

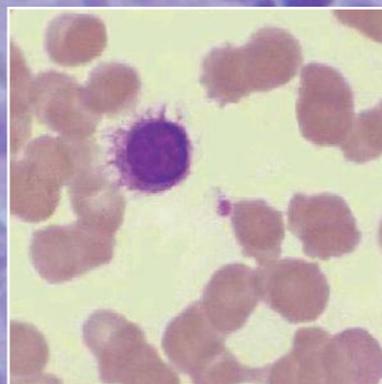
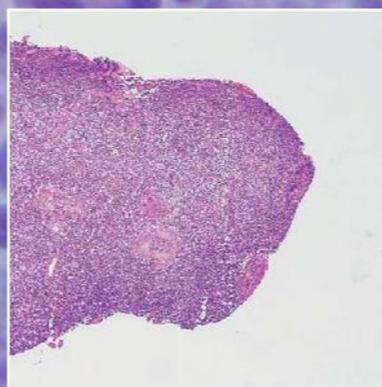
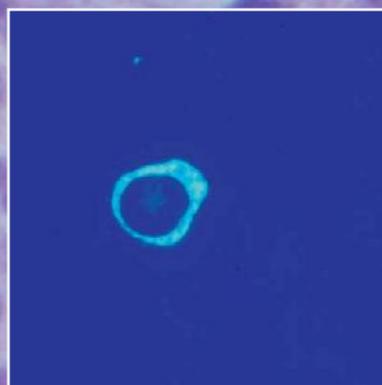
Evidence-based Handbook of Investigation and Diagnosis

Lymphoid Malignancies

- A highly illustrated guide and reference for haematologists, oncologists and clinical scientists
- Guiding investigation, differential diagnosis, prognosis and treatment options

Meeting the needs of haematologists, oncologists and clinical scientists for an up-to-date reference, this atlas provides a visual presentation of lymphoproliferative disorders, lymphoid leukaemias and plasma cell neoplasms. Each malignancy is surveyed based on molecular and cellular changes, including histochemistry, cytochemistry and relevant radiographs. Pertinent clinical information relating to clinical presentation, differential diagnosis and prognostic indicators are concisely outlined, using numerous graphics and citing key references in the field.

CONTENTS: The molecular basis of lymphoma, Acute lymphoblastic leukaemia, Chronic lymphocytic leukaemia/small lymphocytic lymphoma and monoclonal B-cell lymphocytosis, B-cell prolymphocytic leukaemia, Follicular lymphoma, Mantle cell lymphoma, Lymphoplasmacytic lymphoma, Nodal marginal zone lymphoma, Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), Splenic marginal zone lymphoma, Hairy cell leukaemia, Hairy cell leukaemia variant and splenic diffuse red pulp small B-cell lymphoma, Burkitt lymphoma, Diffuse large B-cell lymphoma, Other B-cell lymphomas, AIDS-related and other immunodeficiency-related lymphomas, Adult T-cell leukaemia/lymphoma, Mycosis fungoides, Sézary syndrome and other cutaneous T-cell lymphomas, T-cell large granular lymphocytic leukaemia and chronic lymphoproliferative disorder of NK cells, Aggressive NK-cell leukaemia, T-cell prolymphocytic leukaemia, T follicular helper cell lymphomas, Anaplastic T-cell lymphoma, Other T-cell lymphomas, Multiple myeloma (plasma cell myeloma), Monoclonal gammopathies of undetermined significance, Other plasma cell neoplasms, Hodgkin lymphoma



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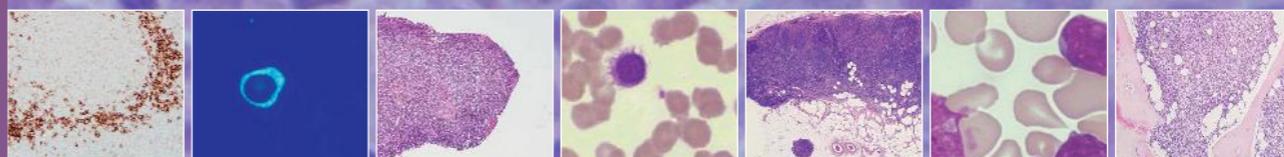
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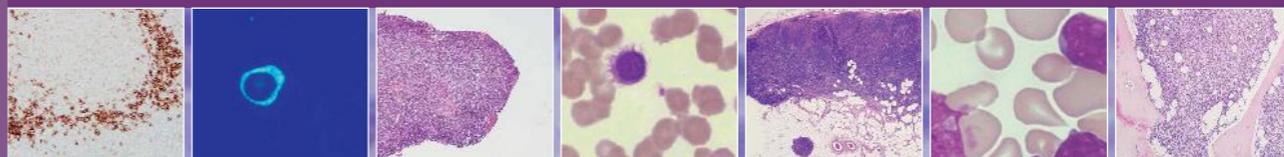
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Lymphoid Malignancies

Second Edition

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Andrew Wotherspoon



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Estella Matutes, Barbara J Bain, Andrew Wotherspoon, September 2020

Abbreviations

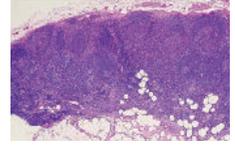
ABC activated B cell	GCB germinal centre B cell
ABCM doxorubicin (Adriamycin), BCNU, cyclophosphamide and melphalan	HAART highly active antiretroviral therapy
AIDS acquired immune deficiency syndrome	HCL-V hairy cell leukaemia variant
AITL angioimmunoblastic T-cell lymphoma	HL Hodgkin lymphoma
ALCL anaplastic large cell lymphoma	H&E haematoxylin & eosin
ALL acute lymphoblastic leukaemia	HGBL high-grade B-cell lymphoma
AML acute myeloid leukaemia	HHV8 human herpesvirus 8
APAAP alkaline phosphatase–anti-alkaline phosphatase	HIV human immunodeficiency virus
ATLL adult T-cell leukaemia/lymphoma	HTLV-1 human T-cell lymphotropic virus 1
BCR B-cell receptor	Ig immunoglobulin
B-PLL B-cell prolymphocytic leukaemia	IGH immunoglobulin heavy chain
CAR-T chimeric antigen receptor-T	IGK immunoglobulin kappa chain
CHAD cold haemagglutinin disease	IGL immunoglobulin lambda chain
CHOP cyclophosphamide, doxorubicin, vincristine and prednisone or prednisolone	IPI International Prognostic Index
CLA cutaneous lymphocyte antigen	IPSID immunoproliferative small intestinal disease
CLL chronic lymphocytic leukaemia	KIR killer immunoglobulin-like receptor
CLPD-NK chronic lymphoproliferative disorder of NK cells	KSHV Kaposi's sarcoma-associated herpesvirus
CNS central nervous system	LBL lymphoblastic lymphoma
CT computed tomography	L&H lymphocytic and histiocytic Reed–Sternberg variant
DLBCL diffuse large B-cell lymphoma	LDH lactate dehydrogenase
EATL enteropathy-associated T-cell lymphoma	LGLL large granular lymphocytic leukaemia
EBER Epstein–Barr virus-encoded RNA	LMP1 latent membrane protein 1
EBV Epstein–Barr virus	MALT mucosa-associated lymphoid tissue
EGIL European Group for the Immunological Characterization of Leukemias	MBL monoclonal B-cell lymphocytosis
EMA epithelial membrane antigen	MCL mantle cell lymphoma
EORTC European Organization for Research and Treatment of Cancer	MEITL monomorphic epitheliotropic intestinal T-cell lymphoma
ESMO European Society for Medical Oncology	MF mycosis fungoides
FAB French–American–British (classification)	MGUS monoclonal gammopathy of undetermined significance
FISH fluorescence <i>in situ</i> hybridization	MHC major histocompatibility complex
FLIPI Follicular Lymphoma International Prognostic Index	MIPI Mantle cell lymphoma International Prognostic Index
	NHL non-Hodgkin lymphoma
	NK natural killer

NLPHD nodular lymphocyte predominant Hodgkin lymphoma	SH2 src-like homology 2
NOS not otherwise specified	SLL small lymphocytic lymphoma
PAS periodic acid–Schiff	SmIg surface membrane immunoglobulin
PCR polymerase chain reaction	SMZL splenic marginal zone lymphoma
PEL primary effusion lymphoma	SS Sézary syndrome
PET positron emission tomography	TCR T-cell receptor
PLL prolymphocytic leukaemia	TdT terminal deoxynucleotidyl transferase
POEMS Polyneuropathy, Organomegaly (hepatomegaly, splenomegaly, lymphadenopathy), Endocrinopathy, M-protein and Skin changes (syndrome)	TFH T follicular helper
PTCL, NOS peripheral T-cell lymphoma, not otherwise specified	T-LGLL T-cell large granular lymphocytic leukaemia
PUVA psoralen plus ultraviolet light	Treg Regulatory T cells
RT-PCR reverse transcriptase polymerase chain reaction	T-PLL T-cell prolymphocytic leukaemia
SDRPL splenic diffuse red pulp small B-cell lymphoma	TRA T cell receptor alpha
	TRB T cell receptor Beta
	TRG T cell receptor gamma
	VAD vincristine, doxorubicin (Adriamycin) and dexamethasone
	VEGF vascular endothelial growth factor
	WHO World Health Organization

This atlas is dedicated to Daniel Catovsky, Peter Isaacson, the late David Galton and the late Dennis Wright, who devoted their scientific lives to lymphoid malignancies.



