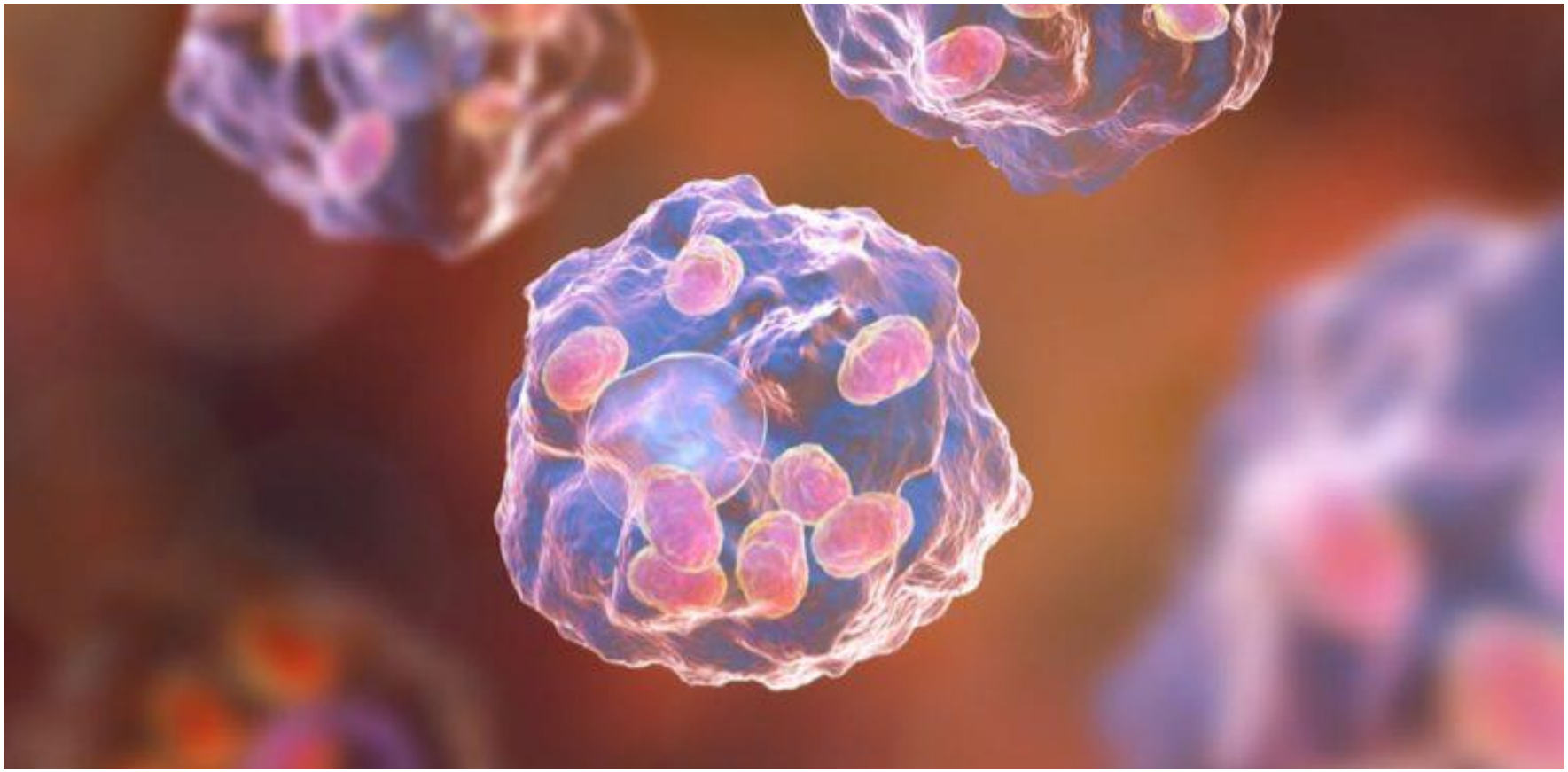


Inflammation III.

Balázs Csernus

Outcomes of acute inflammation

- **Complete resolution**
  - due to elimination of the offending agent and regeneration of injured tissue with normal function
- **Healing** by connective tissue replacement (fibrosis/scar formation)
  - Occurs after large tissue destruction,
  - fibrinous exudation into serous cavities
  - tissue without regeneration capabilities
- **Progression to chronic inflammation**
  - Resulting in granuloma formation to wall off injurious agent and tissue fibrosis (scar formation)

Definition of chronic inflammation

an inflammatory response of prolonged duration (weeks – months - years)

usually provoked by the persistence of the causative stimulus

simultaneous presence of inflammation, tissue destruction and repair (fibrosis)

Causes of chronic inflammation

- **Resistant microorganisms**
  - e.g *Mycobacterium tuberculosis*, *Actinomycosis, treponema palidum* and *Staph aureus*
- **Exposure to irritant inorganic material**
  - wound debris (wood splinters), inhaled materials (silica, asbestos), iatrogenic implants (suture material or dental implants), tatoos
- **Autoimmune diseases**
  - Type I diabetes mellitus, autoimmune thyreoditis, autoimmune gastritis
- **Degenerative diseases**
  - Atherosclerosis, Alzheimer's disease, neoplasia

Characteristics of acute and chronic inflammation

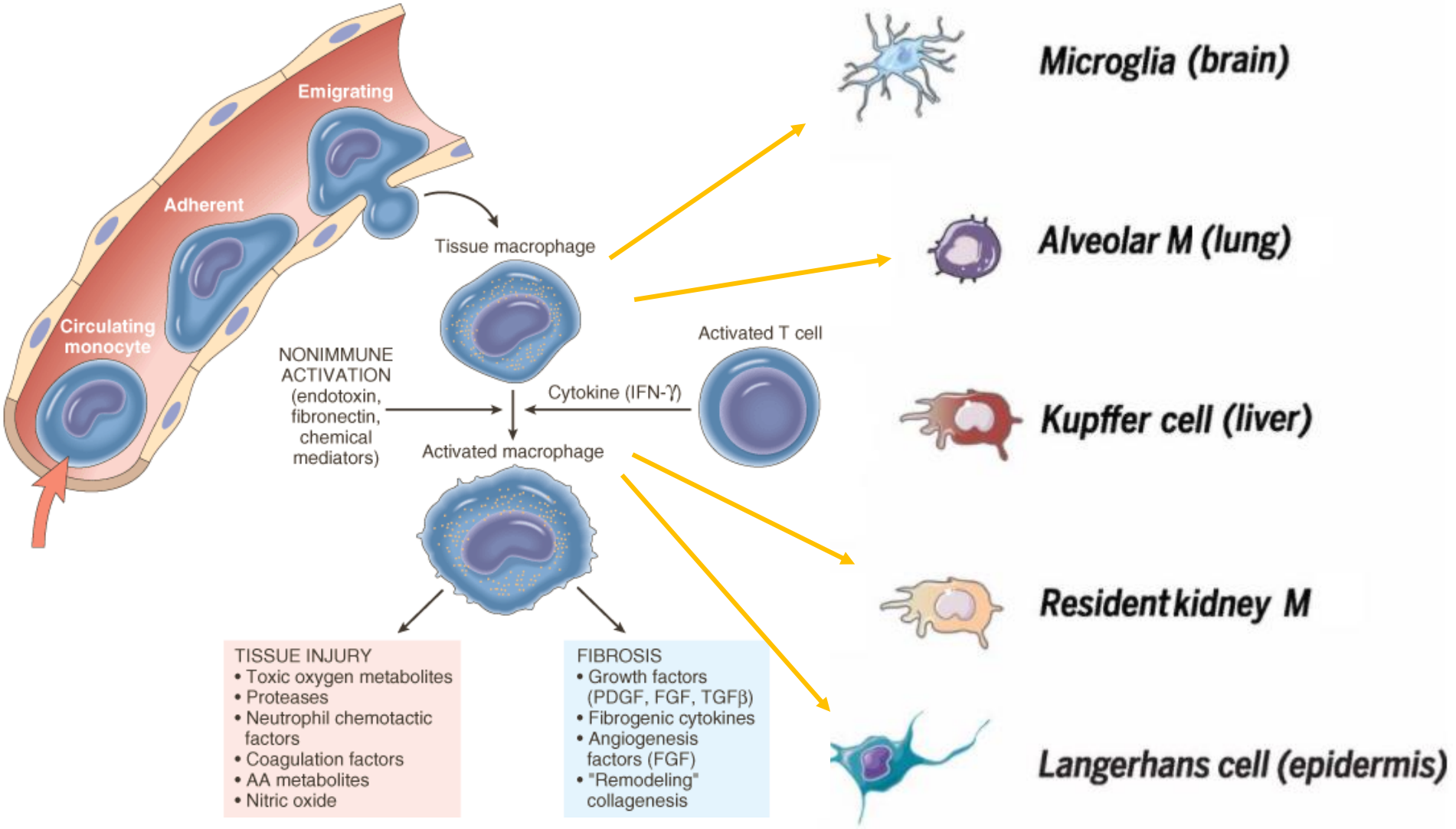
	Acute	Chronic
Duration	Short (days)	Long (weeks to months)
Onset	Rapid	Prolonged
Inflammatory cells	Neutrophils, macrophages	Lymphocytes, plasma cells, macrophages, fibroblasts
Vascular changes	Vasodilation, increased permeability	New vessel formation (granulation tissue)
Presence of exudate	+	-
Tissue necrosis	Usually none (except: abscess or necrotizing inflammation)	Countinuous
Fibrosis	-	+
Host responses	None specific: neutrophils, macrophages, complement	Adaptive: lymphocytes, plasma cells, immunoglobulins
Systemic manifestations	Fever	Mild fever, weight loss, anemia
Changes in peripheral blood	Neutrophil leukocytosis; lymphocytosis (in viral infections)	Not characteristic

