Understanding Lymphoma from a Lab Perspective

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Lymphoproliferative Disorders

- **Malignant lymphoma**
  1. **Non-Hodgkin lymphoma (NHL)**
  2. **Hodgkin (disease) lymphoma**
  3. **Multiple myeloma**

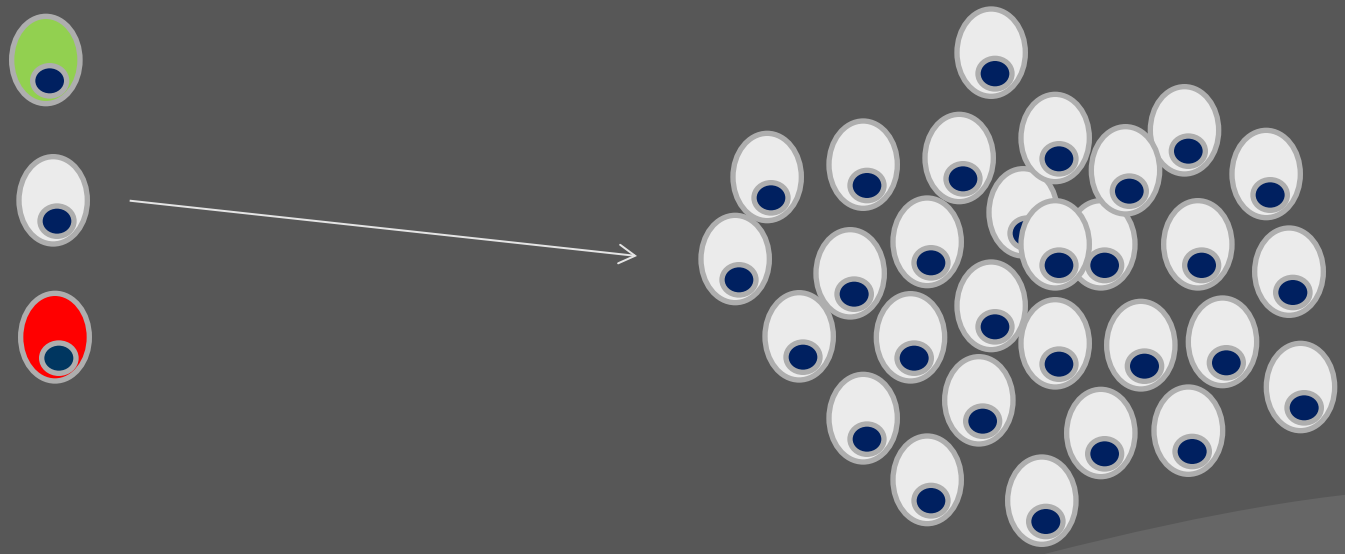
Basic concepts

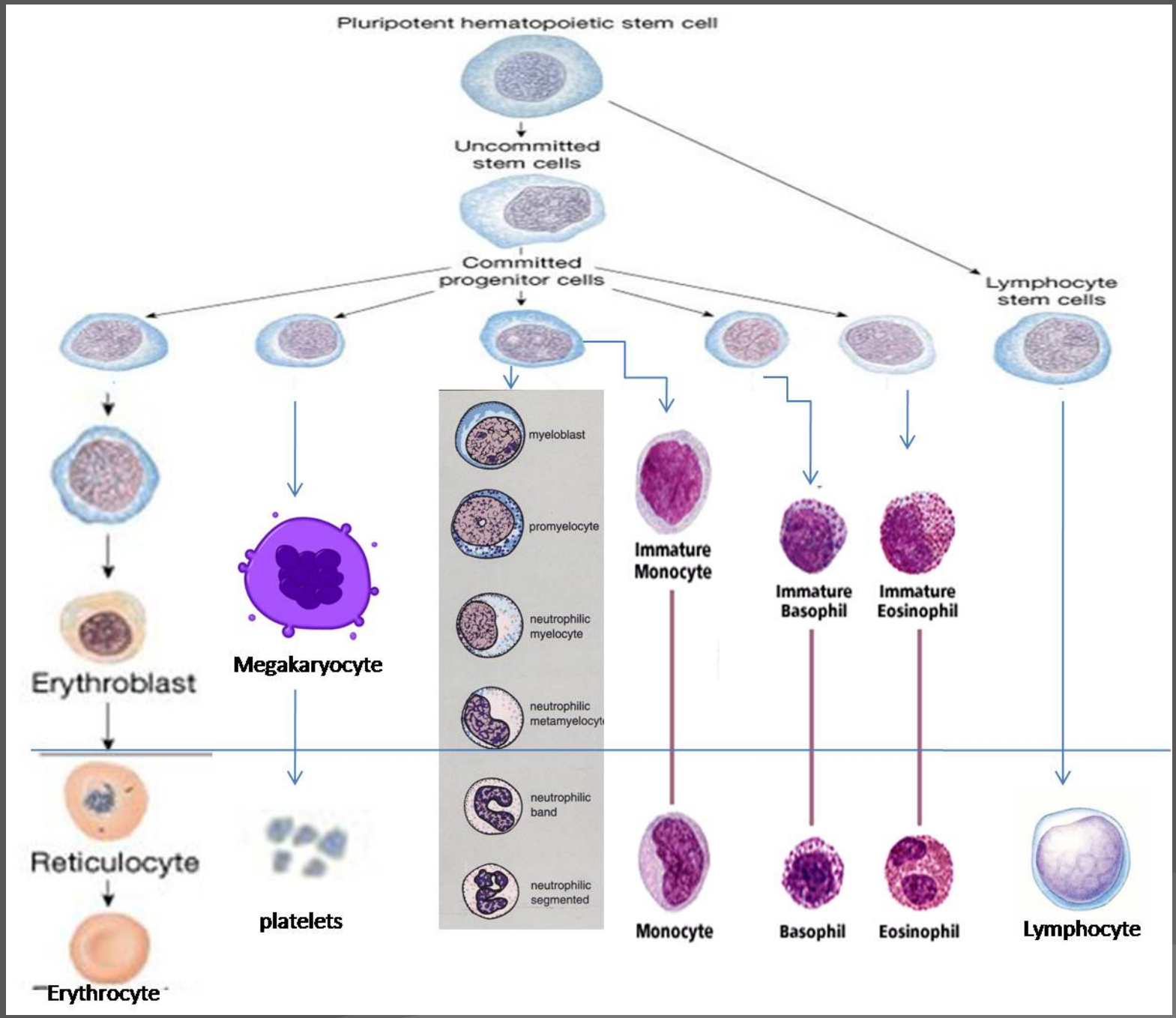
- Lymphomas are solid tumors of the hematopoietic system. Neoplasms of lymphoid origin, typically causing lymphadenopathy

- leukemia vs. lymphoma
    - Leukemias as systemically distributed neoplasms of white cells

Very important concept……

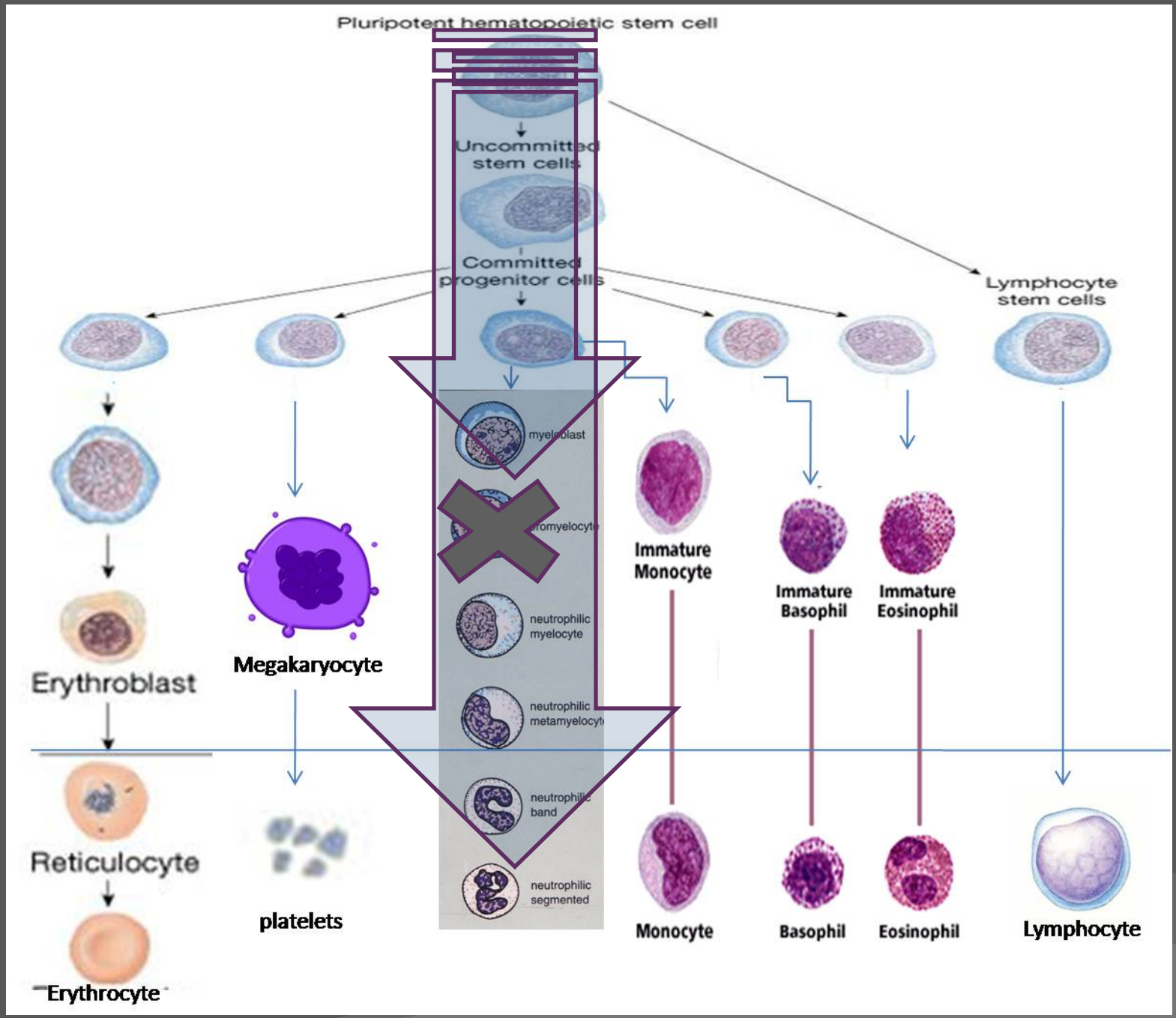
- lymphomas and leukemias are clonal expansions of cells at certain developmental stages



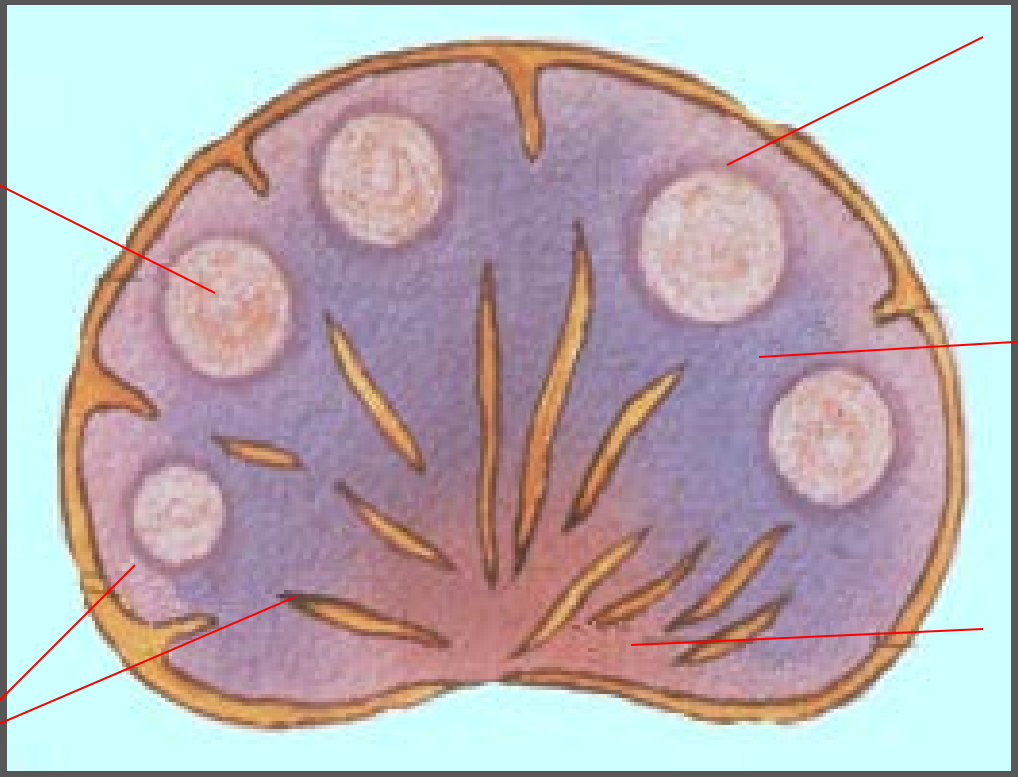

Pluripotent hematopoietic stem cell
Uncommitted stem cells
Committed progenitor cells
Lymphocyte stem cells
myeloblast
promyelocyte
neutrophilic myelocyte
neutrophilic metamyelocyte
neutrophilic band
neutrophilic segmented
Erythroblast
Megakaryocyte
Immature Monocyte
Immature Basophil
Immature Eosinophil
Reticulocyte
platelets
Monocyte
Basophil
Eosinophil
Lymphocyte
Erythrocyte

Bone Marrow

Peripheral Blood



Follicle / germinal center (B cell)



