Pathology of Infectious Diseases

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Host involvement

Endogenous infection from the colonizing flora

Exogenous infection from invasion of host by microorganisms from external sources

Nosocomial infection acquired during hospitalization (urinary tract infections, infections of the respiratory organs, wound infection, sepsis)

Systemic infection

- example: immunocompromised host, *Cladophialophora* mycotic infection („black fungus“)
- portal of entry – lung, skin
- generalisation - haematogenous
- organotropism – brain abscesses
  lung abscesses
- superinfection by bacteria

Host factors in pathogen transmission

- **Age (old age, extreme youth – prematurity, infancy)**
- **Immune status (inborn and/or acquired defects, incl. immunosuppressive therapy, stress, etc.)**
- **Concurrent illness or infirmity**
- **Genetic background**
- **Pregnancy**
- **Nutritional status**
- **Demographics of the exposed population (density, etc.)**
- **Social and behavioral traits**

Sensitive populations – increased infectious disease risks

- **Infants and young children**
- **Elderly**
- **Immunocompromized**
  - **Persons with AIDS**
  - **Cancer patients**
  - **Transplant patients**
- **Pregnant**
- **Malnourished**

INFECTIOUS DISEASES

- **SYMPTOMS -** subjective evidence of disease as sensed by the patient.
- **SIGNS -** objective evidence of disease as noted by an observer.
- **SYNDROMES -** a specific group of symptoms or signs which accompany a particular disease.

Common signs and symptoms

Signs	Symptoms
Fever	Chills
Septicemia	Fatigue, soreness
Skin eruptions	Itching
Chest sounds	Dyspnoea

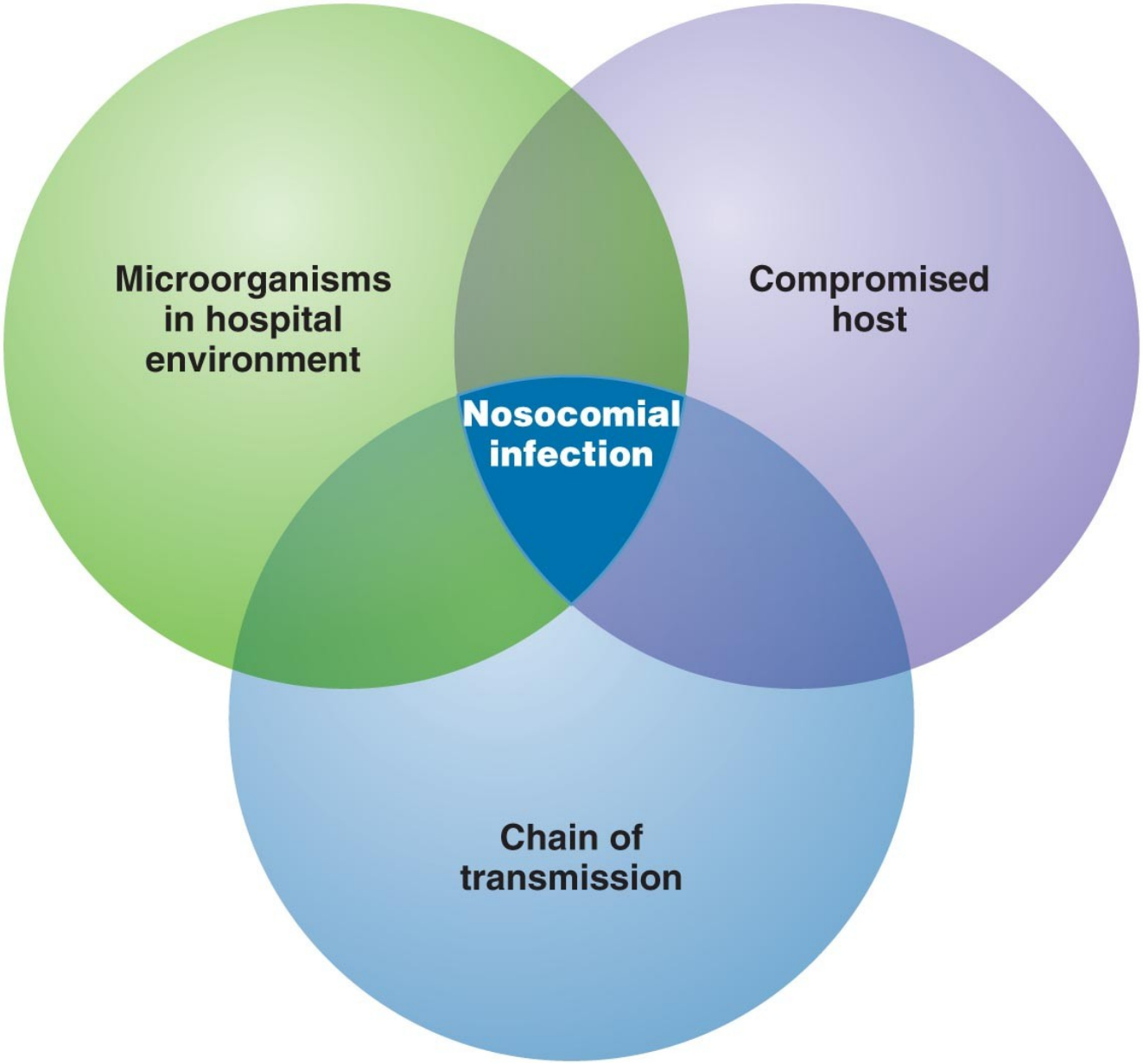
Health outcomes of microbial infection

- **Acute outcomes**
  - **Diarrhea, vomiting, rash, fever, etc.**
- **Chronic outcomes**
  - **Paralysis, hemorrhagic uremia, reactive arthritis, encephalitis, heart disease, etc.**
- **Hospitalizations**
- **Deaths**

Portals of entry

- Skin
- Gastrointestinal tract
- Respiratory
- Urogenital
- Via placenta
- Parenteral (injection, bite)

Nosocomial infections



Nosocomial infections

- ~ 10% of patients acquire a clinically significant nosocomial infection
- 10-30% in developing countries
- Enterobacterias incl. Klebsiella pneumoniae ~ 10% of nosocomial infections, ! multidrug resistant
- Burkholderia + Pseudomonas – urinary catheter – pyelonephritis; necrotizing pneumonia, wound infections; G-sepsis; rapid resistence
- Staph. aureus MRSA

Nosocomial infections consequences

- Additional morbidity/mortality
- Prolonged hospitalisation
- Permanent damage possible
- Increased cost

Nosocomial infections

- Colonies of hospital bacterial strains develop on patient‘s skin, in respiratory and genitourinary tract within hours after admission
- **Risk factors**: patient related
  iatrogenic
  organisational

Patient related risk factors

- Type and severity of illness
- Immunodeficiency (age, malnutrition, alcoholism, heavy smoking - ↓ wound healing, …)
- Lenght of hospital stay
- Sex (females ↑ UTI)

Iatrogenic risk factors

- Medical personnel hands as source!! – hand hygiene
- Invasive procedures
- Antibiotics use + prophylaxis

Organisation risk factors

- Contaminated air (air-conditioning), water, food, …
- General situation in the hospital (staffing, number/closeness of beds…)

Nosocomial infections

- **Source**: endogenous
- exogenous: hands of healthcare workers
  contaminated surfaces/devices
  other patients (incl. contaminated biological material)
  visitors
  vectors

First principle of infection prevention

At least 35-50% of all healthcare-associated infections are associated with only 5 patient care practices:

- Use and care of urinary catheters
- Use and care of vascular access lines
- Therapy and support of pulmonary functions
- Surveillance of surgical procedures
- Hand hygiene and standard precautions

New and emerging infectious diseases

- SARS-CoV-2
- Diseases that are new, increasing in incidence, or showing a potential to increase in the near future (Zika, monkeypox)
- Newly recognised infectious causes of known diseases (other Coronaviruses, Borrelia; hepatitis viruses – HEV; etc.)
- Opportunistic infections in immunocompromised patients (MAC, Pneumocystis, HHV-8)

Emerging infectious diseases

- Geographic spread of known infections (West Nile virus, Plasmodium falciparum)
- Local spread – environmental changes (bats – rabies; ticks – encephalitis, Lyme borreliosis)
- Crossing of interspecies barrier (coronavirus SARS-CoV-2, SARS-CoV-1, MERS-CoV, Ebola, BSE)
- Re-emerging infections, new strains event. resistant (TBC, Vibrio cholerae, influenza H5N1,H1N1,H7N9; polio)

Emerging infectious diseases

- Contributing factors
  - Genetic recombination
    - *E. coli* O157, avian influenza (H5N1), pandemic influenza (H1N1), Zika virus
  - Evolution of new strains
    - *V. cholerae* O139, Candida auris
  - Inappropriate use of antibiotics and pesticides
    - Antibiotic-resistant strains incl. MRSA, TB
  - Climatic changes
    - tick-borne encephalitis*, West Nile fever*

Emerging infectious diseases

- Modern transportation
  - West Nile virus
- Ecological disaster, war, and expanding human settlement
  - Cholera (Haiti – earthquake), coccidioidomycosis
- Animal control measures
  - Lyme disease; ↓rabies→ ↑echinococcus
- Public health failure, decline in vaccination rates
  - Diphtheria, pertussis, measles, poliomyelitis acuta ant.
  - outbreak of Salmonella from salmon; mycotic encephalitis/arthritis from corticosteroid injection
  - Legionella, non-TB mycobacteria (water)

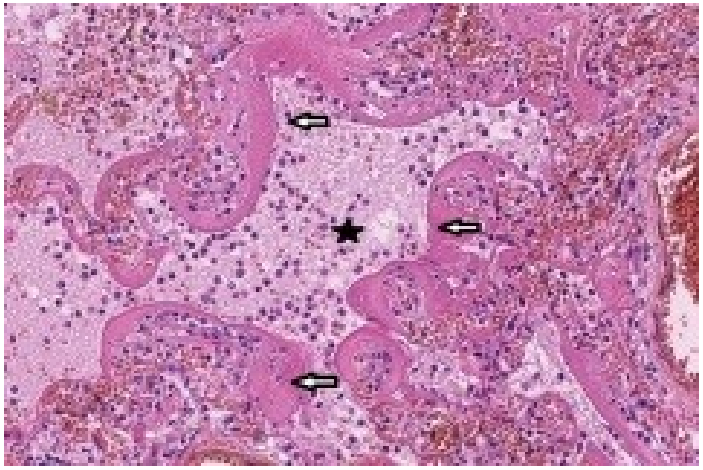
SARS-CoV-2 / COVID-19

- major risk factors:
  - age
  - males
  - obesity
  - DM
  - cardiovascular diseases (IHD, chronic heart failure, cardiomyopathy)
  - chronic lung diseases
  - cancer
  - chronic renal diseases
  - solid organ transplantation, esp. lungs

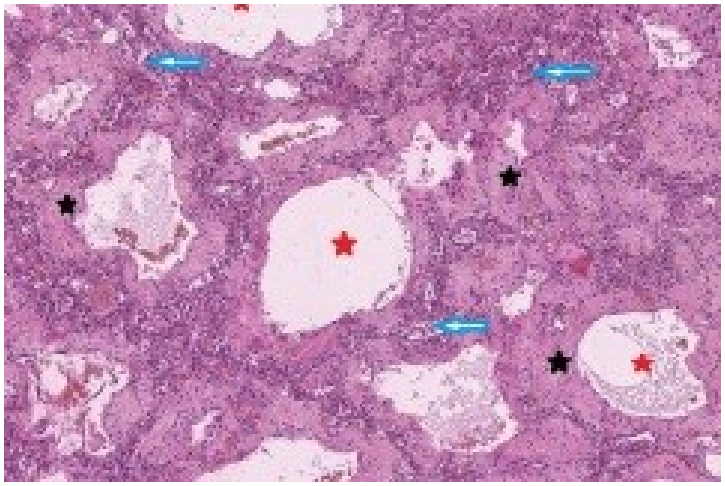
Major pathologic findings in COVID-19

- pneumonitis with acute lung injury, organising pneumonia, and lung fibrosis;
- secondary bacterial pneumonia in some
- systemic inflammatory response syndrome (SIRS) with haemophagocytosis (by marrow and splenic macrophages and liver Kupffer cells) and splenic white pulp atrophy – reflecting a cytokine storm
- thrombophilia and tissue infarction, particularly affecting small vessels in the lungs and brain
  - apart of complement acivation possible co-factor - hyperproduction of neutrophilic extracellular nets – NET

DAD – 14th day



Chronic DAD – lung fibrosis

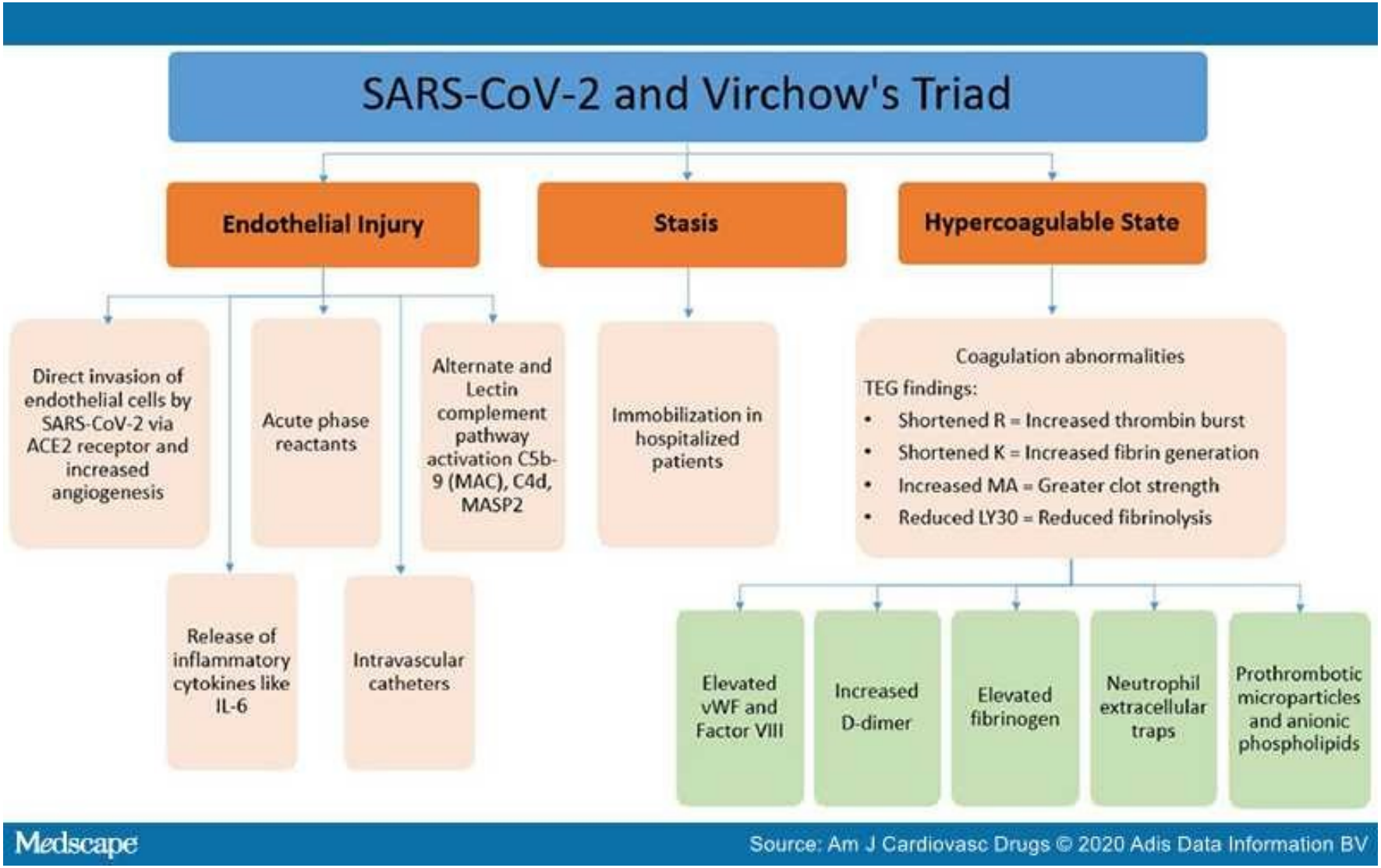


Vasculopathy, thrombosis in COVID-19

- microangiopathy
  - endotheliitis
  - diffuse microthrombosis (platelets + fibrin), lungs in ARDS, kidney, heart, liver
  - capillary congestion
  - angiogenesis

- coagulopathy /hypercoagulability w. thrombosis, thrombembolisation
  - endothelial damage, circulating prothrombotic factors, blood stasis
  - deep venous thrombosis
  - infarctions inc. stroke

Thrombosis in COVID-19



Heart and COVID-19

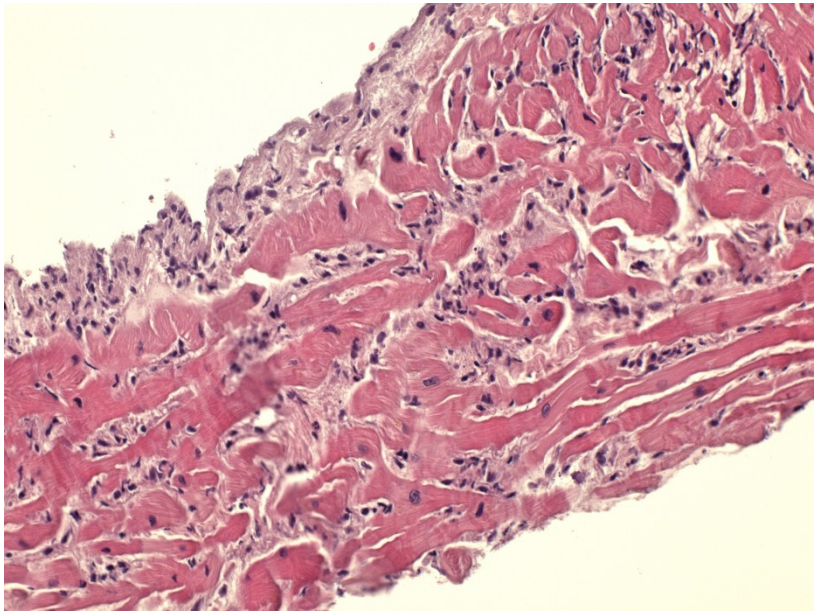
- patients w.preexisting cardiovascular lesions in increased risk of worse course (approx. ½ in hostpitals)
- general common cardiovascular lesions
  - 10-20 %, raised troponin, arrythmia in acute stage
  - cardiomyopathy in „Long COVID syndrome“ 30-90 d. afrer dg., abnormities on MRI, atypical stenocardias, dyspnoea
- etiology
  - hypoxia + ischemia due to lung lesions (pneumonia, ARDS)
  - lymphocytic myocarditis
  - microvasculopathy + thrombosis
- in children and teens possible part of COVID-associated multisystem inflammatory syndrome in children (MIS-C)

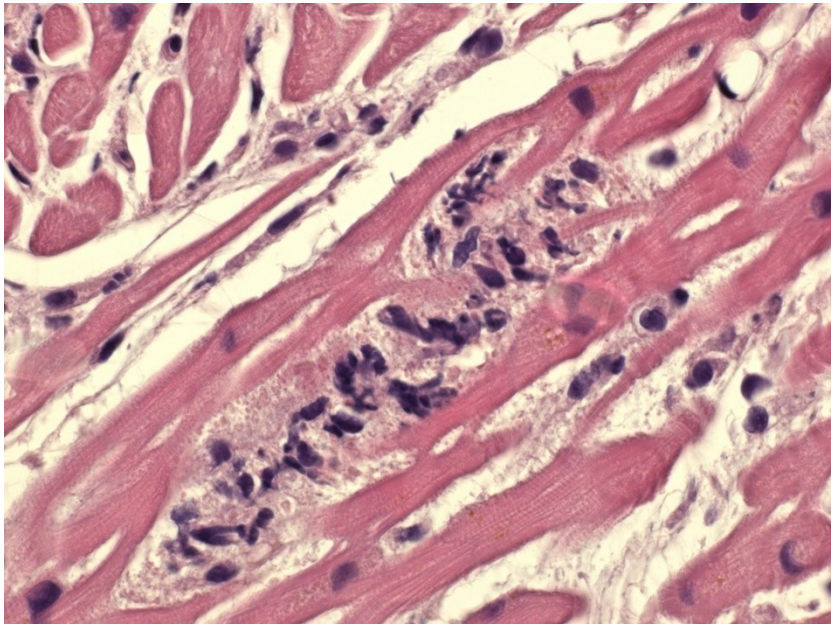
MIS-C

- Kawasaki-like disease
- delayed signs, some weeks after infection (commonly 3-4)
- fever, inflammatory signs in lab tests, lesion up to failure in min. 2 organ systens (heart in 80 %, renal, GIT, lung, neurological, ...), association w. SARS-CoV-2
- commonly acute heart failure, shock, peri-myocarditis
- rare (cca 10 %) coronary aneurysms
- micro: myocarditis w. oedema, mixed infl. reaction w. neutrophils, macrophages, lymphocytes, eosinophils), possible cardiomyocyte necrosis
- most patients survive, rapid recovery

MIS-C

- male, age 19
- EMB





COVID-19 and metabolic disorders

- Patients w. diabetes :
  - ↑ mortality, incl. indirect effects (controlling medications, DM complications treatment...)
  - more severe course both in DM1, DM2
- Obesity
  - ↑ risk of infection, severe course, mortality
- Hypothyroidism as possible complication (thyroiditis)

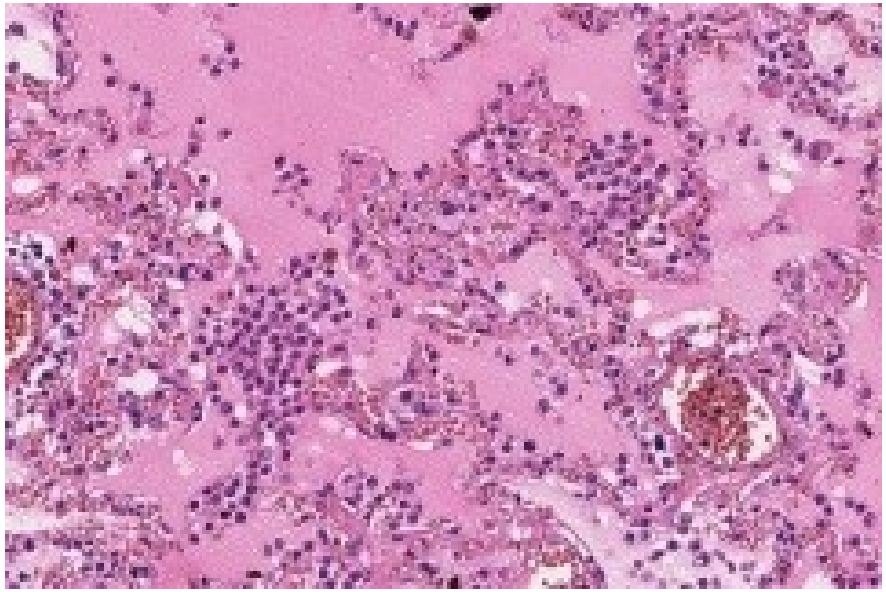
COVID-19 and other organs

- acute renal failure
  - direct damage due to microthrombi and/or tubular damage by the virus
  - consequences of systemic damage (decreased amount of extracellular fluid, shock w. multiorgan failure)
- brain damage
  - stroke
  - rare encephalitis, Parkinson‘s disease, ...
- skin exanthema, COVID fingers
- acute hepatitis
- splenic white pulp atrophy
- subacute thyroiditis (de Quervain)

Cell virus-induced changes

- Multinucleated enlarged pneumocytes (or other cells incl. endothelial - syncytia) with large nuclei, prominent nucleoli in alveolar spaces and other tissues
- Intranuclear inclusions

Acute capillaritis/alveolitis



COVID-19 and other organs

- GIT: edema, lymphocytic infiltrate, possible vascular changes. Diarrhea common. Virus in the stool – possible transmission!

