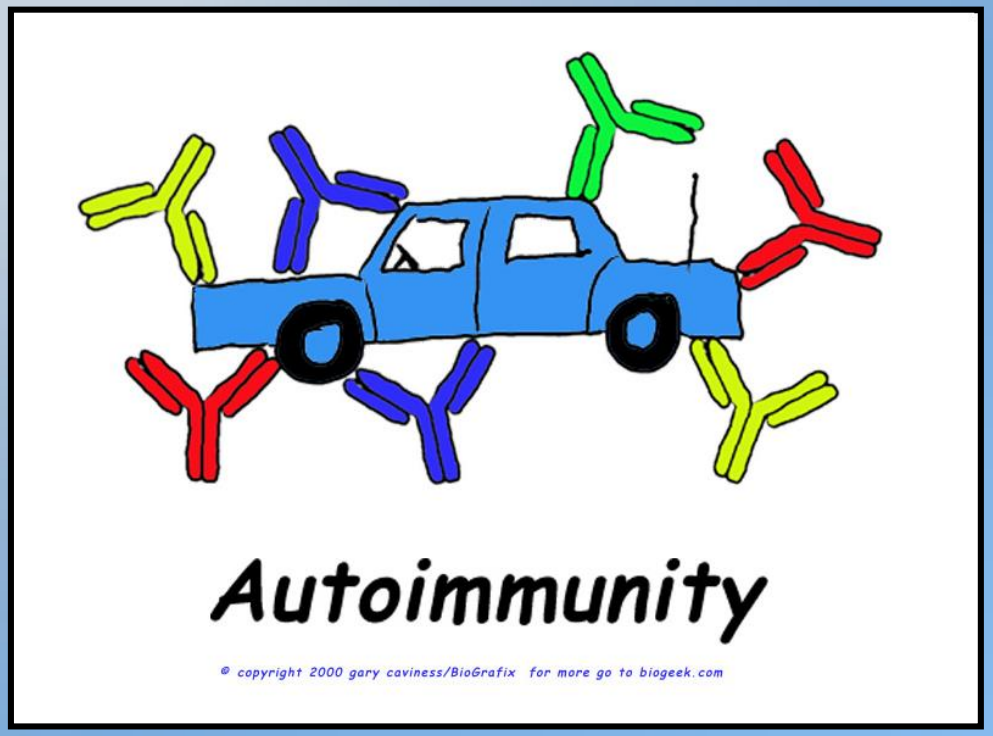
Diseases of the immune system



Lecture II.

Ágota Szepesi

I. Department of Pathology

Autoimmune diseases

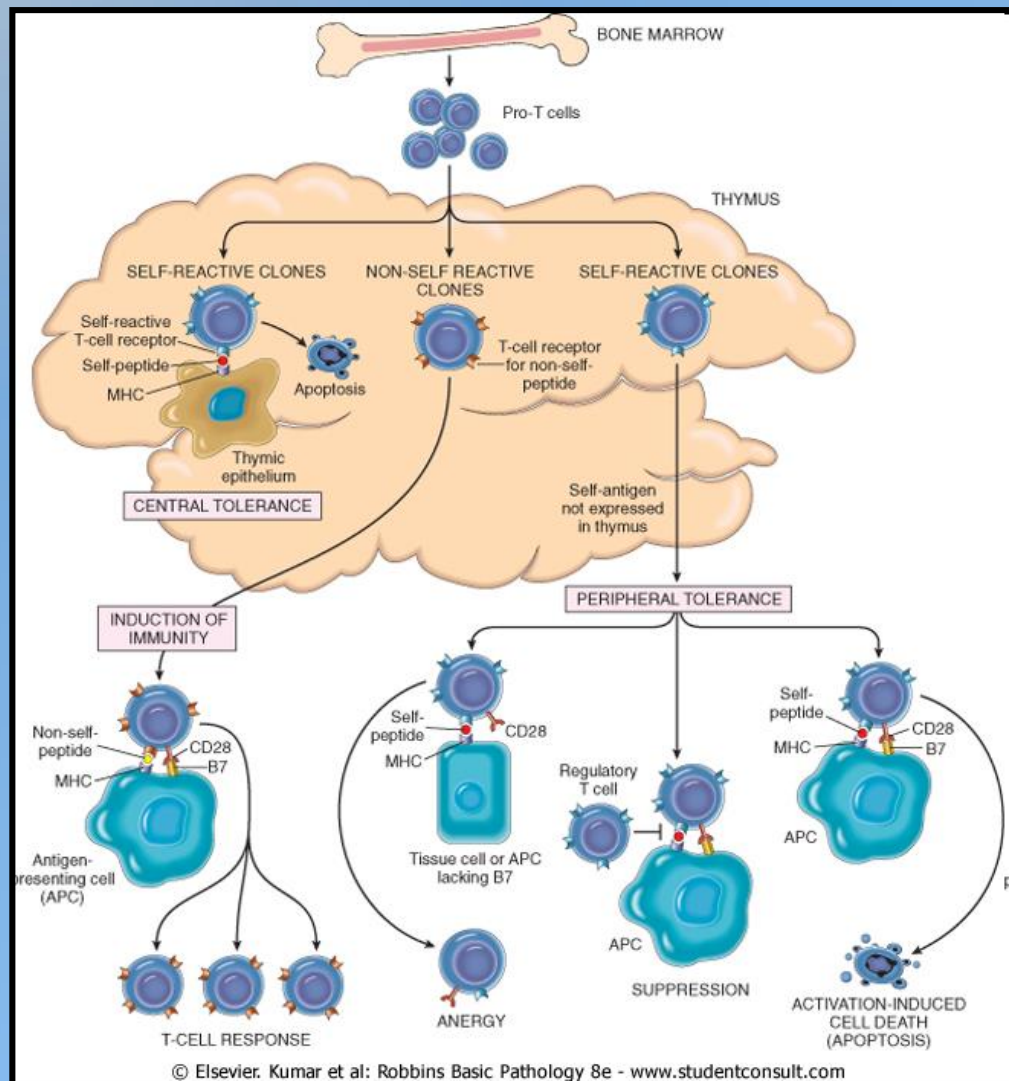
- Definition:
  - immune reaction to *self-antigens*
- Pathomechanism:
  - failure of *self-tolerance*
- Consequence
  - inflammation- tissue damage,
  - loss of function /rarely: increased function due to cell activation, cell proliferation
- Self tolerance
  - No immun reaction against self antigens=*anergy*:

Development of self-tolerance

Tolerance=unresponsiveness

CENTRAL TOLERANCE
develops in primary lymphoid organs

PEERIPHERAL TOLERANCE
1. anergy
2. supression by regulatory T cells
3. apoptosis



Failure of self-tolerance

=Presence of self-reactive B, T lymphocytes

GENETIC background:

Inheritance of susceptibility genes: HLA, immun regulatory genes,
example: HLA-DR4 linked to rheumatoid arthritis

INFECTIONS:

1. Molecular mimicry- rheumatic fever
2. Breakdown of T-cell anergy-infections upregulate APCs

TISSUE INJURY:

Tissue injury can release or change self-antigens:
Traumatic uveitis (sympathetic ophtalmia), orchitis.

Autoimmune diseases

- Systemic diseases

  affect principally the connective tissue and blood vessels: „collagen vascular" or "connective tissue" disorders

- Organ specific

  directed against one particular organ or cell type, that results in localized tissue damage

In general

- Female predominance
- Young adults
- Chronic course
- Immunsupression
- Intercurrent infections
- Autoantibodies
- Overlapping syndromes (systemic forms)

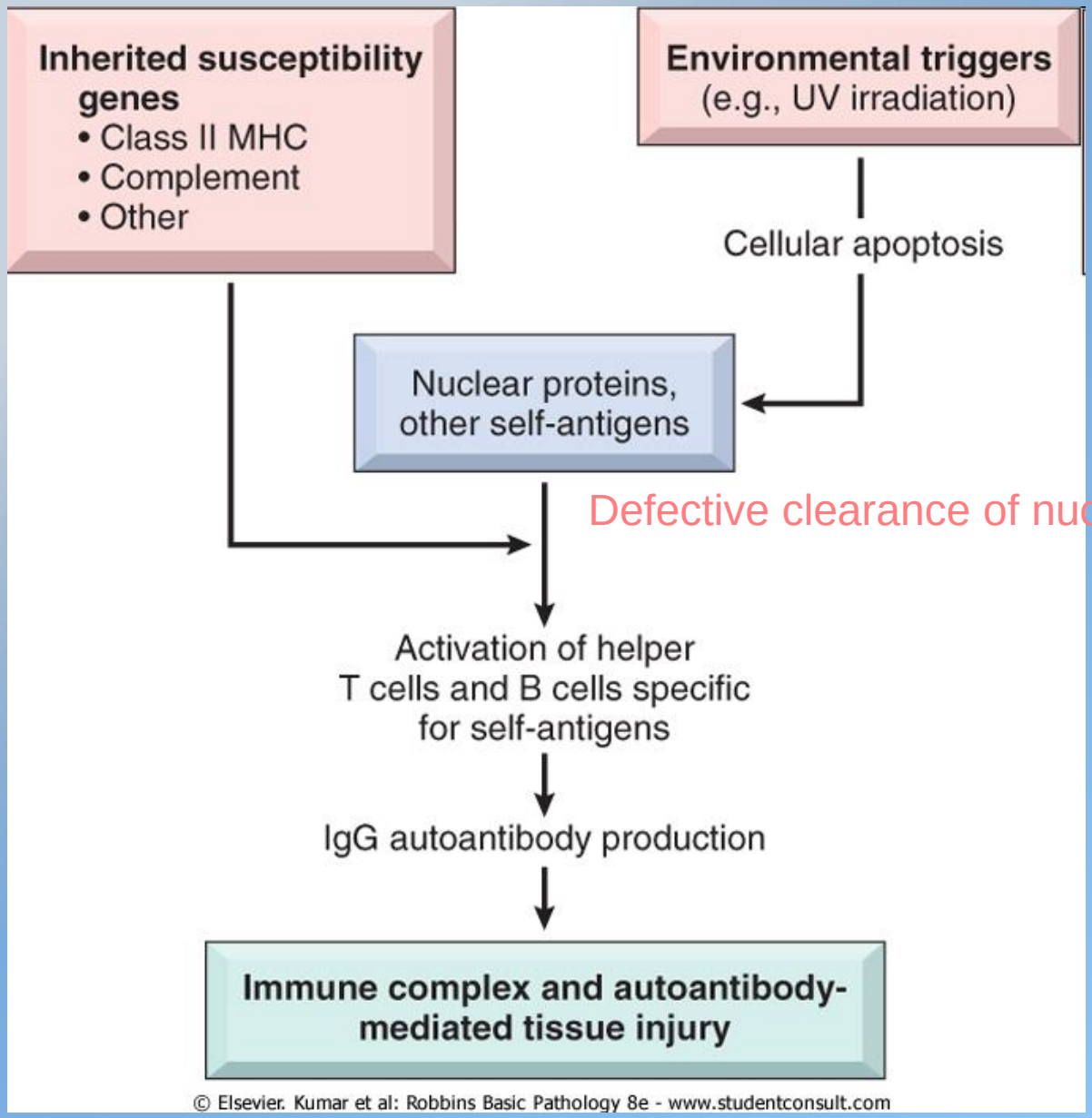
Most important systemic autoimmun diseases

- Systemic lupus erythematosus- SLE
- Systemic sclerosis- SS
- Rheumatoid arthritis- RA
- Dermatomyositis

Systemic Lupus Erythematosus-SLE

- Common disease; 1 case per 2500, female predominance 9:1
- Any organ can be affected : skin, kidneys, serosal membranes, joints, and heart.
- Discoid lupus- only skin involvement
- Genetic predisposition: HLA-DR2 or HLA-DR3 3-5 xrisk
- Clinical presentation variable, overlaps with other autoimmune diseases (rheumatoid arthritis, polymyositis, and others)