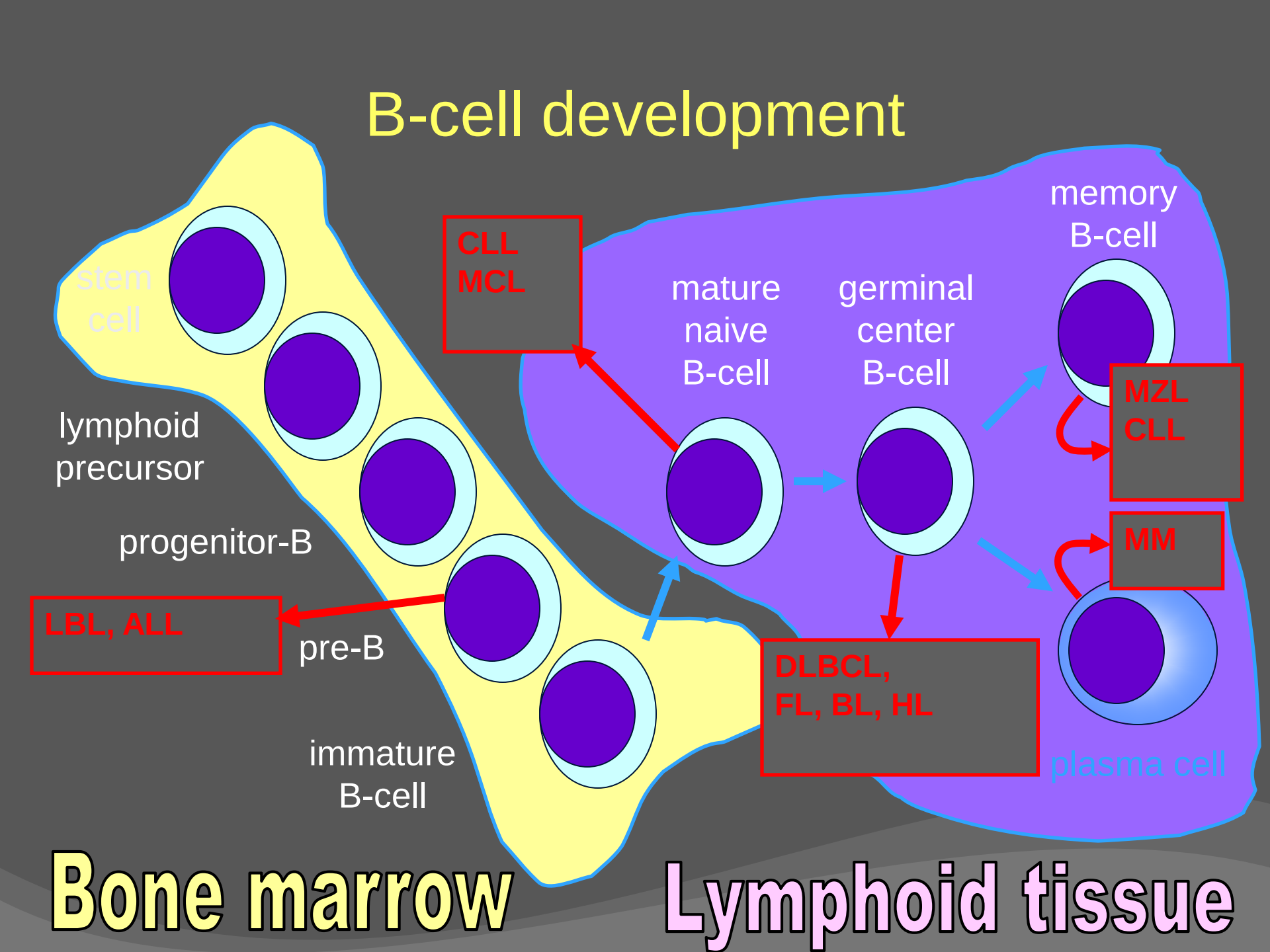
Mantle zone (B-cell)

Paracortex (T-cell)

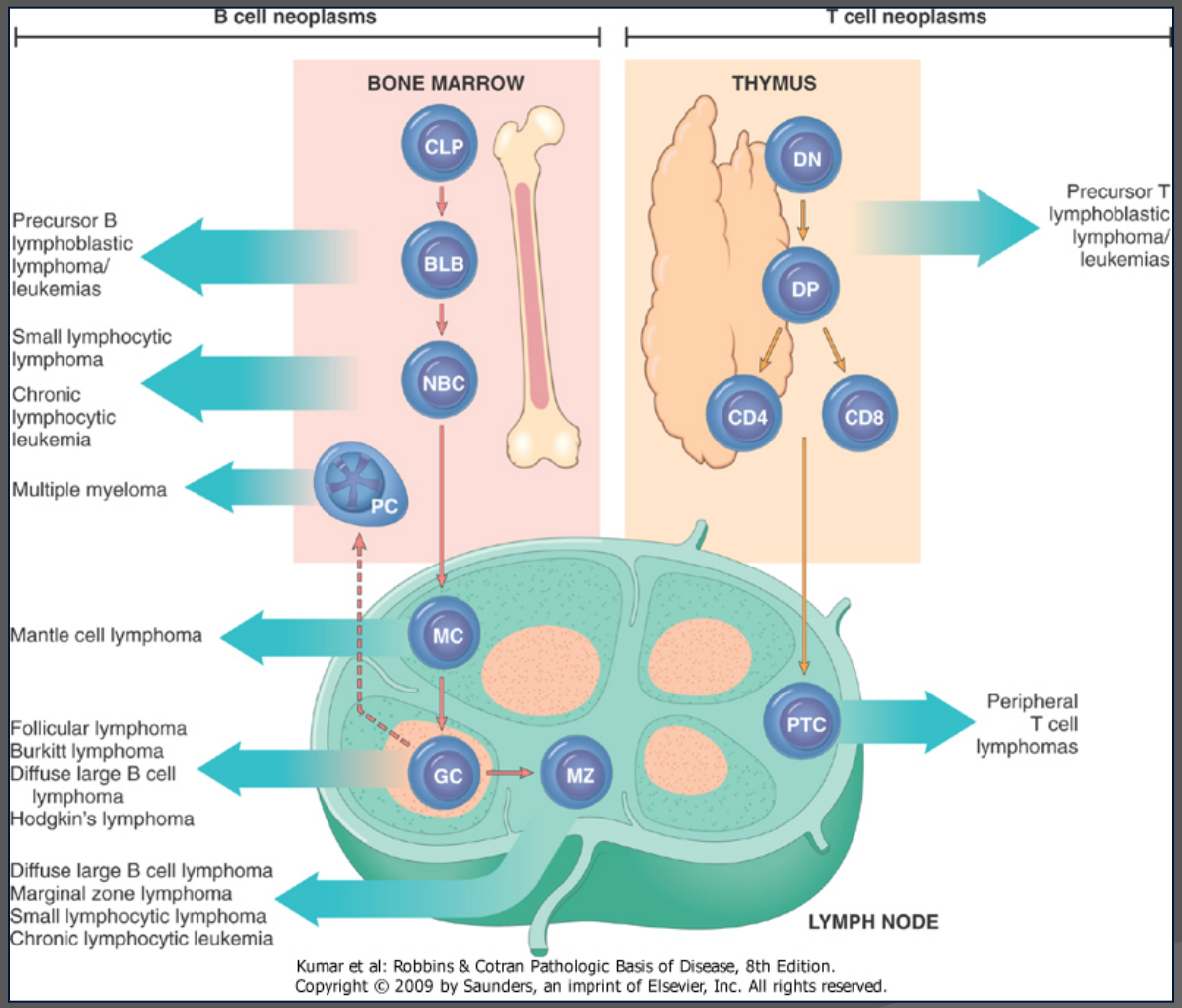
Medullary cord (B-cell)

Lymphatic sinus

NORMAL LYMPH NODE


B-cell development
stem cell
lymphoid precursor
progenitor-B
pre-B
immature B-cell
CLL
MCL
mature naive B-cell
germinal center B-cell
memory B-cell
MZL
CLL
MM
plasma cell
LBL, ALL
DLBCL,
FL, BL, HL
Bone marrow
Lymphoid tissue

Origin of lymphoid neoplasms



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

A practical way to think of lymphoma

Category		Survival of untreated patients	Curability	To treat or not to treat
Non-Hodgkin lymphoma	Indolent	Years	Generally not curable	Generally defer Rx if asymptomatic
	Aggressive	Months	Curable in some	Treat
	Very aggressive	Weeks	Curable in some	Treat
Hodgkin lymphoma	All types	Variable – months to years	Curable in most	Treat

Non-Hodgkin Lymphomas

How do we diagnose and classify these types of lymphoproliferative disorders?

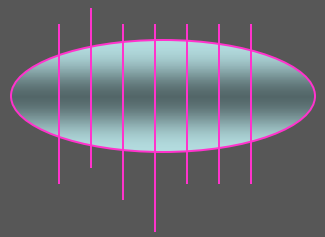
- Architectural pattern
- Cytologic (cellular) morphologic appearance
- Immunophenotypic (antigenic) characteristics
- Molecular / genetic characteristics

