

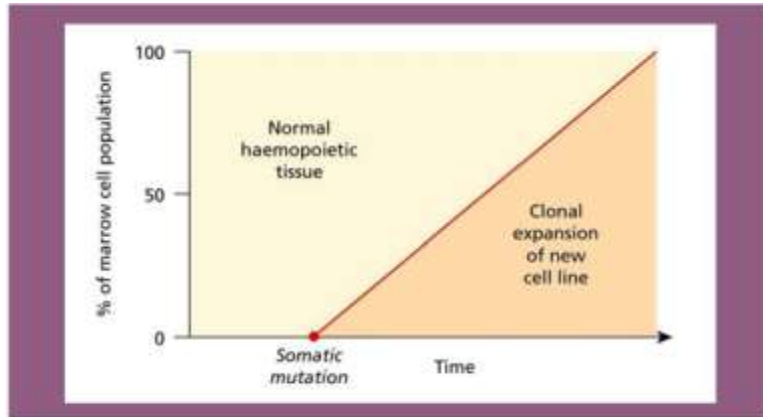


Dr. Khaled Al-Qaoud

Chapter 11

The Etiology and Genetics of Hematological Malignancies

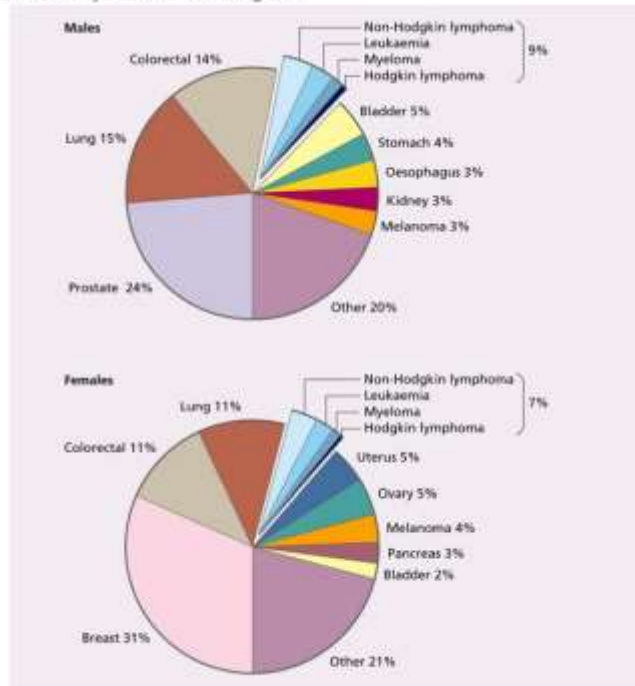
Malignancies are clonal diseases



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Malignancies are clonal disease

- A rise from a single cell in the marrow or peripheral lymphoid tissue due to genetic alteration



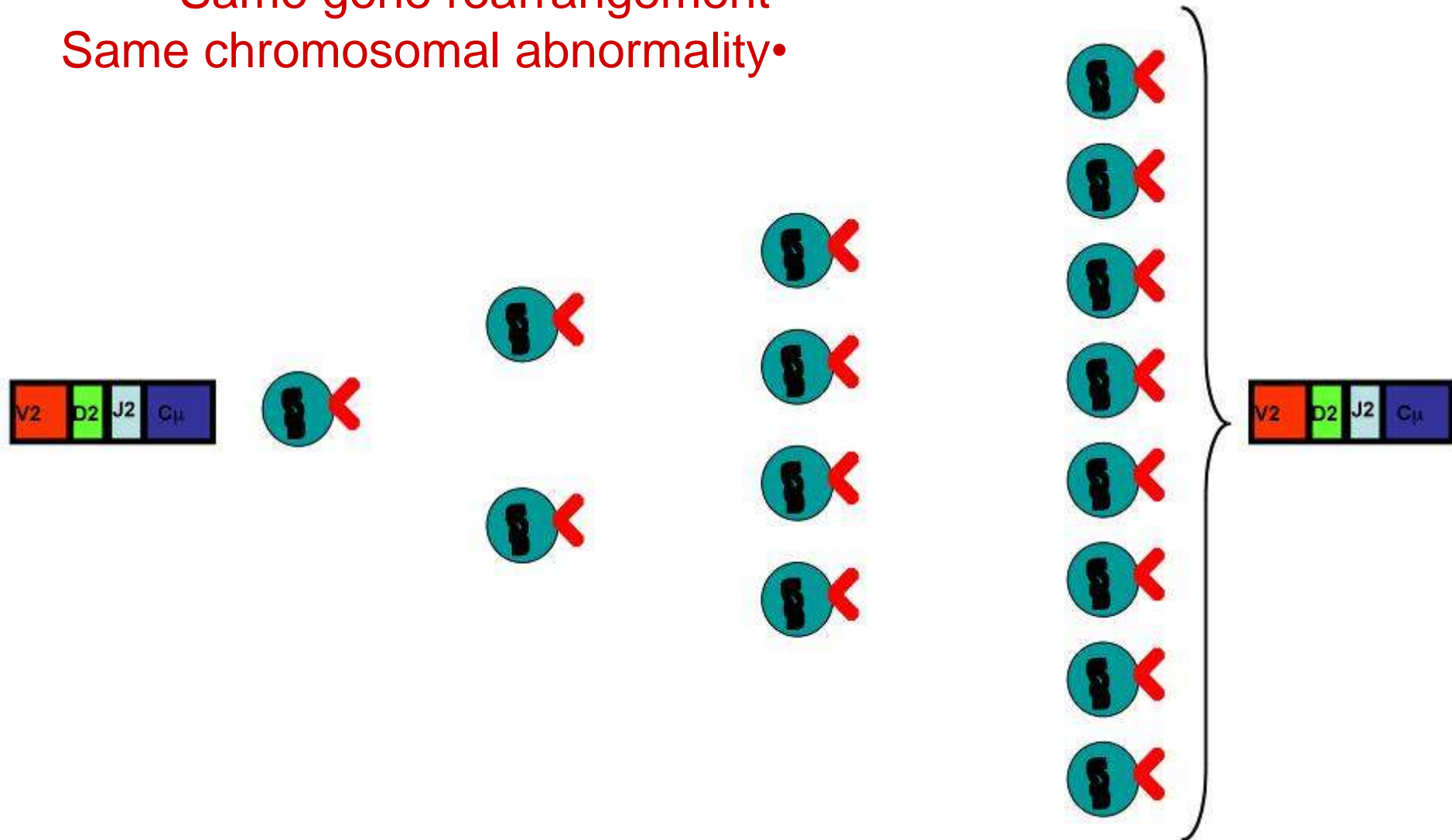
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Malignancies incidence

