

Contents

Chapter 1

Heme Metabolism: Factors Affecting the *in Vivo* Oxidation of Heme

Mahin D. Maines

1.1. Introduction	1
1.2. Heme and Bile Pigments	1
1.3. Mechanism of Heme Oxidation	6
1.3.1. Nonenzymatic Heme Oxidation	6
1.3.2. Enzymatic Heme Oxidation	9
1.3.3. Substrate Specificity	13
1.3.4. Heme Oxygenase: Postulated Mode of Action	15
1.4. Factors Regulating Heme Degradation	17
1.4.1. Heme (Hemoglobin, Hematin, Methemalbumin)	17
1.4.2. Metals	19
1.4.3. Hormonal and Metabolic Factors	23
1.4.4. Effect of Endotoxins and Drugs on Heme Degradation	27
1.5. Catabolism of Heme Compounds <i>in Vivo</i>	29
1.5.1. Hemoglobin	29

1.5.2. Microsomal Cytochromes	31
1.5.3. Myoglobin and Mitochondrial Cytochromes	36
References	38

Chapter 2

Hemoglobin Synthesis in Normal and Abnormal States

Michael L. Freedman

2.1. Normal Hemoglobin Synthesis	47
2.1.1. Ontogeny of Hemoglobin Synthesis	47
2.1.2. Hemoglobin Synthesis during Erythropoiesis	48
2.1.3. Transcription, Processing, and Translation of Globin Messenger RNA	53
2.1.4. Assembly of Hemoglobin	60
2.1.5. Molecular Control Mechanisms in Normal Hemoglobin Synthesis	62
2.2. Abnormal Globin Synthesis	71
2.2.1. Synthesis of Globin in Thalassemia and Related States	71
2.2.2. Synthesis of Structurally Abnormal Hemoglobins	78
2.2.3. Synthesis of Hemoglobin in Heme-Deficient States	82
References	85

Chapter 3

Clinical Significance of 2,3-Diphosphoglycerate in Hematology

Frank A. Oski and Julia A. McMillan

3.1. Oxygen Transport and Delivery	104
3.2. Factors Modifying Hemoglobin's Affinity for Oxygen	107
3.3. Clinical Conditions Associated with Alterations in Red Cell 2,3-DPG	110
3.3.1. Cardiac Disease	111
3.3.2. Hypoxemia of Altitude or Pulmonary Disease	115
3.3.3. Anemia	117
3.3.4. Abnormalities of Serum Inorganic Phosphate	118
3.3.5. Liver Disease	119
3.3.6. Endocrine Disorders	120
3.3.7. Blood Storage and Transfusion	120
3.3.8. The Newborn Infant	121

3.4. Physiologic Significance of Shifts in the Oxygen-Hemoglobin Dissociation Curve	124
References	125

Chapter 4**The Interaction of Folate Ligands with Macromolecules**

Maria da Costa and Sheldon P. Rothenberg

4.1. Introduction	131
4.2. Methods of Identification of Folate Binding Macromolecules	132
4.3. Definition of Terminology	133
4.4. Nonspecific Folate Binder Complexes in Serum	135
4.5. Specific Folate Binder Complexes in Serum	136
4.6. Properties of the Specific Folate Binder in Serum	138
4.7. Significance of the Serum Folate Binder	139
4.8. Serum Folate Binders and Radioassay for Folate	140
4.9. Folate Binder in Erythrocytes	141
4.10. Folate Binder in Granulocytes	141
4.11. Significance of Intracellular Folate Binder	143
4.12. Folate Binders in Other Tissues	144
4.13. Folate Binder in Milk	145
4.14. Summary	147
References	147

