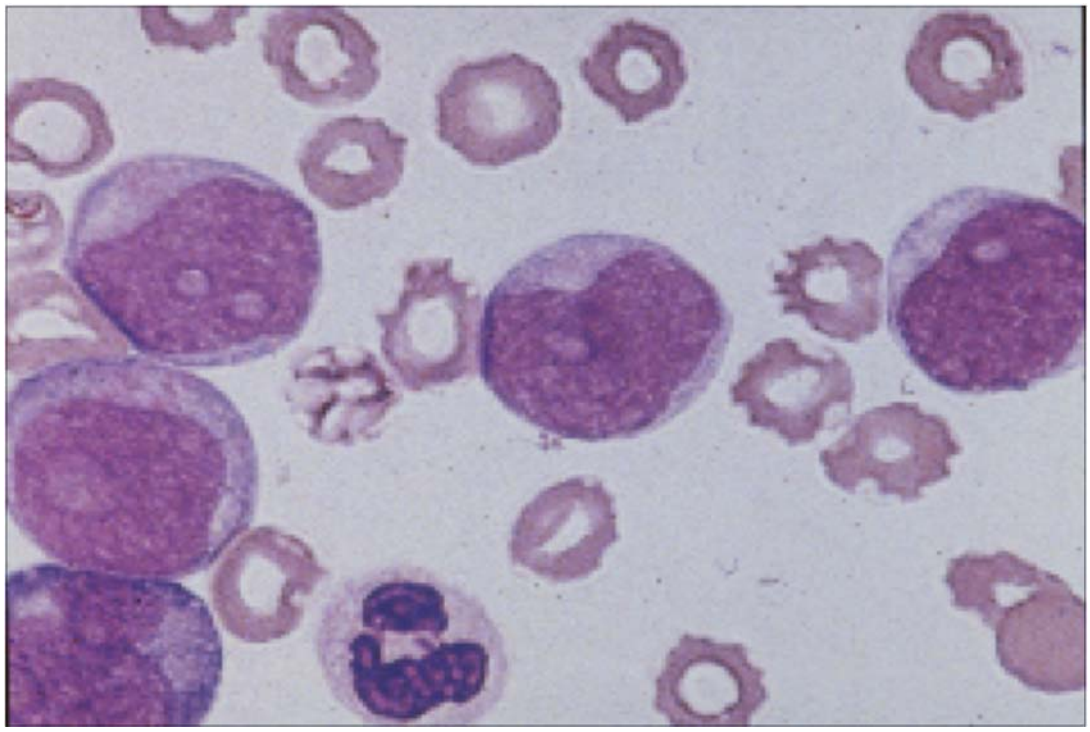
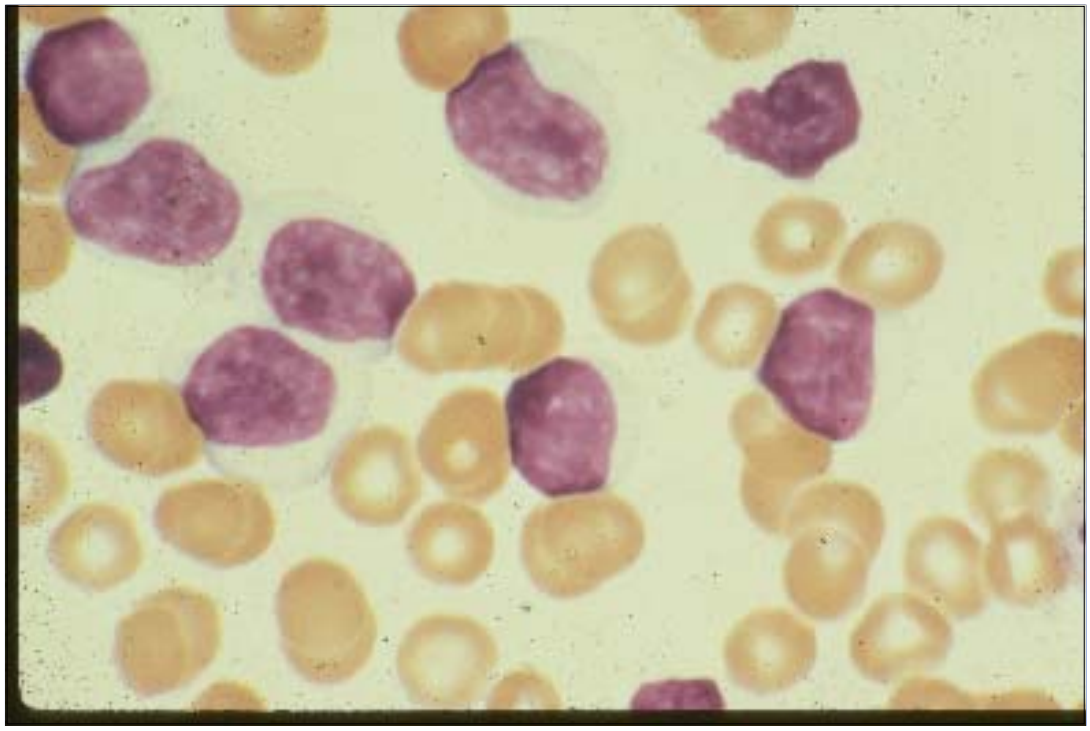
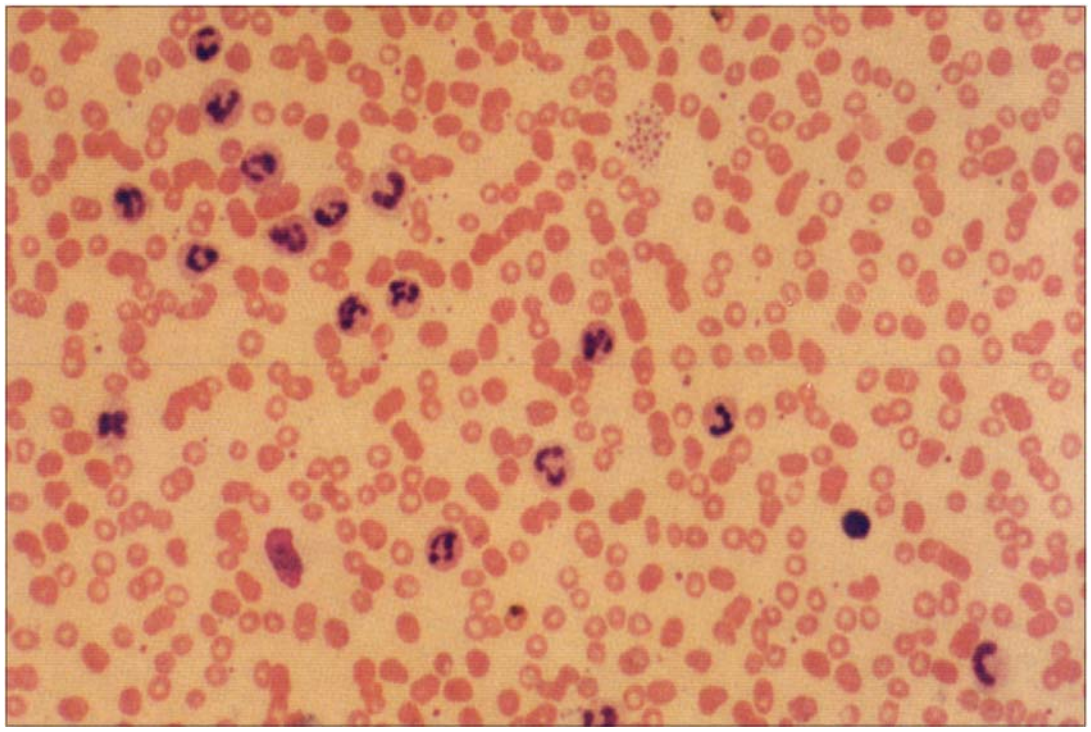


