Hematologic Malignancies

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Objectives

- To review normal peripheral blood, bone marrow, and lymph node pathology
- To briefly review the categories of treatment used to treat these malignancies
- To review the epidemiology, pathology, and clinical findings associate with the following three types of hematologic malignancies:
  - **Leukemia**
  - **Lymphoma**
  - **Multiple Myeloma**

Hematologic Malignancies: Incidence

Estimated New Cases

Males				Females		
Prostate	248,530	26%		Breast	281,550	30%
Lung & bronchus	119,100	12%		Lung & bronchus	116,660	13%
Colon & rectum	79,520	8%		Colon & rectum	69,980	8%
Urinary bladder	64,280	7%		Uterine corpus	66,570	7%
Melanoma of the skin	62,260	6%		Melanoma of the skin	43,850	5%
Kidney & renal pelvis	48,780	5%		Non-Hodgkin lymphoma	35,930	4%
Non-Hodgkin lymphoma	45,630	5%		Thyroid	32,130	3%
Oral cavity & pharynx	38,800	4%		Pancreas	28,480	3%
Leukemia	35,530	4%		Kidney & renal pelvis	27,300	3%
Pancreas	31,950	3%		Leukemia	25,560	3%
All Sites	**970,250**	**100%**		**All Sites**	**927,910**	**100%**

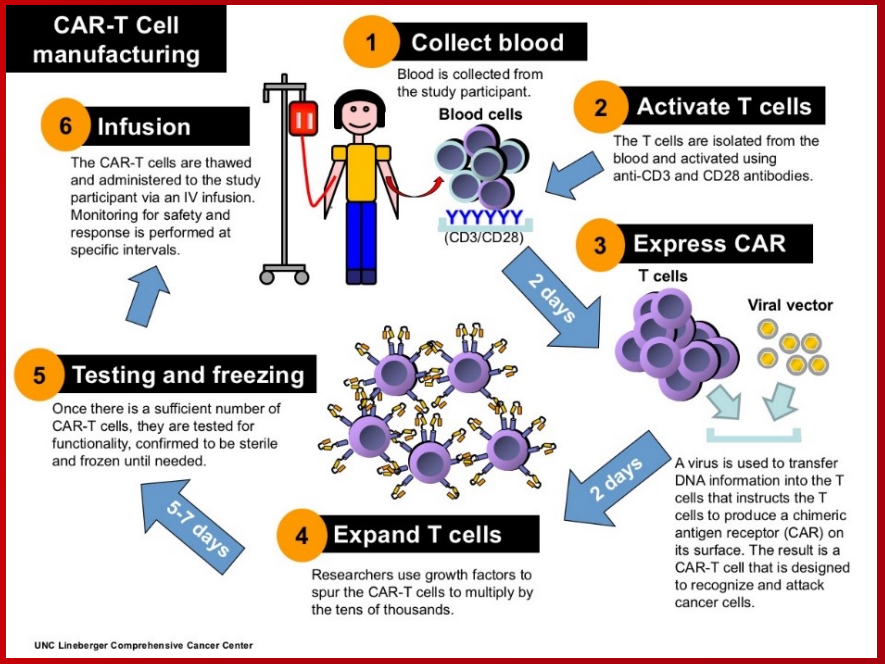
Estimated Deaths

Males				Females		
Lung & bronchus	69,410	22%		Lung & bronchus	62,470	22%
Prostate	34,130	11%		Breast	43,600	15%
Colon & rectum	28,520	9%		Colon & rectum	24,460	8%
Pancreas	25,270	8%		Pancreas	22,950	8%
Liver & intrahepatic bile duct	20,300	6%		Ovary	22,950	5%
Leukemia	13,900	4%		Uterine corpus	12,940	4%
Esophagus	12,410	4%		Liver & intrahepatic bile duct	9,930	3%
Urinary bladder	12,260	4%		Leukemia	9,760	3%
Non-Hodgkin lymphoma	12,170	4%		Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	10,500	3%		Brain & other nervous system	8,100	3%
All Sites	**319,420**	**100%**		**All Sites**	**289,150**	**100%**

https://acsjournals.onlinelibrary.wiley.com/doi/full/10.3322/caac.21654

Treatment

- We will not get into the details of treatment, but…
- In general these disorders are treated with one or more of the following:
  - **Chemotherapy**
  - **Radiation therapy**
  - **Bone marrow transplantation**
  - **Targeted therapy**
  - **CAR-T**
    - Chimeric antigen receptor T-cell therapy
  - **Vaccines *(experimental!)***



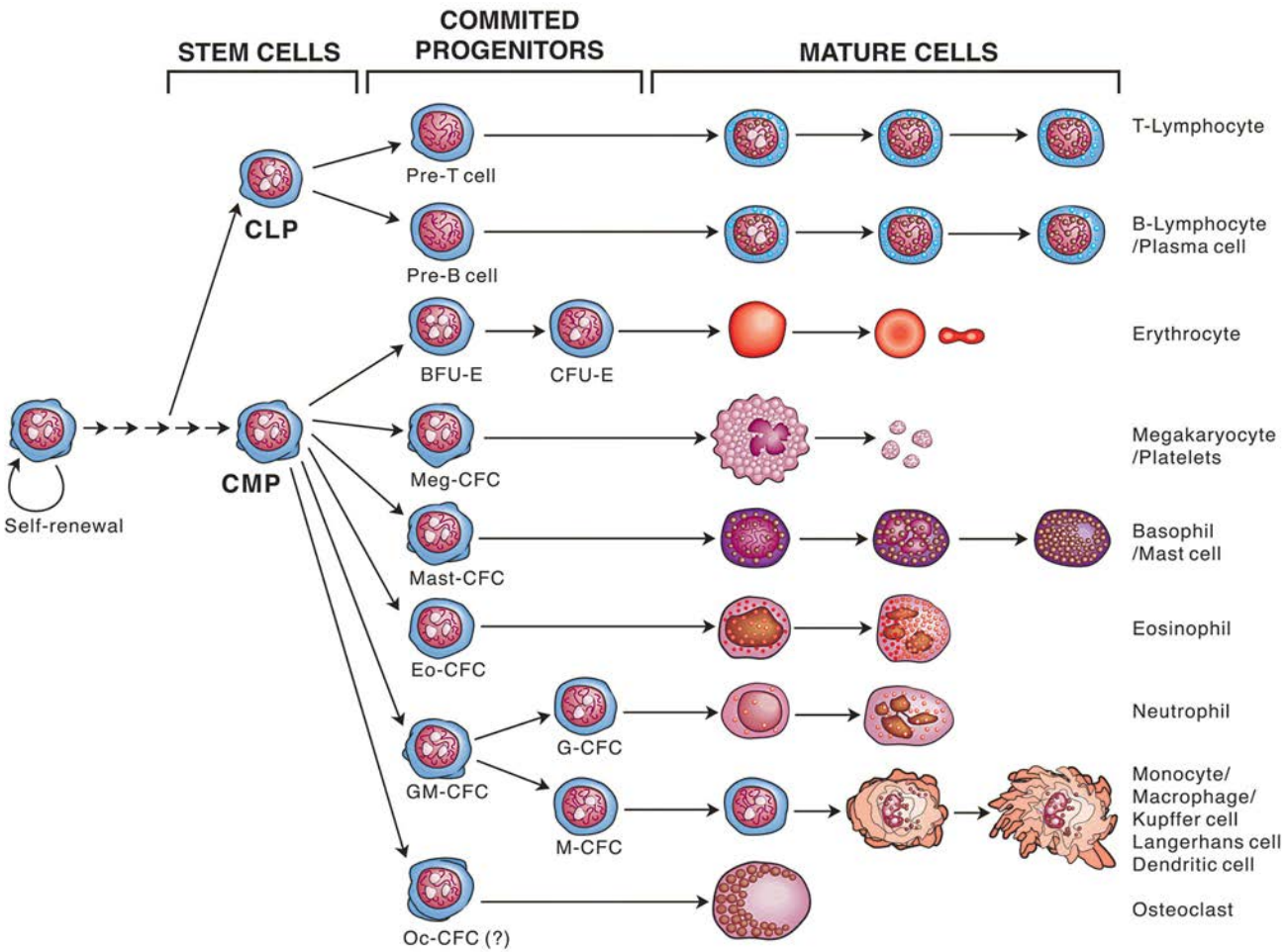
Leukemia

- Myeloid:
  - **Acute**
  - **Chronic**
- Lymphoid:
  - **Acute**
  - **Chronic**

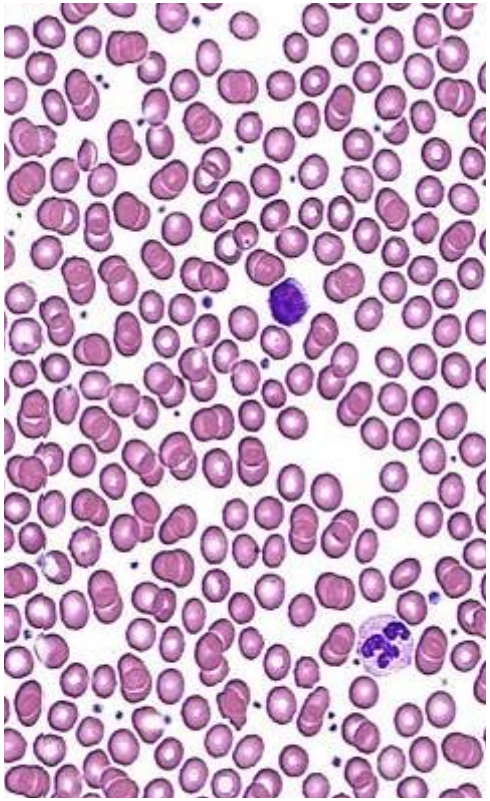
The Leukemias: An Overview

- Leukemia is a neoplastic disease ***composed of malignant blood cells***
- They originate in the ***bone marrow and can involve the patient's peripheral blood***.
- They can manifest clinically over weeks to months: acute leukemia
- They can manifest clinically over months to years: chronic leukemia