Characteristics of chronic inflammation

- Cellular component: mononuclear cells
  - lymphocytes
  - plasma cells
  - Monocyte/macrophage system (MPS)
  - Eosinophils (allergy)
- Tissue destruction
- Proliferative changes (fibrosis, angiogenesis)
- Goal: healing

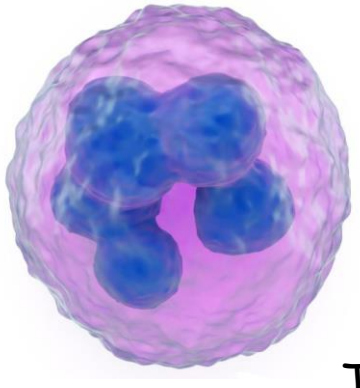
- NO EXUDATE !!!

Key role - monocyte/macrophage system



Key role - monocyte/macrophage system

Classic activation
(microbes, IFNγ)



Th1

Th2

Alternative activation
(IL-4, IL-13)

Goal: eliminate microbes

- killing
- phagocytosis
- proinflammation

Mediators:

Superoxide, lysosomal enzymes
IL-1, IL-12, NO

Goal: repair

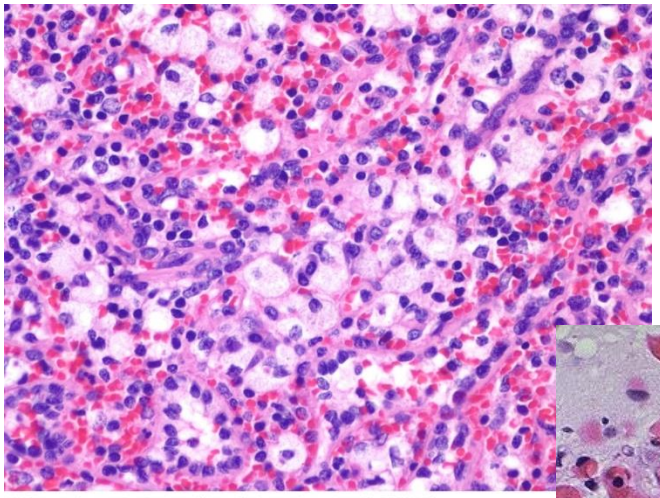
- regeneration
- fibrosis
- anti-inflammatory

Mediators:

Growth factors (FGF, VEGF)
TGFβ, IL10

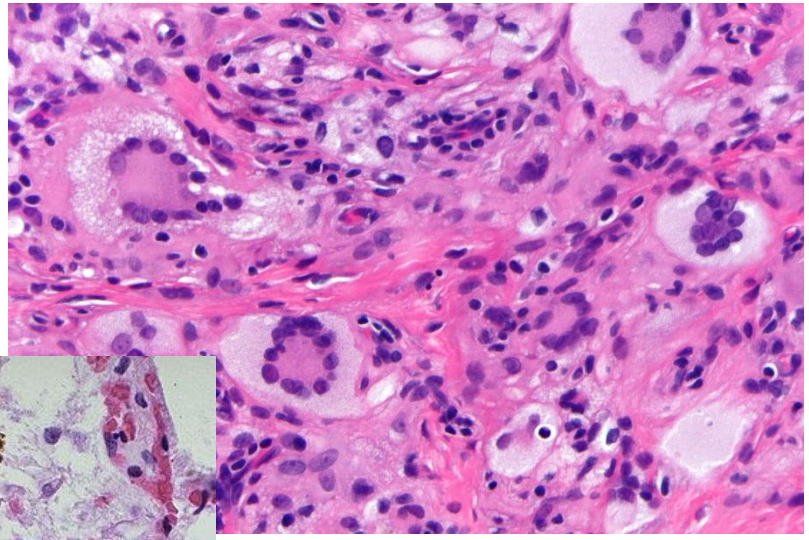
Morphology of macrophages

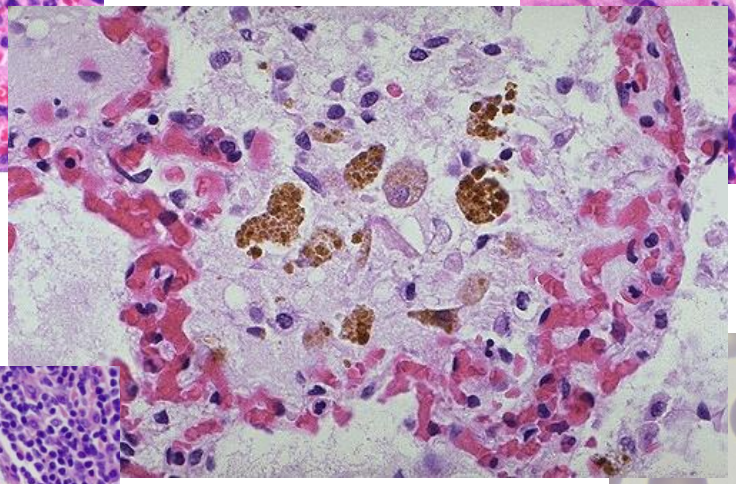
Foam cells



H&E image show small collections of foamy histiocytes in a patient with ITP (40x2)

