Leukaemia

Overview

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Malignancy

- Haematological malignancies are clonal diseases that derive from a single cell in the marrow or peripheral lymphoid tissue which has undergone a genetic alteration.
- The exact aetiology is unknown.
- Possibly due to a combination of genetic abnormalities and environmental factors.
- Environmental factors may include chemicals, drugs, radiation, and infections.

- **Genetic factors**
- The incidence of leukaemia is greatly increased in some genetic diseases, particularly Down's syndrome.
- **Enviromental factors:**

1)Chemicals

- Chronic exposure to benzene may cause chromosome abnormalities, bone marrow hypoplasia, dysplasia and Acute Myeloid Leukaemia (AML).

2)Drugs

- The alkylating agents (e.g. chlorambucil, melphalan) predispose to AML.

3) Radiation

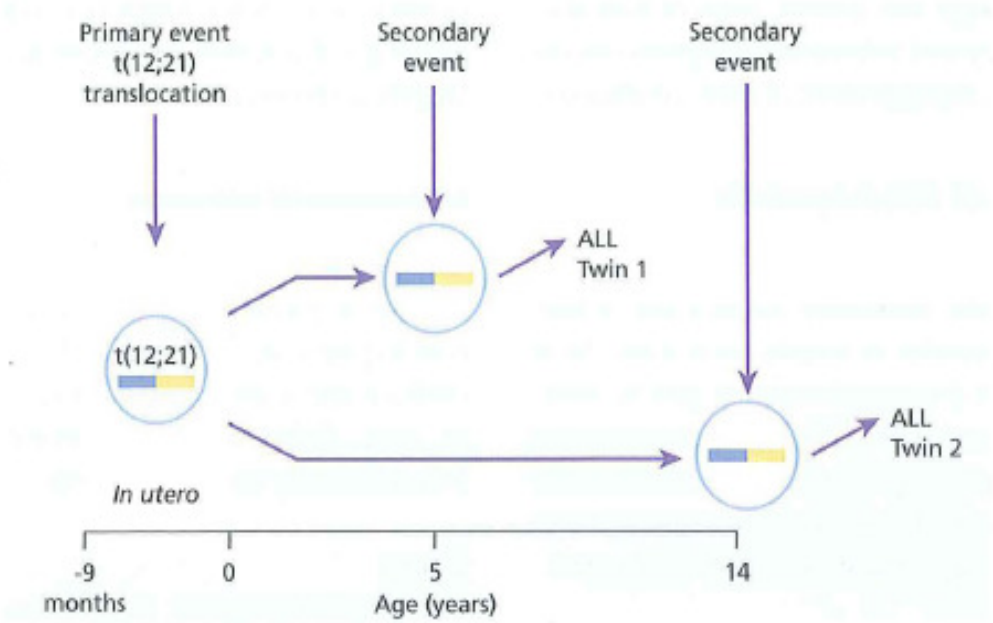
- Radiation, especially to the marrow, is leukaemogenic and cause DNA mutation.

Infections associated with malignancies

Table 10.1 Infections associated with haemopoietic malignancies.

Infection	Tumour
Virus	
HTLV-1	Adult T-cell leukaemia/lymphoma
Epstein–Barr virus	Burkitt's and Hodgkin's lymphomas; PTLD
HHV-8	Primary effusion lymphoma; multicentric Castleman's disease
HIV-1	High-grade B-cell lymphoma
Bacteria	
Helicobacter pylori	Gastric lymphoma (MALT)
Protozoa	
Malaria	Burkitt's lymphoma

Multi-hit theory & malignancy



- Malignancy is not caused by a single abnormality.
- A secondary event is required to cause malignant transformation.
- The mechanism of the second genetic hit within the tumour cell is unclear but an abnormal response of the immune system to infection is suggested.

Genetics of haemopoietic malignancy

- Altered expression of three types of genes underlies multistep pathogenesis of haematological malignancy.
- Malignant transformation occurs as a result of the accumulation of genetic mutations in cellular genes.

1) Oncogenes

- These are genes whose protein products cause neoplastic transformation.
- Oncogenes arise because of gain-of-function mutation in normal cellular genes called *proto-oncogenes* which are normal genes involved in a variety of important cellular processes (examples).
- The transformation of proto-oncogenes to oncogenes can occur in a number of ways including translocation, mutation or duplication.
- ***BCL-2*** proto-oncogene is overexpressed in follicular lymphoma.