Mechanism of autoantibody production



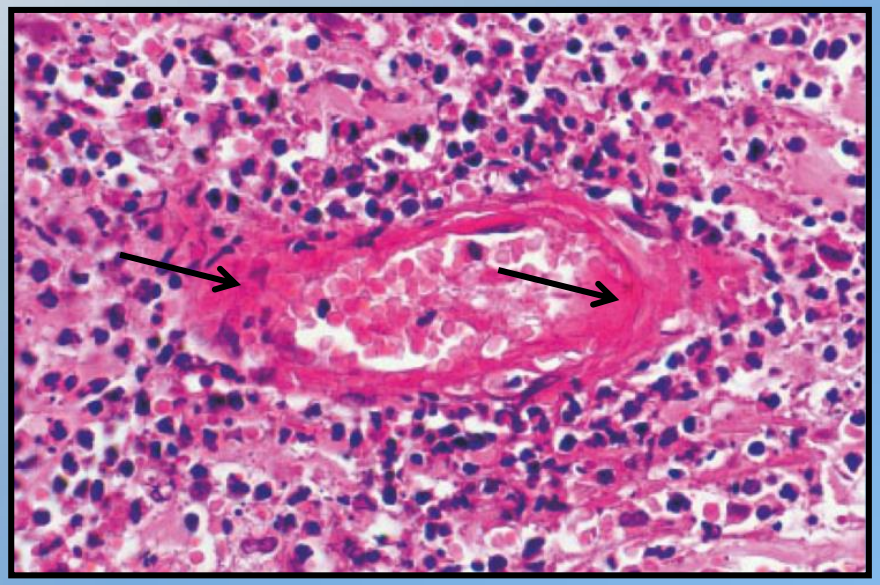
Systemic Lupus Erythematosus

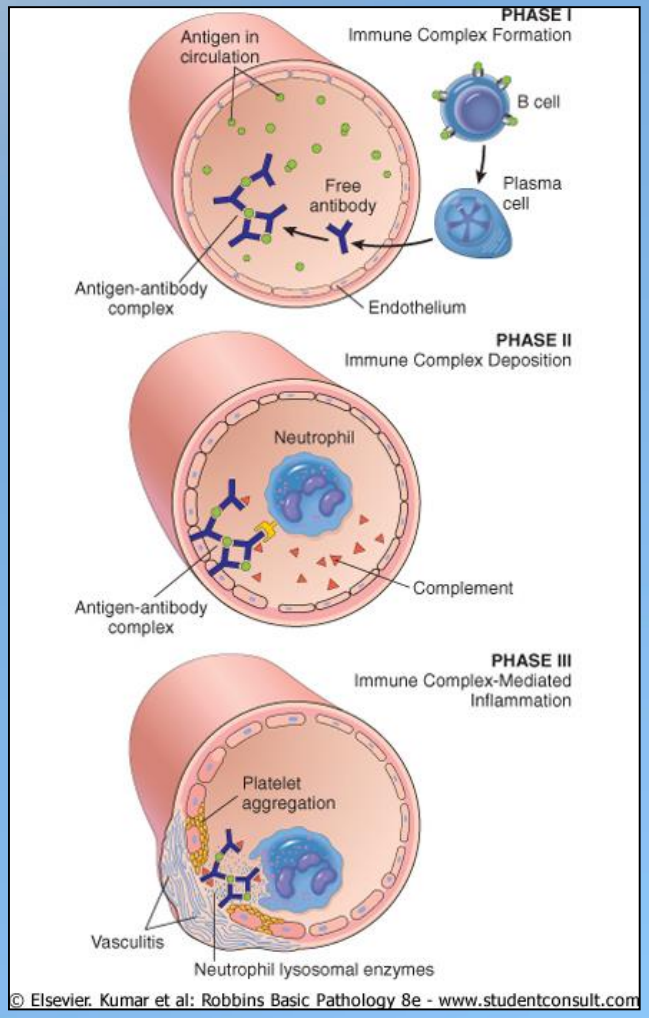
- Autoantibodies:
  - **Antinuclear antibodies (ANAs)** against DNA, histones,nucleolar antigens- immune complex formation -**type III hypersensitivity**
  - **Cell surface antibodies** against blood cells, including red cells, platelets, and lymphocytes-cytopenias -**type II hypersensitivity**
  - **Antiphospholipid antibody** (cell membrane component) "lupus anticoagulants" (prolonged clotting time) prothrombotic state -venous and arterial thromboses -**type II hypersensitivity**
  - **Anticardiolipin antibody**-false + test for syphilis

Vasculitis caused by type III. hypersensitivity

Organs involved: **kidneys, joints**, **skin** and small blood vessels in many tissues.

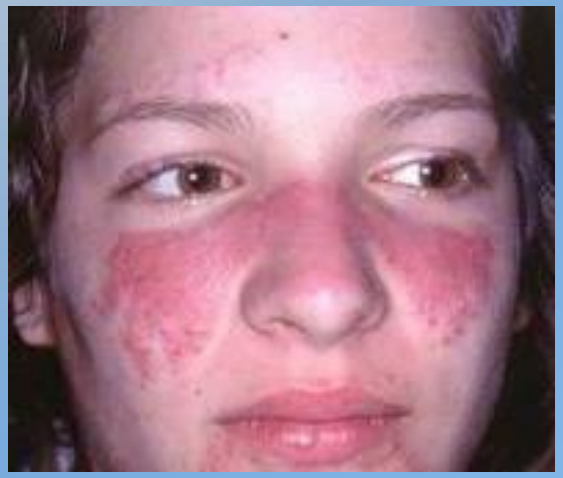
Acute necrotizing vasculitis with **fibrinoid necrosis**





Skin

- Butterfly rash over the face
  - –immuncomplex deposition
- Photosensitivity
  - – UV light causes apoptosis

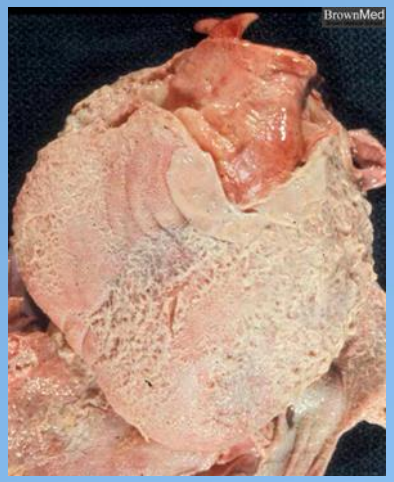


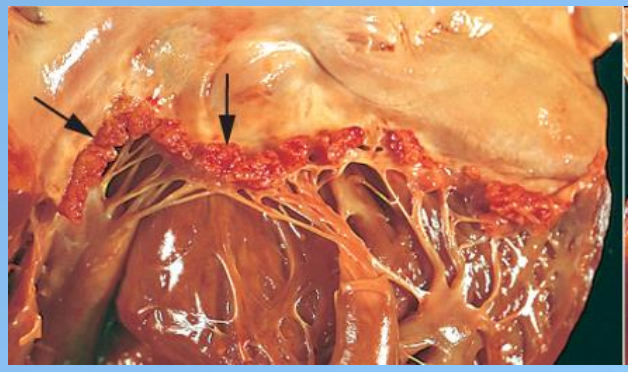
Heart

- Fibrinous pericarditis
- Libman-Sacks endocarditis

  –immuncomplex deposition

  sterile vegetations= small thrombus



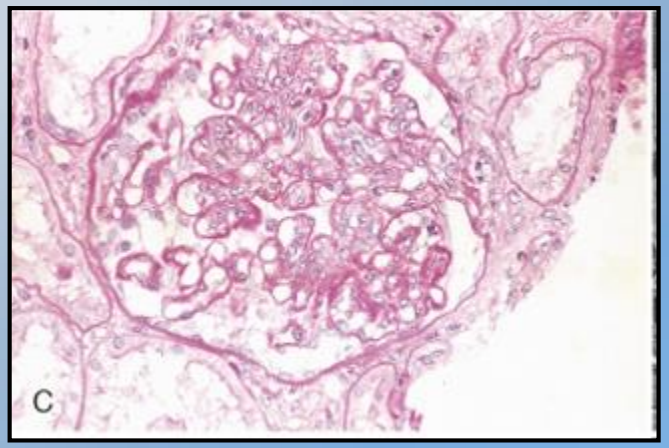


Kidney- Lupus nephritis

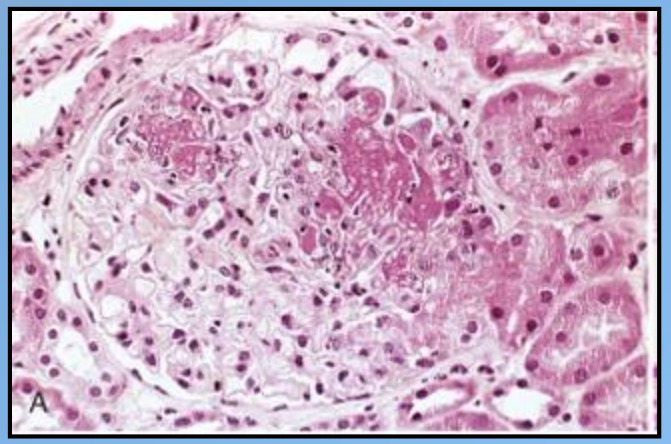
- **Chronic glomerulonephritis**

  – **Histology:**

Membranous glomerulonephritis

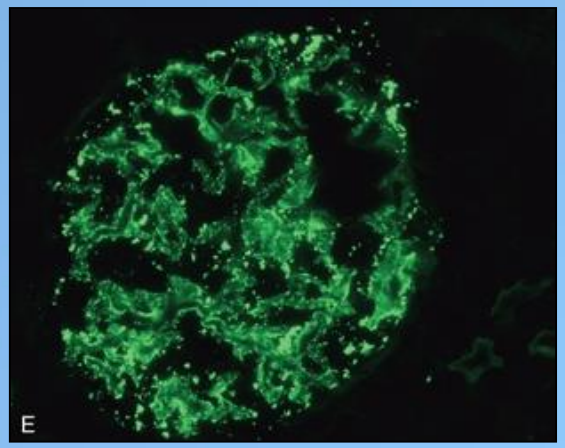


Proliferative



Immunfluorescence microscopy

- deposition of immuncomplexes in the capillary walls



Joints, serosal membranes, CNS

- **Arthritis**: nonspecific
- **Serositis**: serous effusions to fibrinous exudates, pericarditis
- **CNS involvement:** Seizures-vascular lesions caused by microthrombuses- ischemia or multifocal cerebral microinfarcts (antiphospholipid antibodies)

Major causes of death:

1. Renal failure,
2. Intercurrent infections,
3. Diffuse CNS involvement

(5 year survival :95%)

Clinical diagnostic criteria: at least 4 out of 11 symptoms

TABLE 6–8 1997 Revised Criteria for Classification of Systemic Lupus Erythematosus*

Criterion	Definition
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
5. Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	Pleuritis—convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion, or Pericarditis—documented by electrocardiogram or rub or evidence of pericardial effusion
7. Renal disorder	Persistent proteinuria >0.5 gm/dL or >3 if quantitation not performed or Cellular casts—may be red blood cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder	Seizures—in the absence of offending drugs or known metabolic derangements (e.g., uremia, ketoacidosis, or electrolyte imbalance), or Psychosis—in the absence of offending drugs or known metabolic derangements (e.g., uremia, ketoacidosis, or electrolyte imbalance)
9. Hematologic disorder	Hemolytic anemia—with reticulocytosis, or Leukopenia—$<4.0 \times 10^9$ cells/L (4000 cells/mm^3) total on two or more occasions, or Lymphopenia—$<1.5 \times 10^9$ cells/L (1500 cells/mm^3) on two or more occasions, or Thrombocytopenia—$<100 \times 10^9$ cells/L (100×10^3 cells/mm^3) in the absence of offending drugs
10. Immunological disorder	Anti-DNA antibody to native DNA in abnormal titer, or Anti-Sm—presence of antibody to Sm nuclear antigen, or Positive finding of antiphospholipid antibodies based on (1) an abnormal serum level of IgG or IgM anticardiolipin antibodies, (2) a positive test for lupus anticoagulant using a standard test, or (3) a false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by negative *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
11. Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with drug-induced lupus syndrome

*This classification, based on 11 criteria, was proposed for the purpose of identifying patients in clinical studies. A person is said to have systemic lupus erythematosus if any 4 or more of the 11 criteria are present, serially or simultaneously, during any period of observation.

From Tan EM et al: The revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 25:1271, 1982; and Hochberg MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 40:1725, 1997.

