



The Acute Leukemias

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Leukemia

- 19th century European physicians noted a disorder of elevated white blood cells
 - “leukos”=white, “haima”=blood
- Leukemia
 - Cancer of the bone marrow which is the organ for normal blood cell development
 - Results in uncontrolled growth of abnormal blood forming cells in the bone marrow
 - Changes the number of normal cells in the blood



Leukemia--Epidemiology

- 35,000 new cases in US/year
- 90% in adults
 - 10 times more often in adults than in children
- Incidence of leukemia has decreased by 1.1% each year since 1995
- Myeloid vs. Lymphoid
- Acute vs. chronic

Normal Bone Marrow

- Has all of the types of cells necessary to make the blood cells needed in the bloodstream and body
- < 5% blasts in normal bone marrow
- Cells mature in the bone marrow and then enter the blood and carry out their functions

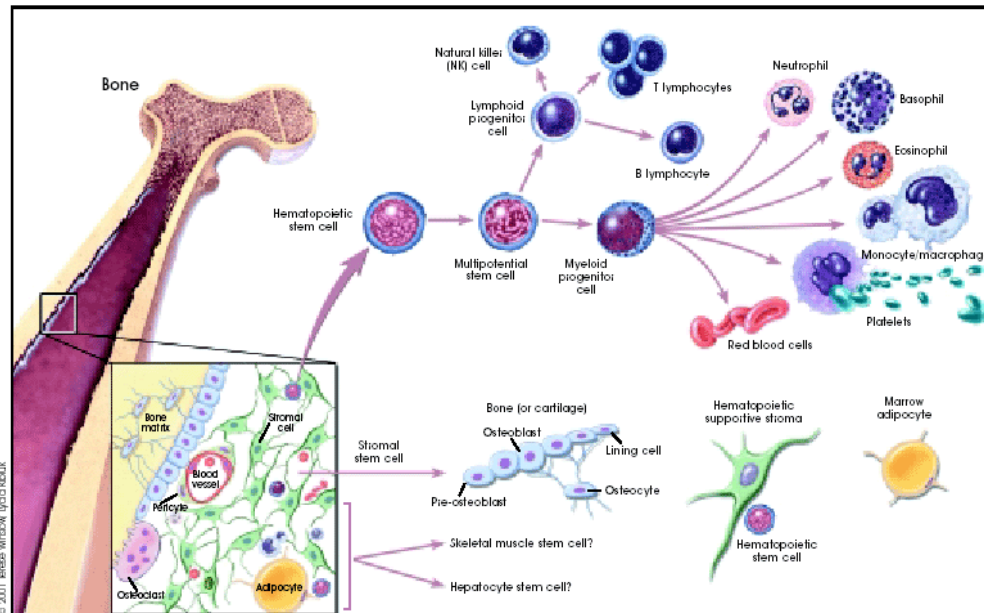
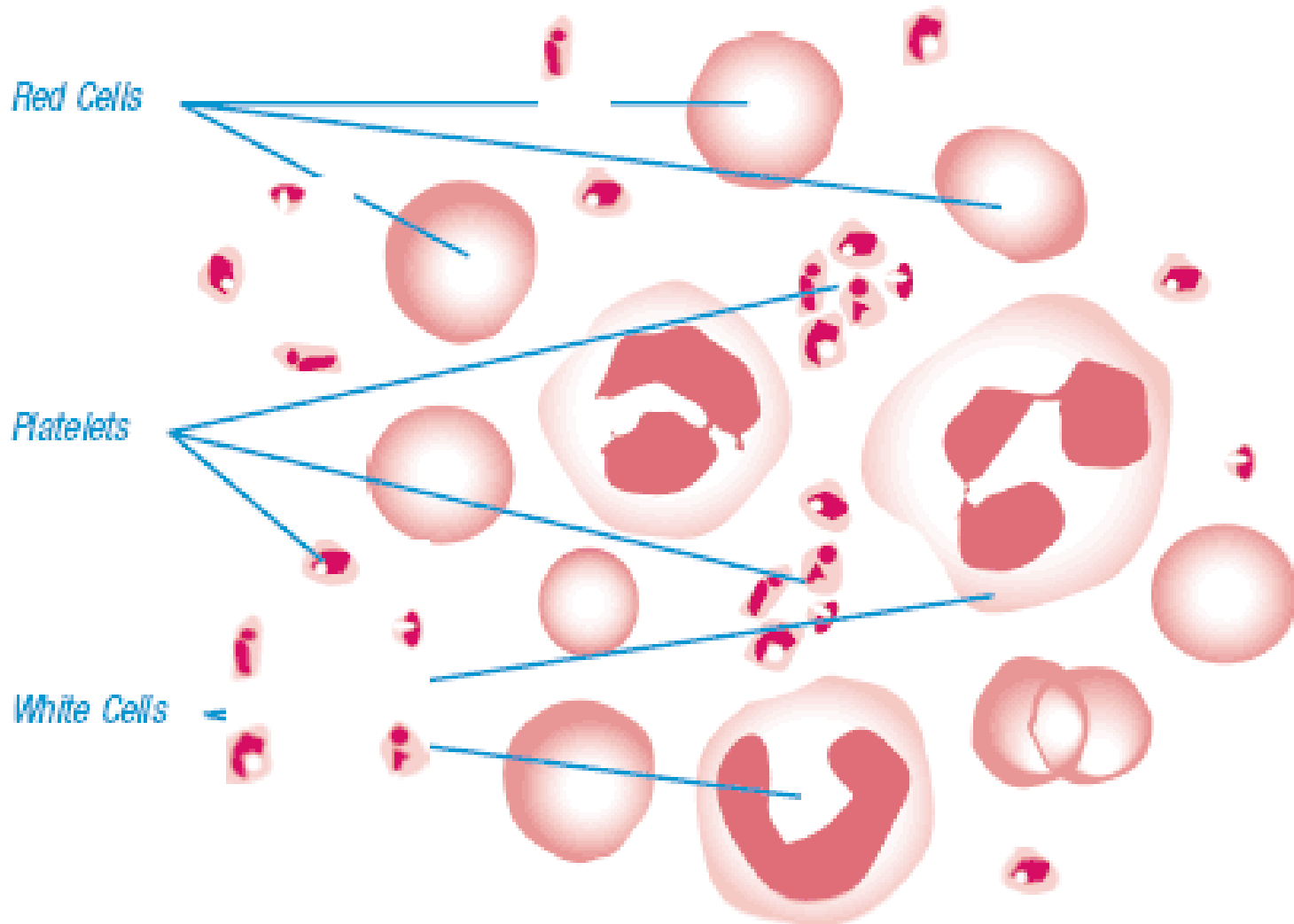


Figure 4.3. Hematopoietic and Stromal Stem Cell Differentiation.

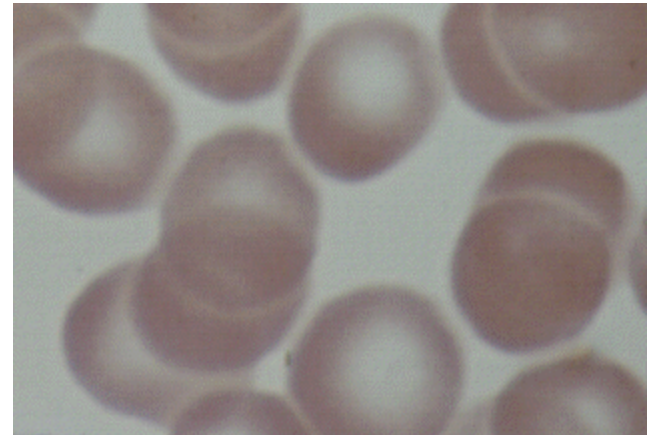
Blood cells



Red blood cells

RBC

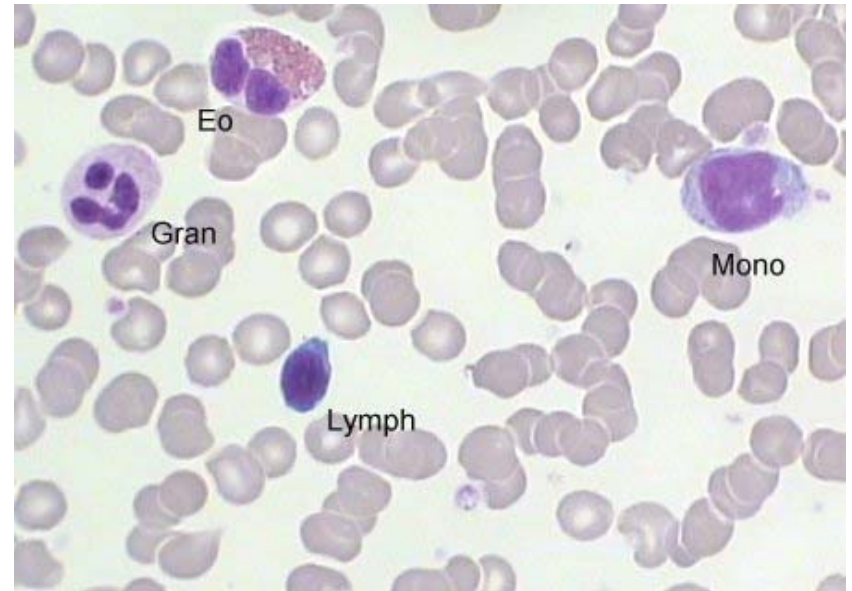
- Carry oxygen
- Contain hemoglobin
 - Normal Hemoglobin 12-16 g/dl
- Without rbc's feel weak, tired



