

Contents

1	Hemostasis Physiology	
Chapter 1	Coagulation Pathway and Physiology	3
	Russell A. Higgins, MD	
	Introduction, 3	
	Constituents of the Hemostatic System, 3	
	Endothelium, 3	
	Prothrombotic Properties of Endothelium, 4	
	Antithrombotic Properties of Endothelium, 5	
	Coordinating Prothrombotic and Antithrombotic Properties of Endothelium, 6	
	Platelets, 6	
	Coagulation Proteins, 7	
	The Extrinsic Pathway and the Prothrombin Time, 9	
	The Intrinsic Pathway and the Activated Partial Thromboplastin Time, 9	
	The Prothrombin Time and Activated Partial Thromboplastin Time Pathways, 9	
	Newer Coagulation Model, 10	
	Initiation, 11	
	Amplification, 12	
	Propagation, 12	
	Regulatory Mechanisms, 13	
	Protein C and Protein S System, 14	
	Protease Inhibitors, 14	
	Operation of the Hemostasis and Thrombosis Pathway, 15	
	Suggested Reading, 15	
Chapter 2	Platelet Structure and Function	17
	Imran Mirza, MD, and Kandice Kottke-Marchant, MD, PhD	
	Platelet Production, 17	
	Megakaryocyte Development and Maturation, 17	
	Platelet Production from Megakaryocytes, 19	
	Platelet Structure, 19	
	Surface Glycoproteins and Plasma Membrane, 19	
	Von Willebrand Receptor (GPIb/IX/V), 19	
	Collagen Receptors (GPVI and GPIa/IIa), 20	
	Adenosine Diphosphate Receptors, 21	
	Alpha-2 Adrenergic Receptors for Epinephrine, 21	
	Thrombin Receptors (PAR-1 and PAR-4), 21	
	Thromboxane Receptor and Prostaglandin Receptors, 22	
	Fibrinogen Receptor (GPIIb/IIIa), 22	
	CD36 (GPIV), 23	
	CD31 (Platelet Endothelial Cell Adhesion Molecule-1), 23	
	Platelet Cytoskeleton, 24	
	Platelet Membrane Systems, 25	
	Platelet Granules, 25	
	Alpha Granules, 25	
	Dense Granules, 26	

- Platelet Activation, 26
 - Platelet Adhesion, 27
 - Role of GPIb/IX/V and von Willebrand Factor, 27
 - Role of Collagen Receptors, 28
 - Cytoskeletal Changes, 29
 - Platelet Activation and Granule Release, 29
 - Phospholipase Pathway, 29
 - Cyclooxygenase Pathway, 29
 - Platelet Granule Release, 29
 - Platelet Aggregation, 30
 - Platelet Procoagulant Activity, 31
- Immune and Inflammatory Roles of Platelets, 31
- Suggested Reading, 31

Chapter 3	Fibrinolytic System Physiology	33
	Marc D. Smith, MD, and Wayne L. Chandler, MD	
	History, 33	
	Proteins and Function, 33	
	Regulation of Fibrinolysis, 37	
	Fibrinolysis at the Site of a Thrombus, 39	
	Suggested Reading, 39	

2

Basics of Laboratory Testing in Hemostasis

Chapter 4	Specimen Collection and Processing	43
	Jayashree Krishnan, MD, and Dorothy M. Adcock, MD	
	Introduction, 43	
	Specimen Collection Technique for Peripheral Venipuncture, 43 <ul style="list-style-type: none"> Needle Selection for Venipuncture, 44 Tourniquet Effect, 44 Use of Winged Collection Sets, 44 Specimen Labeling, 44 	
	Blood Collection From Indwelling Lines and Catheters, 45	
	Blood Collection Tubes and Anticoagulant Considerations, 45 <ul style="list-style-type: none"> Blood Collection Tubes, 45 Blood Tube Draw Order, 45 Anticoagulant, 46 Volume Effect, 46 Hematocrit Effect, 47 	
	Transportation of Whole Blood Specimens to the Laboratory, 47	
	Sample Processing, 47 <ul style="list-style-type: none"> Preparation of Platelet-Poor Plasma, 48 Effects of Temperature and Time, 48 Causes for Specimen Rejection, 51 Specimen Collection and Storage for Molecular Coagulation Assays, 52 	
	Conclusion, 53	
	Suggested Reading, 53	
	<i>Case Study</i> , 51	