Table 6–8 1997 Revised Criteria for Classification of Systemic Lupus Erythematosus*

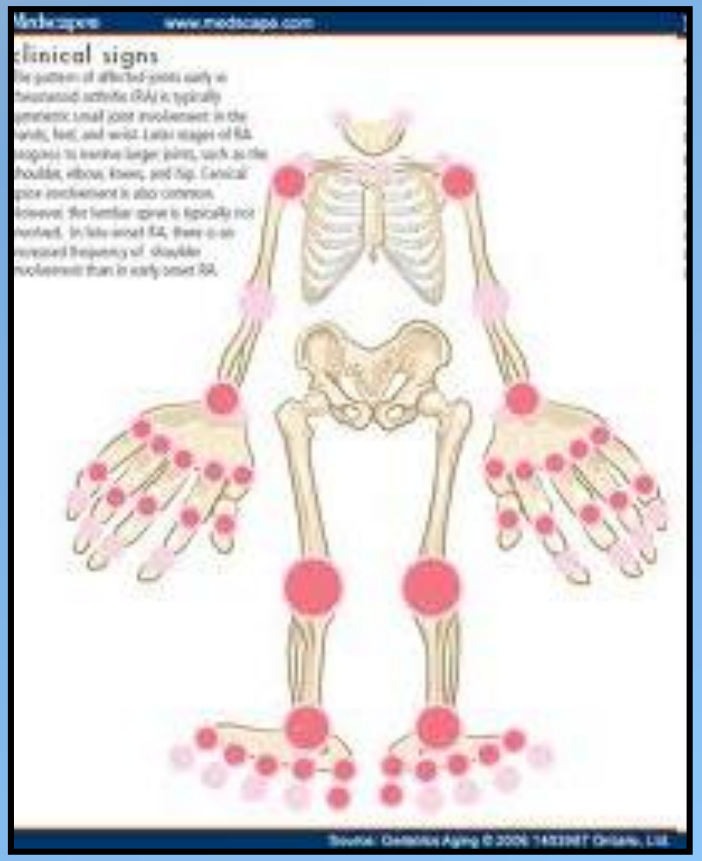
Rheumatoid Arthritis

-1% of the population

-F/M : 3-4/1

-Symmetric chronic arthritis, principally affecting the small joints

-Systemic disease:extra-articular involvement : skin, heart, blood vessels, muscles, and lungs-RA may resemble SLE or scleroderma

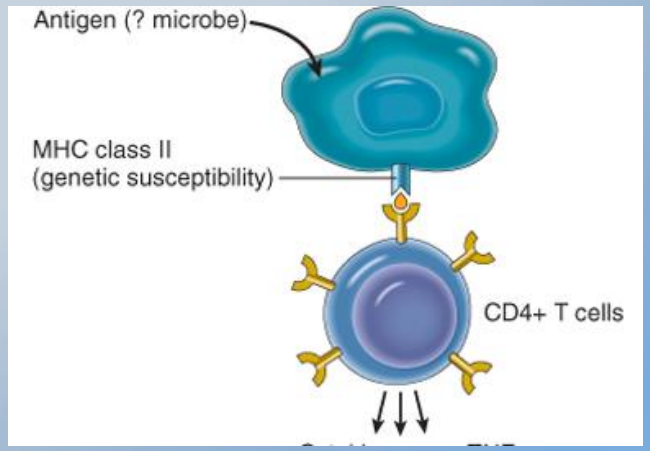


proximal interphalangeal and metacarpophalangeal joints

Chronic inflammatory synovitis

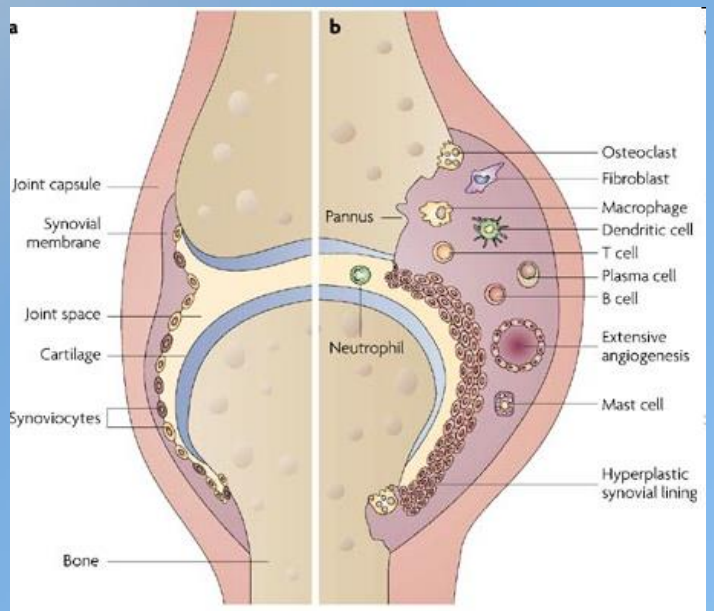
Pathomechasnism: Type IV hypersensitivity
CD4+ helper T cell mediated

HLA-DR4

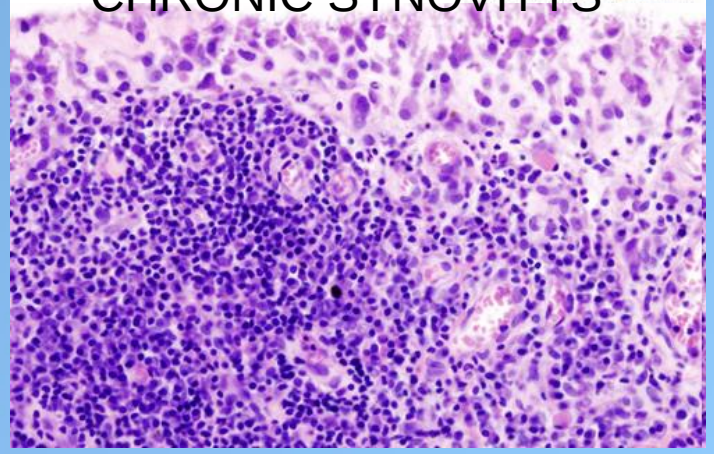


Activation- macrophage
endothel cells
B-cell

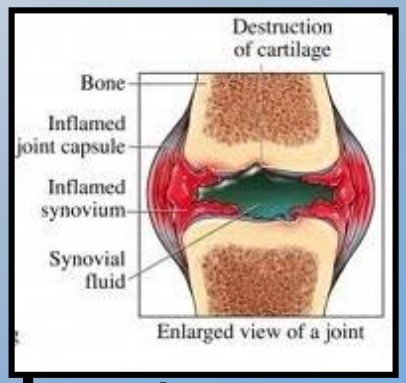
Production of autoantibodies:
rheumatoid factor *(RF)- IgM/ IgG* against Fc portions of their own (self) IgG

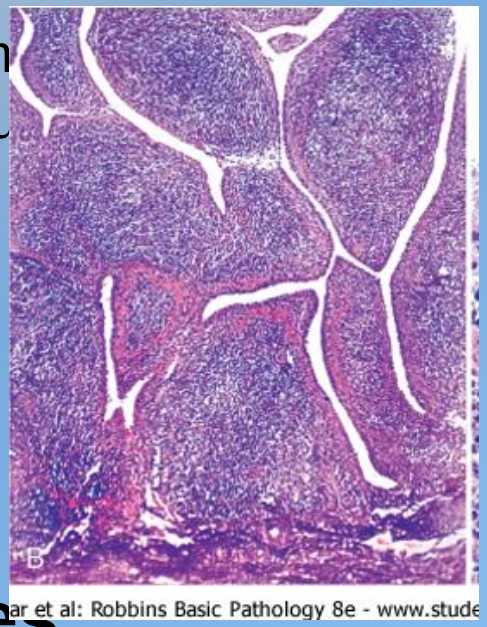


CHRONIC SYNOVITYS



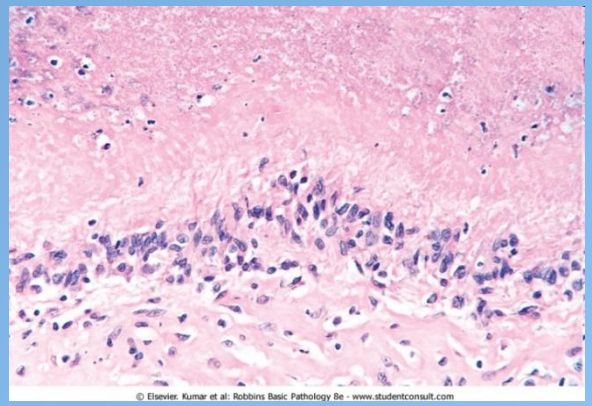
- **Chronic inflammatory synovitis**
  - **Pannus**: proliferating synovial-lining cells adm
    inflammatory cells, granulation tissue, and fibrou
    tissue;





ar et al: Robbins Basic Pathology 8e - www.stude

- **Rheumatoid subcutaneous nodules**
  - **Granulomas** ~2 cm diam.
    with necrobiotic
    center.



- **Serositis: fibrinous pleuritis or pericarditis**

Late consequences:

- **Progressive joint destruction** leading to disability after 10-15 years.

Ankylosis: loss of flexibility due to fibrosis and calcification
Ulnar deviation

- 5-10% **amyloidosis** (chronic inflammation)