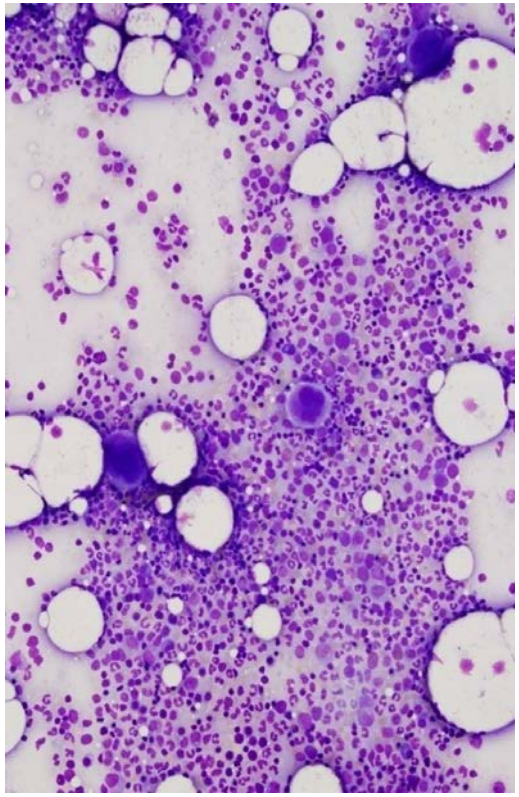
Normal Hematopoiesis



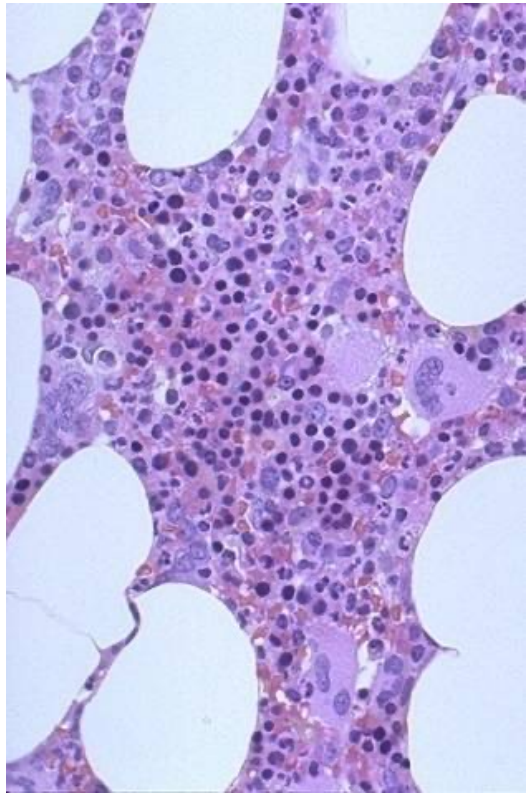
Normal



Peripheral Blood

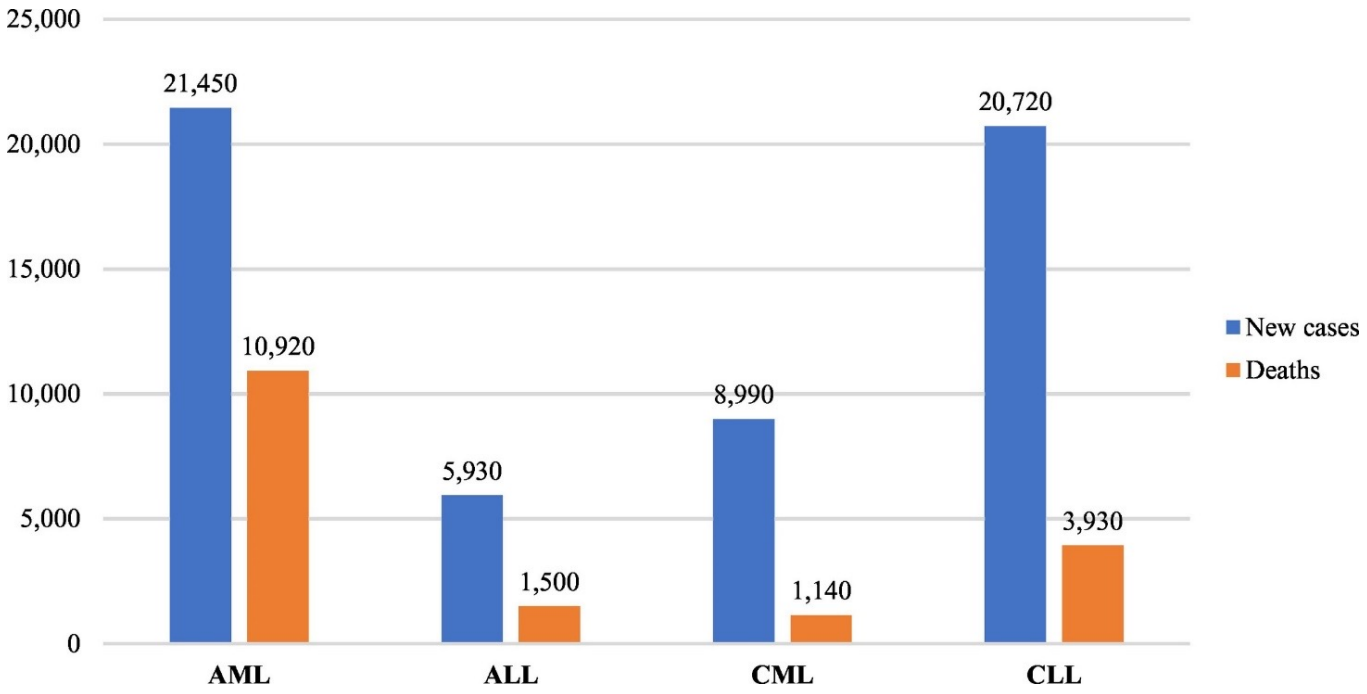


Bone Marrow Aspirate



Bone Marrow Biopsy

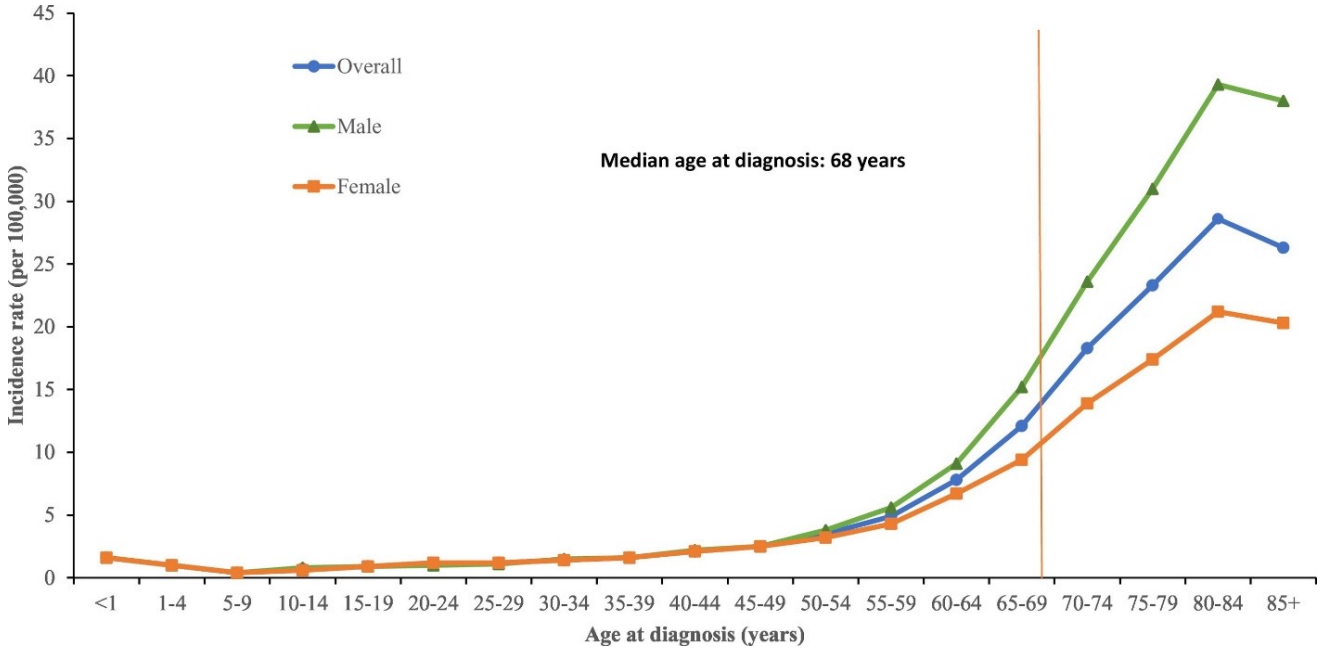
Leukemia: Epidemiology



https://www.sciencedirect.com/science/article/pii/S0268960X18301395?via%3Dihub

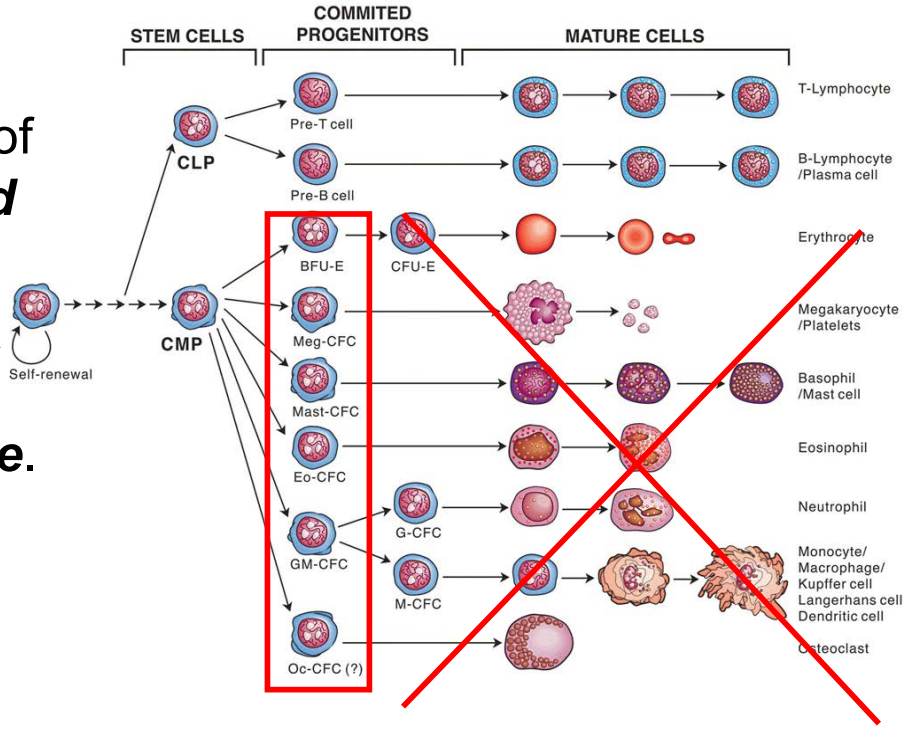
Acute Myeloid Leukemia

AML is a Disease Primarily of Adults



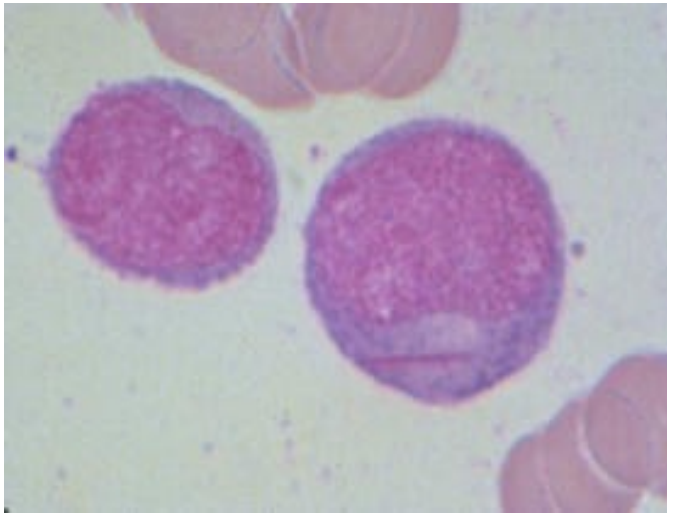
Origins of AML

- AML is a malignancy of a ***committed myeloid progenitor cell***.
- In AML, the malignant cells largely ***lose the ability to differentiate***.
  - **Morphologically <u>homogeneous</u>** population of myeloblasts.

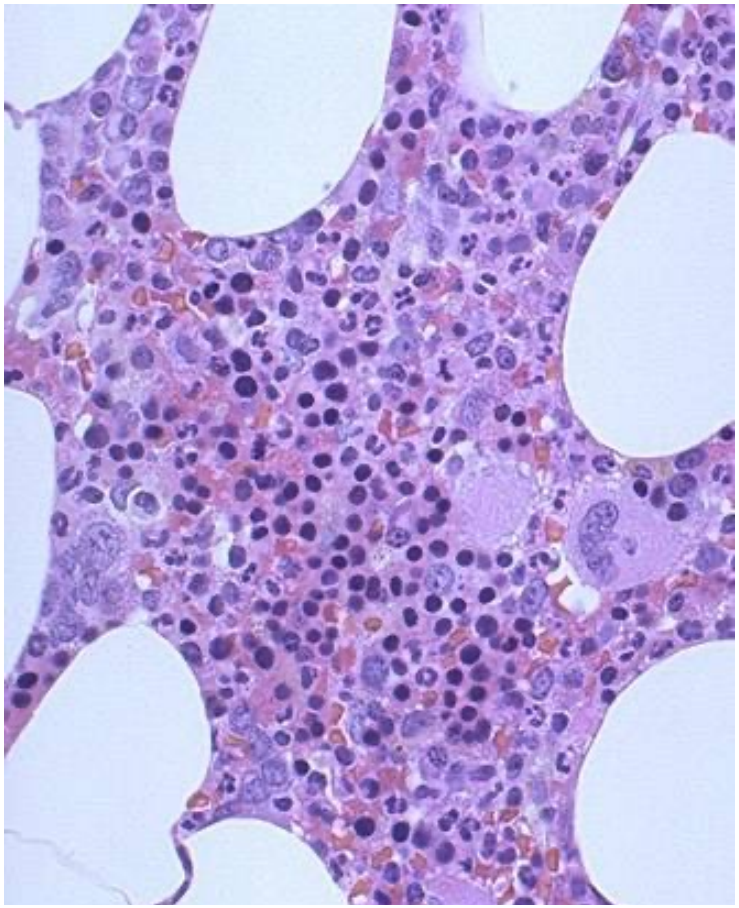


Acute Myeloid Leukemia

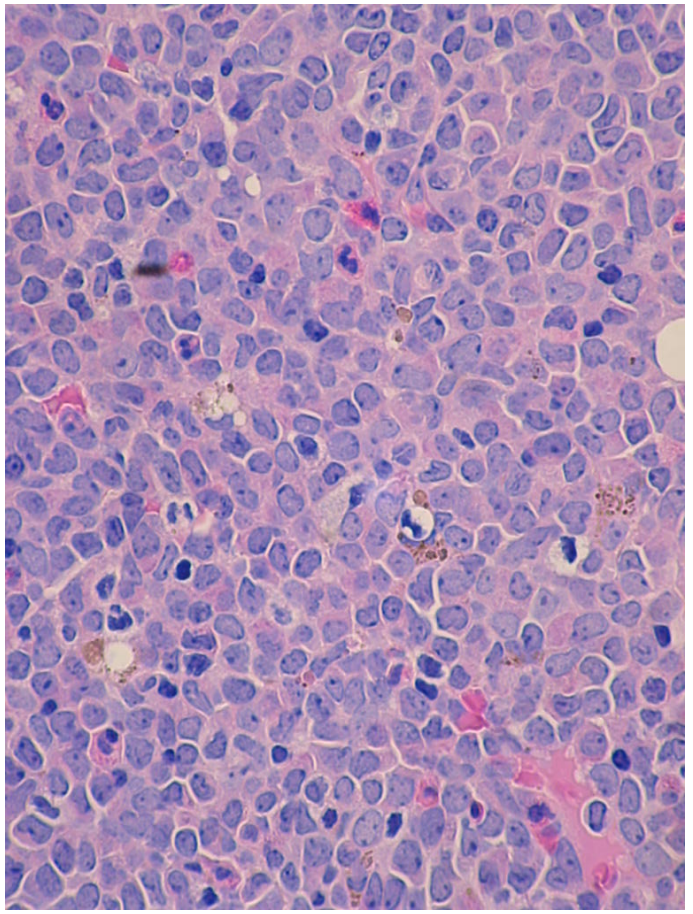
- **Clonal expansion of myeloid blasts**
- Can arise *de novo* or as a consequence of underlying disorder (such as: a bone marrow failure syndrome, myelodyplastic syndrome, myeloproliferative disorder)



Bone Marrow Biopsy



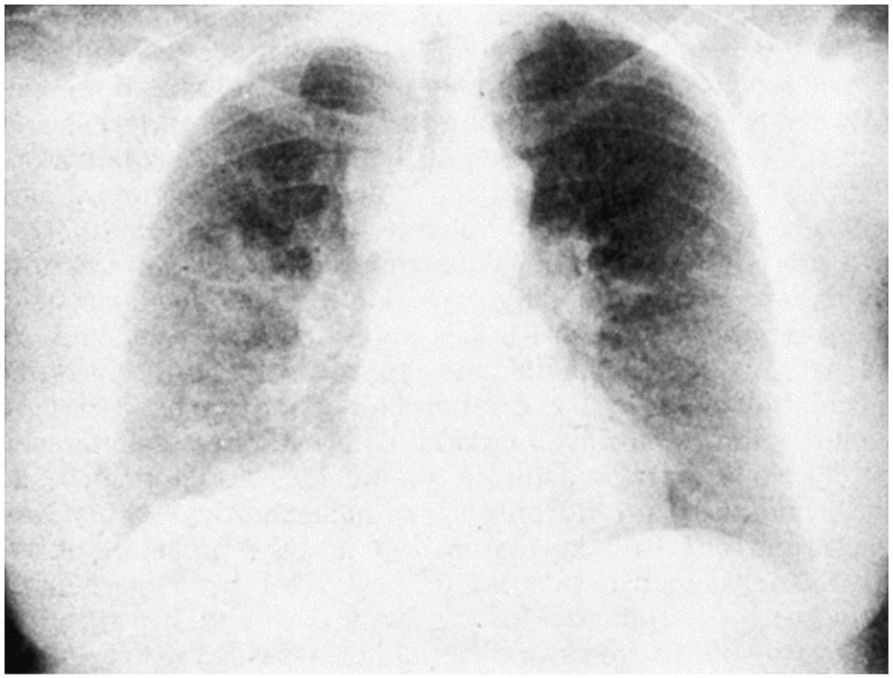
- NORMAL
  - Trilineage hematopoiesis



- ABNORMAL
  - Monotonous population of mononuclear cells

Clinical Manifestations

- **Anemia -- severe**
  - Fatigue, dyspnea
- **Neutropenia -- severe**
  - Infections
- **Thrombocytopenia – severe (decreased platelets)**
  - brusing, petechiae, mucocutaneous bleeding
- **Hyperleukocytosis**
  - Increased white blood cells
  - Mental status changes (somnolence).
  - Dyspnea with bilateral infiltrates on CXR.
  - Due to stasis of blood flow.
  - More likely in AML.
- **Acute Disseminated intravascular coagulation (DIC)**



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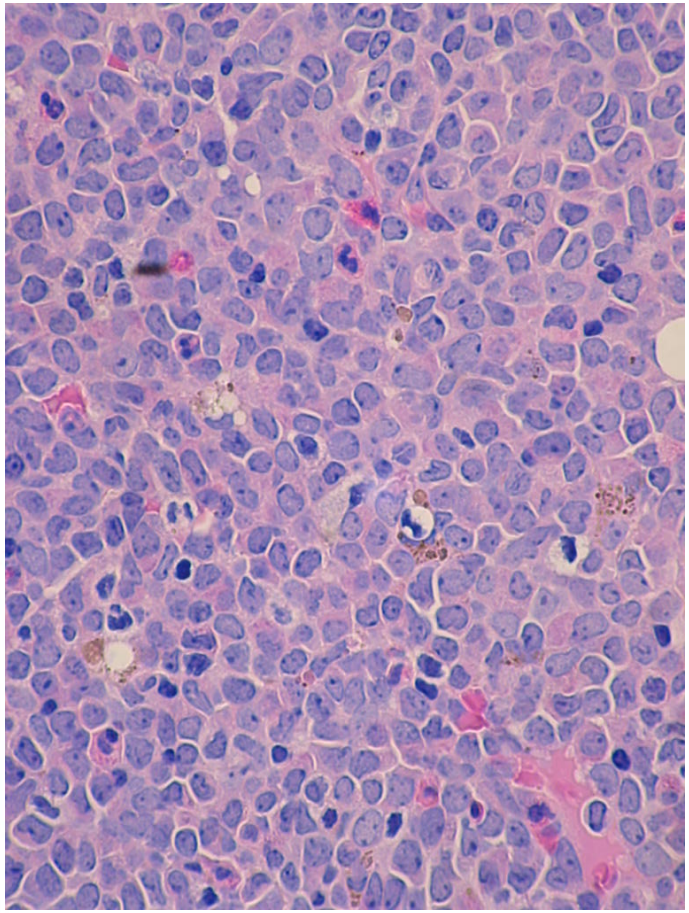
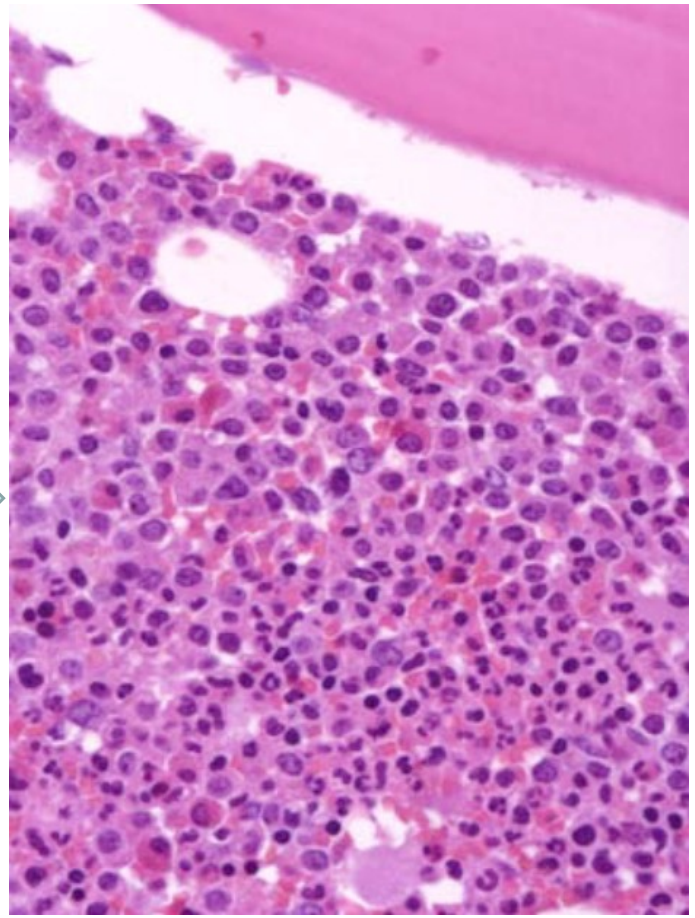
Hyperleukocytosis in a patient with AML

Bone Marrow Biopsy: AML vs. CML



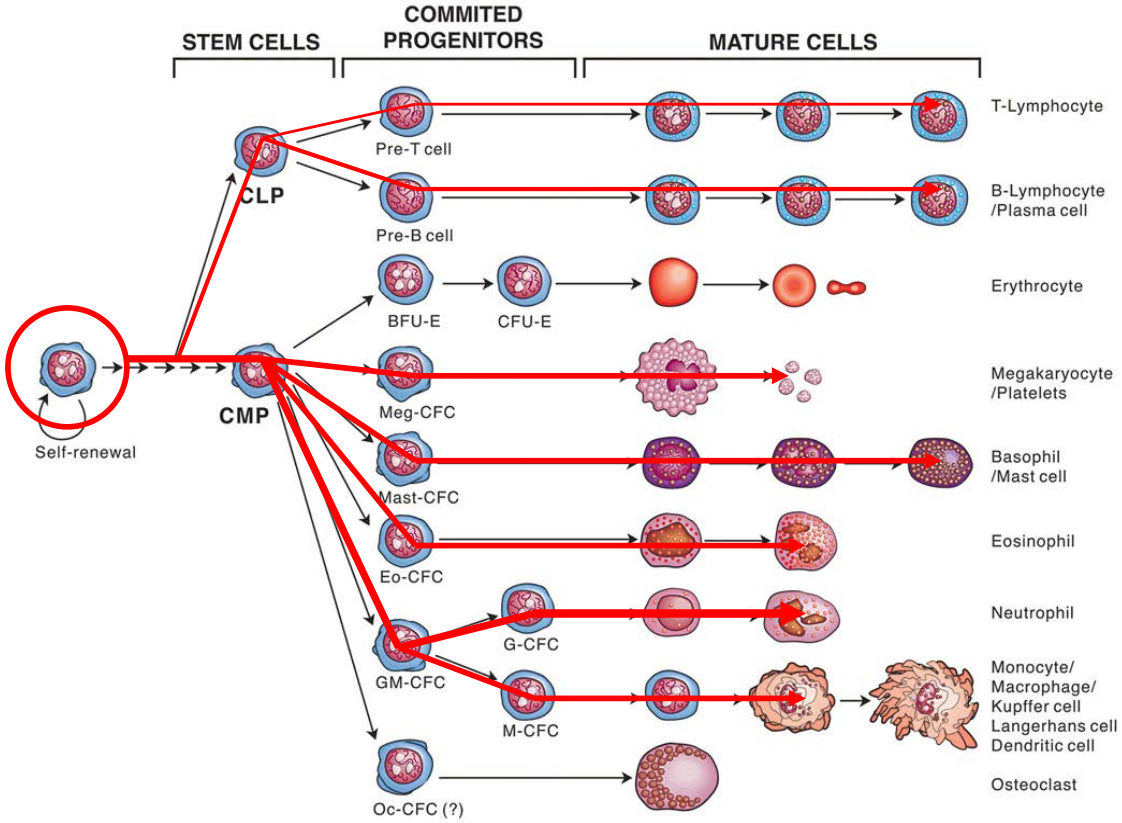


- ABNORMAL:AML
  - Monotonous population
- ABNORMAL:CML
  - Maturing granulocytes

Chronic Myelogenous Leukemia

Origins of CML

- Neoplastic transformation of a hematopoietic progenitor cell (HPC).
- The malignant cells ***maintain the ability to differentiate***.



CML: Epidemiology

- Incidence: 1 to 2 / 100,000
  - 4830 new cases in US in 2008.
  - 450 deaths.
- Median age at diagnosis: 66 yrs.
- Male/Female ratio: 1.4 / 1
- Risk Factors
  - Ionizing radiation exposure

Jemal A, et al. *CA Cancer J Clin*. 2008 Mar-Apr;58(2):71-96.