Chapter 5	Clinical History in Hemostasis and Thrombosis	55
	Vandita Johari, MD	
	Introduction, 55	
	Clinical History in Bleeding Patients, 55 <ul style="list-style-type: none"> Bleeding Scores (Bleeding Assessment Tool), 55 Determine Whether the Patient Has Excessive Bleeding, 57 <ul style="list-style-type: none"> Extent of Bleeding, 57 Duration of Bleeding Abnormality, 58 Type of Bleeding, 59 	

Bleeding Due to Connective Tissue and Vascular Disorders, 59
Posttraumatic and Spontaneous Bleeding, 60
Hemarthrosis and Body Cavity Hematomas, 60
Epistaxis, 60
Surgical Procedures, 60
Gingival/Dental Bleeding History, 61
Menstrual History, 61
Obstetric History, 61
Bleeding Due to Organ System Disorders, 61
Medication and Food Habits, 62
Family History, 62
Previous Coagulation Test Results, 64
Pediatric Considerations, 64
Clinical History in Patients With Thrombosis, 64
Family History, 65
Age of Onset, 65
Ethnicity, 65
Location and Type of Thrombosis (Venous, Arterial, or Embolic), 65
Recurrences, 67
Acquired Thrombophilic Risk Factors, 67
Medical History, 67
Malignancy, 68
Obstetric History and Hormone Therapy, 68
Medication History, 68
Surgery and Trauma, 69
Elevated Levels of Homocysteine, 69
Summary, 69
Suggested Reading, 69

Chapter 6 Coagulation Testing

71

Sandra C. Hollensead, MD, Jayashree Krishnan, MD, and Kandice Kottke-Marchant, MD, PhD
Introduction, 71
Laboratory Measurement of Clot-Based Coagulation Tests, 71
Coagulation Analyzers, 71
Principles of Performance, 71
How to Select and Validate a Coagulation Analyzer, 72
Prothrombin Time, 72
Reagent Considerations, 73
Reporting of Prothrombin Time, 74
Calculation of International Normalized Ratio, 74
Clinical Utility of Prothrombin Time, 78
Point-of-Care Monitors for Oral Anticoagulant Therapy, 78
Activated Partial Thromboplastin Time, 79
Principle, 79
Reagents, 79
Method, 80
Reference Range, 80
Clinical Utility of Activated Partial Thromboplastin Time, 80
Point-of-Care Testing for Activated Partial Thromboplastin Time, 81
Steps to Take in the Evaluation of a Prolonged Activated Partial Thromboplastin Time, 81
Evaluation of Unfractionated Heparin Sensitivity, 81
Thrombin Time, 82
Method, 82
Reagents, 83
Reference Range, 83
Clinical Utility of Thrombin Time, 83

- Fibrinogen Assay, 83
 - Clinical Utility of Fibrinogen Assays, 85
- Assay of Specific Factors, 85
 - Principle, 85
 - Factor II (Prothrombin), 86
 - Factors V, VII, and X, 86
 - Factors VIII, IX, XI, XII, High-Molecular-Weight Kininogen, and Prekallikrein, 86
 - False-Positives and False-Negatives in Factor Assays, 87
 - Factor XIII, 87
 - Von Willebrand Factor, 87
- Mixing Studies, 88
 - Principle, 88
 - Technical Considerations, 88
 - Procedure, 90
 - Criteria for Interpretation of Mixing Studies, 90
- Specific Inhibitor Studies, 90
 - Bethesda Assay, 90
 - Nijmegen Modification, 91
 - Reporting of Results, 91
- Establishing Reference Ranges and Validating Coagulation Laboratory Testing, 92
 - Preanalytic and Postanalytic Considerations, 92
 - Reference Range, 92
 - Accuracy, 92
 - Precision, 93
 - Linearity, 93
 - Interfering Conditions, 93
 - Issue of Duplicate Testing, 95
 - Turnaround Time, 95
 - Reporting of Results, 96
- Summary, 96
- Suggested Reading, 97
- Case Study, 95

Chapter 7 Platelet Testing

- Megan O. Nakashima, MD, and Kandice Kottke-Marchant, MD, PhD
- Patient History, 99
 - Clinical History for Patients With a Bleeding Diathesis, 99
 - Clinical History for Patients With Thrombosis, 99
- Platelet Count, Indices, and Morphology, 100
 - Specimen Collection and Processing Considerations, 100
 - Test Performance and Interpretation, 101
- Bone Marrow Analysis, 102
 - Specimen Collection and Processing Considerations, 102
 - Bone Marrow Interpretation, 103
- Platelet Function Testing, 103
 - Bleeding Time, 103
 - PFA-100, 104
 - Specimen Considerations, 104
 - Test Performance and Interpretation, 104
- Platelet Aggregation, 106
 - Light Transmission Aggregation, 107
 - Specimen Considerations, 107
 - Test Performance and Interpretation, 107
 - Whole Blood Aggregometry, 109
 - Plateletworks, 110
 - VerifyNow, 110

