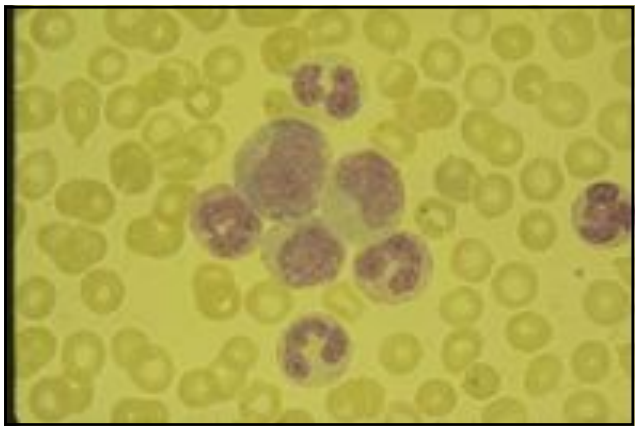
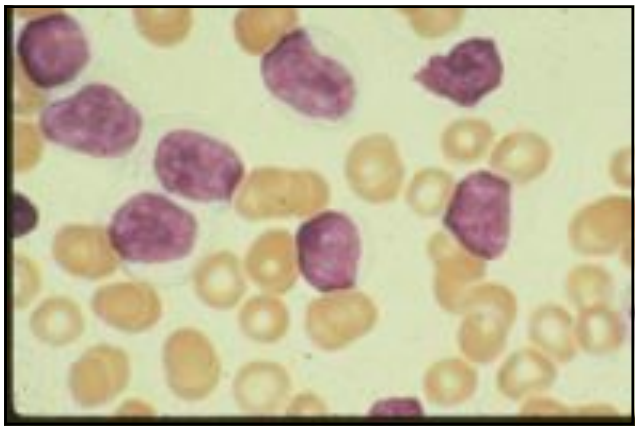
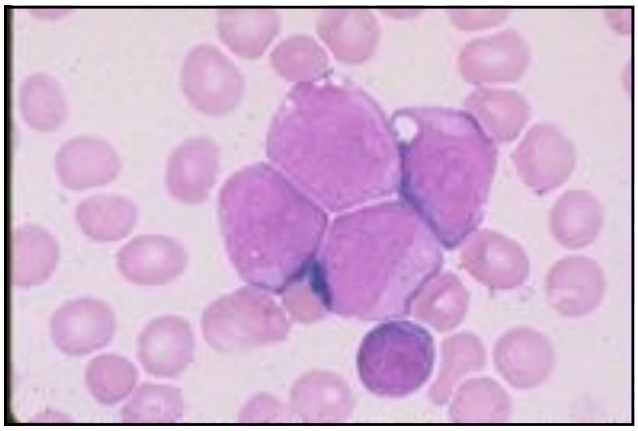
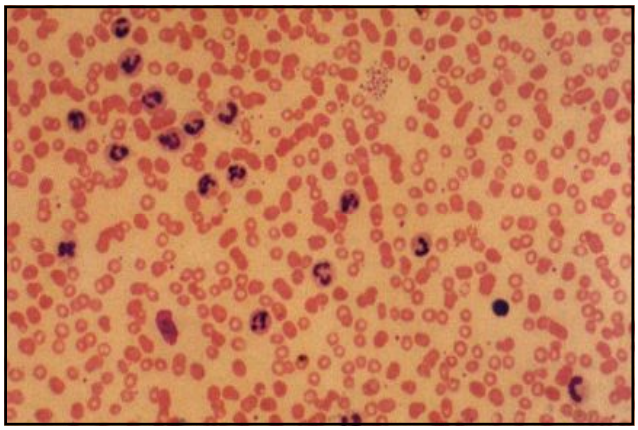
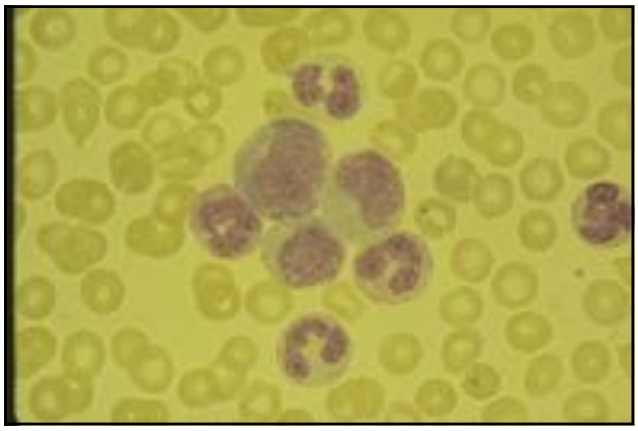


