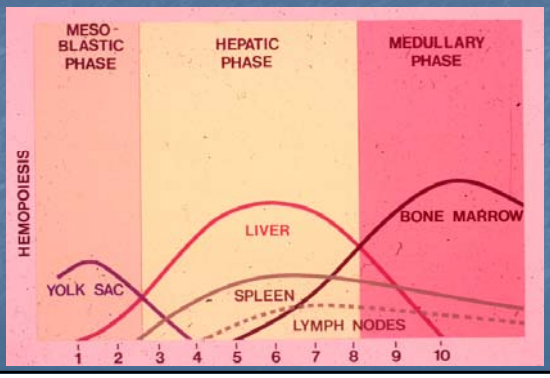
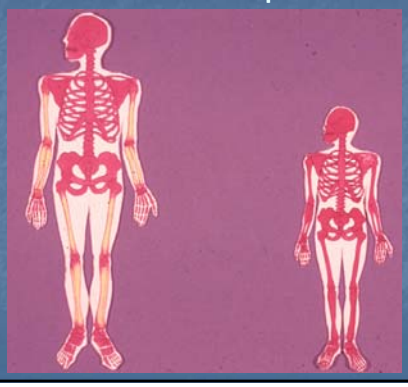
Hematopoietic and Lymph Node Pathology

