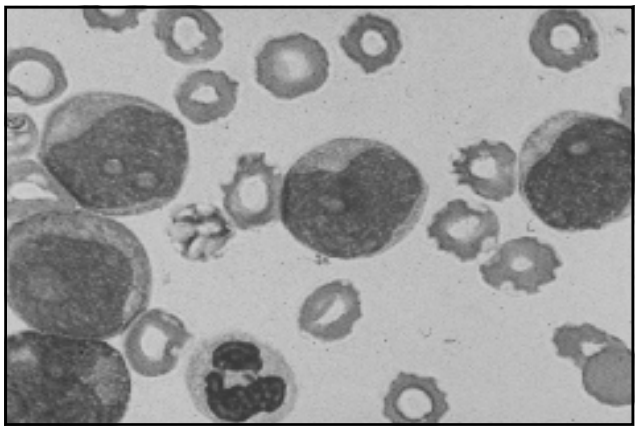
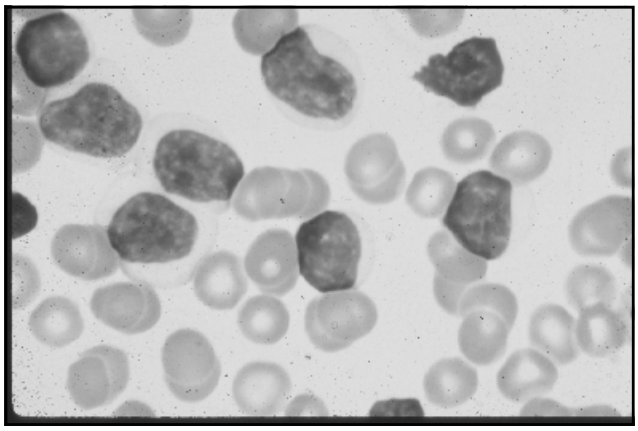
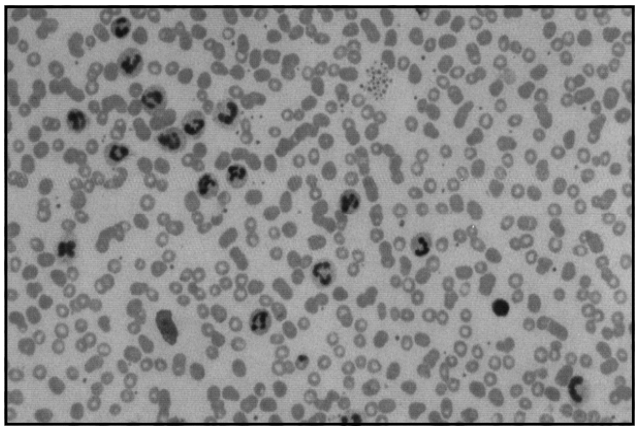
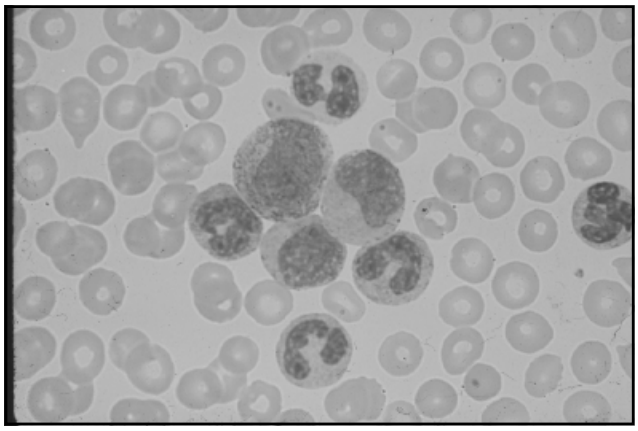
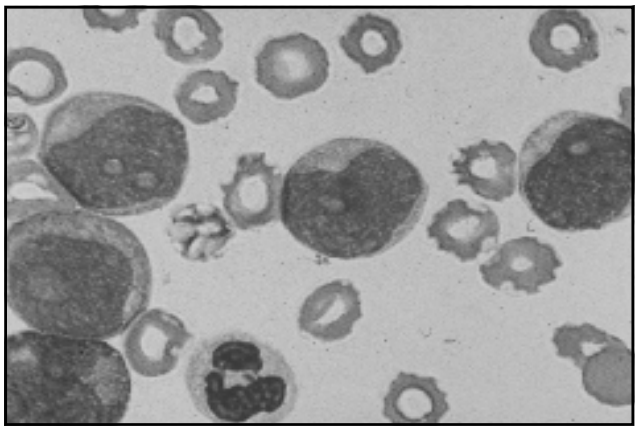
Acute Leukemia - D Savage - 8 January 2002





