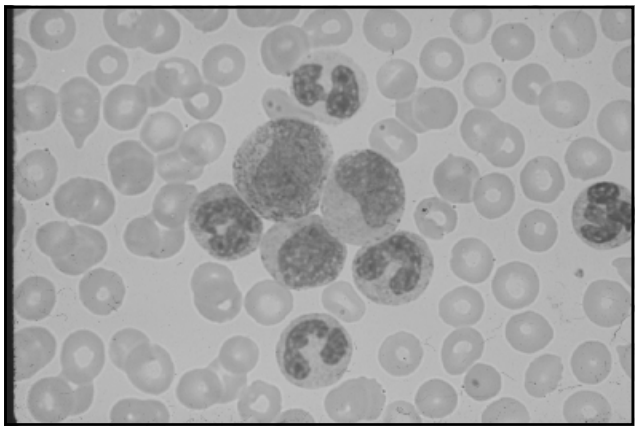
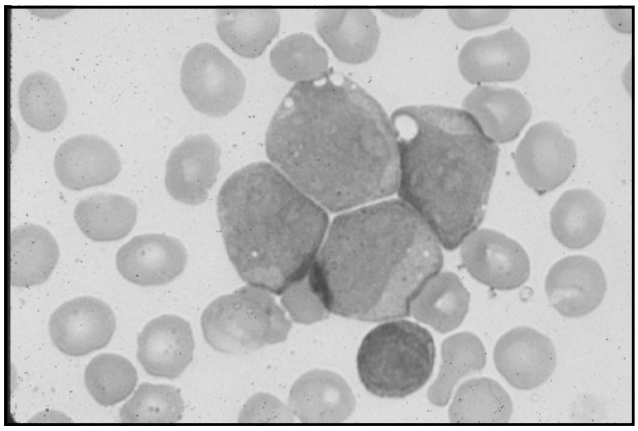
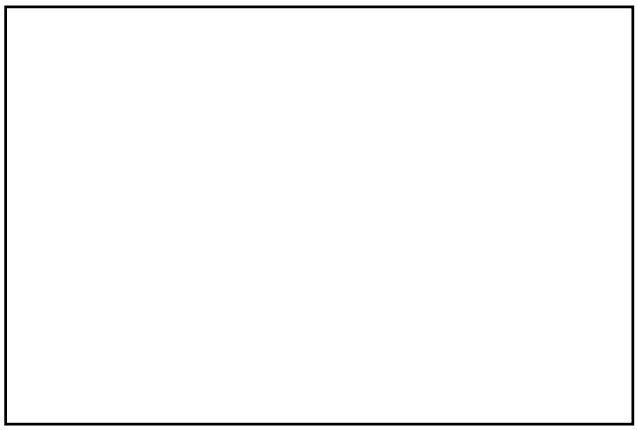
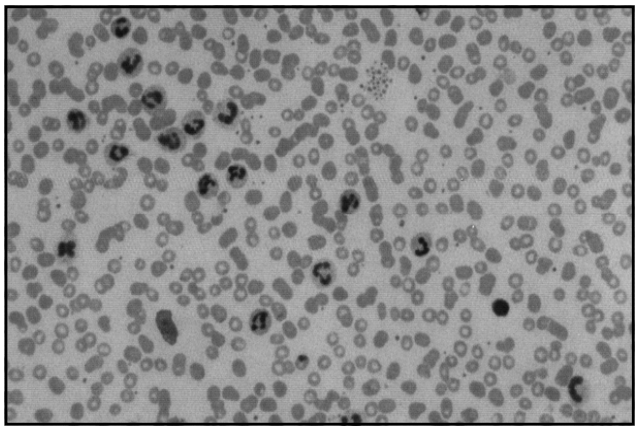
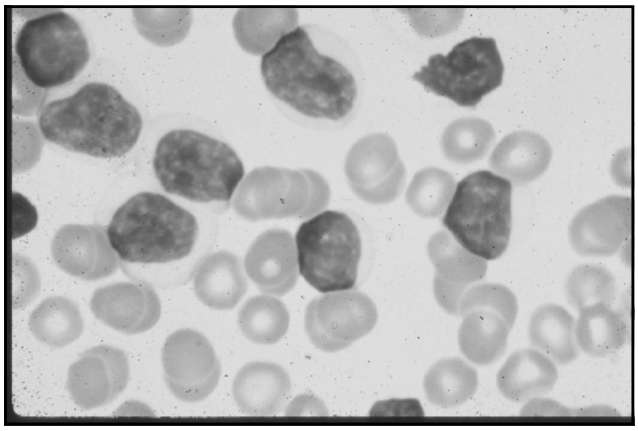
Myeloproliferative Disorders - D Savage - 9 Jan 2002