	Release Assays, 111	
	Lumiaggregation, 111	
	Release Markers, 111	
	P-selectin, 111	
	Thromboxane Metabolites, 112	
	Adhesion Assays, 112	
	Platelet Adhesion Chambers, 112	
	Impact Cone and Plate(let) Analyzer, 112	
	Platelet Mechanical Assays, 113	
	Hemostasis Analysis System, 113	
	Whole Blood Viscoelastometry, 113	
	Flow Cytometry, 114	
	Platelet Turnover (Platelet Reticulocyte Analysis), 115	
	Electron Microscopy, 116	
	Platelet Genetic Testing, 117	
	Summary, 118	
	Suggested Reading, 118	
Chapter 8	Fibrinolysis Testing	121
	Wayne L. Chandler, MD	
	Clinical History Suggesting the Need for Fibrinolytic Testing, 121	
	Sample Collection and Processing for Fibrinolytic Testing, 121	
	D-Dimer and Fibrin Split Product Assays, 123	
	Plasminogen Assays, 125	
	Alpha-2 Antiplasmin Assays, 126	
	Tissue Plasminogen Activator Assays, 126	
	Plasminogen Activator Inhibitor-I Assays, 128	
	Global Tests of Fibrinolysis, 129	
	Lipoprotein (a), 130	
	Genomic Assays, 131	
	Research Assays, 131	
	Suggested Reading, 131	
Chapter 9	Laboratory Aspects of Thrombophilia Testing	133
	Charles Eby, MD	
	Introduction, 133	
	Inherited Thrombophilias: Natural Anticoagulants, 133	
	Protein C, 133	
	Protein C Functional Assays, 133	
	Protein C Antigen Assays, 135	
	Protein S, 136	
	Protein S Activity Assays, 137	
	Protein S Antigen Assays, 137	
	Antithrombin, 138	
	Antithrombin Functional Assays, 138	
	Antithrombin Antigen Assays, 139	
	Activated Protein C Resistance, 139	
	Activated Protein C Resistance Assays, 139	
	Factor VIII Activity, 140	
	Fibrinogen Abnormalities, 140	
	Lupus Anticoagulant, 141	
	Factor V Leiden and Prothrombin G20210A Mutations, 141	
	Plasma Homocysteine Concentration, 142	
	Global Tests of Hypercoagulability, 143	
	Endogenous Thrombin Potential, 143	
	Undiluted Activated Protein C Resistance, 143	
	Activated Partial Thromboplastin Time, 143	
	Activation and Degradation Peptides, 144	

	Conclusion, 144	
	Suggested Reading, 144	
Chapter 10	Quality in Hemostasis Laboratory Testing	147
	Paul Allison, MD, and Kandice Kottke-Marchant, MD, PhD	
	History of Hemostasis Laboratory Quality Initiatives, 147	
	Quality Management Programs, 147	
	Purpose of a Quality Plan, 147	
	Implementing a Hemostasis Quality Plan, 148	
	Quality Management for Coagulation Screening Tests, 149	
	Standard Operating Procedures, 150	
	Quality Control, 151	
	Frequency of Quality Control Testing, 153	
	Quality Assurance, 153	
	Evidence of Compliance, 153	
	External Quality Assessment, 154	
	Laboratory Quality Data in Patient Care, 156	
	Summary, 157	
	Suggested Reading, 157	
3	Algorithmic Approach to Bleeding Disorders	
Chapter 11	Abnormal Activated Partial Thromboplastin Time	161
	Russell A. Higgins, MD, and John D. Olson, MD, PhD	
	Introduction, 161	
	Clinical Etiologies, 161	
	Coagulation Factor Deficiency Associated With Significant Hemorrhage, 161	
	Von Willebrand Disease, 161	
	Factor VIII Deficiency, 162	
	Factor IX Deficiency, 163	
	Factor XI Deficiency, 163	
	Other Inherited and Acquired Deficiencies, 163	
	Coagulation Factor Deficiencies Not Associated With Bleeding, 163	
	Prolongation of aPTT Due to Inhibitors, 164	
	Medications, 164	
	Lupus Anticoagulant, 164	
	Specific Coagulation Factor Inhibitors, 165	
	Alloantibodies in Hemophilic Patients, 165	
	Autoantibodies to Factor VIII and Other Factors, 166	
	Spurious Causes of an Elevated aPTT, 166	
	Laboratory Testing Algorithm, 167	
	Accelerated aPTT, 170	
	Spurious, 170	
	Treatment With Activated Clotting Factors, 170	
	Consumptive Coagulopathy, 170	
	Summary, 170	
	Suggested Reading, 171	
	<i>Case Studies, 170, 171</i>	
Chapter 12	Prolonged Prothrombin Time	173
	Mark T. Cunningham, MD, and Marc D. Smith, MD	
	Introduction, 173	
	Differential Diagnosis of a Corrected Mixing Study, 173	
	Hereditary Disorders: Factor Deficiency, 174	
	Factor II Deficiency, 174	
	Factor V Deficiency, 175	
	Factor V and Factor VIII Deficiency, Combined, 175	
	Factor VII Deficiency, 176	
	Factor X Deficiency, 176	