Red Blood Cell Maturation
&
Anemias

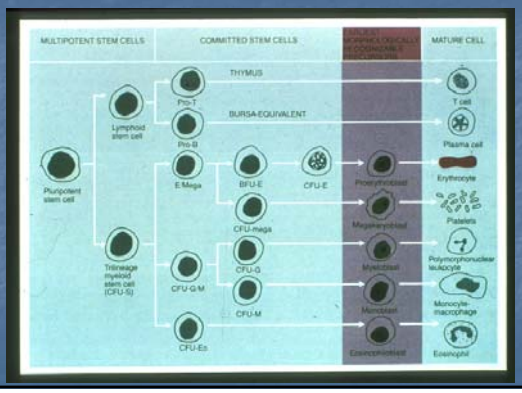
Normal Development



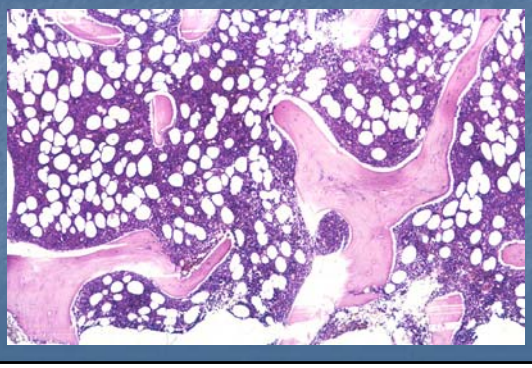
Normal Development



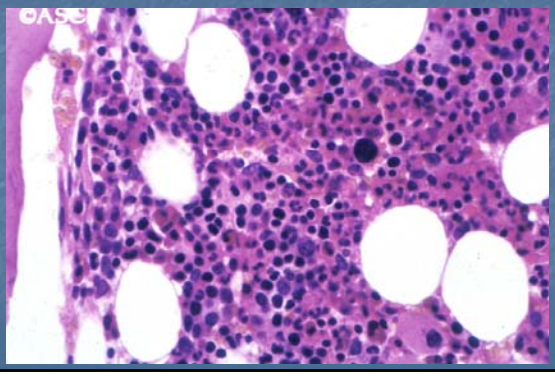
Differentiation of Hematopoietic Cells

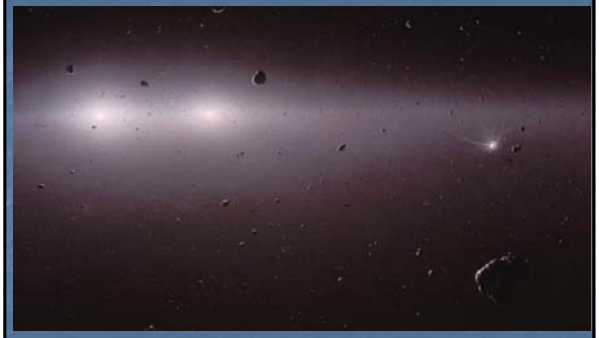


Bone Marrow

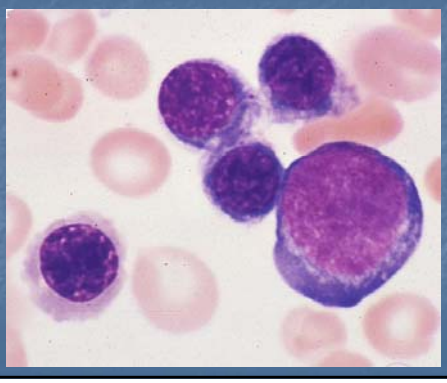


Bone Marrow

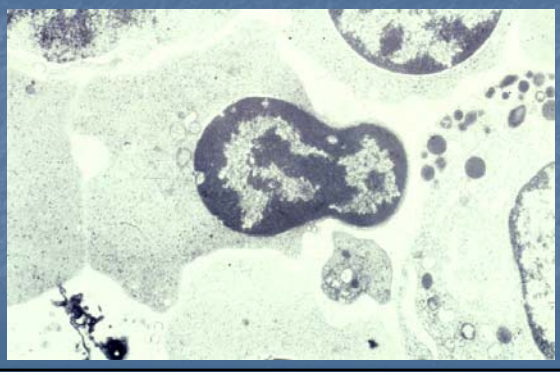




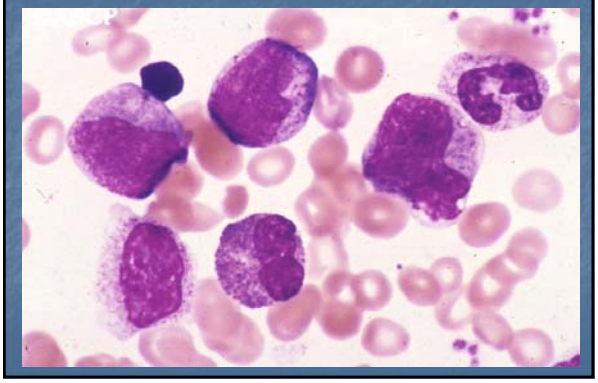
Bone Marrow, RBC Precursors



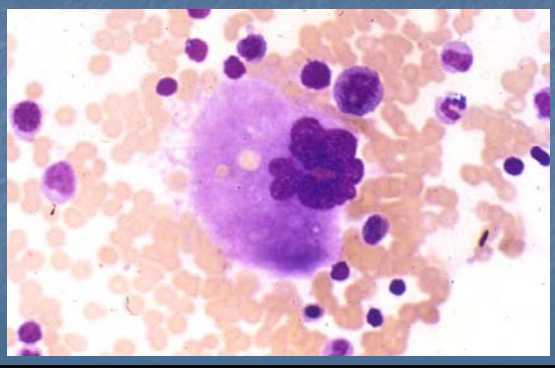
RBC Expelling the Nucleus

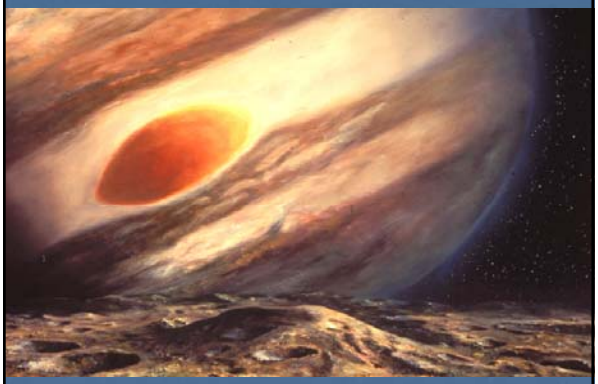


Myeloid Maturation



Megakaryocyte





Anemias

- Not a disease in itself
- Just a symptom, like a fever
- Must Understand why.
- Fix underlying cause
- Unpredicted outcomes

Anemia

- Acute
  - Trauma
    - Blood loss, either internal or external
    - Reticulocytes 10-15% in a week
- Chronic
  - Time to adapt
  - GI bleeds, colon ca
  - Increased demands of pregnancy

Anemia Workup

- History, History & More History
  - Age, sex, medications, duration….
- Physical
  - Nailbeds, mucus membranes…..
- Lab
  - CBC
    - RBC size, shape, HgB, RDW, MCV, MCHC
  - Reticulocyte count
  - Chemistries
    - Iron, B-12, Folate
  - Bone marrow
  - Fancy stuff

Erythrocytes

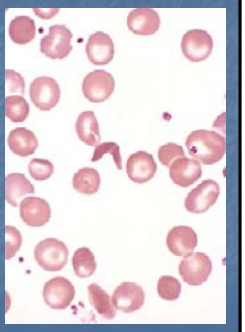
- Size
  - Anisocytosis (an/iso/cytosis)
- Shape
  - Poikilocytosis (poikilo/cytosis)
  - Fragmented cells
- Hemoglobin content of cells and whole blood
  - HBG and HCT
  - MCH & MCHC
- Mean volume of the RBCs (MCV)
  - Uniformity (RDW)
- Cytoplasmic inclusions
  - Congenital problems
    - Sickle cell among others

Anemias by Etiology

- Blood loss
  - Acute, no time to accommodate
    - Trauma
    - Massively bleeding ulcer or esophageal varices
  - Chronic, slow with some adaptation
    - GYN loss
    - Ulcer
    - Colon cancer
- RBCs are 'normocytic'
- Retic count better go up
- History and Physical

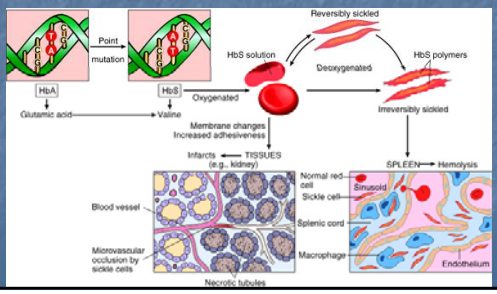
Anemias by Etiology

- Congenital
- Hemoglobin
  - Sickle cell
- Enzyme
  - G6PD
- Membrane
  - Spherocytosis

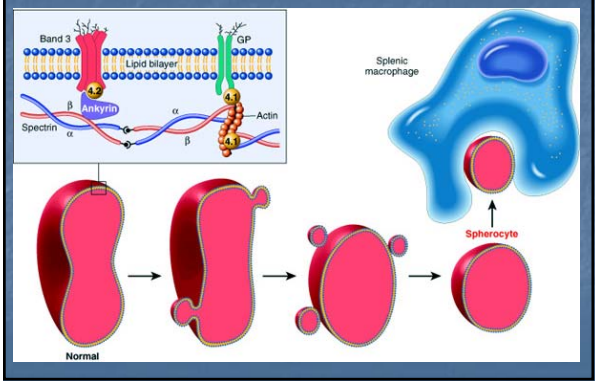


Sickle Cell Disease

- Homozygous vs. heterozygous
- Chronic anemia
- Acute crisis
- Microvascular occlusion
- Infections
- Relative malaria resistance for AS