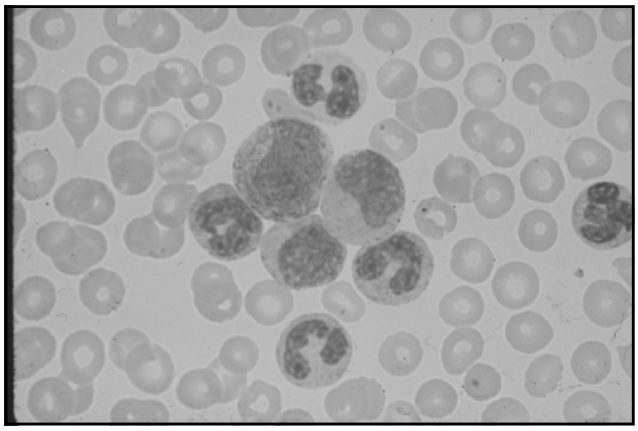






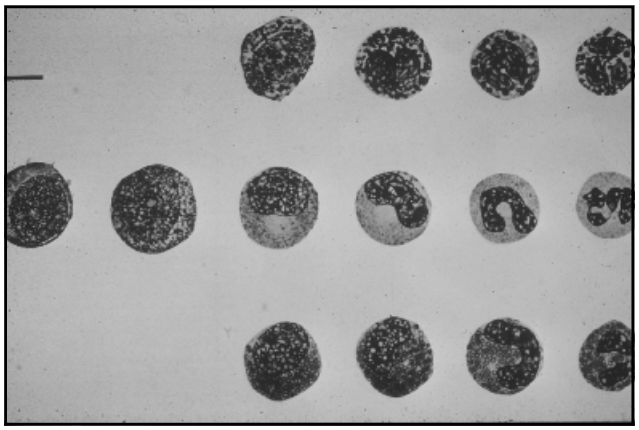






Leukemias - evidence of damage to DNA

- 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)

Chronic myeloid leukemia

Chronic phase

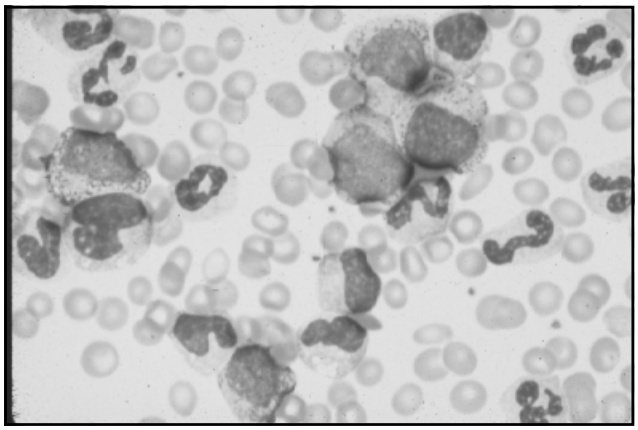
increased pool of clonal precursors committed to become myeloid cells