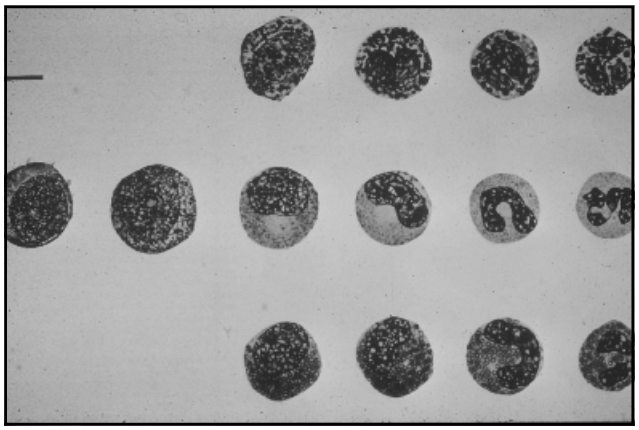






Acute Leukemia

- imbalance between proliferation and differentiation
- majority of cells not dividing
  - therapeutic dilemma



Leukemias - evidence of damage to DNA

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

Acute leukemias

- ***Major Categories***:

ALL = acute lymphocytic, lymphoid or lymphoblastic leukemia

versus

ANLL = acute non-lymphocytic leukemia = acute myeloid leukemia (AML)
- includes granulocytic, erythroid, and megakaryocytic lineages

Types of Genetic Damage (DNA mutations)

- rearrangements
- translocations
- point mutations
- deletions

Genetic damage in leukemias

- Causes
  - radiation
  - carcinogens
    - » benzene
    - » chemotherapy
  - hereditary chromosome disorders
  - hereditary disorders of DNA repair
  - viruses (eg, HTLV-I)
- Proto-oncogenes → oncogenes
- Inactivation of 'tumor suppressor genes'
- Multiple events

Gene Products of Oncogenes

- Growth factors
- Receptors for growth factors
- Molecules involved in signal transduction
- Proteins that bind DNA and regulate nuclear functions (e.g., transcription factors)

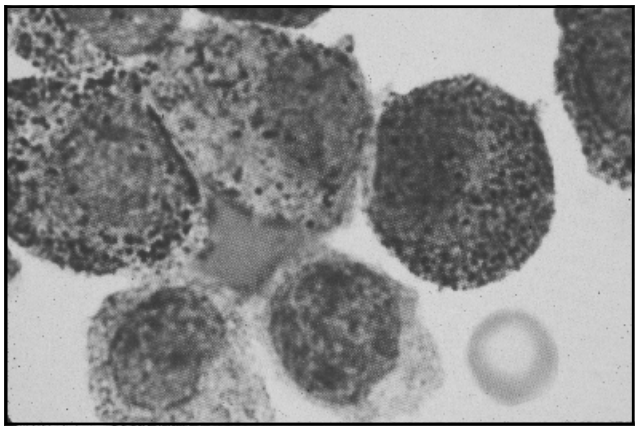
Proto-oncogenes

- Human genes homologous with genes in viruses which cause cancer in animals
  - e.g., *abl* is homologous with genetic material in the Abelson murine leukemia virus
- Protein product of proto-oncogenes may have an important normal function in humans:
  - e.g., tyrosine kinase activity of *abl*
  - e.g., transcriptional regulation by *myc*
- Conversion to oncogenes by mutational events → enhanced or disturbed function

