ACUTE MYELOID LEUKEMIA

What is an Acute Myeloid ? Leukemia

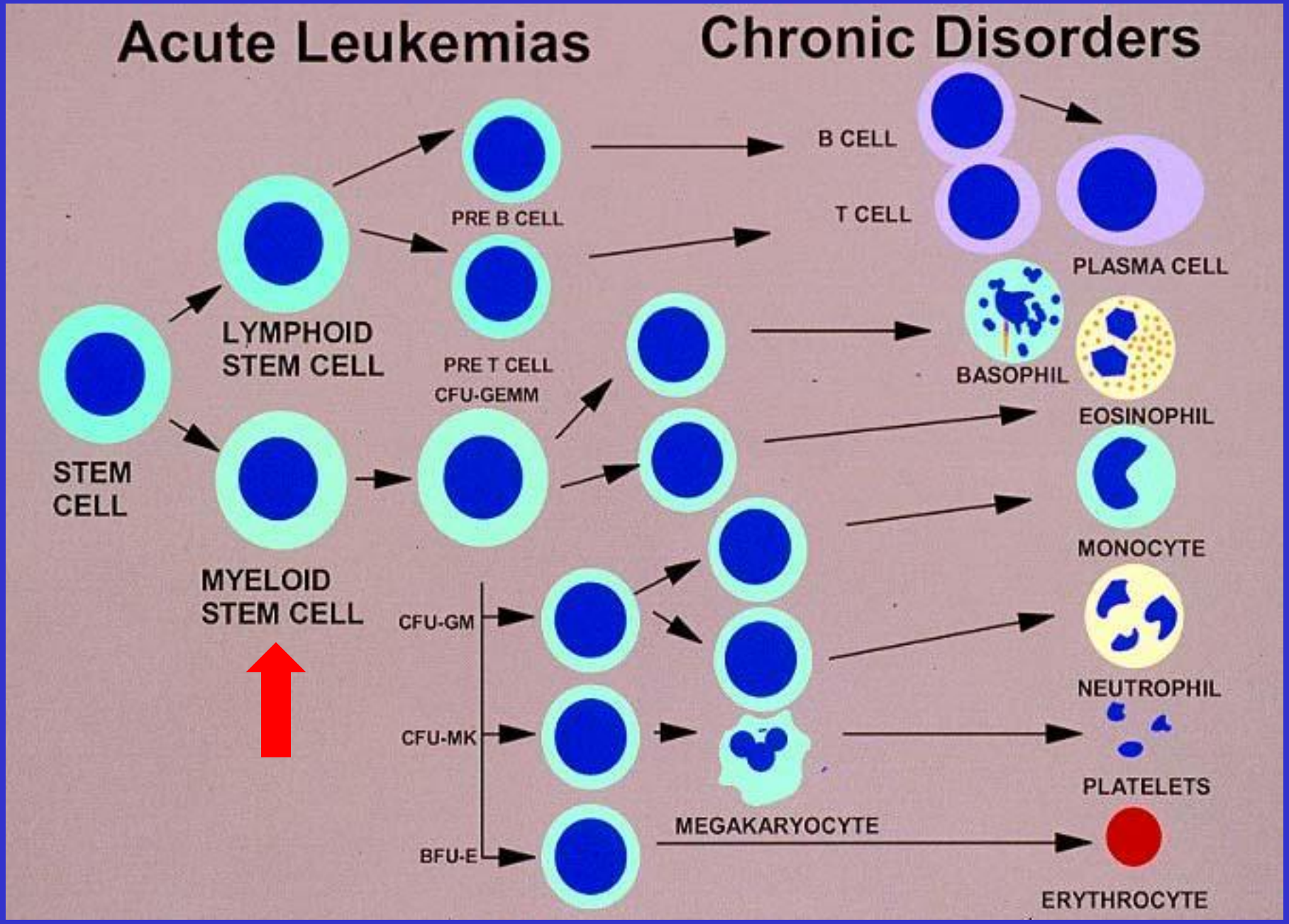
Accumulation of early myeloid progenitors (blast cells) in bone marrow and blood

Definition requests presence of 20% or more blasts in BM

Normally- less than 5%

ETIOLOGY

- Environment: irradiation, chemotherapeutic agents, organic solvents – benzene etc.
- Genetic diseases: neurofibromatosis, Wiscott-Aldrich synd., defective DNA repair – Fanconi, Down synd.
- Acquired disorders: Aplastic Anemia, PNH
- **MOST OF THE CASES APPEAR WITH NO APPARENT RISK FACTORS!!!**


Acute Leukemias
Chronic Disorders
B CELL
PRE B CELL
T CELL
PLASMA CELL
LYMPHOID STEM CELL
PRE T CELL
CFU-GEMM
BASOPHIL
EOSINOPHIL
STEM CELL
MONOCYTE
MYELOID STEM CELL
CFU-GM
NEUTROPHIL
CFU-MK
PLATELETS
MEGAKARYOCYTE
BFU-E
ERYTHROCYTE

AML

Aggressive disease with an acute onset

Can occur De Novo

or

following a known leukomogemic trigger :(radiation, chemotherapy, diseases)