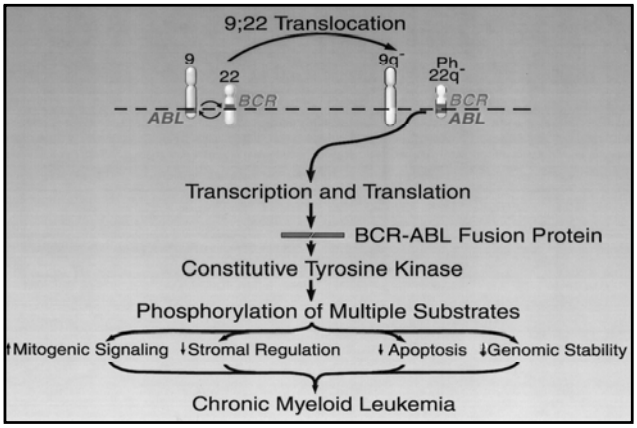
most of the clonal precursors differentiate into mature cells

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**

Introduction of BCR-ABL gene into mice

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

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**

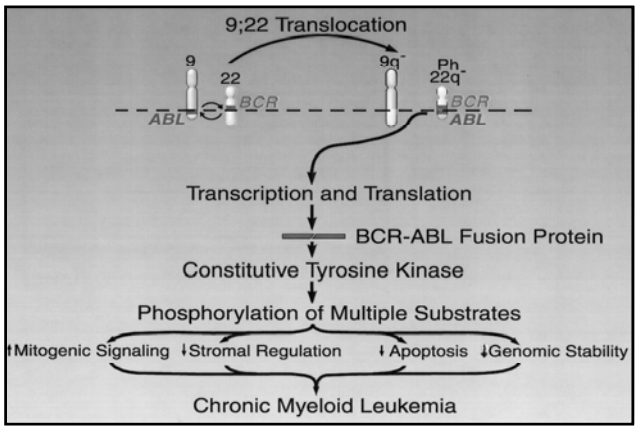
bcr-abl protein differs from *abl* protein

- 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

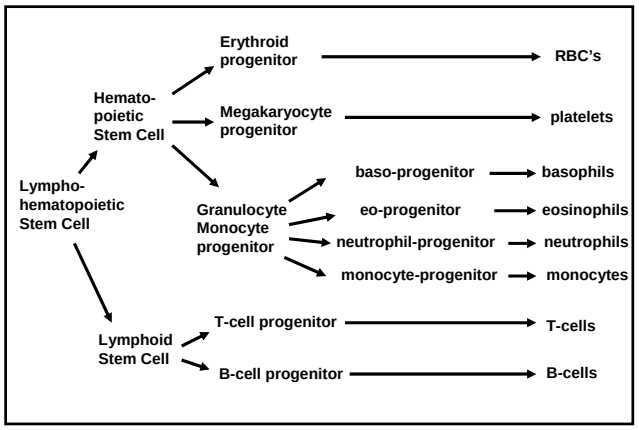
Ph chromosome present in precursors of:

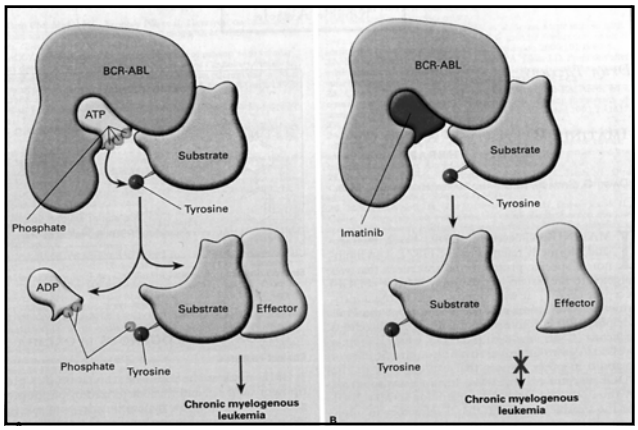
- granulocytes
- monocytes/macrophages
- basophils
- eosinophils
- erythrocytes
- platelets
- some B lymphocytes