Chapter 5**Pure Red Cell Aplasia**

Sanford B. Krantz and S. Donald Zaentz

5.1. Definition	153
5.2. Classification	154
5.2.1. Congenital PRCA	154
5.2.2. Acquired Primary PRCA	155
5.2.3. Acquired Secondary PRCA	155
5.3. Laboratory Manifestations	159
5.3.1. Blood and Bone Marrow Morphology	159
5.3.2. Other Laboratory Abnormalities	160
5.4. Pathogenesis	162
5.4.1. Congenital PRCA	162
5.4.2. Acquired PRCA	164
5.5. Treatment	174

5.5.1. Congenital PRCA	174
5.5.2. Acquired PRCA	175
5.6. Conclusion	182
References	184

Chapter 6

Neutrophil Function: Normal and Abnormal

Thomas P. Stossel and Harvey J. Cohen

6.1. Some General Comments Concerning Normal and Abnormal Neutrophil Function	192
6.2. The Humoral Dimension of Neutrophil Function	192
6.2.1. Factors with Chemotactic Activity for Neutrophils	192
6.2.2. Inhibitors of Chemotactic Activity	194
6.2.3. Opsonins	195
6.2.4. Other Serum Factors	195
6.3. The Cellular Dimension of Neutrophil Function	197
6.3.1. Structure and Metabolism of Neutrophils	197
6.3.2. Neutrophil Locomotion	200
6.3.3. Ingestion	201
6.3.4. Degranulation	202
6.3.5. The Chediak–Higashi Syndrome	203
6.4. Oxygen Metabolism and Microbicidal Activity	205
References	210

Chapter 7

Phagocytosis: Role of C3 Receptors and Contact-Inducing Agents

Alfred G. Ehlenberger and Victor Nussenzweig

7.1. Introduction	221
7.2. Role of Contact and Surface Forces in Phagocytosis	224
7.3. Role of C3 in Opsonization	225
7.4. The Effect of Binding and Contact-Inducing Agents on Ingestion	230
References	236

Chapter 8

Leukocyte 5'-Nucleotidase

Maryrose Conklyn and Robert Silber

8.1. Introduction	241
-------------------------	-----

8.2. The Enzyme	241
8.2.1. The 5'N Reaction	241
8.2.2. Properties of the Enzyme	242
8.2.3. Representative Methods Utilized in 5'N Assays	244
8.3. Studies on 5'N in Leukocytes	245
8.3.1. Distribution of the Enzyme in Leukocytes	245
8.3.2. Subcellular Localization of 5'N in Leukocytes ..	251
8.3.3. Studies of 5'N in Pathological Conditions	252
8.3.4. Function of 5'N in Leukocytes	255
8.4. Summary and Conclusions	256
References	258

Chapter 9

Metabolism and Functions of Monocytes and Macrophages

Martin J. Cline and David W. Golde

9.1. Proliferation and Maturation	263
9.1.1. Monoblast	264
9.1.2. Promonocyte	264
9.1.3. Blood Monocyte	264
9.1.4. Tissue Macrophages	265
9.2. Kinetics	265
9.3. Metabolism	266
9.4. Functions	268
9.5. Defense against Microorganisms	268
9.6. Removal of Damaged Cells and Inorganic Materials	270
9.7. Cooperative Functions in Immune Responses	271
9.8. Cell-Mediated Cytotoxicity and Antitumor Immunity	272
9.9. Control of Granulopoiesis	274
9.10. Mononuclear Phagocyte Dysfunction Syndromes	275
9.11. Malignant Mononuclear Phagocytes	276
9.12. Summary	278
References	278

Chapter 10

The Production of Immunoglobulins by Mouse Myeloma Cells

W. Cieplinski and M. D. Scharff

10.1. Introduction	287
10.2. Plasma Cell Tumors and Cell Lines	288
10.3. Types and Frequency of Spontaneous Variants	290
10.4. Effect of Mutagenizing Agents on Mouse Myeloma Cells	292
10.5. Relationship to Human Heavy-Chain Disease	293

10.6. Regulation of Immunoglobulin Synthesis, Assembly, and Secretion	293
10.7. Posttranscriptional Events in the Production of Immunoglobulin	297
10.8. Conclusions	300
References	301

