Lymphoma

Overview

- Concepts, classification, biology
- Epidemiology
- Clinical presentation
- Diagnosis
- Staging
- Three important types of lymphoma

How Cancer Develops

- Normal cells are programmed to multiply, die when they're old
- Signals to multiply and die are controlled by specific genes
- Mutations can occur in these genes
- If enough mutations occur in genes controlling growth or cell death a cell begins to **multiply uncontrollably**
- The cell has then become cancerous or "malignant"

Features common to cancer cells

- Growth in the absence of “go” signals
- Growth despite “stop” signals
- Locally invasive growth and metastases to distant sites

Bone Marrow

- Present in the soft inner part of some bones such as the skull, shoulder, blade, ribs, pelvis, and backbones. (Occupies central cavity of bone)

- The bone marrow is made up of blood-forming stem cells, lymphoid tissue, fat cells, and supporting tissues that aid the growth of blood forming cells.

Bone Marrow

- Spongy tissue where development of all types of blood cells takes place
- All bones have active marrow at birth
- Adulthood - vertebrae, hip, shoulders, ribs, and skull contain marrow

Hematopoietic Malignancies

- **Lymphoma is a general term for hematopoietic solid malignancies of the *lymphoid* series.**

- **Leukemia is a general term for liquid malignancies of either the *lymphoid* or the *myeloid* series.**

Conceptualizing lymphoma

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

What is Lymphoma

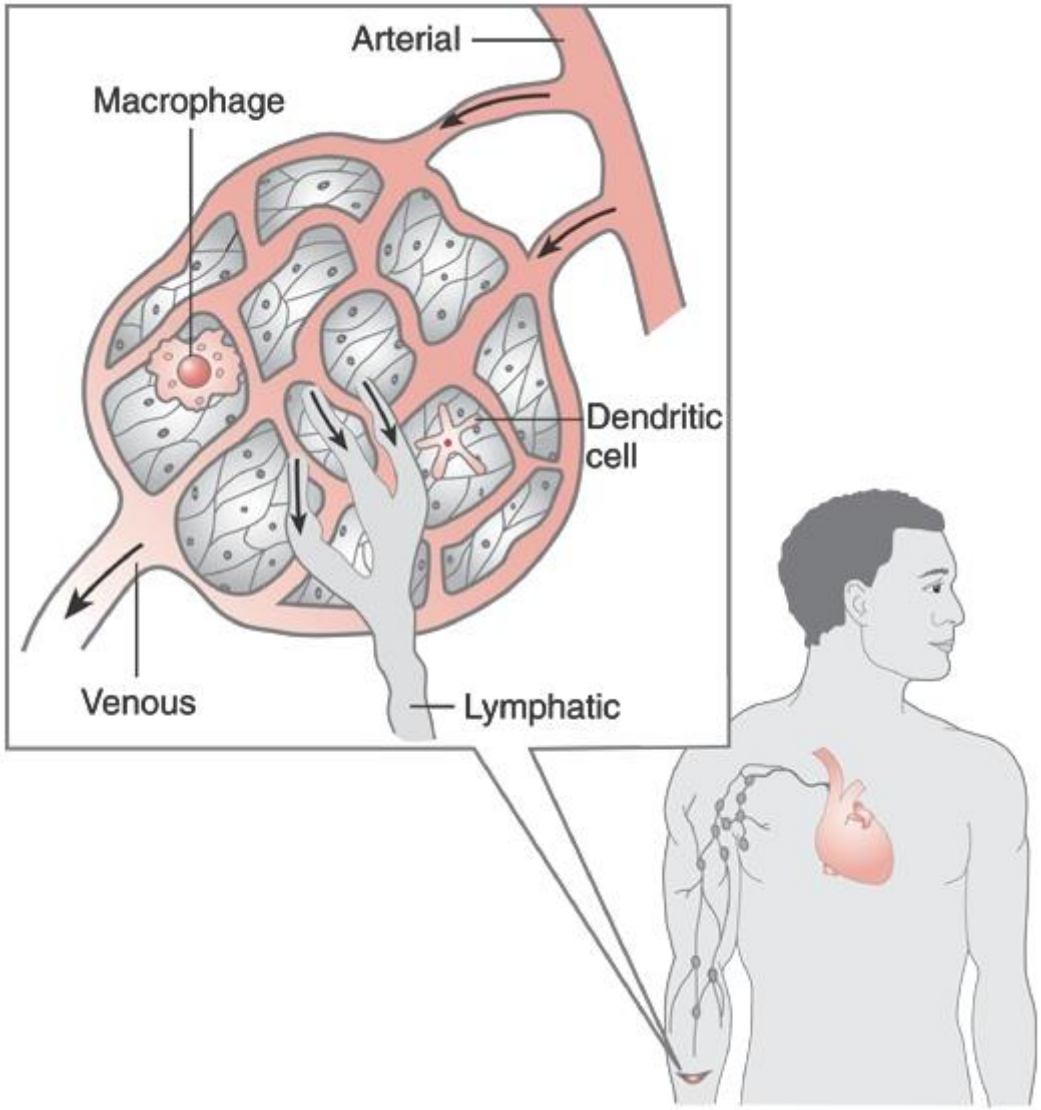
- Lymphomas are cancers that begin by the “malignant transformation” of a lymphocyte in the lymphatic system
- Many lymphomas are known to be due to specific genetic mutations
- Follicular lymphoma due to overexpression of BCL-2 (gene that blocks programmed cell death)

What is the Lymphatic System?

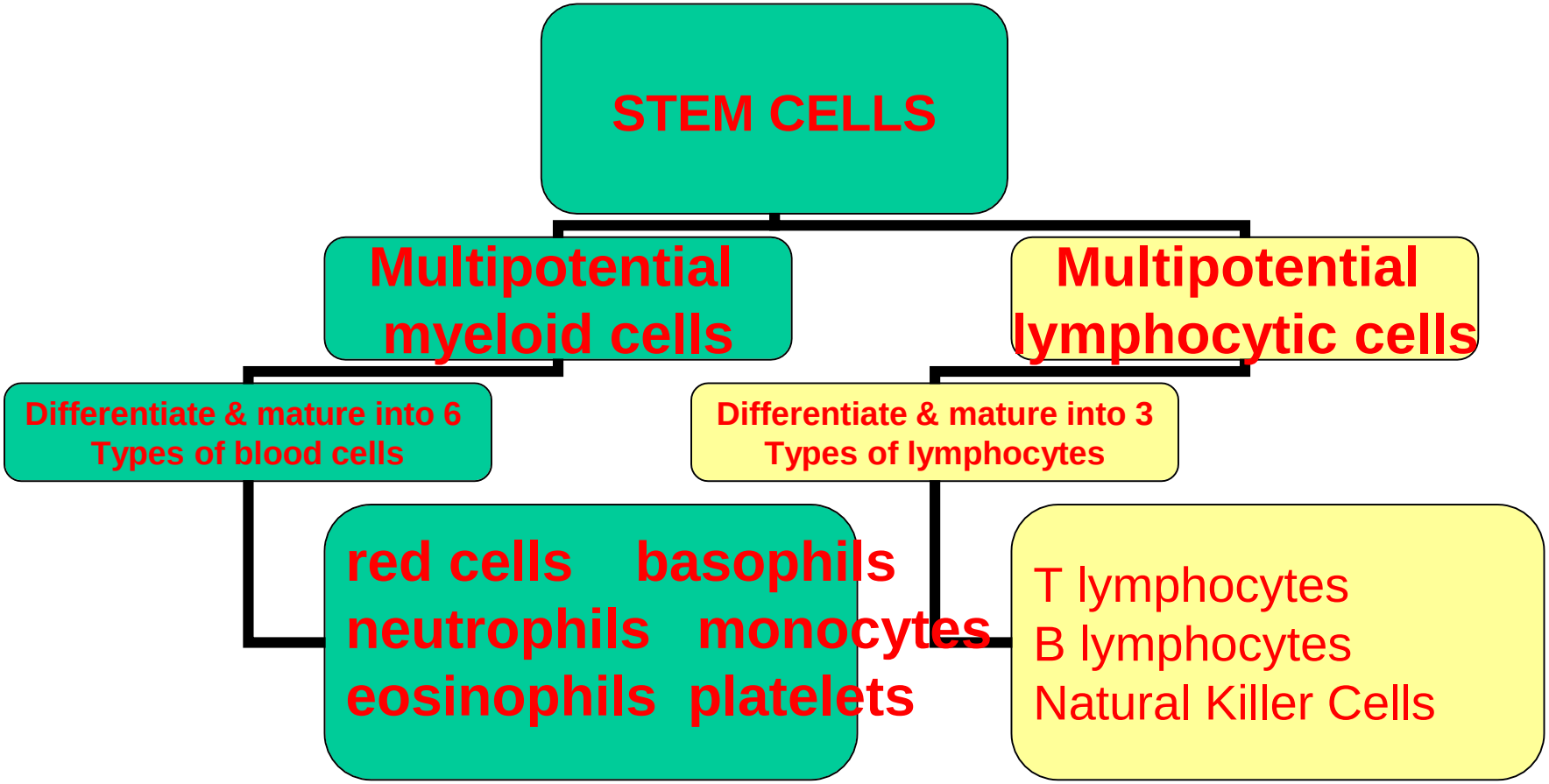
- Made up of organs, such as the tonsils, spleen, liver, bone marrow and a network of lymphatic vessels that connect glands, called lymph nodes
- Lymph nodes located throughout the body
- Lymph nodes filter foreign particles out of the lymphatic fluid
- Contain B and T lymphocytes

