# Heme-Lymph Lab: Acute Leukemias/MDS/MPN

## Objectives

Laboratory instructors:

1. Facilitate lab discussion and answer questions

Students:

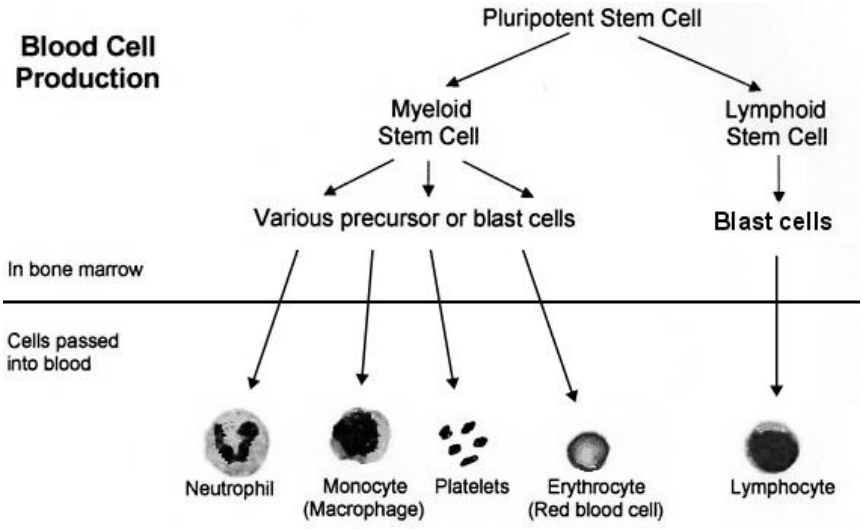
1. Review the introductory material below
2. Study and review the assigned cases and questions in small groups before the Lab. This includes the pathological material using Virtual Microscopy
3. Be prepared to present your cases, questions and answers to the rest of your Lab class during the Lab

## Acute Leukemia: Pathophysiology

- Defined by the presence of ≥ 20% blasts in the blood or bone marrow
- Develops when acquired defects result in clonal expansion without significant maturation beyond the blast stage
- Blasts rapidly accumulate in the marrow
- The expansion of blast cells compromises normal hematopoiesis resulting in bone marrow failure:
  - Anemia
  - Neutropenia
  - Thrombocytopenia
- Infiltration of lymph nodes by leukemic cells leading to lymphadenopathy is commonly seen in acute lymphoblastic leukemia

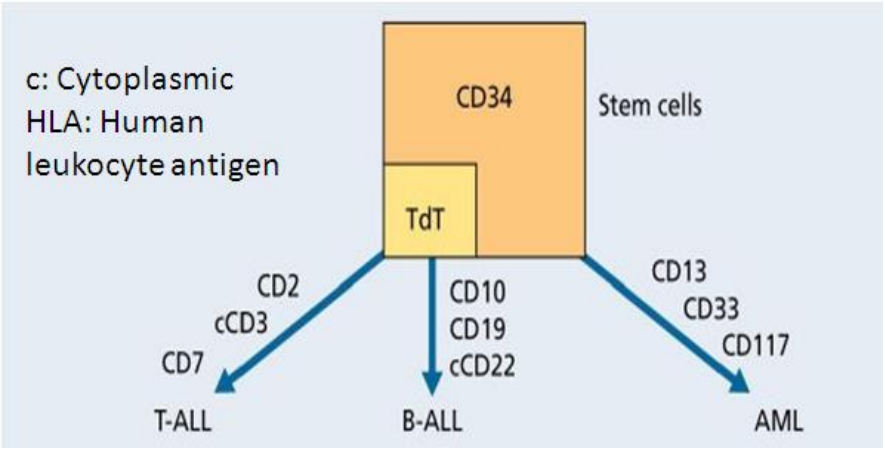
**Consequences of leukemic transformation:**

- Increased proliferation (at the blast level, diagram below)
- Blocked differentiation
- Decreased cell death (decreased apoptosis)
- Bone marrow failure
- Infiltration of organs by leukemic cells



