# Disorders of the lymphoid tissue

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# Overview

- General approach to generalized lymphadenopathy
- Causes
- Investigations
- Lymphomas
  - Diagnosis
  - Staging
  - Three important types of lymphoma

# What is lymphadenopathy?

- Lymph nodes abnormal in
  - size
  - consistency
  - number

# Lymphadenopathy

- Is it serious?
- Most often not
- History and examination is all whats necessary: in most

- Do  not over investigate

# Normal people

- Over 600 nodes
- Submandibular
- axillary
- inguinal Palpable in normal people

# PHYSIOLOGY AND ANATOMY

Lymph nodes are populated predominantly by
macrophages,
dendritic cells,
B lymphocytes, and
T lymphocytes.

- B lymphocytes are located primarily in the follicles and perifollicular areas,

- T lymphocytes are found primarily in the interfollicular or paracortical areas of the lymph node.

# Palpable Lymph nodes

In young children palpable lymphadenopathy is the rule.

In fact, the absence of palpable lymphadenopathy would be considered abnormal

In adults, lymph nodes larger than 1 to 2 cm in diameter are generally considered abnormal.

However, lymph nodes 1 to 2 cm in diameter in the groin are sufficiently frequent to often be considered "normal.“

# Generalised adenopathy has been defined as

- involvement of three or more noncontiguous lymph node areas.
- generalized lymphadenopathy is frequently associated with nonmalignant disorders

# Lymphadenopathy

Generalized immune proliferation and lymphadenopathy can occur with a

systemic disorder of the immune system,

disseminated infection, or

disseminated neoplasia.

Malignancies of the immune system might be manifested as:

localized or

disseminated lymphadenopathy.

# Causes of Lymphadenopathy

**Infection**

**Bacterial (e.g., all pyogenic bacteria, cat-scratch disease, syphilis, tularemia)**

**Mycobacterial (e.g., tuberculosis, leprosy)**

**Fungal (e.g., histoplasmosis, coccidioidomycosis)**

**Chlamydial (e.g., lymphogranuloma venereum)**

**Parasitic (e.g., toxoplasmosis, trypanosomiasis, filariasis)**

**Viral (e.g., Epstein-Barr virus, cytomegalovirus, rubella, hepatitis, HIV)**

**Benign disorders of the immune system (e.g., rheumatoid arthritis, systemic**

# Causes of Lymphadenopathy

- SLE
- Drug reactions such as to phenytoin,
- Histiocytosis,
- Kawasaki syndrome,
- Malignant disorders of the immune system (e.g., chronic and acute myeloid and lymphoid leukemia, non-Hodgkin's lymphoma, Hodgkin's disease, T-cell lymphoma
- Waldenström's macroglobulinemia, multiple myeloma
- Other malignancies
- Storage diseases (e.g., Gaucher's disease
- Endocrinopathies (e.g., hyperthyroidism, adrenal insufficiency, thyroiditis)
- Miscellaneous (e.g., sarcoidosis, amyloidosis, dermatopathic lymphadenitis)

# .MOST FREQUENT CAUSES OF LYMPHADENOPATHY IN ADULTS

**Unexplained**

**Infection**

**In drainage area of infection (e.g., cervical adenopathy with pharyngitis)**

- **Tuberculosis**
- **Disseminated (e.g., mononucleosis, HIV infection)**

**Immune disorders (e.g., rheumatoid arthritis)**

**Neoplasms**

- **Immune system malignancies (e.g., leukemia and lymphomas)**
- **Metastatic carcinoma or sarcoma**

# Clinical Evaluation

- a careful history
- a thorough physical examination
- laboratory tests
- imaging studies to determine the extent and character of the
- lymphadenopathy
- age of the patient
- The occurrence of fever, sweats, or weight loss
- of a site of infection, a particular medication, a travel history, or a previous malignancy.

# Physical examination

- localized or generalized
- size of nodes
- Texture
- presence or absence of nodal tenderness
- signs of inflammation over the node
- skin lesions
- splenomegaly.

# Investigations

- Basic Investigations
- Imaging
  - Chest radiography
  - Lymphangiography
  - Ultrasonography
  - Computed tomography
  - Magnetic resonance imaging
  - Positron emission tomography
- Sampling
  - Needle aspiration
  - Cutting needle biopsy Excisional biopsy

# Lymphadenopathy

lymph nodes that are ***tender*** are more likely to be due to an infectious process,

whereas ***painless*** adenopathy raises the concern of malignancy.