Lymphatic System

- Lymph nodes act as a filter to remove bacteria, viruses, and foreign particles
- Most people will have had “swollen glands” at some time as a response to infection



Blood Cell and Lymphocyte Development

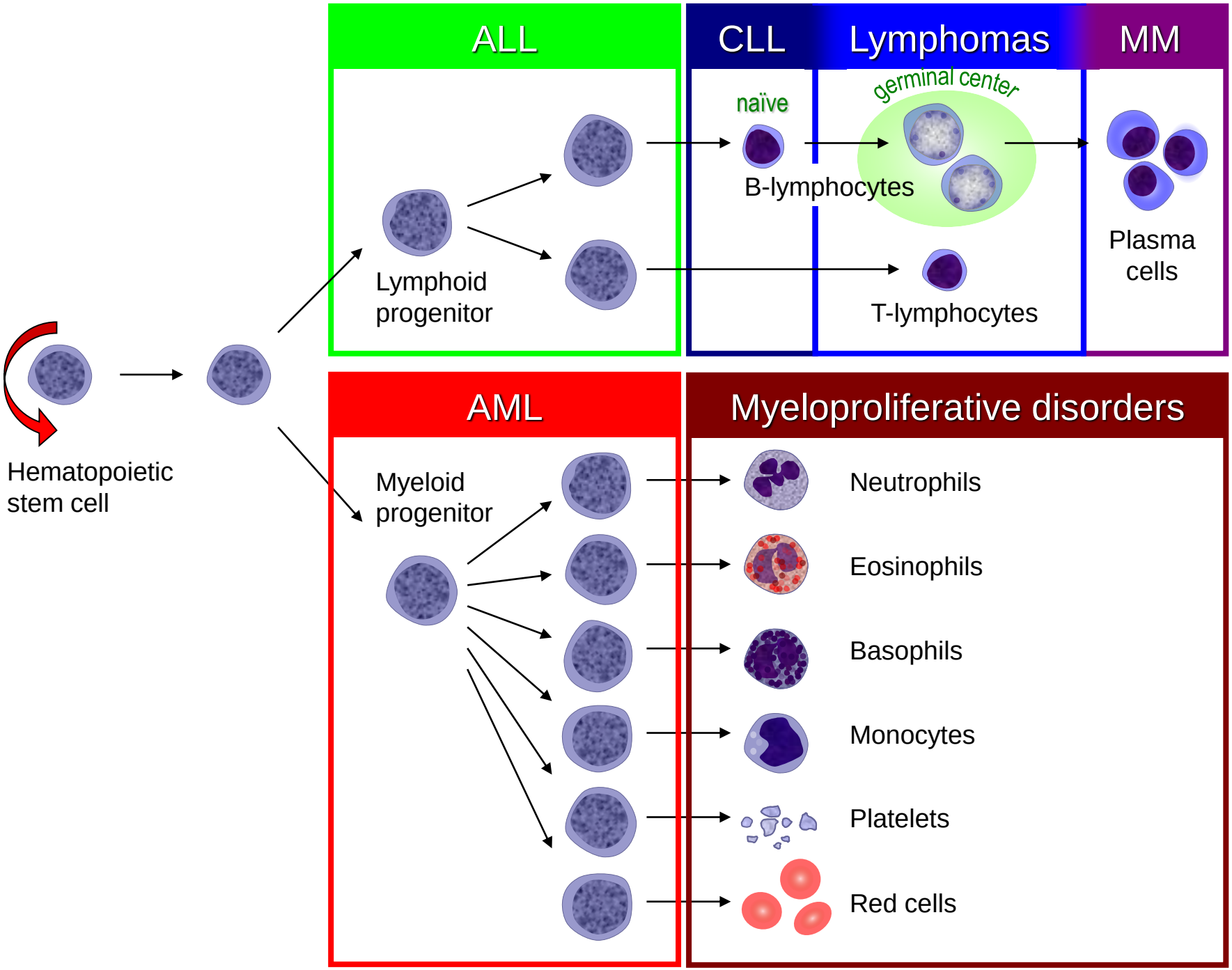


Lymphocytes

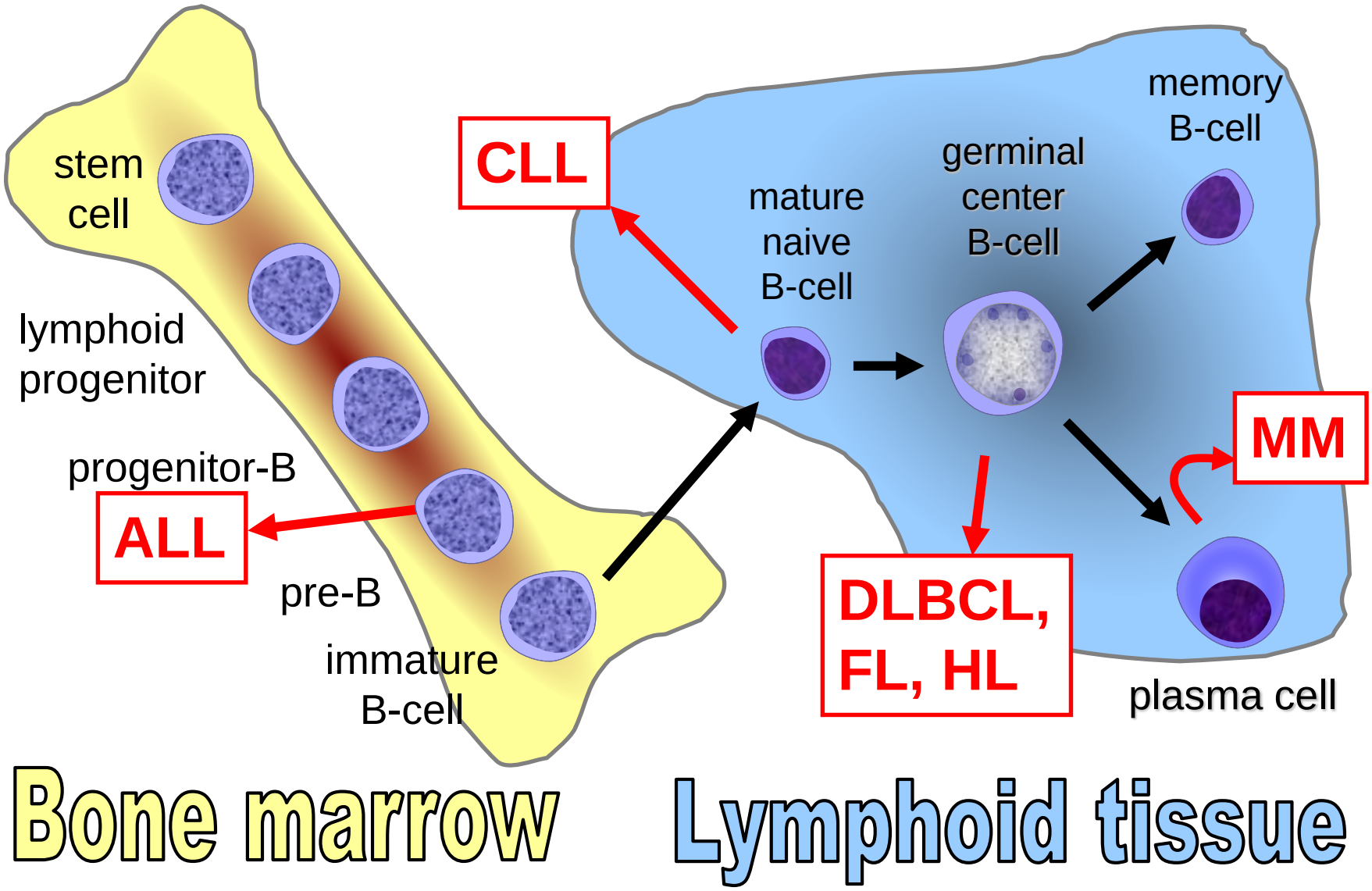
- Most lymphocytes are in lymph nodes, spleen, bone marrow and lymphatic vessels
- 20% of white blood cells in blood are lymphocytes
- T cells, B cells, natural killer cells
- B cells produce antibodies that help fight infectious agents
- T cells help B cells produce antibodies and they fight viruses

T-Cells and B-Cells

- **Immature lymphocytes that travel to the thymus differentiate into T-Cells**
  - **“T” is for thymus**
- **Immature lymphocytes that travel to the spleen or lymph nodes differentiate into B cells**
  - **"B" stands for the bursa of Fabricius, which is an organ unique to birds, where B cells mature.**


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



Classification

Biologically rational classification	Clinically useful classification