## Acute Leukemia: Classification

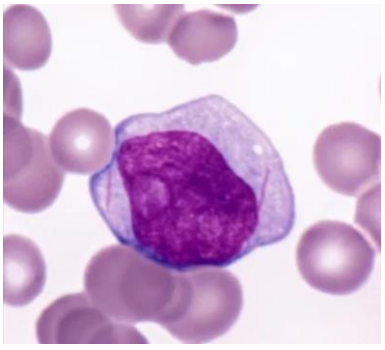
- Acute leukemia is divided into two broad categories:
  - Acute lymphoblastic leukemia (ALL): consists of blasts of either T cells or B cells
  - Acute myeloid leukemia (AML) consists of blasts with characteristics of myeloid cells (granulocytes, monocytes, megakaryocytes, erythrocytes)
- Further subclassification is according to World Health Organization (WHO) system which incorporates morphology, cytochemistry, flow cytometry, genetic markers and clinical features



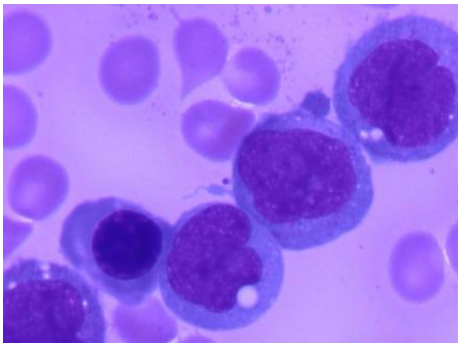

Distinguishing the origin of blasts based on expression of cellular antigens, typically done by flow cytometry

## AML Morphology

(a)

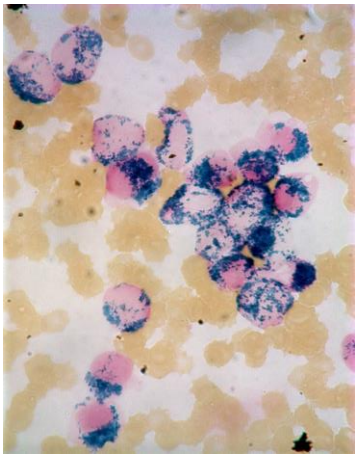


(b)

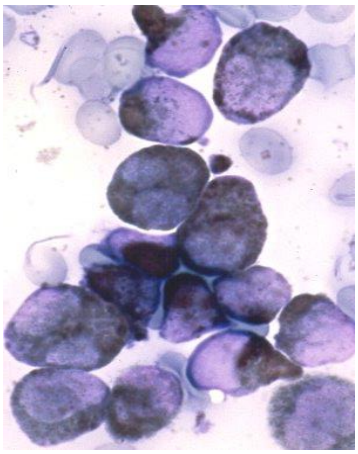


Morphological examples of acute myeloid leukemia. (a) Blast cells with few granules but may show Auer rods, as in this case; (b) Monoblastic leukemia with large blasts with irregular nuclear shapes and a few vacuoles in the cytoplasm

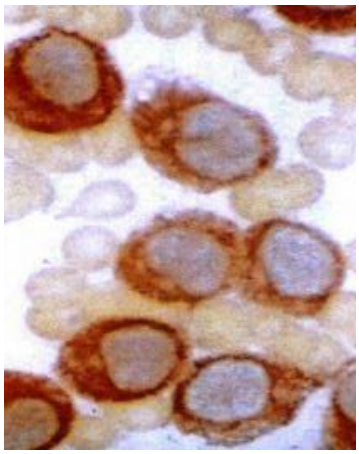
## AML: Cytochemistry



Myeloperoxidase (MPO): specific for myeloid differentiation



Sudan Black: positive in myeloid cells (Courtesy of: www.hmds.org.uk/aml.html)

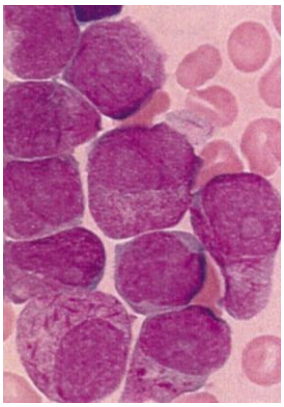


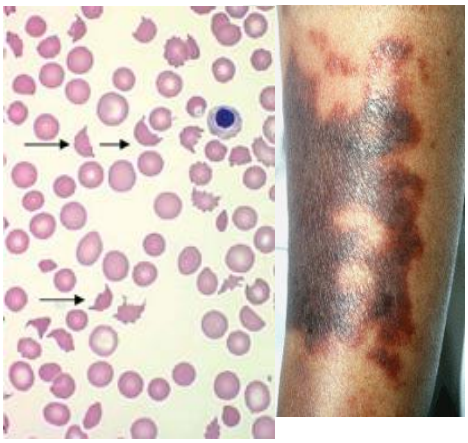
Non-specific esterase (NSE): Positive in monocyte lineage