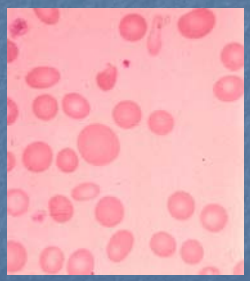


Shperocytosis



Hemolytic Anemias

- Premature destruction or removal of RBCs
- Genetic
  - SS
  - Spherocytosis
- Acquired
  - Antibody mediated
- Intravascular
  - Antibody mediated
  - Free hemoglobin
- Extravascular



Problems of RBC Production

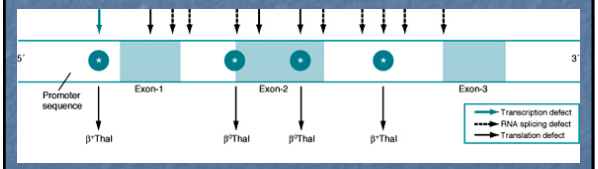
- Genetic related
- Nutritional deficits
  - Iron
  - B12
    - Dietary or problems of absorption?
    - Chronic gastritis
  - Folic acid
- Chronic renal failure (no erythropoietin)
- Aplasia of RBC line in bone marrow

Nutrient Deficit

- Inadequate dietary source?
- Absorption?
- Utilization?

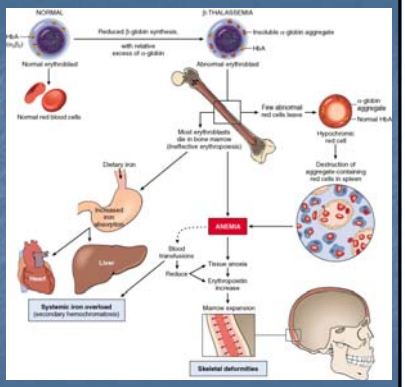
Thalassemia

- Genetic
- Collection of problems of production of one of the hemoglobin chains.
- Beta and Alpha chains

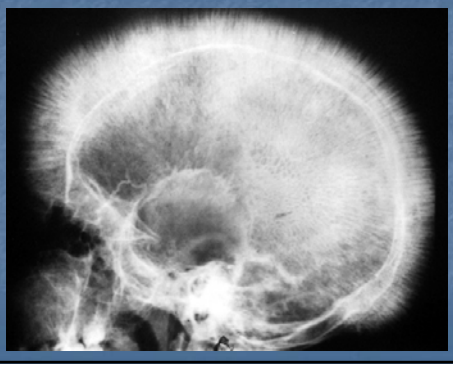


Thalassemia

- Microcytic
  - Small RBCs
- Target cells
- Mismatched production of β and α chains
- Hemoglobin globs in RBC
- Reduced RBC survival

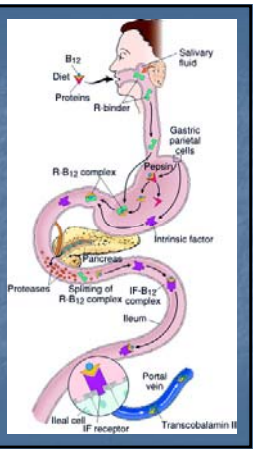


Thalassemia



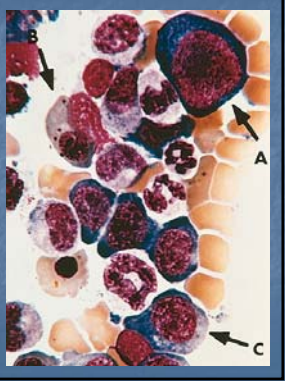
B12 Deficiency

- Dietary
- Pernicious Anemia
  - Absorption
  - Binding factor missing
  - Chronic gastritis
- Macrocytic anemia
  - Large cells
  - Delayed nuclear maturation
- Neurological signs
  - Myelin production

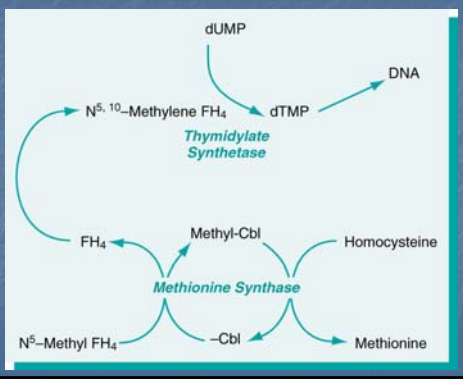


Macrocytes and Megaloblasts

- Macrocyte
  - Large RBC
- Megaloblast
  - Large BM precursor
- Folic acid can have similar look
- CNS with B12 only
  - Be careful correcting B12 deficiency with folic acid.
  - Anemia corrects, but neurological problems progress.