- Nearly 40% of population develop cancer in their lifetime
- Majority is epithelial malignancies
- Hematological malignancies represent about 7% of malignant diseases
- Differences in geographical distribution and sex
- CLL is the most common in western but rare in far east

A neoplastic lymphocyte proliferation is **clonal**

- Same gene rearrangement•
- Same chromosomal abnormality•



Accumulation of genetic mutations



Dr. Khaled Al-Qaoud

- Cancer is characterized by an accumulation of multiple genetic mutations in a population of cells undergoing neoplastic transformation.
- After the first mutation, there is limited expansion
- After subsequent mutations, there is greater proliferation potential.

Inherited factors in malignancy

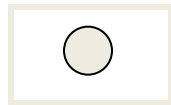
- In downs syndrome, acute leukemia occurs with 20-30 fold increased frequency
- Familial tendency to develop some leukemias as AML

Environmental influences

- **Chemicals:** exposure to Benzene and high incidence of AML
- **Drugs:** alkylating drugs predispose to AML
- **Radiation:** marrow radiation is leukemogenic
- **Infection:** ALL development in children who are exposed to infection is higher
- **Viruses:** EBV is associated with Burkett lymphoma, HIV is associated with lymphoma
- **Bacteria:** H. pylori gastric mucosa B cell lymphoma.
- **Protozoa:** malaria may predispose to tumors

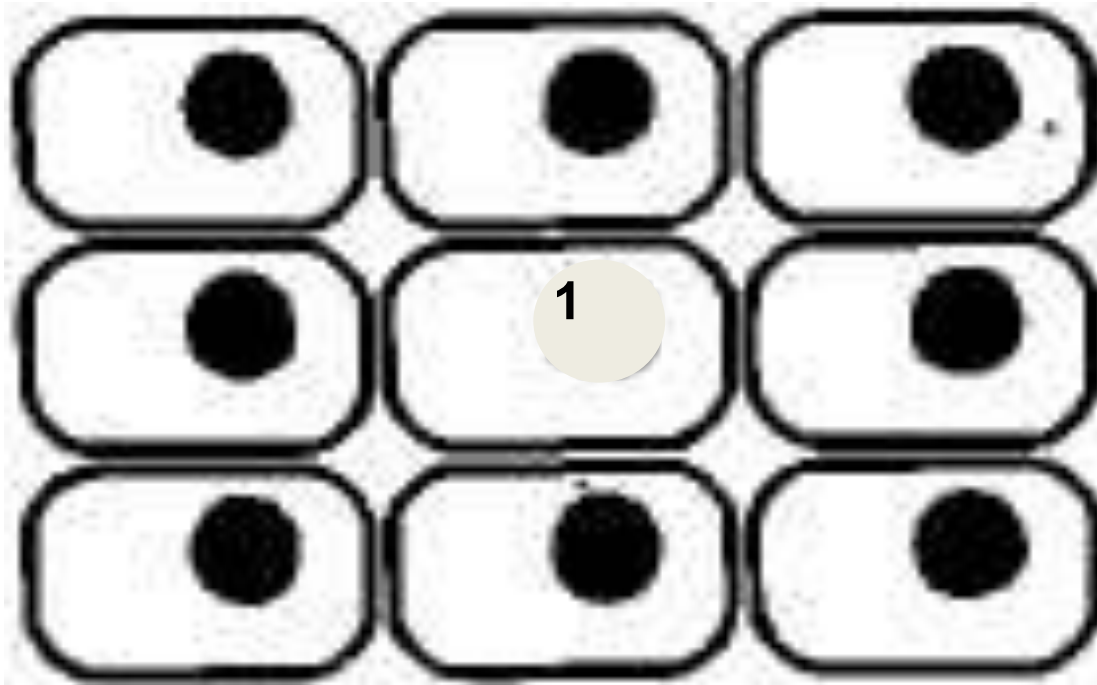
How does this happen?

In the following slides:



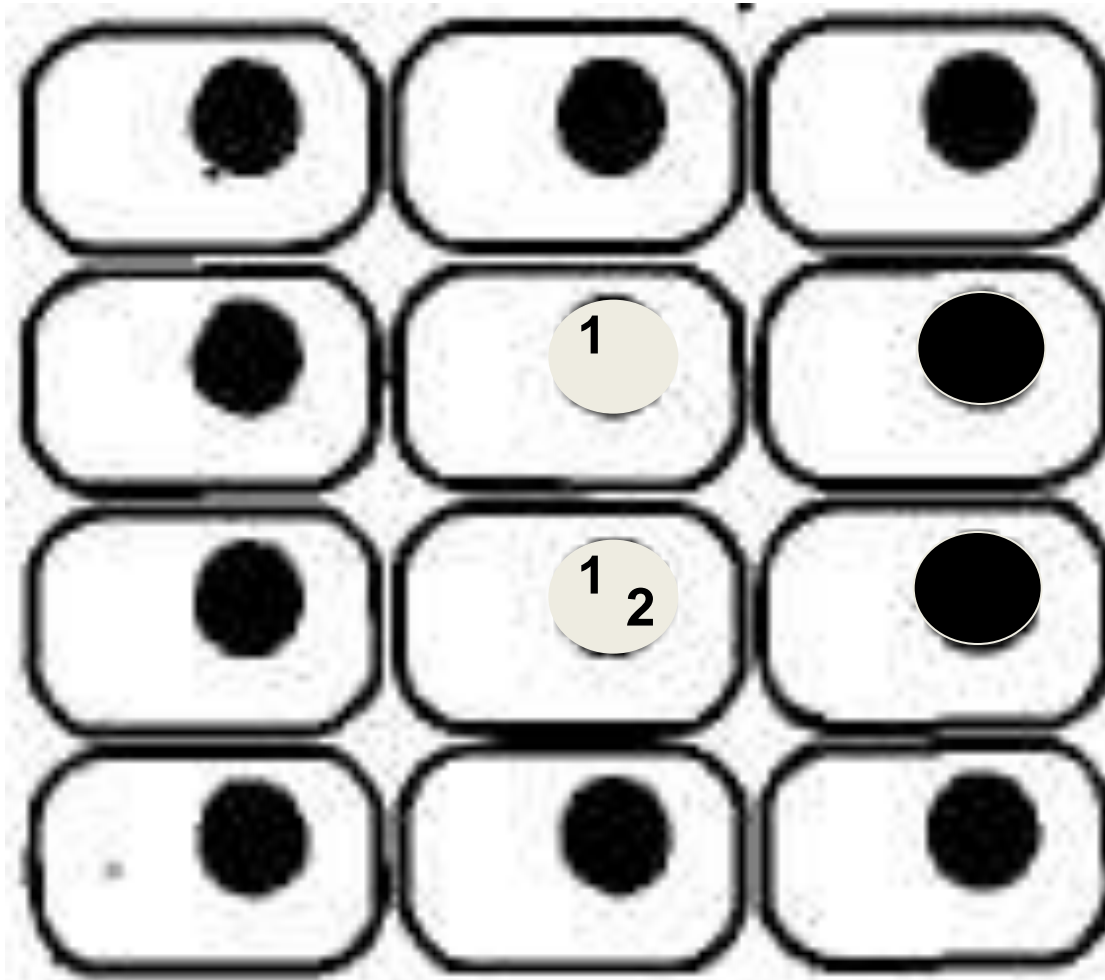
= a non- dividing cell

1, 2, 3 = successive mutations, each contributing in some way to an increased rate of cell division or decreased rate of cell death.



