Chronic Inflammation

Gábor Lotz MD Ph.D.

Phasis of inflammation

- Acute
- Subacute
- Chronic

Description of chronic inflammation

- Under conditions in which the inflammatory response is unable to eliminate the injurious agent or restore injured tissue to its normal state, the process may become chronic.
- Chronic inflammation may occur
  - as a sequel to acute inflammation or
  - as a primary immune response to certain foreign or autoantigens *(e.g. viruses, parasites, autoantigens, malignant tumor cells – neoantigens)*.
- Chronic inflammation primarily serves to contain and remove a pathologic agent or process within a tissue.

Causes of chronic inflammation

- recurring acute inflammatory episodes (pyelonephritis); acute inflammation in persons with impaired healing capacity (weaken, cachectic patients)
- Persistent infections

  viruses (hepatitis C)
  - inflammatory infiltrate which is rich in lymphocytes, plasma cells and macrophages

  TB, syphilis, fungi
  - Deleyed type hypersensitivity (T-cells), and macrophages (granuomatous reactions)
- Prolonged expositions of toxic agents

  (exogenous: silica – silicosis; endogenous: lipids - atherosclerosis)
- Immun-mediated inflammatory diseases
  - Autoimmun diseases (rheumatoid arthritis, PBC, PSC, SLE, etc.)
  - Diseases caused by exogenous allergens (asthma bronchiale)

Chronic inflammation:

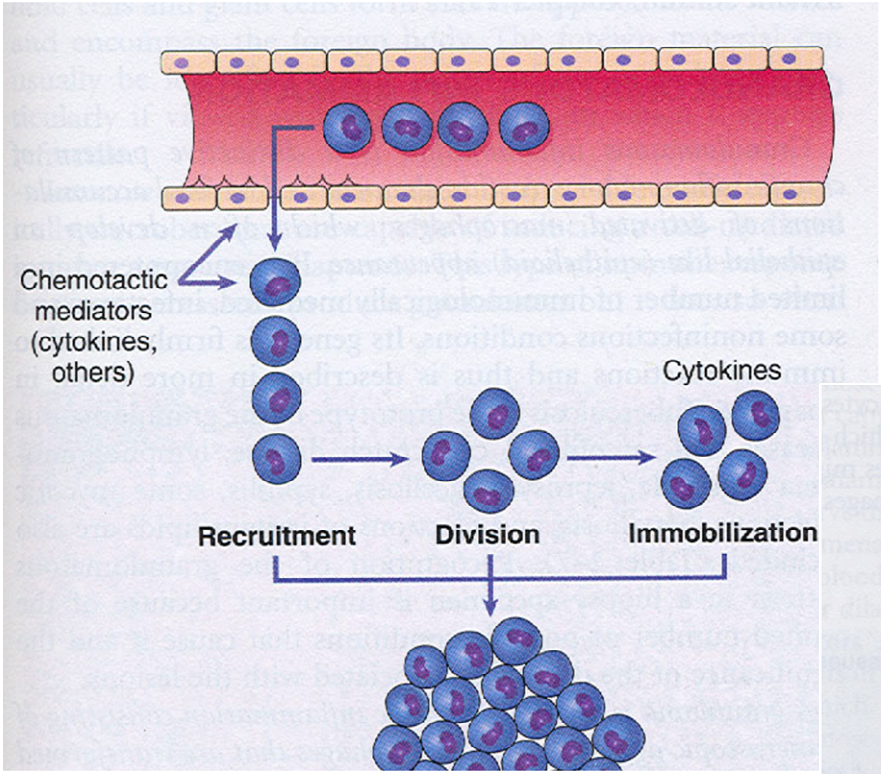
- Inflammation of prolonged duration (weeks, months, years)
- Simultaneously occurs:
  - inflammation,
  - tissue destruction,
  - repair
- Cells: Mononuclear cell („small round cell”) infiltrate (macrophages, lymphocytes, plasma cells), secondary lymphoid follicles

  Other cells can occur under special conditions:
  mast cells (Fc-IgE), eosinophils (IgE- parasitic, allergic), neutrophils (PMNs), multinucleated giant cells

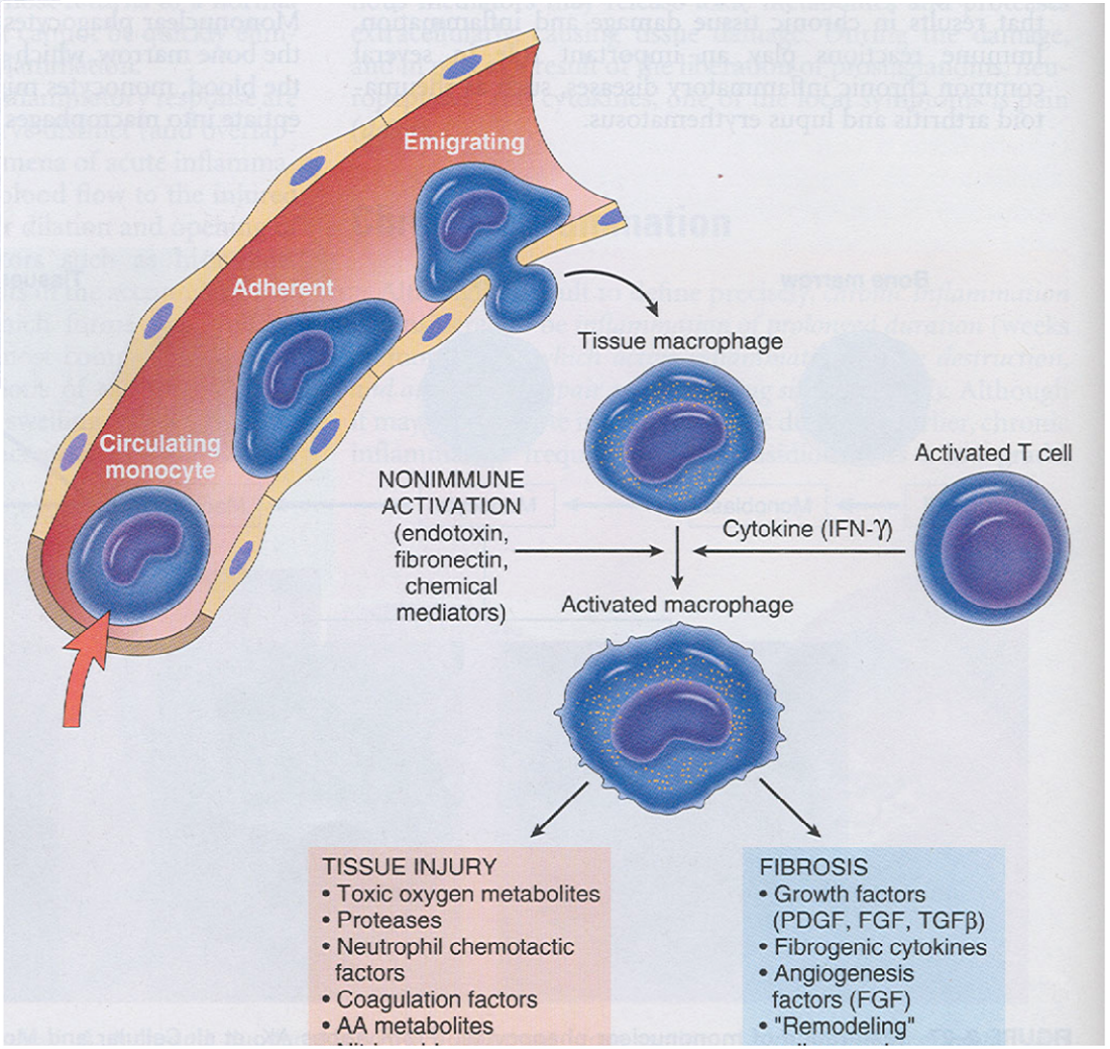
Accumulation of macrophages (Ma)