1 The Molecular Basis of Lymphoma



Lymphomas are neoplasms of T, B or natural killer (NK) lymphoid cells and their precursors. Although having different characteristics from their normal counterparts, the neoplastic cells of many lymphomas have the features of lymphoid cells at a particular stage of differentiation. In addition, lymphoma cells can have the characteristics of lymphocytes that normally reside in a particular organ or tissue. Neoplastic lymphocytes tend to ‘home’ to the tissues and specific locations where their normal counterparts reside. Lymphomas arise as a result of a series of mutations in a single lymphoid cell. Usually, this is a cell already committed to the B, T or NK lineage although rarely the mutation is in a pluripotent myeloid-lymphoid stem cell or in a common lymphoid stem cell. In the former case, exemplified by the 8p11 syndrome (*FGFR1* rearranged), patients can have a B-cell precursor or T-cell precursor leukaemia/lymphoma during one phase of the disease and an acute or chronic myeloid leukaemia during another phase [1]. In the latter instance, exemplified by mixed lineage acute leukaemia (designated mixed phenotype acute leukaemia in the WHO classification), neoplastic cells express various combinations of B-lineage, T-lineage and myeloid markers on cells of the same clone [2]. Lymphomas differ from lymphoid leukaemias in that the predominant disease manifestations are in lymphoid organs or tissues whereas in lymphoid leukaemias, the predominant manifestations are in the bone marrow and the blood.

The mutations leading to lymphoma are very variable. Invariably, they involve oncogenes and often there is also loss of function of tumour suppressor genes. It is the nature of the molecular events that is the crucial factor determining the nature of the lymphoma. Sometimes, these molecular changes are the result of major chromosomal rearrangements, such as a translocation or inversion, and can be predicted by standard cytogenetic analysis [3].

An understanding of the normal immune system necessarily underpins an understanding of the nature of lymphoma.

The normal immune system

The immune system includes lymph nodes, spleen and thymus and, in addition, lymphoid cells in many other organs, including particularly the bone marrow, the liver, the gastrointestinal tract, the upper and lower respiratory tracts and the genitourinary system. Mucosa-associated lymphoid tissue (MALT) includes (1) discrete lymphoid structures such as the appendix, Peyer’s patches in the submucosa of the intestine, and the tonsils and adenoids (collectively referred to as Waldeyer’s ring) in the pharynx and (2) lymphocytes in the submucosa of various organs that do not form any macroscopically recognizable structure. The various components of the immune system are interconnected by lymphatic channels and by the blood stream. In addition to lymphoid cells and certain plasma proteins, the normal immune system includes other cells with phagocytic and antigen-presenting function, including neutrophils, monocytes, macrophages and dendritic cells [4]. The immune system has both innate and adaptive components, and both of these systems have cellular and humoral elements (Table 1.1). Innate immunity does not require prior antigen exposure and provides an immediate response; it includes phagocytic cells, NK cells, gamma/delta T cells and the plasma proteins of the complement system. Adaptive immunity occurs as a response to antigen exposure; it is characterized by specificity and immunological memory with the response being delayed. It is dependent on B cells (which differentiate into antibody-producing plasma cells), CD8-positive T cells (which damage or destroy target cells

Table 1.1 The normal immune system.

	Innate	Adaptive
Characteristics	Does not alter with repeat exposure to antigens	Is characterized by specificity and immunological memory; response enhanced by repeat exposure to an antigen
Components	Phagocytic cells (neutrophils, monocytes, macrophages, interdigitating dendritic cells), cells that release inflammatory mediators (eosinophils, basophils, mast cells) Natural killer cells Gamma/delta T cells Complement components and acute phase reactants Cytokines including chemokines Interferons	B cells and plasma cells T cells Antigen-presenting cells (interdigitating dendritic cells including Langerhans cells ^a , follicular dendritic cells ^b , macrophages and B lymphocytes ^a) Immunoglobulins
Main sites	Blood stream and tissues	Lymph nodes, spleen, mucosa-associated lymphoid tissue

^aPresent antigen to T cells.

^bPresent antigen to B cells.

expressing the relevant antigen) and CD4-positive T cells (which possess effector capability and also enhance and regulate the function of other cells involved in the immune response). Immune responses to self-antigens can also occur. These are maladaptive and often give rise to disease. The bone marrow and thymus, being the sites of B and T lymphocyte

development, are referred to as primary lymphoid organs. The lymph nodes and other peripheral lymphoid tissues comprise the secondary lymphoid tissues.

The structure of a normal or reactive lymph node is shown diagrammatically in Figure 1.1 and in histological sections in Figures 1.2–1.4. Lymph nodes

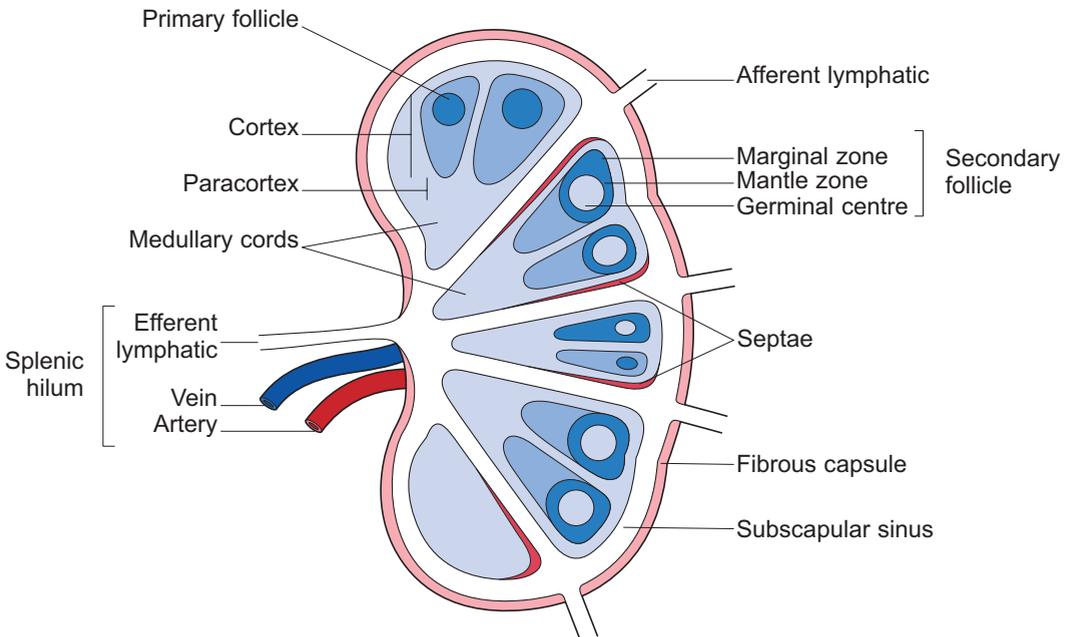


Figure 1.1 Diagram showing the structure of a normal lymph node.

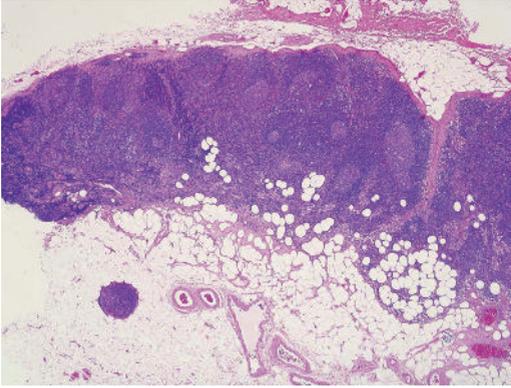


Figure 1.2 Histological section of a lymph node from a patient with reactive lymphadenopathy showing the cortex (containing primary and secondary follicles) and the medulla. Haematoxylin and eosin (H&E) stain, $\times 4$ objective.

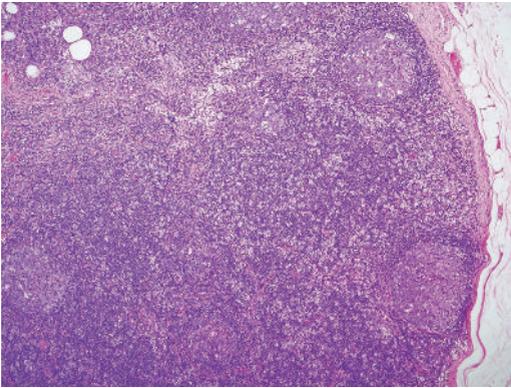


Figure 1.3 Histological section of a lymph node from a patient with reactive lymphadenopathy showing the cortex (containing secondary follicles) and the medulla. H&E stain, $\times 10$ objective.

are divided into cortex, paracortex and medulla. Within the cortex are primary follicles, which are composed of naïve B lymphocytes, which are usually CD5-positive, and follicular dendritic cells. On antigen exposure, proliferation and maturation of B cells causes the primary follicle to develop into a secondary follicle comprising a germinal centre surrounded by a mantle zone of small B lymphocytes. Germinal centre B centroblasts switch off BCL2 and express BCL6. Centroblasts mature to centrocytes, which are located in the light zone of the germinal centre and re-express BCL2. MYC, expressed in centrocytes in the light zone in reactive lymph nodes, plays a key role in the formation and

