We'll cover these in this lecture

Myelodysplasia
Acute Myeloid Leukemia
Chronic Myelogenous Leukemia

Non Hodgkin Lymphoma
Chronic Lymphocytic Leukemia
Plasma Cell (Multiple) Myeloma
Hodgkin Lymphoma

APPROVED

Overview

We'll do this with each disease

- **Case**
- **Pathophysiology**
- **Diagnosis**
- **Prognosis**
- **Epidemology/Statistics**
- **Clinical**
- **Treatment**

Pathology Clinical

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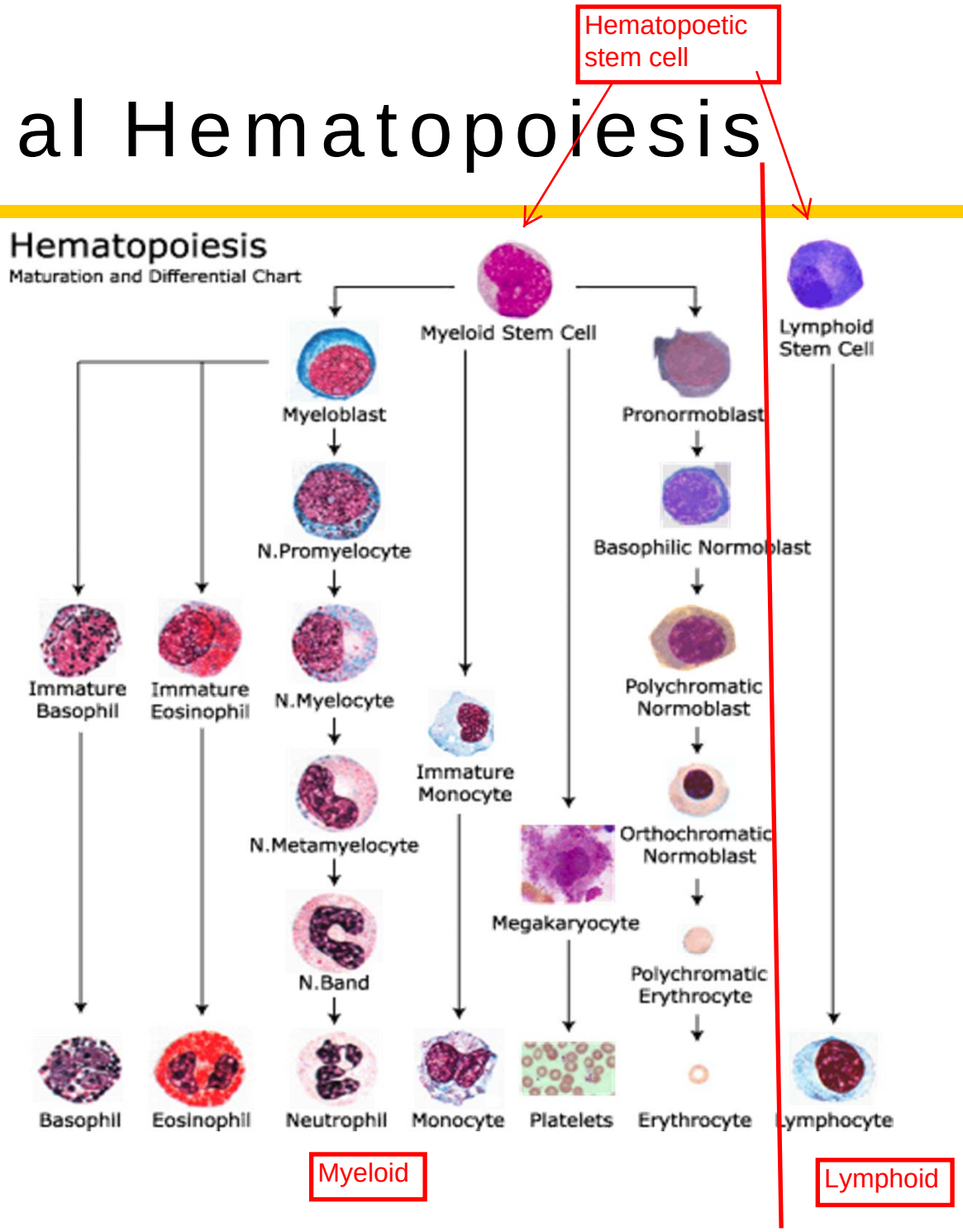
Introduction

Normal Hematopoiesis



Leukemia

- **Monoclonal neoplasm of bone marrow cells typically characterized by a proliferation of immature cells (blasts) in bone marrow/blood**
- **Major types are *lymphoid* and nonlymphoid (the latter commonly called "*myeloid*" leukemia)**
- **Divided into *acute* (develops over weeks to months) and *chronic* (develops over months to years)**

2 basic types (per the previous gaph)

Operational definitions for prognosis (ie there is overlap; they are not specific descriptors)

In general

Lymphoma

- **Monoclonal neoplasm of lymphocytes**

Usually present as masses or lumps, but some can have leukemic ("liquid") phase

These lymphocyte proliferations usually form tumors (-omas) in lymph nodes and/or in extranodal lymphoid tissues

Major categories are *T-cell* lymphomas and *B-cell* lymphomas

Tools

Tools of the Trade

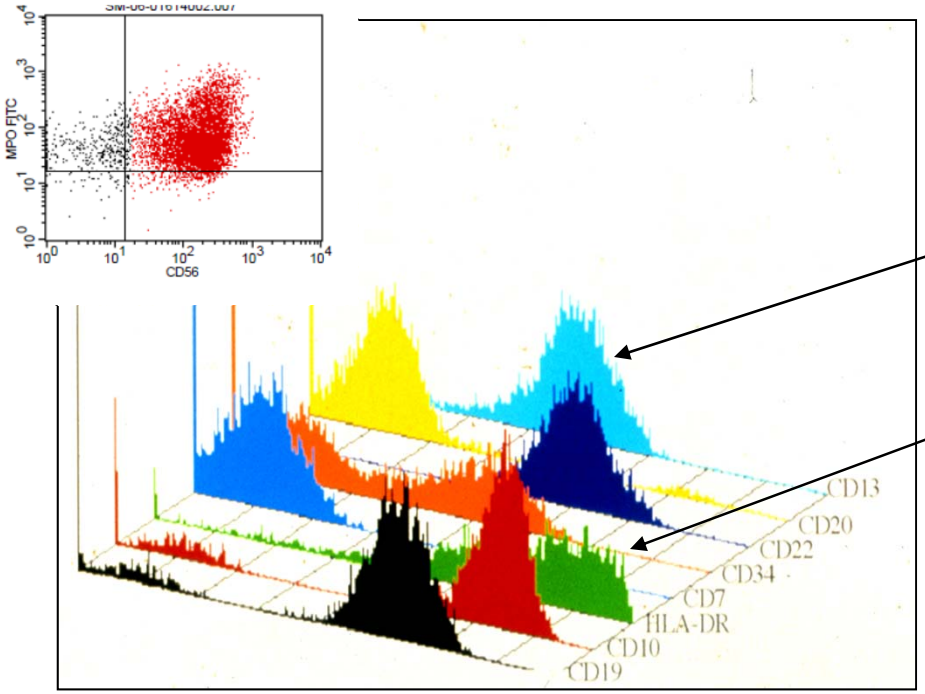
Techniques used for the diagnosis of hematopoietic and lymphoid disorders

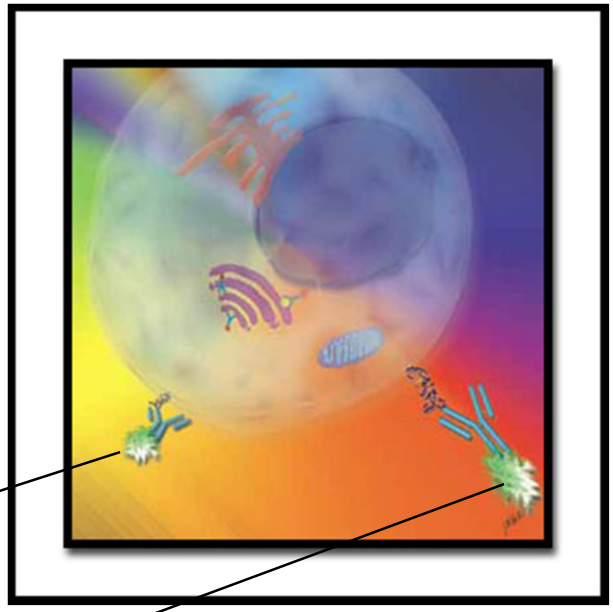
Morphology

Gives you lots of info and helps determine what other tests should be performed (you don't want to do unnecessary tests)

Flow Cytometry

Labels Abs to cell specific cellular Ags in a liquid suspension
Can do 8 Ags on one cell at once
Cells flow in a stream past some lasers and you get these pretty colors below





Fluorochrome-labeled antibodies to cell surface antigens activated by lasers

Flow Cytometry Example:

Acute Leukemia

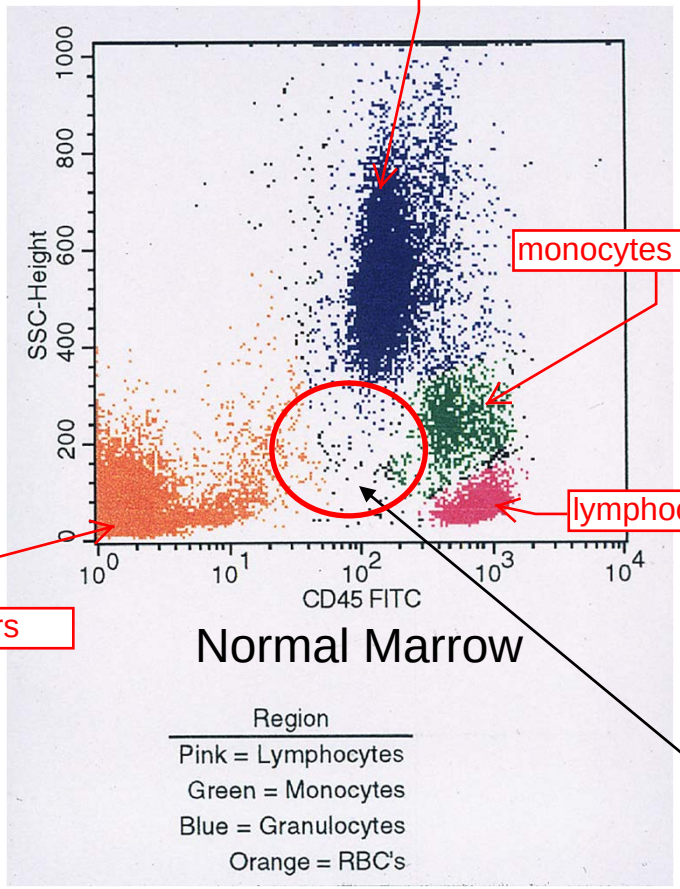
You can separate cells by seeing how strongly they express CD45 (leukocyte Ag). Anything born in the blood marrow has CD45.
You can also tell how complex a cell is, like if it has granules which scatter light even without an Ab on its surface.

Granulocytes

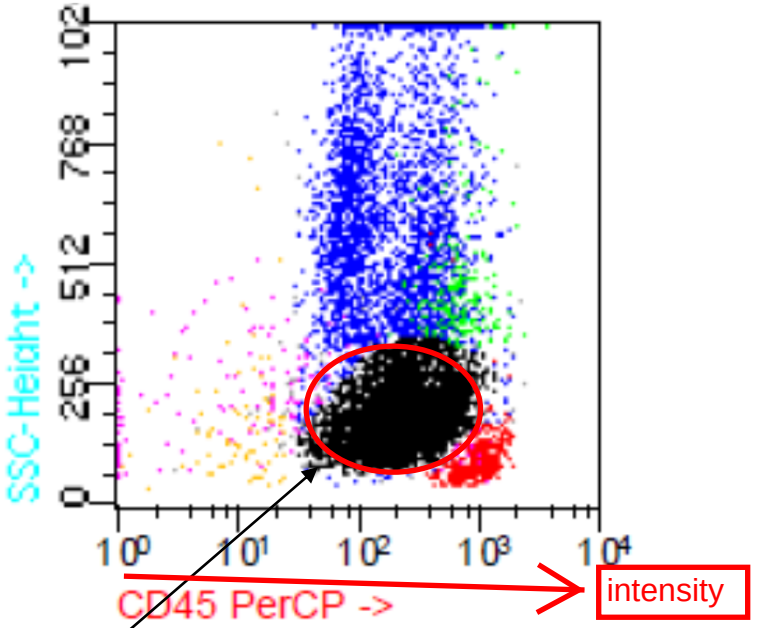
monocytes

lymphocytes

RBC precursors



Normal Marrow



Acute Leukemia

Blast Region

Immature granulocyte precursors (important to look for!)

Immunohistochemistry

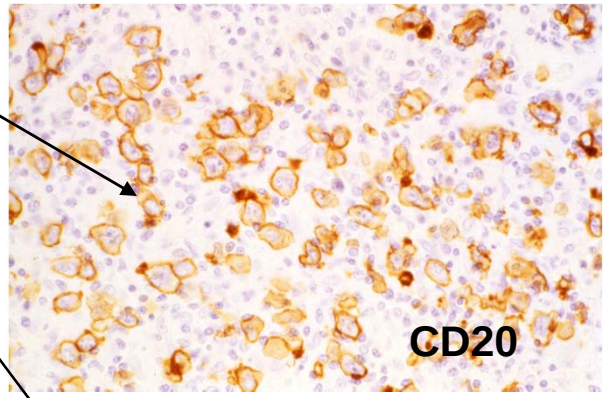
"flow cytometry on a slide"
Tissue sections are Ab-labeled then stained so you can see

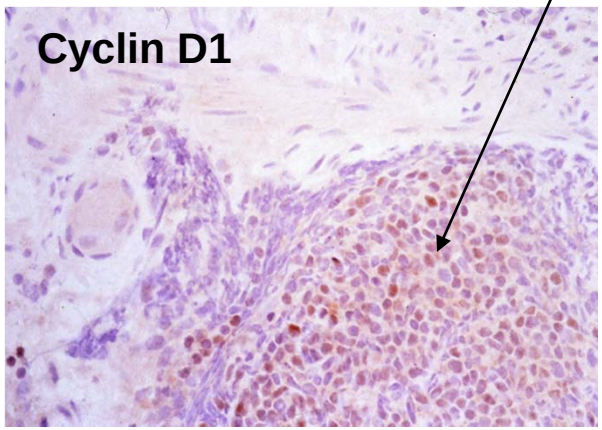
Antibodies to:

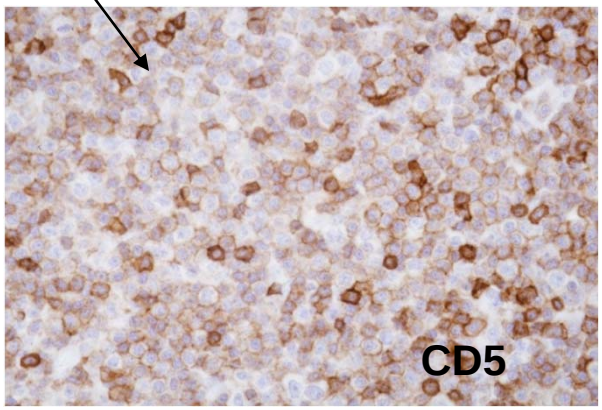
B-cell antigens

T-cell antigens

Nuclear antigens

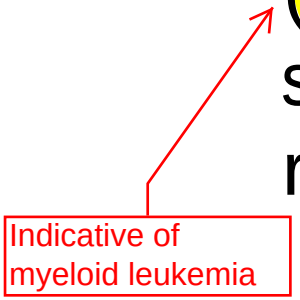




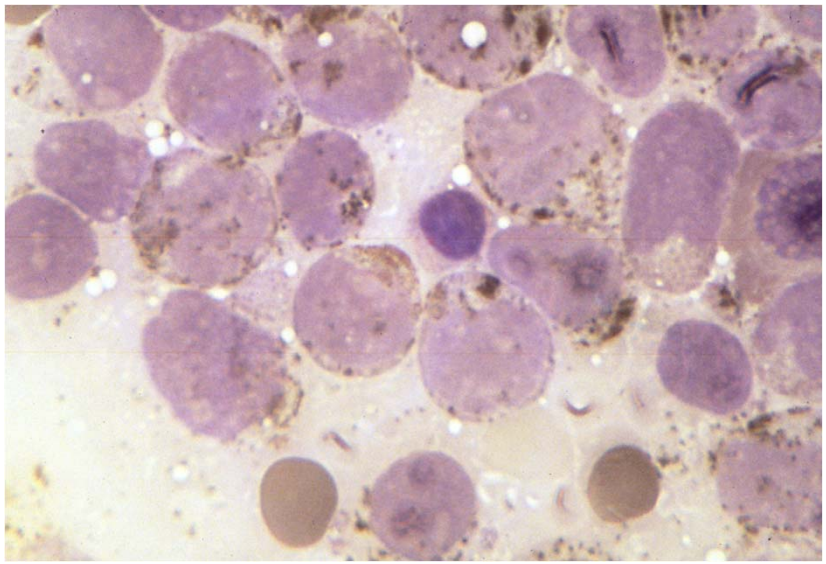


Cytochemistry

- Detection of substances (usually enzymes) associated with certain cell types
- Used to determine cell lineage in acute leukemia (myeloperoxidase/monocyte esterase) but sometimes for other purposes e.g., tartrate resistent acid phosphatase in hairy cell leukemia



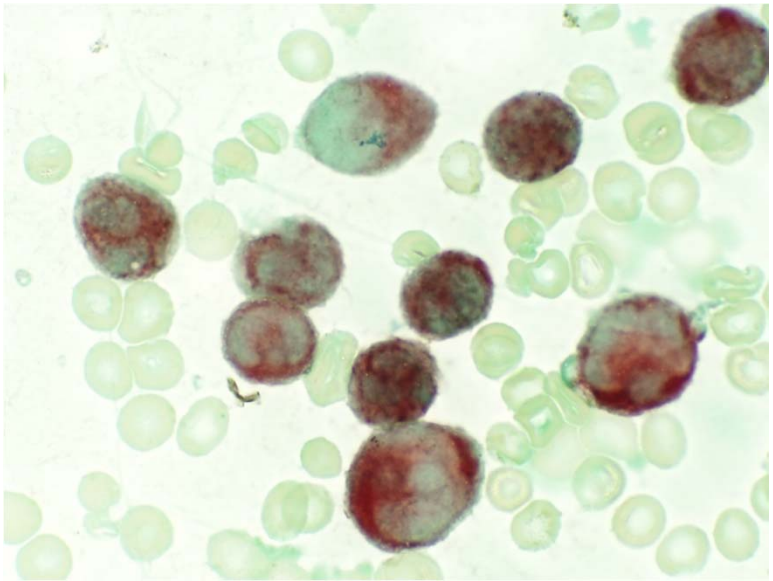
Cytochemistry



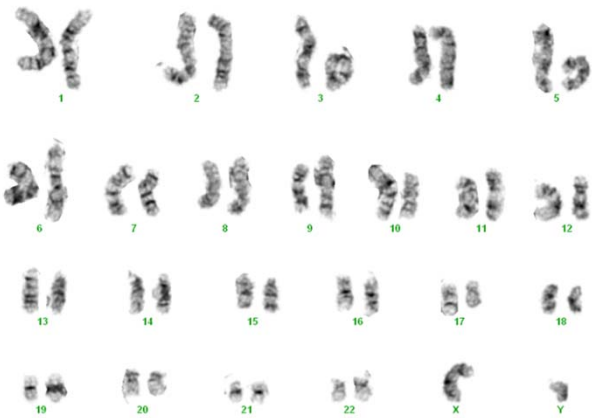
Myeloperoxidase in AML

Look for Ags that should be there but aren't, or Ags that are there but shouldn't be.
Also look at the number of cells

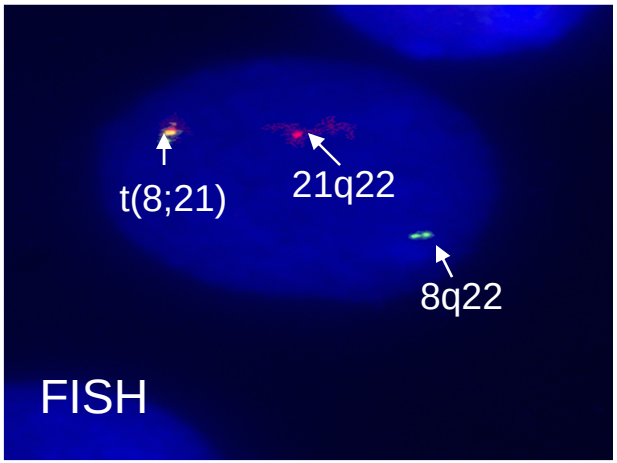
Monocyte esterase in acute monocytic leukemia



Cytogenetics



Standard karyotype



Probes labelling specific parts of the chromosome

Cytogenetics and molecular genetics: some chromosomal changes detected by standard cytogenetics (karyotype analysis) and **FISH** are of diagnostic and prog-nostic importance

Molecular Techniques

Glossed over. Just know we'll keep seeing more in the future of medicine

- B- and T-cell clonality studies by pcr to help diagnose lymphoma
- Detecting translocations (e.g., bcr-abl in CML) and mutations by pcr
- Sequencing genes (e.g., IgH in CLL)
- Gene expression studies
- ....and more to come

Molecular Techniques

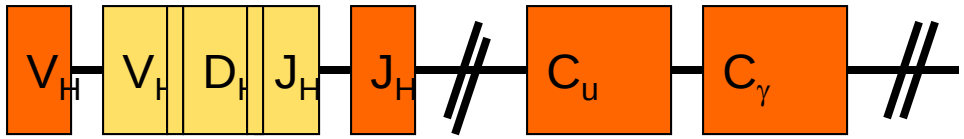
Clonality

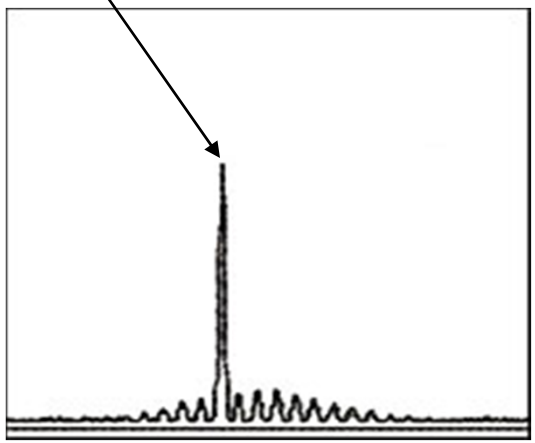
If all B-cells have the same Ig receptor gene, then they are clonal

For example, determining that all the B cells in a tissue have the same IgH gene re-arrangement allows a diagnosis of lymphoma (as opposed to a poly-clonal = reactive pro-cess)

Rearranged IgH Gene

(From Michael Datto, MD, PhD, with permission)





Capillary electrophoresis of pcr products

Molecular tests for clonality

Disease 1

Myelodysplasia

Case 1 Read it

- Patient 1: 68 year old man seen for pancytopenia picked up during an annual physical examination. One year ago his WBC 4,100, Hct 40.4% and platelet count 145,000. His MCV was 101. He is well.

