Pathology of the lymphatic and hematologic systems

V. Žampachová
I. ÚP

Lymph nodes

- Normal LN soft, nonpalpable
- Lymphadenopathy – enlarged palpable LN
- Tender LN – usually in acute reaction (hyperemia, edema of LN), commonly neck
- Nontender LN – palpable firmer lump – mostly chronic reaction (neck LN, inguinal LN, …), chronic inflammation (TB, …), cancer
- Past medical history of the client important

Lymph nodes

- changes in size (>10 mm), shape (fused together), consistency important, must be reported

- LN in front or behind of ears, supraclavicular, pectoral – usually not affected by local inflammation – changes more suspicious

Disorders of the lymphatic system

- Lymphadenitis – inflammation of LN
- Lymphadenopathy – reactive enlargement of LN (immune reaction)
- Lymphangitis – inflammation of lymphatic vessel
- Lymphedema – increased amount of lymph fluid in soft tissue

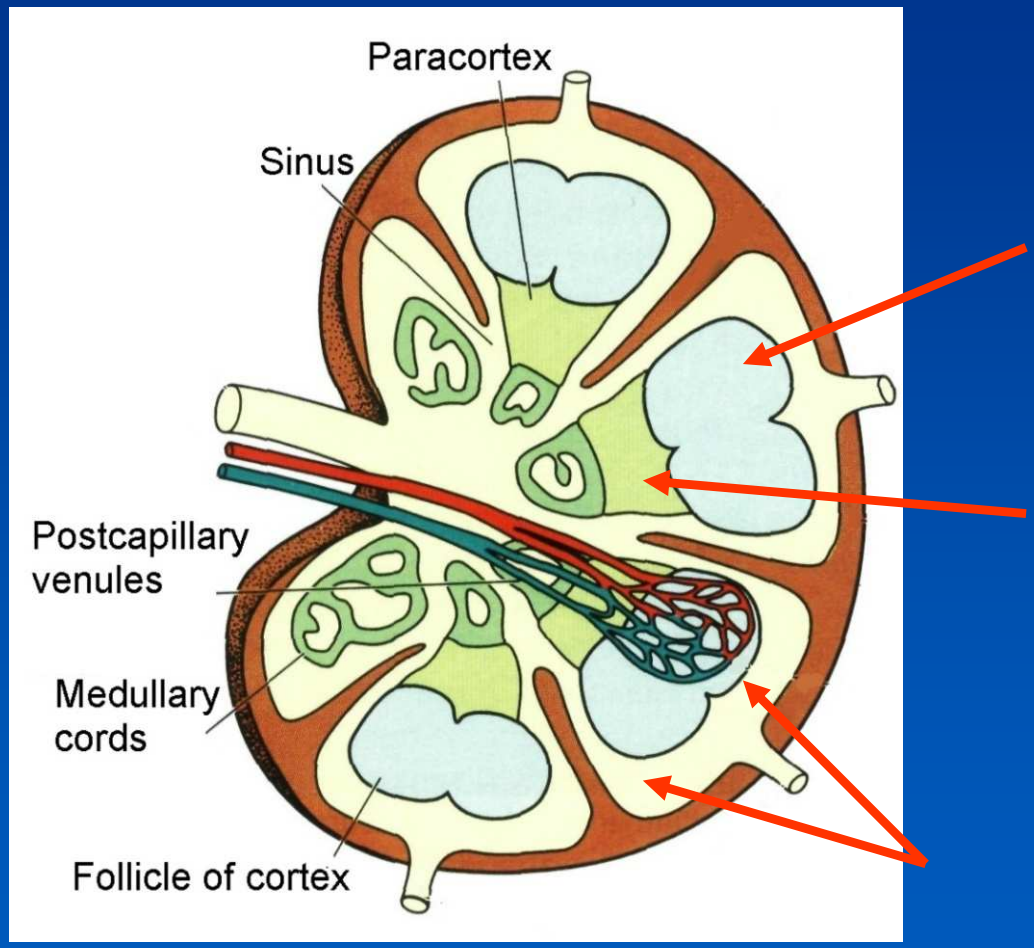
Lymphadenopathy

- LN – defense barrier
- Regional LN in focal infection /reaction, focal malignant tumor (reactive cervical lymphadenopathy in infection of oral cavity, pharynx, ears, head, skin or soft tissue
- Generalized lymphadenopathy - ≥ 2 groups of LN; in systemic infection, immunologic reaction, spread of a malignant tumor

Non-specific reactive lymphadenopathy

- regional or systemic response of lymphatic tissue on antigenic stimulation (inflammation, tumor, foreign material)
- Gross : acute lymphadenopathy (enlarged LN), hyperaemia, soft consistency, tender
- Micro: according to the cause – lymph. follicles activation and hyperplasia, sinus hyperplasia („histiocytosis“), T-zone activation

Reactive lymphadenopathy



- **Reactive hyperplasia:**

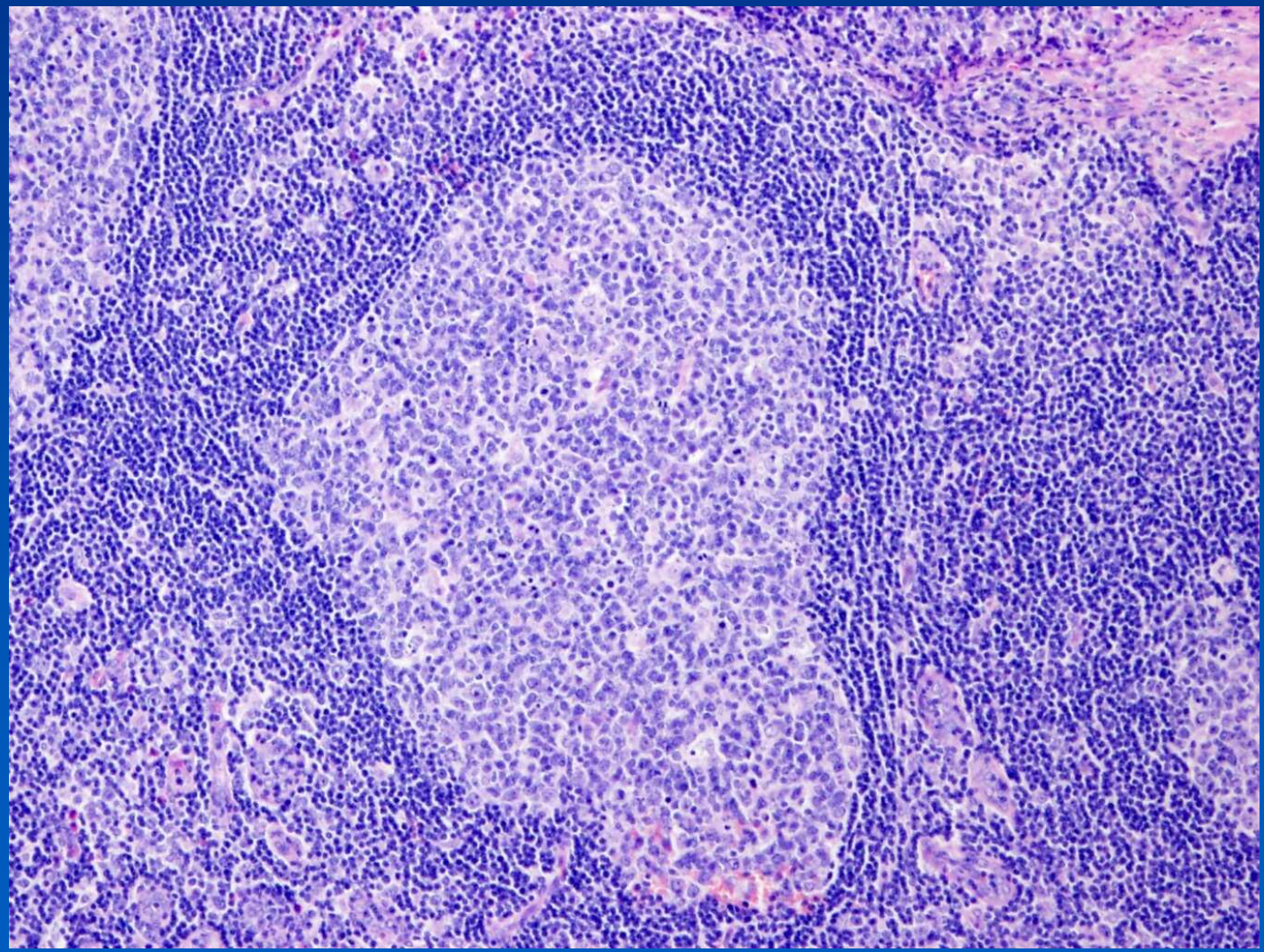
  Follicular (B)
  (bacteria, sterile inflammation)

  Paracortical (T)

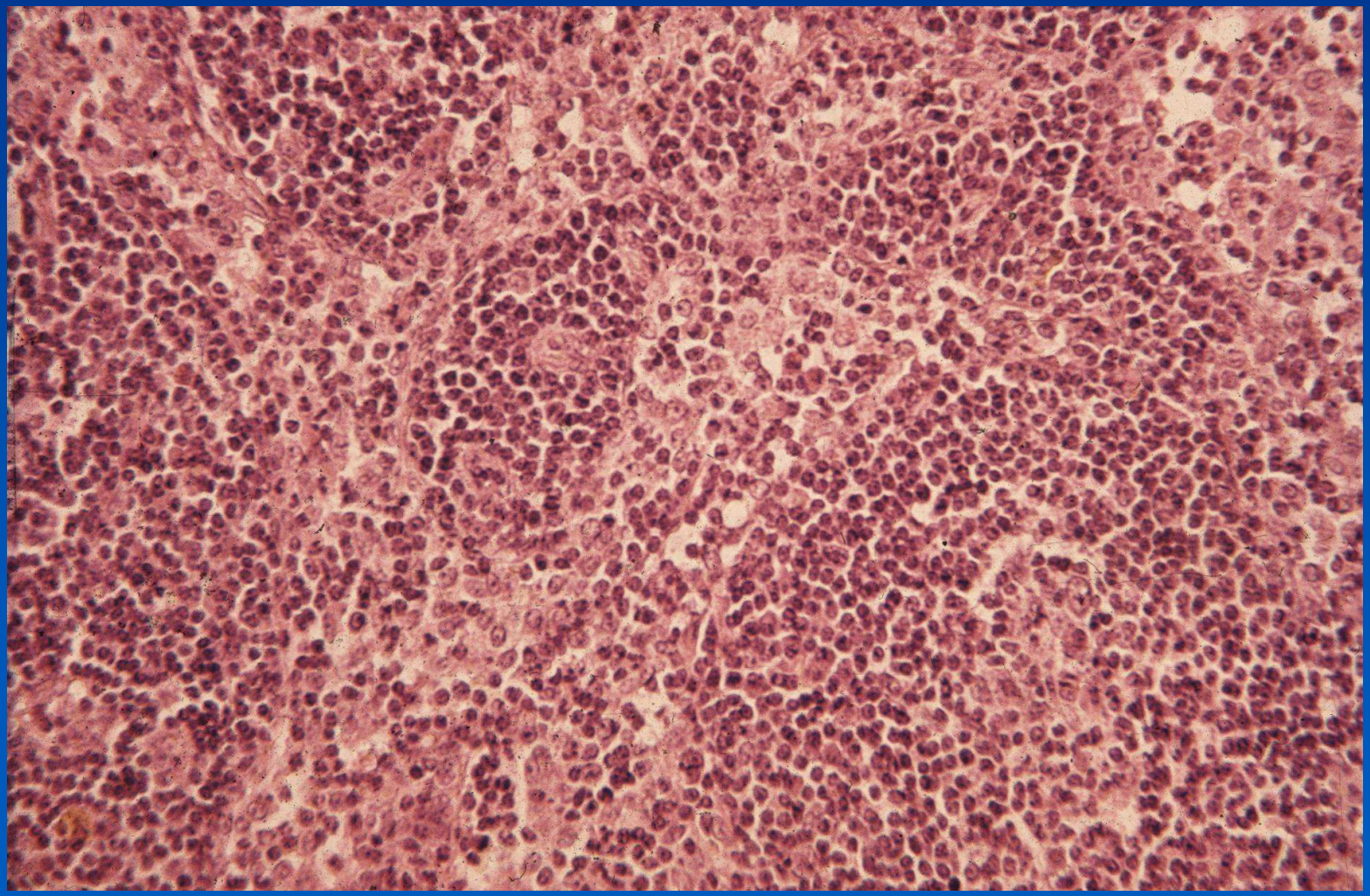
  (viruses, chronic inflammations)