Disease	Usual phenotype
acute leukemia	precursor
chronic leukemia low grade lymphoma myeloma	differentiated

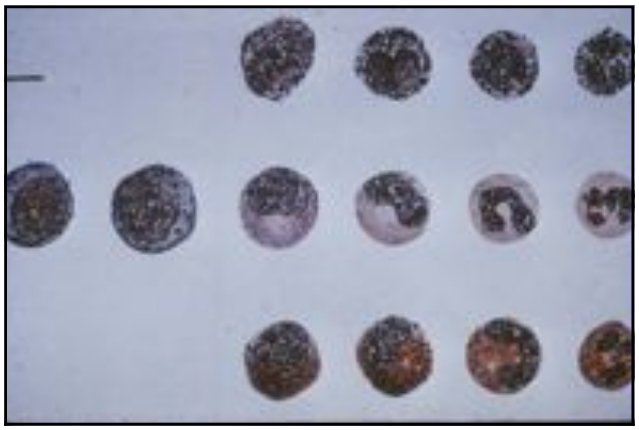








Total WBC ≥ 60	Blast	Pro	Myel	Meta	Band	Seg	Lymph
leukemoid reaction	0	0	0	2	13	82	3
acute leukemia	82	0	0	0	3	10	5
CML	2	8	13	18	20	37	2
CLL	0	0	0	0	1	1	98



Chronic myeloid leukemia

Chronic phase

increased pool of clonal precursors committed to become myeloid cells

most of the clonal precursors differentiate into mature cells

Leukemias - evidence of damage to DNA

- majority have visible chromosomal abnormality
- tumor-specific chromosomal translocations, e.g.,
  - t(15;17) acute promyelocytic leukemia
  - t(8;14) Burkitt's lymphoma/leukemia
  - t(9;22) chronic myeloid leukemia (and ALL)

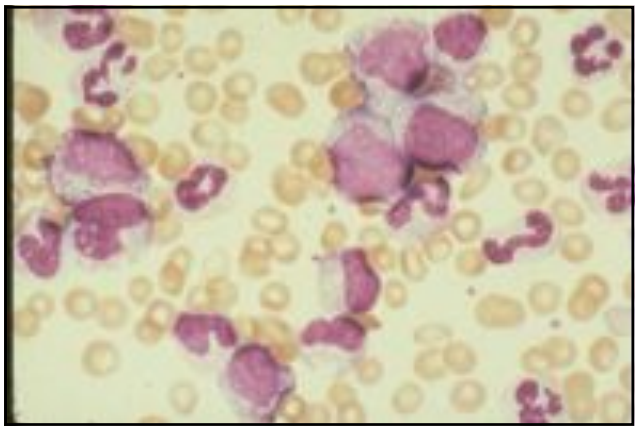
Conversion of proto-oncogene to oncogene

- Possible mechanisms
  - Unaltered gene product (e.g., *myc* in Burkitt's)
  - Altered gene product
    - » usually a fusion protein (e.g., *bcr-abl* in CML)

CML - chronic phase

- weakness, weight loss, purpura
- thrombocytosis
- anemia - normal MCV
- splenomegaly
- priapism

- median duration 3-4 yrs

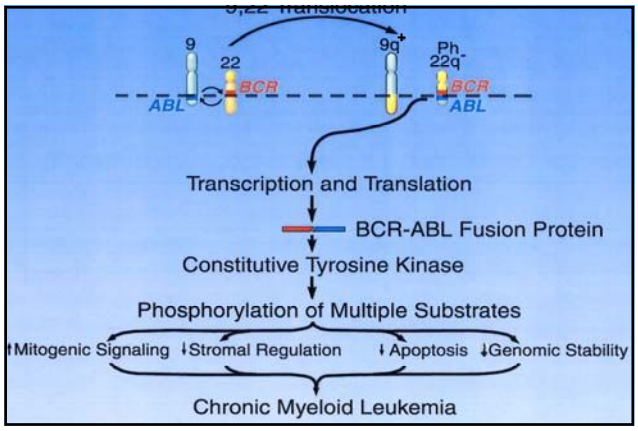


CML - chronic phase

- WBC increased
- Entire granulocytic spectrum on blood film
- Marrow hyperplasia
  - expanded myeloid series
  - eo and basophil precursors
  - megakaryocytes
- Low neutrophil alkaline phosphatase
- Ph chromosome [t(9;22)] present