- Physical examination:
  - LN: not enlarged
  - ABD: no organomegaly

- LAB:
  - Hct: 38.2%
  - WBC: 3985
  - Platelet: 104,000
  - MCV: 102.3

Case 1

- Patient 1: 68 year old man seen for pancytopenia picked up during an annual physical examination. One year ago his WBC 4,100, Hct 40.4% and platelet count 145,000. His MCV was 101. He is well.

Picked up asymptomatically

All 3 cell lines affected (anemia, leukopenia, thrombocytopenia)

- Physical examination:
  - LN: not enlarged
  - ABD: no organomegaly
- LAB:
  - Hct: 38.2%
  - WBC: 3985
  - Platelet: 104,000
  - MCV: 102.3

Case 1

- History:
  - 68 year old man seen for pancytopenia picked up during an annual physical examination. One year ago his WBC 4,100, Hct 40.4% and platelet count 145,000. His MCV was 101. He is well.
  - Five years ago he had a medical evaluation with WBC 5,300 cells/mm3, Hct 45.5%, platelet count 278,000 cells/mm3 and MCV 92.

Normal

- **Social History**: worked in the manufacture of rubber products from 1953 to 1965. Used to use benzene

- Physical examination:
  - LN: not enlarged
  - ABD: no organomegaly

- LAB:
  - Hct: 38.2%
  - WBC: 3985
  - Platelet: 104,000
  - MCV: 102.3

Case 1

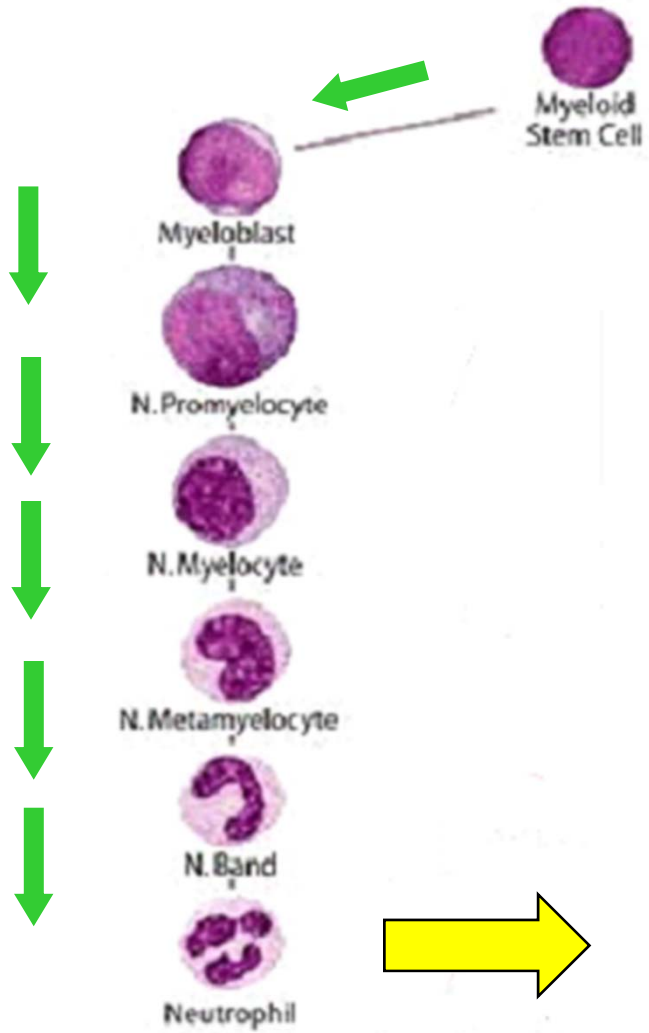
Date	WBC	Hct	Platelet	MCV
5 years ago	5300	45.5	278,000	92
1 year ago	4100	40.4	145,000	101
Now	3985	38.2	104,000	102.3

Gradual decrease

Gradual increase in cell size

Myelodysplasia: Pathophysiology

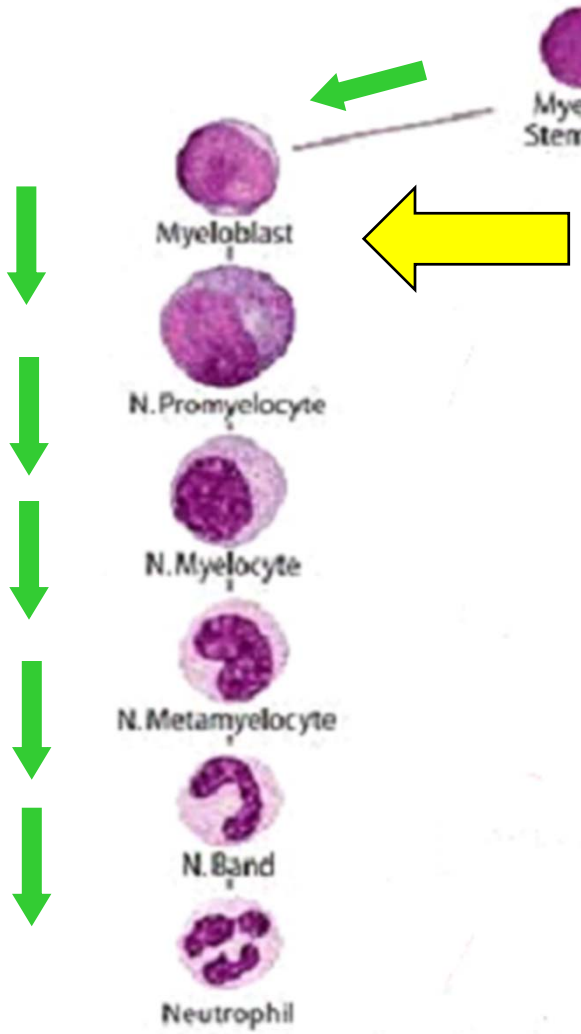
Normal Apoptosis



Apoptosis
Programmed cell death

Myelodysplasia: Pathophysiology

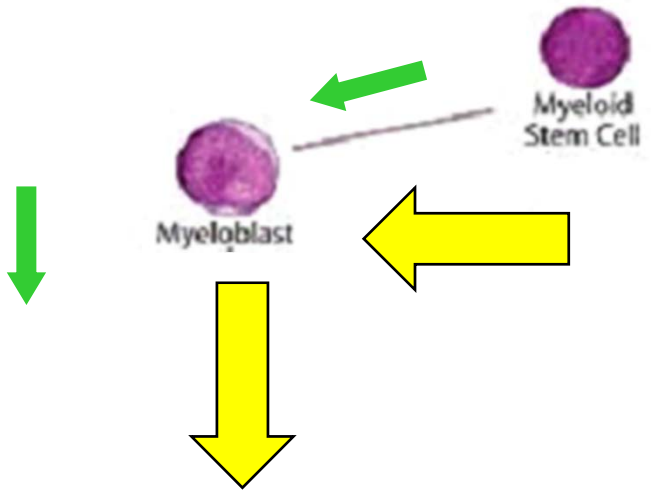
Apoptosis Defective: Occurs Early



Apoptosis
Programmed cell death

Pancytopenia b/c you don't get maturation of cell types.

Myelodysplasia: Pathophysiology
Apoptosis Defective: Occurs Early



Apoptosis
Programmed cell death

No Mature Cells

Pancytopenia

Definition - Standard

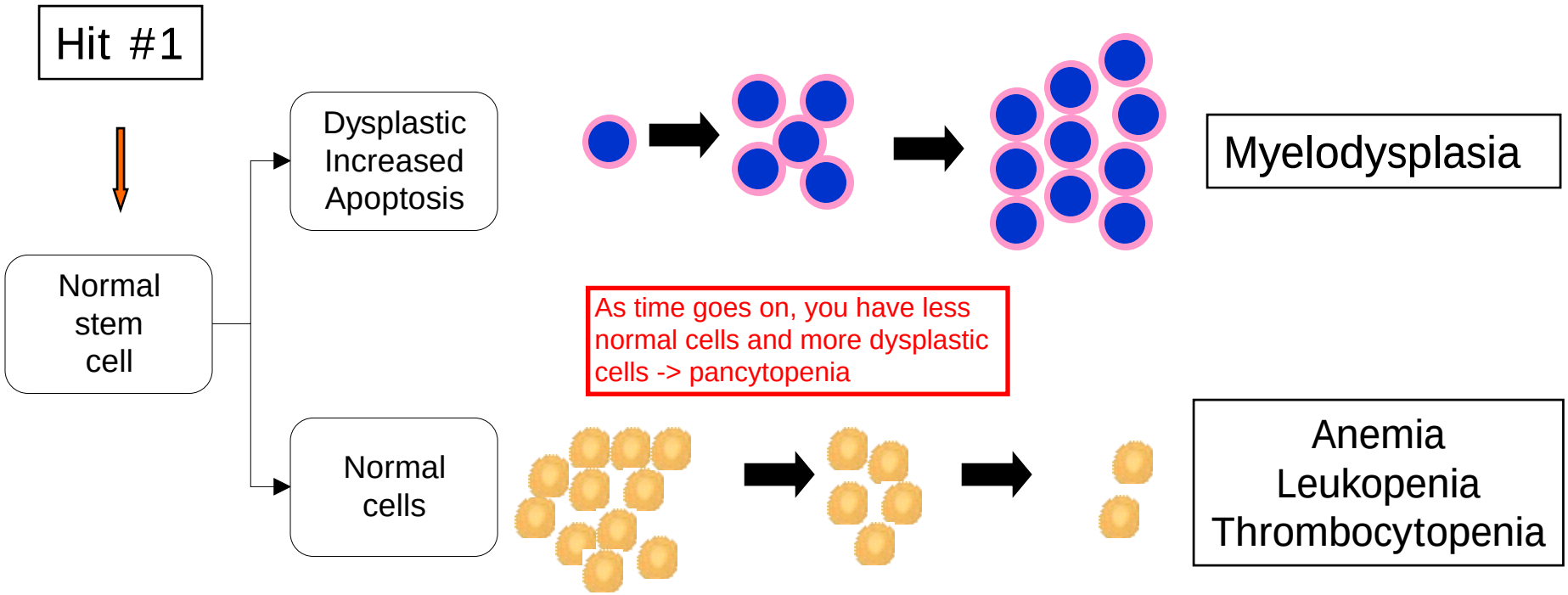
Prof finds this definition of little use and gives his own on the next slide

- Myelodysplastic syndromes (MDS) are clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis and peripheral cytopenias.
  - Clonal: All abnormal cells come from a single, common, precursor cell
  - Ineffective hematopoiesis: Immature cells do not develop effective develop into mature cells or the mature cells die early, resulting in too few effective peripheral blood cells

Definition - Explanatory

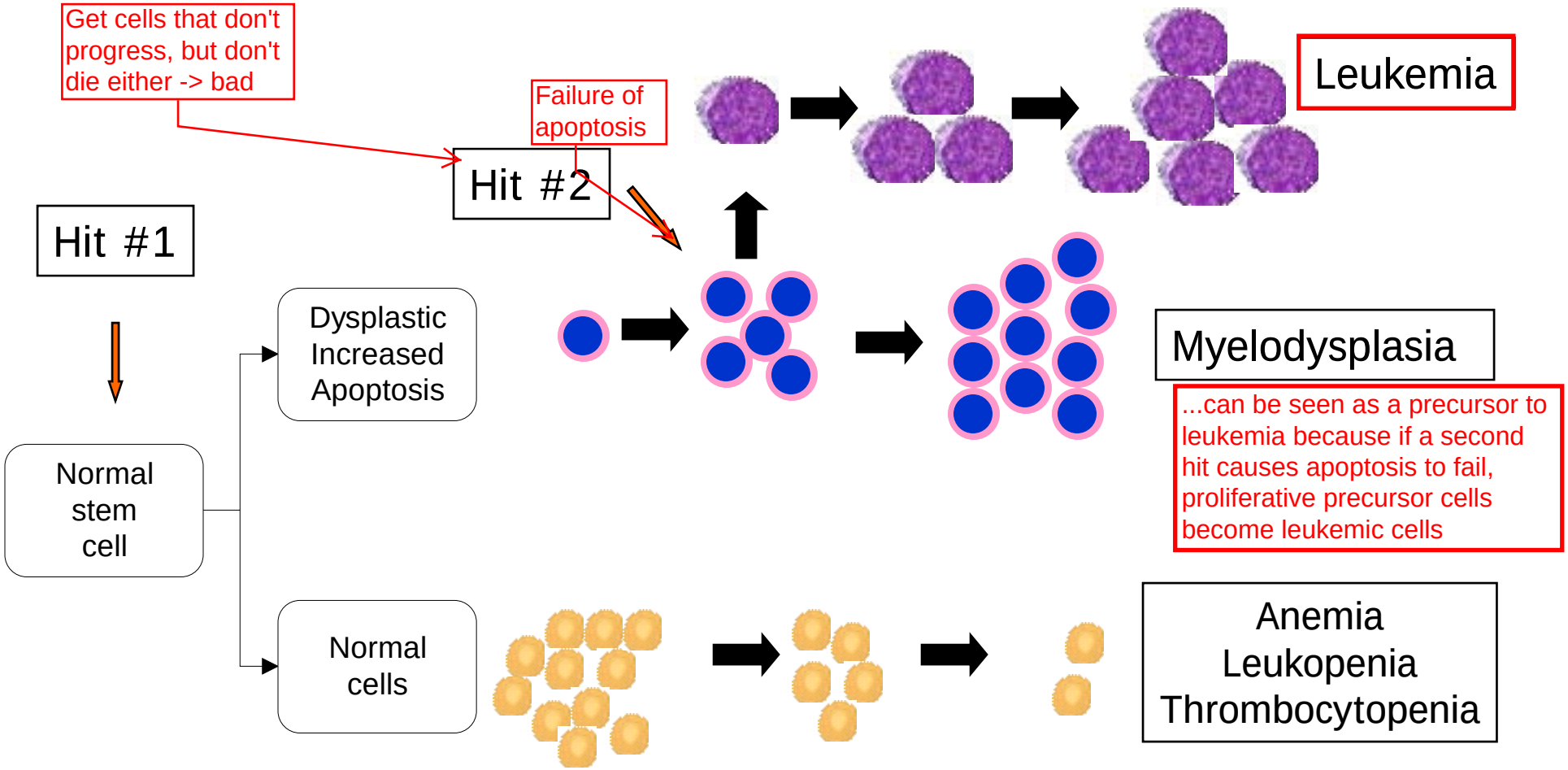
- The developing hematopoietic cell dies before it reaches maturity. High yield!

Myelodysplasia: Pathophysiology
Genetic Defect #1: Apoptosis Defect



Rosenfeld,List. Leukemia 2000 Jan;14(1):2-8

Myelodysplasia: Pathophysiology #2: Apoptosis/Maturation Defect



Rosenfeld,List. Leukemia 2000 Jan;14(1):2-8

Myelodysplasia Diagnosis

- Morphology
- Cytogenetics

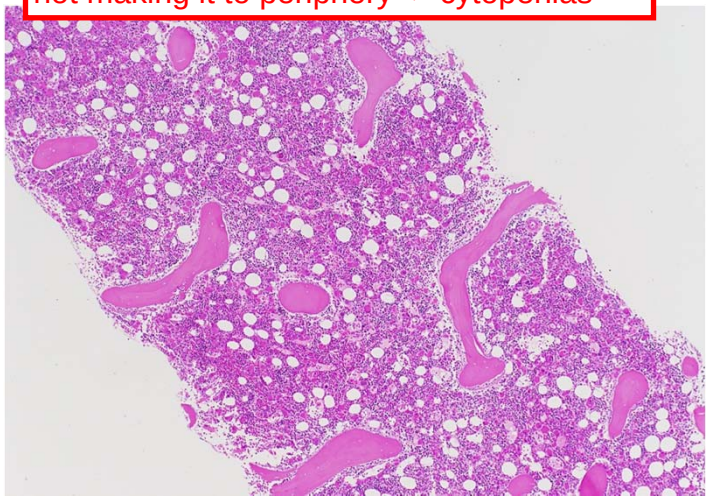
Pathology

Myelodysplasia

Morphology

Myelodysplastic Syndrome

You see too many cells growing in the bone marrow, but they're also dying and not making it to periphery -> cytopenias

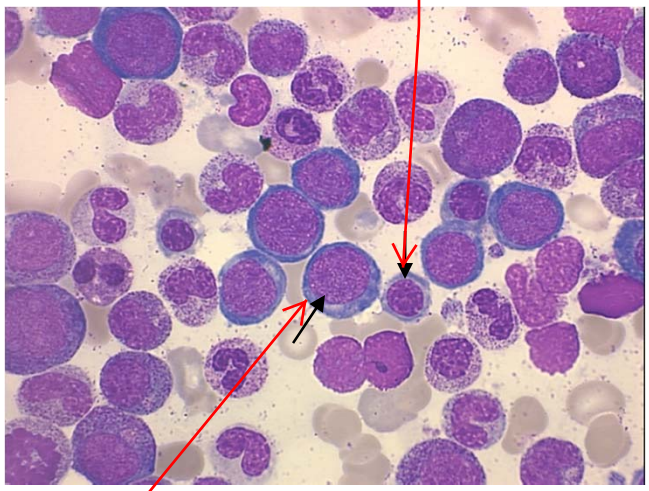


Hypercellular bone marrow with in increased cell turn-over and death (apoptosis) = ineffective hematopoiesis

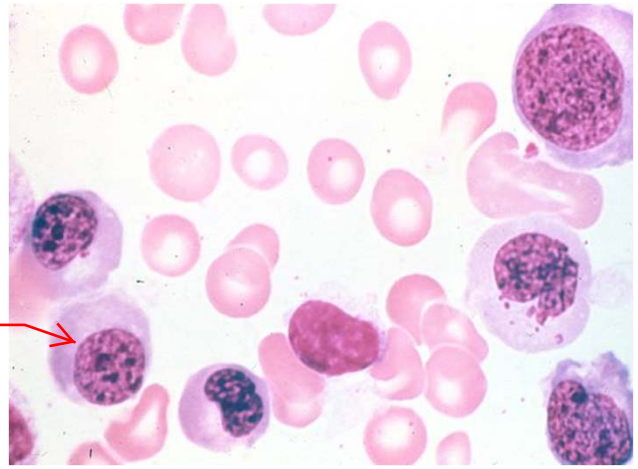
- Anemia
- Thrombocytopenia
- Leukopenia

Dysplastic Erythroid Precursors

relatively mature

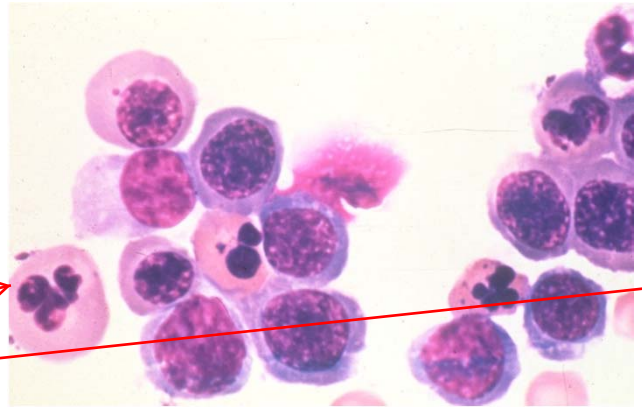


Normal Erythroid Precursors

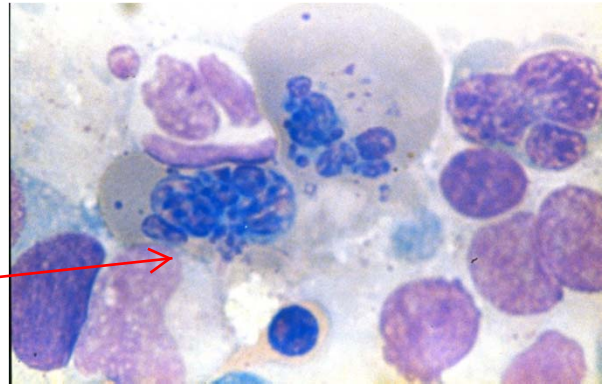


Nucei not as round. Loss of synchrony between maturation of nucleus and cytoplasm (megaloblastic/ megaloblastoid)

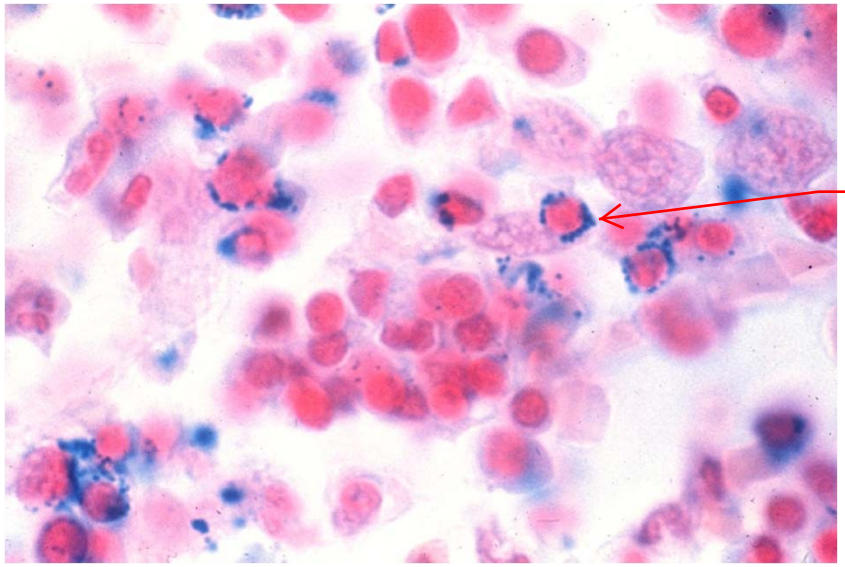
Immature, have nice round nuclei and are all together



mickey mouse ears, falling apart, = karyorrhexis

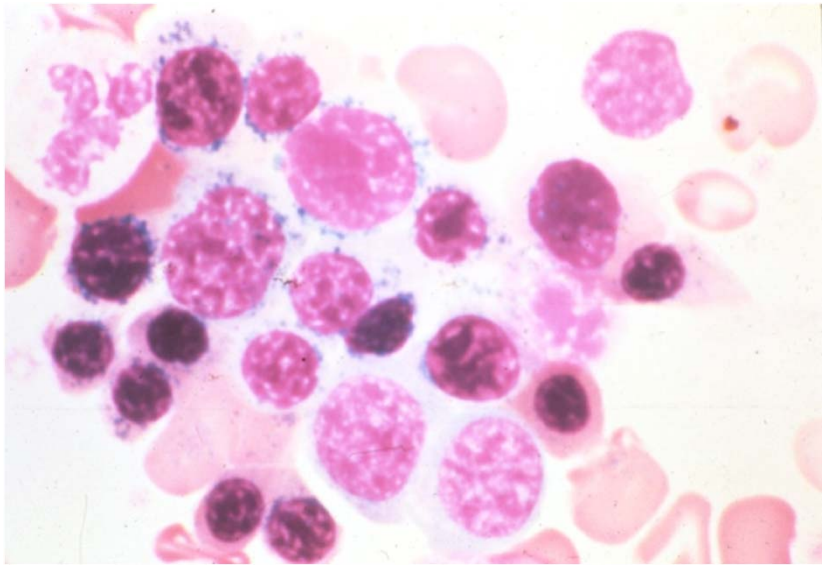


Dysplastic Erythroid Precursors: Ringed Sideroblasts

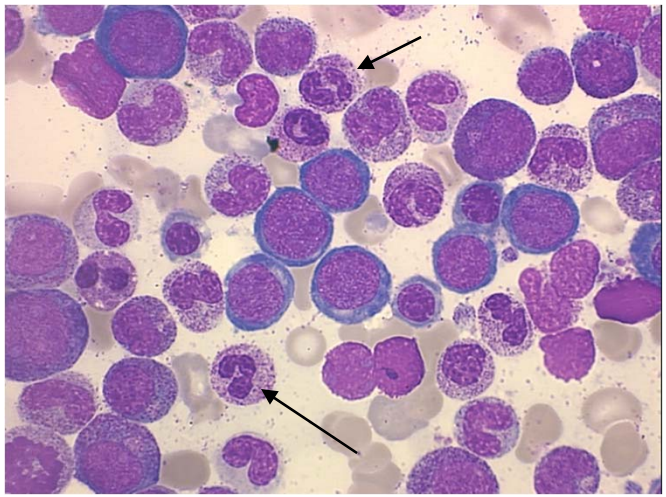


Ringed sideroblasts. Abnormal deposition of iron in mitochondria

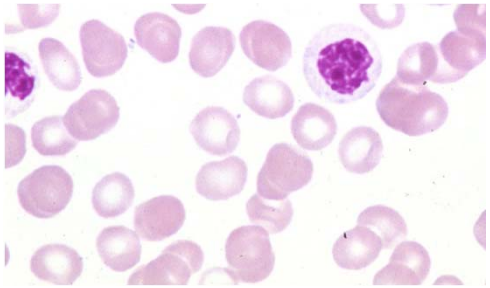
Abnormal deposition of iron in mitochondria



