## Contents

xvii

Defenses of the Skin

31

xix

xxi

Preface

In Memoriam

About the Authors

CH	HAPTER 1 The Power of Bacteria	2
	Why Are Bacteria So Much in the Public Health Spotlight Nowadays? 3	
	Bacteria, a Formidable Ancient Life Form 4	
	Pressing Current Infectious Disease Issues Emerging and Reemerging Infectious Diseases Foodborne and Waterborne Infections Modern Medicine as a Source of New Diseases Postsurgical and Other Wound Infections  Bioterrorism  10	
	A New Respect for Prevention 10 Surveillance: An Early Warning System 11 Making Hospitals Safe for Patients 12	
	And Now for Some Good News: You've Got a Bacterial Infection! 12  The Helicobacter pylori Revolution 12  The Aftermath 13  Microbiota Shift Diseases 13	
	A Brave New World of Pathogenesis Research The New Age of Genomics 16 Insights into Pathogen Evolution 17 Modeling the Host-Pathogen Interaction in Experimental Animals 17 Correlation Studies 18	
	Selected Readings 18	
	Questions 20	
21	HAPTER 2 Skin and Mucosa: The First Lines of Defense against Bacterial Infections	22
	The Best Defense: Avoid, Reduce, and Prevent Exposure! 23	
	Barriers: Skin and Mucosal Membranes The Layers of Cells That Protect the Body Normal Microbiota of the Skin and Mucosa  24  25	

Defenses of Mucosal Surfaces 32 Special Defenses of the Gastrointestinal Tract 34 Special Defenses of the Urogenital Tract 36 Special Defenses of the Respiratory Tract 36 Immune Defenses of the Skin and Mucosa 37
Models for Studying Breaches of Barrier Defenses 38
Selected Readings 39
Questions 39
CHAPTER 3 The Innate Immune System: Always on Guard
Triggering Innate Immune Defenses 41
Innate Immune Cells That Defend Blood and Tissue 42  Neutrophils (PMNs) 42  Monocytes, Macrophages, and Dendritic Cells (DCs) 42  Granulocytes: Basophils, Mast Cells, and Eosinophils 47  Transmigration—How Do Phagocytes Know When and Where to Go? 47  Natural Killer (NK) Cells 48
The Lymphatic System 50
How Phagocytes Recognize and Respond to Bacteria 50
How Phagocytes Recognize and Respond to Bacteria 50  How Phagocytes Kill Bacteria 54  Oxidative Burst in Phagolysosomes 54  Autophagy—Another Pathway for the Killing of Intracellular Pathogens 56
The Complement Cascade 57 Complement Proteins 57 Overview of Complement Pathways and Their Function 58 Steps in Complement Activation 60 Controlling Complement Activation 62
Cytokines and Chemokines—Mediators of Immune Responses 63 Roles of Cytokines and Chemokines in Directing Innate Immune Responses 63 Inflammation and Collateral Damage 65
Septic Shock: The Dark Side of the Innate Defenses 66
Other Innate Defenses of the Body—Nutritional Immunity 69
Selected Readings 70
Questions 70
CHAPTER 4 The Adaptive Defenses: Antibodies and Cytotoxic T Cells
The Specialists: Adapting to a Particular Pathogen Challenge 73
B Cells: Producers of Antibodies 74  The Humoral (Antibody) Immune Response 74  Characteristics of Antibodies and Their Diverse Roles in Preventing Infection 74  Serum Antibodies 76  Secretory Antibodies: Antibodies That Protect Mucosal Surfaces 78  Pathogen and Toxin Neutralization by Antibodies 79  Affinity and Avidity 80
Cytotoxic T Cells, Also Known as Cytotoxic T Lymphocytes (CTLs) 81 Cytotoxic T Lymphocytes: Critical Defense against Intracellular Pathogens 81
Antigen Presentation to the Immune System 82 Processing of Protein Antigens by Dendritic Cells 82 Interaction between APCs and T Cells: The T-Cell-Dependent Response 84 Th-(Th1/Th2/Th17)-Cell-Mediated Immunity 86 Production of Antibodies by B Cells 87
Links between the Innate and Adaptive Defense Systems 88