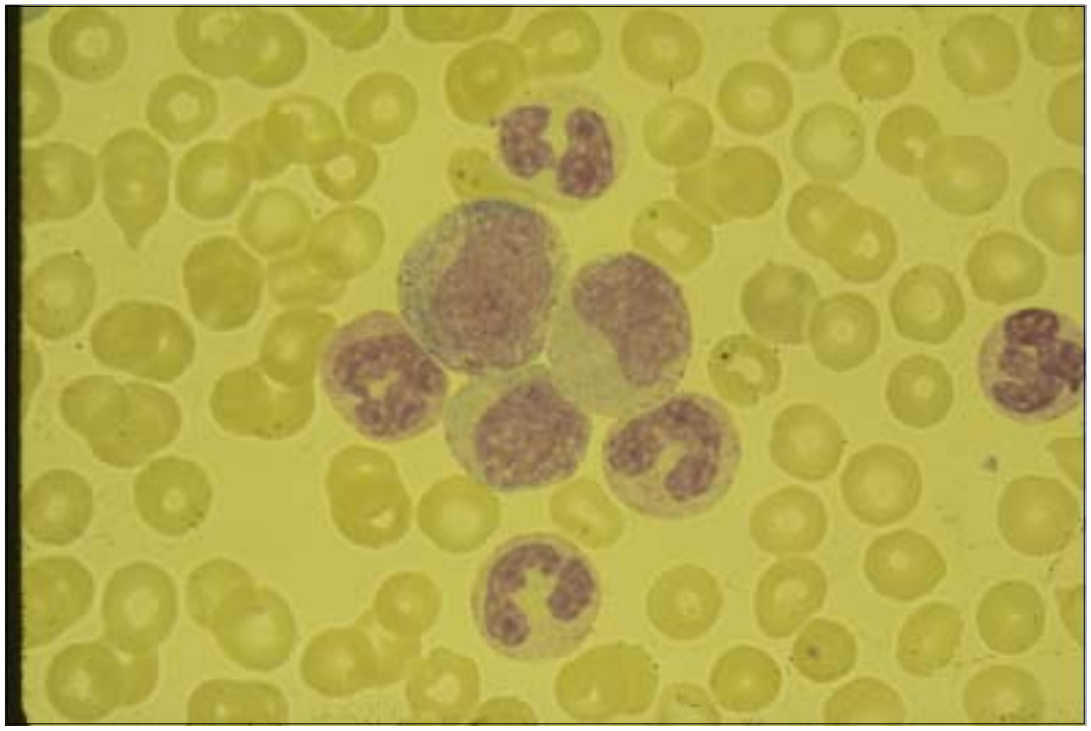
Disease	Usual phenotype
acute leukemia	precursor
chronic leukemia lymphoma myeloma	differentiated

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

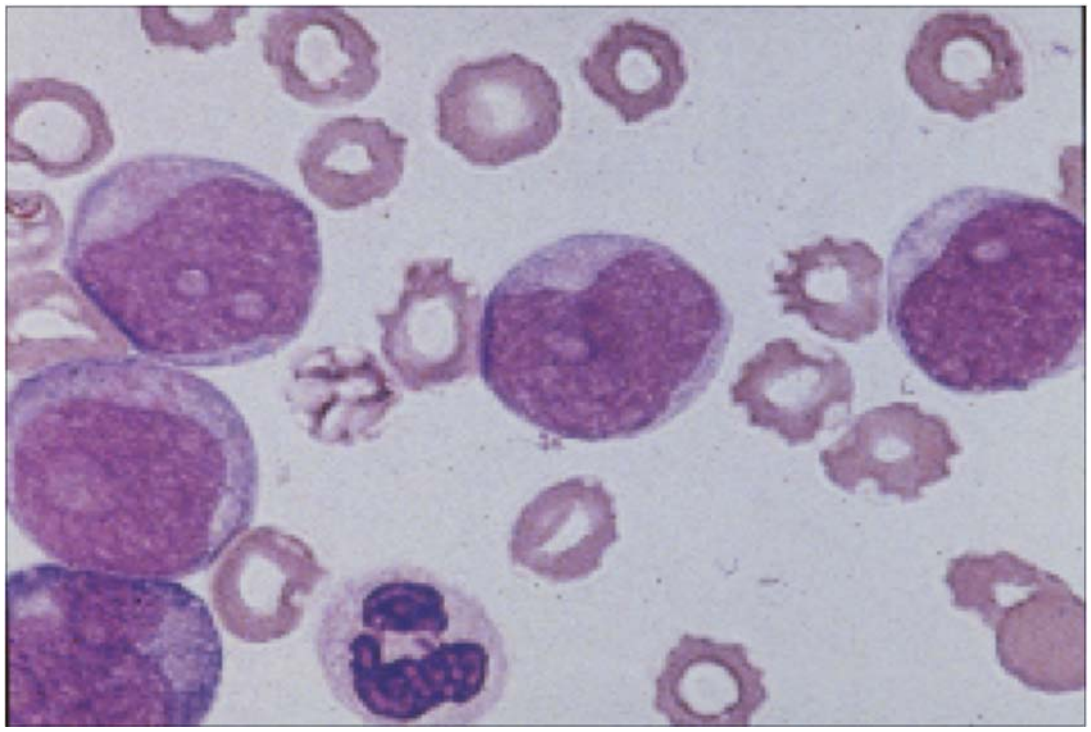


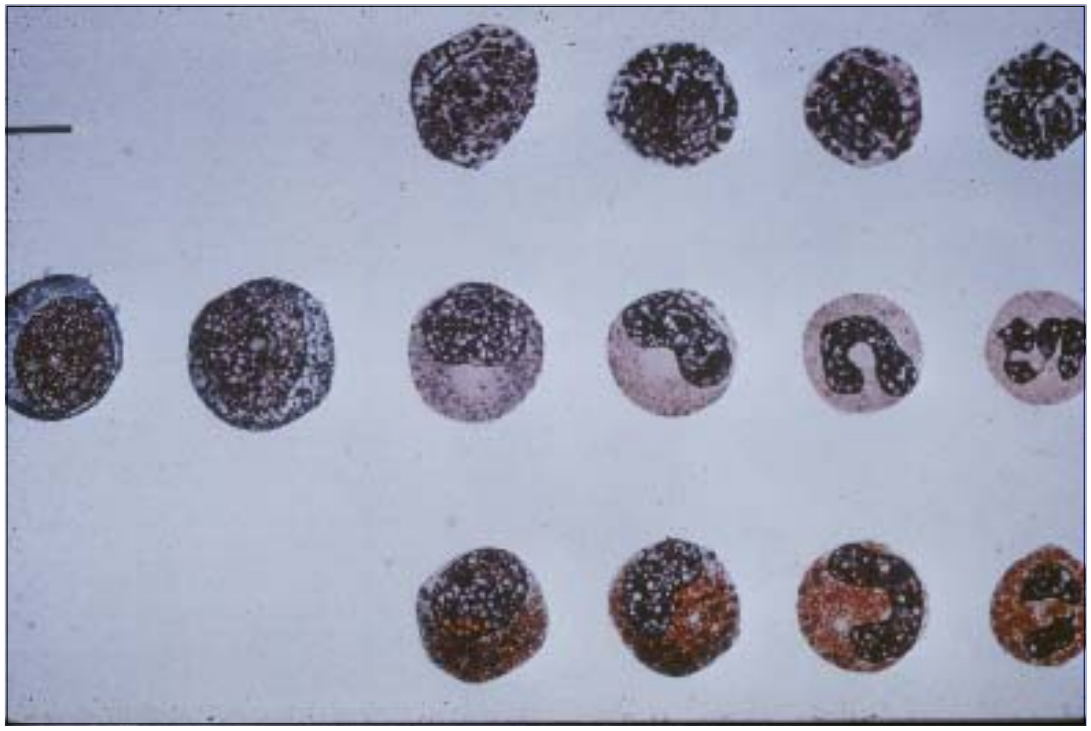
Acute Leukemia - D Savage - 8 January 2002





Acute Leukemia - D Savage - 8 January 2002





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

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

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

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

Conversion of proto-oncogene to oncogene

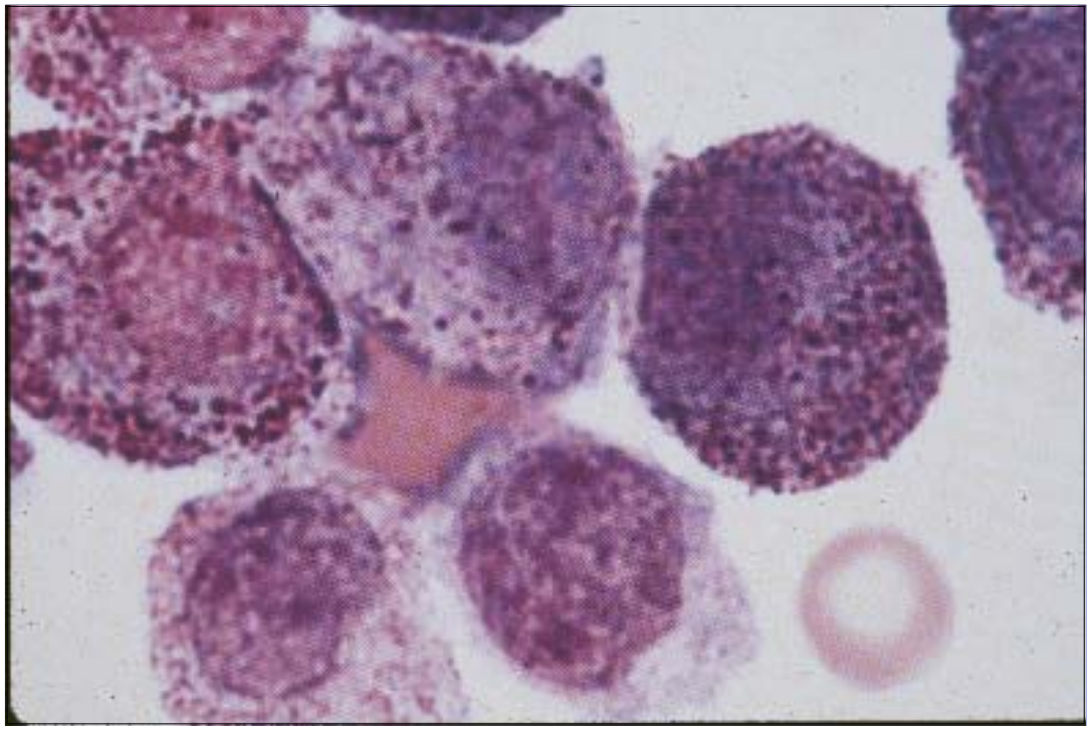
- Possible mechanisms
  - Unaltered gene product (e.g., *myc* in Burkitt's)
  - Altered gene product
    - » usually a fusion protein (e.g., *bcr-abl* in CML)