White Blood Cells

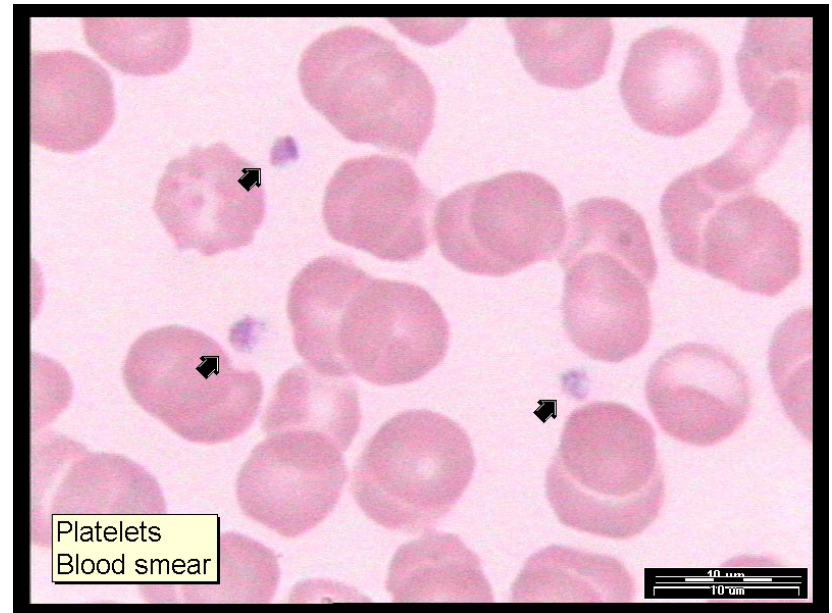
WBC

- important to the immune system
- Several different types
 - Granulocytes/neutrophils
 - lymphocytes
 - monocytes
- 4,000-10,000/ μ l
- Without healthy functioning wbc's, unable to properly fight infections

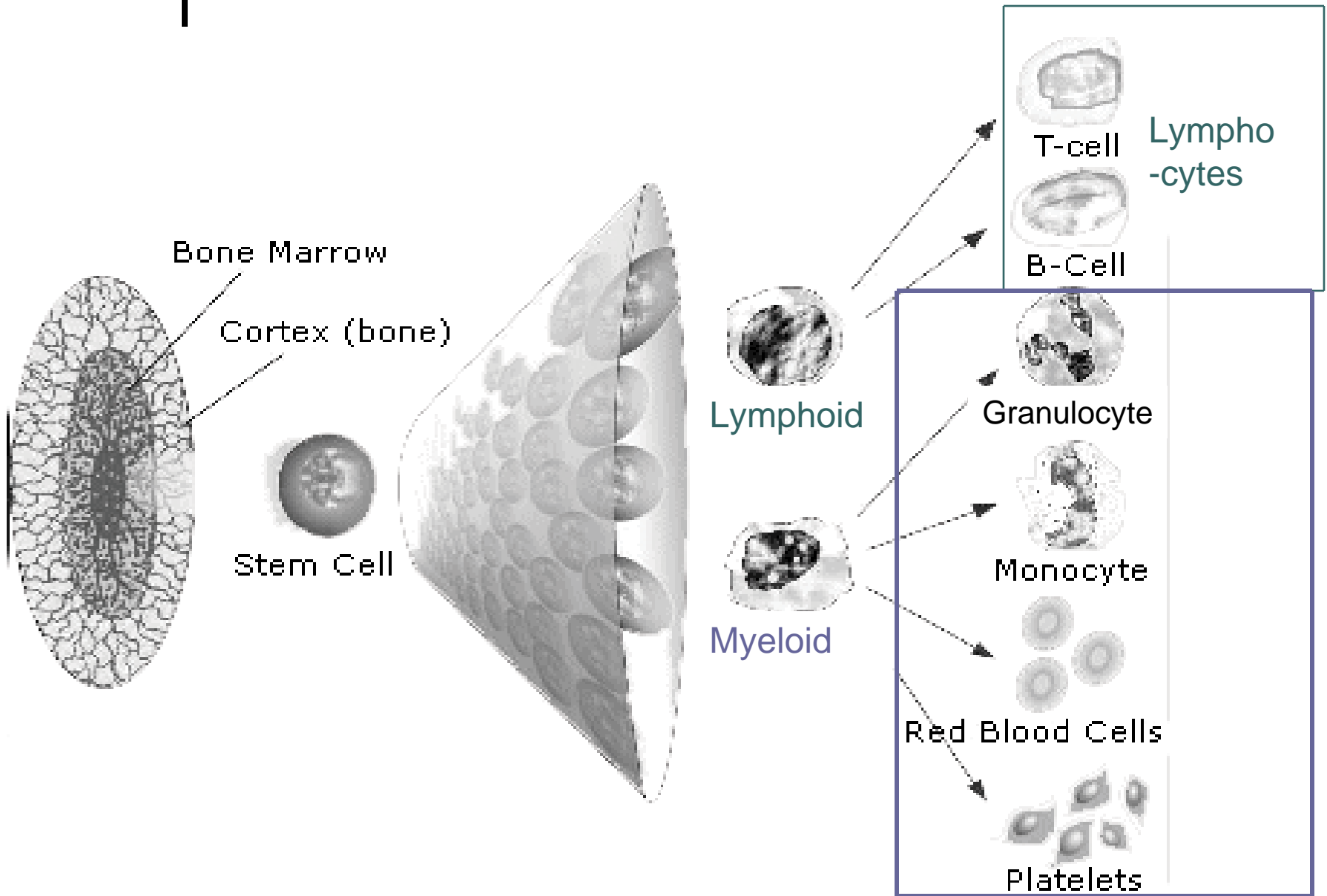


Platelets

- Help blood clot properly
- Prevent excessive bleeding when injured
- 140,000-450,000 / μl
- If insufficient, excessive bleeding at wound site, spontaneous bleeding



Normal blood cells





Classification of leukemias

Acute

Chronic

Myeloid
origin

Acute Myeloid
Leukemia (AML)

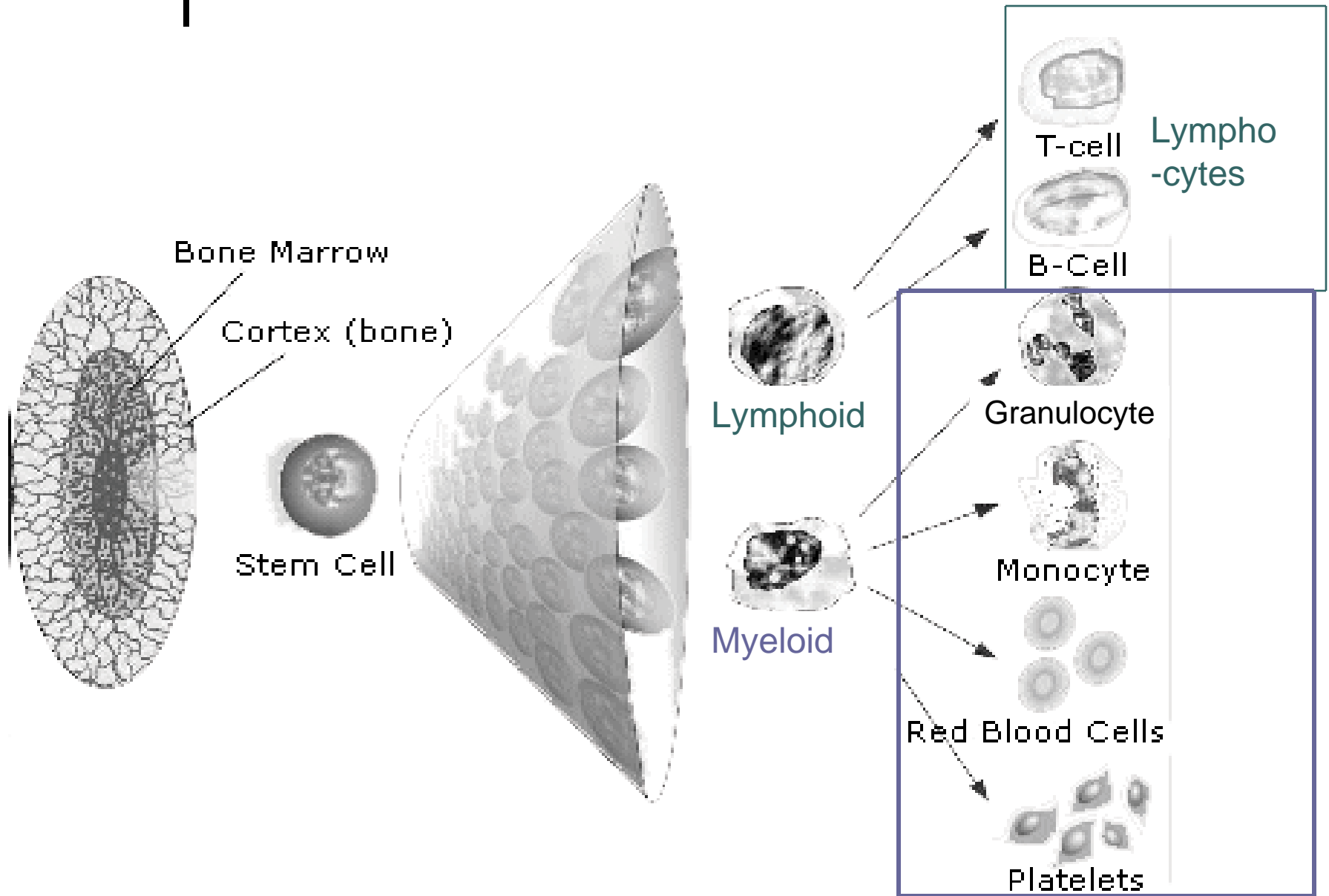
Chronic Myeloid Leukemia
(CML)

Lymphoid
origin

Acute Lymphoblastic
Leukemia (ALL)

Chronic Lymphocytic Leukemia
(CLL)

Normal blood cells





Chronic Leukemia

- Increased number of mature, although abnormal white blood cells
- In its early stages, many patients without symptoms
 - Even though there are too many mature cells, early on the disease has no effect on the other blood counts
- Course variable
- May be controllable for years, with or without medication