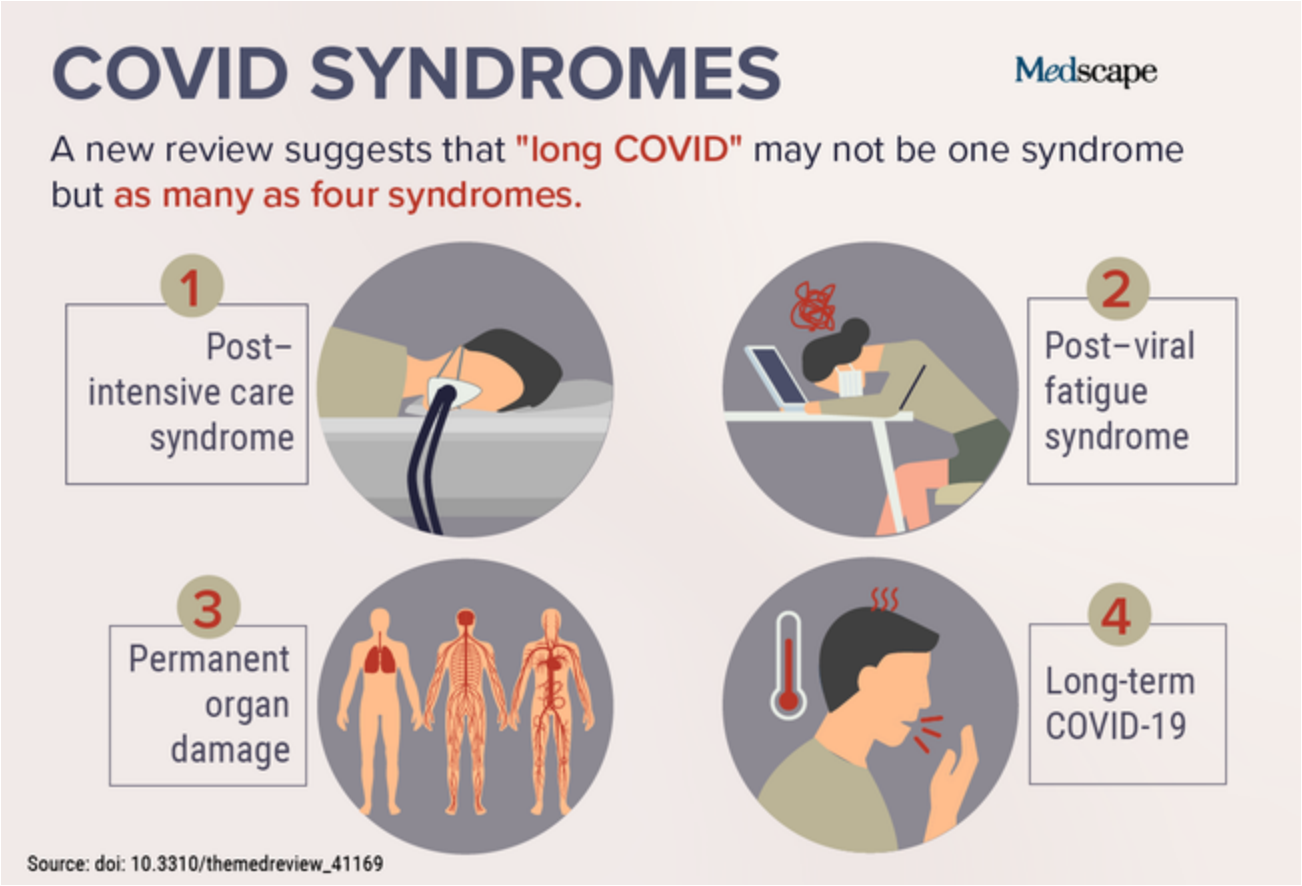
Covid-19 and pregnancy

- possible maternal vascular malperfusion (intervillous thrombi, maternal vessel injury)
- villous edema, placental hematoma
- risk of intrauterine fetal death
- risk of premature birth

Long COVID syndrome

- different mechanisms, different impacts
- chronic symptoms of fatigue, breathlessness, muscle weakness, joint pains, mental confusion, depression (↓ serotonin
- possible evolution of lung fibrosis, cardiomyopathy
- immune dysregulation, incl. complement system
- nervous system abnormalities (similar to chronic fatigue syndrome
- vaccination (esp. ≥ 3 doses) reduces the risk of long COVID

Long COVID syndrome



Monkeypox

- recent outbreak, human-to human transmission
- mostly MSM – sexual transmission
- prodromal stage – high fever, chills, headache, cough, dyspnoe, ...
- lymphadenopathy within 2-3 days after the fever.
- vesicular rash within 1-10 days after the onset of fever, → pustules, common start on the face
- sexual transmission – painless vesicles in the anogenital region, without lymphadenopathy
- complications – secondary bacterial infection, encephalitis, blindness, scars
- self-limited in 2-4 wks

Mosquito-borne infections

- in Europe:
  - invasive mosquitoes: chikungunya (long-lasting fever + joint pain), dengue (fever for 7 days, 390 million infected in the world, possibility of haemorrhagic organ failure), zika
  - local mosquitoes: West Nile fever (older more in risk of severe disease); malaria (but in Europe 99% of cases travel-related; 450.000 of deaths worldwide)

Zika, West Nile: transmission

- bite of an infected *Aedes* species mosquito (*Ae. aegypti* and *Ae. albopictus*)
- Mosquito in Europe: Madeira (+ Dengue epidemics), Italy (+ Chikungunya epidemics), Greece, Croatia, south Switzerland, Netherlands, spread into north
- Czech Republic: single mosquitoes in South Moravia, no stable population (yet?!), single cases of West Nile fever incl. death

Zika: transmission

- Sexual transmission: both sexes, even without symptoms
- No sex/safe sex for 3-6 months after possible contact with the virus
- No sex/safe sex during the whole pregnancy
- By blood transfusion, organs + tissue donation (semen!)

Zika: pathology

- Adults: commonly asymptomatic (80%)
- Incubation: 3-12 days
- few days - 1 week, self-limited
  - fever
  - maculopapular rash
  - conjunctivitis
  - joint, muscle pain, headache
- Guillain-Barré syndrome – very rare, muscle weakness - paralysis

Zika: pathology

- Infection during pregnancy - risk of birth defects
  - severe brain defects incl. microcephaly, hearing loss,eye defects,
  - growth defects

EBOLA

- Virus sensitive to drying out – no distant droplet spread
- Direct or close contact, contaminated material – injured skin; mucosa
- Incubation period 2-21 d.
- Symptomatic patient infectious
- Commonly duration 8 days
- Surviving patient may transmit e. (up to 4 months in semen)

EBOLA PATHOLOGY

- Infection of dendritic cells (disruption of the antigen presentation, interferon system)
- Infection of macrophages (release of cytokines, NO)
- Infection of endothelial cells (bleeding)

EBOLA PATHOLOGY

- Inflammatory changes in the liver (↓ coagulative proteins)
- Adrenal gland (↓ cortical steroids, ↓ of blood pressure regulation, circulation failure)
- GIT (diarrhea)

EBOLA PATHOLOGY

- Disruption of regulation systems – uncontrolled viral replication – rapid death

Ebola treatment

- Recombinant vaccines (highly effective in nonhuman primates) – VZV, adenovirus, rabies virus-based
- Passive immunization – therapeutic vaccines (coctail of monoclonal atibodies), immunoglobulins from the survivor‘s blood
- Antivirotic drugs

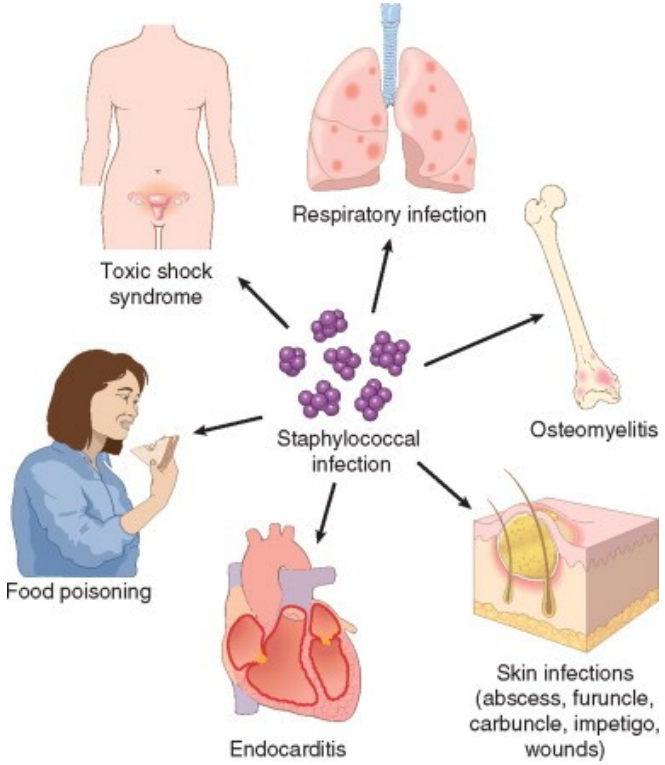
Bioterrorism

- Microorganisms that pose the greatest danger as weapons
- Efficiency of transmission
- Possibility of production and distribution
- Possibility of defence
- Extent of possible public alarm and widespread fear production.

Bioterrorism

- Anthrax *(Bacillus anthracis)*
- Botulism *(Clostridium botulinum* toxin)
- Plague *(Yersinia pestis)*
- Smallpox *(Variola major virus)*
- Tularemia *(Francisella tularensis)*
- Viral hemorrhagic fevers (filoviruses [e.g., Ebola, Marburg] and arenaviruses [e.g., Lassa, Machupo])

Staphylococci



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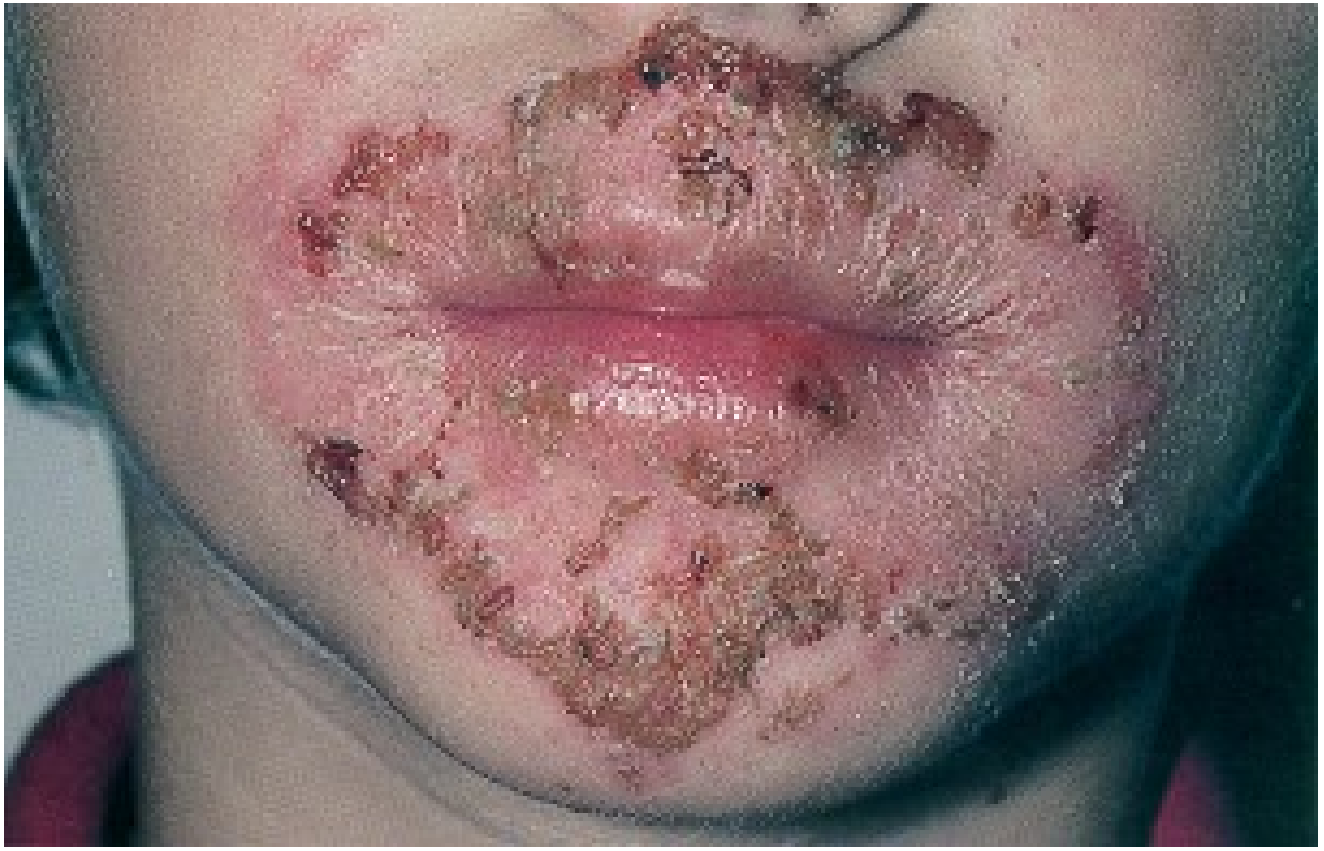
Staphylococci

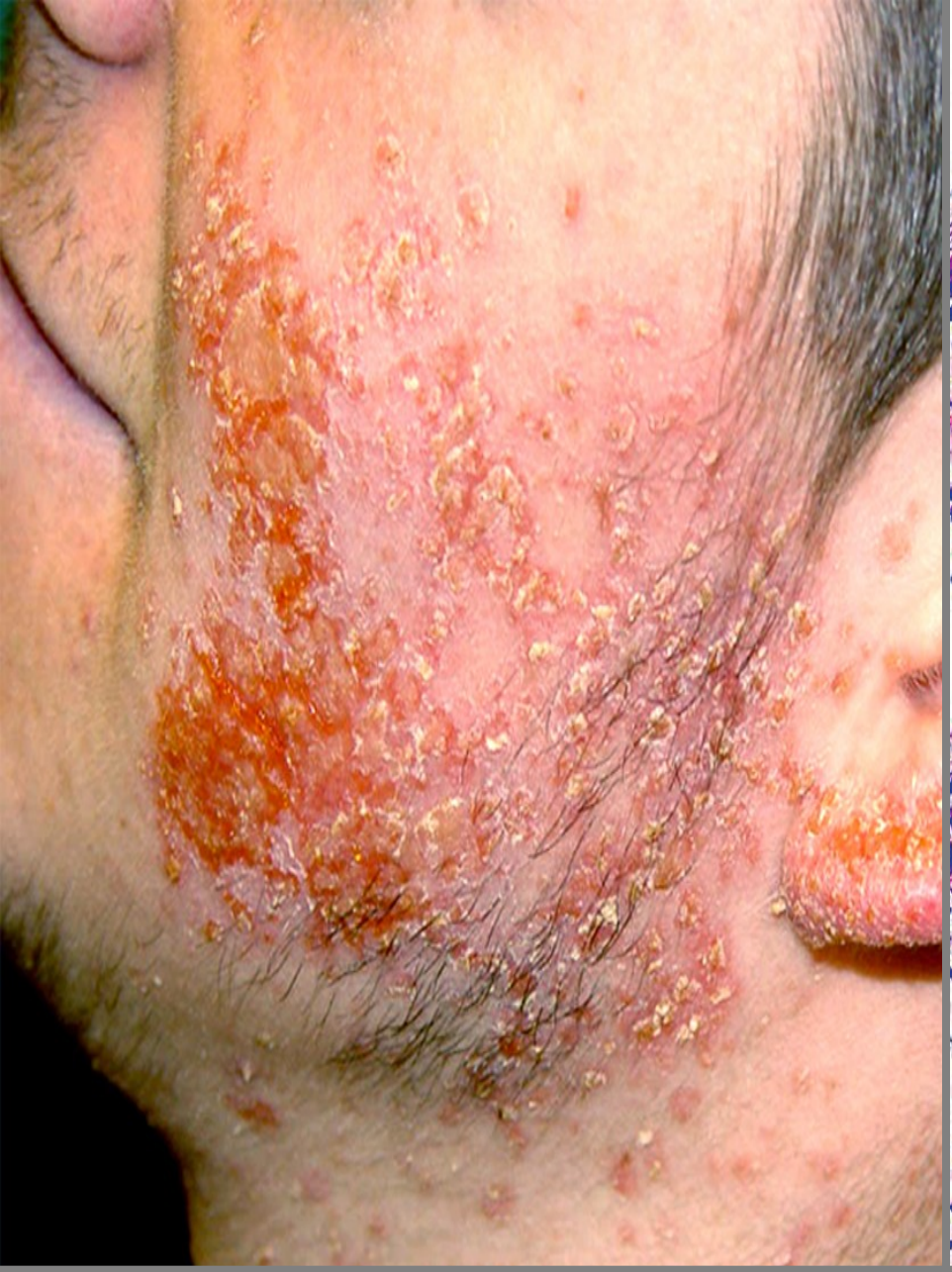
- Destructive pyogenic inflammation
- Abscess, furuncle, impetigo on skin
- **Carbuncle**: deeper suppurative infection spreading laterally beneath the deep subcutaneous fascia
- **Hidradenitis:** chronic suppurative infection of apocrine glands, most often in the axilla.

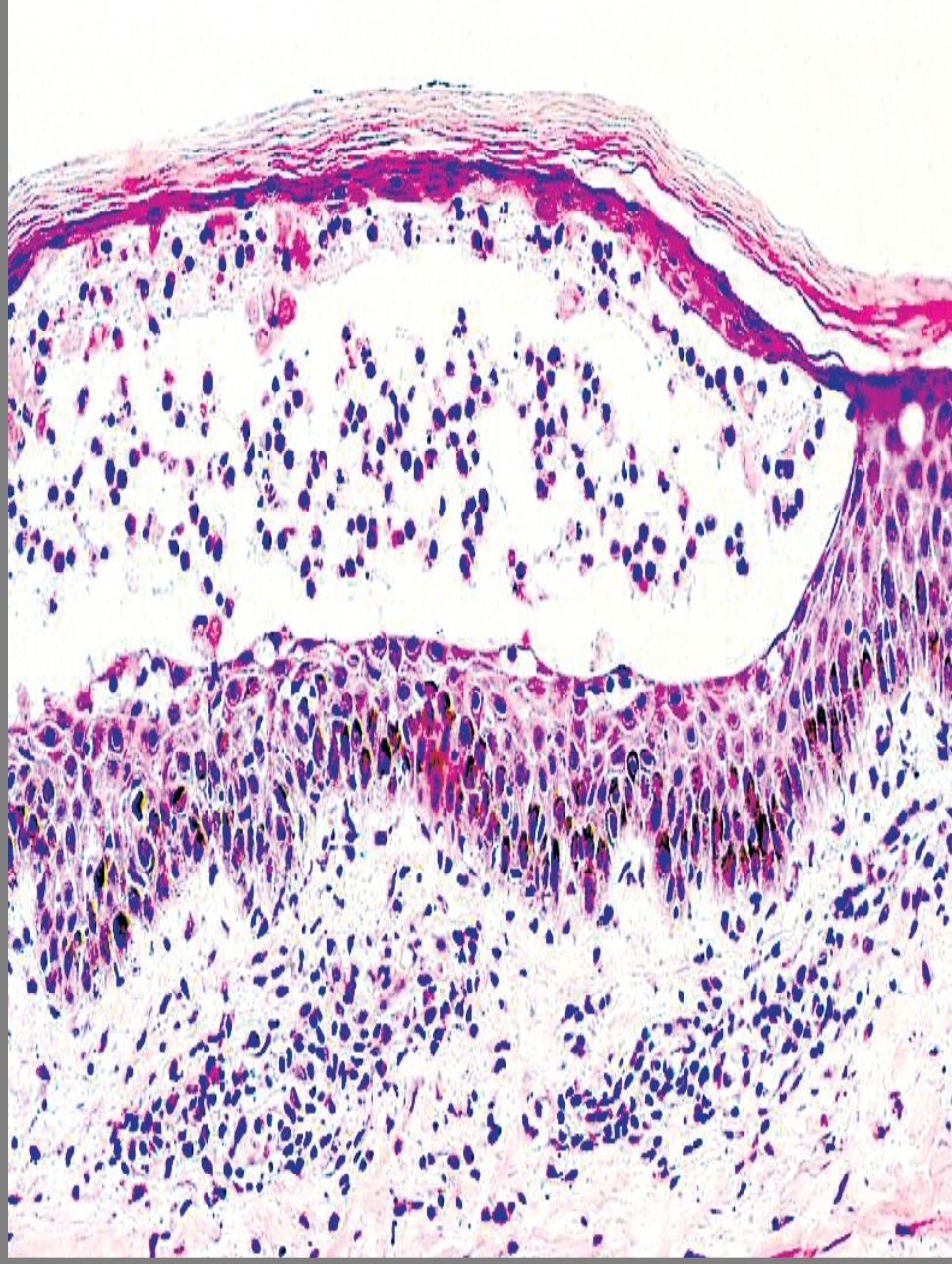
Staphylococci

- osteomyelitis
- pneumonia
- endocarditis incl. prosthetic valves
- urinary tract infections
- sepsis
- food poisoning (rapid, GIT symptoms incl. severe diarrhea, vomiting)
- toxic shock syndrome

Impetigo







Bullous impetigo

Staphylococci

- **Staphylococcal scalded-skin syndrome** (**Ritter disease)** in children with staphylococcal infections of the nasopharynx or skin. Diffuse sunburn-like rash → fragile bullae → partial or total skin loss.
- Purulent bronchopneumonia, +/abscesses

Staphylococci

- Methicillin-resistant *S. aureus* (MRSA)
- Sepsis + systemic infection possible
- Further antibiotic resistance growing

Streptococci

- Suppurative infections of the skin, oropharynx, lungs, heart valves.
- Post-infectious syndromes, incl. rheumatic fever, immune complex glomerulonephritis, erythema nodosum

Streptococci

- *S. pyogenes* (group A): pharyngitis, scarlet fever, erysipelas, impetigo, rapidly progressive necrotizing fasciitis, rheumatic fever, glomerulonephritis
- *S. agalactiae* (group B) colonizes the female genital tract → possible sepsis and meningitis in neonates, chorioamnionitis in pregnancy.