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

Lymph Node Protocol

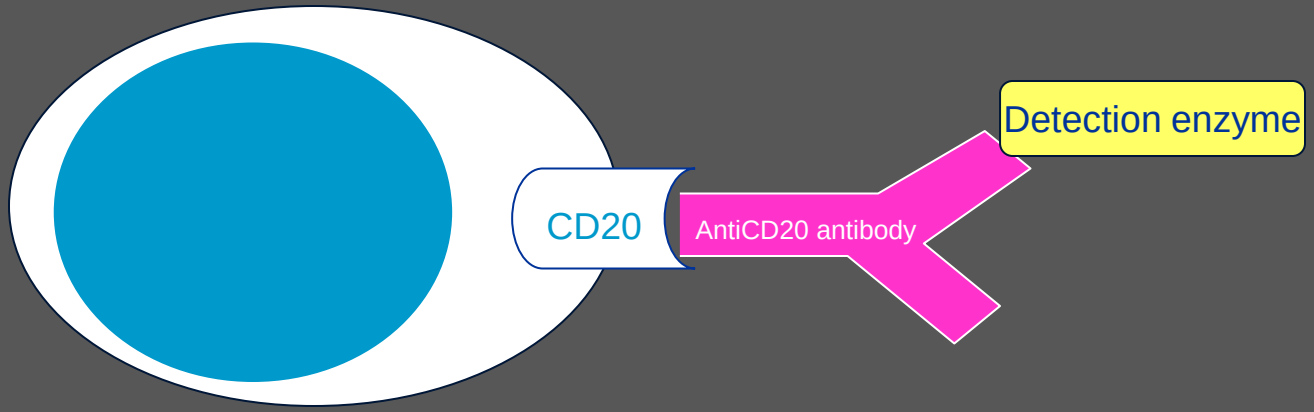


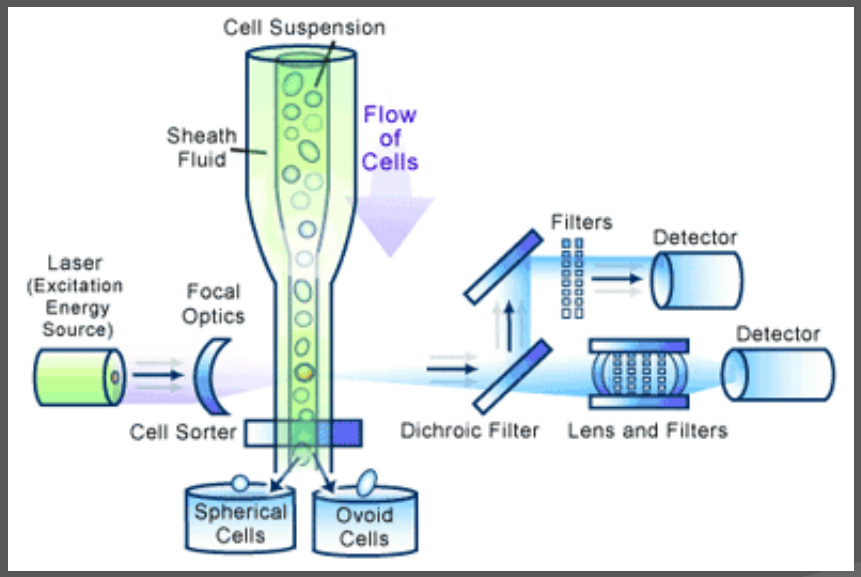
Permanent sections

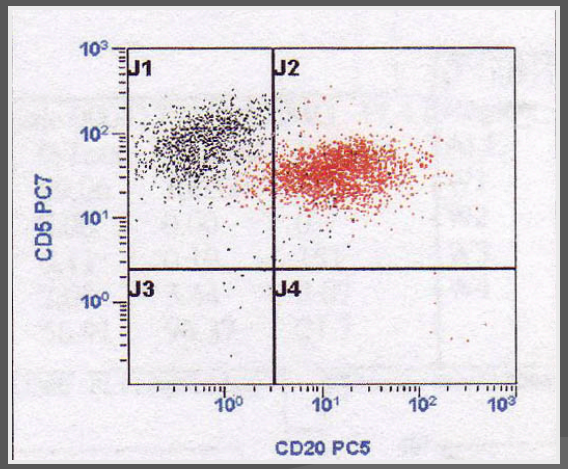
Morphologic evaluation

- Flowcytometry
- Immunostains
- Cytogenetics
- Molecular

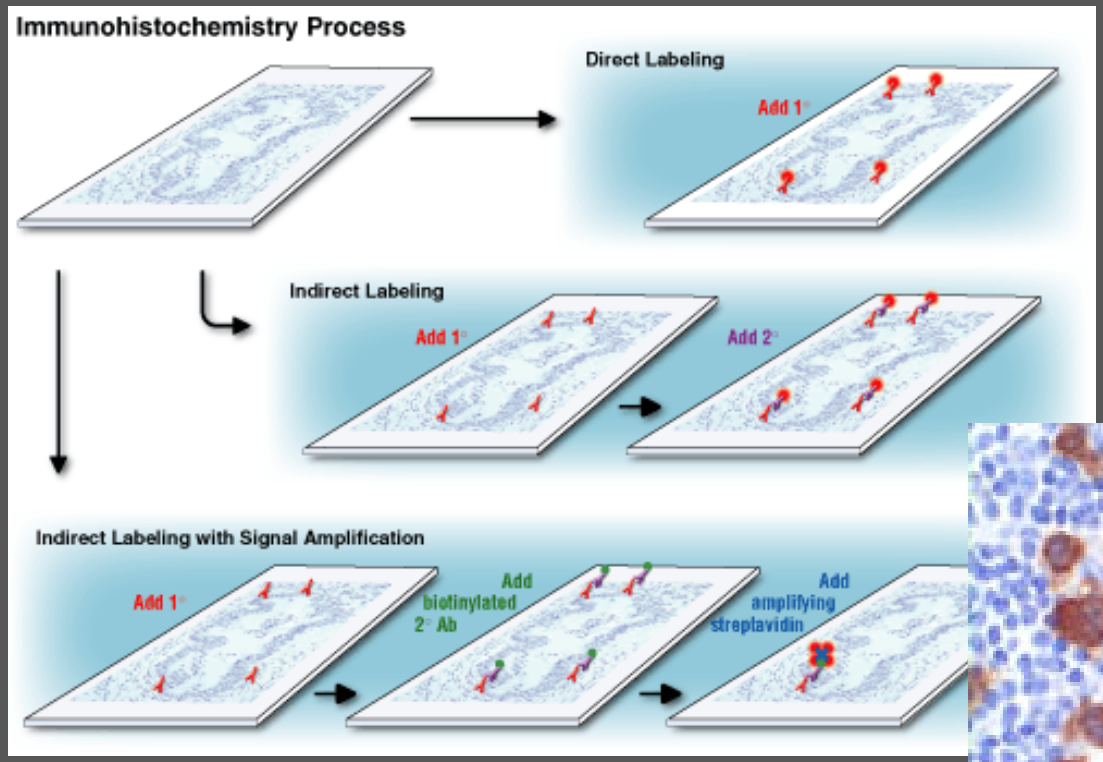
Flow-cytometry

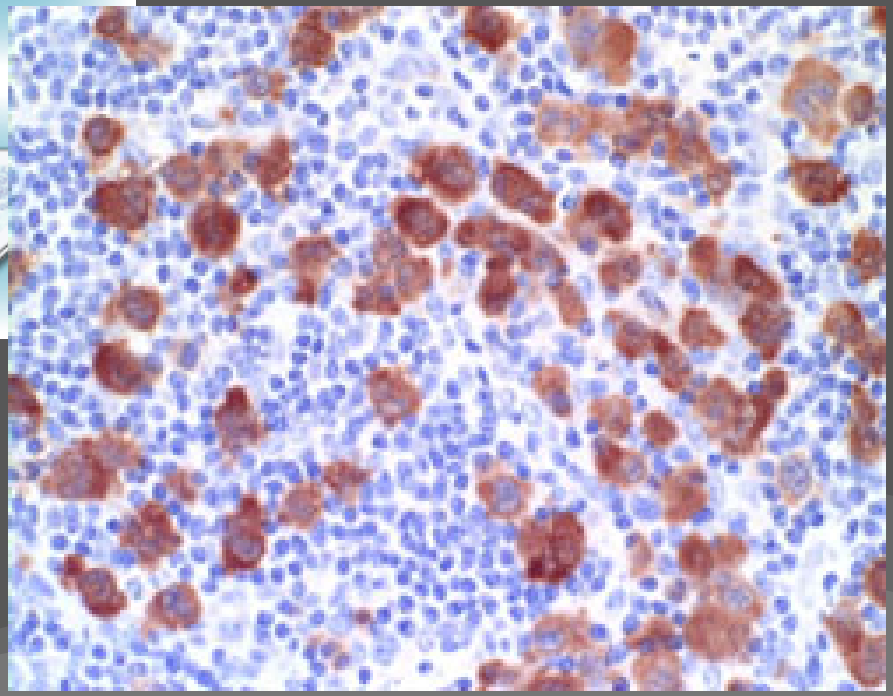






Immunostains





Non-Hodgkin Lymphomas

- Neoplasm of the immune system
- B-cells, T-cells, histiocytes
- Usually begin in the lymph nodes, but may arise in other lymphoid tissues such as spleen, bone marrow, or extranodal sites

Clinical Findings

- Enlarged, painless lymphadenopathy
- B-symptoms-fever, weight loss
- Impingement or obstruction of other structures

Subtypes of Non-Hodgkin Lymphoma

TABLE 4: WHO classification of the mature B-cell, T-cell, and NK-cell neoplasms (2008)

Mature B-cell neoplasms

Chronic lymphocytic leukemia/small lymphocytic lymphoma
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Splenic lymphoma/leukemia, unclassifiable
    *Splenic diffuse red pulp small B-cell lymphoma**
    Hairy cell leukemia-variant*
Lymphoplasmacytic lymphoma
Waldenström macroglobulinemia
Heavy chain diseases
    Alpha heavy chain disease
    Gamma heavy chain disease
    Mu heavy chain disease
Plasma cell myeloma
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone lymphoma
Pediatric nodal marginal zone lymphoma
Follicular lymphoma
Pediatric follicular lymphoma
Primary cutaneous follicular center lymphoma
Mantle cell lymphoma
Diffuse large B-cell lymphoma (DLBCL), NOS
    T-cell/histiocyte-rich large B-cell lymphoma
    EBV+ DLBCL of the elderly
    DLBCL associated with chronic inflammation
    Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
Primary cutaneous DLBCL, leg type
ALK+ large B-cell lymphoma
Plasmablastic lymphoma
Large B-cell lymphoma arising in HHV-8–associated multicentric Castleman disease
Primary effusion lymphoma
Burkitt lymphoma
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classic Hodgkin lymphoma

Mature T-cell and NK-cell neoplasms

T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells*
Aggressive NK cell leukemia
Systemic EBV+ T-cell lymphoproliferative disease of childhood
Hydroa vacciniforme-like lymphoma
Adult T-cell leukemia/lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30+ T-cell lymphoproliferative disorders
    Lymphomatoid papulosis
    Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous gamma-delta T-cell lymphoma
*Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma**
*Primary cutaneous CD4+ small/medium T-cell lymphoma**
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
Anaplastic large cell lymphoma, ALK+
*Anaplastic large cell lymphoma, ALK−**

Hodgkin lymphoma

Nodular lymphocyte-predominant Hodgkin lymphoma
Classic Hodgkin lymphoma
    Nodular sclerosis classic Hodgkin lymphoma
    Lymphocyte-rich classic Hodgkin lymphoma
    Mixed cellularity classic Hodgkin lymphoma
    Lymphocyte-depleted classic Hodgkin lymphoma

Posttransplantation lymphoproliferative disorders (PTLDs)

Early lesions
Plasmacytic hyperplasia
Infectious mononucleosis-like PTLD
Polymorphic PTLD
Monomorphic PTLD (B and T/NK-cell types)†
Classic Hodgkin lymphoma type PTLD†

*Provisional entities for which the WHO Working Group thought there was insufficient evidence to recognize as distinct diseases at this time.
†These lesions are classified according to the leukemia or lymphoma to which they correspond. Diseases shown in italics were newly included in the 2008 WHO classification.

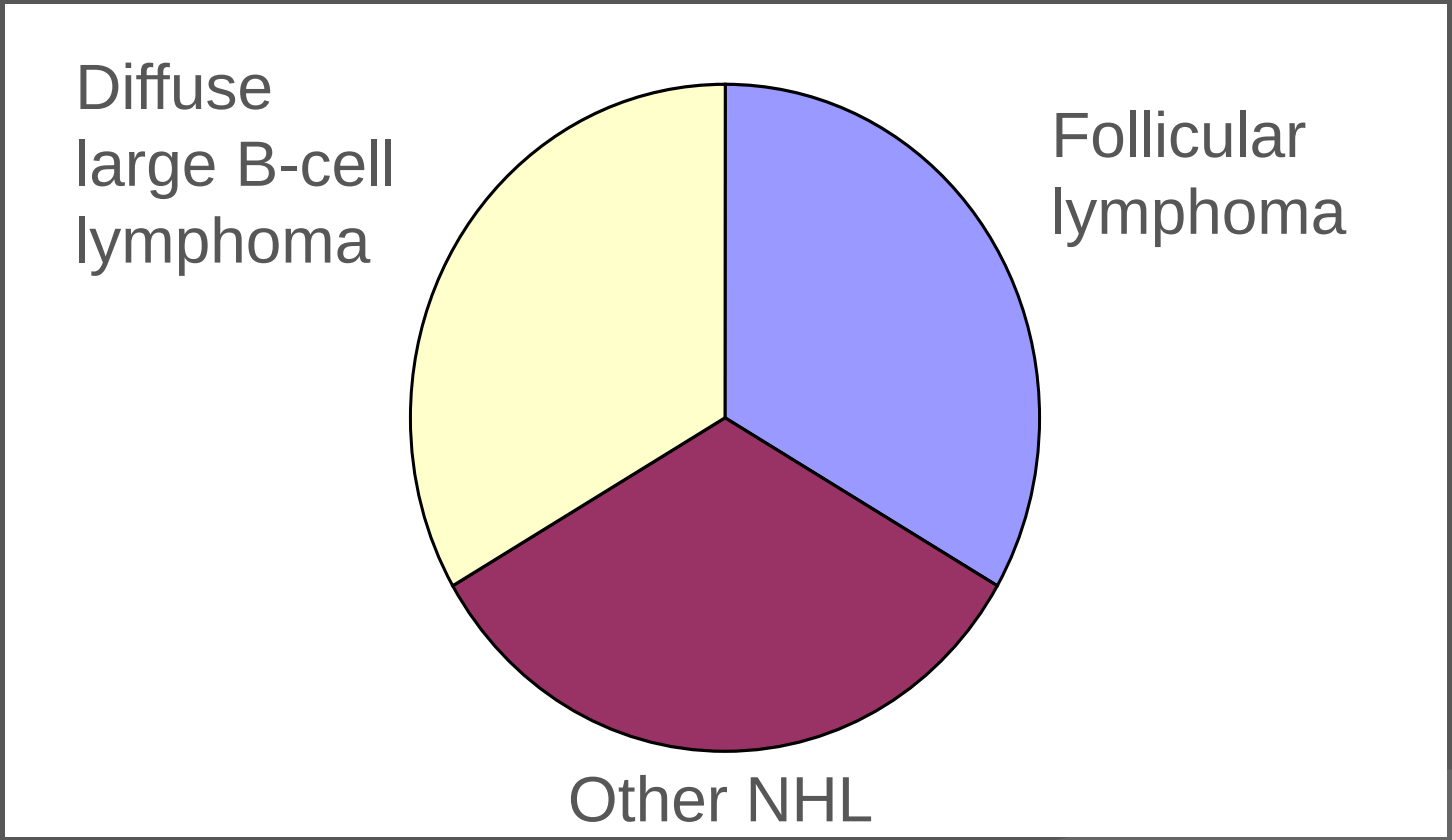
Most common types of lymphoma

1. Non-Hodgkin lymphoma (NHL)
   - SLL/CLL
   - Follicular lymphoma
   - Diffuse large B cell lymphoma
   - Burkitt's lymhoma