***Consistency***

lymph nodes containing metastatic carcinoma are rock hard,

lymph nodes containing lymphoma are firm and rubbery,

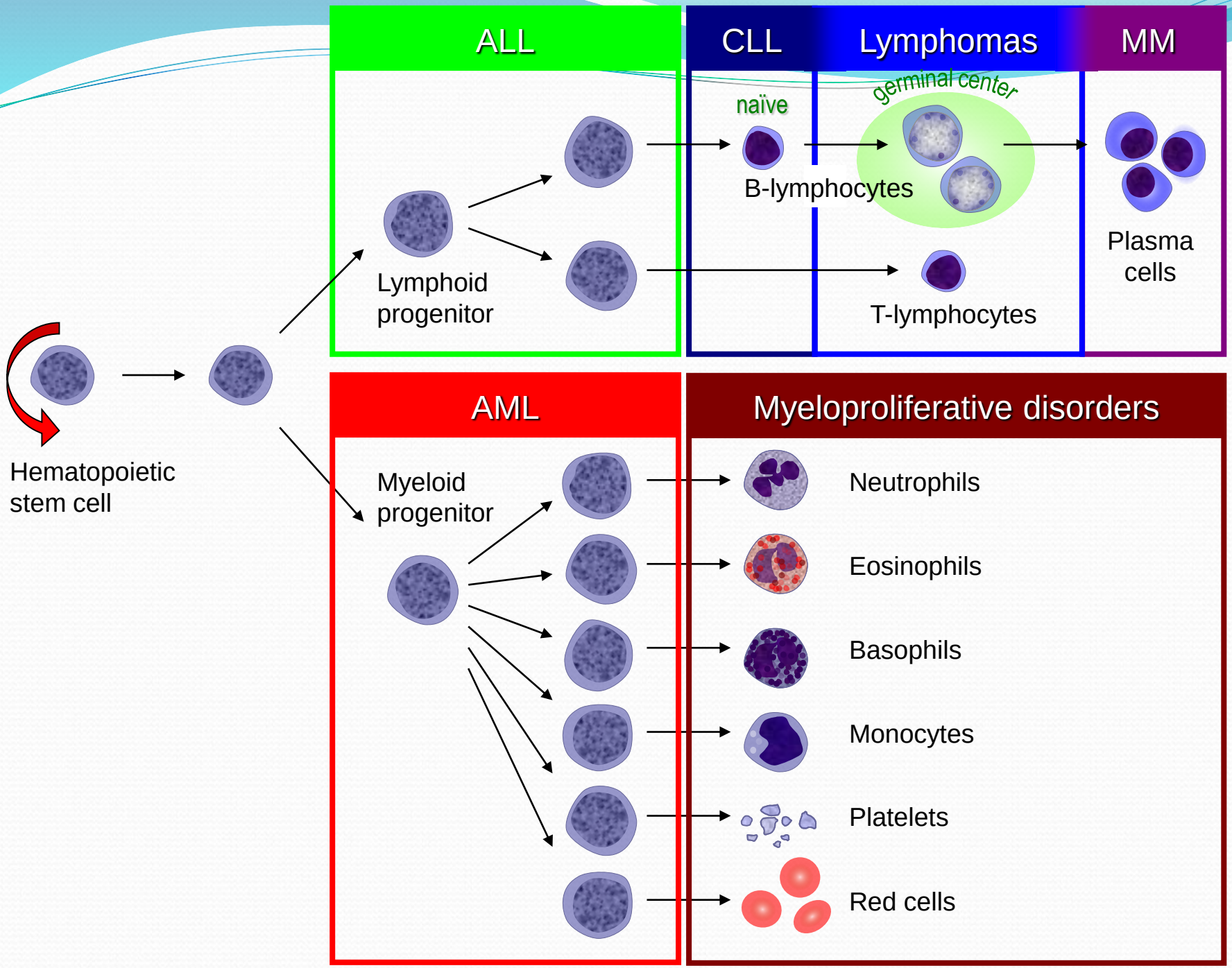
lymph nodes enlarged in response to an infectious process are soft.

The ***larger*** the lymph node, the more likely a serious underlying cause exists

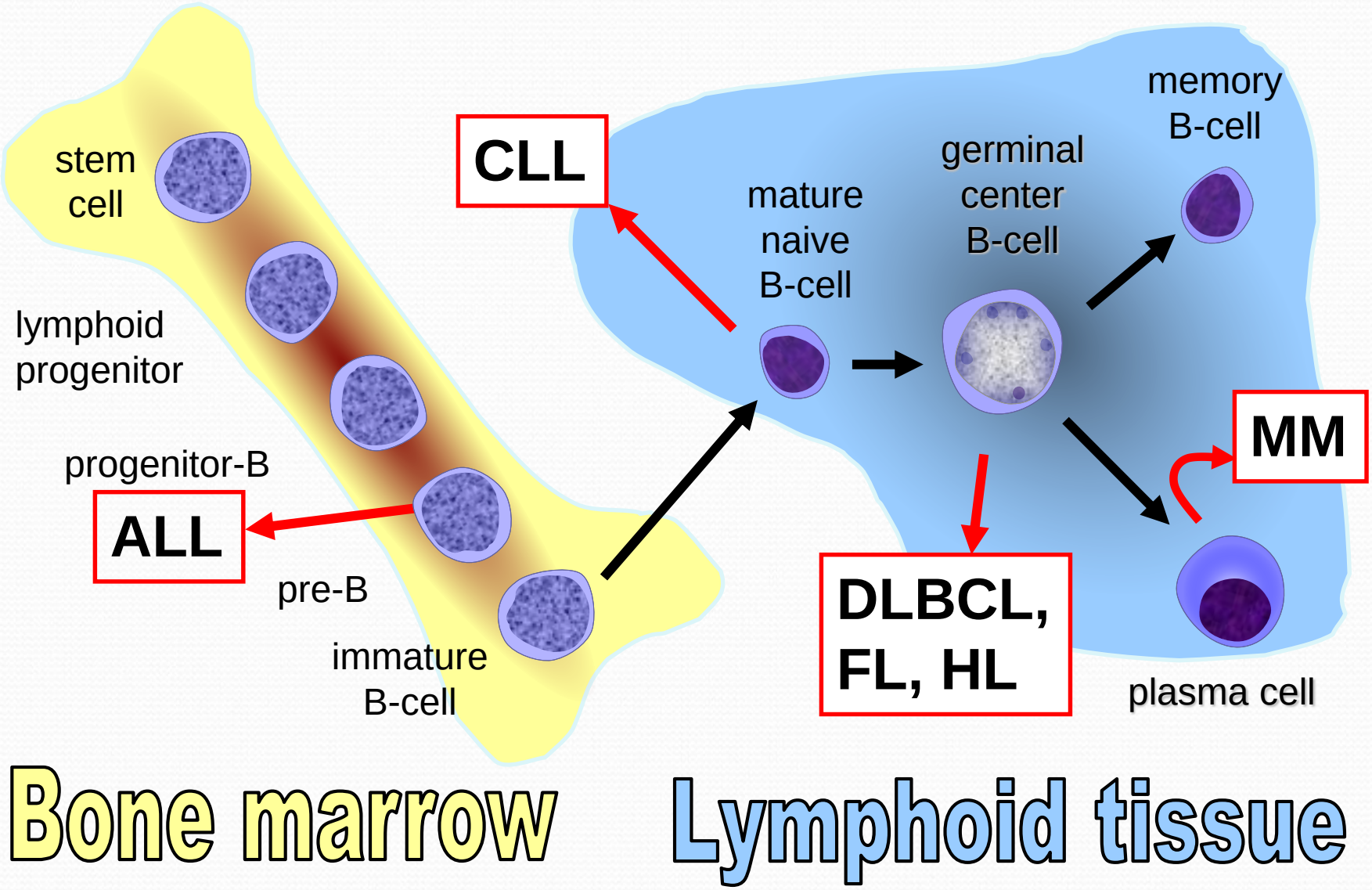
# Lymphoma

# Lymphoma

- neoplasms of lymphoid origin, typically causing lymphadenopathy
- leukemia vs lymphoma
- lymphomas as clonal expansions of cells at certain developmental stages