Secondary AML

Leukemia

Malignant Transformation

↓

Proliferation and Accumulation

↙ ↘

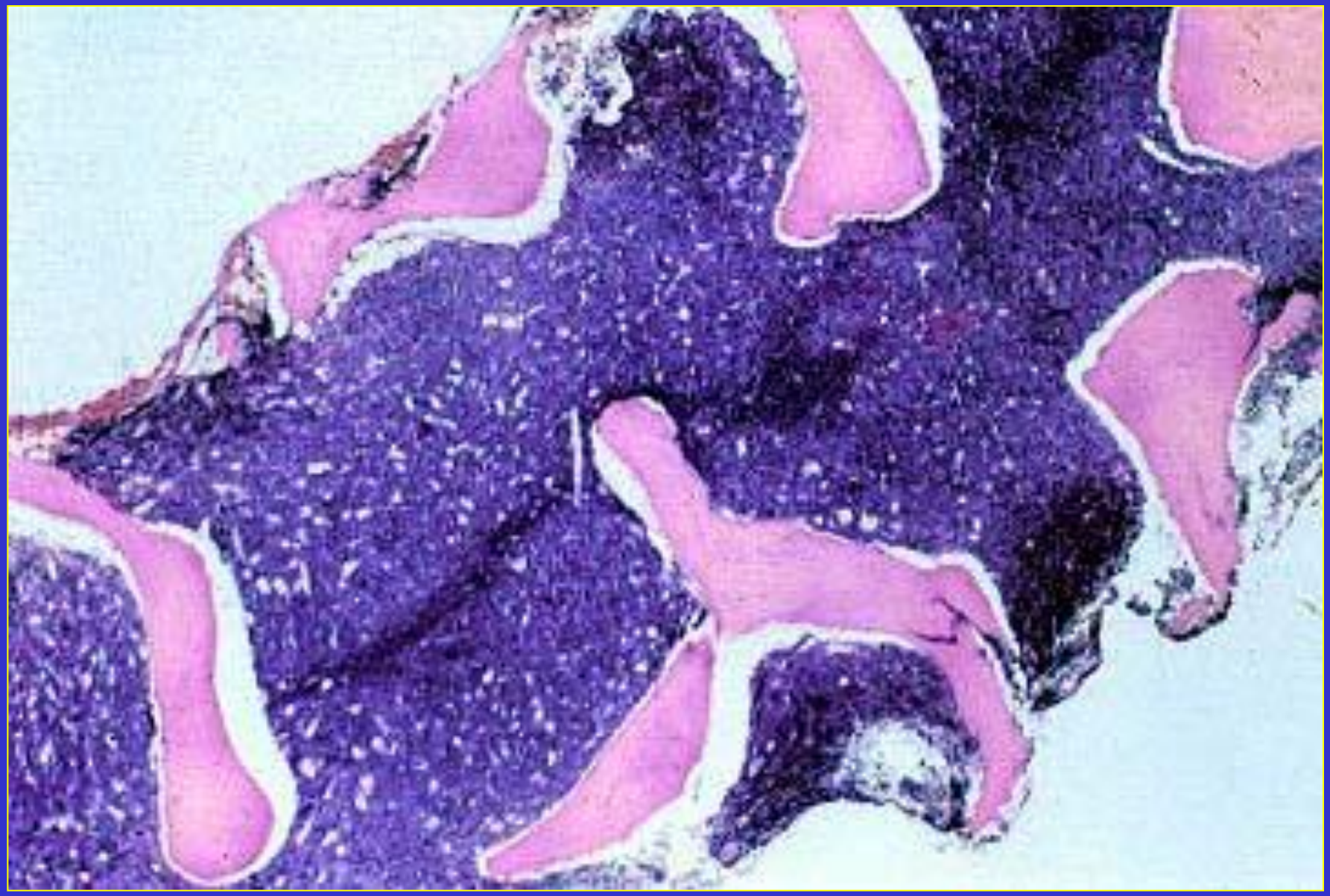
Peripheral blood

Bone marrow

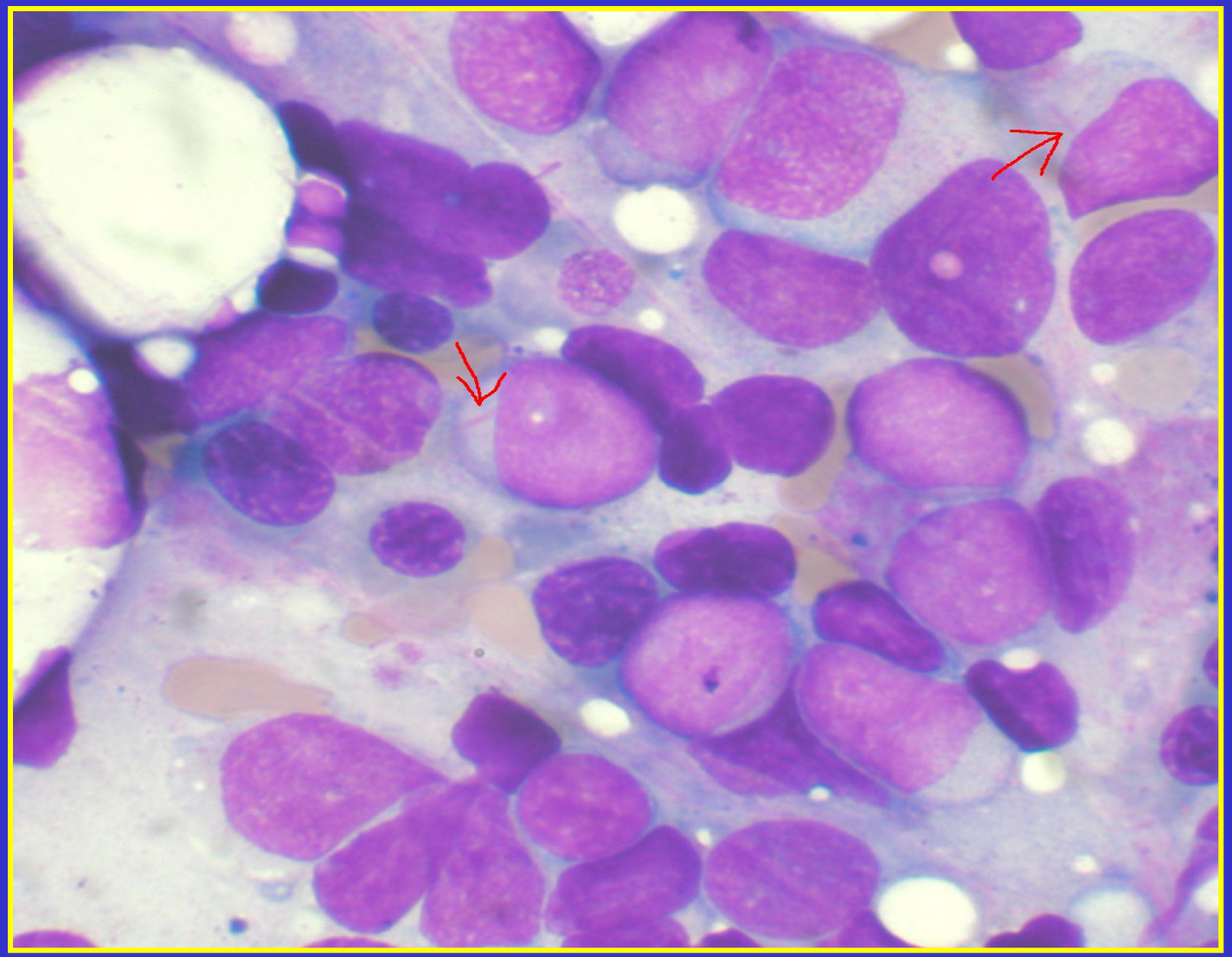
Visceral organs

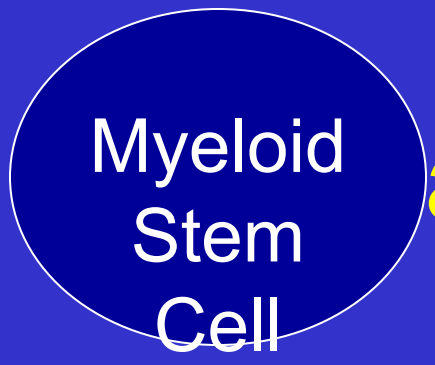
Cytopenias

BM - Acute Leukemia (low power)



Morphology AML





athophysiology

Radiation
Chemotherapy
Viruses

chromosomal damage

t(8;21),M2
t(15;17) M3
Inv 16;M4e

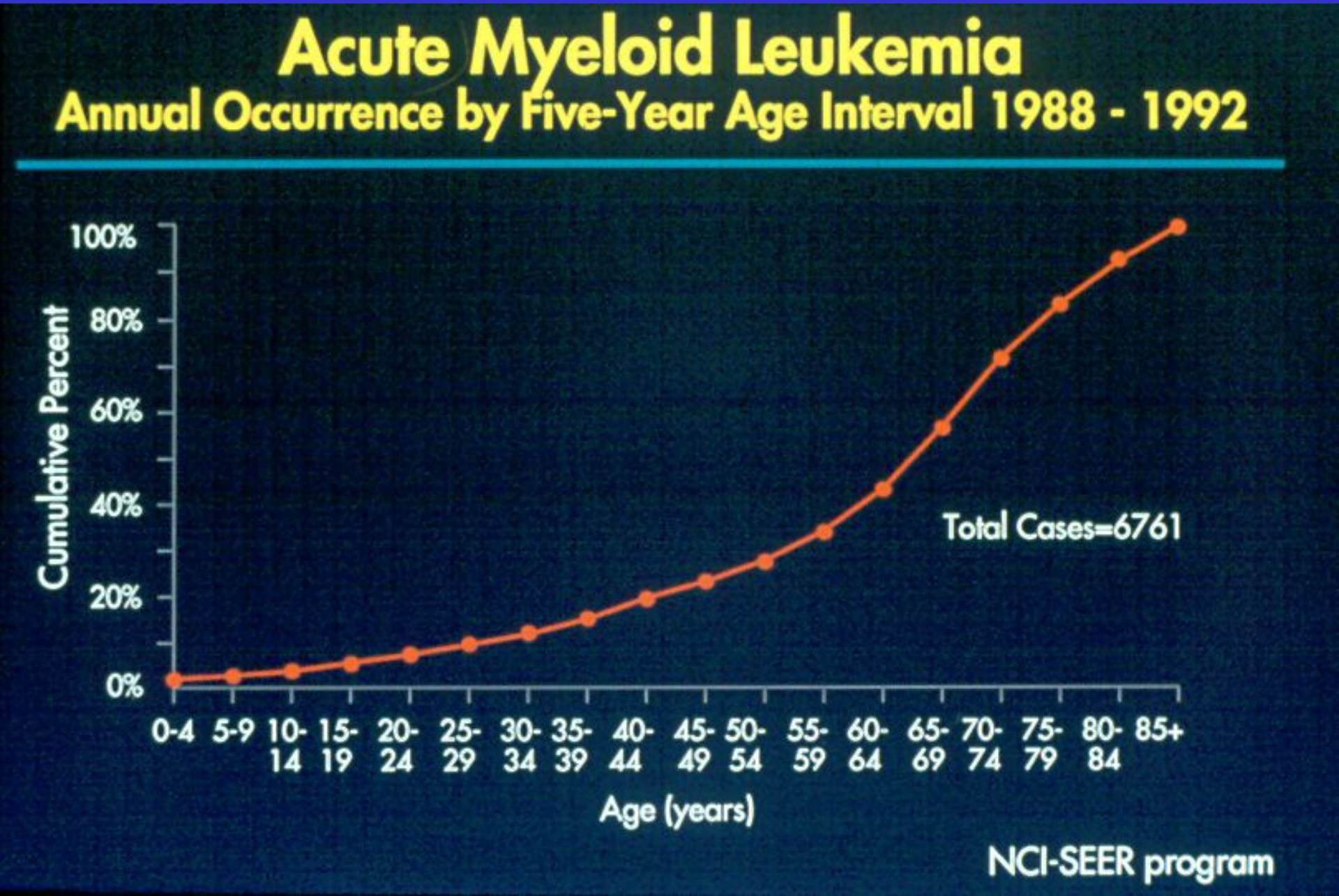
protooncogen
Inhibition/Enhancements of regulatory genes

Inhibition of suppressor genes

Enhancements of proliferation

Inhibition of apoptosis

Epidemiology



Predisposing factors

Environmental Benzen, herbicies

Chemotherapy :AK ; NU;PRC

Radiation

Acquired diseases Meyloproliferative(CML;PV..)

Aplastic anemia

Genetic Congenital abnormality

: *to repair DNA*

Down syndrome

Ashkenazi Jews >> orientals

Relatives(1st degree x3)