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)

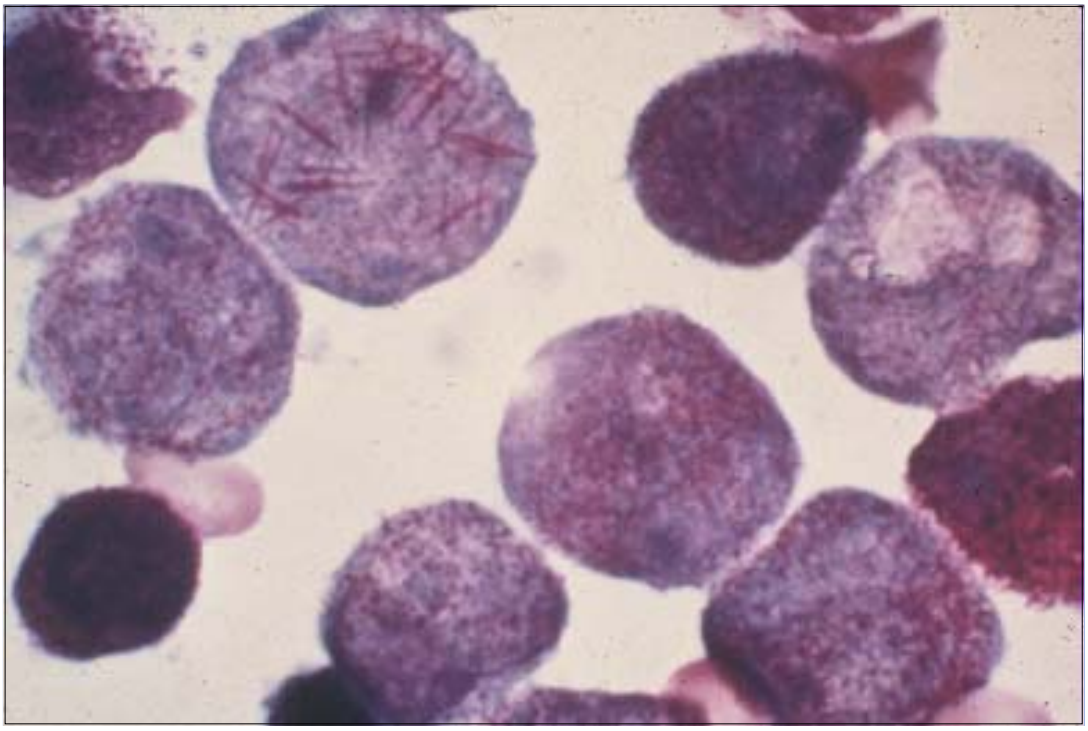
Oncogene Activation

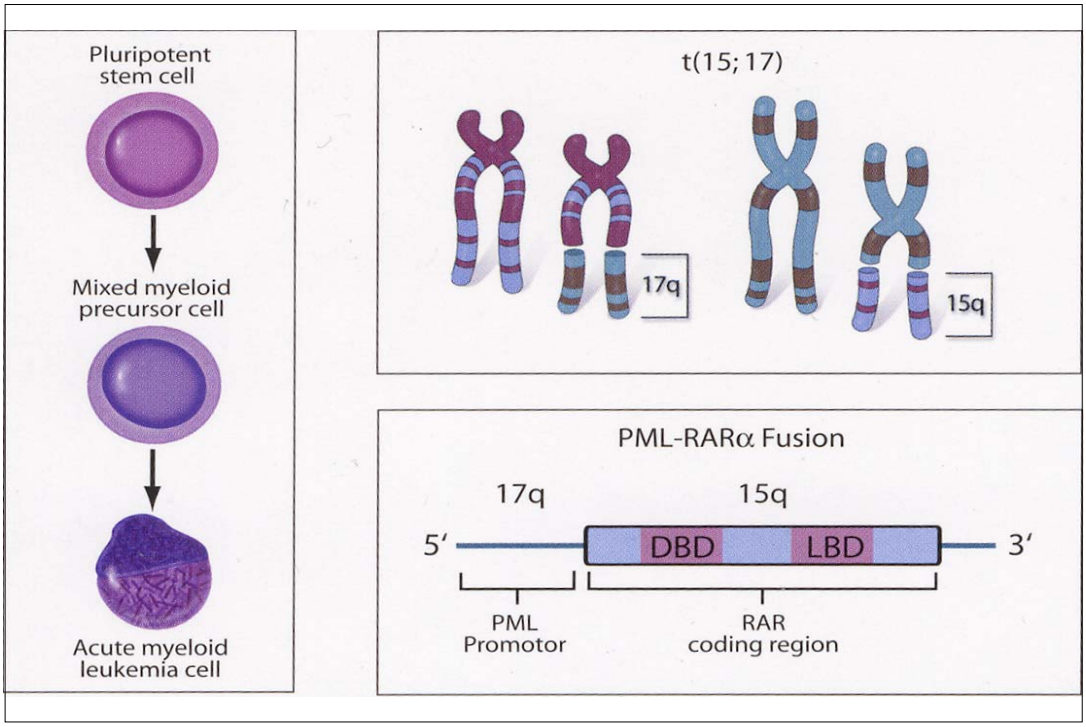
Trans-location	Disease	Proposed mechanism
t(8;14)	some B-cell lymphomas, ALL	↑expression of transcription factor (*myc*)
t(9;22)	CML, some ALL	chimeric signalling molecule (*bcr-abl*)
t(15;17)	acute promyelocytic leukemia	chimeric transcription factor (*pml-rarα*)



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



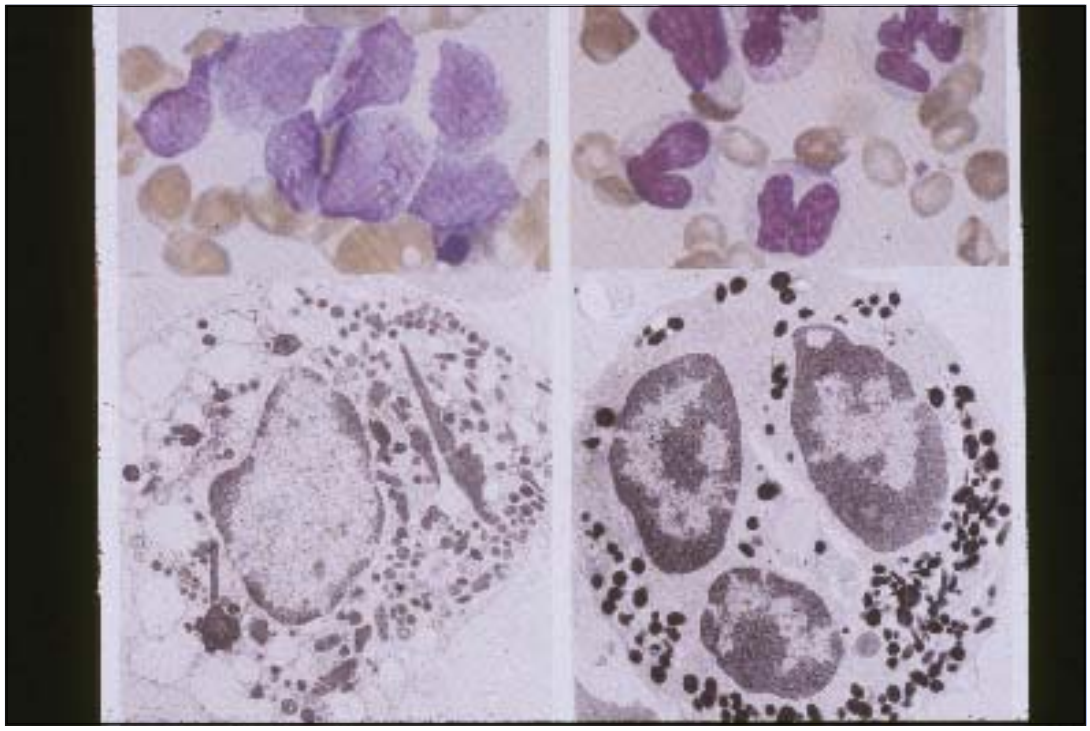


Acute Promyelocytic Leukemia t(15;17)