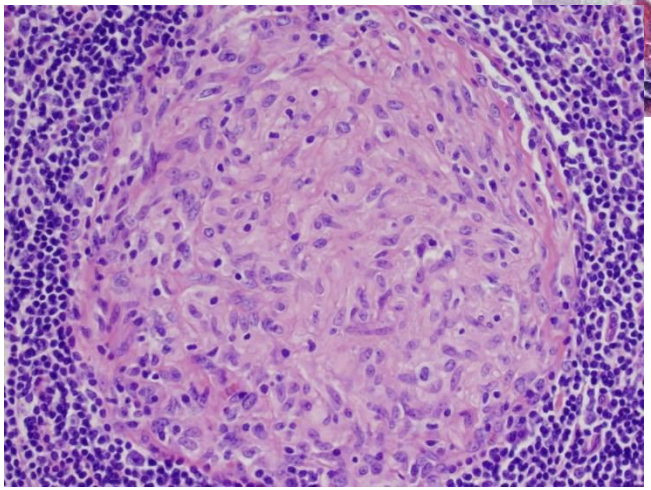
Giant cells



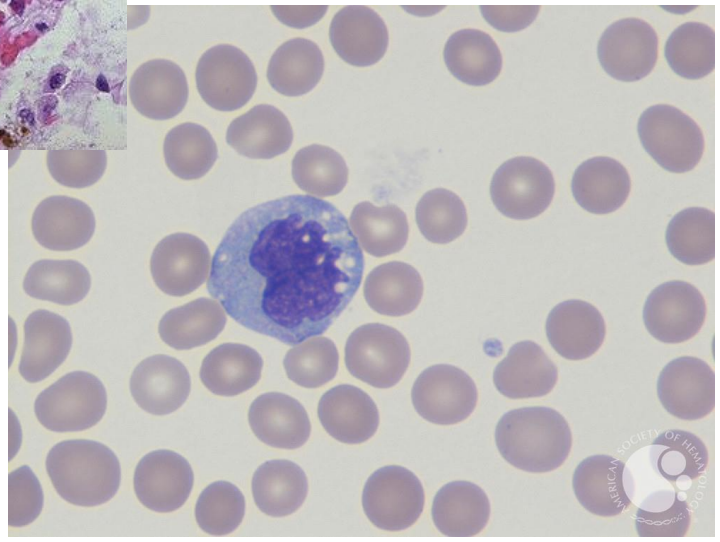


Hemosiderin macrophage

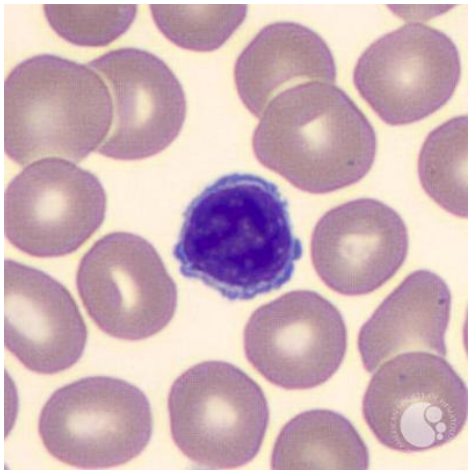
Epitheloid cells



Circulating monocytes

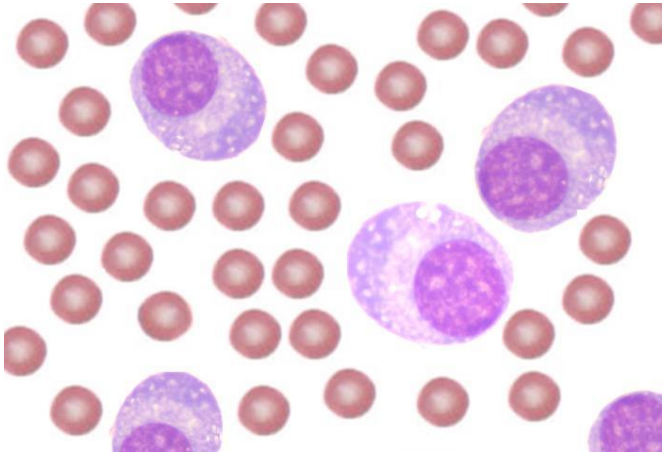


Other players – mediate specific recognition



Lymphocytes

- T and B cells
- surface receptors allow specific Ag recognition
- coordinate immune response
- effector functions

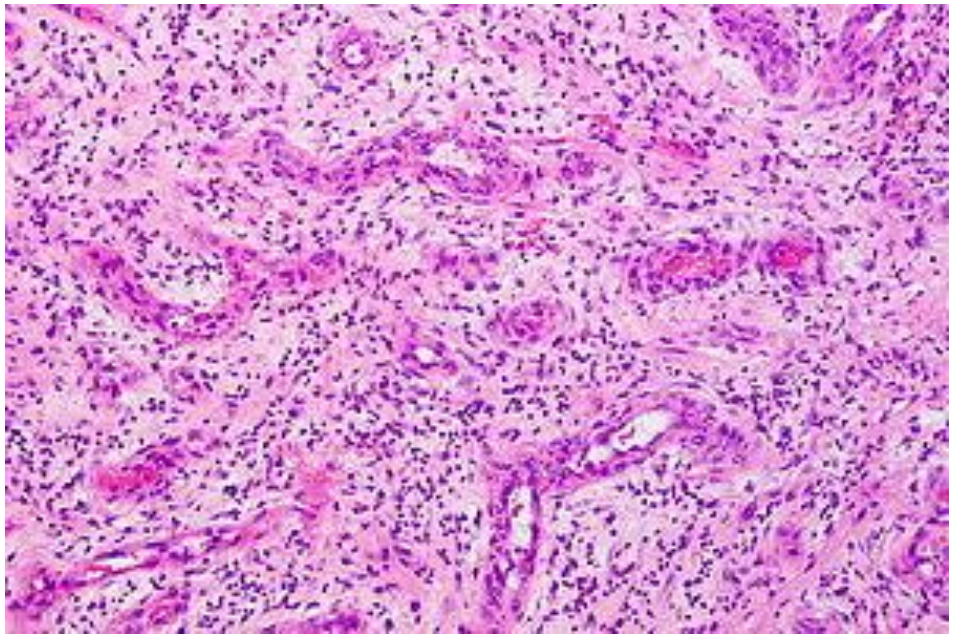


Plasma cells

- produce immunoglobulins
- opsonisation
- immunocomplex formation

Histology of chronic inflammation

GRANULATION TISSUE (non-specific)



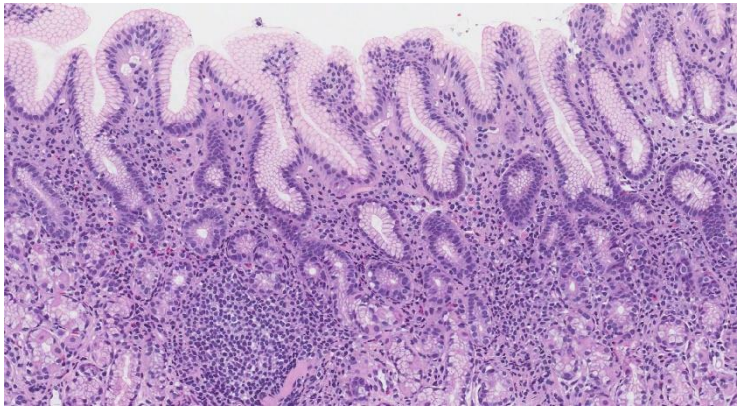
- Inflammatory cells
- Fibroblasts
- Newly formed collagen
- Vessel proliferation

Inflammation and repair

Main types of chronic inflammation

Non-specific

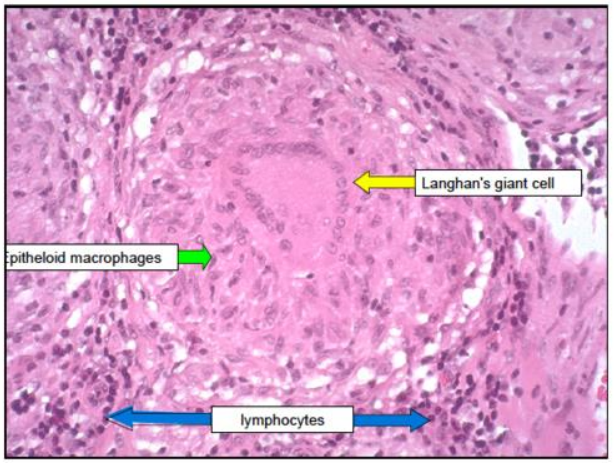
90%



Histology is not-specific to etiology

Specific or granulomatous

10%



Histology hold clues for etiology

Examples of chronic inflammatory diseases

Non-specific

- Chronic gastritis
- Chronic hepatitis
- Chronic pancreatitis

Granulomatous (specific)