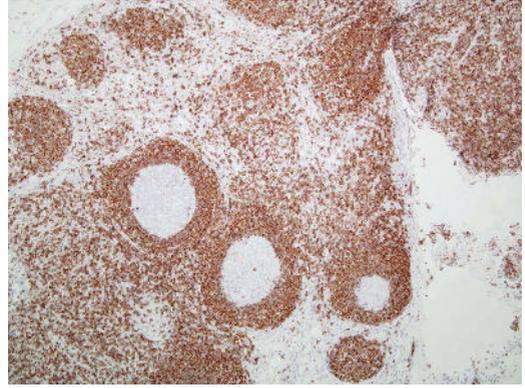


Figure 1.4 Histological section of a lymph node from a patient with reactive lymphadenopathy showing that follicle centres are BCL2 negative. Immunoperoxidase, $\times 10$ objective.

maintenance of germinal centres. Outside the mantle zone, some lymph node and extranodal germinal centres (and particularly splenic germinal centres) have a marginal zone, also composed of B lymphocytes. The network of follicular dendritic cells in the germinal centre presents antigen to B cells. T cells occupy the paracortex, which surrounds and underlies the primary and secondary follicles. The paracortex also has abundant dendritic cells. The centre of the lymph node is the medulla, composed of medullary cords and sinuses. The medullary cords are occupied by B and T lymphocytes, plasma cells and macrophages. Lymph, derived from interstitial fluid and containing a variable number of lymphocytes, is brought to the lymph nodes by a number of afferent lymphatics and is transported from the lymph node by an efferent lymphatic, exiting from the hilum of the node. Lymphocytes are also brought to the lymph node by its arterial supply, entering the interstitium of the node through high endothelial venules. Lymphocytes characteristically recirculate, from lymph nodes or other lymphoid tissues through the lymphatics and the blood stream back to lymphoid tissues. Homing of lymphocytes to tissues similar to those from which they originated (e.g. skin or gastrointestinal submucosa) is usual.

The spleen is a lymphoid and reticuloendothelial organ of major importance [5]. Its functions include phagocytosis of abnormal circulating cells, 'pitting' of micro-organisms and other inclusions from red cells, phagocytosis of antibody-coated bacteria and

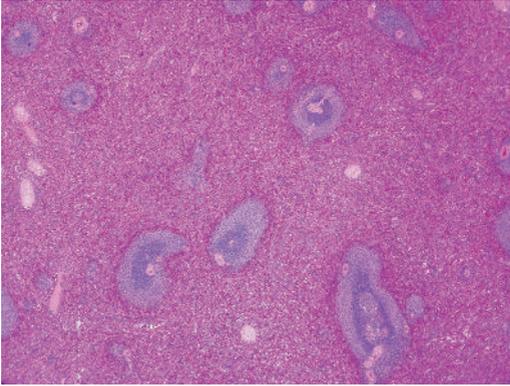


Figure 1.5 Histological section of a normal spleen showing the red pulp and the white pulp. The paler marginal zone is clearly apparent. H&E stain, $\times 4$ objective.

antibody production. It is divided into the white pulp and the red pulp (Figure 1.5). The white pulp surrounds arteries and arterioles, being composed of a peri-arterial and peri-arteriolar sheath of T lymphocytes (among which CD4-positive T cells predominate) within which, between the branching arterioles, there are lymphoid follicles. The primary lymphoid follicles of the spleen have a well-developed marginal zone composed mainly of B lymphocytes but also containing T lymphocytes, macrophages, dendritic cells and plasma cells. With antigenic stimulation, germinal centres and a more prominent mantle zone develop. The white pulp is the major site of antigen presentation and antibody production. The red pulp is composed of venous sinuses and splenic cords, the latter containing dendritic cells, macrophages, stromal cells, red cells and a small transitory population of neutrophils, monocytes, lymphocytes (including B cells and CD8-positive T cells) and plasma cells; it is the major site of phagocytosis, and is an important component of the reticuloendothelial system. In addition to lymphoid cells, the spleen contains significant numbers of red cells and about 10% of circulating platelets.

The thymus is a lymphoid organ of major importance in T-cell maturation and in the selection of T cells recognizing peptides derived from foreign rather than self-antigens. The thymus is composed of a cortex and a medulla. It contains functionally important epithelial elements, as well as lymphoid cells. Maturation and selection of T cells start in the cortex and continue in the medulla.

The normal development of a B lymphocyte is shown schematically in Figure 1.6 [4,6,7]. B lymphocytes originate in the bone marrow from haemopoietic stem cells, which give rise to B-cell precursors (B lymphoblasts or 'haematogones'), which in turn give rise to naïve B lymphocytes. These travel to the primary follicle of the lymph node or other secondary lymphoid tissue. There they either meet a cognate antigen (presented by a follicular dendritic cell), and proliferate and differentiate further, or die by apoptosis. B cells that encounter antigen are thought to migrate to the mantle zone surrounding the primary follicle. Interaction with antigen-specific T cells results in proliferation followed by migration of the activated lymphocytes to form a primary focus of clonal expansion within the follicle centre. These B lymphocytes develop into centroblasts and centrocytes, leading to formation of the germinal centre of the secondary follicle. Immunoglobulin (Ig) class switching (isotype switching) and somatic hypermutation occur in the germinal centre. Ongoing IGHV mutations and *BCL6* mutations are the hallmark of germinal centres. Further maturation can occur in the marginal zone where the lymphoid cell may assume a monocytoïd appearance. Thereafter, the cell either becomes a long-lived circulating memory B cell or develops into a plasma cell in the bone marrow or other tissue. During this process of differentiation, there are genetic, immunophenotypic and functional changes occurring in the B cell.

The normal development of a T cell is shown in Figure 1.7. A haemopoietic stem cell (CD34+, CD38+) of bone marrow origin migrates to the corticomedullary junction of the thymus where development into a T-cell precursor occurs. At this stage, the cell, now known as a thymocyte, expresses terminal deoxynucleotidyl transferase (TdT), CD7 and cytoplasmic CD3, and does not express either CD4 or CD8, that is 'double negative' [8]. It migrates into the cortex where rearrangement of T-cell receptor (TCR) genes (*TRA*, *TRB*) commences and expression of CD1a, CD4 and CD8 occurs, producing a 'double positive' cortical thymocyte. During maturation in the thymus, the cell expresses membrane CD3 and either CD4 or CD8. The thymocyte migrates towards the thymic medulla, encountering cortical thymic epithelium expressing MHC class I or class II molecules, which present peptides. Cells that are not actively selected through encounter

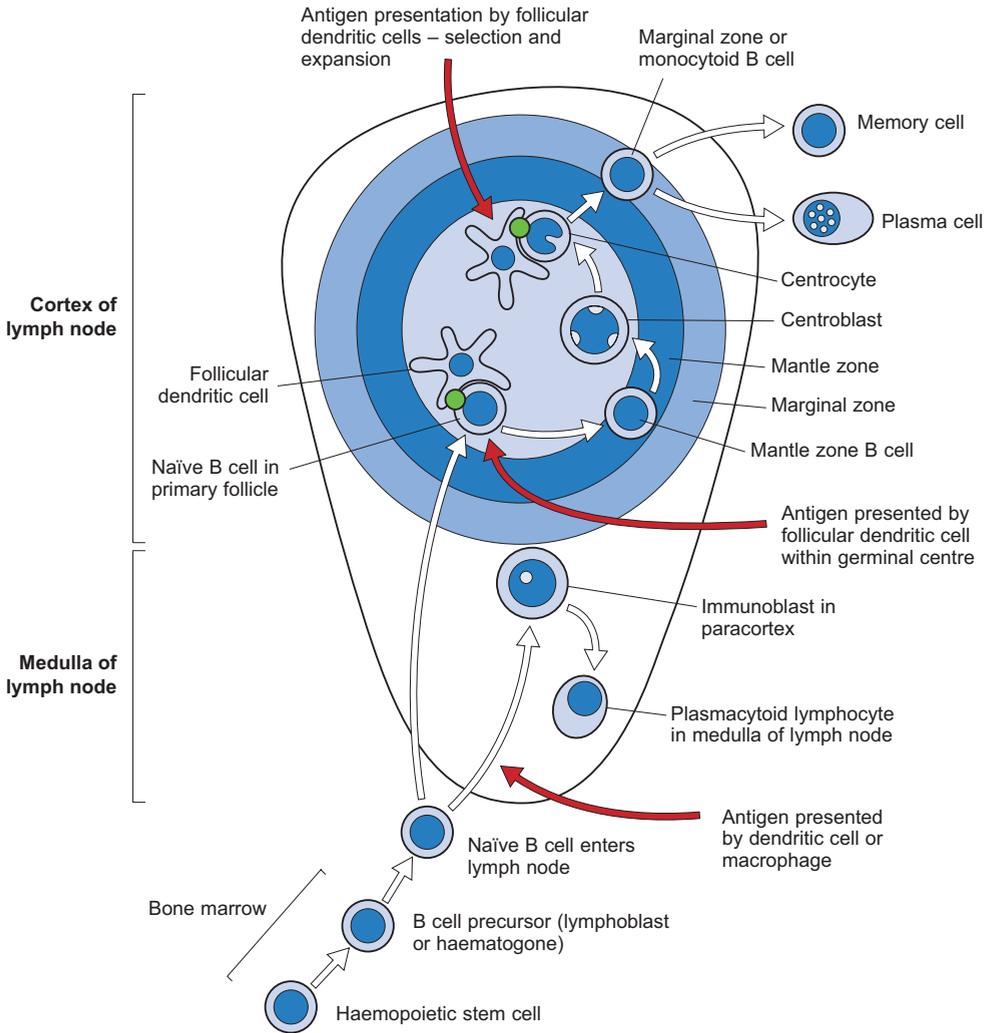


Figure 1.6 Diagram showing the normal development of a B lymphocyte. A haemopoietic stem cell in the bone marrow gives rise to a B-cell precursor and then to a naïve B cell, which migrates to either secondary lymphoid tissues such as a lymph node primary follicle or medulla. If the B cell is presented with antigen by a dendritic cell or macrophage, further development occurs. A naïve, immunoglobulin (Ig) M- or IgD-expressing B cell in the primary follicle responds to antigen by class switching and migration to the mantle zone. The mantle zone B cell then migrates back into the germinal centre and transforms to a centroblast and then a centrocyte within what is now a secondary follicle containing a germinal centre. These germinal centre cells undergo somatic hypermutation before migrating to the marginal zone and then the blood stream. Post-germinal centre B cells become memory cells in blood or tissues or plasma cells in tissues.