### Acute Promyelocytic Leukemia (APL)

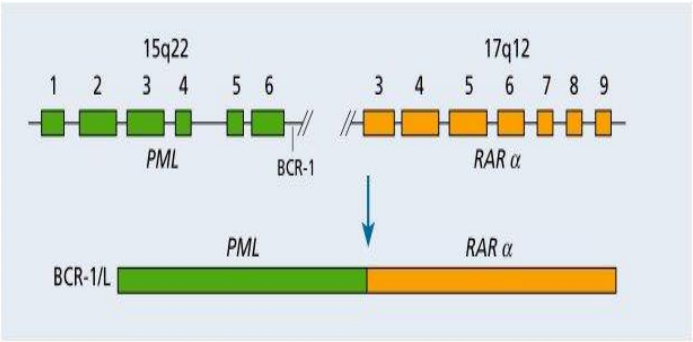
Characterized by:

- Characteristic morphology
- t (15;17) chromosomal translocation
- Disseminated intravascular coagulation
  - Microangiopathic blood picture (schistocytes)
  - Microvasculature thrombosis (tissue necrosis)
  - Bleeding





Above: Left; typical APL leukemic cell morphology showing abundant granules and Auer rods; Middle: Blood film showing irregular-shaped, broken RBCs (schistocytes, arrows) typical of microangiopathic hemolytic anemia associated with APL; Right: Large areas of ecchymosis and skin necrosis secondary to disseminated intravascular coagulation (DIC) associated with APL




Above: Generation of the t(15;17) translocation. The PML gene at 15q22 may break at one of three different breakpoint cluster regions (BCR-1, -2 and -3) and join with exons 3-9 of the RARα gene at 17q12. Three different fusion mRNAs are generated (termed long (L), variable (V) or short (S)) and these give rise to fusion proteins of different size. In this diagram only the long version resulting from a break at BCR-1 is shown.

## Acute Lymphoblastic Leukemia

Morphology, cytochemistry and immunophenotyping of acute lymphoblastic leukemia (ALL).

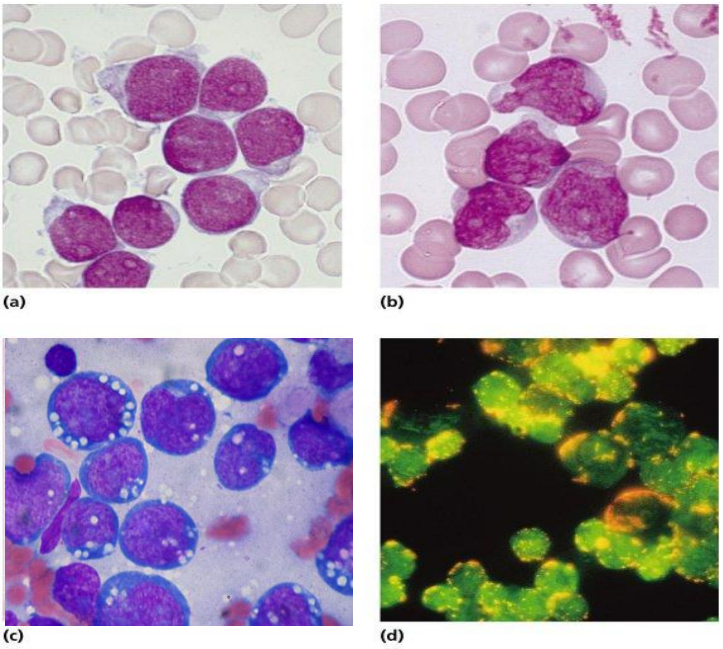
(a) Lymphoblasts show scanty cytoplasm without granules.

(b) Lymphoblasts can be large and heterogeneous with abundant cytoplasm.

(c) Lymphoblasts are deeply basophliic with cytoplasmic vacuolation. This is known as L3 morphology. This is now classified as Burkitt lymphoma not ALL

(d) Indirect immunofluorescence reveals nuclear terminal deoxynucleotidyl transferase (TdT) (green) and membrane CD10 (orange).