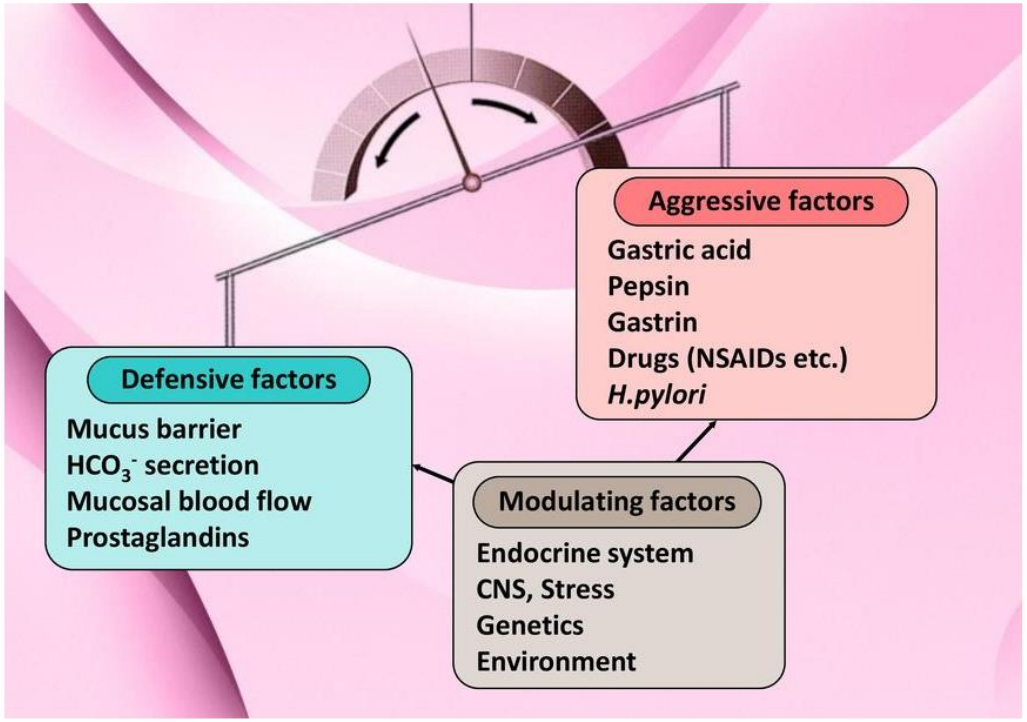
- Tuberculosis
- Sarcoidosis
- Rheumatic fever
- Foerign body granuloma

Non-specific

Chronic gastritis

- Chronic inflammation of the gastric mucosa that may lead to mucosal atrophy, and epithelial metaplasia
- Most common histological diagnosis – very frequent

- Patomechanism: imbalance of mucosal offensive and defensive factors on mucosal surface



Non-specific

Chronic gastritis

Forms

A: **Autoimmune gastritis** (10%)

- autoantibodies against the parietal cells
- decreased HCL production
- mucosal atrophy – intestinal metaplasia

B: **Bacterial** – **H. pylori**

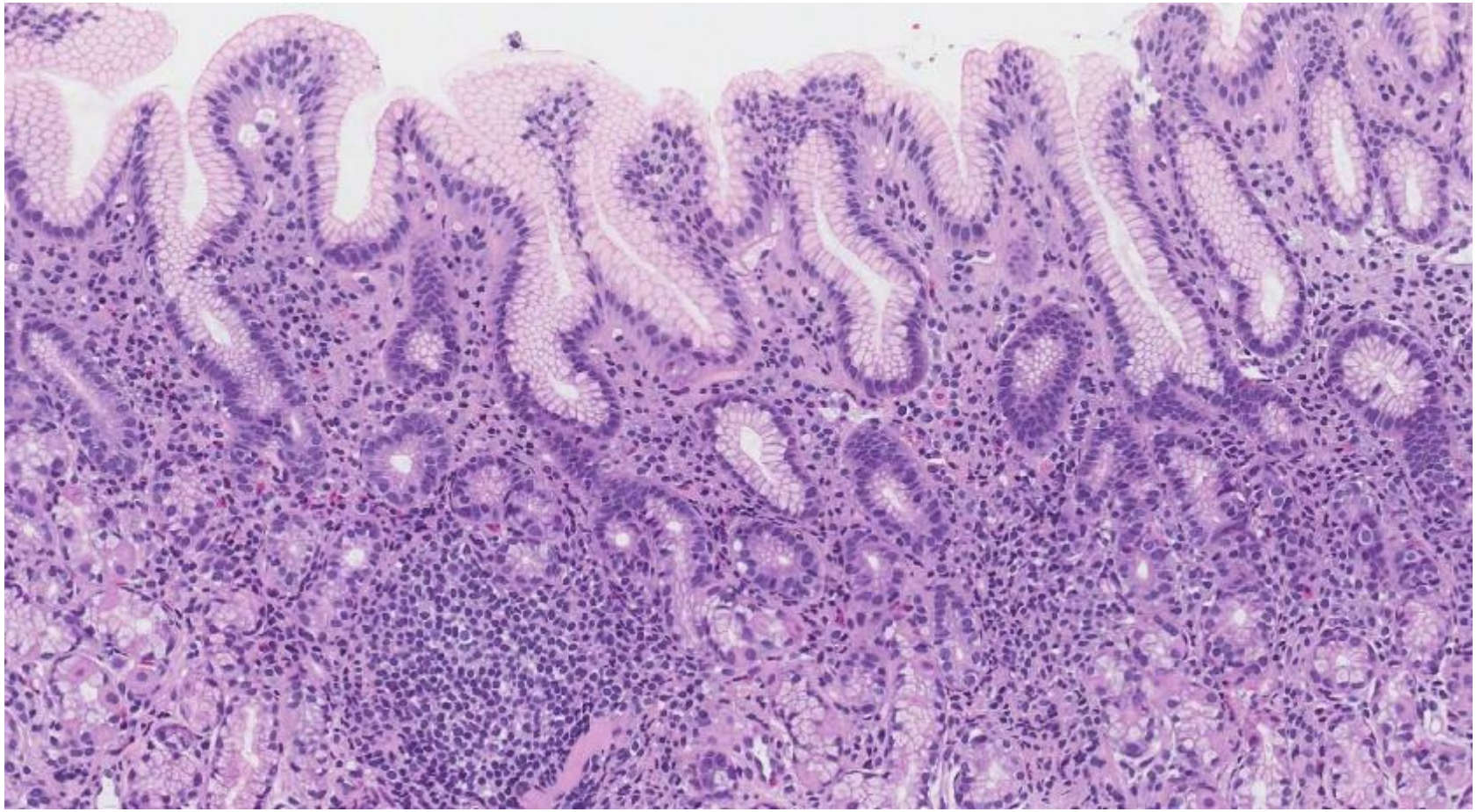
- G-, non-invasive, spiral bacterium on mucosal surface
- ammonia production leads to mucosal injury
- eradication by combined antibotics
- gastric ulcer, gastric cancer, MALT lymphoma

C: **Chemical** – most common

- hyperacidity
- hot or spicy foods, alcohol
- bile reflux
- mucosal hypoperfusion (congestion, NSAID)

Non-specific

Chronic gastritis



Non-specific

Chronic hepatitis

Definition: inflammation of the liver that lasts at least 6 months.