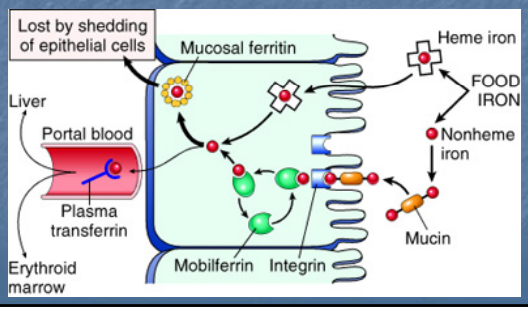


Folic Acid and B12



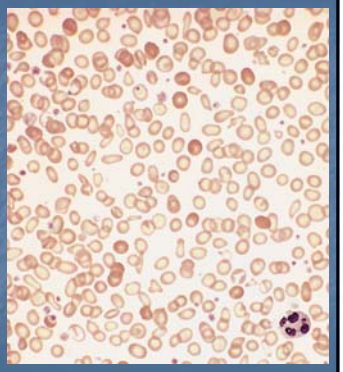
Microcytic Anemia

- Small RBCs
- Iron deficiency
- Thalassemia



Iron Deficiency

- Dietary?
  - Rarely in US
  - How much anyway?
- Blood loss
  - Chronic
  - GYN
  - Colon cancer
- RBCs are
  - Microcytic
  - Hypochromic
- Lack iron for hemoglobin production

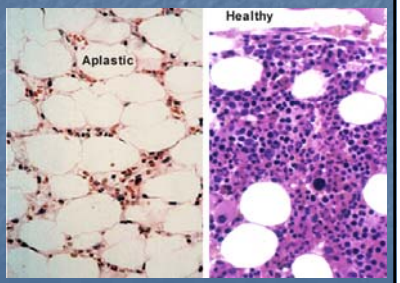


Anemia of Chronic Disease

- Problem is of excessive drive to store iron.
- Chronic inflammation
  - Arthritis
  - TB
  - Even cancer
- Most of incoming iron is sent to storage
  - Part of the normal response to inflammation.
- In time anemia develops because of
  - Reduced iron for utilization
  - Not dietary lack or
  - Failed absorption

Aplastic Anemia

- Something kills precursor in BM.
  - Virus
  - Radiation
  - Chemotherapy



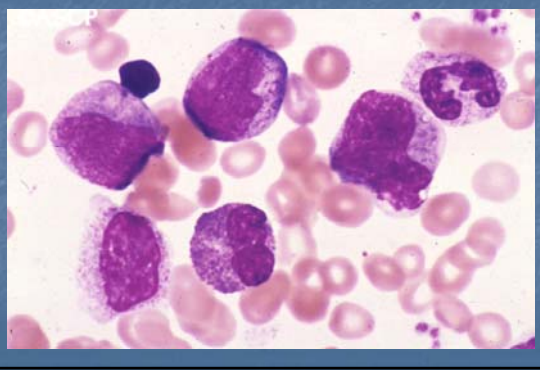
Over Production of RBCs

- Believe it or not, it's not a good thing.
- Response to increased need
  - High altitude living
  - Lung disease
    - Emphysema
- Over production of erythropoietin.
  - Renal disease
  - Tumors
- Uncontrolled production at bone marrow level

Hemolytic Disease of Newborn

- Pregnant mother is Rh^-, fetus is Rh^+
- If mom should have antibodies to the Rh factor, they will cross the placenta.
- Destruction of baby's RBCs
- Previous maternal exposure
  - Miscarriage
  - Previous delivery
  - Wrong transfusion
- Treatment: Mom gets Rhogam

WBC Disorders



WBC Disorders

- Quantity
  - Do we have enough WBCs
- Quality
  - If the number looks right, are the cells working?
- Higher than expected number (leukocytosis)
  - Cell type
  - Reactive or
  - Neoplastic
    - Benign
    - Malignant
- Leukopenia

Leukopenia

- Low WBC count
  - Under 3,000 per mm^3
- Causes
  - Production problem
    - Sick BM
    - Replacement of BM space
  - Peripheral destruction
    - Autoimmune destruction
  - Sequestration of cells
    - Large spleen
      - Rheumatoid arthritis

Leukocytosis

- High WBC count in peripheral blood
  - >12,000 per mm^3
- Cell type?
- Healthy Cells?
- Reaction to need
  - Pneumonia
  - Incr granulocytes; bacterial infection, necrosis
  - Incr monocytes; TB, brucella, rickettsia
  - Incr lymphocytes; virus, tumor response
  - Incr eosinophil; allergic, parasite

Distinguish Malignant Proliferation

- History and physical
- Maturity of cells
  - Visual inspection of blood smear
  - Flow cytometry
  - Nuclear maturity
    - Nucleoli
  - Cellular inclusions
- Chromosomal studies
- Bone marrow

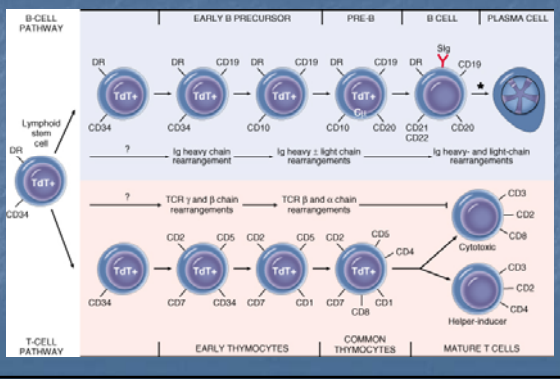
Leukemia

- Malignant proliferation of WBCs and/or precursors.
- Classification
  - Cell line
    - Granulocytes or Lymphocytes
  - Cell population:
    - Chronic, mature, slower developing
    - Acute, immature cells, rapidly developing
- The big three features: All three cell lines affected
  - RBC
  - WBC
  - Platelets
- Causes
  - Chromosomal breaks, but why?
  - Viruses, chemical exposure, radiation.....