Dysplastic Granulocytes

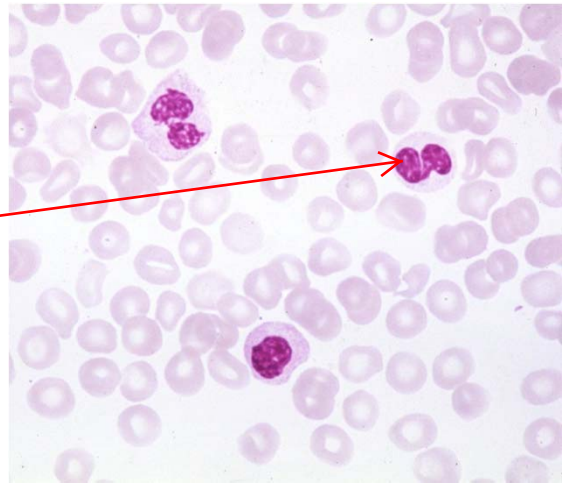


Normal granulocyte precursors
In bone marrow



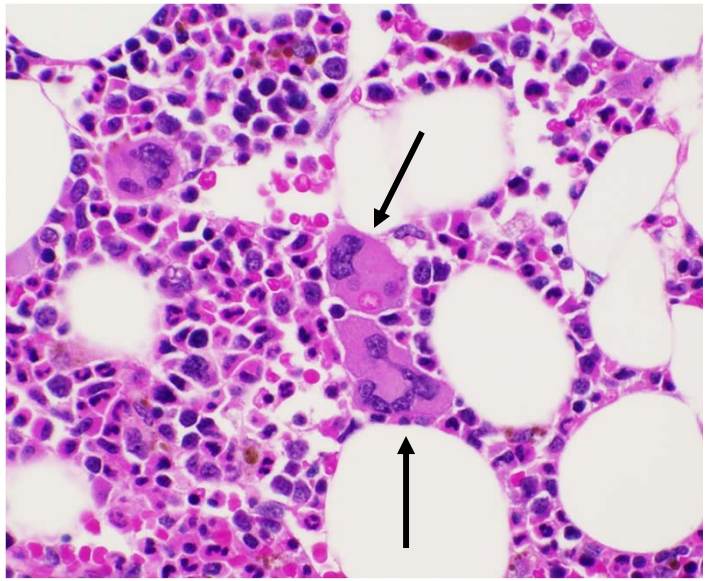
Decreased number of hypogranular, hypolobated granulocytes in blood

Best viewed in periphery



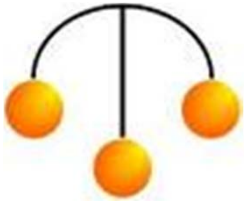
Binucleated look: pseudo pelger-hewitt cells

Dysplastic Megakaryocytes

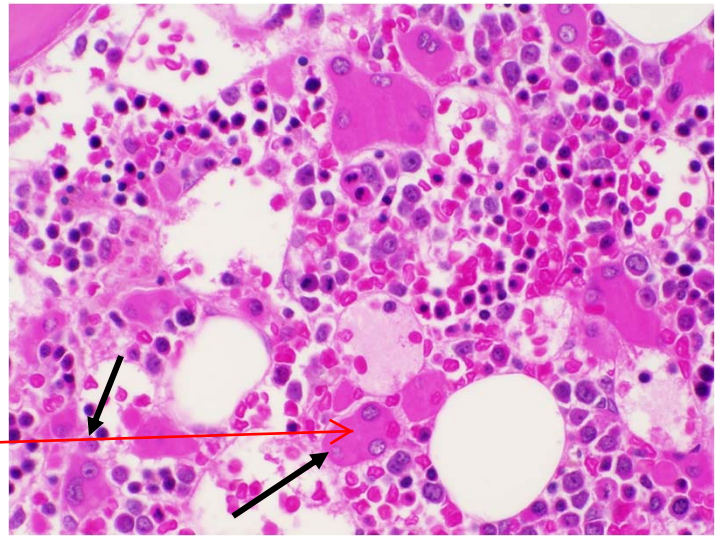


Normal megakaryocytes

Should have connected nuclei



Small, dysplastic “pawn ball-like” megakaryocytes



separated nuclear lobes

Myelodysplasia: Diagnosis Cytogenetic

You can have normal cytogenetics and still have myelodysplasia, or you can have very different abnormalities with myelodysplasia

Karyotype	
Normal	53%
Abnormal	47%
Complex	11%
Single/double	36%
Single abnormalities	
Del (5q)	6%
-7/del (7q)	4%
-7	3%
del(7q)	1%
+8	6%
-Y	2%

Sole, Haematologica 90:1168-1178, 2005

Myelodysplasia Classification

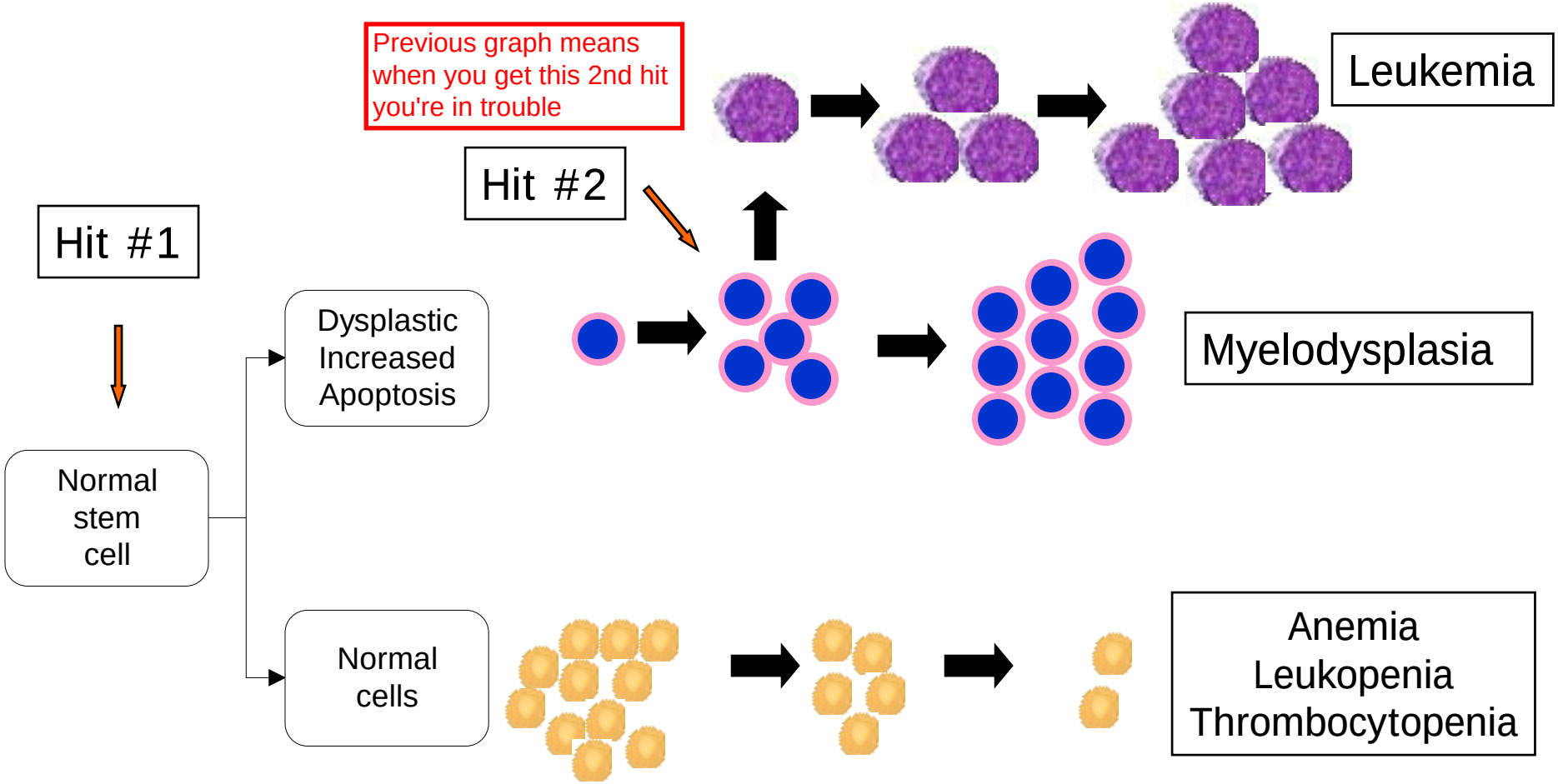
Old scheme that we've since updated to add more features

Disease	*No affected cell lines*	*Cell ularity*	*No lines with dysplasia*	*Percent blasts Blood*	*Percent blasts BM*	*Median Survival Years*
RA with ringed sideroblasts	1	N or I	1	< 1%	<5%	6.9
Refractory anemia (RA)	1	N or I	1	< 1%	<5%	4.2
RA with Excess Blasts (RAEB)	≥ 2	I	3	< 5%	5-20%	1.5
RA in Transformation (RAEB-T)	≥ 2	I	3	> 5%	21-30%	.6

This is the kicker: higher % blasts in bone marrow = worse prognosis

In prognosis: The most important thing is the number of blasts.

Myelodysplasia: Classification
Classification and Pathophysiology



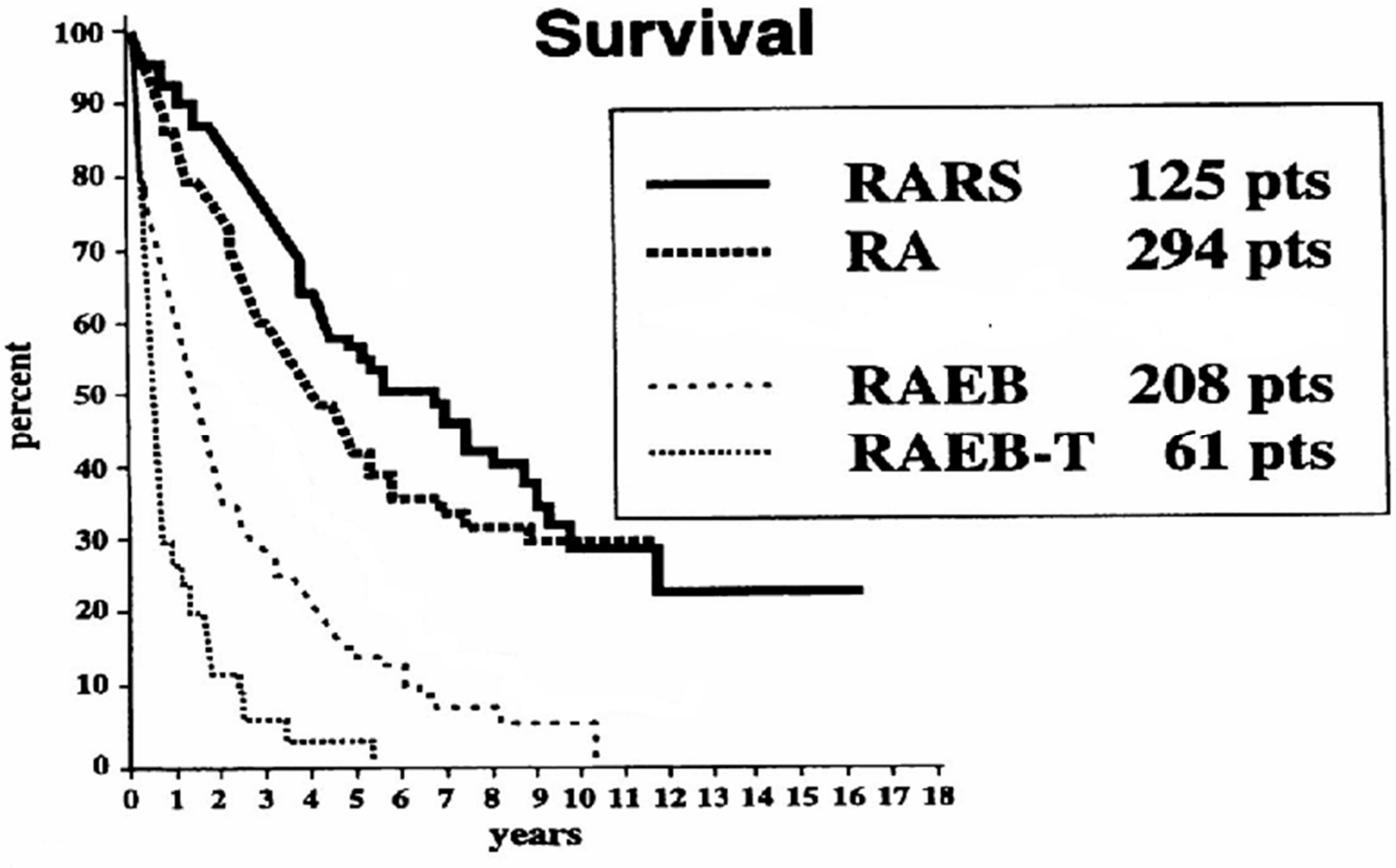
Rosenfeld,List. Leukemia 2000 Jan;14(1):2-8

Classification & Prognosis

- Classification
  - Cell lines affected
  - Blasts in bone marrow
- Prognosis
  - Blasts most important factor!
  - Cytogenetics
  - Cytopenias

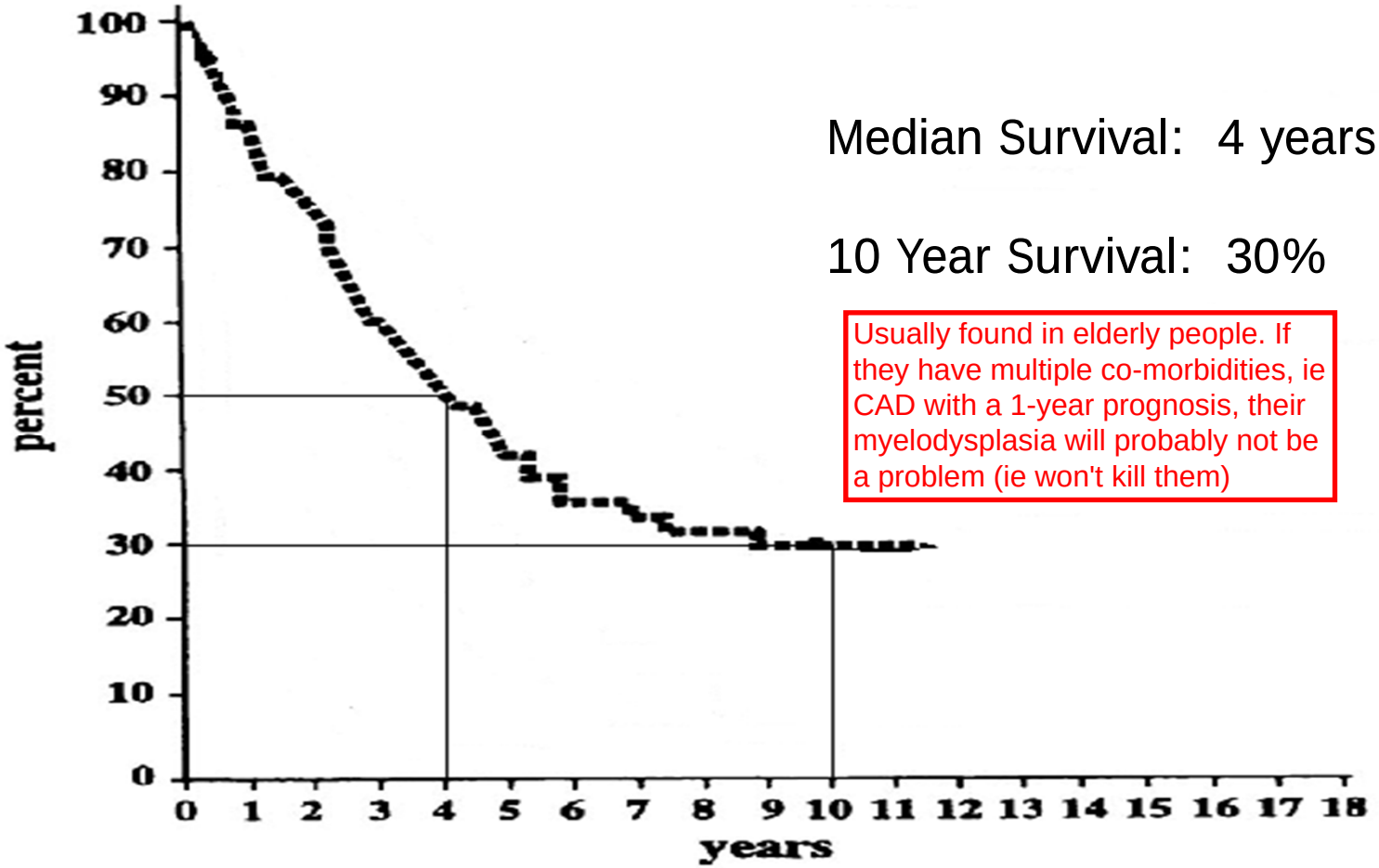
Myelodysplasia:Prognosis
Overall Surivival

All go relentlessly downhill



Blood, Vol. 89 No. 6 (March 15), 1997: pp. 2079-2088

Myelodysplasia:Prognosis Overall Surivival RARS



Median Survival: 4 years

10 Year Survival: 30%

Usually found in elderly people. If they have multiple co-morbidities, ie CAD with a 1-year prognosis, their myelodysplasia will probably not be a problem (ie won't kill them)

Blood, Vol. 89 No. 6 (March 15), 1997: pp. 2079-2088

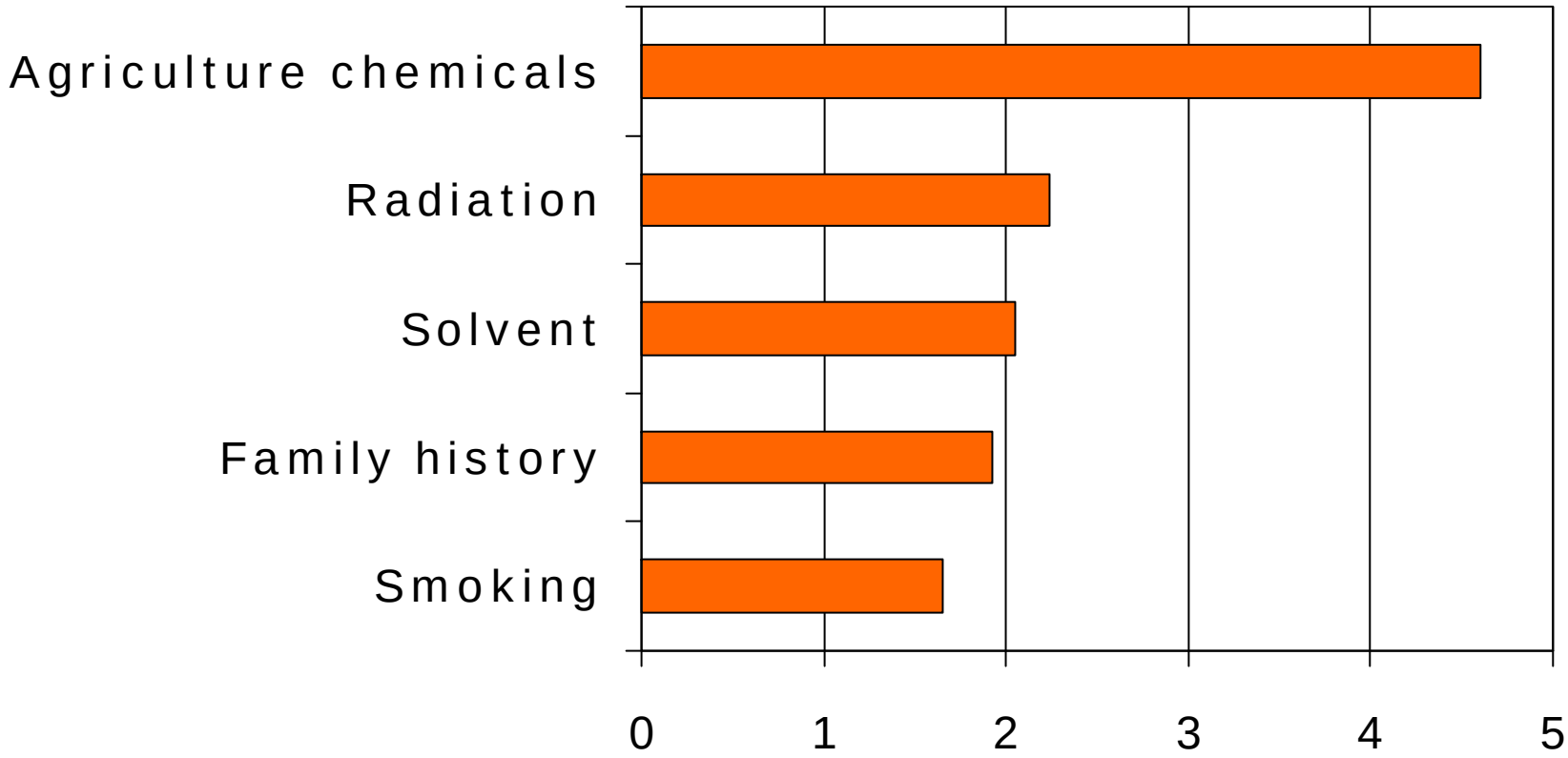
Myelodysplasia: Statistics Incidence

- 1/10,000 people per year
- 7% patients treated with alkylator chemotherapy
  - incidence peaks at 7 years
- Increasing

Probably more, but we can't pick them all up

1% of the 100,000 cases of breast cancer treated with alkylator chemo will get myelodysplasia