- 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

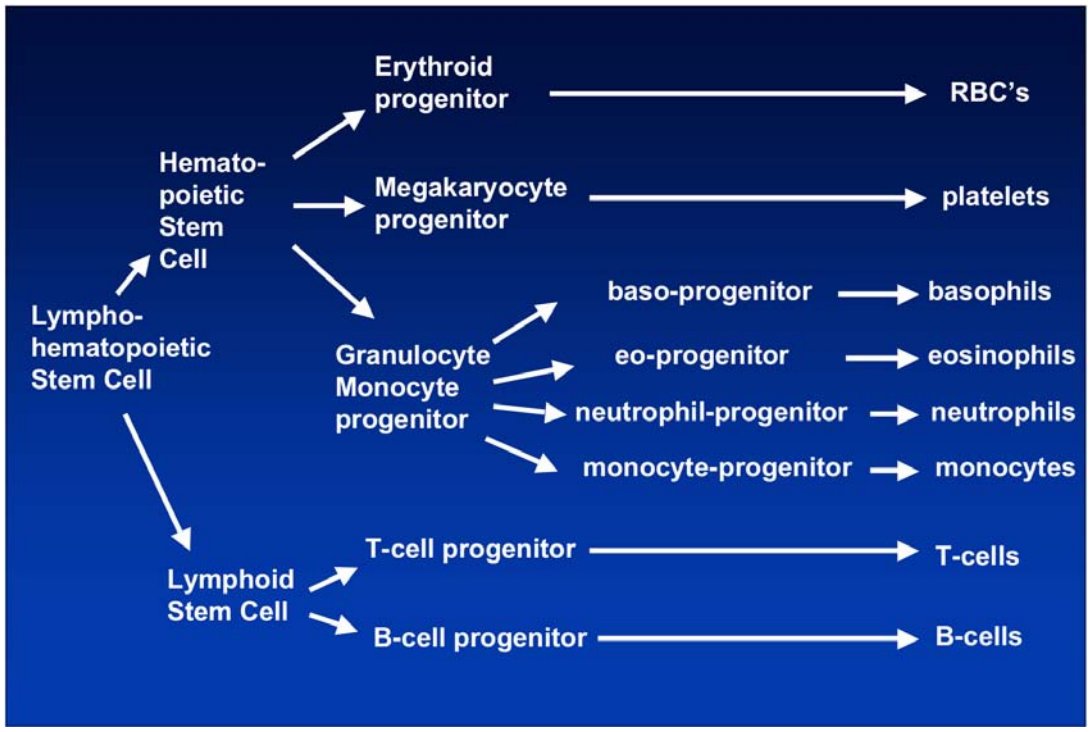


Tumor-suppressor genes

- 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

How is Lineage & Stage Specificity Achieved?

Acute non-lymphocytic leukemia	clonal marker expressed in:	progenitor cell of origin
most patients	neutrophils, monocytes	granulocyte - monocyte progenitor
minority	neutrophils, monocytes, RBC's, platelets	multipotent hemato-poietic progenitor



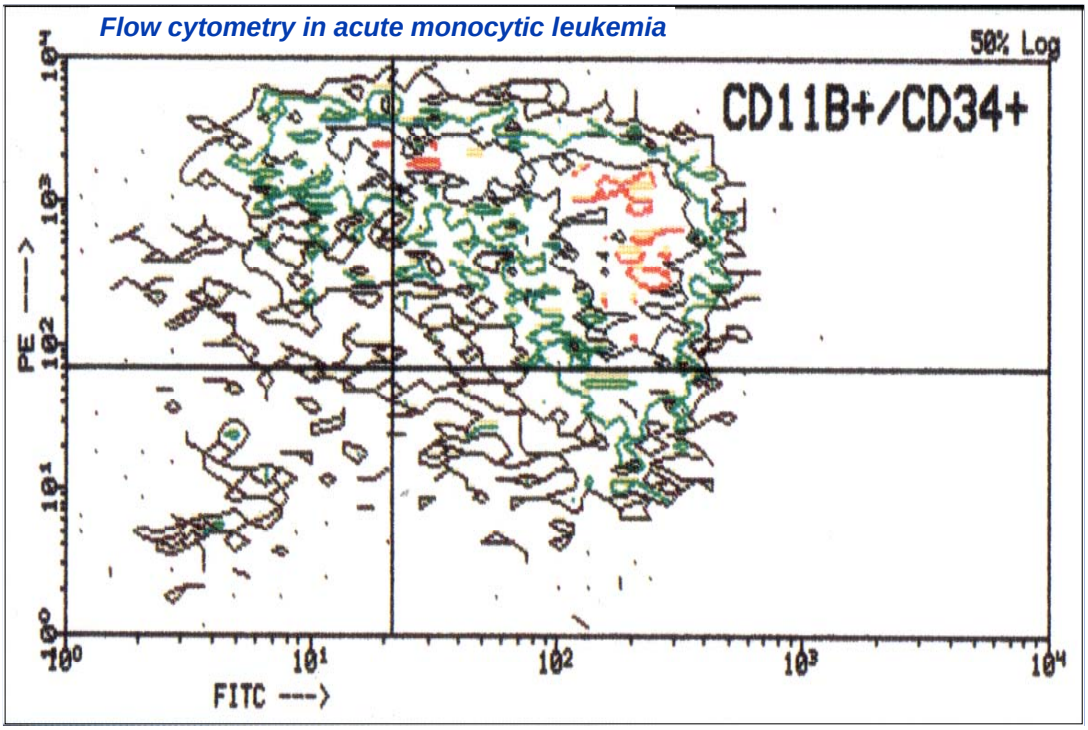
Lineage & Stage Specificity in ALL

Acute lymphocytic leukemia

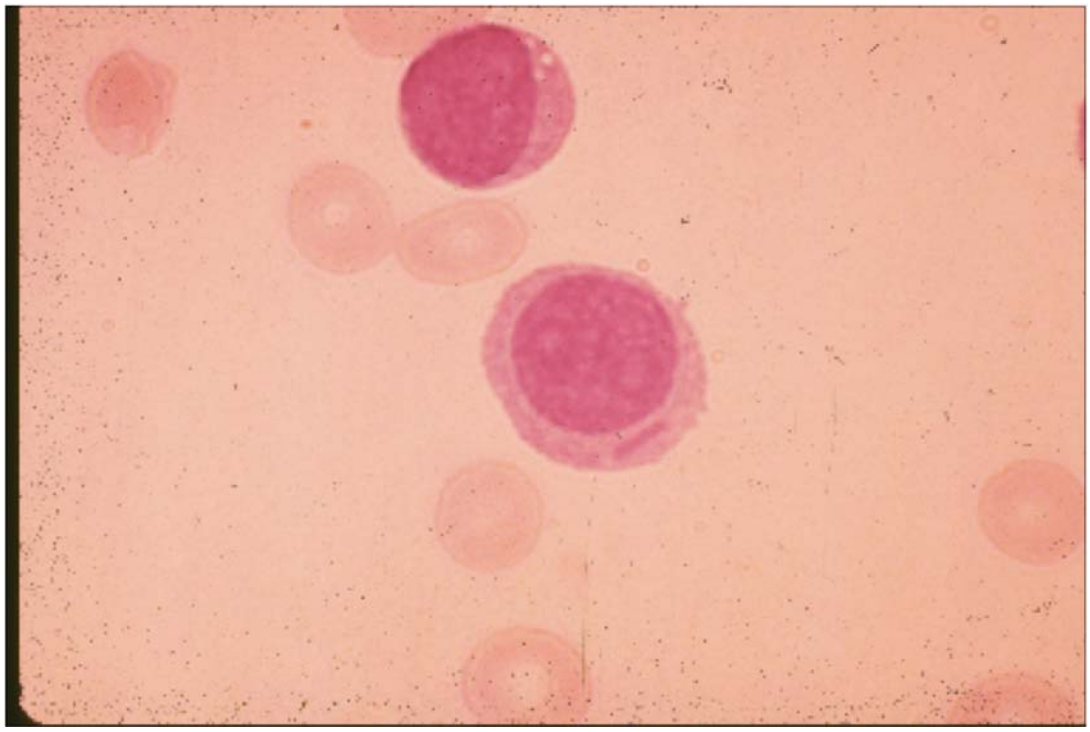
- usually arises in early progenitor B or T cell
- B:T 4:1
- occasional mixed B and T cell phenotype, suggesting malignant event at earlier multipotent lymphoid progenitor cell