Courtesy of Professor G Janossy




## Acute Lymphoblastic Leukemia: Fast Facts

- The most common malignant disease of childhood. 75% of cases occur before age 6
- Eighty-five percent of the cases are of B-cell lineage, the rest are T-cells
- The chromosome number in leukemic cells is prognostic: higher is favorable (>50= hyperdiploidy)
- Overall, 85% of children are now expected to be cured of ALL; adults with ALL have worse prognosis

## Myeloproliferative Neoplasms (MPN)

Definition: Hematopoietic stem cell disorders characterized by proliferation of one or more of the myeloid lineages

- Granulocytic
- Erythroid
- Megakaryocytic
- Mast cells

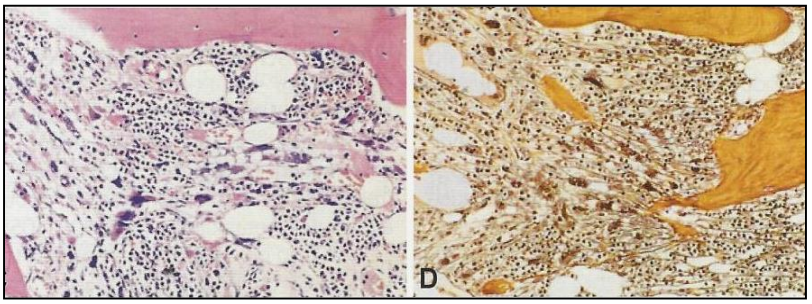
MPN's typically present with:

- Hypercellular bone marrow with maturation of cells
- Increased numbers of peripheral blood neutrophils, red blood cells and/or platelets
- Hepatosplenomegaly
- Each has the potential to progress, resulting in marrow fibrosis and/or acute leukemia

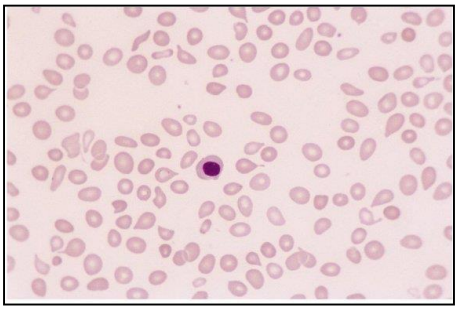
Classification:

- Chronic Myelogenous Leukemia
- Polycythemia Vera
- Primary Myelofibrosis
- Essential Thrombocythemia
- Mastocytosis

## Primary Myelofibrosis

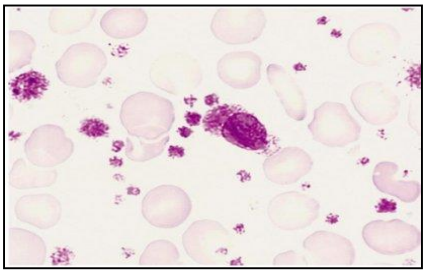


Above: Bone marrow biopsy showing loss of normal architecture. Hematopoietic cells surrounded by increased fibrous tissue streaming through the marrow (right: sliver staining)



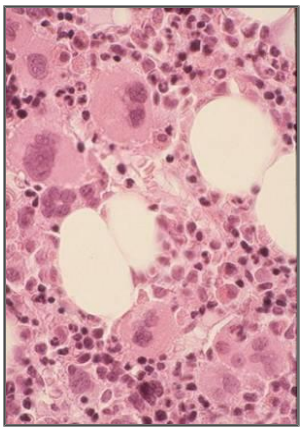
Peripheral blood film showing tear-drop RBCs characteristic of this diagnosis and a normoblast (as part of leukoerythroblastic picture)

## Essential Thrombocythemia (ET)



Left: Peripheral blood film in essential thrombocythemia showing increased numbers of platelets and a nucleated megakaryocytic fragment.