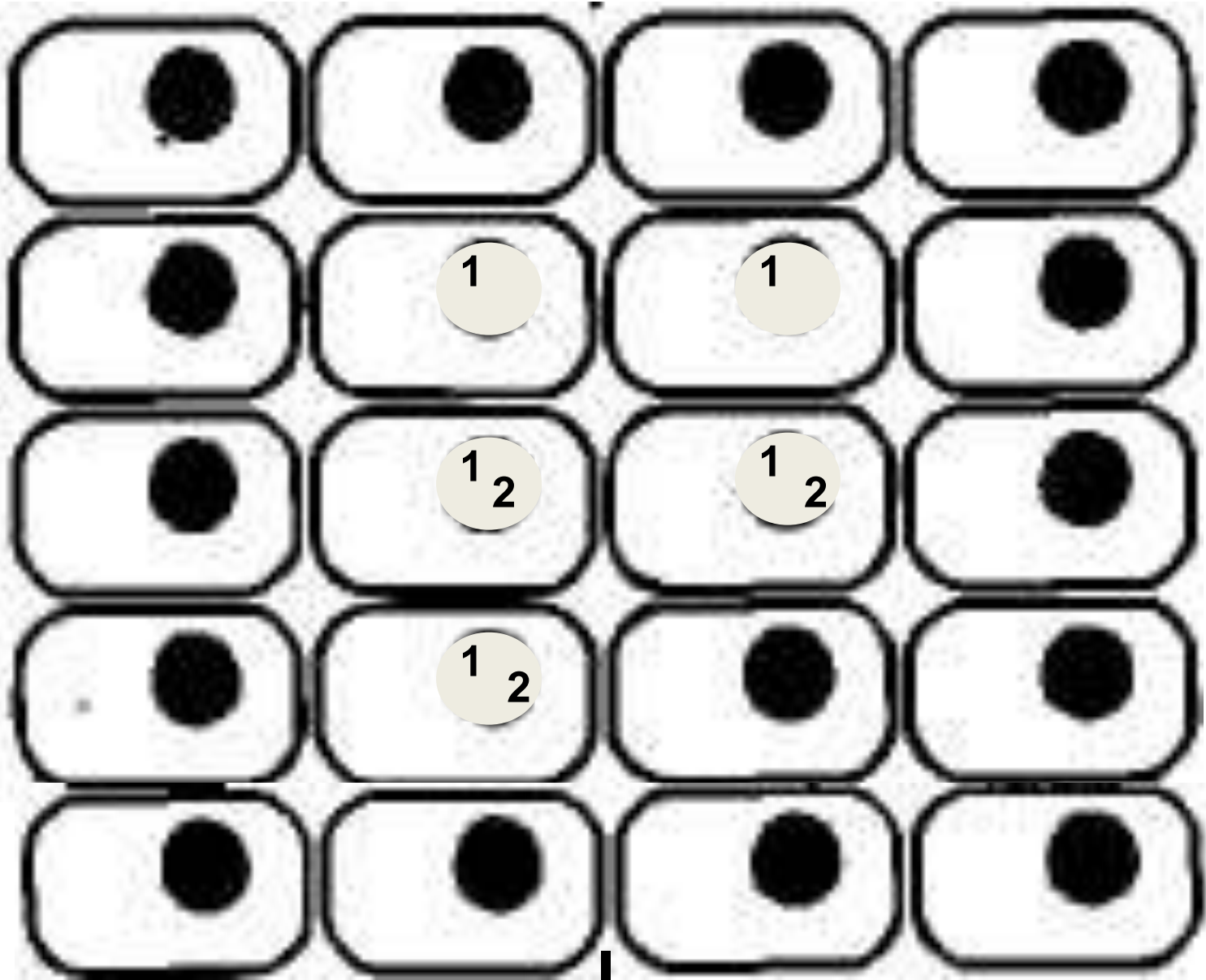
**Non-dividing
cells**

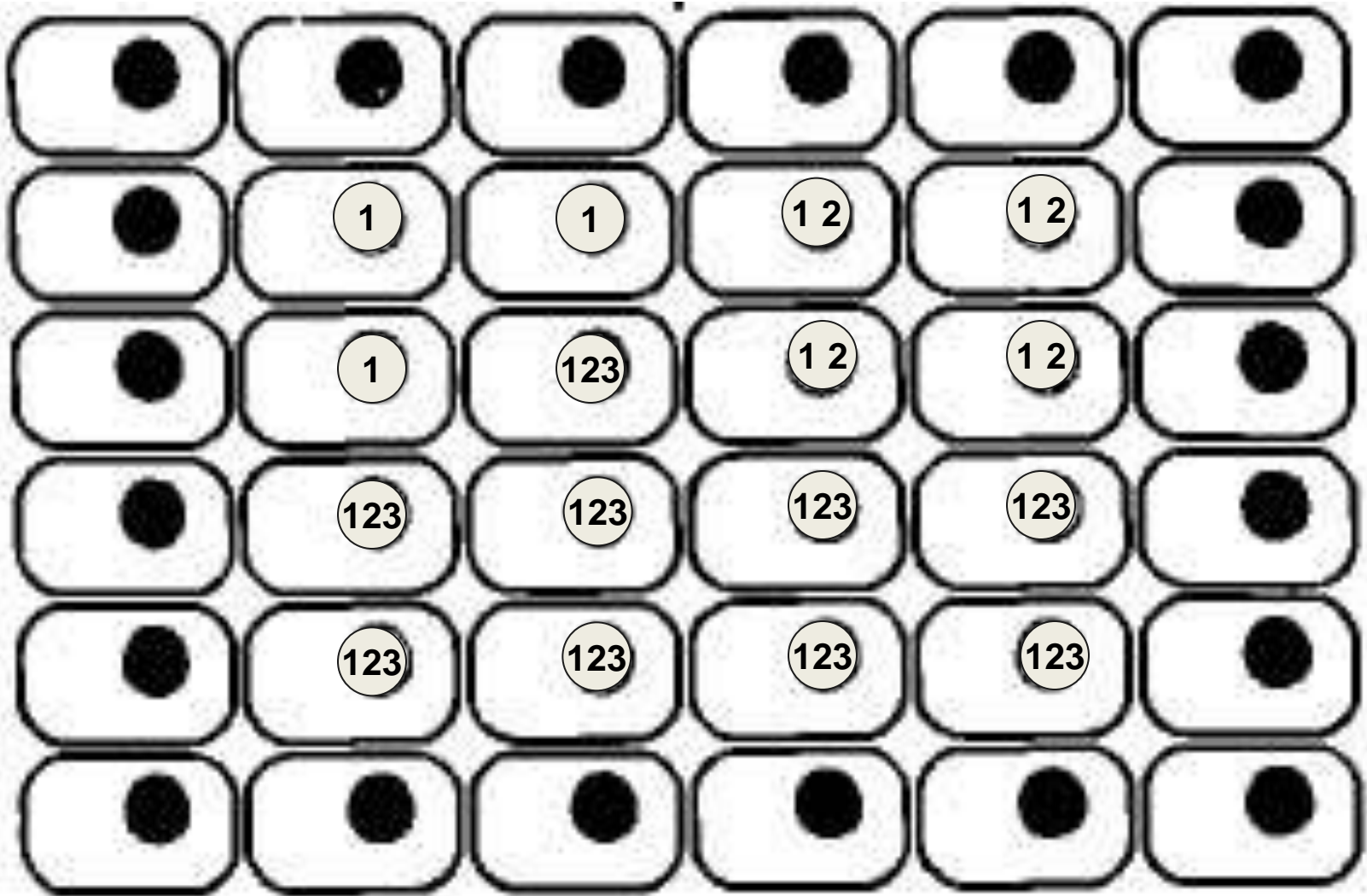




**Non-dividing
cells**







This process continues, with each successive mutation leading to a faster rate of cell division, slower rate of cell death, and eventually loss of cell adhesion.

A sort of summary of the previous four slides.

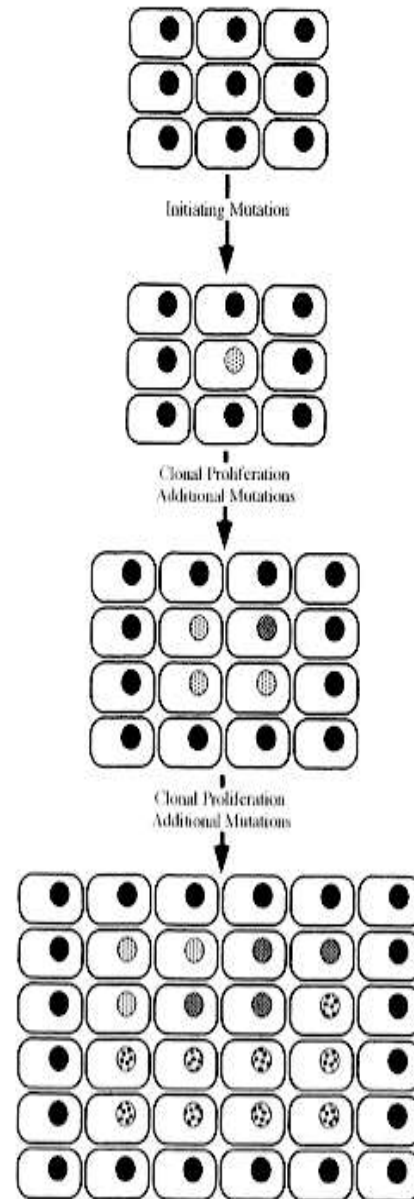


Fig. 1. Clonal selection and proliferation of cell populations in neoplastic development. ●, normal epithelial cell; ⊙, epithelial cell harboring a single genetic lesion; ⊚, epithelial cell harboring two genetic lesions; ⊛, epithelial cell with multiple genetic lesions.