T-Cell-Independent Antibody Responses 89	
Mucosal Immunity: IgA/sIgA Antibodies 89	
Development of the Adaptive Immune System from Infancy to Adulthood 92	
Adaptive Defense Systems in Nonmammals 93	
The Dark Side of the Adaptive Defenses: Autoimmune Disease 93	
Selected Readings 94	
Questions 94	
Solving Problems in Bacterial Pathogenesis 95	
HAPTER 5 The Microbiota of the Human Body: Microbiomes and Beyond 98	
Importance of the Normal Resident Microbial Populations (Microbiota) of the Human Body 99	
Characterization of the Body's Microbiota 100	
Taking a Microbial Census by Using Microbial rRNA Gene Sequence Analysis 101  Characterizing Microbiamos by Using Metagonomic Analysis 115	
Characterizing Microbiomes by Using Metagenomic Analysis 115  Beyond the Metagenome 117	
Overview of the Human Microbiota 123	
Skin Microbiota 124	
Oropharyngeal Microbiota 125	
Microbiota of the Small Intestine and Colon 125	
Microbiota of the Vaginal Tract 128	
The Other Microbiota: The Forgotten Eukaryotes 130	
Selected Readings 130	
Questions 131	
Solving Problems in Bacterial Pathogenesis 133	
HAPTER 6 Microbes and Disease: Establishing a Connection 134	
HAPTER 6 Microbes and Disease: Establishing a Connection  History and Relevance of Koch's Postulates  136	
History and Relevance of Koch's Postulates Early Germ Theory 136	
History and Relevance of Koch's Postulates 136	
History and Relevance of Koch's Postulates 136  Early Germ Theory 136  Koch's Postulates: A Set of Criteria Used To Establish a Microbe-Disease Connection 137  Challenges to Satisfying Koch's Postulates 138	
History and Relevance of Koch's Postulates 136  Early Germ Theory 136  Koch's Postulates: A Set of Criteria Used To Establish a Microbe-Disease Connection 137  Challenges to Satisfying Koch's Postulates 138  Easier Said than Done 138	
History and Relevance of Koch's Postulates 136  Early Germ Theory 136  Koch's Postulates: A Set of Criteria Used To Establish a Microbe-Disease Connection 137  Challenges to Satisfying Koch's Postulates 138  Easier Said than Done 138  The First Postulate: Association of the Microbe with Lesions of the Disease 139	
History and Relevance of Koch's Postulates 136  Early Germ Theory 136  Koch's Postulates: A Set of Criteria Used To Establish a Microbe-Disease Connection 137  Challenges to Satisfying Koch's Postulates 138  Easier Said than Done 138	
History and Relevance of Koch's Postulates 136  Early Germ Theory 136  Koch's Postulates: A Set of Criteria Used To Establish a Microbe-Disease Connection 137  Challenges to Satisfying Koch's Postulates 138  Easier Said than Done 138  The First Postulate: Association of the Microbe with Lesions of the Disease 139  The Second Postulate: Isolating the Bacterium in Pure Culture 140  The Third Postulate: Showing that the Isolated Bacterium Causes Disease Experimentally in Humans or Animals 141	
History and Relevance of Koch's Postulates 136  Early Germ Theory 136  Koch's Postulates: A Set of Criteria Used To Establish a Microbe-Disease Connection 137  Challenges to Satisfying Koch's Postulates 138  Easier Said than Done 138  The First Postulate: Association of the Microbe with Lesions of the Disease 139  The Second Postulate: Isolating the Bacterium in Pure Culture 140  The Third Postulate: Showing that the Isolated Bacterium Causes Disease Experimentally in Humans or Animals 141  The Fourth Postulate: Reisolating the Bacterium from the Intentionally Infected Animal 143	
History and Relevance of Koch's Postulates 136  Early Germ Theory 136  Koch's Postulates: A Set of Criteria Used To Establish a Microbe-Disease Connection 137  Challenges to Satisfying Koch's Postulates 138  Easier Said than Done 138  The First Postulate: Association of the Microbe with Lesions of the Disease 139  The Second Postulate: Isolating the Bacterium in Pure Culture 140  The Third Postulate: Showing that the Isolated Bacterium Causes Disease Experimentally in Humans or Animals 141  The Fourth Postulate: Reisolating the Bacterium from the Intentionally Infected Animal 143  Modern Alternatives To Satisfy Koch's Postulates 143	