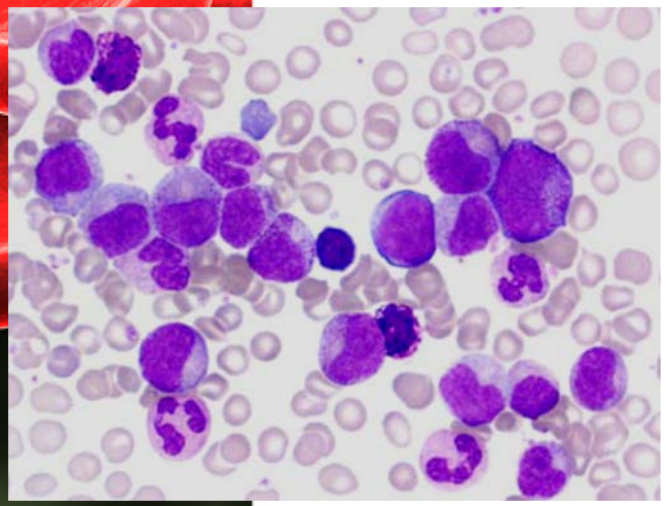
Clinical Presentation of CML

- **Common Symptoms**
  - Fatigue, sweats, fevers
  - Weight loss/anorexia
  - Abdominal fullness, early satiety
- **Physical Exam Findings**
  - Splenomegaly
  - Hepatomegaly
- **Common Laboratory Findings**
  - **Leukocytosis** (high WBC count)
    - **Neutrophilia**
    - **Basophilia**
    - **Eosinophilia**
  - Anemia
  - Thrombocytosis

***20-40% of patients are asymptomatic**

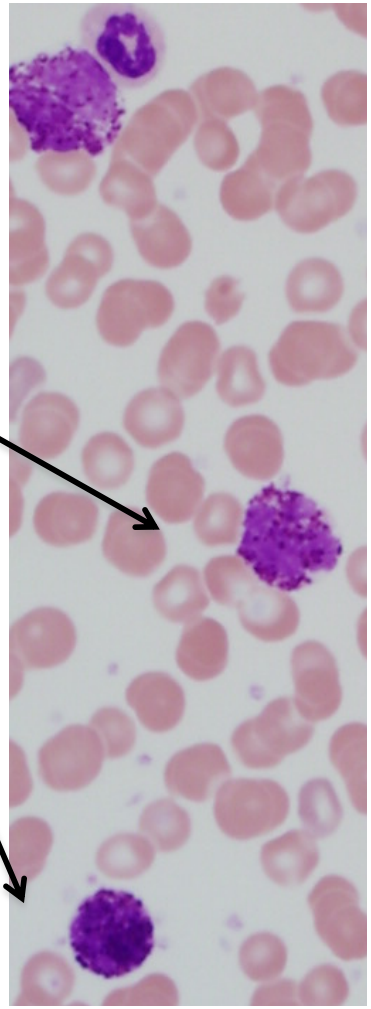
Chronic Myelogenous Leukemia

Peripheral blood

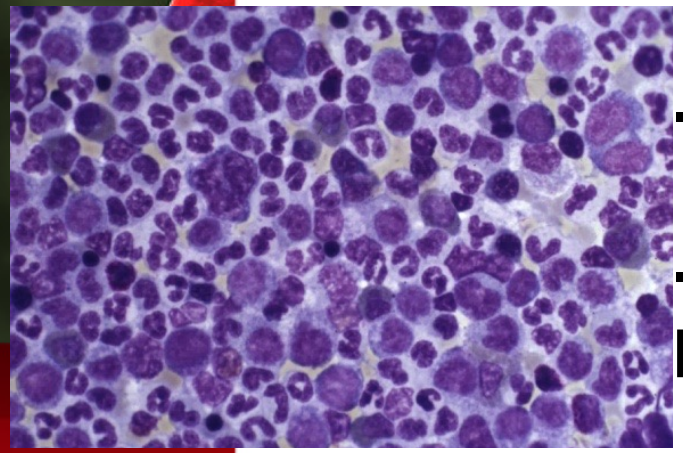


-Numerous immature granulocytes

-Increased basophils



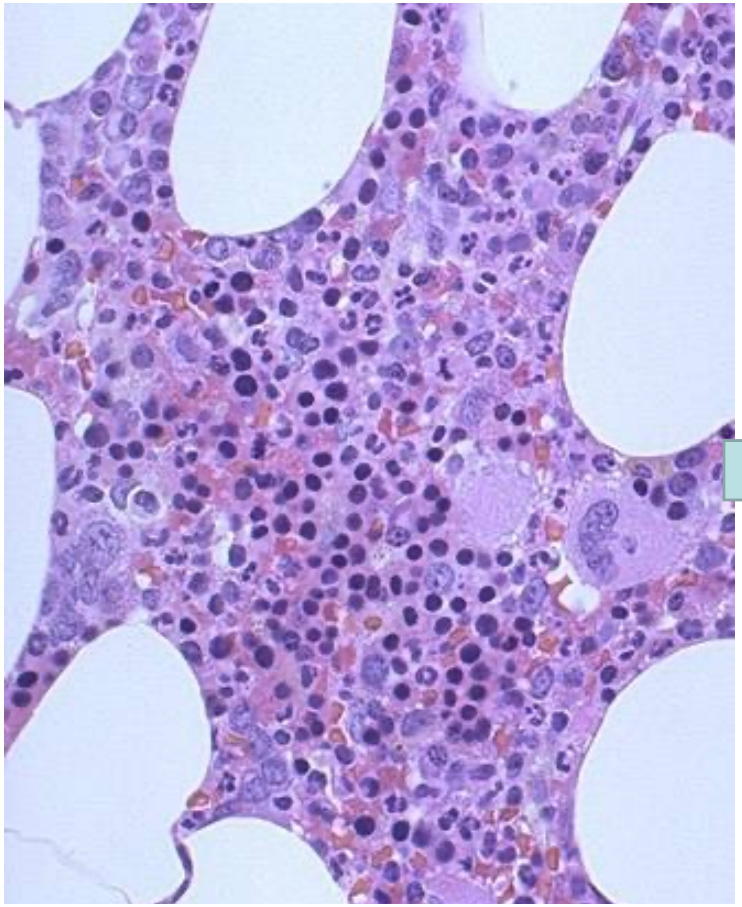
Bone marrow aspirate

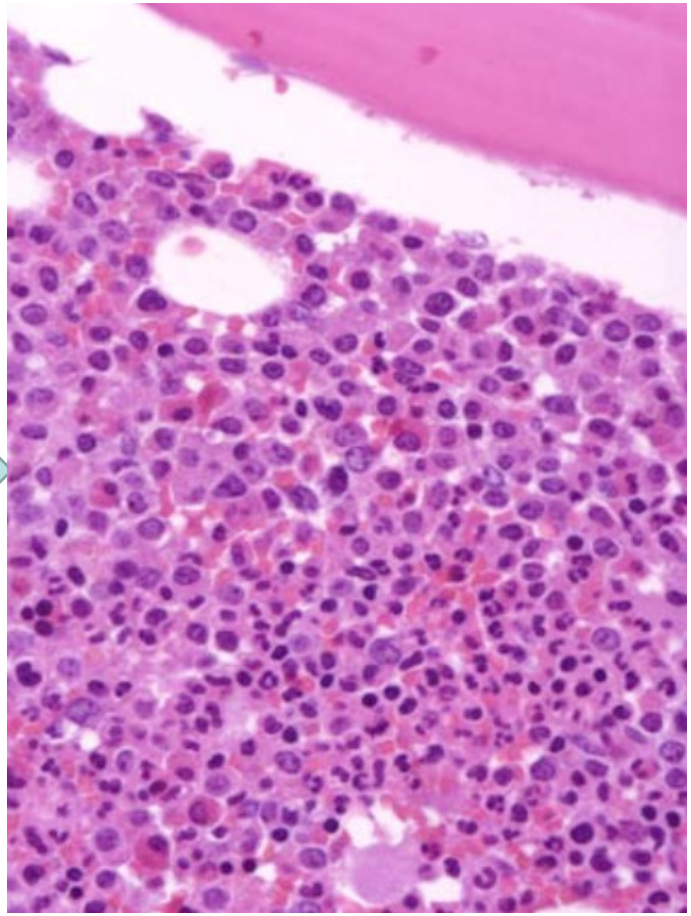


-Hypercellular

-Increased M:E

Bone Marrow Biopsy: Normal vs. CML





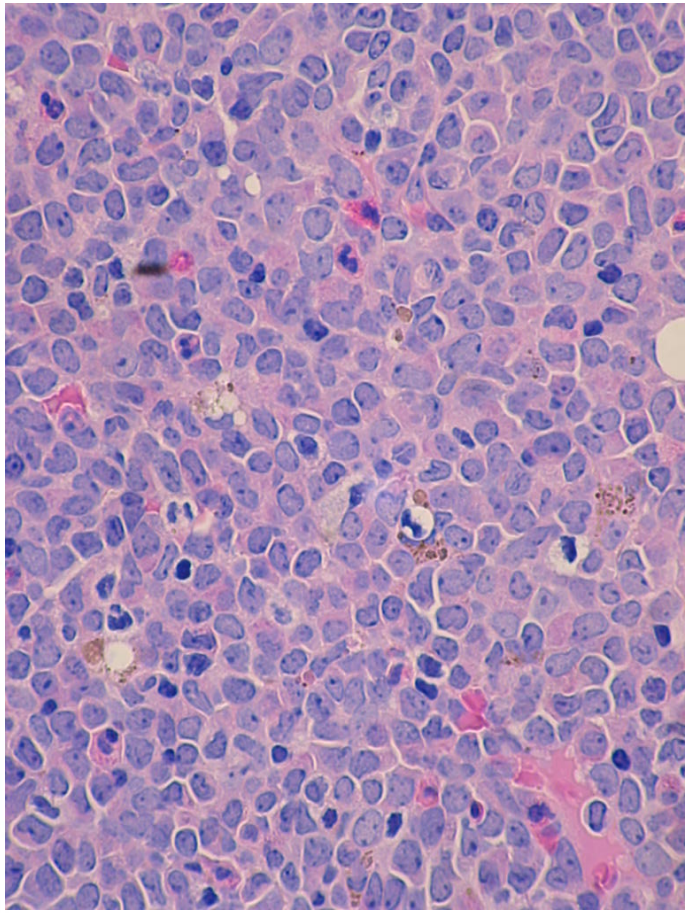
NORMAL

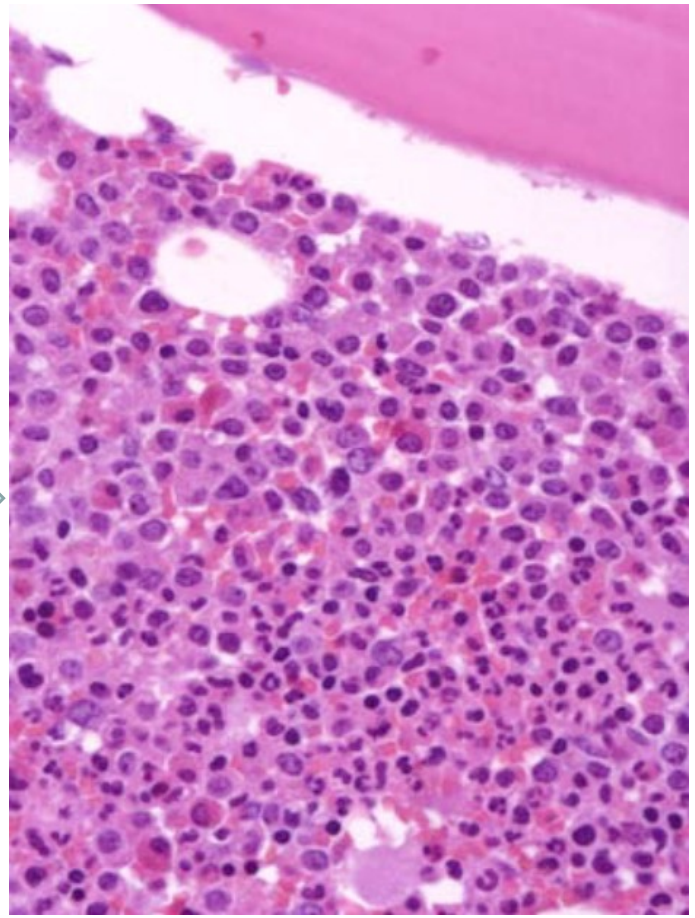
- Trilineage hematopoiesis

ABNORMAL: CML

- Maturing granulocytes

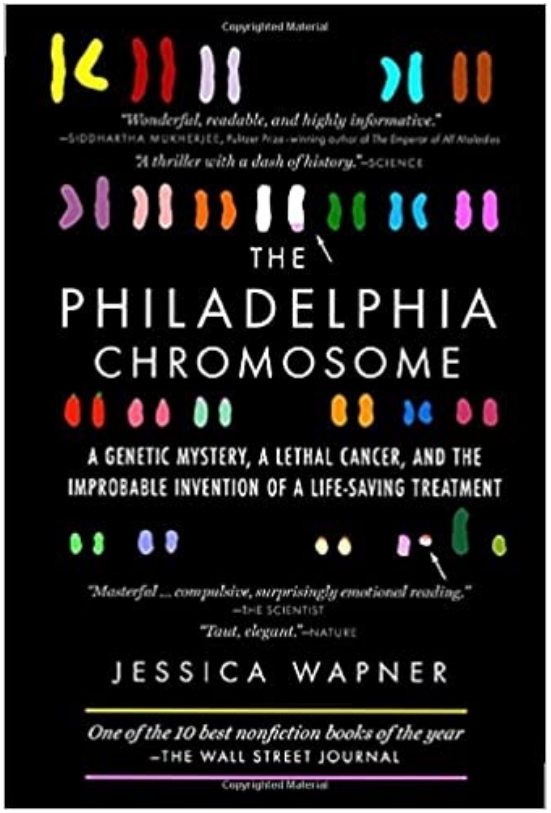
Bone Marrow Biopsy: AML vs. CML

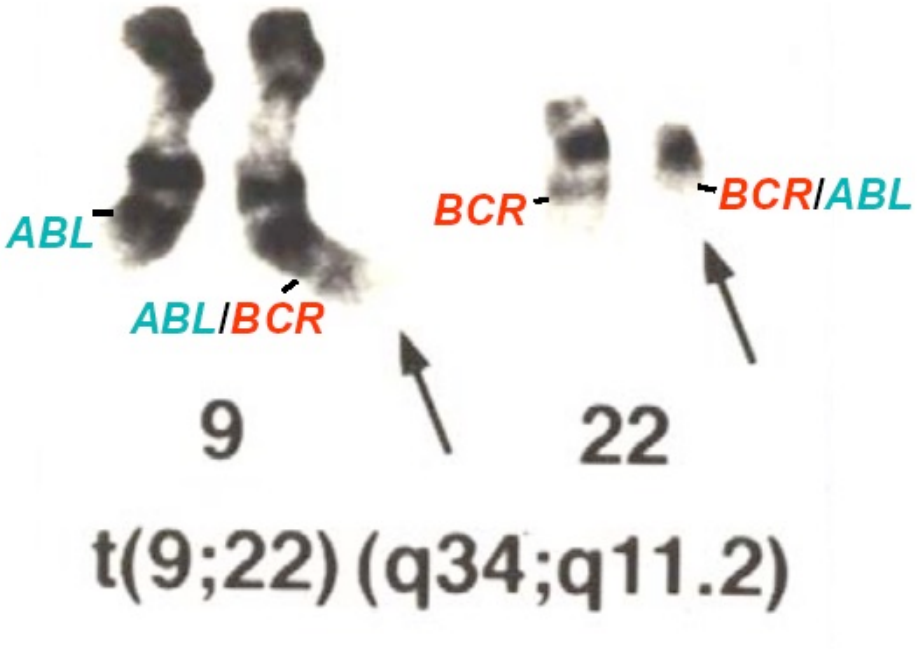




- ABNORMAL:AML
  - Monotonous population
- ABNORMAL:CML
  - Maturing granulocytes

Pathogenesis: The Philadelphia Chromosome



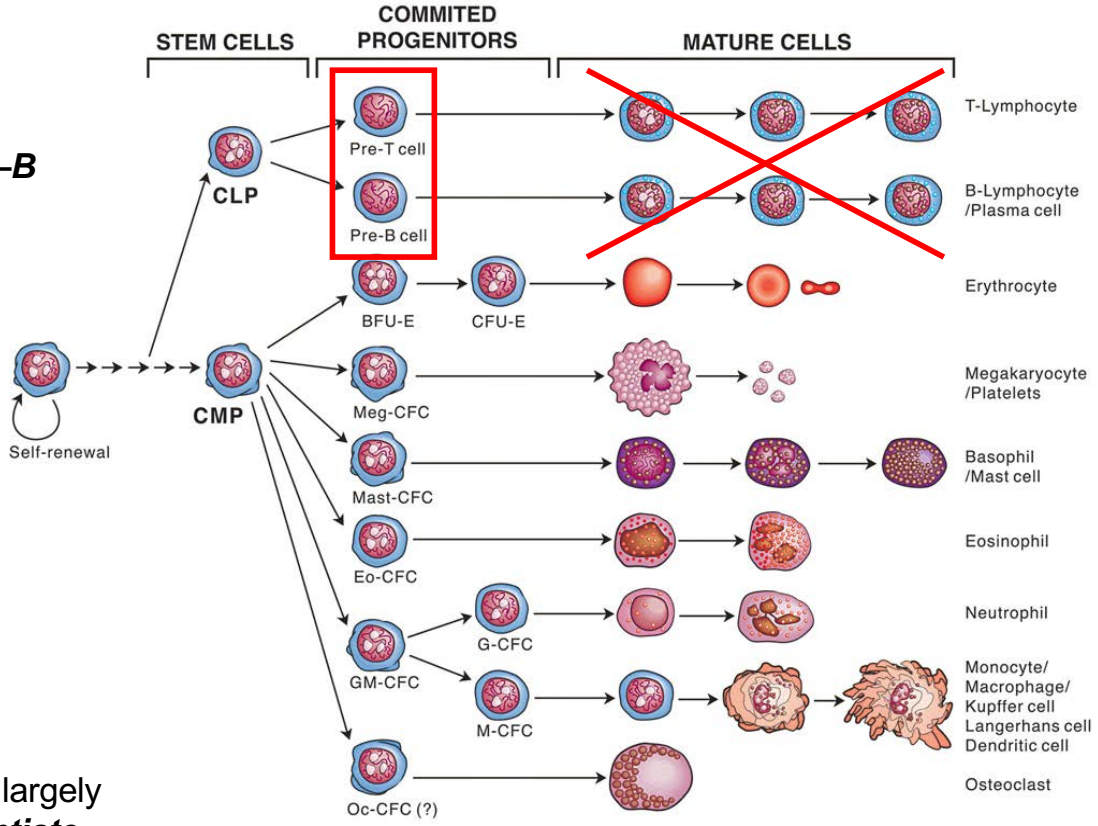


FUSION PROTEIN WITH CONSTITUTIVE TYROSINE KINASE ACTIVITY

Acute Lymphoblastic Leukemia

Origins of ALL

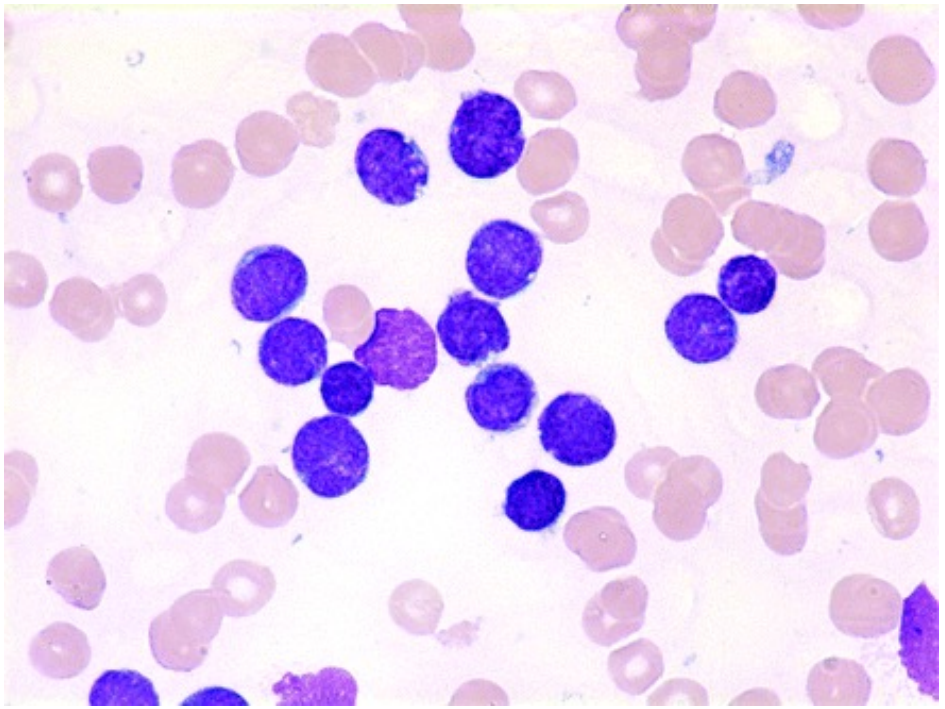
- ALL is a malignancy of a ***committed lymphoid progenitor cell (pre-T or –B cell)***.