- **Sinus histiocytosis**

Follicular hyperplasia - reactive



Sinus histiocytosis



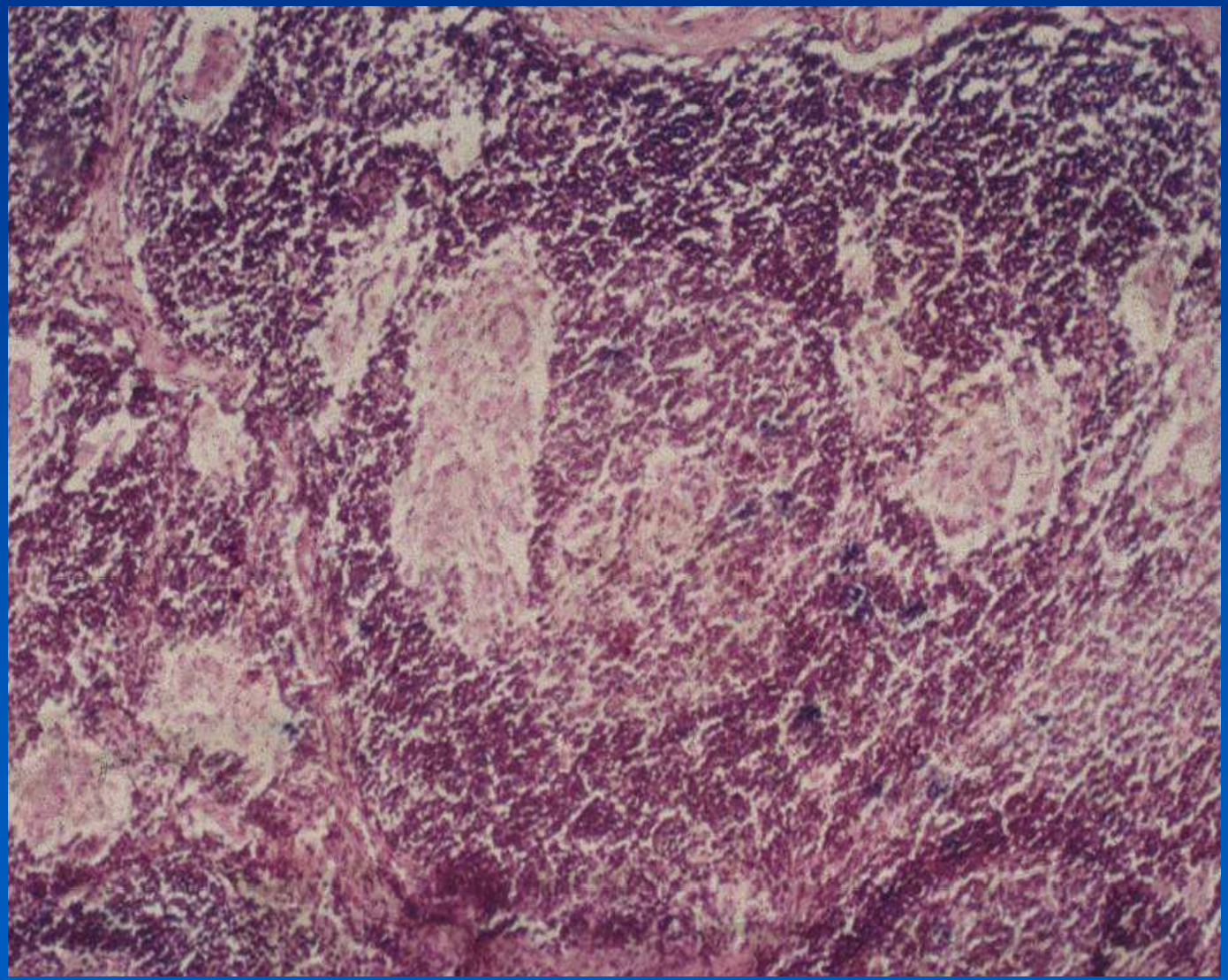
Lymphadenitis

- Acute – LN region warm, reddened, LN enlarged, tender
- Usually in more aggressive local infection, which affects even the LN (cervical in acute tonsillitis, inguinal in infection of extremities). Abscess possible.
- Short duration (approx. 2 weeks), if the cause progresses → possible transformation into chronic lymphadenitis

Lymphadenitis

- Non-specific: without specific microscopic patterns
- Specific: micro picture +/- specific for one cause – granulomatous inflammation (TB, sarcoidosis, mycotic infection,…)
- Chronic - LN enlarged, nontender, firmer
- Long duration, even persistent

TBC lymphadenitis

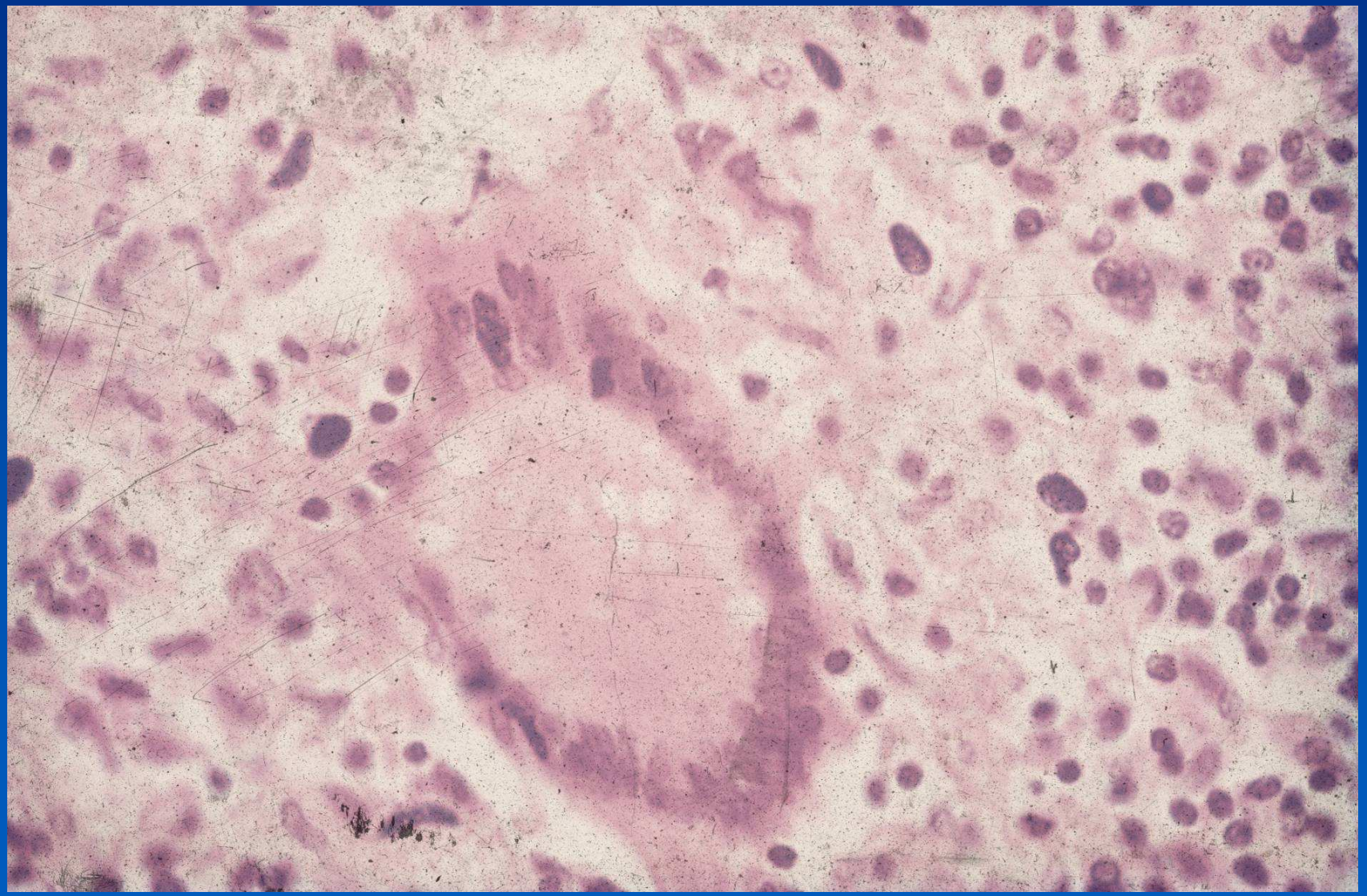


Tuberculosis

- Tuberculous granuloma - basic morphology:
  central caseous necrosis (soft), transformed epithelioid macrophages + multinucleated Langhans‘ giant cells (fusion of macrophages), rim of T-cells