- Ma are key cells in chr infl, components of mononuclear phagocytic system
  - Bone marrow: stem cells,
  - Blood: monocytes,
  - Tissue: macrophages (microglia, Kupffer cells, alveolar Ma, sinus histiocytes, osteoclasts),
  - activated Ma (secretion of biologically activated products)
- Cont. recruitment of monocytes from the circulation (chemotactic fators, GFs etc)
- Local proliferation of Ma (atheromatous plaque)
- Immobilization of Ma (cytokines, oxidized lipids)

Role of the activated macrophages in chronic inflammation



Accumulation of macrophages (Ma)



Tissue alterations in chronic inflammation

- Tissue destruction
- Regeneration
  - Integrity of the ECM is preserved:
    complete healing - restitutio ad integrum
  - The ECM is damaged - reparation:
    - Healing by fibrosis directly or via granulation tissue (in the case of significant damage of the basic tissue structure)

      Granulation tissue: richly vascular, newly formed connective tissue

      (proliferating capillaries /angiogenesis/, macrophages /sometimes granulocytes, lymphocytes/, abundant fibroblasts, collagen synthesis & maturation, subseqently scar formation)

Fibr**in**ous pleuritis - acute inflammation (fibrin on the surface)

↓

Healing via granulation tissue
(organisation – scar formation)

↓

Fibrous pleuritis
- chronic inflammation:

Pleuritis chronica adaesiva. (Adhaesiones)

Granulomatous inflammations

- Gr.Infl.: specific type of chr.infl. Characterized by accumulation of modified Ma (epitheloid cells), initiated by a variety of infectious and noninfectious agents
- Granuloma: circumscribed mass (focal area) of granulomatous inflammation, aggregation of infl cells
- Cell types:
  - Epitheloid cells: epithelial-like Ma (pink cytoplasm with distinct cell boundaries)
  - Giant cells: fused epitheloid cells (40-50 um, 20 or more Nu) – foreign body type, Langhans-type, Touton-type)
  - Lymphocytes, plasma cells
  - Fibroblasts (in older granulomas)

GRANULOMATOUS INFLAMMATION

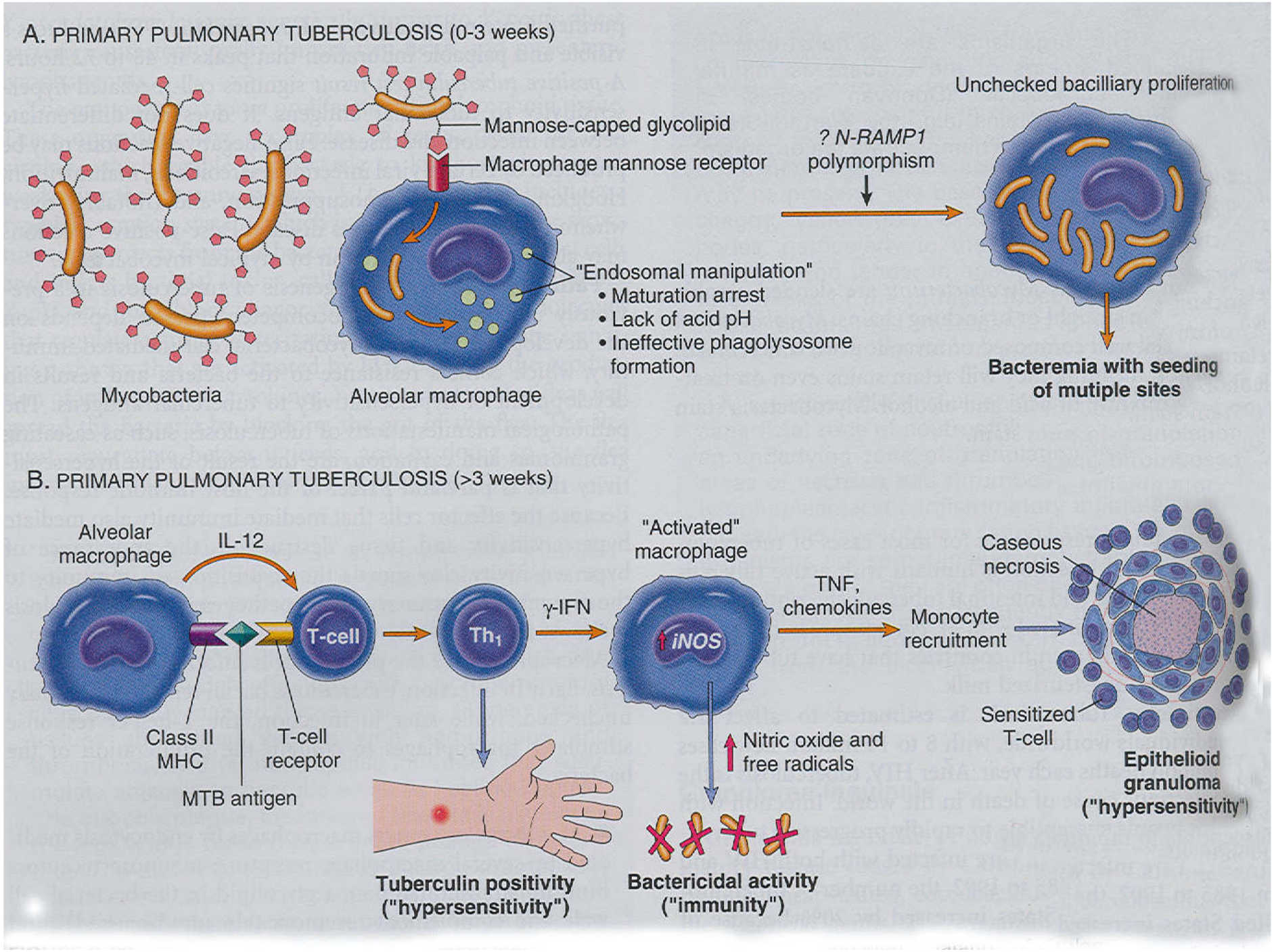
- **Foreign body granuloma** („walls off" the agent)
- **Immune granuloma: Infectious granulomas**
  - **Tuberculosis**
  - **Syphilis**
  - **Lepra**
  - Cat-scratch disease
  - Whipple-disease
  - Brucellosis
  - Leishmaniasis
  - Schistosomiasis
  - Fungal infections
- **Immune granuloma: Non infectious granulomas**
  - Unknknown (?) etiology (**sarcoidosis**, Crohn-disease, PBC etc)
  - **Rheumatic fever**
  - Granulomas associated with vasculitis (Wegener- gr, polyarteritis nodosa, etc)
  - Hypersensitiv pneumonitis
  - Others (panniculitis, malakoplakia, paraneoplastic syndrome, berilliosis etc)

TUBERCULOSIS (TB or TBC)

- Agent: Mycobacterium tuberculosis (Koch bacillus, 0,2-0,6 um x 1-10 um rods, waxy cell wall, high lipid content – acid fast (retain stains, Ziehl-Neelsen stain - carbol fuchsin)
- Epidemiology: 8-10 million new cases/yr, 1,7 billion infected individuals, person-person inf, delayed hypersensitivity
- Pathogenesis: depends on the exposition (previous inf.: anti-mycobacterial cell-mediated immunity)
  - (1) M.tbc. enters Mas,
  - (2) replication – blocks phagolysosome formation
  - (3) 3 weeks: Th1 cells produce IFN-gamma
  - (4) Ma iNOS↑ – NO↑ – Mas become bactericidal
  - (5) granuloma formation, caseation (TNF-epitheloid cells)

Forms of tuberculosis

- Primary TB: develops in previously unexposed, unsensitized (immunocompetent) person
  - Primary complex (Gohn-Ranke complex):
    - (1) tuberculum (Ghon focus, middle, close to pleura, central caseation),
    - (2) lymphangitis tuberculosa,
    - (3) lymphadenitis tuberculosa
- Secondary : develops in previously sensitized host, after primary TB or reactivation/superinfection
  - Apical, both lungs, tuberculum (first 1-2 cm) , central caseation – cavitation (bacteria in sputum!), fibrosis, fibrocalcification
  - Low grade fever (systemic symptom), night sweats, hemoptoe, pleuritic pain
  - Progressive pulmonary tuberculosis