Oncogene Activation

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)

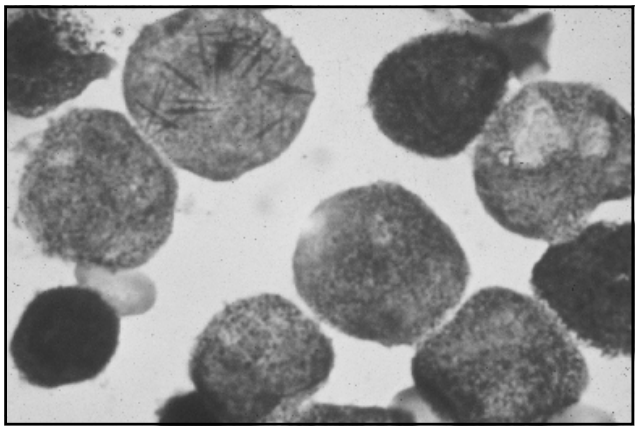


Acute Promyelocytic Leukemia

- about 7% of all ANLL
- malignant clone shows early differentiation
- cells often contain multiple Auer rods
- disseminated intravascular coagulation common
- t(15;17) almost always present
- sensitivity to arsenical trioxide and retinoic acid

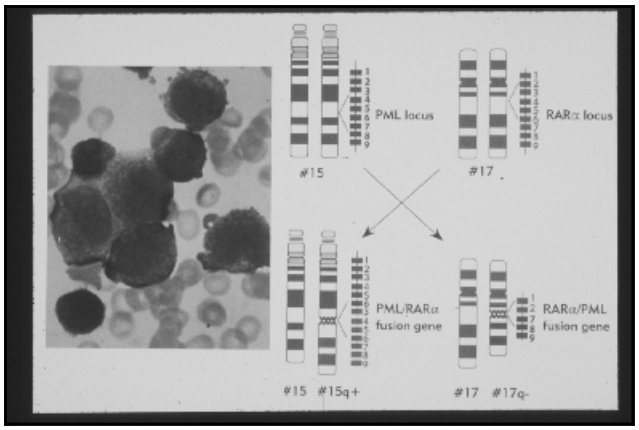
Acute Promyelocytic Leukemia t(15;17)

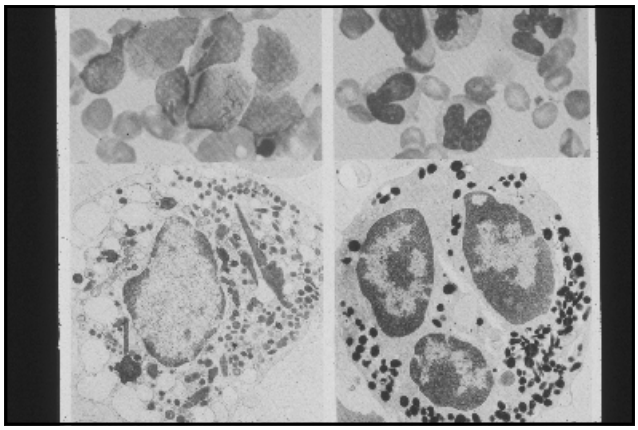
- retinoic acid receptor-α (RAR-α) gene on 17q in normal cells
- RAR-α gene product is a nuclear receptor protein acting as transcription enhancer in myeloid differentiation when bound to retinoic acid
- in t(15;17), part of RAR-α gene on 17q is translocated to 15q and fused to another gene, PML
- PML is normally a tumor suppressor gene which modulates transcriptional activation and promotes apoptosis
- the fusion gene product (*pml-rarα*) of APL causes failure of promyelocytes to differentiate and blocks apoptosis



Retinoic acid induces remissions in APL

- marrow hypoplasia not mandatory
- malignant clone matures to PMN
- leukemic clone replaced by normal cells in marrow
- t(15;17) no longer readily detected
- 'differentiating agent'
- relapse occurs, necessitating chemotherapy