Fibrinogen Deficiency, 176	
Vitamin K-Dependent Coagulation Factor Deficiency, Hereditary, 177	
Acquired Disorders, 177	
Dilutional Coagulopathy, 177	
Disseminated Intravascular Coagulation, 177	
Liver Disease, 177	
Vitamin K Antagonists and Vitamin K Deficiency, 178	
Warfarin, 178	
Superwarfarin Poisoning, 178	
Vitamin K Deficiency, 179	
Newborns, 179	
Adults, 180	
Differential Diagnosis of a Noncorrected Mixing Study, 180	
Inhibitor Drugs, 180	
Direct Thrombin Inhibitors, 180	
Direct Factor Xa Inhibitors, 181	
Heparin, 181	
Factor Inhibitors, 181	
Factor II Inhibitor, 181	
Factor V Inhibitor, 182	
Factor VII Inhibitor, 182	
Factor X Inhibitor, 184	
Lupus Anticoagulant, 184	
Algorithm, 184	
Suggested Reading, 184	
<i>Case Studies, 174</i>	

Chapter 13 Abnormal Thrombin Time **187**

Mark T. Cunningham, MD, and Sandra C. Hollensead, MD

Introduction, 187	
Clinical Indications, 187	
Differential Diagnosis, 187	
Amyloidosis, 187	
Autoantibodies, 187	
Drugs, 188	
Bovine Thrombin, Topical, 188	
Direct Thrombin Inhibitors, 189	
Heparin, 189	
Plasminogen Activators, 189	
Volume Expanders, 189	
Fibrin Degradation Products, 190	
Fibrinogen Abnormalities, 190	
Dysfibrinogenemia, 190	
Hypofibrinogenemia, 190	
Afibrinogenemia, 193	
Hyperfibrinogenemia, 193	
Radiocontrast Agents, 193	
Algorithm, 193	
Suggested Reading, 193	
<i>Case Studies, 190, 191</i>	

Chapter 14 Normal Prothrombin Time and Activated Partial Thromboplastin Time **195**

Vandita Johari, MD

Introduction, 195	
Clinical Evaluation, 195	
False-Negative (Normal) PT and aPTT, 196	
Patient-Specific Causes, 196	
Preanalytic Causes, 196	
Analytic Causes, 196	