The genetics of hematopoietic malignancies

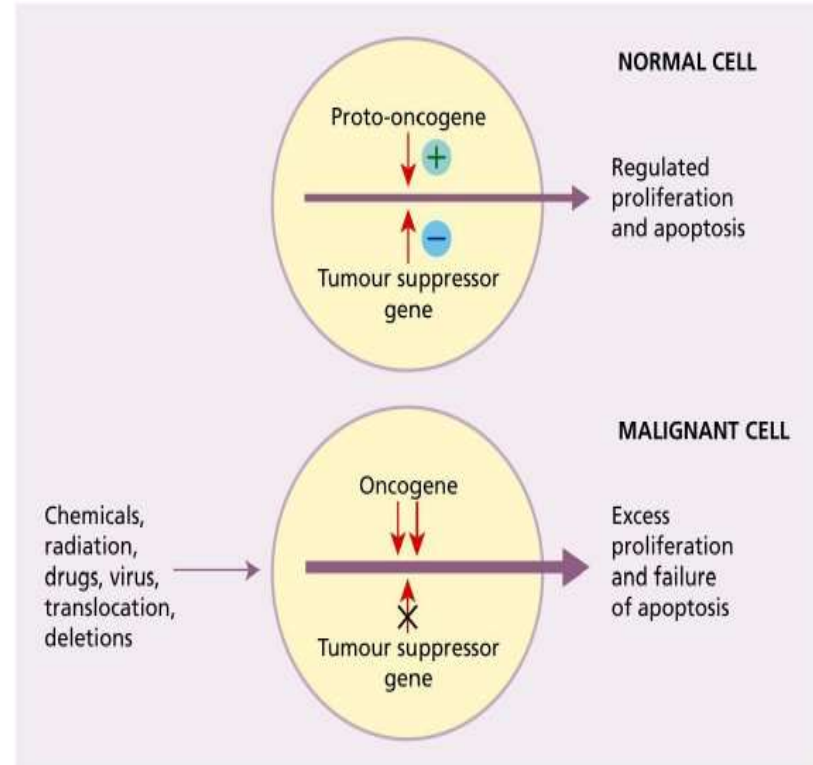
Accumulation of genetic mutations:
Genes involved are:

1. **Oncogenes**
2. **Tumor suppressor genes**

Oncogenes

An **oncogene** is a gene that has the potential to cause cancer. In tumor cells, they are often mutated or expressed at high levels

proto-oncogene is a normal gene that can become an oncogene due to **mutations**, **translocations**, **deletions** or increased expression



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A balance between **proto-oncogene** and **tumor suppressor gene** guarantee normal cell proliferation

Chromosomes

Karyotype

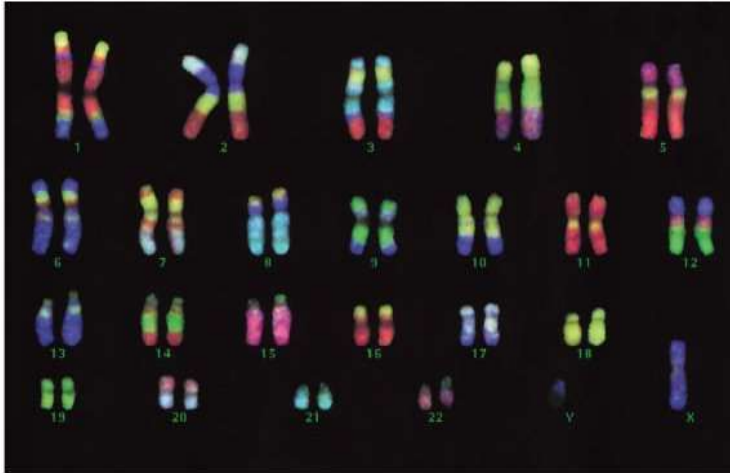
- Describes the chromosomes derived from mitotic cell which have been set out in numerical order

Somatic cell

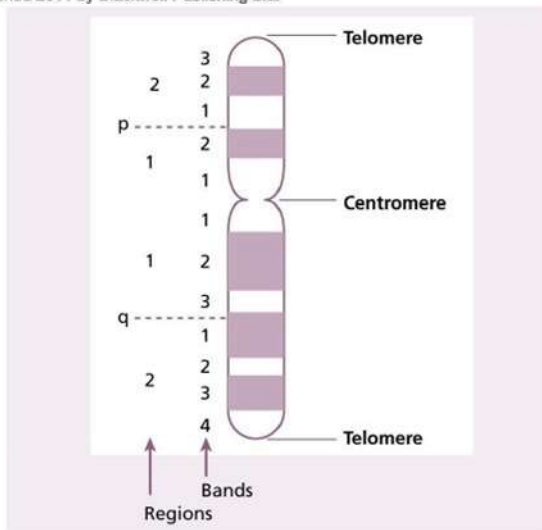
- Diploid: cell with 46 chromosomes
- Haploid: cell with 23 chromosomes
- Aneuploidy: more or less than 46 chrom
 - Hyperploidy: more
 - Hypoploidy: less