Streptococci

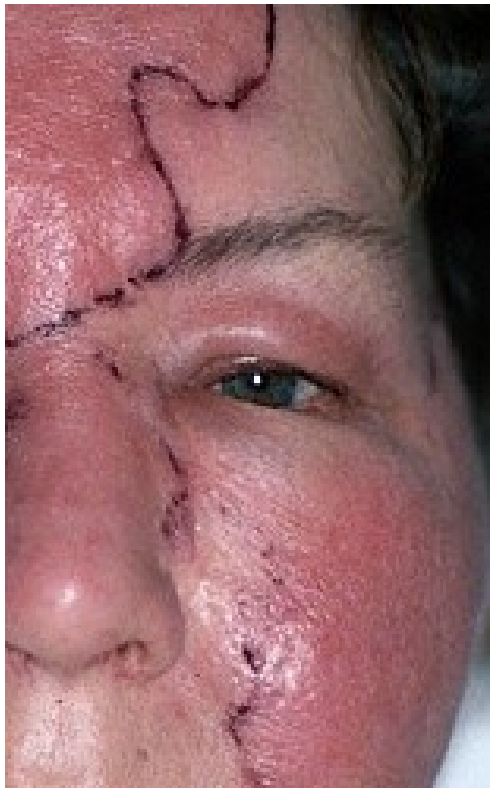
- *S. pneumoniae*: community-acquired pneumonia and meningitis in adults.
- Viridans group streptococci: several species of α-hemolytic and nonhemolytic streptococci,in normal oral flora, common cause of endocarditis.
- *S. mutans* is the major cause of dental caries, metabolization of sucrose to lactic acid causes demineralization of tooth enamel.

Erysipelas

- Most common in middle-aged persons in warm climates
- Exotoxins from superficial infection with *S. pyogenes*.
- Rapidly spreading erythematous cutaneous swelling with well-demarcated border
- Diffuse, edematous, neutrophilic inflammatory reaction in the dermis and epidermis extending into the subcutaneous tissues. Microabscesses may be formed, but tissue necrosis is usually minor.

Erysipelas

- Well-demarcated cellulitis with fever and malaise
  - upper dermal oedema lifts epidermis except where staked down by hair follicles or sweat glands
  - leads to the typical “peau d'orange” appearance



Scarlet fever

- Hemolytic streptococcus B group A
- Systemic bacterial infection, result of an erythrogenic toxin → capillary damage
- Most common in children
- Complication: local spread (otitis media, abscess)

systemic spread (pneumonia, septicemia, toxic shock syndrome);

poststreptococcal heart, kidney and joints diseases

Scarlet fever

- Incubation period: 2-3days (1-7days)
- Typical type:

Fever: 39°C, 1 week

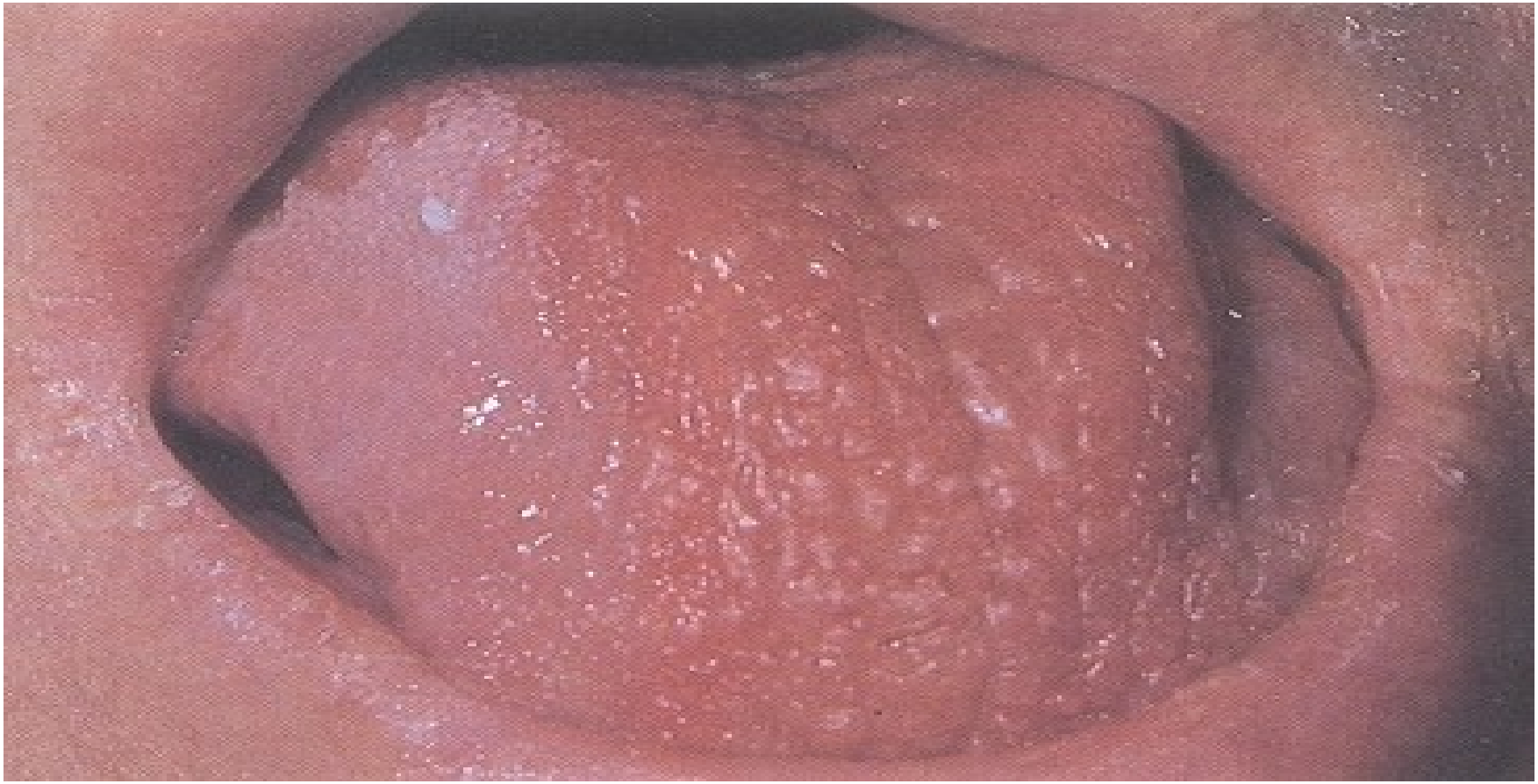
Vascular dilation and damage with an erythematous macular rash on the skin (chest area), after 1 week desquamation.

Face →flushed except for zone of circumoral pallor

Pharyngitis, tonsillitis: red enanthema, edema, yellow exudate

Cervical lymphadenitis

Scarlet fever



Post-streptococcal complications (immune-mediated)

- **Rheumatic fever** – follows overt or subclinical pharyngitis in children; carditis with extensive valve damage possible, arthritis, chorea, fever
- **Acute glomerulonephritis** – nephritis, increased blood pressure, occasionally heart failure; can become chronic leading to kidney failure

Respiratory tract infections

- ↓ local host defences – mucociliary clearance (smoking, cystic fibrosis, preexisting inflammation), phagocytosis
- immunodeficiency – mycotic infections
- evasion by microorganisms – influenza virus binding to mucus; cilia paralyzing toxin (Bordetella pertussis, H. influenzae); TB intracellular parasite;

Respiratory tract infections

- **Viral**

  Rhinoviruses, Influenza,

- **Bacterial**

  Str. pneumoniae, Haemophilus infl., Chlamydia, TB,

- **Fungal**

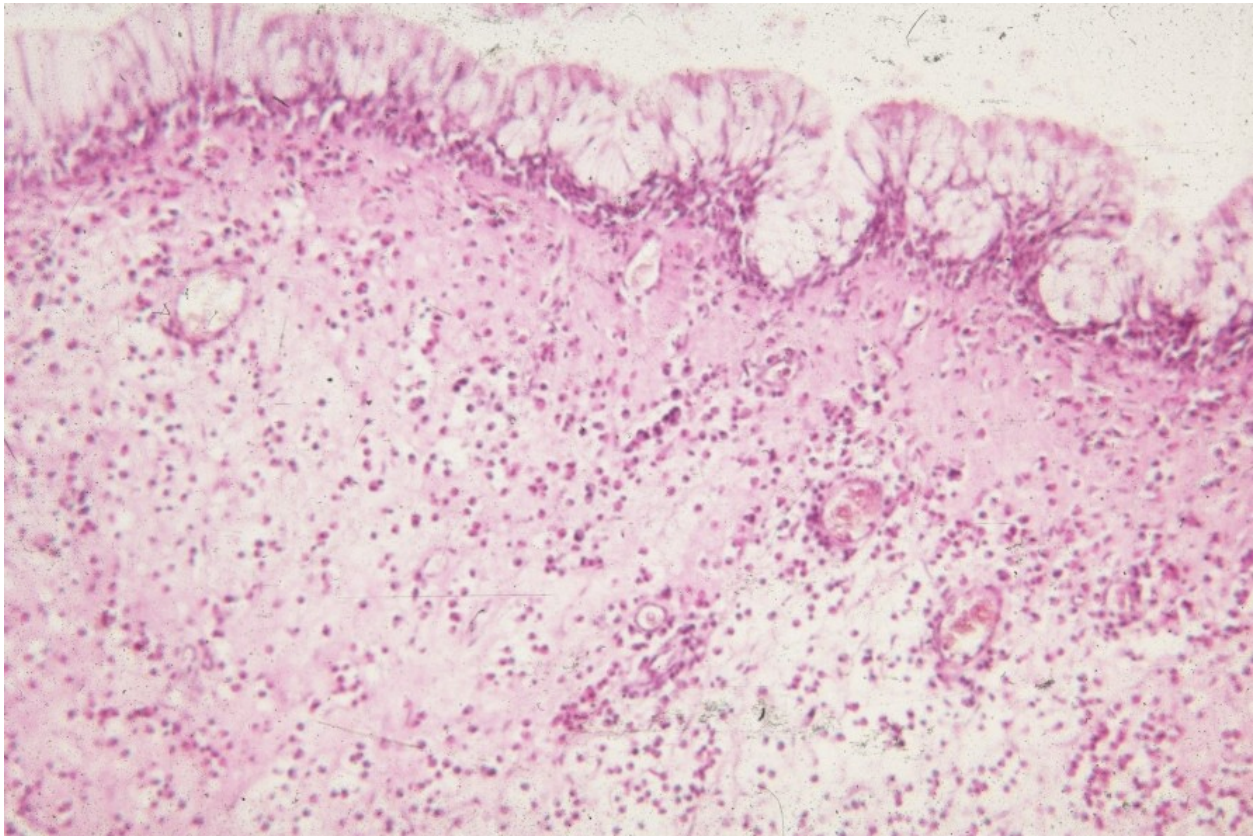
  Histoplasmosis, Coccidioimycosis, Pneumocystis

Upper respiratory tract

- Rhinitis + Sinusitis serous – viral (rhinoviruses, RSV, etc.); purulent – bacterial (Haemophilus, etc.); granulomatous – fungal (Aspergillus, Mucor, etc.)
- Laryngitis – pseudomembranous (Diphteria); acute epiglottitis in children (H. influenzae); papillomatosis - HPV

Upper respiratory tract

- Rhinitis



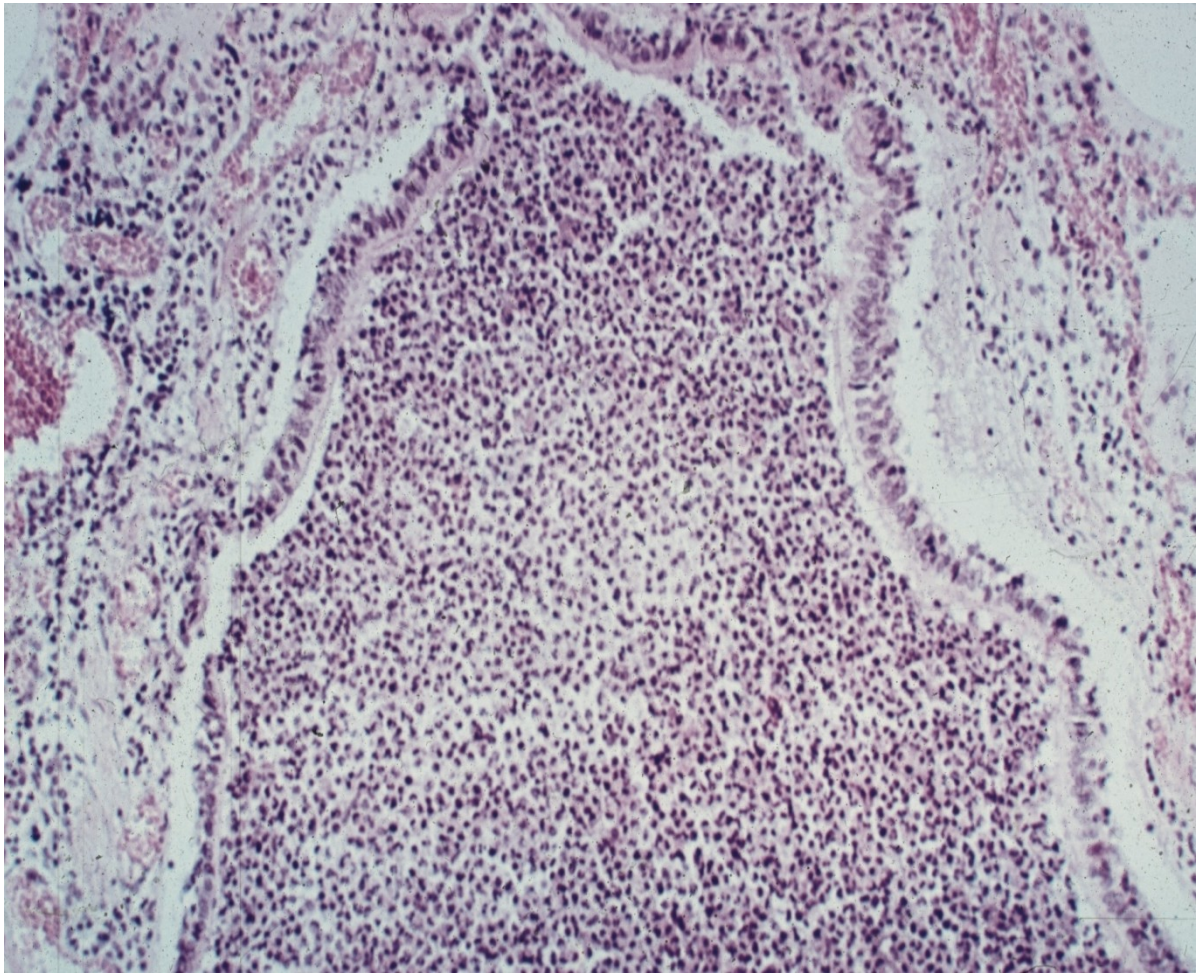
Lower respiratory tract

- Bronchitis – nonpurulent viral - RSV;
  purulent H. influenzae, Str. pneumoniae,
  Pertussis - ↑ incidence, peripheral lymphocytosiis, laryngotracheobronchitis

- fungal (mycetoma in bronchiectasis – Aspergillus)

Lower respiratory tract

- Bronchitis



Lower respiratory tract

- Pneumonia – lobar (pneumococcus, Klebsiella); bronchopneumonia (Staph., H. infl., Str.)

  atypical (interstitial): viral – Infl., RSV, adenovirus, CMV, HSV,

  Mycoplasma, Legionella, Chlamydia,

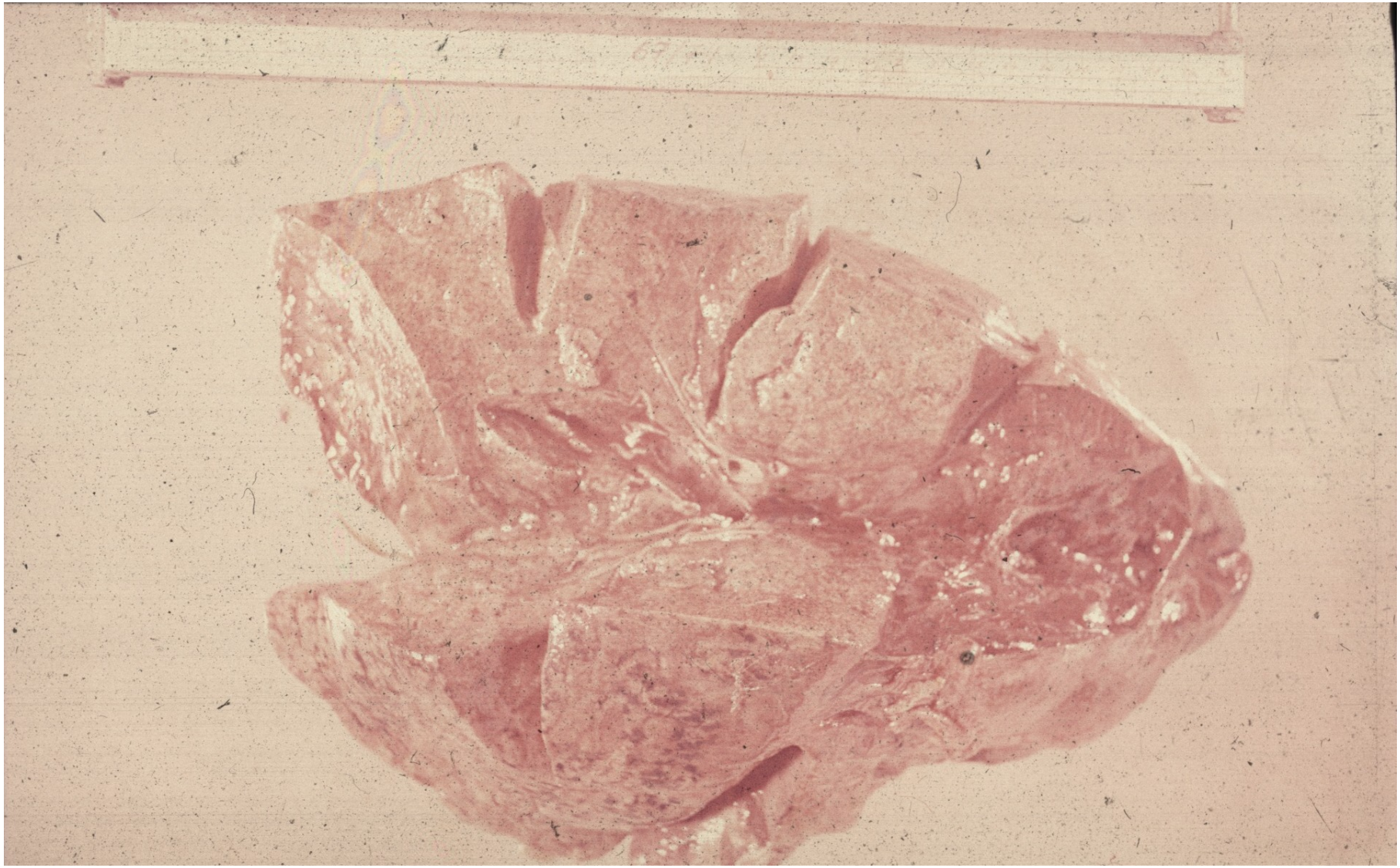
  fungal – Aspergillus, Pneumocystis, Cryptococcus, Candida,