Types of genetic abnormalities in haematological malignancies

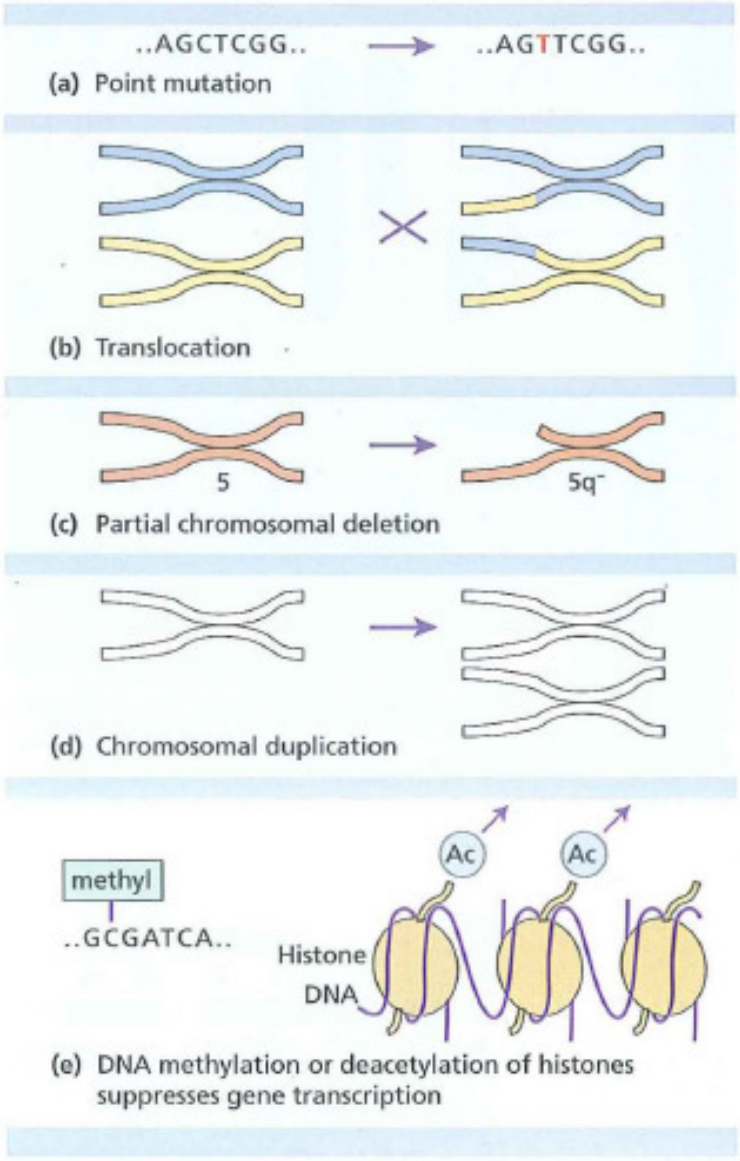
1- point mutation.

2-Translocation.

3- Deletion.

4- Duplication.

5- DNA methylation.