Clinical symptoms of Acute Leukemia

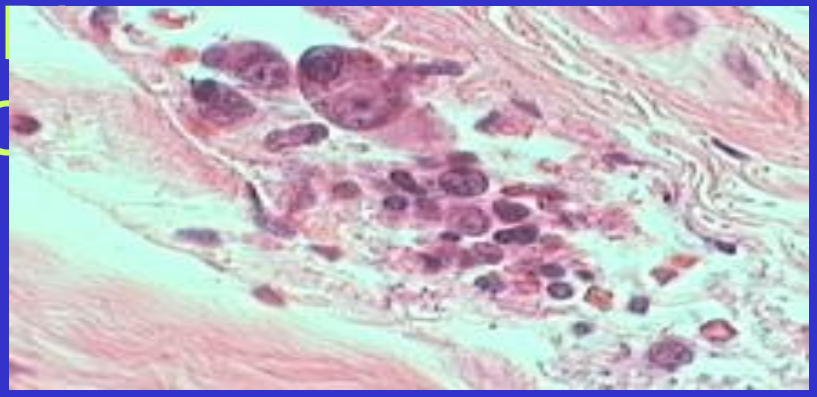
Bone marrow expansion Bone pain

Bone marrow failure Leucopoenia infections

Thrombopenia bleeding

Anemia

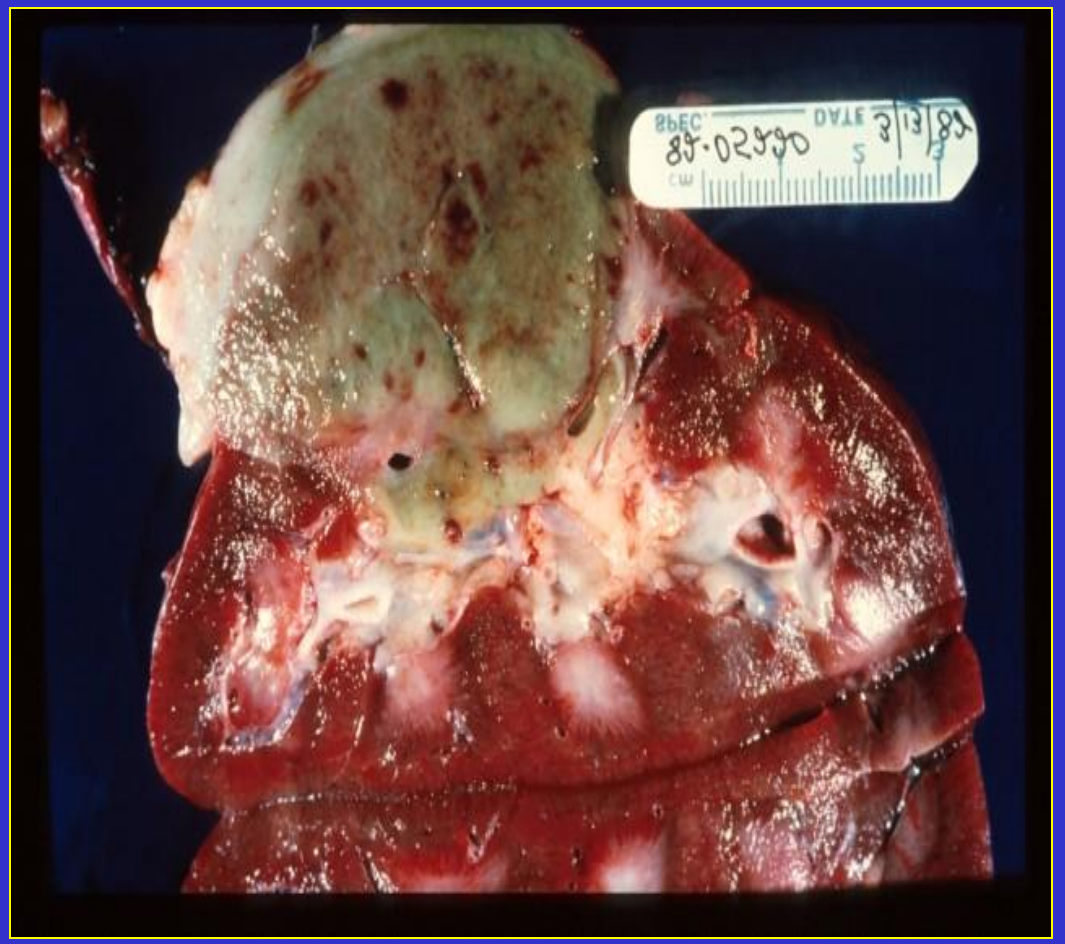
Leucostasis >50,000 blasts



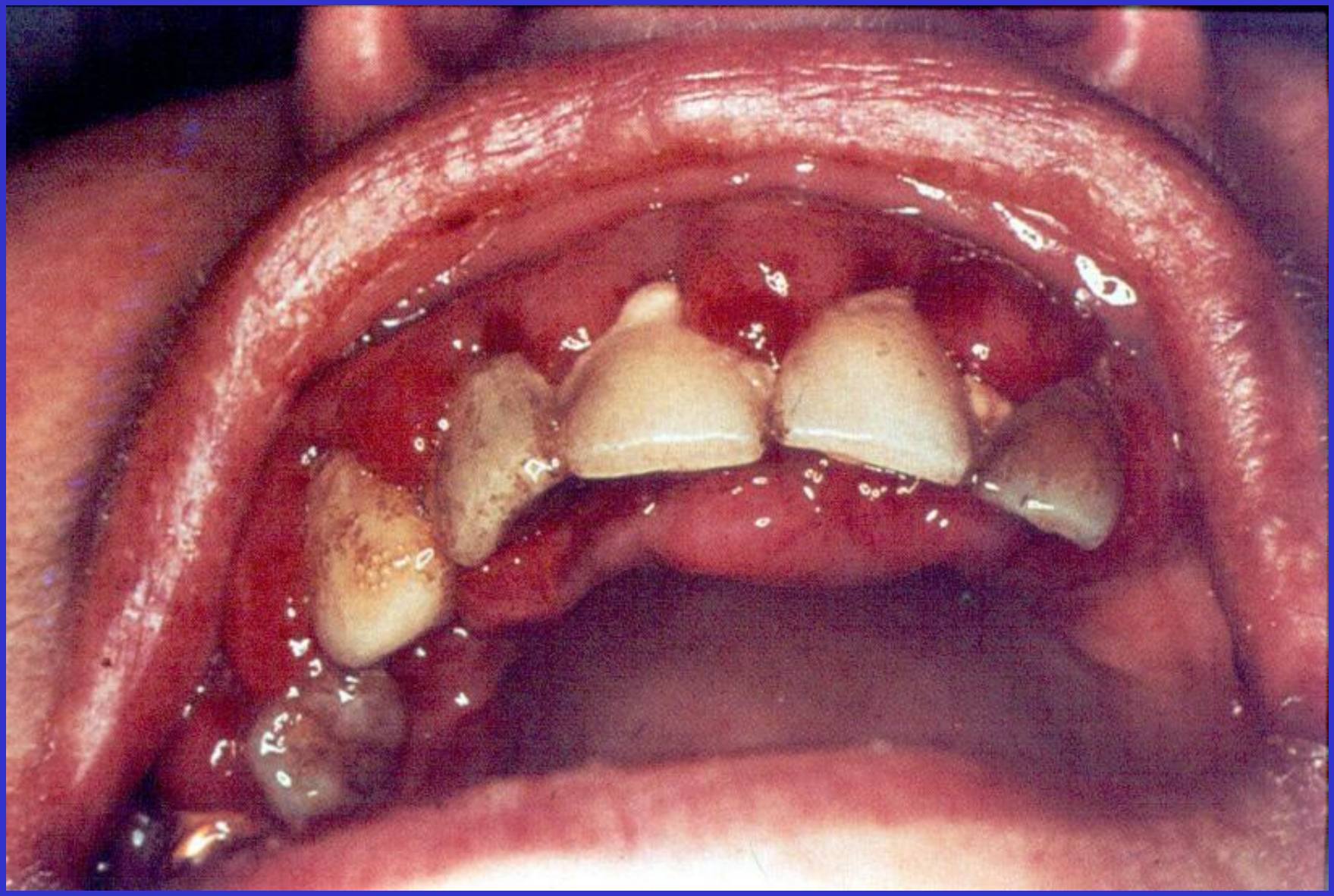
Clinical symptoms

Extramedullary
(Chloroma)