A. PRIMARY PULMONARY TUBERCULOSIS (0-3 weeks)
Mycobacteria
Mannose-capped glycolipid
Macrophage mannose receptor
Alveolar macrophage
"Endosomal manipulation"
• Maturation arrest
• Lack of acid pH
• Ineffective phagolysosome formation
? N-RAMP1 polymorphism
Unchecked bacilliary proliferation
Bacteremia with seeding of mutiple sites
B. PRIMARY PULMONARY TUBERCULOSIS (>3 weeks)
Alveolar macrophage
IL-12
T-cell
Class II MHC
T-cell receptor
MTB antigen
Th1
γ-IFN
"Activated" macrophage
iNOS
TNF, chemokines
Monocyte recruitment
Caseous necrosis
Sensitized T-cell
Epithelioid granuloma ("hypersensitivity")
Nitric oxide and free radicals
Tuberculin positivity ("hypersensitivity")
Bactericidal activity ("immunity")

Localization of primary TB

- Lung: most common: right lobe, middle, subpleural
- Pharynx: through the tonsilles
- Intestines: through the terminal ileum, M.bovis, mesenterial lymph node involvement („tabes mesaraica”)
- Skin: occupational disease (in stockmen)

Outcome of primary TB

- Elimination of bacteria and healing of the primary lesions (scar)
- Dormant Mycobacteria in the residual fibrotic lesions (this is the most common outcome; reactivation of bacteria: secondary TB)
- Progressive primary TB (in case of impaired immunoreactivity; the symptoms are resembling to the progressive secondary TB: cavitation in the lung, massive hematogenous dissemination - miliary TB)

Forms of tuberculosis

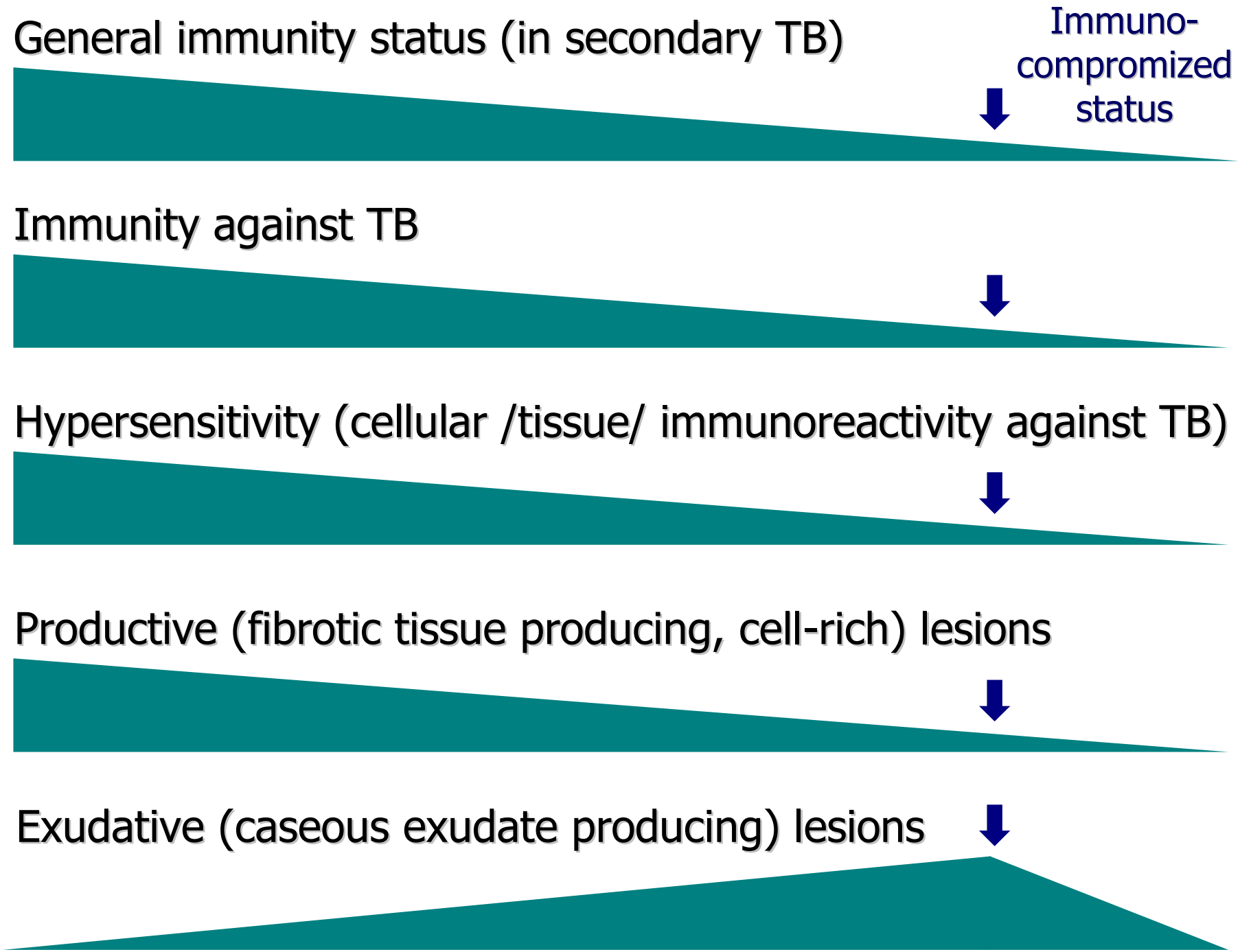
- Primary TB: develops in previously unexposed, unsensitized (immunocompetent) person
  - Primary complex (Ranke-Ghon):
    - (1) tuberculum (middle, close to pleura, central caseation),
    - (2) lymphangitis tuberculosa,
    - (3) lymphadenitis tuberculosa
- Secondary (postprimer): develops in previously sensitized host , after primary TB or reactivation/superinfection
  - Apical, one or both lungs, tuberculum (first 1-2 cm) , central caseation – cavitation (bacteria in sputum!), fibrosis, fibrocalcification
  - Low grade fever (systemic symptom), night sweats, hemoptoe, pleuritic pain
  - Progressive pulmonary tuberculosis (next slide)