Leukemia

- Organs involved
  - BM
  - Blood
  - Nodes
  - Liver and Spleen
  - Brain.....
- Common presenting symptoms
  - Recurrent serious infections
    - Pneumonia
  - Bleeding tendency
  - Anemia
  - Fever with no obvious cause
  - Bone pain

Lymphocyte Maturation

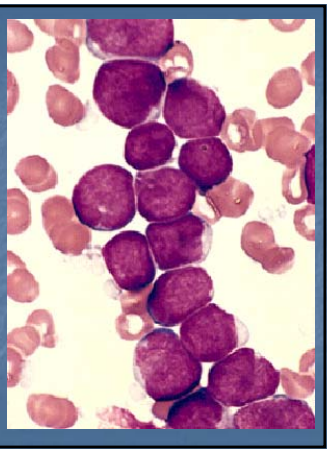


Lymphoid Malignancies

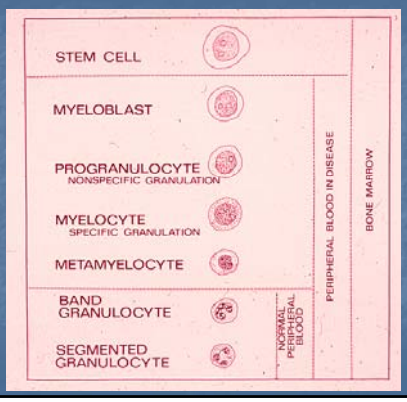
- 'Solid' vs. 'Liquid'
  - Leukemia
    - Bone marrow predominately
  - Lymphoma
    - Lymph nodes
- Cell type and level of maturation
  - Cell size
  - CD typing
  - Where did it come from in the follicle?

Acute Lymphobalstic Leukemia

- Children
  - Less common, but does occur in adults
- Precursor B leukemia
  - CD19, TdT +
  - Ig locus t(12:21)
  - Marked BM replacement
- Precursor T leukemia
  - CD1 and TdT +
  - Chromosomal breaks
  - Adolescent males
  - Mediastinal mass
  - +/- spleen and liver

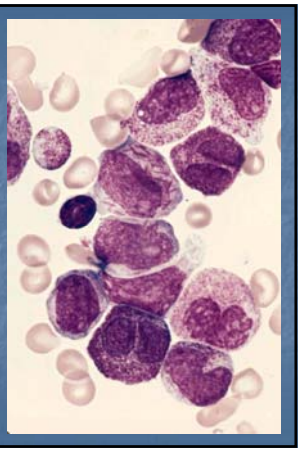


Acute Myelogenous Leukemia



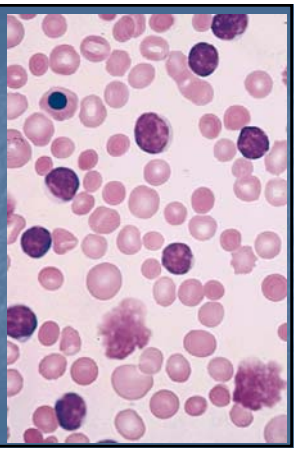
Acute Myelogenous Leukemia

- Myeloid line
  - Many subtypes
  - Level of maturation determines what malignant cells look like.
- Adults
- Aure rods ->
- Adults
- Rarely pure monocytic
- Symptoms
  - Infections
  - Mouth ulcers
  - Gingival hypertrophy (mono)

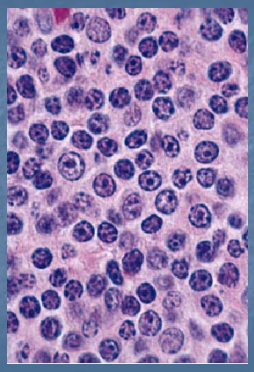


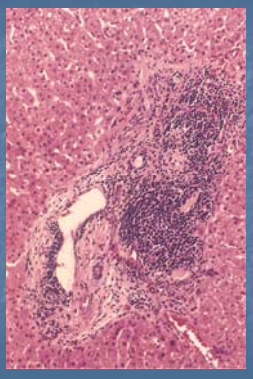
Chronic Lymphocytic Leukemia

- Mature lymphocytes
- High WBC count
- B-Cells
- Adult and older
- Indolent course
- Tissues
  - BM
  - Nodes
  - Liver and Spleen
- May accelerate
  - Blast crisis
  - Richter's syndrome