Causes: - viral (Hepatitis virus B and C)
- alcohol
- autoimmune

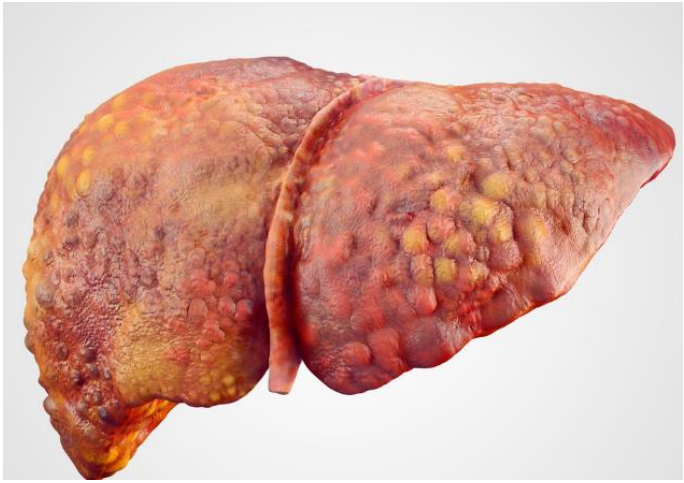
Clinical: vague symptoms, such as a general feeling of illness
poor appetite, and fatigue

Laboratory: elevated liver enzymes (ALT, AST, GGT)
elevated bilirubin (jaundice)

Morphology:

- Lymphocytic infiltration of portal areas
- Bridgeing necrosis
- Fibrosis- chirrosis

Outcome: fibrotic remodeling – cirrhosis
liver failure (vascular, parenchymal)



Non-specific

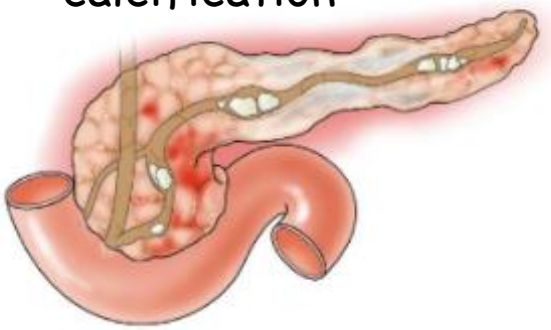
Chronic pancreatitis

Definition is a long-standing inflammation of the **pancreas** that alters the organ's normal structure and functions.

- Repeated incidences of inflammation lead to atrophy and fibrosis of the parenchyma
- Functional consequence will be exocrine (malabsorption) and endocrine (carbohydrate metabolism) dysfunction

Etiology: - 70% alcohol
- autoimmune
- cystic fibrosis
- gallstones

Morphology: - parenchymal atrophy
- fibrosis
- duct strictures
- calcification



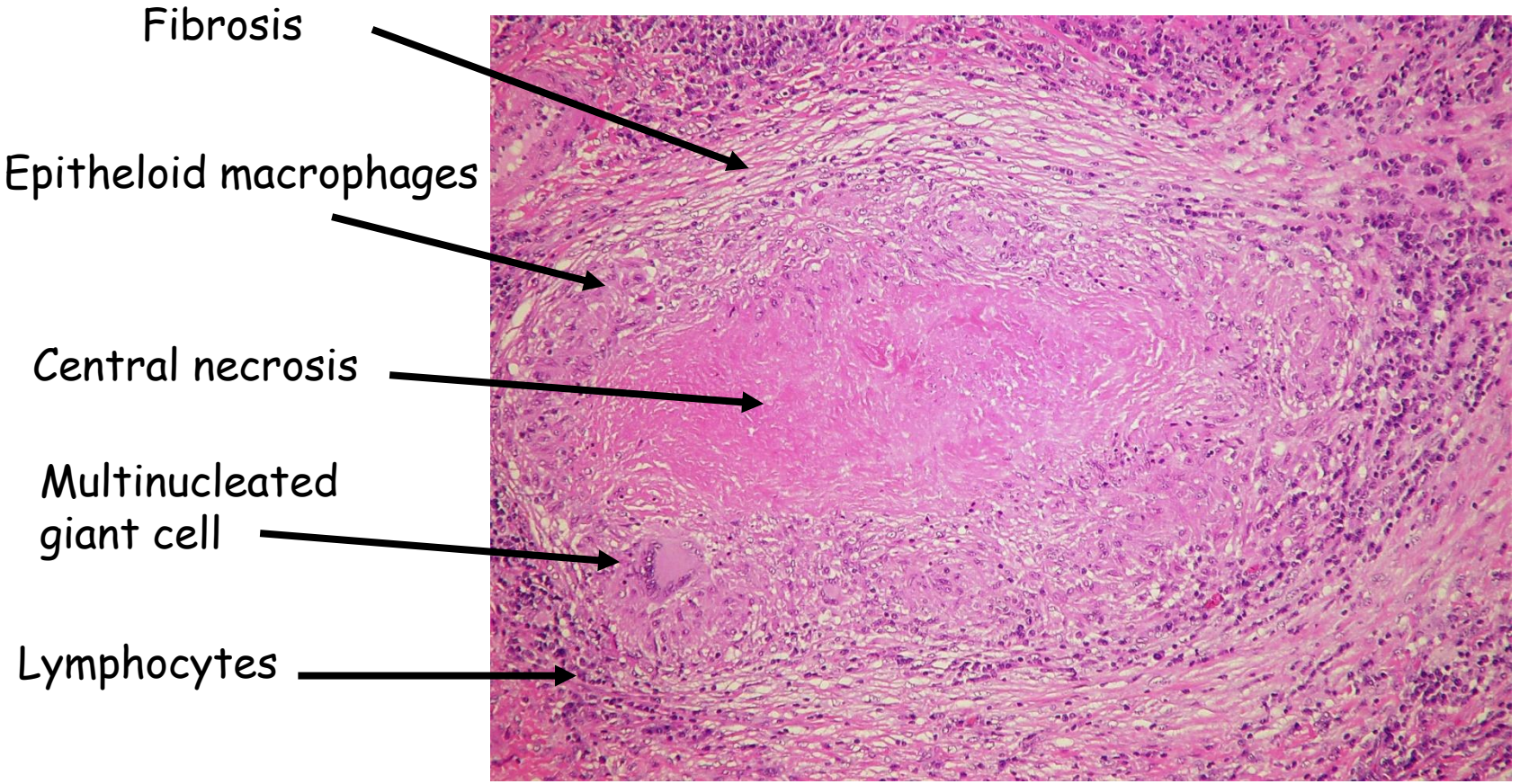
Clinical: - vague symptoms
- epigastrial pain
- malabsorption, weight loss

Granulomatous inflammation

- distinctive pattern of chronic inflammation
- encountered in a limited number of infectious and non-infectious conditions (specific inflammation)
- characterized by granulomas formed by epitheloid histiocytes (activated macrophages)
- immune reactions are involved in formation of granulomas (type IV hypersensitivity)

Granuloma is a cellular attempt to control an offending agent that is difficult to eradicate. – immunological prison

Sructure of a granuloma



Specific

Types of granulomas

A. Immune granulomas

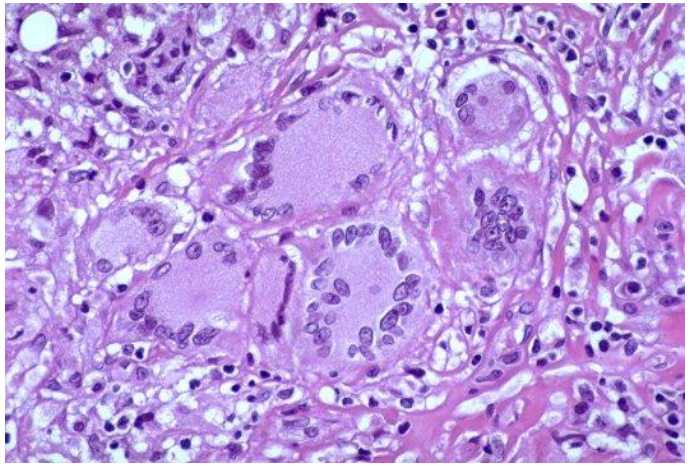
- Infectious
  - Tuberculosis
  - Syphilis
  - Leprosy
  - Cat-scratch disease
- Non-infectious
  - Sarcoidosis
  - Rheumatic fever
  - Crohn's disease (GIT granulomas)