  granulomatous: TB, MAC, Histoplasma

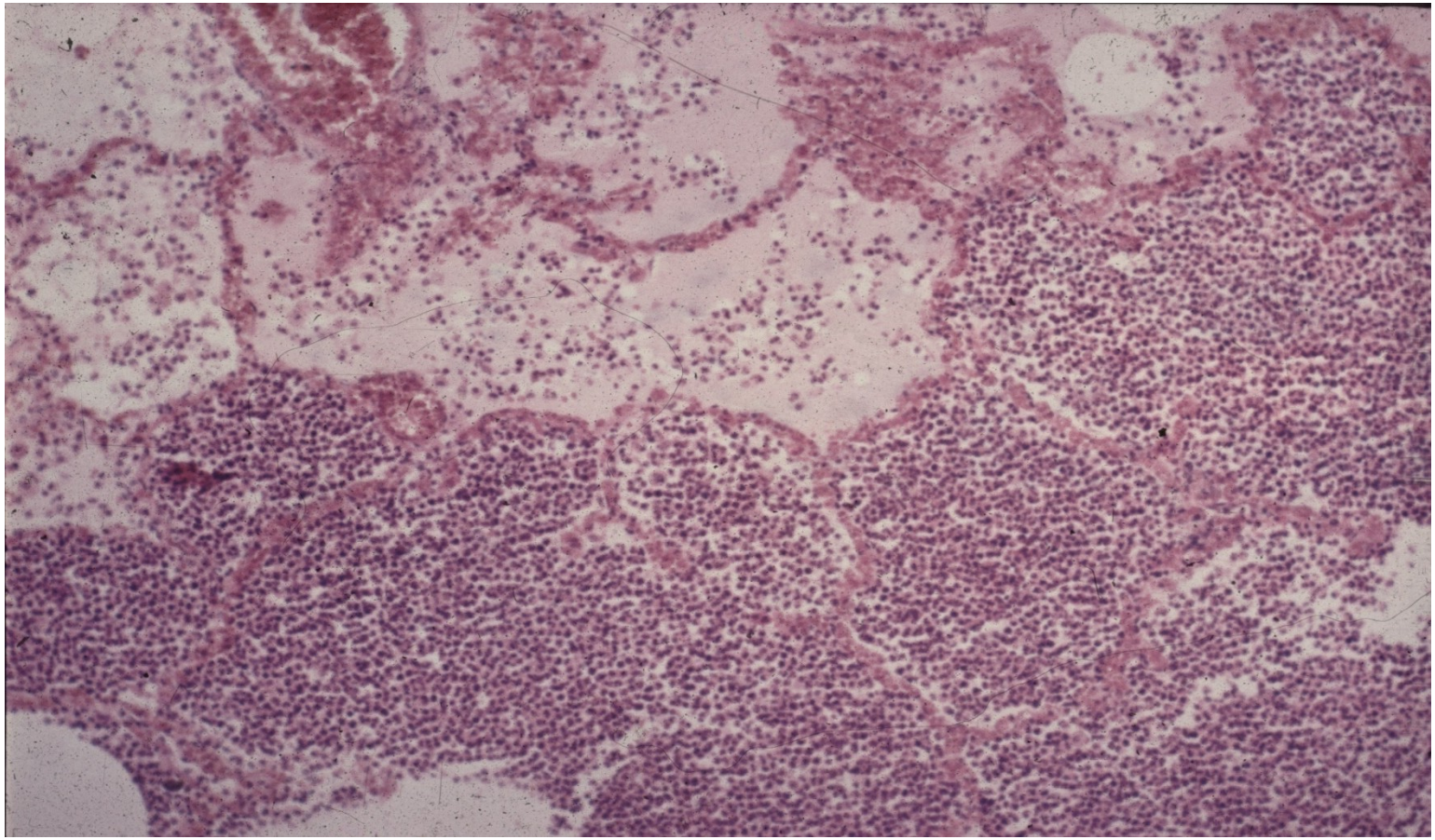
COMMUNITY-ACQUIRED ACUTE PNEUMONIA

- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Moraxella catarrhalis*
- *Staphylococcus aureus*
- *Legionella pneumophila*
- Enterobacteriaceae (*Klebsiella pneumoniae*) and *Pseudomonas* spp.

Lobar pneumonia



Bronchopneumonia



COMMUNITY-ACQUIRED ATYPICAL PNEUMONIA

- *Mycoplasma pneumoniae*
- *Chlamydia* spp. (*C. pneumoniae*, *C. psittaci*, *C. trachomatis*)
- *Coxiella burnetii* (Q fever)
- Viruses: respiratory syncytial virus, parainfluenza virus (children); influenza A and B (adults); adenovirus (military recruits); SARS virus

HOSPITAL-ACQUIRED PNEUMONIA

- Gram-negative rods, Enterobacteriaceae (*Klebsiella* spp., *Serratia marcescens*, *Escherichia coli*) and *Pseudomonas* spp.
- *Staphylococcus aureus* (usually penicillin resistant)

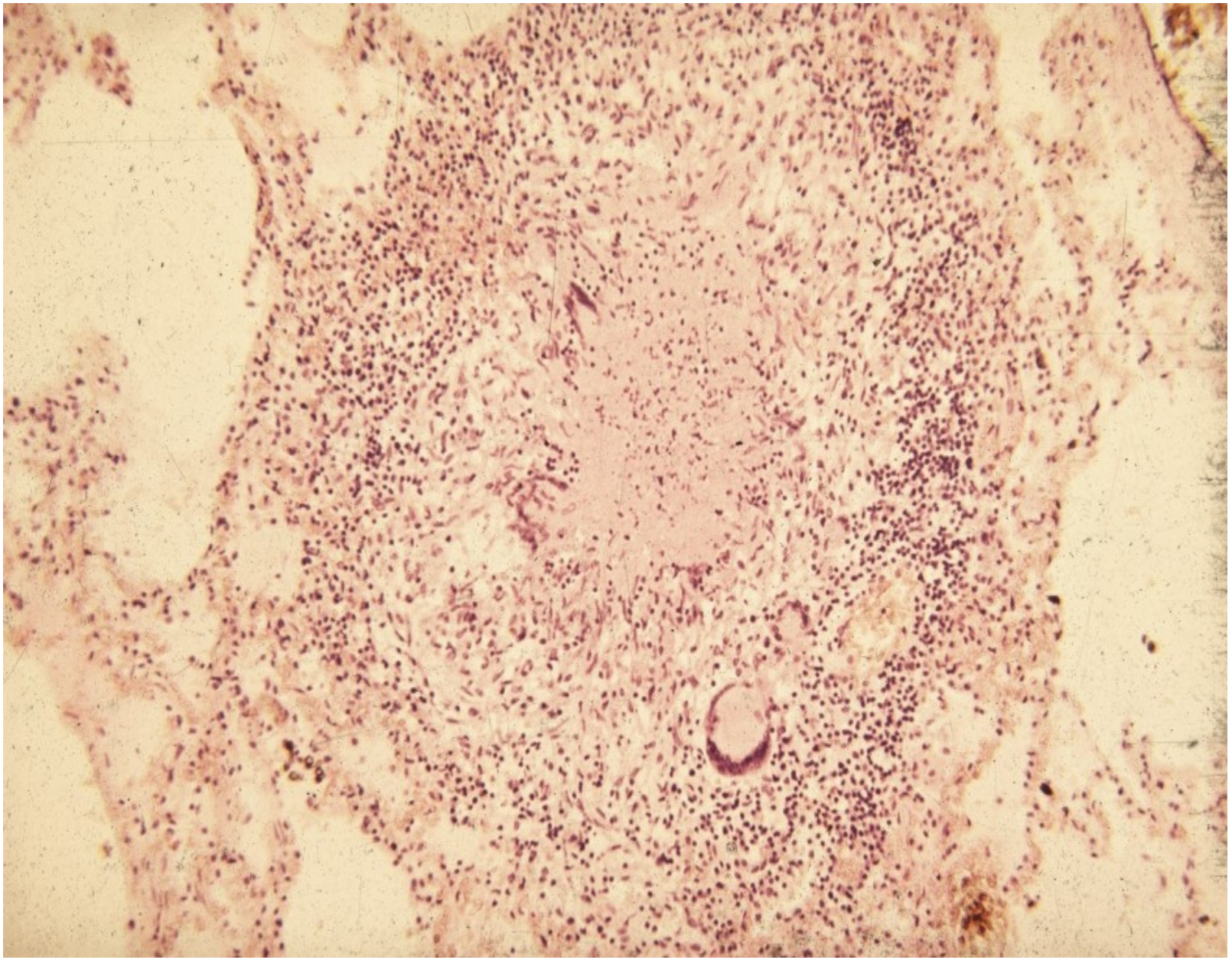
ASPIRATION PNEUMONIA

- Anaerobic oral flora (*Bacteroides*, *Prevotella*, *Fusobacterium*, *Peptostreptococcus*), admixed with aerobic bacteria (*Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa*)

CHRONIC PNEUMONIA

- *Nocardia*
- *Actinomyces*
- Granulomatous: *Mycobacterium tuberculosis* and atypical mycobacteria, *Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitidis*

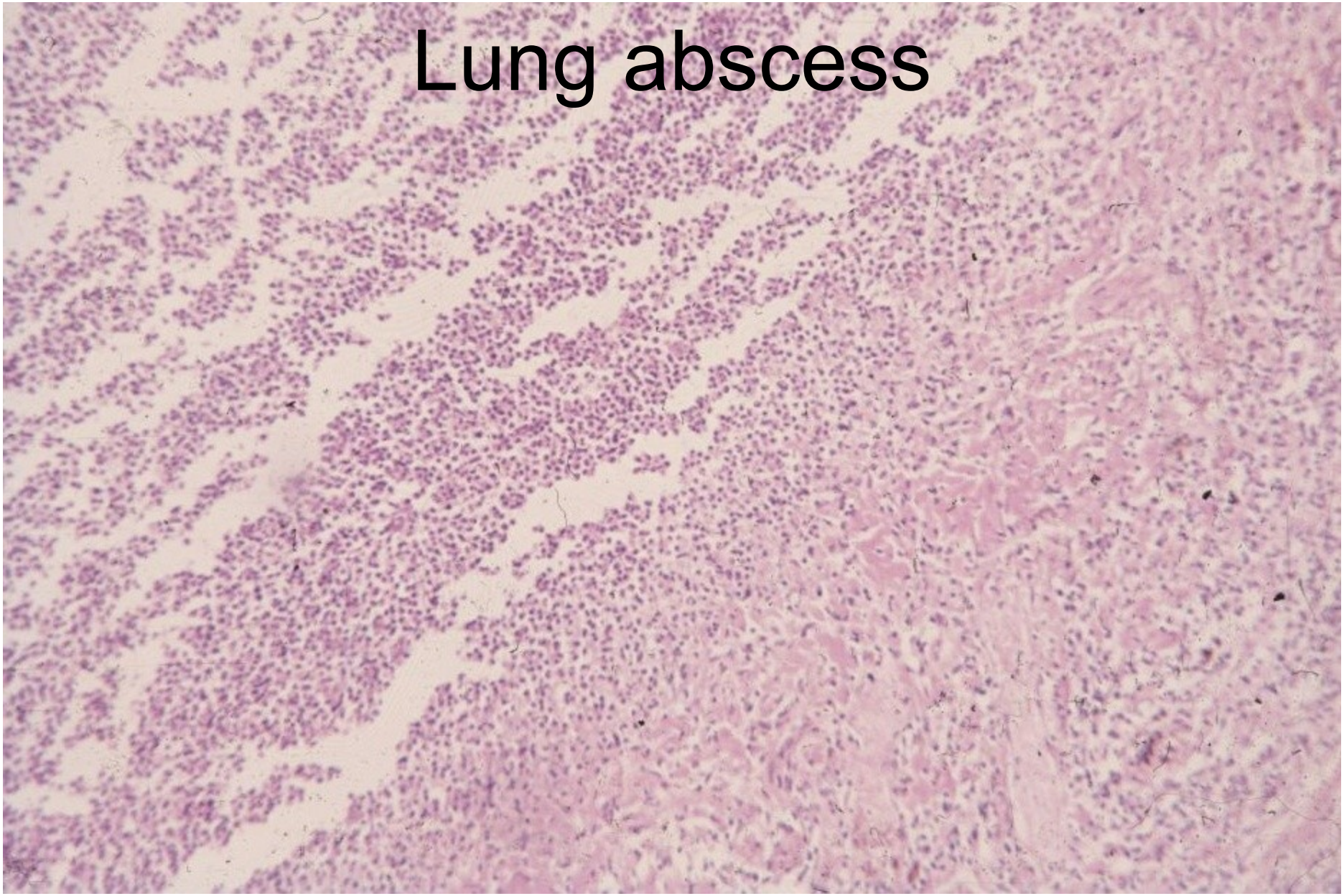
TB



NECROTIZING PNEUMONIA AND LUNG ABSCESS

- Anaerobic bacteria (extremely common), with or without mixed aerobic infection
- *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pyogenes*, and type 3 pneumococcus (uncommon)

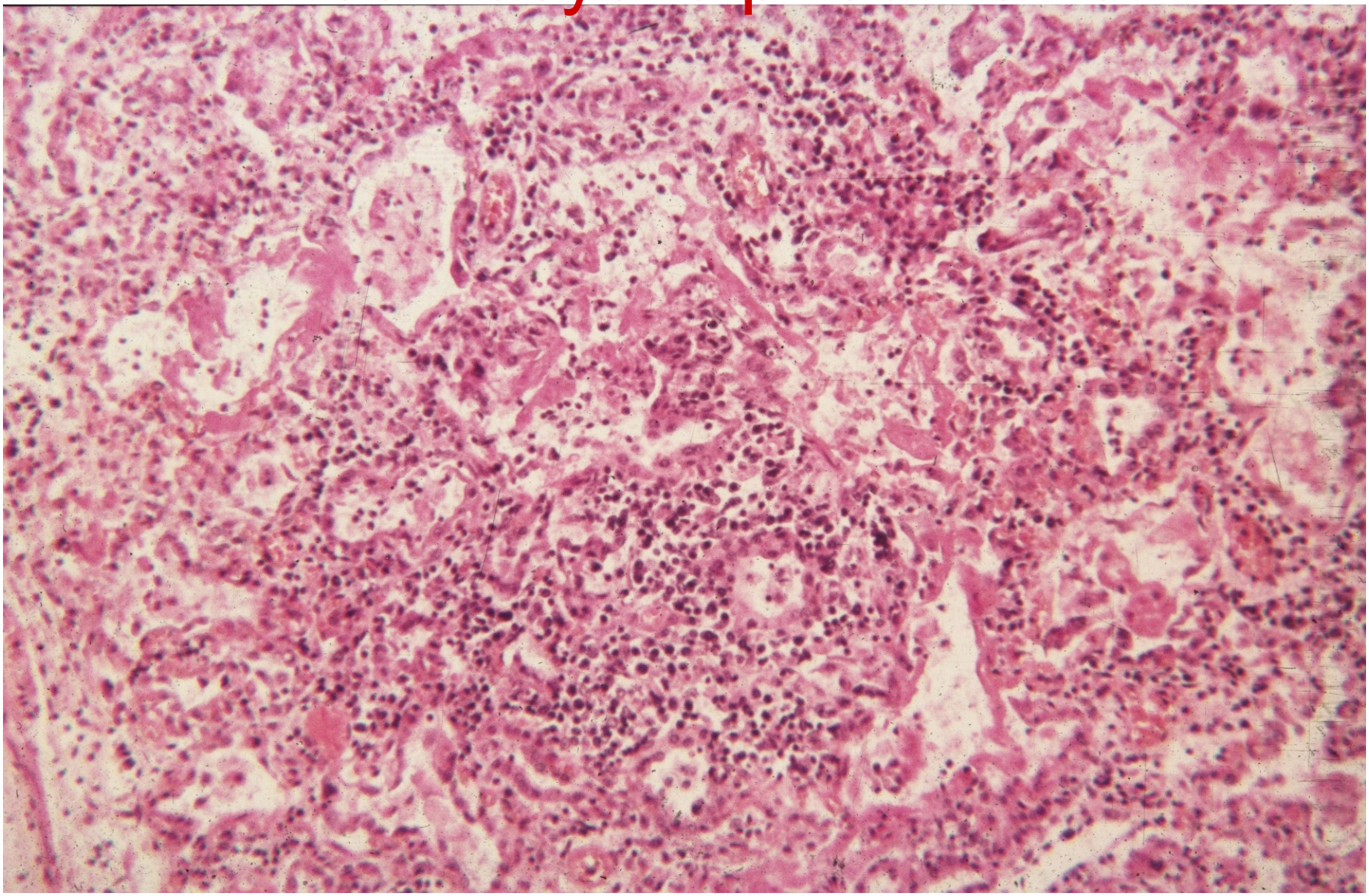
Lung abscess



PNEUMONIA IN THE IMMUNOCOMPROMISED HOST

- Cytomegalovirus
- *Pneumocystis jiroveci*
- *Mycobacterium avium-intracellulare*
- Invasive aspergillosis
- Invasive candidiasis
- “Usual” bacterial, viral, and fungal organisms

Pneumocystis pneumonia



Influenza

- Acute respiratory illness caused by influenza viruses.
- Typical symptoms-fever, chills, myalgia, headache, sore throat, cough.
- Serious cases in young children and elderly.

Influenza pathogenesis

- Histopathology: degenerative cell changes, incl. granulation, vacuolization, swelling, pyknotic nuclei.
- The severity of illness correlates with the quantity of virus shed in secretions;
- Rarely detected in extra-pulmonary sites (trachea).
- Primary influenza viral pneumonia (risk patients) interstitial lymphoplasmocytic infiltration, ARDS posible.

Influenza manifestations

- Incubation period: 1-3 days
- Typical influenza

abrupt onset of systemic symptoms.

Headache, fever, chills, myalgia, or malaise,

respiratory tract signs, particularly cough and sore throat.

Ocular signs and symptoms include pain on motion of the eyes, photophobia, and burning of the eye.

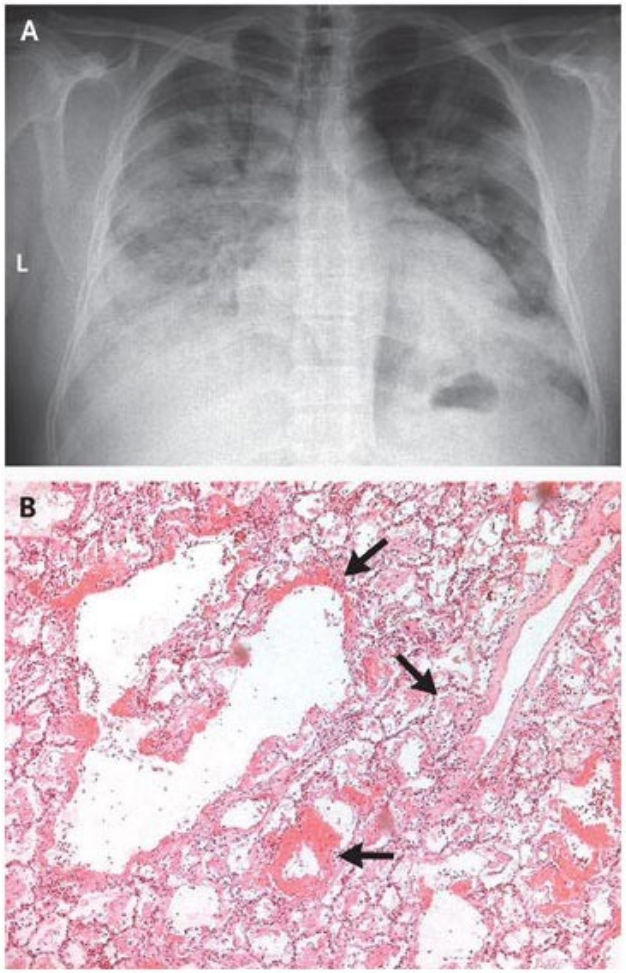
Influenza manifestations

- Primary influenza virus pneumonia:

  presents as acute influenza, not resolving, progression with persistent fever, dyspnea, eventual cyanosis. Sputum production generally scanty. ARDS + respiratory failure.

Possible cardiac failure, liver failure and renal failure.

Physical findings: no consolidation signs.



Influenza manifestations

- Mild form influenza
- Other forms:

  stomach flu

  encephalitis, transverse myelitis,

  myocarditis and pericarditis,

  myositis

Influenza complications

- Secondary bacterial infection:

  pneumonia: cough, purulent sputum, physical and x-ray signs of consolidation.

  Most common bacterial pathogens are Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae.

