

CONTENTS

PREFACE **xi**

I MOLECULAR BIOLOGY OF THE CELL **I**

- Compartmentalization of the Cell, 1
 - The Nucleus, 1*
- Gene Transcription and Messenger RNA Translation: The Production and Journey of mRNA, 3
- DNA Mutations can Alter Protein Synthesis by a Number of Mechanisms, 6
- Transcriptional Control of Gene Expression, 6
 - Cis-Elements and Transcription Factors, 8*
 - Chromatin and Epigenetic Control of Gene Expression, 9*
- Transcription Factors, Control of Gene Expression, and Lineage Commitment, 14
- Micro-RNAs, 16
- Regulatory Noncoding RNAs, 16
- DNA Replication and Telomeres, 16
- Mutations and How They Result in Disease, 17
- Cell Cycle, 19
- Apoptosis, 20
- Organelles in Cells, 21
 - Mitochondria, 21*
- Link Between Metabolism and Gene Expression, 22
- Removal Of Circulating and Cellular Debris by Lysosomes, 26
- Protein Ubiquitination, 26

2 HEMATOPOIESIS **27**

- Sites of Hematopoiesis, 27
- Road Maps of Hematopoiesis, 27
 - Cellular Pathways as HSCs Differentiate Into Terminally Mature Cells, 27*
- Transcriptional Control of Hematopoiesis, 32
- The Hematopoietic Niche, 33

3 GROWTH FACTOR SIGNALING **37**

- Signaling at Different Stages of Hematopoiesis, 37
- Cytokine Receptors, 38
- Signaling Pathways Downstream of Receptors, 39
 - WNT Pathway, 39*

- Cytokine Signaling Pathways, 40*
- The RAS/MAP Kinase Pathway, 41*
- Phosphatidylinositol 3-Kinase Pathway, 41*
- JAK-STAT Pathway, 41*

Mutations in Signaling Components Leading to Clonal Hematologic Disorders, 46

4 ERYTHROPOIESIS AND EXAMINATION OF THE PERIPHERAL BLOOD AND BONE MARROW **47**

- Erythropoiesis, 47
- Examination of Peripheral Blood and the Bone Marrow, 49
- Erythroid Cells in the Bone Marrow and Peripheral Blood, 49

5 HYPOCHROMIC ANEMIAS **53**

- Iron Metabolism, 53
- Iron Absorption, 55
- Hepcidin, 55
- Iron Homeostasis, 55
- Iron-Deficiency Anemia, 55
 - Blood and Bone Marrow Appearances, 56*
 - Causes of Iron Deficiency, 57*
 - Iron-Refractory Iron-Deficiency Anemia (IRIDA), 62*
- Sideroblastic Anemia, 62
 - Congenital Sideroblastic Anemia, 63*
- Alcohol, 67
- Lead Poisoning, 67
- Differential Diagnosis of Hypochromic Microcytic Anemias, 68

6 THE PORPHYRIAS AND IRON OVERLOAD **69**

- Congenital Erythropoietic Porphyria, 69
- Congenital Erythropoietic Protoporphyrinemia, 71
- Iron Overload, 71
 - Genetic Hemochromatosis, 71*
 - Rare Causes of Iron Overload, 74*
 - Hereditary Hyperferritinemia with Autosomal Dominant Congenital Cataract Syndrome, 74*