Genetics of haemopoietic malignancy

2) Tumour-suppressor genes

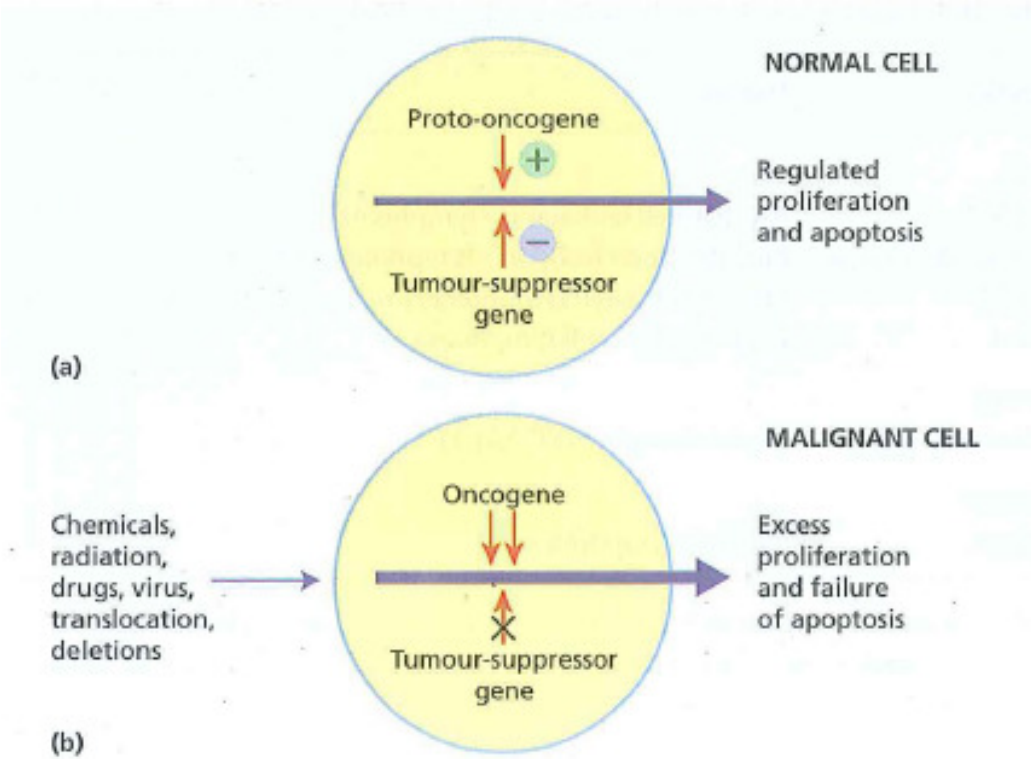
- Genes encoding proteins which have a critical role in suppressing cell growth.

- Tumour-suppressor genes commonly act as components of control mechanisms which regulate cell division (entry to cell cycle).

- Tumour-suppressor genes are inhibited or acquire loss-of function mutations, usually by point mutation or deletion, which lead to malignant transformation.

- The most significant tumour-suppressor gene in human cancer is ***p53*** which is mutated or inactivated in over 50% of cases of malignant disease.

Malignant transformation



Malignant cells often show resistance to apoptosis. The BCL-2 gene product inhibits apoptosis and its over-expressed in malignacies like follicular lymphoma.