Diseases that have distinct • morphology • immunophenotype • genetic features • clinical features	Diseases that have distinct • clinical features • natural history • prognosis • treatment

Classification

- Usually classified by how the cells look under a microscope and how quickly they grow and spread
  - Aggressive lymphomas (high-grade lymphomas)
  - Indolent Lymphomas (low-grade lymphomas)

Lymphoma classification (2001 WHO)

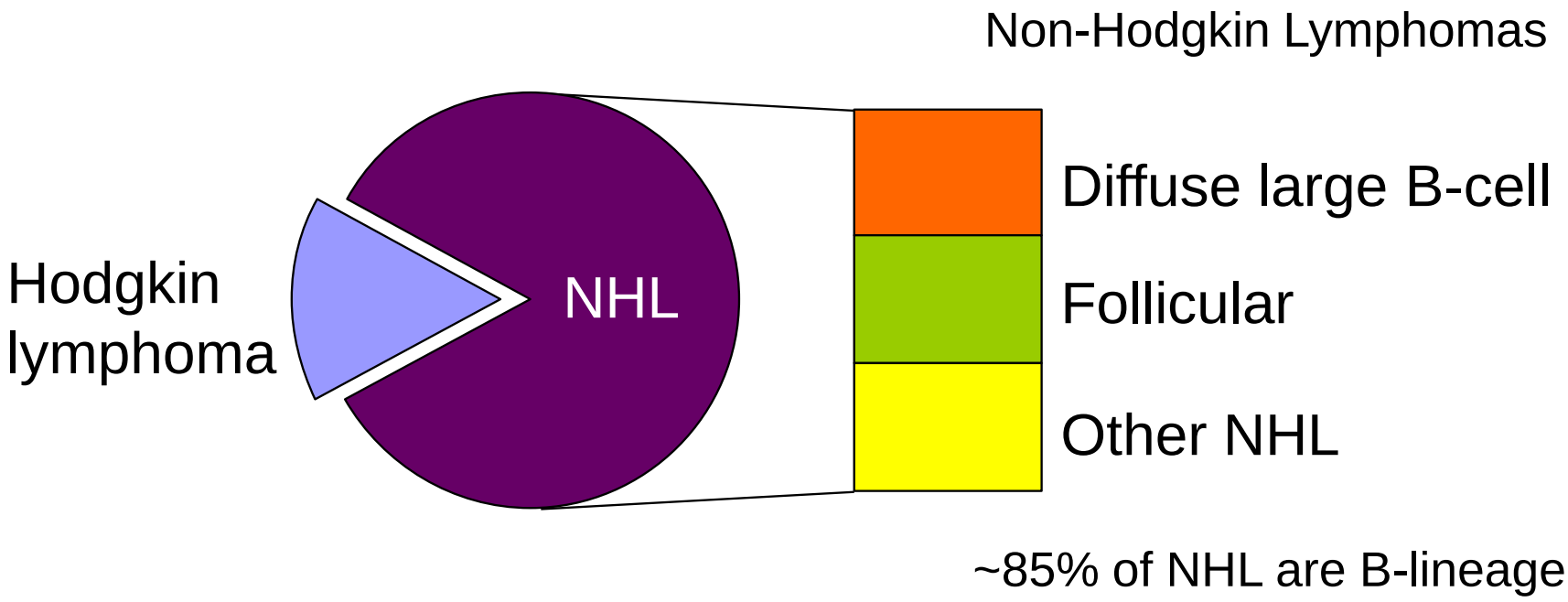
- B-cell neoplasms
  - precursor
  - mature
- T-cell & NK-cell neoplasms
  - precursor
  - mature
- Hodgkin lymphoma

Non-Hodgkin Lymphomas

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%

B-Cell Lymphoma (80%)

- B-Cells help make antibodies, which are proteins that attach to and help destroy antigens
- Lymphomas are caused when a mutation arises during the B-cell life cycle
- Various different lymphomas can occur during several different stages of the cycle
  - Follicular lymphoma, which is a type of B-cell lymphoma is caused by a gene translocation which results in an over expressed gene called BCL-2, which blocks apoptosis.

