

1st volume

1 IN VITRO AND IN VIVO HEMATOPOIESIS	1	2 ERYTHROCYTES	39
Embryonic hematopoiesis	3	PART 1 GENERAL ASPECTS OF ERYTHROPOIESIS	41
Hepatic hematopoiesis	3	Introduction	41
Bone marrow ontogeny	7	Fetal erythropoiesis	41
Umbilical cord blood	9	Generation of erythroid cells	
Biology of hematopoiesis	9	in post-natal life	43
Hematopoietic stem cells (HSC)	11	Regulation of erythroid differentiation	44
<i>In vitro</i> HSC assays	11	Morphology	46
Phenotype of hematopoietic		Light microscope cytology,	
stem cells	13	cytochemistry and ultrastructure	46
Regulation of stem cell self-renewal		The structure of the red cell	
and differentiation	14	membrane	49
Kit Ligand-KL (stem cell factor,		The erythroblastic island	65
Steel factor)	15	Erythrocyte inclusions	66
Flk-2/Flt-3 ligand (FL)	15	Physiologic (reversible) changes	
Plasticity of hematopoietic		in red cell shape	66
stem cells	15	Red cell shape changes associated with	
Hematopoietic stem cell migration .	16	pathologic states	77
Hematopoietic stem cell			
proliferation, telomerase			
and proliferative senescence	17		
Bone marrow microenvironment	19	PART 2 ABNORMALITIES OF RED CELL	
Hematopoietic progenitor cells	21	PRODUCTION	81
Granulocyte-macrophage progenitors .	21	Aplastic myelopathies	81
Granulocyte-macrophage colony		Pure red cell aplasia	81
stimulating factor (GM-CSF)	21	Parvovirus B19 infection	81
Granulocyte colony-stimulating			
factor (G-CSF)	22	Abnormalities of DNA synthesis.	
Macrophage colony-stimulating		Megaloblastic anemias	81
factor (M-CSF, CSF-1)	22	Megaloblastic erythropoiesis	83
Interleukin 3 (IL3)	25	Cytochemical and ultrastructural	
Erythroid progenitors	28	features	83
Erythropoietin (Epo)	28	Drug-induced megaloblastic changes	83
Megakaryocyte and platelet			
progenitors	28	Disorders related to disturbances	
Thrombopoietin (Tpo)	28	of erythroid development	90
Interleukin 11 (IL11)	30	Dyserythropoiesis	
<i>In vivo</i> action of hematopoietic		and dyserythropoietic anemias	90
growth factors	32	Sideroblastic anemias	
References	34	“Synartesis”	99
		Congenital dyserythropoietic anemias .	100
		CDA type I	100

CDA type II	100	Phagocytosis	203
CDA type III	102	Ehrlichiosis	206
Porphyrias	108	The lupus erythematosus (LE) cell phenomenon	207
Acute attack (inducible porphyrias)	109	Crystal phagocytosis	207
Cutaneous porphyrias	109	Neutrophil metabolism	208
Iron deficiency anemia	110	Apoptosis (programmed cell death)	213
Abnormalities of globin synthesis	110	NEUTROPHIL PATHOLOGY	214
Thalassemia syndromes	110	Acquired abnormalities (non-neoplastic)	214
Abnormal hemoglobin: sickle cell anemia	115	Nuclear abnormalities	215
Unstable hemoglobins	125	Cytoplasmic abnormalities	216
Hyperproliferative and neoplastic erythropoiesis	126	Toxic granulation and Döhle bodies	216
Acute erythremic myelosis and erythroleukemia	126	Lipid inclusions	216
Morphologic features	126	Labyrinths	217
Polycythemia vera	133	Anti-neutrophil cytoplasmic antibodies (ANCA)	218
Myelofibrosis with metaplasia	136	Disorders of neutrophil function	218
PART 3 ABNORMALITIES OF RED CELL DESTRUCTION	137	Hereditary abnormalities	221
Hereditary hemolytic anemias	137	Pelger-Hüet anomaly	221
Hereditary spherocytosis	137	May-Hegglin anomaly	221
Hereditary elliptocytosis and pyropoikilocytosis	140	Chediak-Higashi-Steinbrink anomaly	222
Acanthocytosis	141	Alder-Reilly anomaly	226
Enzyme deficiencies	141	References	226
Paroxysmal nocturnal hemoglobinuria	144	PART 2 THE MYELOGENOUS LEUKEMIAS	233
Acquired hemolytic disorders	146	The chronic myelogenous leukemias	233
Anemia due to infection and infestation	146	Classical (<i>BCR-ABL</i> positive) chronic myelogenous leukemia	233
Hemophagocytic histiocytosis	152	Blood	233
Chemical and drug-induced anemias	152	Marrow	237
Autoimmune hemolytic anemias (AIHAs)	154	<i>BCR-ABL</i> positive thrombocythemia	239
Erythrocyte abnormalities associated with acanthocytosis	154	Neutrophilic chronic myelogenous leukemia	239
The erythrocyte fragmentation syndromes	154	Minor- <i>BCR</i> breakpoint (m-bcr)-positive CML	239
Myelophthisic anemias	157	Hyperleukocytosis	240
References	163	Concurrence of lymphoid malignancies	240
3 NEUTROPHILS	177	Accelerated phase and blast crisis	240
PART 1 NORMAL STRUCTURE AND PATHOLOGY	179	Blood findings	241
Differentiation and maturation	179	Marrow findings	241
Sex chromatins	193	Extramedullary blast crisis	241
Cytoplasm and cytochemistry	194	Marrow blast crisis	241
Chemotaxis, locomotion and adhesion	195	Chronic neutrophilic leukemia	247
		Juvenile myelomonocytic leukemia	247
		Chronic myelomonocytic leukemia	248
		Chronic eosinophilic leukemia	248
		Indolent clonal hemopathies and oligoblastic myelogenous leukemia (the myelodysplastic diseases)	248
		Acute myelogenous leukemia	252