Acute Leukemia

- Uncontrolled proliferation of a malignant clone of immature hematopoietic cells
 - >20% bone marrow cells are blasts
- Diseased cells incapable of normal differentiation
- Leukemic cells prevent the maturation and differentiation of other bone marrow cells
- Disease progresses rapidly and is fatal without treatment

Myeloid maturation

myeloblast

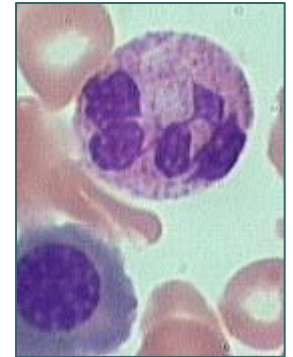
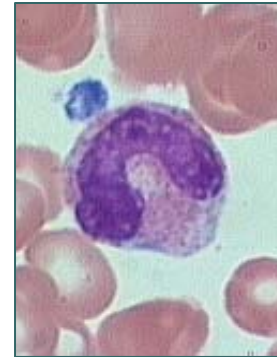
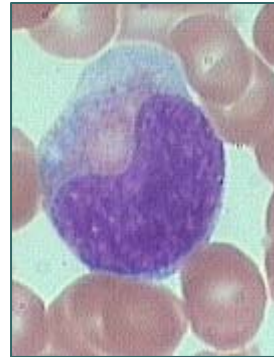
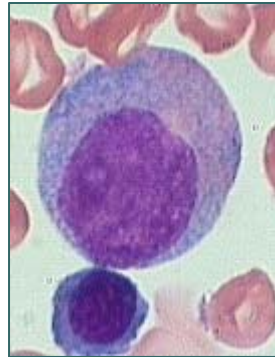
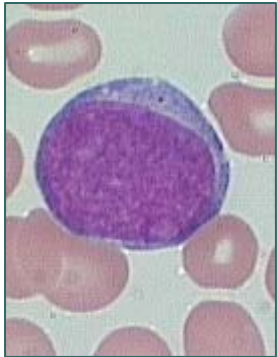
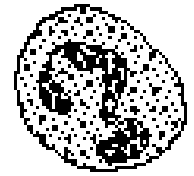
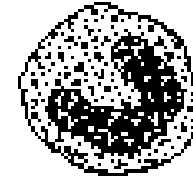
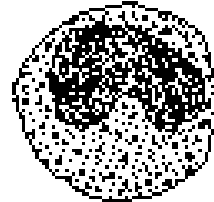
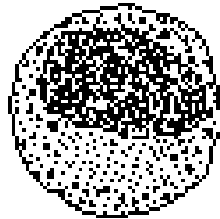
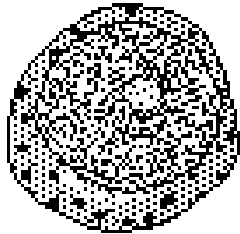
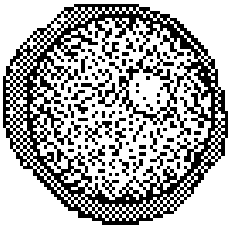
promyelocyte

myelocyte

metamyelocyte









band

Neutrophil or
granulocyte



MATURATION

PB in AL vs CML vs normal

	CML	AL	normal
blasts		+	
promyelocytes			
myelocytes			
metamyelocytes			
bands			
neutrophils			





ALL

- Acute leukemia where blasts are lymphoid in origin
- 3000-5000 new cases per year in US
- 20% of adult leukemias
- 75% childhood leukemias
 - Childhood cancer is leading non-accidental cause of death in children
 - most common childhood malignancy
 - Peak age is 4 years old



AML

- Acute leukemia where $>20\%$ of the bone marrow cells are non-lymphoid blasts
- The most common type of leukemia diagnosed in adults
 - 80% of adult leukemias
 - 11,000 cases per year



Acute Leukemia--Signs & Symptoms

- Anemia (low red cells) results in fatigue, pallor, shortness of breath, chest pain
- Thrombocytopenia (low platelets) results in easy bruisability, gum or nose bleeds
- White blood count can be low or high
 - Neutropenia (low neutrophil count) results in recurrent infections or poor healing
 - Occasionally patients may present with symptoms related to a high white blood count



How is the diagnosis made?

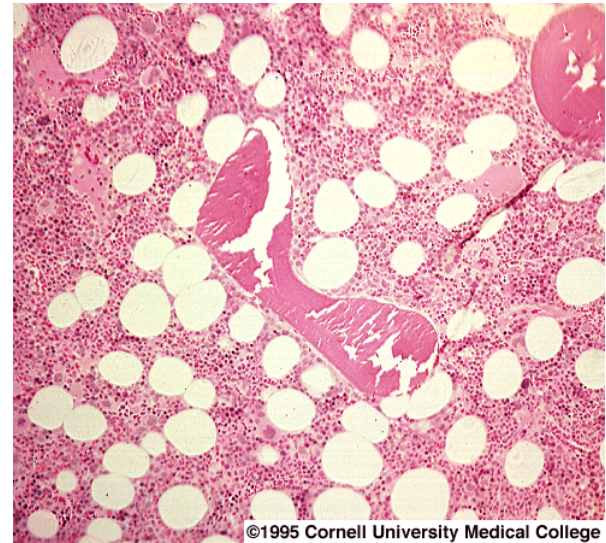
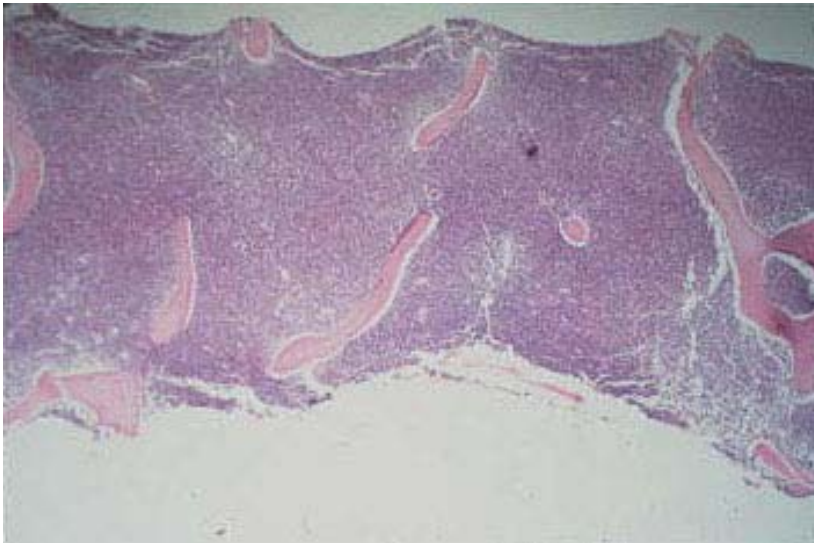
- Look in the blood
 - Sometimes we can see leukemia cells in the blood
 - Anemia, and low platelet count
- Bone marrow tests
 - Bone marrow biopsy
 - Bone marrow aspirate



Bone marrow in acute leukemia

- necessary for diagnosis
- useful for determining type
- useful for prognosis
- Acute leukemias are defined by the presence of $> 20\%$ blasts in bone marrow

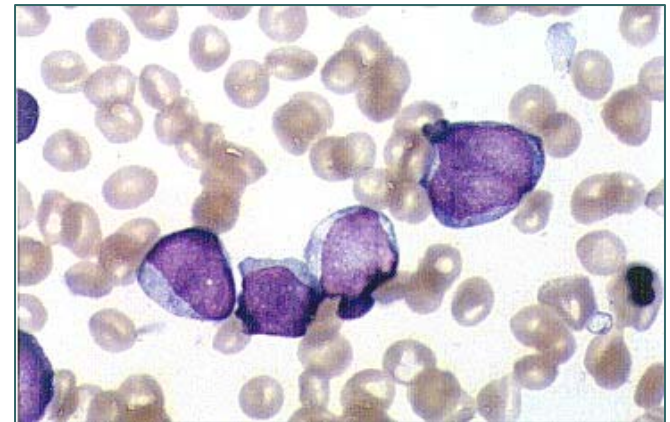
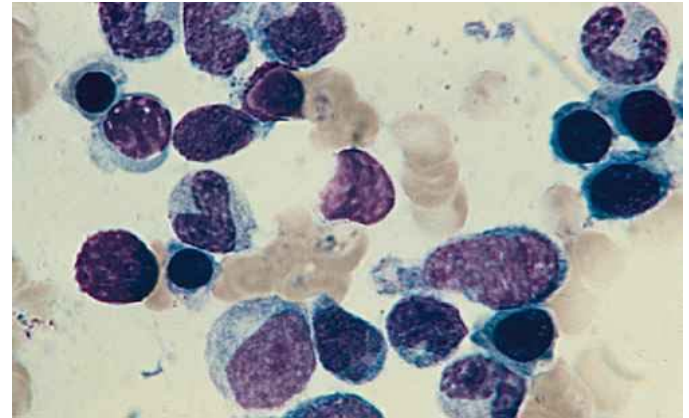
Bone marrow biopsy



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Bone marrow aspirate

- Looks at the types of cells in the bone marrow
- Normal bone marrow contains cells at various stages of maturation
- Acute leukemia results in an accumulation of blasts in the marrow