T-Cell Lymphoma (15%)

- The T-cells are born from stem cells, similar to that of B-cells, but mature in the thymus.
- They help the immune system work in a coordinated fashion.
  - These types of lymphomas are categorized by how the cell is affected
    - Anaplastic Large cell Lymphoma, t-cell lymphoma caused by a gene translocation in chromosome 5

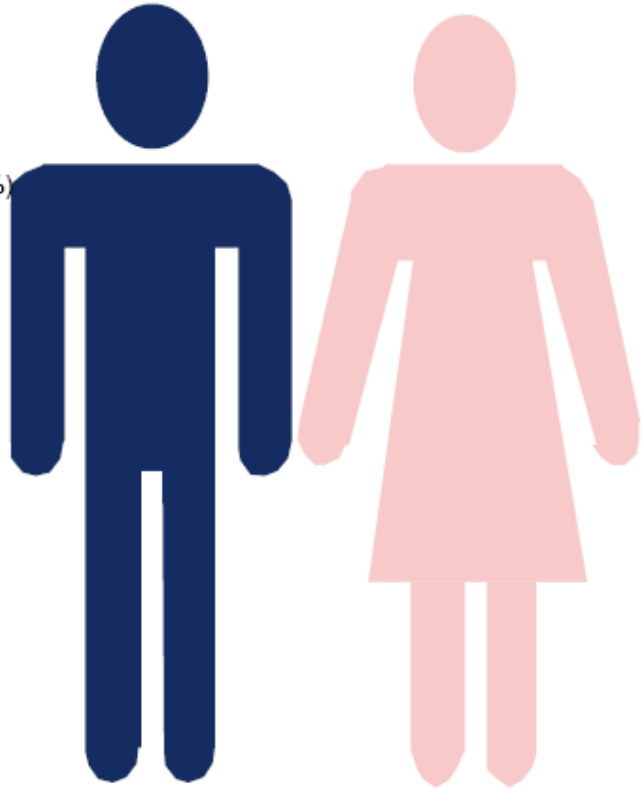
Mechanisms of lymphomagenesis

- Genetic alterations
- Infection
- Antigen stimulation
- Immunosuppression

Epidemiology of lymphomas

- males > females
- incidence
  - NHL increasing
  - Hodgkin lymphoma stable
- in NHL: 3rd most frequently diagnosed cancer in males and 4th in females
- in HL: 5th most frequently diagnosed cancer in males and 10th in females

DISTRIBUTION OF 20 MOST COMMON MALIGNANCIES
2005 ANALYTIC CASES (TOTAL CASES = 2,336)



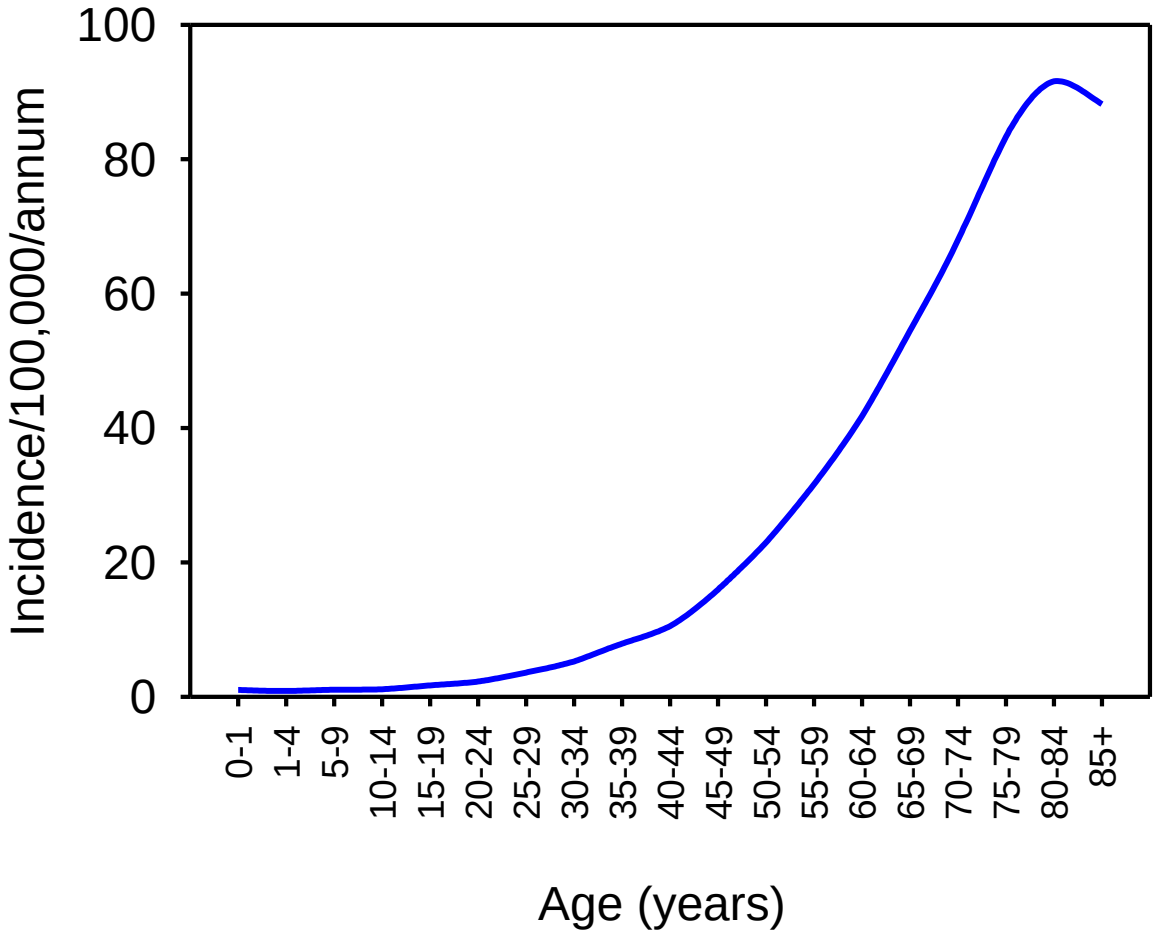
MALE

LEUKEMIA 92 (8.5%)
COLON, RECTUM 90 (8.3%)
NHL 83 (7.7%)
BRAIN, CNS 67 (6.2%)
HODGKIN'S LYMPHOMA 63 (5.8%)
BLADDER 62 (5.7%)
PROSTATE 61 (5.6%)
ORAL CAVITY 58 (5.4%)
NASOPHARYNX 58 (5.4%)
LUNG, PLEURA 55 (5.1%)
THYROID 44 (4.1%)
BONE, CARTILAGE 43 (4.0%)
STOMACH 37 (3.4%)
LARYNX 31 (2.9%)
SOFT TISSUE 31 (2.9%)
SKIN NON-MELANOMA 31 (2.9%)
KIDNEY, URINARY 26 (2.4%)
LIVER 20 (1.8%)
TESTIS, GENITAL 19 (1.8%)
PANCREAS 16 (1.5%)
ESOPHAGUS 16 (1.5%)

FEMALE

BREAST 344 (27.4%)
THYROID 141 (11.2%)
COLON, RECTUM 77 (6.1%)
NHL 76 (6.1%)
UTERUS, GENITAL 58 (4.6%)
ORAL CAVITY 53 (4.2%)
LEUKEMIA 53 (4.2%)
BRAIN, CNS 52 (4.1%)
CERVIX 44 (3.5%)
HODGKIN'S LYMPHOMA 44 (3.5%)
OVARY 40 (3.2%)
KIDNEY, URINARY 28 (2.2%)
LUNG, PLEURA 26 (2.1%)
BONE, CARTILAGE 25 (2.0%)
ESOPHAGUS 24 (1.9%)
SKIN NON-MELANOMA 23 (1.8%)
NASOPHARYNX 21 (1.7%)
SOFT TISSUE 21 (1.7%)
STOMACH 15 (1.2%)
LIVER 12 (1.0%)
OTHER G.I. 12 (1.0%)