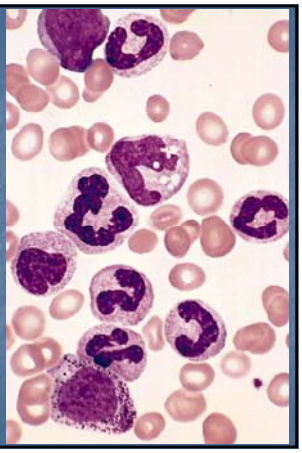
Chronic Lymphocytic Leukemia



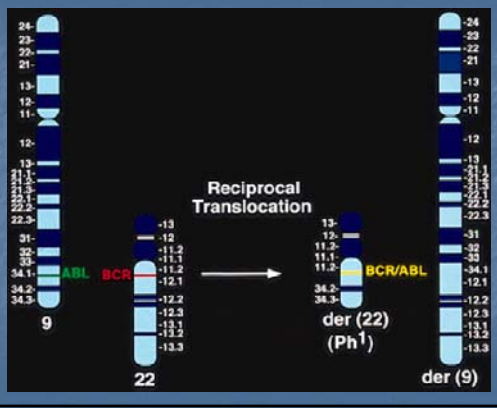


Chronic Myelocytic Leukemia

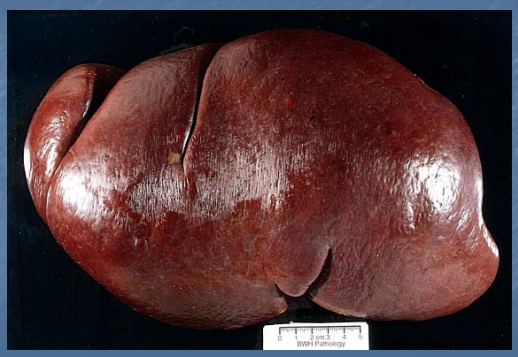
- Middle age and older
- High WBC count
- Stem cell is malignant
- All phases present
- Low LAP (cells don't work)
- Ph' Chromosome
  - t(9:22)
- Organs
  - BM
  - Spleen
- Blast crisis
- Soft tissue met
  - Chloroma



Ph' Chromosome



Splenomegally in Chronic Granulocytic Leukemia

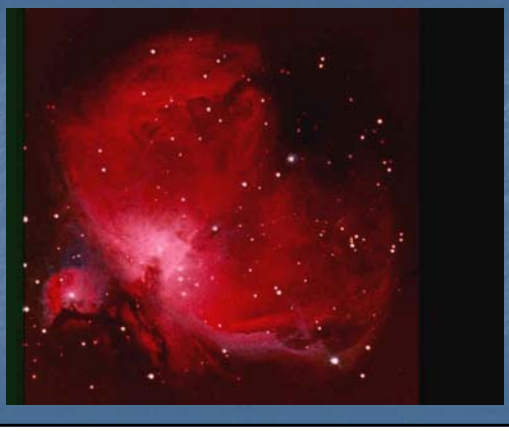


Myelofibrosis Etc

- Myelofibrosis
  - Scarring process
  - Reticulum fibers
  - Loss of marrow space
  - Extramedullary hematopoiesis
- Metastatic cancer

Preleukemia

- RBC abnormalities easiest to spot.
- All cell lines have abnormal maturation.
- Chromosomal abnormalities
- Some end in leukemia
- Most end with myelofibrosis

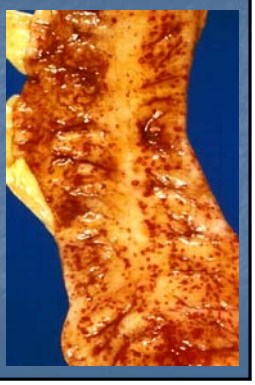


Bleeding Disorders

- Takes three things working for hemostasis
  - Platelets
  - Clotting proteins
  - Vessels
- The question is always
  - Quantity
  - Quality

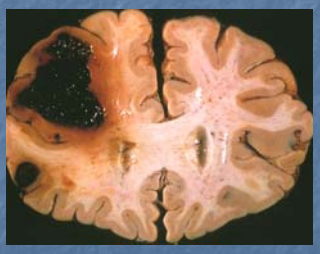
Platelet Related Bleeding

- Platelet problems
  - Petichae
  - Bruises (purpura)
- Quantity
  - 120,000-400,000
  - Production
  - Destruction
- Quality
  - Aspirin
  - Renal failure



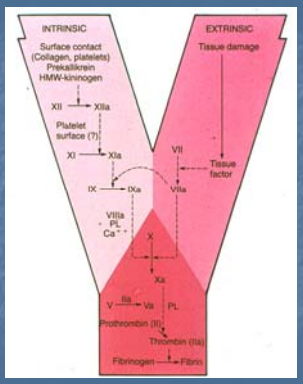
Clotting Factor Related Bleeding

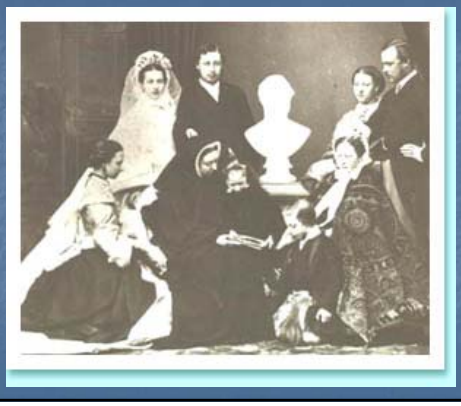
- Hematoma
  - Deep muscle
- Joint bleeds
- Bleeding gums
- Poor wound healing
- Quantity
  - Can you make it
  - Genetics
  - Liver disease
- Quality



Hemophilia A & B

- Hemophilia A
  - X-linked recessive
  - Boys express
  - Factor VIII enzymatic
- Hemophilia B
  - Christmas Disease
  - Factor IX
  - Also X-linked recessive
  - Not as severe as VIII





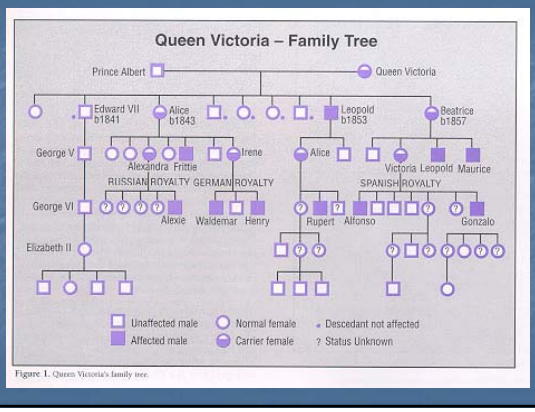
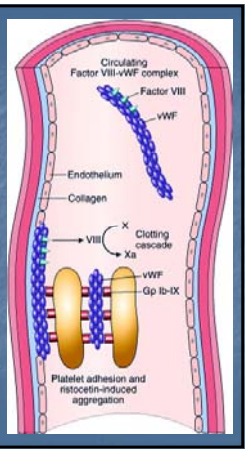


Figure 1. Queen Victoria's family tree.