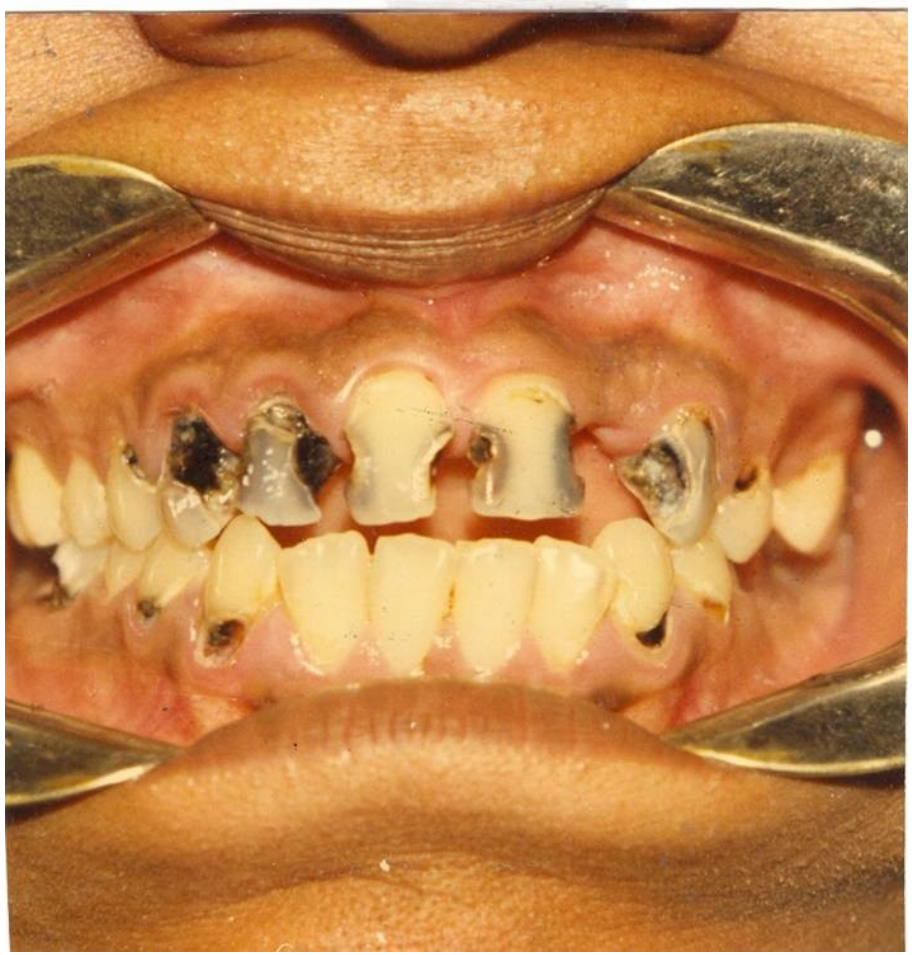
GIT infections

- mostly by contaminated food or water
- ↓ local host defences (↓ gastric acidity, ↓ enzymatic and mucus secretion, loss of local defensins and IgA, loss of normal flora, obstruction)
- general immunodeficiency (→ fungal, CMV, MAC infection)
- resistant microorganisms (hepatitis A virus, rotavirus, H. pylori, protozoan cysts,…)

Oral cavity and oesophagus infections

- Viral – herpetic stomatitis (HSV-1, less common HSV-2), vesicles → ulcers; herpes zoster; EBV, CMV, measles
- Fungal – superficial pseudomembranous oral candidiasis
- Sialoadenitis – non-purulent viral (mumps); purulent bacterial (Stph. aureus, Str. viridans)

Dental caries



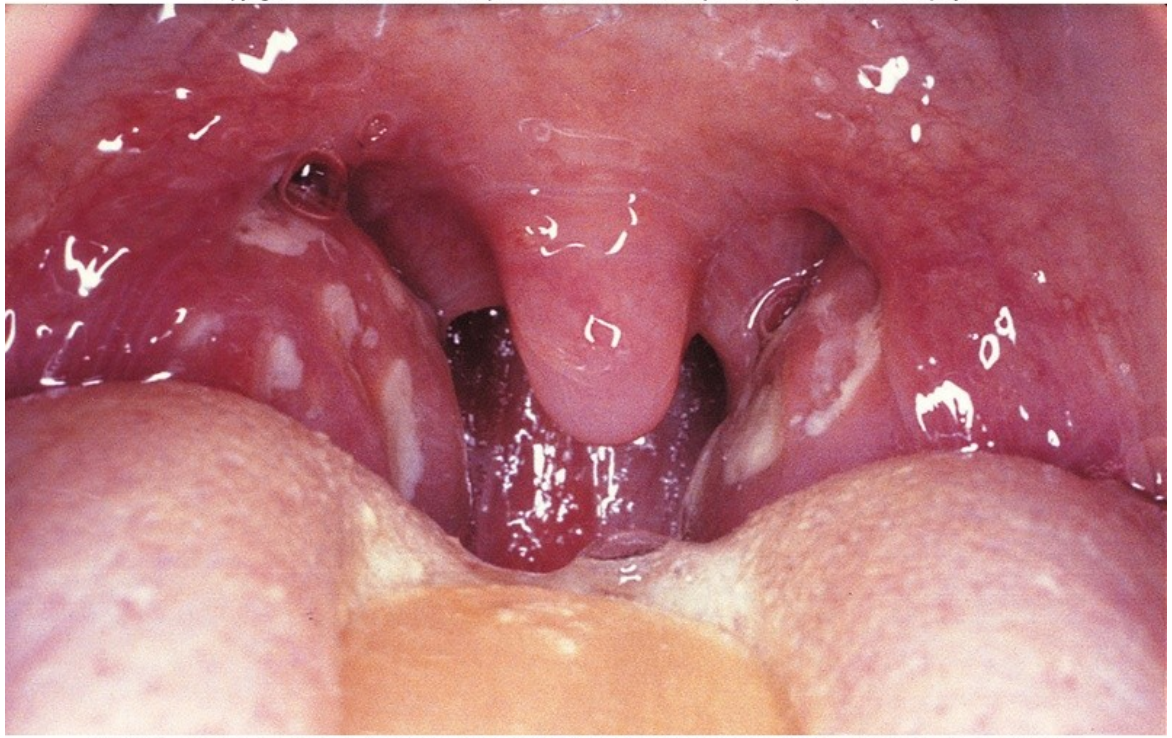
Dental caries

- Multifactorial dynamic process
- Involves the interaction of inborn or acquired host factors (tooth surface, saliva, acquired pellicle), diet, dental plaque (biofilm) – oral infection.
- Caries does not occur in the absence of either plaque or dietary fermentable carbohydrates.

Tonsillitis and pharyngitis

- bacterial (Str. – 25%, Staph., dipthteria…)
- viral (EBV, influenza, adenoviruses, …)
- Clinical – sore throat, dysphagia, red + swollen tonsils + focal/confluent yellowish exudate, cervical lymhadenopathy, fever, malaise, …
- In viral + rhinitis, laryngitis

Tonsillitis



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Diphtheria

- **Pathology**
  Pseudomembrane over the mucosal membranes (nose, tonsils, oropharynx, larynx, genital), adherent to the tissue, bleeding by removal attempt.
  Damage by exotoxins to heart muscle, liver, kidneys, and adrenals. Also nerve damage resulting in paralysis of the soft palate, eye muscles or extermities.

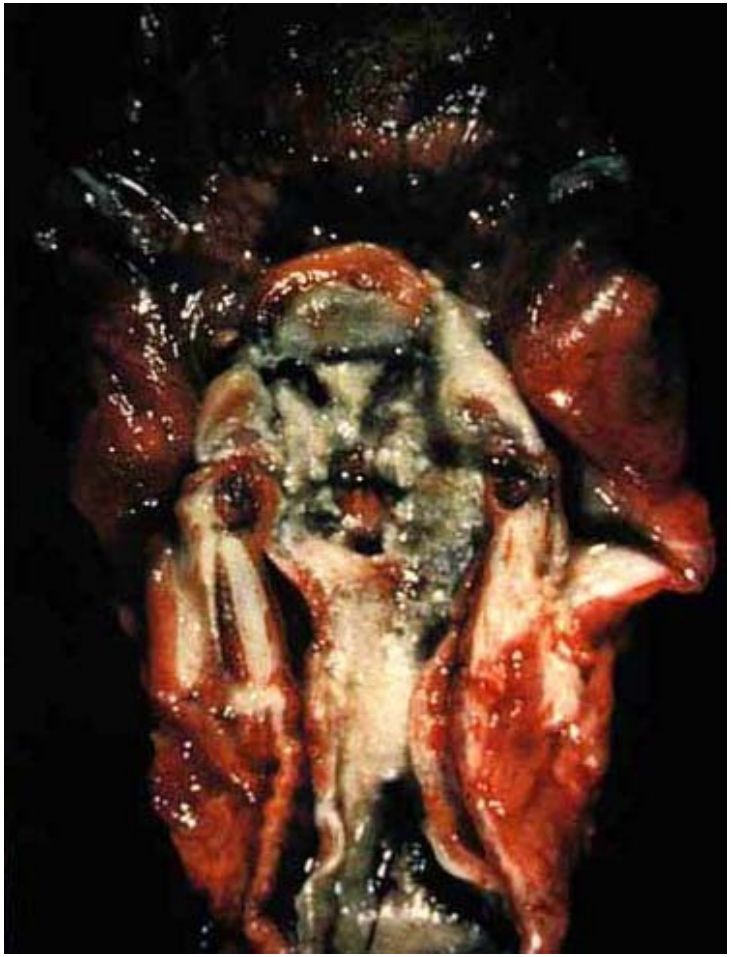
Diphtheria

- **Clinical findings**
  Fever, sore throat, dyspnea (obstruction by the membrane). Later on difficulties with vision, speech, swallowing, or movement of the arms or legs. Var. gravis more severe.

Pharyngeal diphtheria

- The most common type, >80%.
- Sites of infection: tonsils, pharynx.
- Usually + substantial systemic absorption of toxin.
- Within 2-3 days, small patches of white pseudomembrane on the tonsils
- Var. gravis: Large, thick pseudomembrane, greyish-green or black (if bleeding), covering the tonsils, uvula, and some soft palate, odoriferous in mouth.
  - With enlarged lymph nodes in the submandibular areas of neck.

Diphtheria



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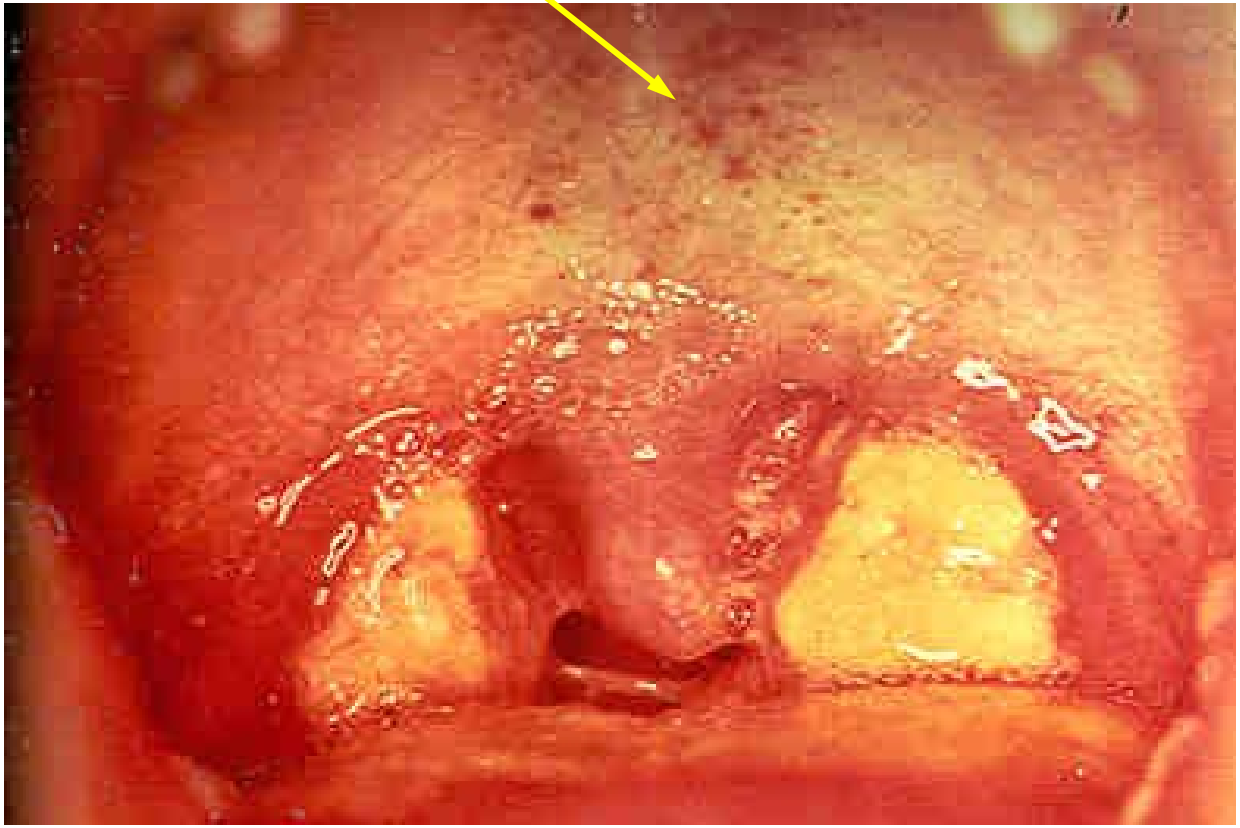
Infectious mononucleosis

- Caused by Epstein-Barr Virus (EBV)
- Acute self limiting disease of adolescents, young adults (cytomegalovirus has a similar picture → serological separation)

- <u>Infection characterised by</u>
  - Fever, sore throat + generalised lymphadenopathy
  - Reactive leukocytosis (atypical morphology)
  - Humoral antibody response

- <u>Epidemiology</u>
  - Low socio-economic populations
    - Asymptomatic infection in early life
    - 50% become virus shedders
  - Developed regions
    - Infection delayed → adolescent/adulthood
    - More effective immune response to virus → prolongs infection
    - 20% become virus shedders

Pseudomembranous tonsillitis, Forsheimer spots



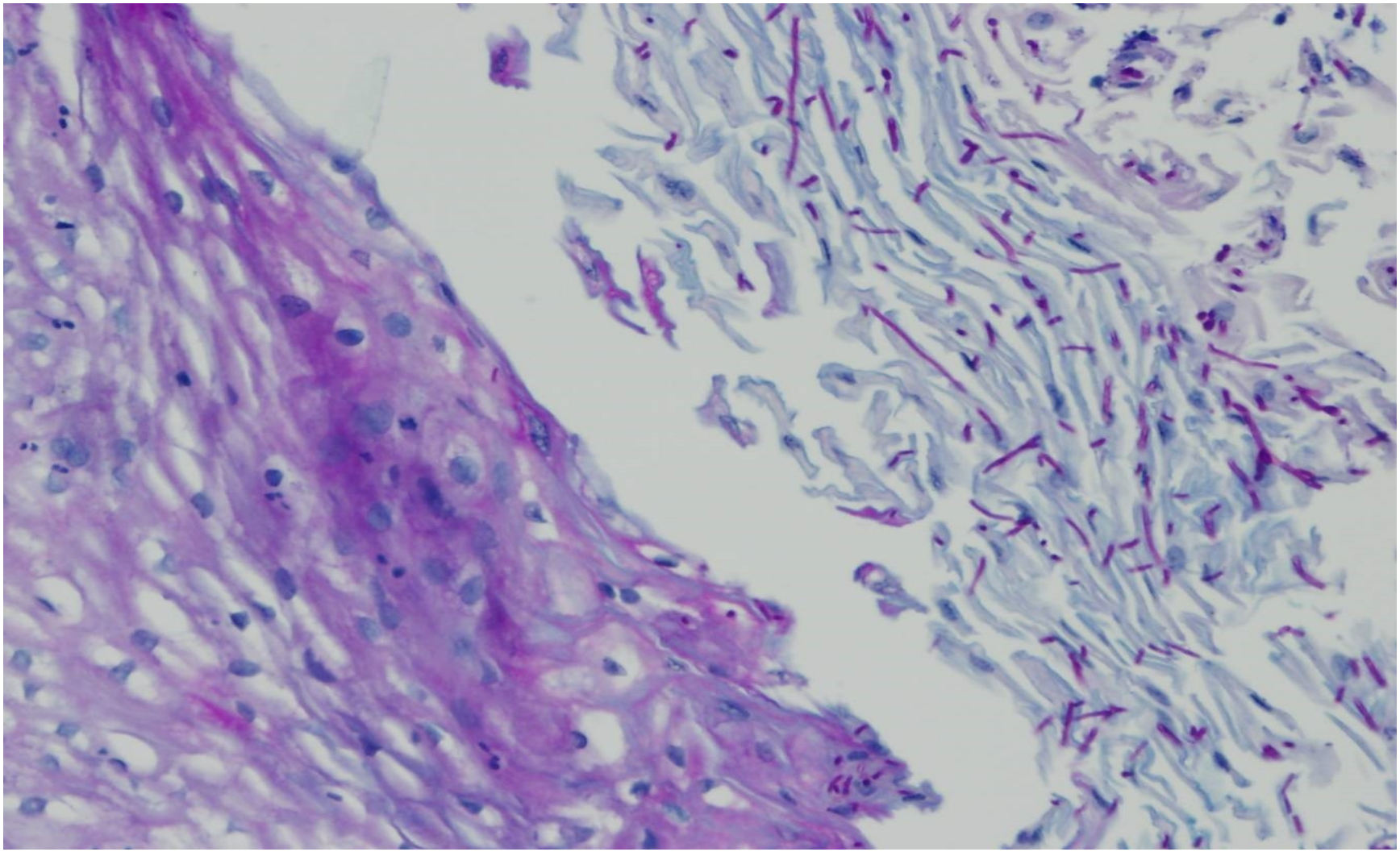
EBV complications

- Predisposed patients
  - E.g. HIV/AIDS; immunosuppressive therapy
  - Can easily die from the infection
- EBV- potent transforming virus
  - True monoclonal B-cell lymphomas
  - Nasopharyngeal carcinoma
- X-linked lymphoproliferative syndromes
  - Immunodeficieny
  - Inherited
  - Inability to maintain immune response against EBV
  - Fatal infection

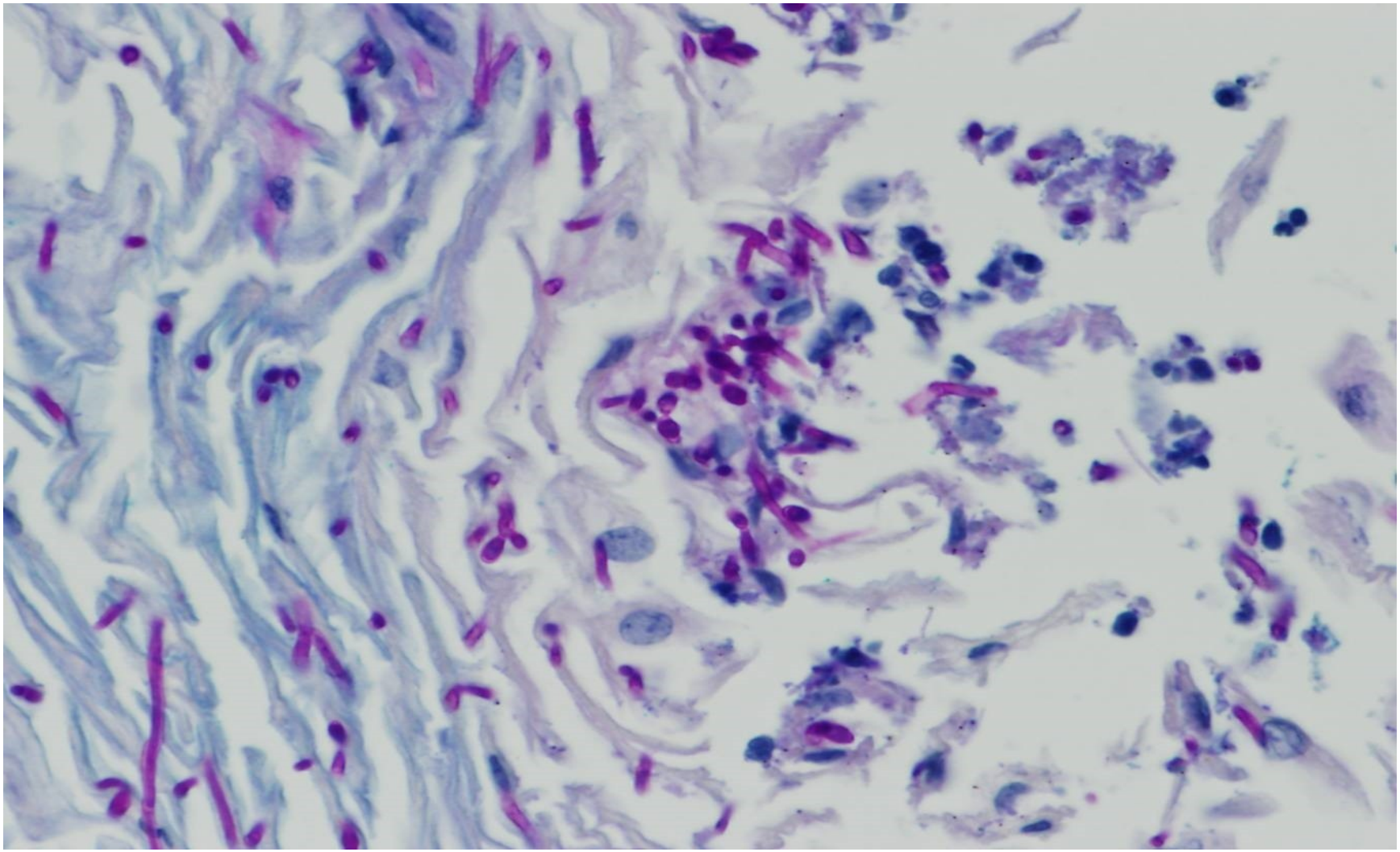
Fungal GIT infections

- oral cavity, pharynx, oesophagus, anus – candidiasis
- intestines – Candida + others

