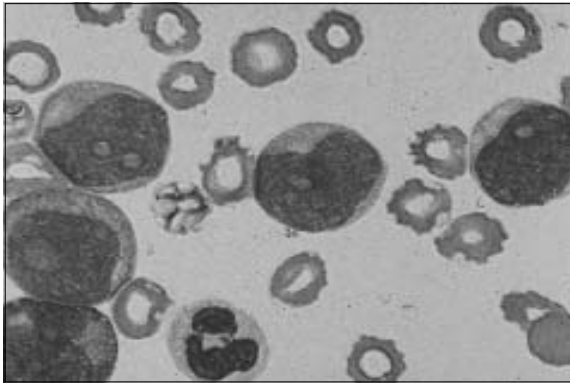
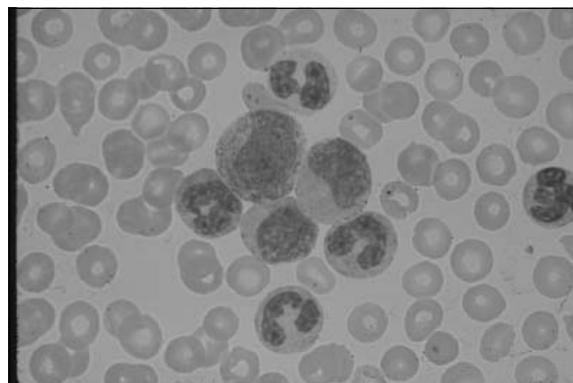
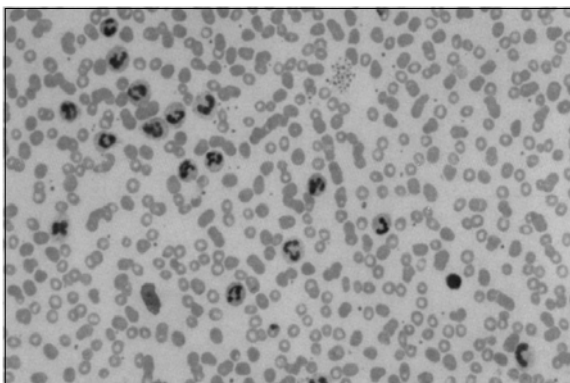
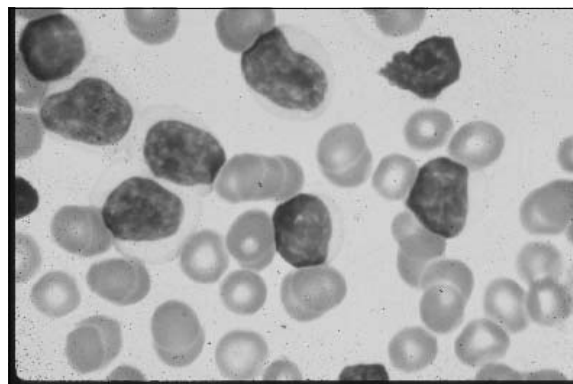


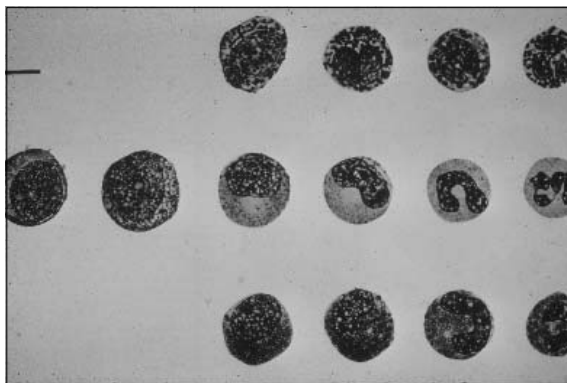
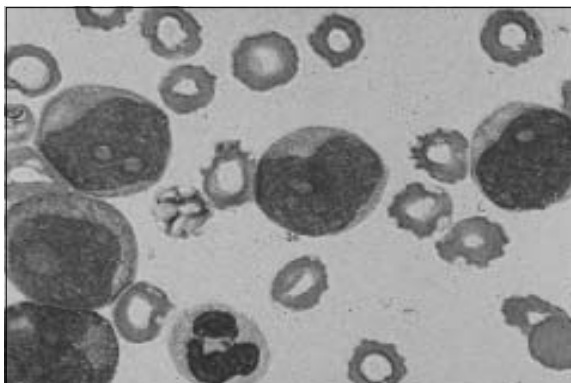
**Acute Leukemia - D Savage - 8 January 2002**