7 MEGALOBLASTIC ANEMIAS 76

Clinical Features, 77

Blood Count and Blood Film Appearances, 79

Bone Marrow Appearances, 81

Causes of Megaloblastic Anemia, 81

Vitamin B₁₂ Deficiency, 81

Folate Deficiency, 84

Abnormalities of Vitamin B₁₂ or Folate

Metabolism, 84

Other Causes, 86

8 HEMOLYTIC ANEMIAS 89

Hereditary Hemolytic Anemia, 91

Normal Red Cell Membrane, 91

Red Cell Blood Group Antigens, 91

Hereditary Spherocytosis, 92

Hereditary Elliptocytosis, 92

Normal Red Cell Metabolism, 94

Hemolytic Anemias Associated with Inherited Defects of Enzymes, 96

Acquired Hemolytic Anemia, 99

Autoimmune Hemolytic Anemias, 99

Evans Syndrome, 101

Drug-Induced Immune Hemolytic Anemia, 101

Isoimmune Hemolytic Anemia, 101

Red Cell Fragmentation Syndromes, 101

Secondary Hemolytic Anemias, 102

Paroxysmal Nocturnal Hemoglobinuria, 103

Other Hemolytic Anemias, 104

9 GENETIC DISORDERS OF HEMOGLOBIN 106

Thalassemia, 106

β-Thalassemia Major, 108

β-Thalassemia Intermedia (Nontransfusion-Dependent Thalassemia), 115

β-Thalassemia Trait, 117

β-Thalassemia with A Dominant Phenotype, 117

Antenatal Diagnosis, 118

α-Thalassemia, 118

X-linked α-Thalassemia and Mental Retardation Syndrome, 119

Structural Hemoglobin Variants, 122

Sickle Cell Anemia, 122

Other Structural Hemoglobin Defects, 128

F-Cells, 128

Methemoglobinemia, 129

10 BENIGN DISORDERS OF PHAGOCYTES 130

Granulopoiesis and Monocyte Production, 130

Neutrophils (Polymorphs), 131

Mononuclear Phagocytic System, 133

Reticuloendothelial System, 133

Hereditary Variation in White Cell Morphology, 137

Pelger–Huët Anomaly, 137

May–Hegglin Anomaly, 138

Chédiak–Higashi Syndrome, 139

Alder (Alder–Reilly) Anomaly, 139

Myeloperoxidase Deficiency, 139

Neutrophil-Specific Granule Deficiency, 139

Mucopolysaccharidoses VI and VII, 139

Dorfman–Chanarin Syndrome, 140

Lysinuric Protein Intolerance, 140

Disorders of Phagocytic Function, 140

Chronic Granulomatous Disease, 140

Papillon–Lefevre Syndrome, 141

Lazy Leukocyte Syndrome, 141

Leukocyte Adhesion Deficiency, 141

Card9 Deficiency, 142

Leukocytosis, 142

Neutrophil Leukocytosis (Neutrophilia), 142

Hyperthermia, 143

Eosinophil Leukocytosis (Eosinophilia), 143

Monocytosis and Basophil Leukocytosis, 143

Leukemoid Reaction, 144

Leukoerythroblastic Reaction, 145

Neutropenia, 146

Severe Congenital Neutropenia, 146

Idiopathic Cytopenias of Undetermined Significance, 148

Myelokathexis, 149

Whim Syndrome, 149

Lysosomal Storage Diseases, 150

Gaucher Disease, 150

Niemann–Pick Disease, 151

Sea-Blue Histiocyte Syndrome, 153

11 BENIGN DISORDERS OF LYMPHOCYTES AND PLASMA CELLS 155

T Cells, 155

PD-1–PD-L1, 156

Chimeric Antigen Receptor Cells, 157

B Cells, 157

Natural Killer Cells, 160

Lymphocyte Proliferation and Differentiation, 162

Somatic Hypermutation In Normal B Cells, 164

Lymphocyte Circulation, 164

Complement, 165

Lymphocytosis, 165

Infectious Mononucleosis, 165

Lymphadenopathy, 167

Kikuchi Disease, 168

Sinus Histiocytosis with Massive Lymphadenopathy (Rosai–Dorfman Disease), 168

Primary Immunodeficiency Disorders, 168

Acquired Immunodeficiency Syndrome, 170

Autoimmune Lymphoproliferative Syndrome, 180

12	APLASTIC AND DYSERYTHROPOIETIC ANEMIAS	185			
	Aplastic Anemia, 185				
	<i>Acquired Aplastic Anemia, 185</i>				
	<i>Inherited Aplastic Anemia, 186</i>				