Age distribution of new NHL



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

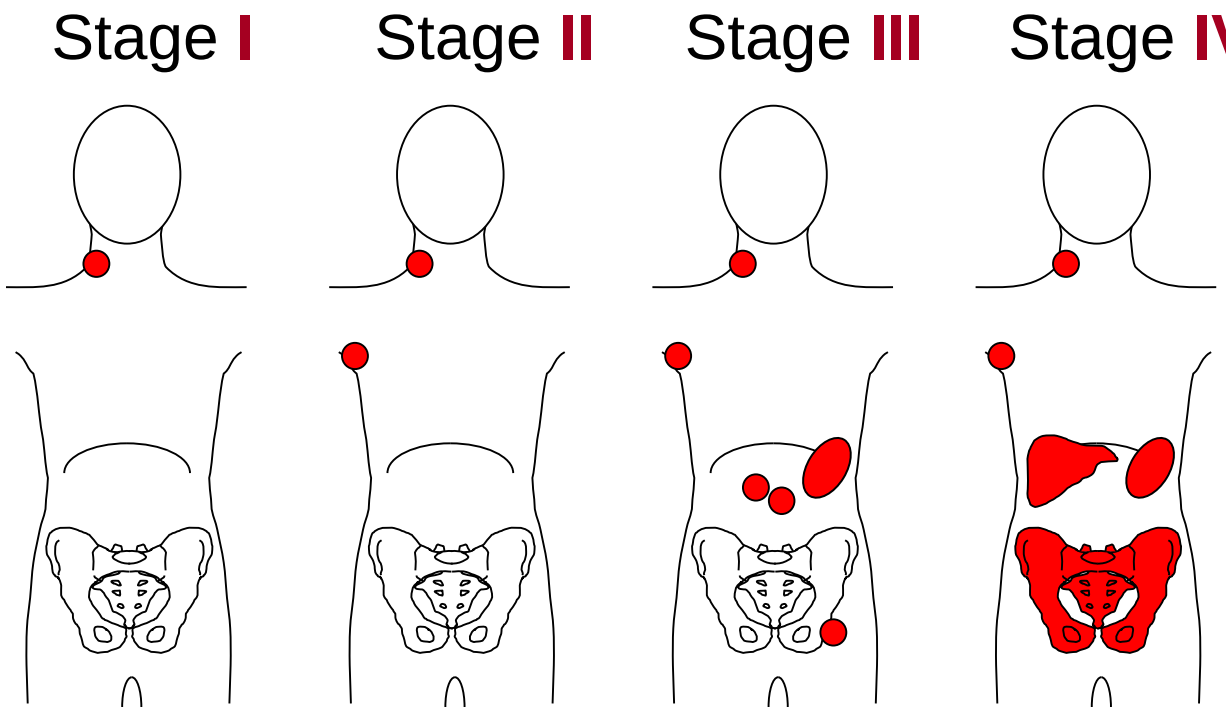
Other complications of lymphoma

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

Non-Hodgkin's Lymphoma Staging

- Stage is the term used to describe the extent of tumor that has spread through the body (**I** and **II** are localized where as **III** and **IV** are advanced.
- Each stage is then divided into categories **A**, **B**, and **E**
  - **A**: No systemic symptoms
  - **B**: Systemic Symptoms such as fever, night sweats and weight loss
  - **E**: Spreading of disease from lymph node to another organ

Staging of lymphoma



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

Staging

Stages of Non-Hodgkin's Lymphoma

Stage I (early disease): the cancer is found only in a single lymph node region OR one organ or area outside the lymph node.

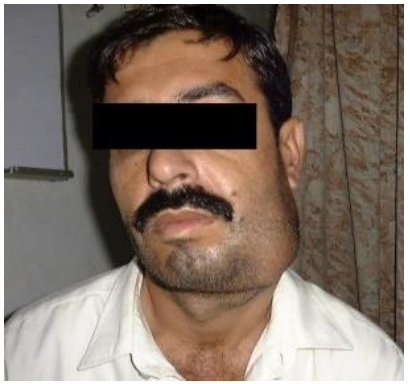
Stage II (locally advanced disease): the cancer is found in two or more lymph node regions on one side of the diaphragm (the breathing muscle that separates the abdomen from the chest), OR the cancer is found in one lymph node region plus a nearby area or organ.

Stage III (advanced disease): the disease involves lymph nodes both above and below the diaphragm OR one nodal area and one organ on opposite sides of the diaphragm.

Stage IV (widespread disease): the lymphoma is outside the lymph nodes and spleen AND has spread to one or more organs such as bone, bone marrow, skin, or other organs.

Symptoms

- Painful Swelling of lymph nodes located in the neck, underarm and groin.
- Unexplained Fever
- Night Sweats
- Constant Fatigue
- Unexplained Weight loss
- Itchy Skin



Cancer Sourcebook

Causes and Risk Factors

- The Exact causes are still unknown
  - Higher risk for individuals who:
    - Exposed to chemicals such as pesticides or solvents
    - Infected w/ Epstein-Barr Virus
    - Family history of NHL (although no hereditary pattern has been established)
    - Infected w/ Human Immunodeficiency Virus (HIV)

Diagnosis
Staging Studies

- Bone marrow aspiration and biopsy
- Radionuclide scans:
- GI x-rays
- Spinal fluid analysis
- CT scans
- Magnetic Resonance Imaging (MRI)
- Biopsy

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

Treatment

- Non-Hodgkin's Lymphoma is usually treated by a team of physicians including hematologists, medical oncologists and a radiation oncologist.

- In some cases such as for Indolent lymphomas, the Doctor may wait to start treatment until the patient starts showing symptoms, known as "watchful waiting"

Treatment Options

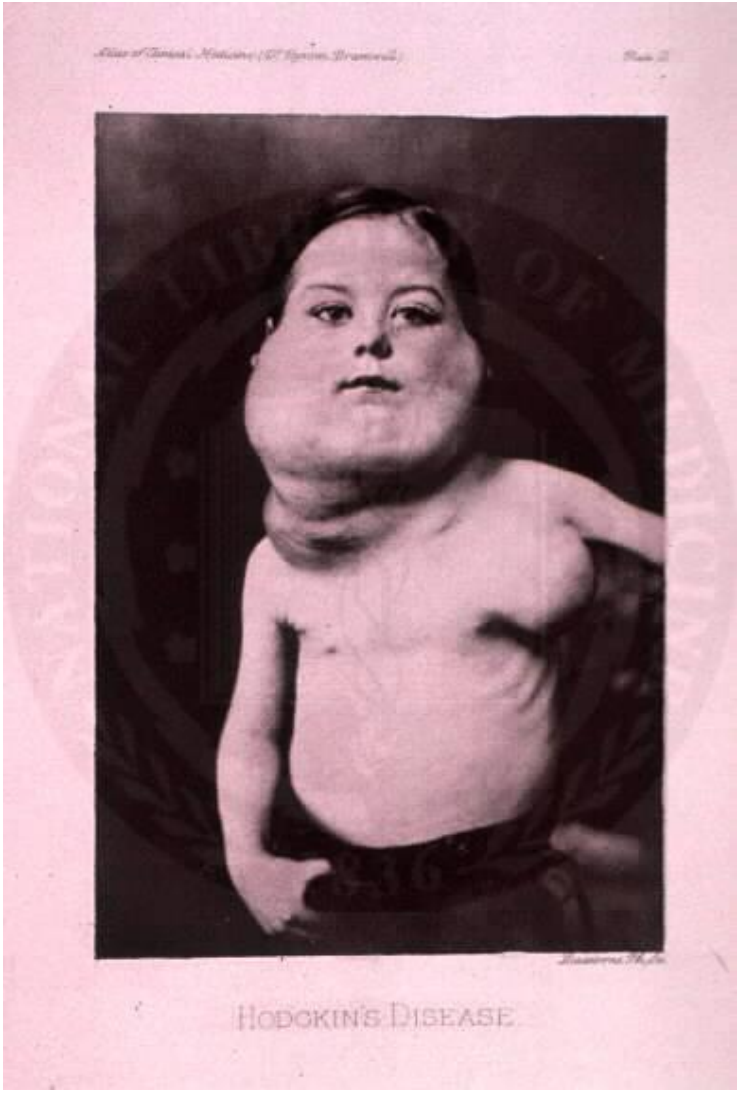
- Chemotherapy
- Radiation
- Bone Marrow Transplantation
- Surgery
- Immunotherapy
- Using the bodies own immune system combined with material made in a lab.