- In ALL, the malignant cells largely ***lose the ability to differentiate*** and from a **morphologically <u>homogeneous</u>** population of lymphoblasts.

ALL: Epidemiology

- Most common cancer in children.
  - Peak incidence between ages 2 to 5.
- Median age at diagnosis: 11.
- Risk factors
  - Prior radiation
  - Prior chemotherapy
  - Familial syndromes
    - (e.g. Down syndrome)

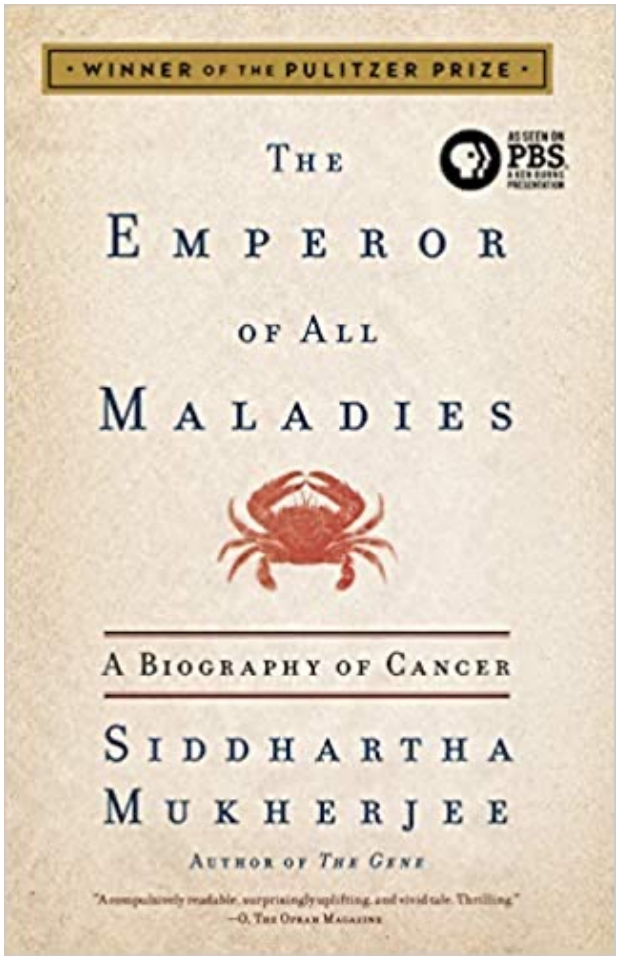


Clinical Manifestations

- **Anemia -- severe**
  - Fatigue, dyspnea
- **Neutropenia -- severe**
  - Opportunistic infections (staph, gram negatives, fungal)
- **Thrombocytopenia – severe (decreased platelets)**
  - bruising, petechiae, mucocutaneous bleeding
- **Hepatosplenomegaly**
  - Abdominal pain, early satiety

ALL Treatment

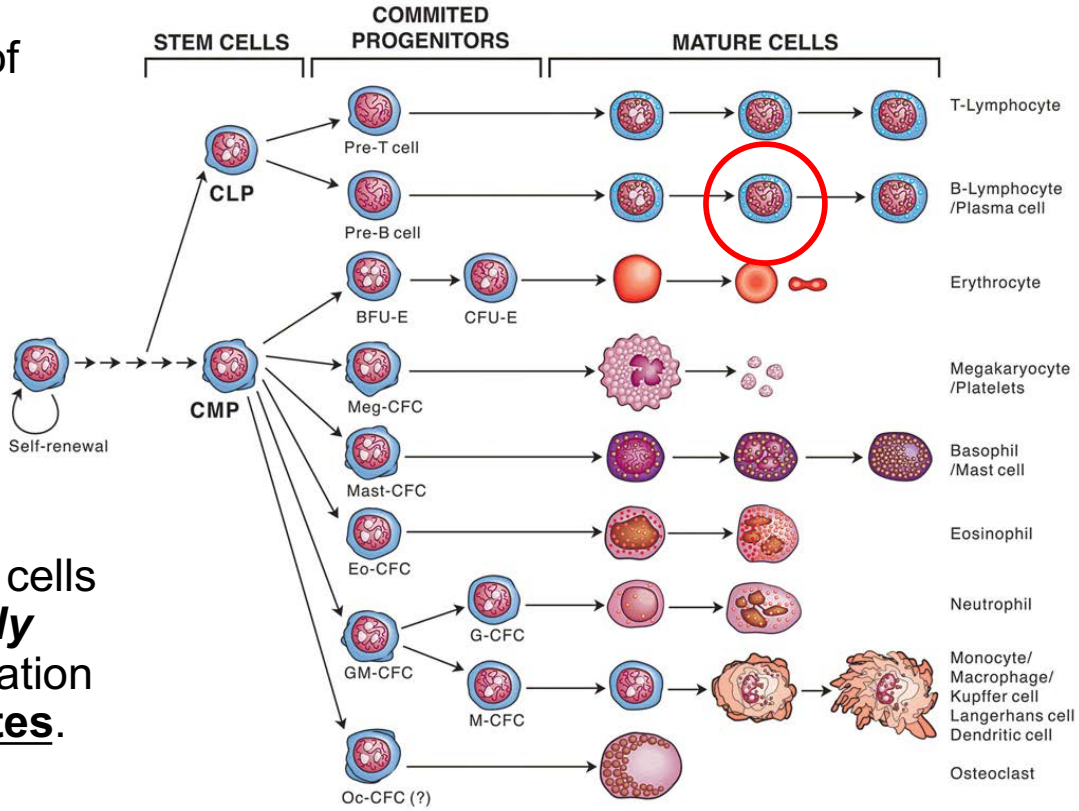
- The great success story for cancer chemotherapy in the 21st century
- Childhood ALL was a death sentence until the late 1960s
- This story is beautifully told in *The Emperor of All Maladies.*
- The majority of childhood ALL patients are cured but disparities exist impacting patients of color



Chronic Lymphocytic Leukemia

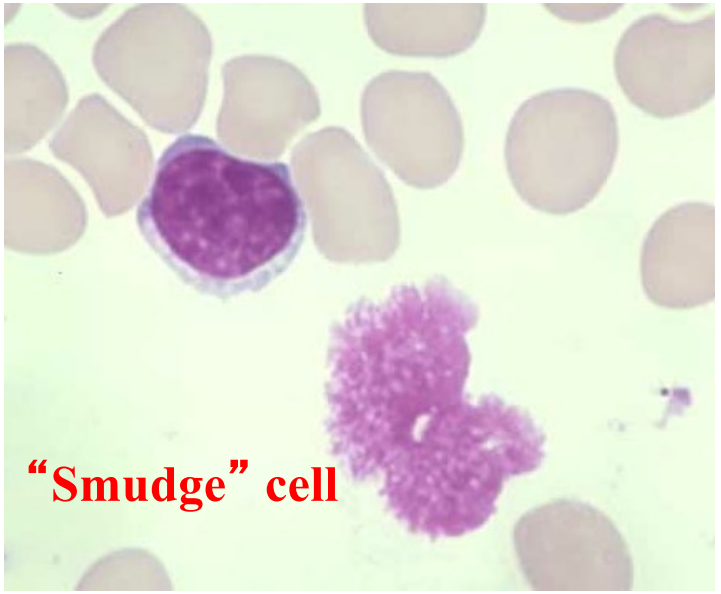
Origins of CLL

- CLL is a malignancy of **mature B-cells**.
- In CLL, the malignant cells ***are a morphologically*** **homogeneous** population of **mature lymphocytes**.



CLL: Epidemiology

- **The most common adult leukemia**
  - 15,110 new US cases in 2008
  - 4,390 deaths from CLL
- **Median age at diagnosis: 72**
- Risk Factors
  - Familial
  - Environmental
    - Agent Orange



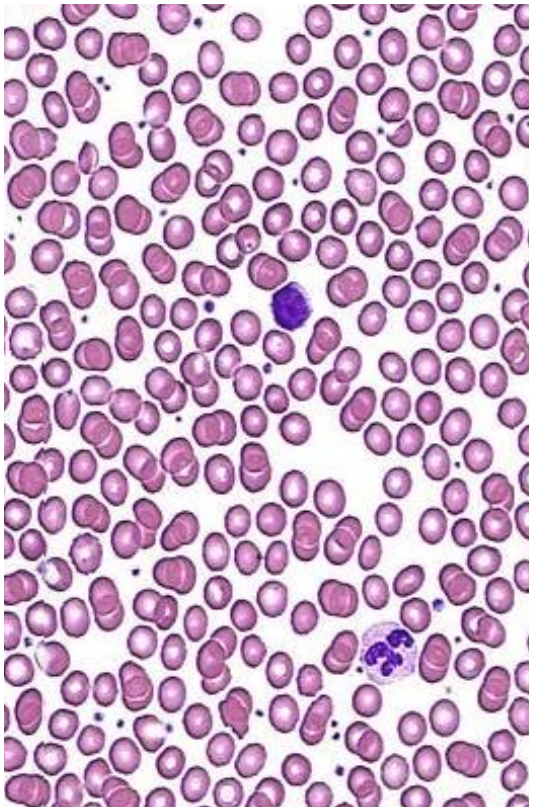
Jemal A, et al. *CA Cancer J Clin*. 2008 Mar-Apr;58(2):71-96.

Clinical Presentation of CLL*

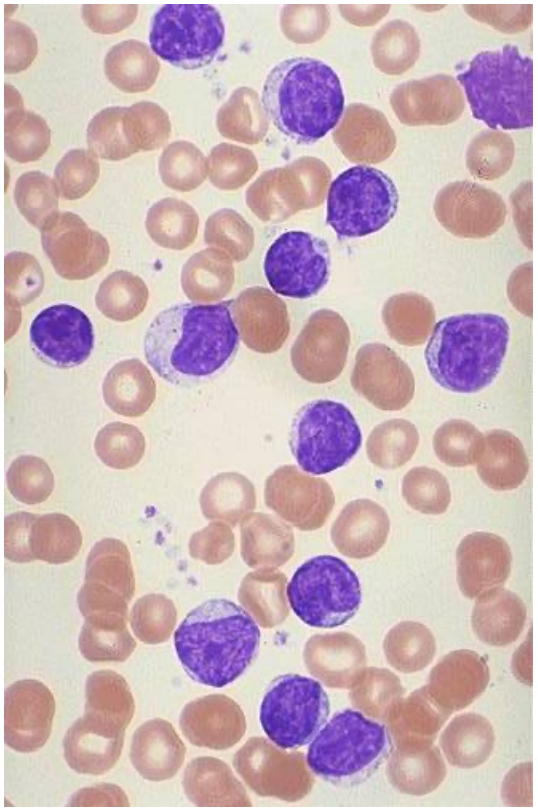
- **Common Symptoms**
  - Fatigue, sweats, fevers
  - Weight loss/anorexia
  - Abdominal fullness, early satiety
  - Frequent infections
    - Respiratory infections
    - Encapsulated organisms
  - **Incidental lab finding in ~20%**
- **Common Physical Exam Findings**
  - Lymphadenopathy
  - Splenomegaly
  - Hepatomegaly
- **Common Laboratory Findings**
  - Leukocytosis (high WBC count)
    - **Lymphocytosis**
  - Anemia
  - Thrombocytopenia
  - Hypogammaglobulinemia

*** CLL characterized by accumulation of mature, homogeneous, mature lymphocytes.**

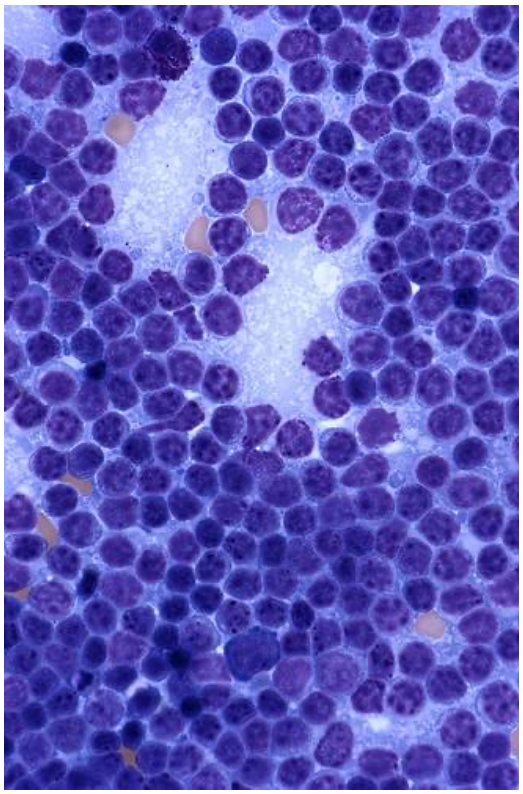
Morphology



Normal blood:
-mostly neutrophils
-scattered lymphs



Peripheral blood: CLL
-usually diagnostic
-lymphocytosis



Bone Marrow Aspirate: CLL
-variable involvement
-loss of heterogeneity

Lymphoma

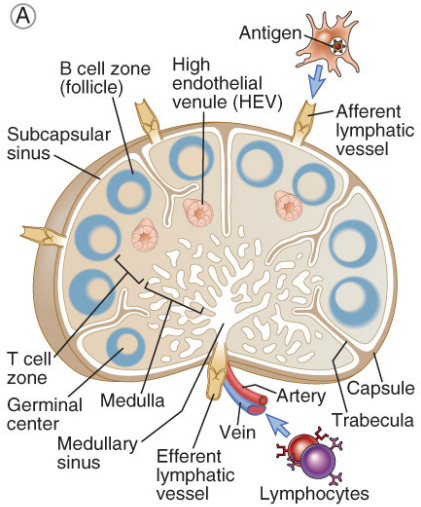
- To review the epidemiology, pathology, and clinical findings associate with the following three types of hematologic lymphomas:
  - **Low grade**
  - **Intermediate grade**
  - **High grade**

Differential Diagnosis of an Enlarged Lymph Node

Causes of **lymphadenopathy** include:

- Reactive (benign such as seen with Strep throat, mononucleosis, etc)
- Lymphoma
  - Hodgkin disease
  - Non-Hodgkin lymphoma
- Metastatic disease

The Lymph Node



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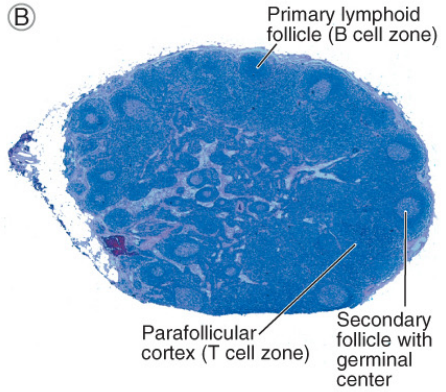