	<i>Bone Marrow Appearances, 191</i>				
	Red Cell Aplasia, 193				
	<i>Diamond–Blackfan Anemia, 193</i>				
	Congenital Dyserythropoietic Anemias, 195				
13	THE HEMATOLOGIC NEOPLASMS: LABORATORY TECHNIQUES AND ACUTE MYELOID LEUKEMIA	198			
	Diagnostic Techniques, 198				
	<i>Immunohistochemistry, 198</i>				
	<i>Flow Cytometric Immunophenotyping, 199</i>				
	<i>Cytogenetic Analysis, 201</i>				
	<i>Fluorescence in Situ Hybridization, 201</i>				
	<i>Molecular Genetic Analysis, 201</i>				
	Acute Myeloid Leukemia, 208				
	<i>Classification, 212</i>				
	<i>Clinical Features, 212</i>				
	<i>Microscopic Appearances, 214</i>				
	<i>WHO 2016 Subgroups, 214</i>				
	<i>Classification of Myeloid Neoplasms with Germline Predisposition, 225</i>				
	<i>Acute Leukemias of Ambiguous Lineage, 229</i>				
	<i>Specific Diagnostic Aspects in AML, 229</i>				
14	ACUTE LYMPHOBLASTIC LEUKEMIA	241			
	Classification, 241				
	<i>B-Lymphoblastic Leukemia/Lymphoma, BCR-ABL1-Like, 241</i>				
	<i>B-ALL with Intrachromosomal Amplification of Chromosome 21, 242</i>				
	<i>T-Lymphoblastic Leukemia/Lymphoma, 242</i>				
	<i>Early T-Cell Precursor ALL, 242</i>				
	<i>Acute Natural Killer Cell Leukemia, 242</i>				
	Clinical Features, 242				
	Microscopic Appearances, 244				
	Immunology, 246				
	Cytogenetics, 247				
	Fluorescence in Situ Hybridization, 248				
	Molecular Findings, 248				
	<i>B-ALL, 248</i>				
	<i>T-ALL, 248</i>				
	Minimal Residual Disease, 250				
	<i>Flow Cytometry, 250</i>				
	<i>Molecular Methods, 252</i>				
15	MYELOYDYSPLASTIC SYNDROMES	256			
	Clinical Features, 256				
	<i>Microscopic Features, 256</i>				
	<i>Cytogenetic Abnormalities, 263</i>				
	Molecular Genetics, 263				
	<i>Splicing Factors, 266</i>				
	<i>Epigenetic Regulators, 266</i>				
	<i>Cohesins, 266</i>				
	<i>Transcription Factors, 268</i>				
	<i>Signal Transduction, 268</i>				
	<i>Molecular Genetics During Follow-Up, 268</i>				
	Mirage Syndrome, 268				
	Clonal Hematopoiesis of Indeterminate Potential, 269				
16	MYELOPROLIFERATIVE NEOPLASMS	271			
	Chronic Myeloid Leukemia, BCR-ABL1+, 271				
	<i>Clinical Features, 272</i>				
	<i>Accelerated Phase, 273</i>				
	<i>Blast Transformation, 276</i>				
	Chronic Neutrophilic Leukemia, 277				
	The Nonleukemic Myeloproliferative Diseases, 277				
	<i>Etiology, 279</i>				
	<i>Polycythemia Vera, 282</i>				
	<i>Essential Thrombocythemia, 283</i>				
	<i>Primary Myelofibrosis, 288</i>				
	Leukemic Transformation of Polycythemia Vera and Myelofibrosis, 295				
	Chronic Eosinophilic Leukemia, Not Otherwise Specified, 300				
	Myeloproliferative Disorder Unclassifiable, 300				
17	MASTOCYTOSIS, MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND SPECIFIC CYTOGENETIC REARRANGEMENTS, MYELOYDYSPLASTIC/MYELOPROLIFERATIVE NEOPLASMS	302			
	Mastocytosis, 302				
	<i>Types of Mastocytosis, 303</i>				
	<i>Prognosis, 309</i>				
	Paraneoplastic Pemphigus, 309				
	Myeloid/Lymphoid Neoplasms with Eosinophilia and Abnormalities of PDGFRA, PDGFRB or FGFR1, or with PCMI-JAK2, 309				
	<i>Chronic Myelomonocytic Leukemia, 312</i>				
	<i>Atypical Chronic Myeloid Leukemia, BCR-ABL1-, 312</i>				
	Myelodysplastic/Myeloproliferative Neoplasms With Ring Sideroblasts and Thrombocytosis, 312				
	Juvenile Myelomonocytic Leukemia, 314				
	<i>Noonan Syndrome, 314</i>				
	<i>Neurofibromatosis 1, 315</i>				