  therapy: cytokine (TNF) antagonists

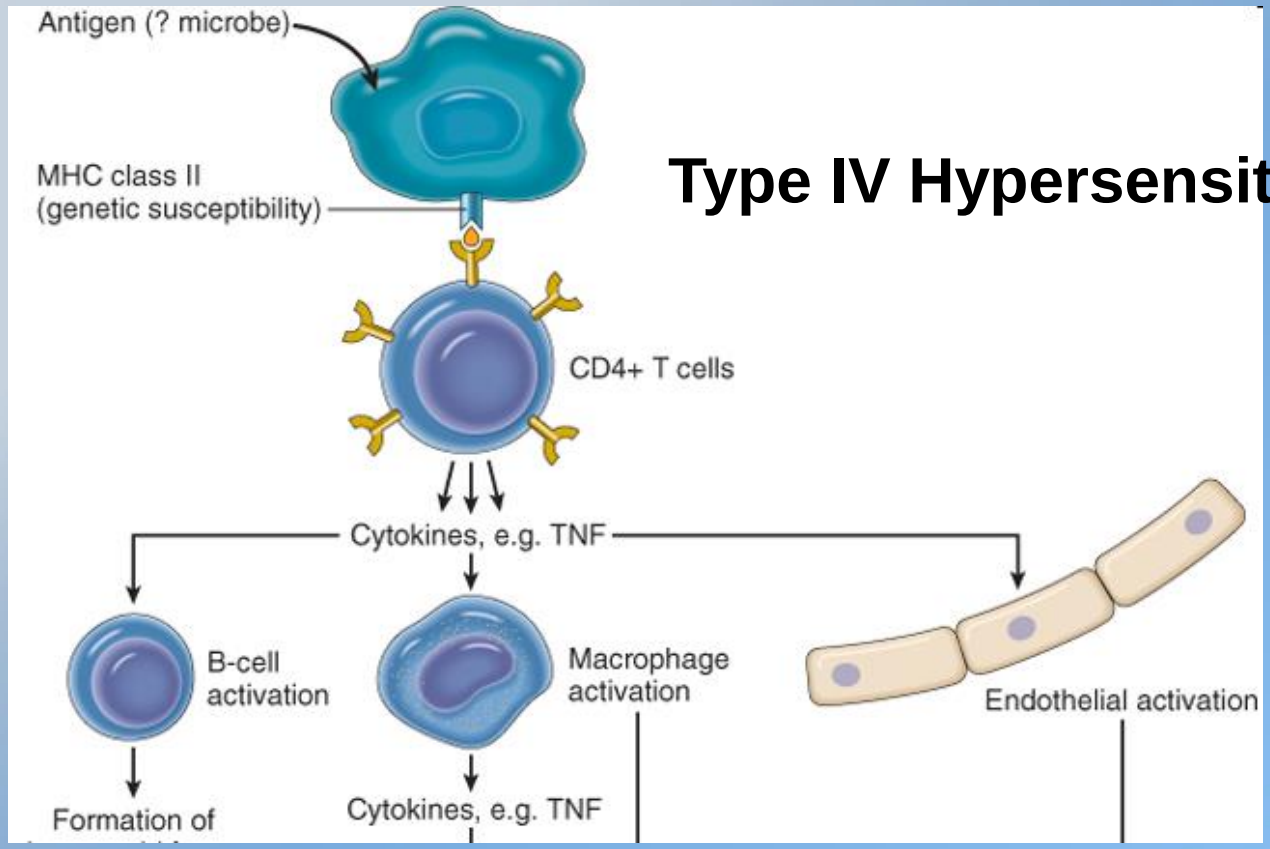
Systemic Sclerosis/ SS Scleroderma

- Fibroblast activation with excessive fibrosis, microvascular injury

1. Limited scleroderma: Skin

2. Diffuse scleroderma: Skin+ gastrointestinal tract, lungs, kidneys, heart, and skeletal muscles

Pathomechanism: CD4+ T cell activation



Type IV Hypersensitivity

Autoantibodies
ANAs

Immune complex

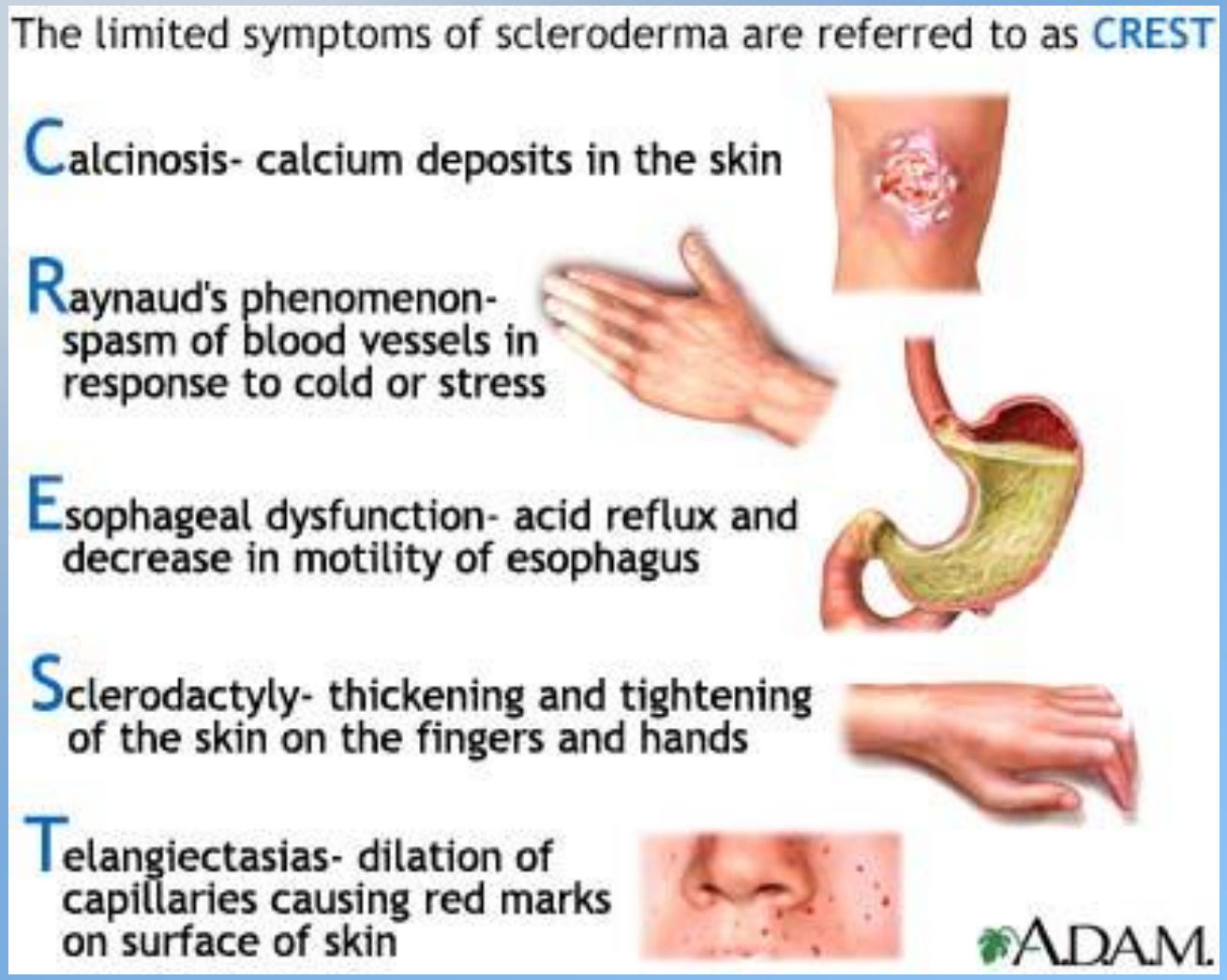
Type III Hypersensitivity

PDGF, TGFβ
IL1, FGF

Damage
periadventitial fibrosis
and narrowing
ischemic injury

Inflammation,fibrosis, atrophy

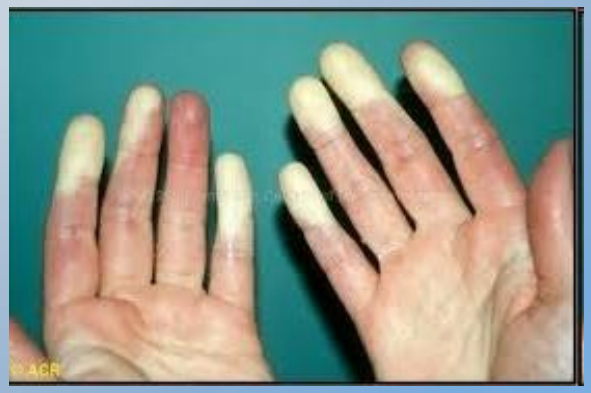
Limited Scleroderma- CREST syndrom



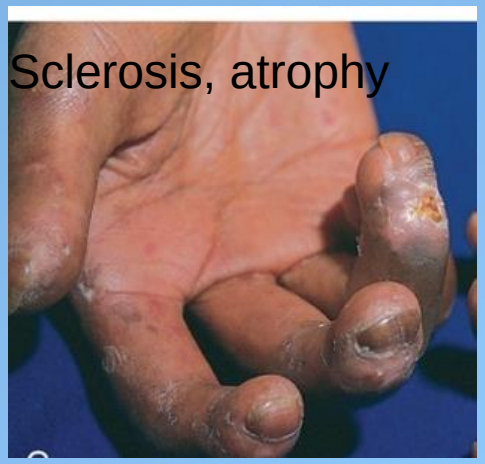
Limited scleroderma-Skin

Raynaud's phenomenon: In 70% of the patients this is the first symptom
Induced by cold, emotion
Results: vasoconstriction, hypoxia ➔ ulcers, gangrene

EARLY phase



LATE phase

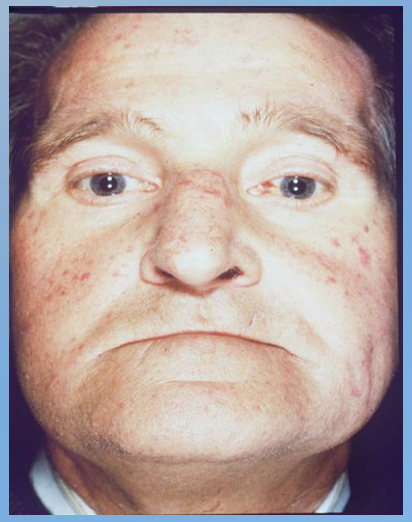


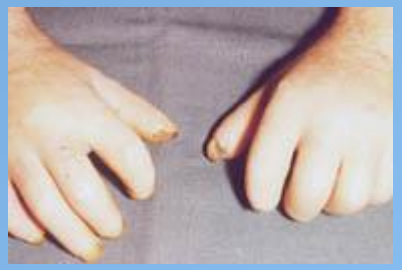
Skin involvement:

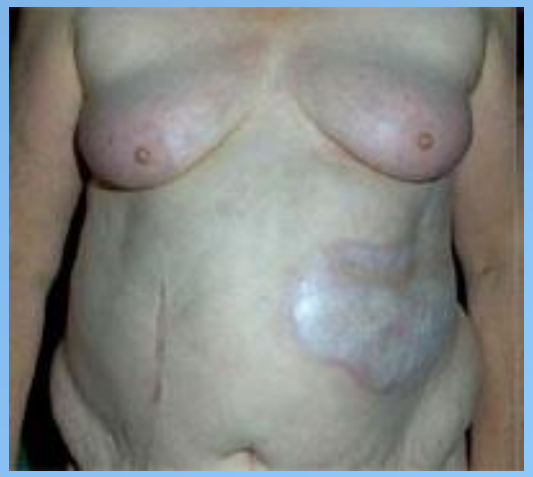
1. Involvement of the fingers and hands to wrist- acrosclerosis
   - Face- mask like
   - Fingers: sclerodactily

2. Proximal extremity: ascending sclerosis including the forearm

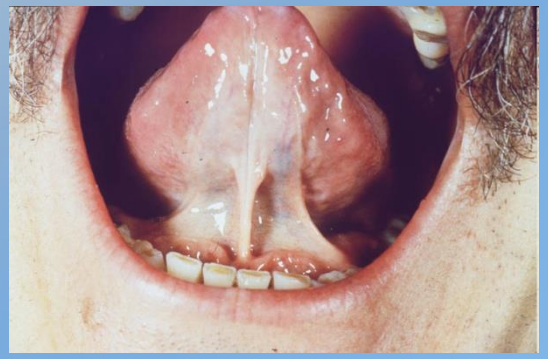
3. Sclerosis at the trunk.







Diffuse scleroderma- visceral involvement



GI tract involvement:
in 90% of the patients
Tongue: sclerosis of the frenulum
Oesophagus: dysmotility: fibrosis,
gastroesophageal reflux- Barrett metaplasia

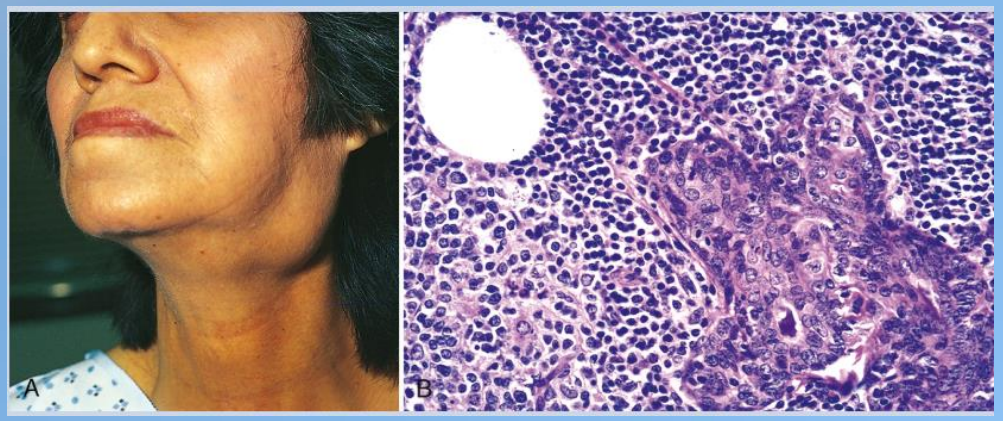
Lung: 50% of the patients
Interstitial fibrosis- pulmonary hypertension

Diagnosis: serology, detection of autoantibodies:

- Diffuse Scleroderma specific ANA :
  - **DNA-topoisomerase** (70%)
- Limited scleroderma spesific ANA:
  - **anticentromere antibody** (90%)

Sjögren syndrome

- Dry eyes -keratoconjunctivitis sicca
- Dry mouth- xerostomia
- Pathomechanism: Type IV. HS, CD4+ T
- Diagnosis:
  - Histology of small salivary glands: lymphocytic infiltration, fibrosis
  - Serology: SS-A, SS-B- anti-ribonucleoprotein antibodies (70%-reumatoid factor)



Xerostomia

- Causes:
  - Sjögren s,
  - radiation therapy
  - medications! (anticholinergic, antidepressant/antipsychotic, diuretic, antihypertensive, sedative)
- Consequence:
  - atrophy of the papillae of the tongue, with fissuring and ulcerations,
  - dental caries, candidiasis,
  - difficulty in swallowing and speaking.

Organ-spesific autoimmune diseases

- Liver: autoimmune hepatitis, PBC, PSC
- Pancreas: autoimmune pancreatitis
- Suprarenal gl: autoimmune adrenalitis
- Thyroid gland: Hashimoto thireoiditis, Graves disease

Autoimmune hepatitis

- Pathomechanism: CD4+ helper T cell mediated reaction
  - Association with other autoimmune diseases (60%): RA, IBD, Sjögren sy.
- Female predominance (70%)
- Clinical picture: Mild-severe chronic hepatitis, 5% of the cases progress to cirrhosis and death.
- Diagnosis: Presence of autoantibodies: anti-SMA, liver/kidney microsomal antobodies.