Ph chromosome: t(9;22)

- reciprocal translocation between long arms of chromosomes 9 and 22
- Ph-negative CML: 9;22 translocation present but not visible
- ABL sequences from 9 translocated into BCR gene on 22 → FUSION GENE



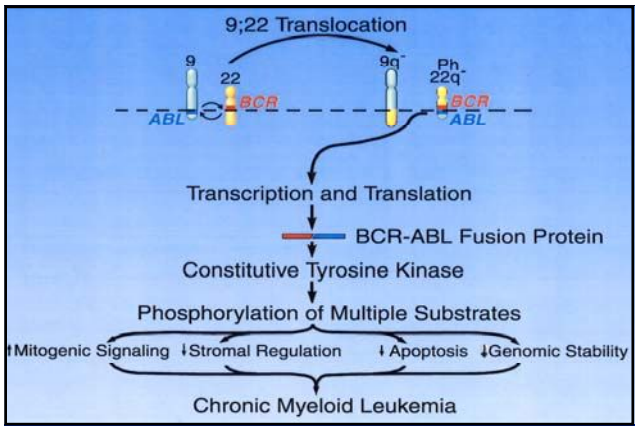
Introduction of BCR-ABL gene into mice

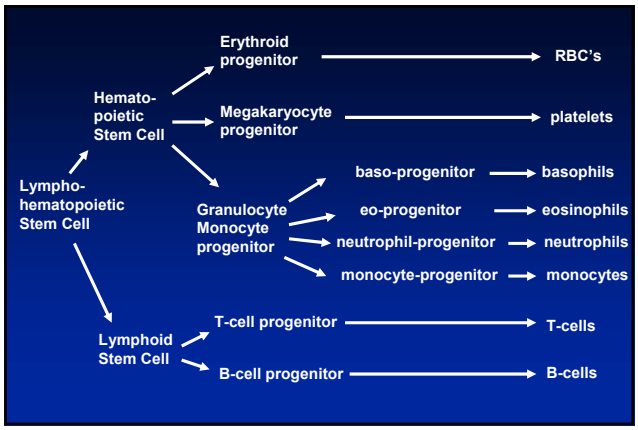
- trans-genic model
- *bcr-abl* product expressed
- animals develop CML and/or ALL

	molecul weight	tyrosine kinas activity
normal ABL chromosom	145,000	weak
fusion gene chromosom	210,000	strong

bcr-abl protein differs from *abl* protein

- cytoplasmic location
- transforms cells *in vitro*
- constitutive (continuous) increased tyrosine kinase activity
- new substrates and binding proteins
- *ras* is activated
- *bcr* component contributes to transforming activity





Chronic myeloid leukemia

Ph chromosome present in precursors of:

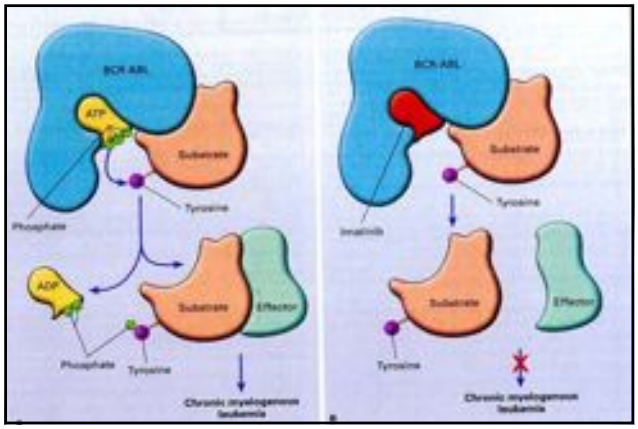
- granulocytes
- monocytes/macrophages
- basophils
- eosinophils
- erythrocytes
- platelets
- some B lymphocytes

Treatment of CML - chronic phase

- hydroxyurea
- interferon-$\alpha \rightarrow$ 10-20% become Ph-negative
- survival better with hydroxyurea or interferon