with a compatible peptide-presenting MHC molecule die by apoptosis. This is the fate of more than 98% of the initial thymocyte population. Those that do encounter a matching peptide-presenting MHC class I molecule develop into CD8-positive medullary thymocytes. Those that encounter a matching peptide-presenting MHC class II molecule develop into CD4-positive medullary thymocytes. Self-reactive

T cells are deleted, probably in the thymic medulla. Mature CD4-positive or CD8-positive T cells migrate from the thymus to lymph nodes and other lymphoid organs where they are located preferentially in the paracortex and the medulla. The mature T cells express in the membrane a complete TCR complex, which is composed of TCR chains and a CD3 complex, which contains gamma, delta and epsilon

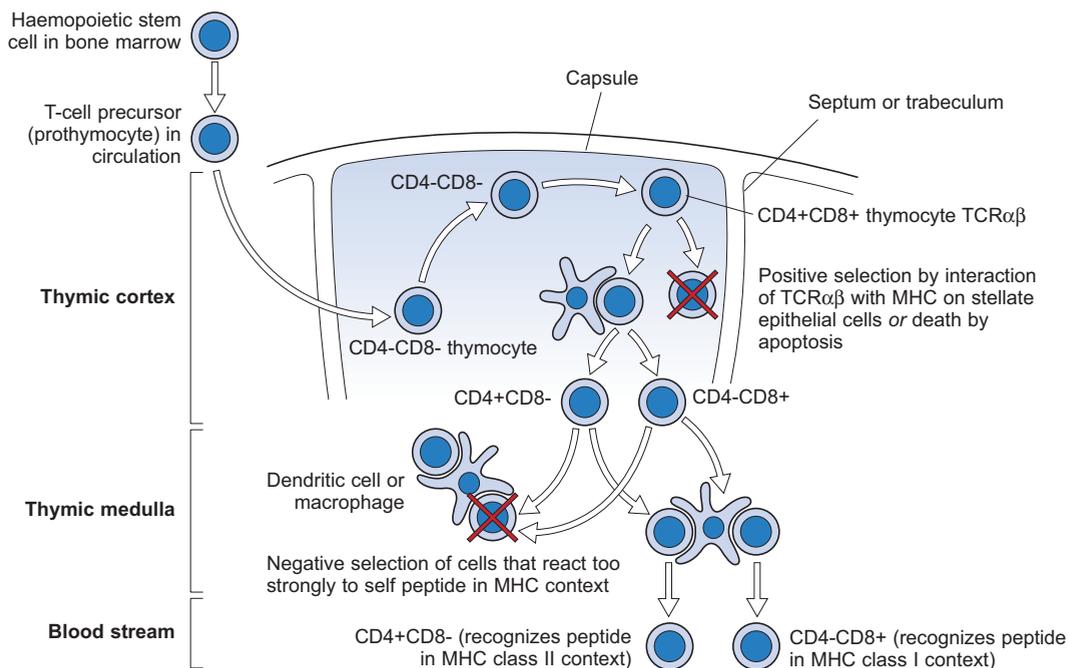


Figure 1.7 Diagram showing the normal development of a T lymphocyte in the thymus. Haemopoietic stem cells in the bone marrow give rise to T-cell precursors, which enter the thymic medulla and then migrate from the medulla to the cortex. Cortical thymocytes undergo positive selection. If they recognize a specific foreign peptide presented in an MHC I or II context by a thymic epithelial cell, they survive; if not, they undergo apoptosis. Surviving cells develop into either CD4+CD8- or CD4-CD8+ cells, which migrate to the thymic medulla. Medullary thymocytes undergo negative selection. Cells with a strong affinity for a self-peptide presented by a dendritic cell or a macrophage in an MHC context undergo apoptosis and are thus deleted. Surviving cells leave the thymus as T cells, which migrate to secondary lymphoid tissues where they undergo clonal expansion if they recognize a peptide presented by a dendritic cell in an MHC context.

chains. There are two groups of mature T cells according to the TCR, the alpha/beta and the gamma/delta. Gamma/delta-expressing T cells account for about 5% of T cells and are found in the splenic red pulp, mucosae and intestinal and skin epithelia; a minority are circulating in the peripheral blood. Among CD4-positive cells, there are particular sub-populations characterised by a distinct immunophenotype, function and/or localization. For instance, the regulatory T cells (Treg) suppress the immune response to cancer and express CD25 and the transcription factor FOXP3, and the T follicular helper (TFH) cells have a distinct immunophenotypic profile with expression of BCL6, CD10, CD57 and PD1 (CD279) and provide help to B lymphocytes within the context of germinal centre reaction.⁷

NK cells originate in the bone marrow, probably being derived from a lymphoid precursor that is shared with B and T lymphocytes and being ultimately derived from a haemopoietic stem cell. They do not have a

complete TCR complex but activated NK cells express, in the cytoplasm, the epsilon and zeta chains of CD3.

T and B lymphocyte precursors have germline genes that are unusual in that they are divided into segments. These must be assembled into functional genes by a process of deletion and rearrangement of gene segments to form the genes that encode the various chains of immunoglobulin molecules (IGH, IGK and IGL) and, similarly, the TCR genes (*TRA*, *TRB*, *TRG*, *TRD*); surface membrane immunoglobulin molecules (SmIg) are part of a complex that functions as a B-cell receptor. The segments that comprise a heavy chain gene are a variable region segment (VH), a diversity segment (D), a joining segment (JH) and a constant region segment (C); the latter is specific for each heavy chain class (C μ , C δ , C γ 3, C γ 1, C α 1, C γ 2, C γ 4, C ϵ and C α 2). These gene segments are assembled as shown in Figure 1.8. The process of VDJ recombination occurs in the bone marrow leading to a cytoplasmic μ -expressing

pre-B cell. The *RAG1* and *RAG2* genes are then re-activated leading to rearrangement of an *IGK* gene, or if this fails, an *IGL* gene. The rearranged light chain-encoding *IGK* and *IGL* genes are composed of a variable region and a joining region only,

$V\kappa + J\kappa$ or $V\lambda + J\lambda$. Once a light chain gene has been effectively rearranged, immunoglobulin is expressed on the surface of the cell and the pre-B cell becomes an IgM-expressing B cell. The next stage of B-cell differentiation, class or isotype switching (Figure 1.9), occurs within a germinal centre,

leading to a cell that expresses IgG, IgA or IgE rather than IgM with or without IgD. The final event in the genetic development of a B cell is somatic hypermutation, a process of multiple point mutations and, to a lesser extent, deletions and duplications, occurring in the variable region of the gene. Somatic hypermutation occurs in germinal centres, for example in lymph nodes, spleen and tonsils, when a naïve B lymphocyte recognizes antigen presented in an MHC context by an antigen-presenting cell such as a dendritic cell. The result of this process is

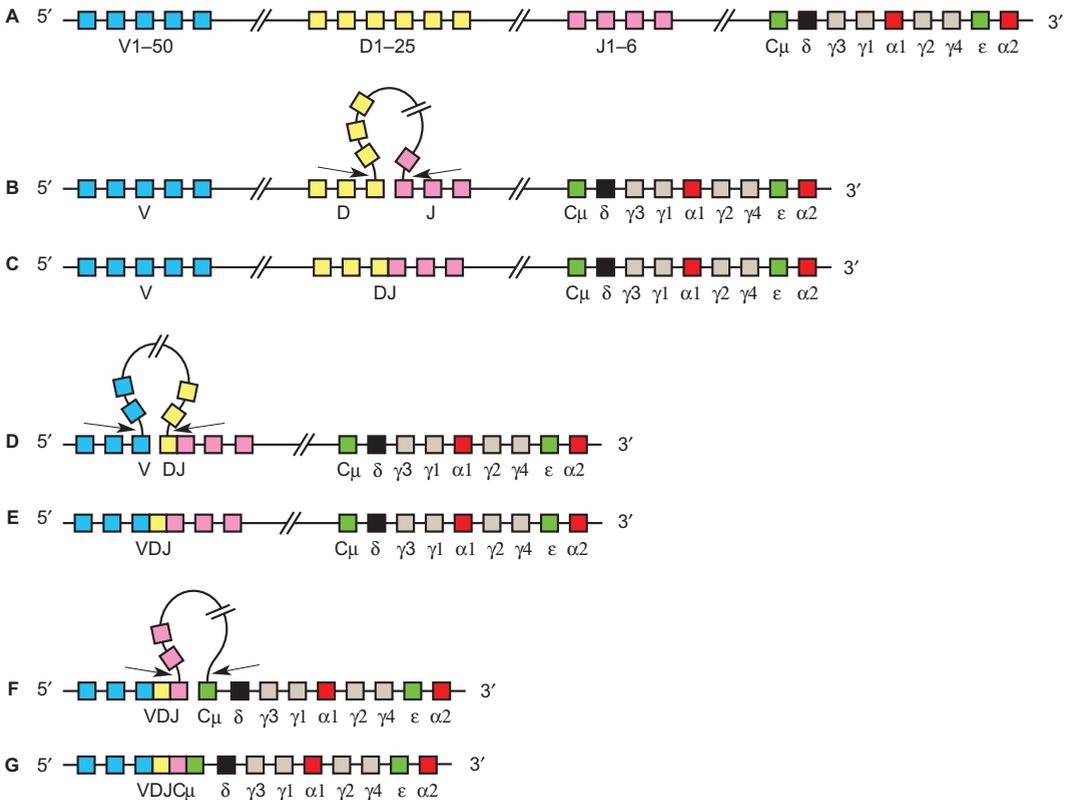


Figure 1.8 Diagram showing the rearrangement of an immunoglobulin heavy-chain locus (IGH) in a B-cell precursor in the bone marrow.