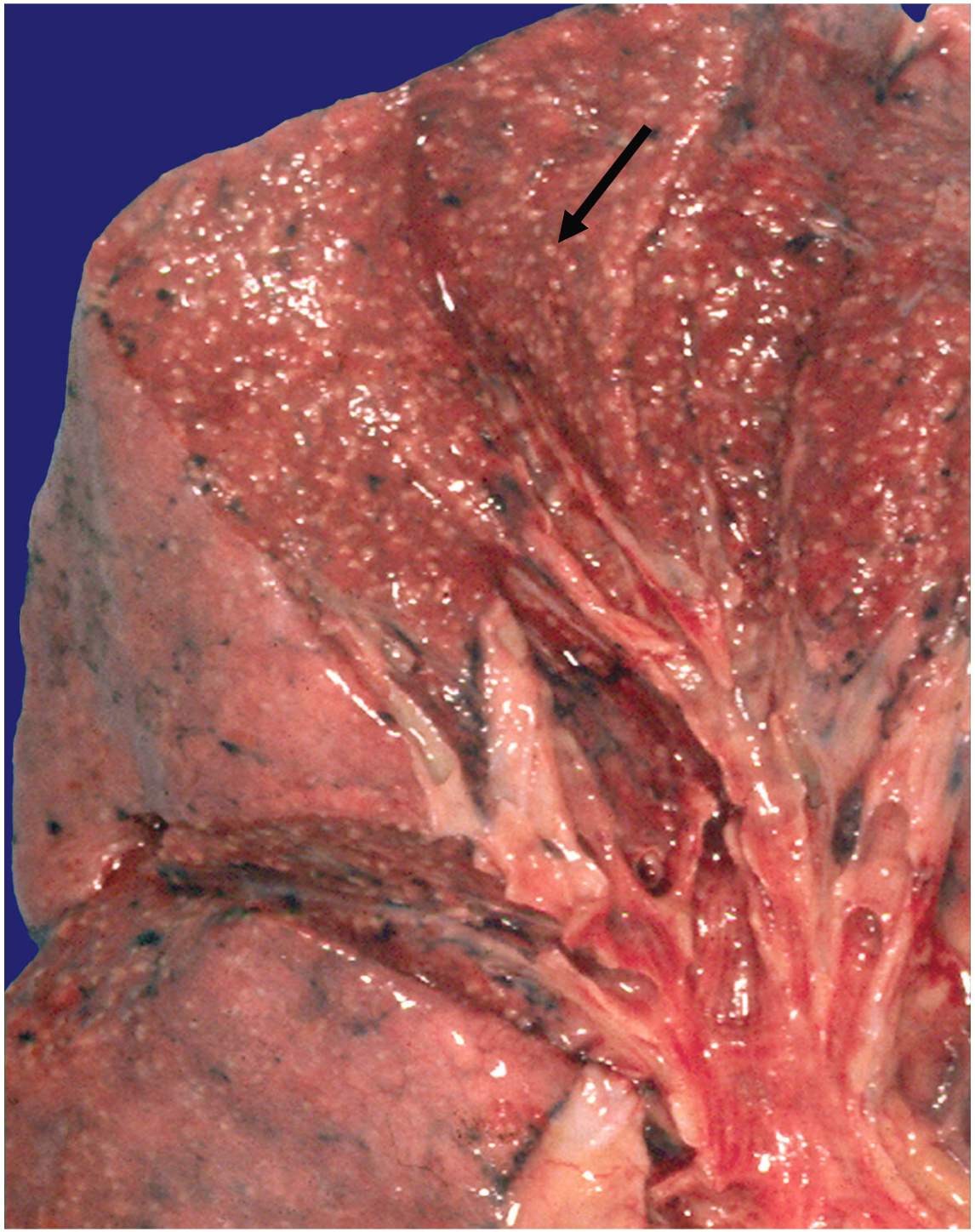
Progression of TB

- Directly to the adjacent structures
- Lymphogen
- Haematogen
- Canalicular (bronchogen, urinary, genital organs)
- On serous membranes (pleural, peritoneal)

Progressive pulmonary tuberculosis

- Apical lesion enlarges,
  - Erosion into bronchi, cavity formation (caseous material lined)
  - erosion of blood vessels (bleeding), (cor pulmonale)
- Miliary tuberculosis (hematogenous spread)
  - Milium (millet seeds): lesions of 1-2 mm, yellow-white through the parenchyma ,
  - Extension of the infection: miliary TB in other organs (liver, kidney serous membranes, fallopian tubes, epididymis etc)
- Isolated organ tuberculosis
  - In any organ (seeded hematogenously)
  - Most common: tuberculous meningitis, renal TB, adrenal, bones, fallopian tubes TB
  - Pott's disease: vertebrae affected
  - „cold" abscess: paraspinal caseous mass along the spine
  - Lymphadenitis: common form of extrapulmonary TB, in cervical region: „scrofula"
  - Intestinal TB: from contaminated food/milk


General immunity status (in secondary TB)
Immuno-compromized status
Immunity against TB
Hypersensitivity (cellular /tissue/ immunoreactivity against TB)
Productive (fibrotic tissue producing, cell-rich) lesions
Exudative (caseous exudate producing) lesions



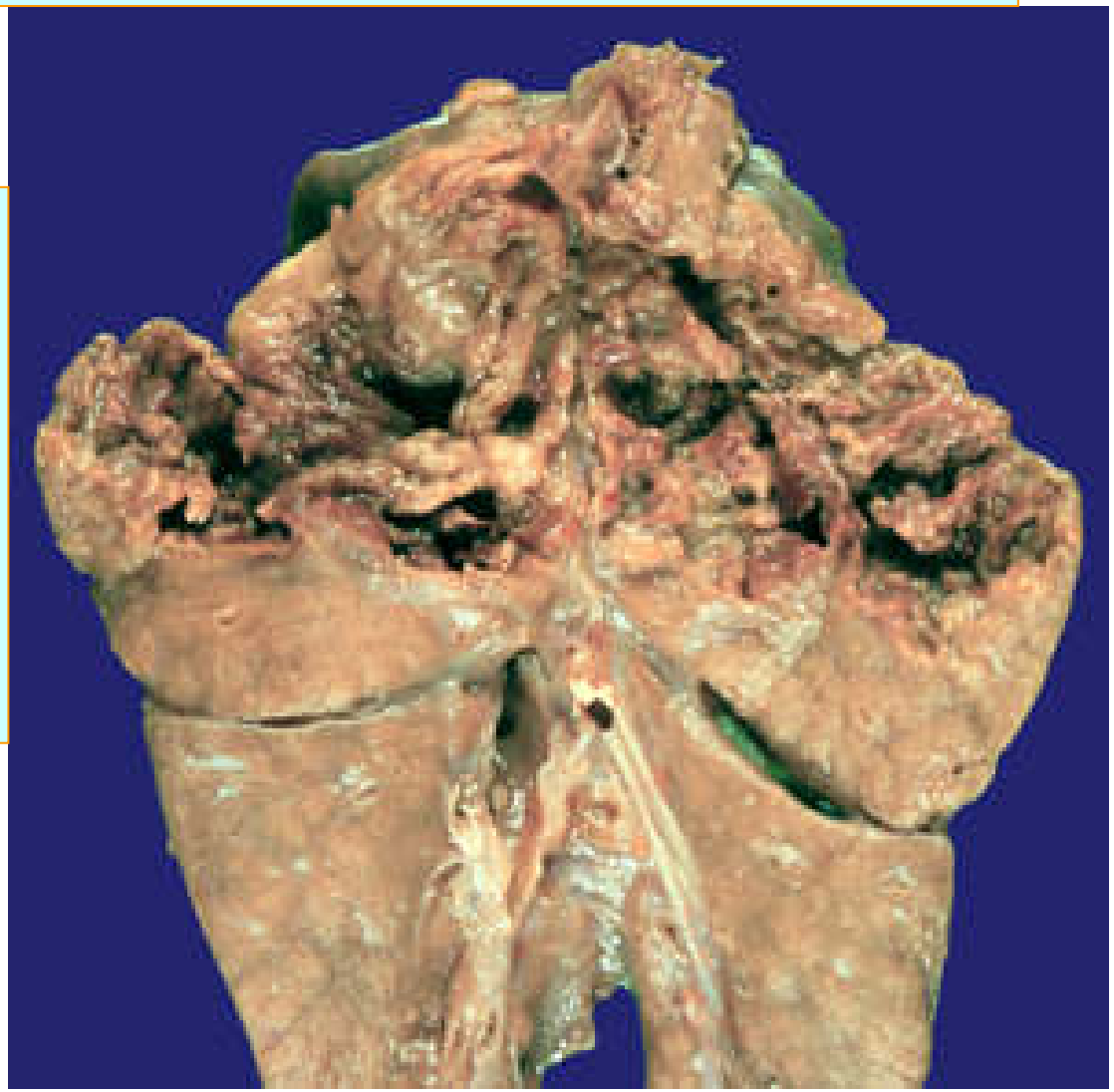
Miliary TB

(10.26.)

Caverna (cavitation)

Cavity containing air, communicating with the bronchial tree.
Caseous inner surface in the early stage.

Formation:
Tuberculotic inflammation destroys the wall of a bronchus and the caseous necrotic mass of fused granulomas empties via the bronchial tree.