Acute leukemia classification

- ALL

- AML

- M0

- M1 myelocytic without differentiation

- M2 myelocytic

- M3 promyelocytic

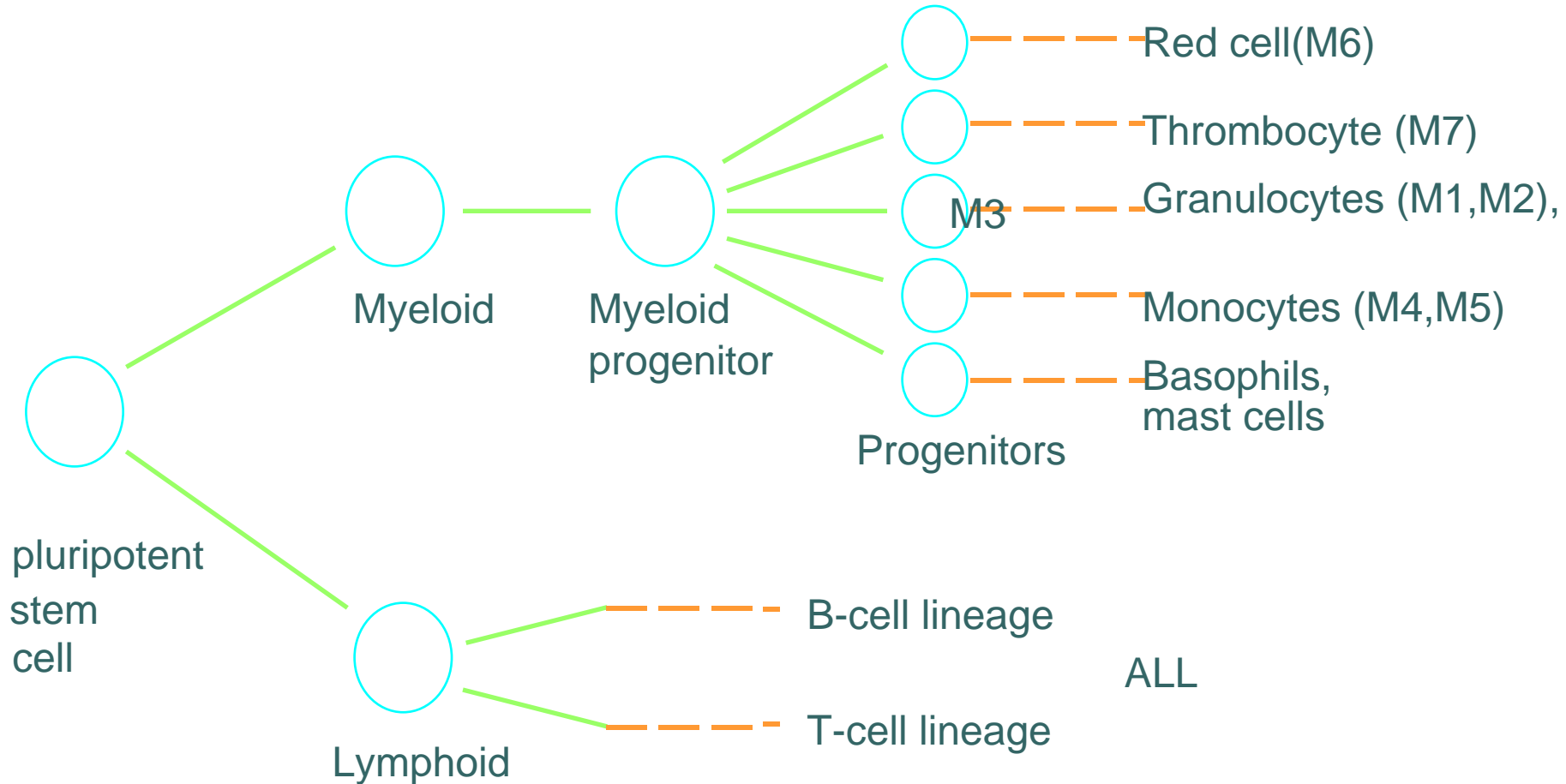
- M4 monomyelocytic

- M5 myelomonocytic

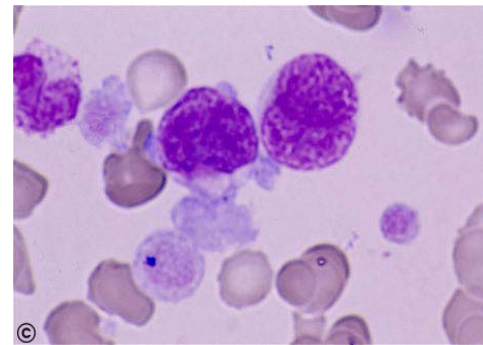
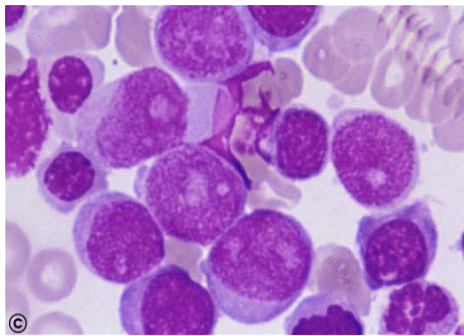
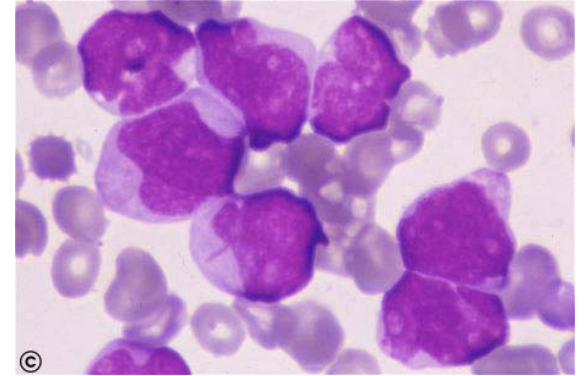
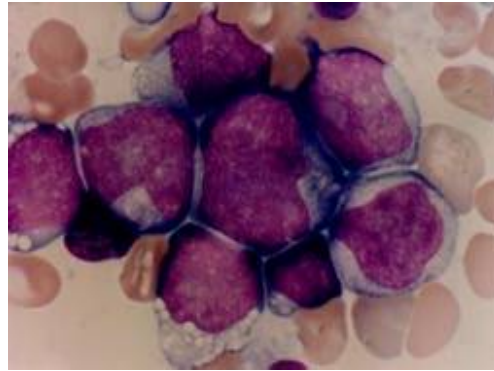
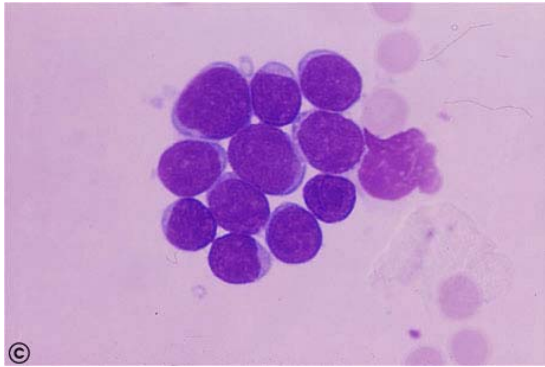
- M6 erythroblastic

- M7 megakaryoblastic

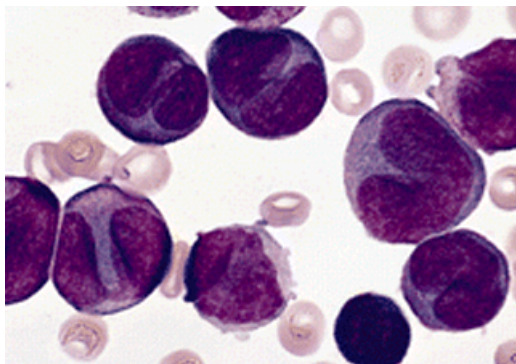
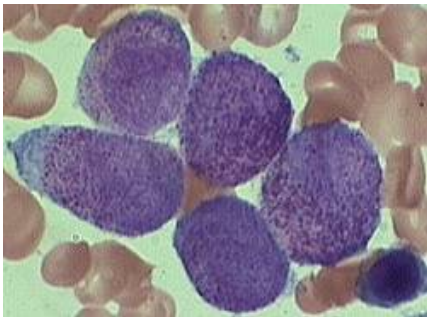
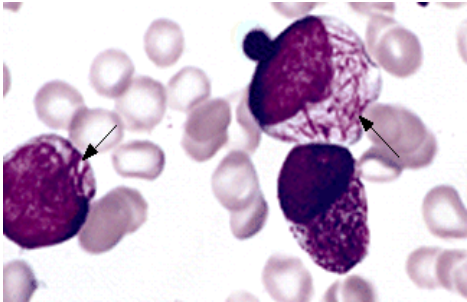
Leukemic Hematopoiesis



● ● ● | M0, M1, M2, M6, M7

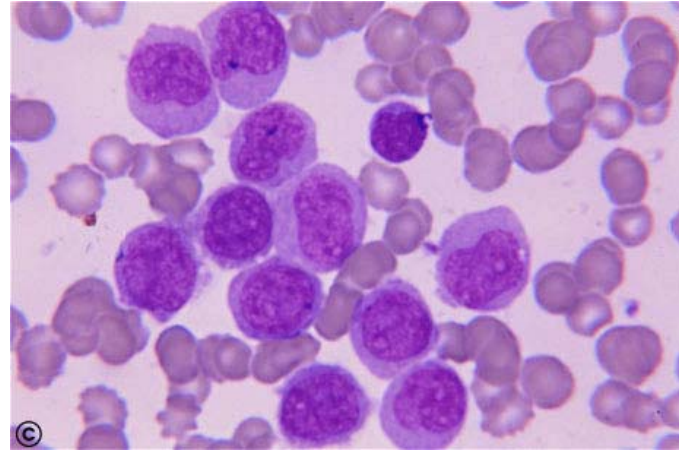
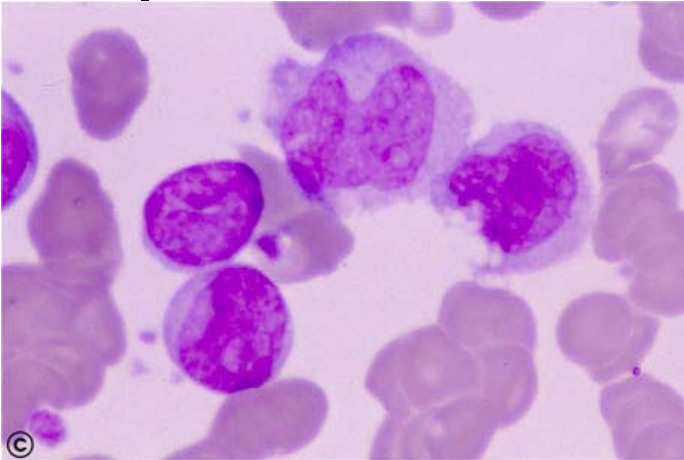