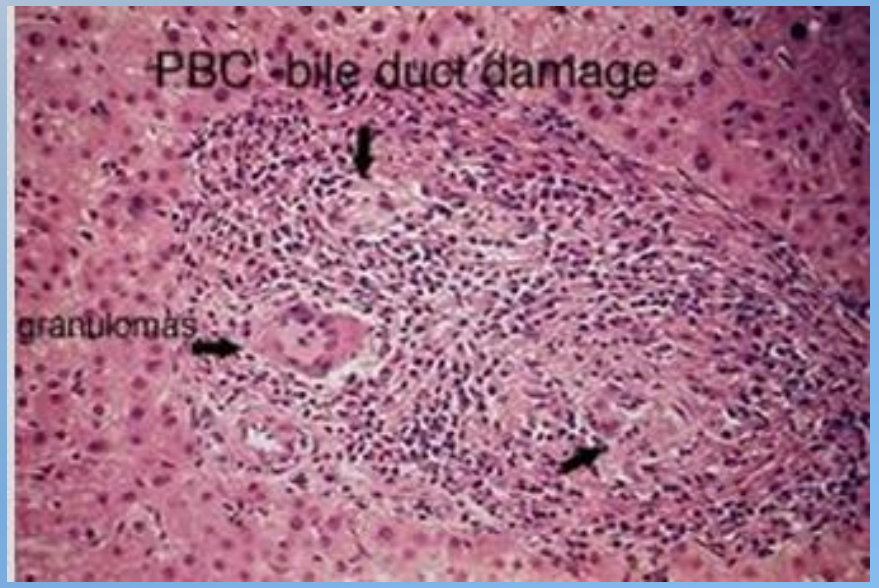
Primary biliary cirrhosis -PBC

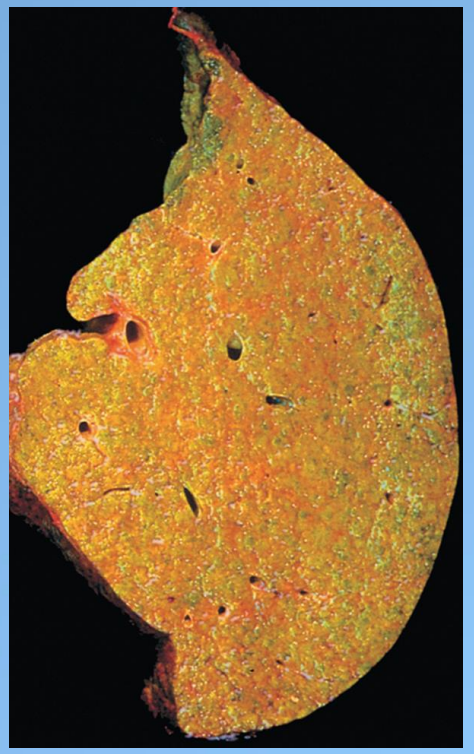
Chronic, progressive liver disease- middle aged women

Diagnosis:

Serology, anti-mitochondrial antibodies –AMA- 90%

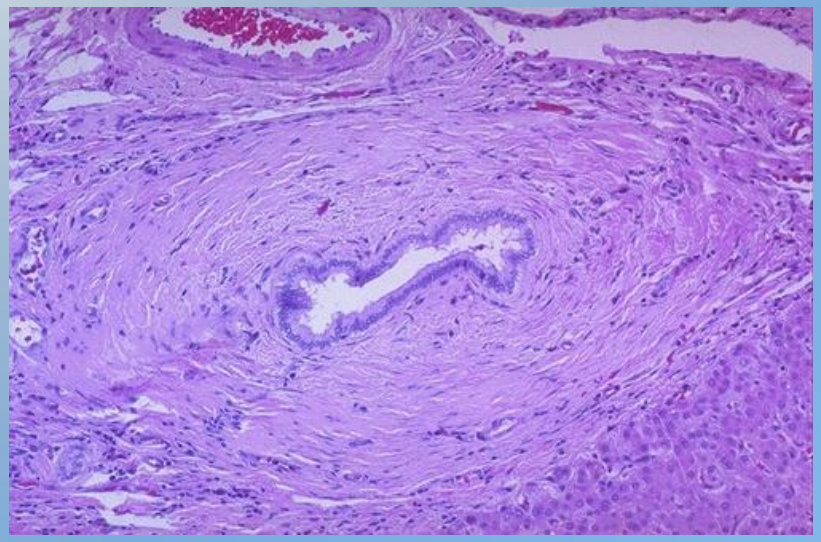
Histology: Chronic cholangitis, cholestasis (green liver), micronodulare cirrhosis



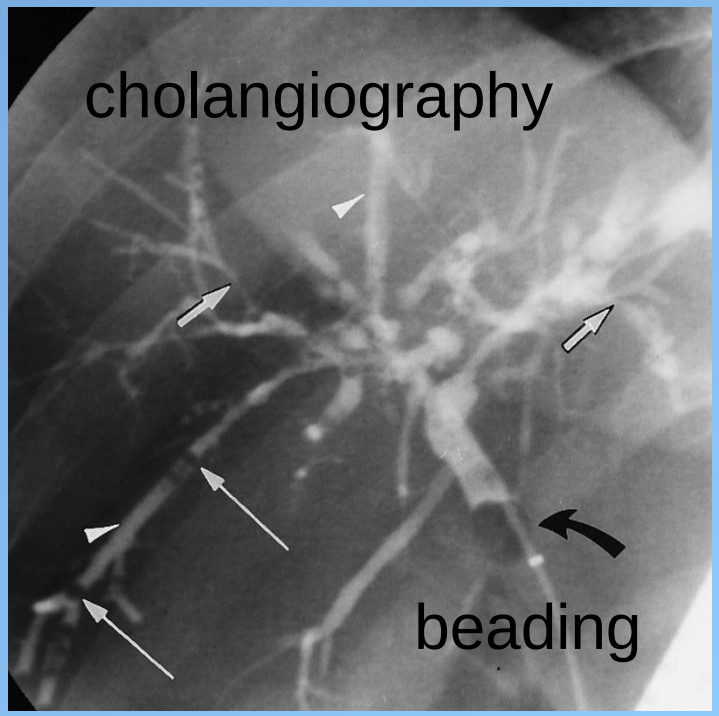


Primary sclerosing cholangitis PSC

-Chronic cholestatic liver disease associated with destruction of intra- and extrahepatic bile ducts of all size, leading to secundary biliary cirrhosis
-Association with ulcerative colitis (70%)
Diagnosis: Histology, cholangiography



Onion skinning



Addison disease

- Primary insuffitiency of the adrenal cortex
  - Autoimmune adrenalitis- 60-70% of primary adrenal insuffitiency
  - Other causes of adrenal insuffitiency:TBC, AIDS, metastasis-lung cancer
- Cause: genetic: mutation of the autoimmune regulator gene, FAILURE OF CENTRAL SELF-TOLERANCE
- Histology: lymphocytic infiltration,
- Symptoms: weight loss, fatigue, anorexia, depression, skin hyperpigmentation

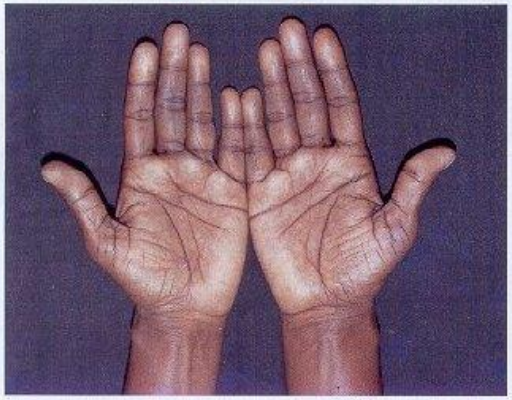
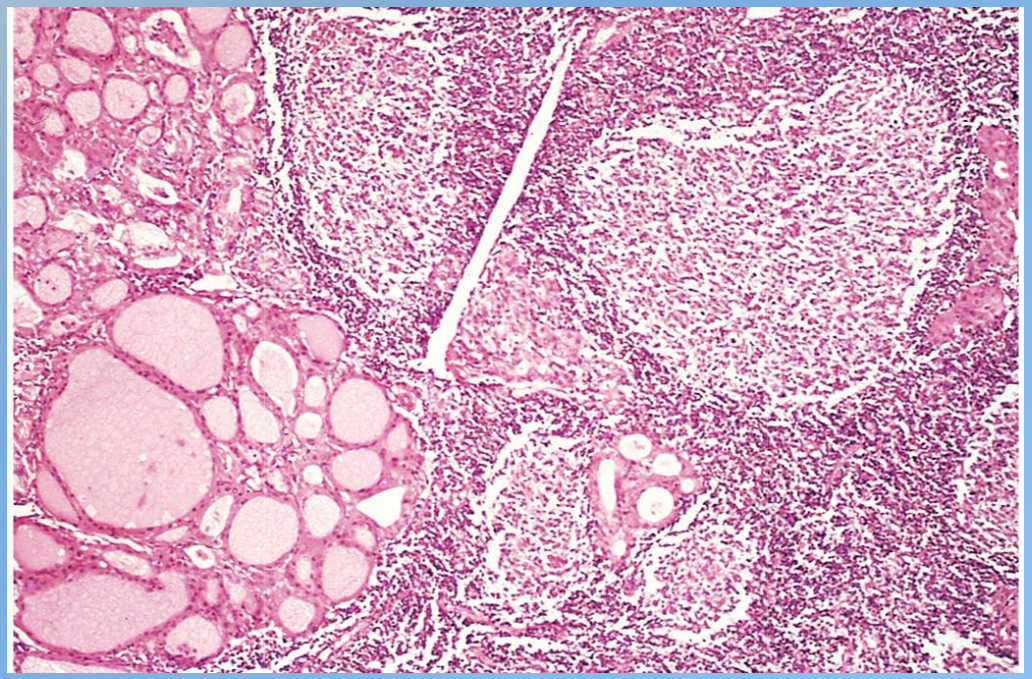


Fig. 2 Addison's disease – hyperpigmentation involving the palms of the hand.

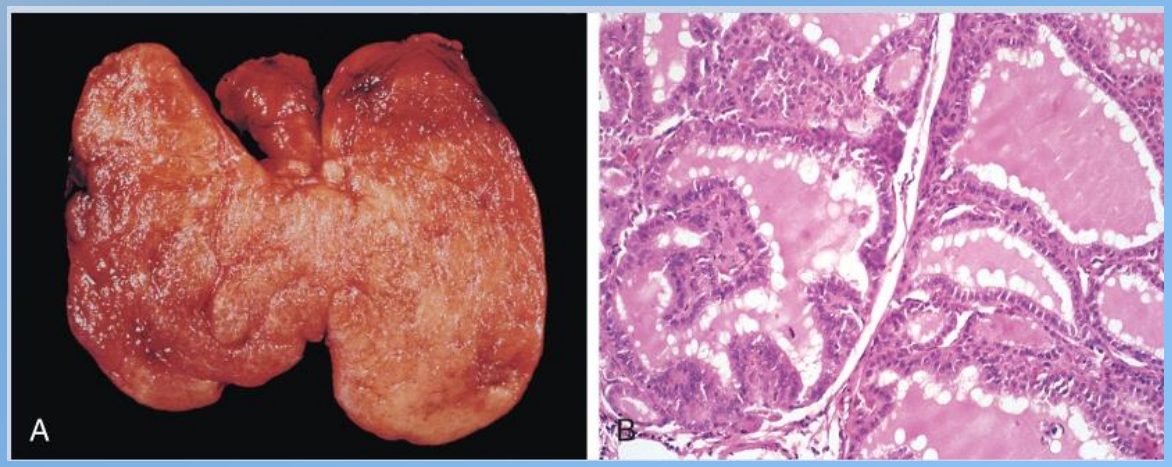
Hashimoto thyreoiditis

- CD8+ and CD4+ T-cell and antibody mediated tissue injury (*anti-thyroglobulin antibodies)*
- Histology: lymphocytic infiltration with germinal centers



Graves disease- diffuse goiter

- Mediated by anti-TSH receptor stimulating antibodies- TYPE II. HS
- Clinical symptoms (triad):
  - Symmetric enlargment of the gland+hyperthiroidism
  - Exophtalmus
  - Pretibial myxoedema



IMMUNODEFICIENCY

- primary
  - inherited defects affecting immune system development

SEVERE

- secondary
  - effects of other diseases
    - 1. infections/sepsis
    - 2. immunosuppressiv therapy-transplantation!
    - 3. chemotherapy
    - 4. malignant tumors
    - 5. autoimmunity

SEVERE-MODERATE

    - 6. aging
    - 7. malnutrition
    - 8. chronic diseases (liver, kidney)

MILD

Primary immunodeficiency

- Early diagnosis (6 month-2 years)
- Pathological T cell, B cell development and mixed diseases
- Clincal symptoms: Infections
  - T cell deficiency: Viral (herpes,varicella/zoster), fungal (candida, cryptococcus), protozoal (toxoplasma) intracellular bacteria (tuberculosis).
  - B cell def.: streptococcus, staphylococcus, haemophilus

X-Linked Agammaglobulinemia: Bruton Disease

- Failure of B cell differentiation
- X-linked disease- women are carriers
- Underdevelopment of lymphoid tissues,
- Absence of immune globulins , normal T cell-mediated responses
- Bacterial infections
- Increased risk for autoimmune diseases

Thymic Hypoplasia: DiGeorge Syndrome

- Congenital defect in thymic development with deficient T cell maturation.
- Infections: Viral (varicella/zoster), fungal (candida, cryptococcus), and protozoal (toxoplasma) infections and infection with intracellular bacteria (tuberculosis).
- Treatment: transplantation of thymic tissue

Severe combined immundeficiency (SCID)

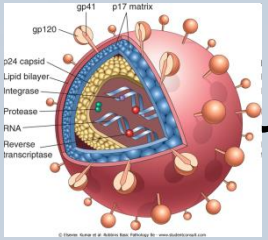
- Different genetic background (mutation of the immun regulatory molecules- IL)
- Hypoplasia of all lymphoid tissues
- Early death due to infections
- Opportunistic infections: candida, pneumocystis, CMV, pseudomonas.