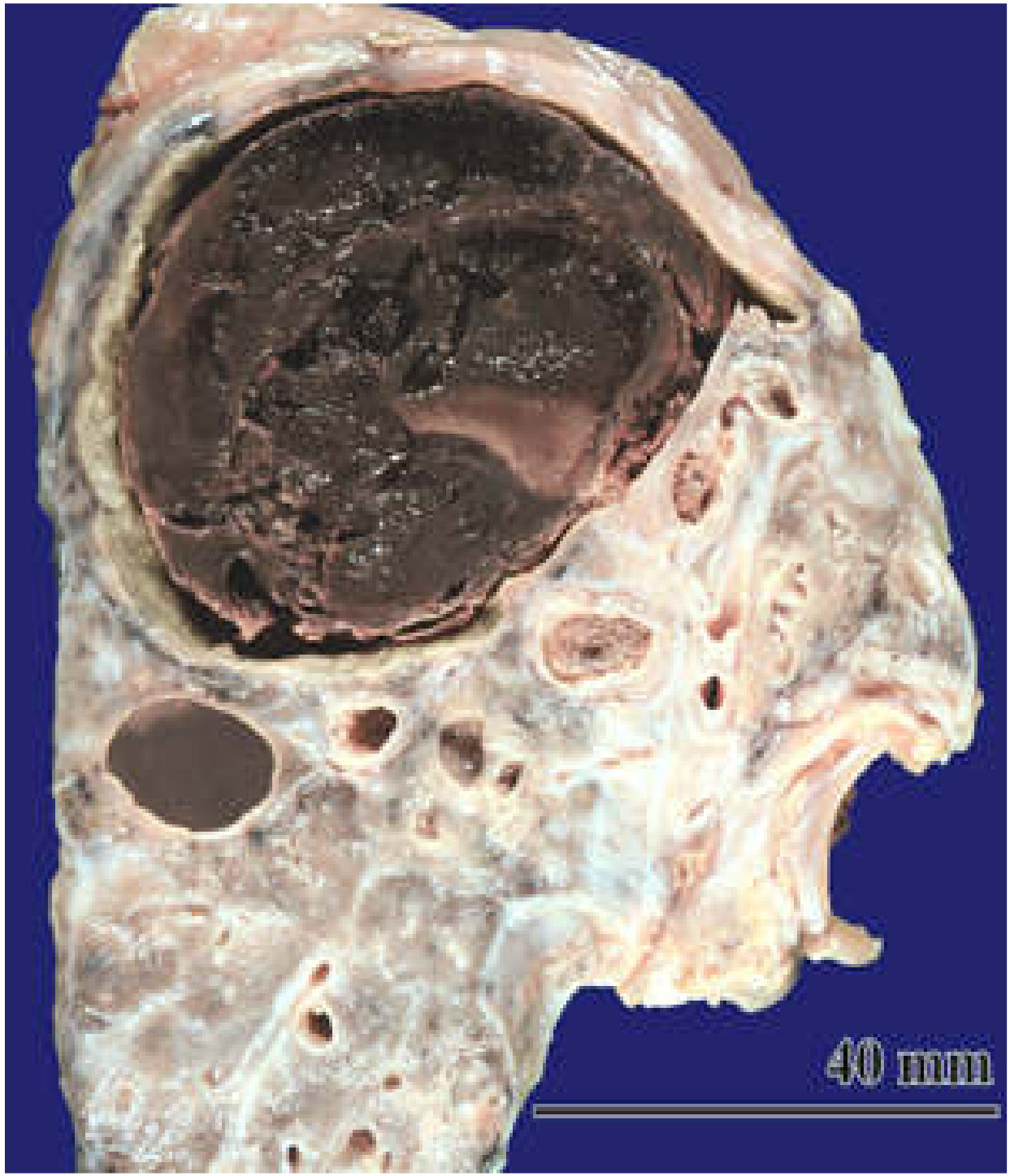
Progressive pr.TB. Apical cavernas

Complication of secondary TB

- Infection of caverna (cavities) with other bacteria (abscessus, gangraena) or fungi (Aspergilloma)
- Empyema pleurae, pyopneumothorax
- Haemoptoe, pulmorrhagia due to extensive bleeding from Rasmussen's aneurysm (Dilation of a branch of a pulmonary artery in a tuberculous cavity due to tuberculotic inflammation of the arterial wall. It may lead to rupture and haemorrhage.)
- Cavernacarcinoma (via squamous metaplasia of the lining bronchial epithelium of the healed inner surface of caverna)
- Canalicular progression of lung TB to contralateral lung and other organs (larynx, pharynx, intestine etc)

Large cavity in the upper lobe is filled with hematoma:

Bleeding from a Rasmussen aneurysm

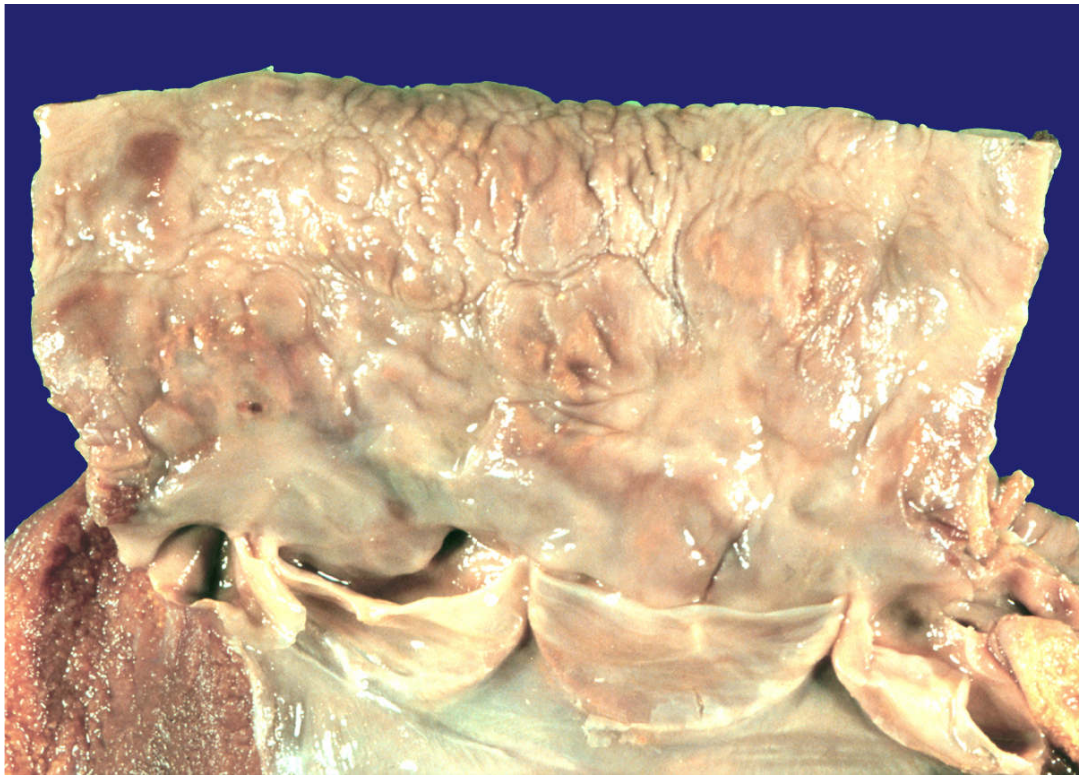


Secondary TB in extrapulmonal localizations

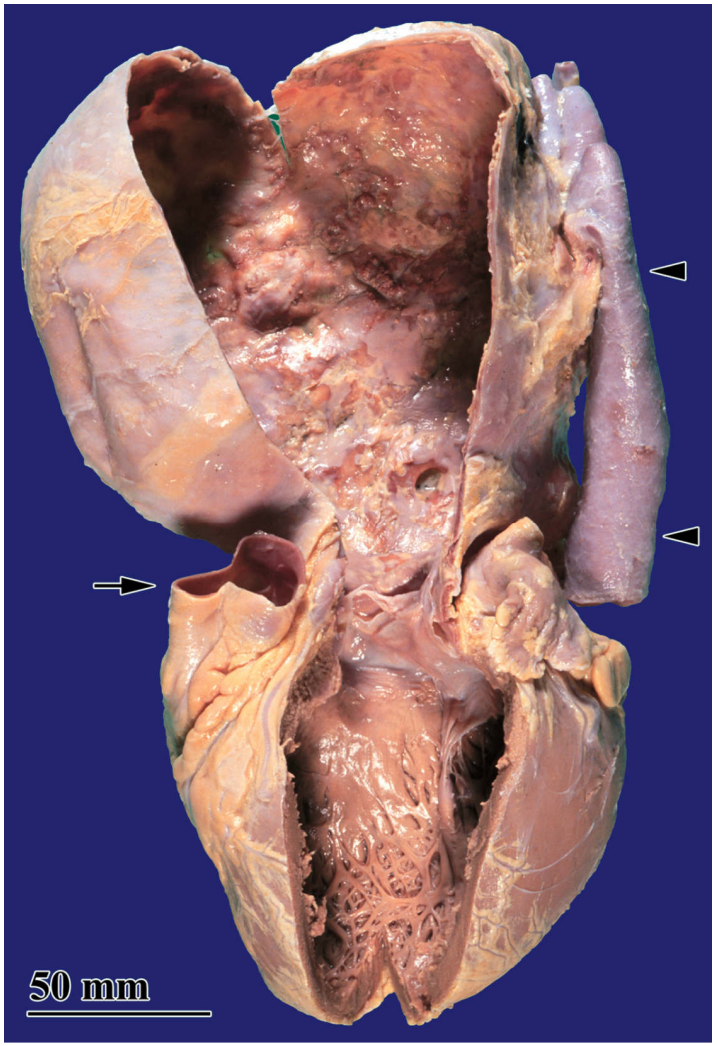
- Kidney
- Reproductive system:
  - Female (fallopian tube),
  - Male (epididymis)
- Bone
- Central nervous system

SYPHILIS (Lues)

- Agent: Treponema pallidum (slender corkscrew-shaped, 0,1-0,2x6-20 um)
- Stages: sexually transmitted disease (STD), chr venereal disease
  - Primary: 3 weeks after contact (9-90days)
    - Endarteritis and inflammation,
      - Ulcus durum (chancre: firm, red lesion at the site of the invasion),
      - bubo indolens (enlarged, painless lymphnode)
    - Heals in 3-6 weeks (without therapy)
    - Spreading through the body by hematologic and lymphatic dissemination
  - Secondary: 10-12 weeks after the primary
    - Skin, mucous membrane lesions: Maculopapulous exanthemes, condyloma latum (broad based elevated paques), lymphadenopathy
    - infectious
  - Tertiary: Years after infection (5 or more)
    - Cardiovascular: syphilitic aortitis, aneurysm
    - Neurosyphilis: meningovascular, tabes dorsalis (myelopathy - damage of the posterior column of spinal cord + peripheral nerves, loss of proprio-ceptive feedback of the cerebellum; stamping gait), general paresis
    - Gummas: hepar lobatum, in bone, skin etc



Syphilis (tertiary): Aortitis luetica
- tree-bark pattern
  on the inner surface



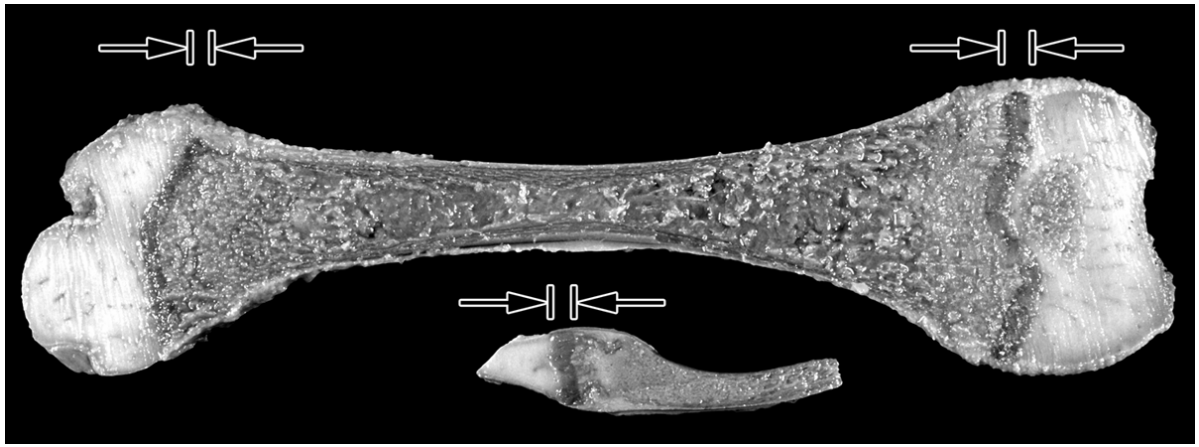
Syphilis (tertiary):
Aorta aneurysm

Congenital syphilis

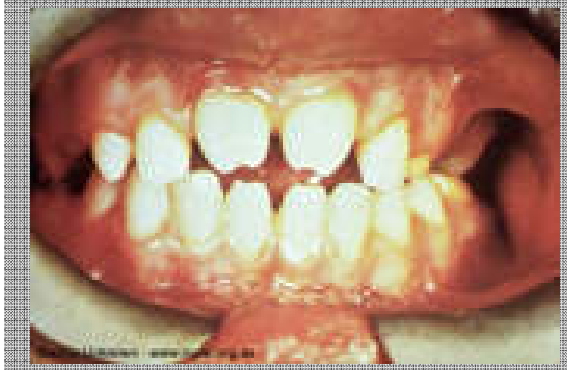
- Transplacental infection mainly in 3. trimester
- Manifestations:
  - (1) Early (infantile, Treponema sepsis),
    - Intrauterine death, perinatal death
    - Pemphigus syphiliticus (bullous rash of the skin of the hands, feet etc)
    - Hepatosplenomegaly
    - Pneumonia alba
    - Dubois abscesses in the thymus
  - (2) Late (tardive)
    - Hutchinson triad (notched central incisors, interstitial keratitis with blindness, deafness)
    - Osteochondritis luetica, skeletal abnormalitis

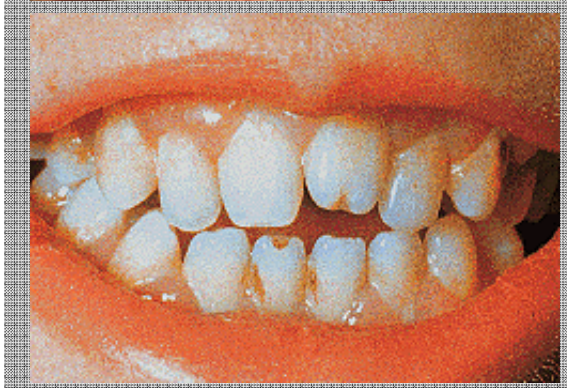
Congenital syphilis

Osteochondritis luetica: Broadened bone-cartilage border in the femur and in a rib