Mycotic oesophagitis



Mycotic oesophagitis



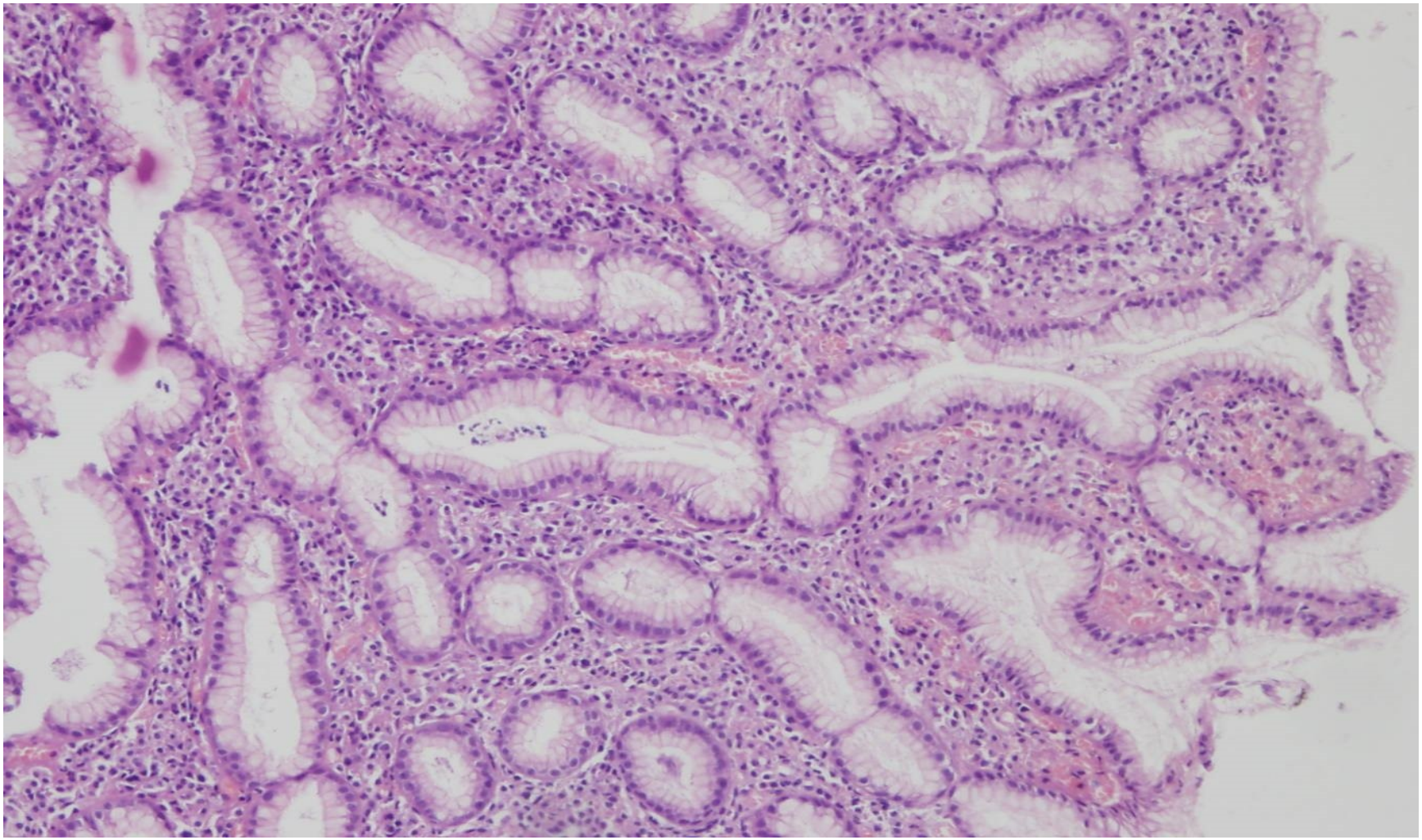
Stomach infections

- H. pylori – acute infection mostly asymptomatic; chronic infection may lead to chronic gastritis
- Viral gastroenteritis – acute; rotavirus, adenovirus, calicivirus (Norwalk-like)
- eosinophilic gastritis – may be due to parasites

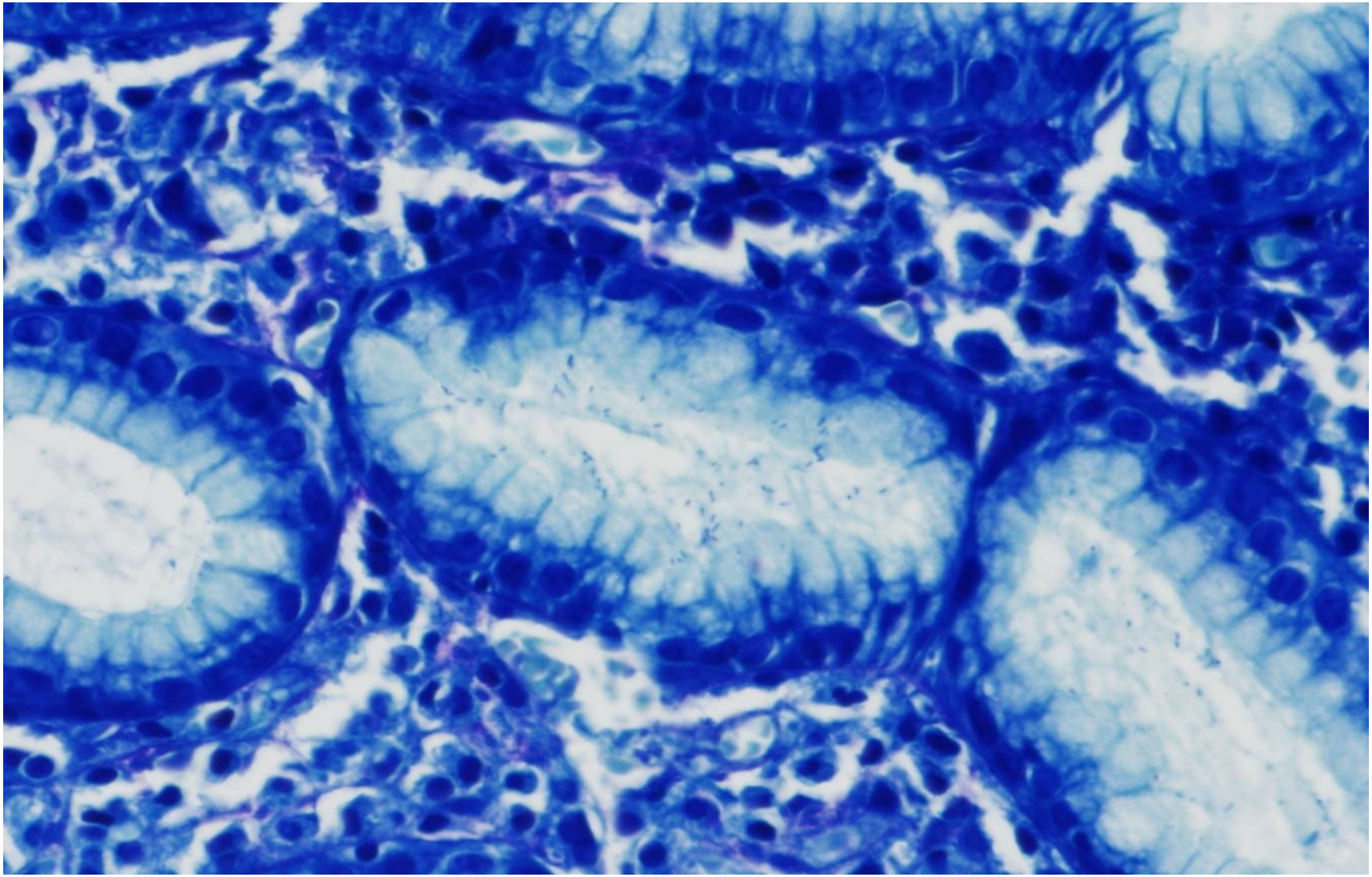
Gastritis

- acute: ac. mucosal inflammation, usually transient
  - chemical injury (drugs, alcohol, smoking, uraemia), **infection,** ischaemia, stress, physical injury (irradiation, burn, mechanic trauma)
    - mucosal hyperaemia, oedema, haemorrhage, erosion, mixed or neutrophilic infiltrate in epithelium above the basement membrane (activity of the process)
    - usually rapid healing by regeneration
    - clinically epigastric pain, nausea, vomiting, in severe cases haematemesis
    - rarely haemorrhagic shock, death

Helicobacter pylori gastritis



Helicobacter pylori gastritis



Intestinal infections

- Enterocolitis – usual manifestation as diarrhea, may be pseudomembranous, ulcerative, non-purulent
- worldwide more than 3 millions deaths annually, mainly children ≤ 5 yrs
- chronic or recurrent enterocolitis – parasites, protozoa

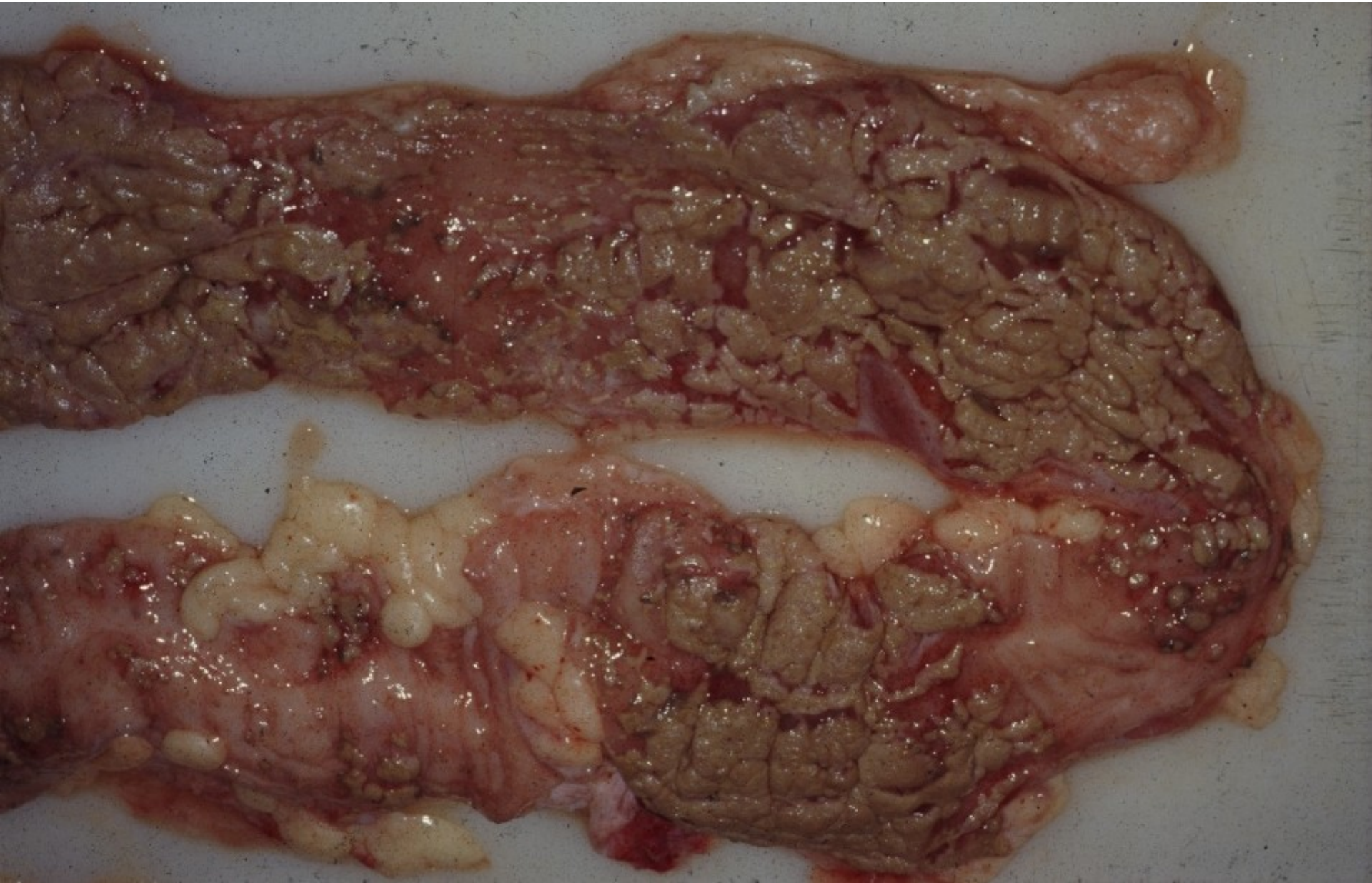
Infectious diarrhea

- **Viral**: rotavirus, enteric adenovirus, echovirus
- **Bacterial**: Salmonella sp., Shigella,E. coli (enterotoxigenic, enteropatgogenic), Campylobacter jejuni, Vibrio cholerae, Yersinia enterocolica, Clostridium difficile
- **Parasitic**: Giardia lamblia, Entamoeba histolytica

Enteropathogenic bacteria

- Staphylococcal strains release enterotoxins → food poisoning.
- *V. cholerae* and toxigenic *E. coli* multiply inside the mucous layer → exotoxins → fluid secretion by epithelium → watery diarrhea.
- *Shigella*, *Salmonella*, and *Campylobacter* invade and damage the intestinal mucosa and lamina propria → ulceration, inflammation, and hemorrhage, clinically manifested as dysentery.
- *Salmonella typhi* passes from the damaged mucosa through Peyer patches and mesenteric lymph nodes and into the bloodstream, resulting in a systemic infection.

Pseudomembranous colitis



Intestinal protozoa

- Cysts resist stomach acid
- *Giardia lamblia* attaches to the epithelial brush border
- *Entamoeba histolytica*:contact-mediated cytolysis through a channel-forming pore protein ulceration, invasion of the colonic mucosa
- Cryptosporidia taken up by enterocytes, in which they form gametes and spores.

Intestinal helminths

- Disease only when present in large numbers or in ectopic sites
- *Ascaris lumbricoides* – gut obstruction, or invasion + damage of the bile ducts
- Hookworms: iron deficiency anemia by chronic loss of blood sucked from intestinal villi
- *Diphyllobothrium latum* (fish tapeworm) depletes its host of vitamin B12, → illness resembling pernicious anemia.
- *Trichinella spiralis* larvae encyst in muscle, *Echinococcus* species larvae in the liver or lung.

Types of diarrhea

- Secretory – isotonic, persist during fasting, etiology: viral; bacterial enterotoxin (cholera, E. coli, Clostridium perfringens, etc.)
- Exudative – purulent + bloody stools, persist during fasting

  etiology: Shigella spp., Salmonella spp., Campylobacter spp., Entamoeba histolytica
- Malabsorption – Giardia lamblia

Infectious hepatitis

- Viral hepatitis – part of systemic disease (EBV, CMV, yellow fever, rarely rubella, herpesvirus, etc.
- Viral hepatitis – liver specific (HAV, HBV, HCV, HDV, HEV, …)
- Bacterial – Stph. aureus, Salmonella typhi, Treponema pallidum
- Parasitic – abscesses - Entamoeba, Echinococcus; malaria, schistosomiasis, cryptosporidiosis, etc.

Viral hepatitis

- Acute asymptomatic infection with recovery
- Acute symptomatic infection with recovery
- Fulminant hepatitis – acute hepatic failure (mostly HAV, HBV, HEV in pregnancy), noninfectious causes (toxic); high mortality (~80%)
- Chronic hepatitis
- „Carrier state“ – no manifest symptoms, usually very mild chronic hepatitis, non- or low-progressive, reservoir for infection

Urogenital tract infections

FLORA of the URINARY SYSTEM

- *Staphylococcus, Streptococcus, and coliforms.*
- In females, flora exists only in the first portion of urethra, the remainder of the tract is sterile.
- In males, the entire reproductive and urinary tract is sterile except for a short portion of the anterior urethra.

FLORA of the REPRODUCTIVE SYSTEM

- *Lactobacillus, Strptococcus, Corynebacterium, Mycobacterium.*
- *Candida albicans*
- In females and males , flora occupies the external genitalia. Internal reproductive structures normally remain sterile.

Urogenital tract infections

- Ascending infection via urethra most usual (G- fecal bacteria – E. coli, Proteus,…)
- Anatomy – 5 cm lenght in women, 20 cm in men
- Predisposing factors – obstruction, reflux, loss of protective vaginal flora, mucosal microtraumata

Urogenital tract infections

- Hematogenous spread (septicemia – Stph., bacteremia, viremia, rare fungal inf. - Candida)
- Immunocompromised – CMV, polyomavirus (kidney transplant), etc.
- Acute pyelonephritis – purulent
- Chronic pyelonephritis – chronic tubulointerstitial inflammation + renal scarring

Sexually Transmitted Infections

- Sexually Transmitted Disease - STD
- Infection transmitted through vaginal, anal or oral sex
- Every sexually active individual is at risk
- Women acquire infections from men more than men from women
- 2/3 of STD occur in people under 25 yrs of age
- Infection by multiple agents common (↑ risk)
- Fetus or infants – vertical transplacental or perinatal transmission of STD → abortus, inborn defects, neonatal infection. Diagnosis + treatment!!

STI

- **Viruses**: HSV, HPV, HIV, hepatitis B,C
- **Chlamydiae**: Ch. trachomatis
- **Mycoplasmas**: U. urealyticum
- **Bacteria**: Neisseria gonorrhoeae, Treponema pallidum, Haemophilus ducreyi (chancroid), Klebsiella granulomatis (granuloma inguinale)
- **Protozoa**: Trichomonas vaginalis (urethritis, balanitis, vaginitis)

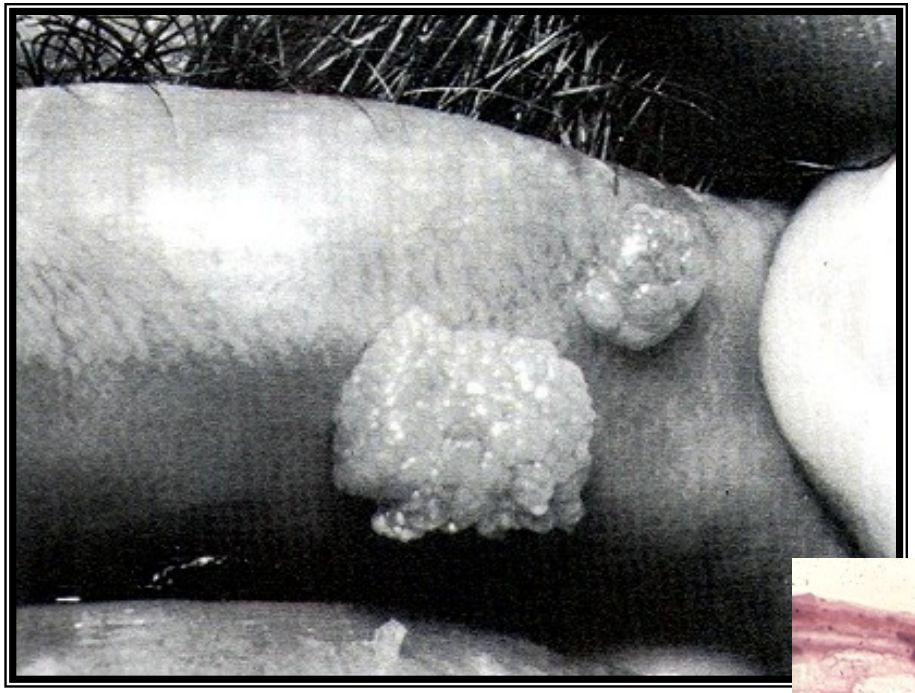
STI - viruses

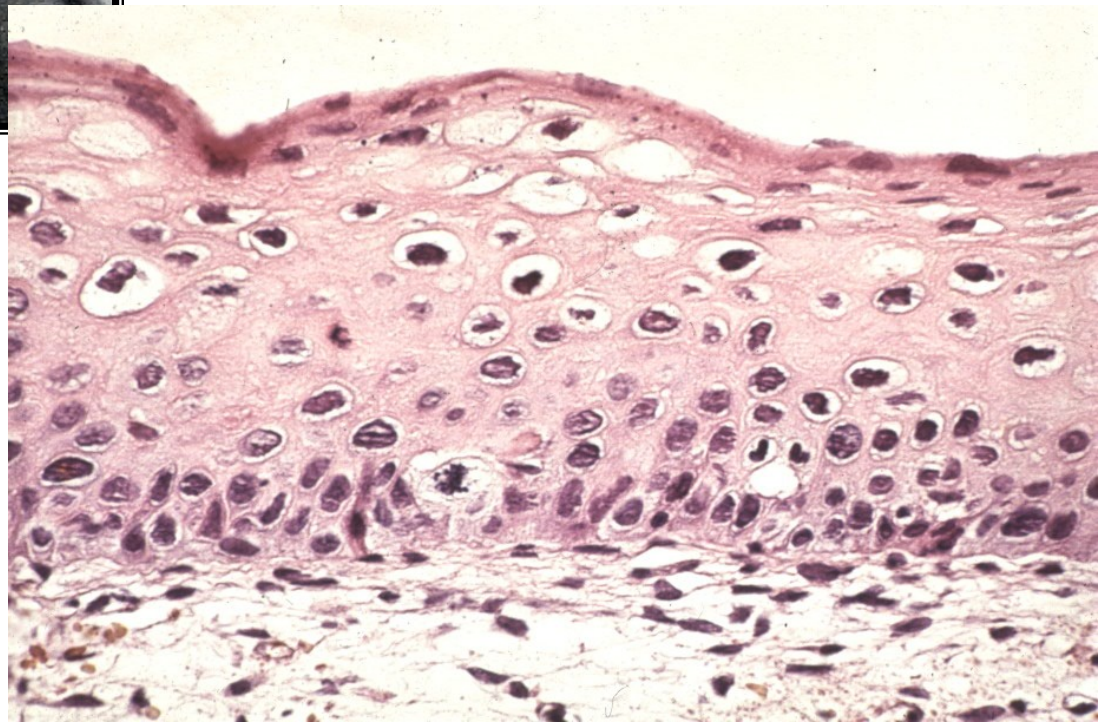
- Herpes simplex virus: Primary and recurrent herpes, neonatal herpes
- Hepatitis B,C virus: Hepatitis
- Human papillomavirus: Cancer of penis (some cases), cervical dysplasia and cancer, vulvar cancer. Condyloma acuminatum
- Human immunodeficiency virus: Acquired immunodeficiency syndrome

Genital warts

- Condyloma acuminatum - HPV
- Most HPV infections asymptomatic or unrecognized
- Mostly found in young, sexually active; associated with early onset of sexual activity, multiple sexual partners
- Transmitted by all types of sexual contact

Condyloma accuminatum (venereal vart)





Koilocytes – HPV productive infection, low-risk types

Genital warts: Complications

- Possible urethral obstruction or destruction of normal tissue
- Can be transferred to fetus during pregnancy or delivery
- Large warts may obstruct the birth canal; cesarean section may be necessary
- Infants infected may develop a chronic respiratory condition – laryngeal papillomatosis

Genital herpes

- About a week after exposure, painful red, fluid-filled blisters in the genital area (vagina, labia, cervix, penis, anus)
- Blisters filled with clear fluid containing the virus, highly contagious
- Rupture → ulcers may last up to 6 weeks
- The first outbreak - the first episode infection
- Subsequent episodes (recurrent infections) usually less severe