Tumor-suppressor genes

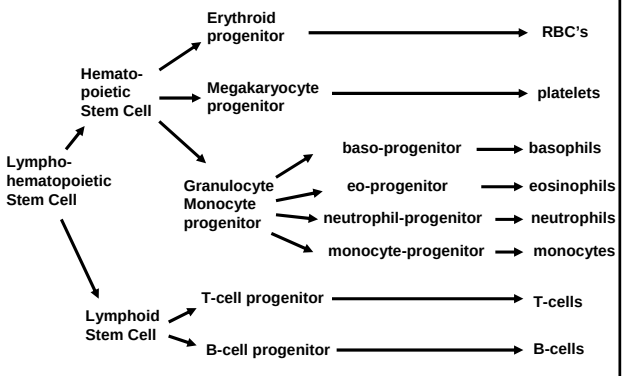
- **inactivation of both alleles of gene allows tumor growth**
  e.g., p53
  minor DNA damage - promotes repair
  major DNA damage - promotes apoptosis
  e.g., retinoblastoma gene
  modulates cell cycling
- **? deleted in therapy-related acute leukemia**

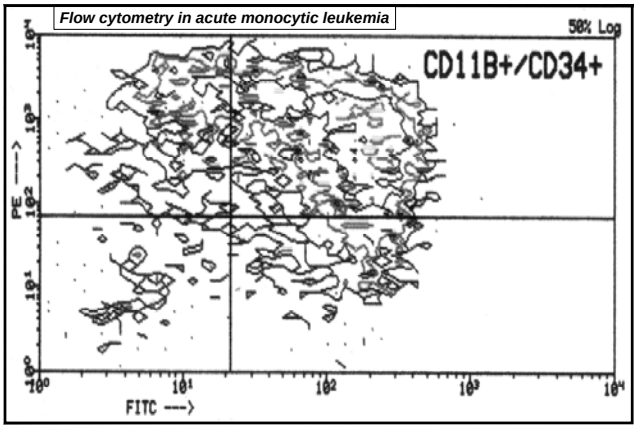
Lineage & Stage Specificity in ALL

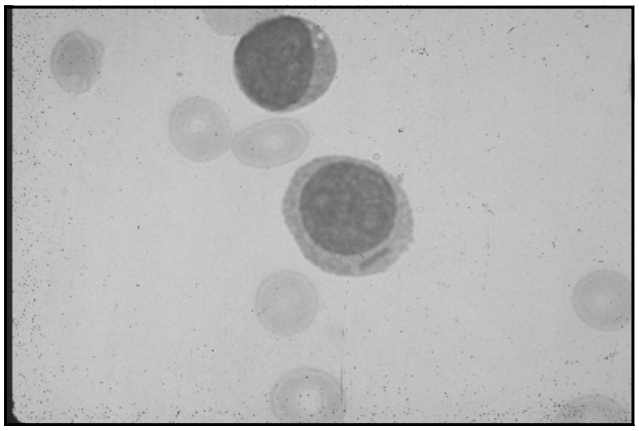
Acute lymphocytic leukemia

- **usually arises in early progenitor B or T cell**
- **B:T 4:1**
- **occasional mixed B and T cell phenotype, suggesting malignant event at earlier multipotent lymphoid progenitor cell**

How is Lineage & Stage Specificity Achieved?