Von Willebrand's

- Factor VIII, 'structural'
- Platelet binding
  - Collagen of damaged vessel
  - Platelet – platelet binding
- Clinically, bleeding looks more like platelet abnormality.
- Autosomal dominant
- Multiple types
  - Type I
    - Most common
    - Reduced quantity of vWF
  - Type II
    - Problem with multimeric form of vWF

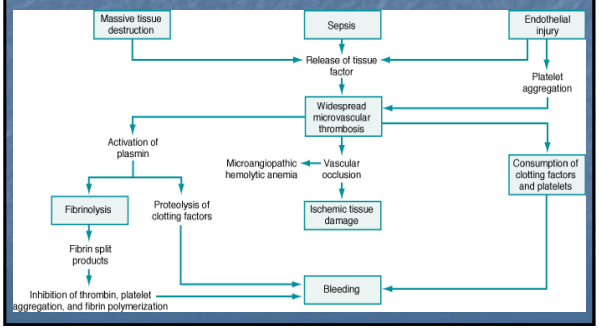


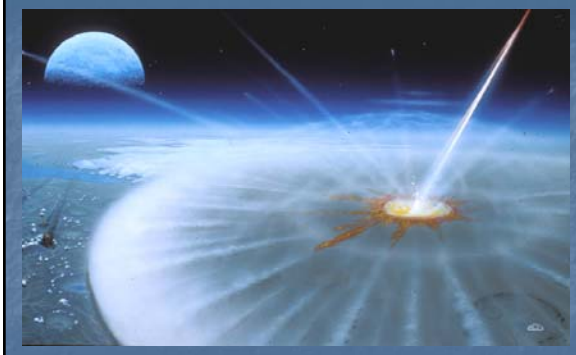
Generic Platelet Problems

- Quantity (thrombocytopenia)
  - Lack of bone marrow production
  - Autoimmune destruction (ITP)
  - Heparin induced thrombocytopenia
  - Lack of stabilizing factor (TTP)
- Quality
  - Aspirin induced platelet dysfunction

Disseminated Intravascular Coagulation

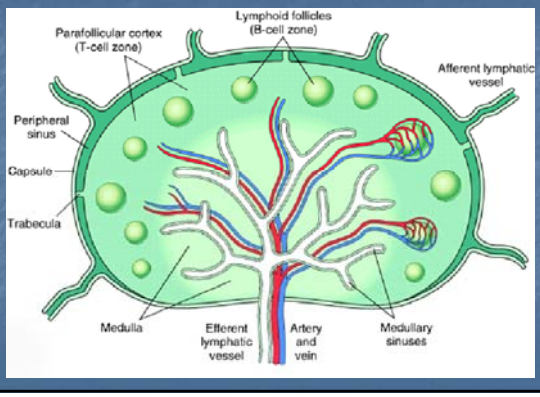
- Runaway train
  - OB disaster
  - Sepsis and endothelial cell injury
  - Massive muscle injury



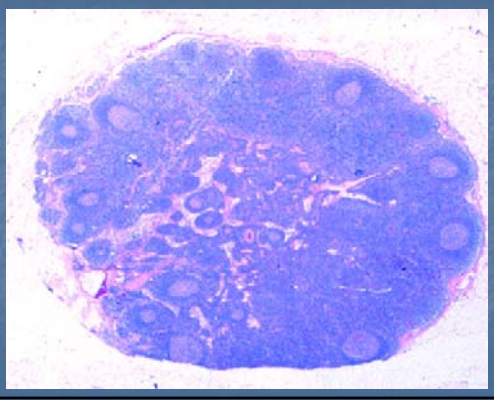


Diseases of Lymph Nodes

Basic Node



Basic Node



Lymph Node Disorders

- Reactive vs. Neoplastic
- History & Physical Exam
- Histological pattern
  - Nodal architecture recognizable?
    - Effaced?
  - Diagnostic inflammatory changes

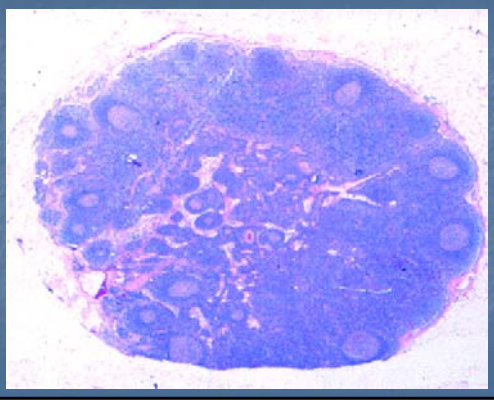
Reactive Conditions

- Non-neoplastic reaction to
  - Infections, necrosis, tumors
- Histological pattern
  - Follicular
  - Sinusoidal
  - Specific patterns
    - Abscess
    - Granuloma