Myelodysplasia: Statistics
Epidemology: Environmental



Strom, Leukemia 19:1912, 2005

Myelodysplasia: Statistics
Epidemology: Chemotherapy

- Alkylator therapy
- Topoisomerease inhibitors

Myelodysplasia Clinical Features

Characteristic	***Value***
Age	69+/- 10
Sex (M/F)	1/1
Disease duration (mo)	9.3 +/- 9.8
Hb (g/dL)	8.64 +/- 11.7
ANC x 10(9)/L	2.2 +/-1.8
Platelet count x 10(9)/L	213 +/- 168

Usually low Hg (fatigue) brings them in

Often normal when they're diagnosed

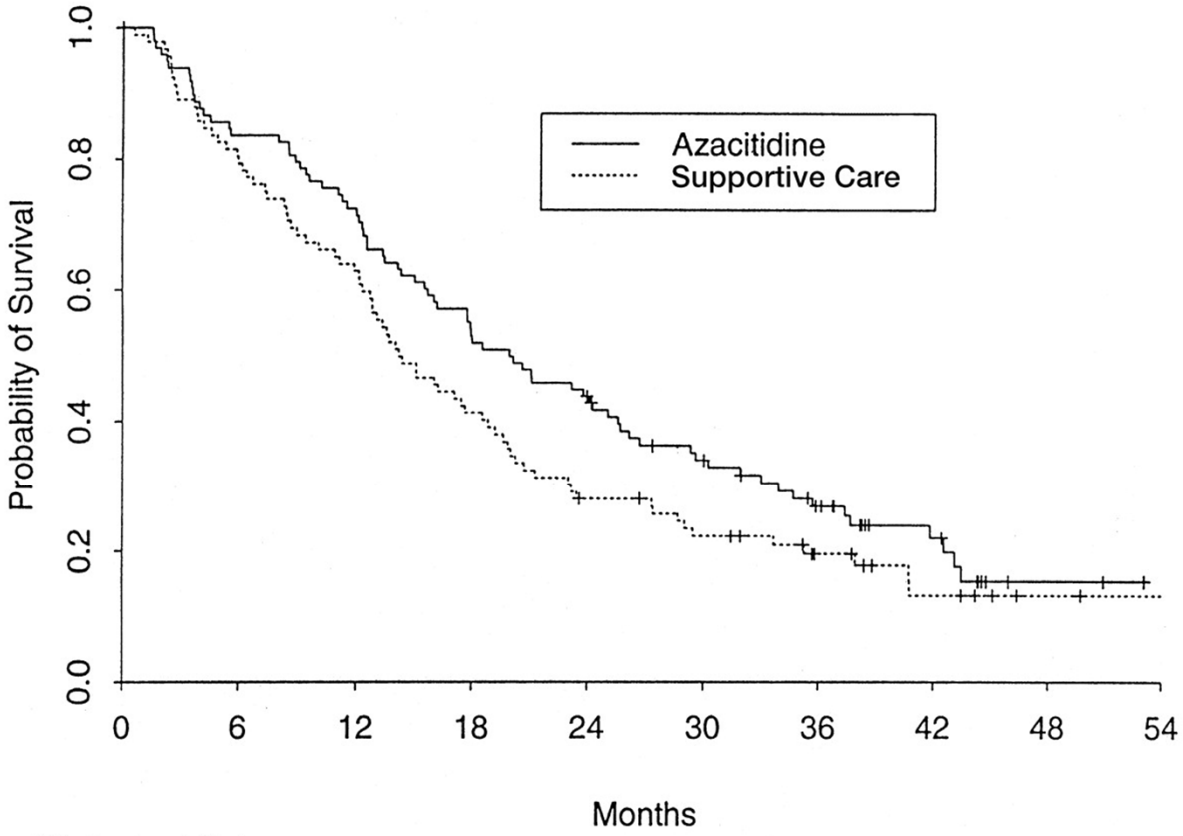
Absolute neutrophil count

Hellstrom-Lindberg, Blood 92 (July) 1998:68-75.

Myelodysplasia: Treatment

- Supportive care
  - Growth factors
- Transfusions
  - Red blood cells
  - platelets
- Infection treatment
- Drug therapy

Myelodysplasia: Treatment
Azacitadine: Overall Survival

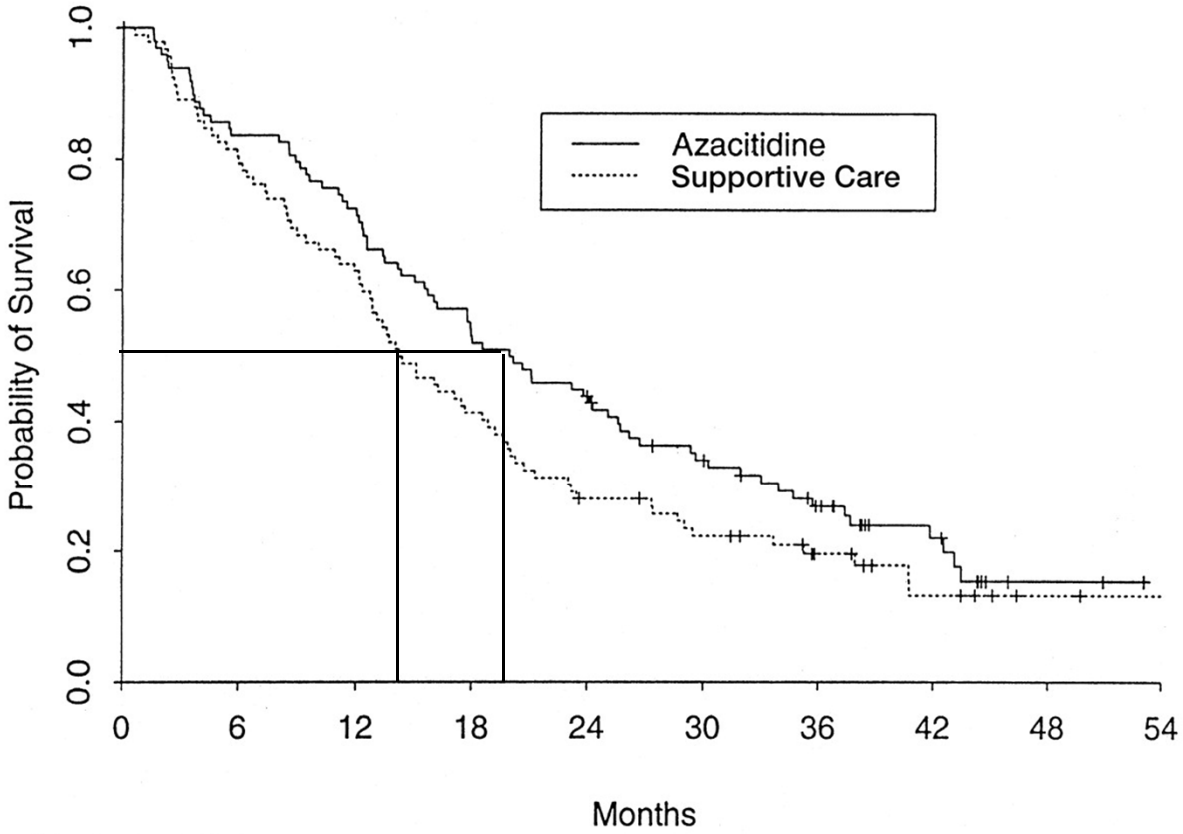


Number of Patients at Risk

Azacitidine	99	82	71	52	42	30	21	11	2	0
Observation	92	73	58	38	25	19	12	6	2	1

Silverman (CALGB) J Clin Oncol 20:2429-2440, 2002

Myelodysplasia: Treatment
Azacitadine: Overall Survival



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Silverman (CALGB) J Clin Oncol 20:2429-2440, 2002

MDS Treated with Azacitidine

Quality of Life

Decreased need for transfusions and increased QOL, despite only extending life by a few months

	#	*Fatigue*	*Dyspnea*	*Social Function*	*Overall QOL*
Azacitidine	99	42.8	36.7	60.8	53.6
Observation	92	47.4	43.0	43.1	38.3

Difference between staying in bed all day and being able to do everyday activities

Silverman (CALGB) Proceedings ASCO, 1998, Abstract #53
Silverman (CALGB) J Clin Oncol 20:2429-2440, 2002

Myelodysplasia: Treatment Lenalidomide (Revlimid)

- 43 patients
- Anemia
  - Transfusion dependent
  - Symptomatic
- Erythropoietin resistant or not eligible
- Lenalidomide dosing
  - 25 mg daily PO
  - 10 mg daily PO
  - 10 mg daily for 21/28 days PO
- Response
  - 24 (56%) responded
    - 20 independence from transfusion
    - 1 Hb increase of 2 g
    - 3 had 50% decrease in transfusion
  - Interstitial deletion involving chromosome 5q31.1
    - 83% response
- Adverse events
  - Neutropenia 65%
  - Thrombocytopenia 74%

List, N Engl J Med 352:549-557, 2005

Myelodysplasia: Treatment
Lenalidomide (Revlimid)

Table 3. Erythroid Responses.

Lenalidomide Dose	No. of Patients	Erythroid Response			Weeks to Response	
		Major	Minor	Total	Median ±SD	Range
		number (percent)				
25 mg/day	13	6	0	6 (46)	9.0±5.8	2.5–18.5
10 mg/day	13	6	1	7 (54)	10.5±6.4	2–17.5
10 mg/day for 21 days	17	9	2	11 (65)	11.5±10.3	6–24
Total	43	21 (49)	3 (7)	24 (56)	—	—

List, N Engl J Med 352:549-557, 2005

Myelodysplasia: Treatment Lenalidomide (Revlimid)

Myelodysplastic cells went away in 83% of patients who had this cytogenetic abnormality, though some had later recurrence

Cytogenetic Responses According to Chromosomal Abnormality.

Chromosomal Abnormality	No. of Patients	≥50% Decrease in Abnormal Cells in Metaphase	Complete Cytogenetic Response
		number of patients (percent)	
Del(5)(q31.1)	12	10 (83)	9 (75)
Isolated	11	9	8
With trisomy 21	1	1	1
Del(20)(q11.2)	2	0	0
t(1;22)(q21p11.2)	1	1	1
Other*	5	0	0
Total	20	11 (55)	10 (50)

List, N Engl J Med 352:549-557, 2005

Myelodysplasia: Treatment Lenalidomide (Revlimid)

Table 5. Cytogenetic Responses According to Chromosomal Abnormality.

Chromosomal Abnormality	No. of Patients	≥50% Decrease in Abnormal Cells in Metaphase	Complete Cytogenetic Response
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Other*	5	0	0
Total	20	11 (55)	10 (50)

List, N Engl J Med 352:549-557, 2005

Myelodysplasia: Treatment

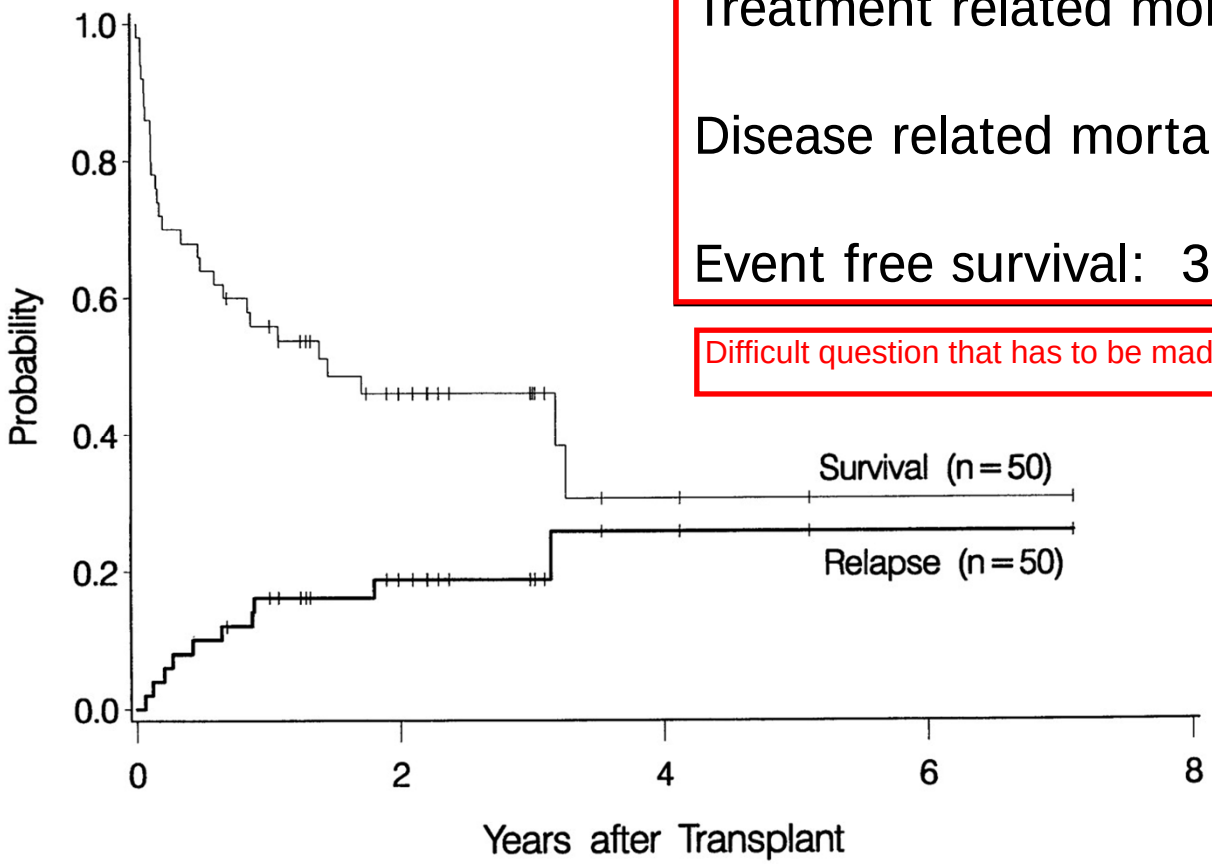
Stem Cell Transplant

Treatment related mortality: 33%

Disease related mortality: 33%

Event free survival: 33%

Difficult question that has to be made quickly



Blood, Vol. 95 No. 4 (February 15), 2000: pp. 1188-1194

Myelodysplasia Summary

- Developing hematopoietic cells die early
- No mature cells Causes the Sx
- Slowly the normal cells go away
- Tendency toward leukemia Biggest prognostic factor
- Survival
  - Long if early and favorable
  - Short if late and unfavorable

Disease 2

Acute Myeloid Leukemia

Case 2 Read it

- 64 year old man, previous healthy, referred for pancytopenia. He notes some fatigue, progressive dyspnea and easy bruising on the trunk as well as the back and legs.
- PMH: non contributory
- PE: normal except for multiple ecchymosis
- LAB:
  - WBC 2,300
    - Neut 32%
    - Lymph 45%
    - Mono 15%
    - Atypical lymphs 8%
  - Hct 25%
  - Platelet 45,000

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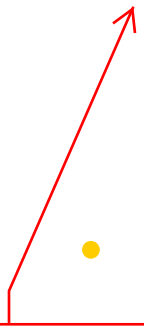
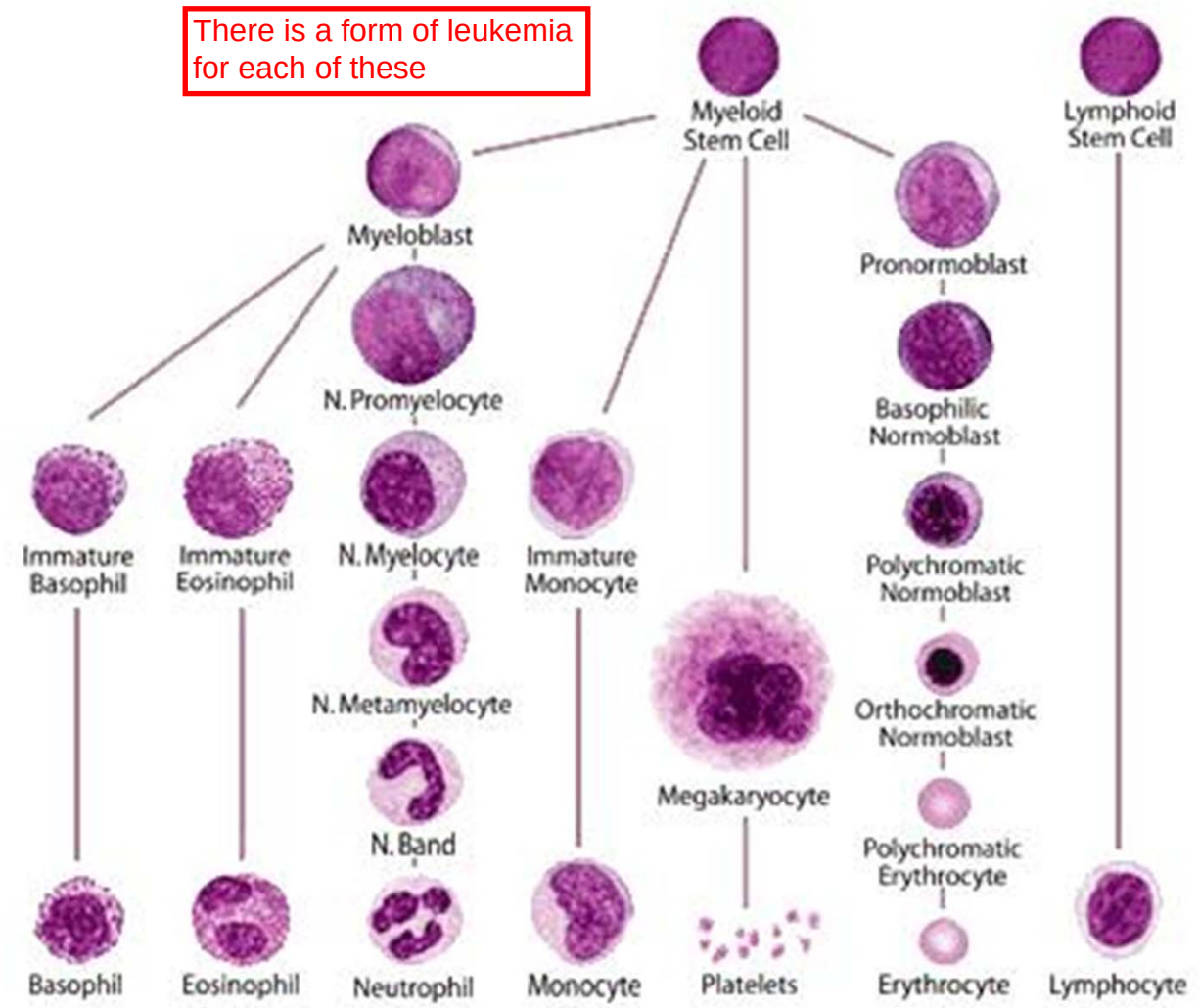


Abnormal. Most don't people knock their chest against things like with their shins or arms

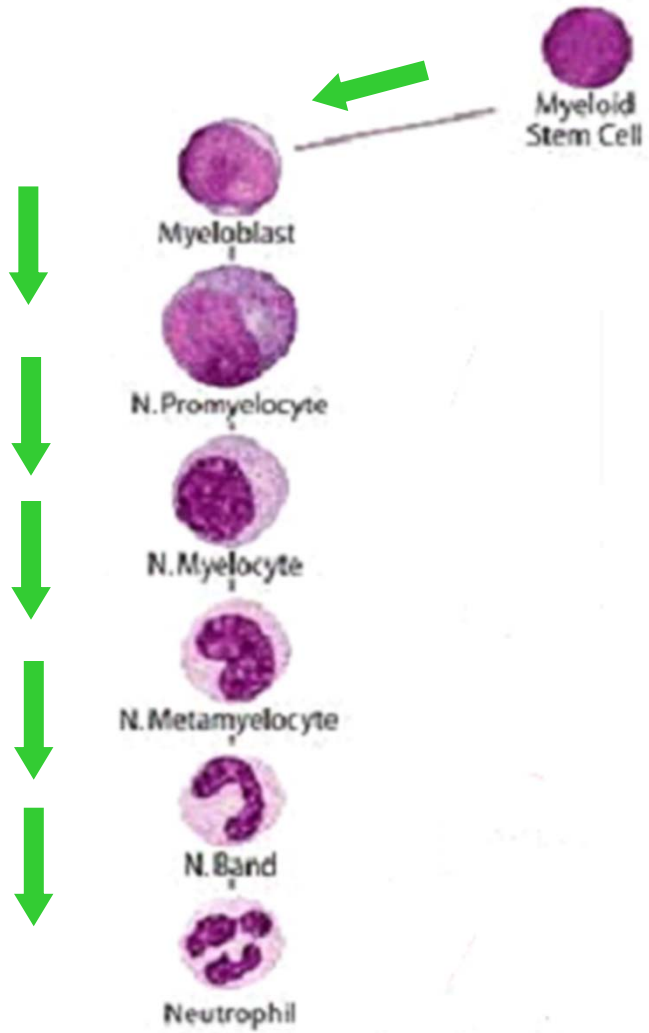
Myeloid Cell Development

There is a form of leukemia for each of these



http://focosi.altervista.org/blood-cell-development.jpg

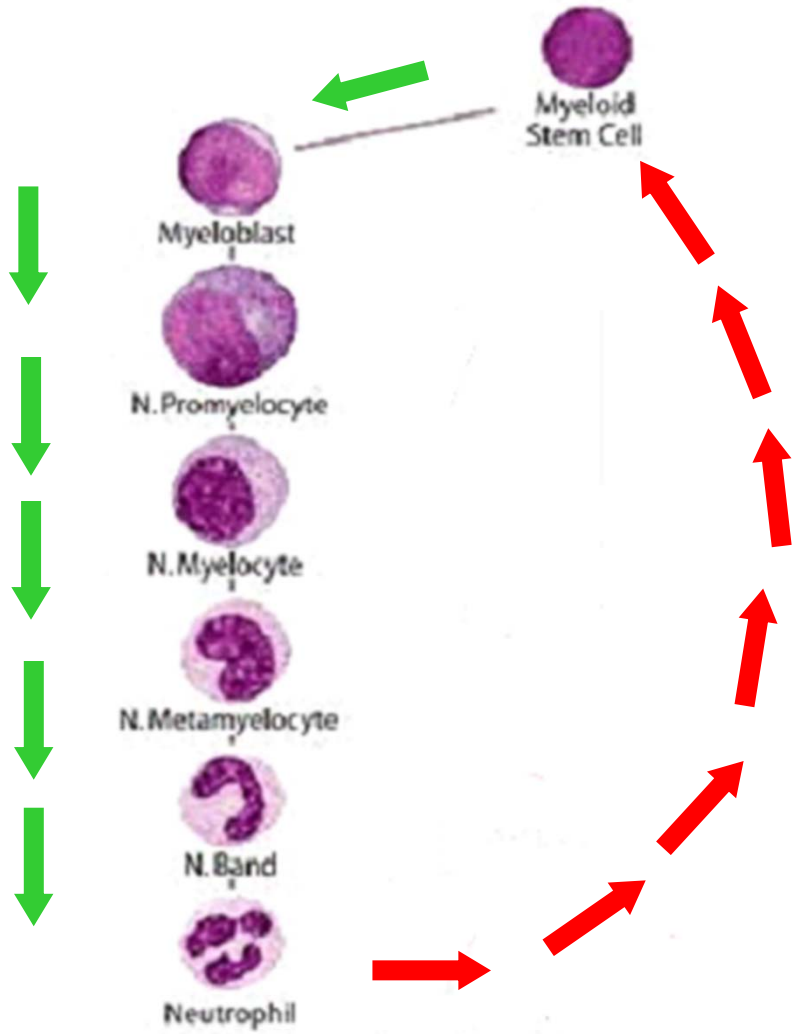
Acute Myeloid Leukemia: Pathophysiology Proceed Through Development Cycle