Definition	252	Heredity anomalies	331
Pathogenesis	252	Malignant or primary eosinophilia	331
Techniques for identification		Hypodense eosinophils	332
of variants	252	Conclusion	335
Blood findings	252	References	337
Marrow findings	253		
Mixed and hybrid leukemias	259		
Morphologic variants	259		
Myeloblastic leukemia	261		
Promyelocytic leukemia	261	5 BASOPHILS	341
Myelomonocytic leukemia	269		
Monocytic leukemia	269	Introduction	343
Erythroleukemia	276	Light microscopy	343
Megakaryoblastic leukemia	278	Electron microscopy	346
Eosinophilic leukemia	279	Fluorescence activated cell sorter (FACS) analysis	352
Basophilic and mast cell leukemia	279	Basophil development	353
References	280	Relationship to mast cells	357
		Mediators	359
		Function	359
		Activation/degranulation	359
PART 3 THE MYELODYSPLASTIC SYNDROMES	285	Endocytosis - Transport - Storage	362
The myelodysplastic syndromes	285	Locomotion - Chemotaxis	363
Morphologic features	285	Clinical abnormalities affecting	
Classification of MDS	286	basophils	366
Refractory anemia with excess blasts (RAEB) and refractory anemia with excess blasts in transformation (RAEB-t)	289	Basophilia	366
Chronic myelo-monocytic leukemia	289	Basophilia in inflammatory and immunological reactions	366
The 5q- syndrome	291	Chronic myeloproliferative diseases	368
Secondary MDS: therapy-related myelodysplastic syndromes	294	Basophilic leukemias	368
MDS associated with myelofibrosis	296	Basophilopenia	371
References	297	Role in immune responses	372
		Acute reactions	372
		Late-phase reactions	375
		Basophils in parasite infestations	378
4 EOSINOPHILS	299	References	381
Introduction	301		
Normal eosinophils	301	6 MONOCYTES – MACROPHAGES	387
Eosinophil structure and maturation	301		
Eosinophil granule proteins	305	PART 1 MONOCYTES	389
Major basic protein (MBP)	305	Introduction	389
Eosinophil ribonucleases	310	Development and function	
Eosinophil peroxidase (EP)	310	of monocytes	389
Maturation of granule structure	310	Receptors	398
Ultrastructure of mature eosinophils	312	Pathology	404
Nucleus	312	Abnormal phagocytosis and metabolism	404
Granules	313	References	408
Morphologic correlates of eosinophil function	317		
Pathology of eosinophils	321	PART 2 MACROPHAGES	411
Charcot-Leyden crystals (CLC)	326	Introduction	411
		Differentiation <i>in vivo</i>	411

Progenitors and sublineages	411
Ontogeny	416
Resident MØ in the normal adult	416
Lympho-hematopoietic organs	416
Non-lymphoid organs	421
Recruitment of monocytes	
to peripheral sites by local	
and systemic stimuli	428
General features	428
Phagocytosis and endocytosis <i>in vivo</i> .	434
Granuloma formation	434
Modified forms of inflammation	434
Proliferation/accumulation of MØ	
as a result of malignancy	435
Differentiation of macrophages	
and their modulation <i>in vitro</i>	435
Isolation and culture	435
Human bone marrow	435
Mouse bone marrow	439
Modulation by non-phagocytic/	
endocytic stimuli	442
Membrane traffic	442
Secretion and endocytosis	442
Phagocytosis in the absence	
of infection	442
Phagocytosis and invasion	
by infectious agents	442
Conclusion	445
References	445
 7 DENDRITIC CELLS	
Introduction	449
Cytology	451
Nomenclature	451
Development	455
Endocytosis and antigen processing	
compartments	457
DC markers	469
DC migration	469
The DC-T cell interaction	472
Generating large numbers of DCs	
in culture and the use of DCs	
in immunotherapy	472
References	474