Chapter 11**The Origin of RNA Tumor Viruses and Their Relation to Human Leukemia**

Robert C. Gallo and David H. Gillespie

11.1. Origin of RNA Tumor Viruses	305
11.1.1. RNA-Containing Viruses Coded by Genes of Normal Cells	306
11.1.2. Type C RNA-Containing Viruses Not Coded by Genes of Normal Cells	309
11.1.3. Class 2 Viruses Arise from Class 1 Viruses	311
11.1.4. Type C RNA Viruses Are Transmitted among Hosts of Different Species in the Wild	313
11.1.5. Primate Type C RNA Tumor Viruses	314
11.2. Type C RNA Viruses in Human Cells	318
11.2.1. Detection of Type C RNA Virus Components in Tissue of Leukemic Patients	318
11.2.2. Natural Antibodies in Humans to Primate Type C Viruses	327
11.3. Summary and Interpretations	329
11.4. Deductions Concerning Viral Etiology of Human Leukemia	330
References	336

Chapter 12**Immunological Aspects of Leukemia**

Ronald B. Herberman

12.1. Introduction	345
12.2. Normal Cell Surface Markers and Leukemia-Associated Antigens	346
12.2.1. Experimental Animal Systems	347
12.2.2. Human Leukemia	357

12.3. Immunosuppression in Leukemia	362
12.3.1. Experimental Animal Systems	362
12.3.2. Human Leukemia	365
12.4. Immune Responses to Experimental Leukemias	368
12.4.1. Humoral Immune Responses	368
12.4.2. Cell-Mediated Immune Responses	369
12.5. Clinical Studies on Immune Response to Leukemia-Associated Antigens	370
12.5.1. Humoral Antibodies	370
12.5.2. Cell-Mediated Immune Responses	373
12.6. Practical Clinical Applications of Immunology to Leukemia	378
12.6.1. Diagnostic and Prognostic Tests	378
12.6.2. Immunotherapy	379
References	380

Chapter 13

Antihemophilic Factor

Oscar D. Ratnoff

13.1. Introduction	399
13.2. Assays for Antihemophilic Factor	400
13.3. The Site of Synthesis of AHF	402
13.4. Purification of AHF	403
13.5. Chemical and Physical Properties of AHF	403
13.5.1. Subcomponents of AHF	405
13.6. The Antigenicity of AHF Preparations	407
13.7. Functions of AHF	408
13.7.1. Procoagulant Activity	408
13.7.2. Ristocetin-Induced Platelet Aggregation	409
13.7.3. Platelet Retention by Glass Bead Columns and Platelet Adhesion to Subendothelial Structures	411
13.8. The AHF-like Properties of Platelets	411
13.9. Variations in AHF in Physiologic and Nonhereditary Pathologic States	412
13.10. Classic Hemophilia	413
13.10.1. The Nature of the Defect in Hemophilic Plasma	414
13.10.2. The Hereditary Nature of Classic Hemophilia and Detection of the Carrier State	415
13.10.3. Clinical Picture	417
13.10.4. Laboratory Diagnosis	418

13.10.5. Therapy	419
13.10.6. Circulating Anticoagulants against AHF in Hemophilia and Nonhemophilic States	421
13.10.7. The Heterogeneous Nature of Classic Hemophilia	423
13.11. Von Willebrand's Disease	424
13.11.1. The Nature of von Willebrand's Disease	424
13.11.2. Diagnosis	427
13.11.3. Therapy	427
13.11.4. Variants of von Willebrand's Disease	428
13.12. Acquired von Willebrand's Disease	429
13.13. Combined Deficiency of Antihemophilic Factor and Proaccelerin	430
13.14. Combined Deficiency of Antihemophilic Factor and Plasma Thromboplastin Antecedent	430
13.15. Animal Models of Hemophilia and von Willebrand's Disease	431
References	431