	<ul style="list-style-type: none"> Postanalytic Causes, 196 Additional Testing, 196 <ul style="list-style-type: none"> Primary Hemostasis Defects, 196 Secondary Hemostasis Defects, 197 <ul style="list-style-type: none"> Factor Assays, 197 Factor XIII Deficiency, 197 Fibrinolysis Defects, 199 Vascular Disorders, 199 Algorithm, 199 Suggested Reading, 200 <i>Case Studies</i>, 199, 200 	
Chapter 15	Fibrinolytic Bleeding Disorders	201
	<ul style="list-style-type: none"> Wayne L. Chandler, MD Introduction, 201 Clinical Evaluation of Fibrinolytic Bleeding Disorders, 201 Plasminogen Activator Inhibitor-1 Deficiency, 201 Alpha 2-Antiplasmin Deficiency, 203 Quebec Platelet Disorder, 203 Factor XIII Deficiency, 203 Acquired Causes of Fibrinolytic Bleeding, 203 <ul style="list-style-type: none"> Mechanisms of Acquired Fibrinolytic Bleeding, 203 Cardiovascular Surgery and Cardiopulmonary Bypass, 204 Cirrhosis and Liver Transplantation, 205 Monitoring Fibrinolysis, 205 Menorrhagia, 205 Trauma, 206 Disseminated Intravascular Coagulation, 206 Suggested Reading, 210 <i>Case Studies</i>, 205, 206 	
Chapter 16	Platelet Disorders	211
	<ul style="list-style-type: none"> Kandice Kottke-Marchant, MD, PhD Introduction, 211 Platelet Dysfunction With Normal Platelet Count (Qualitative Platelet Disorders), 211 <ul style="list-style-type: none"> Glycoprotein Disorders, 213 <ul style="list-style-type: none"> Glanzmann Thrombasthenia (GPIIb/IIIa Deficiency), 213 GPIb/IX/V (Bernard-Soulier Syndrome), 218 Platelet-Type von Willebrand Disease, 218 Collagen Receptor Disorders (GPIa/IIa and GPVI), 218 Adenosine Disphosphate Receptor Abnormalities, 219 Platelet Release Defects, 219 <ul style="list-style-type: none"> Storage Pool Disorders (Alpha and Dense Granule Disorders), 219 Signal Transduction Disorders, 221 Disorders of Platelet Procoagulant Activity (Scott Syndrome), 222 Platelet Disorders With Thrombocytosis, 222 <ul style="list-style-type: none"> Reactive Thrombocytosis, 222 Myeloproliferative Neoplasms Associated With Thrombocytosis, 223 Platelet Disorders With Thrombocytopenia, 224 <ul style="list-style-type: none"> Thrombocytopenia With Increased Platelet Size (Macrothrombocytopenia Disorders), 224 <ul style="list-style-type: none"> Macrothrombocytopenias With Neutrophilic Inclusions (<i>MYH9</i>-Related Diseases), 224 Bernard-Soulier Syndrome, 227 Gray Platelet Syndrome (Alpha Granule Storage Pool Disorder), 228 Thrombocytopenia With Decreased Platelet Size, 229 <ul style="list-style-type: none"> Wiskott-Aldrich Syndrome and X-Linked Thrombocytopenia, 229 Thrombocytopenia With Normal Platelet Size, 229 	

	Peripheral Platelet Destruction, 230	
	Immune Destructive Thrombocytopenias, 230	
	Nonimmune Destructive Thrombocytopenias, 232	
	Decreased Platelet Production, 233	
	Inherited Thrombocytopenias With Decreased Platelet Production, 233	
	Defects of Platelet Production, 233	
	Acquired Thrombocytopenias With Decreased Platelet Production, 234	
	Platelet Dysfunction Associated With Other Illnesses, 234	
	Platelet Disorders Associated With Thrombosis or Platelet Activation, 234	
	Platelet Activation, 235	
	Genetic Polymorphisms Associated With Thrombosis and Cardiovascular Disease, 235	
	Cardiovascular Devices, 236	
	Summary, 236	
	Suggested Reading, 237	
	<i>Case Study</i> , 211	
Chapter 17	Von Willebrand Disease	241
	Elizabeth M. Van Cott, MD, and Arnaud Drouin, MD	
	Introduction, 241	
	Von Willebrand Factor, 241	
	Clinical Features, 241	
	Classification, 242	
	Inheritance, 244	
	Laboratory Testing, 244	
	Laboratory Findings in Type 1 von Willebrand Disease, 248	
	Laboratory Findings in Type 2 von Willebrand Disease, 248	
	Laboratory Findings in Type 3 von Willebrand Disease, 249	
	The Molecular Basis of von Willebrand Disease, 249	
	Acquired von Willebrand Disease, 250	
	Treatment, 250	
	Suggested Reading, 251	
	<i>Case Study</i> , 244	
Chapter 18	Emergency Assessment of Hemostasis in the Bleeding Patient	253
	Wayne L. Chandler, MD	
	Clinical Situation, 253	
	Clinical Criteria for Emergency Hemostasis Testing, 253	
	Options for Testing Locations, 253	
	Testing Methodology for Emergency Hemostasis Evaluation, 254	
	Standard Assays, 254	
	Point-of-Care Analyzers, 256	
	Viscoelastic Global Hemostasis Assays, 256	
	Platelet Function Assays, 257	
	Summary, 258	
	Suggested Reading, 258	
4	Algorithmic Approach to Thrombophilic Disorders	
Chapter 19	Arterial and Venous Thrombosis in Adults	261
	Russell A. Higgins, MD, and John D. Olson, MD, PhD	
	Introduction, 261	
	General Considerations, 261	
	Consent and Counseling, 261	
	Assay Calibration, Reference Range, and Assay Reliability, 261	
	Combined Deficiency, 262	
	Testing for Thrombophilic Risk in Patients With Venous or Arterial Thrombosis, 262	
	Thrombophilic Risk Factor Testing in Venous Thromboembolism, 262	
	How Does Thrombophilia Testing Impact Medical Decisions?, 262	