Survival Rates

- Survival Rates vary widely by cell type and staging.
  - 1 Year Survival Rate: 77%
  - 5 Year Survival Rate: 56%
  - 10 Year Survival Rate: 42%

Cancer.org

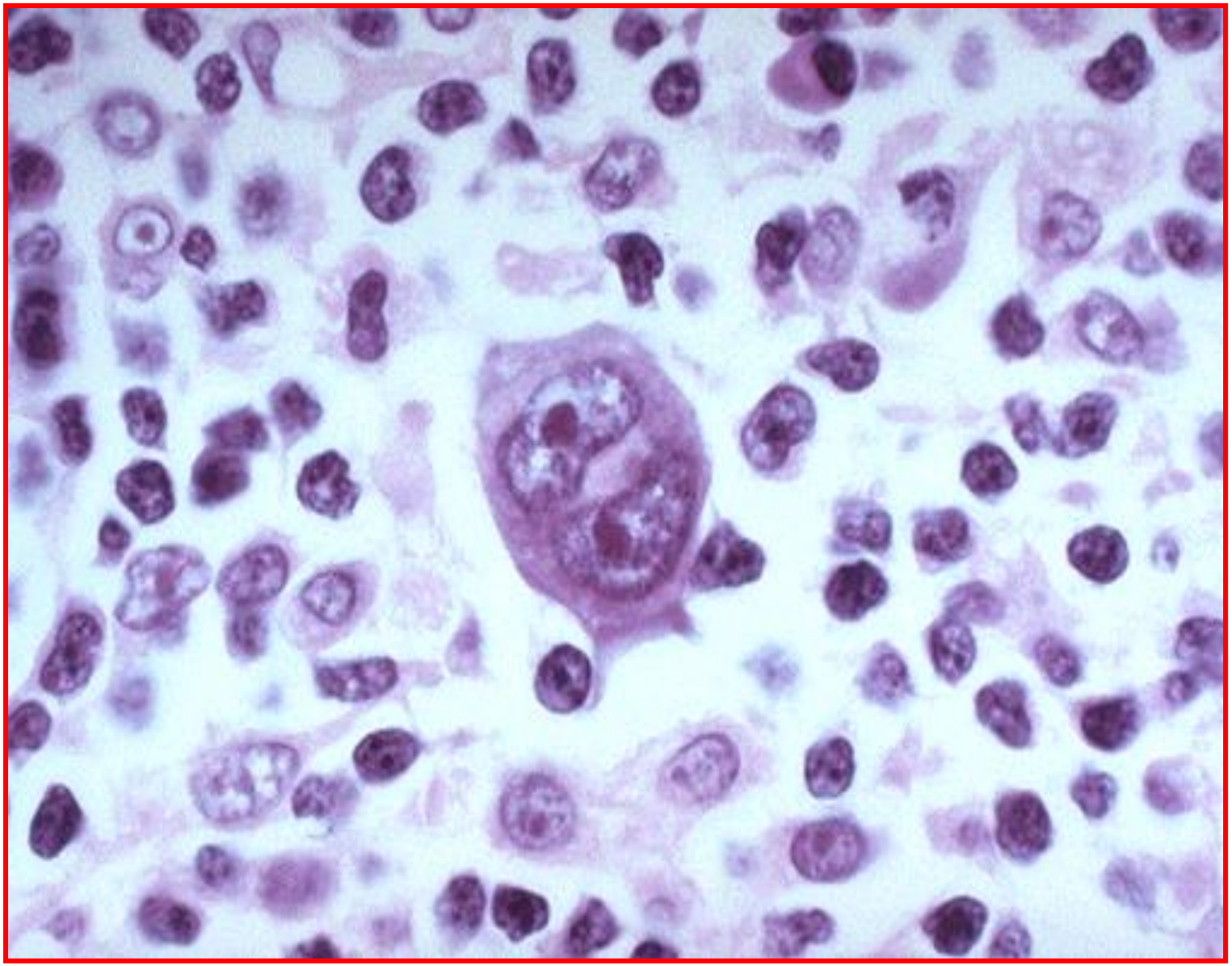
Classical Hodgkin Lymphoma



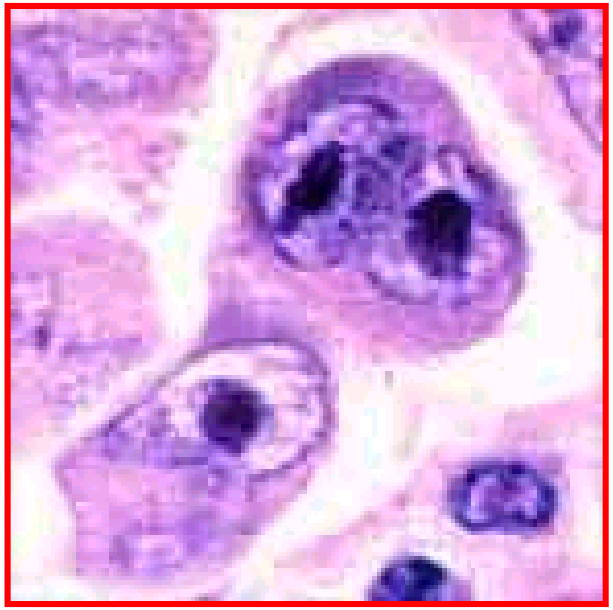
Hodgkin lymphoma

- 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

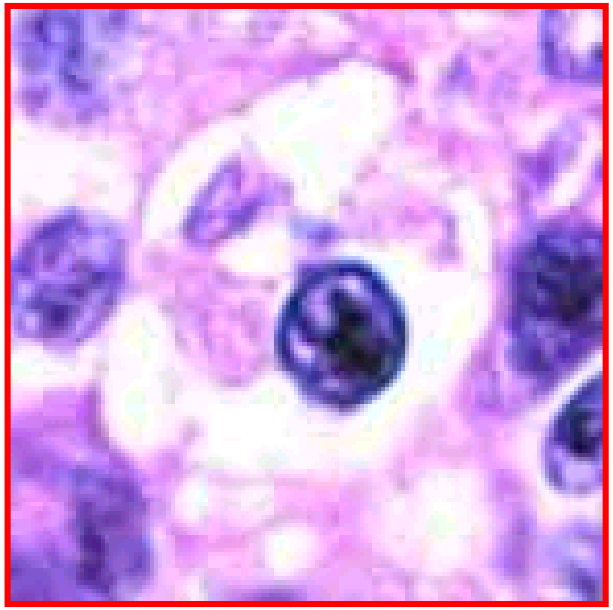


RS cell and variants



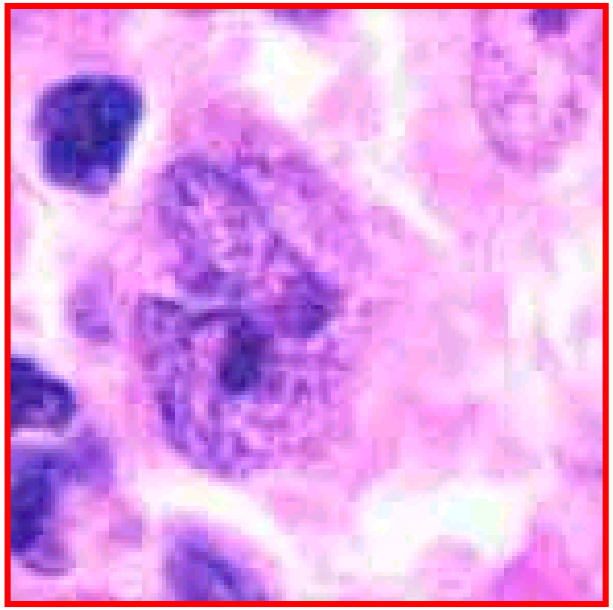
classic RS cell

(mixed cellularity)



lacunar cell

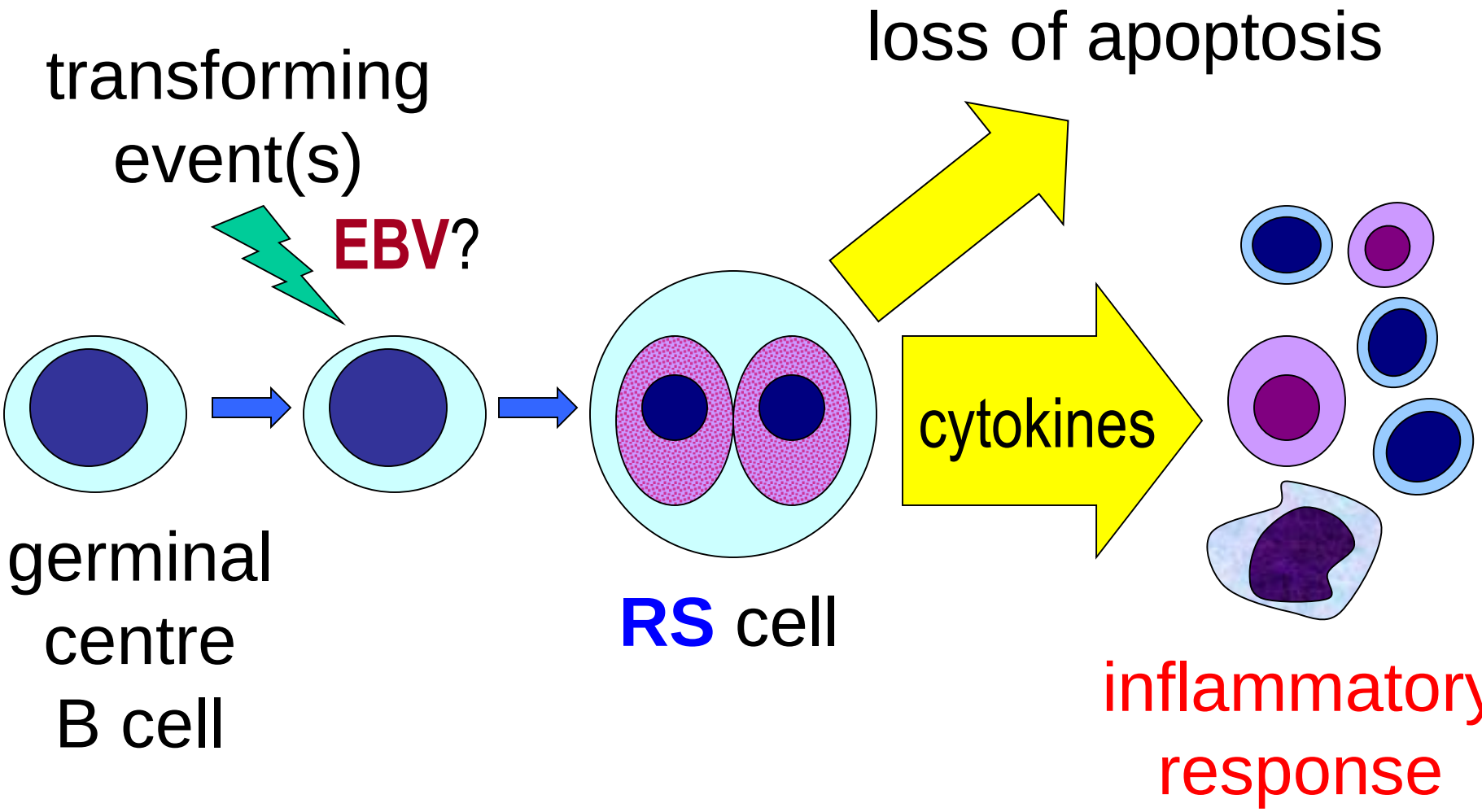
(nodular sclerosis)



popcorn cell

(lymphocyte predominance)

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

Age distribution of new Hodgkin lymphoma cases

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

Hodgkin's Disease/Lymphoma Treatment

With appropriate treatment about 85% of patients with Hodgkin's disease are curable

⑩I A,B	Radiation Therapy
⑩II A	Combination Chemo + Radiotherapy
⑩IIB; IIIA,B; IVA,B	Combination Chemo (+/- radiotherapy)

Hodgkin's Disease/Lymphoma Treatment

- Radiation therapy (35-40 Gy) 80-90% RC
- Mantle field
- Paraaortic field
- Pelvic field

- Combination chemotherapy
- ABVD 80% RC
- BEACOPP 90% RC

Hodgkin's Disease
Stanford V

Doxorubicin	25 mg/m2	IV	Days 1& 15
Vinblastine	6 mg/m2	IV	Days 1 & 15
Mechorethamine	6 mg/m2	IV	Day 1
Vincristine	1.4 mg/m2	IV	Days 8 & 22
Bleomycin	5 u/m2	IV	Days 8 & 22
Etoposide	60 mg/m2	IV	Days 15 & 16
Prednisone	40 mg/m2	PO	QOD