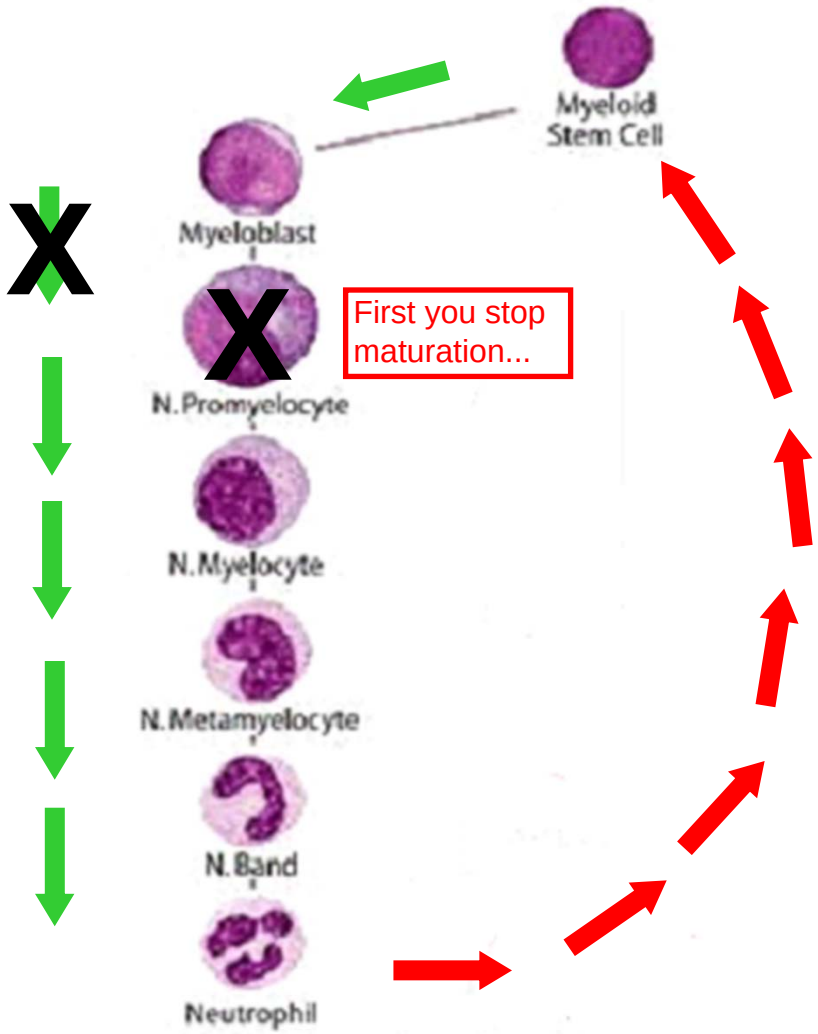
Acute Myeloid Leukemia: Pathophysiology

Feedback Control

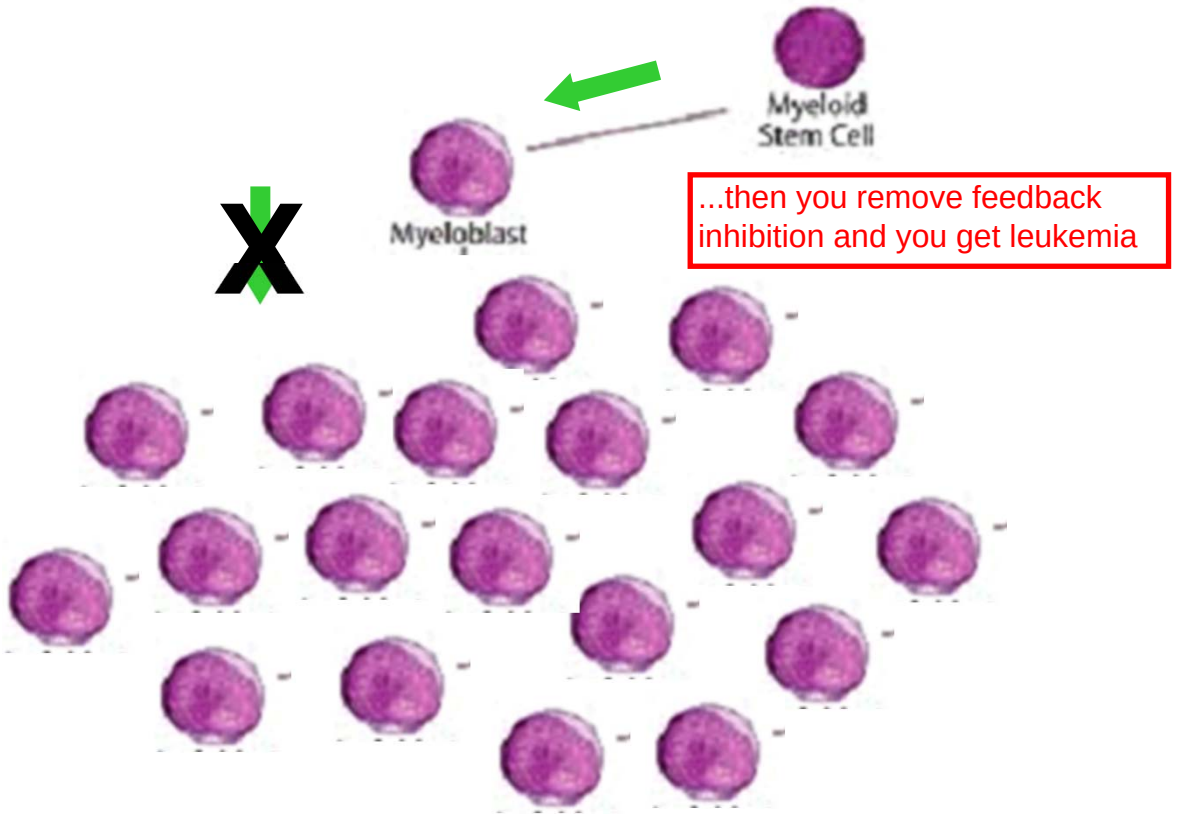
Ye olde negative feedback loop



Acute Myeloid Leukemia: Pathophysiology Proceed Through Development Cycle Broken



Acute Myeloid Leukemia: Pathophysiology Proceed Through Development Cycle Defective



Definition - Explanatory

- Overproduction of an immature cell that does not develop into a normal mature cell

Acute Myelogenous Leukemia: Diagnosis Diagnosis

- Morphology
- Immunophenotype
- Cytogenetics

Pathology

Acute Myeloid Leukemia (AML)

Classification and Morphology

AML

- The World Health Organization (WHO) classifies AML according to the presence of certain recurrent genetic abnormalities and whether they arose in the setting of MDS or after chemotherapy
  - myelodysplasia
  - Like alkylating chemo before
- All other AML is classified by morphology and stage of differentiation based on the French-American-British (FAB) system

SKIP

AML Without Maturation

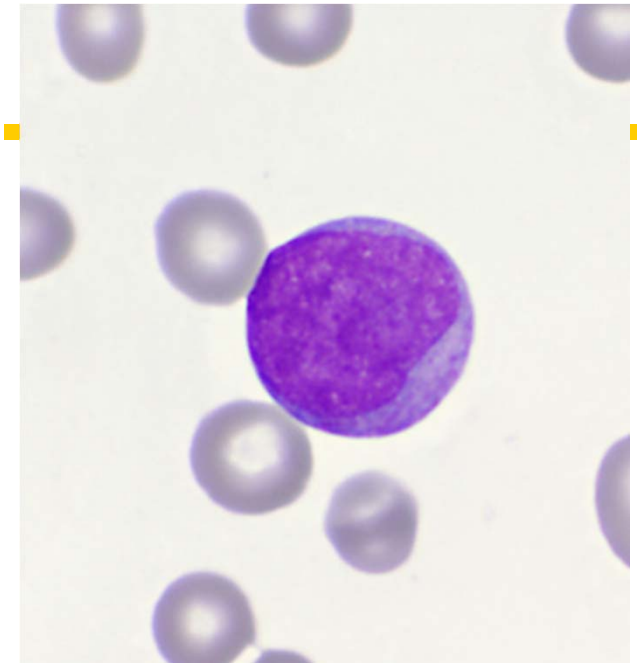
(for comparison with other subtypes)

(FAB AML M1)

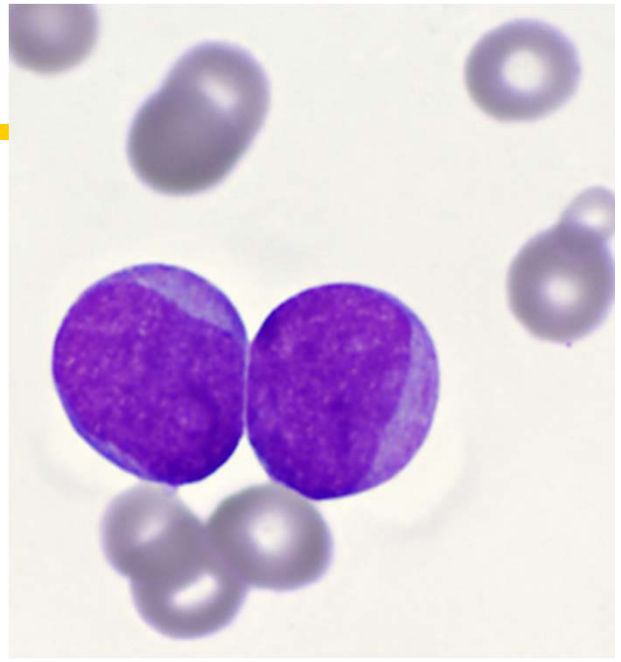
SKIP

M1 Bone Marrow Biopsy: Increased Blasts

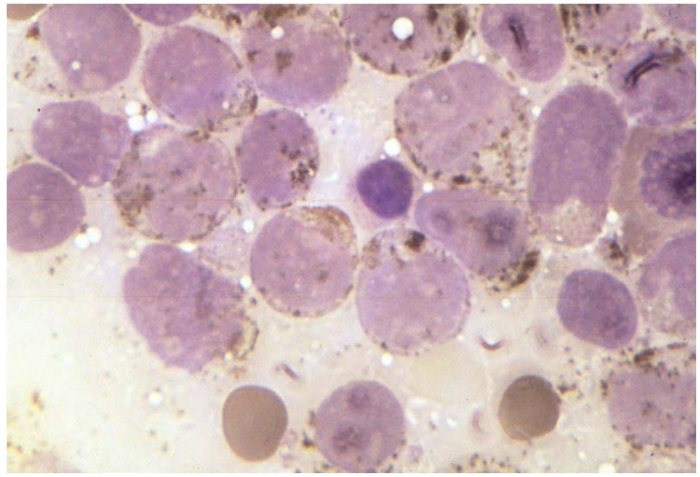
SKIP



M1 Blood (Blasts)

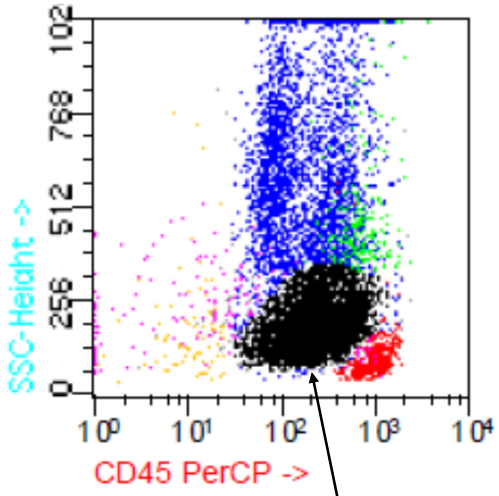


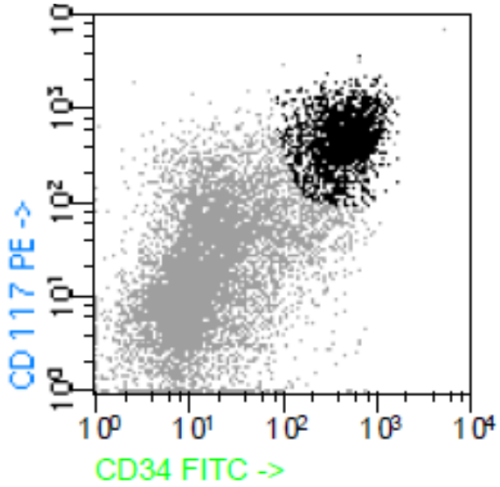
M1 Myeloperoxidase Stain

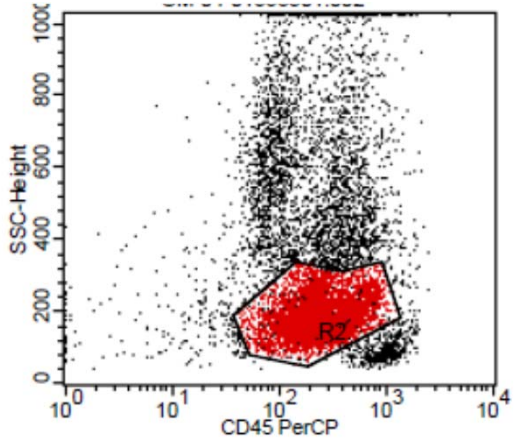


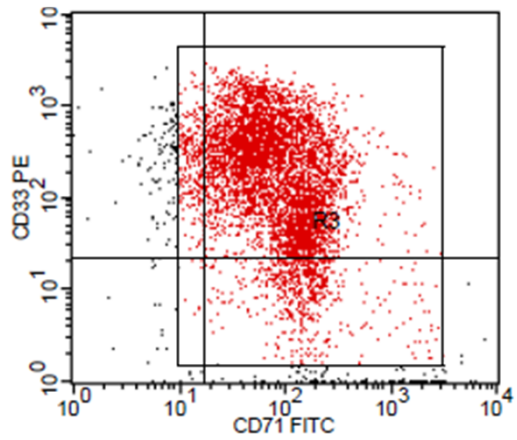
SKIP

AML M1: Flow Cytometry









SKIP

AML with Recurrent Genetic Abnormalities

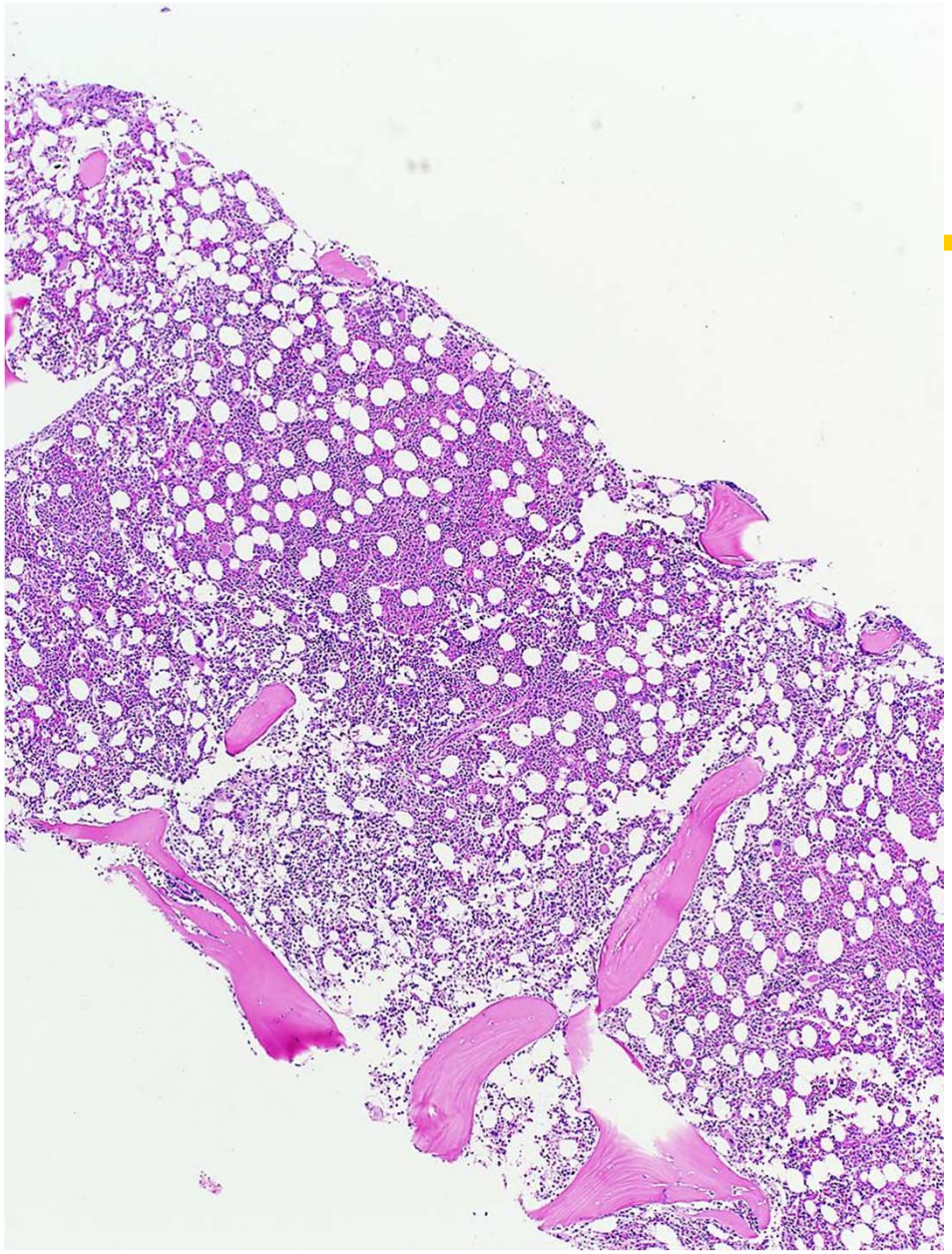
AML with t(8;21)(q22;q22)

(Core binding factor alpha/ETO)

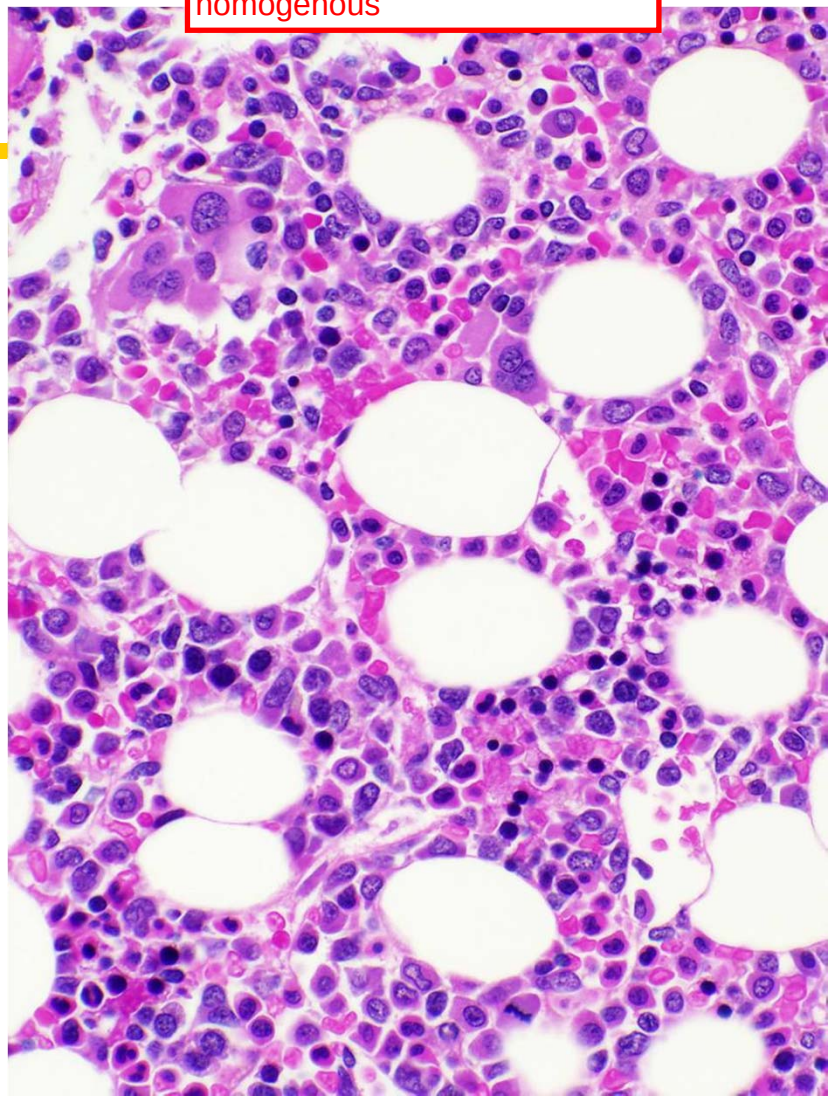
10% of “AML with Maturation”

(FAB AML M2)

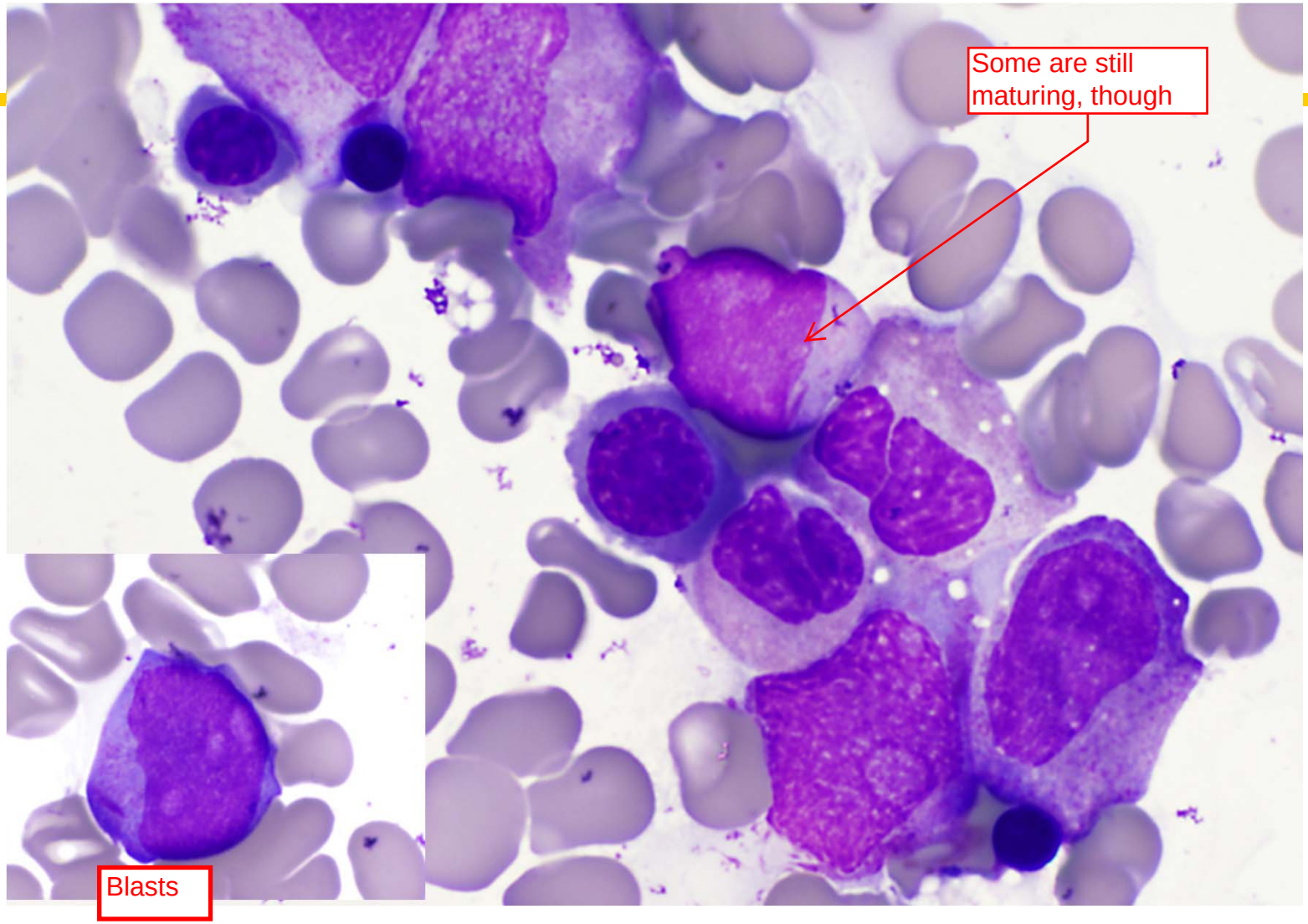
Looks like blasts with a little maturation