Malignant transformation

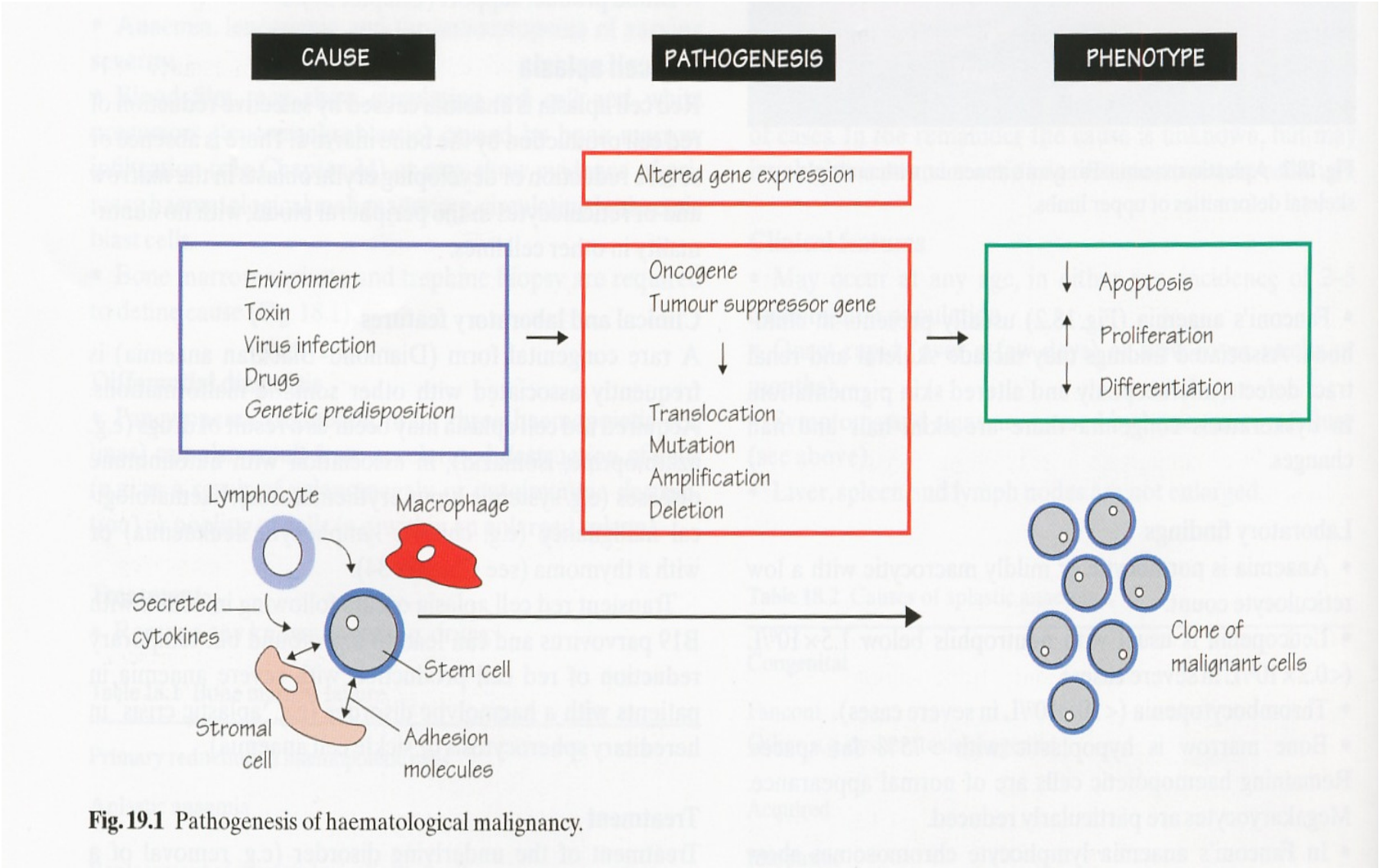


Fig. 19.1 Pathogenesis of haematological malignancy.

Examples of oncogenes in haeamtological malignacies

Disease	Genetic abnormality*	Oncogene(s) involved
Myeloid		
AML M_2	t(8; 21)	*ETO* and *CBFα* (*AML1*)
	t(6; 9)	*DEK, CAN*
AML M_3	t(15; 17)	*RARα, PML*
AML M_4	inv(16), del(16q)	*CBFβ, MYH11*
AML M_5	del(11q); t(9; 11); t(11; 19)	*MLL*
AML (all types)	Nucleotide insertion	Nucleophosmin
	Mutation, ITD	*Flt3*
MDS	–5/del(5q)	Unclear
	–7/del(7q)	
	Point mutation	*N-RAS*
Secondary myeloid leukaemia	11q23 translocations	*MLL* gene
CML	t(9; 22)	*ABL, BCR*
Myeloproliferative disease	Point mutation	*JAK2*
	20q–	
Chronic eosinophilic syndrome	4q12 del	*FIP1L1-PDGFRA* fusion
Lymphoid		
Precursor B lineage ALL	t(12; 21)	*TEL, AML1*
	t(4; 11)	*AF4, MLL* (*ALL1, HRX*)
	t(9; 22)	*ABL, BCR*
	t(1; 19)	*PBX-1, E2A*
	Hyperdiploidy	
	Hypodiploidy	
Burkitt's lymphoma, B-ALL	t(8; 14)†	*MYC* to *IgH* locus
	t(2; 8)	*MYC* to *IgK* locus