Treatment of CML - chronic phase

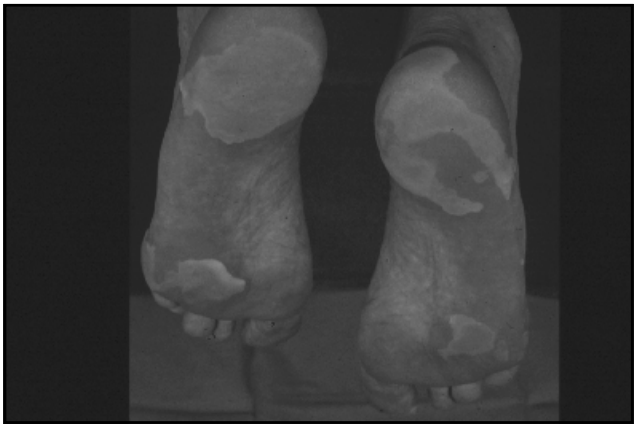
- hydroxyurea
- interferon-α → 10-20% become Ph-negative
- survival better with hydroxyurea or interferon
- imatinib (Gleevec) - targets ABL, potent, low toxicity
- allogeneic transplantation potentially curative

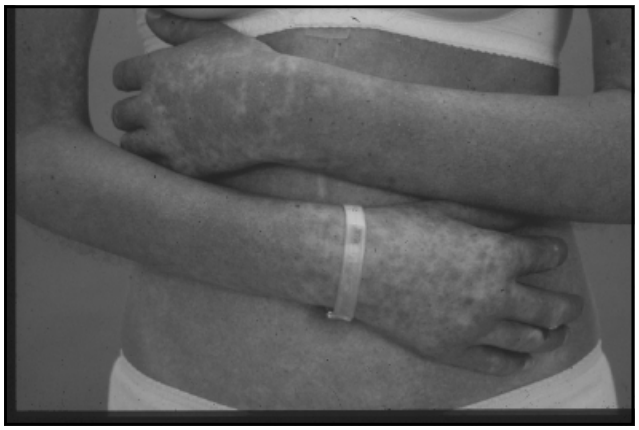


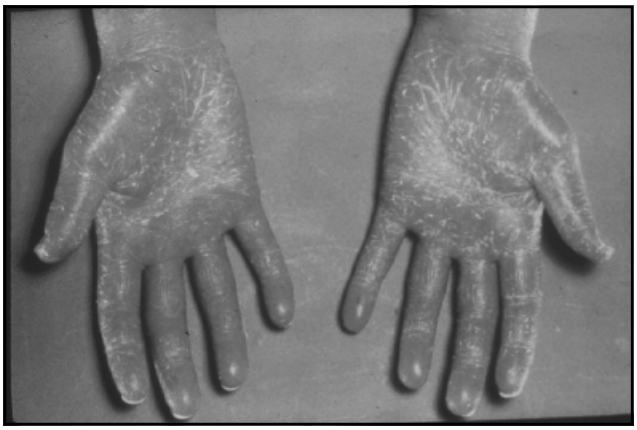


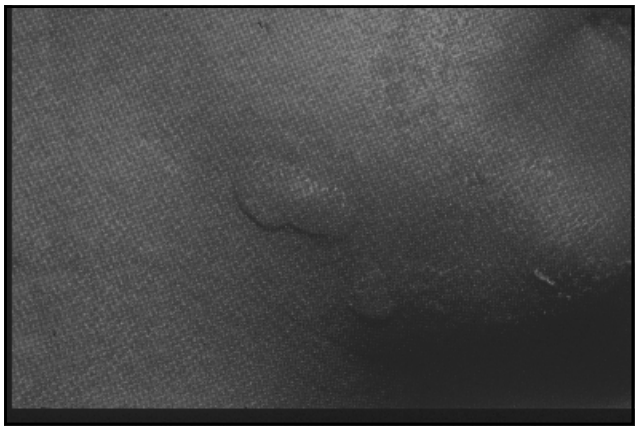
Marrow and Blood Stem Cell Transplantation