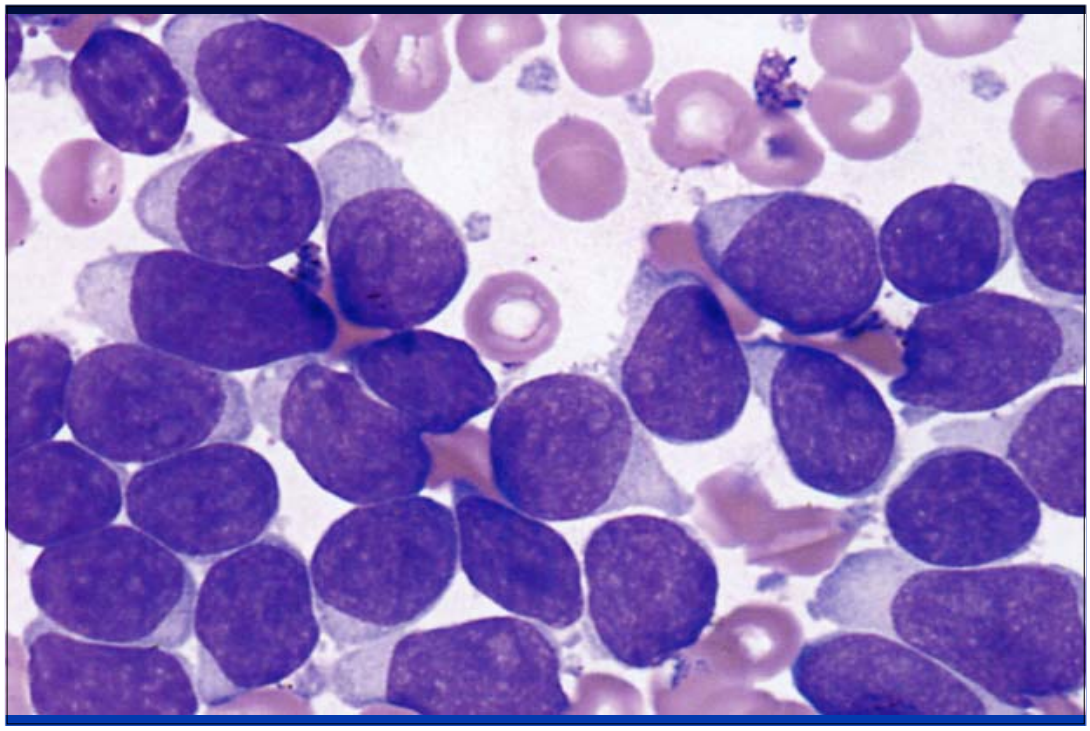
Feature	ALL	ANLL
usual age group	children	adults
myeloperoxidase stain	-	+
Auer rods	-	+
terminal transferase (TdT)	+	-
cell surface Ag's	B or T	myeloid
Ig or T cell receptor gene rearrangement	+	-

Flow cytometry in acute monocytic leukemia



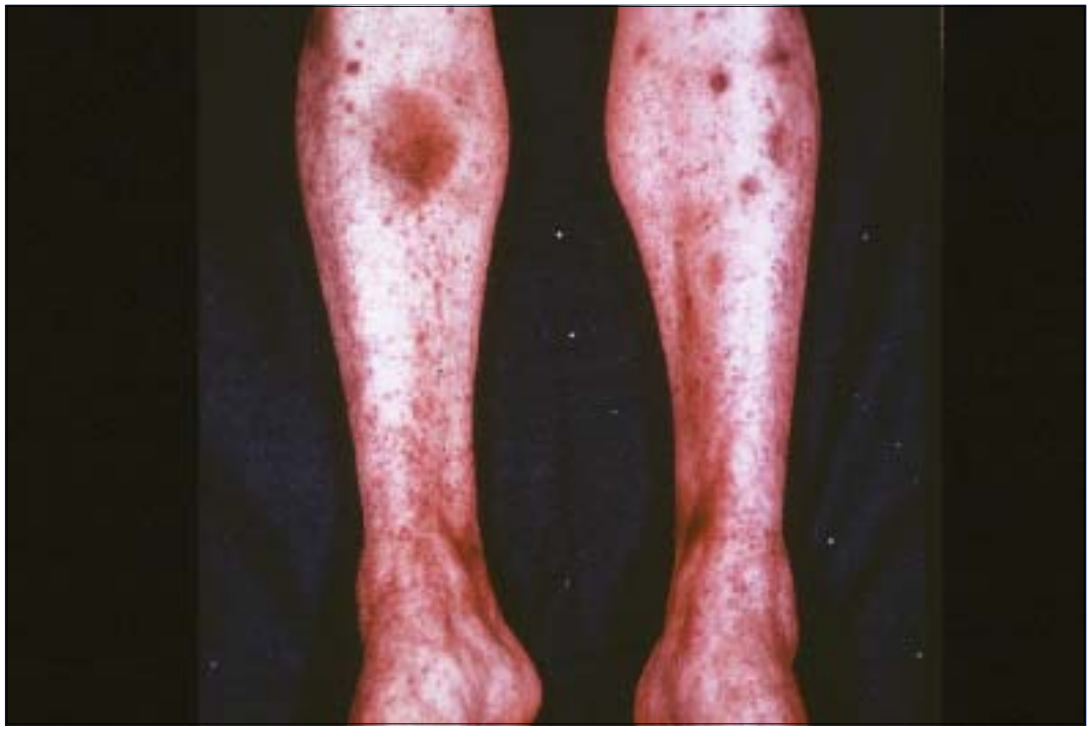
Acute Leukemia - D Savage - 8 January 2002





Acute Leukemia

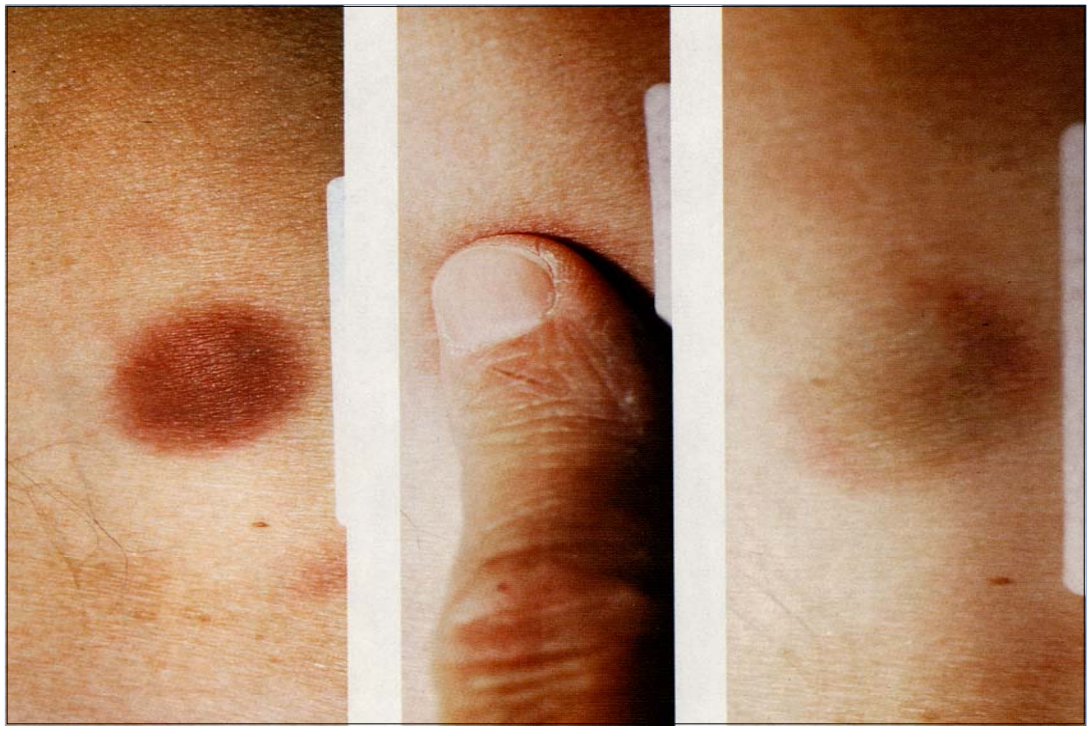
Event	Consequences	
Marrow failure	neutropenia anemia ↓platelets	infection weakness, fatigue bleeding
Hyper-uricemia	tubular damage	acute renal failure
DIC	↓platelets abnormal clotting	bleeding