ALL
CLL
Lymphomas
MM
naïve
germinal center
B-lymphocytes
Plasma cells
Lymphoid progenitor
T-lymphocytes
Hematopoietic stem cell
AML
Myeloproliferative disorders
Myeloid progenitor
Neutrophils
Eosinophils
Basophils
Monocytes
Platelets
Red cells

# B-cell development



# Lymphoma classification (2001 WHO)

- B-cell neoplasms
  - precursor
  - mature
- T-cell & NK-cell neoplasms
  - precursor
  - mature
- Hodgkin lymphoma

Non-Hodgkin Lymphomas

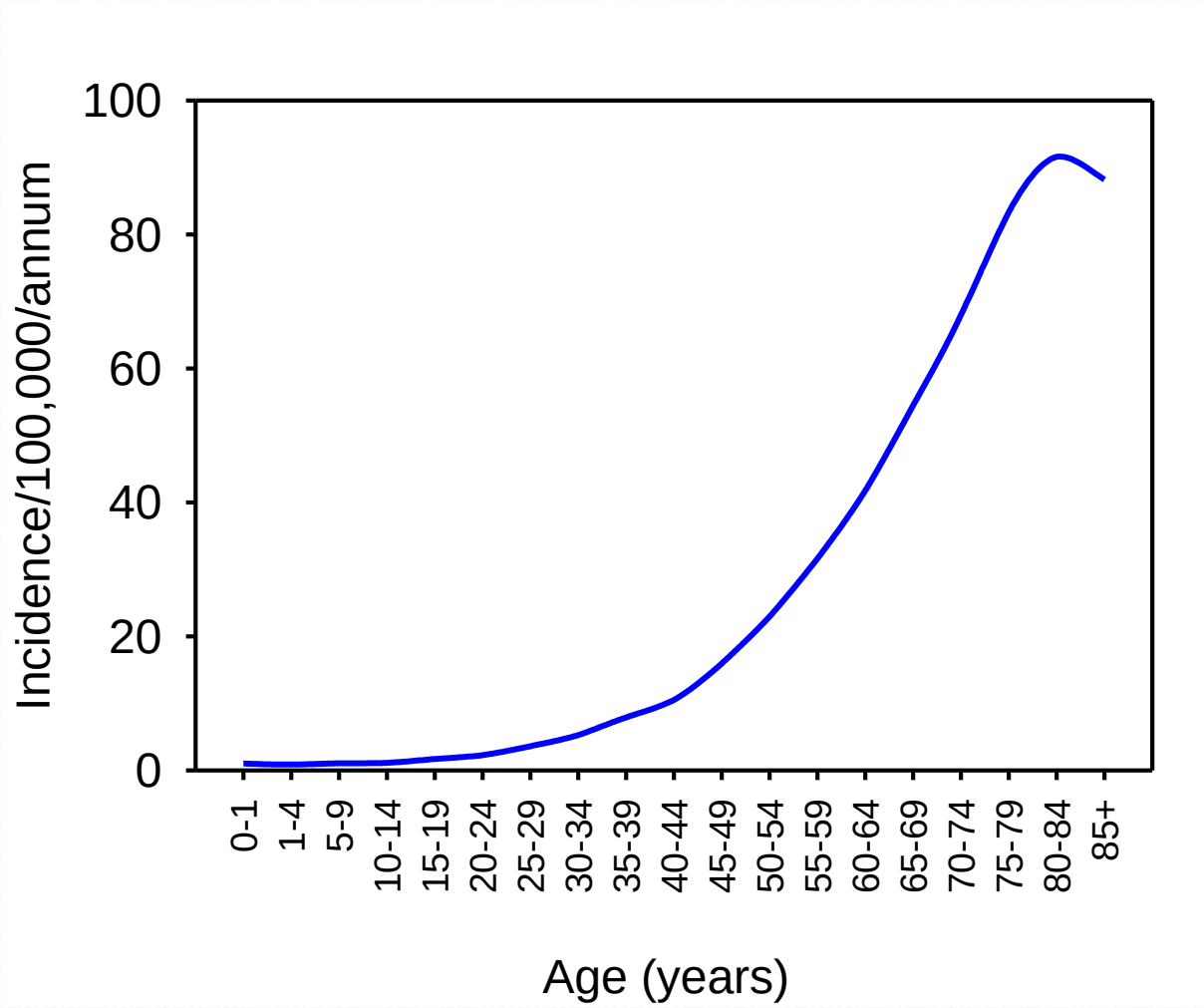
# Mechanisms of lymphomagenesis

- Genetic alterations
- Infection
- Antigen stimulation
- Immunosuppression

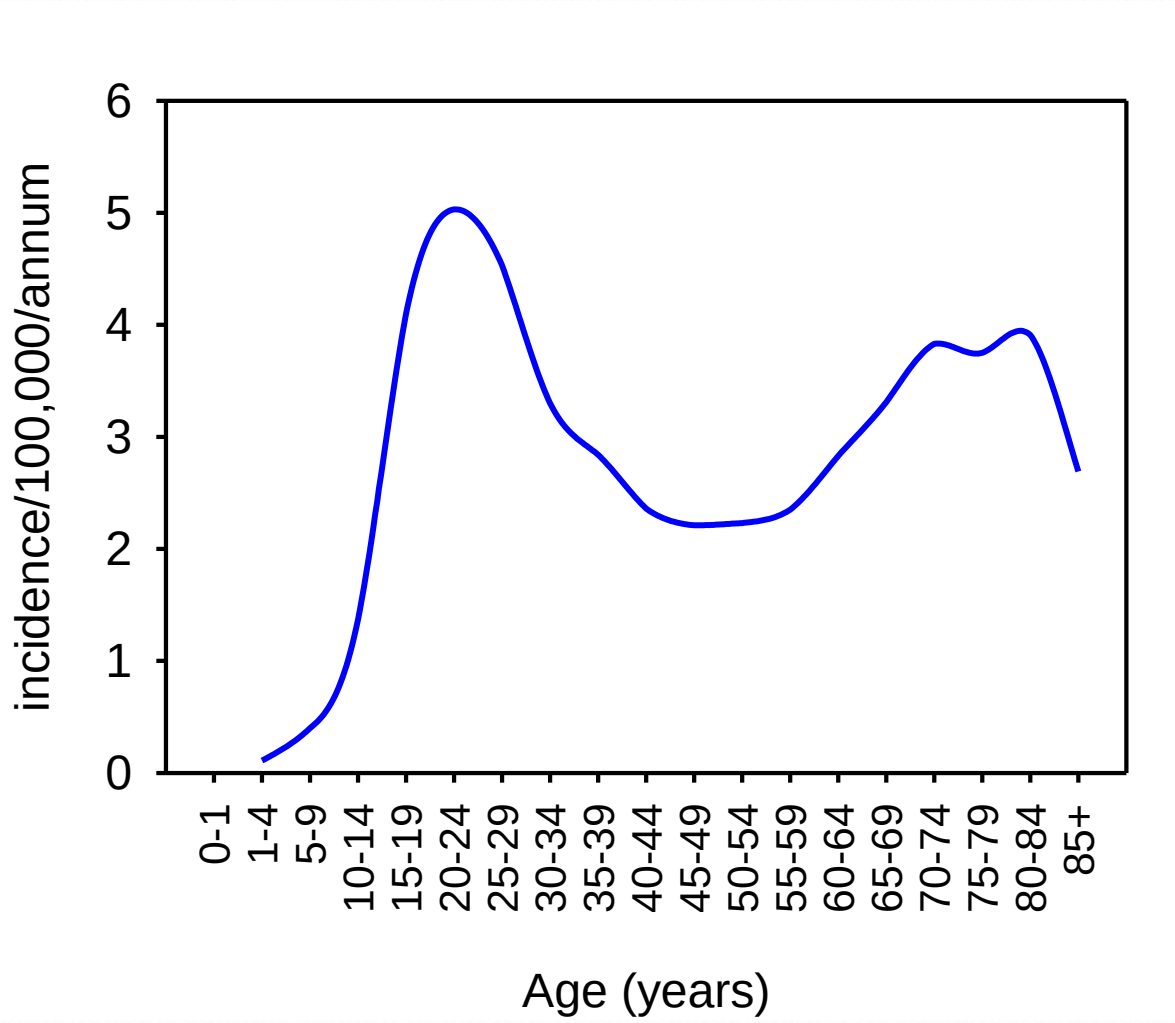
# Epidemiology of lymphomas

- 5th most frequently diagnosed cancer in both sexes
- males > females
- incidence
  - NHL increasing
  - Hodgkin lymphoma stable

# Age distribution of NHL



# Age distribution of HL



# Risk factors for NHL

- immunosuppression or immunodeficiency
- connective tissue disease
- family history of lymphoma
- infectious agents
- ionizing radiation

# Clinical manifestations

- Variable
  - severity: asymptomatic to extremely ill
  - time course: evolution over weeks, months, or years
- Systemic manifestations
  - fever, night sweats, weight loss, anorexia, pruritis
- Local manifestations
  - lymphadenopathy, splenomegaly most common
  - any tissue potentially can be infiltrated