2. Hodgkin lymphoma (HL)

Non-Hodgkin Lymphomas

Incidence



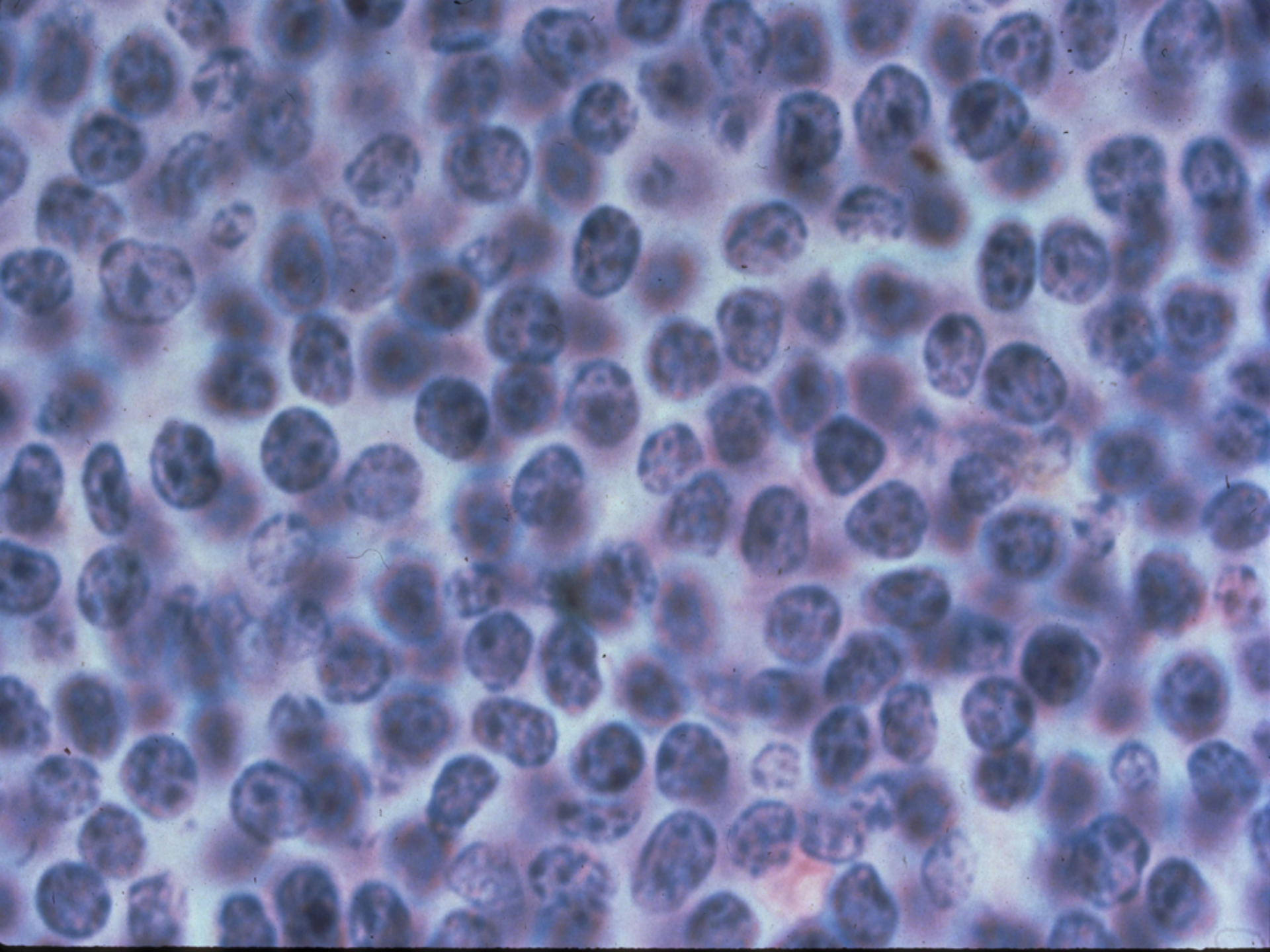
General Feature

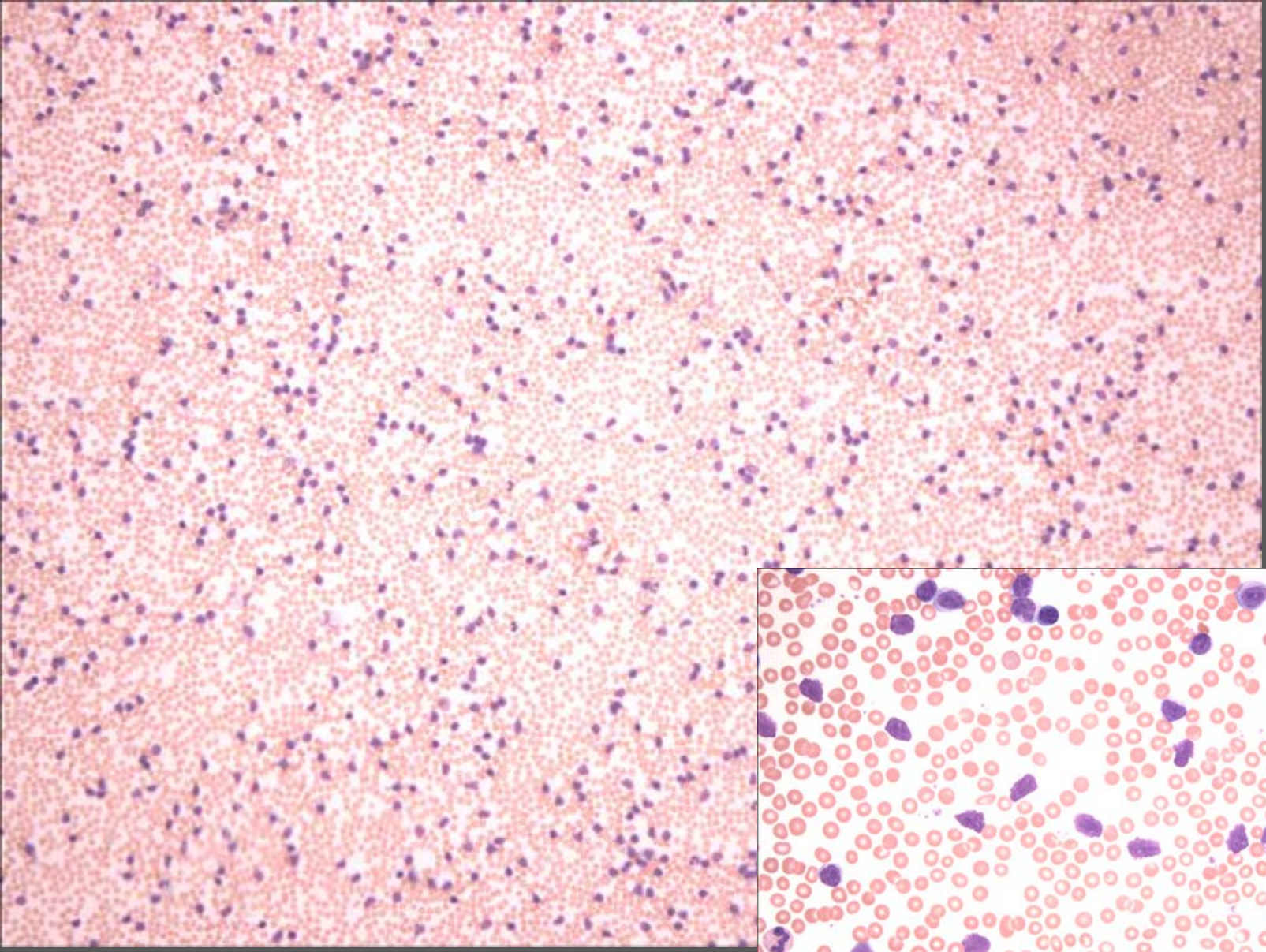
Low Grade Lymphomas

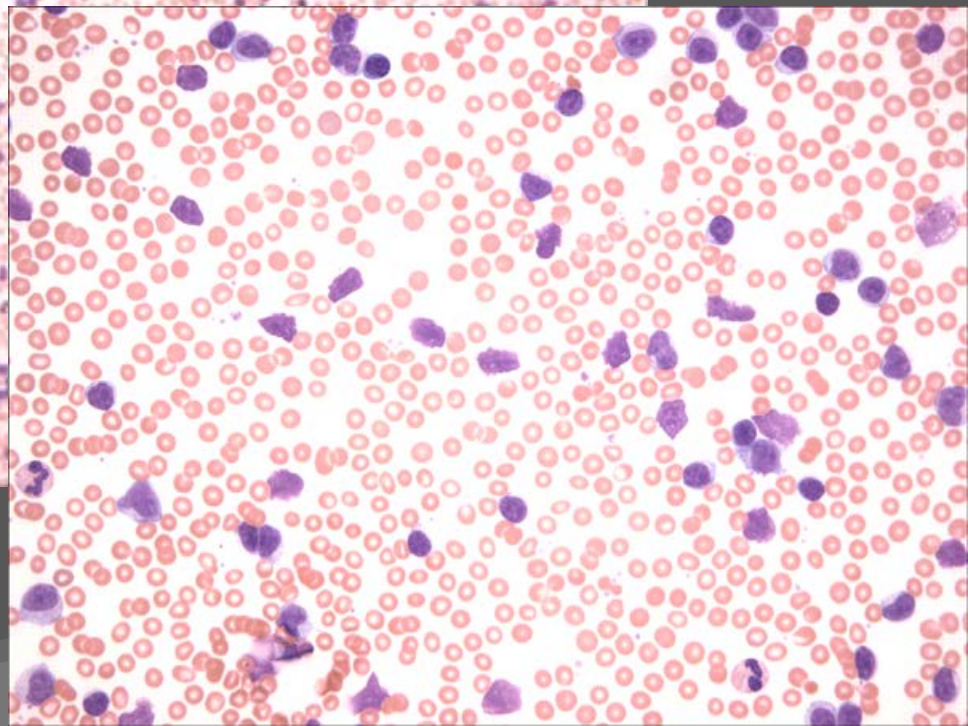
- Adult population affected (median age, 50-70 years)
- Rare in children
- High stage disease (III/IV) is most common
- Indolent course with relatively long survival
- Generally incurable
- Transformation to higher grade NHL may occur

Small Lymphocytic Lymphoma

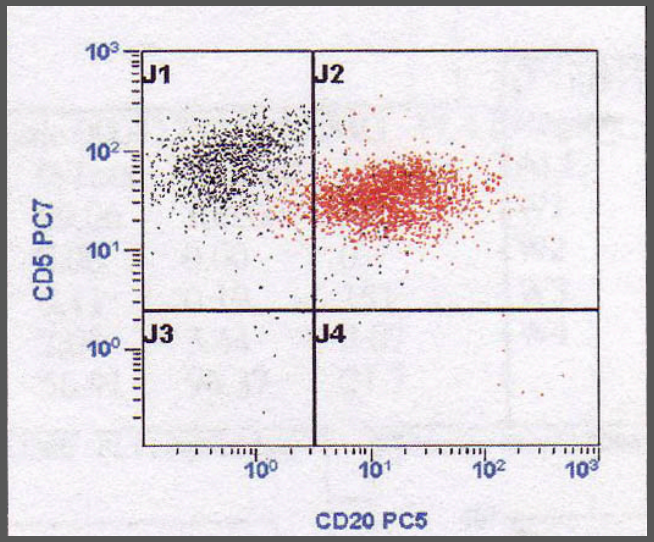
- Low grade B-cell malignancy
- Similar to chronic lymphocytic leukemia (CLL)
- Frequency - ~ 4% of NHL
- Older age group (median, 60.5 years)
- Bone marrow involvement: Common
- Indolent course

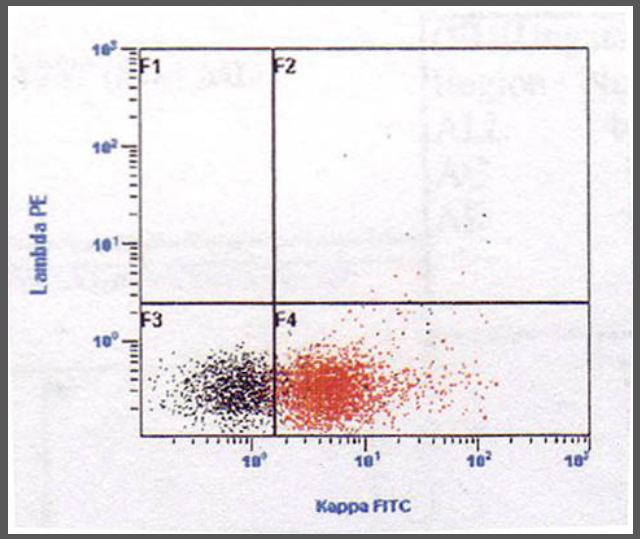






Flow cytometry

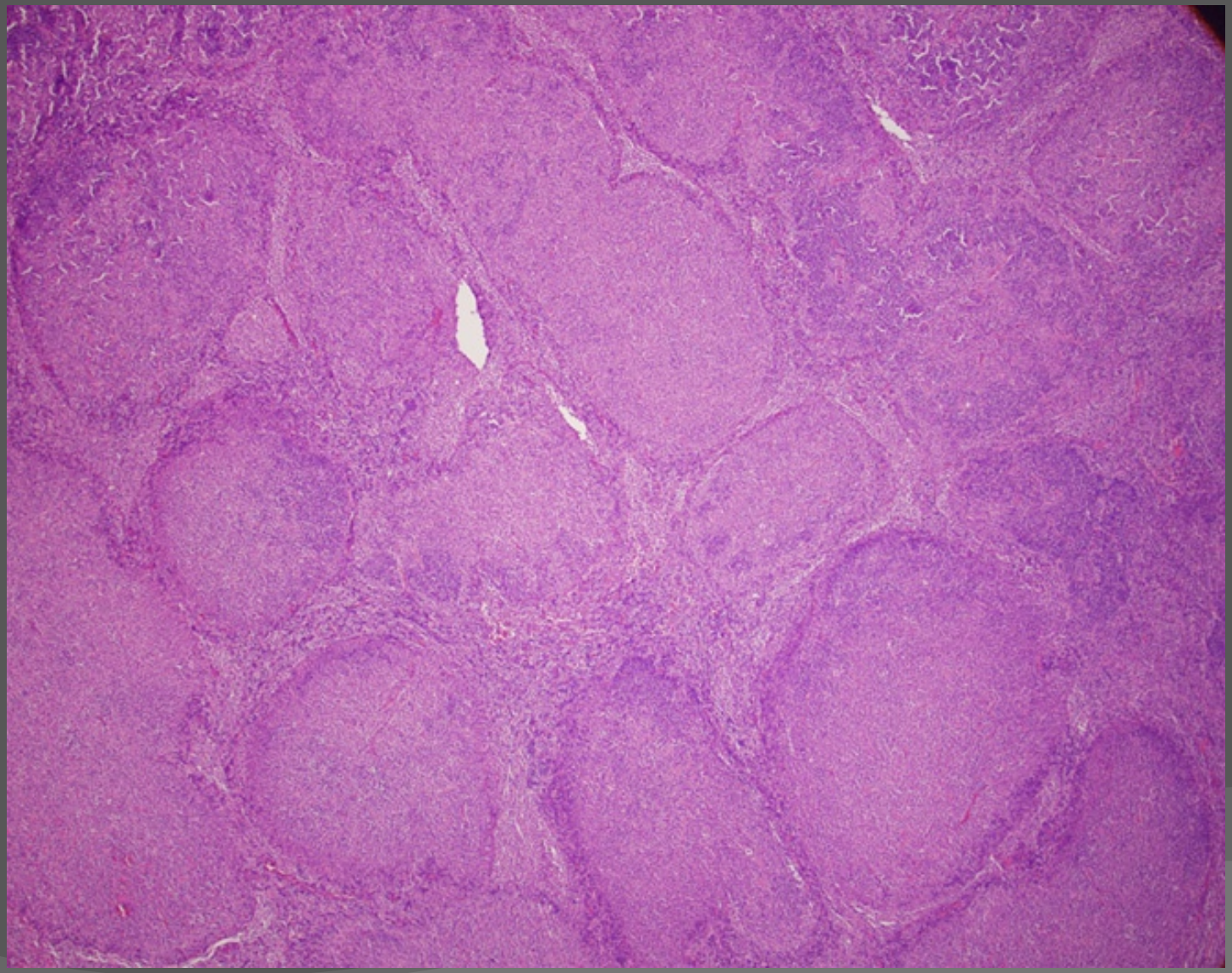




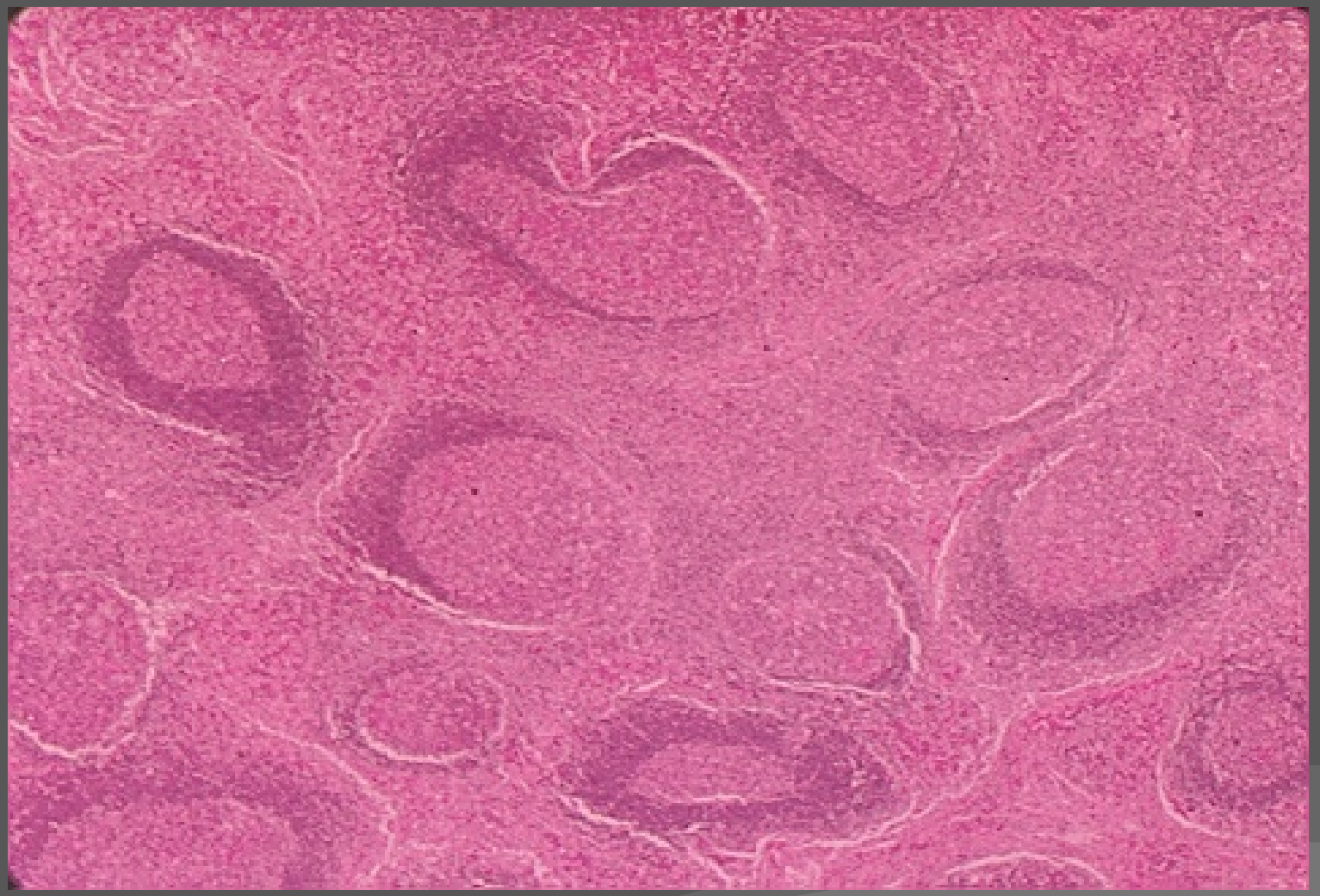
Follicular Lymphomas

- Frequency -~40% of NHL (most common)
- Older age group (median, 55 years)
- Often asymptomatic
- Bone marrow involvement: Common
- Indolent Course
- Chromosomal translocation, t(14;18)
- Transformation to more aggressive B-cell lymphoma