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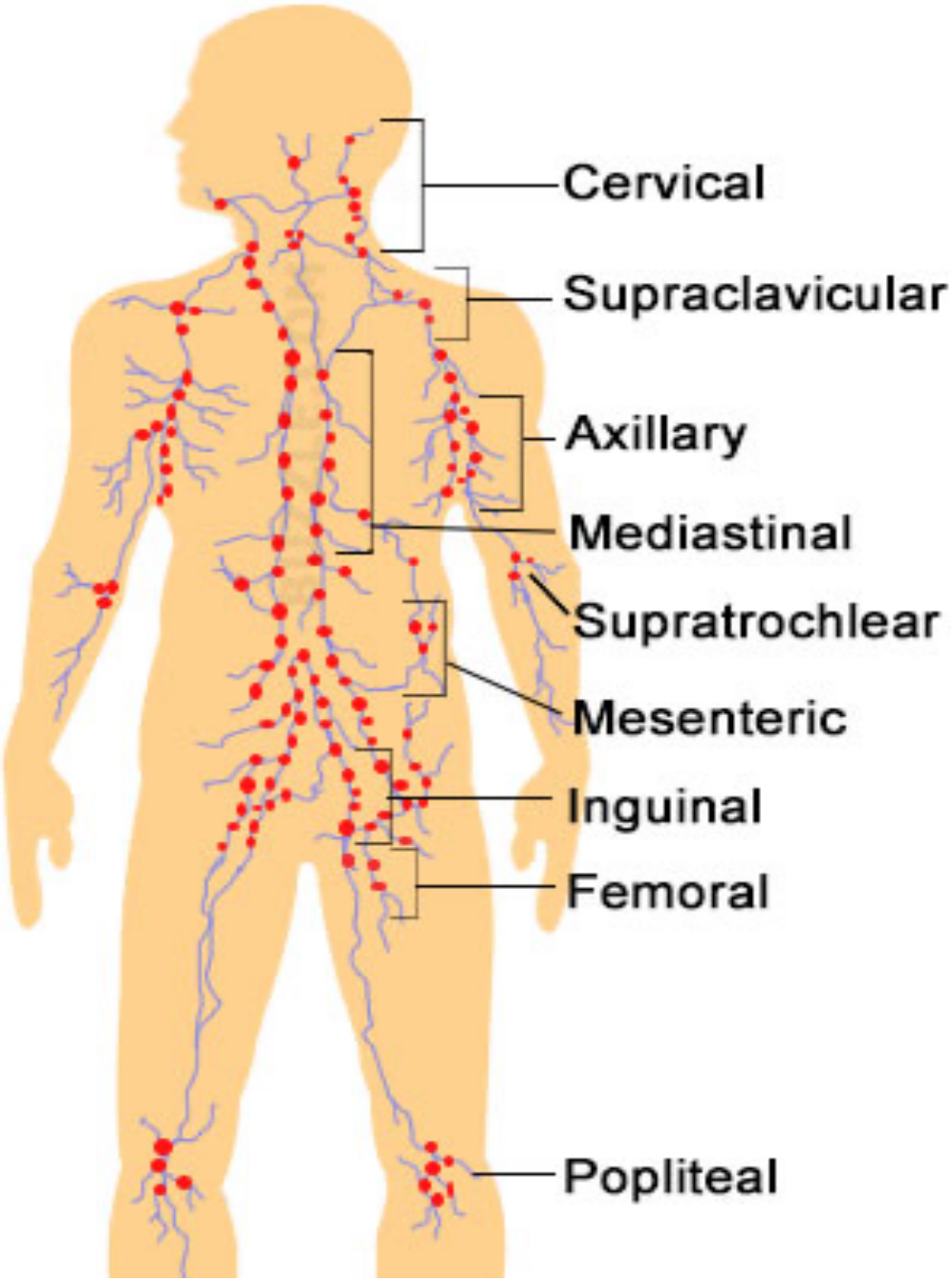
Lymph Node Groups



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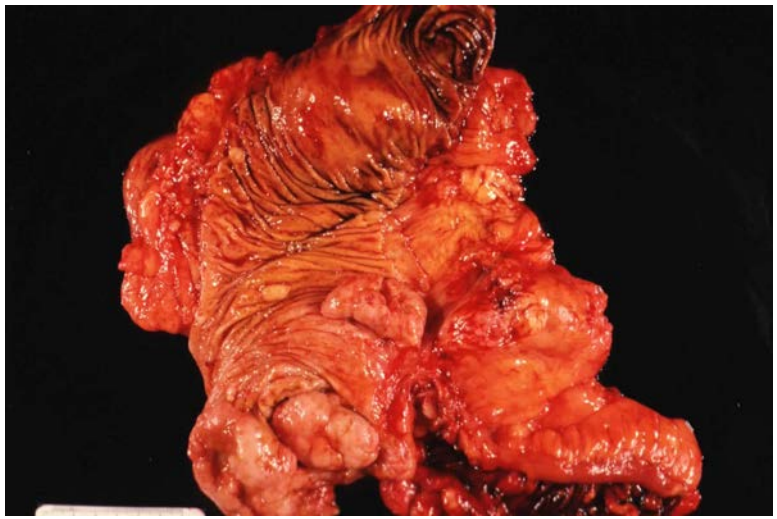
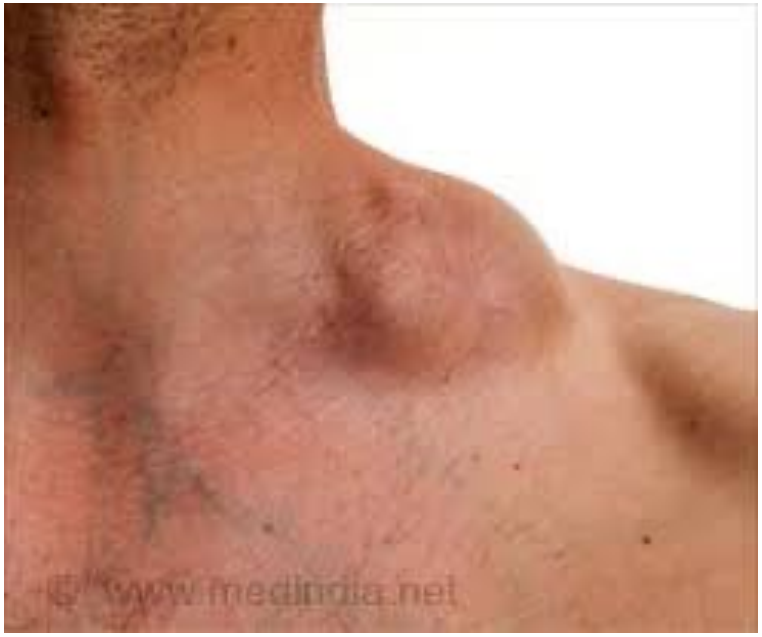
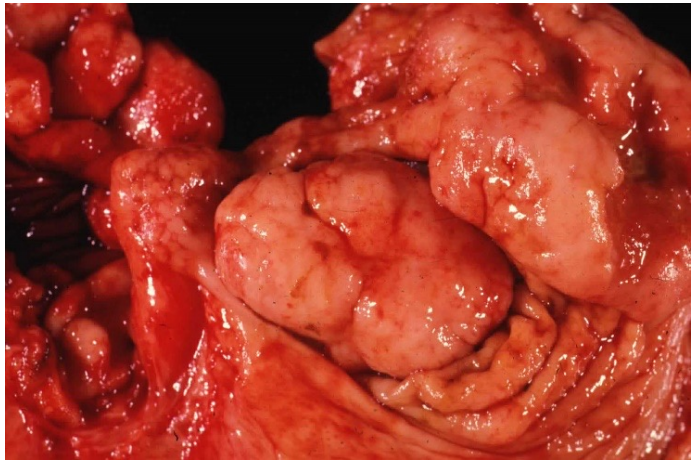
Lymphoma

Extra Nodal, Colon



Nodal

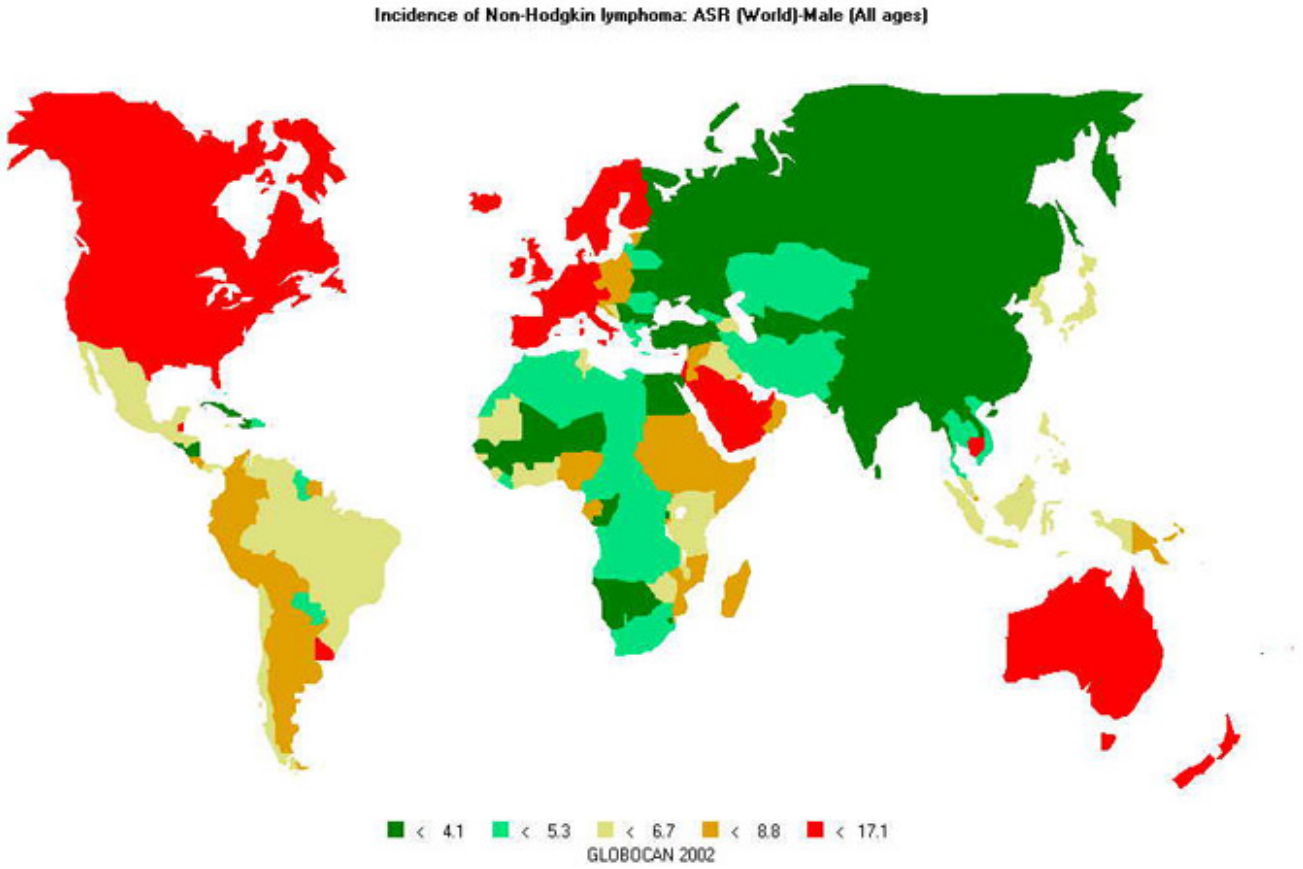




Lymphoma Epidemiology

- Lymphoma definition: malignant neoplasm of lymphocytes associated with a solid mass or infiltrate
- 6th most common cancer in America
- Approximately 77,000 new lymphoma cases diagnosed a year in US
  - 42,000 males
  - 35,00 females
  - 65,000 Non-Hodgkin
  - 9,000 Hodgkin
- Approximately 20,000 deaths a year in US due to lymphoma (11,000 males, 9,000 females)
- Approximately 1,000 people worldwide are diagnosed with lymphoma every day.

Incidence of Non-Hodgkin Lymphoma Varies Worldwide



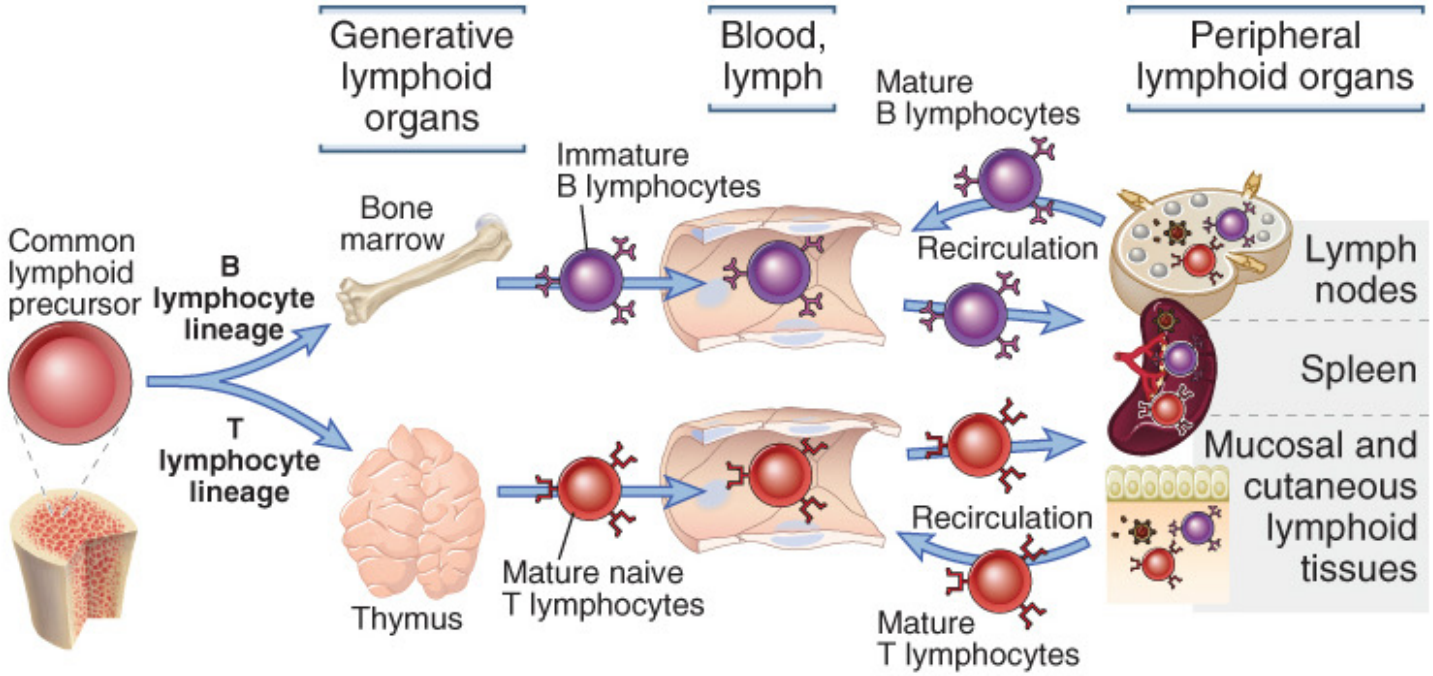
Non-Hodgkin Lymphoma: Risk Factors

- Infections
  - HIV
  - Epstein-Barr virus (EBV), virus associated with mononucleosis
  - *Helicobacter pylori*
  - Hepatitis B
  - Hepatitis C
  - Human T-cell leukemia virus type 1 **(**HTLV-1)
  - HHV-8
- Medical conditions that compromise the immune system
  - HIV
  - Autoimmune disease (e.g. Hashimoto thyroiditis, Sjögren syndrome)
  - Use of immune suppressive therapy (e.g. associated with organ transplant)
  - Inherited immunodeficiency diseases (e.g. severe combined immunodeficiency, ataxia telangiectasia, IgA deficiency, many others)
- Toxic chemicals
  - Pesticides, herbicides, or benzene
  - Hair dye use in patients who started to use the dyes before 1980
- Age
- While risk factors are important, **most patients have no identifiable risk factor**

Lymphoma Types: WHO Classification

- **Non-Hodgkin**
  - B-cell (85% of North-American lymphomas)
  - T-cell (15% of North-American lymphomas)
- **Hodgkin Disease**

Maturation of Lymphocytes



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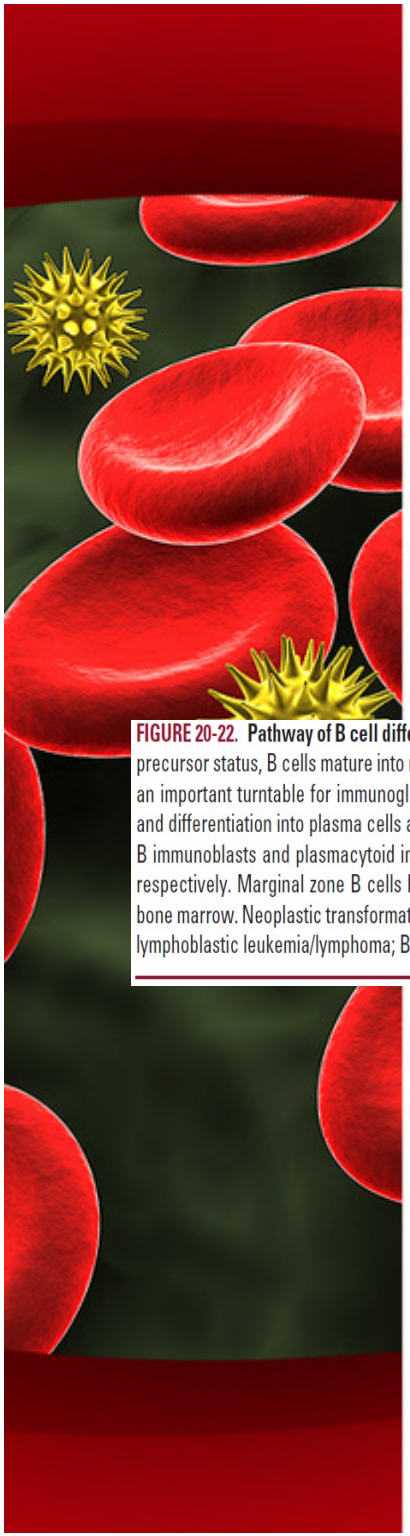
Lymphoma Types: WHO Classification Non-Hodgkin

- **B-cell**
  - Precursor B-cell neoplasms
  - Mature B-cell neoplasms
- **T-cell**
  - Precursor T-cell neoplasms
  - Mature T-cell neoplasms



B-cell Malignancie
Cells of Origin

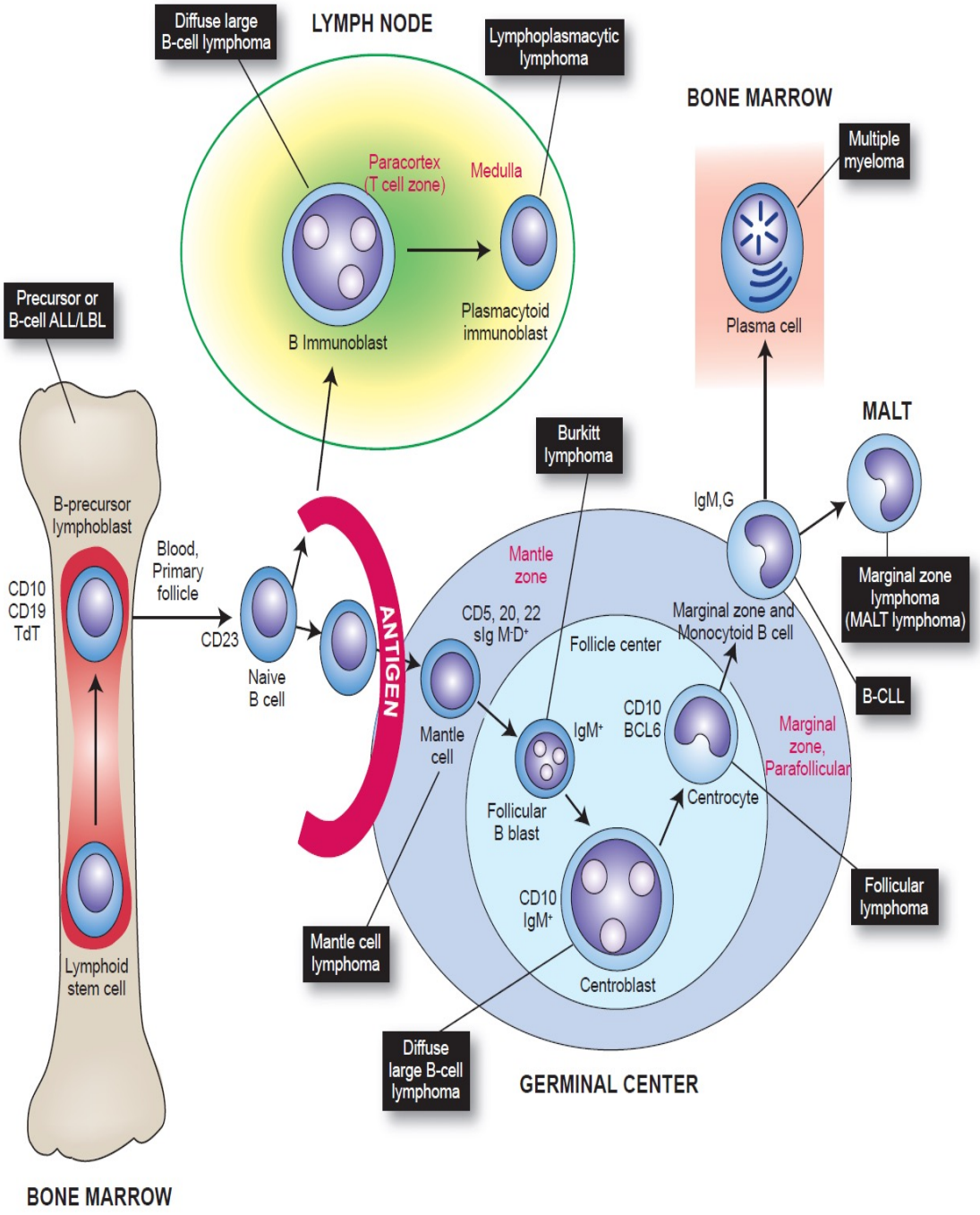


FIGURE 20-22. Pathway of B cell differentiation and corresponding B-cell lymphomas. Following the precursor status, B cells mature into naive B lymphocytes. The germinal-center response represents an important turntable for immunoglobulin variable region gene mutations, Ig heavy-chain switch, and differentiation into plasma cells and memory cells. Cluster designation (CD) markers are shown. B immunoblasts and plasmacytoid immunoblasts reside in the T-cell-rich paracortex and medulla, respectively. Marginal zone B cells home to mucosa-associated lymphoid tissue (MALT) sites and bone marrow. Neoplastic transformation occurs at all phases of B-cell differentiation. ALL/LBL, acute lymphoblastic leukemia/lymphoma; B-CLLB-cell, chronic lymphocytic leukemia; Ig, immunoglobulin.