A Germline IGH showing V (variable), D (diversity), J (joining) and C (constant) regions (only a few representative segments are shown; double lines indicate a non-existent break in the gene).

B Lymphocyte-specific enzymes, *RAG1* and *RAG2*, cleave the DNA at one point within the D region and at another within the J region (arrows).

C The intervening segments having been excised, the two ends are rejoined by enzymes encoded by ubiquitously expressed genes, to give DJ fusion.

D *RAG1* and *RAG2* are reactivated and cleavage occurs within the V and D regions.

E Rejoining occurs to give VDJ fusion.

F Cleavage occurs within the J region and between the final J segment and the first (μ) exon of the C region.

G Rejoining results in a VDJC μ gene, encoding μ heavy chain (a switch region, S μ , upstream of C μ , is also included in the sequence so that the sequence can also be represented as VDJ μ C μ – see Figure 1.9).

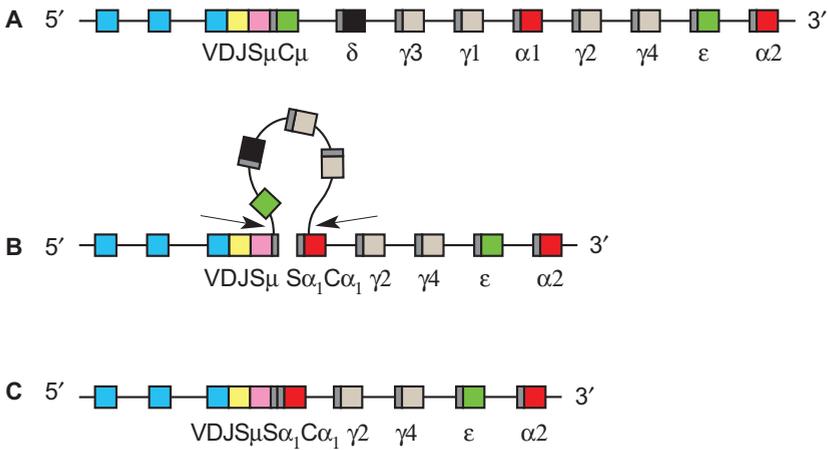


Figure 1.9 Class or isotype switching of a B cell, which occurs within a germinal centre. **A** Gene that has undergone VDJ recombination and is expressing IgM (IGK or IGL having also been effectively rearranged); the sequence is VDJ μ C μ ; the switch region of each gene segment is represented in grey. **B** As a result of activation-induced deamination, DNA cleavage occurs between the switch region and the coding region of C μ and also upstream of the switch region of one of the other C segments, in the case illustrated C α 1. **C** The intervening sequence having been excised, there is rejoining of two switch regions, in this case S μ and S α 1 resulting in the sequence VDJ μ S α 1C α 1; the cell is now able to express IgA1.

that the immunoglobulin expressed on the surface membrane of the B cell more closely matches the antigen that has been presented and binding affinity is thereby increased. Naïve B cells that reach germinal centres but do not find a matching antigen die by apoptosis (Figure 1.10). Each mutation that increases affinity for antigen selects for cell survival rather than cell death. Continuing cycles of selection and mutation produce cells with a high affinity for the antigen. It is these high-affinity B cells that differentiate into plasma cells and give rise to memory B cells. Plasma cells home to the bone marrow, spleen, lymph nodes and gastrointestinal tract. Memory cells comprise about 40% of circulating B cells, the other 60% being naïve B cells.

The process of rearrangement of gene segments also occurs in T cells, which rearrange V, D and J segments in genes encoding α , β , γ and δ chains. Somatic hypermutation and class switching do not occur and it has been hypothesized that it is the greater degree of genetic rearrangement occurring in B cells that make B-cell lymphomas far more common than T-cell lymphomas. Most mature T cells have a surface membrane complex composed of α and β chains of the TCR together with CD3 and either CD4 or CD8, which recognize specific peptides in an appropriate MHC context, MHC class I

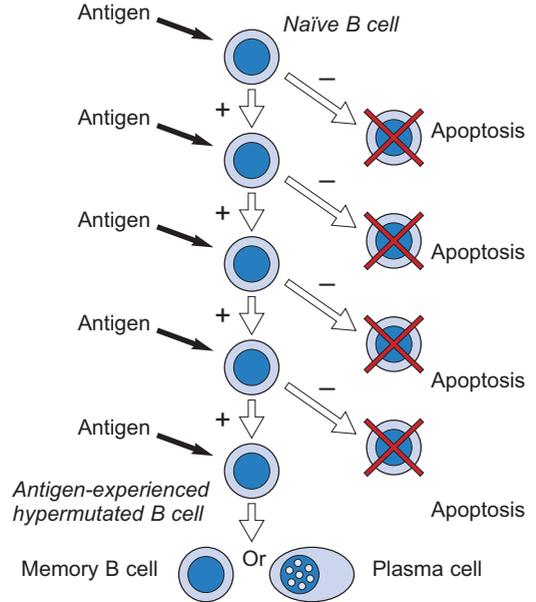


Figure 1.10 The process of somatic hypermutation, which occurs within the germinal centre on exposure to antigen. Cells that are capable of binding to that antigen are selected for survival (+) and cells that are not (-) die by apoptosis; cells that undergo mutation of V H and V L segments that lead to a higher binding affinity for the antigen are selected for survival (+) rather than those with a lower affinity (-); this leads to progressive expansion of a clone of antigen-experienced cells that have a high affinity for the antigen.

in the case of CD8-positive cells and MHC class II in the case of CD4-positive cells [4].

NK cells, being part of the innate rather than the adaptive immune system, appear not to undergo any gene rearrangement.

The genetic rearrangement that occurs in B and T cells is paralleled by alterations in expression of surface membrane and cytoplasmic antigens [7, 8]. These changes are illustrated in Figures 1.11 and 1.12.

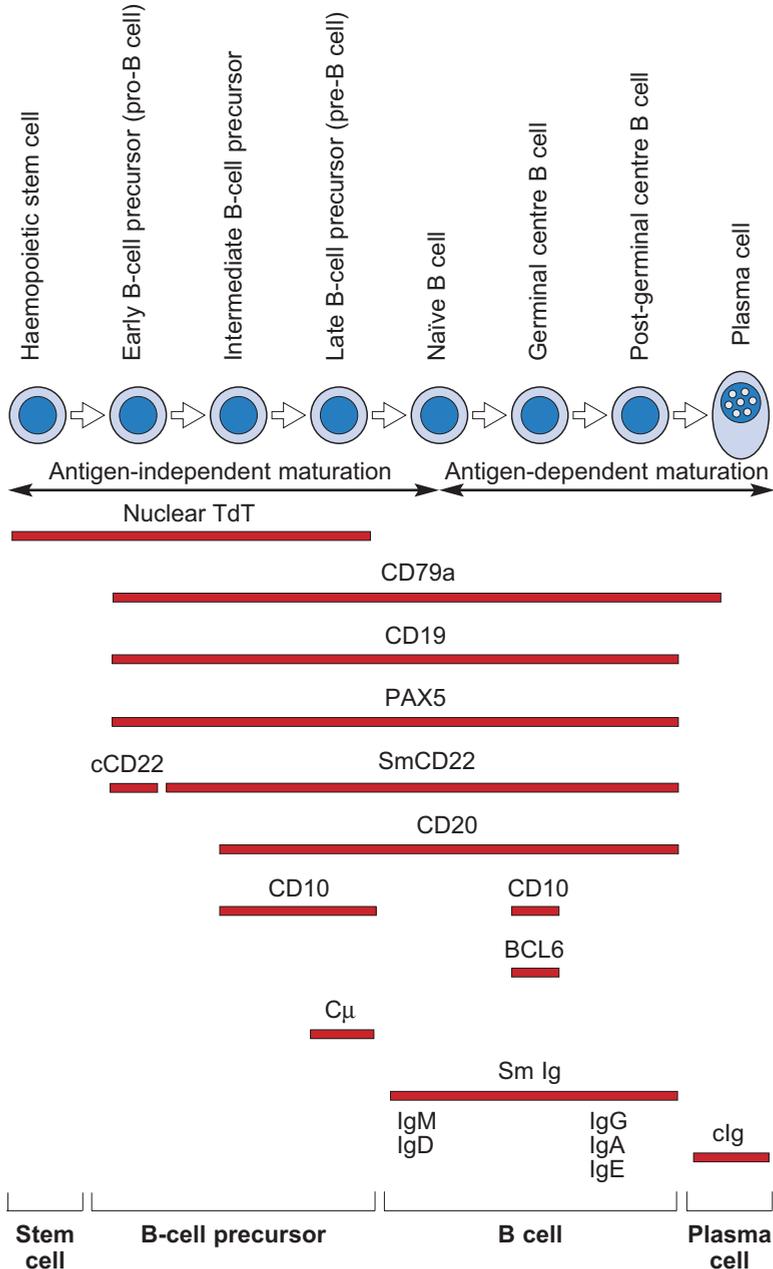


Figure 1.11 Alterations in the expression of surface membrane and cytoplasmic antigens that occur with B-cell maturation. c, cytoplasmic; Ig, immunoglobulin; Sm, surface Membrane; TdT, terminal deoxynucleotidyl transferase.