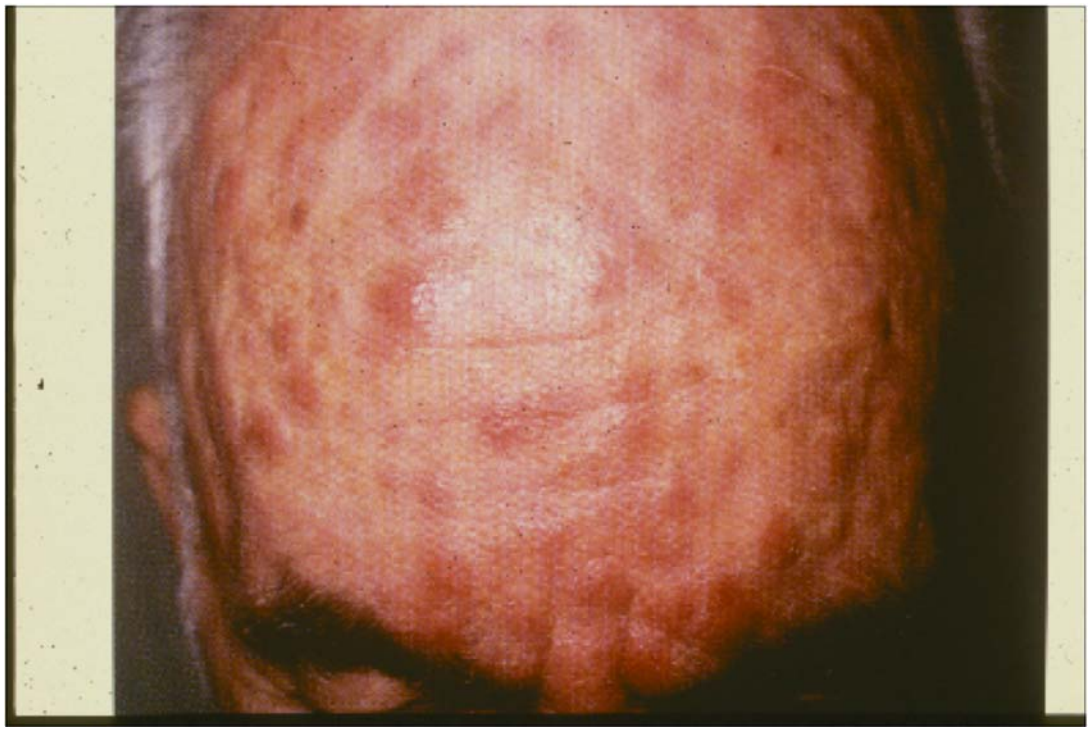
Acute Leukemia

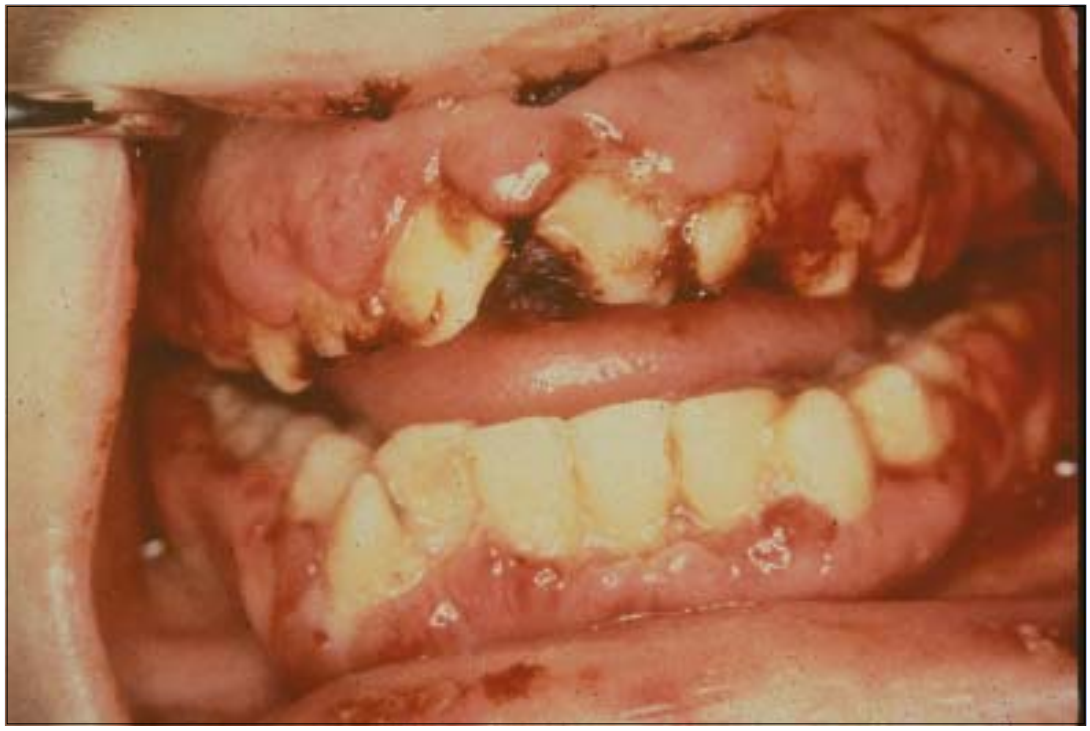
Organ infiltration

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

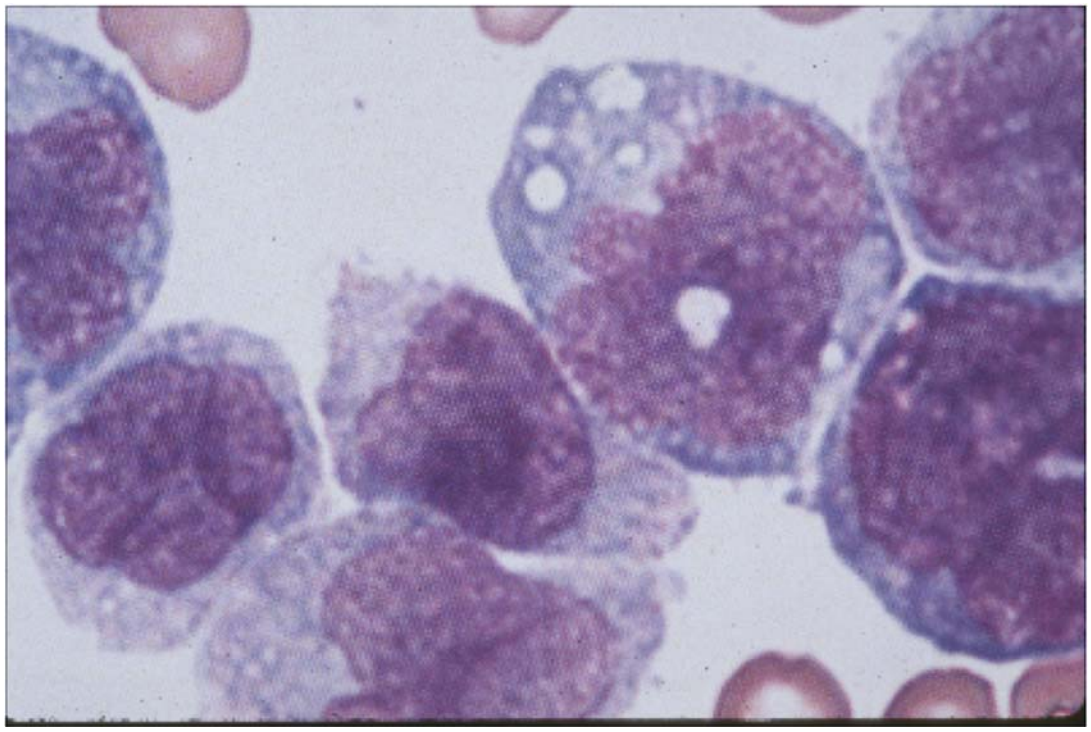


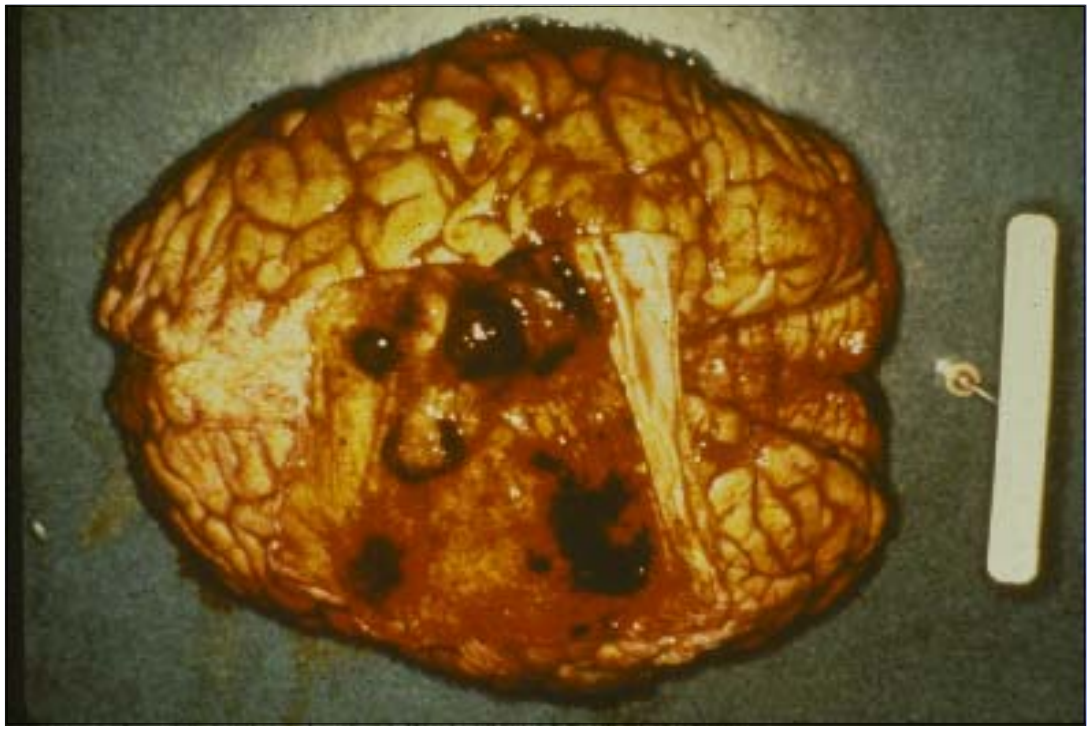
Acute Leukemia - D Savage - 8 January 2002





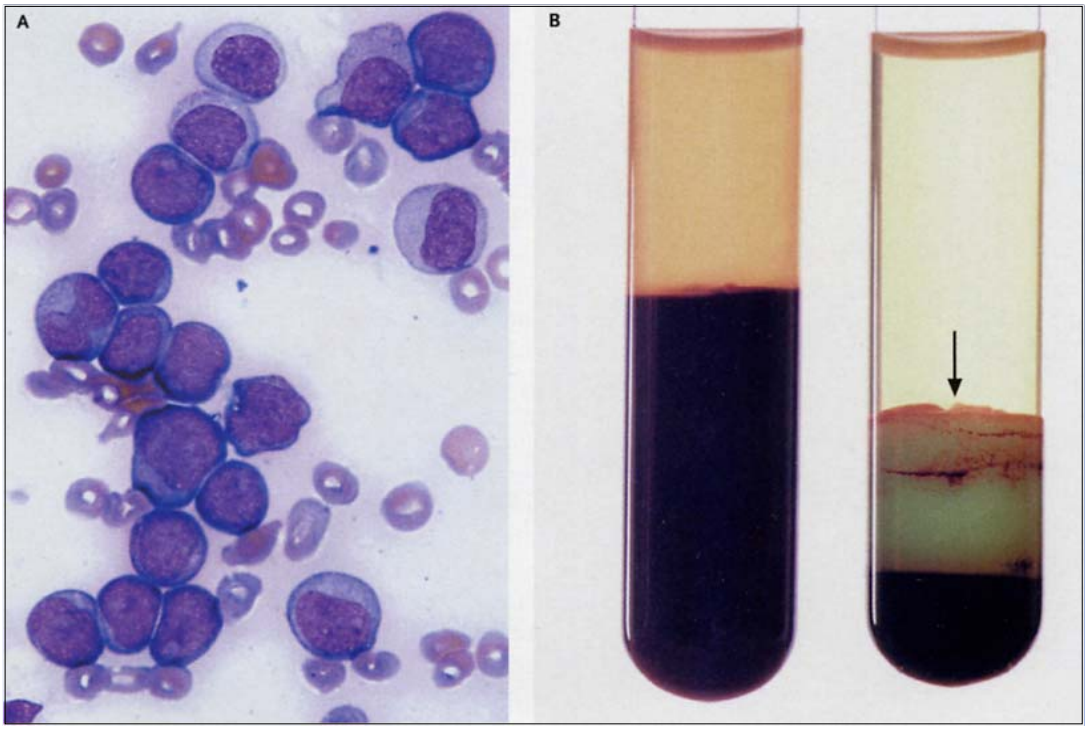
Acute Leukemia - D Savage - 8 January 2002