Skin
CNS
Gingiva
Kidney



Extramedullary: Gingival hypertrophy



Clinical symptomes

DIC

Bleeding

Thrombosis

Metabolic

Hyperuricemia

Tumor lysis syndrome

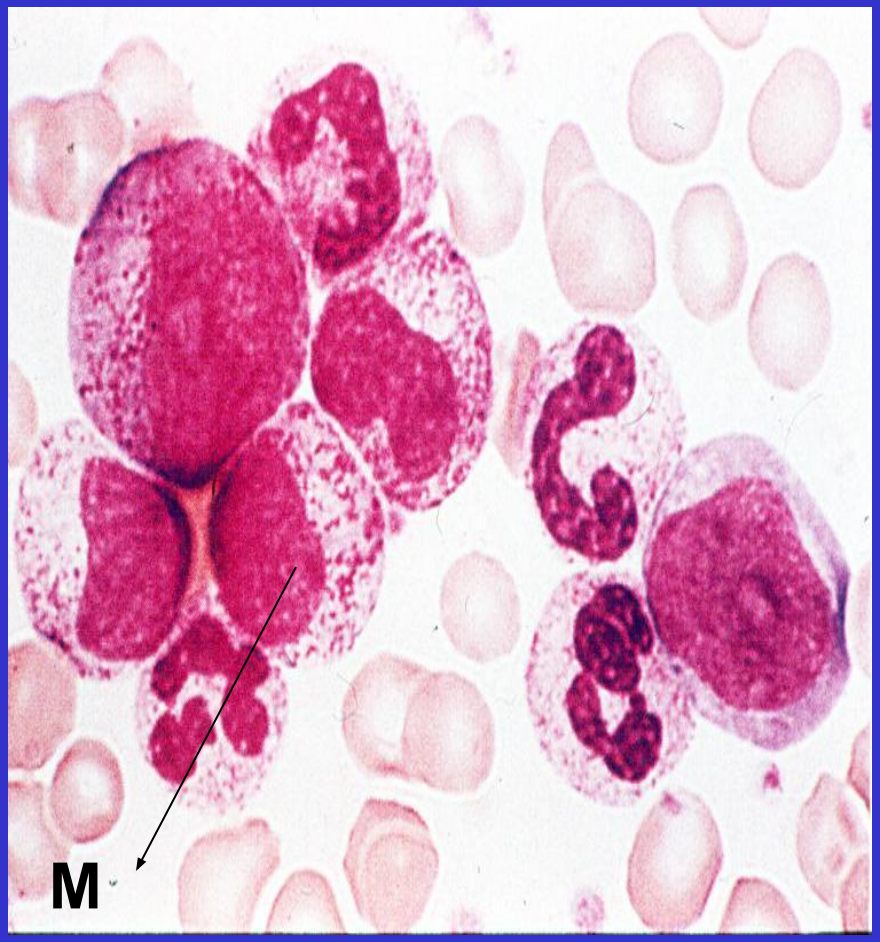
↑ K, ↑ phosphor, Ca↓

↑ Uric Acid

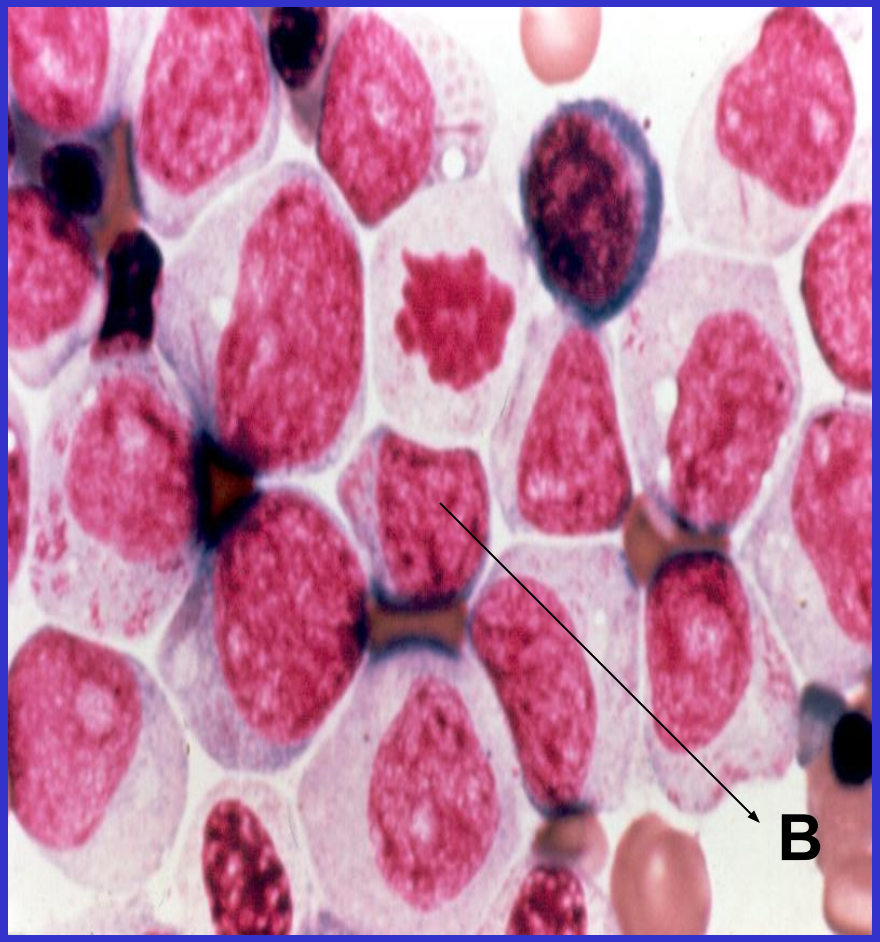
Diagnosis

(*blasts* in bone marrow/peripheral blood 20%<

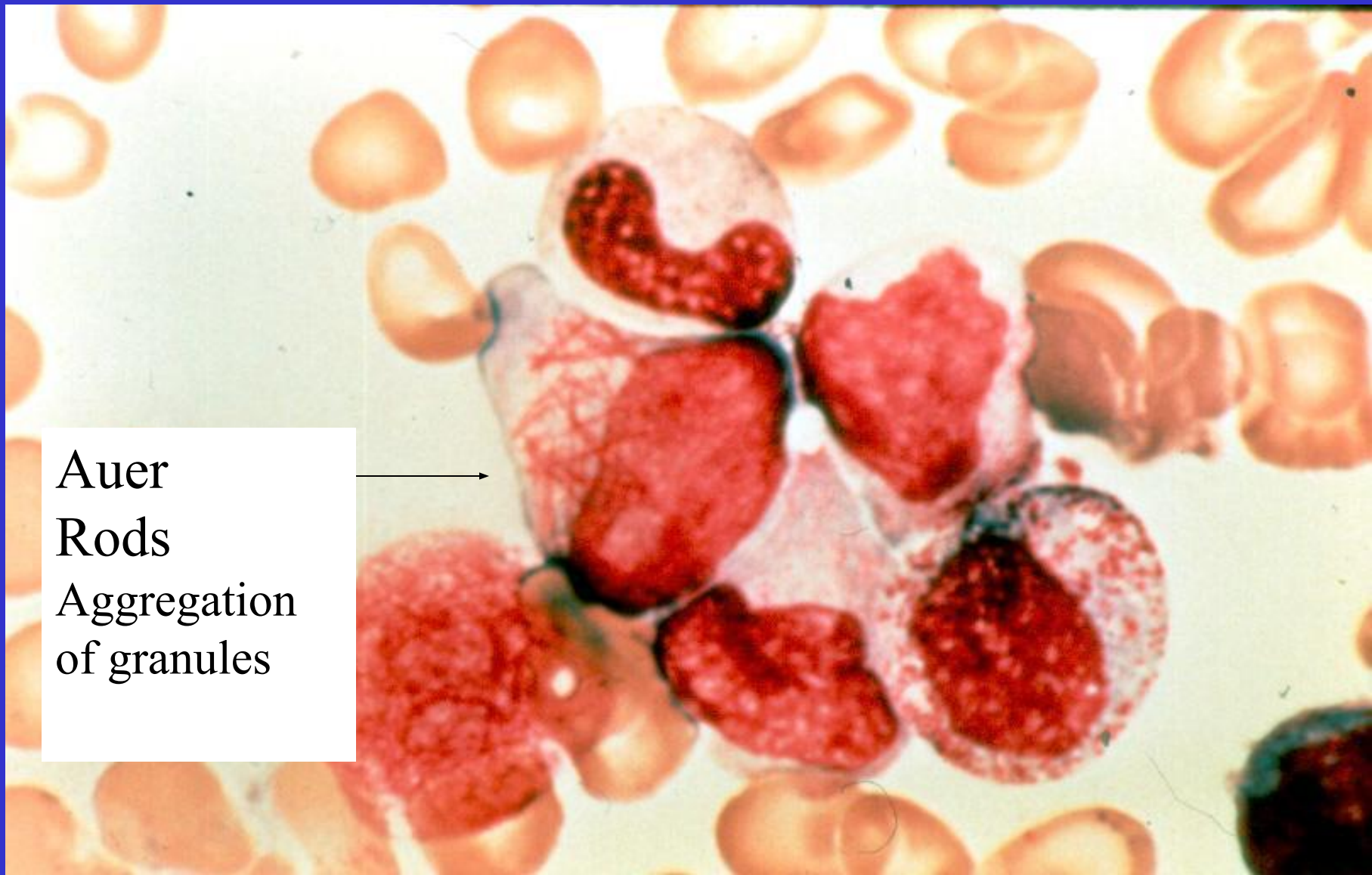
Normal bone marrow



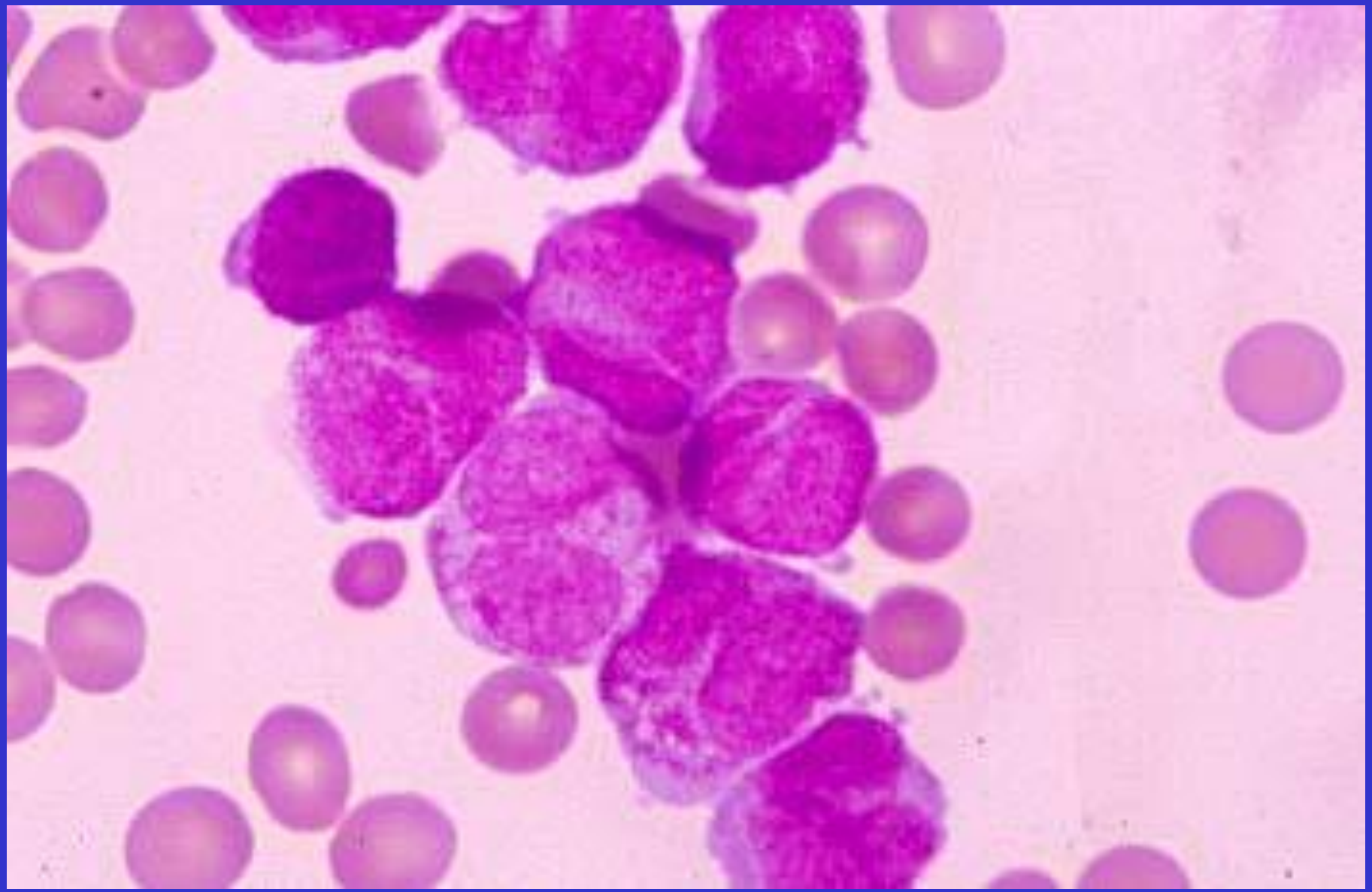
AML ;blasts



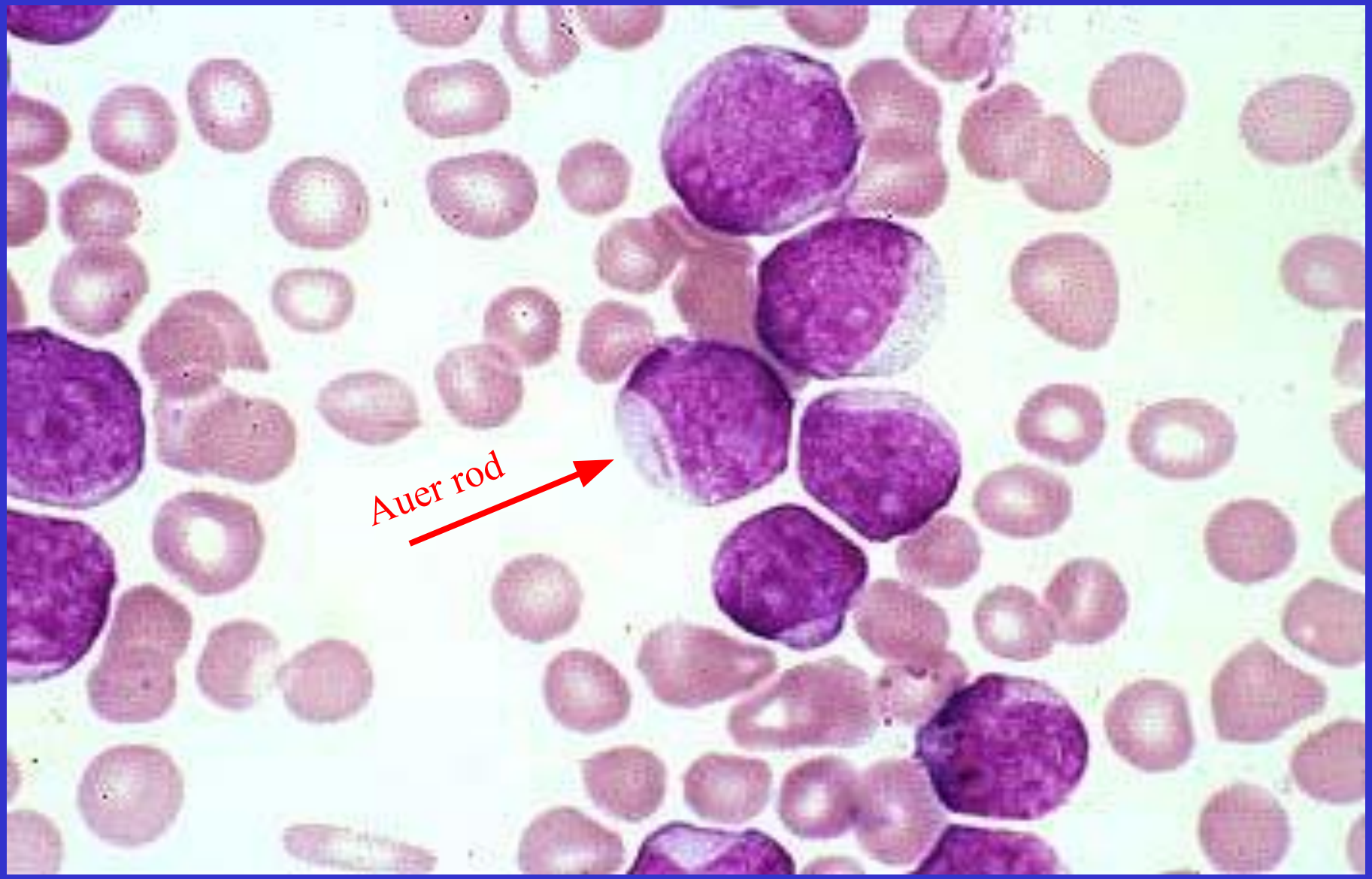
Acute leukemia - AUER Rods (FAB;AML M3)