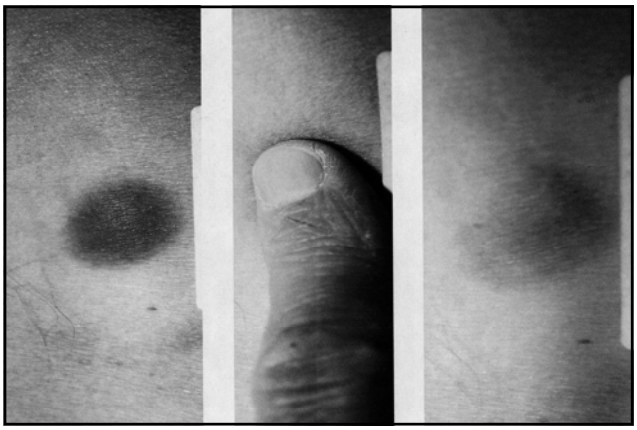


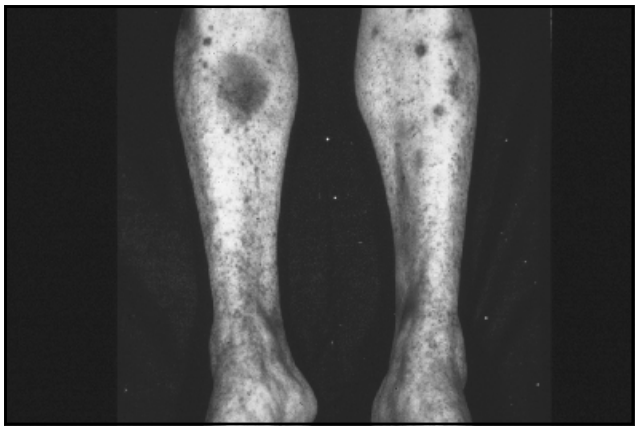
Acute Leukemia

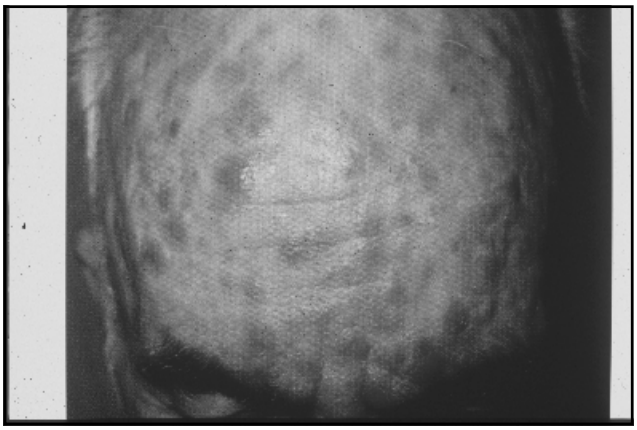
Organ infiltration

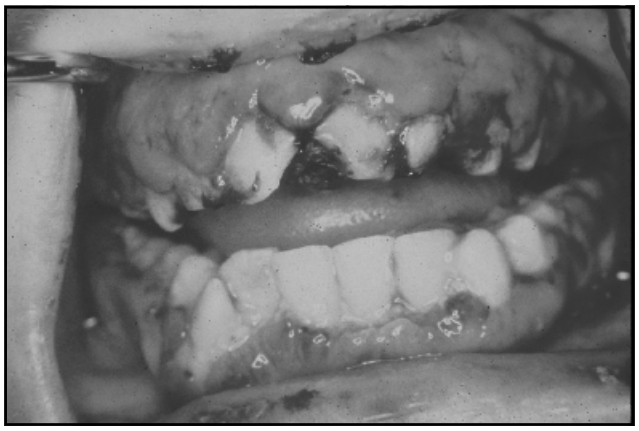
- **marrow involvement**
  - **bone pain**
- **enlarged liver, spleen, nodes**
- **hypertrophied gums**
- **meningeal infiltration**
  - **headache, cranial nn. palsies**