2nd volume

8 LYMPHOCYTES	479	
PART 1 NORMAL LYMPHOCYTES	481	
Normal lymphocytes	481	
Lymphocyte heterogeneity	481	
Lymphocyte identification	485	
Mechanisms of antigen receptor gene rearrangement in B and T cells	488	
The B cell receptor (BCR) complex and signal transduction	488	
The T cell receptor (TCR) complex and signal transduction	491	
Formation of B cell receptor and T cell receptor	492	
BCR: the bone marrow events	495	
BCR: the peripheral events	497	
TCR: the thymic events	500	
B lymphocytes	501	
B cell ontogeny and bone marrow microenvironment	501	
B cell subsets	507	
B cell memory and terminal B cell differentiation	509	
T lymphocytes	514	
T cell ontogeny and the thymic microenvironment	514	
A brief survey of the thymus	514	
Development of T cells in the thymus	517	
T cell subsets	520	
T cell activation, inactivation and anergy	525	
Loss of T cell clones	527	
Natural killer (NK) cells	530	
Definition of NK cells	530	
NK cell morphology and phenotype	530	
NK cell ontogeny	534	
Receptors that regulate the cytotoxic function of NK cells	534	
Lymphocyte-mediated cytotoxicity	537	
Molecular mechanisms of cell-mediated cytotoxicity	537	
References	544	
PART 2 LYMPHOCYTE MIGRATION	553	
Overview of lymphocyte migration	553	
Multistep cascades involved in migration of naive lymphocytes to secondary lymphoid tissues	556	
Multistep cascades involved in migration of memory/effector lymphocytes to tertiary lymphoid tissues	557	
Multistep navigation through chemoattractant fields in tissues	563	
References	564	
PART 3 LYMPHOPROLIFERATIVE DISORDERS	567	
Classification and biological characterization	567	
Classification of lymphoid neoplasms by their developmental phenotype	567	
Leukemia/lymphoma-specific antigens	570	
Clonal rearrangements of B and T cell antigen receptor genes	570	
Is monoclonality an invariant and exclusive characteristic of malignant clones?	573	
What is the sensitivity of the assays for detecting monoclonal populations admixed with polyclonal cells?	573	
Are Ig and TCR gene rearrangements specific for B and T cells respectively?	573	
Acute lymphoblastic leukemia	575	
Morphology, cytochemistry and ultrastructure of ALL cells	576	
Immunobiological subsets	578	
Prognostic factors	583	

Molecular genetics of ALL: practical relevance	584
Chronic lymphoid leukemias	
of B cell type	587
B cell chronic lymphocytic leukemia (B-CLL)	587
Prolymphocytic leukemia (PLL)	594
Hairy cell leukemia (HCL)	594
Non-Hodgkin lymphoma in leukemic phase	601
Waldenström macroglobulinemia	601
Multiple myeloma	607
Amyloidosis	625
Heavy chain diseases	627
Adult T cell leukemia/lymphoma (ATLL)	632
Introduction	632
Virology	633
Epidemiology	634
Clinical features of ATLL	637
The ATLL cell	637
Chronic lymphoproliferative disorders	
of mature (post-thymic) T cells	641
Sézary syndrome	642
T cell chronic lymphocytic leukemia (T-CLL)	643
Autoimmune lymphoproliferative syndrome (ALPS)	647
References	651
PART 4 LYMPH NODES: REACTIVE AND NEOPLASTIC CONDITIONS	663
Introduction	663
Reactive lymphoid hyperplasias	665
Neoplasms of lymph nodes:	
malignant lymphomas	667
Precursor lymphoid neoplasms	673
Mature B cell lymphomas	674
Mature T cell lymphomas	687
Hodgkin disease (Hodgkin lymphoma)	701
Nodular lymphocyte predominance Hodgkin lymphoma (NLPHL)	703
Classical Hodgkin lymphoma, nodular sclerosis (NSHL)	705
Classical Hodgkin lymphoma, mixed cellularity (HLMC)	706
Classical Hodgkin lymphoma, lymphocyte-rich (HLLR)	709
Classical Hodgkin lymphoma, lymphocyte depletion (HLLD)	711
Neoplasms of lymph nodes: histiocytic sarcoma and related disorders	712
References	713
9 ACQUIRED IMMUNODEFICIENCY SYNDROME	719
AIDS	721
Historical background	721
Properties of the virus and mechanisms of infection	721
Clinical and laboratory observations	724
Bone marrow	729
Lymph nodes	733
Thymus	733
Dendritic cells	733
Kaposi sarcoma	741
B cell lymphomas	743
Opportunistic infections	746
Other histopathologic observations	747
References	750
10 MEGAKARYOCYTES AND PLATELETS	753
Megakaryocytes	755
Normal megakaryocytes	
and thrombocytopoiesis	755
Nucleus	758
Cytoplasm	759
Surface membrane of megakaryocytes	772
Thrombocytopoiesis	777
Megakaryocyte pathology	785
Congenital disorders	785
Acquired disorders	793
Extrinsic	793
Intrinsic	794
Multinucleation	807
Platelets	810
Platelet formation	812
Platelet surface membrane	814
Granules	824
Microtubules	830
Contractile system	832
“Open” canalicular system (OCS), endocytosis, exocytosis and the “release” phenomenon ..	835
Platelet functions subserved	
by synergy of various structures	844
Histochemistry	845
Platelet pathology	846