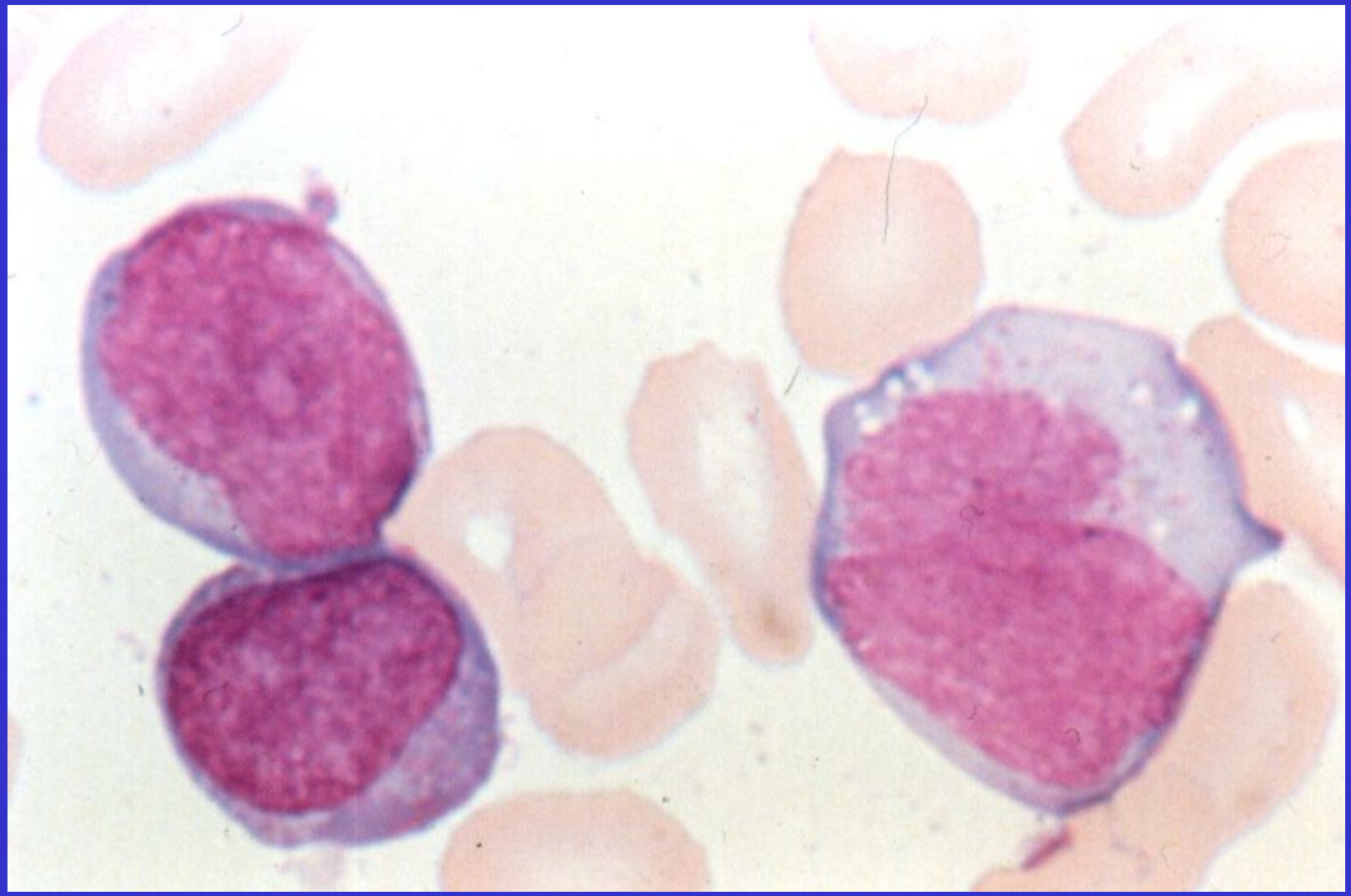
Acute promyelocytic leukemia - AML M3



Myeloblasts - AML



AML M2 blasts



French American British (FAB) classification

Based on morphology and staining- (cytochemistry)

Divides patients into 7 AML subtypes-

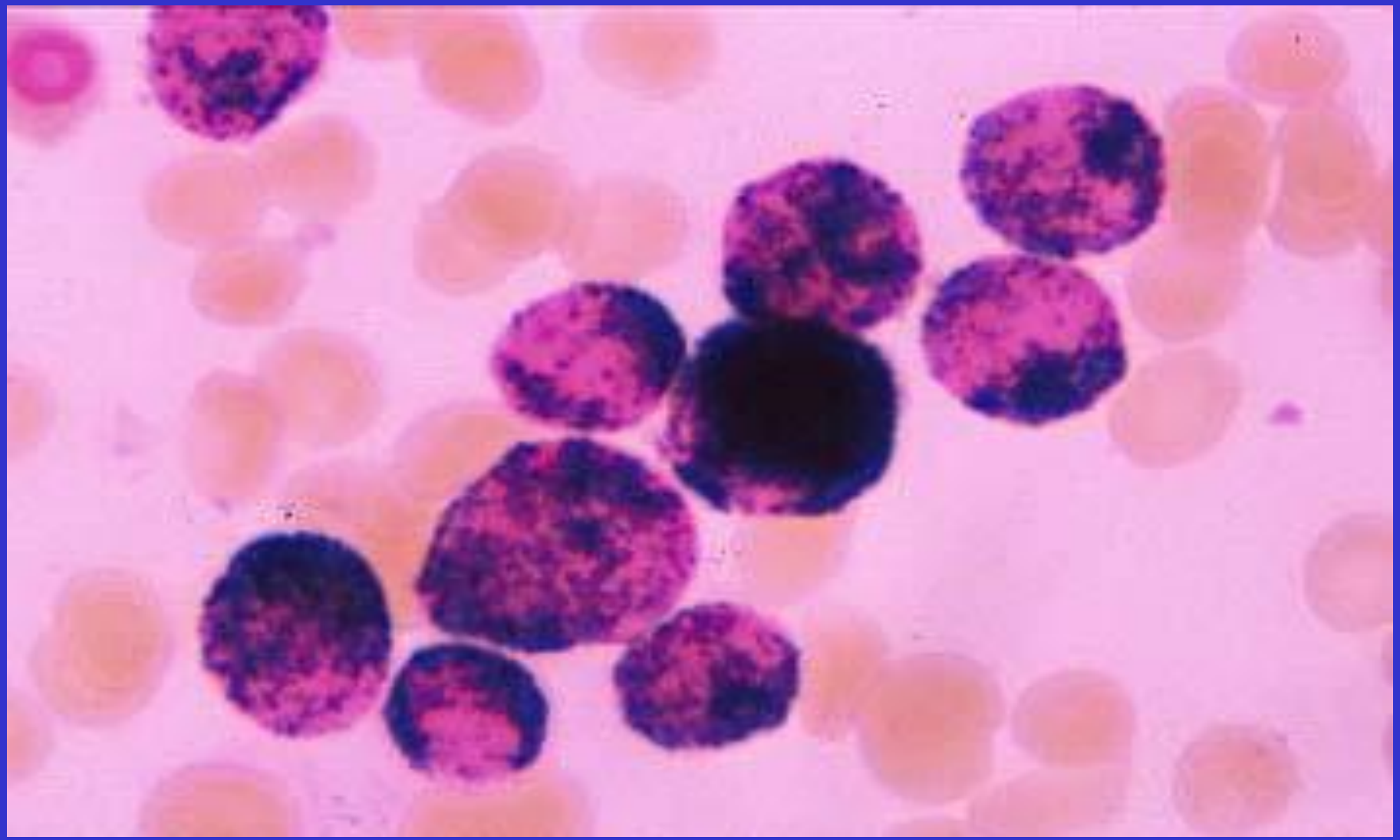
A morphological rather than biological- classification

Correlation between morphological and- biological characteristics may exist , but not always

AML – WHO classification

- AML with recurrent cytogenetic translocations – M2 with t(8;21), M3 with t(15;17) and variants, M4eo with (inv16), AML with 11q23 abnormalities
- AML with multilineage dysplasia ± MDS
- AML or MDS therapy related (alkylating agents, epydiphylotoxin, other)
- FAB subtypes without other features
- Acute biphenotypic leukemia