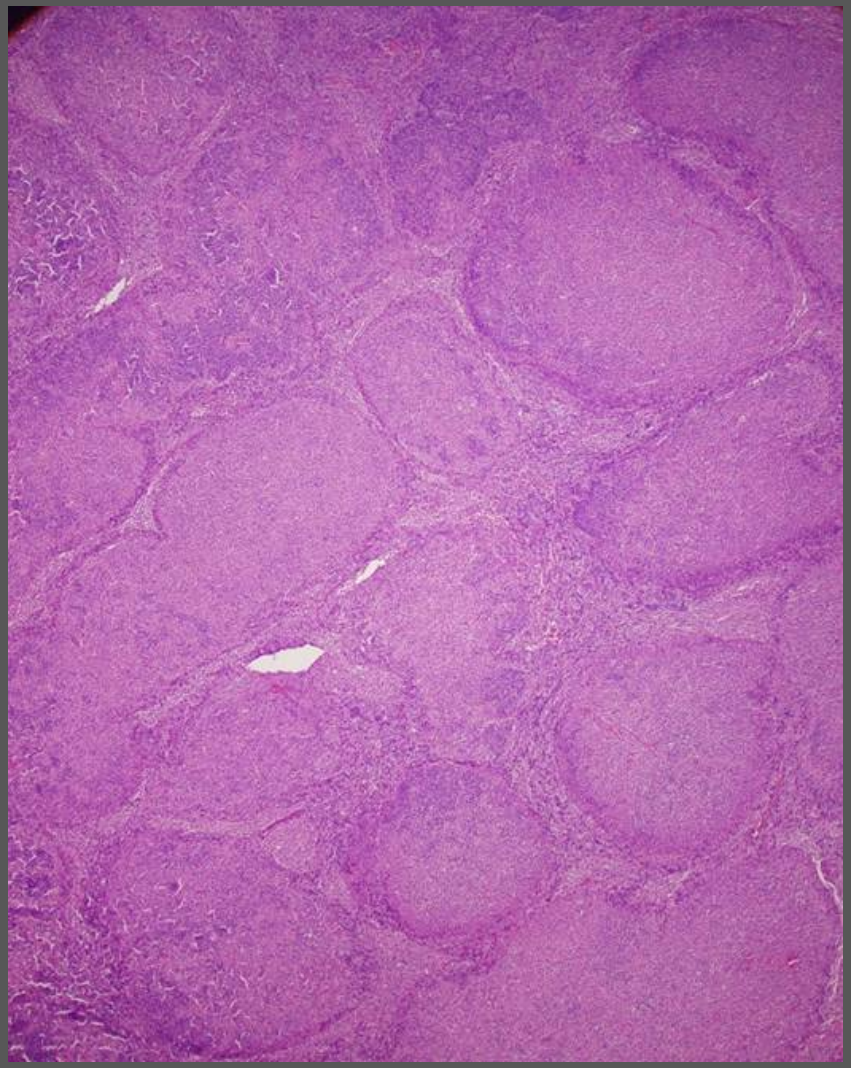
Follicular Lymphoma



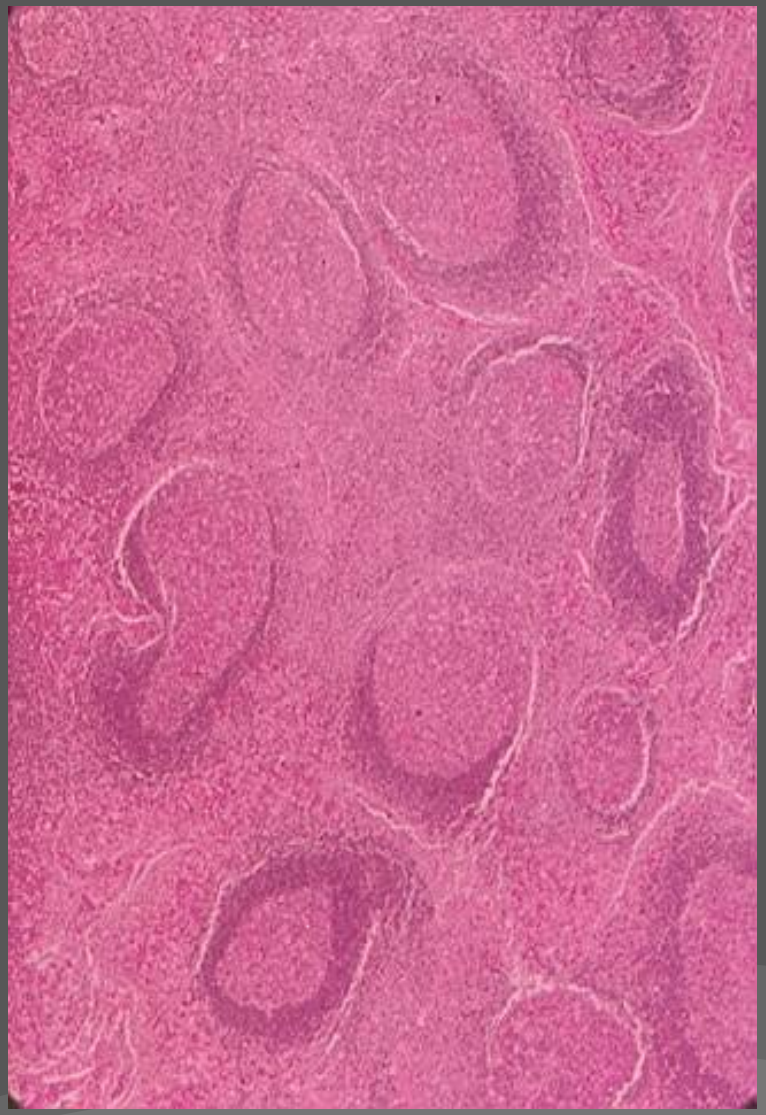
Reactive Follicular Hyperplasia



Follicular Lymphoma



Reactive



Architectural Features Distinguishing Reactive Follicular Hyperplasia and Follicular NHL

	Reactive Follicular Hyperplasia	Follicular NHL
Nodal Architecture	Preserved	Effaced
Germinal Center Size & Shape	Marked variation	Slight to moderate variation
Capsular infiltration	None or minimal	Invasion with extension into pericapsular fat
Density of follicles	Low, with intervening lymphoid tissue	High, with back to back follicles
Morphology of follicles	Sharply defined, mantle zone	Ill defined, no mantle zone

Treatment: Indolent

- No standard approach proven better than others
  - Treatment individualized accounting for lymphoma and patient characteristics, co-morbidities, etc
- Local irradiation for localized symptoms
- Systemic treatment for systemic disease
  - Chemotherapy, single agent or combination
    - Combination = better responses at expense of increased toxicity
- Monoclonal antibodies
  - Rituximab
  - Single most important breakthrough in B-cell NHL treatment

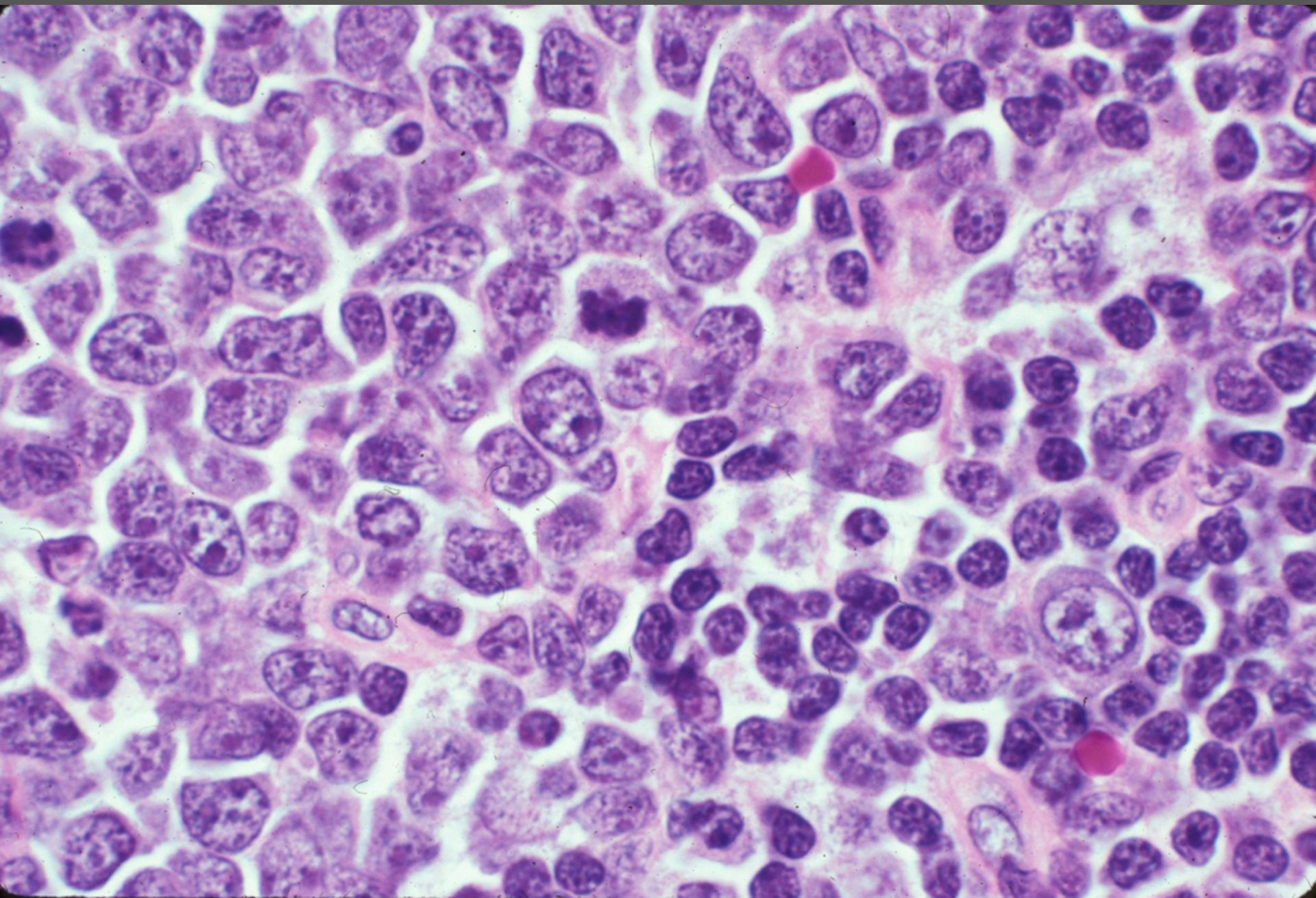
Intermediate Grade/ Aggressive

- **Mantle cell lymphoma**
  - **t(11;14) translocation results in over- expression of cyclin D1 protein**
- **Diffuse large cell lymphoma**