	Who Should Be Tested for Thrombophilic Risk?, 263	
	What Tests Should Be Performed?, 268	
	When Should Thrombophilia Testing Be Performed?, 268	
	Recommendations for Testing of Individual Analytes, 269	
	Protein C, Protein S, and Antithrombin Deficiency, 269	
	Factor V Leiden and Prothrombin G20210A Mutations, 270	
	Hyperhomocysteinemia and High Concentrations of Factor VIII, 271	
	Acquired Thrombophilic Risk Factors, 271	
	Antiphospholipid Antibodies, 271	
	Heparin-Induced Thrombocytopenia, 271	
	Thrombophilic Risk Factor Test Selection in Arterial Thrombosis, 272	
	Antiphospholipid Antibodies, 272	
	C-Reactive Protein, 273	
	Lipoprotein (a), 273	
	Homocysteine, 273	
	Prothrombin G20210A Mutation, 274	
	Factor V Leiden (Activated Protein C Resistance), 274	
	Deficiencies of Protein C, Protein S, and Antithrombin, 275	
	Coagulation Factors, 275	
	Heparin-Induced Thrombocytopenia, 275	
	Thrombophilic Risk Factor Test Selection in Neurovascular Thrombosis, 276	
	Antiphospholipid Antibodies, 276	
	Lipoprotein (a), 276	
	Homocysteine, 276	
	Prothrombin G20210A Mutation, 277	
	Factor V Leiden (Activated Protein C Resistance), 277	
	Deficiencies of Protein C, Protein S, and Antithrombin, 277	
	Heparin-Induced Thrombocytopenia, 278	
	Additional Considerations for Thrombosis in Unusual Sites, 278	
	Myeloproliferative Neoplasms and <i>JAK2V617F</i> , 279	
	Paroxysmal Nocturnal Hemoglobinuria, 279	
	Warfarin-Induced Skin Necrosis, 280	
	Suggested Reading, 280	
	<i>Case Studies</i> , 263, 264	
Chapter 20	Unique Issues of Thrombophilia in Women and Children	285
	S. Kate Hartman, MD, and John D. Olson, MD, PhD	
	Introduction, 285	
	Pregnancy and Hormonal Therapy, 285	
	Baseline Thrombotic Risk in Women, 285	
	Oral Contraceptives and Risk of Thromboembolism, 288	
	Hormone Replacement Therapy and Venous Thromboembolism, 291	
	Thrombophilia in the Pediatric Setting, 292	
	Description of the Problem, 292	
	Testing for Thrombophilia in Children, 294	
	Suggested Reading, 296	
	<i>Case Studies</i> , 291, 292	
Chapter 21	Laboratory Diagnosis of Inherited Thrombophilia	299
	Charles Eby, MD	
	Introduction, 299	
	Algorithmic Approach to Laboratory Diagnosis of Thrombophilic Risk Factors, 299	
	Protein C, 300	
	Protein S, 302	
	Antithrombin, 303	
	Factor VIII, 305	
	Activated Protein C Resistance and Factor V Leiden, 305	

	Prothrombin G20210A Mutation, 306	
	Homocysteine, 306	
	Suggested Reading, 308	
	<i>Case Study</i> , 302	
Chapter 22	Fibrinolytic Thrombotic Disorders	309
	Vandita Johari, MD	
	Introduction, 309	
	Thrombosis and Defects of Fibrinolysis, 309	
	Plasminogen Deficiency, 309	
	Tissue Plasminogen Activator Deficiency, 310	
	Tissue Factor Pathway Inhibitor Deficiency, 310	
	Plasminogen Activator Inhibitor Excess, 310	
	Alpha 2-Antiplasmin Excess, 311	
	Thrombin Activatable Fibrinolysis Inhibitor Increase, 311	
	Dysfibrinogenemia, 311	
	Lipoprotein (a) Excess, 312	
	Antifibrinolytic Medications, 312	
	Disseminated Intravascular Coagulation, 312	
	The Role of D-Dimer in Excluding Venous Thromboembolism, 312	
	D-Dimer Testing, 313	
	Variations in the Types of D-Dimer Assays, 313	
	Selecting the Appropriate Cutoff and Units for Excluding Venous Thromboembolism, 314	
	Summary, 314	
	Suggested Reading, 315	
	<i>Case Studies</i> , 310, 311, 314	
Chapter 23	Heparin-Induced Thrombocytopenia	317
	Marc D. Smith, MD, and Karen A. Moser, MD	
	Introduction, 317	
	Clinical Presentation, 317	
	Pathophysiology, 318	
	Clinical Laboratory Diagnosis and Algorithm, 319	
	Enzyme Immunoassay, 319	
	Rapid HIT Immunoassays, 322	
	Serotonin Release Assay, 323	
	Heparin-Induced Platelet Aggregation, 323	
	Other HIT Assays, 323	
	Treatment, 324	
	Suggested Reading, 325	
	<i>Case Study</i> , 322	
Chapter 24	Antiphospholipid Antibodies	327
	Elizabeth M. Van Cott, MD, and Charles Eby, MD	
	Introduction, 327	
	Laboratory Testing for Antiphospholipid Antibodies, 327	
	Lupus Anticoagulant Testing and Guidelines, 327	
	Preanalytic Variables, 329	
	Testing for a Lupus Anticoagulant, 331	
	Exclusion of Other Abnormalities (Factor Inhibitors), 333	
	When Results Do Not Agree, 333	
	Anticardiolipin Antibody Testing and Other Antiphospholipid Antibody Immunoassays, 333	
	Clinical Features and Diagnosis, 334	
	Monitoring Anticoagulation in Patients With Lupus Anticoagulants, 335	
	Suggested Reading, 335	
	<i>Case Study</i> , 328	