Acute Leukemia



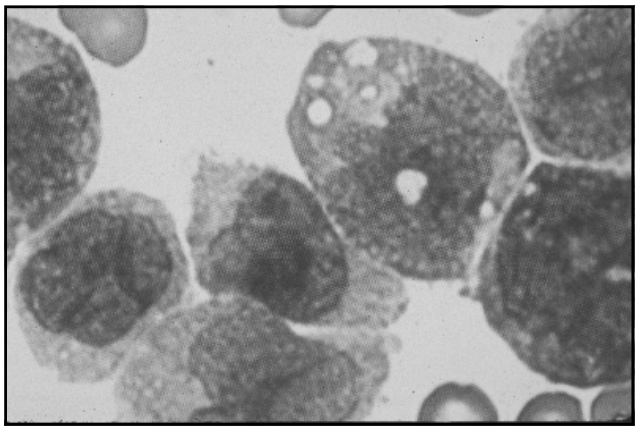


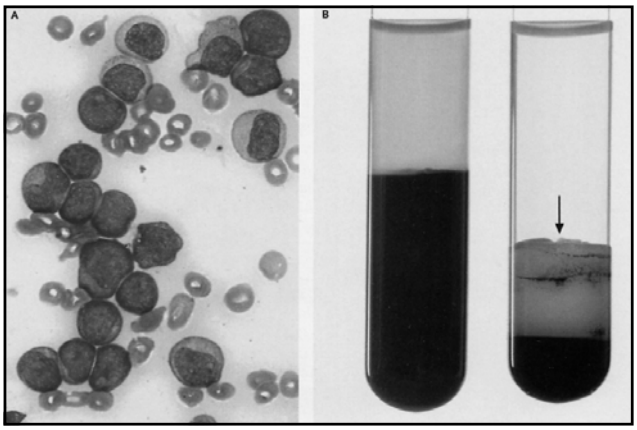


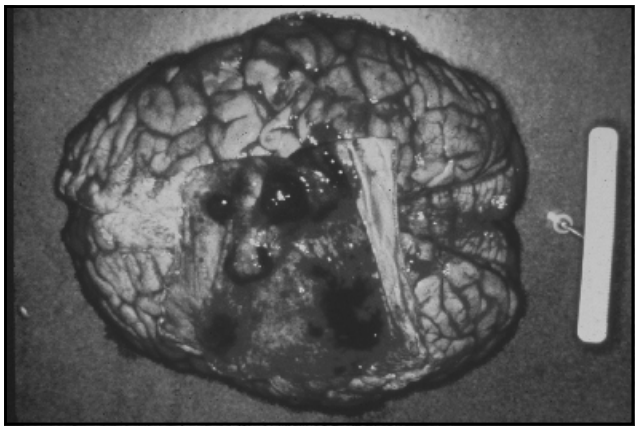


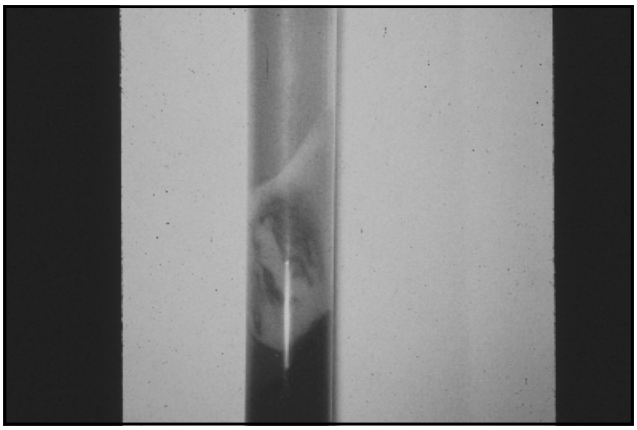
Acute Leukemia

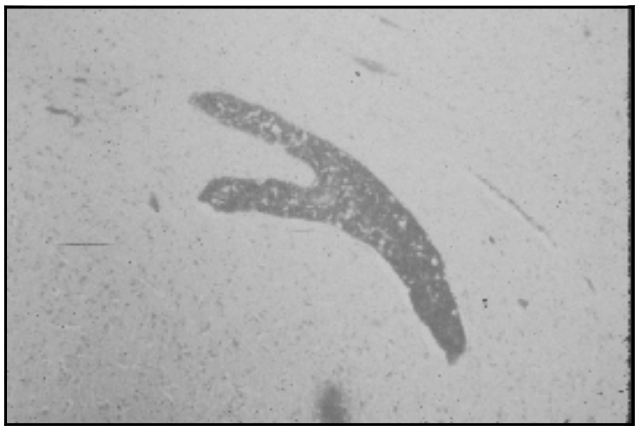
- **blast leukocytosis**
- **leukostasis in small blood vessels:**
  - **tachypnea**
  - **dyspnea**
  - **tinnitus**
  - **lethargy**
  - **stupor**