M3



- Higher risk of bleeding from the leukemia before or after treatment has started
- Advances in the last decade have allowed us to treat this type differently from all of the other AML's

M4, M5



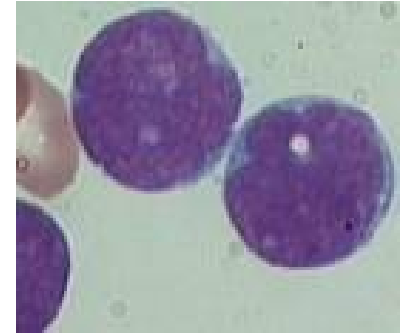
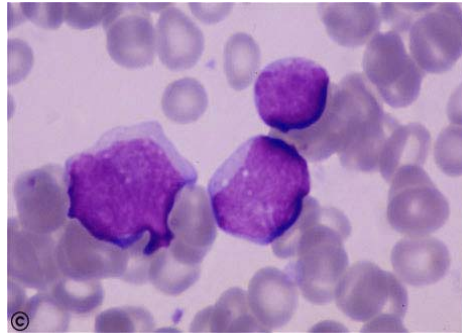
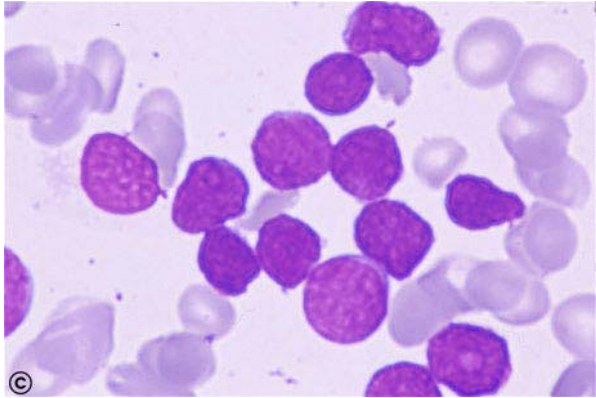
- Can have leukemia cells in places other than the blood or bone marrow
 - Gum swelling
 - Spinal fluid

- ● ● | Gum hypertrophy



- Can be associated with M4 or M5 leukemia

ALL

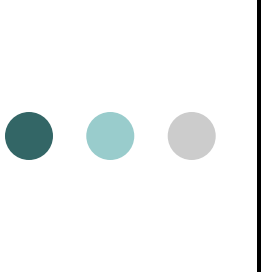


- Treated differently than AML
- Has a significant risk of disease in the spinal fluid, requiring treatment of the spinal fluid whether or not it's there



Acute leukemia—Studies

- Blood counts
- Blood tests to determine if the leukemia is causing other complications
 - Tumor lysis—waste products of the leukemia cells can clog the kidneys
 - Abnormal clotting (DIC)
- Look for infections
- Spinal taps
- Marrow aspirate/biopsy



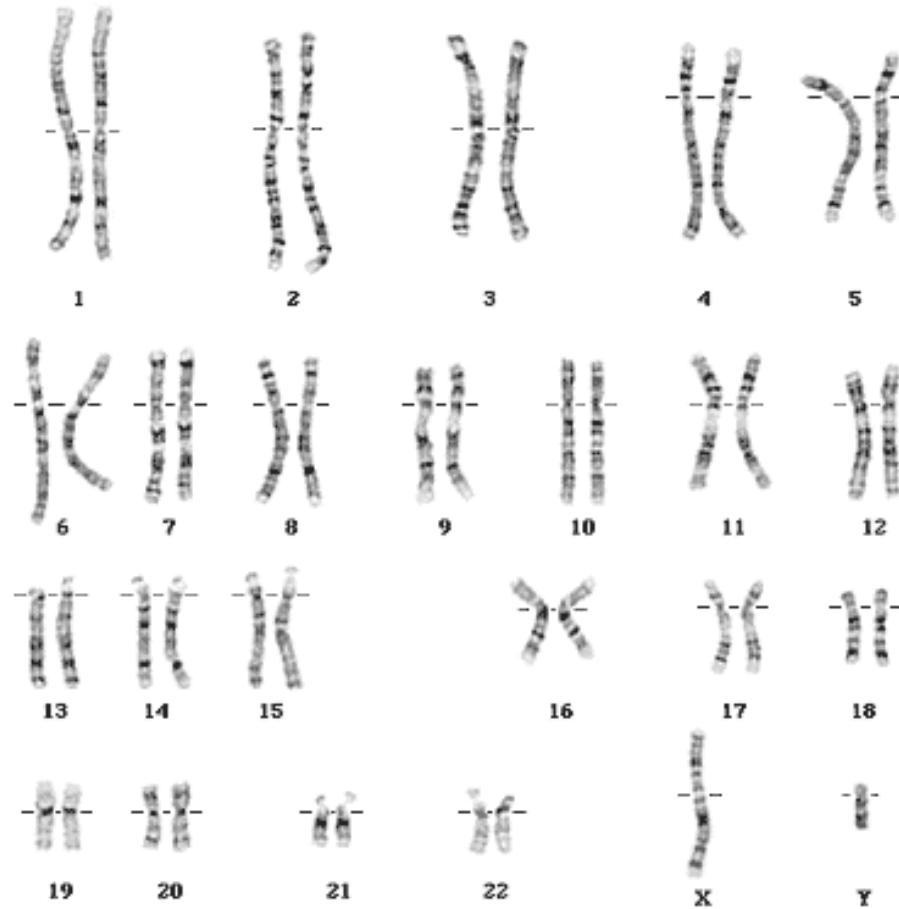
Acute Leukemia—Bone marrow studies

- Morphology—look at the cells to try and determine what type of leukemia it is
- Cytohistochemistry--Stain the cells with substances that are specific for specific types
- Immunophenotype—look of proteins on the cell surface that help us identify the cell type
- Cytogenetics—analysis of chromosomes in the leukemia cells
 - Diagnostic
 - prognostic
- Gene mutation studies



Chromosomes

- Small bodies in the nucleus of the cell that contain wound up strands of DNA
- Instructs cells on how to make copies of themselves and get copied every time a new cell of that type is made
- DNA carries information that controls the production of proteins and other molecules essential to cell function



- Normally each cell has 22 pairs of chromosomes and 2 additional chromosomes.



Inherited chromosomal abnormalities

- You are born with one chromosome of each number from each parent
 - When you are born you have the same chromosomes in every cell in your body.
 - These determine different things, like hair color, height, eye color etc.
 - Some chromosomes that you inherit carry information that make it more likely that you get certain diseases like diabetes, arthritis etc.
 - If you inherit the wrong number of chromosomes you can get “genetic” diseases. For example in Down’s syndrome, there are 3 copies of chromosome 21 instead of 2.

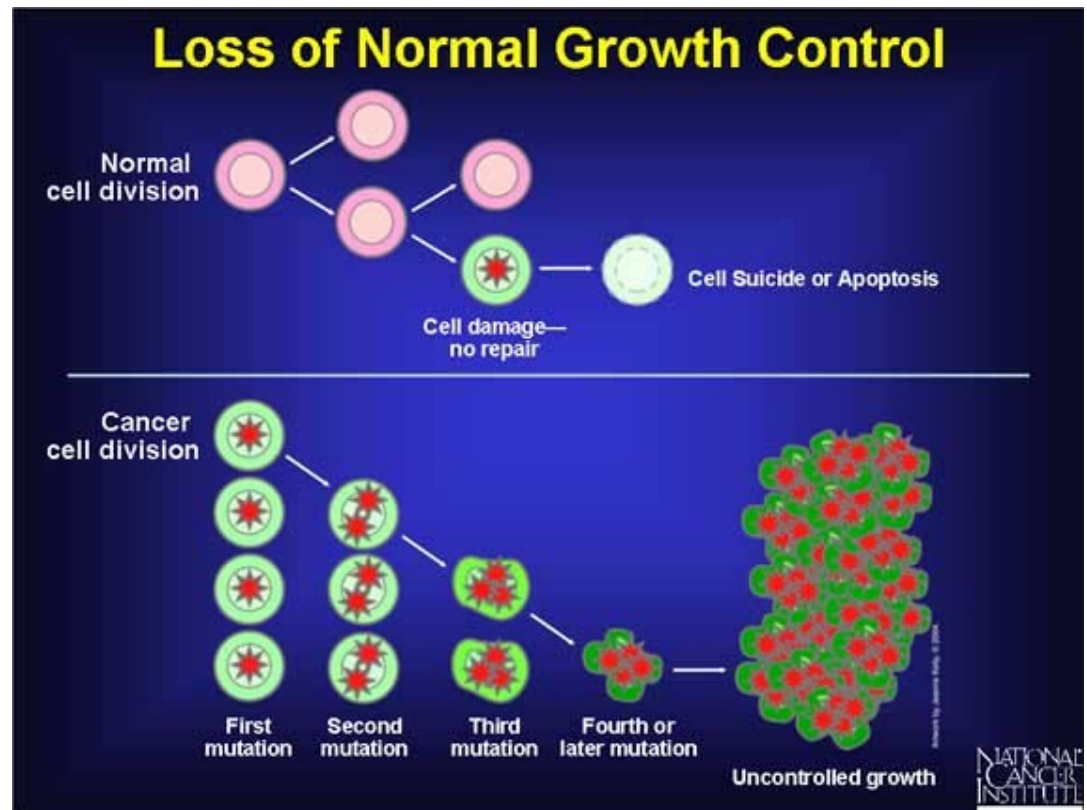


Chromosomes and Cancer

- It is possible for the DNA in some cells to get damaged over time.
 - Certain things are known to damage DNA
 - Excessive radiation—e.g. atomic bomb
 - Chemotherapy
 - Benzene
 - Other times DNA is damaged without any clear reason
- The body is very good at repairing damaged DNA
 - BUT--if repair is not carried out properly, genes or whole chromosomes can become abnormal.
- The cells that contain the abnormal DNA and chromosomes can become cancerous and grow uncontrollably