Conclusions	857	Hairy cell leukemia (HCL)	932
References	857	B cell prolymphocytic leukemia	932
11 CHROMOSOME REARRANGEMENTS IN HEMATOLOGICAL DISEASES 865		Non-Hodgkin lymphomas (NHL)	932
Introduction	867	Hodgkin disease (HD)	936
Methodology	867	T cell leukemia and lymphoma	936
Application of conventional and molecular cytogenetics to diagnosis, prognosis and response to treatment	878	Natural killer (NK) lymphoma/leukemia	937
Myeloproliferative disorders	878	Anaplastic large cell lymphoma (ALCL)-ALK-positive lymphoma	937
Chronic myelogenous leukemia (CML)	878	Conclusions and future directions	938
Chronic phase of CML	878	References	939
Acute phase of CML	887		
Acute myeloid leukemia (AML)	888		
Chromosome gain or loss in AML	889		
Acute myeloid leukemia M2 and t(8;21)(q22;q22)	890		
Acute promyelocytic leukemia (APL), (15;17)(q22;q21) and variant translocations: t(11;17)(q23;q21), (5;17)(q35;q21) and t(11;17)(q13;q21)	895		
Acute myelomonocytic leukemia with excess eosinophils (M4Eo); inv(16)(p13q22), t(16;16)(p13;q22) and del(16)(q22)	900		
(16;21)(p11;q22)	902		
t(9;22)(q34;q11.2)	902		
Acute monocytic leukemia (M5) and translocations involving 11q23 and <i>MLL</i> gene	903		
AML with an increased number of basophils and t(6;9)(p23;q34)	906		
t(1;22)(p13;q13)	906		
AML in children	906		
AML in the elderly	906		
Therapy-related AML	906		
Other myeloproliferative disorders	911		
Polycythemia vera (PV)	911		
Myelodysplastic disorders (MDS)	914		
Rearrangements of t(8)(p11)	916		
Lymphoproliferative disorders	917		
Acute lymphoblastic leukemia (ALL)	917		
B cell ALL in children	917		
B cell ALL in adults	924		
Chronic lymphocytic leukemia (CLL)	925		
Multiple myeloma (MM)	928		
Hairy cell leukemia (HCL)	932		
B cell prolymphocytic leukemia	932		
Non-Hodgkin lymphomas (NHL)	932		
Hodgkin disease (HD)	936		
T cell leukemia and lymphoma	936		
Natural killer (NK) lymphoma/leukemia	937		
Anaplastic large cell lymphoma (ALCL)-ALK-positive lymphoma	937		
Conclusions and future directions	938		
References	939		
12 HEMATOPOIETIC CELL TRANSPLANTATION 949			
History	951		
Pre-transplant studies	952		
Aplastic anemia	953		
Myelodysplastic syndromes and myelofibrosis	955		
Solid tumors	957		
Post-transplant considerations	958		
Engraftment and mixed chimerism	958		
Rejection	959		
Relapse and minimal residual disease	961		
Use of multiparameter flow cytometry in assessing relapse	963		
Graft-versus-host disease (GVHD) of marrow	963		
Influence of exogenous cytokines on assessment of marrow and blood post-transplant	966		
Complications of stem cell transplantation	966		
Toxicity of preconditioning regimen	966		
Graft-versus-host disease	966		
Acute GVHD	966		
Chronic GVHD	967		
Pulmonary GVHD	968		
Pseudo-GVHD	968		
Infections in the immuno-compromised transplant recipient	969		
General	969		
Infections of marrow	969		
Post-transplant lymphoproliferative disorders	970		
Technical notes	972		
Future prospects	972		
References	974		
SUBJECT INDEX		977	