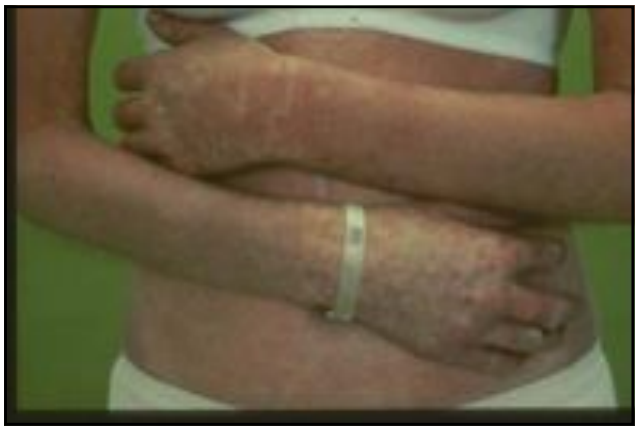
- imatinib (Gleevec) - targets ABL, potent, low toxicity

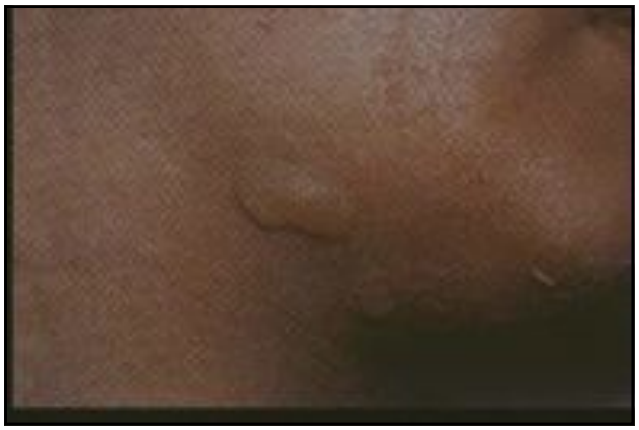
- allogeneic transplantation potentially curative

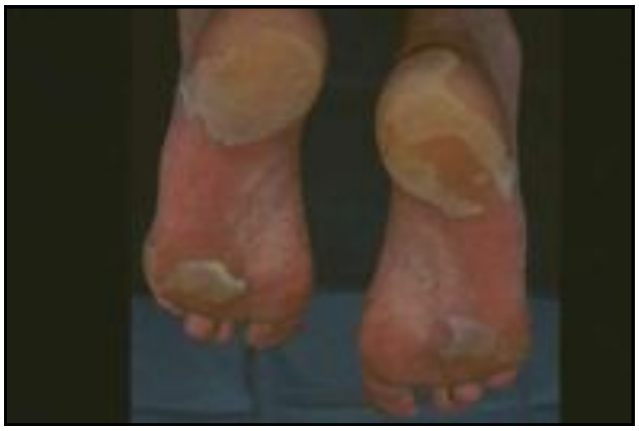


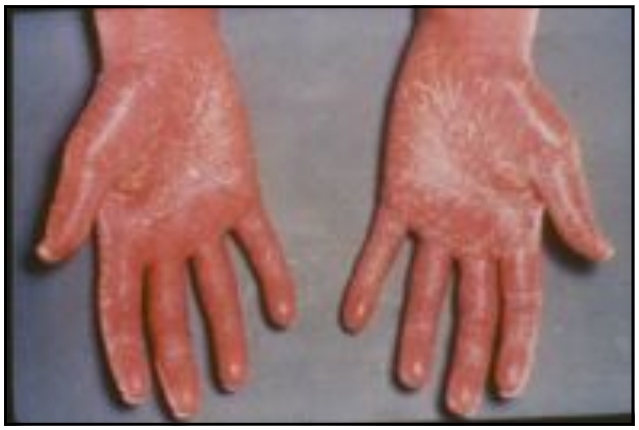
Marrow and Blood Stem Cell Transplantation

	Autologous (autograft)	Allogeneic (allograft)
Source of cells	Patient	Normal donor
Myeloablative conditioning	Yes	Usually
Transplant-related mortality	2-4%	10-30%
Graft-vs-host disease	No	Yes
Graft-vs-malignancy	No	Yes
Greatest curative potential	Lymphoma	Inherited disease, CML