- *Mycobacterium tuberculosis*
  Ziehl-Neelsen staining, acid-resistant bacteria

TBC lymphadenitis



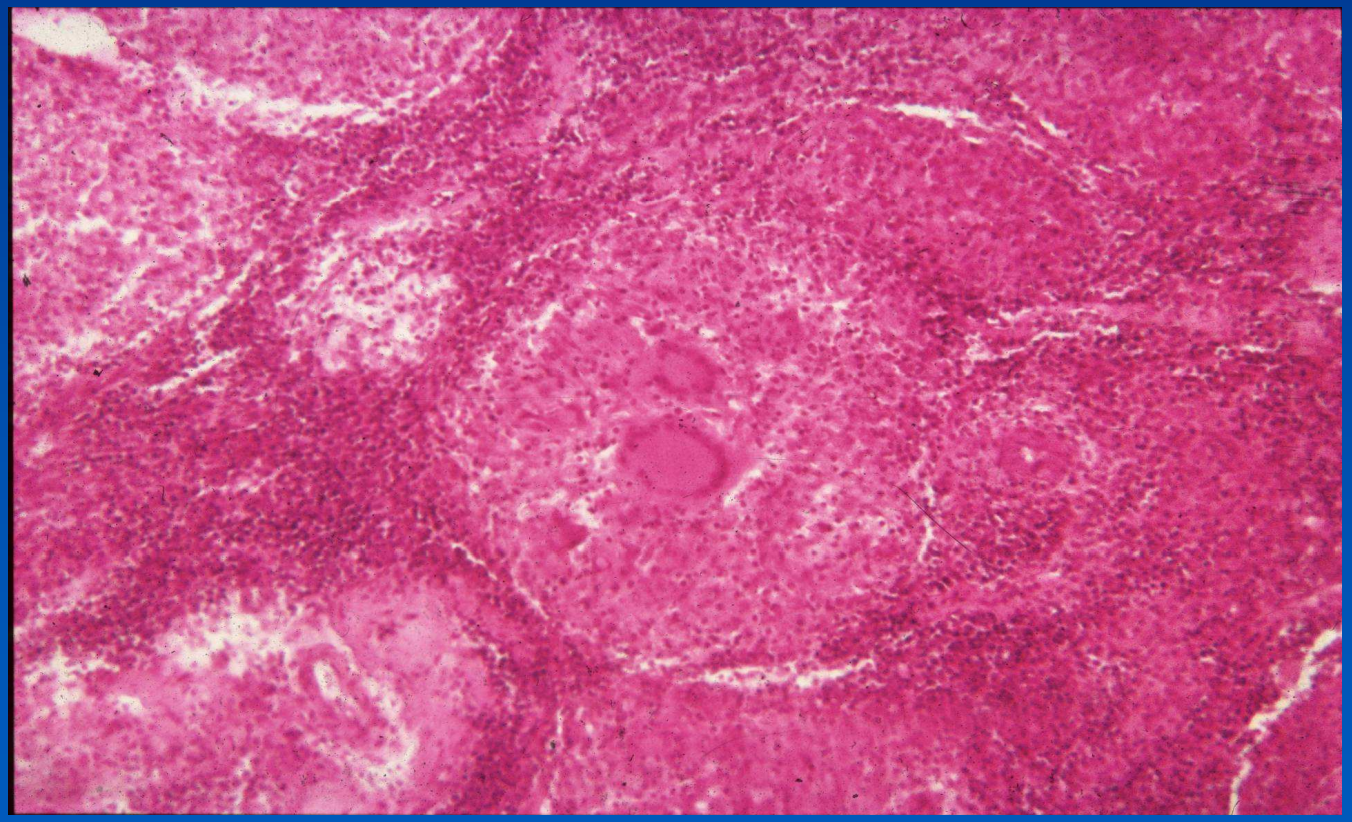
Sarcoidosis

- Chronic granulomatous inflammatory disease, direct etiology unknown
- Mostly in mediastinal LN, lung, skin, eye; any localisation possible
- Regular small „tuberculoid“ granulomas without caseous necrosis

Sarcoidosis

- May be asymptomatic, chest X-ray: bilateral lymphadenopathy (diff. dg. x lymphoma, cancer metastasis)
- Slow progression or remission + healing
- 10% mortality (lung fibrosis, cor pulmonale), 20% lung or ocular dysfunction

Sarcoidosis



Lymphangitis

- Acute inflammation of subcutaneous lymphatic vessels
- Usually from local wound/infection

- Red streak under the skin („blood poisoning“)
- Involved regional LN
- Systemic manifestation possible (fever, chills, malaise), bacteremia
- Risk of lymphedema

Lymphedema

- Swelling of the soft tissues due to accumulation of protein-rich fluid in the extracellular space
- Cause: ↓ lymphatic transport capacity and/or increased amount of lymph
- Extremities common; head, neck, abdomen, genitalia posssible

Lymphedema

- Primary (idiopathic): result of lymphatic maldevelopment, rare.
  - ⇨ *May be present at birth (connatal)*
  - ⇨ *Can develop later in life without known cause*

- Secondary (acquired) more common.
  - ⇨ *Result of surgery, radiation, injury, trauma, scarring, or infection of the lymphatic system*

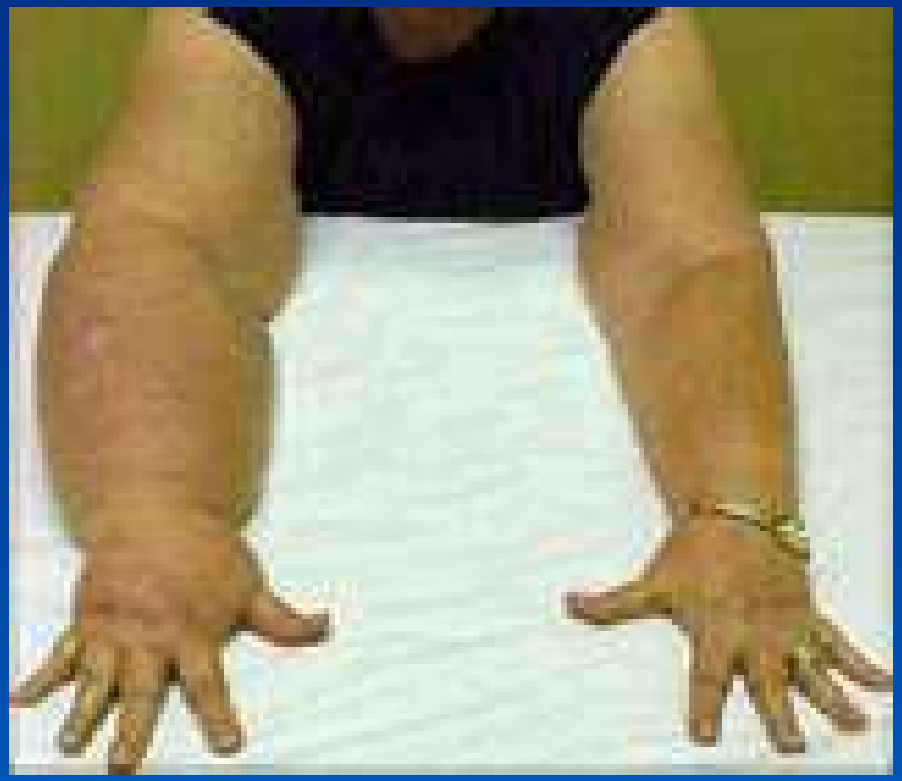
Secondary lymphedema

- Surgery: breast cancer, melanoma, prostate/bladder cancer, lymphoma, ovarian cancer, hip replacements
- Radiation therapy
- Drugs (steroid, etc.)
- Trauma – scarring, crush injury
- Infection: filariasis, etc.
- Chronic venous insufficiency
- Obesity
- Self-induced

Lymphedema staging

- Stage 0 – latent: reduced transport capacity, no edema present
- Stage I: pitting edema present, reversible (elevation)
- Stage II: nonpitting edema + fibrotic tissue, irreversible
- Stage III: lymphostatic elephantiasis, severe fibrotic edema, skin changes – folds, hyperkeratosis

Lymphedema



Lymphedema

- Lymphedema is a disease.
- Untreated l. is progressive
- Early diagnosis necessary
- If fully evolved, no definitive cure possible.
- Management strategies exist: treat the causing disorder;
- Proteolysis, surgery, …
- Lymphatic drainage – manual, compression bandage, pump

Malignant complications

- After long-standing lymphedema possible evolution of malignant vessel tumor – angiosarcoma

- Signs: reddish-blue and dark nodules, rapid growth, bleeding, ulceration
- Bad prognosis

Tissue changes in lymphedema

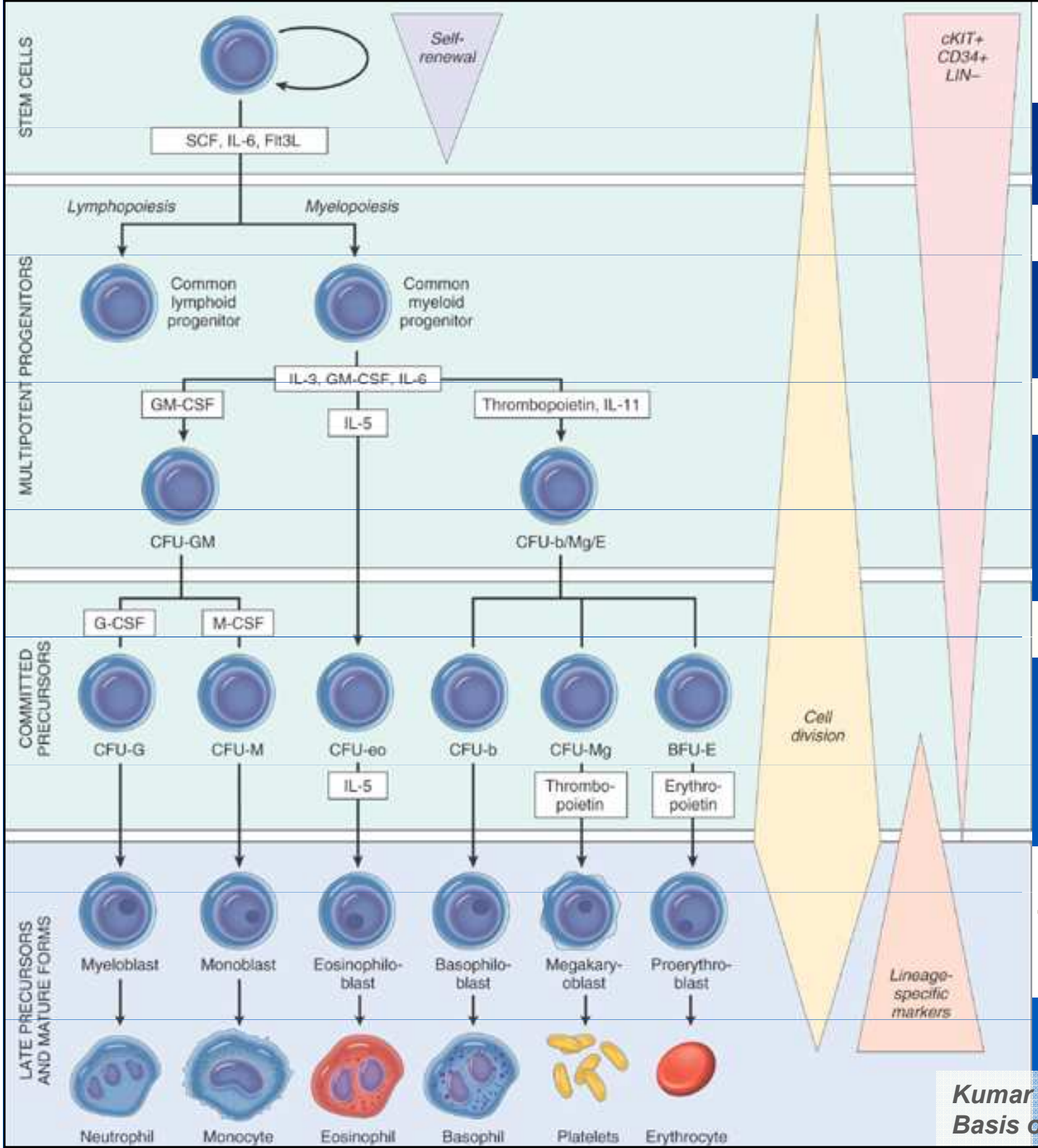
- Hypoxemia, loss of functional cells
- Proliferation of connective tissue cells (fibroblasts)
- Production of collagen fibers
- Fibrotic changes, sclerosis and induration
- Fatty tissue increase

Hematopoiesis

- from **hematopoietic stem cell**
- **HSC**s (***H****ematopoietic* ***S****tem* ***C****ells*)*:* ***pluripotent****, ability of self-renewal (replication)*

  ⇒ *due to asymetric cell division variable progenitor cells arise :*
  - **fenotypically identical cells –** HSCs
  - **fenotypically different cells –** multipotent cells **(progenitors of myeloid cell line or progenitors of lymhoid cell line)**

  - *Regulation of hematopoiesis through specific growth factors*



Hematopoetic stem cells

• in BM (<0,1% of cells)

Multipotent progenitors

Multipotent progenitors

Committed precursors

Late precursors and mature forms

•morphologically differentiated

Kumar et al.: Robbins&Cotran Pathologic Basis of Disease, 8th Edition.