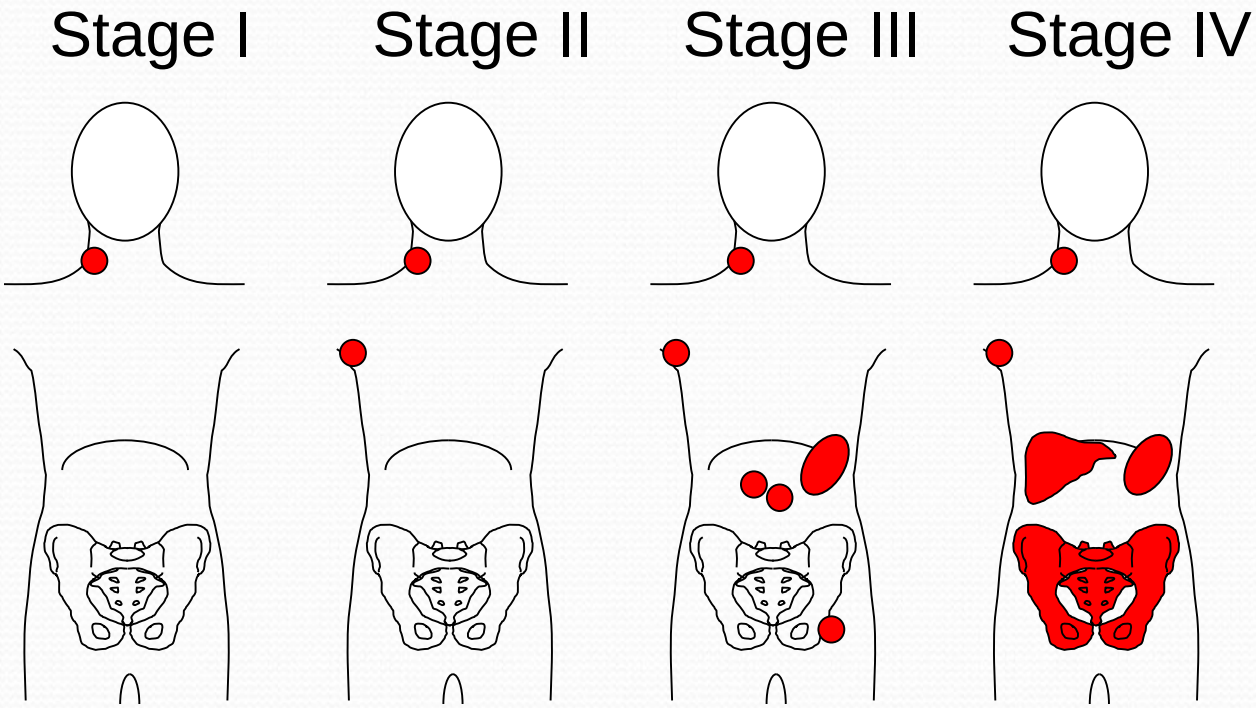
# Other complications of lymphoma

- bone marrow failure (infiltration)
- CNS infiltration
- immune hemolysis or thrombocytopenia
- compression of structures (eg spinal cord, ureters)
- pleural/pericardial effusions, ascites

# Diagnosis requires an adequate biopsy

- Diagnosis should be biopsy-proven before treatment is initiated
- Need enough tissue to assess cells and architecture
  - open bx vs core needle bx vs FNA

# Staging of lymphoma




A: absence of B symptoms
B: fever, night sweats, weight loss

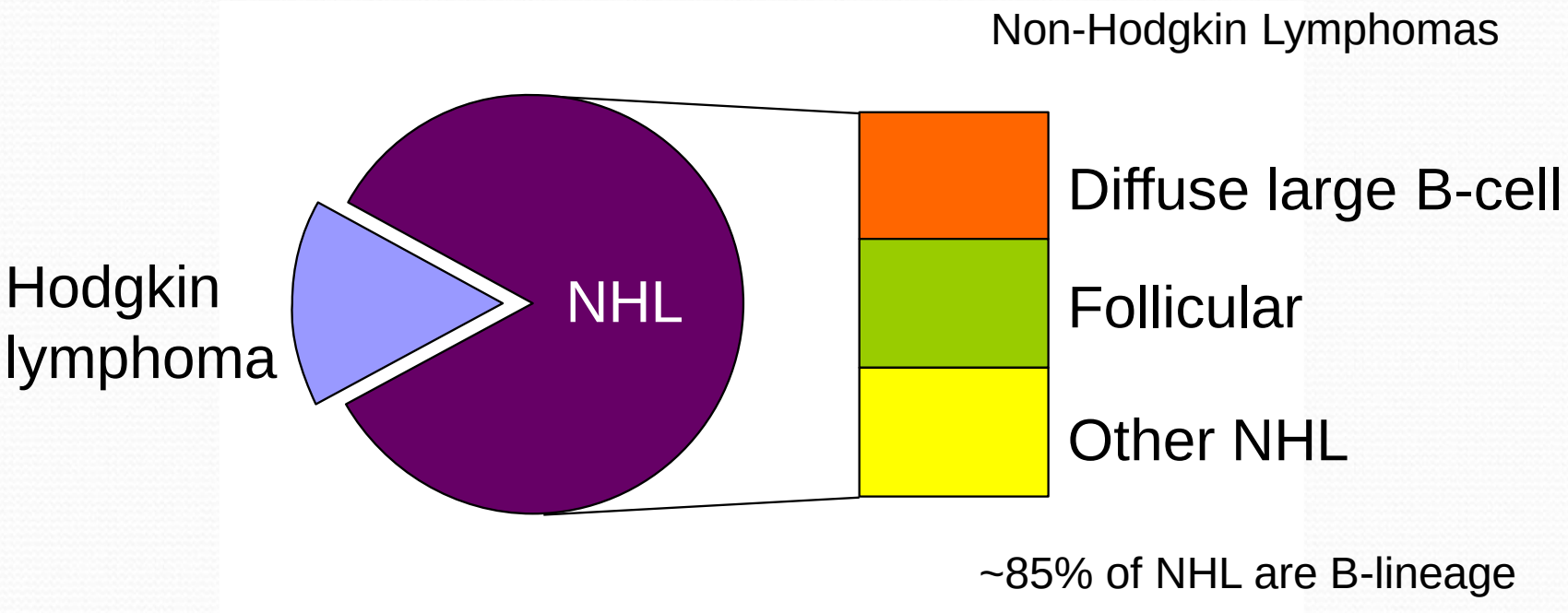
| TABLE 179–4. ANN ARBOR STAGING SYSTEM | |
|---|---|
| **Stage I** | **Involvement of a single lymph node region (I) or a single extralymphatic organ or site (IE)** |
| **Stage II** | **Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site (IIE)** |
| **Stage III** | **Involvement of lymph node regions on both sides of the diaphragm (III) or localized involvement of an extralymphatic organ or site (IIIE), the spleen (IIIS), or both (IIISE)** |
| **Stage IV** | **Diffuse or disseminated involvement of one or more extralymphatic organs with or without associated lymph node involvement** |

**Identification of the presence or absence of symptoms should be noted with each stage designation. A = asymptomatic; B = fever, sweats, or weight loss greater than 10% of body weight.**