Disease	Usual phenotype
acute leukemia	precursor
chronic leukemia lymphoma myeloma	differentiated

Total WBC ≥ 50	Blasts	Pro	Myel	Meta	Band	Seg	Lymph
acute leukemia	0	0	0	0	0	0	0
chronic leukemia	0	0	0	0	0	0	0
lymphoma	0	0	0	0	0	0	0
myeloma	0	0	0	0	0	0	0





### 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

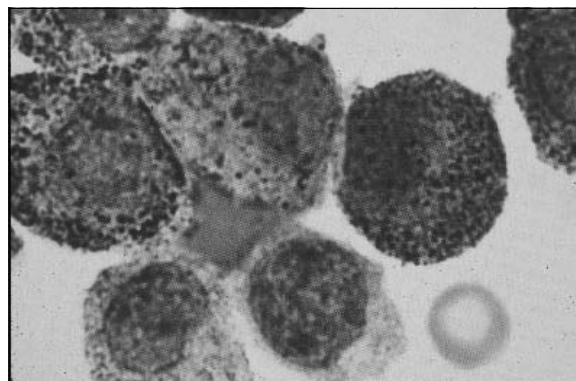
- Possible mechanisms
  - Unaltered gene product (e.g., *myc* in Burkitt's)
  - Altered gene product
    - » usually a fusion protein (e.g., *bcr-abl* in CML)

### 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)

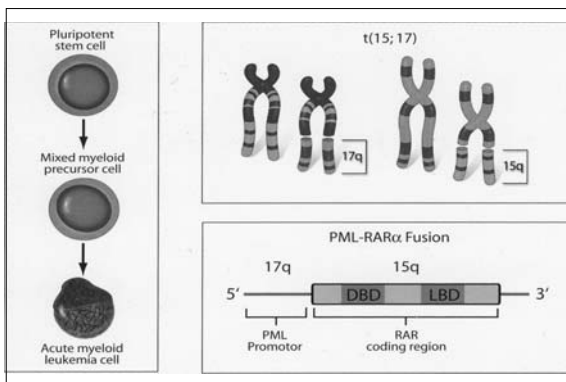
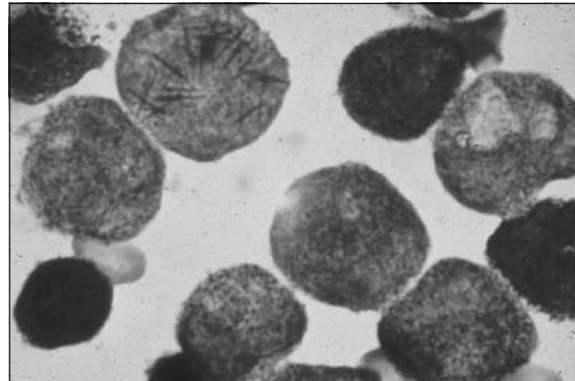
### Oncogene Activation

Translocation	Disease	Proposed mechanism
(2;4)(11;14)	some B-cell lymphomas, CLL	expression of transcription factor ( <i>myc</i> )
(9;22)	CLL, some AML	cellular signalling molecule ( <i>Bcr/Abi</i> )
(6;5)(14)	acute promyelocyte leukemia	cellular transcription factor ( <i>plutiva</i> )