Principles of leukemogenesis

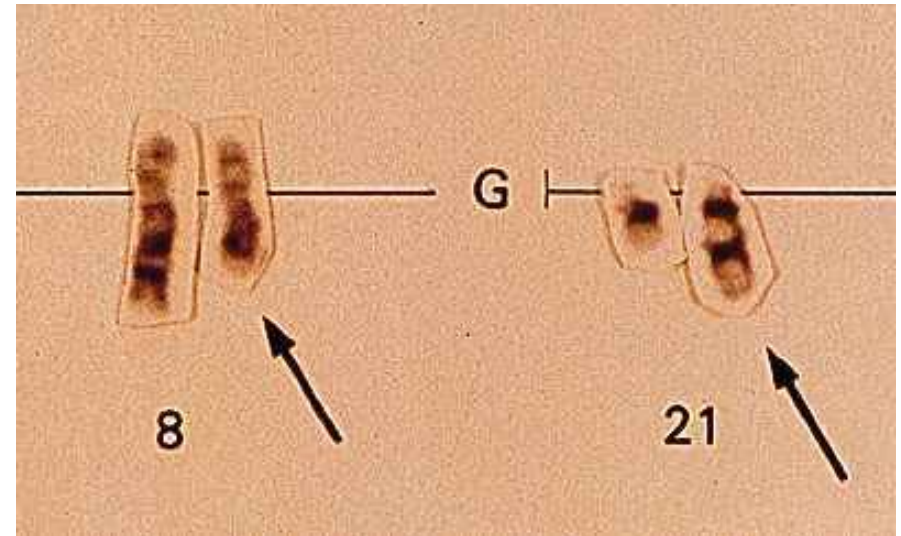
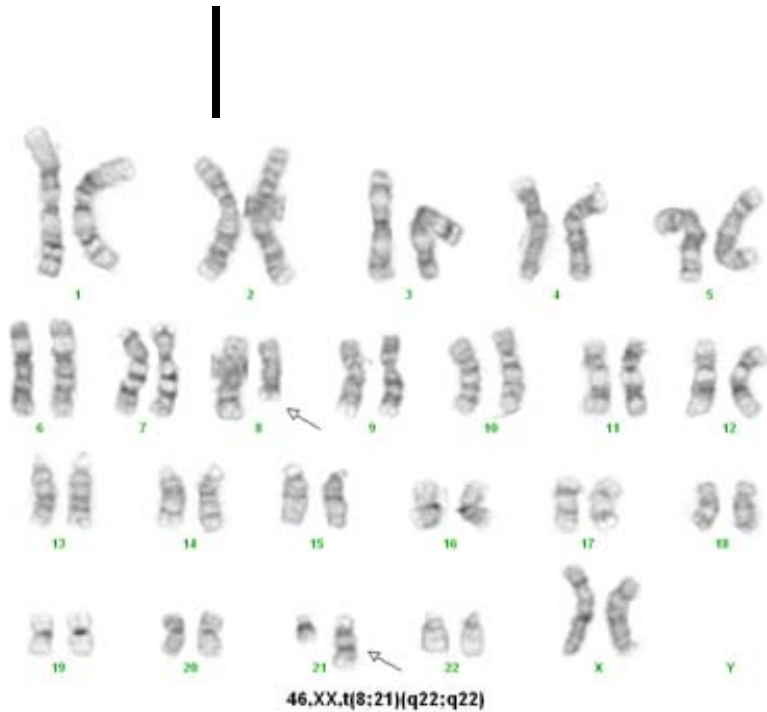
- a multistep process
- dysregulation of cell growth and differentiation (associated with mutations in DNA)



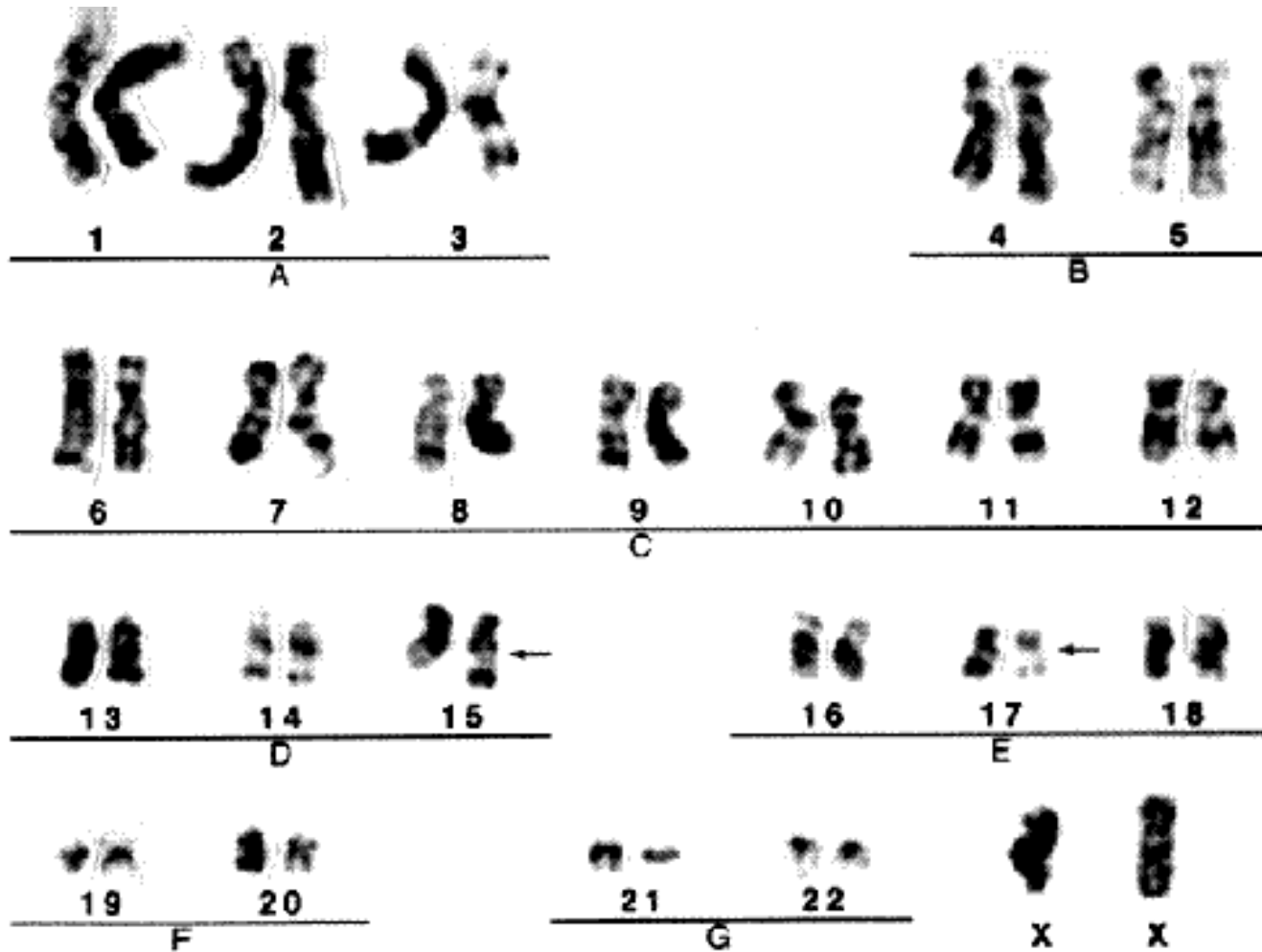


Leukemia and chromosomes

- From studying the chromosomes of thousands of patients with leukemia and we have learned that
 - certain chromosome abnormalities are associated with specific leukemia types
 - the chromosomal changes can be important in prognosis

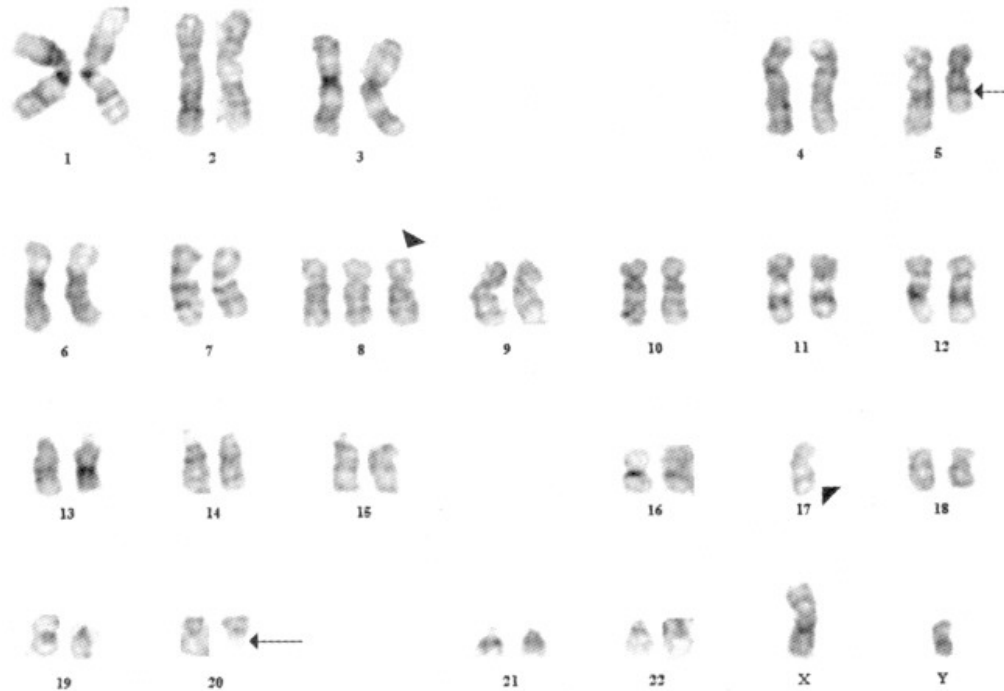


This chromosome abnormality is found in leukemia cells of patients with AML and is associated with a better than normal chance of getting into remission and a better chance of staying in remission with our treatments.