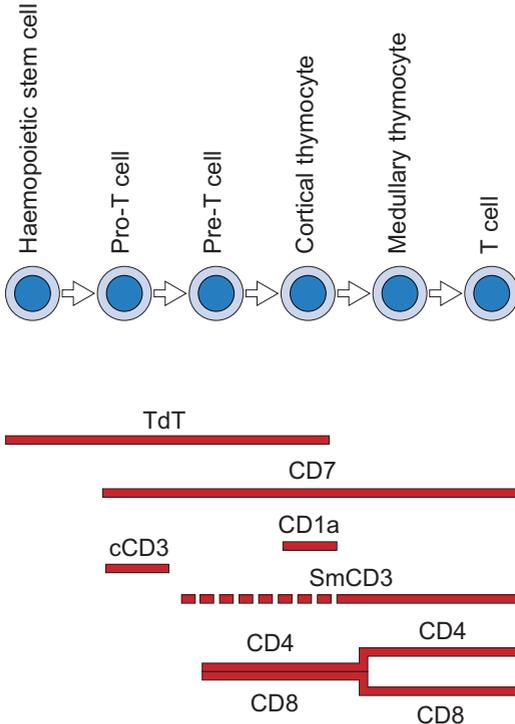


Figure 1.12 Alterations in expression of surface membrane and cytoplasmic antigens that occur with T-cell maturation. c, cytoplasmic; Sm, surface membrane; TdT, terminal deoxynucleotidyl transferase.

Relationship of lymphomas to putative normal homologues

The putative relationship between the normal stages of B-cell and T-cell differentiation and B- and T-lineage neoplasms is shown in Figures 1.13 and 1.14.

The molecular basis of acute lymphoblastic leukaemia/lymphoblastic lymphoma

The molecular basis of acute lymphoblastic leukaemia (ALL) and the related lymphoblastic lymphomas varies between T- and B-lineage cases and also between different subtypes. Often, there is a mutation that leads to either dysregulated expression of a

normal transcription factor gene or to expression of a gene encoding an abnormal transcription factor. More than one mutation is needed in order to give rise to an acute leukaemia. One mutation may interfere with transcription factor function and another with intracellular signalling so that cells continue to proliferate but differentiation does not occur.

The two most common subtypes of B-lineage ALL are those associated with hyperdiploidy and with a cryptic reciprocal translocation, $t(12;21)(p13.2;q22.1)$. The molecular mechanism of leukaemogenesis of the former is unknown while the latter is associated with fusion of two transcription factor genes to give an *ETV6-RUNX1* (previously known as *TEL-AML1*) fusion gene. Several other less common subtypes of ALL are also associated with the formation of a fusion gene. The subtype associated with $t(4;11)(q21;q23.3)$ has a *KMT2A-AFF1* (previously known as *MLL-AF4*) fusion gene, whereas the subtype associated with $t(1;19)(q23;p13.3)$ has an *TCF3-PBX1* (previously known as *E2A-PBX1*) fusion gene. In adults, about one-quarter of cases of B-lineage ALL are associated with $t(9;22)(q34.1;q11.2)$ and a *BCR-ABL1* fusion gene; it is likely that there are other undiscovered molecular events in this subtype, explaining why the phenotype is that of ALL since the dysregulated tyrosine kinase activity of *BCR-ABL1* usually leads to chronic myeloid leukaemia.

In T-lineage ALL, the two abnormalities most often observed are $t(5;14)(q35.1;q32.2)$, in about 20% of cases, and *TAL1* cryptic deletion/fusion in about one-third of cases. The mechanism of leukaemogenesis in the former is dysregulation of *TLX3* (previously known as *HOX11L2*), probably by proximity to the transcription regulatory elements of *BCL11B* (previously known as *CTIP2*) at 14q32.2. In the case of *TAL1*, there is a cryptic deletion that results in most of the sequences of *TAL1*, a transcription factor gene on chromosome 1, being fused with the promoter of an upstream gene, *SIL*. This leads to dysregulation of *TAL1*, which is not normally expressed in T cells. Another frequent mechanism of leukaemogenesis in T-lineage ALL is dysregulation of a transcription factor gene by proximity to a TCR gene (*TRA*, *TRB*, *TRG* or *TRD*); genes that can be dysregulated in this manner include *TAL1*, *TLX1*, *TLX3*, *MYC*, *LMO1* and *LMO2*.

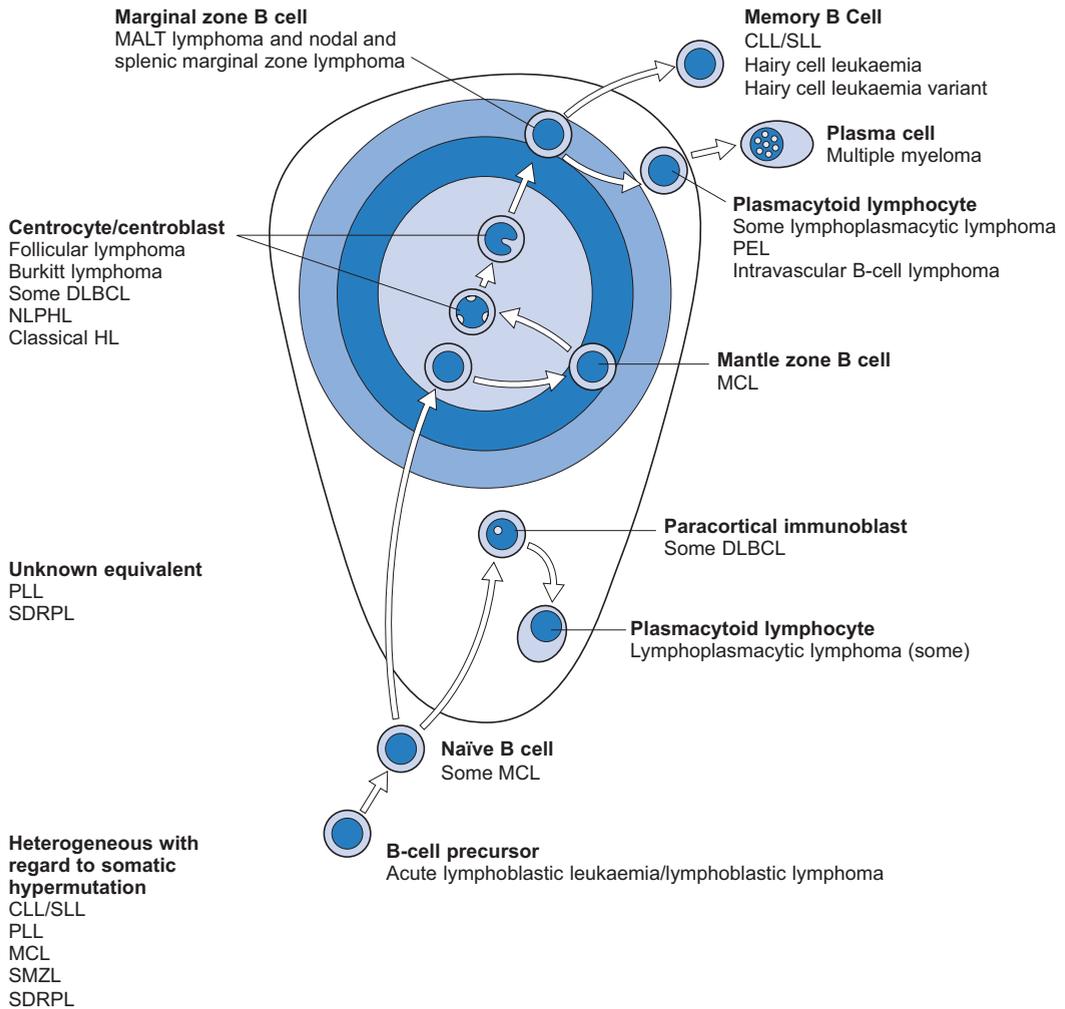


Figure 1.13 Putative relationship between normal B-cell differentiation and B-lineage neoplasms. CLL, chronic lymphocytic leukaemia; DLBCL, diffuse large B-cell lymphoma; classical HL, classical Hodgkin lymphoma; MALT, mucosa-associated lymphoid tissue; MCL, mantle cell lymphoma; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma; PEL, primary effusion lymphoma; PLL, prolymphocytic leukaemia; SLL, small lymphocytic lymphoma; SDRPL, splenic diffuse red pulp lymphoma; SMZL, splenic marginal zone lymphoma.

Second mutations occurring in the cell that gives rise to the leukaemic clone may or may not be specific to a cytogenetic/molecular genetic subtype. For example, in B-lineage ALL associated with *ETV6-RUNX1* there has often also been deletion of the second *ETV6* allele whereas in T-lineage ALL an activating mutation of *NOTCH1* has been found as a second event in all major cytogenetic/molecular genetic subtypes. *NOTCH1* encodes a membrane receptor that regulates normal T-cell development.