### 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

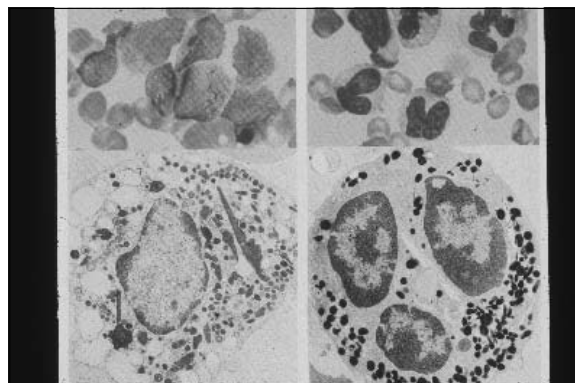


### Acute Promyelocytic Leukemia t(15;17)

- retinoic acid receptor- $\alpha$  (RAR- $\alpha$ ) gene on 17q in normal cells
- RAR- $\alpha$  gene product is a nuclear receptor protein acting as transcriptional enhancer in myeloid differentiation when bound to retinoic acid
- in t(15;17), part of RAR- $\alpha$  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-rara*) 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

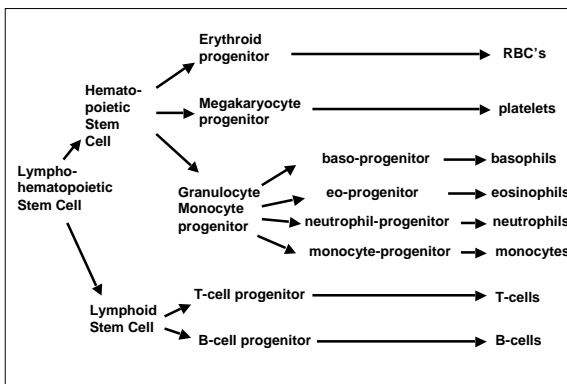


### Tumor-suppressor genes

- 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	abnormal marker expressed	progenitor cell of origin
most patients	neutrophils, monocytes	granulocyte or monocyte progenitor
minority	neutrophils, monocytes, RBCs, platelets	multilineage primitive progenitor

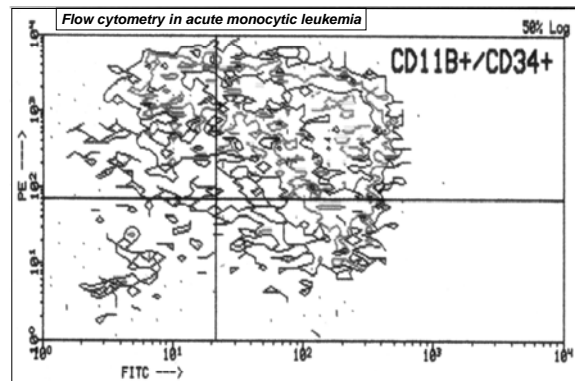


### Lineage & Stage Specificity in ALL

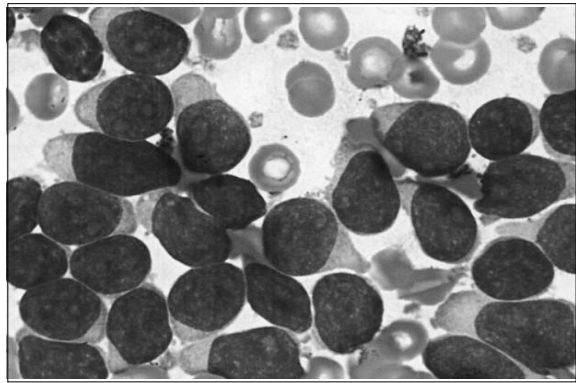
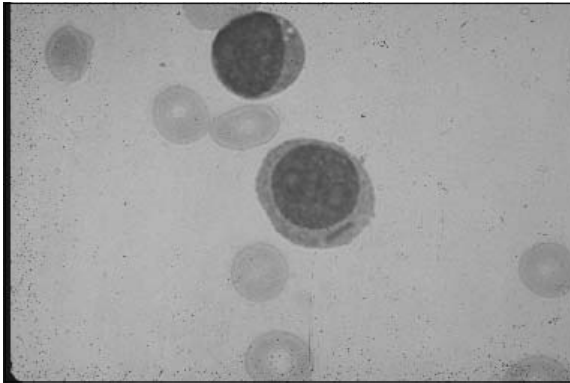
#### Acute lymphocytic leukemia