From the Hutchinson triad:
notched central incisors

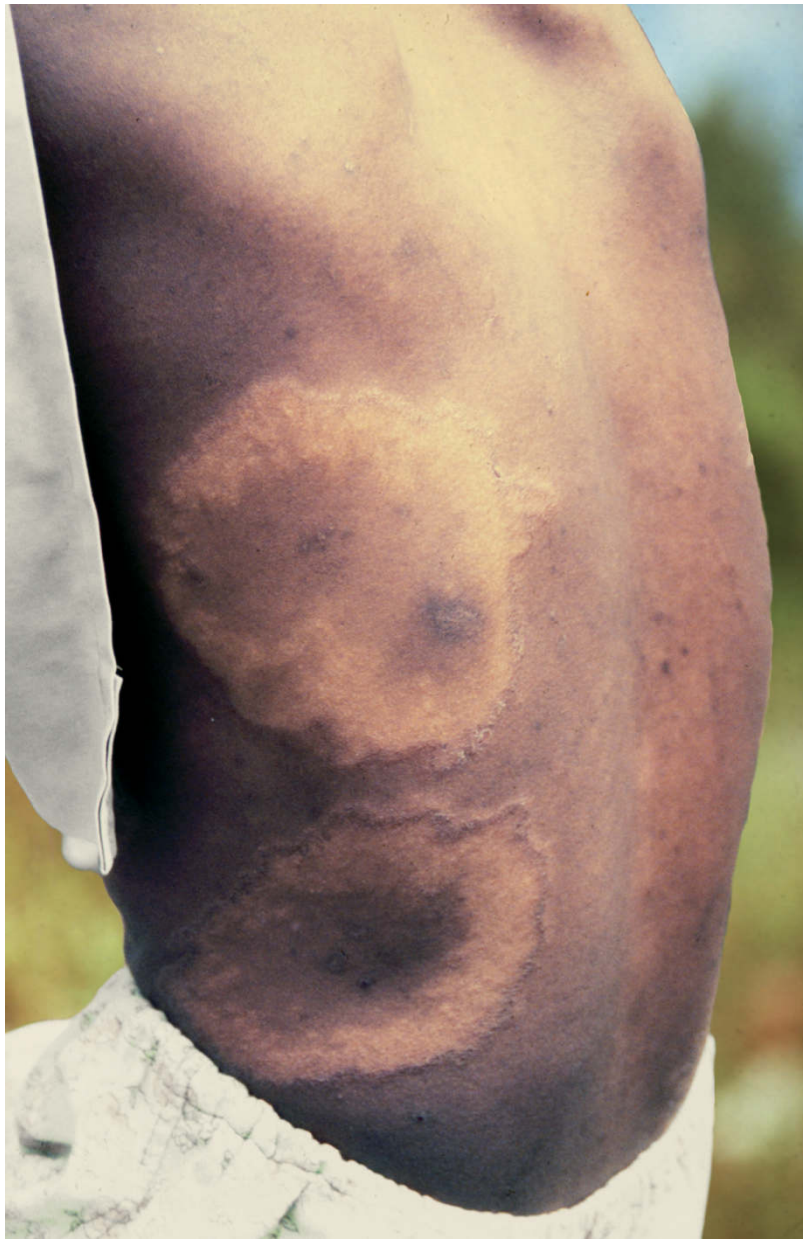




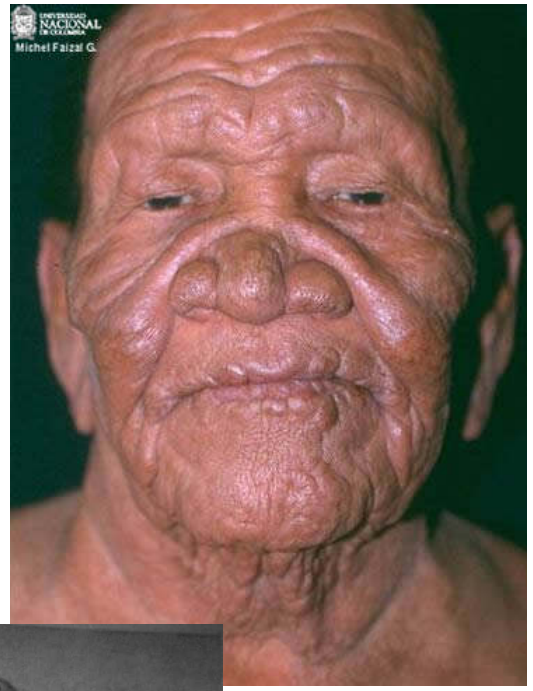
LEPROSY (Lepra)

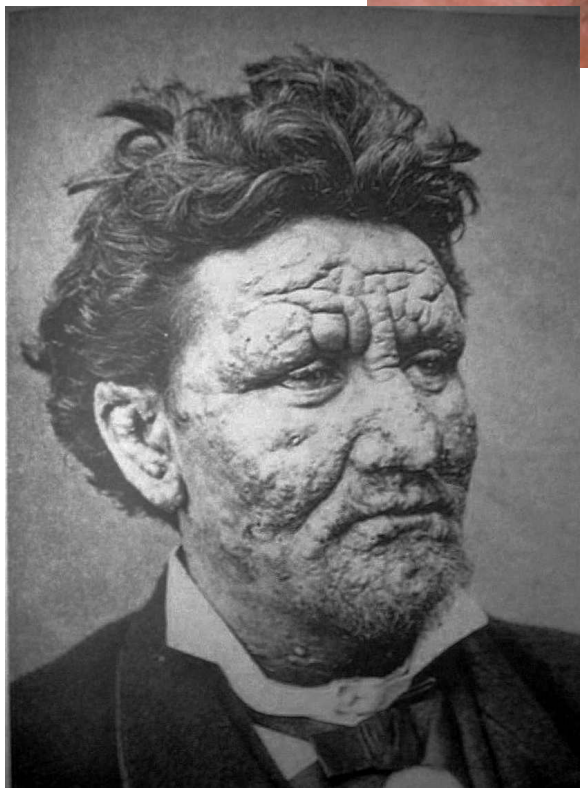
- Infectious agent: Mycobacterium leprae (Hansen 1873), temperature optumum 32-34 °C
- Entrance: bronchi, skin,
- long incubation periode (for yrs), slow progression
- Forms
  - Tuberous (tuberculoid) leprosy (in persons with good immunoreactivity against M. leprae): granulomas, affecting superficial nerves and skin, marginally active (indurated, elevated, hyperpigmented), centrally depressed, depigmented lesions in the skin
  - Lepromatous leprosy (in persons with impaired immunoreactivity against M. leprae): bacteria laden clear, foamy macrophages in the dermis (skin deformities - leonine facies, peripheral nerve lesions); eyes, upper airways and testes can also be affected

Tuberculoid leprosy



Lepromatous leprosy
(leonine facies)