	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



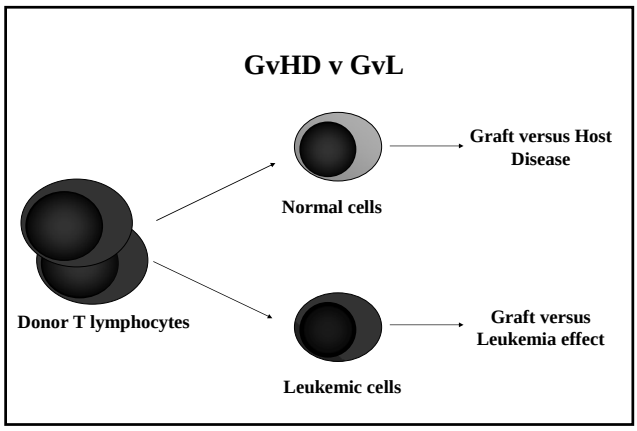






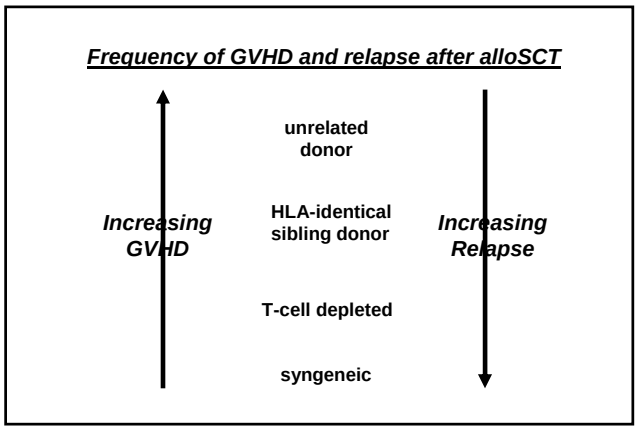
CML - allogeneic transplantation

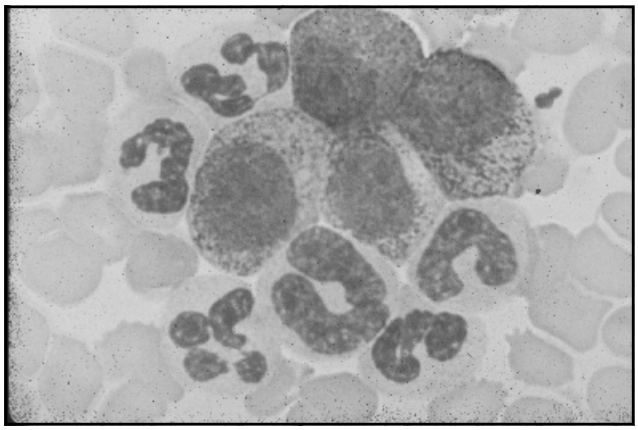
- may result in cure
- 10-25% transplant-related mortality
- age, donor limitations
- mechanisms of cure
  - high dose chemoradiotherapy
  - graft vs leukemia



But I must go and meet with danger there,
Or it will seek me in another place,
And find me worse provided.

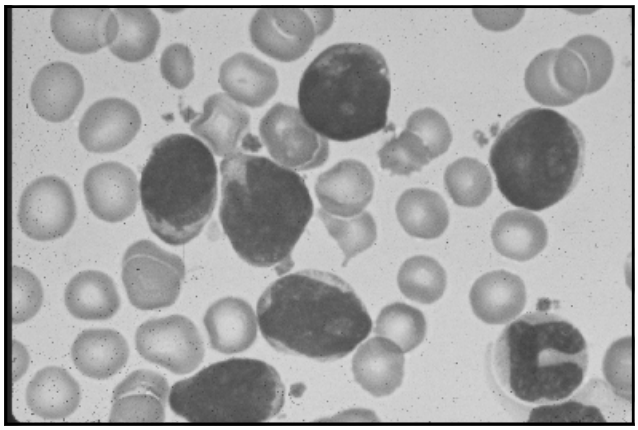
William Shakespeare,
Henry IV





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 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

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)