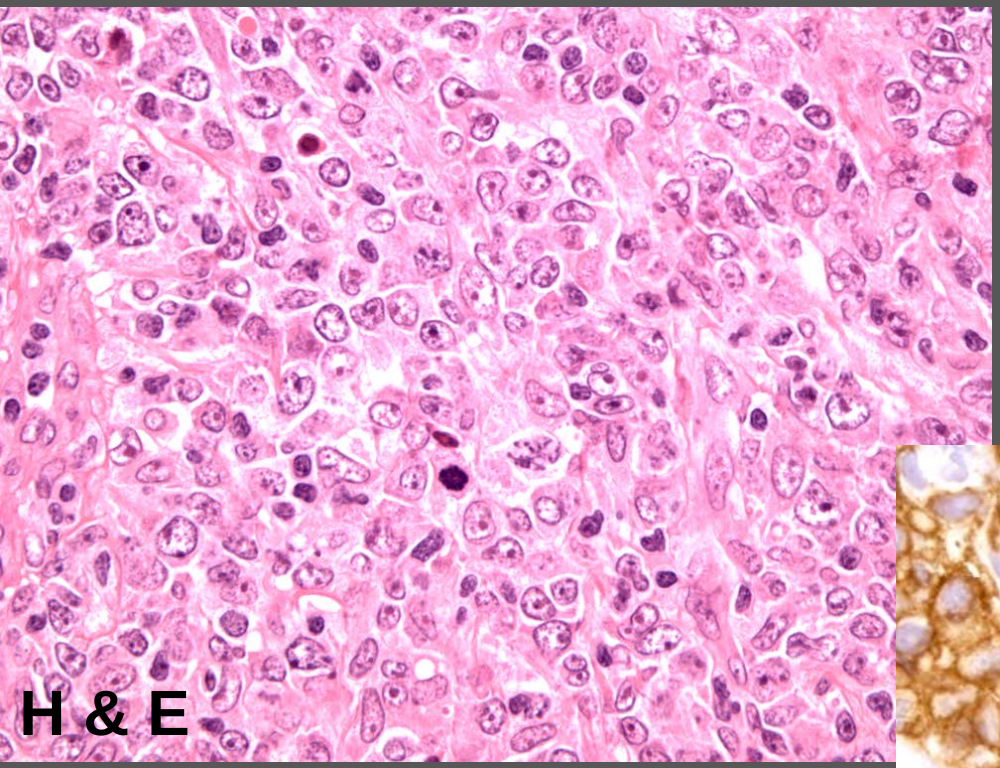
Diffuse Large Cell

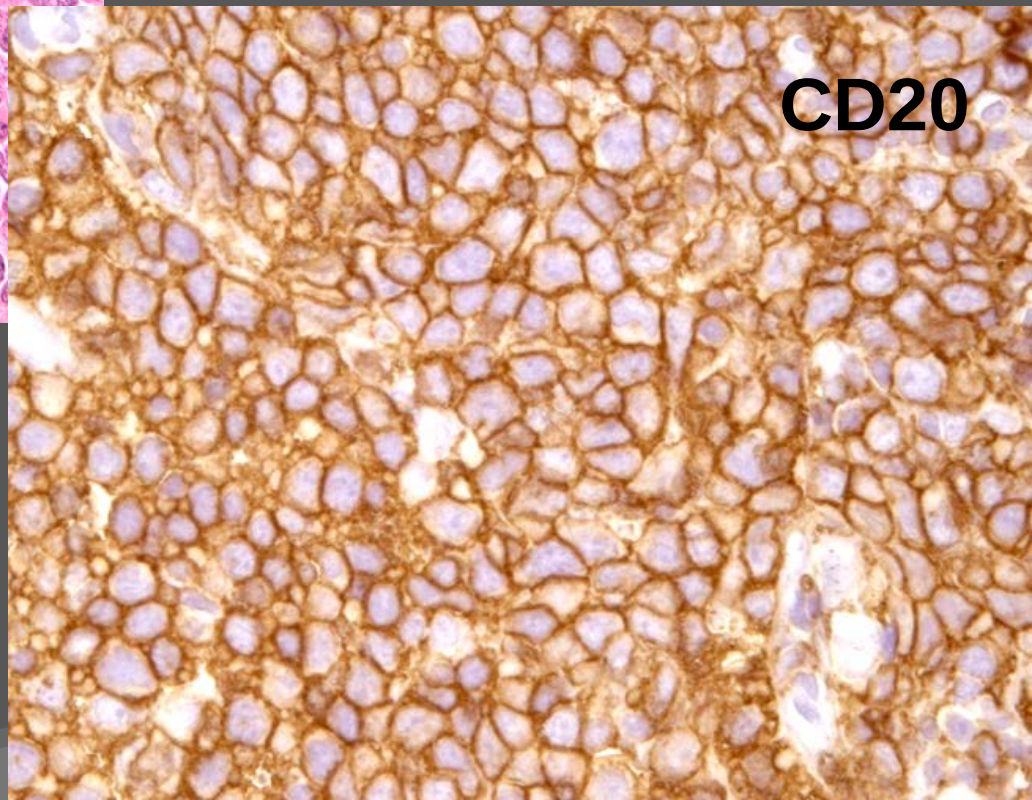
- 60-70% derived from B-cells
- Often stage I or II at diagnosis
- More likely to have extranodal sites
- Peripheral blood involvement is rare

Diffuse Large B-cell Lymphoma

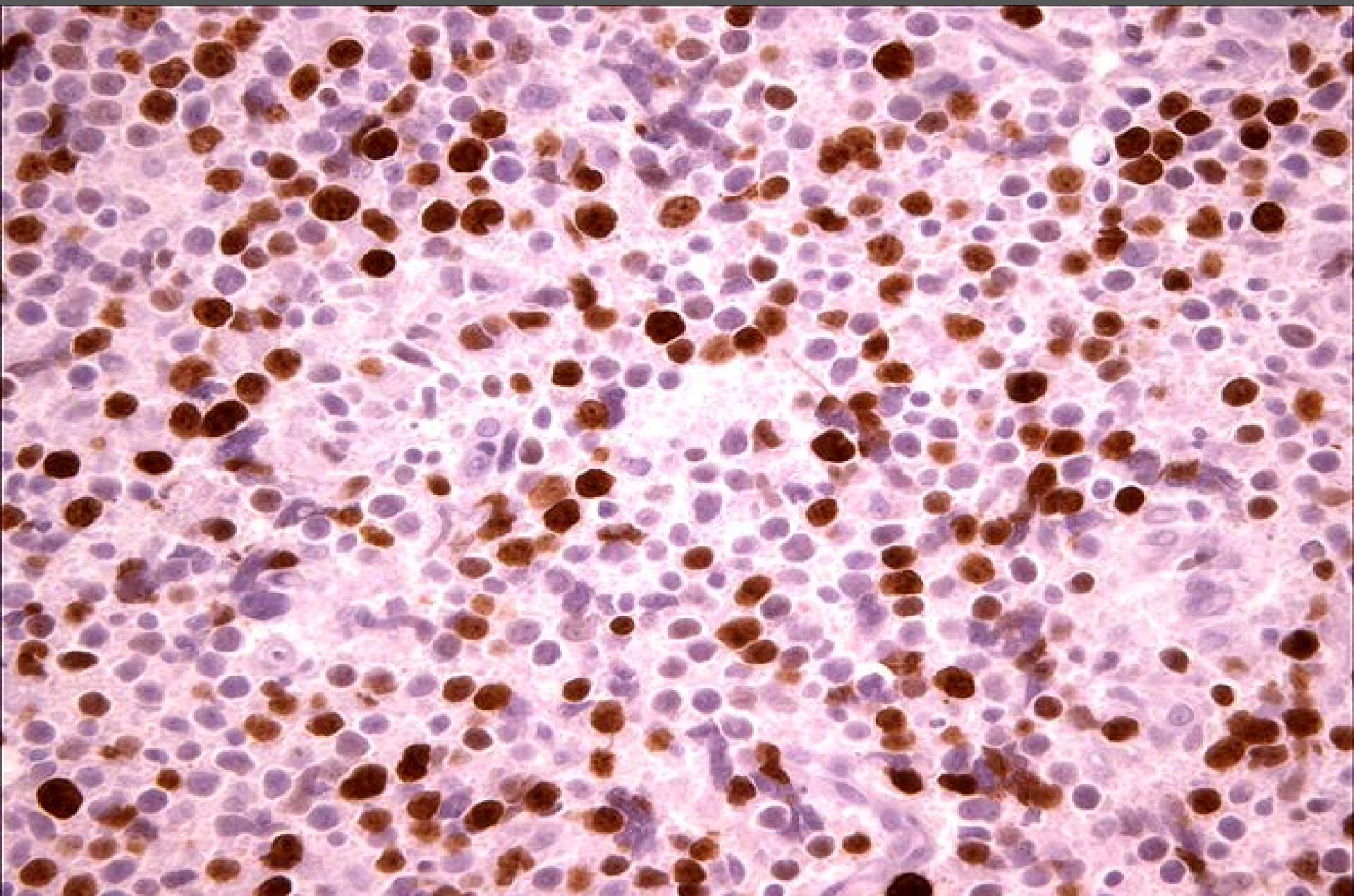


Diffuse Large B-cell Lymphoma



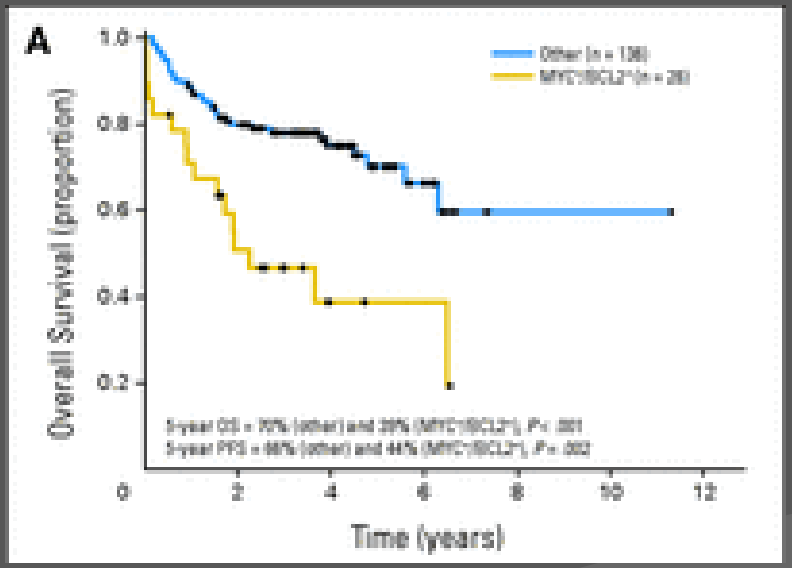


MIB-1

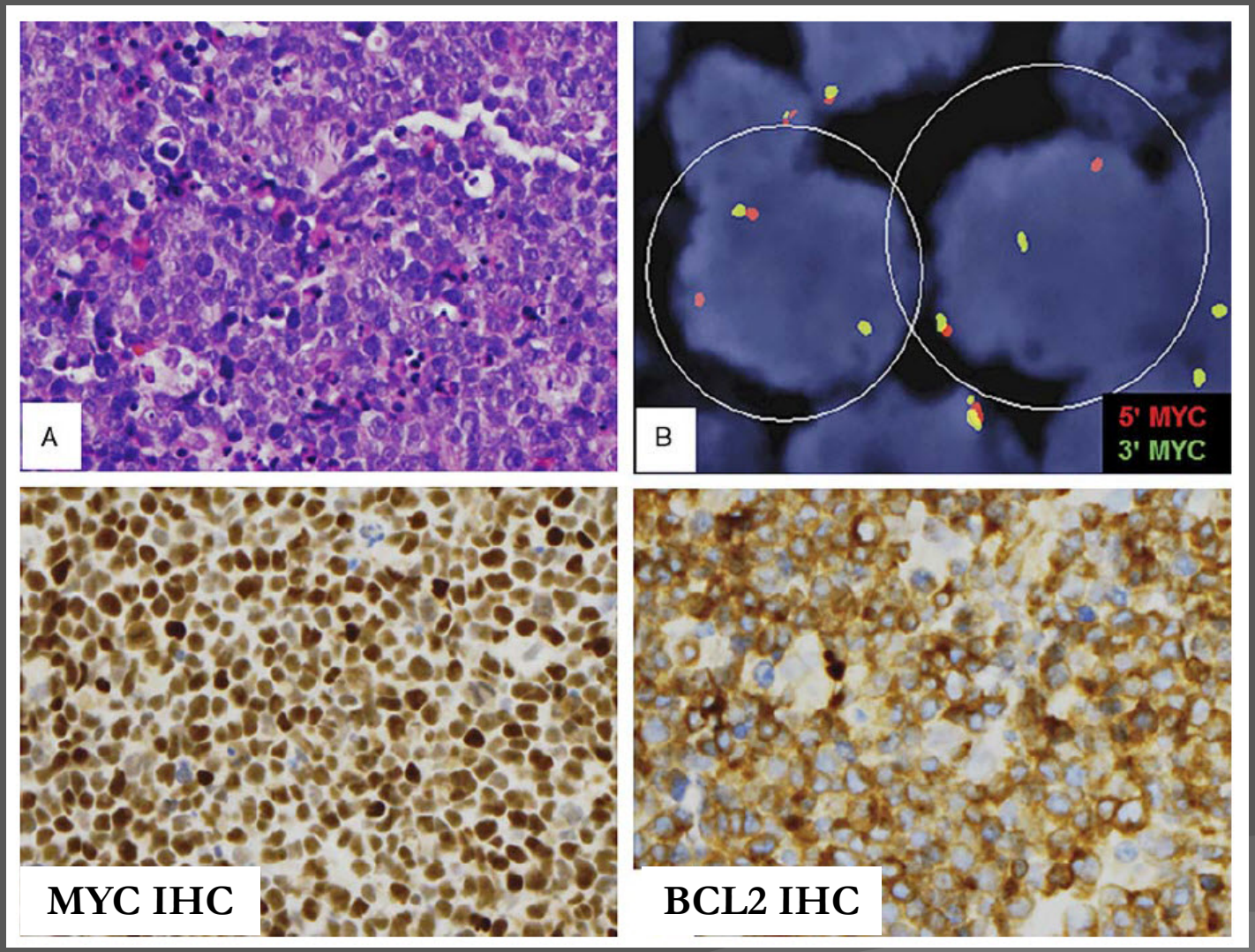


Prognosis

- Cell of origin
  - IHC – CD10, BCL6 &MUM-1
- BCL2 / MYC expression



DLBCL Prognostic Testing



High grade

- Burkitt lymphoma
  - Endemic in Africa
  - Seen in children and related to Epstein-Barr virus
  - B-cell phenotype
  - t(8:14) MYC/IgH
  - Usually extranodal
  - High mitotic rate (starry-sky)
  - Could be HIV associated
- Lymphoblastic lymphoma

Clinical Findings

- Enlarged painless lymphadenopathy
- B-symptoms, fever, sweats, weight loss
- Impingement or obstruction of adjacent structures (mass effect)
- Extranodal presentation (30% of cases) GI tract, spleen, salivary gland