Possible signs of hematologic disorders

- Congestion
- Infarction
- Thrombosis, embolism
- Bleeding, bruising
- Lymphadenopathy
- Splenomegaly
- Fatigue, dyspnoea
- Edema:
  - ⇨ ***lymphedema***
  - ⇨ ***cerebral edema***
  - ⇨ ***inflammatory edema***
  - ⇨ ***pulmonary edema***

Emergency disorder

- Shock: acute circulatory failure causing hypoperfusion of vital organs
- Cardiogenic or hypovolemic
  - ⇨ *Hypotension*
  - ⇨ *Rapid, weak pulse*
  - ⇨ *Pallor*
  - ⇨ *Moist, cooler skin*
  - ⇨ *Bleeding foci possible, if shock due to bacterial toxemia (pinpoint bleeding into the skin)*

Shock

- Ischemic injury of multiple organs
- Serious clinical problem, commonly fatal
- Consequences:
  - ⇨ ***Renal failure***
  - ⇨ ***Acute pancreatitis***
  - ⇨ ***Irreversible neuronal injury, risk of cerebral infarction***
  - ⇨ ***Risk of myocardial infarction***
  - ⇨ ***Lung insufficiency – acute respiratory distress syndrome***

Multiorgan failure (MOF) possible

Hematologic disorders

- Alteration of the oxygen-carrying capacity of the blood
- Changes of the structure, consistency of the blood
- Alteration of the blood flow

- Increased workload of the heart and/or lungs
- Alteration of tissue perfusion
- Increased risk of thrombosis
- Increased risk of bleeding

Modifications of therapy according to the blood + other tests necessary

Disorders of erythrocytes (RBC)

Anaemia

Reduction of the oxygen-carrying capacity of the blood due to decreased quantity and/or quality of RBC

- Posthemorrhagic: trauma, cancer (GIT, urinary, genital, lung), ulcers, varices, coagulopathy…
- Hemolytic (destruction of RBC): mechanical (artificial heart valve), autoimmune, inborn defects (of hemoglobin etc.), infection (malaria), hypersplenism
- Decreased production of RBC: nutritional deficiency; bone marrow failure – due to neoplasia, drugs (antineoplastic), endocrine disorders; chronic diseases – anaemia of inflammation

Implications for the therapist

- Diminished exercise tolerance + easy fatigability
- Combination with other problems common (cardiovascular, renal, …)
- Risk of combination with bleeding disorders - !manual therapy
- Impaired healing of wounds
- Monitoring of vital signs and mental status necessary
- In young athletic clients iron-deficiency anemia possible (females, dietary choices, drugs, etc.)

Disorders of leukocytes

Leukocytosis

↑ number of WBC, usually of specific group

- Acute haemorrhage (after 1-2 hrs)
- Infection (mostly bacterial for neutrophils, viral for lymphocytes)
- Inflammatory reaction in tissue necrosis, trauma
- Immune-mediated disorders (incl. allergic reaction – eosinophils)
- Malignancies, incl. hematologic
- Reaction to stress, incl. exercise

Disorders of leukocytes

Leukopenia

- ↓number of WBC (≤5000/ml)
- Infection (HIV, other viruses – destruction of WBC)
- Alcohol
- Nutritional status
- Drugs (antineoplastic, immunosuppressive, NSAID, antibiotic)
- Malignancies incl. hematologic, carcinomas
- Radiation therapy

Implications for the therapist

Immune deficiency – risk of infection!

Disorders of hemostasis - hypocoagulative

↑ tendency to bleeding, ↓ coagulation – doesn‘t stop normally

- Von Willebrand disease – problems in formation of the primary platelet plug
- Hemophilia – lack of clotting factor for secondary hemostasis; arthropathy, spontaneous bleeding, major bleeding after minor trauma
- Acquired coagulopathy – common due to therapy (aspirin, antithrombotic drugs), liver problems
- Thrombocytopenia / thrombocytopathy – mucosal bleeding common, easy bruising, heavy menstruation bleeding, GIT bleeding
- Vessel wall problems – easy rupture, bruising; inborn, acquired (vitamin C)

Disorders of hemostasis - hypercoagulative

Thrombosis, risk of emboli into other organs

- inborn (coagulative factors mutations – Leiden f.)
- more common acquired – smoking, drugs (incl. contraceptive), ↓ blood flow (bedridden, limb fracture, airplane,...), infections (microangiopathy, thrombosis in COVID-19), immune mediated (vasculitis)
- most commonly combination of several factors (incl. venous sinus thrombosis in predisposed people after antiCOVID vaccination)

Implications for the therapist

- Individual exercise planning according to the client stage

TUMORS of HAEMATOPOETIC and LYMPHATIC TISSUES

- Broad spectrum of entities
- **WHO classification**

  - clinical, morphologic, imunophenotypic and genetic features defining distinct diseases.

Etiopathogenesis of hematooncological diseases

- **???**
- **hereditary syndromes**
  - ***Inherited genetic instability*** *(Bloom´s sy, ataxia teleangiectasia…)*, ***Down´s sy, NF type I…***
- **oncogenic viruses**
  - ***HTLV-1, EBV, HSV-8***
- **chronic stimulation of immune system**
  - ***Helicobacter pylori, gluten-sensitive enteropathy (celiac sprue)***
- **iatrogenicity**
  - ***radiotherapy, chemotherapy***
- **smoking**

Hematooncology

- **Leukemia (hemoblastosis)**
  - ***Diffuse replacement of normal BM by leukemic cells with their subsequent variable accumulation in peripheral blood (=leukemization)***
  - ***Infiltration of peripheral organs (liver, spleen, lymph nodes, meninges, gonads,….), tissue infiltration → organ enlargement without solid foci.***

Hematooncology

- **Lymphoma (hemoblastoma)**
  - ***Neoplastic/lymphoma cells form tumor/neoplastic mass (nodal and/or extranodal)***
  - ***solid tumorous foci, dissemination in form of metastasis. Usually lymphoid origin, rare histiocytic***

! Lymphomas may also present by leukemic infiltrates and leukemias also form solid neoplastic massess

Hematooncological diseases classification

- **Myeloid neoplasms**

- Monoclonal proliferations from stem cells that normally give rise to the formed blood elements
- Replacement of normal bone marrow
- 3 categories
  → acute myelogenous leukemias
  → myeloproliferative disorders
  → myelodysplastic syndromes

- **Lymphoid neoplasms**

→ non-Hodgkin lymphomas
(incl. lymphocytic leukemias and plasma cell dyskrasias)
→ Hodgkin lymphomas

- **Histiocytic neoplasms**

Hematooncology

- Myeloid neoplasms
  - Cells of the myeloid line
    (erythrocytes, granulocytes, monocytes, platelets)
  - Primary involvement of bone marrow
    (secondary spleen, liver and lymph nodes)

Hematooncology

- **General clinical signs in acute leukaemia**

  rapid onset; marrow failure →
- Anaemia (fatigue, dyspnea, palor)
- Neutropenia (bacterial, fungal infection – fever, repeated oral/respiratory inflammation),
- Thrombocytopenia (bleeding, epistaxis, haematomas)

- Weight loss (increased cell turn-over)
- Hepatomegaly, splenomegaly (compression of adjacent organs)

Hematooncology

- **Acute myeloid (myeloblastic) leukaemia**
- primarily in older adults (median age 50), incidence rises with age
- leukemic infiltrates in bone marrow, liver, spleen, lymph nodes
- possible solid tumor manifestation (myeloid sarcoma)
- generally poor prognosis

Hematooncology

- Myelodysplastic syndromes: clonal stem cell disorders, ineffective haematopoesis→ cytopenias; dysplastic maturation. De novo or after radio/chemotherapy. Progressive marrow failure. May → AML.

- Myelodysplastic/myeloproliferative diseases overlapping features, variably effective haematopoesis, dysplasia

Hematooncology

- **Chronic myeloproliferative diseases**

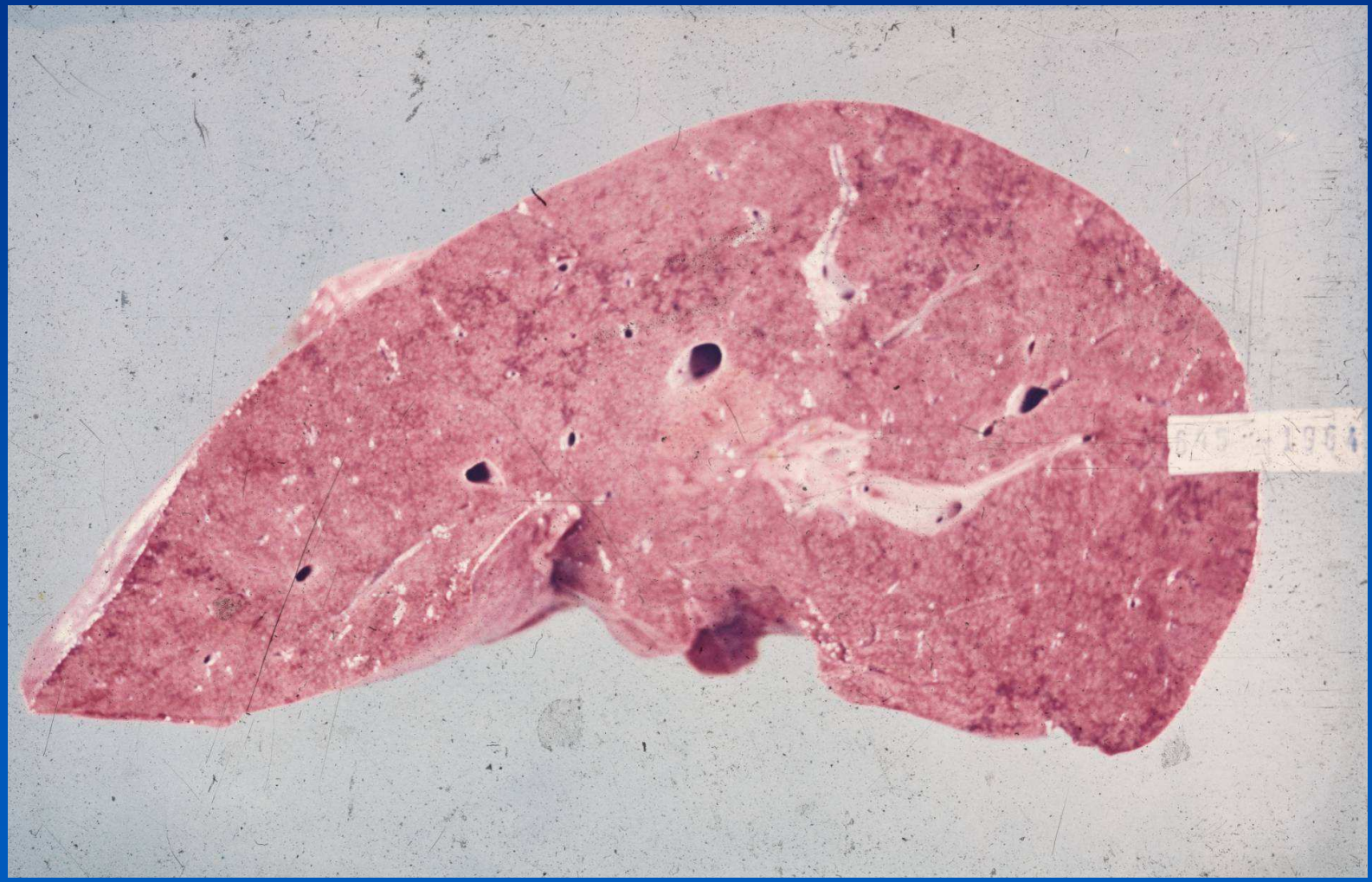
  clonal stem cell disorders – hypercellular marrow with maturation, no dysplasia, effective haematopoesis → elevated blood levels of one or more cell lines, usually hepatosplenomegaly, lymphadenopathy