Chronic myeloproliferative disorders

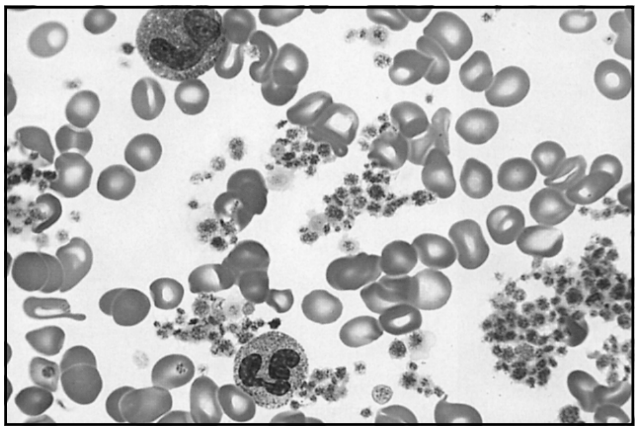
- chronic myeloid leukemia
- myelofibrosis with myeloid metaplasia
- polycythemia vera
- essential thrombocythemia

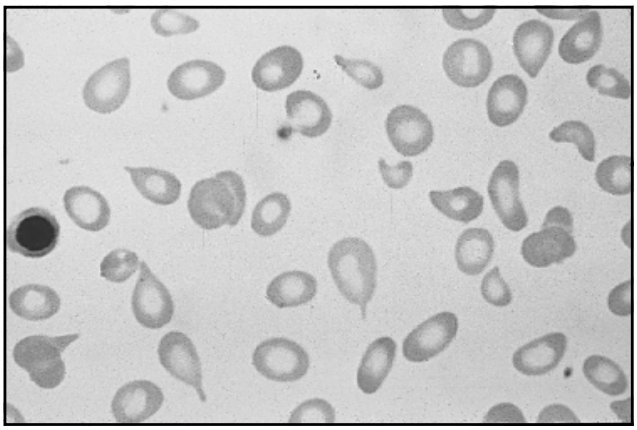
Ph-positive ALL

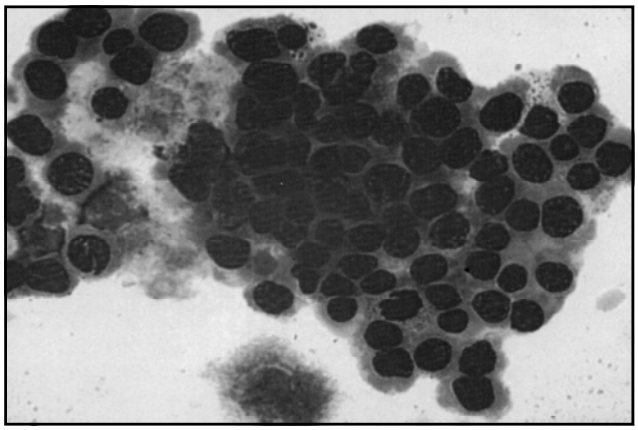
- 30-40% of adult ALL
- poor prognosis
- some have same fusion gene as in CML
- different fusion gene in others
  - –breakpoints more 5' in BCR
  - –gene product 190,000 daltons
  - –even stronger tyrosine kinase activity

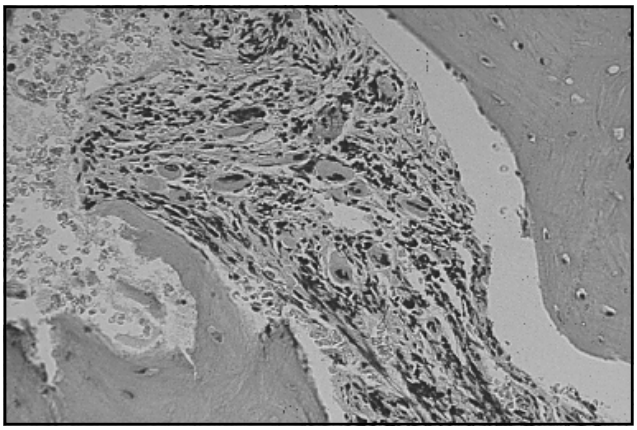
CML, myeloid metaplasia, P vera, essential thrombocythemia

- 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**

Myeloproliferative Disorders - D Savage - 9 Jan 2002