Wiskott-Aldrich syndrome combined immundeficiency with thrombocytopenia and ekcema

- X-linked recessive disease-males
  - Mutation of the Wiskott-Aldrich syndrome protein- links several membrane receptors to the cytoskeleton
- Progressive age-related combined immundefficiency
  - depletion of T lymphocytes, decreased antobody production-
- Early death- infections, malignant lymphoma

Isolated IgA Deficiency

- Most common , 1:700
- Block of differentiation of B cells to IgA secreting plasma cells
- Lack of IgA- weakened mucosal defenses predispose patients to recurrent sinopulmonary infections and diarrhea.
- Increased risk for autoimmune diseases



uired Immunodeficiency Syndrome

- Infection: human immunodefficiency virus (HIV) human retrovirus (RNA)
- depletion of CD4+ T lymphocytes, and by profound immunosuppression leading to -
  - secondary neoplasms,
  - opportunistic infections
  - neurologic manifestations
- 95% of HIV infections are in developing countries
- 35 million people infected, new infections 5 million/ year
- new anti-retroviral drugs!

Transmission

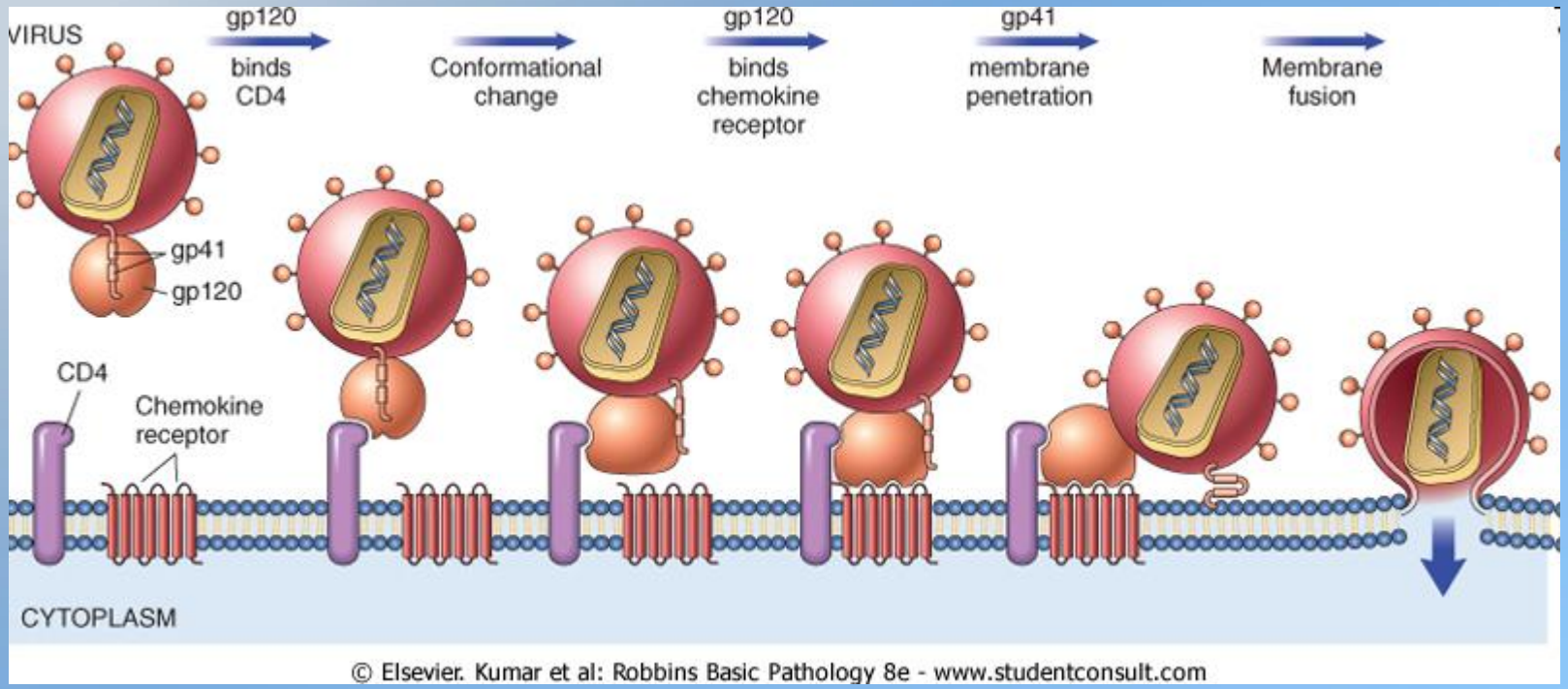
CLOSE CONTACT NEEDED

Exchange of blood or body fluids (seminal fluid) that contain the virus or virus-infected cells

- Sexual Transmission- homosexual and heterosexual contacts-increasing!
- Parenteral Transmission- intravenous drug abusers , (recipients of blood transfusion)
- Mother-to-Infant Transmission (>10%)
- Through nonintact skin - health care workers
  - accidental needle-stick injury or exposure of nonintact skin to infected blood
  - seroconversione rate about 0.3% per accidental exposure- antiretroviral drugs!!!

Infection

CD4 molecule- high-affinity receptor for the virus
Infected cells: CD4+ T cells, macrophages , dendritic cells.



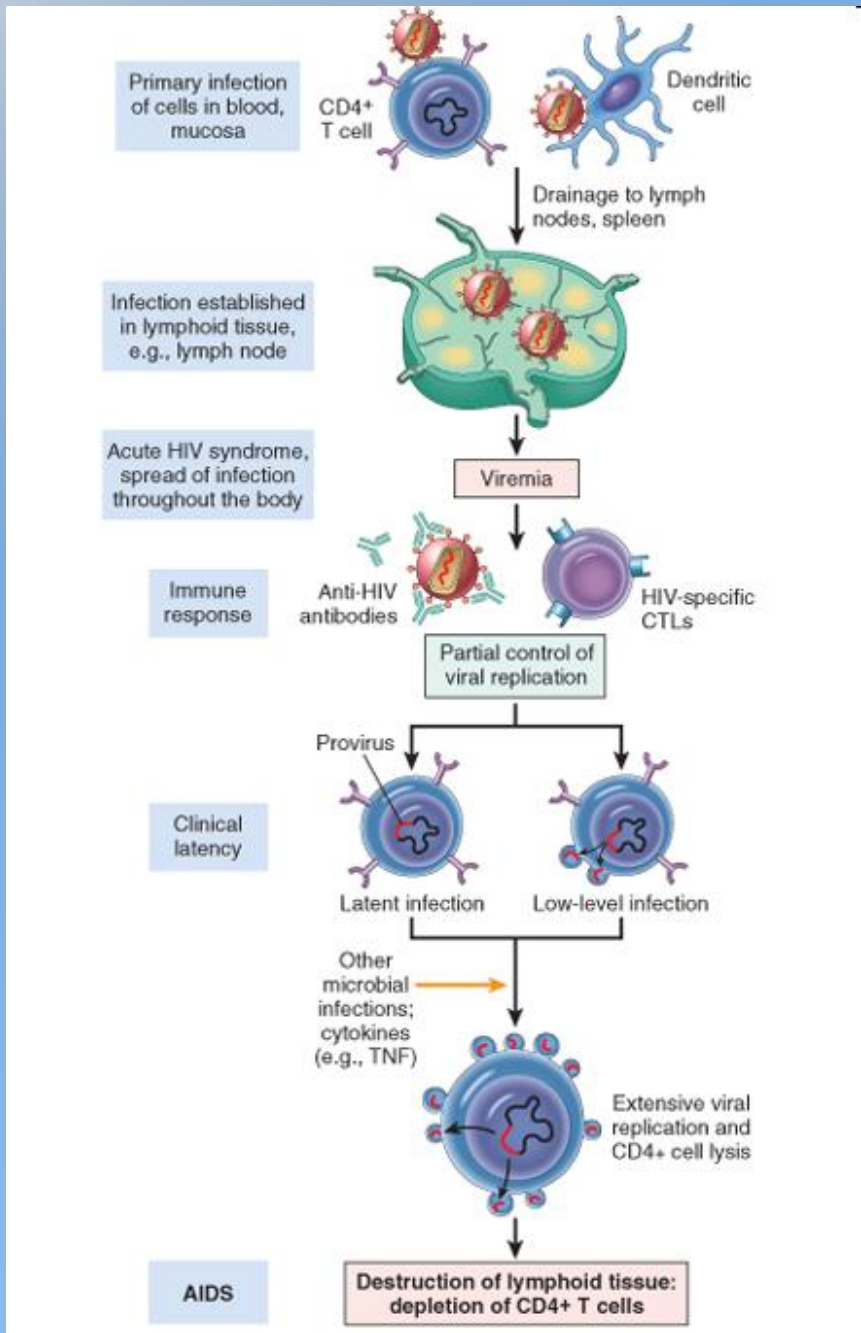
Disease course

- 1. Latent infection (3-6 week):
- HIV proviral cDNA in quiescent T cells
- Dividing T cells: integrated into the host genome

- 2. Acut phase/ productive infections (influenza-like syndrome):

- 3. chronic phase (silent): lymph nodes and the spleen are sites of continuous HIV replication and cell destruction

- 4. AIDS- decline in the number of CD4+ T cells >200/ μl blood

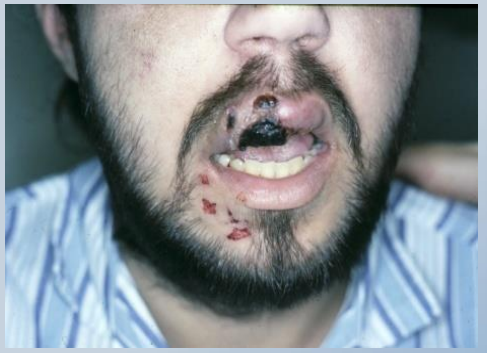


Opportunistic infections

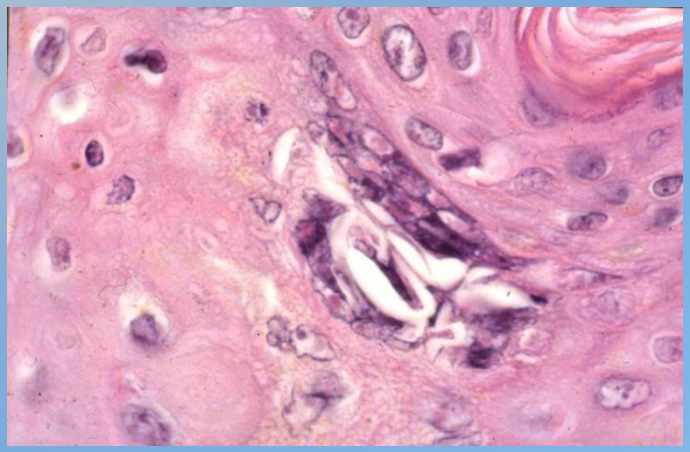
- **Viral**: Herpes simplex, herpes zoster, cytomegalovirus
- **Bacterial**: tuberculosis-mycobacterium avium intracellulare
- **Fungal**: Candidiasis, pneumocystis, cryptococcus, aspergillus
- **Protozoon**: toxoplasma