Treatment Repeated q 28 days

Vincristine max dose = 2.0 mg

Velban dose reduced to 4 mg/m2, VCR to 1 mg/m2, cycle 3, pts>50 yrs

Prednisone tapered beginning week 10

Bartlett, JCO 1995;13:1080

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

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

Lab Diagnostic Studies

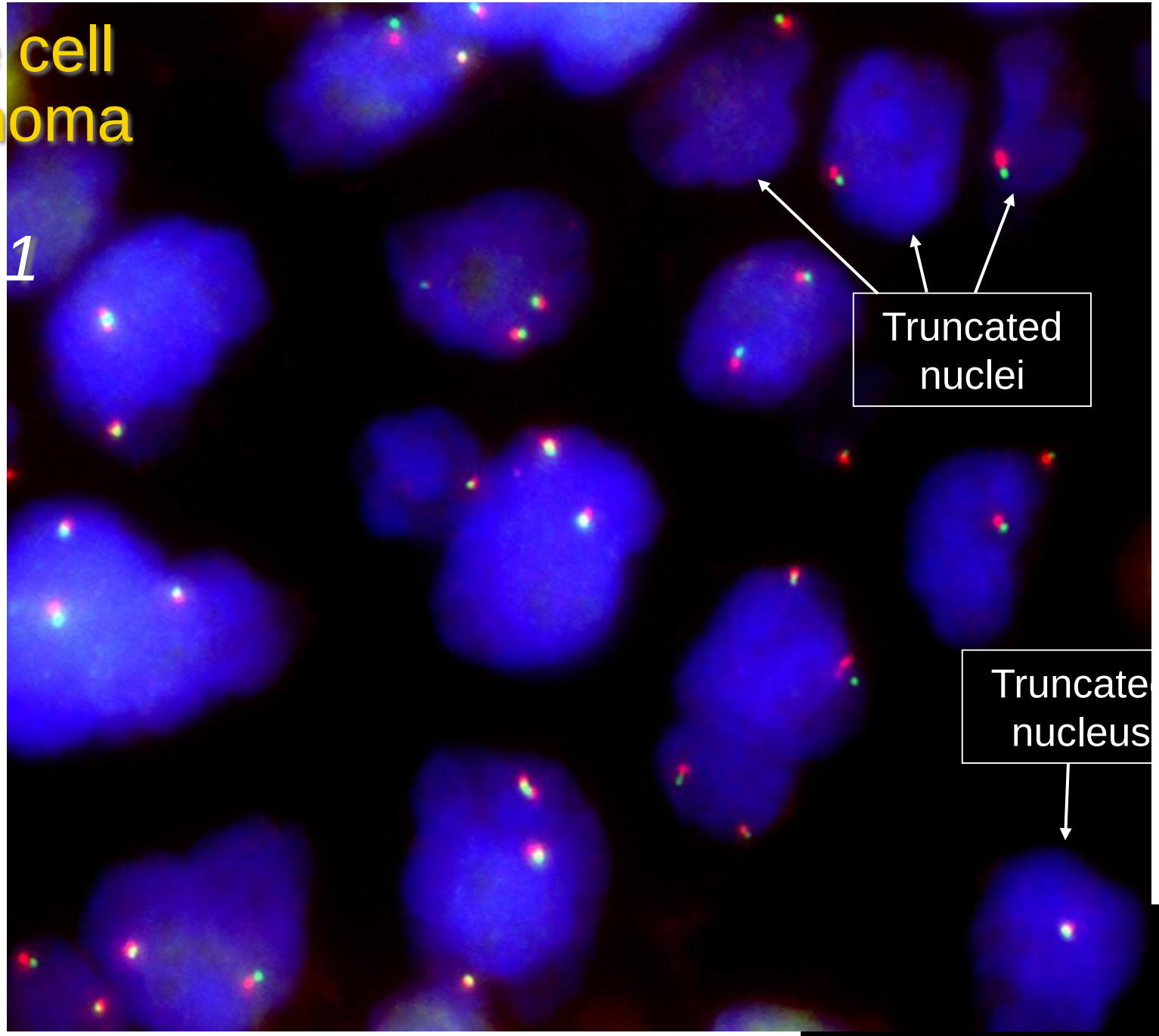
- Lymph node biopsy
- Bone marrow aspiration and biopsy
- Immunohistochemistry
- Flow cytometry
- Molecular Genetic studies
- Cytogenetics

Cytogenetic Lab

- t(14,18) common (about 30%)
  - *Bcl-2*
  - Follicular growth pattern
- t(8,14) ! common in Burkitt's ! *c-myc*
- Multiple anomalies common
- Correlation between cytogenetic change and outcome is variable

Large cell lymphoma

Case 1



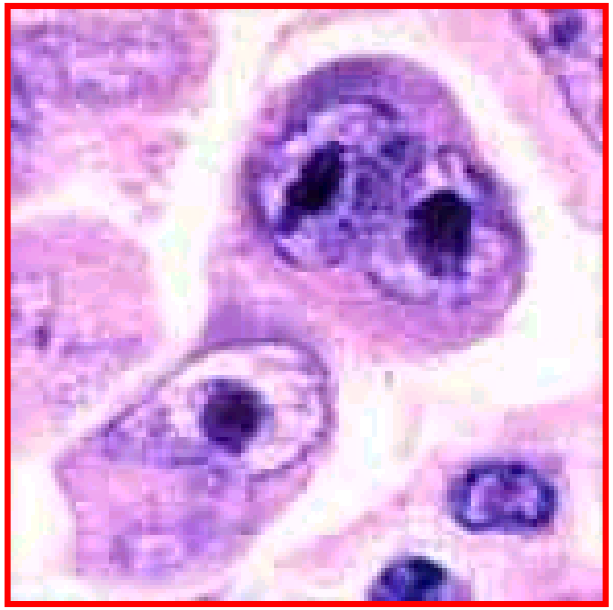
Myc split-apart probe:

Molecular Cytogenetic Lab

Recurrent molecular abnormalities in lymphoma

- **t(14;18) / Bcl2 - JH in follicular lymphoma**
- **t(11;14) / Bcl1 - JH in Mantle Zone lymphoma**
- **t(3;14) / Bcl6 - JH in Diffuse Large Cell lymphoma**
- **t(8;14) / cMyc - JH in Burkitt lymphoma**
- **t(2,5) / ALK-NPM in Anaplastic Large Cell Lymphoma**

Histology Lab
RS cell and variants



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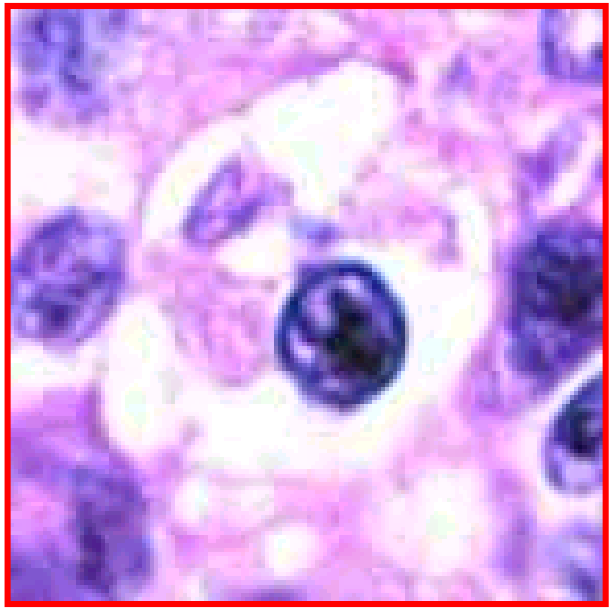

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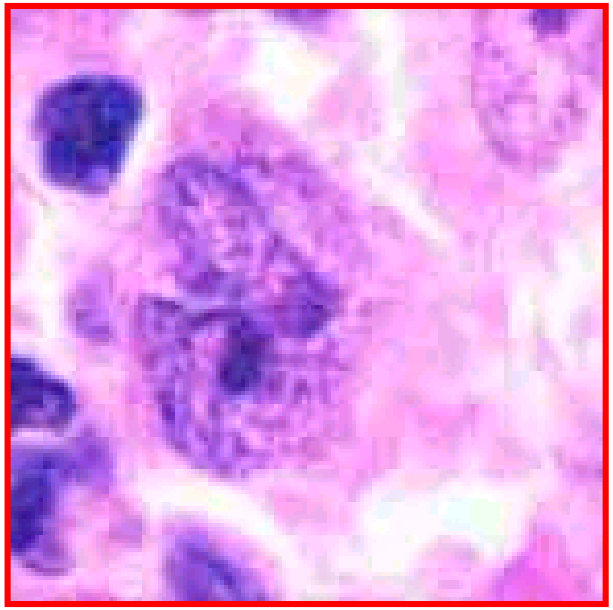

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