18 CHRONIC LYMPHOCYTIC LEUKEMIA AND OTHER MATURE B- AND T-CELL LEUKEMIAS 317

- Mature B-Cell Leukemias, 317**
 - Chronic Lymphocytic Leukemia, 317*
 - B-Cell Prolymphocytic Leukemia, 325*
 - Hairy Cell Leukemia, 327*
- Mature T-Cell Leukemias, 328**
 - T-Cell Prolymphocytic Leukemia, 328*
 - T-Cell Large Granular Lymphocytic Leukemia, 330*
 - Adult T-Cell Leukemia/Lymphoma, 333*
 - Aggressive NK-Cell Leukemia, 333*

19 SMALL B-CELL LYMPHOMAS 335

- Epidemiology, 336**
- Etiologic Factors, 336**
- Genetic and Molecular Abnormalities, 337**
- Clinical Features and Diagnosis, 337**
- Imaging, 341**
- Diagnosis, 342**
- Lymphoplasmacytic Lymphoma/
Waldenström Macroglobulinemia, 345**
- Monoclonal Gammopathy of Undetermined
Significance IgM+, 346**
- Heavy Chain Diseases, 346**
- Splenic Marginal Zone Lymphoma, 348**
- Extranodal Marginal Zone Lymphoma
of Mucosa-Associated Lymphoid Tissue
(Malt Lymphoma), 349**
- Nodal Marginal Zone B-Cell
Lymphoma, 351**
- Follicular Lymphoma, 352**
 - Other Subtypes of Follicular Lymphomas, 355*
- Mantle Cell Lymphoma, 356**

20 AGGRESSIVE MATURE B-CELL NEOPLASMS 361

- Diffuse Large B-Cell Lymphoma, Nos, 361**
- T-Cell/Histiocytic-Rich Large B-Cell
Lymphoma, 365**
- Primary Cutaneous Diffuse Large B-Cell
Lymphoma, Leg Type, 365**
- Lymphomatoid Granulomatosis, 365**
- Primary Mediastinal (Thymic) Large B-Cell
Lymphoma, 365**
- Intravascular Large B-Cell Lymphoma, 366**
- ALK-Positive Diffuse Large B-Cell
Lymphoma, 366**
- Plasmablastic Lymphoma, 370**
- Primary Effusion Lymphoma and Other
HHV8-Related Disorders, 370**
- Burkitt Lymphoma, 371**
- High Grade B-Cell Lymphoma, 372**

21 MYELOMA AND RELATED NEOPLASMS 376

- Multiple (Plasma Cell) Myeloma, 376**
 - Plasma Cell Leukemia, 383*
 - Prognosis, 383*
 - Smoldering (Asymptomatic) Myeloma, 383*
- Other Plasma Cell Tumors, 383**
 - Solitary Plasmacytoma of Bone, 383*
 - Extraosseous (Extramedullary) Plasmacytoma, 383*
- Hyperviscosity Syndrome, 384**
- Other Causes of Serum M-Proteins, 384**
 - Monoclonal Gammopathy of Uncertain
Significance, 387*
 - Cryoglobulinemia, 389*
- Amyloidosis, 389**
 - Primary (AL) Amyloidosis, 392*
 - Localized AL Amyloidosis, 392*
 - Reactive Systemic (AA) Amyloidosis, 394*
 - Light Chain Deposition Disease, 394*