Viral infections

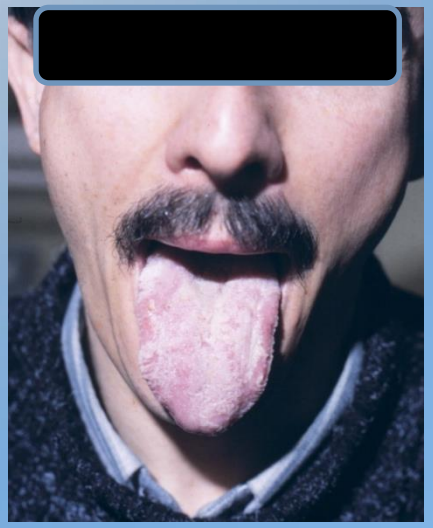
Herpes labialis
Herpes simples virus 1

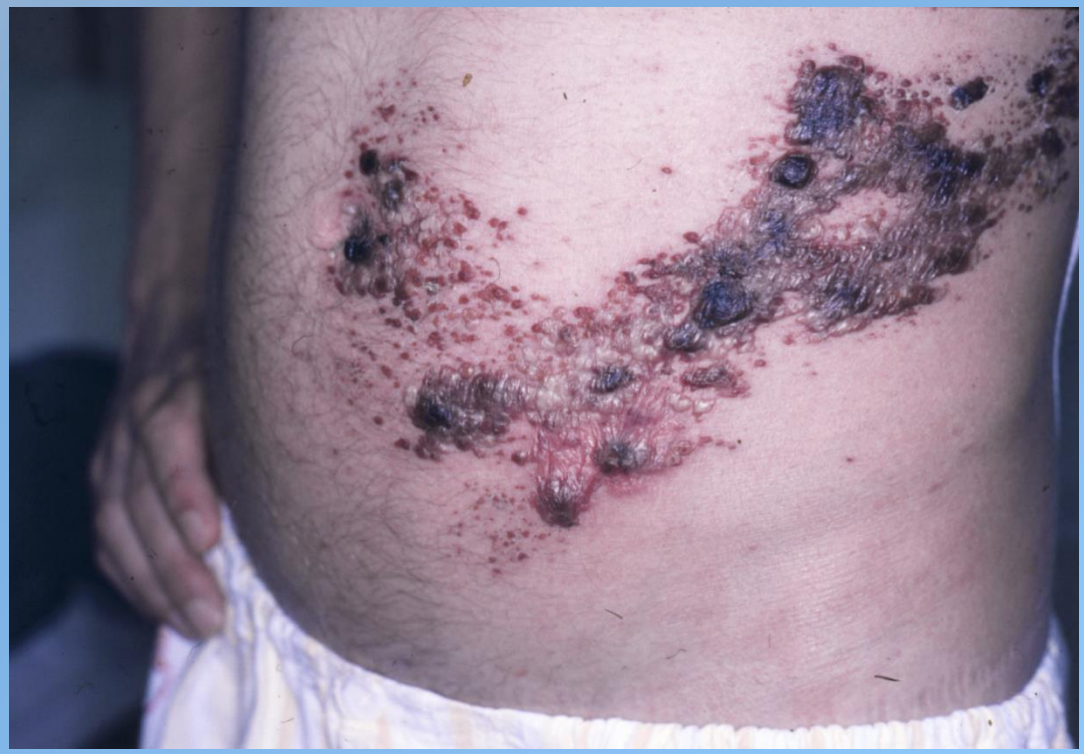


Herpes zoster varicella



Oral hairy leukoplakia
EBV

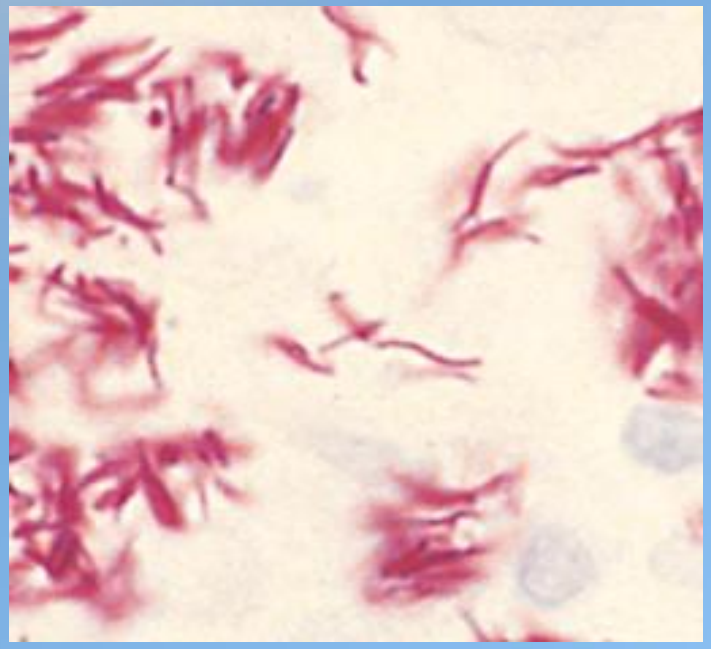




Bacterial infections

Atypical mycobacteriosis: mycobacterium avium intracellulare complex (MAC)
Disseminated disease- lungs+GI
No granulomatosus reaction