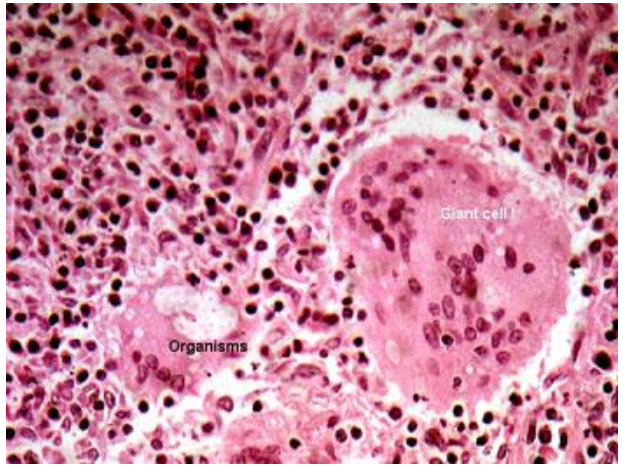
B. Foreign-body granulomas

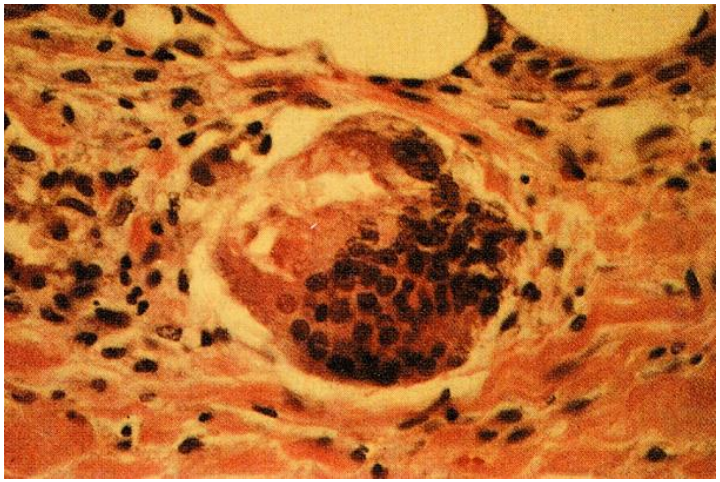
- Suture granuloma
- Lipogranuloma
- Drugs (allopurinol)

Types of giant cells

- Langhans type
- Foreign body type
- Touton type



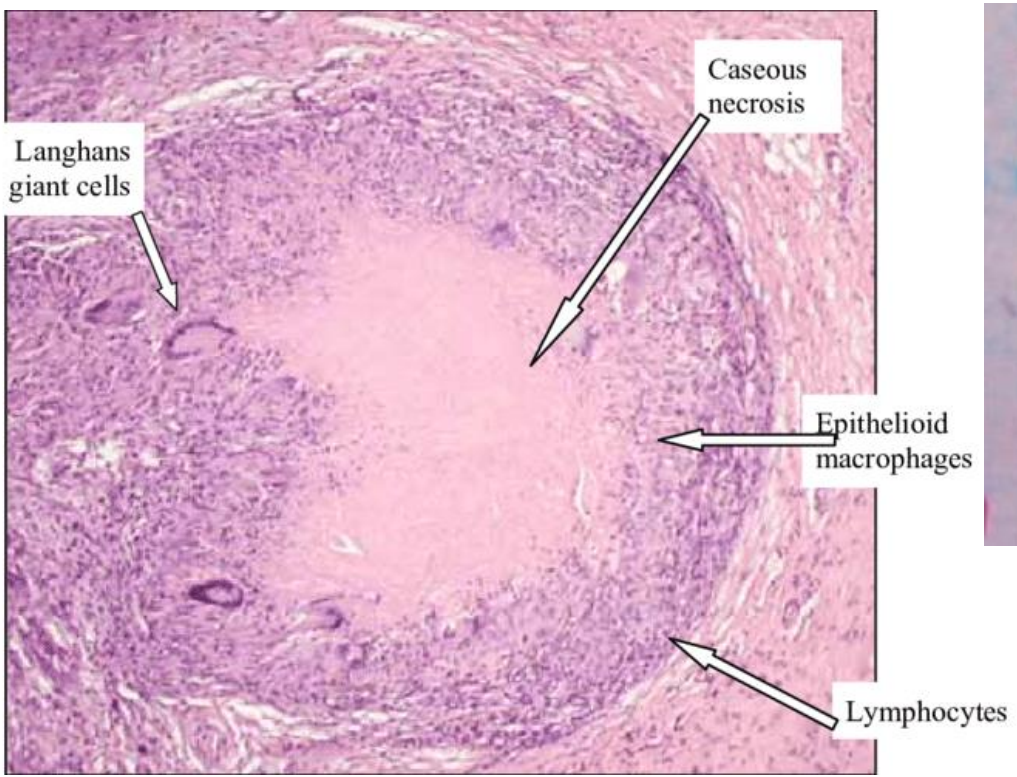


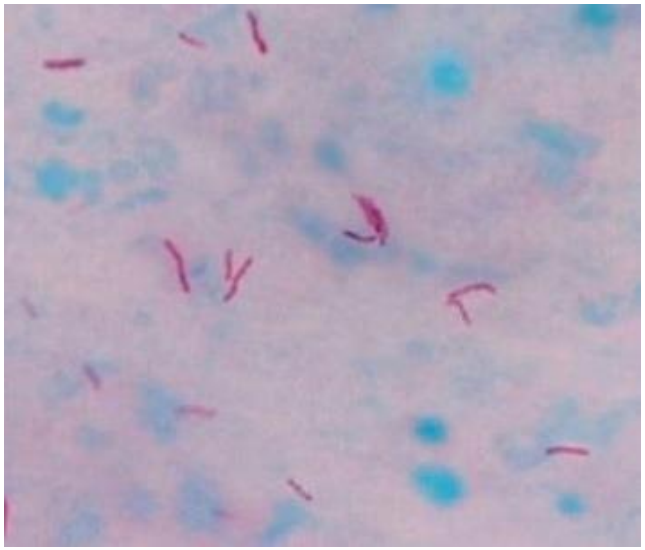


xanthogranuloma

Tuberculosis

- Chronic granulomatous inflammation caused by Mycobacteria (tuberculosis, avium, bovis)
- Acid-fast, rod shaped bacterium – Ziehl-Neelsen staining
- Caseous necrotizing granulomas
- Langhans type giant cells





Ziehl-Neelsen

Tuberculosis

Sites of primary infection – lung (common), skin, gastrointestinal tract

Stages:

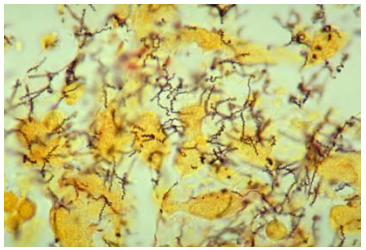
Primary: primary focus – formation of caseating granulomas (subpleural)
Ranke-Ghon's complex (primary focus, lympangitis, lympadenitis)
granulomas may undergo calcification

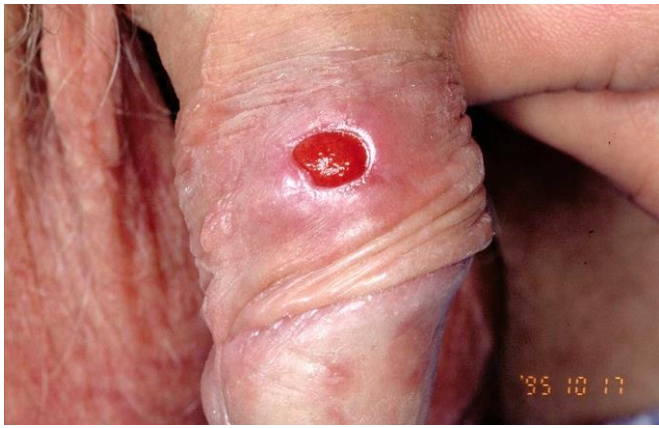
Post-primary: result of reactivation - immune weakness
exudative process – apex of lung – caseation
cavitation