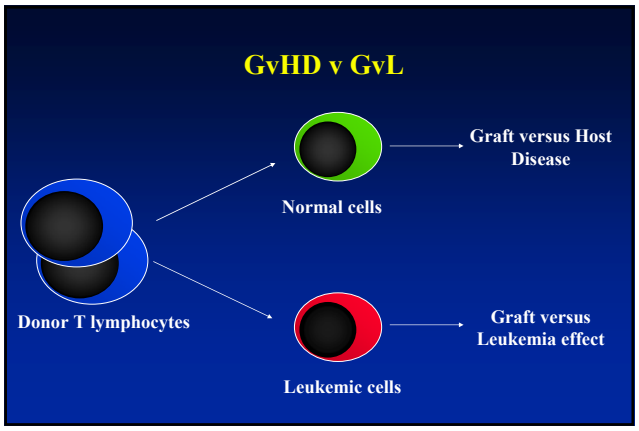


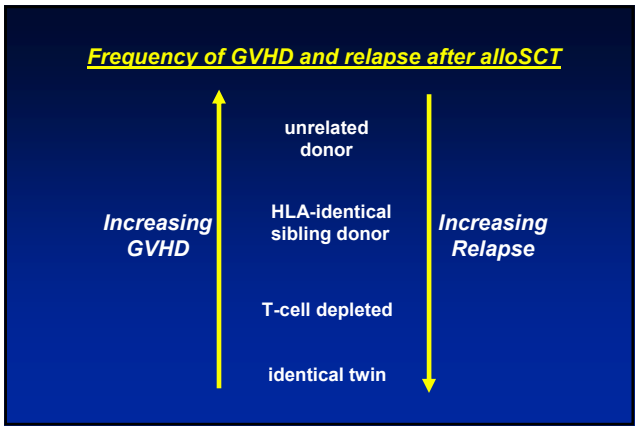




CML - allogeneic transplantation

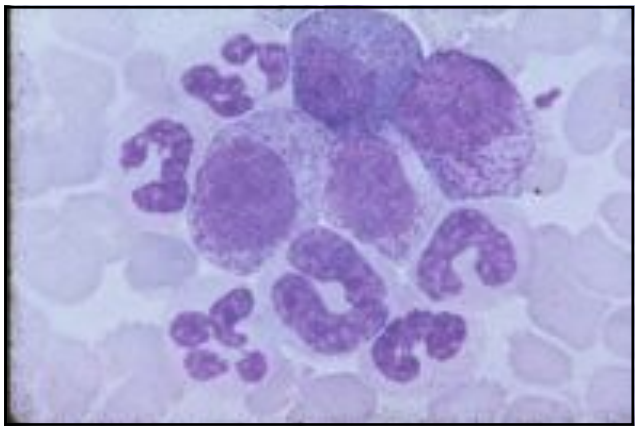
- may result in cure
- 10-25% transplant-related mortality
- age, donor limitations
- mechanisms of cure
  - high dose chemoradiotherapy
  - graft vs leukemia

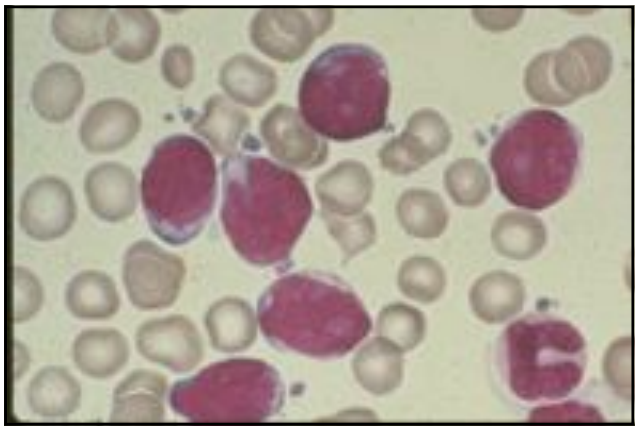




Evidence for an immunologically mediated GVL effect

- Inverse correlation between GVHD and relapse
- In patients whose CML relapses after alloSCT, transfusion of lymphocytes from stem cell donor *without additional chemoradiotherapy* often induces a complete remission





CML in blastic transformation

- unstable disease
- weight loss, fever, sweats, bone pain
- worsening
  - splenomegaly
  - anemia
  - platelet counts
  - blast and promyelocyte counts
  - basophilia and eosinophilia
- resistance to therapy
- 'blastic crisis' develops in most

- death in weeks or months

CML in blastic transformation

- Blasts of variable phenotype
  - myeloid
  - lymphoid (early B cell)
  - megakaryocytic
  - erythroid
- 'Clonal evolution'
  - Ph chromosome with additional mutations (e.g., double Ph, trisomy 8, p53 alteration)

Ph-positive ALL

- 30-40% of adult ALL
- poor prognosis
- some have same fusion gene as in CML
- different fusion gene in others
  - –breakpoints more 5' in BCR
  - –gene product 190,000 daltons
  - –even stronger tyrosine kinase activity