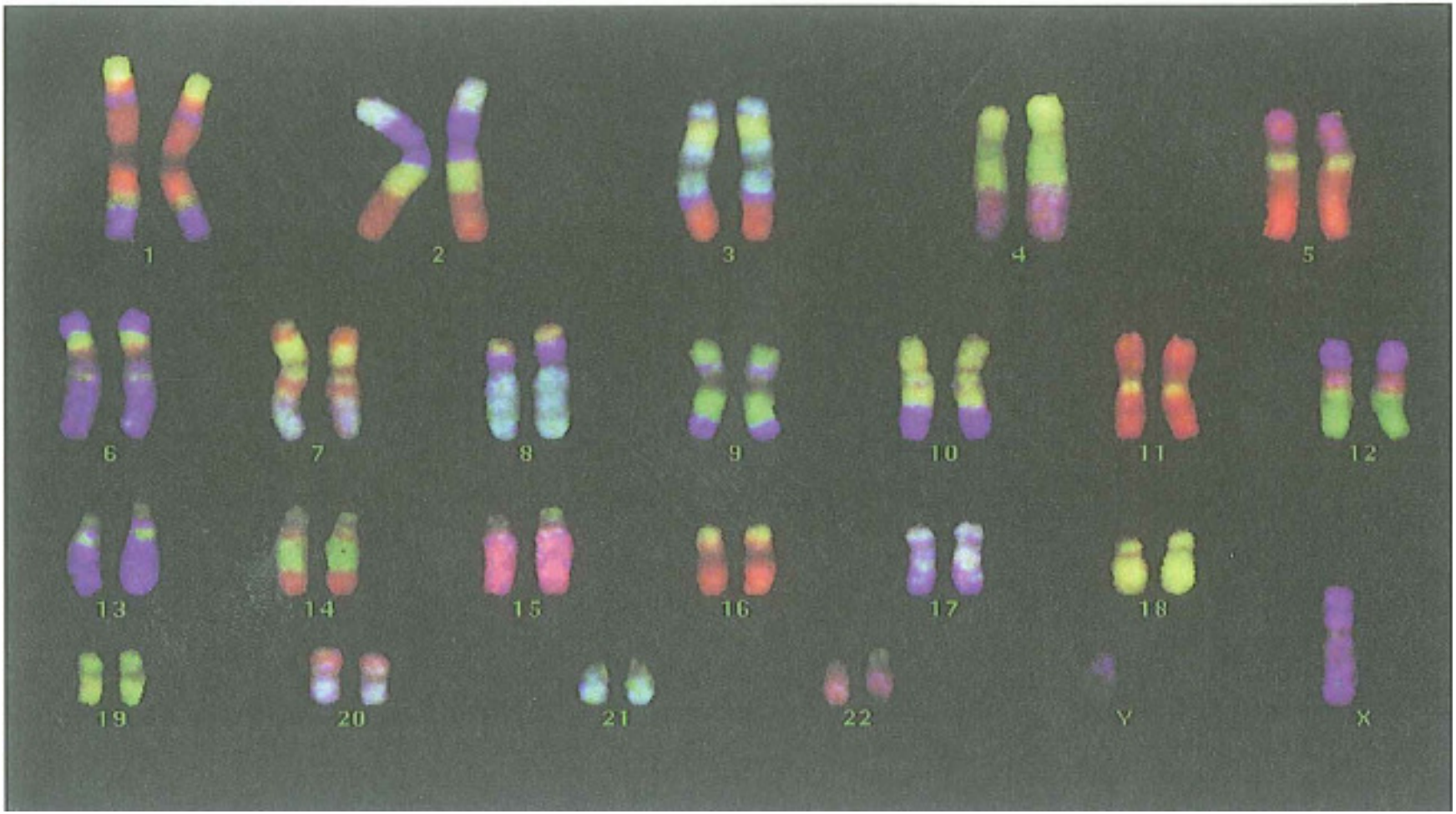
How normal cells become malignant?

- Haematological malignancies are clonal.
- This means that they arise from a single cell (clone) in the bone marrow, thymus or lymphoid tissues.
- This cell undergoes genetic mutation leading to malignant transformation.
- Successive & uncontrolled mitotic divisions give rise to a clone of cells derived from the parent cell.
- Further mutations may give rise to sub-clones (clonal evolution).
- Transformed cells either proliferate in a an uncontrolled fashion or are resistant to apoptosis.