Chapter 25	Thrombotic Microangiopathies	337
	Dorothy M. Adcock, MD, Karen A. Moser, MD, and Dong Chen, MD, PhD	
	Introduction, 337	
	Definition and Clinical Features of Thrombotic Microangiopathies, 337	
	Thrombotic Thrombocytopenic Purpura, 338	
	Biology of von Willebrand Factor and ADAMTS13, 338	
	A Brief History of Thrombotic Thrombocytopenic Purpura, 340	
	Clinical Presentation of Thrombotic Thrombocytopenic Purpura, 341	
	Laboratory Testing in Thrombotic Thrombocytopenic Purpura, 342	
	ADAMTS13 Testing, 342	
	ADAMTS13 Activity Assays, 342	
	ADAMTS13 Activity Assay Interferences, 346	
	Interpretation of ADAMTS13 Activity Results, 346	
	ADAMTS13 Antigen Assays, 347	
	Anti-ADAMTS13 Autoantibody Assessment, 347	
	Mutation Analysis of <i>ADAMTS13</i> , 347	
	Thrombotic Thrombocytopenic Purpura Treatment, 347	
	Prediction of Severity and Mortality of Acute Thrombotic Thrombocytopenic Purpura, 348	
	Prediction of Thrombotic Thrombocytopenic Purpura Relapse, 348	
	Thrombotic Microangiopathies Other Than TTP, 349	
	Shiga Toxin–Associated Hemolytic Uremic Syndrome, 349	
	Atypical Hemolytic Uremic Syndrome, 350	
	Pregnancy-Related Thrombotic Microangiopathies, 351	
	Hematopoietic Stem Cell Transplant–Associated Thrombotic Microangiopathy, 351	
	Malignancy-Associated Thrombotic Microangiopathy, 352	
	Other Considerations, 352	
	Suggested Reading, 352	
	<i>Case Study</i> , 338	
Chapter 26	The Value of Consultation in Hemostasis Testing	357
	Kandice Kottke-Marchant, MD, PhD, and Marc D. Smith, MD	
	Introduction, 357	
	The Drive for Added Value in Laboratory Testing, 357	
	Institutions Influencing Change in Health Care Delivery, 357	
	The New Laboratory Value Focus, 358	
	Unique Features of Hemostasis Testing That Make Consultation Valuable, 359	
	Basic Elements and Benefits of an Interpretive Hemostasis Service, 360	
	Operational Process for an Interpretive Hemostasis Service, 361	
	Model Algorithm for an Elevated aPTT Panel, 363	
	Model Algorithm for a Hypercoagulation Panel, 365	
	Elements of the Interpretive Report, 366	
	Impact of an Interpretive Hemostasis Service, 367	
	Quality Assessment in Interpretive Reporting, 367	
	Summary and Conclusion, 368	
	Suggested Reading, 368	
	<i>Case Study</i> , 366	
5	Antiplatelet and Anticoagulant Drugs	
Chapter 27	Overview of Antithrombotic Agents	373
	Karen A. Moser, MD	
	Introduction, 373	
	Target Therapeutic Range and Monitoring Considerations, 373	
	Common Clinical Settings Where Antithrombotic Agents Are Used, 374	
	Acute Venous Thromboembolism, 374	
	Prophylaxis for Venous Thromboembolism, 375	