- chronic myeloid (myelogenous) leukaemia
- essential thrombocythaemia
- polycythaemia vera (rubra) (RBC)
- chronic idiopatic myelofibrosis

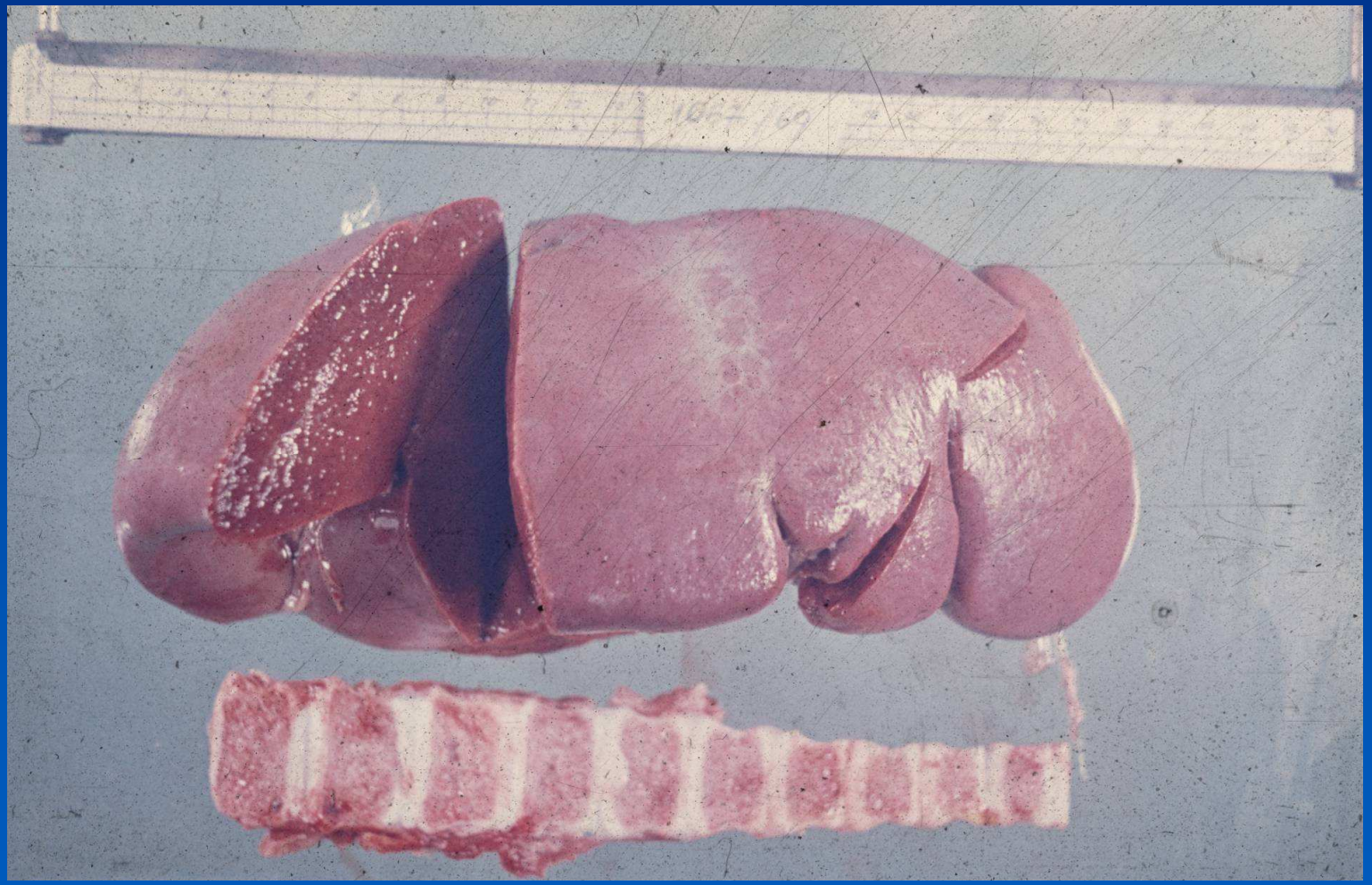
Chronic myelogenous leukemia

- adults, peak incidence in 4th and 5th decade
- elevated leukocyte count
- 15-20% all leukaemias
- huge spleen (~5-7 kg), liver enlargement
- clinical picture: anemia, hypermetabolism due to increased cell turnover: fatigability, weakness, weight loss, anorexia…..slow progression-accelerated phase - blastic crisis (AML-like)
- poor prognosis;
- therapy: transplantation of bone marrow, specific drug available

CML in the liver



CML – splenomegaly, spine infitrates



Implications for the therapist

Leukemia

Problems due to neoplasia + therapy

Immune deficiency – risk of infection!

Thrombocytopenia – bleeding

Anaemia

Other possible side effects of therapy (mood changes; muscle weakness in corticosteroid therapy)

Joint problems (arthralgia, arthritis)

Exercise necessary for improvement in health-related quality of life, mental health, reduced symptoms

Hematooncology

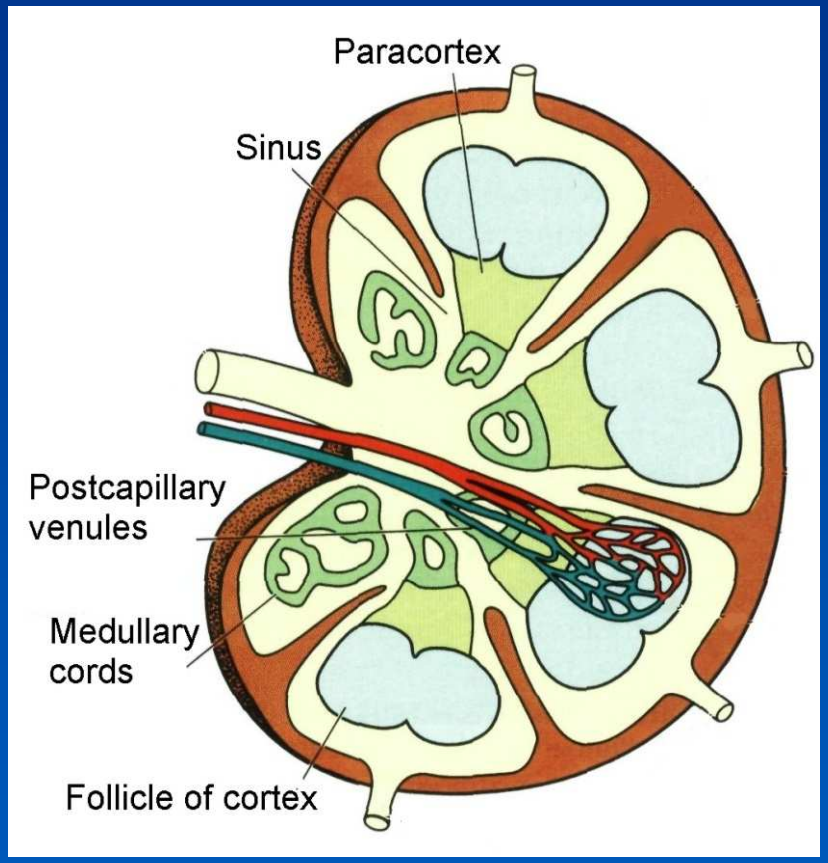
- ***Histiocytic and dendritic cell neoplasms***
- from mononuclear phagocytes – common bone marrow precursor
- follicular dendritic cells non-myeloid, from mesenchymal stem cell
- true histiocytic neoplasm uncommon (Langerhans cell histiocytosis)

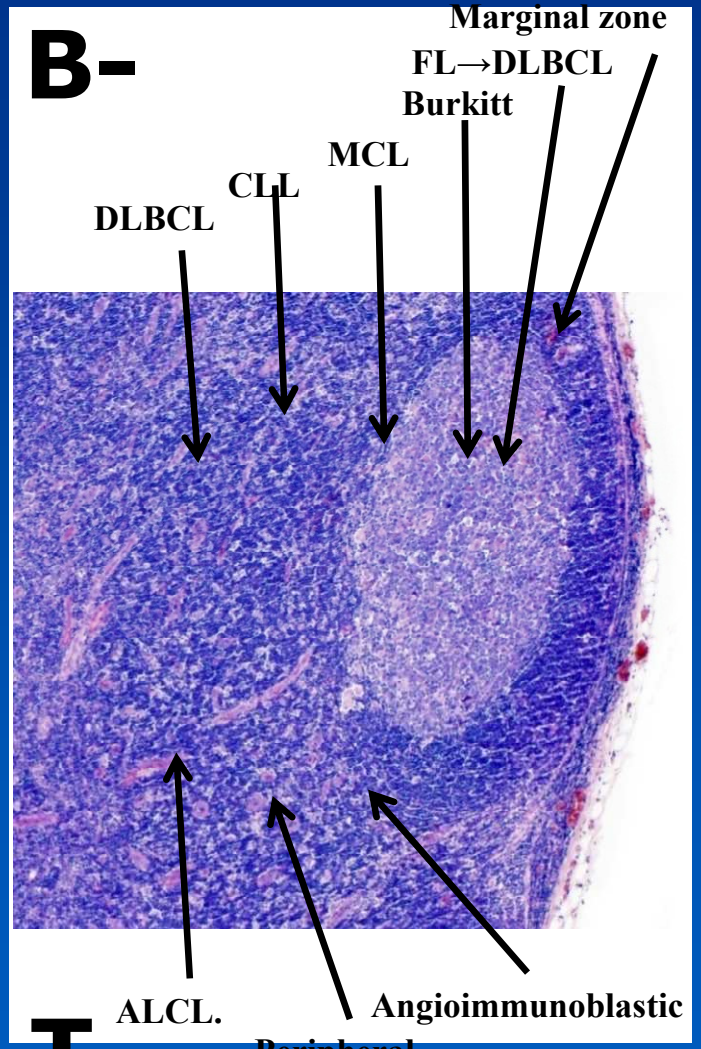
Non-Hodgkin lymphomas/ WHO classification