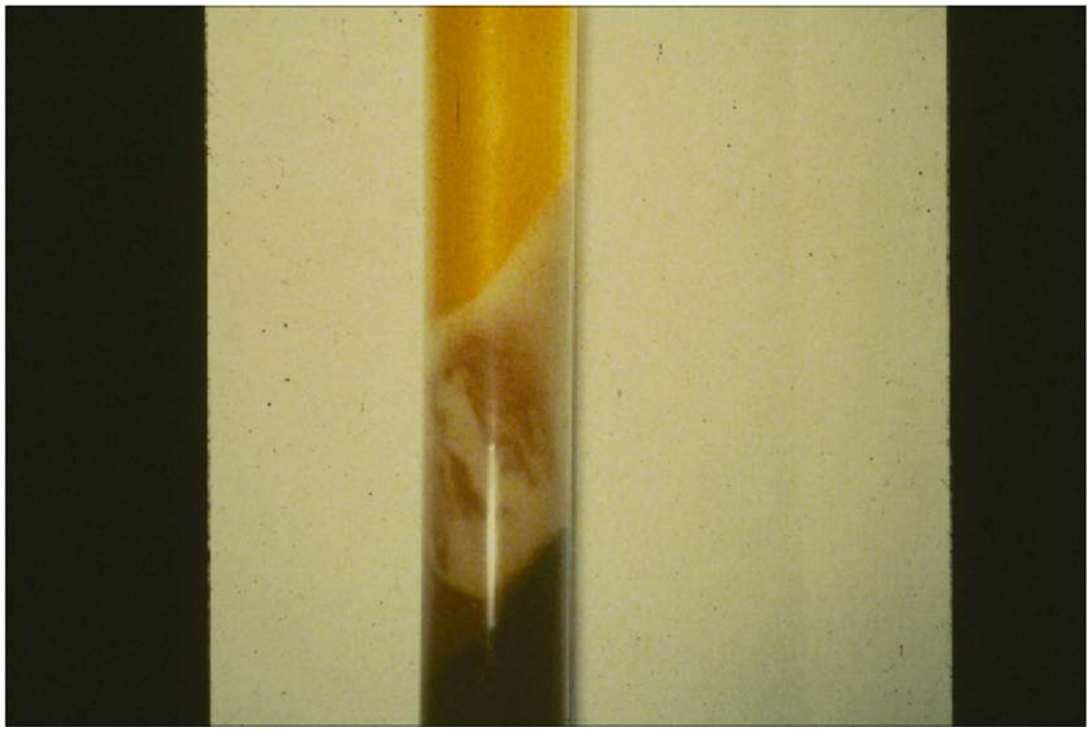


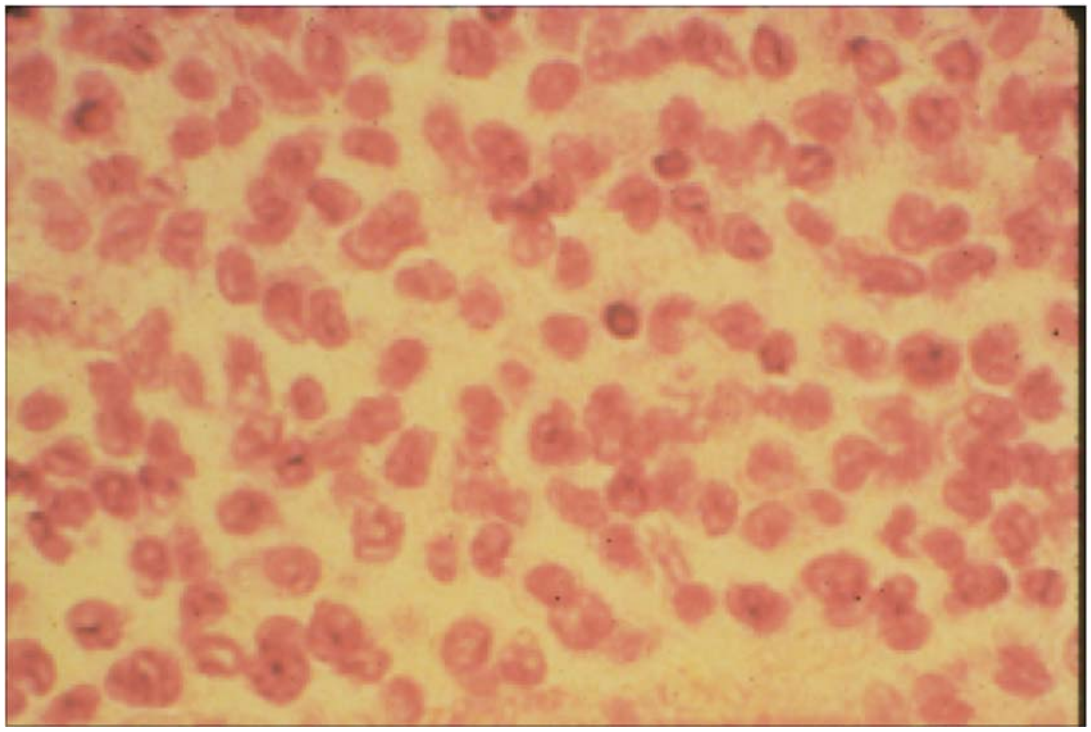
Acute Leukemia

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



Acute Leukemia - D Savage - 8 January 2002

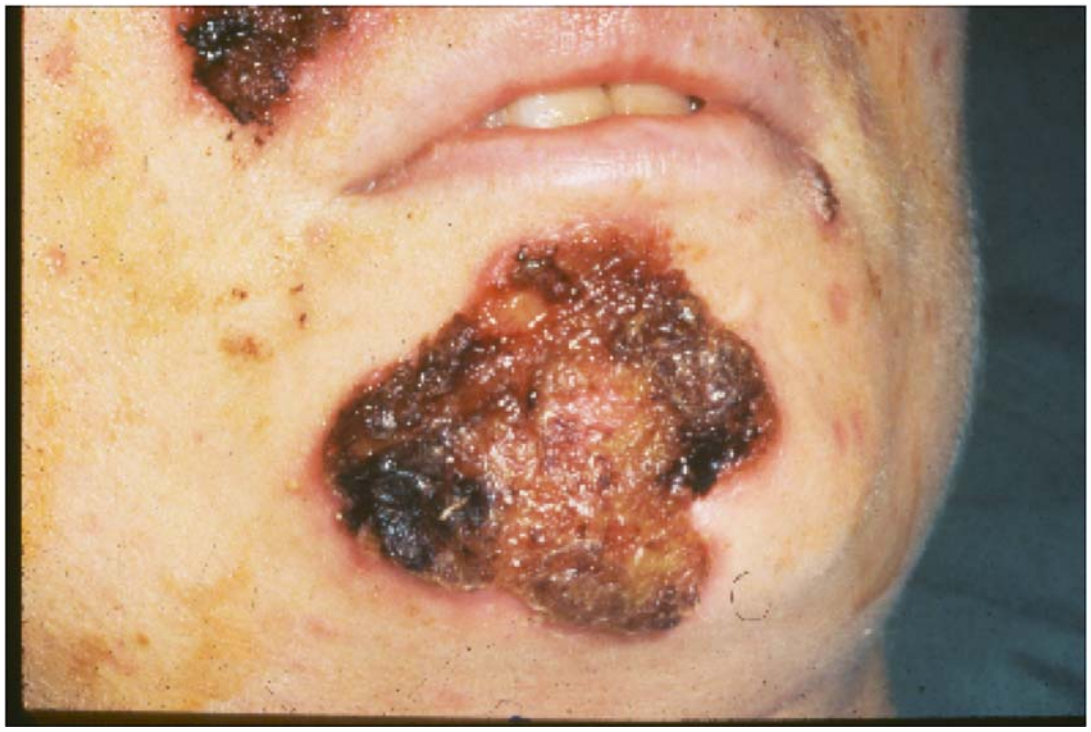


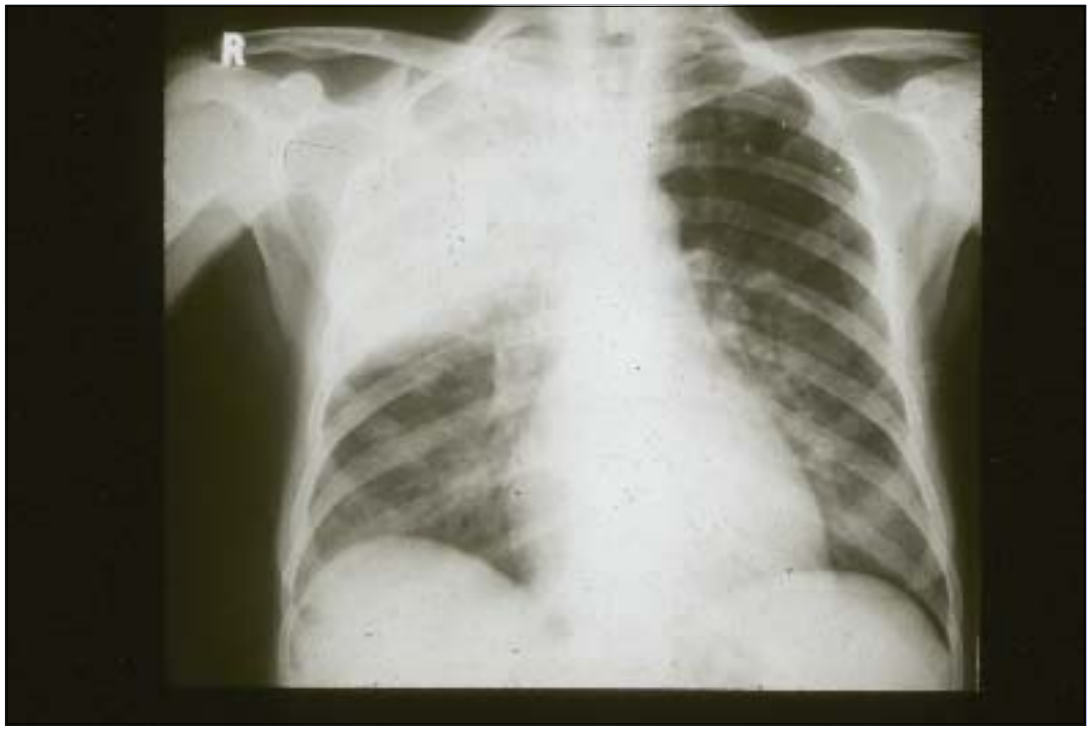


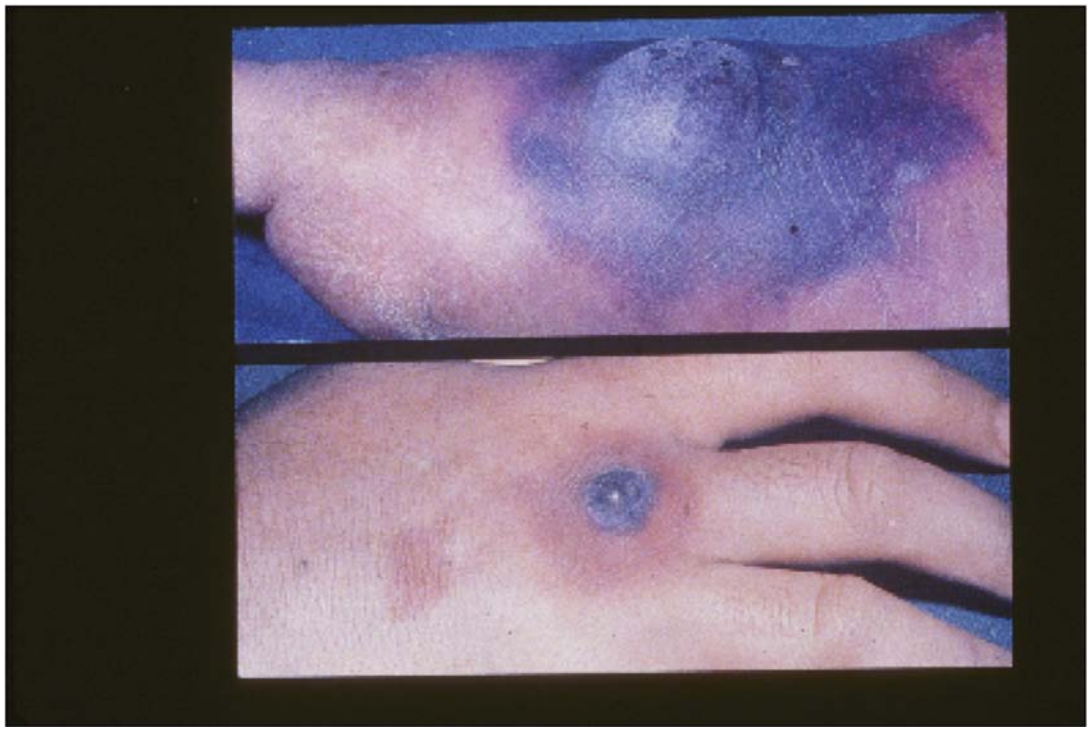
Acute Leukemia - treatment

- 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 - D Savage - 8 January 2002







Acute Leukemia - results of treatment

	ALL		ANLL
	children	adults	adults
complete remission	90%	75%	65%
median survival	6+ yrs	1-2 yrs	1-2 yrs
5 yr disease-free survival	70%	20-45%	10-20%