	Prophylaxis in Patients With Atrial Fibrillation, 375	
	Acute Coronary Syndromes, 376	
	Peripheral Vascular and Cerebrovascular Disease, 376	
	Extracorporeal Circulation, 376	
	Implantation of Mechanical Heart Valves, 377	
	Effects on Tests of Hemostasis, 377	
	Summary, 377	
	Suggested Reading, 377	
Chapter 28	Mechanism and Monitoring of Anticoagulant Agents	379
	Dorothy M. Adcock, MD, and Karen A. Moser, MD	
	Introduction, 379	
	Unfractionated Heparin, 379	
	Laboratory Detection and Monitoring of Unfractionated Heparin, 380	
	Acute Venous Thromboembolism, 384	
	Acute Coronary Syndromes, 384	
	Renal Dialysis, Percutaneous Coronary Intervention, and	
	Cardiopulmonary Bypass, 385	
	Low-Molecular-Weight Heparins, 385	
	Laboratory Detection and Monitoring of Low-Molecular-Weight Heparin, 385	
	Fondaparinux, 386	
	Laboratory Detection and Monitoring of Fondaparinux, 387	
	Direct Thrombin Inhibitors, 387	
	Hirudins (Peptide Direct Thrombin Inhibitors), 387	
	Laboratory Detection and Monitoring of Hirudin Analogues, 388	
	Argatroban, 389	
	Laboratory Detection and Monitoring of Argatroban, 389	
	Dabigatran, 390	
	Laboratory Detection of Dabigatran, 391	
	Vitamin K Antagonists, 392	
	Laboratory Detection and Monitoring of Vitamin K Antagonists, 393	
	Direct Anti-Xa Inhibitors, 394	
	Rivaroxaban, Apixaban, and Edoxaban, 394	
	Laboratory Detection of Rivaroxaban and Apixaban, 396	
	Interference of Direct Thrombin Inhibitor and Direct Anti-Xa Inhibitor	
	Anticoagulants in Special Coagulation Assays, 397	
	Direct Thrombin Inhibitors, 397	
	Direct Xa Inhibitors, 397	
	Suggested Reading, 399	
Chapter 29	Antiplatelet Agents	403
	Kandice Kottke-Marchant, MD, PhD	
	Introduction, 403	
	Parenteral Agents, 403	
	Glycoprotein IIb/IIIa Inhibitors, 403	
	Mechanism of Action, 403	
	Effect on Platelet Function Tests, 406	
	Clinical Uses, 406	
	Role of Monitoring, 407	
	Special Issues, 407	
	Oral Agents, 407	
	Aspirin, 407	
	Mechanism of Action, 407	
	Clinical Uses, 408	
	Laboratory Tests Used to Assess Effect, 408	
	Laboratory Monitoring, 409	
	P2Y ₁₂ Inhibitors, 410	

- Thienopyridines, 410
 - Mechanism of Action, 410
 - Clinical Uses, 411
 - Laboratory Monitoring, 412
- Nonthienopyridine P2Y₁₂ Inhibitors (Ticagrelor), 414
 - Mechanism of Action, 414
 - Clinical Uses, 414
 - Laboratory Monitoring, 414
- An Algorithmic Approach to Use of P2Y₁₂ Antagonists in Patients With Acute Coronary Syndromes, 414
- PAR-1 Inhibitors, 416
- Vorapaxar, 416
 - Mechanism of Action, 416
 - Clinical Utility, 416
 - Laboratory Monitoring, 416
- Dipyridamole, 416
 - Mechanism of Action, 416
 - Clinical Uses, 416
 - Monitoring Issues, 417
- Iloprost, 417
- Cilostazol, 417
 - Mechanism of Action, 417
 - Clinical Uses, 417
 - Monitoring Issues, 417
- New Antiplatelet Drugs in Development, 418
- Antiplatelet Effect of Other Drugs and Herbal Remedies, 419
- Summary, 420
- Suggested Reading, 420

Chapter 30 Antifibrinolytic and Thrombolytic Agents

425

Wayne L. Chandler, MD

- Introduction, 425
- Therapeutic Uses of Antifibrinolytic Drugs, 427
 - Cardiovascular Surgery and Cardiopulmonary Bypass, 427
 - Liver Transplantation, 427
 - Trauma, 428
 - Orthopedic and Spinal Surgery, 428
 - Genitourinary Bleeding, 428
 - Gastrointestinal Bleeding, 428
 - Other Indications, 429
- Monitoring of Antifibrinolytic Drugs, 429
- Thrombolytic Agents, 429
 - Monitoring of Thrombolytic Agents, 432
- Suggested Reading, 432
- Case Studies*, 431

6

Appendices and Index

- Appendix A. Acronyms List, 437
- Appendix B. Example Reference Ranges, 440
- Index, 441