B-Cell Neoplasms	T-Cell Neoplasms
Precursor B-Cell Neoplasms - precursor B-cell leukemia/lymphoma (B-cell acute lymphoblastic leukemia)	**Precursor T-Cell Neoplasms** - precursor T-cell leukemia/lymphoma (T-cell acute lymphoblastic leukemia)
Peripheral B-Cell Neoplasms	**Peripheral T-/NK-Cell Neoplasms**

Nodal lymphomas

different cell type/stage of immunologic maturation → different lymphoma type





B-cell acute lymphoblastic leukemia/lymphoma (B-ALL)

- **most frequent malignancy in children (peak at age 4)**
- Infiltration of **bone marrow**, **lymph nodes, liver, spleen…**
- **Highly aggressive**, but chemosensitive

  (⇒ children 2 to 10 years – best prognosis)

  - ⇨ **chemo-, radiotherapy generally carcinogenic in itself**
  - ⇨ **! increased risk of secondary malignancy (other type of leukemia/lymphoma, lung cancer, etc.) after several years - decades**

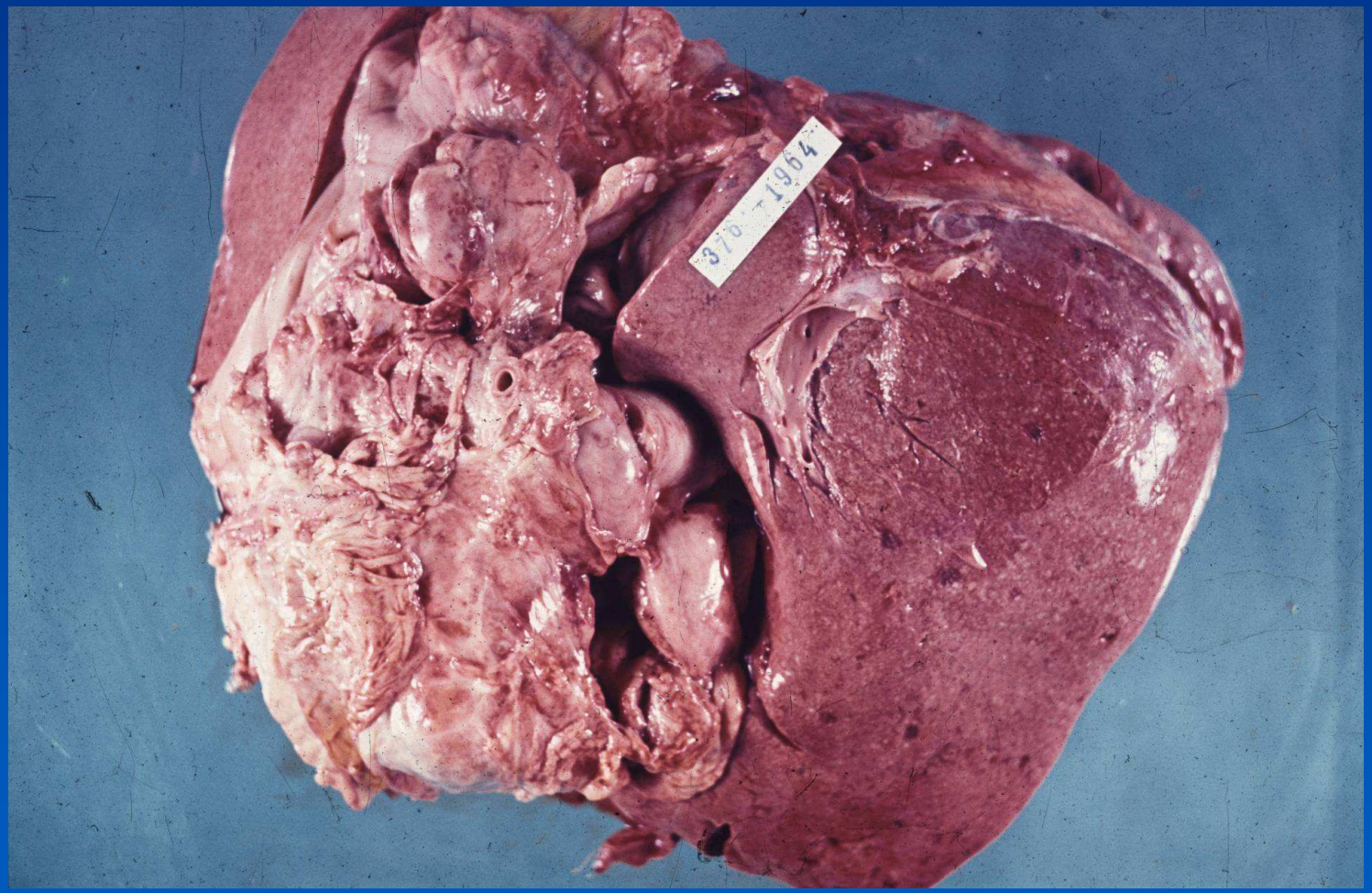
Peripheral B-cell lymphomas (selected)

- Chronic lymphocytic leukemia / small cell lymphoma
- Follicular lymphoma
- MALT lymphoma
- Plasma cell neoplasms
- Diffuse large B-cell lymphoma

Chronic lymphocytic leukemia (CLL)

- Mature B-cell neoplasm, same cellular morphology and genotype in small lymphocytic lymphoma (in CLL lymphocytosis in peripheral blood)
- Most common chronic leukaemia, common protracted course (~10 yrs), in >50 yrs old. Possible transformation to high grade ML
- Hypercellular bone marrow, generalised lymphadenopathy, hepatosplenomegaly

CLL- hepatic and nodal infiltrates



Follicular lymphoma

- Mature B-cell non-Hodgkin lymphoma;
- common type (40%)

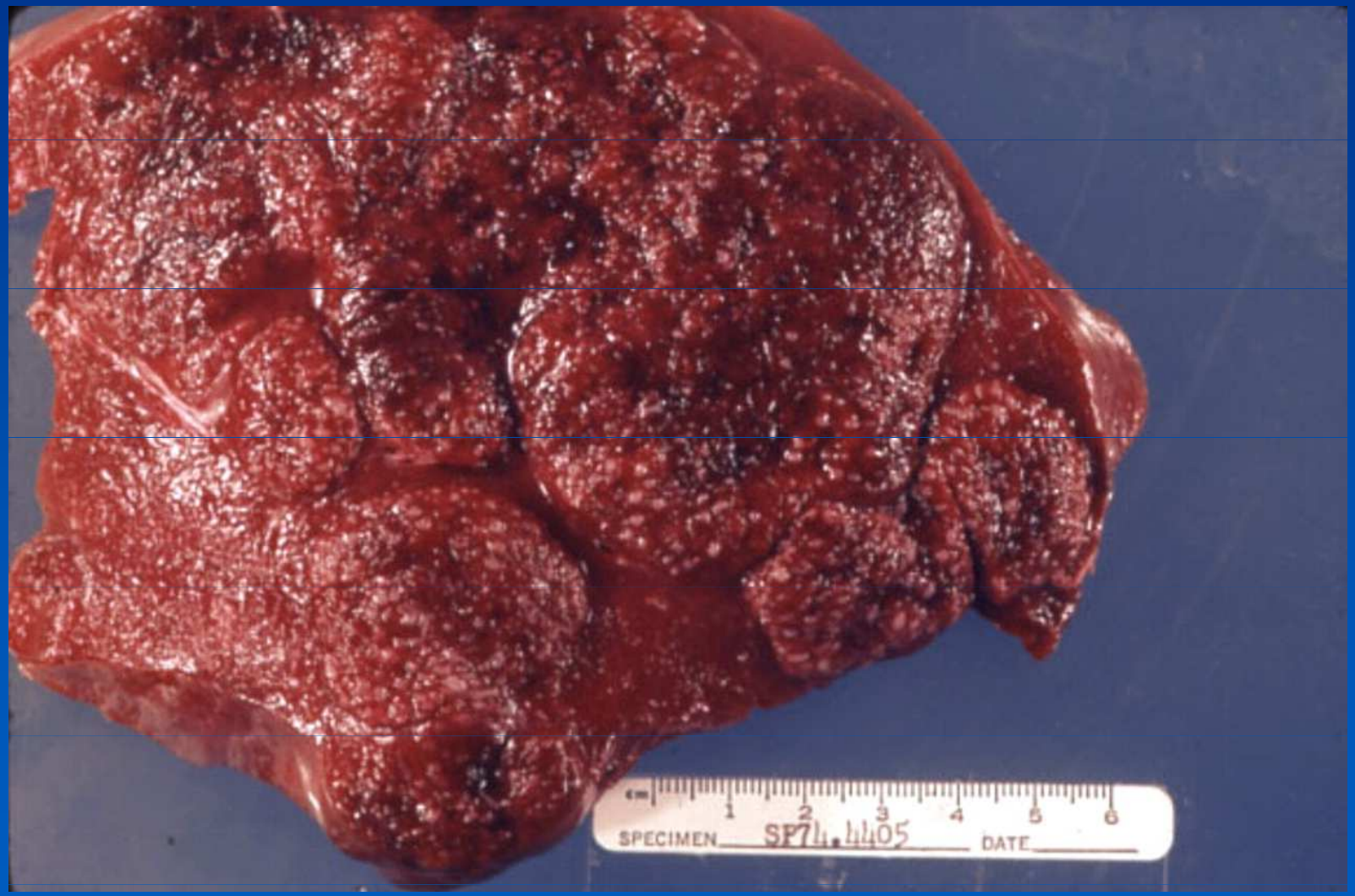
- Neoplasia of follicle centre B-cells In LN - predominantly follicular pattern, sm. diffuse. May be in spleen, Waldeyer‘s ring,…

Follicular lymphoma

- Clinically: nontender generalised lymphadenopathy, commonly widespread disease at diagnosis (incl. liver, bone marrow), middle → late age adults.