Chromosomal description

- q long arm
- P short arm
- i inversion
- t translocation

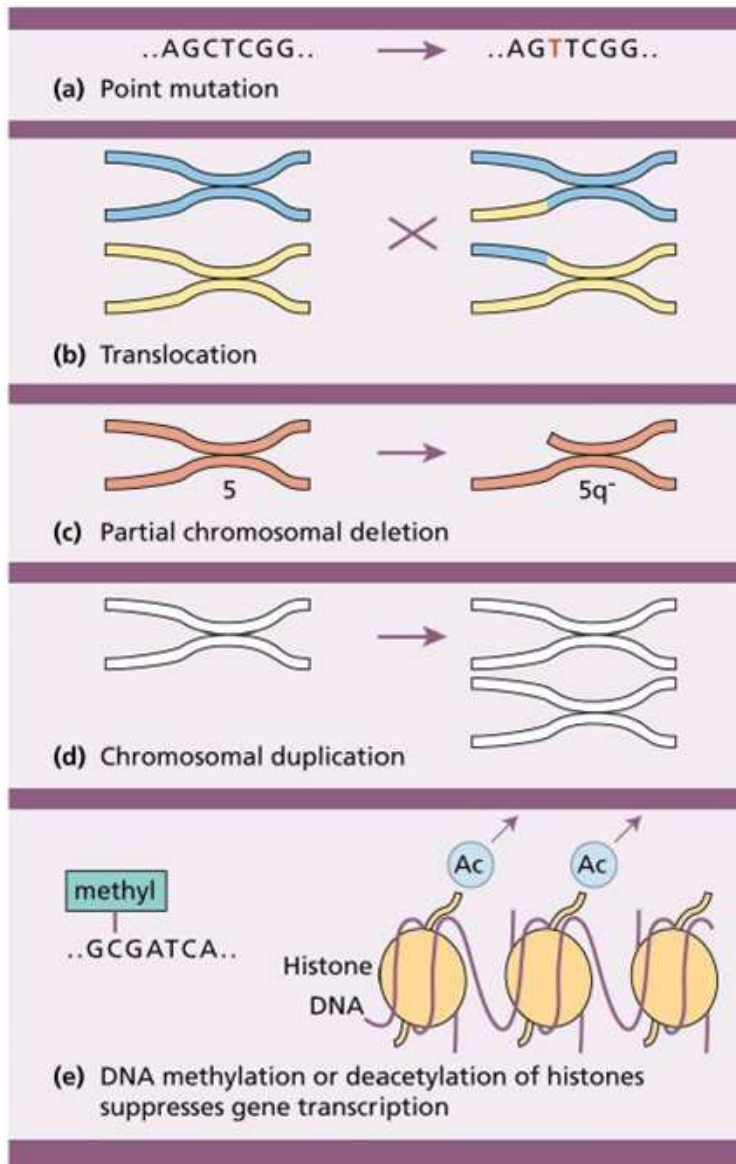


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Genetic abnormalities and hematological Malignancies



Point Mutation

- Change in one or more base pair
- TET-2 is a tumor suppressor gene, mutation lead to Chronic myeloid Leukemia (CML)
- RAS is oncogene, mutation associated with hematopoietic malignancies

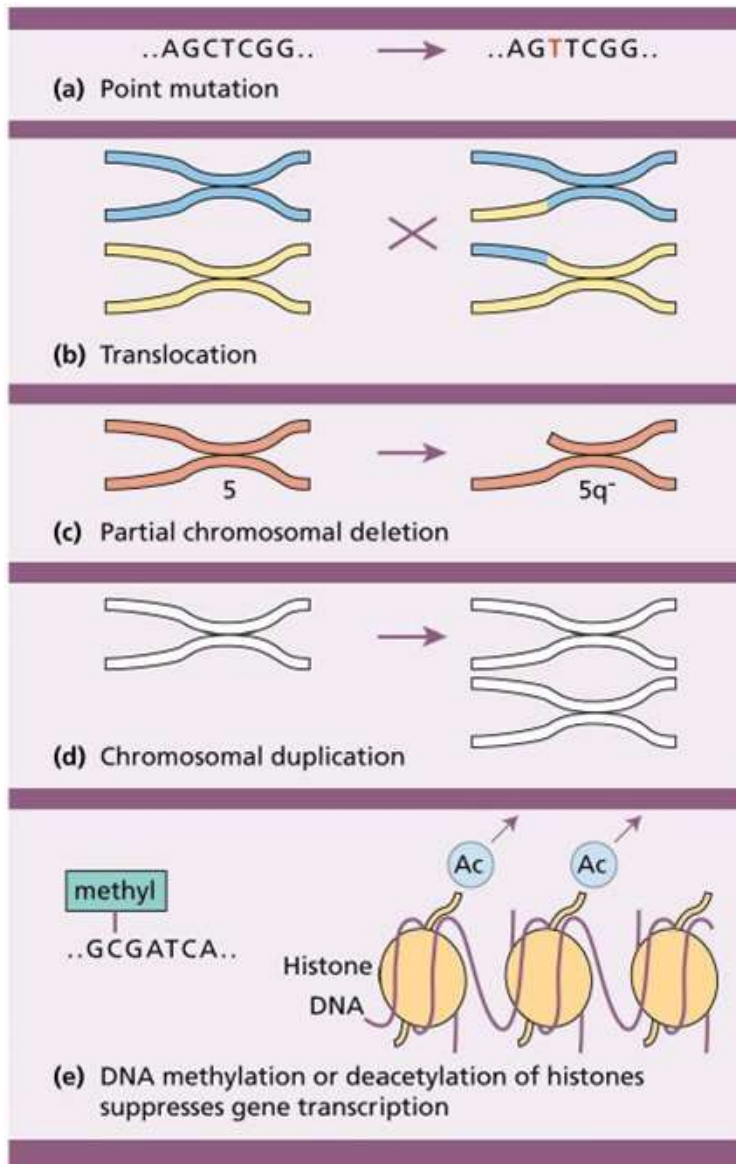
Translocation

- Exchange of part of chromosome with adjacent one.
- Overexpression of Bcl2 genes in t(14,18) translocation of follicular lymphoma

Deletions

- May involve small part of the chromosome (5q-) or the whole chromosome (monosomy 7)
- Loss of tumor suppressor gene as in 13q14 deletions in CML