Cytochemistry
Myeloblasts - myeloproxidase positive



Diagnosis

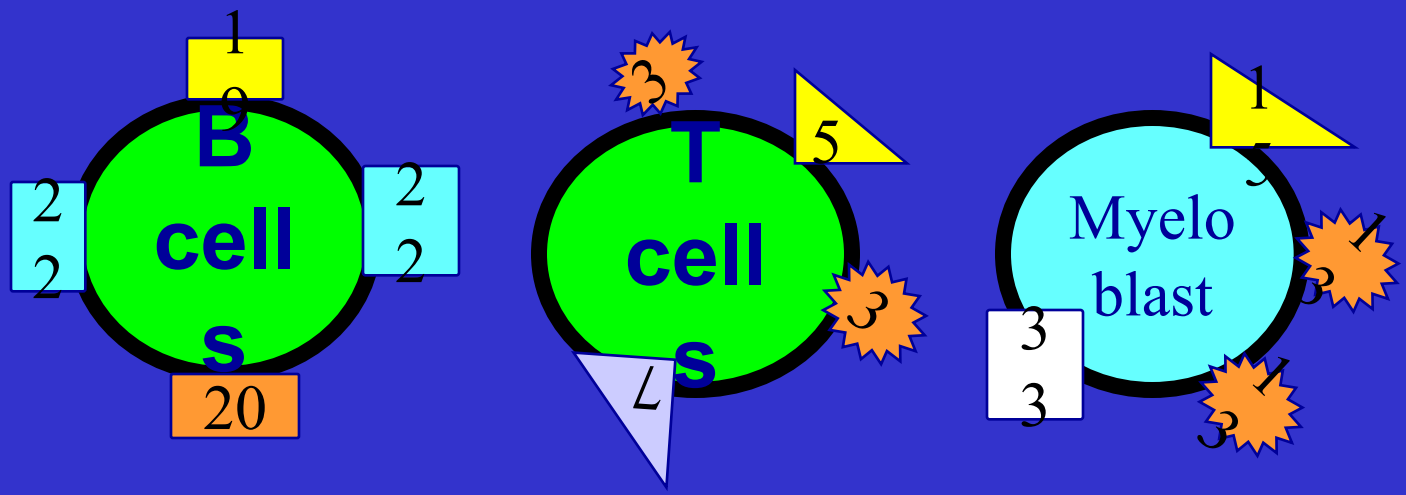
Diagnosis :>20% blasts in BM

: Cytochemical stains

- ALL TdT +, MPO

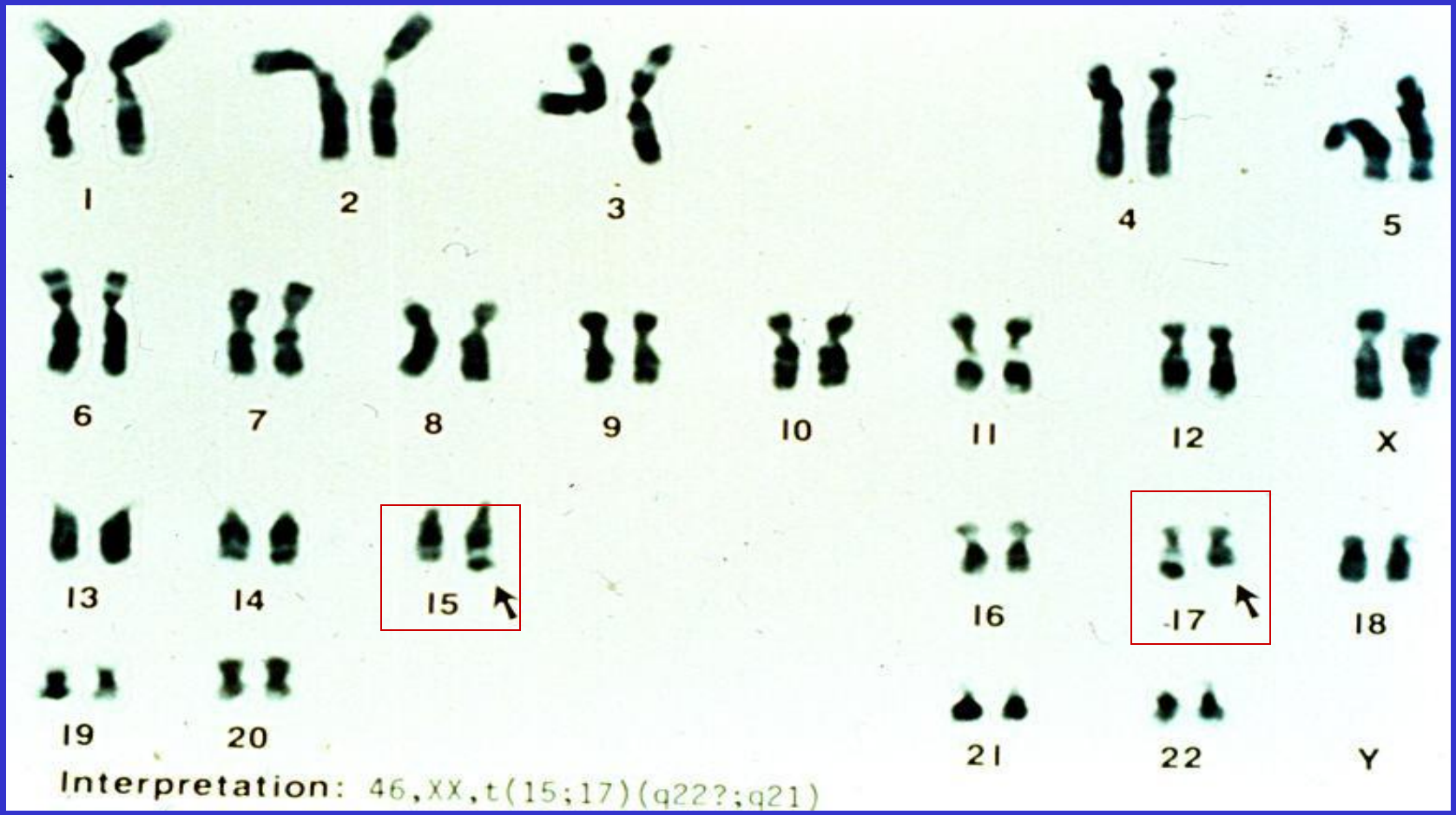
PO

FAC S

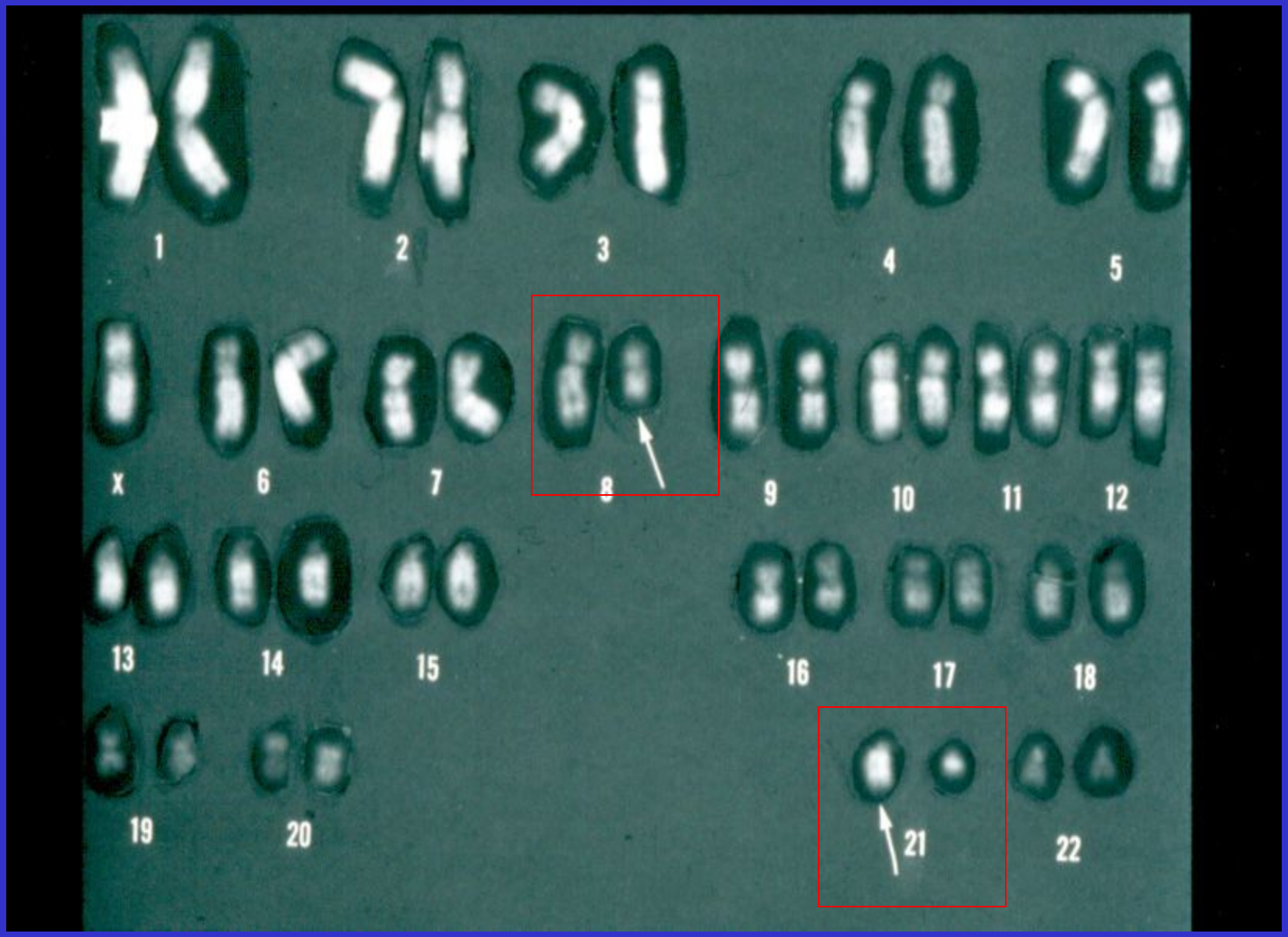


Classified into subgroups based on cell surface markers and cytogenetics

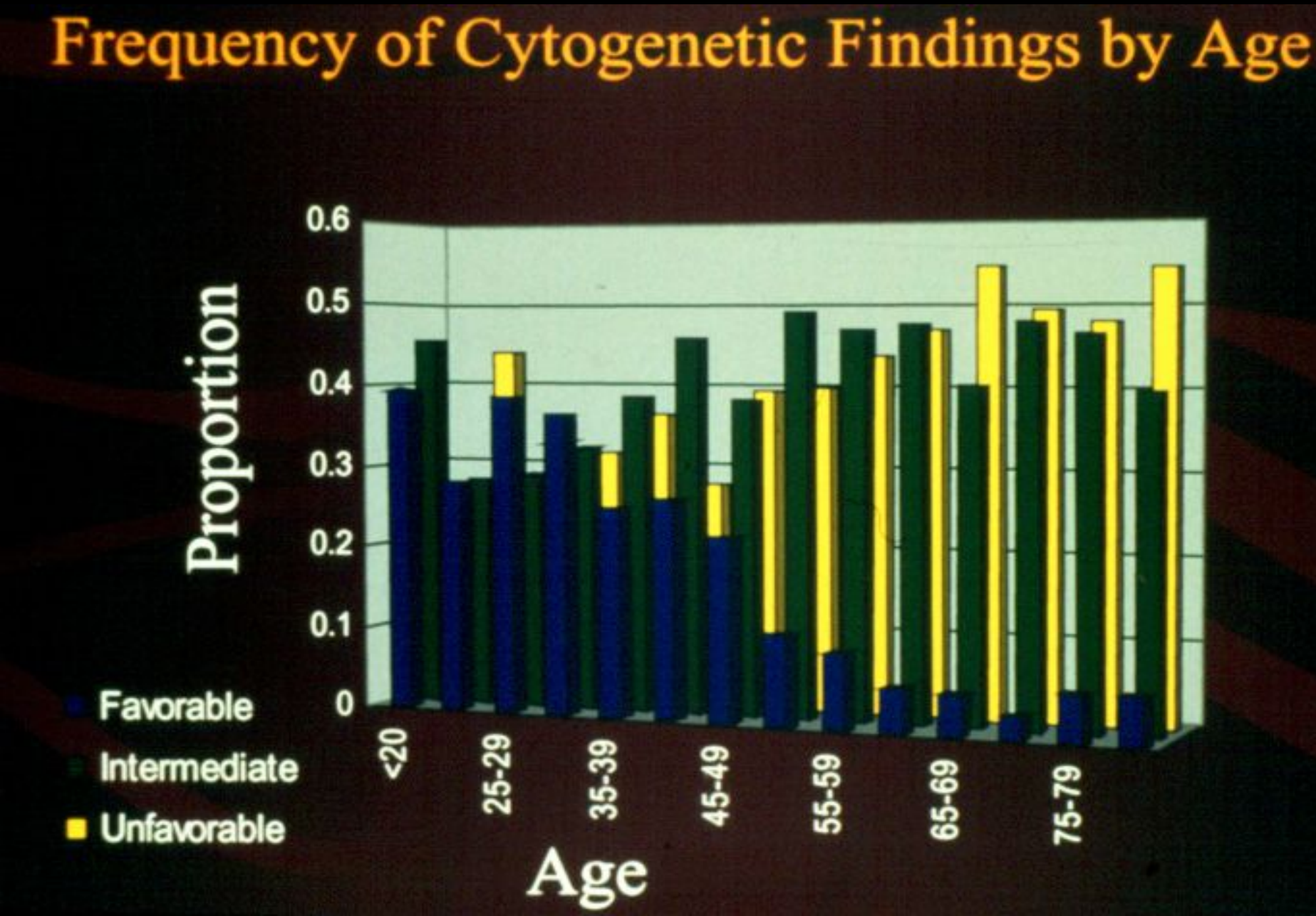
Diagnosis : Karyotype, cytogenetics chromosomal abnormalities: M3



AML M2



Chromosomal abnormalities (cytogenetics)



Prognosis
Risk factors

Cytogentics

Flt-3 mutation

Age

White blood cell count at presentation

FAB classification