- 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

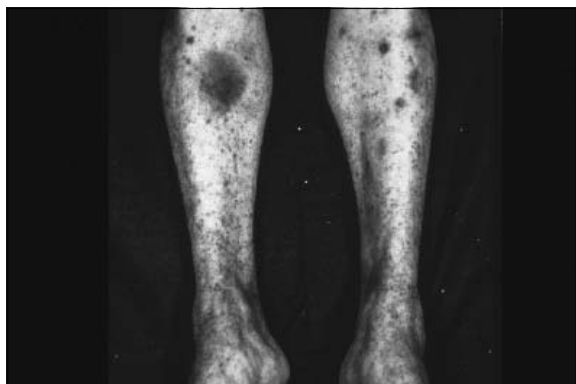
Feature	ALL	AML
usual age group	children	adults
myeloblasts	..	..
blast cell transferrase (TdT)	..	..
cell surface AIGs	..	..
lymphoid cell receptor gene rearrangement	..	..



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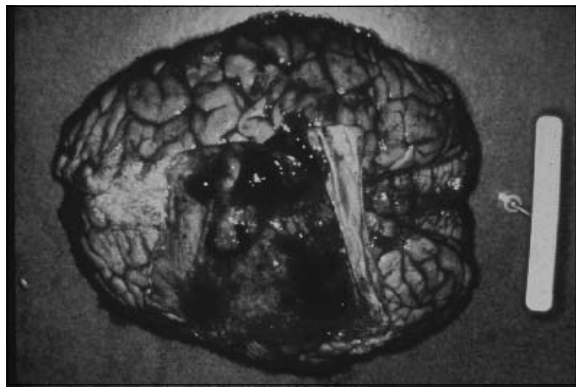
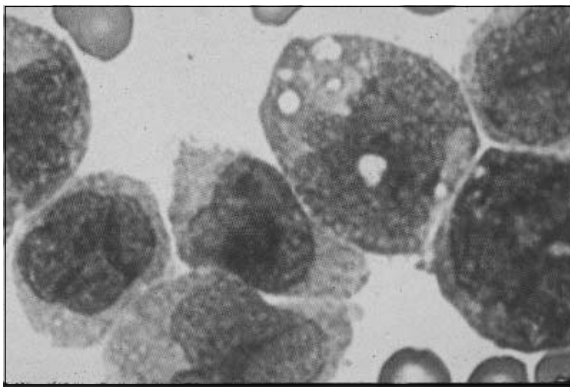
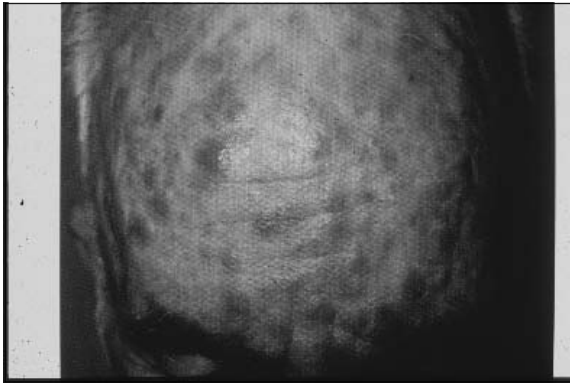