The molecular basis of B-lineage non-Hodgkin lymphoma, chronic B-lineage leukaemias and multiple myeloma

The molecular basis of B-lineage non-Hodgkin lymphoma (NHL) often involves dysregulation of an oncogene as the result of a translocation that

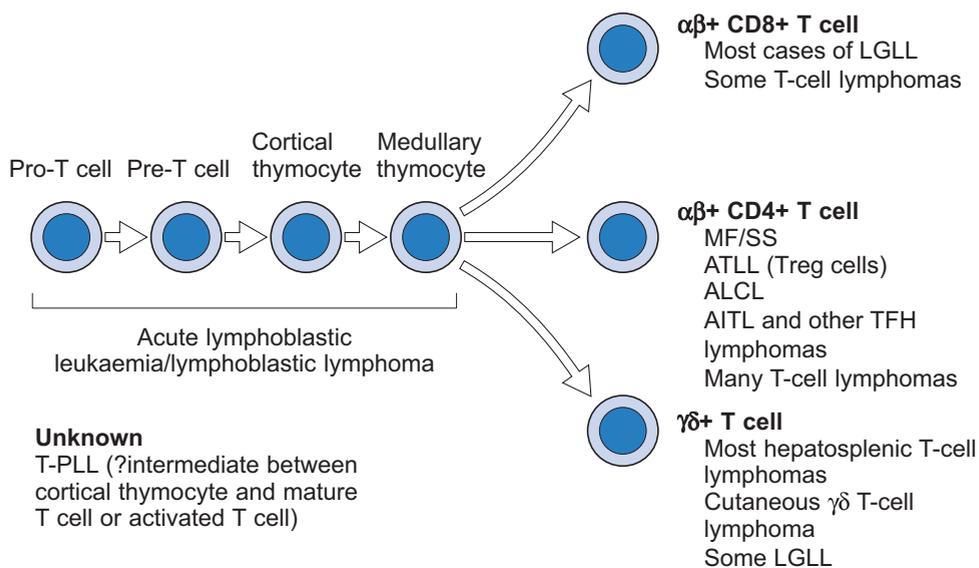


Figure 1.14 Putative relationship between normal T-cell differentiation and T-lineage neoplasms. AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; ATLL, adult T-cell leukaemia/lymphoma; LGLL, large granular lymphocytic leukaemia; MF, mycosis fungoides; SS, Sézary syndrome; TFH, T follicular helper cell; T-PLL, T-cell prolymphocytic leukaemia.

brings it under the influence of an enhancer of the immunoglobulin heavy chain gene (IGH) at 14q32.33 or of the kappa (κ) or lambda (λ) genes (IGK and IGL) at 2p12 and 22q11.22, respectively. Examples of this mechanism include the three translocations that can underlie follicular lymphoma, dysregulating *BCL2*, and the three that can underlie Burkitt lymphoma, dysregulating *MYC*. An alternative mechanism is formation of a fusion gene as the result of a translocation, such as the *BIRC3-MALT1* (previously *API2-MALT*) fusion gene in gastric MALT-type lymphoma with t(11;18)(q22.2;q21.32). Sometimes, different molecular abnormalities affect a common signalling mechanism, for example dysregulation of *MALT1* by proximity to IGH is an alternative to formation of a *BIRC3-MALT1* fusion gene. In some B-lineage lymphomas and leukaemias, the molecular mechanisms of oncogenesis are largely unknown. This is so for small lymphocytic lymphoma/chronic lymphocytic leukaemia (SLL/CLL), in which many cytogenetic and molecular abnormalities have been described (mainly deletions or gene amplification rather than translocations) without a primary oncogenic event yet being identified. In some leukaemias and lymphomas, characteristic chromosomal abnormalities have similarly

been recognized without an associated oncogenic molecular change yet being identified. This is so for trisomy 3 and deletion 7q31.2 in splenic marginal zone lymphoma and for trisomy 12 in CLL.

Cytogenetic and molecular analysis can be very important in diagnosis, for example confirming a diagnosis of Burkitt lymphoma so that specific treatment regimes can be used, identifying cases of double or triple hit high grade B-cell lymphomas with prognostic implications or confirming a diagnosis of follicular lymphoma or mantle cell lymphoma if other features are not diagnostic.

The molecular basis of multiple myeloma often involves translocations that bring oncogenes under the influence of enhancers of IGH, for example t(4;14)(p16.3;q32), t(6;14)(p21;q32), t(11;14)(q13;q32), t(14;16)(q32;q23) and t(14;20)(q32;q11). Cytogenetic analysis has demonstrated the same chromosomal rearrangements in cases of monoclonal gammopathy of undetermined significance. The mechanism of oncogenesis in plasma cell tumours differs somewhat from that in other B-cell neoplasms since translocations usually involve the switch region and thus separate an intrinsic and a 3' enhancer; there can therefore be an oncogene under the influence of an enhancer on both of the derivative chromosomes

rather than just on one. This is the case, for example in t(4;14)(p16.3;q32) when both *FGFR3* on chromosome 14 and *MMSET* on chromosome 4 are dysregulated. Other unknown oncogenic mechanisms relate to loss of 13, 13q or 13q14, any of which is associated with a worse prognosis (at least when detected in metaphases).

Cytogenetic and molecular analysis in NHL can reveal not only initial or early events in oncogenesis but also genetic alterations that are of prognostic significance or correlate with disease progression, such as loss or inactivation through mutation of the tumour suppressor gene, *TP53*. Cytogenetic/molecular analysis also gives information as to the nature of apparent high-grade transformation. It has been found, for example, that transformation of follicular lymphoma to diffuse high-grade B-cell lymphoma does indeed represent transforming events in a cell of the neoplastic clone, whereas in CLL, many examples of 'Richter's transformation' (about 20–25%) actually represent an independent neoplasm,

sometimes Epstein–Barr virus (EBV)-related, resulting from immunosuppression.

In addition to the putative oncogenic events, molecular analysis will show whether or not somatic hypermutation has occurred. This gives information as to the nature of the cell in which the oncogenic mutations occurred, that is whether pre-germinal centre, germinal centre or post-germinal centre, and may throw some light on possible aetiology. Such information can also be of prognostic significance, for example in CLL somatic hypermutation correlates with a better prognosis.

Cytogenetic and molecular genetic analysis often yields information of prognostic significance, for example in CLL and multiple myeloma. Sometimes, specific abnormalities indicate likely refractoriness to treatment, for example cases of gastric MALT lymphoma with t(11;18) do not usually respond to elimination of *Helicobacter pylori* infection. Some genetic abnormalities observed in B-lineage NHL are summarized in Table 1.2.

Table 1.2 Cytogenetic and molecular genetic abnormalities observed in different subtypes of B-lineage non-Hodgkin lymphoma.

Lymphoma	Cytogenetic abnormality	Molecular abnormality
Follicular lymphoma	t(14;18)(q32.33;q21.33)	Dysregulation of <i>BCL2</i> by proximity to <i>IGH</i>
	t(2;18)(p11.2;q21.33)	Dysregulation of <i>BCL2</i> by proximity to <i>IGK</i> at 2p11.2
	t(18;22)(q21.33;q11.22)	Dysregulation of <i>BCL2</i> by proximity to <i>IGL</i> at 22q11.22)
Mantle cell lymphoma	t(1;14)(q13.3;q32.33)	Dysregulation of <i>CCND1</i> , the gene encoding cyclin D1, by proximity to <i>IGH</i>
Diffuse high grade B-cell lymphoma	t(14;18)(q32.33;q21.33)	Dysregulation of <i>BCL2</i> by proximity to <i>IGH</i>
	t(3;14)(q27.3;q32.33)	Dysregulation of <i>BCL6</i> by proximity to <i>IGH</i>
Burkitt lymphoma	t(8;14)(q24.21;q32.33)	Dysregulation of <i>MYC</i> by proximity to <i>IGH</i> at 14q32.33
	t(2;8)(p11.2;q24.21)	Dysregulation of <i>MYC</i> by proximity to <i>IGK</i> at 2p11.2
	t(8;22)(q24.21;q11.22)	Dysregulation of <i>MYC</i> by proximity to <i>IGL</i> at 22q11.22
Gastric and sometime pulmonary or intestinal MALT-type lymphoma	t(11;18)(q22.2;q21.32)	<i>BIRC3-MALT1</i> fusion
MALT lymphoma of ocular adnexae, skin or thyroid	t(1;14)(p22.3;q32.33)	Dysregulation of <i>BCL10</i> by proximity to <i>IGH</i>
MALT lymphoma of salivary gland	t(3;14)(p13;q32.33)	Dysregulation of <i>FOXP1</i> by proximity to <i>IGH</i>
MALT lymphoma of salivary gland	t(14;18)(q32.33;q21.32)	Dysregulation of <i>MALT1</i> by proximity to <i>IGH</i>

The molecular basis of T-lineage and NK-lineage non-Hodgkin lymphoma and leukaemia

The molecular basis of T-lineage NHL is less well established than that of B-lineage neoplasms.

Recurring cytogenetic/molecular genetic abnormalities have been observed in association with T-cell prolymphocytic leukaemia (T-PLL). About three-quarters of cases show either *inv(14)(q11.2q32.13)* or *t(14;14)(q11.2;q32.13)*. These chromosomal rearrangements involve the TRAD locus at 14q11.2 and two oncogenes, *TCL1A* and *TCL1B*, at 14q32.13. *TCL1A* and *TCL1B* are dysregulated and, when overexpressed, inhibit apoptosis.