Chapter 14

Research on the Biochemical Basis of Platelet Function

Thomas C. Detwiler and Israel F. Charo

14.1. Introduction	455
14.2. Current Concepts of Platelet Function	456
14.2.1. The Physiological Role of Platelets	456
14.2.2. Platelet Morphology	456
14.2.3. <i>In Vitro</i> Responses of Platelets to Stimulation ..	458
14.2.4. Platelet Stimuli	460
14.2.5. Inhibitors of Platelet Function	460
14.3. Membranes	460
14.3.1. Fluid Mosaic Model of Membranes	460
14.3.2. Platelet Membranes	461
14.4. Physiological Stimuli	463
14.4.1. Thrombin	463
14.4.2. Collagen	467
14.4.3. ADP	471
14.4.4. Conclusion	471
14.5. Intracellular Regulatory Mechanisms	472
14.5.1. Calcium	472
14.5.2. Cyclic Nucleotides	473

14.5.3. Prostaglandins, Endoperoxides, and Thromboxanes	475
14.5.4. Protein Kinases	479
14.5.5. Conclusion	480
14.6. Contractility	480
14.6.1. Platelet Actomyosin	481
14.6.2. Function of Platelet Contractile Proteins	485
14.6.3. Microtubules	486
14.6.4. Summary	487
References	487

Chapter 15

Significance of Platelet Volume Measurements

Simon Karpatkin

15.1. Summary	497
15.2. Introduction	499
15.3. <i>In Vivo</i> Kinetic Studies during Basal Conditions	501
15.4. Kinetic Studies during Thrombopoietic Stress ("Thrombopoietin" Injection)	504
15.5. Kinetic Studies during Thrombopoietic Stress Induced by Blood Loss and/or Iron Deficiency	505
15.6. Clinical Methodology for Platelet Volume Distribution Analysis of Human Platelets	509
15.7. Clinical Significance of Megathrombocyte Measurements	511
15.8. Functional Capacity of Megathrombocytes	514
15.9. Preferential Splenic Sequestration of Megathrombocytes	514
15.10. Platelet and Red Blood Cell Fragmentation in Severe Autoimmune Thrombocytopenia	516
References	520

Chapter 16

Mechanisms of Polycythemia

John W. Adamson

16.1. Introduction	523
16.2. Oxygen Transport and Erythropoietin Production in Normal Man	523
16.3. Definition and Classification of Polycythemia	525
16.3.1. Normal Red Cell Mass	526

16.3.2. Increased Red Cell Mass	527
16.4. Tissue Hypoxia	527
16.4.1. O ₂ Loading Defects	527
16.4.2. O ₂ Transport Defects Due to Impaired Flow ..	530
16.4.3. O ₂ Unloading Defects	531
16.5. Autonomous Erythropoietin Production	537
16.5.1. Neoplasms	537
16.5.2. Recessively Inherited Polycythemias	538
16.6. Autonomous Marrow Function	540
16.6.1. Pathogenesis	540
16.6.2. Response to Humoral Regulators	541
16.7. Overview	543
References	544

Chapter 17

Nutritional Anemias Overview; Megaloblastic Anemias

Victor Herbert, Neville Colman, and Elizabeth Jacob

17.1. Nutritional Anemias Overview	549
17.2. Folate (Folic Acid) Deficiency	553
17.2.1. Frequency	553
17.2.2. Diagnostic Aspects	553
17.2.3. Metabolic Aspects	555
17.2.4. Clinical Aspects	557
17.3. Vitamin B ₁₂ Deficiency	558
17.3.1. Inadequate Ingestion	559
17.3.2. Stomach	561
17.3.3. Small Bowel	563
17.3.4. Pancreas	567
17.3.5. Drugs	567
17.3.6. Inadequate Utilization	568
17.3.7. Increased Excretion	568
17.3.8. Increased Requirement	569
17.3.9. Increased Destruction	569
References	569
Index	583