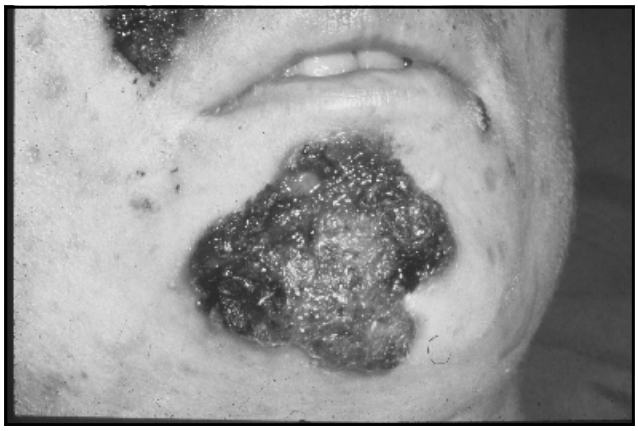


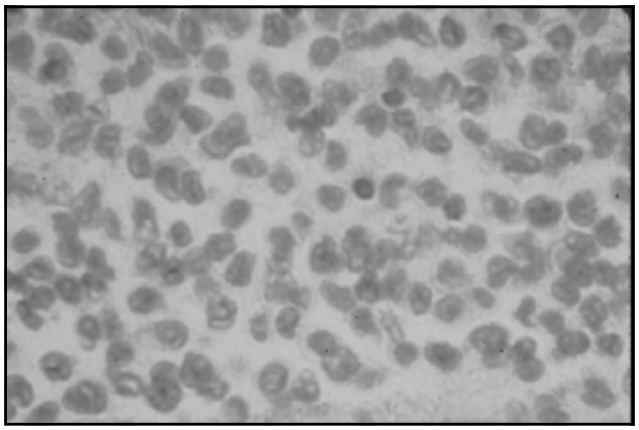


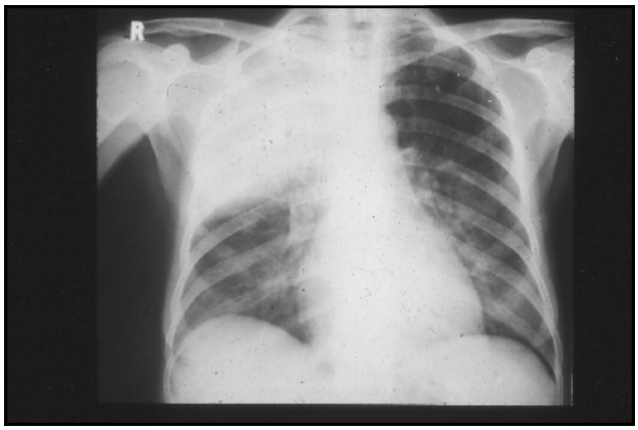






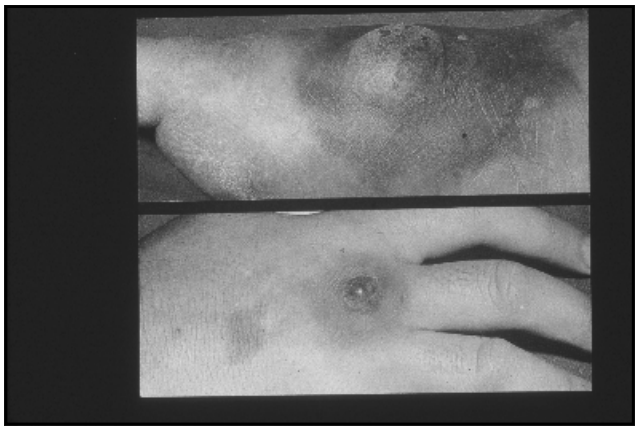






Acute Leukemia - treatment

- intensive combination therapy
- chemotherapy continued beyond remission
- central nervous system prophylaxis (ALL)
- bone marrow transplantation in selected patients
- therapy is dangerous
- supportive measures
  - allopurinol
  - rbc and platelet transfusions
  - antimicrobials



Acute Leukemia - results of treatment