- Low grade – longer course (5-10 years), usually incurable
- High grade – aggressive, potential for cure (remission), but possible transformation into diffuse large B-cell lymphoma

Spleen, follicular lymphoma



Extranodal marginal zone lymphoma (MALT lymphoma)

- **derived from mucosa-associated lymphatic tissue** (salivary glands, thyroid, stomach, intestine, …)
- **chronic stimulation of immune system**
  - e.g.: chronic gastritis associated with Helicobacter pylori (HP) infection
  - some autoimmune inflammations (thyroiditis, salivary glands, ...)
- low grade/aggressive lymphoma

Diffuse large B-cell lymphoma (DLBCL)

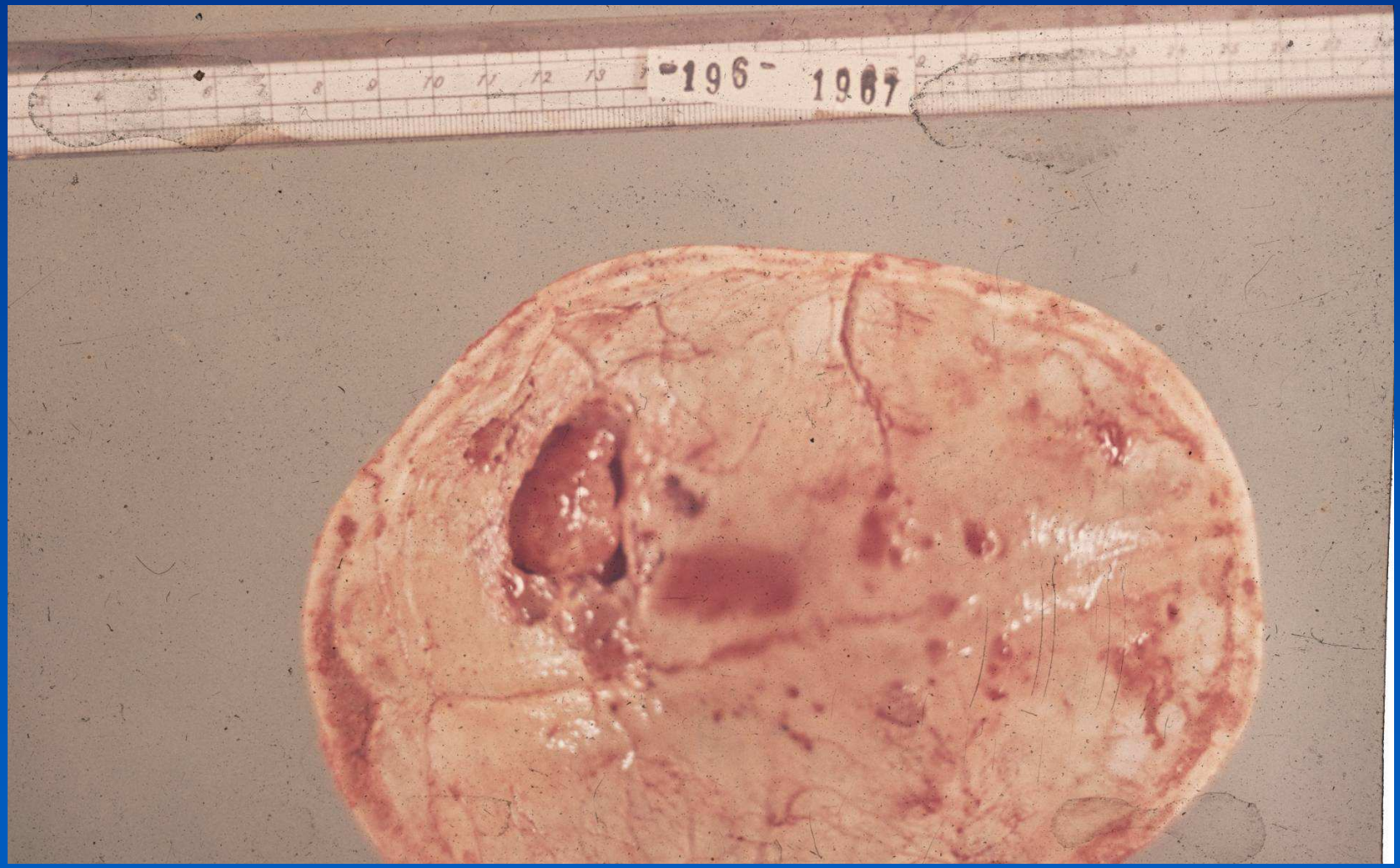
- **older adults**, most frequent lymphoma
- **highly aggressive**
- *de novo* or high grade transformation of low grade lymphoma (CLL, FL, MALToma…)
- nodal or **extranodal** (tonsil, adenoid lymphatic tissue, GIT, skin, bones, thyroid, …)

Plasma cell neoplasms

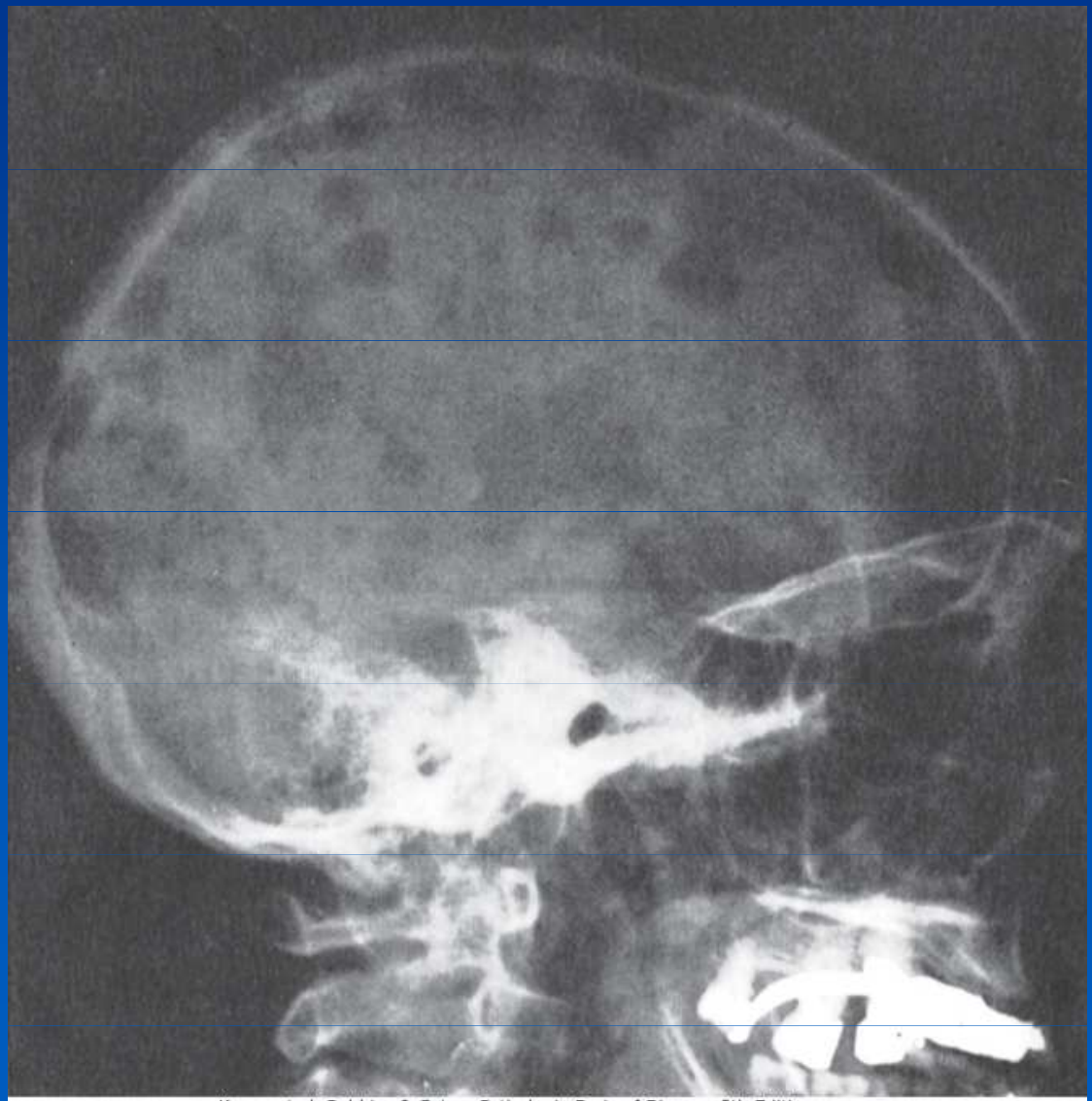
- Included in mature B cell neoplasms, clonal prolif. of immunoglobulin secreting end-stage B cell. Most common plasma cell (multiple) **myeloma**

- Bone marrow-based, multifocal, in older adults, destructive skeletal (osteolytic) lesion, common in foci of active haematopoesis (vertebrae, ribs, skull, …)
- Pathological fractures, hypercalcaemia, anaemia
- Renal complications

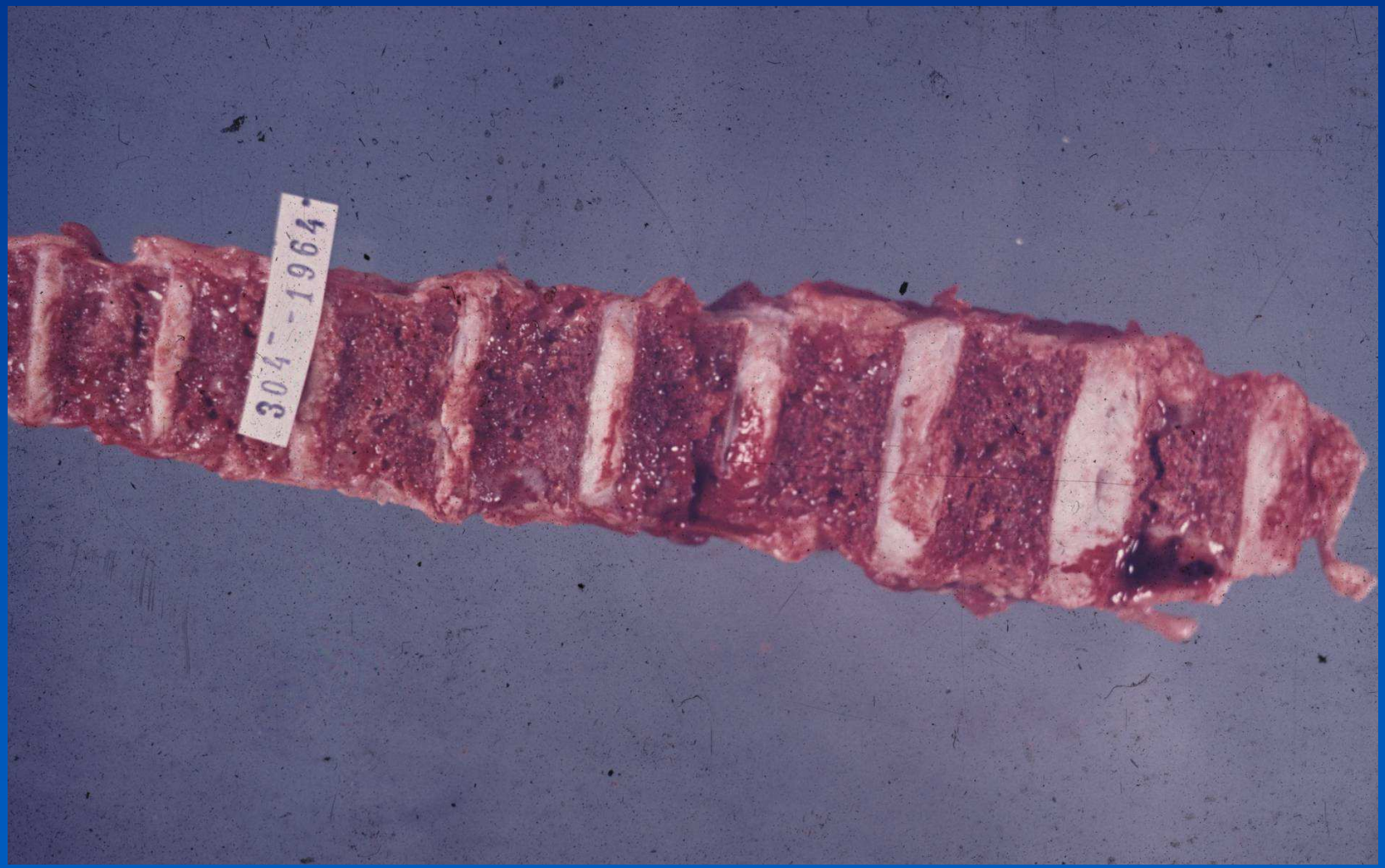
Multiple myeloma in skull



Multiple myeloma in skull – X-ray



Multiple myeloma in spine



T-cell lymphomas
(selected entities)