# Three common lymphomas

- Follicular lymphoma
- Diffuse large B-cell lymphoma
- Hodgkin lymphoma

# Relative frequencies of different lymphomas



# Follicular lymphoma

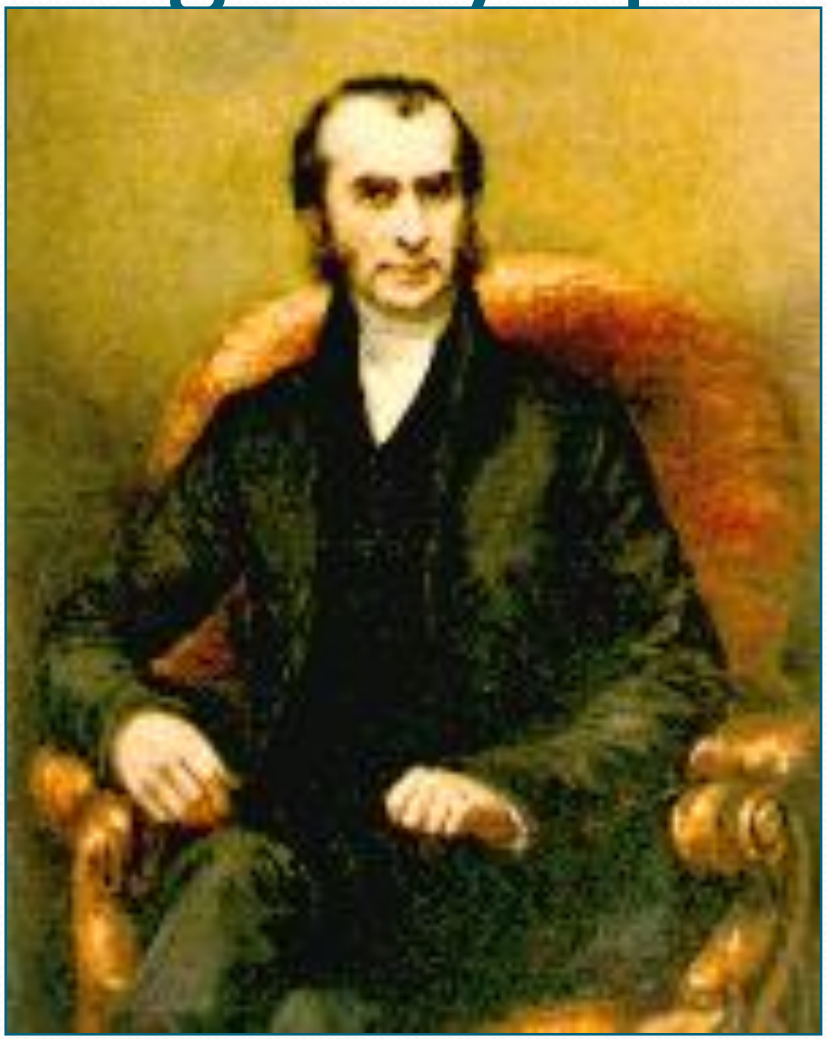
- most common type of “indolent” lymphoma
- usually widespread at presentation
- often asymptomatic
- not curable (some exceptions)
- associated with BCL-2 gene rearrangement [t(14;18)]
- cell of origin: germinal center B-cell

- defer treatment if asymptomatic (“watch-and-wait”)
- several chemotherapy options if symptomatic
- median survival: years
- despite “indolent” label, morbidity and mortality can be considerable
- transformation to aggressive lymphoma can occur

# Diffuse large B-cell lymphoma

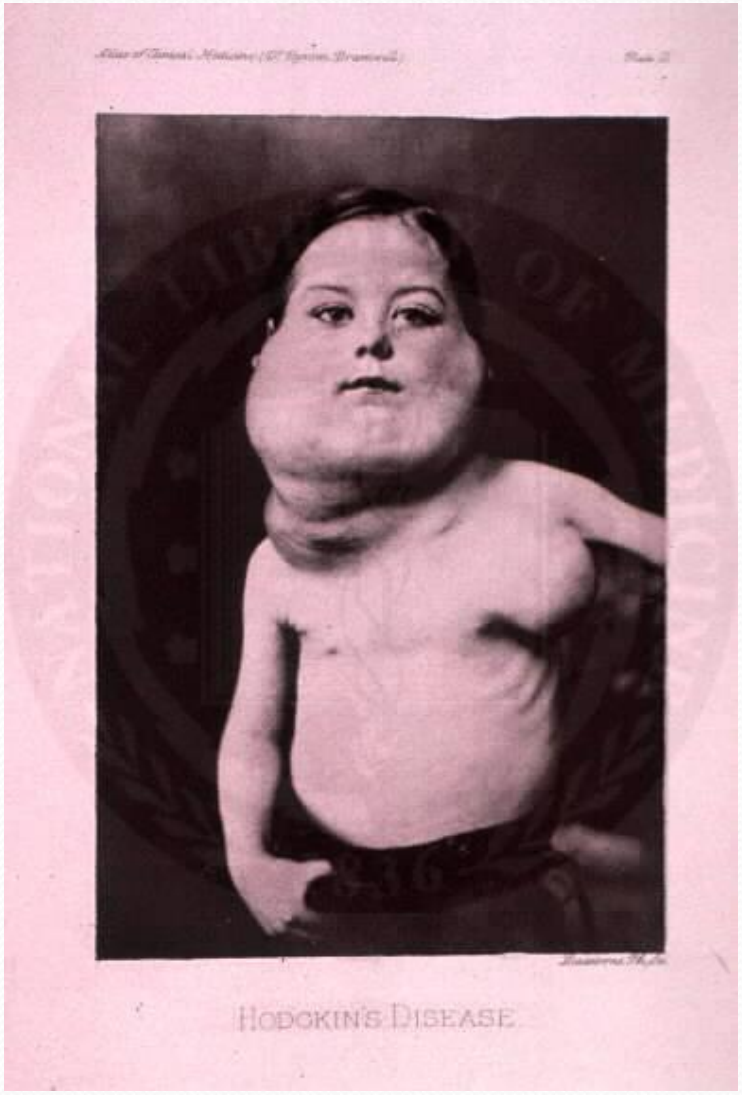
- most common type of “aggressive” lymphoma
- usually symptomatic
- extranodal involvement is common
- cell of origin: germinal center B-cell
- treatment should be offered
- curable in ~ 40%