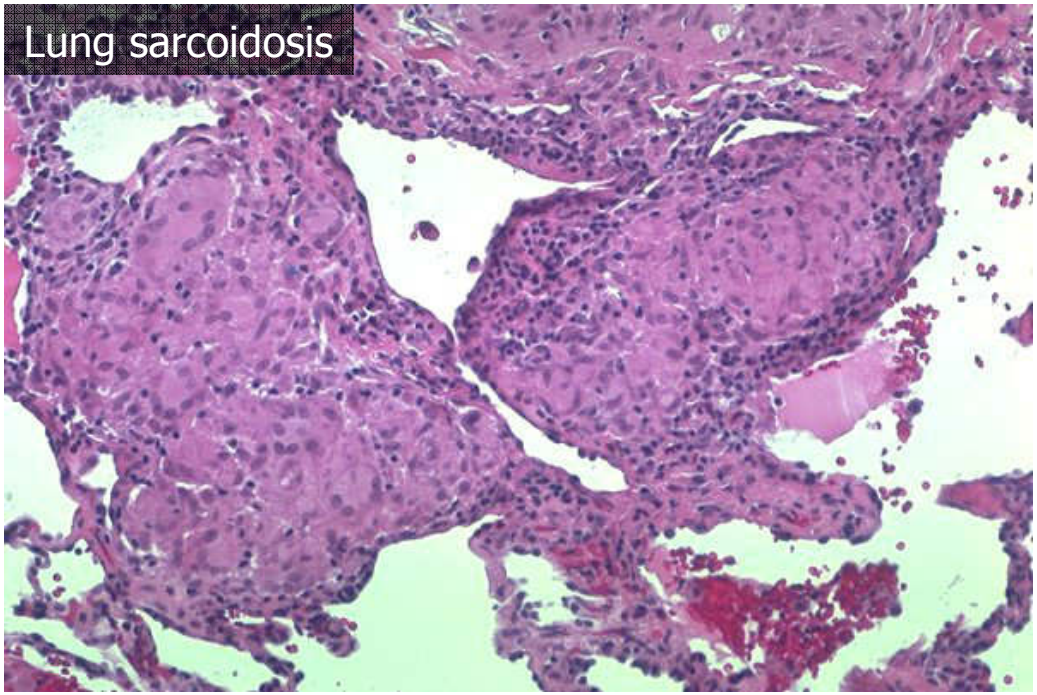


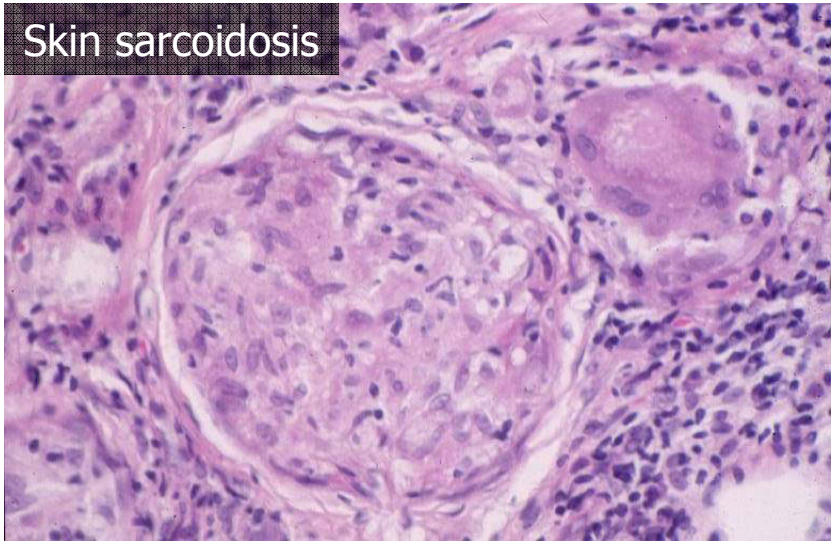


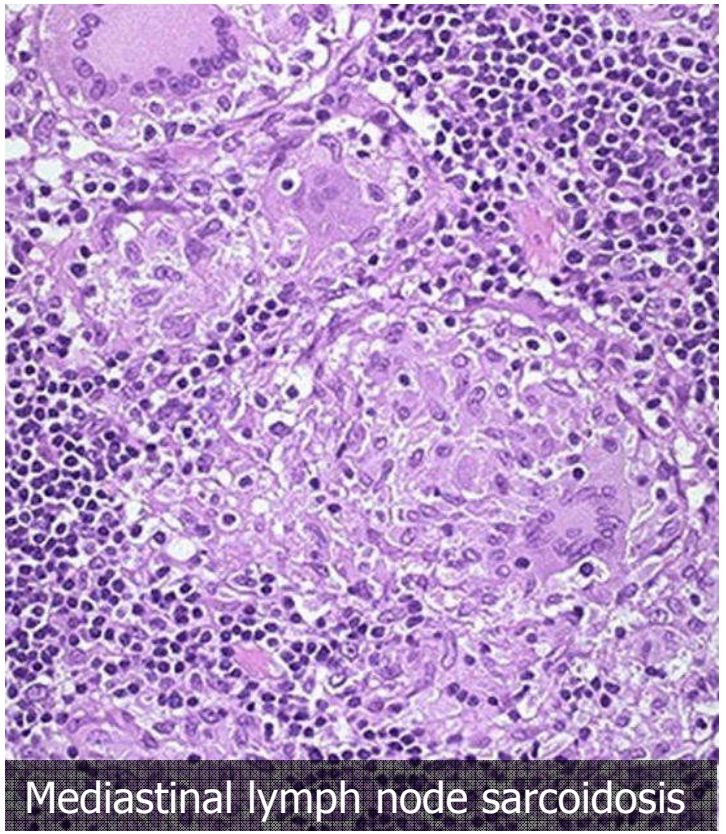
Non-infectious immune granulomas

- Unknknown (?) etiology (**sarcoidosis**, **Crohn-disease**, PBC etc)
- **Rheumatic fever**
- Granulomas associated with vasculitis (Wegener- gr, polyarteritis nodosa, etc)
- Hypersensitiv pneumonitis
- Others (panniculitis, malakoplakia, paraneoplastic syndrome, berilliosis etc)

Sarcoidosis: Non-necrotizing (non-caseous) granuloma



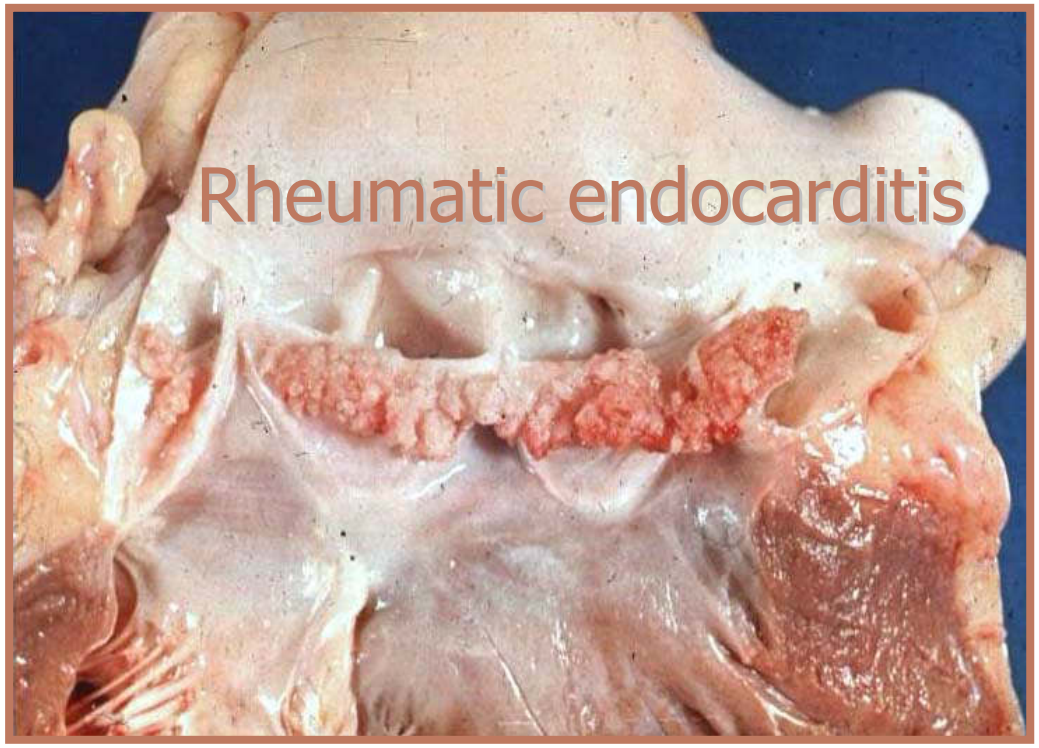




Rheumatic fever

- Immunologically mediated, multisystem inflammatory disease
- Occurs a few week after an episode of group A streptococcal pharyngitis
- Antibodies directed against the M protein of streptococci are cross-react with autoantigens in the heart
- Main pathologic features of the rheumatic heart disease:
  - endocardial lesions: sterile endocarditis on the left sided valves (long-term consequences: valvular deformation, stenosis and insufficiency)
  - myocardial lesions: granulomas (Aschoff bodies) with Anitschkow cells (charcteristic macrophages with abundant cytoplasm and caterpillar-like nucleus or nuclei)
  - pericardial lesions: fibrinous pericarditis and Aschoff bodies in the subepicardial fat tissue

Rheumatic fever



Rheumatic granuloma
(Aschoff body)
in the myocardium