World Health Organization 2016
B-cell Neoplasms

- *Precursor B-cell neoplasm*
  - Precursor B-cell acute lymphoblastic leukemia or lymphoma
- *Mature B-cell neoplasms*
  - Chronic lymphocytic leukemia/small lymphocytic lymphoma
  - Monoclonal B-cell lymphocytosis
  - B-cell prolymphocytic leukemia
  - Splenic marginal zone lymphoma
  - Hairy-cell leukemia
  - Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia
  - Monoclonal gammopathy of undetermined significance (IgM, IgG, IgA)
  - Heavy chain diseases (Mu, Gamma, Alph)
  - Plasma-cell myeloma
  - Solitary plasmacytoma of bone
  - Extraosseous plasmacytoma
  - Monoclonal immunoglobulin deposition diseases
  - Extranodal marginal-zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
  - Nodal marginal-zone B-cell lymphoma
  - Follicular lymphoma
  - Pediatric-type follicular lymphoma
  - Primary cutaneous follicle center lymphoma
  - Mantle-cell lymphoma
  - Diffuse Large B-cell lymphoma (DLBCL)
  - Primary mediastinal large B-cell lymphoma (DLBCL)
  - T cell/histiocyte-rich large B-cell lymphoma
  - Primary DLBCL of the CNS
  - Primary cutaneous DLBCL, let type
  - EBV positive DLBCL, NOS
  - DLBCL associated with chronic inflammation
  - Lymphomatoid granulomatosis
  - Primary medicastinal (thynic) large B-cell lymphoma
  - Intravascular large B-cell lymphoma
  - ALK positive large B-cell lymphoma
  - Plasmablastic lymphoma
  - Primary effusion lymphoma
  - Burkitt's lymphoma
  - B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma
  - High grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements
  - High grade B-cell lymphoma, NOS
  - B-cell lymphoma, unclassifiable with features intermediate between DLBCL and Hodgkin lymphoma

T-cell Malignancies
Cells of Origin

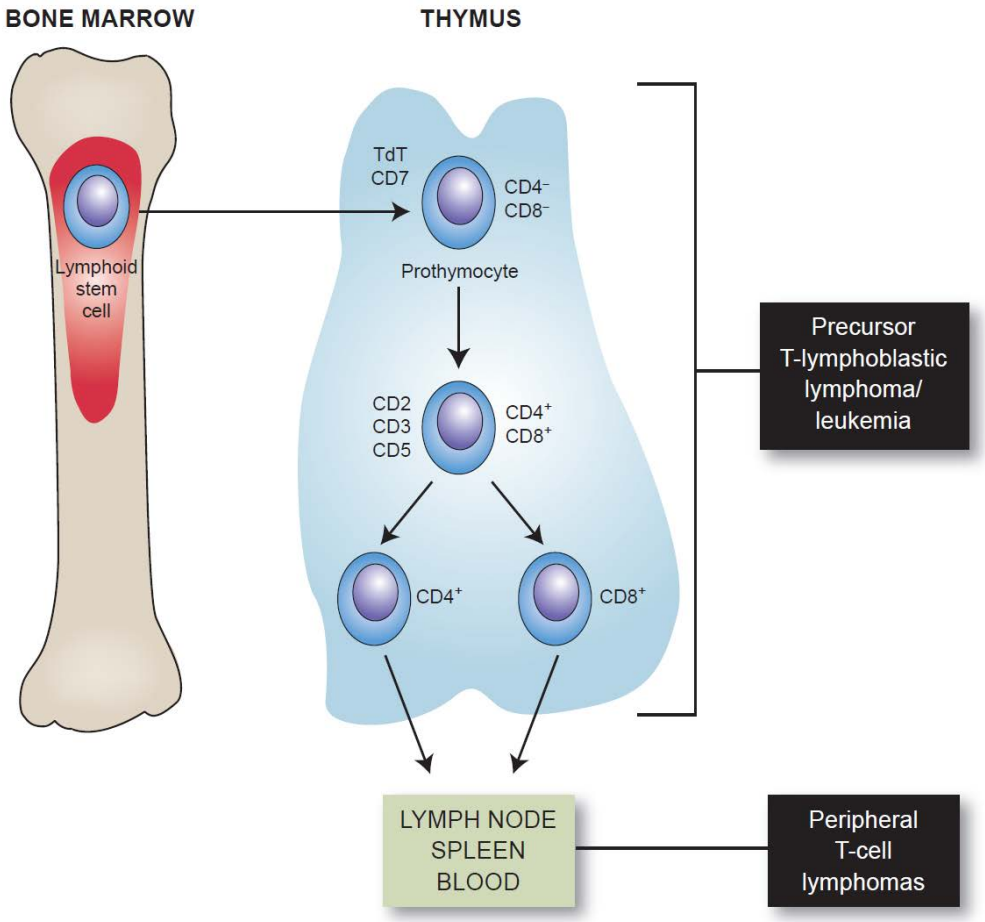
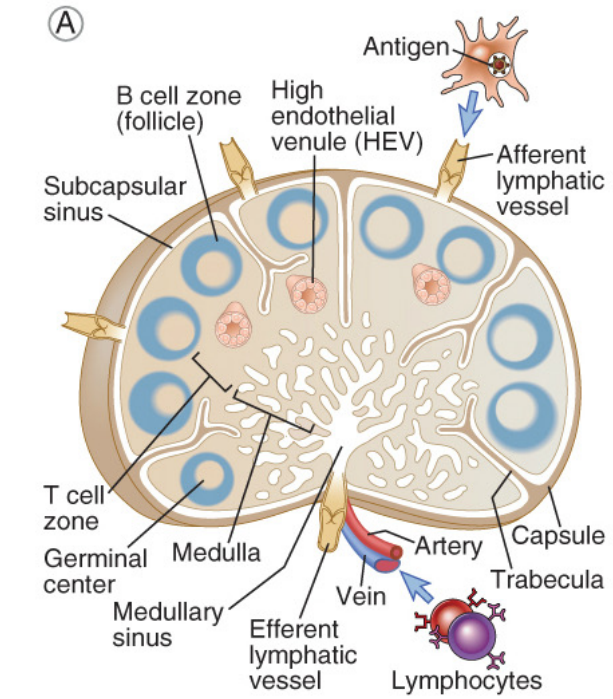


FIGURE 20-23. Pathways of T-cell development and corresponding lymphomas. CD, cluster designation; TdT, terminal deoxynucleotidyl transferase.

World Health Organization 2016
T-cell Neoplasms

- *Precursor T-cell neoplasm*
  - Precursor T-cell acute lymphoblastic leukemia or lymphoma
- *Mature (peripheral) T-cell neoplasms*
  - T-cell prolymphocytic leukemia
  - T-cell granular lymphocytic leukemia
  - Aggressive natural-killer cell leukemia
  - Systemic EBV+ T-cell lymphoma of childhood
  - Hyroa vacciniforme-like lymphoproliferative disorder
  - Adult T-cell leukemia/lymphoma
  - Extranodal natural-killer/T-cell lymphoma, nasal type
  - Enteropathy-type T-cell lymphoma
  - Monomorphic epitheliotropic intestinal T-cell lymphoma
  - Hepatosplenic T-cell lymphoma
  - Subcutaneous panniculitis-like T-cell lymphoma
  - Mycosis fungoides
  - Sezary syndrome
  - Primary cutaneous CD30 positive T-cell lymphoproliferative disourders
  - Primary cutaneous gamma-delta T-cell lymphoma
  - Peripheral T-cell lymphoma, not otherwise characterized
  - Angioimmunoblastic T-cell lymphoma
  - Anaplastic large-cell lymphoma, ALK positive
  - Anaplastic large-cell lymphoma, ALK negative

The Lymph Node



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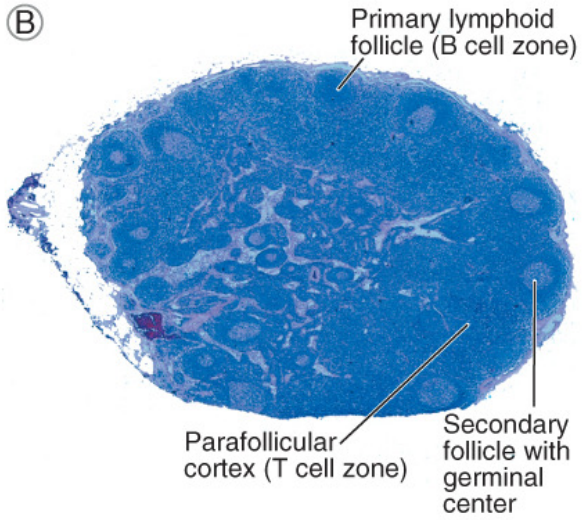

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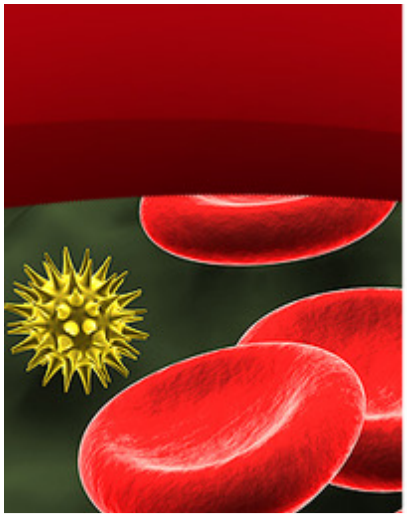
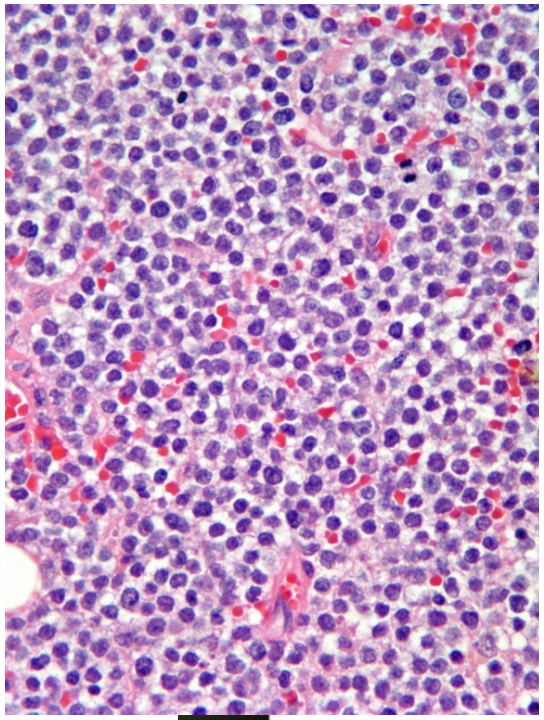
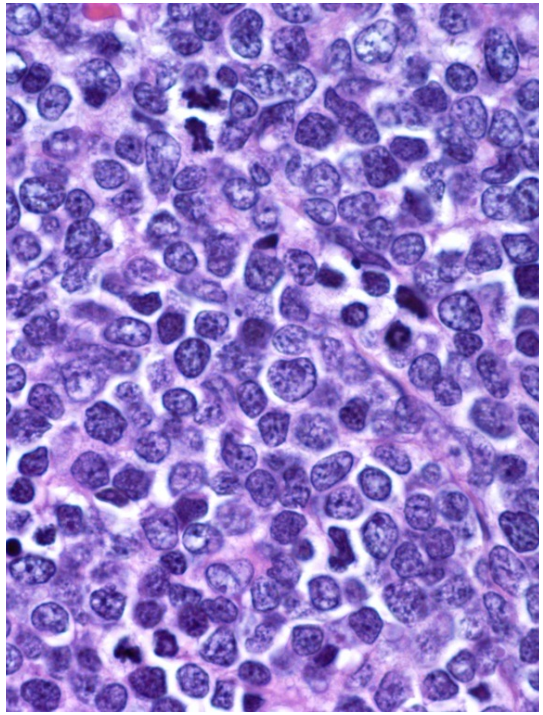


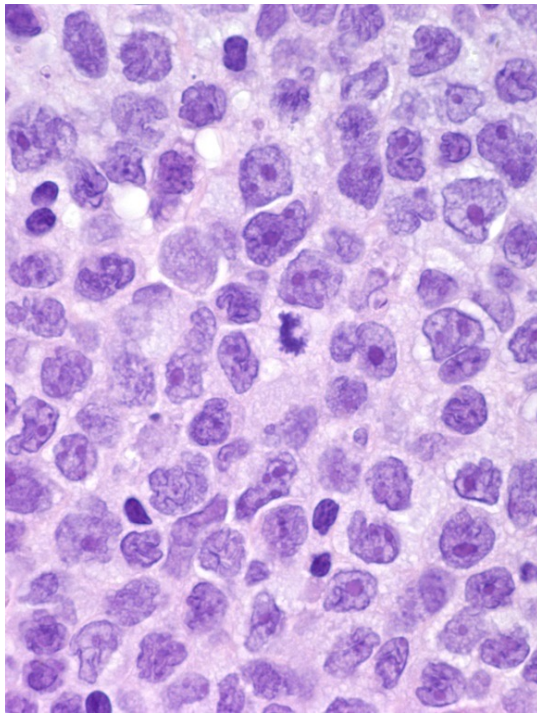
Histologic Classification: Cell Size



Small



Intermediate



Large

Lymphoma Grades

- Low Grade *(indolent, slow growing)*
  - Small lymphocytic lymphoma
  - Follicular small cleaved lymphoma
- Intermediate Grade *(in between, prognosis depends on stage)*
  - Diffuse large cell lymphoma
- High Grade *(aggressive, fast growing)*
  - Burkitt lymphoma
  - Lymphoblastic lymphoma

The Working Formulation

	Natural History	Cure Rate
Low Grade (Follicular, Small lymphocytic)	Many years	Incurable
Intermediate Grade (Diffuse Large B-Cell)	A few years	Curable (20 to 80%)
High Grade (Burkitt, Lymphoblastic)	Months	Curable (≥ 80%)