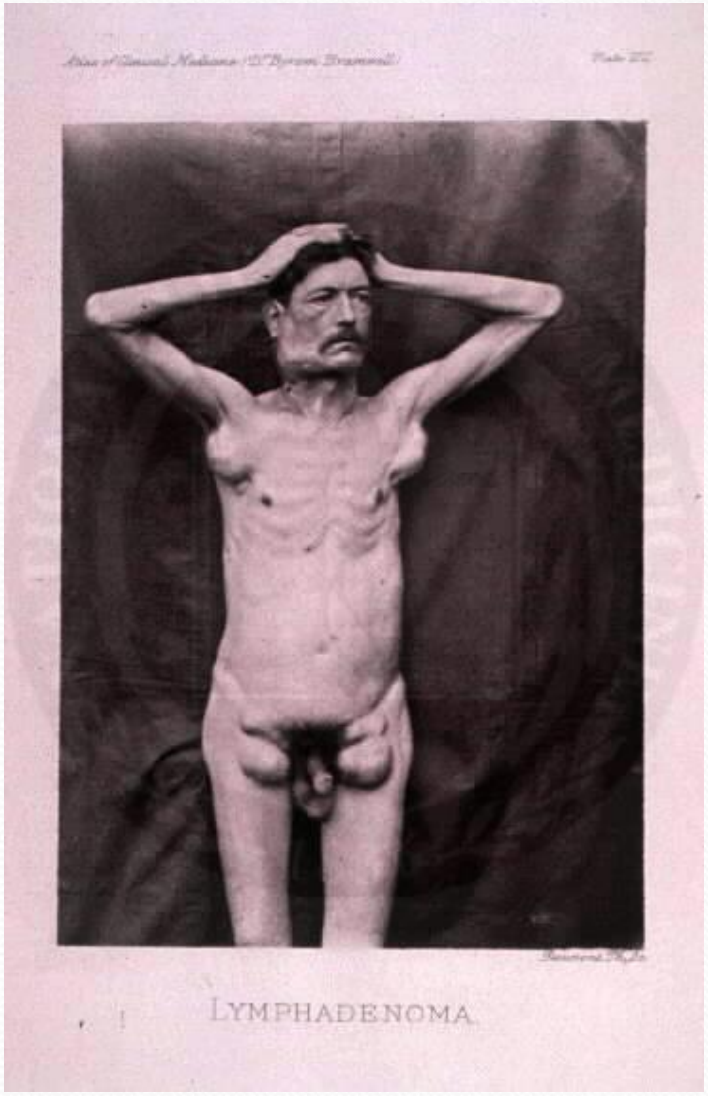
# Hodgkin lymphoma



Thomas Hodgkin
(1798-1866)