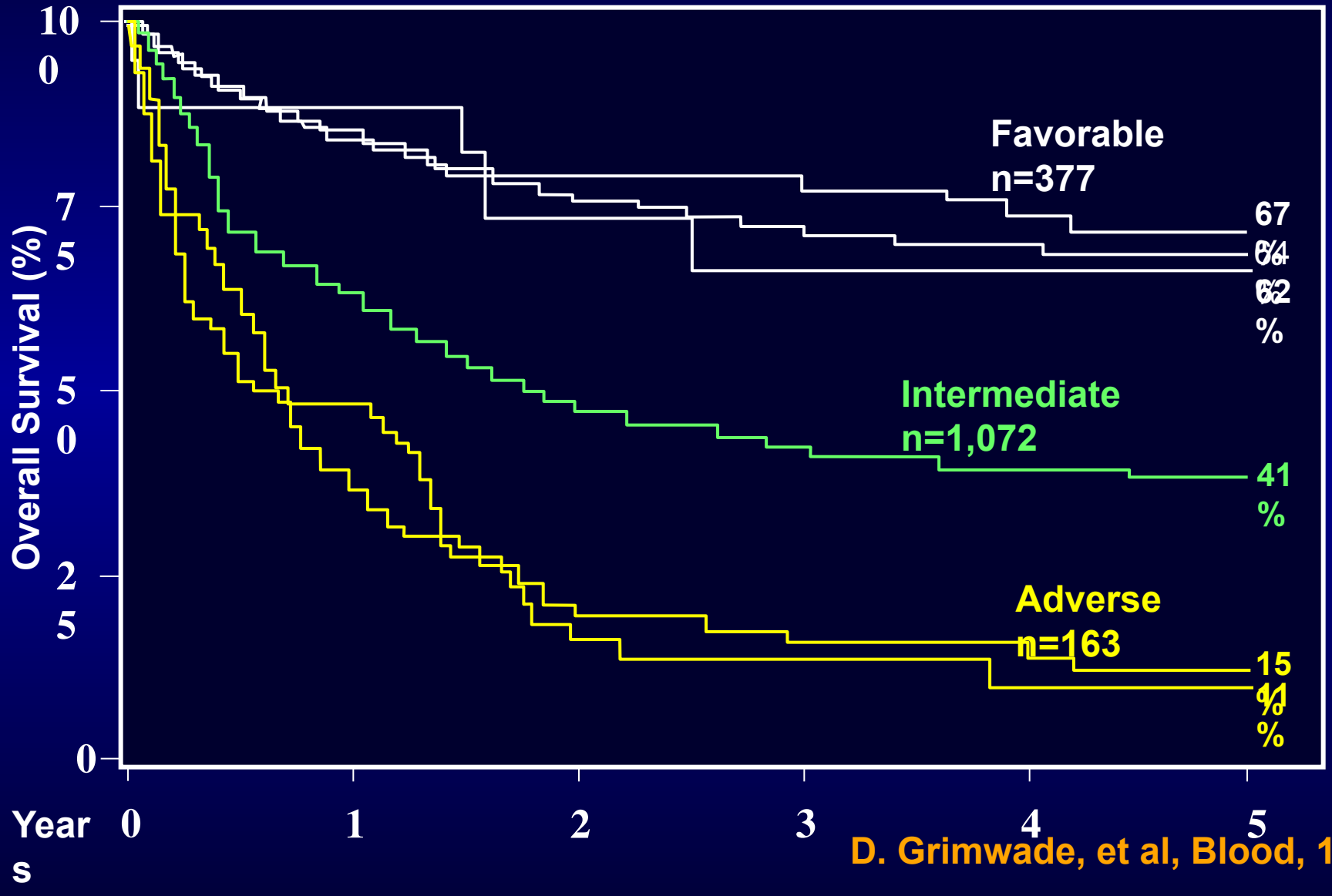
De-novo /secondary

Response to first course of chemotherapy

Cytogenetic Classification

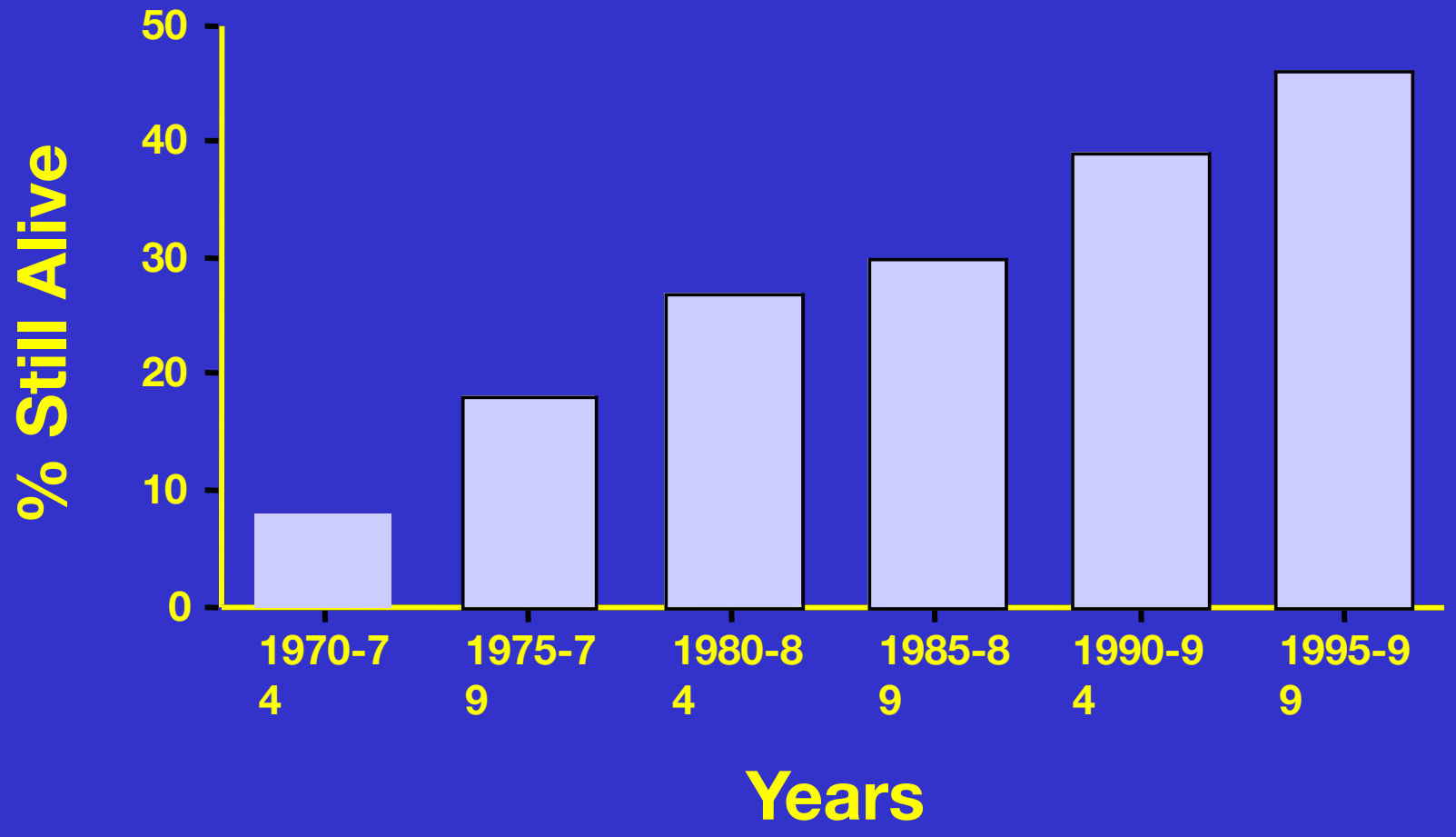
	SWOG	*MRC ; As for SWOG, except:-*
Favorable	t(15;17) Inv(16) t(8;21)-	t(8;21) — ± other abnormality
Intermediate	+8 normal karyotype	11q23 del(9q), del(7q) — alone Complex karyotypes (> 3 abn, but < 5 abn)
Unfavorable	-5/del(5q), -7/del(7q), inv(3q), 11q23, 20q, 21q, del(9q), t(6;9) t(9;22), 17p, Complex (> 3 abn)	All abnormalities of unknown prognostic significance Complex karyotypes (> 5 abn)
Unknown	All other clonal chromosomal aberrations with less than 3 abn	