Hodgkin's Disease is similar to intermediate grades with 60 to 95% cure

Small Lymphocytic Follicular

Low Grade

Mantle Cell

Low/Intermediate Grade

Diffuse Large B-Cell

Intermediate Grade

Burkitt's, Lymphoblastic

High Grade

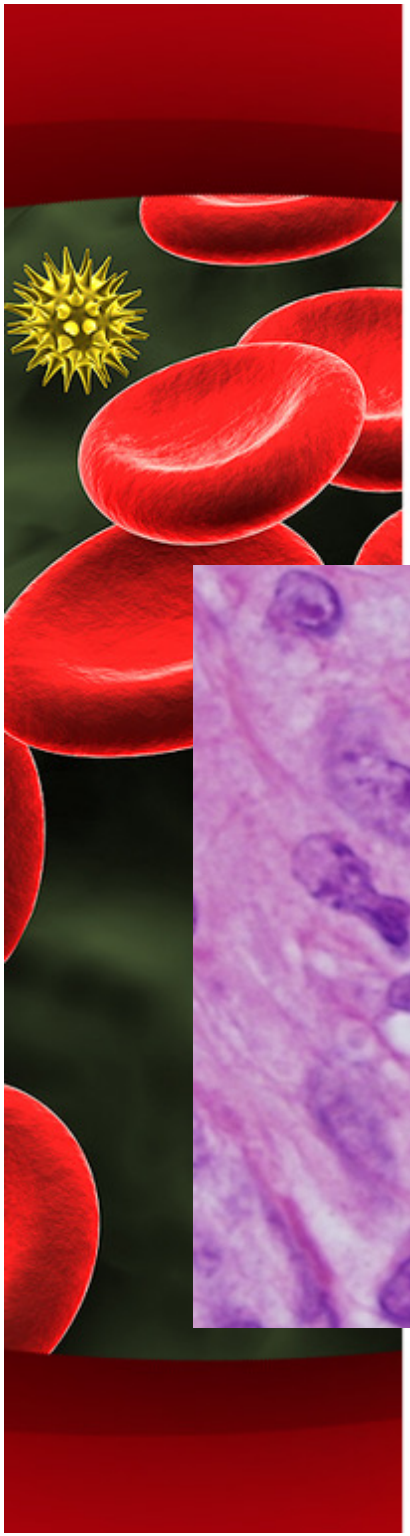
Hodgkin's Disease

Presents like an intermediate grade

Asymptomatic

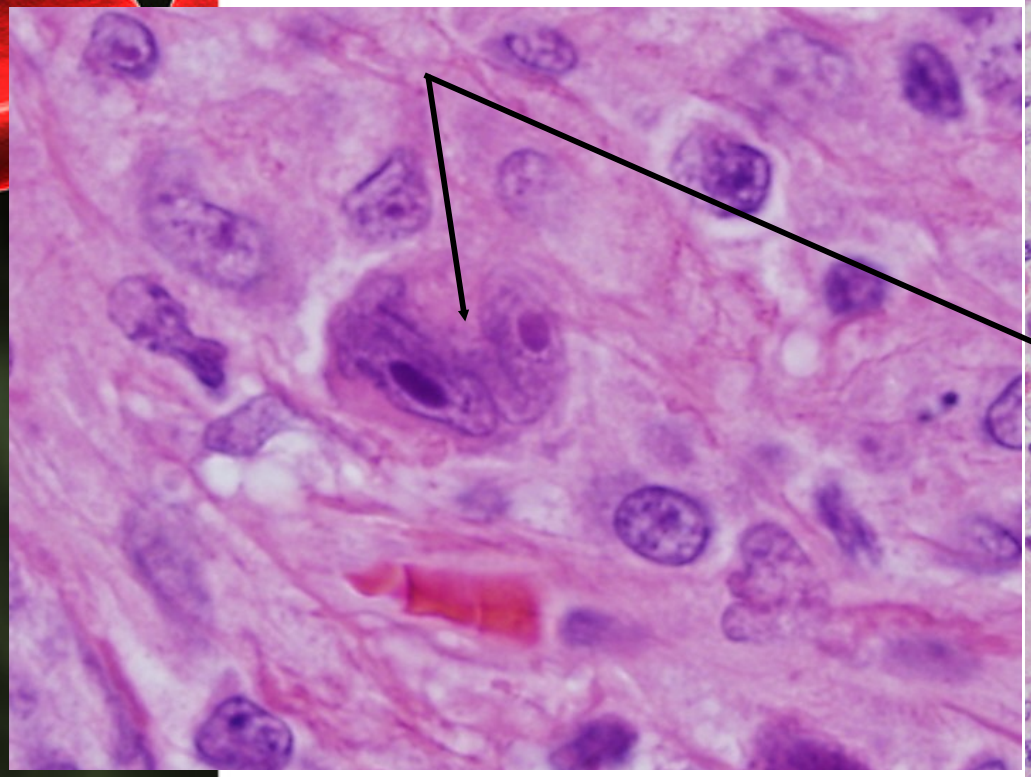
B Symptoms

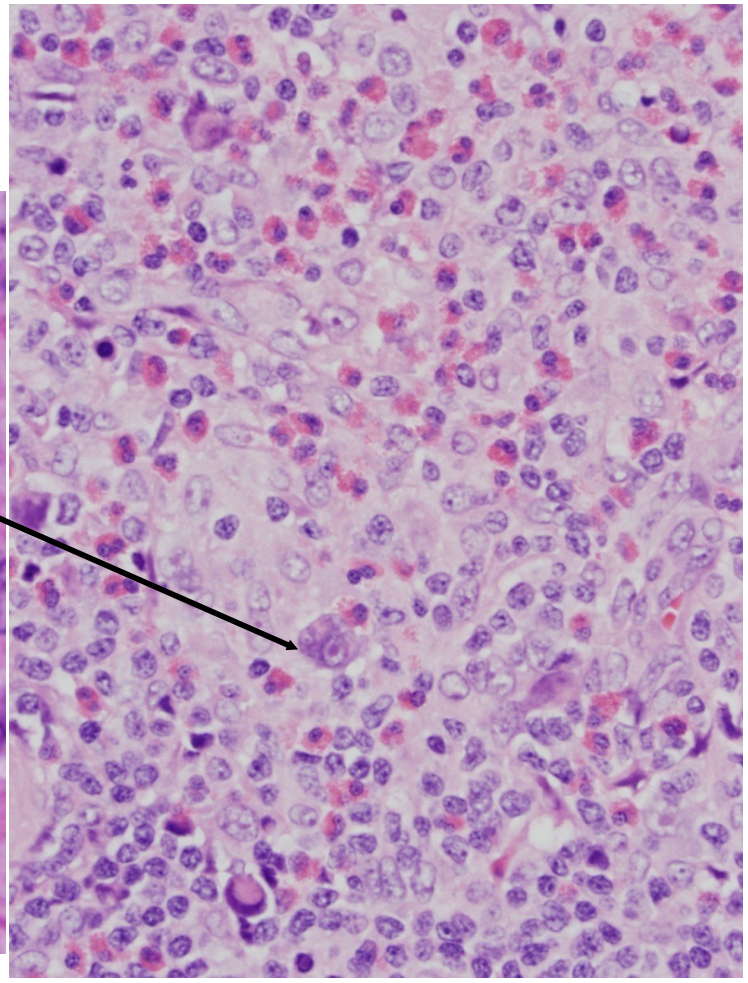
Masses



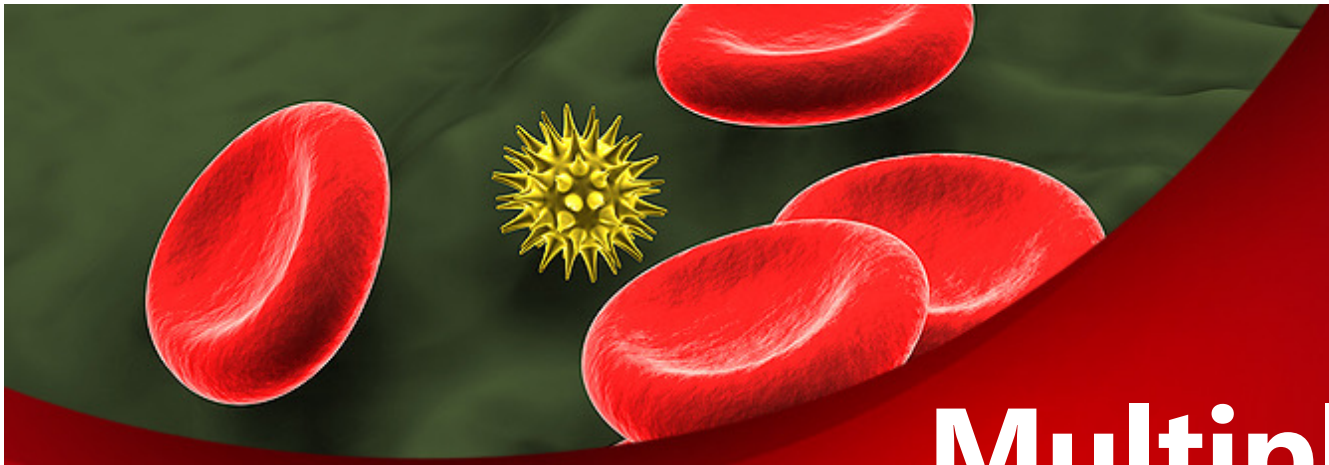
Hodgkin Lymphoma

Reed-Sternberg Cell





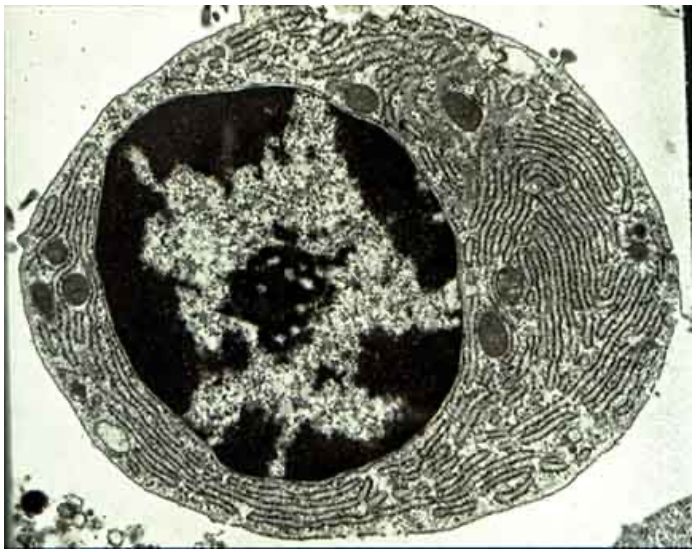
Tumor is primarily composed of benign reactive cells with rare malignant Reed-Sternberg Cell

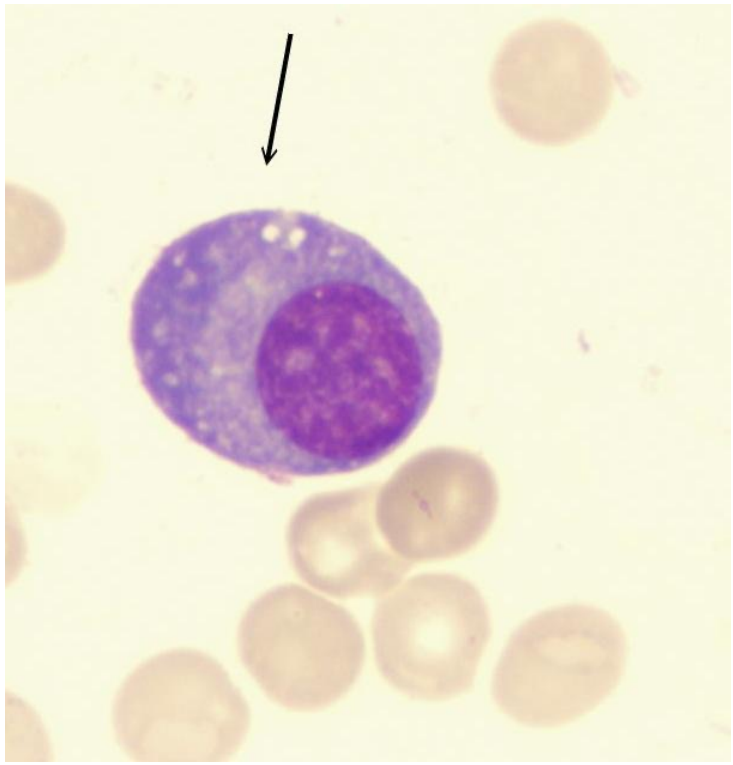


Multiple Myeloma

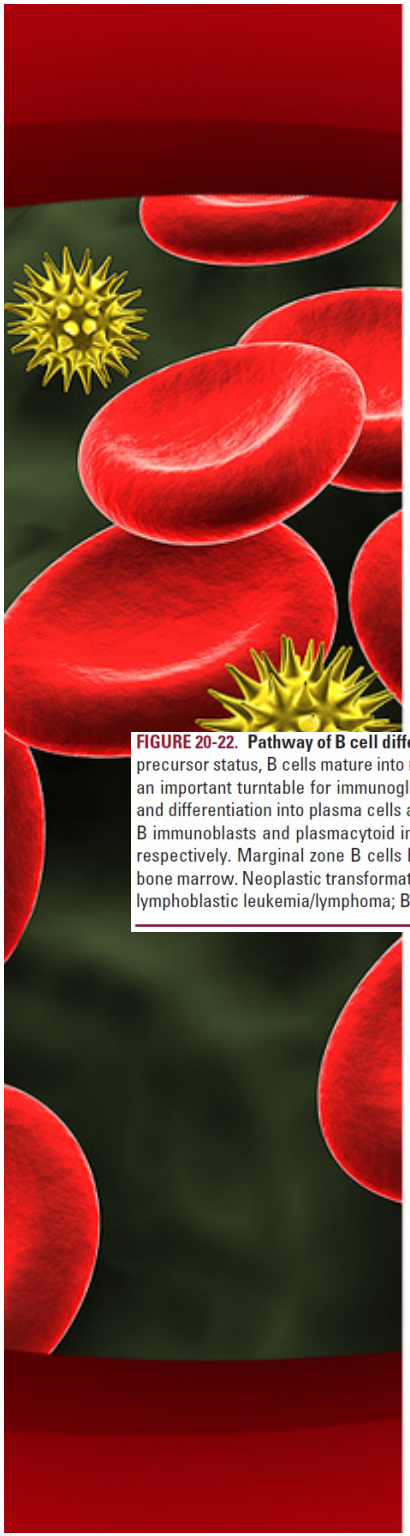
- To review normal peripheral blood, bone marrow, and lymph node pathology of multiple myeloma
-

Multiple Myeloma is a Malignancy of Plasma cells





Cells of origin of B-cell malignancies



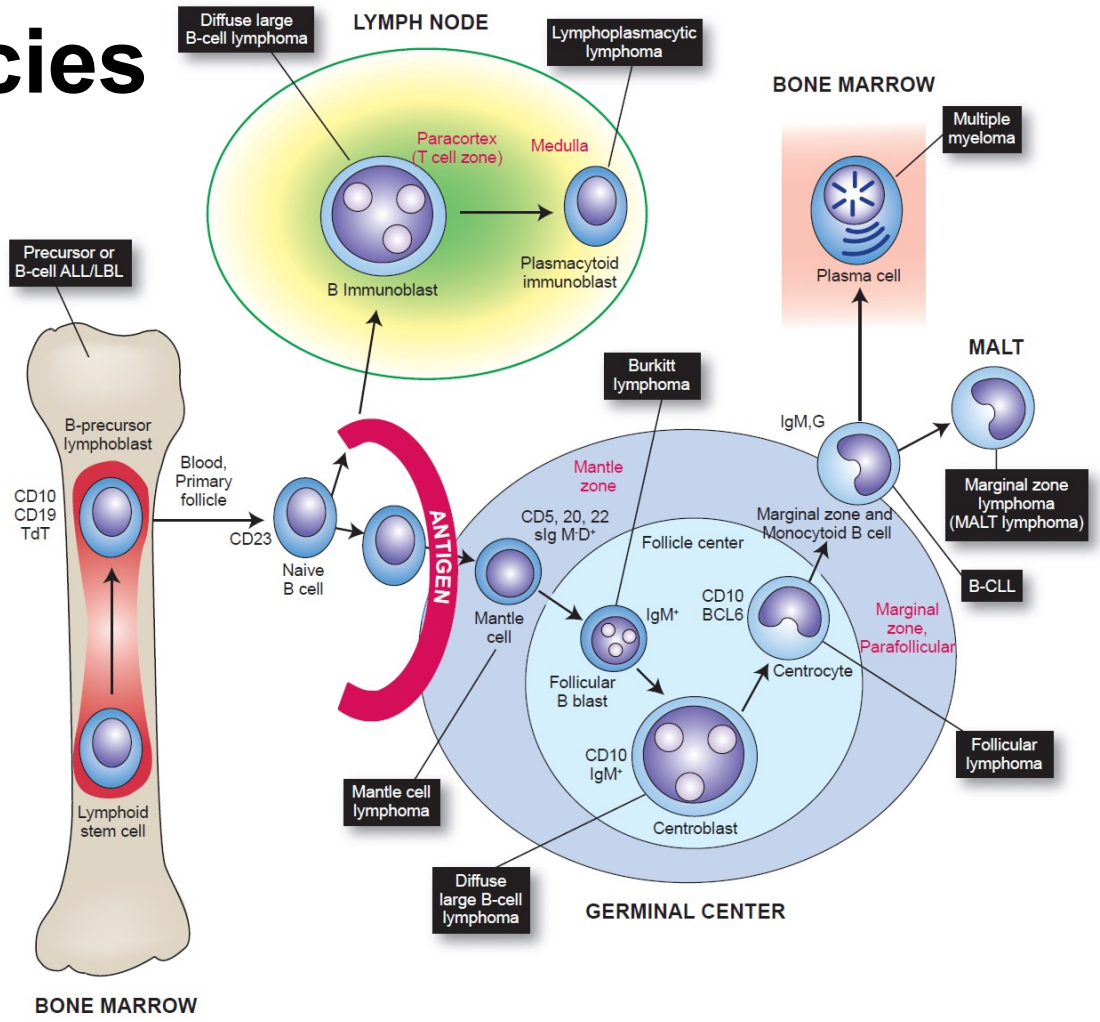


FIGURE 20-22. Pathway of B cell differentiation and corresponding B-cell lymphomas. Following the precursor status, B cells mature into naive B lymphocytes. The germinal-center response represents an important turntable for immunoglobulin variable region gene mutations, Ig heavy-chain switch, and differentiation into plasma cells and memory cells. Cluster designation (CD) markers are shown. B immunoblasts and plasmacytoid immunoblasts reside in the T-cell-rich paracortex and medulla, respectively. Marginal zone B cells home to mucosa-associated lymphoid tissue (MALT) sites and bone marrow. Neoplastic transformation occurs at all phases of B-cell differentiation. ALL/LBL, acute lymphoblastic leukemia/lymphoma; B-CLLB-cell, chronic lymphocytic leukemia; Ig, immunoglobulin.