CML as a model of human malignancy

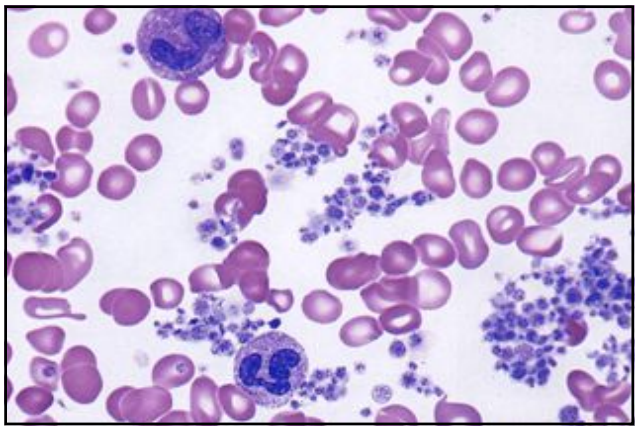
- origin in a stem cell
- tumor cell phenotype is differentiated (variably)
- clonal
- proliferative advantage
- genetic instability
  - –tendency to become less differentiated

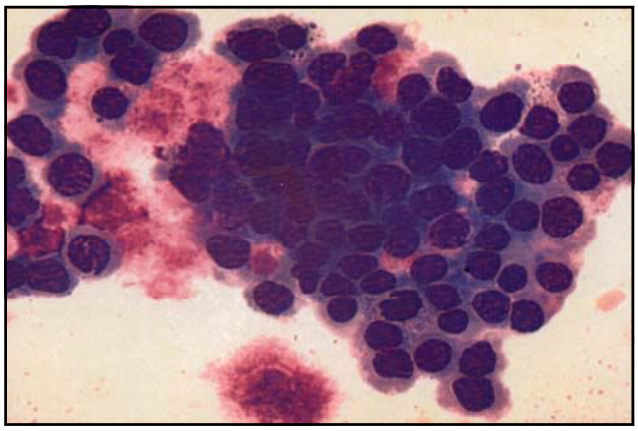
Chronic myeloproliferative disorders

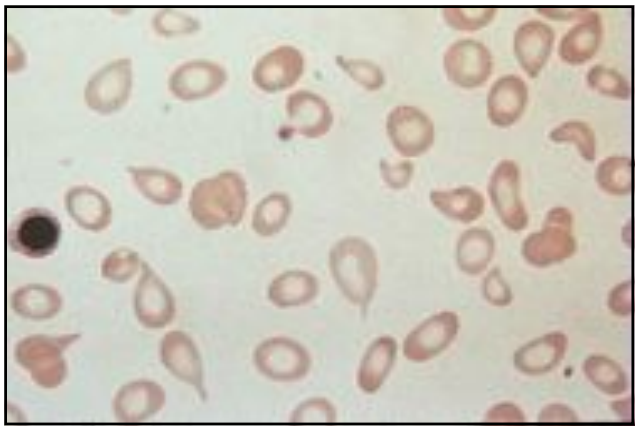
- chronic myeloid leukemia
- myelofibrosis with myeloid metaplasia
- polycythemia vera
- essential thrombocythemia

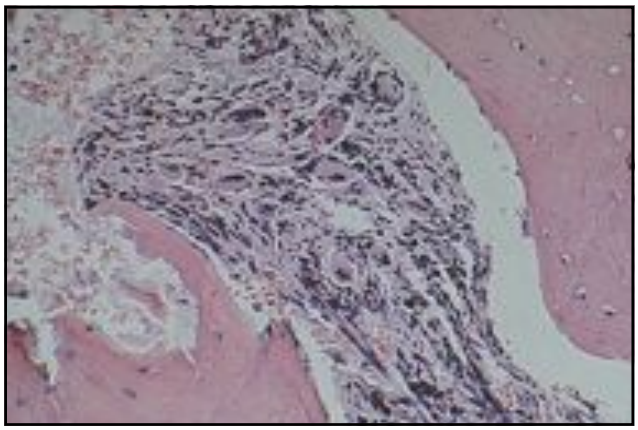
CML, myeloid metaplasia, P vera, essential thrombocythemia

- clonal
- arising in stem cells, with involvement of several cell lines
- JAK2 mutation common
- leukocytosis, thrombocytosis and platelet dysfunction
- splenomegaly
- tendency to convert to acute leukemia









Myelofibrosis with Myeloid Metaplasia

- WBC increased, normal, or decreased
- Differential similar to CML

- anisopoikilocytosis
- tear-drop RBC's
- nucleated RBC's

- fibrosis of marrow
  - fibroblasts not part of clone