Tertiary: systemic dissemination (testis, CNS)
high mortality rate

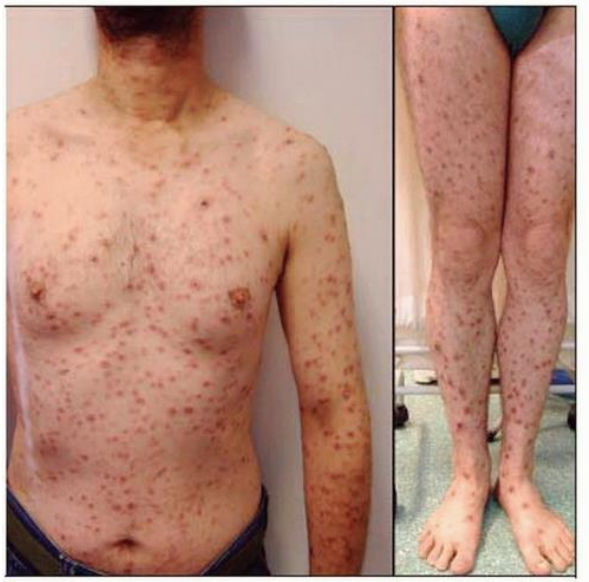
Special form: Primary progressive tuberculosis – severely immuncompromised skips the primary stage and starts with exudative process

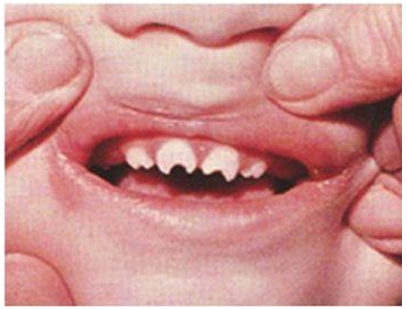
Syphilis





- bacterial infection spread by sexual contact
- Cause: Treponema pallidum (spiral shape)
- typically affects genitals, rectum or mouth
- 3 stages
  - Primary syphilis
    - genital sore (chancre) – site of entry
    - three weeks after exposure
    - painless
  - Secondary syphilis
    - weeks after healing of sore
    - disseminated skin rash (palm, soles also)
    - general symptoms, fever, lymphadenomegaly
  - Latent syphilis
    - Hidden stage, lasts for years, no symptoms
  - Tertiary syphilis
    - Late stage in those without prior treatment
    - Affects: brain, nerves, eyes, heart, blood vessels, liver, bones and joints (aorta ascendens aneurysm)
  - Neurosyphilis
    - At any stage
    - Nervous system and eye damage (progressive

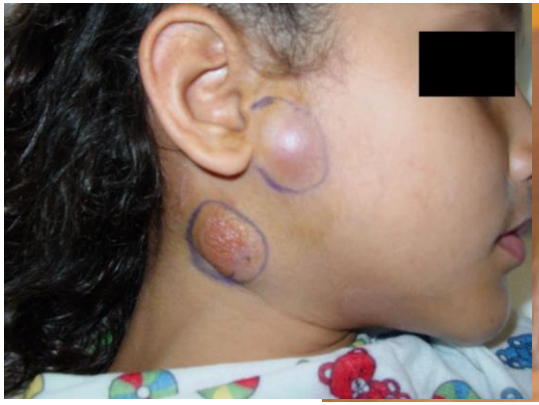




* Congenital syphilis – transplacental- deafness, teeth deformities and saddle nose

Suppurative granulomas

Pus (granulocytes associated with granulomas)



Cat-scratch disease

- Bartonella hensleae
- Spread by cats (cat is not sick)
- Enlarged axillary, neck lymph nodes, fever
- Granulomatous lymphadenitis

Lymphogranuloma venerum

- Sexually transmitted disease
- Chlamidia trachomatis
- Primary stage: painless genital ulcer
- Secondary stage: 10–30 days later
  - tender inguinal and/or femoral lymphadenopathy (buboes)
  - salpingitis (sterility)

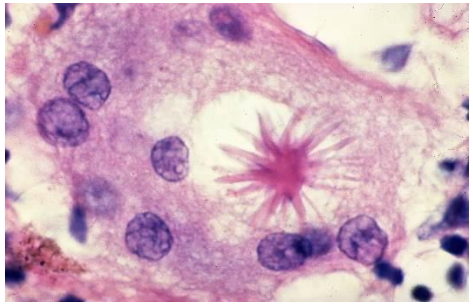
Tularemia (rabbit fever)

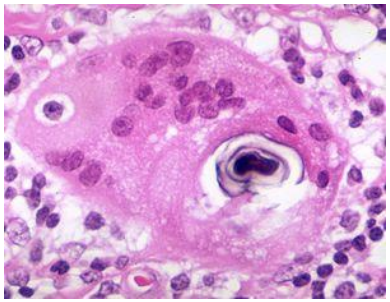
- infection caused by Francisella tularensis (facultative intracellular bact.)
- spread by tick, deer flies from animal host
- fever, skin ulcers, and enlarged lymph nodes (ulceroglandular form)
- sepsis – may cause death without treatment (60%)