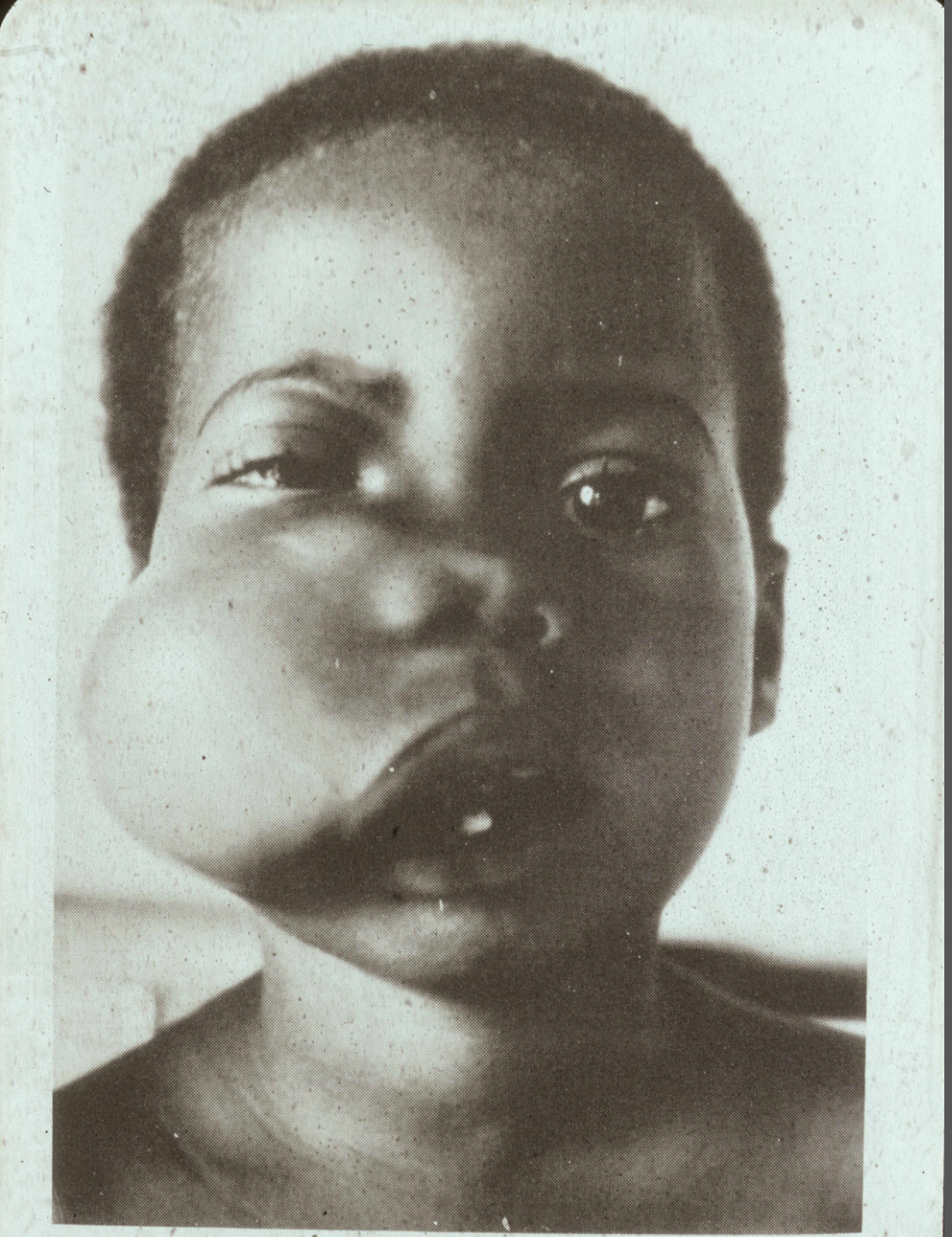
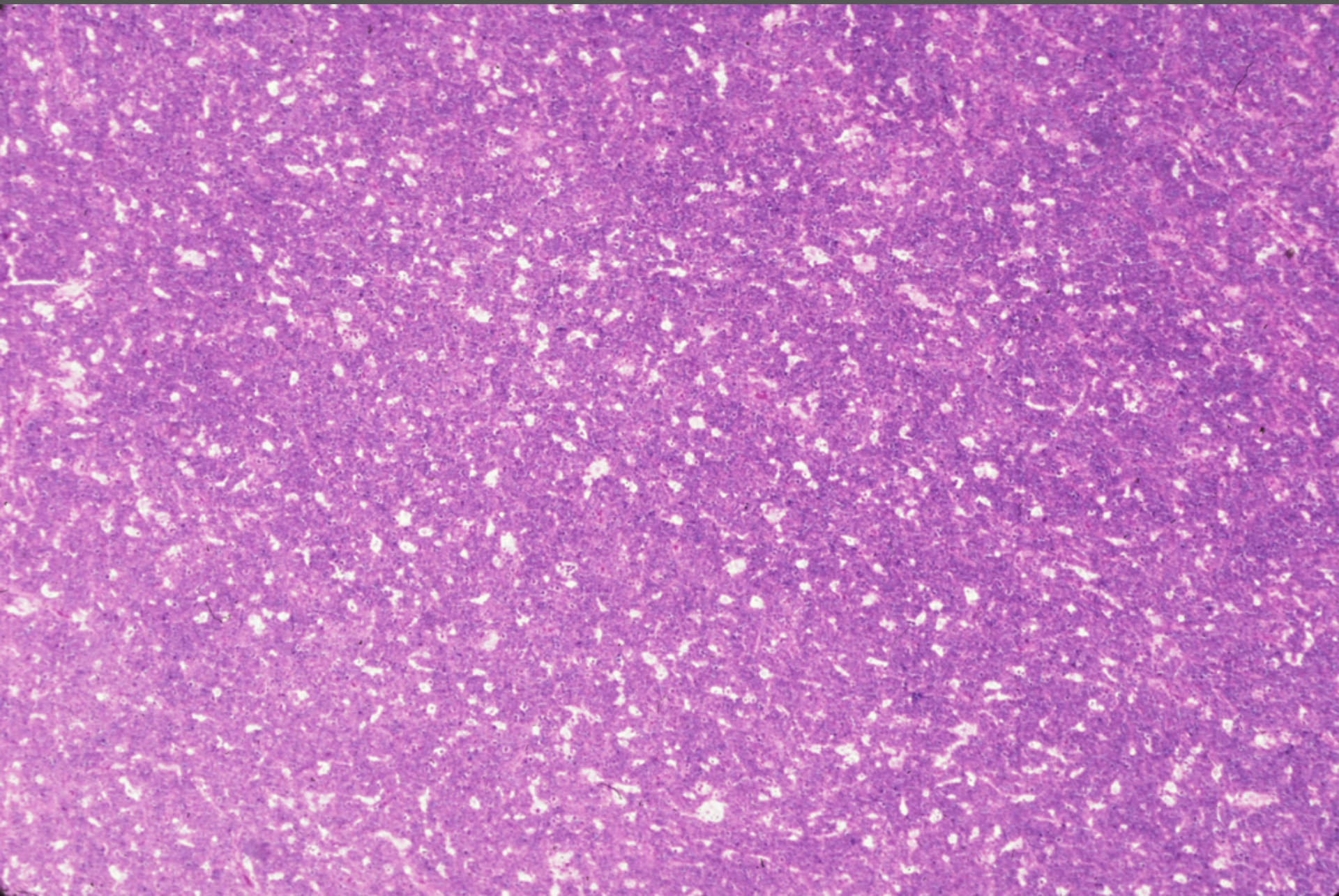


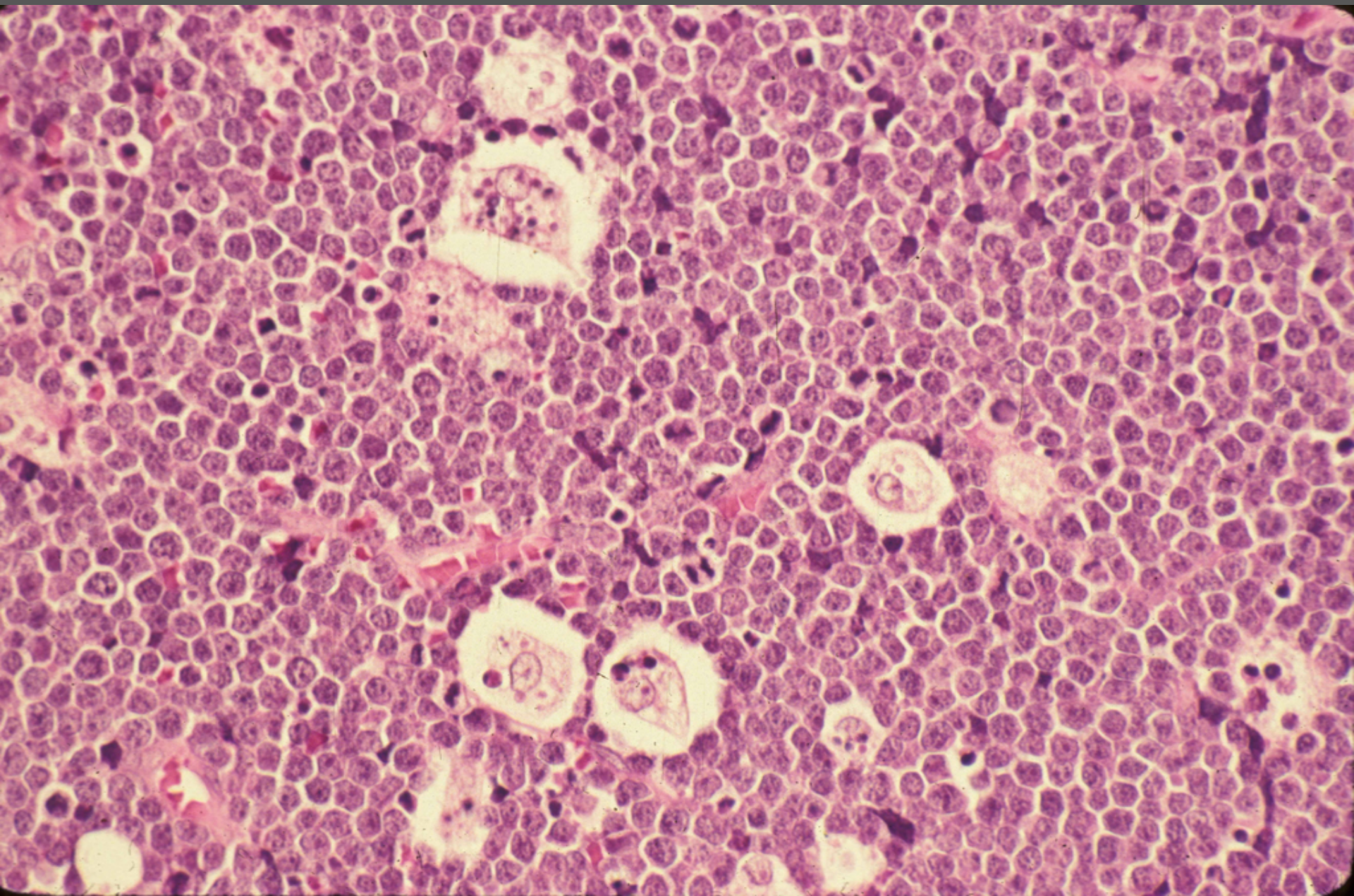
FIGURE 10–6. Burkitt's lymphoma in a nine-year-old child. The maxillary tumor mass is a characteristic presentation of this disease.

Burkitt lymphoma involving jaw

Burkitt lymphoma - Starry-sky pattern



Burkitt lymphoma tingible-body macrophages



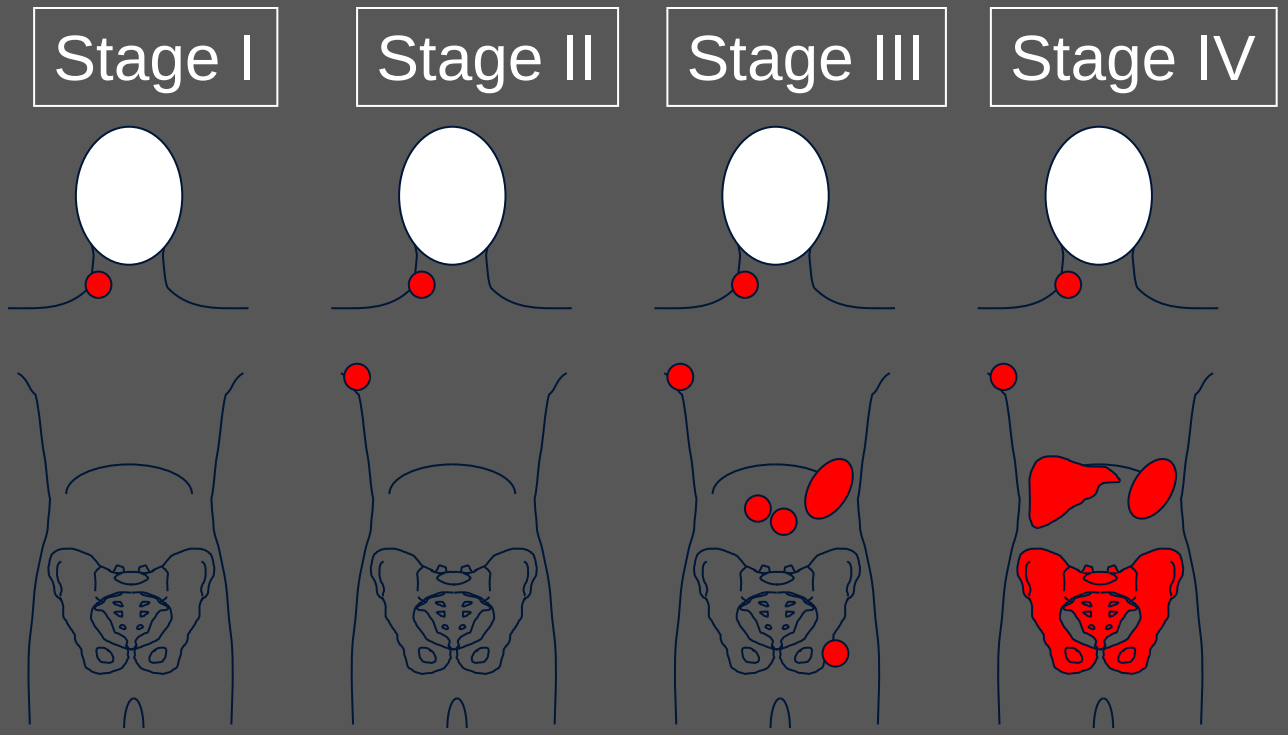
NHL Treatment: Aggressive

- Combination chemotherapy is mainstay of therapy
- R-CHOP is proven standard
  - Rituximab
  - Cyclophosphamide
  - Hydroxdaunomycin = doxorubicin
  - Oncovin = vincristine
  - Prednisone
- Additional treatment depending upon individual circumstances:
  - XRT for bulky lesions
  - CNS prophylaxis with IT chemotherapy (MTX, ara-C)
    - if liver, BM, testicular, sinus involvement or multiple extra-nodal sites
- CURE is the goal!

Sum…

- Indolent Lymphomas
  - Very slow growing, over years.
  - Follicular lymphoma, grades I/II is prototype.
  - If can’t cure, goal is to control disease/symptoms.
  - Decision of WHEN to treat is important.
- Aggressive Lymphomas
  - Rapidly growing, over days, months.
  - Diffuse large B cell lymphoma is prototype.
  - Cure is possible.
  - About 50% with multi-agent chemotherapy.