Cytogenetic and prognosis



D. Grimwade, et al, Blood, 1998

Treatment


% Still Alive
50
40
30
20
10
0
1970-74
1975-79
1980-84
1985-89
1990-94
1995-99
Years

Treatment of acute leukemia (I)

: Supportive care

Hydration

Allopurinol to prevent hyperuricemia

Cytopharesis

Blood products

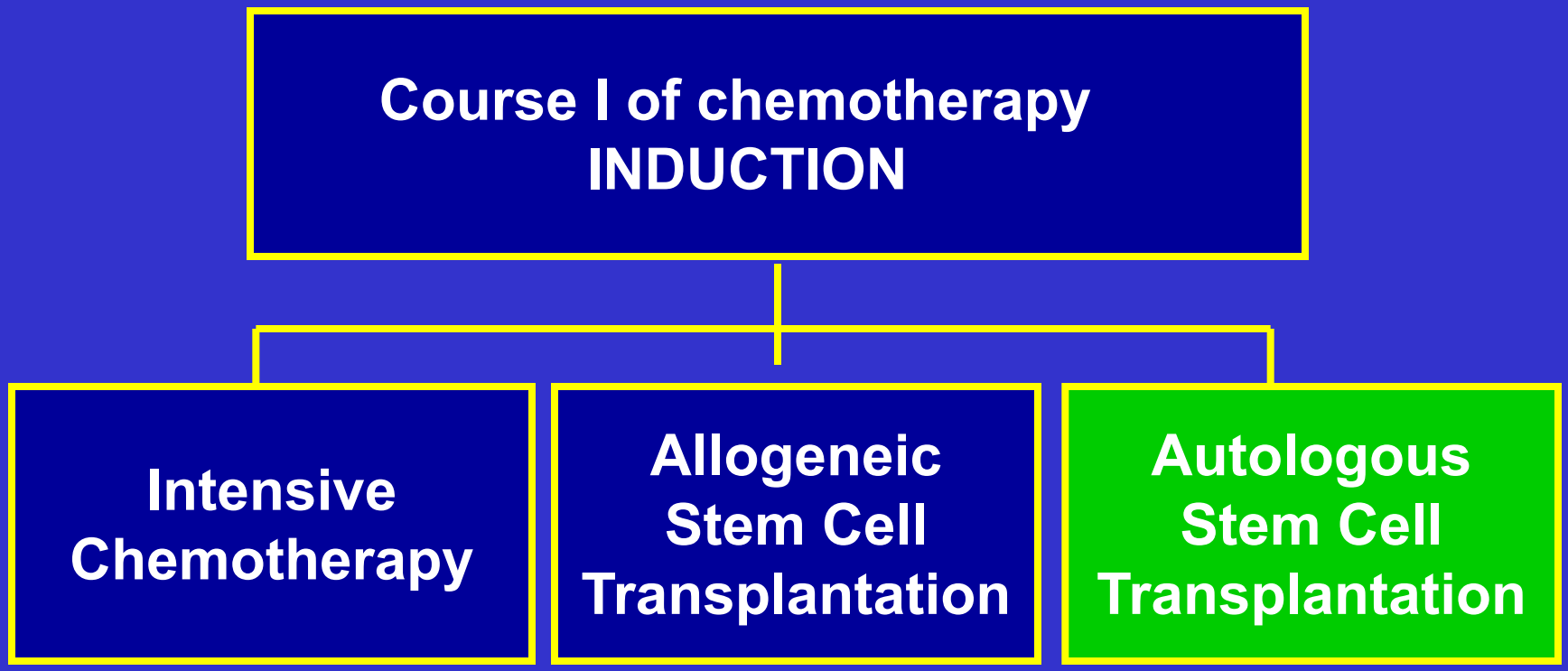
:Patient workup

History for occupational exposure or exposure

Bone marrow aspiration and biopsy

Bone marrow sample for cytogenetic, FACS, PCR

Treatment in the Younger AML Patient<60yrs



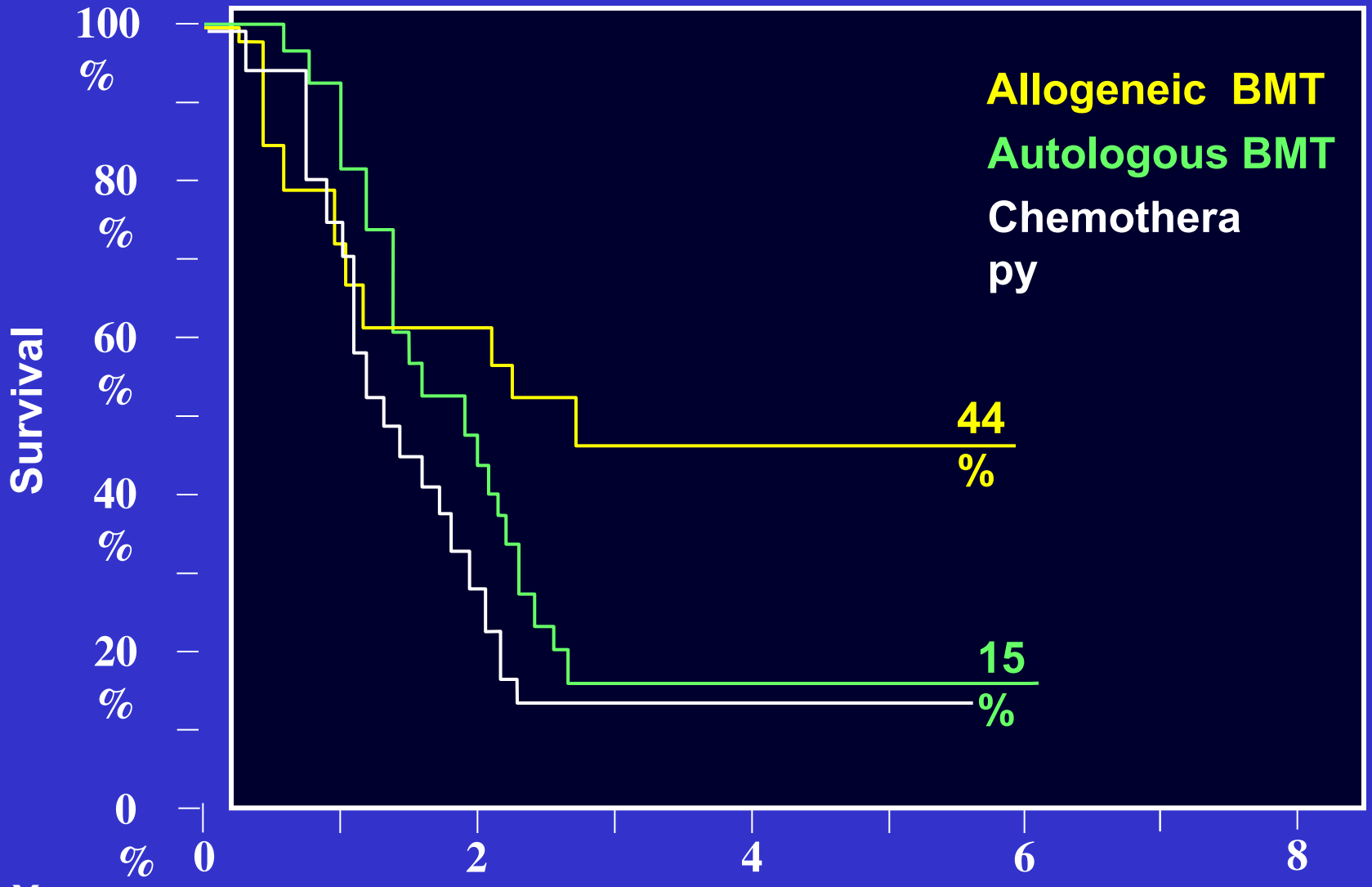
Outcome at 5 years

	Allo	Chemotherapy
Relapse	20-30%	40-60%
Overall survival	50%	50%
TRM	20-30%	5%

So how to choose which therapy ?to a specific patient

use the prognostic factors
to estimate
relapse rate and survival

Unfavorable Cytogenetics



Slovak M., et al, Blood, 2000

?What is the best treatment

Who should have a matched related Allo ? SCT

Patients with poor risk and standard risk younger than 35/40 years in CR1

Patients in CR2 or beyond

Who should have an ?Auto SCT

Favourable/standard risk patients who relapsed, responded again to chemotherapy and have no matched donor

? Patients in CR1

AML in Elderly patients(>60 years)

The majority of the patients are older than 60

Lower remission rate

Higher treatment –related morbidity & mortality

Very poor outcome

higher frequency of poor risk cytogenetics & resistance to chemotherapy

Future directions

Identify new prognostic factors

New therapies : Modulation of drug resistance

:Biological, specific treatments

Monoclonal antibodies

ATRA in APL, t (15;17)

Summary

The majority of patients still die of their disease (significantly poor outcome in elderly patients)

:Further improvement is needed

Better ability to predict patients outcome

Tailoring treatment to patient's risk factors

Improving therapy & supportive care

New strategies for elderly patients

Suggested Reading

Hoffbrand Hematology

Williams Hematology

Harrison's Text book of Internal Medicine