Neoplastic Diseases

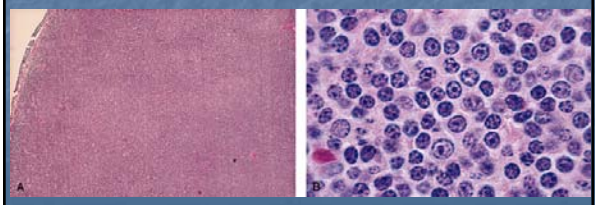
- Classification is very important
  - Treatment options
  - Predicting outcome
- Histological pattern
  - Hodgkin Lymphoma vs. Non-Hodgkin Lymphoma
  - Cell type (where did it come from in the node?)
  - Degree of differentiation (grade)
  - Diffuse or Follicular
- Stage (extent of spread)
  - Know the difference between stage and grade
- Systemic symptoms (so-called B symptoms)
  - Fever
  - Night sweats
  - Weight loss

Basic Node



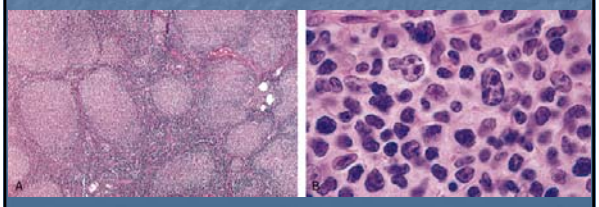
Non-Hodgkin Lymphoma, SLL

- Small cell lymphocytic lymphoma
- Tissue phase of CLL
- Diffuse replacement of nodal architecture
- Long-lived B-cells (CD19, CD20)
- Surface immunoglobulins



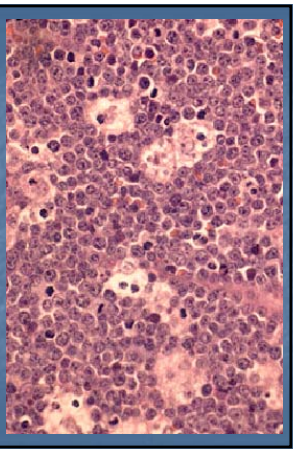
Non-Hodgkin Lymphoma, Follicular Pattern

- Nodal architecture is effaced
- Nodular or follicular pattern
- 'Centrocytic' cells (from germinal centers)
- B-cell markers
- Surface immunoglobulins

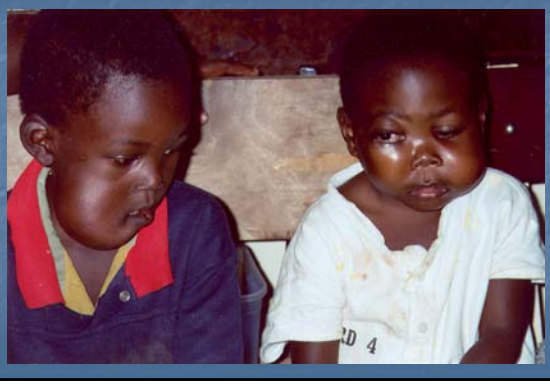


Burkitt's Lymphoma

- Two types
- American
  - Retroperitoneal
- African
  - Jaw
  - EB virus association?
- 'Starry sky' appearance
- B-cell

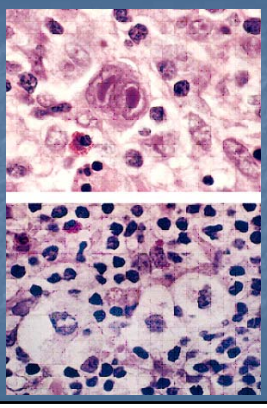


African Burkitt's

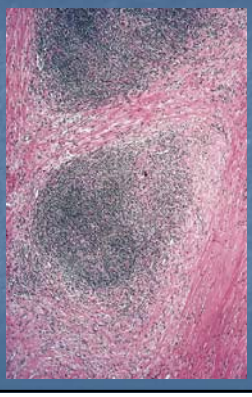


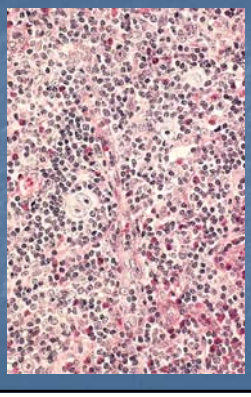
Hodgkin's Disease

- Distinguished from NHL by
- Reed-Sternberg cell ->
  - In its proper background
  - This is the malignant cell
  - The others are reactive
- Bimodal age distribution
- Distinctive patterns
  - Nodular sclerosis
    - Lacunar cells ->
  - Mixed-cellularity
  - Lymphocyte predominate



Hodgkin's Disease





Hodgkin's Staging

- Stage I
  - Single node or single extranodal site (I-e)
- Stage II
  - Two or more nodal regions on the same side of the diaphragm
- Stage III
  - Both sides of the diaphragm
  - +/- Splenic involvement (III-s)
  - +/- Extranodal (III-e)
- Stage IV
  - Multiple disseminated foci

Multiple Myeloma

- Plasma cell malignancy
- Term refers to holes in the bone because of nest of plasma cells ->
- The replace marrow space.
- The cells make an intact, or fragment, of immunoglobulin.
- Real problems with infections
  - No inflammatory cells
- Bleeding
  - Protein coats platelets
- Renal failure
  - protein clogs tubules

Multiple Myeloma

- Protein electrophoresis
- Large amount of abnormal protein in blood.
- Immunoglobulin
- Patient sample
  - Huge gamma band
  - All of it is kappa light chain