# Classical Hodgkin Lymphoma

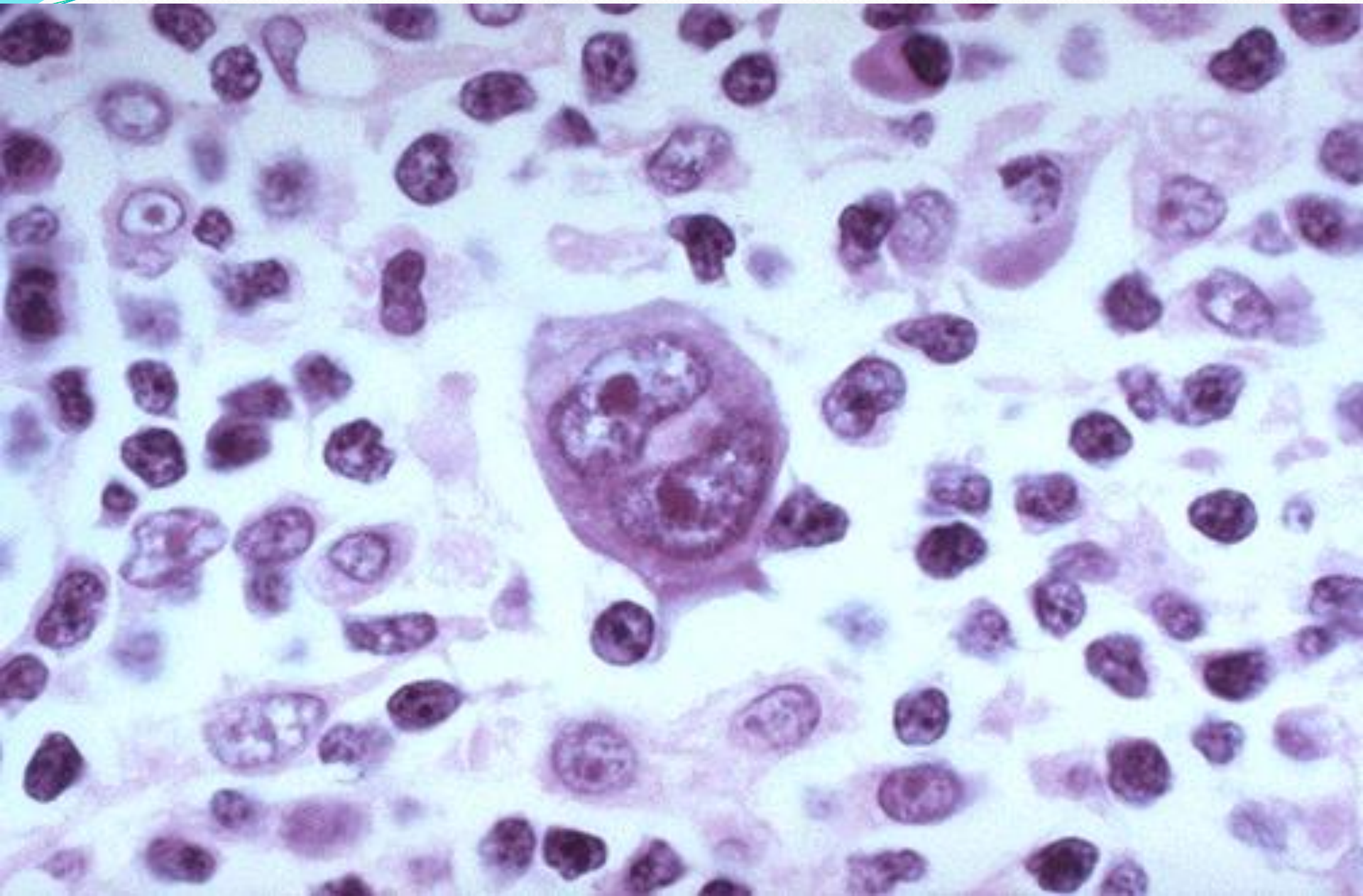


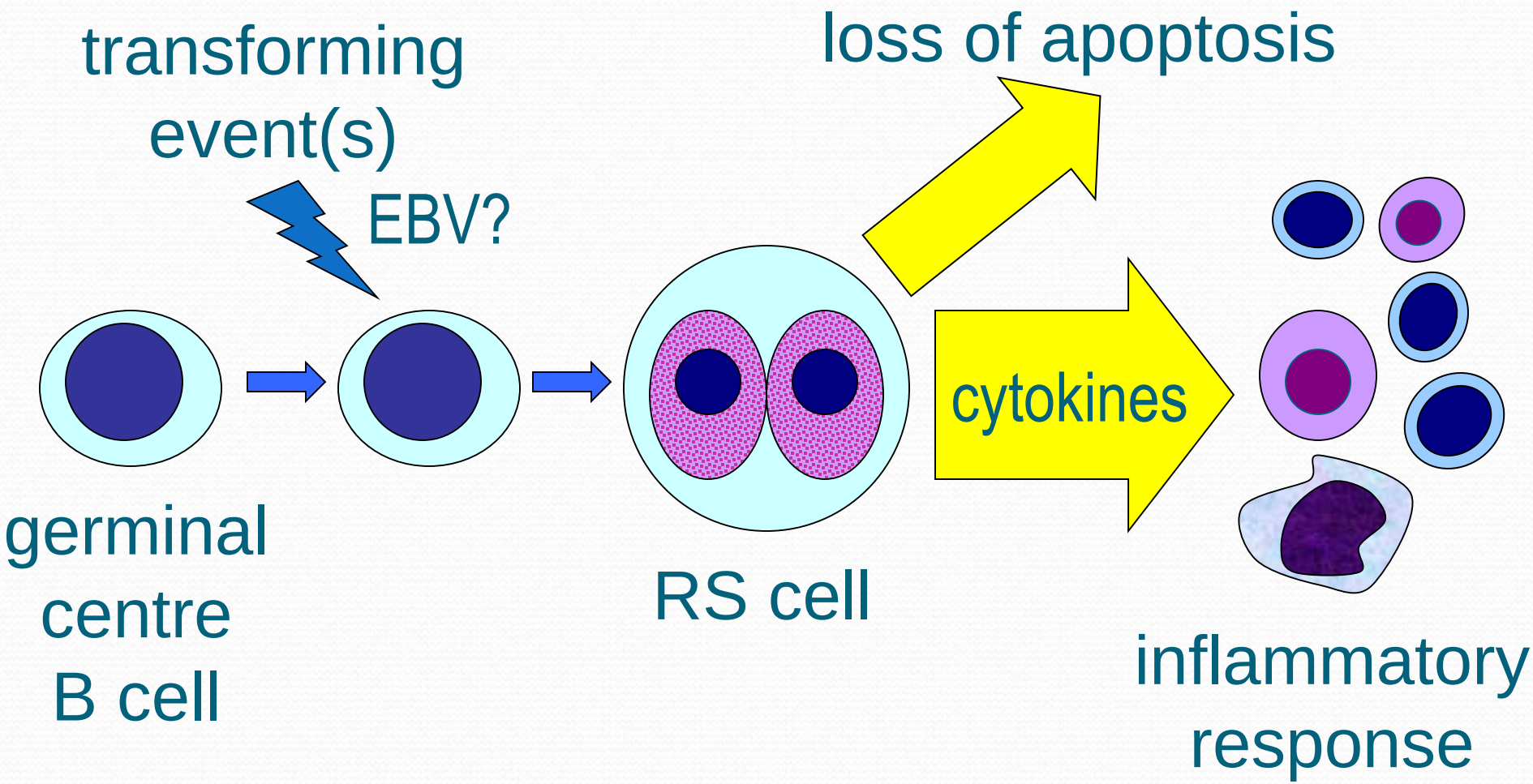
# Hodgkin lymphoma

- cell of origin: germinal centre B-cell
- Reed-Sternberg cells (or RS variants) in the affected tissues
- most cells in affected lymph node are polyclonal reactive lymphoid cells, not neoplastic cells

# Reed-Sternberg cell



# A possible model of pathogenesis



# Hodgkin lymphoma
# Histologic subtypes

- Classical Hodgkin lymphoma
  - nodular sclerosis (most common subtype)
  - mixed cellularity
  - lymphocyte-rich
  - lymphocyte depleted

# Epidemiology

- less frequent than non-Hodgkin lymphoma
- overall M>F
- peak incidence in 3rd decade

# Associated (etiological?) factors

- EBV infection
- smaller family size
- higher socio-economic status
- caucasian > non-caucasian
- possible genetic predisposition
- other:  HIV? occupation? herbicides?

# Clinical manifestations:

- lymphadenopathy
- contiguous spread
- extranodal sites relatively uncommon except in advanced disease
- “B” symptoms

# Treatment and Prognosis

| Stage | Treatment | Failure-free survival | Overall 5 year survival |
|---|---|---|---|
| I,II | ABVD x 4 & radiation | 70-80% | 80-90% |
| III,IV | ABVD x 6 | 60-70% | 70-80% |

# Long term complications of treatment

- infertility
  - MOPP > ABVD;  males > females
  - sperm banking should be discussed
  - premature menopause
- secondary malignancy
  - skin, AML, lung, MDS, NHL, thyroid, breast…
- cardiac disease