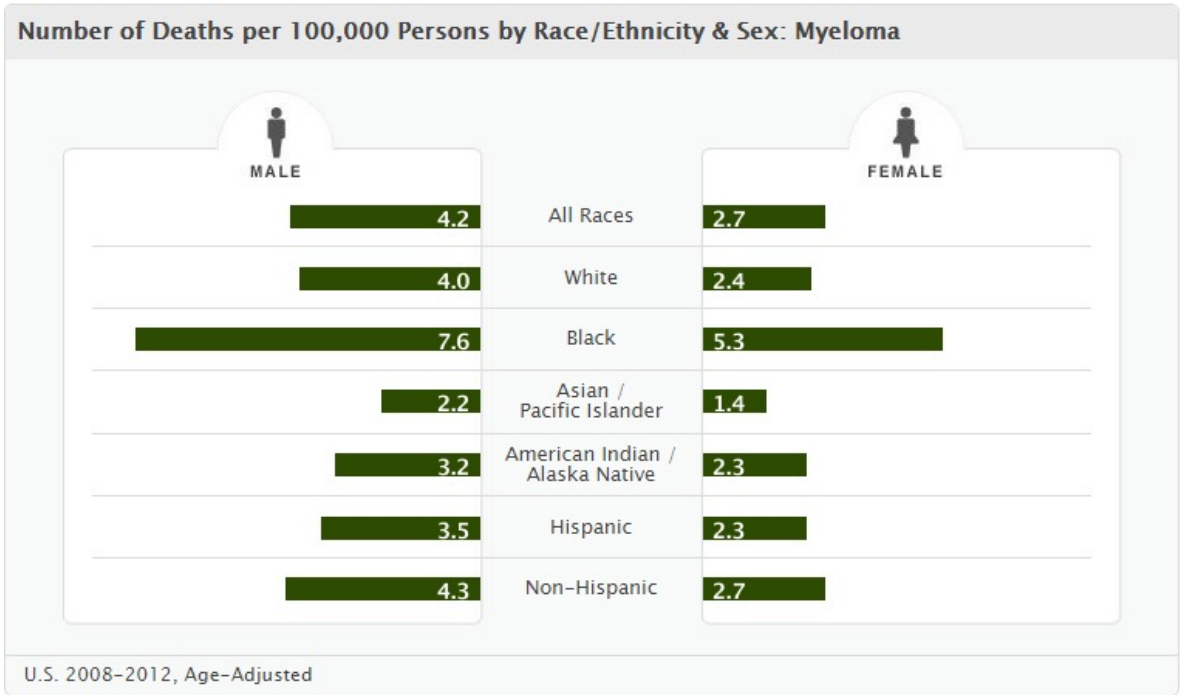
Multiple Myeloma: Epidemiology

- Approximately 1% of all malignancies
- Approximately 10% of hematological malignancies
- Approximately 20,000 cases a year
- Primarily incurable, but survival has increased in the past decade

Multiple Myeloma: Risk factors

- Risk factors include:
  - Age (peak incidence between 65 and 70)
  - Gender (males>females)
  - Genetic ancestry (Blacks>Whites≥Hispanic>Asian)
  - Family history
  - Radiation exposure
  - Chronic antigenic stimulation

Demographics*

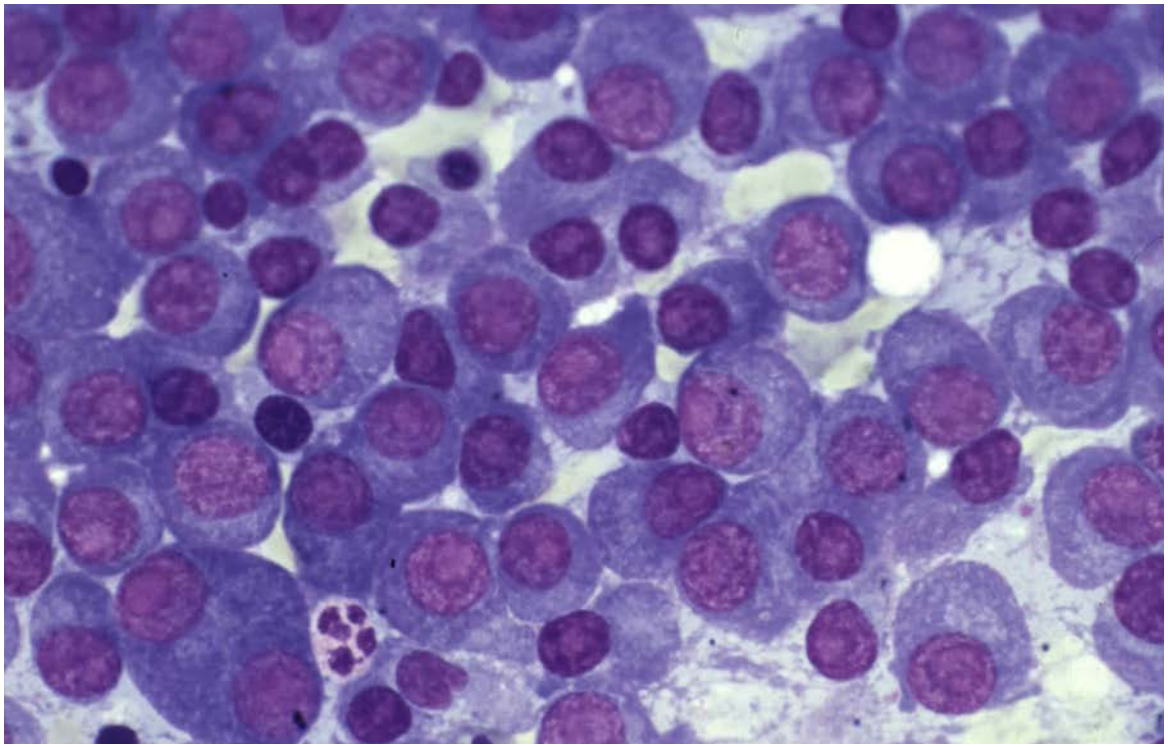


***Substitute genetic ancestry for race**

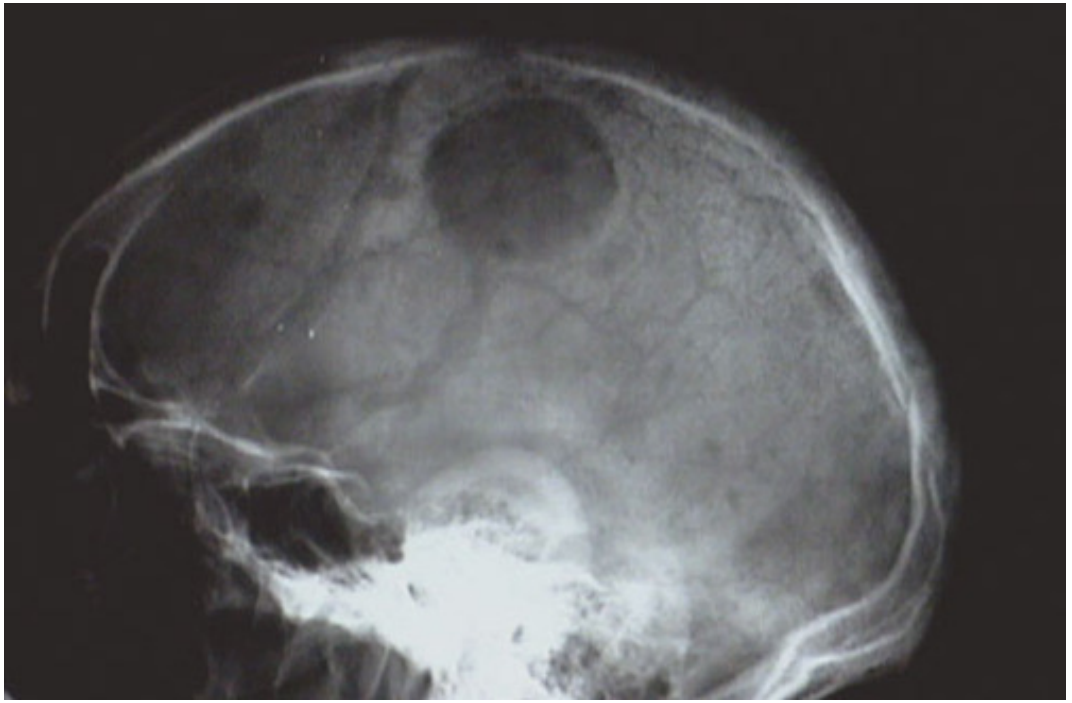
Multiple Myeloma

- The clinical and pathologic findings associated with multiple myeloma are in large part a consequence of:
  1) Tumor mass effect of the malignant plasma cells proliferating in the bone marrow or from:
  2) Abnormal secretory products from the malignant plasma cells including monoclonal immunoglobulins and cytokines

Bone Marrow Clonal Plasmacytosis

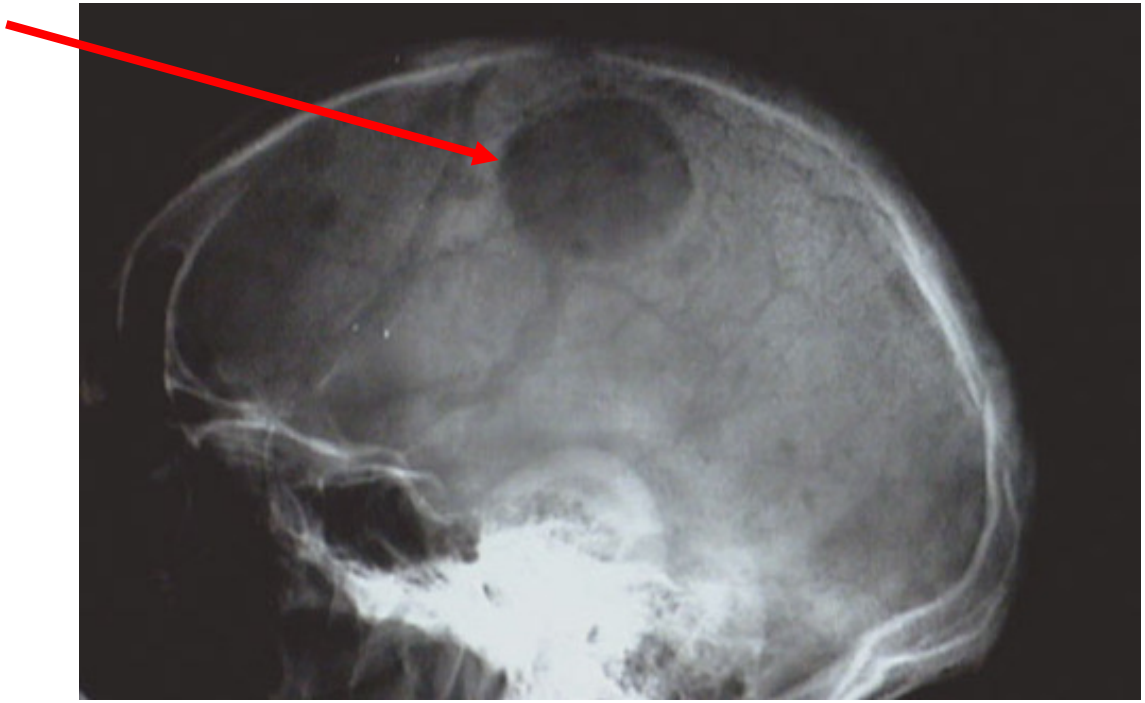


Lytic Skull Lesion



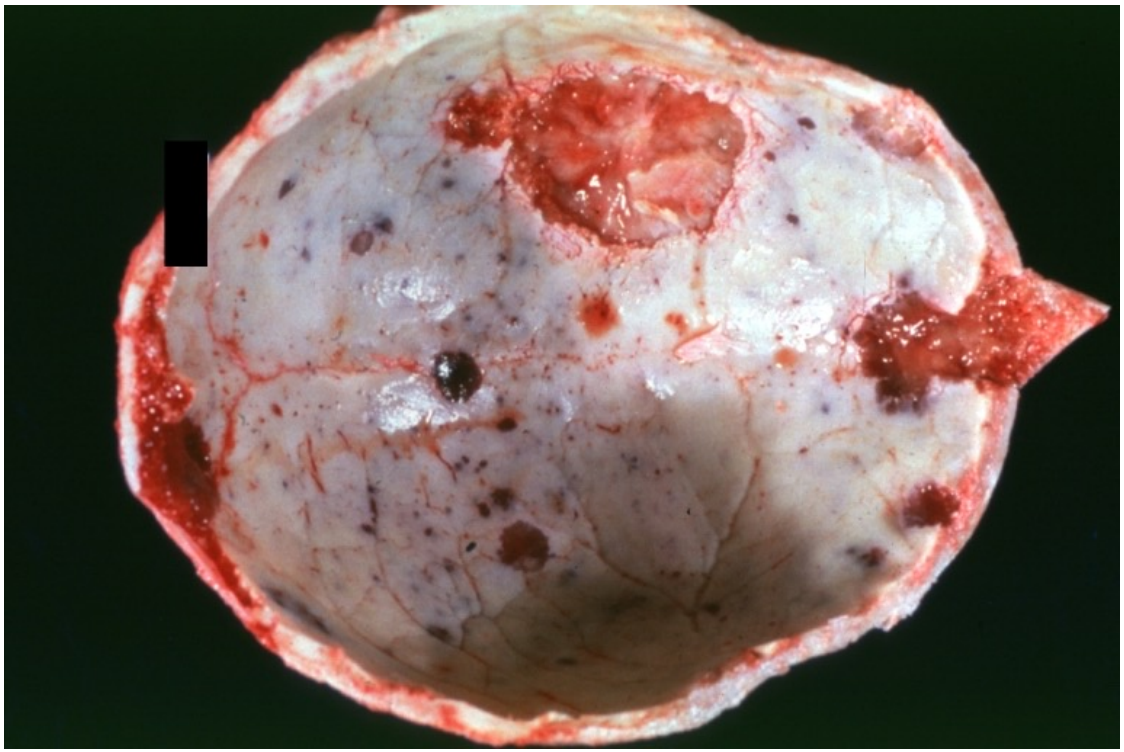
Lytic lesions see on skeletal survey, but not bone scans

Lytic Skull Lesion



Lytic lesions see on skeletal survey, but not bone scans

Multiple Myeloma – Lytic lesions in skull



Multiple Myeloma Laboratory Studies

- Complete blood count (CBC)
- Chemistries, especially calcium and creatinine
- Serum and urine protein electrophoresis and immunofixation
- Bone marrow for morphology, immunophenotyping and cytogenetics
- Bone imaging studies (skeletal radiography, CT, or PET-CT)

Colin Powell & Multiple Myeloma

- Multiple myeloma is associated with suppression of normal immunoglobulins
- This causes patients to be more vulnerable to infections
- They do not make normal immunoglobulins like people with normal immune systems
- They might not make antibodies in response to a vaccine

- https://www.cbsnews.com/news/colin-powell-covid-vaccine-multiple-myeloma-cancer-risk/

Serum protein electrophoresis and immunofixation – IgG Lambda

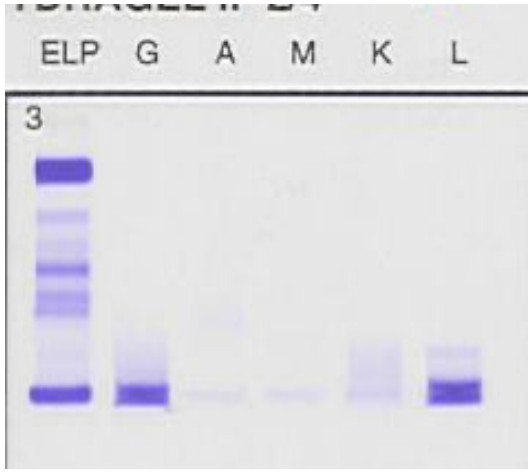
SPEP

P N

Albumin

Band indicating monoclonal immunoglobulin in gamma globulin region

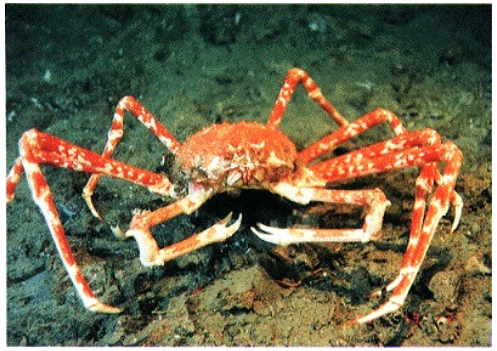
Immunofixation



P=Patient
N=Normal

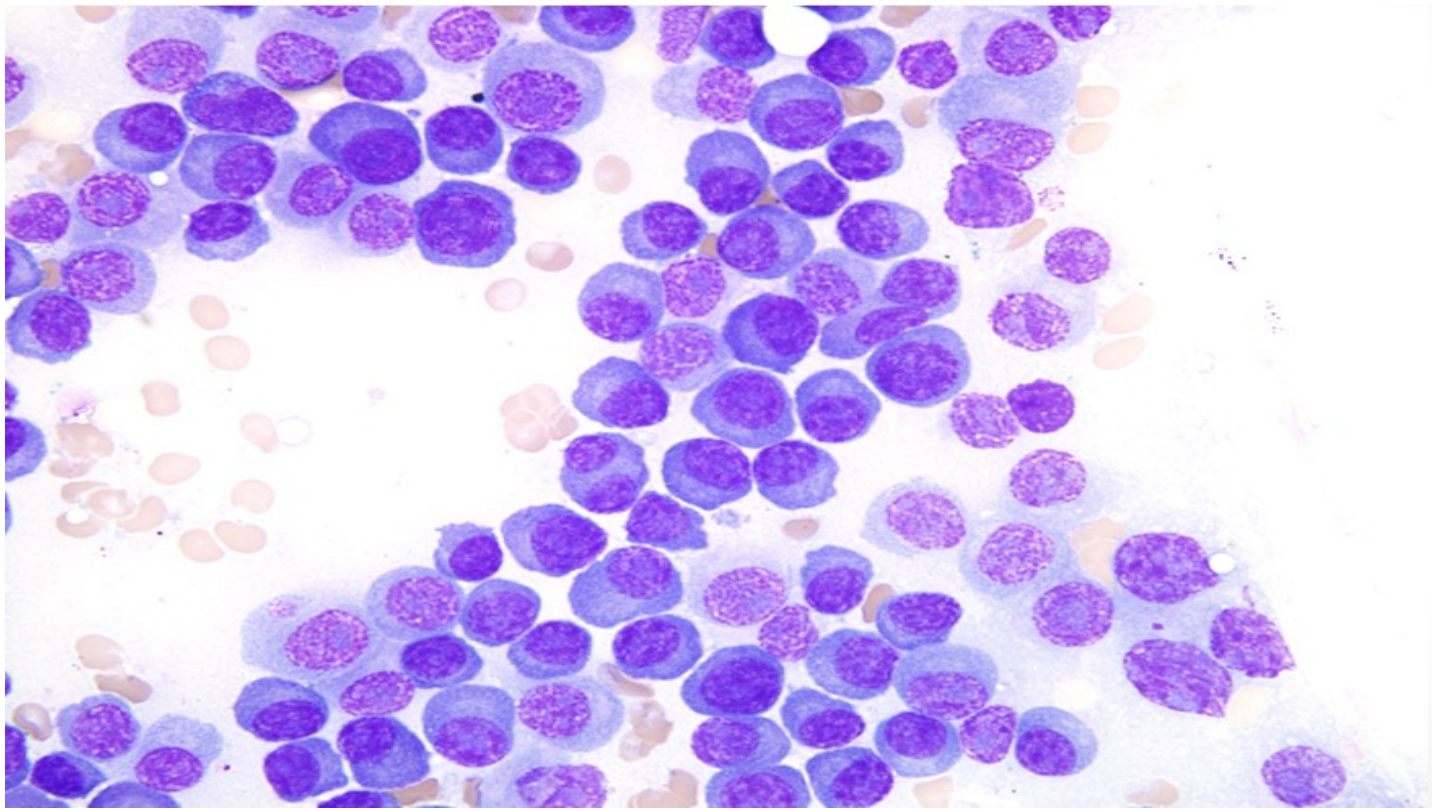
Myeloma Defining Events (MDE)

- Evidence of end organ damage (CRAB)
  - Hypercalcemia
  - Renal disease
  - Anemia
  - Bone disease



- Biomarkers
  - Extreme bone marrow clonal plasmacytosis
  - Elevated free serum light chain level (FLC)
  - More than one focal lesion on MRI

Bone marrow plasmacytosis



Summary

- Hematologic neoplasms include leukemia, lymphoma, and multiple myeloma
- These diseases occur throughout life
- Disparities exist based on socioeconomics and genetic ancestry
- There have been many advances in therapy in the last decades but more work needs to be done
-