Still some variation, unlike some leukemias which can look homogenous



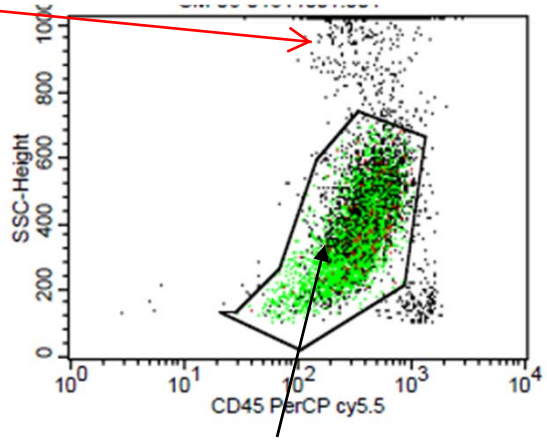
M2: Bone Marrow Biopsy

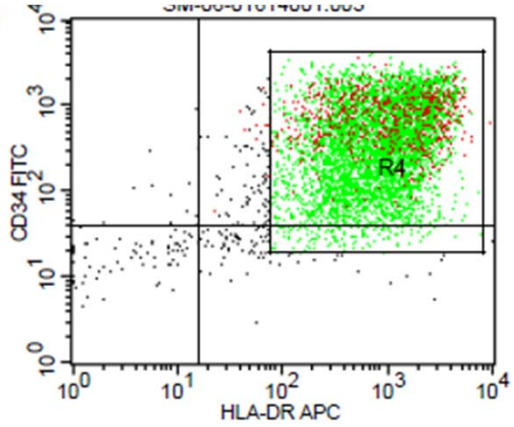


M2 Bone Marrow Aspirate

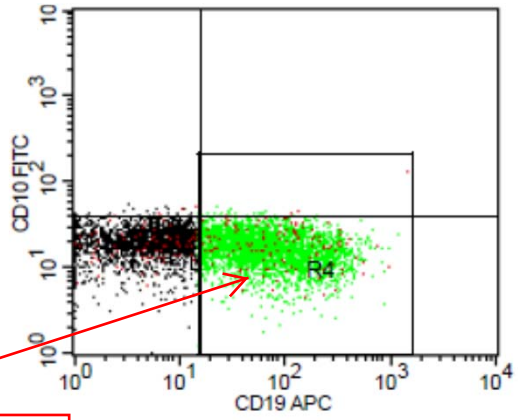
AML M2: Flow Cytometry

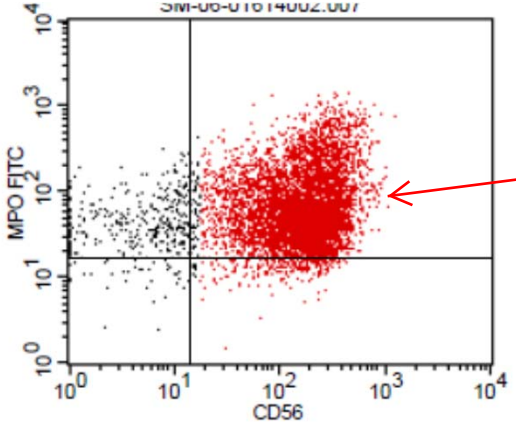
Mature granulocytes





Blasts and more mature granulocytes appear to “merge”





CD56, should be on NKs, not myeloid cells

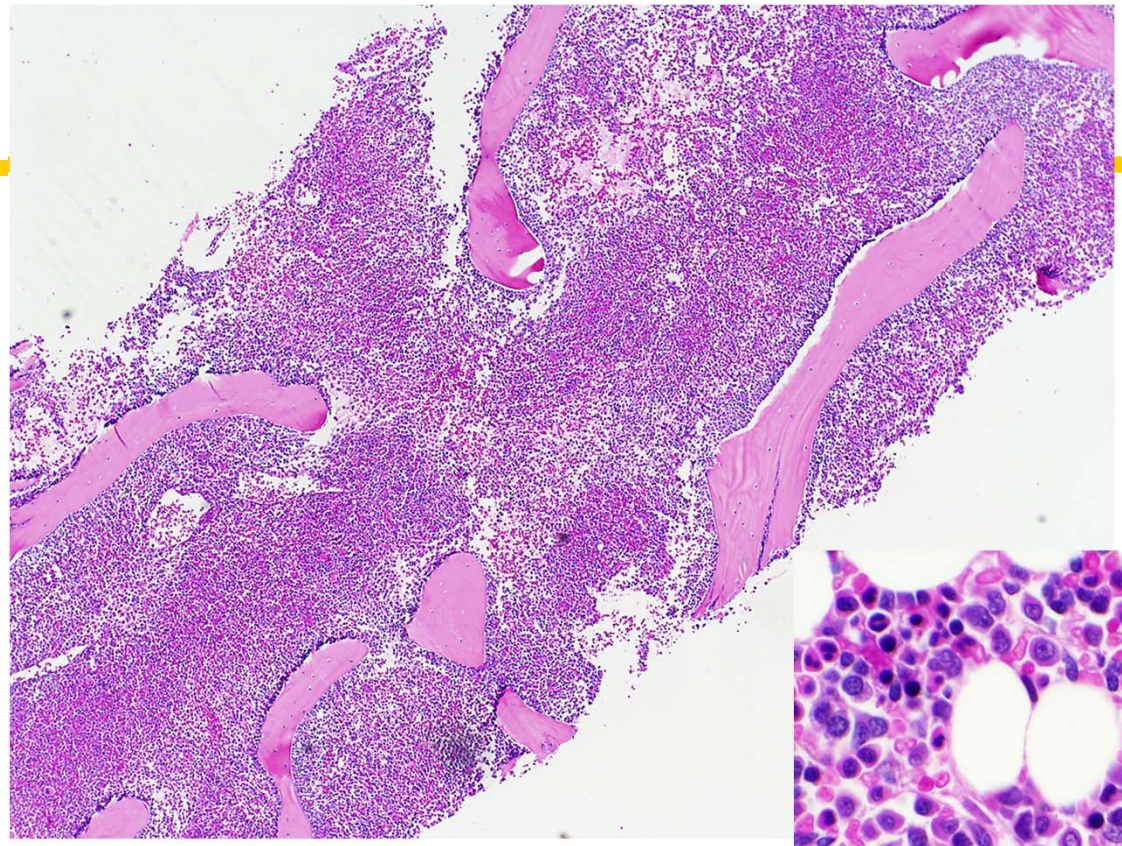
CD19 (B-cell Ag that should not be expressed) indicates leukemia

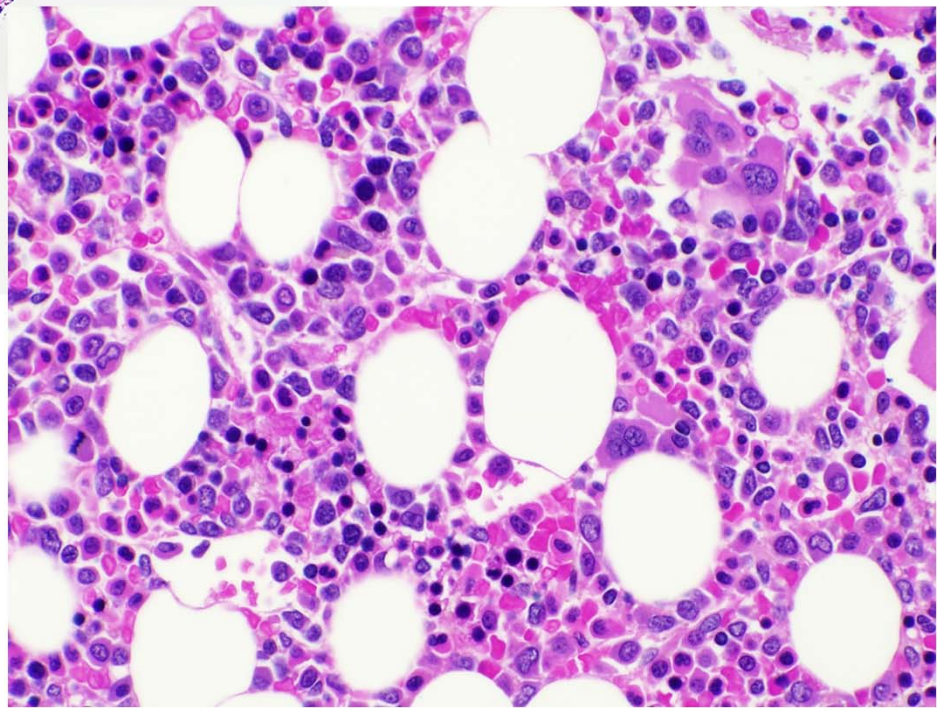
CD19+/CD56+ phenotype suggests t(8;21)

AML with inv(16)(p13.q22)
or t(16;16)(p13.1;q22)
(Core binding factor beta/MYH11)

Acute Myelomonocytic Leukemia
with Eosinophils
(FAB AML $M4_{eos}$)

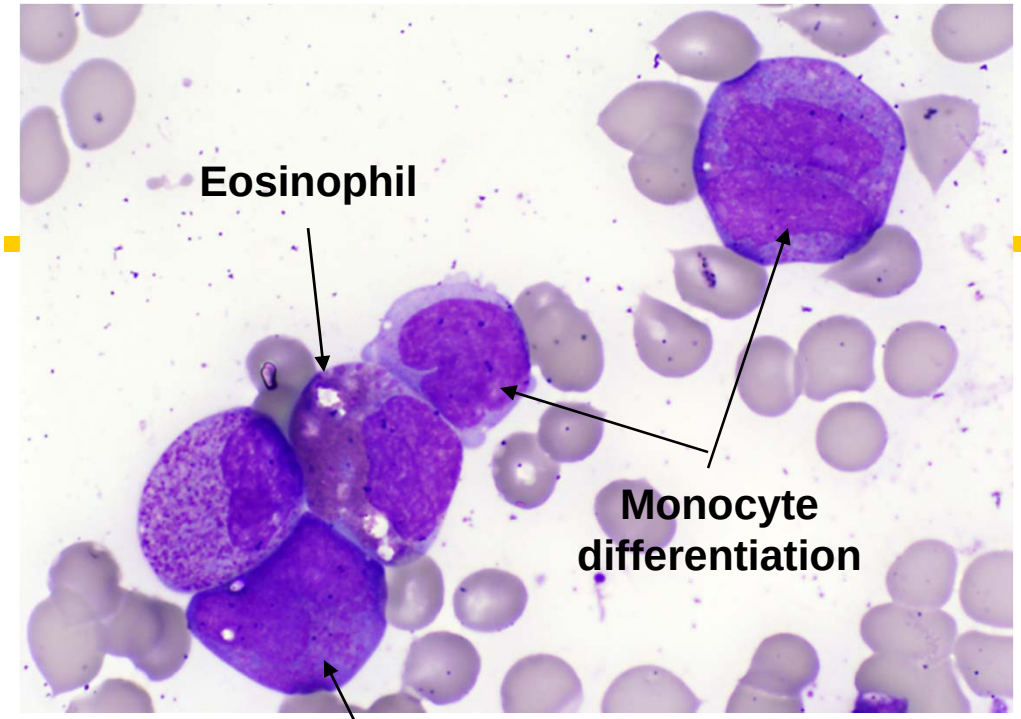
Looks like precursors of monocytes. Very specific subset of AML, but with one of the better prognoses



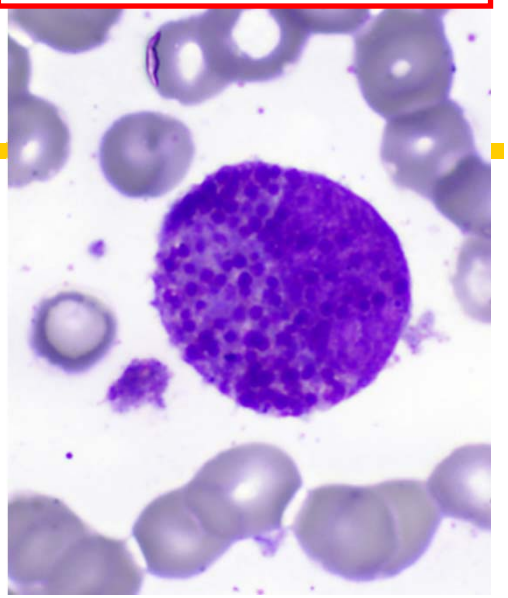


M4 $_{eos}$

Bone Marrow Biopsy

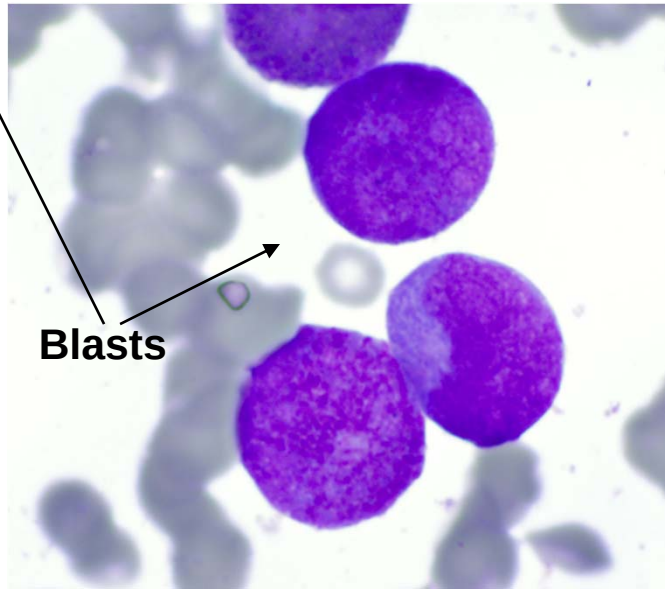


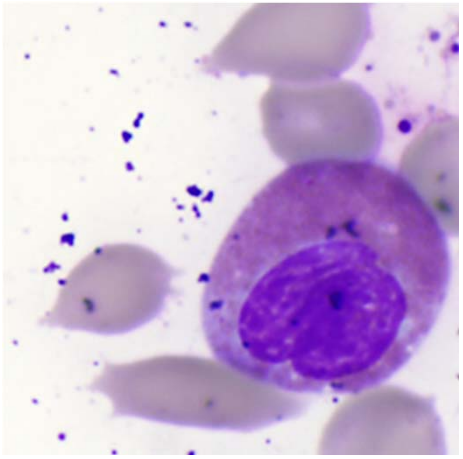
This appearance would indicate inv(16), but "cytogenetics trumps everything"



Abnormal granules

$M4_{eos}$: Bone marrow aspirate

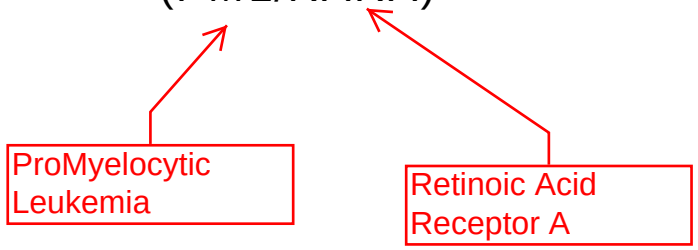




Eosinophil

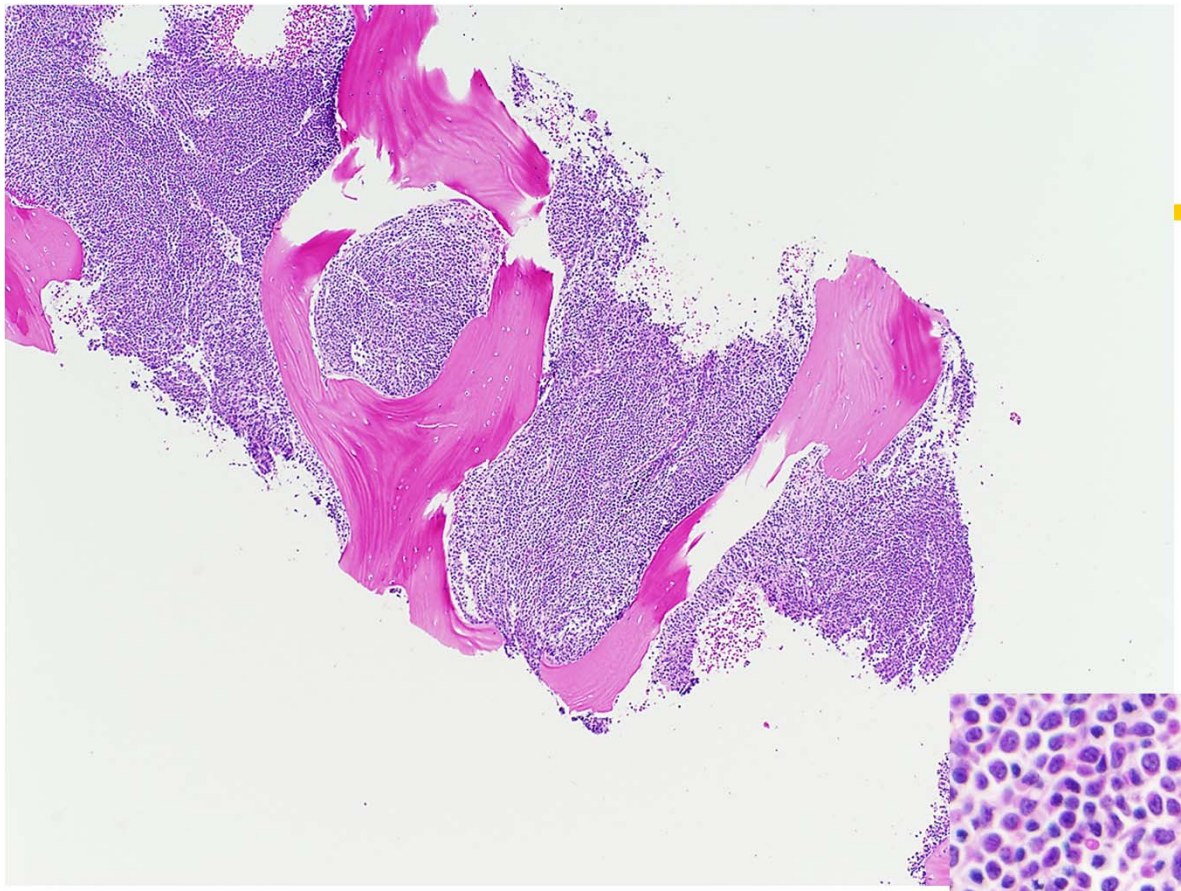
AML with t(15;17)(q22;q12)

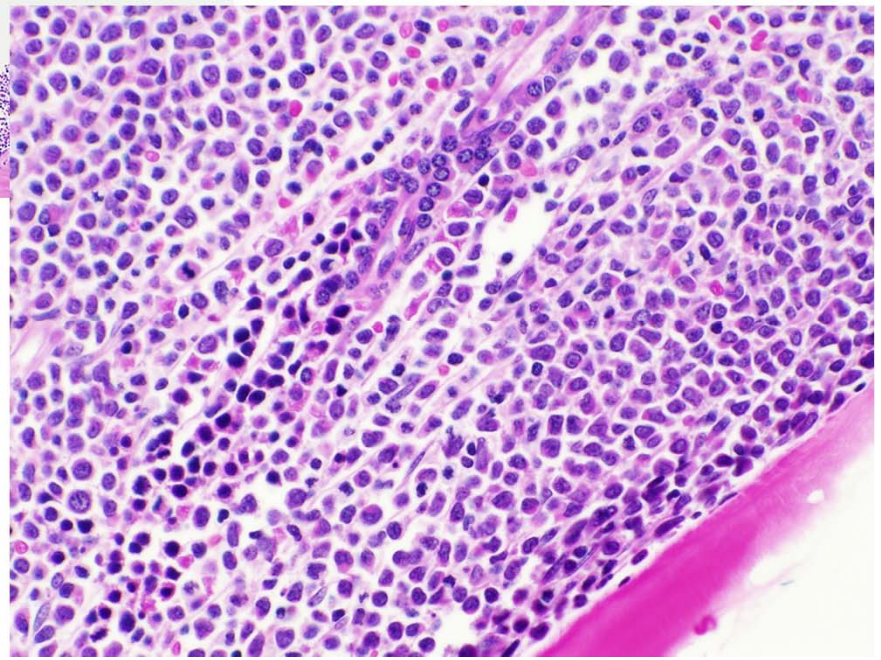
(PML/RARA)



Acute Promyelocytic Leukemia

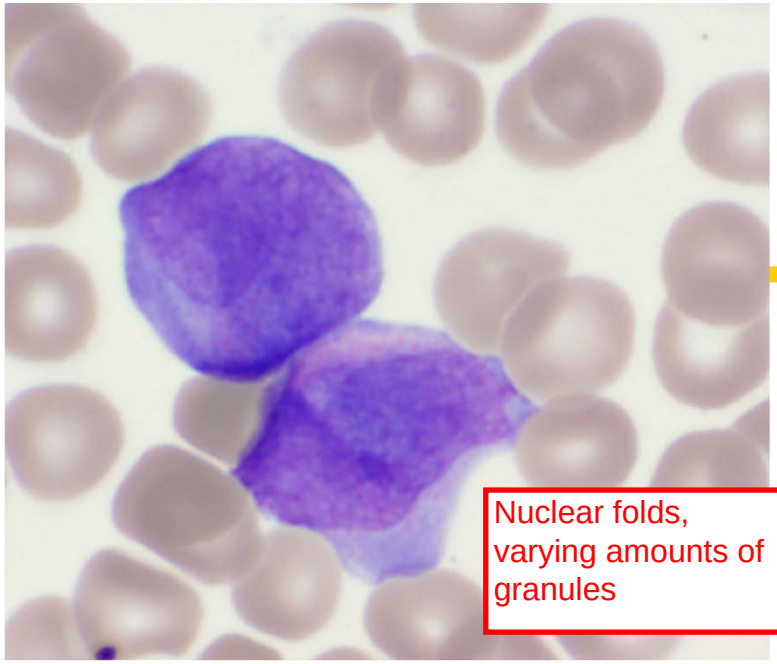
(FAB AML M3)