Genetic abnormalities and hematological Malignancies



Duplication or amplification

- As in trisomy 12 in CLL
- Not common in hematological malignancies

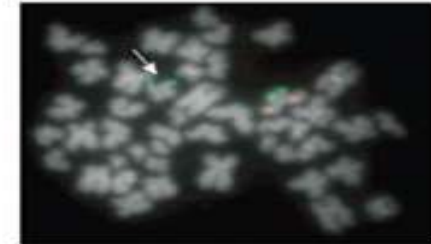
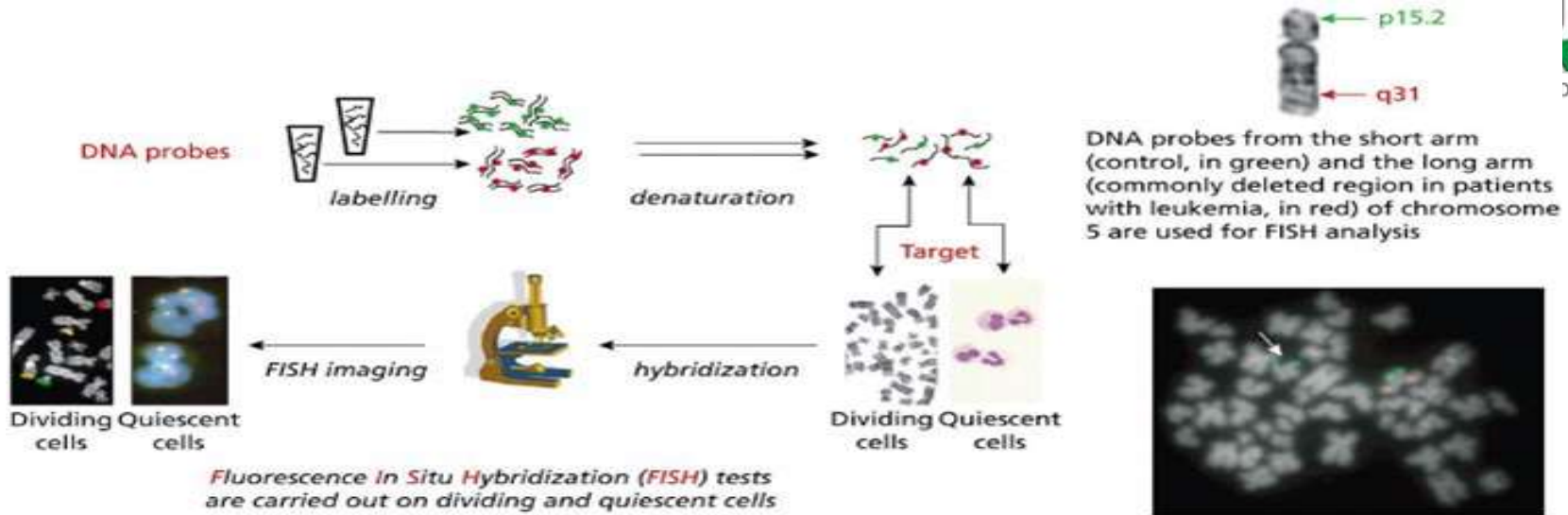
Epigenetic alterations

- Alterations in the mechanism by which genes are transcribed.
- Pass with malignant cell division
- Methylation of cytosine in DNA

MicroRNAs

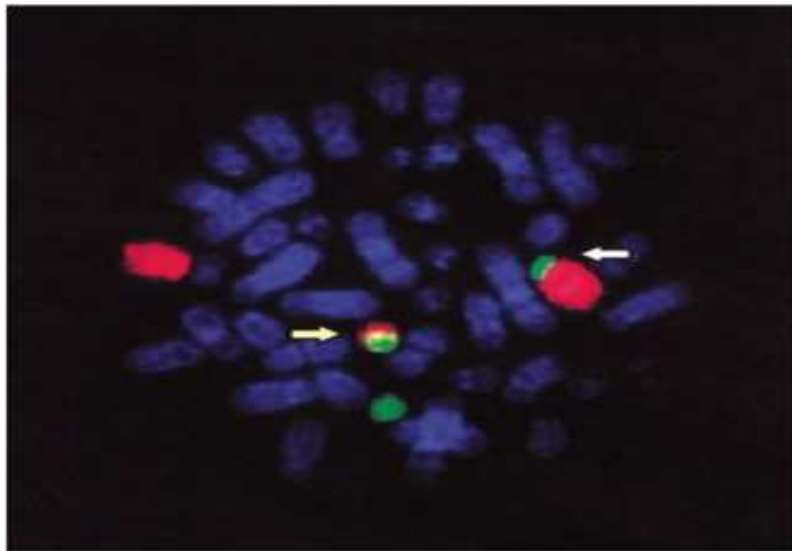
- Short RNAs that are normally transcribed but not translated

Fluorescent in situ hybridization (FISH)



Missing red FISH signal (arrow) shows deletion of the long arm of chromosome 5, while the normal homologue 5 is marked by red & green signals

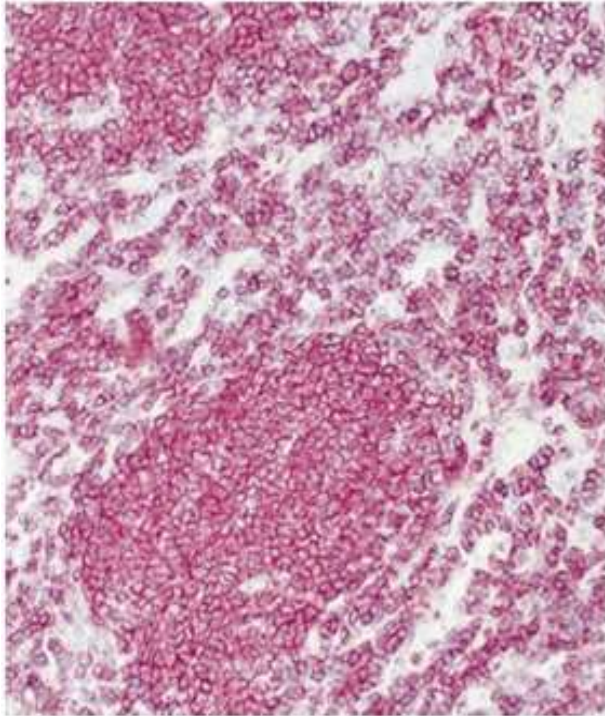
(b)



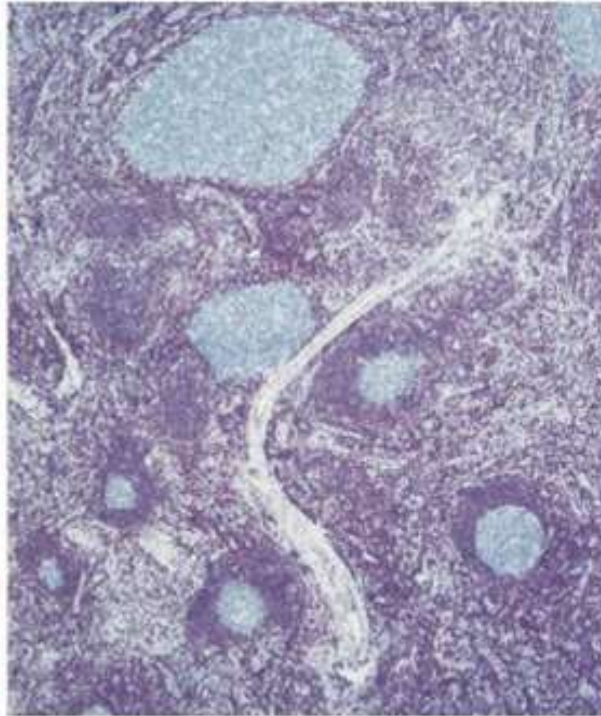
(c)