- Generally uncommon
- Possible origin in the skin
  - *unusual chronic relapsing „dermatitis“*

- **Mycosis fungoides/Sézary syndrome**
  - ***MF: Primary skin lymphoma***
  - ***SS: leukemized, erythroderma***

- **Anaplastic large cell lymphoma**

Hodgkin lymphoma

- One of most common malignancies in young adults
- Non-tender lymhadenopathy (origin in LN), commonly cervical or axillary; usually localised at presentation (1-2 LN groups); in 30% systemic signs (high fever, night sweats, weight loss)
- Continual spread from one group of LN to the next one, diaphragm important barrier for staging, late extralymphatic spread

Differences between HL and NHL

Hodgkin lymphoma	Non-Hodgkin Lymphoma
Usually localized to a single axial group of LN (cervical, mediastinal, para-aortic)	Involvement of multiple peripheral LN
Contiguous spreading	Non-contiguous spreading
Mesenteric LN and Waldeyer ring rarely involved	…… commonly involved
Extranodal rare	Extranodal common
Diagnostic (neoplastic) cells admixed with reactive non-malignant inflammatory cells	Neoplastic/lymphoma cells dominate
B-cell origin	B- or T-cell origin

Hodgkin lymphoma

2 distinctive disease entities:

- **Nodular lymphocyte predominant** HL: 80% males, 30-50 yrs, large neoplastic „popcorn, L&H“B cells among non-neoplastic ly

- Mostly localised at presentation, late relapse or transformation into DLBCL possible

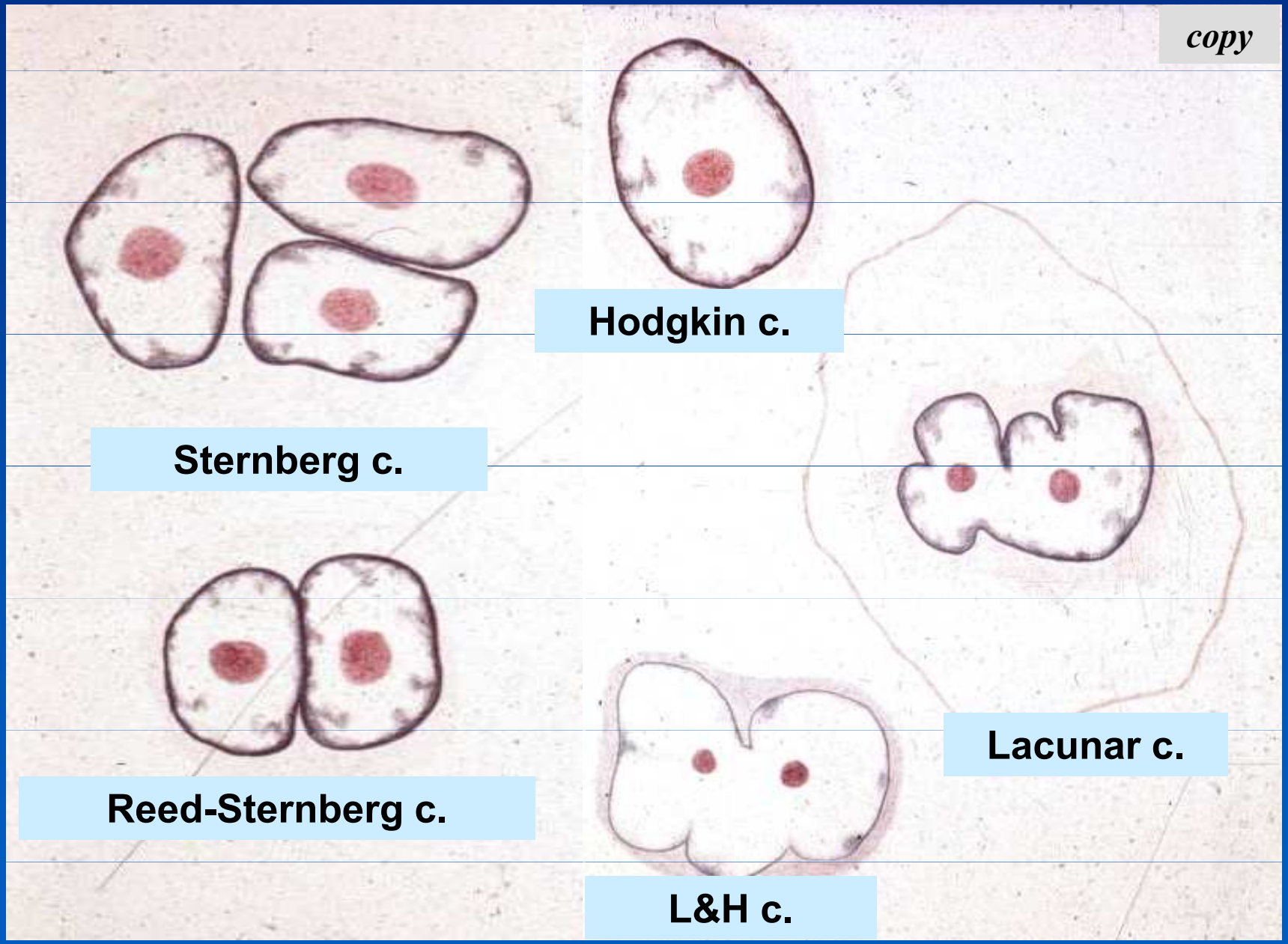
- Stage I+II – 10 year survival in 80%

Hodgkin lymphoma

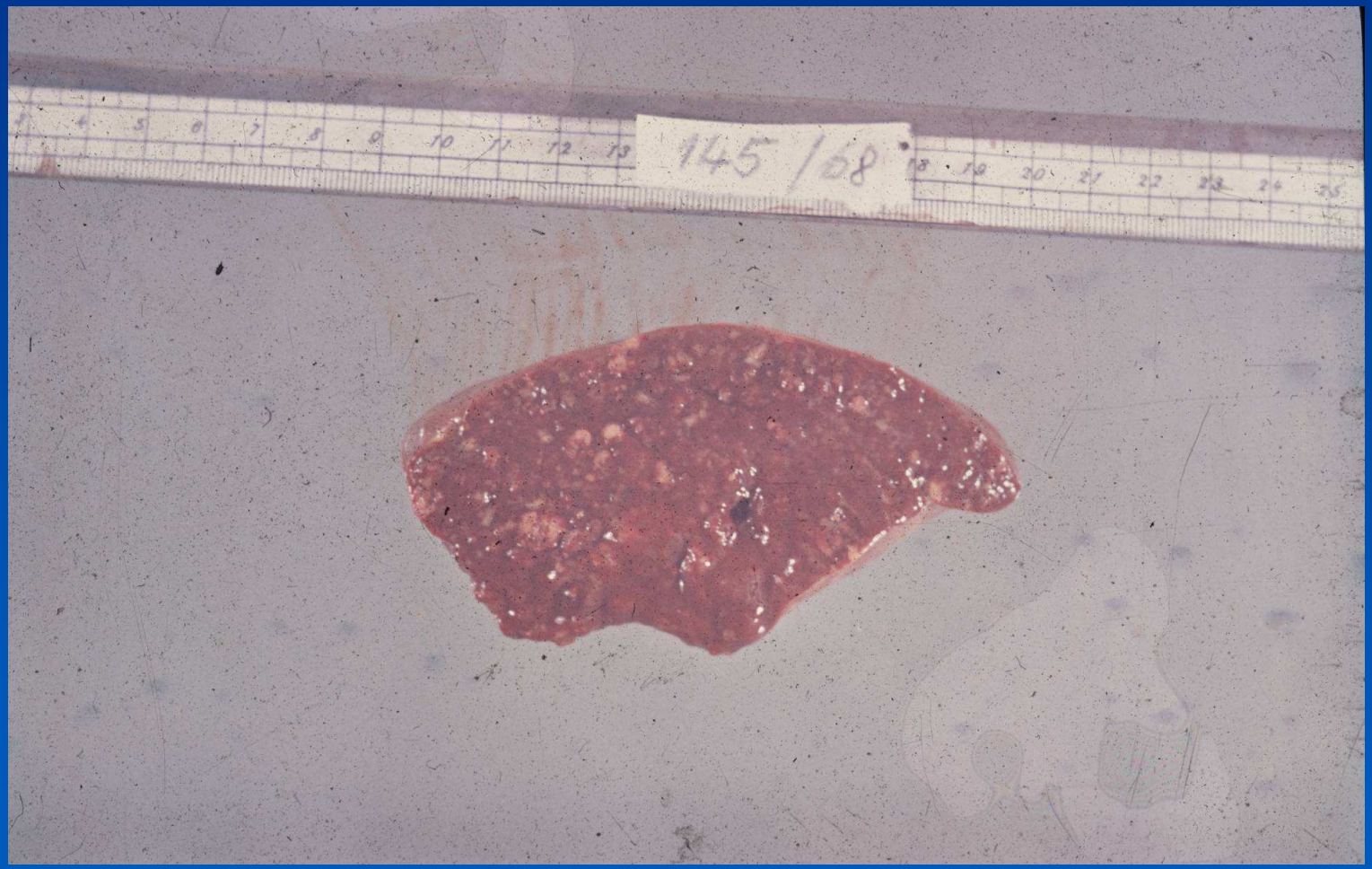
- **classical Hodgkin lymphoma**
  95% of HL, 1. peak 15-35 yrs, 2. elderly; risk factor EBV; 75% in cervical LN

- 4. subtypes
- variable types/numbers of neoplastic Reed-Sternberg cells in the infiltrate
- RT, CHT → excellent prognosis, but risk of secondary malignancies (myelodysplastic sy, acute myeloblastic leukemia, lung ca)

Diagnostic cells of HL



Hodgkin lymphoma – splenic infiltrates



Implications for the therapist

- Lymphadenopathy (diagnosis)
- Infection control
- Mobility + gait training
- Aerobic conditioning
- Respiratory rehabilitation
- Lymphedema management
- Special management in multiple myeloma: muscle wasting, risk of pathological fractures