Acute Leukemia		
Event	Consequences	
<b>Marrow failure:</b>	neutropenia anemia ↓ platelets	infection weakness, fatigue bleeding
<b>Hypertonicity:</b>	tubular damage	acute renal failure
<b>etc</b>	↓ platelets abnormal clotting	bleeding



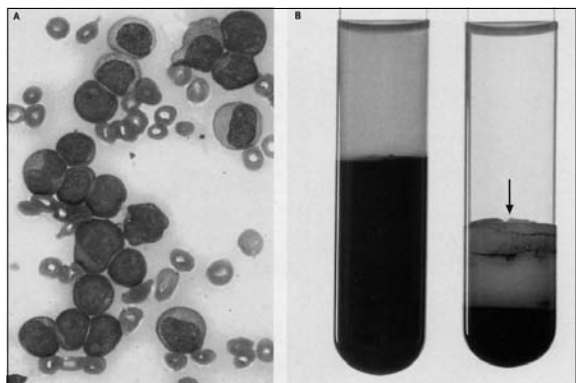
Acute Leukemia	
<b>Organ infiltration</b>	
marrow involvement	
bone pain	
enlarged liver, spleen, nodes	
hypertrophied gums	
meningeal infiltration	
headache, cranial nn. palsies	

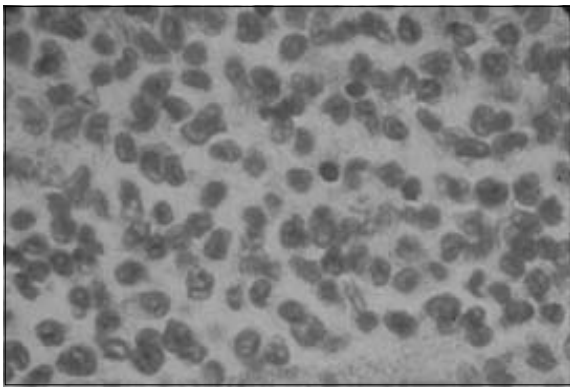
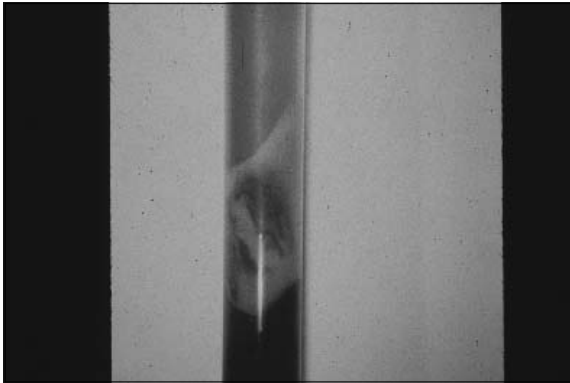




**Acute Leukemia**

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





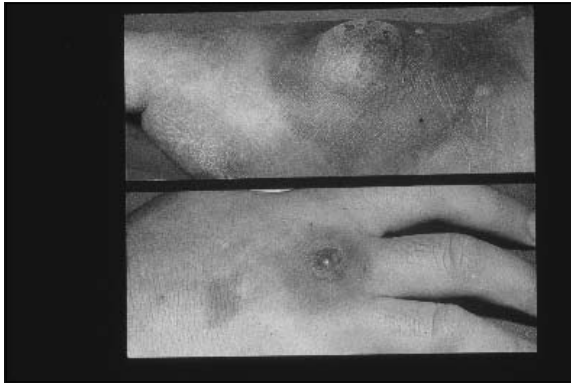
#### Acute Leukemia - treatment

- 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 - D Savage - 8 January 2002**



**Acute Leukemia - results of treatment**

	KNOX		KNOX
	children	adults	adults
conjugate antibody	20%	75%	55%
metformin sulfate	50% <sup>1</sup>	110% <sup>1</sup>	110% <sup>1</sup>
5- $\alpha$ -dihydrotestosterone sulfate	70%	20-55%	10-20%