This chromosome abnormality tells you the patient has M3 AML and needs a specific treatment.

Multiple cytogenetic abnormalities

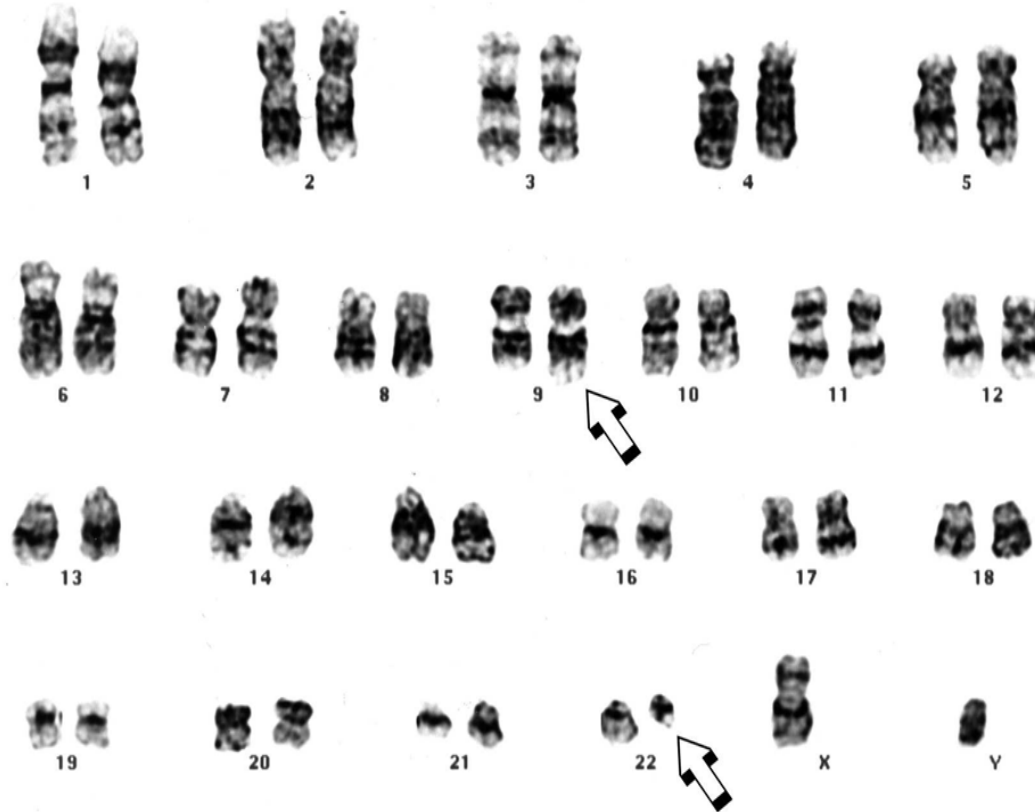


In patients with AML with more than 3 abnormal chromosomes, even if they get into remission, with standard treatment they are unfortunately at a high risk of relapse

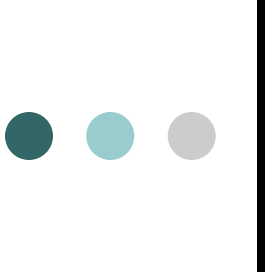
Cytogenetic Abnormality in

ALL:

-



Patients with ALL who have the Philadelphia chromosome need especially aggressive ALL therapy



Acute Leukemia--Treatment Stages

- Remission Induction
 - Initial goal of treatment is complete remission
 - no evidence of leukemia
 - return of normal bone marrow and blood cells
- Postremission Therapy
 - prevent relapse of disease
- Salvage Therapy



Induction Chemotherapy

- Drug therapy
- Destroys rapidly dividing cells
- Non specific
 - Kills off the leukemic cells
 - Also destroys normal blood cells, other rapidly dividing cells, i.e. hair, mucosa
- It can take one or two rounds of chemotherapy to get rid of all of the visible leukemia cells



Toxicity during Induction

- Many side effects
 - Anemia-thrombocytopenia
 - Neutropenia
 - Alopecia
 - Mucositis-stomatitis
 - Nausea and vomiting
 - Fatigue
 - Possible cardiotoxicity
- Supportive Care



Types of Postremission Therapy

- Chemotherapy that is similar to but less intensive than the initial chemotherapy
- Bone marrow transplantation
 - Use of high doses of chemotherapy +/- radiation to kill the patients' bone marrow followed by an "infusion of stem cells"
 - Autologous stem cell transplant
 - Allogeneic stem cell transplant
- Maintenance –low dose long term chemotherapy



Allogeneic Transplant

- Use of someone else's cells to repopulate the bone marrow—requires a “match”
- Benefit of getting the donor's immune system which may help fight the leukemia
- Risk of complications related to having that immune system attack the patient's normal cells—Graft vs. host disease.
- Many patients not eligible
- Research ongoing to see if benefits of the graft versus leukemia effect possible without the risks



Autologous Transplant

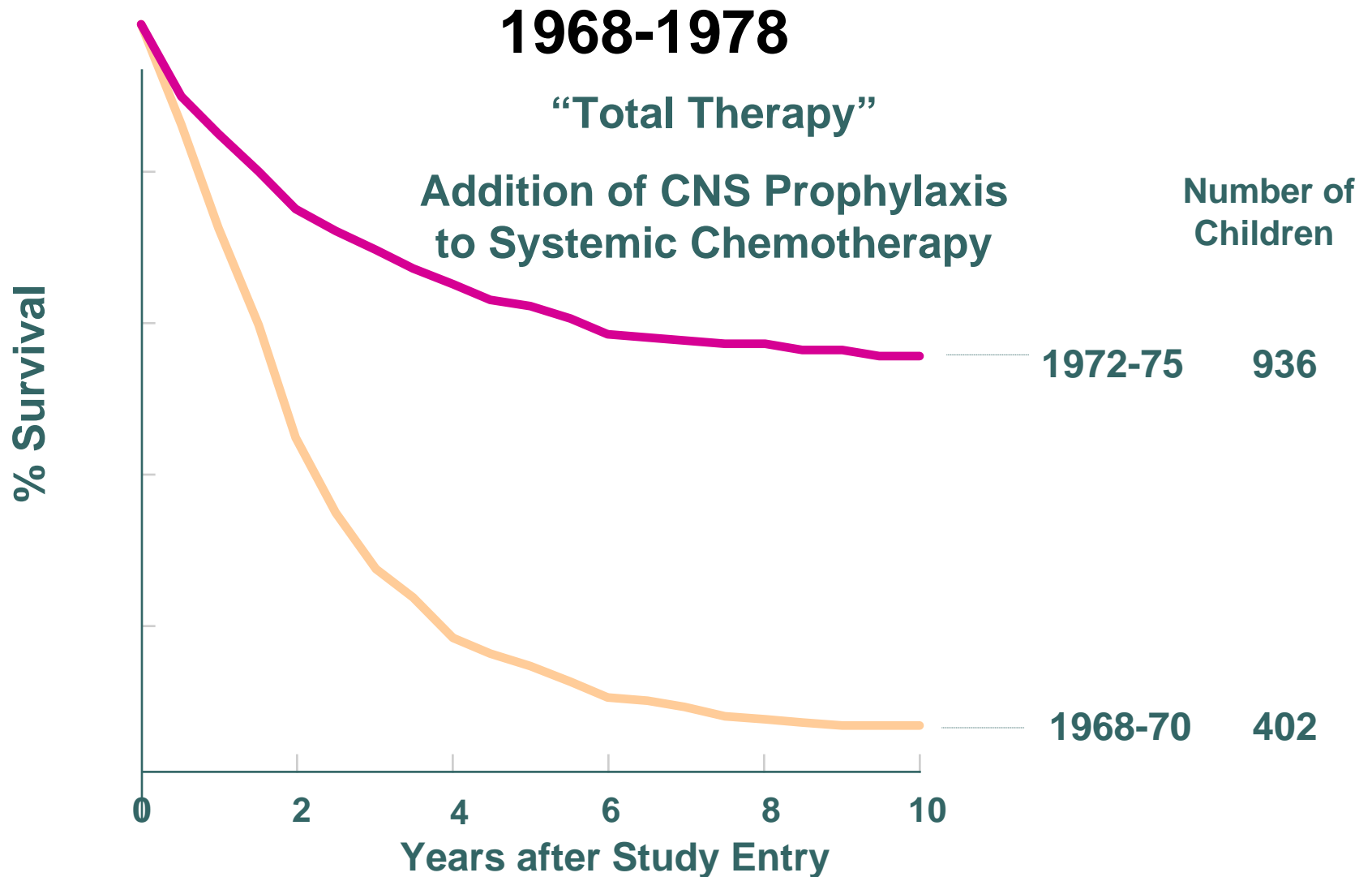
- Use of the patients own cells to repopulate the bone marrow
- Requires healthy patient cells
- Risk of relapse even if the cells look healthy
- Research now focusing on things that can be done to decrease the chances that patient will relapse



History of ALL Therapy

- 1940's: single agent chemotherapy
- 1950's: combination chemotherapy
- 1960's: maintenance chemotherapy, first group of children cured
- 1980's: Induction followed by consolidation followed by reinduction and reconsolidation