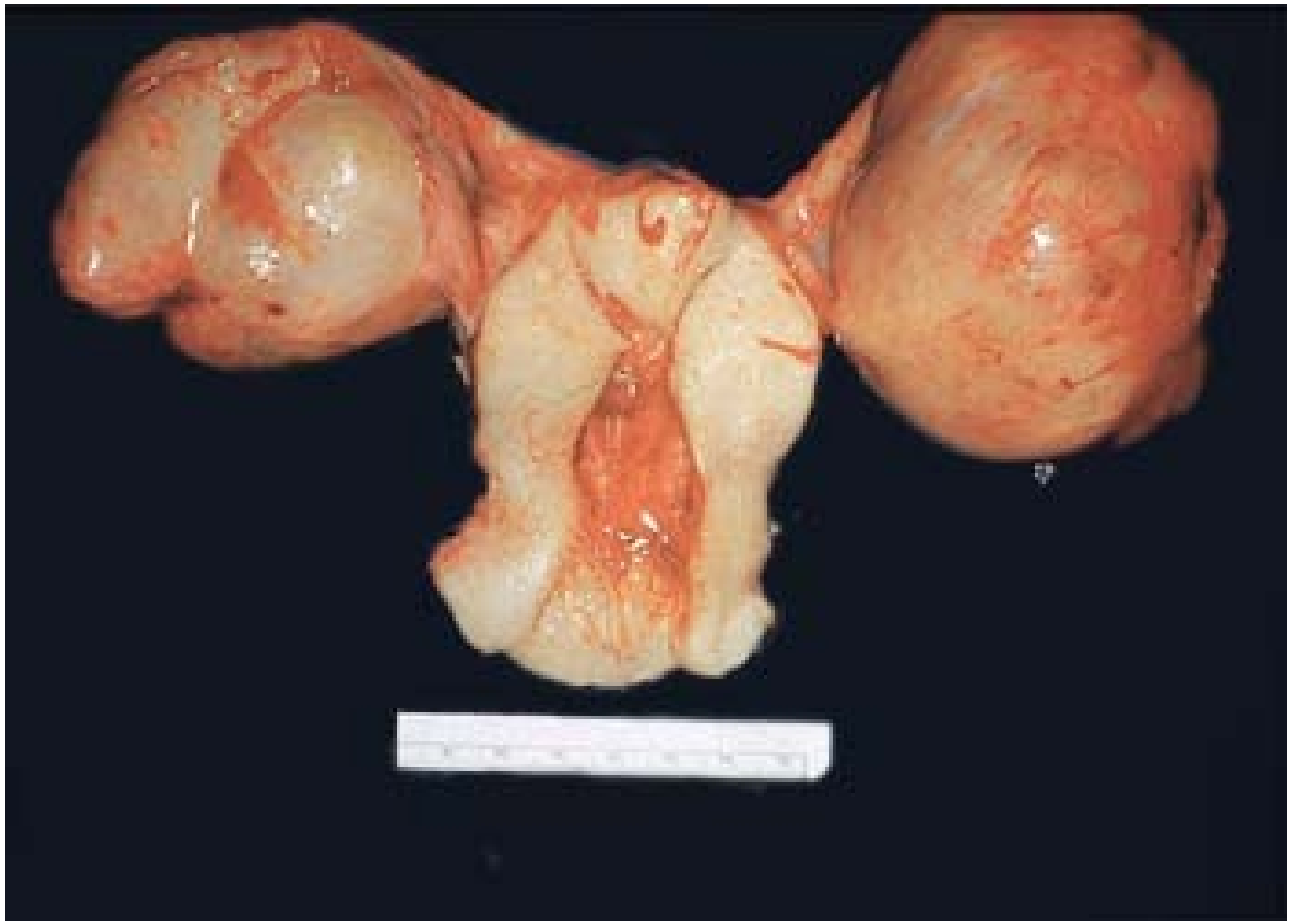
STI

- *Chlamydia trachomatis:* Urethritis, epididymitis, proctitis. Urethral syndrome, cervicitis, bartholinitis, salpingitis and sequelae. Lymphogranuloma venereum
- *Ureaplasma urealyticum:* Urethritis

Chlamydia: Manifestations

- In women often asymptomatic until uterus and tubes infected; may present with dysuria, urinary frequency, vaginal discharge
- 1/3 of men may be asymptomatic; dysuria, urethral discharge, testicular pain
- Patient infectious even if asymptomatic

Acute endometritis and salpingoophoritis



Chlamydia: Complications

- May result in PID (pelvic inflammatory disease)
- Major cause of infertility, ectopic pregnancy in women; may cause stillbirth or spontaneous abortion (miscarriage)
- In men, may result in epididymitis, prostatitis, sterility, Reiter's syndrome
- In neonates, may cause blindness, pneumonia

STI - bacteria

- *Neisseria gonorrhoeae:* Epididymitis, prostatitis, urethral stricture. Cervicitis, endometritis, bartholinitis, salpingitis, and sequelae (infertility, ectopic pregnancy, recurrent salpingitis). Urethritis, proctitis, pharyngitis, disseminated gonococcal infection
- *Treponema pallidum:* Syphilis
- *Haemophilus ducreyi:* Chancroid
- *Klebsiella granulomatis:* Granuloma inguinale (donovanosis)

Gonorrhea

- ‘clap’; one of the most common STDs (second only to Chlamydia)
- Caused by *Neisseria gonorrhoeae*; incubation period is 2-8 days
- Transmitted by sexual contact, during passage through the birth canal
- Usually targets the cervix, male urethra

Gonorrhea

- Female: mostly asymptomatic until advanced disease; dysuria, urinary frequency or abnormal vaginal discharge
- Male: dysuria, serous, milky or purulent urethral discharge; regional lymphadenopathy
- Complications: prostatitis, epididymitis, sterility;

  PID, endometritis, salpingitis, peritonitis;

  in neonates gonorrhea can infect the eyes, nose or anorectal region

Syphilis

- Spirochete *Treponema pallidum*
- Transmitted from open lesions during sexual contact
- Organism can survive days in fluids
- May also be transmitted by infected blood, body fluids, including saliva
- Average incubation is 20-30 days
- Spreads through blood, lymphatic system
- Congenital syphilis - transplacental

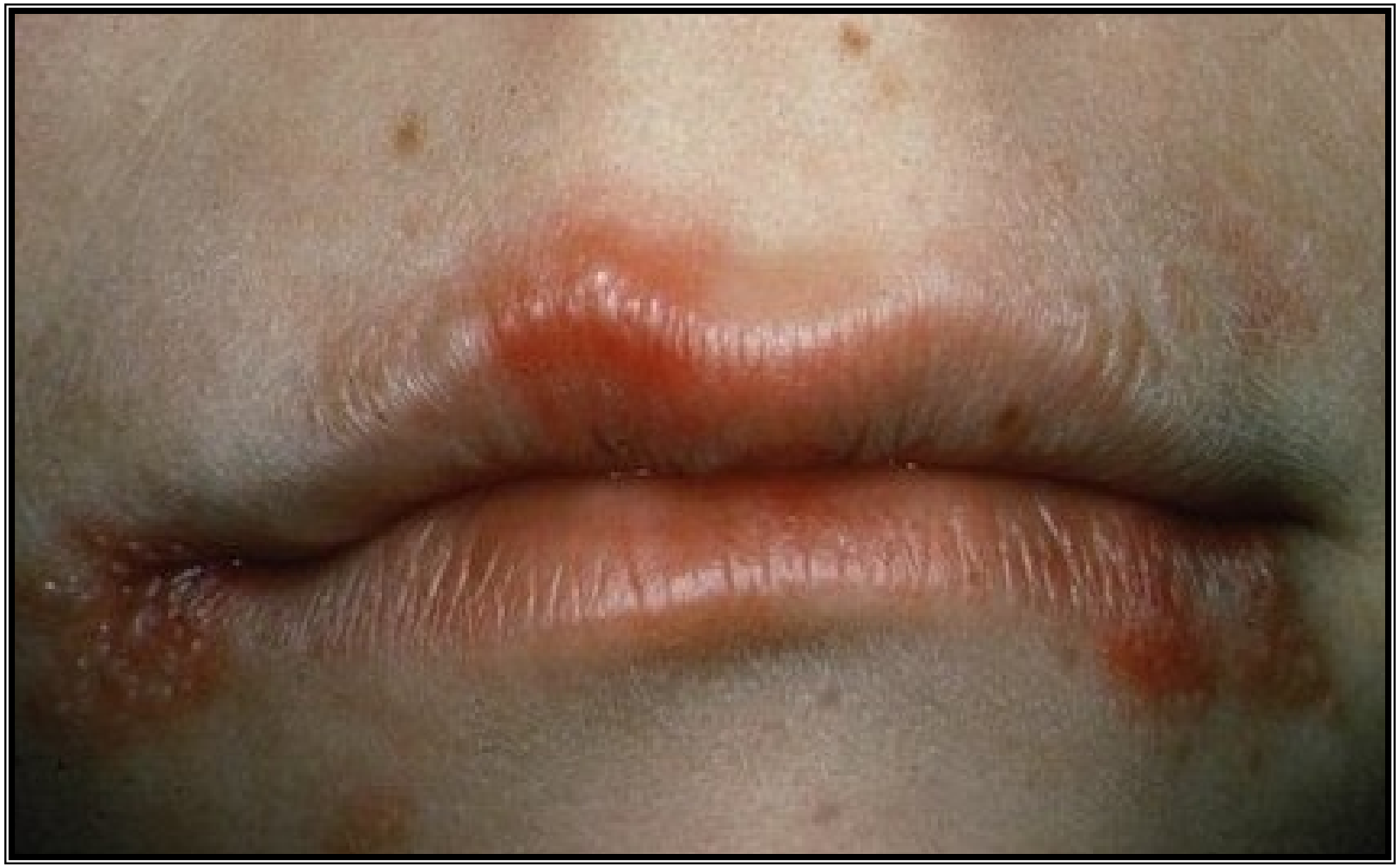
Skin infections

- The dense, keratinized outer layer of skin - natural barrier to infection. Low pH of the skin (5.5) and the presence of fatty acids inhibit growth of microorganisms other than residents of the normal flora.
- Potential opportunists, such as *S. epidermidis* and *Candida albicans*.
- Few microorganisms able to traverse the unbroken skin
- *Most microorganisms penetrate through breaks in the skin*

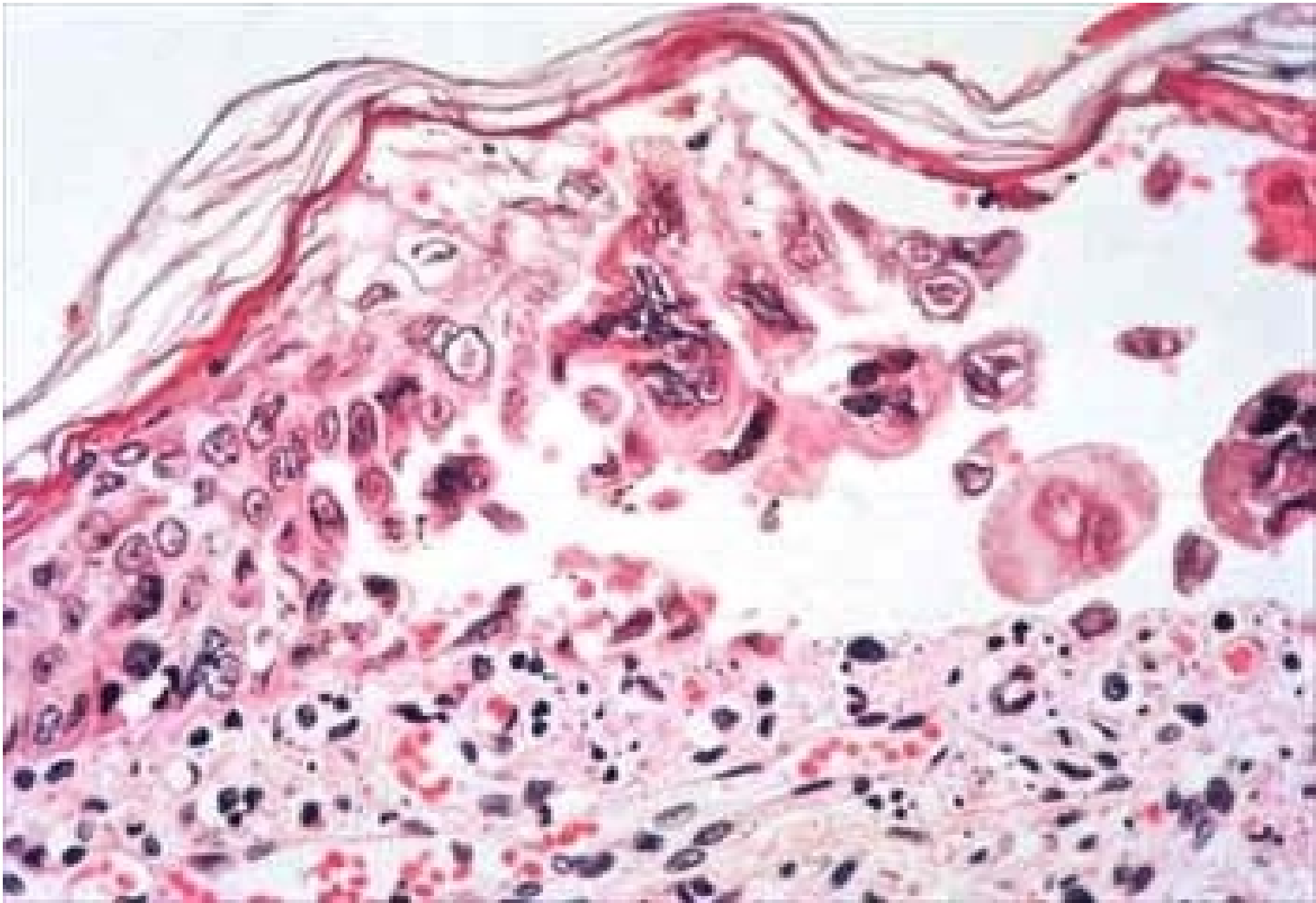
Skin infections

- Viral exanthematic inflammations – HSV, varicella-zoster, etc.
- Viral pseudotumorous lesions – warts (HPV), molluscum contagiosum (poxvirus)
- Bacterial infections – superficial (impetigo – Stph. aureus, blisters + neutrophils), deep (panniculitis, phlegmona)
- Fungal inf. – superficial (Tinea – dermatophytes)
- Parasitic inf. – scabies etc.

Herpetic lesions



HSV



Fungal infections

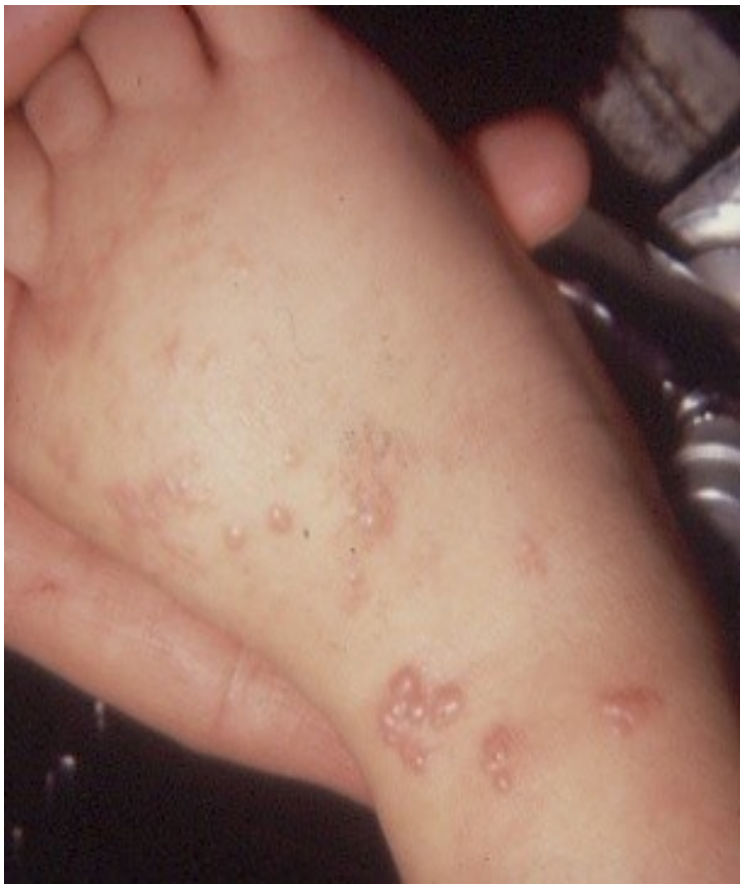
- Superficial infections by dermatophytes : skin, hair, nails.
- The term “tinea” + the area of the body affected (e.g., tinea pedis, “athlete's foot”; tinea capitis, “ringworm of the scalp”).
- Certain fungal species invade the subcutaneous tissue, causing abscesses or granulomas (e.g., sporotrichosis and tropical mycoses).

Common childhood viral infections

- Measles (rubeola, red measles)
- Rubella (German measles)
- *Erythema infectiosum* (Fifth disease)
- Mumps
- Varicella-Zoster (Chickenpox)
- Coxsackievirus and Echovirus associated infections (hand-foot-and-mouth disease)

Chickenpox
Varicella-zoster virus

- Infection is primarily by the airborne route
- Very infectious (90% of non-immune household contacts will become infected).
- Unlike other human herpes viruses almost all infections are symptomatic.
- Infections in immune compromised and neonates can produce encephalitis, pneumonia or disseminated infection.



Coxsackieviruses and Echoviruses

- Enteroviruses
- Infections occur June-October
- Transmission: fecal-oral
- 50-80% of infections are asymptomatic
- Can cause skin rash and can look mimic other virus infections
- Common cause of meningitis, myocarditis
- Hand-foot-and-month disease (vesicular type)
  - Usually secondary to Coxsackie A16
  - Children <10
  - Sore throat, vesicles, fever, cutaneous lesions including hand and feet

CNS infections

- Meningitis

  acute pyogenic (bacterial)

  aseptic (acute viral)

  chronic (+ encephalitis; tbc, borrelia,

  T. pallidum, cryptococcus)
- Brain abscess (bacterial, Naegleria)
- Viral encephalitis (+ meningitis) acute (arboviruses, herpetic, CMV, poliomyelitis, rabies, HIV), persistent (progressive multifocal leukoencephalopathy – JC virus, subacute sclerosing panencephalitis – measles)
- Fungal (cryptococcus etc.), parasitic (Toxoplasma)

Transmission of infection to NS

- blood borne
  - septicaemia, viraemia, infected blood cells, septic embolism (e.g. endocarditis, bronchiectasis, IV drug use)
- direct spread
  - adjacent infection, head injury etc
- trauma (incl. iatrogenic – lumbar punction, ventriculo-peritoneal shunts)
- vertical transmission in pregnancy
- (important role for immunosuppression)

Bacterial infections

- problems arise because of inflammatory reaction or tissue destruction
- result in meningitis or abscess

Meningitis

- inflammation in subarachnoid space (arachnoid and pia mater) strictly speaking = *leptomeningitis*
- *pachymeningitis* = predominantly dural disease
  - usually direct spread of infection from skull (otitis media, mastoiditis or fracture)
  - G- bacilli from middle ear, str. from sinuses; mixed organisms, often + Stph. aureus, from skull fractures.
  - can cause dural abscess

Meningitis (i.e. leptomeningitis)

- usually blood-borne infection, but can be direct spread from the skull bones
- most common bacteria –
  - neonates: coliforms, streptococci
  - 2-5 years: haemophilus
  - older children - adults: meningoccus, pneumococcus
  - old age: pneumococcus
- in immunocompromised
  - pneumococcus, meningococcus, listeria

- (TB and syphilis also important causes)

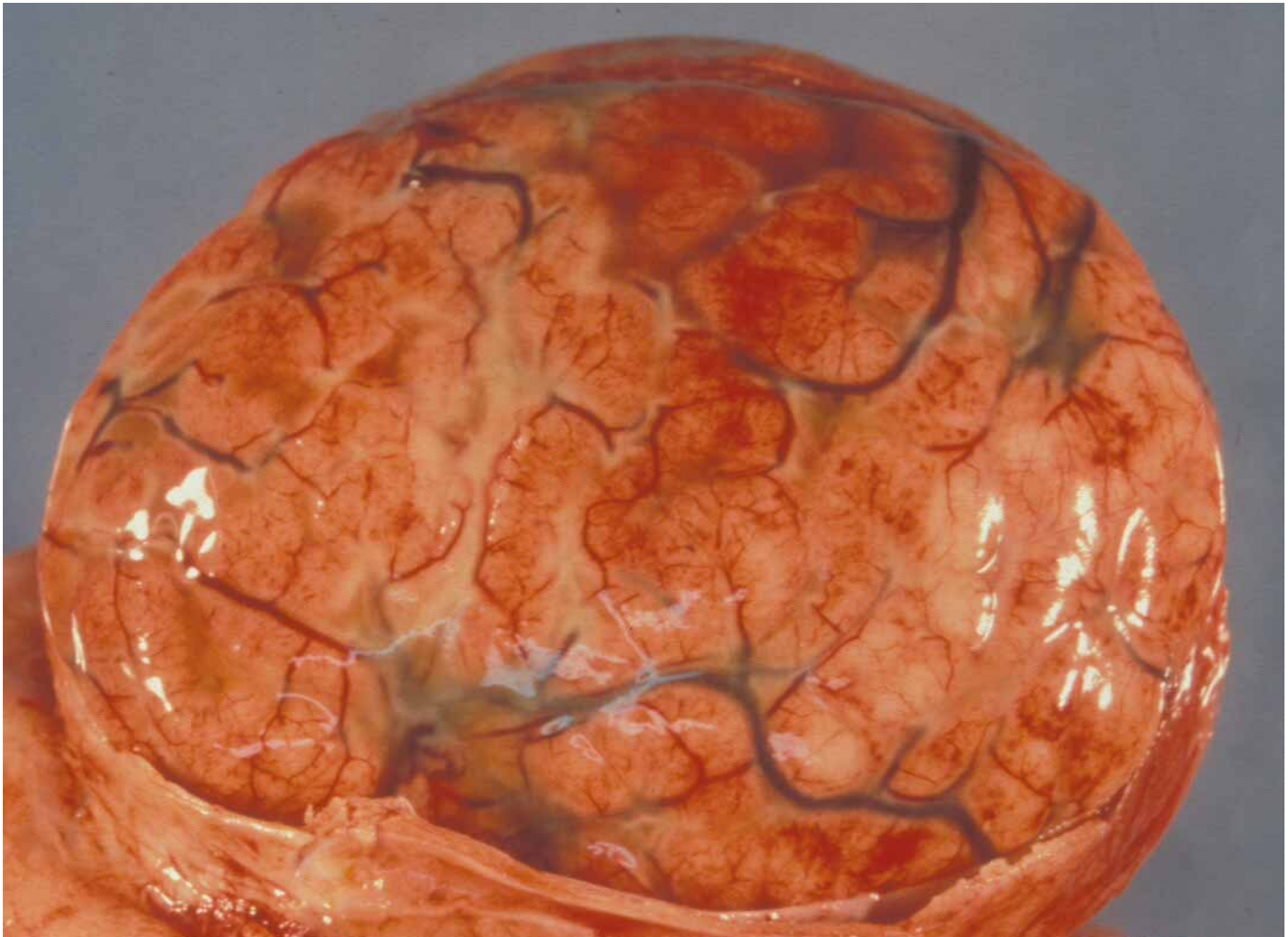
Pathology of bacterial meningitis

- meningeal and superficial cortical vessels congested, often haemorrhagic;event.+ myelitis
- infiltrate of neutrophils, suppuration – basal cisterns and sulci
- CSF often turbid - reduced glucose, increased cells (neutrophils) and increased protein
- complications: DIC if meningococcal

acute: cerebral abscess, subdural empyema, superficial encephalomalatia,

chronic: obstructive hydrocephalus, epilepsy, cranial nerve palsies;