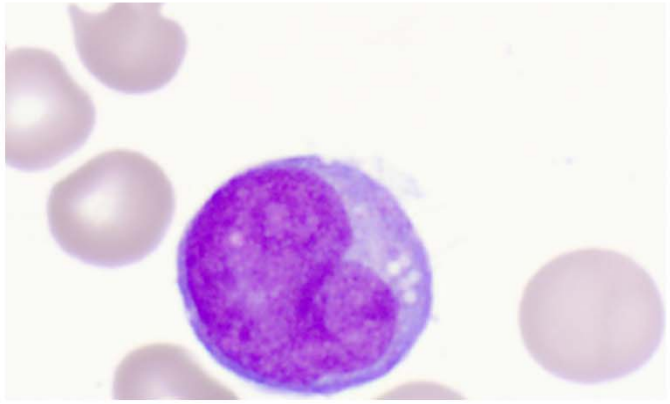


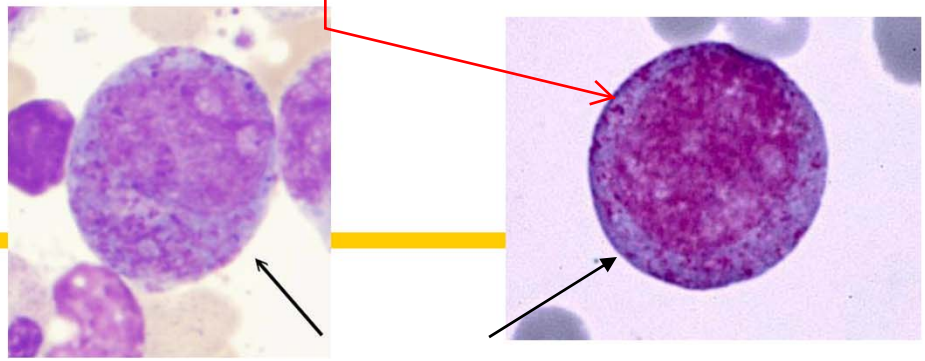
APL: Bone Marrow Biopsy (All Promyelocytes)

1st step beyond blasts. the cells have acquired granules

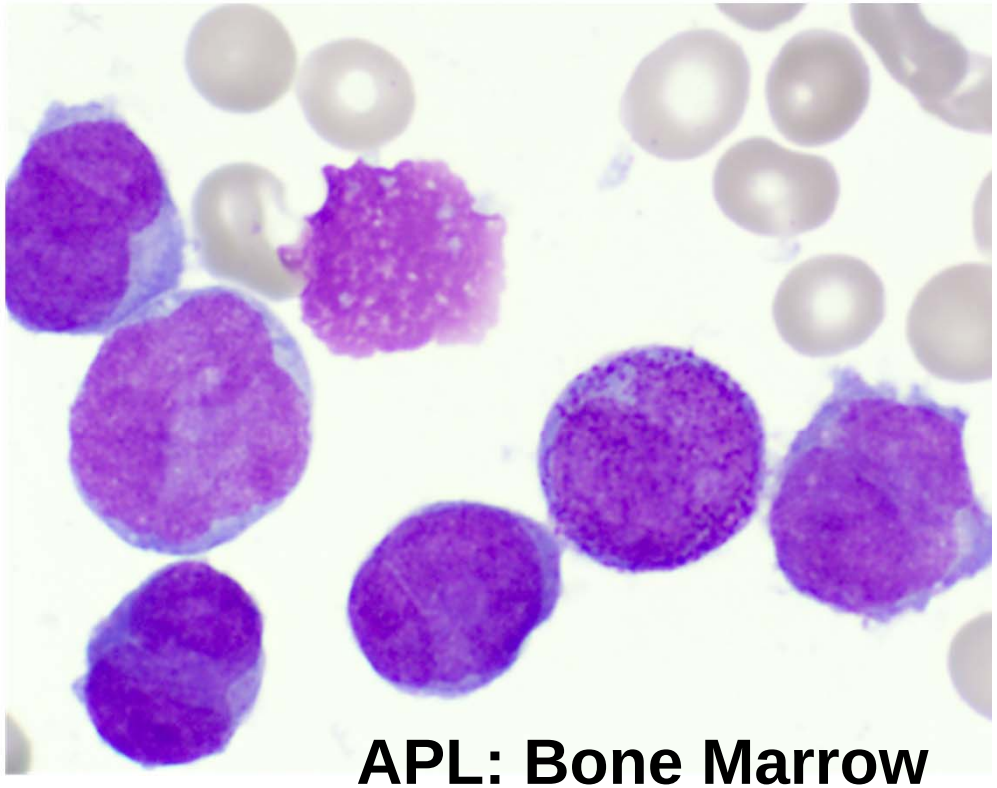


APL Blood
(Abnormal Promyelocytes)

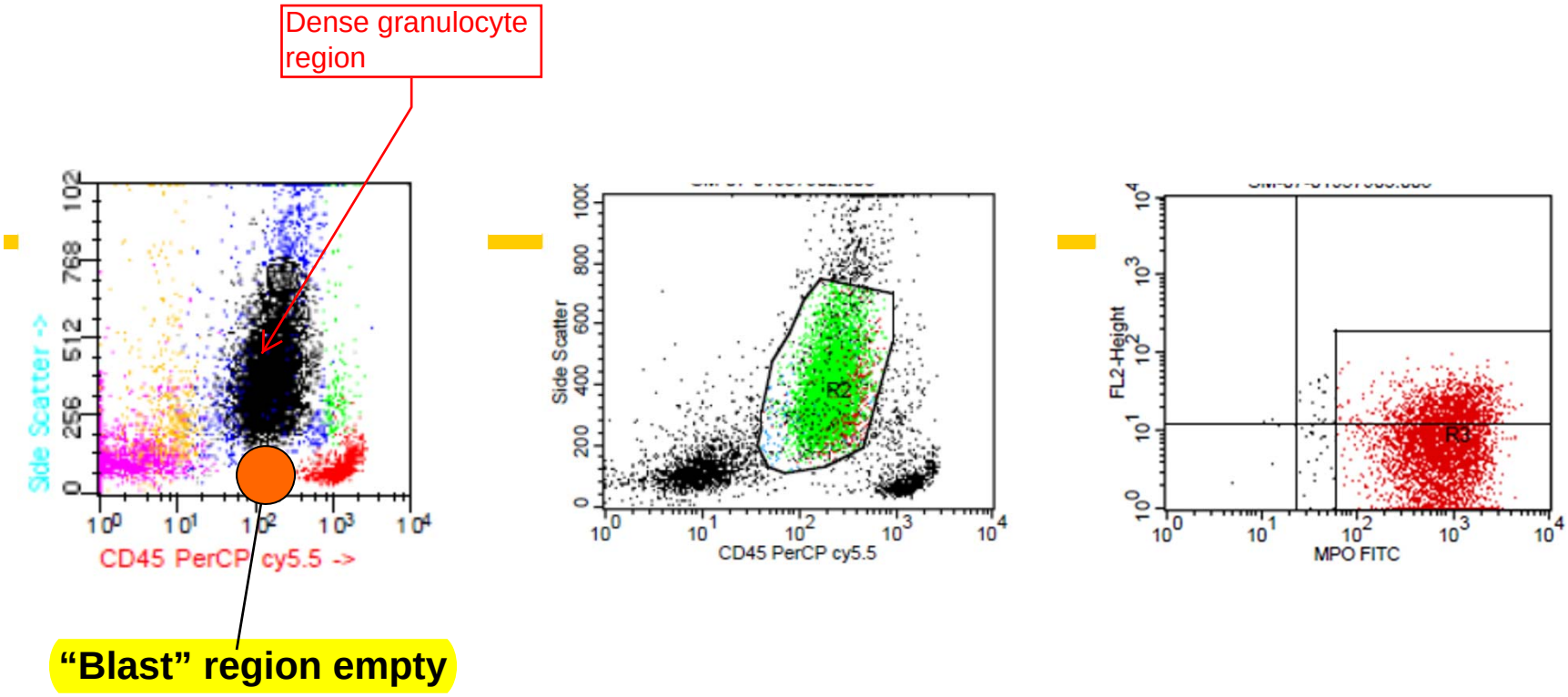




Normal Promyelocytes



APL: Bone Marrow



APL: Flow Cytometry

SKIPPED

Acute Monocytic Leukemia

(associated with translocations of 11q23 in some cases, especially children)

(FAB AML M5)

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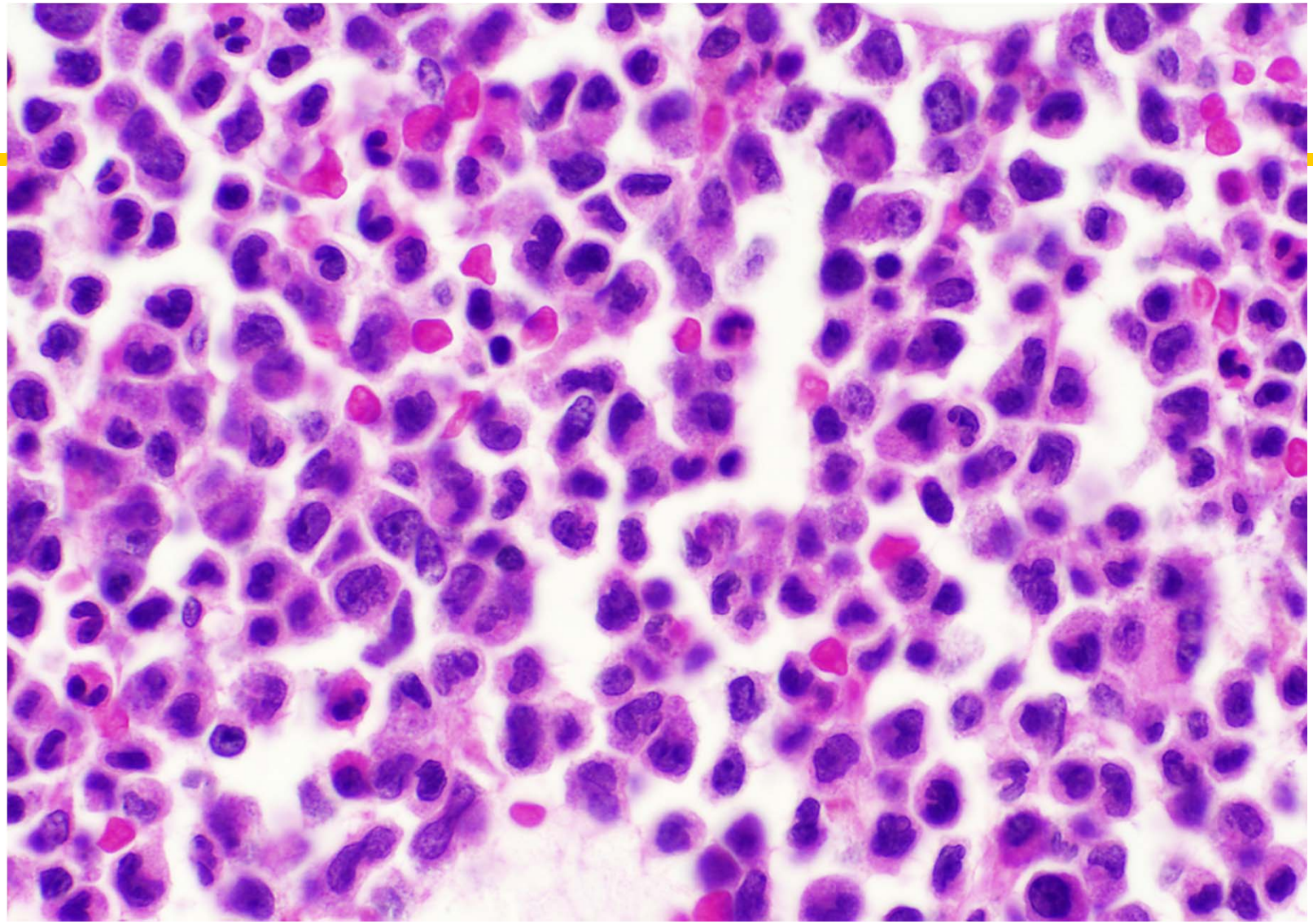
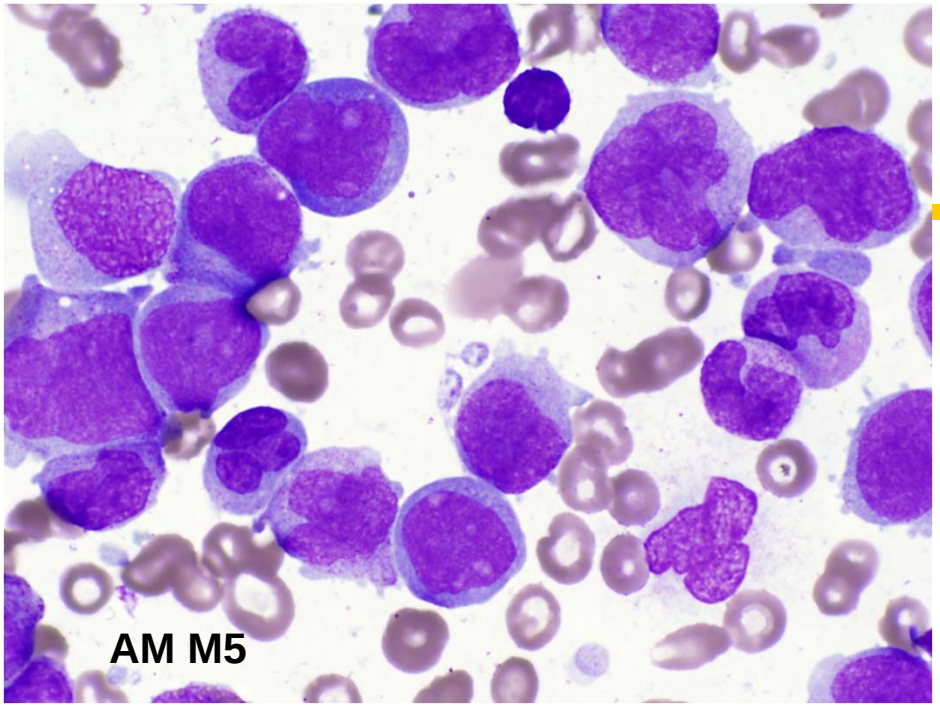


AML M5: Bone Marrow Biopsy



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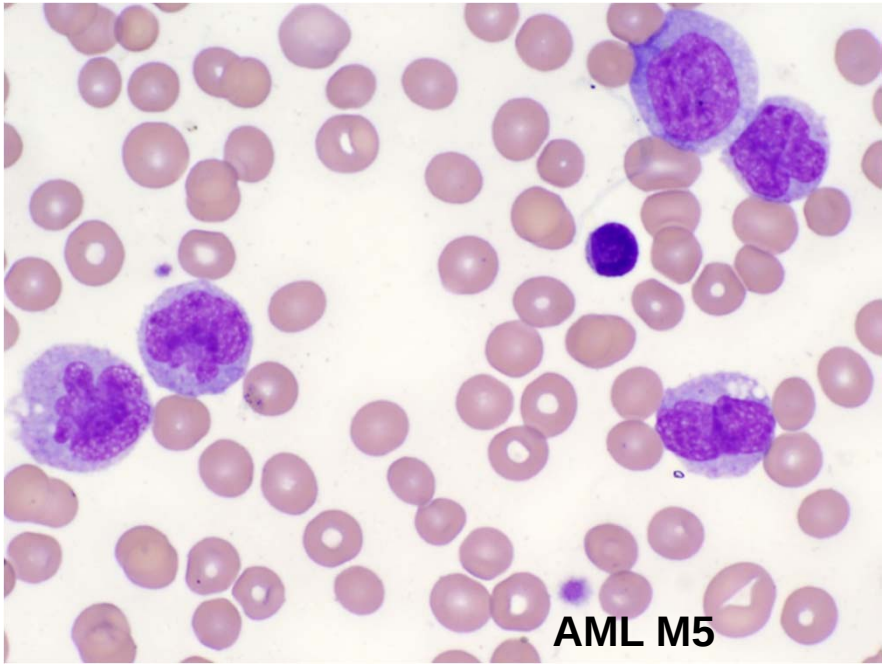
Bone Marrow

Blood



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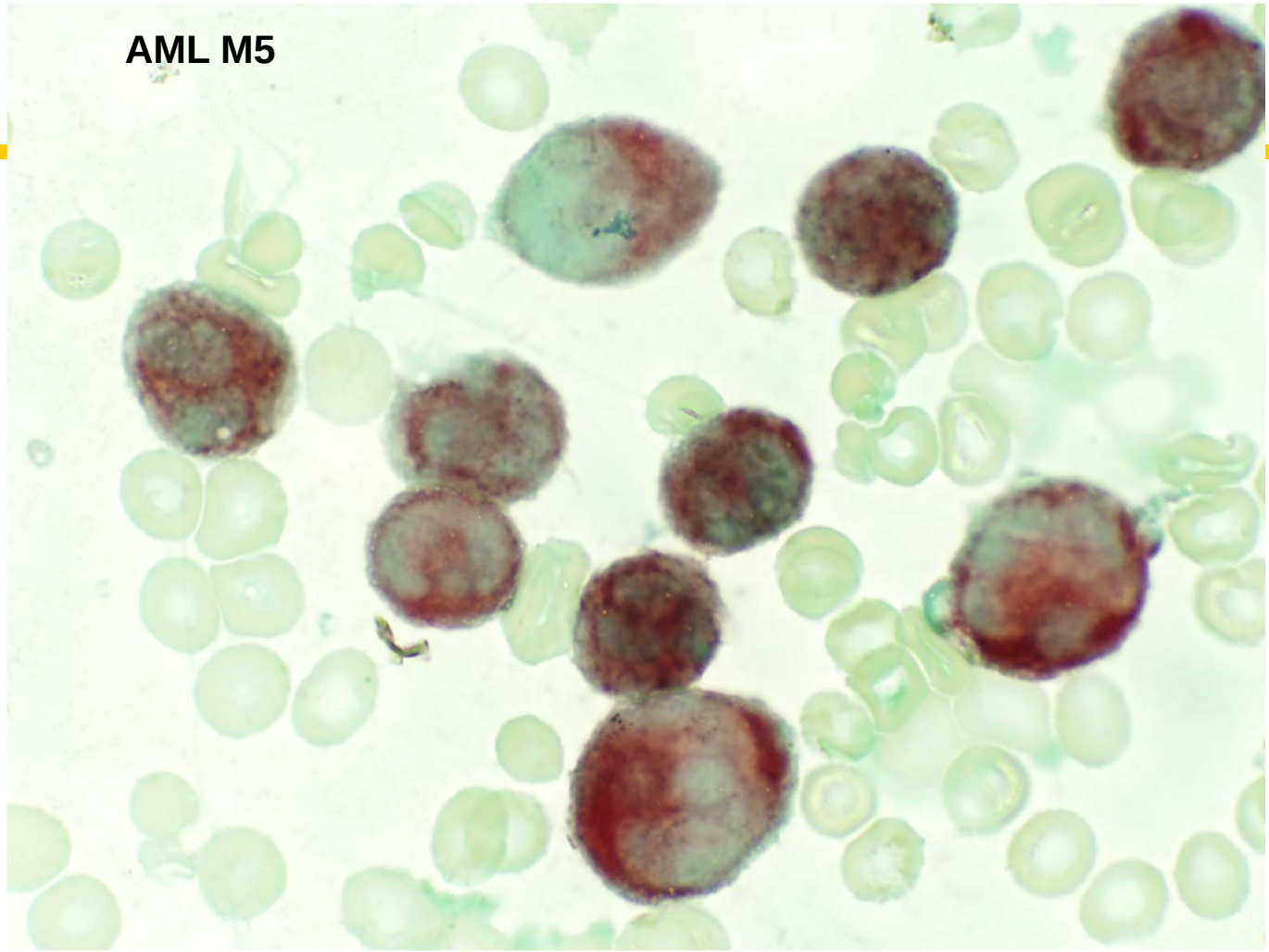

Cytochemical Stain: Monocyte Esterase (ANAE)

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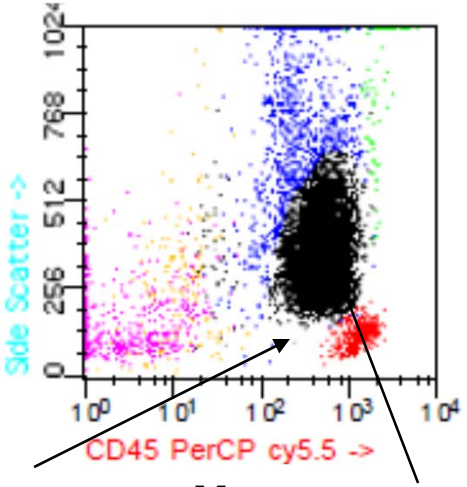
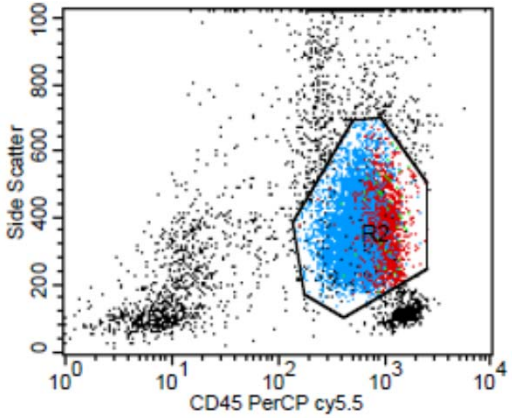
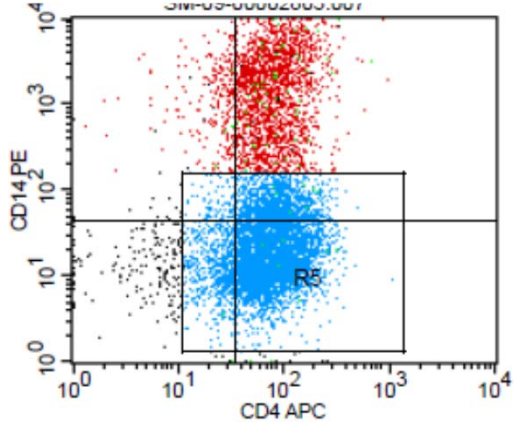
AML M5: Flow Cytometry



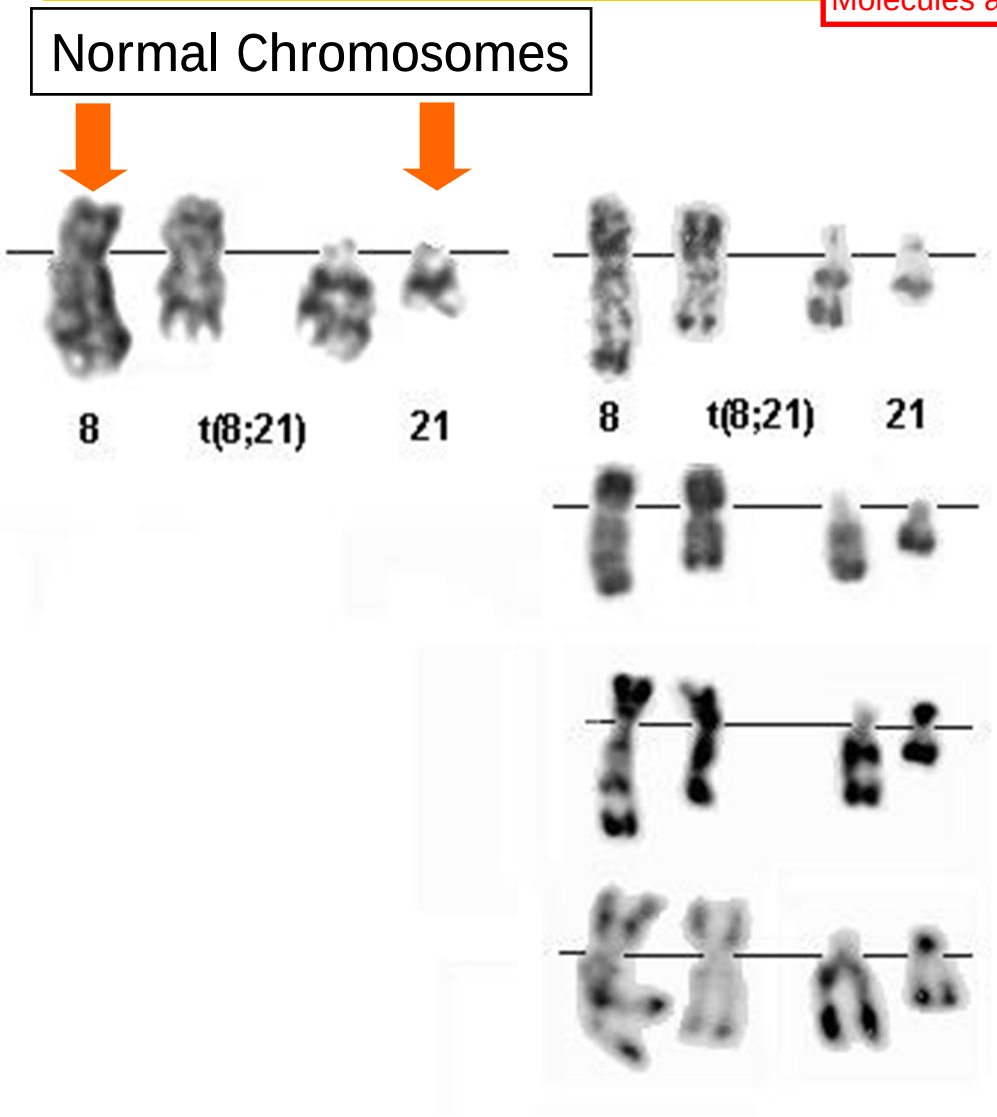




CD4 and CD14 identify monocytes

Acute Myelogenous Leukemia: Diagnosis Cytogenetics t(8;21)

Just an explanation of translocation. Throwback to Molecules and Cells



- An exchange of a piece of the long arm of chromosome 8 (ETO gene at 8q22) and the long arm of chromosome 21 (AML1 gene at 21q22).
- The critical product resulting is bringing the AML1 gene over to chromosome 8. This deregulates the gene product which functions in controlling maturation.
- Hence, the cells do not mature.