TEL gene on chromosome 12- Green Probe
AML1 gene on chromosome 21-Red probe

Immunohistochemistry



(a)



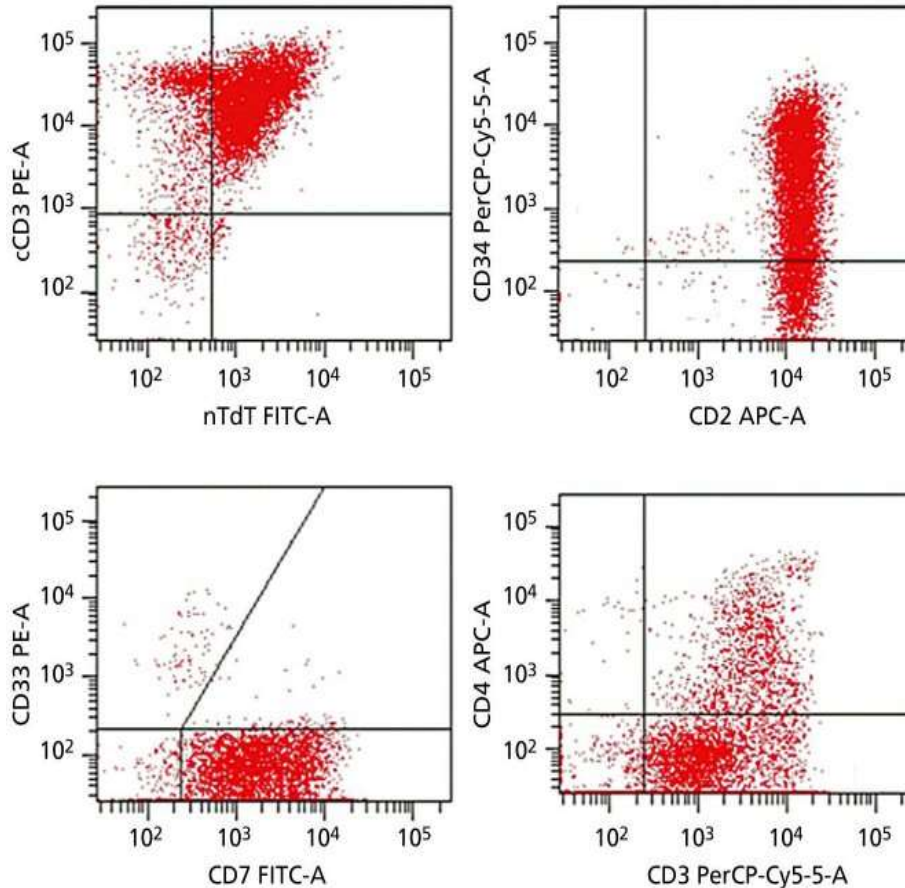
(b)

Formalin Fixed slides:

- Stained with Fluorescent antibodies
- Monitored using Microscopic slides

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Flow Cytometry



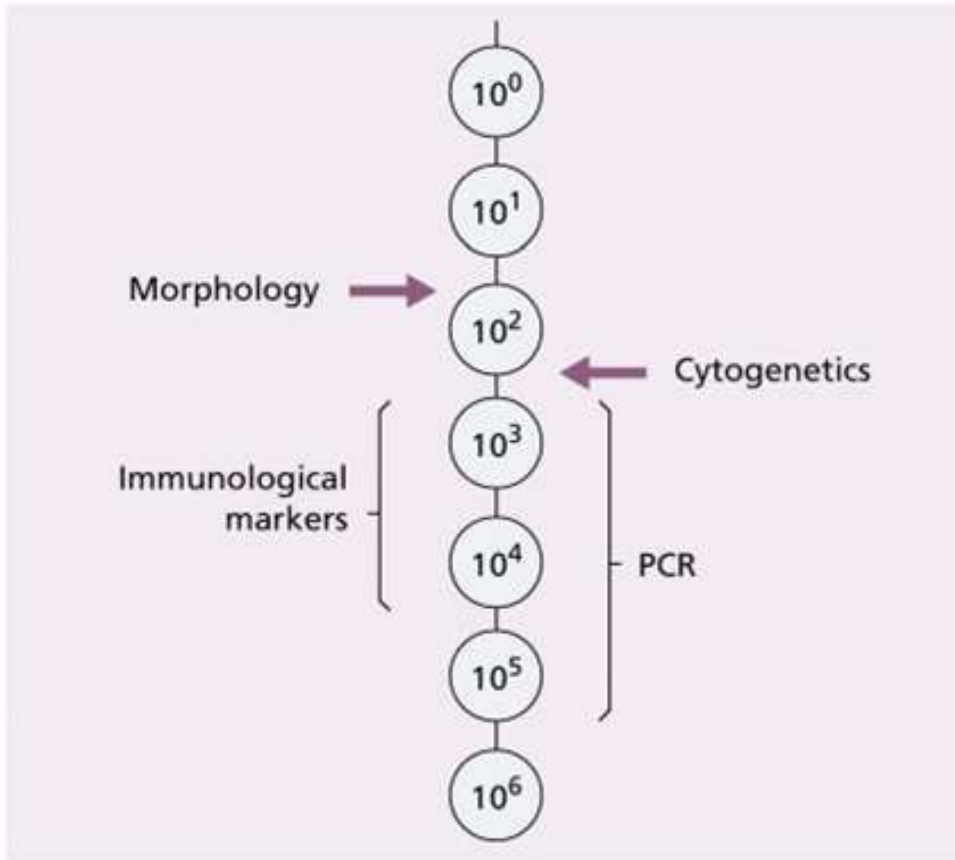
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- distinguish cell population according to phenotypes
- Fluorescence conjugated antibodies are normally used

Cells are identified according to:

- Size: forward scatter
- Granularity: sideward scatter
- fluorescence

Test sensitivities



Sensitivity of different techniques in detecting 1 leukemic cells in 10-1000000 cells

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