Suppurative meningitis



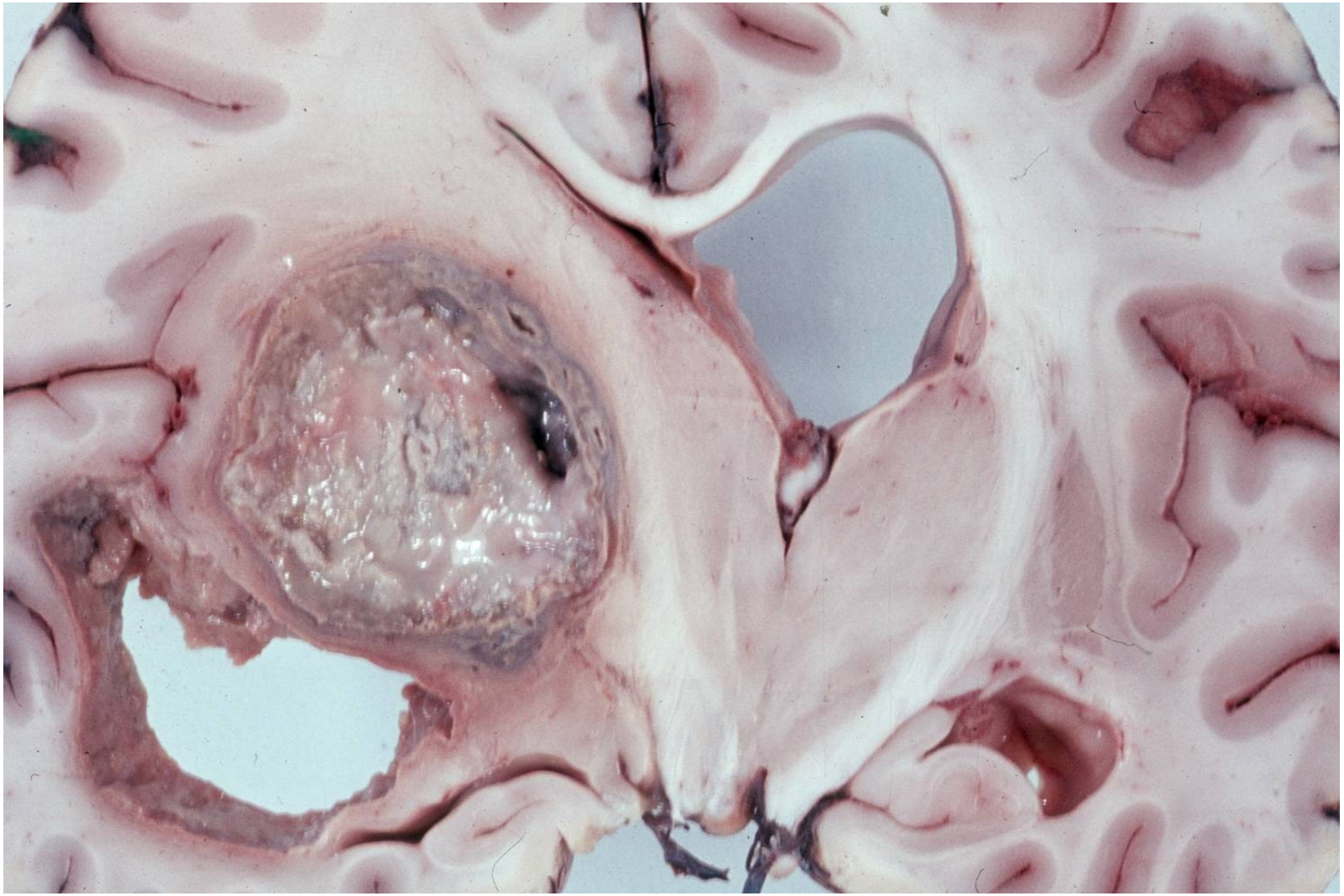
Cerebral abscess

- usually from
  - direct spread - sinuses or middle ear
  - septic sinus thrombosis - spread of infection from mastoid or middle ear via sigmoid sinus
  - blood spread, e.g. infective endocarditis, bronchiectasis etc - often multiple abscesses in parietal lobes
- adjacent brain markedly oedematous
- abscesses frequently enlarge and become multiloculate

Cerebral abscess

- presentation can be similar to meningitis, but often with focal signs, epilepsy and fever
- but also act/present as space-occupying lesions
- complications include –
  - meningitis
  - focal neurological deficit
  - epilepsy
  - herniation of the brain

Cerebral abscess



NS tuberculosis

- secondary to infection (75% primary) elsewhere
- meningitis (espec. in young) and/or abscesses (tuberculomas)
- meningitis from rupture of subependymal tubercles
  - (rarely from direct spread from vertebral body)
  - thick gelatinous exudate in basal cisterns and sulci
  - causes subacute meningitis with occasional isolated cranial nerve palsies
  - but can be non-specific and diagnosed only after LP
- tuberculomas present like other cerebral abscesses

NS syphilis

- blood spread
- effects include –
  - silent meningitis during prim. and sec. stages
  - meningeal thickening in tertiary stage, causing cranial nerve palsies
  - gummata → cerebral or spinal compression
  - tabes dorsalis due to degeneration of dorsal columns
  - “general paralysis of the insane” due to cerebral atrophy in chronic infection

Neuroborreliosis

- variable symptoms
- aseptic meningitis
- facial nerve palsy, polyneuropathy
- encephalopathy

Viral infections of NS

- usually haematogenous spread during viraemia
  - usually cause meningitis or encephalitis
- neural spread along peripheral sensory nerves by retrograde axonal transport, e.g. rabies
- some viruses neurotropic, incl. specific cell types infection; specific site infection
- pathogenetic effects because of multiplication inside NS cells or immune response (with lymphoid infiltration) to virus

Viral infections of NS

- acute infection
- immune-mediated disease
- reactivation of latent viral infection (e.g. zoster)
- latency + subactute-chronic disorders (JC polyomavirus progressive multifocal leukoencephalopathy; measles subacute sclerosing panencephalitis; post-infective parkinsonism,…)

Viral meningitis

- common
- acute onset, but usually less severe than bacterial meningitis
- usually haematogenous spread
- common organisms – arboviruses, herpetic viruses
  - mumps
  - echoviruses
  - coxsackie

Viral meningitis

- meninges infiltrated by mononuclear cells (lymphocytes, plasma cells and macrophages) with typical perivascular lymphocytic cuffing in meninges and superficial brain
- characteristic CSF – normal glucose, increased cells (lymphocytes) and slight protein increase

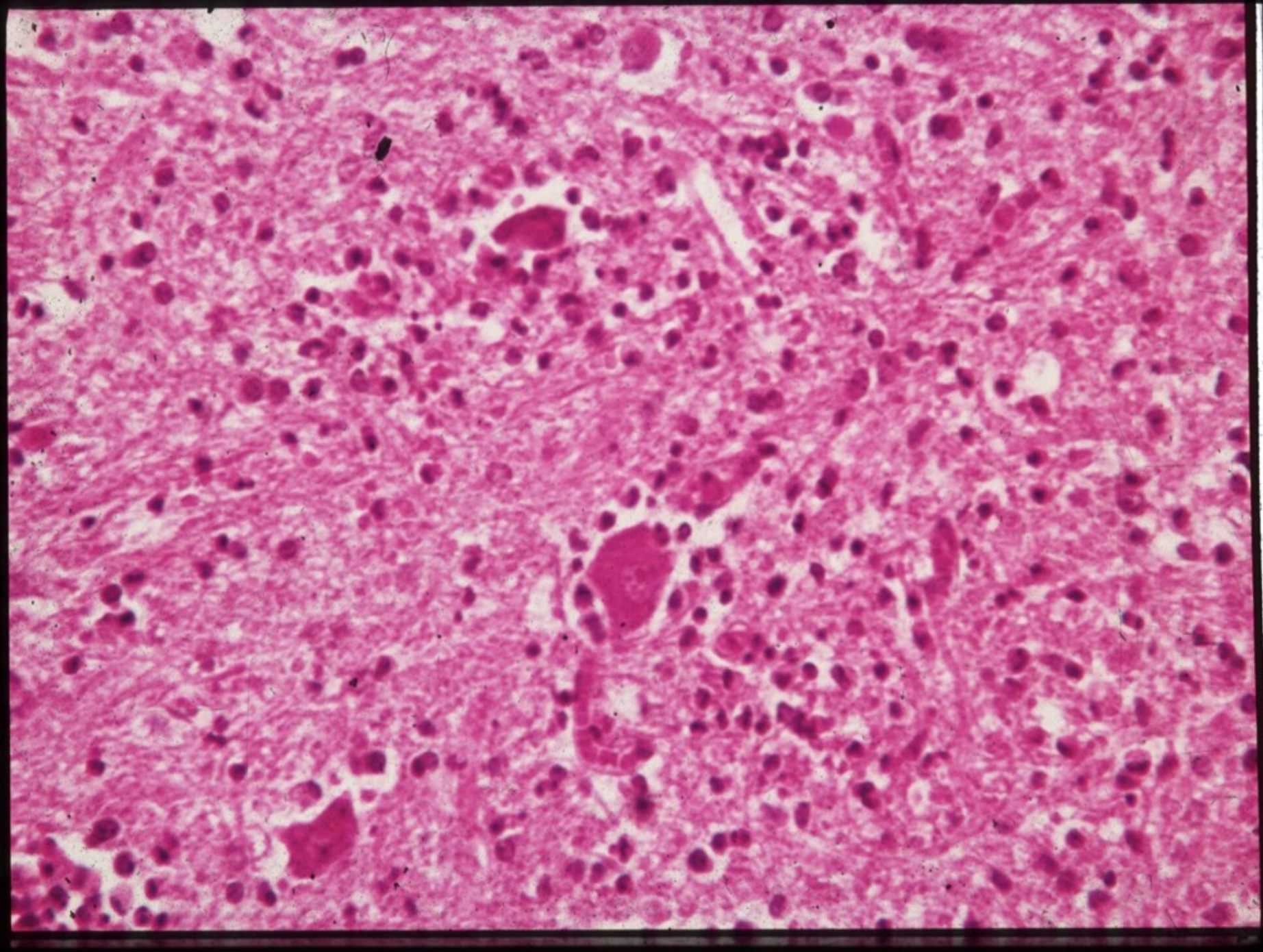
Viral encephalitis

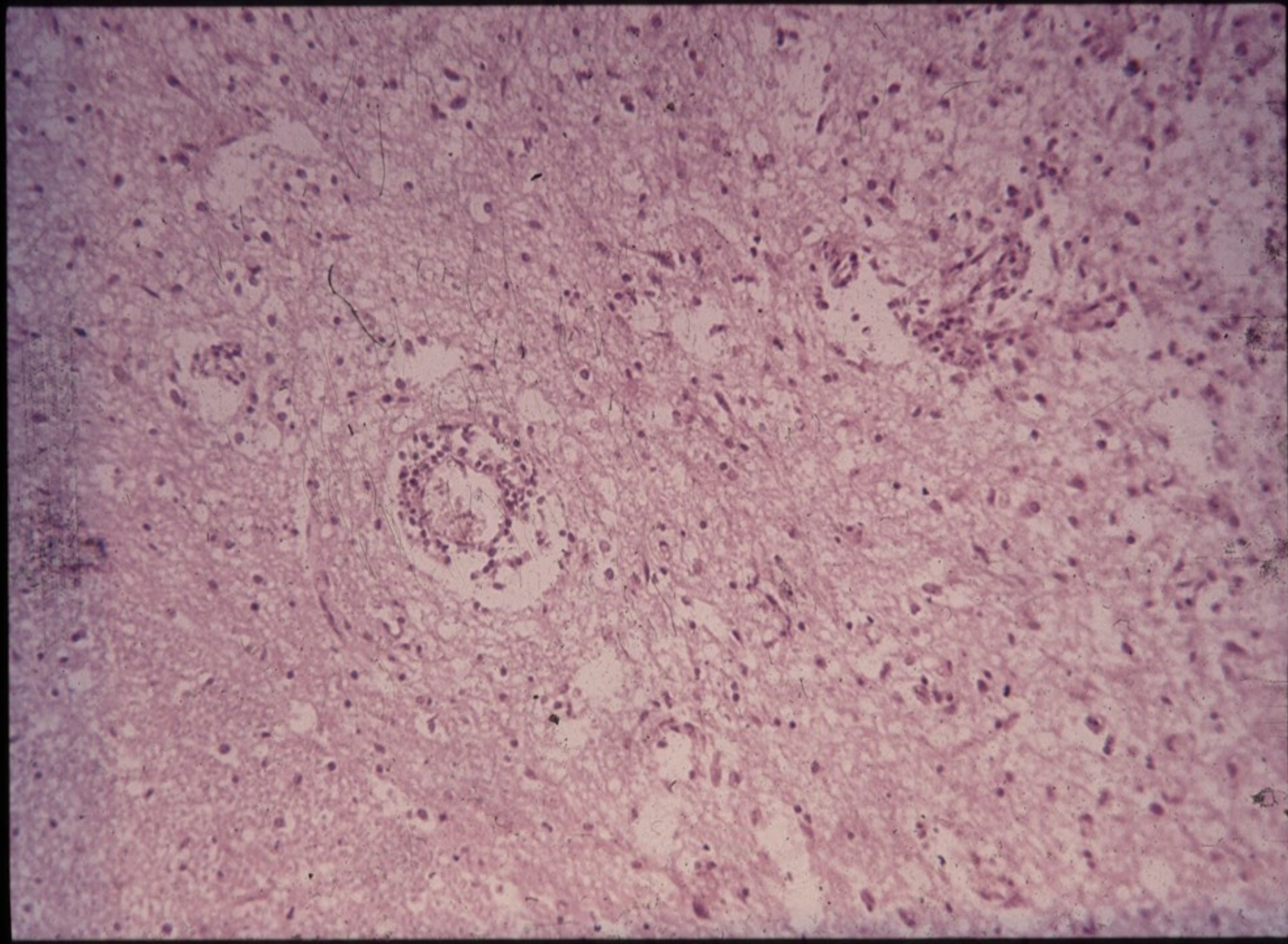
- most commonly HSV, EBV, zoster and arboviruses
  - mode of spread varies with virus
  - viral type may also determine part of brain affected
- pathology
  - mononuclear infiltration - as perivascular cuffing
  - +/- cell lysis and phagocytosis of cell debris by macrophages - when neurones involved, process is known as neuronophagia
  - reactive astrocytes and microglia, often in cell clusters
  - vasogenic oedema
  - viral inclusions may be diagnostic, e.g. 'owl-eyes' CMV and Negri bodies in rabies

Viral encephalitis

- most cases mild, self-limiting conditions, but may result in death or severe
- most common effects – fever, personality change and seizures
- focal neurological signs very unusual

- (some viruses can also damage brain not by invasion, but secondary to an immune mediated demyelination)





Fetal NS infections

- rubella (deafness, blindness, microcephaly)
- CMV (microcephaly)
- toxoplasma (microcephaly)
- syphilis (tertiary forms include GPI, tabes dorsalis and meningovascular syphilis)
- Zika (microcephaly)
- (HIV)

Parasitic infections - toxoplasmosis

- most frequent cause of focal NS disease in AIDS
- ~ 50% patients in Africa and Europe
- often constitutional symptoms/signs at first, but then more obviously neurological ones, sometimes with localising signs
- ICP may be raised with coma/death if untreated

Cerebral malaria

- usually only seen in children under 10 or newcomers to falciparum malarial areas
- acute diffuse parenchymal disease accompanied by fever +/- meningitis
- rapidly fatal in ~ 25-50%
- histological hallmark is sequestration of microcirculation by parasitised/non-parasitised red cells
- causes ring-like lesions in brain

Other parasitic infections

- trypanosomaiasis
  - chronic meningoencephalitis
- entamoeba histolytica
  - amoebic abscess
- echinococcus granulosus
  - hydatid cyst
- toxocara canis
  - eosinophilic meningitis with granulomas

Fungal infections of NS

- more common in immunosuppression
- usually blood spread from lungs, but also direct
- cryptococcus
  - usually causes meningitis
- candida and aspergillus
  - usually cause abscesses
- mucormycosis
  - usually uncontrolled diabetics – granulomatous nasal infection spreading to brain

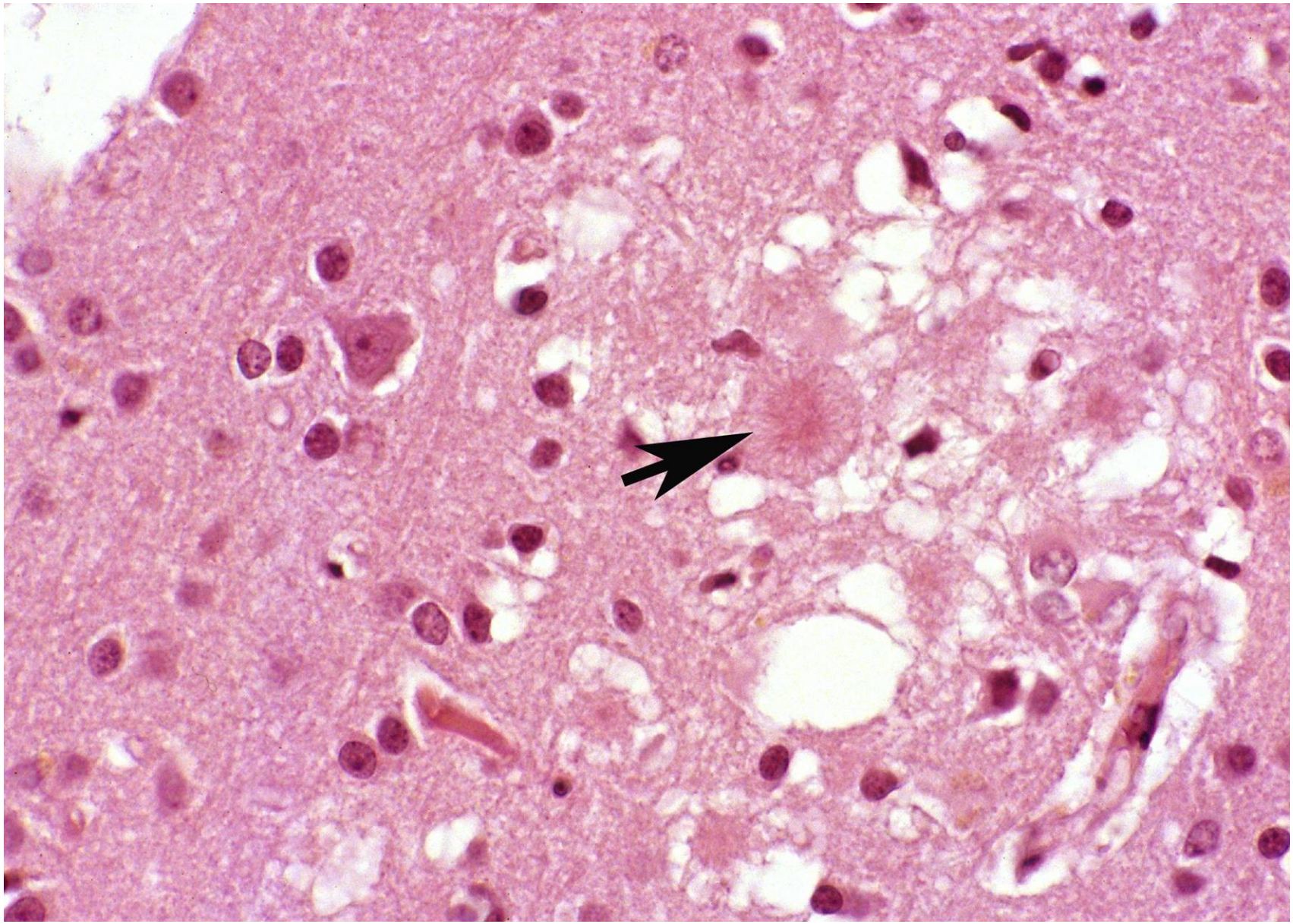
Prion disease

- CJD (Creuzfeldt-Jakob disease
- variant CJD

CJD (Creuzfeldt-Jakob disease)

- presents in adults as rapidly progressive dementia often with focal signs – always fatal
- sporadic disorder in 1:1 000 000 per year worldwide
- transmissible to primates by modified host protein, prion protein
- human-human transmission recorded from electrode implantation, grafts and human growth hormone
- cortical atrophy, neuron loss and reactive proliferation of astrocytes, but no inflammation
- numerous small vacuoles present in neuron and glial processes, so known as spongiform encephalopathy
- akin to kuru in New Guinea

Prion plaques in variant CJD



Variant CJD

- new variant form of CJD identified in young patients in UK
- probably from transmission of BSE (bovine spongiform encephalopathy - 'mad cow' disease) to humans by contaminated beef
- several hundred cases of variant CJD so far - ? in future?