22 PERIPHERAL T- AND NK-CELL NEOPLASMS 399

- Mature T- and NK-Cell Neoplasms, 399**
- Epstein-Barr Virus Positive T-Cell
Lymphoproliferative Diseases
of Childhood, 399**
 - Chronic Active EBV Infection: Hydroa Vacciniforme-Like
Lymphoproliferative Disorder, 399*
 - Systemic EBV+ T-Cell Lymphoma Of Childhood, 400*
- Extranodal NK-/T-Cell Lymphoma, Nasal
Type, 400**
- Enteropathy-Associated T-Cell Lymphoma, 401**
- Hepatosplenic T-Cell Lymphoma, 402**
- Primary Cutaneous T-Cell Lymphomas, 404**
- Subcutaneous Panniculitis-Like T-Cell
Lymphoma, 404**
- Mycosis Fungoides, 405**
 - Folliculotropic Mycosis Fungoides
(Mycosis Fungoides-Associated Follicular
Mucinosi)s, 406*
 - Pagetoid Reticulosis, 406*
 - Granulomatous Slack Skin Disease, 406*
- Sézary Syndrome, 407**
- Primary Cutaneous CD30+ T-Cell
Lymphoproliferative Disorders, 408**
 - Lymphomatoid Papulosis, 409*
 - Primary Cutaneous Anaplastic Large Cell
Lymphoma, 409*
- Primary Cutaneous $\gamma\delta$ T-Cell Lymphoma, 410**
- Primary Cutaneous Aggressive
Epidermotropic CD8+ T-Cell Lymphoma
(Provisional Category), 410**
- Primary Cutaneous Small/Medium CD4+
T-Cell Lymphoproliferative Disorder
(Provisional Category), 411**
- Peripheral T-Cell Lymphoma, Not Otherwise
Specified, 411**
- Angioimmunoblastic T-Cell Lymphoma, 412**

- Anaplastic Large Cell Lymphoma, ALK Positive, 413
 Anaplastic Large Cell Lymphoma, ALK Negative, 414

23 HODGKIN LYMPHOMA 418

- Presentation and Evolution, 418
 Histology, 418
Hodgkin Reed–Sternberg Cell, 419
 Classification of Hodgkin Lymphoma, 421
Nodular Sclerosing Hodgkin Lymphoma, 421
Mixed Cellularity Hodgkin Lymphoma, 422
Lymphocyte-Rich Classic Hodgkin Lymphoma, 422
Lymphocyte-Depleted Hodgkin Lymphoma, 423
Nodular Lymphocyte-Predominant Hodgkin Lymphoma, 423
 Staging Techniques, 424
Deauville Score, 427
 Prognostic Factors, 432

24 HISTIOCYTIC DISORDERS 434

- Hemophagocytic Lymphohistiocytosis (Hemophagocytic Syndrome), 434
 Xanthogranuloma, 435
 Rosai–Dorfman Disease, 435
 Histiocytic and Dendritic Cell Neoplasms, 439
 Histiocytic Sarcoma, 439
 Langerhans Cell Histiocytosis, 439
 Langerhans Cell Sarcoma, 444
 Indeterminate Dendritic Cell Tumor, 444
 Interdigitating Dendritic Cell Sarcoma, 444
 Follicular Dendritic Cell Sarcoma, 446
 Fibroblastic Reticular Cell Tumor, 447
 Disseminated Juvenile Xanthogranuloma, 447
 Erdheim–Chester Disease, 447
 Blastic Plasmacytoid Dendritic Cell Neoplasm, 448

25 STEM CELL TRANSPLANTATION 451

- Human Leukocyte Antigen System, 451
Human Leukocyte Antigen Nomenclature, 451
Typing of Human Leukocyte Antigens, 452
 Other Human Leukocyte Antigens, 452
 Stem Cell Transplantation, 452
Nonmyeloablative (Reduced Intensity) Transplants, 453
Donor Leukocytes, 455
Complications of Stem Cell Transplants, 457
Graft-Versus-Host Disease, 459
Post-Transplant Lymphoproliferative Disorders, 463

26 NORMAL HEMOSTASIS, PLATELET PRODUCTION AND FUNCTION 468

- The Coagulation Cascade, 470
 Regulation of Coagulation, 470
 Megakaryocyte and Platelet Production, 472
 Platelet and Von Willebrand Factor Function, 475