Right: Bone marrow with increased Megakaryocytes in ET



## MDS – General Summary

- Clonal disorder of marrow stem cell
- Occurs mainly in older patients
  - Median age is 70 years
- Symptoms are secondary to cytopenias
- Hallmark is dysplastic features in the hematopoietic cells.
- Increased risk of progression to AML
- Bone marrow is normocellular or hypercellular in >90%, but there is failure to produce mature cells
- Prognostic variables:
  - Blast percent
  - Number and degree of cytopenias
  - Cytogenetic Abnormalities

## MDS: WHO Classification

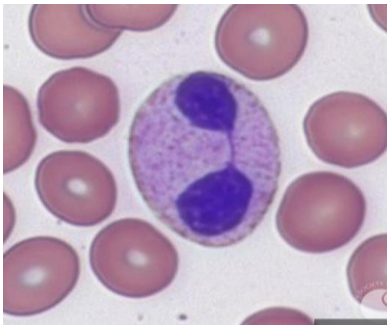
- MDS with Single Lineage Dysplasia
- MDS with Multi Lineage Dysplasia
- MDS with Ring Sideroblasts
- MDS with excess blasts (MDS-EB-1, MDS-EB-2)
- MDS with isolated 5q deletion
- MDS Unclassified

## Diagnosis of MDS

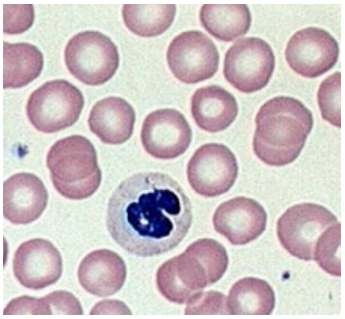
- Unequivocal evidence of dysplasia in one or more cell lineages
- Abnormality should involve ≥ 10% of the affected lineage
- Careful assessment of percentage of blasts

## MDS: Morphological Features

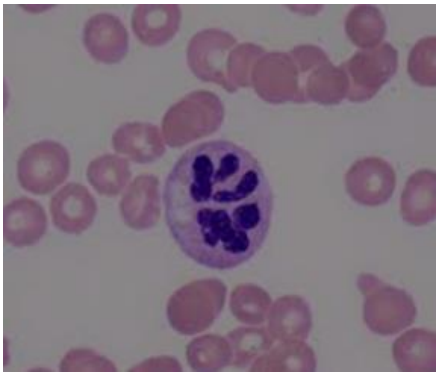
### MDS: Dysplastic Granulopoiesis



Hypolobulated (Pelger-Huet) neutrophils

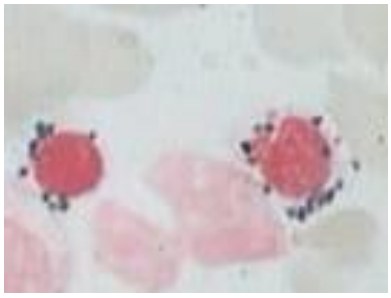


Hypogranular

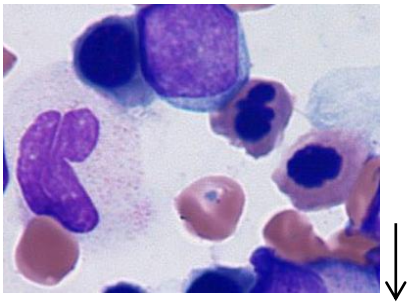


Hypersegmented

### MDS: Dysplastic Erythropoiesis

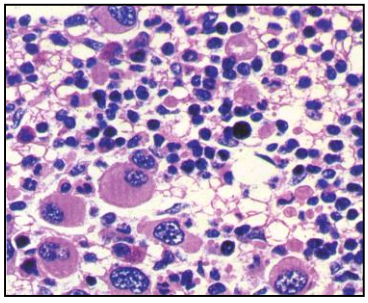


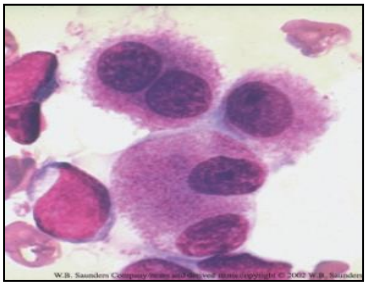
Ring sideroblast



Nuclear irregularity, nuclear budding

### Dysplastic Megakaryocytes





Mononuclear or binucleated megakaryocytes, some with hypogranular cytoplasm

**MDS with Excess Blasts (MDS-EB)**

Cytopenias with uni- or multilineage dysplasia

- **Type 1**:
  - 5-9% blasts in bone marrow
- **Type 2**:
  - 10-19% blasts in bone marrow

Risk of progression to AML:

- **Type 1** - 25%
- **Type 2** - 33%