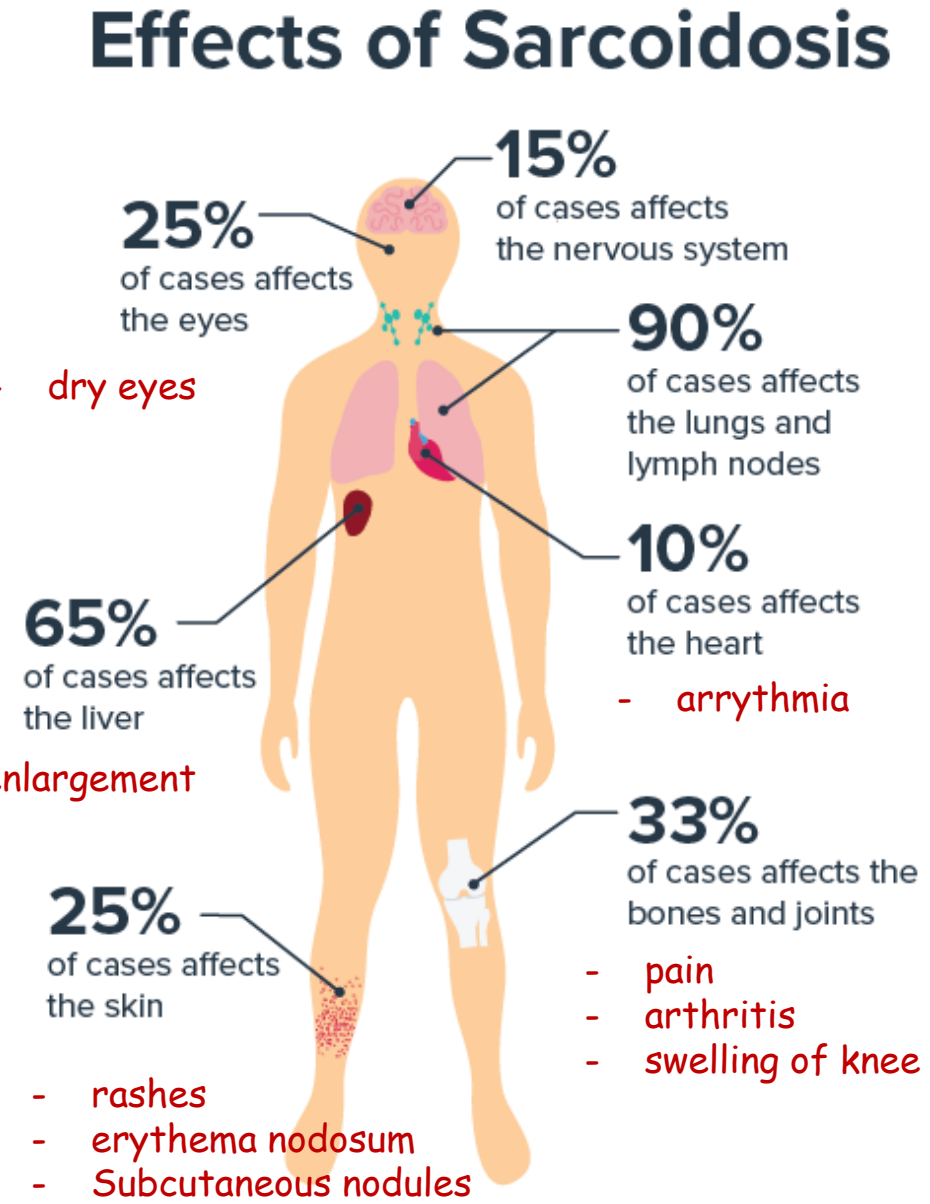
Sarcoidosis

- multisystemic disease
- granulomatous inflammation
- non-caseating granulomas
- unknown etiology
- more common in northern countries
- bilateral hilar lymphadenomegaly
- lung fibrosis

Giant cells may contain:
- Asteroid bodies
- Schaumann bodies







Rheumatic fever

- Poststreptococcal disease with immune mediated systemic tissue damage
- Cause: group A beta-hemolytic Streptococci (contain M-antigen)
- Bacterial infection often causes pharyngitis, follicular tonsillitis or pyoderma

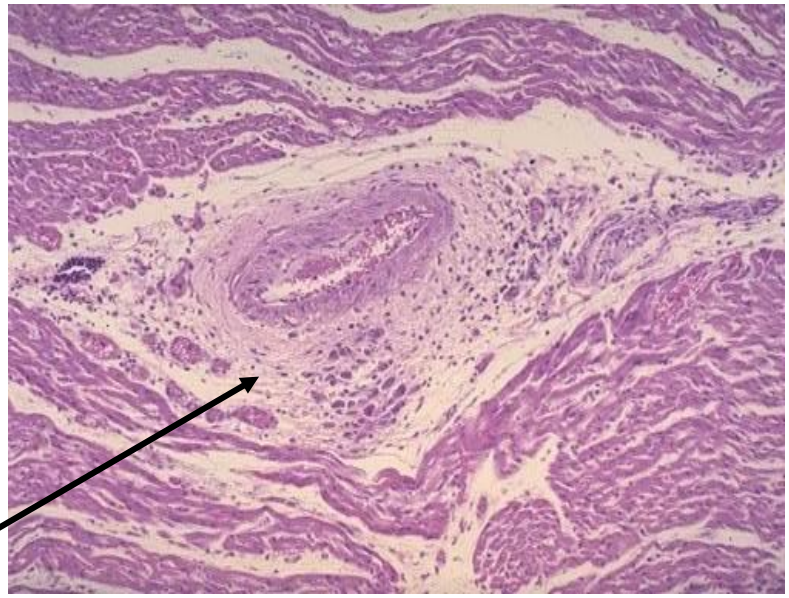
Rheumatic fever occurs 2-3 weeks after acute Streptococcal infection
Pathomechanism: cross reaction of antibodies produced against M-antigen with self antigens (connective tissue)

Symptoms (Jones criteria)

Major	Minor
Polyarthritis	Arthralgia
Carditis	Prolonged PR interval
Chorea	Elevated CRP, ESR
Erythema marginatum	Fever (38-39 C)
Subcutaneous nodules	Elevated WBC

"Licks the joints but bites the heart"

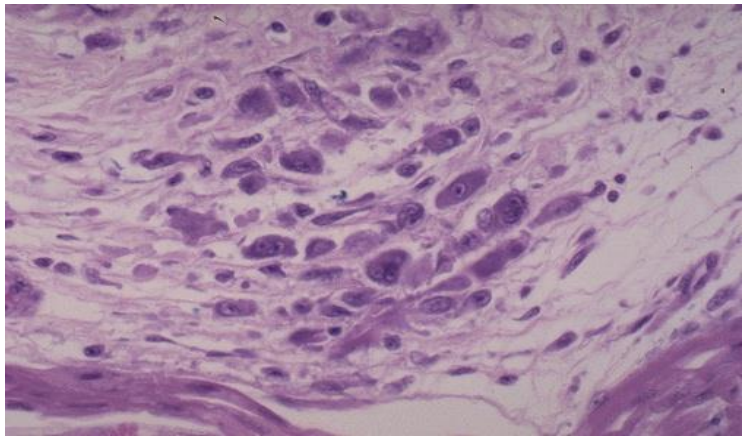
Rheumatic fever

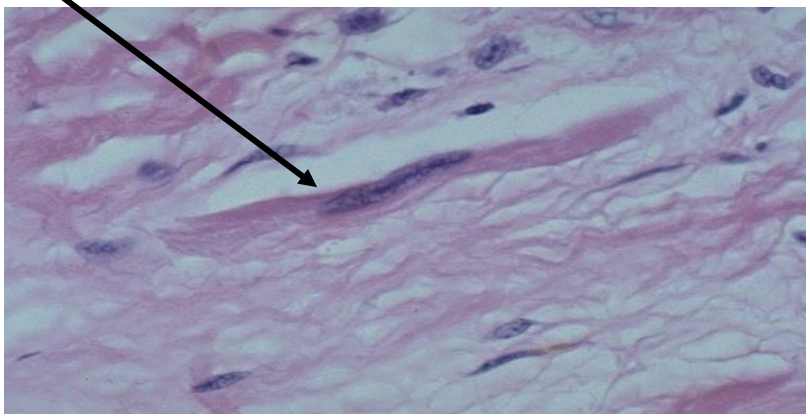


Cardiac manifestation – PANCARDITIS

- Pericarditis – fibrinous
- Myocarditis – granulomatous
- Endocarditis (valves)

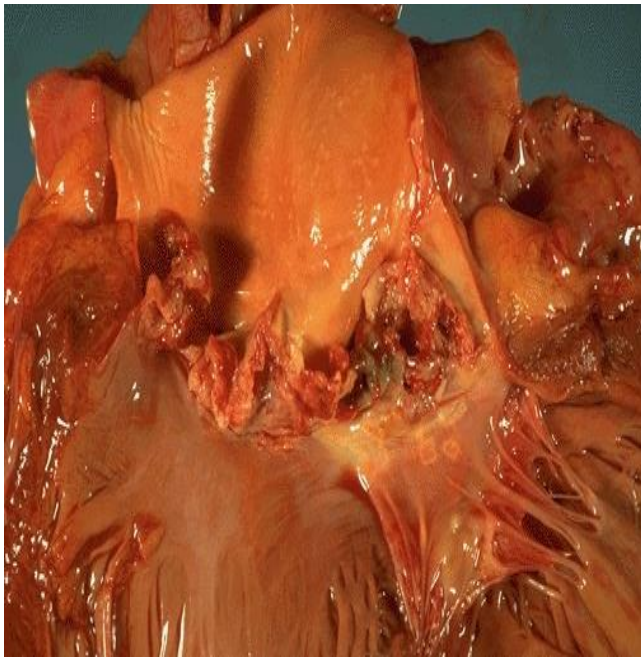
Granulomatous myocarditis – Aschoff bodies (granulomas around vessels)
- fibrinoid collagen necrosis in center of granuloma
- Anitschkov cells (spindly macrophage)





Rheumatic fever

Outcome: all symptoms regress spontaneously
EXCEPT: endocarditis – leads to chronic valve damage (mitral, aortic)



Rheumatic Heart Disease (20-30 years after)

- Scarring of myocardium and valves
- Valve leaflet thickening
- Commissural fusion
- Shortening of cordae tendineae
- Results: valvular stenosis and regurgitation
- Most commonly affects mitral and aortic valve

Complications: heart murmur
arrythmias