Acute Myelogenous Leukemia: Diagnosis Cytogenetics

Outcome depends on the cytogenetics. Can be put in 3 groups (explained later)

Abnormaity	Frequency	CR	Deaths in Remission	Relapse 5 year	OS 5 year
T(15;17)	12	87%	13%	37%	63%
T(8;21)	7	98%	15%	29%	69%
Inv(16)	3	88%	9%	42%	61%
No abn	42	88%	15%	53%	42%
+8	9	84%	12%	44%	48%
11q23	3	87%	9%	46%	45%
+21	2	80%	11%	50%	47%
Del(7q)	1	75%	19%	59%	23%
Del(9q)	1	100%	9%	39%	60%
Complex	5	67%	12%	68%	21%
-7	3	54%	8%	80%	10%
Del(5q)	1	57%	14%	85%	11%
-5	1	42%	12%	90%	4%

Grimwade, Blood 92:2322, 1998

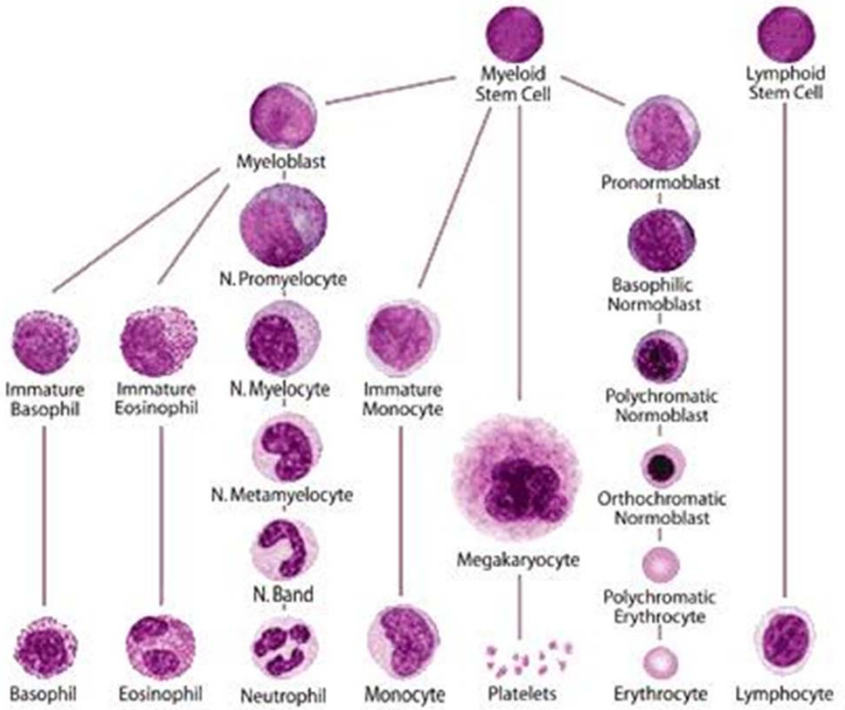
Acute Myelogenous Leukemia: Classification
French American British (FAB) Classification

FAB Type	Name	Comment
M0	Undifferentiated	Primitive cell; no differentiation
M1	Myeloblast	Some differentiation to granulocytic series
M2	Myeloblast with maturation	More differentiation to granulocytic series
M3	Promyelocytic	Differentiation to progranulocyte series
M4	Myelomonocytic	Myeloid and monocytoid series
M5	Monocytic	All monocytic series
M6	Erythroleukemia	Differentiation to erythroid series
M7	Megakaryocytic	Differentiation to megakaryocytic series

One of the "best" forms to have

Myeloid Cell Development versus Classification

The point is you can have any of these



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Acute Myelogenous Leukemia: Prognosis Cytogenetics

Abnormaity	Frequency	CR	Deaths in Remission	Relapse 5 year	OS 5 year
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3 groups (on next slide)

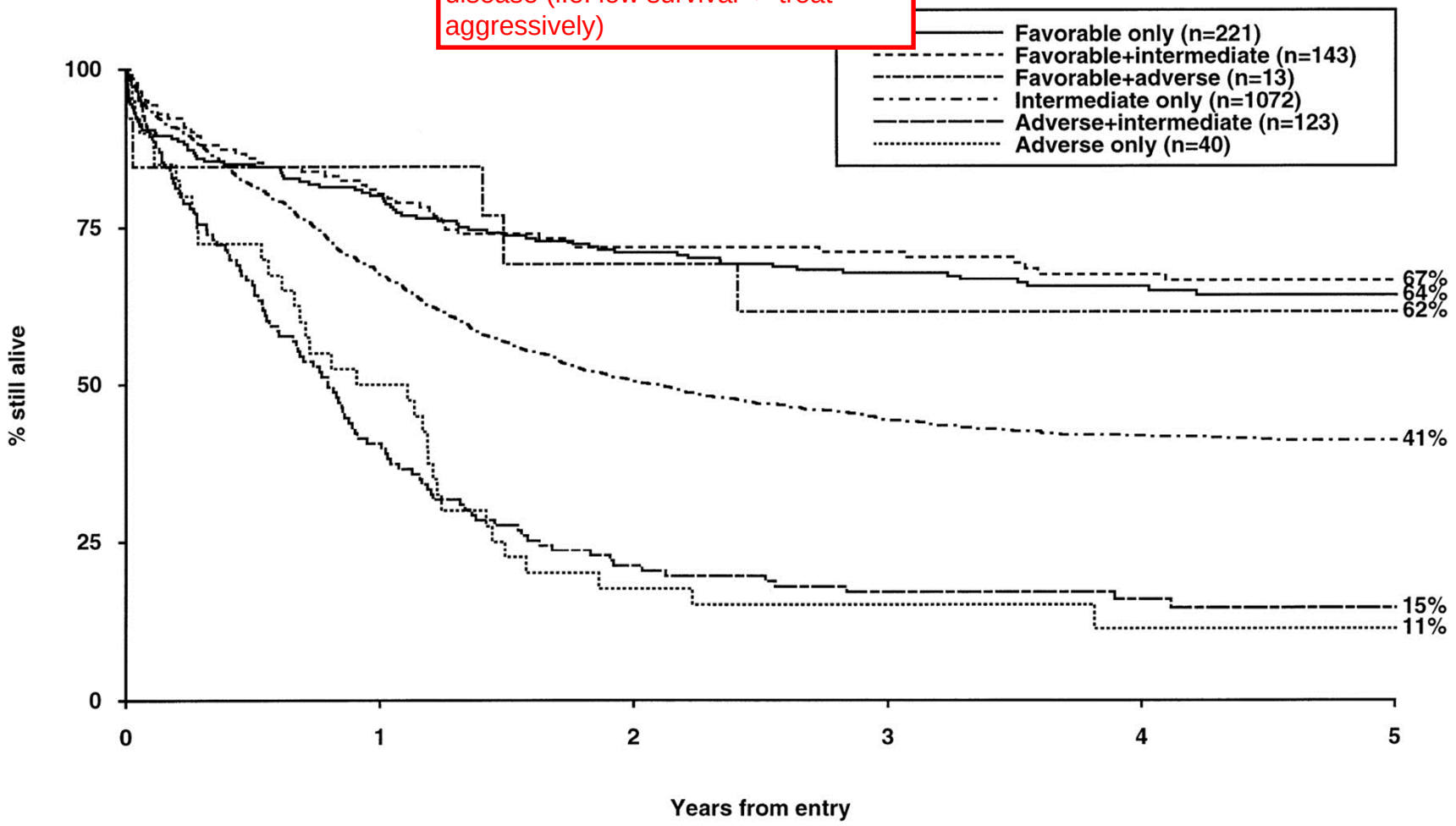
Grimwade, Blood 92:2322, 1998

Acute Myelogenous Leukemia: Prognosis Cytogenetics

Prognostic category	***Abnormality***	***Survival***
Favorable	t(8;21) inv(16) t(15:17)	60%
Intermediate	Normal +8	40%
Poor	-5, -5q -7 11q23 Complex	10%

Acute Myelogenous Leukemia: Prognosis Cytogenetics

Having 3 groups helps you decide how aggressive you should treat the disease (i.e. low survival -> treat aggressively)



Grimwade, Blood 92:2322, 1998

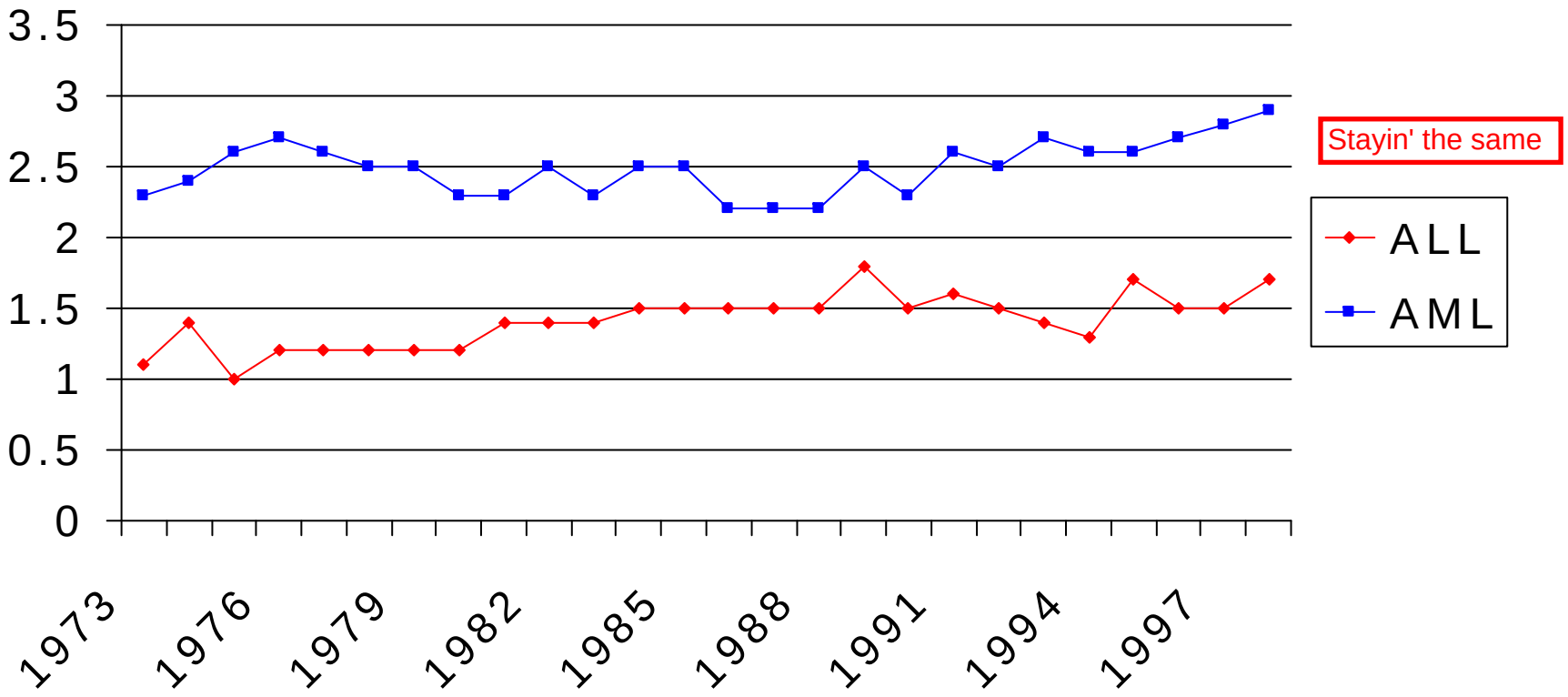
Acute Myelogenous Leukemia: Statistics
Statistics

- Median age: 62-65 Older persons disease
- 1 case per 20,000 people at age 60

- 1% of cancer deaths
- 2.5 deaths per year per 100,000 people

- Slight increase in males
- Slight increase incidence in Eastern European Jews

Acute Myelogenous Leukemia: Statistics
Incidence Rates per 100,000/year



SEER Incidence Rates

Acute Myelogenous Leukemia Epidemiology/Etiology

- Ionizing radiation
- Chemicals
- Drugs
  - alkylating agents
    - cyclophosphamide
    - chlorambucil
    - melphalan
  - topoisomerase II inhibitors
    - etoposide
- Environmental factors
- Genetic abnormalities
  - Down's Syndrome
  - Bloom's Syndrome
  - Fanconi's anemia
- Viruses? No
- Immunological deficiency - No

Acute Myelogenous Leukemia: ClinicalClinical Features I

- Cell deficiency — Causes the Sx
  - RBC - pallor, fatigue, dyspnea
  - Thrombocytopenia - petechiae, hematoma, bleeding
  - Neutropenia - sepsis, cellulitis, pneumonia
- Hyperleukocytosis
  - Blasts > 100,000 - obstruction to capillaries and small arteries

Problematic, i.e. in lungs

- Leukemia cutis — Most common site of infiltration is skin
  - 10-20% of leukemias
- CNS leptomeningeal involvement — 2nd most common
  - headache, mental status — Leukemic meningitis
  - cranial nerves

Acute Myelogenous Leukemia: ClinicalClinical Features II

- DIC — Disseminated intravascular coagulation
  - any form of leukemia
  - very common with M3 (acute promyelocytic leukemia) — ...because the granules are pro-coagulatory and can cause DIC when you treat/lyse the cells
- Tumor lysis syndrome
  - Contents of cells
    - K^+ — Not uncommon to cause [K+] of 7.5 which is lethal
    - PO^4
    - uric acid

Acute Myelogenous Leukemia: ClinicalClinical Features III

- Leukocytosis
  - low pO(2)
  - low glucose
  - high potassium

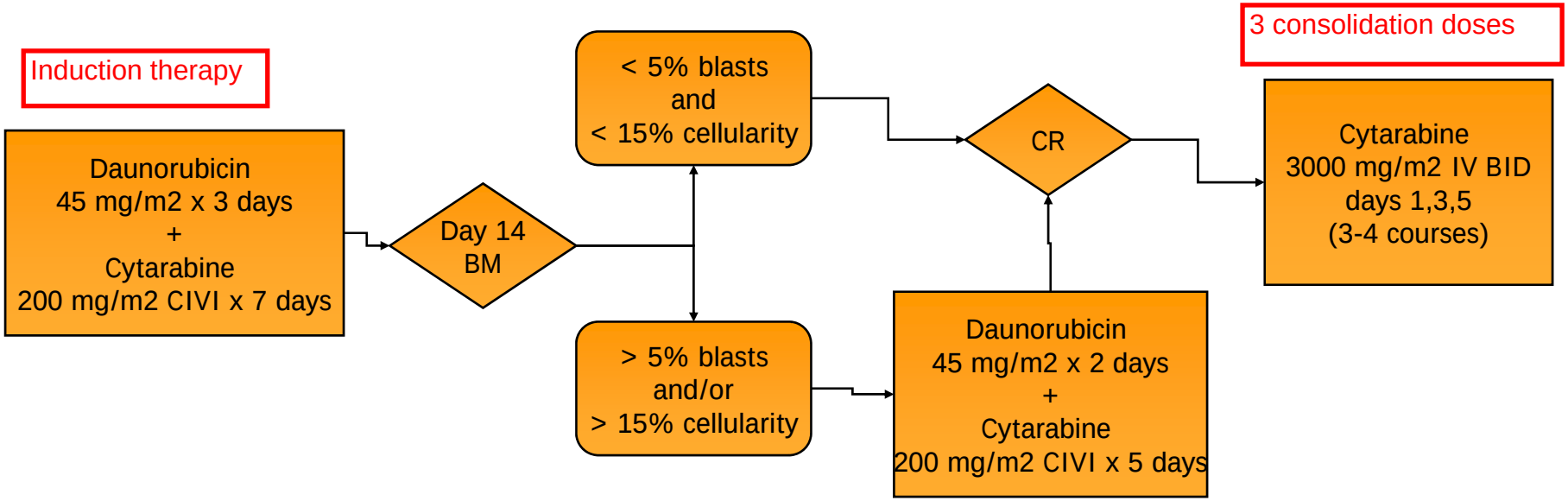
In the test tube, all those cells will use up the O2/glucose.
So if you get a lab reading of O2 = 20 and glucose = 10 and the patient is still talking, don't worry about it.

Acute Myelogenous Leukemia: Treatment Overview

Has stayed the same for 30 years

- Induction
  - 3 days of anthracycline
  - 7 days cytarabine
- Consolidation/Maintenance
  - several more cycles of intensive chemotherapy - highly variable

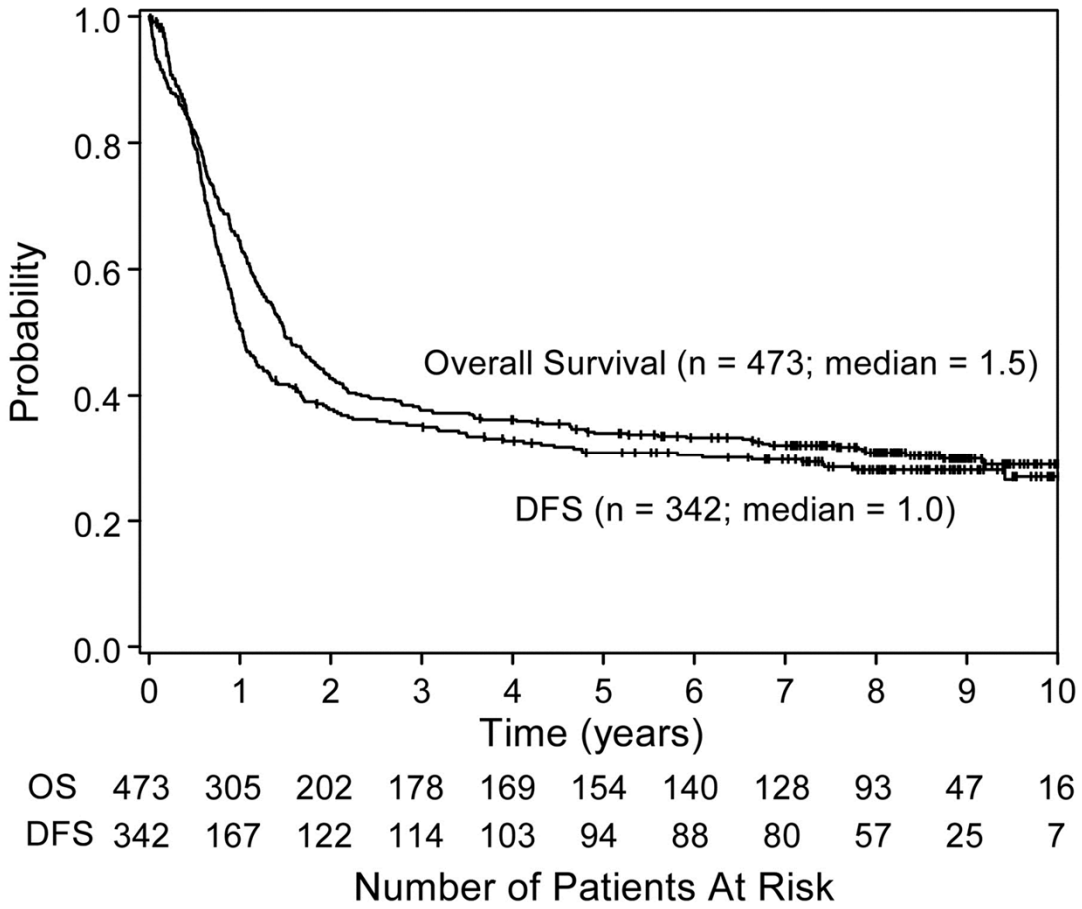
Acute Myelogenous Leukemia: Treatment Schema



CIVI = continuous intravenous
BM = bone marrow biopsy
Blasts = leukemic cells

Mayer (CALGB) N Engl J Med 331:904, 1994

Acute Myelogenous Leukemia: Treatment Overall Survival and Disease Free Survival



30% 10 year survival rate with therapy

Moore, J. O. et al. Blood 2005;105:3420-3427

Acute Myelogenous Leukemia Summary

- Cells do not mature and do not die
- Older individual (can be young)
- Fatigue most common presentation
- Normal physicial exam Usually, but not always
- Pancytopenia Usually, but not always
- Aggressive chemotherapy
- 30% survival

END OF LECTURE I