Survival in CCG ALL Trials





Adult ALL

- Remission induction successful in >80% of patients
- CNS prophylaxis is now standard
- Chance of long term disease free survival (i.e. no relapse) is better if patients receive a bone marrow transplant from a healthy donor
- For patients with the Philadelphia chromosome, risk of relapse is the highest, so need to be very aggressive, if possible.
 - Gleevec blocks the protein made by the Philadelphia chromosome
 - This improves response rate and survival



AML Therapy

- 1962- -6MP/MTX able to induce temporary remission in few AML pts
- 1970's-- Ara-C developed
- Ara-C ± 6TG or DNR---50%CR
- 1980's
 - 3+7 regimen--Anthracycline (DNR/ADR) + Ara-C --CR rate 65-80%
 - high dose Ara-C consolidation resulted in long term survival



Randomized Trials—Conclusion

- Several studies have been done to look at each form of consolidation therapy in first remission AML
 - Allogeneic transplant
 - Autologous transplant
 - Chemotherapy alone
- No clear winner
- Patients who relapse after chemotherapy can often be salvaged by transplant
- Allogeneic transplant early in therapy seems particularly to benefit:
 - Young patients who have poor prognostic disease
 - For everyone else, chemotherapy or autologous transplant offer equivalent outcome, usually with fewer side effects



Advances in AML

Ideal therapy would be one that is toxic to the leukemia cells but not to the normal cells



Acute Promyelocytic Leukemia

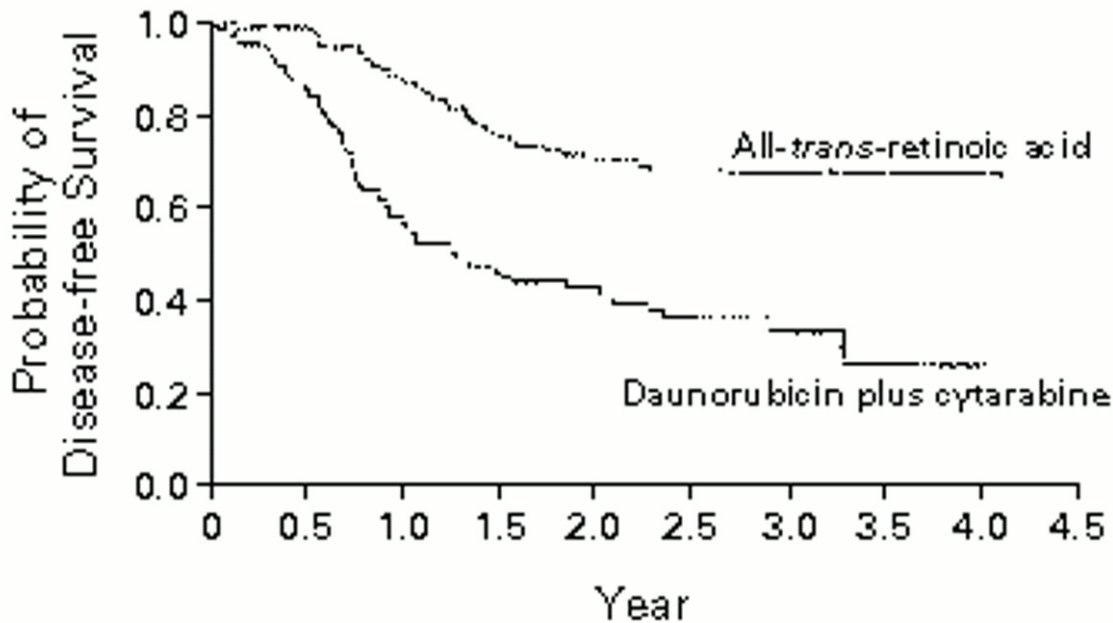
- M3 AML
- Because of complications related to the disease, used to be the type of AML that was the most dangerous
- Now with newer therapies, has become the most treatable AML



APL and ATRA

- t(15;17) determined in the 1970's
 - 1990's it was determined that the 15;17 translocation resulted in an abnormal gene
 - This abnormal gene was found to affect the way the cells handled a chemical in the body called retinoic acid that allowed the cells to mature properly
 - In the presence of the abnormal gene the cells were not able to mature properly
- Through a sequence of clinical trials it was determined that by simply giving a Vitamin A derivative, ATRA, in addition to chemotherapy , we are able to overcome the problem
 - More patients go into remission
 - More patients stay in remission

APL is now one of the most curable forms of leukemia.



	1ST YR	2ND YR	3RD YR	4TH YR	5TH YR
	no. of events/no. at risk				
Daunorubicin plus cytarabine	49/120	14/61	6/35	1/8	0/0
All-trans-retinoic acid	15/124	18/98	2/67	0/21	1/3



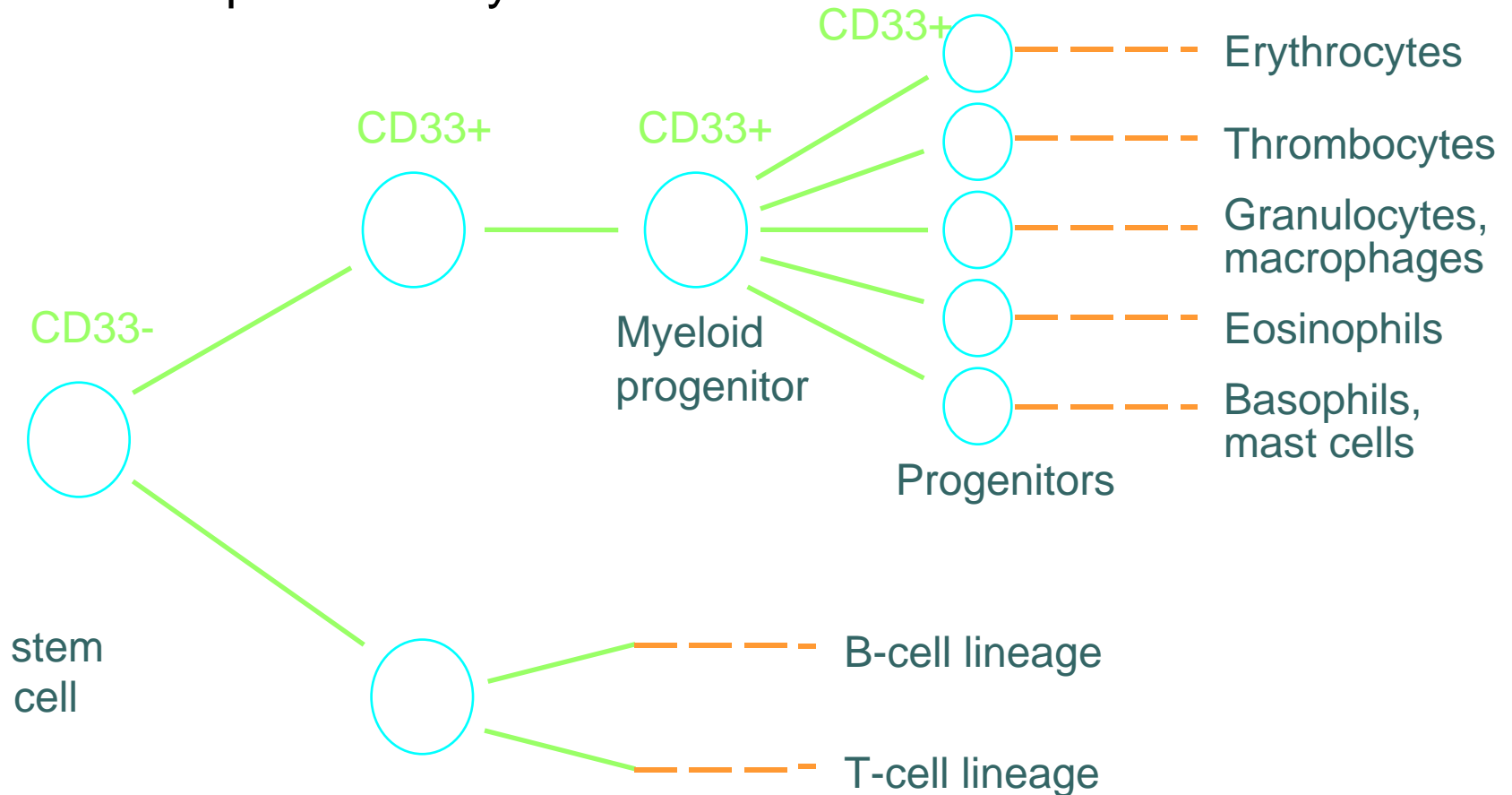


Arsenic and APL

- In the late 1990s, spectacular results were observed in China using arsenic trioxide to treat APL that had relapsed after ATRA therapy.
- A recent randomized study showed the highest cure rate of any adult leukemia in a regimen combining ATRA plus daunorubicin/ara-C followed by arsenic for APL.

Monoclonal Antibodies

- Each cell express antigens on the surface
- Monoclonal antibodies can target antigens present only on leukemia cells





Gemtuzumab Ozogamicin (Mylotarg)

- Attaches to the CD33 molecule on cells
- Has a poison attached to it that gets into those cells and kills them
- Has been approved for use in patients > 60 with relapsed disease
- Being studied in clinical trials as part of the remission therapy in younger patients with AML in first remission



New agents in clinical trials

- Sapacitabine
 - Oral chemotherapy, similar to cytarabine
- KW-2449 and AC220
 - Blocks an enzyme called FLT3 that promotes the growth of AML cells
- Eltrombopag
 - Promotes platelet growth while disrupting leukemic growth
- Sirolimus
 - Blocks an enzyme to help chemotherapy work more effectively



Conclusions

- Treatment of acute leukemia results in significant remissions and long term disease free survival
- Clinical trials have allowed us to learn more about the different types of leukemia and to evaluate new therapeutic options and develop improved regimens
- Newer therapies will hopefully further improve remission rates and decrease toxicities