Clonality of malignant tumours

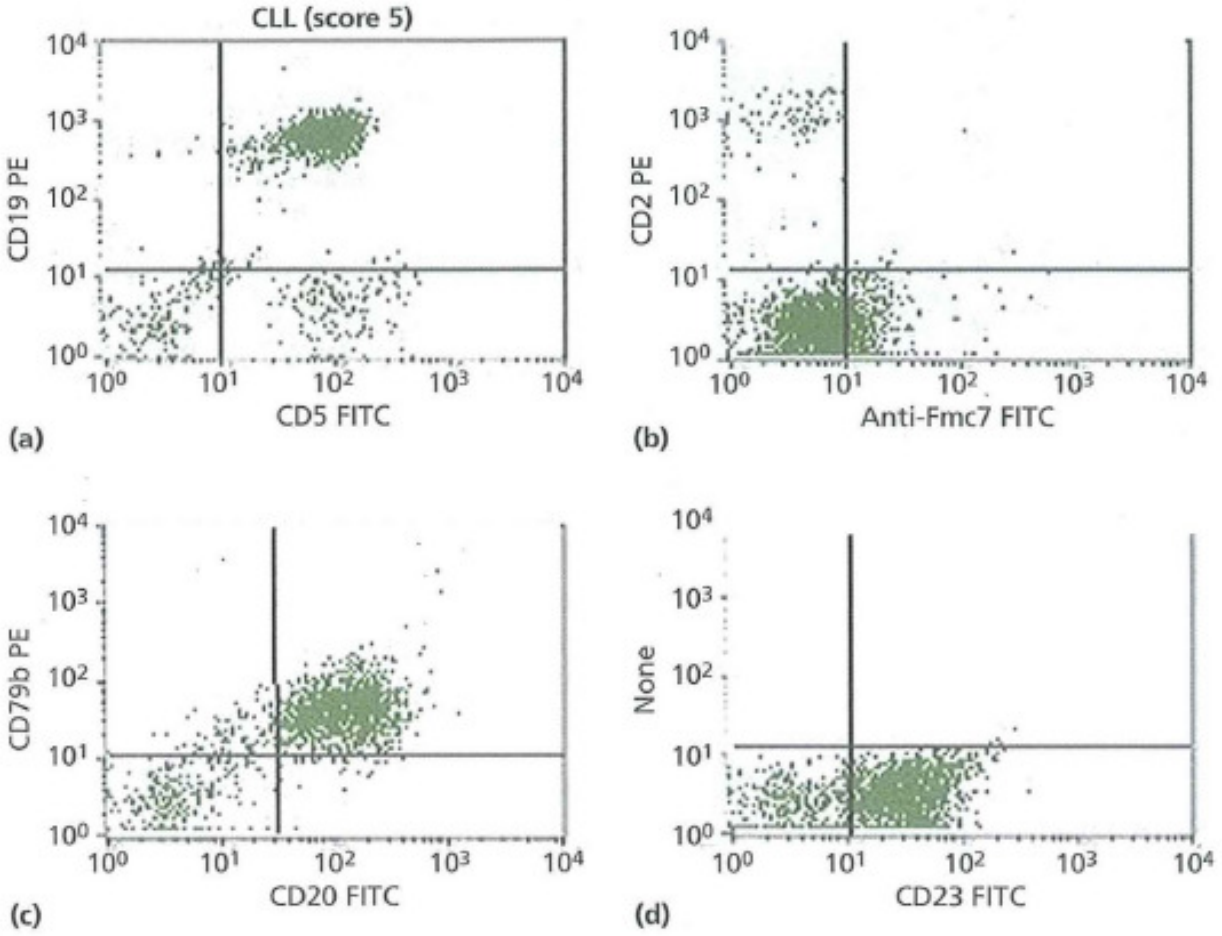
- Clonality means that a tumor is derived from a single transformed cell.
- Usually, it takes several years until a tumor has grown from a single cell to the stage where it can be diagnosed clinically.
- Virtually all hematological neoplasms (leukemias, lymphomas, and myeloproliferative and myelodysplastic syndromes) are clonal.
- Different laboratory techniques are used to identify clonality in haeamtological malignancies including cytogenetics, flow cytometry, and PCR.

Cytogenetics



A colour-banded karyotype from a normal male.

Flow cytometry



Classification of haematological malignancies

Table 19.1 Classification of haematological malignancies.

	Acute	Chronic
Lymphoid	Acute lymphoblastic leukaemia (ALL) and subtypes	Chronic lymphocytic leukaemia (CLL) and variants Non-Hodgkin lymphoma (NHL) Hodgkin lymphoma (HL) Multiple myeloma and variants
Myeloid	Acute myeloid leukaemia (AML) and subtypes	Chronic myeloid leukaemia (CML) and variants Myelodysplasia (MDS) Myeloproliferative disorders