27 VASCULAR AND PLATELET BLEEDING DISORDERS 479

- Vascular Bleeding Disorders, 479
Hereditary Hemorrhagic Telangiectasia (Osler–Weber–Rendu Syndrome), 479
Ehlers–Danlos Syndrome, 479
Senile Purpura, 479
Scurvy, 479
Purpura Associated with Protein Deposition, 479
Immune-Mediated Vessel Wall Purpuras, 480
 Platelet Bleeding Disorders, 480
Thrombocytopenia, 480
Disorders of Platelet Function, 487

28 INHERITED AND ACQUIRED COAGULATION DISORDERS 494

- Hereditary Coagulation Disorders, 494
Hemophilia, 494
Von Willebrand Disease, 503
Other Hereditary Coagulation Disorders, 503
 Acquired Coagulation Disorders, 504
Liver Disease, 504
Overdosage with Anticoagulants, 505
Disseminated Intravascular Coagulation, 505
Acquired Coagulation Factor Inhibitor, 507
Thromboelastometry and Thromboelastography, 509

29 THROMBOSIS AND ANTITHROMBOTIC THERAPY 510

- Atherothrombosis, 510
 Venous Thrombosis, 510
Thrombophilia, 510
 Acquired Risk Factors For Venous Thrombosis, 515
 Antiphospholipid Syndrome, 515
 Diagnosis of Venous Thrombosis, 515
Clinical Probability Assessment, 515
 Diagnosis of Pulmonary Embolus, 516
Clinical Assessment, 516
 Antiplatelet Drugs, 519
Aspirin, 519
Dipyridamole (Persantin), 519
ADP Receptor Inhibitors, 519

Glycoprotein IIB/IIIa Inhibitors, 519
Prostacyclin, 520

Anticoagulant Therapy, 520

Heparin, 520
Warfarin, 522
Indirect Factor Xa Inhibitors, 523
Direct Factor Xa Inhibitors, 523
Direct Thrombin Inhibitors, 523

Fibrinolytic Agents, 523

Post-Thrombotic Syndrome, 527

30 HEMATOLOGIC ASPECTS OF SYSTEMIC DISEASES 528

Anemia of Chronic Disorders, 528
Malignant Diseases (Other than Leukemias, Lymphomas, Histiocytic and Myeloproliferative Disorders), 529
Rheumatoid Arthritis and Other Connective Tissue Diseases, 530
Renal Failure, 533
Liver Disease, 533
Hypothyroidism, 538
Infections, 539
Bacterial Infections, 539
Viral Infections, 541
Parasitic Infections Diagnosed In Blood, 542
Marrow Involvement In Other Infections, 542
Granulomatous Inflammation, 542
Sarcoidosis, 542
Other Granulomas, 543
Osteopetrosis (Albers-Schönberg or Marble Bone Disease), 543
Anorexia Nervosa, 544
Cystinosis, 544
Primary Oxaluria, 547

31 PARASITIC DISORDERS 548

Malaria, 548
Effects of Malaria on Various Organs, 549
Comparative Methods For Malaria Diagnosis, 549
Resistance to Antimalarial Therapy, 552

Toxoplasmosis, 552
Babesiosis, 552
Trypanosomiasis, 553
Bancroftian Filariasis, 553
Loiasis, 554
Bartonellosis, 554
Relapsing Fever, 555

32 BLOOD TRANSFUSION 556

Red Cell Antigens, 556
Red Cell Antibodies, 557
ABO System, 557
Rh System, 558
Blood Grouping and Cross-Matching, 559
Red Cell Components, 559
Clinical Blood Transfusion, 560
Complications of Blood Transfusion, 560
Infections, 561
Iron Overload, 563
Transfusion-Related Acute Lung Injury, 563
Graft-Versus-Host Disease, 563
Other Blood Components, 564
Platelet Concentrates, 564
Leukocytes, 564
Fresh Frozen Plasma, 565
Plasma Derivatives, 565

APPENDIX: 2016 WORLD HEALTH ORGANIZATION CLASSIFICATION OF LYMPHOID AND MYELOID NEOPLASMS 567

INDEX 571