Anaplastic large cell lymphoma is also associated with several recurring cytogenetic abnormalities, of which *t(2;5)(p23.2-23.1;q35.1)* is the most frequent, with known oncogenic mechanisms (Figure 1.15).

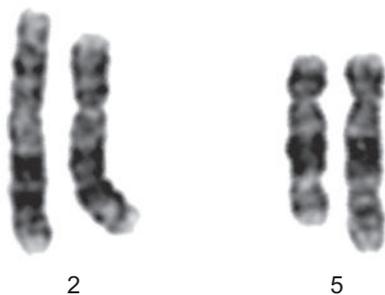


Figure 1.15 Karyogram showing *t(2;5)(p23;q35)* in a patient with anaplastic large T-cell lymphoma. With thanks to Dr John Swansbury.

However, for the majority of T-cell and NK-cell disorders, no recurring abnormality has been discovered and in those instances when recurring cytogenetic abnormalities have been detected, the molecular basis is not yet known.

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Lymphoid Malignancies

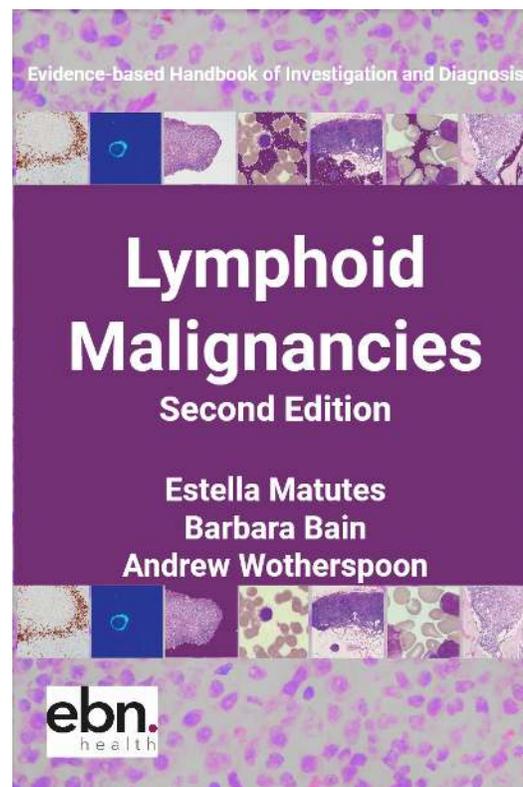
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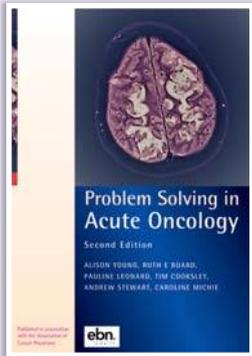
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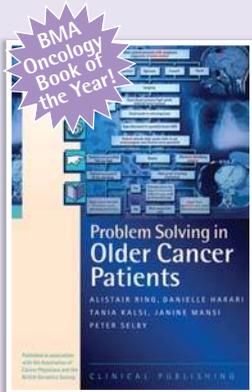
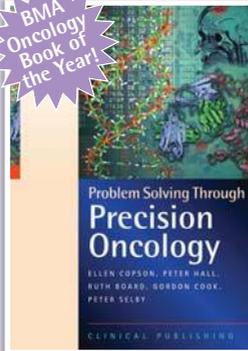
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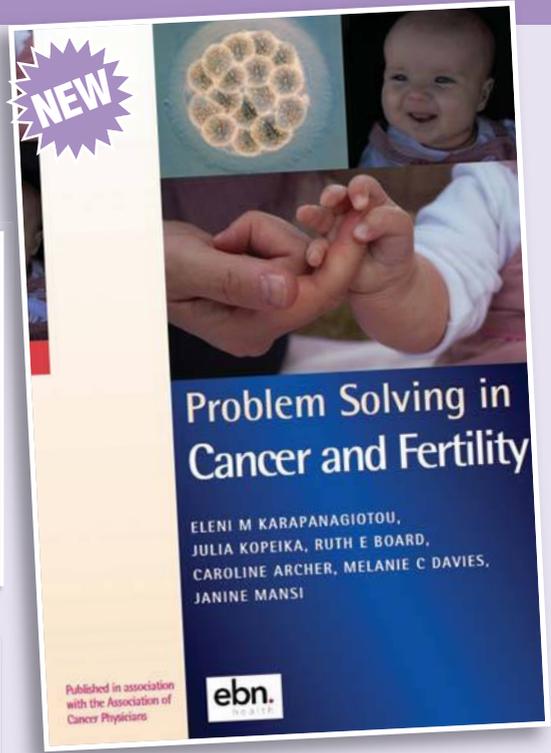
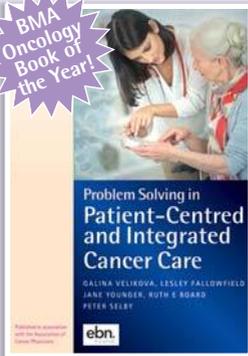
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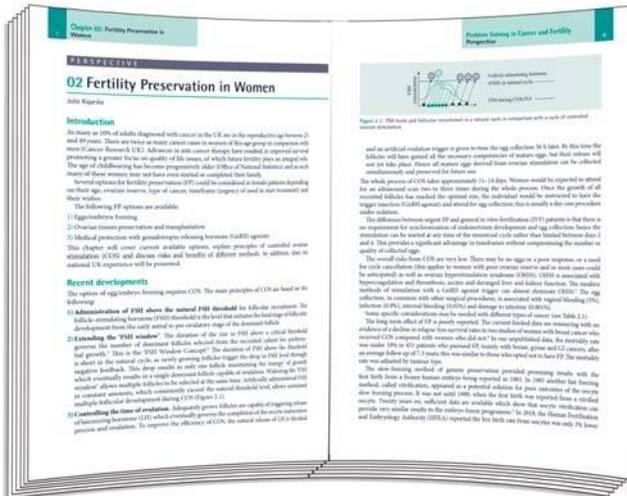
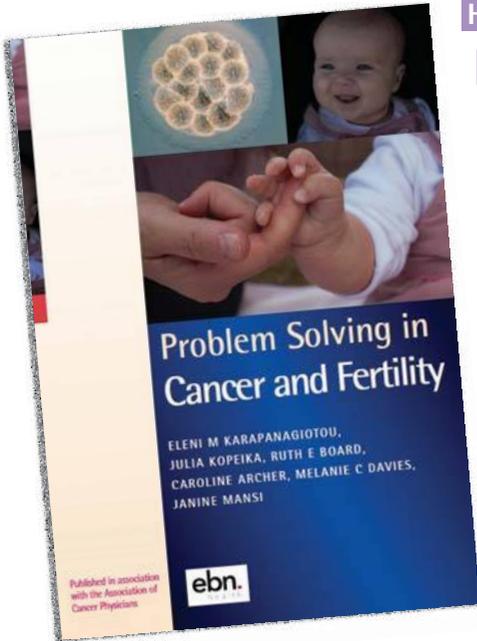
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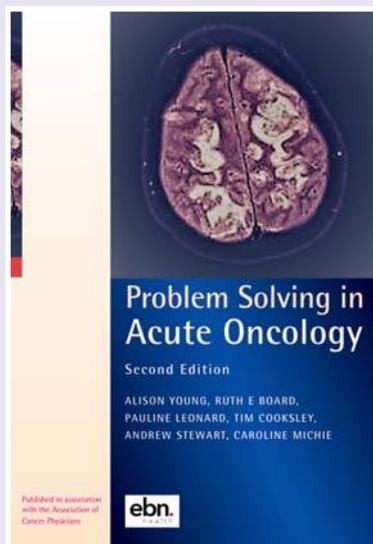
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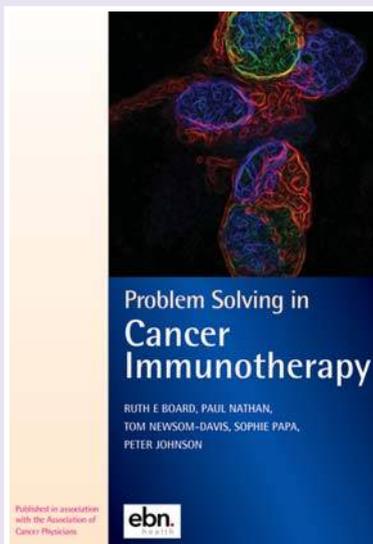


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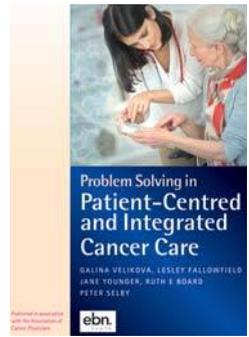
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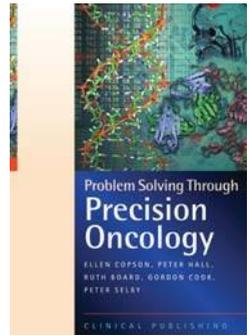
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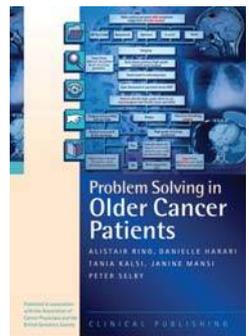
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