Staging of lymphoma



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

Lymphoproliferative Disorders

- **Malignant lymphoma**
  1. **Non-Hodgkin lymphoma (NHL)**
  2. **Hodgkin (disease) lymphoma**
  3. **Multiple myeloma**

Hodgkin lymphoma

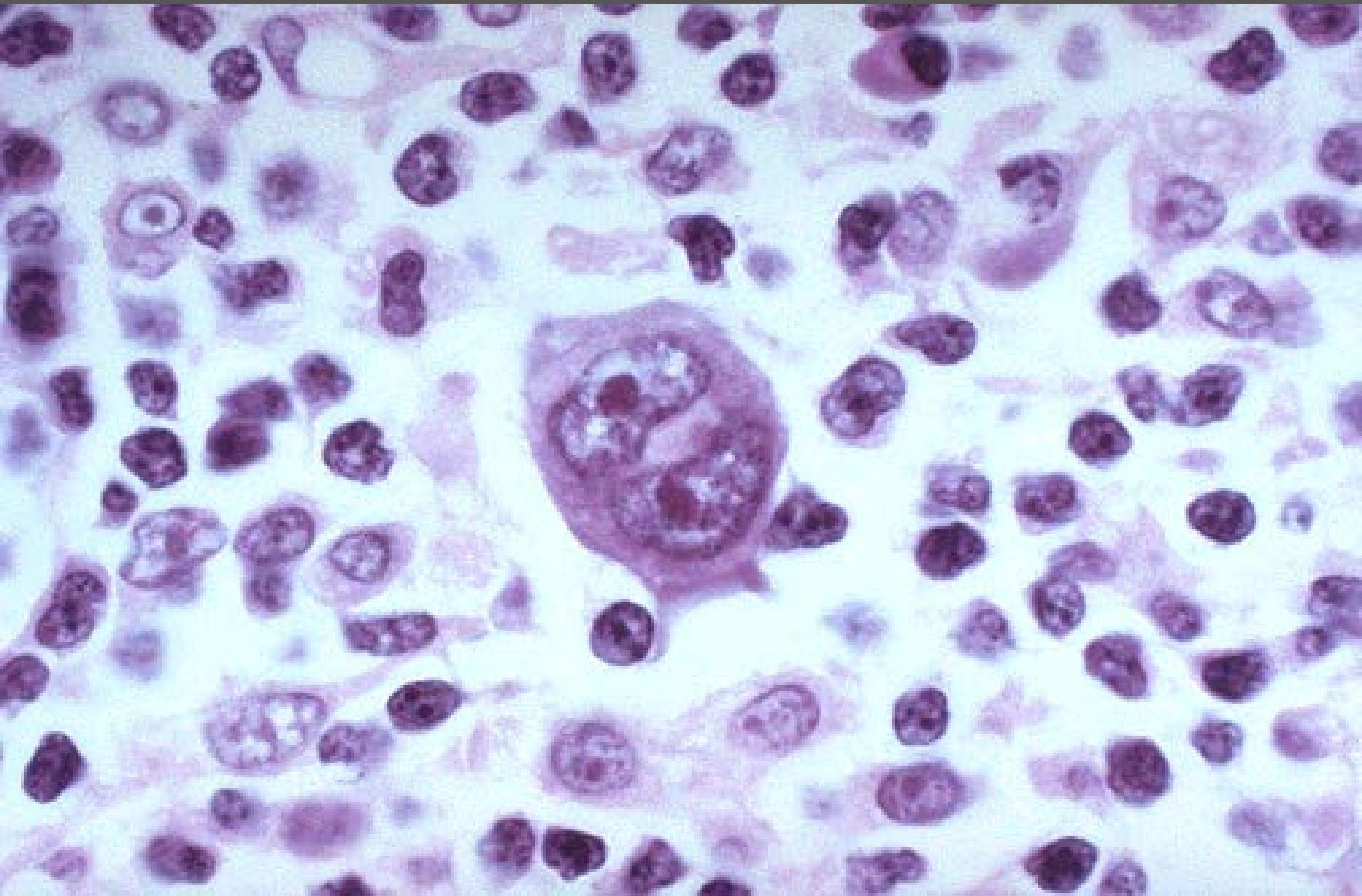
Thomas Hodgkin
(1798-1866)

Hodgkin lymphoma

- Reed-Sternberg cells are the tumor cells

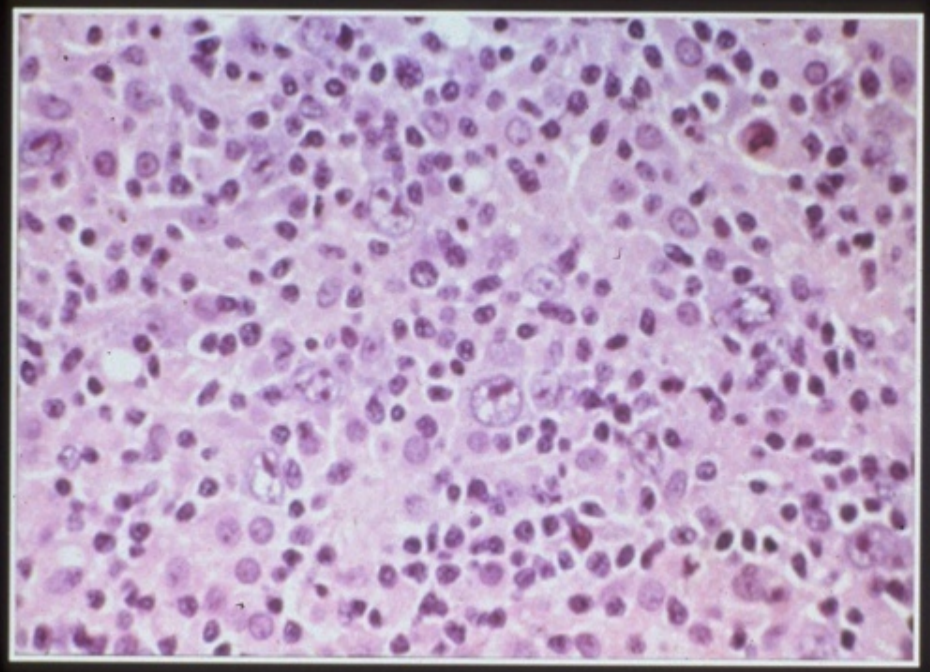
- Large numbers of “reactive” cells are also seen in the background

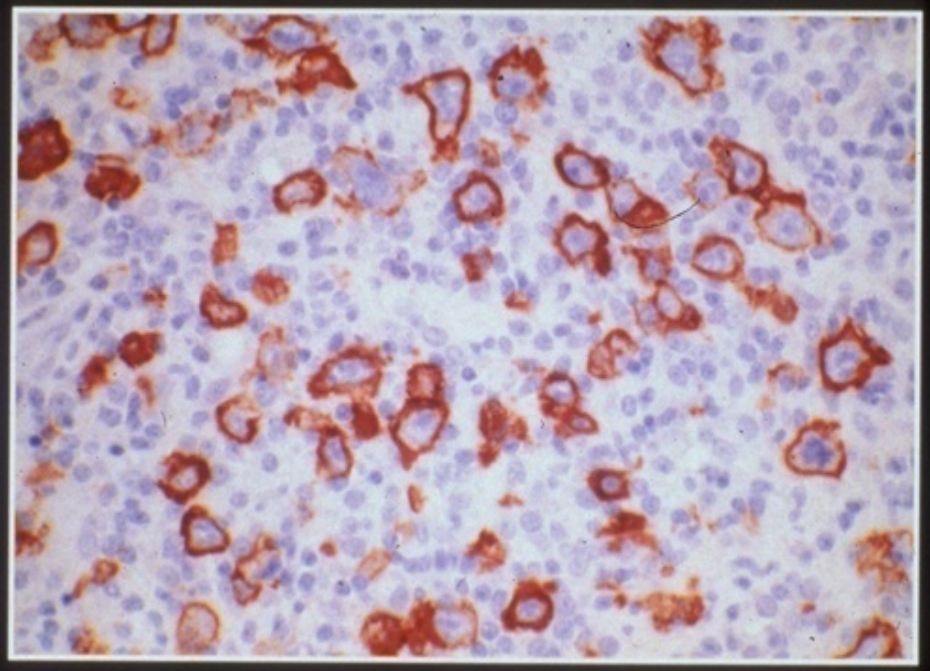
Reed-Sternberg Cells in a Reactive Background



Reed Sternberg Cells

CD30 and CD15 positive

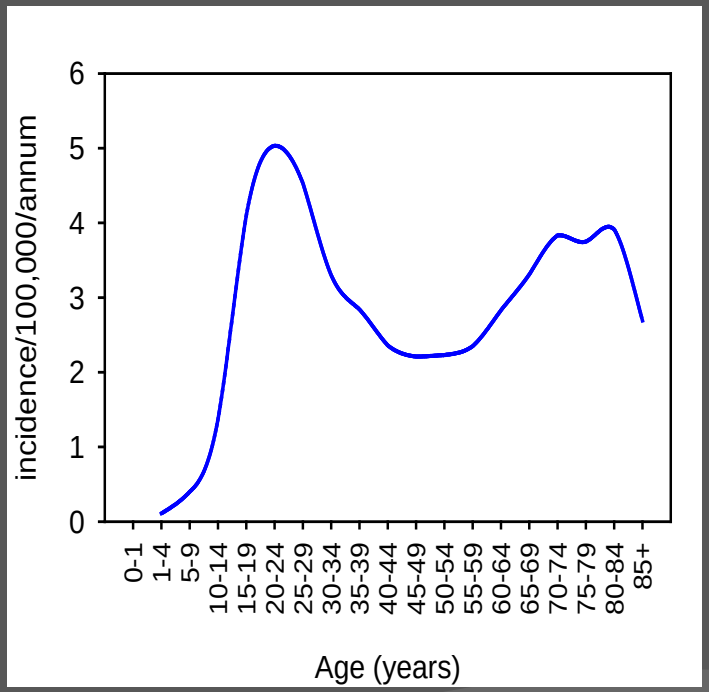




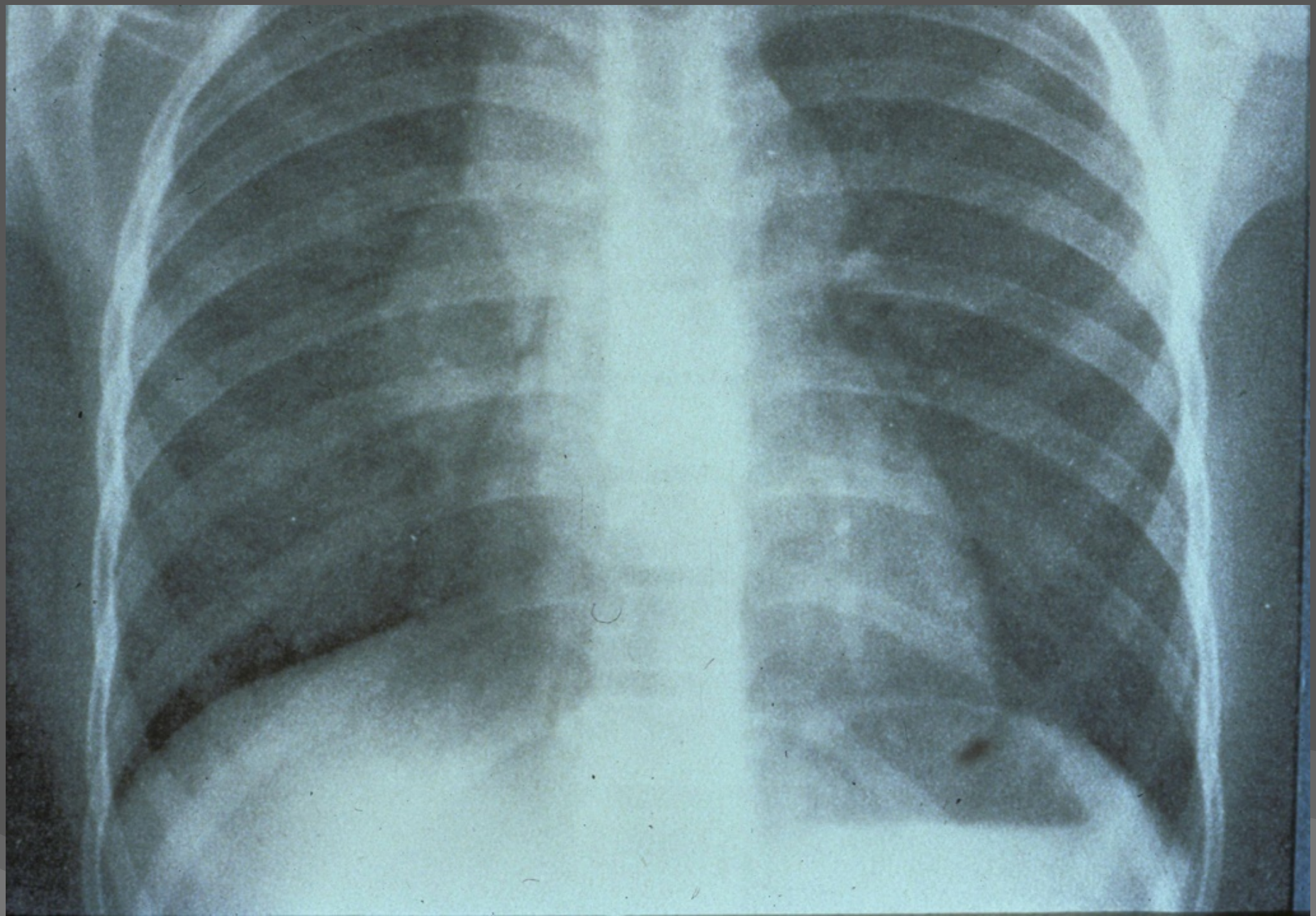
CD30

Clinical Findings

- Males > Females
- Bimodal age distribution 15-45 years old and > 50 years old
- Painless enlargement of lymph nodes, usually in neck
- Constitutional symptoms are common
- Extranodal disease is rare



Mediastinal involvement by HL is common



Subtypes of Hodgkin Lymphoma

- Classical Hodgkin Lymphoma
  - Nodular sclerosis 60-80%
  - Mixed cellularity 15-30%
  - Lymphocyte-rich 5-6%
  - Lymphocyte-depleted <1%

- Lymphocyte predominant, nodular HL 4-5%

Thank you

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