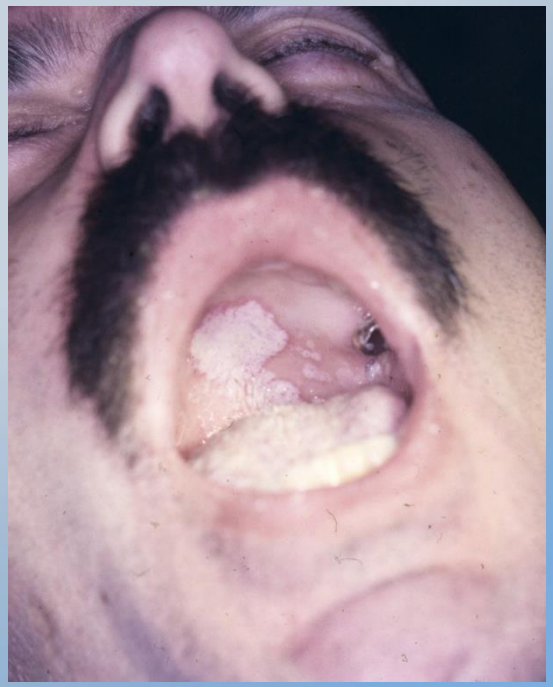
Acid-fast staining- Ziehl-Nielsen



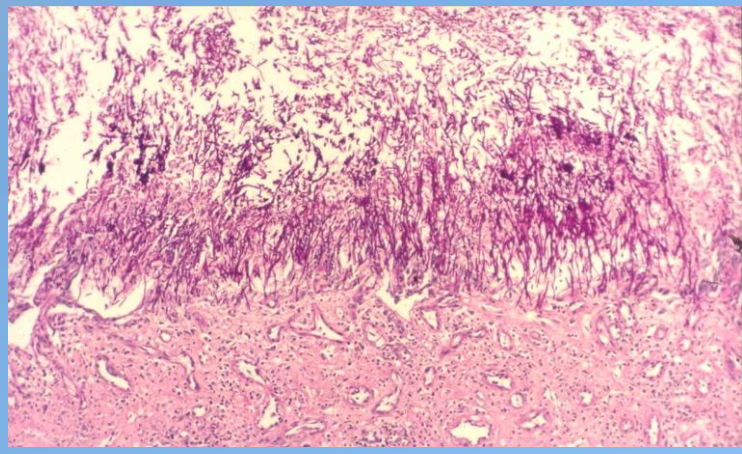
Fungal infections

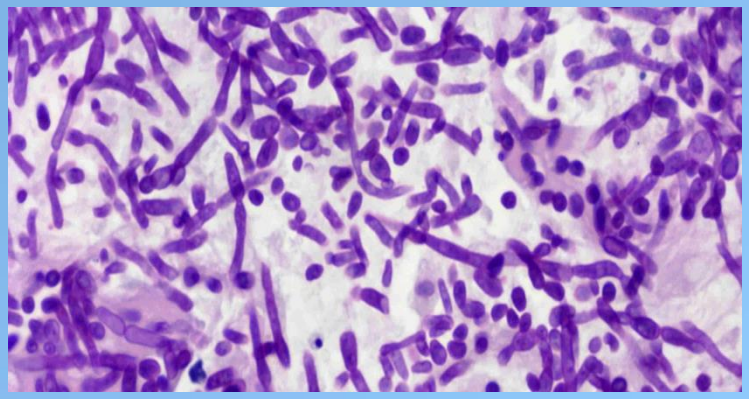
Candidiasis: candida albicans

Soor oris



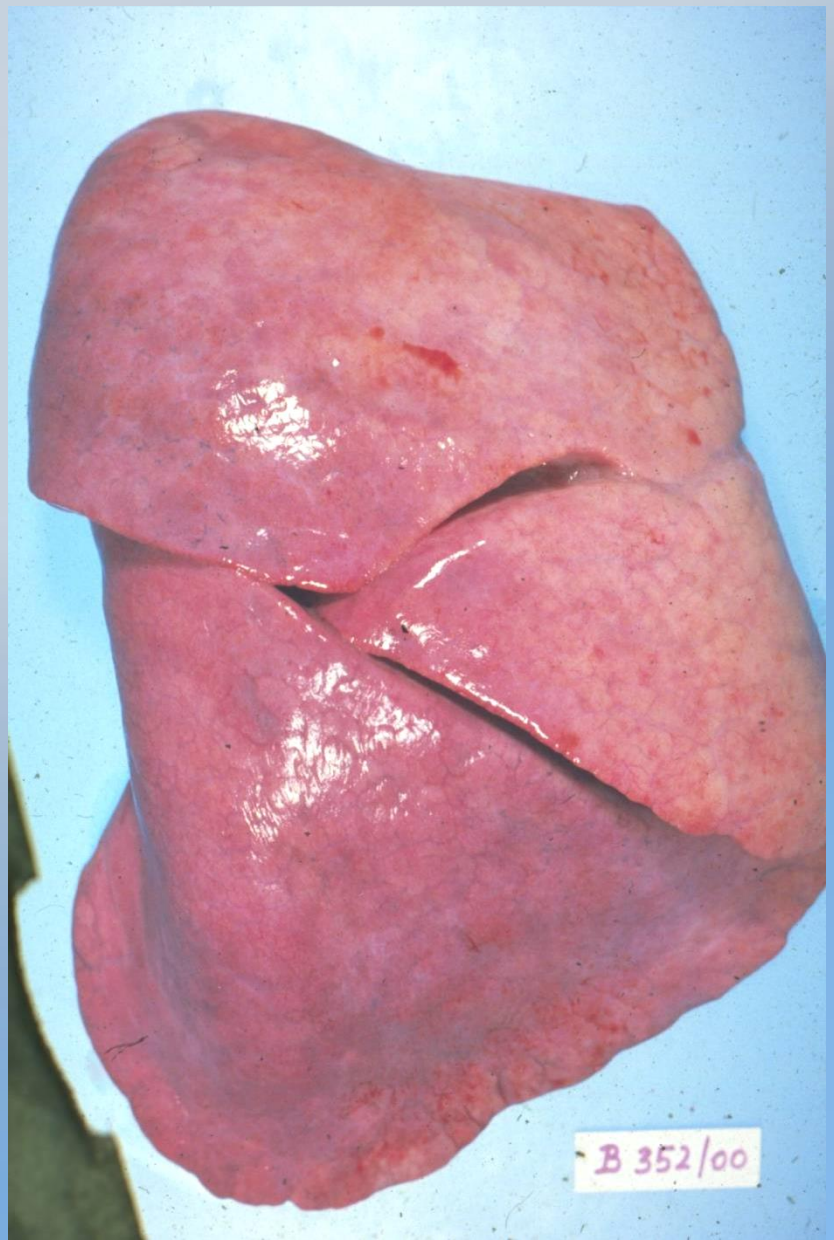
oesophagitis

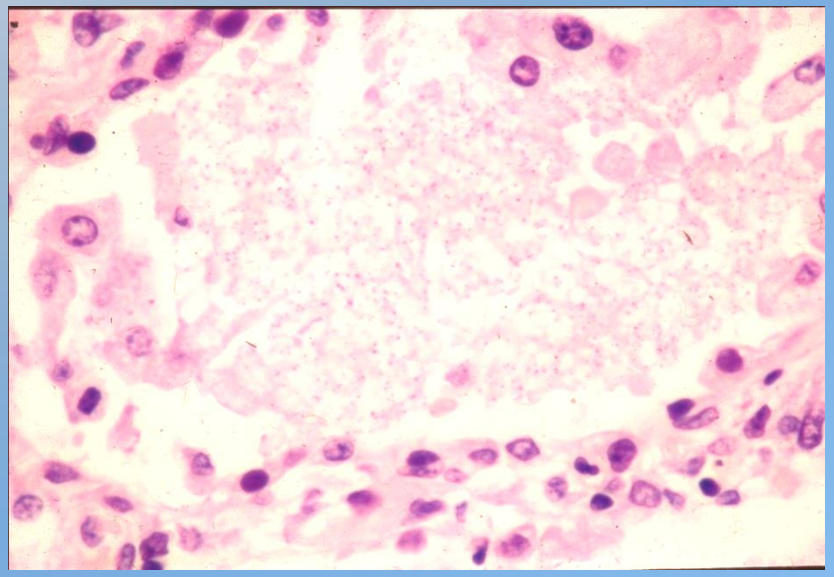




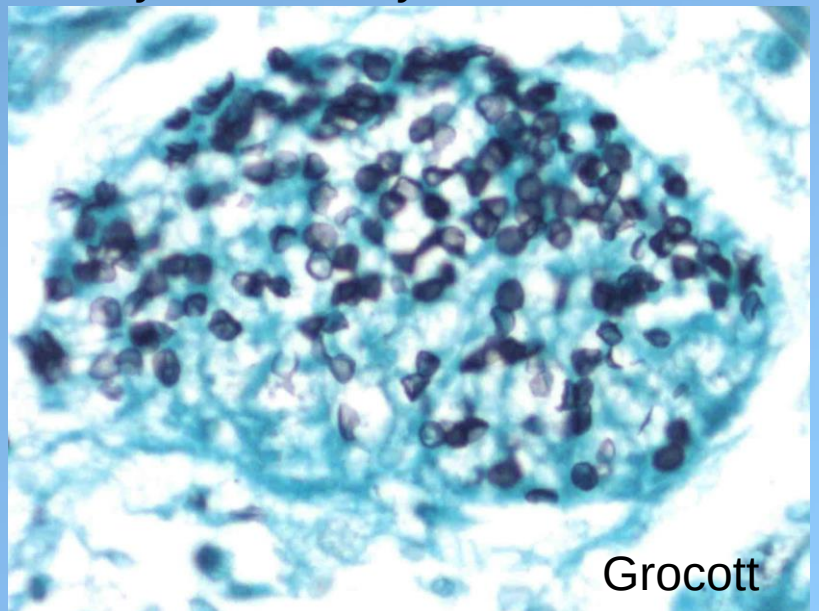
PAS reaction

Pneumocystis jiroveci pneumonia



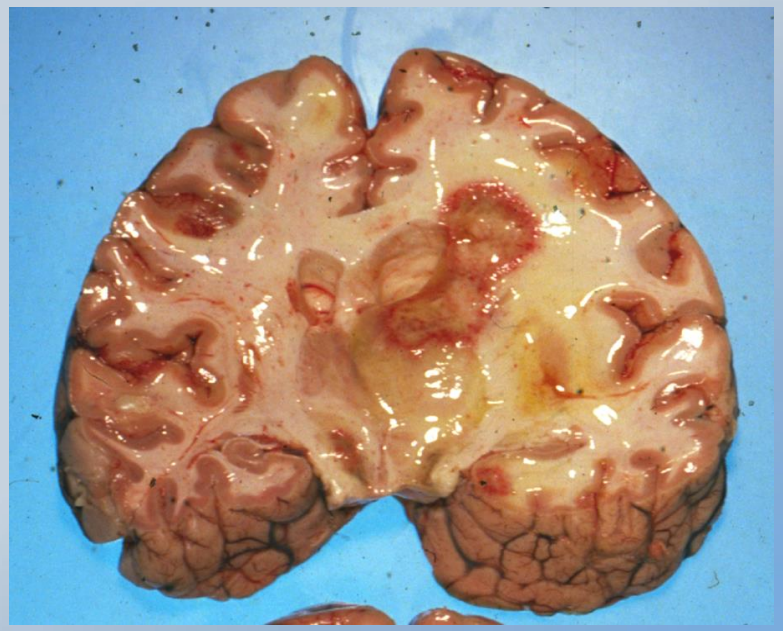


Foamy exudate- cysts with silver stain

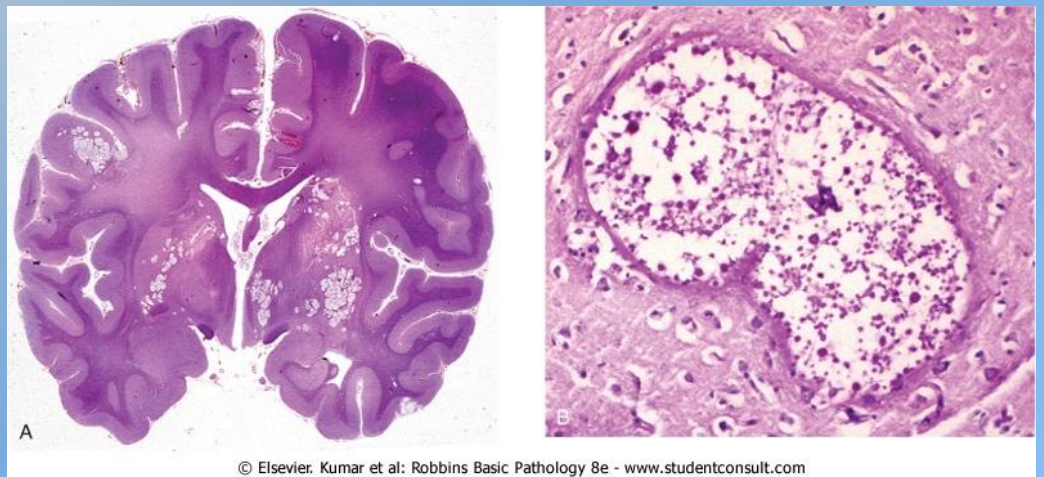


Grocott

PROTOZOAL INFECTION
Toxoplasma encephalitis

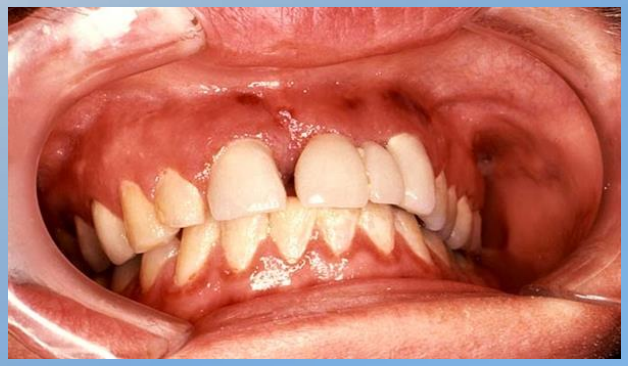


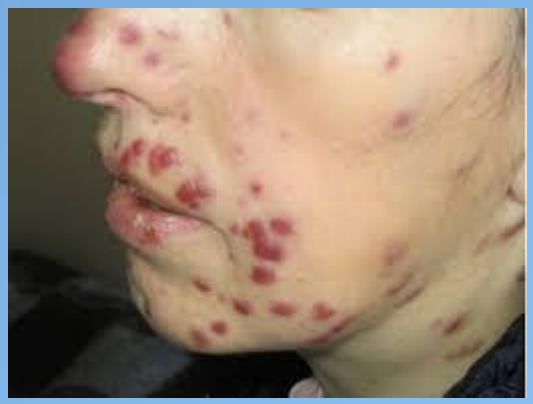
Toxoplasma gondii -is one of the most common causes of neurologic (focal and diffuse) symptoms and morbidity in persons with AIDS
Endogen reinfection
Obligate intracellular protozoon
Source: cat
Histology: abscess:



Increased risk for malignancy

- Kaposi-sarcoma
  - Brownish macules, nodules on the skin
  - Low malignancy, dermal vascular tumor (endothel cells)
  - Localisation: head, face, ears, neck, oral cavity





- Non-Hodgkin lymphoma

Graveyard in Africa- 250000 dead/ 1 year

ORGAN TRANSPLANTATION

- *Allografts*-between same species/human-human (xeno- different species)
- *History*: 1st. 1954-kidney identical twins, 1962 in Hungary
- *Transplanted organs*: kidney, liver, pancreas, lung, heart, bone marrow
- *Source*: brain-dead individuals kept on respiratory maschine (2% alive donors-kidney, liver)

Complications of transplantation

- **Rejection** of the organ (host versus graft)
  - Cell- and antibody-mediated hypersensitivity reactions directed against HLA molecules on the foreign graft
- **Graft versus host disease-** bone marrow transplantation- skin, GI tract, liver
- **Infections** due to immunsupression (secondary immundeficiency)
- Late: post-transplant lymphoproliferative disease (PTLD)

TYPES OF GRAFT REJECTION

Hyperacut rejection- in minutes

Humoral reaction: -mediated by preformed antidonor antibodies

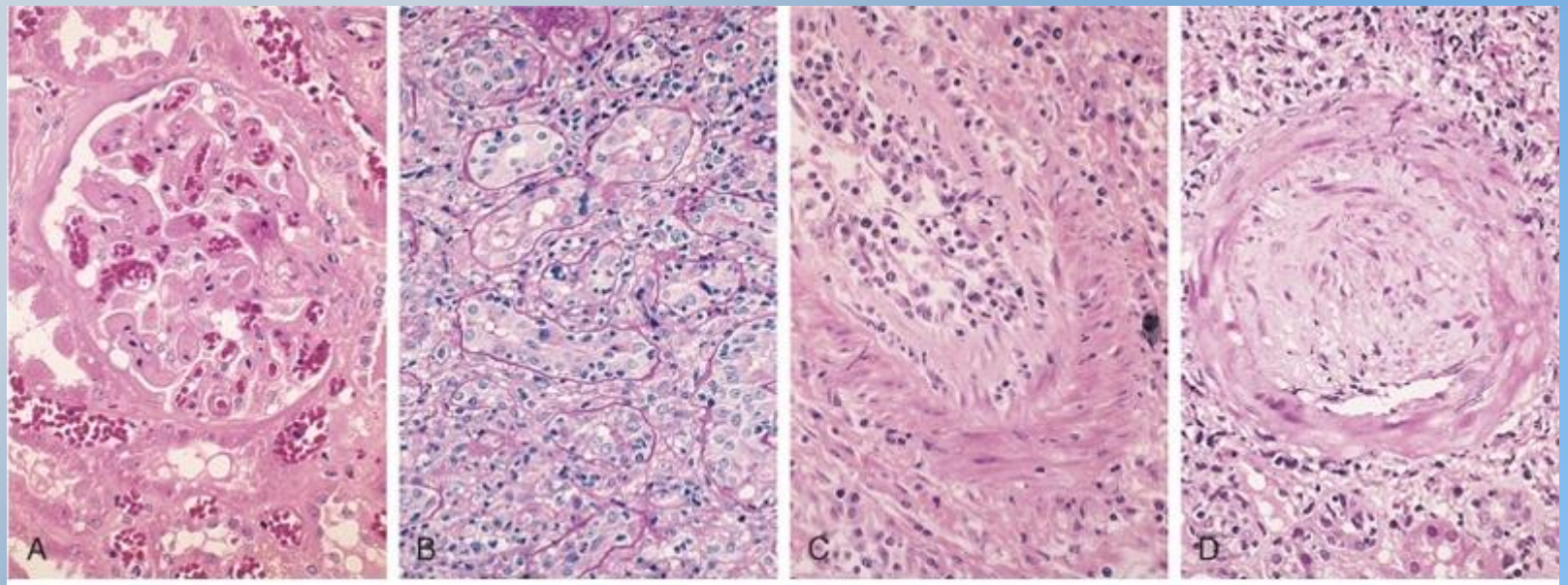
Akut rejection- 0-3 month,

1. Cellular (90%)- -mediated by CD8+, CD4+ **T cells and NK cells** against HLA antigens
2. Humoral (10%)- HLA, endothelial antigens IgG+complement aktivation.

Chronic rejection- month, years

Cellular- T cell reaction/ cytokines

Morphologic patterns of graft rejection



Hyperacute
Vasculitis-Fibrinoid necrosis, thrombosis

Acute cellular
Tubulitis
T cell and macrophage infiltration

Acute humoral
Vasculitis
T cell and granulocytes

Chronic
Arteriolosclerosis, Fibrosis mediated by cytokines


THANK YOU