History and Relevance of Koch's Postulates 136  Early Germ Theory 136  Koch's Postulates: A Set of Criteria Used To Establish a Microbe-Disease Connection 137  Challenges to Satisfying Koch's Postulates 138  Easier Said than Done 138  The First Postulate: Association of the Microbe with Lesions of the Disease 139  The Second Postulate: Isolating the Bacterium in Pure Culture 140  The Third Postulate: Showing that the Isolated Bacterium Causes Disease Experimentally in Humans or Animals 141  The Fourth Postulate: Reisolating the Bacterium from the Intentionally Infected Animal 143  Modern Alternatives To Satisfy Koch's Postulates 143  Detecting the Presence of the Pathogen Only in Diseased Tissues 143	
History and Relevance of Koch's Postulates 136  Early Germ Theory 136  Koch's Postulates: A Set of Criteria Used To Establish a Microbe-Disease Connection 137  Challenges to Satisfying Koch's Postulates 138  Easier Said than Done 138  The First Postulate: Association of the Microbe with Lesions of the Disease 139  The Second Postulate: Isolating the Bacterium in Pure Culture 140  The Third Postulate: Showing that the Isolated Bacterium Causes Disease Experimentally in Humans or Animals 141  The Fourth Postulate: Reisolating the Bacterium from the Intentionally Infected Animal 143  Modern Alternatives To Satisfy Koch's Postulates 143	
History and Relevance of Koch's Postulates 136  Early Germ Theory 136  Koch's Postulates: A Set of Criteria Used To Establish a Microbe-Disease Connection 137  Challenges to Satisfying Koch's Postulates 138  Easier Said than Done 138  The First Postulate: Association of the Microbe with Lesions of the Disease 139  The Second Postulate: Isolating the Bacterium in Pure Culture 140  The Third Postulate: Showing that the Isolated Bacterium Causes Disease Experimentally in Humans or Animals 141  The Fourth Postulate: Reisolating the Bacterium from the Intentionally Infected Animal 143  Modern Alternatives To Satisfy Koch's Postulates 143  Detecting the Presence of the Pathogen Only in Diseased Tissues 143  Eliminate the Pathogen and Prevent or Cure the Disease 144	
History and Relevance of Koch's Postulates 136  Early Germ Theory 136  Koch's Postulates: A Set of Criteria Used To Establish a Microbe-Disease Connection 137  Challenges to Satisfying Koch's Postulates 138  Easier Said than Done 138  The First Postulate: Association of the Microbe with Lesions of the Disease 139  The Second Postulate: Isolating the Bacterium in Pure Culture 140  The Third Postulate: Showing that the Isolated Bacterium Causes Disease Experimentally in Humans or Animals 141  The Fourth Postulate: Reisolating the Bacterium from the Intentionally Infected Animal 143  Modern Alternatives To Satisfy Koch's Postulates 143  Detecting the Presence of the Pathogen Only in Diseased Tissues 143  Eliminate the Pathogen and Prevent or Cure the Disease 144  Comparative Infectious Disease Causation 147  The Microbiota Shift Disease Problem 147  Koch's Postulates and Pathogenic Microbial Communities 147	
History and Relevance of Koch's Postulates 136  Early Germ Theory 136  Koch's Postulates: A Set of Criteria Used To Establish a Microbe-Disease Connection 137  Challenges to Satisfying Koch's Postulates 138  Easier Said than Done 138  The First Postulate: Association of the Microbe with Lesions of the Disease 139  The Second Postulate: Isolating the Bacterium in Pure Culture 140  The Third Postulate: Showing that the Isolated Bacterium Causes Disease Experimentally in Humans or Animals 141  The Fourth Postulate: Reisolating the Bacterium from the Intentionally Infected Animal 143  Modern Alternatives To Satisfy Koch's Postulates 143  Detecting the Presence of the Pathogen Only in Diseased Tissues 143  Eliminate the Pathogen and Prevent or Cure the Disease 144  Comparative Infectious Disease Causation 147  The Microbiota Shift Disease Problem 147	
History and Relevance of Koch's Postulates Early Germ Theory 136 Koch's Postulates: A Set of Criteria Used To Establish a Microbe-Disease Connection 137  Challenges to Satisfying Koch's Postulates 138 Easier Said than Done 138 The First Postulate: Association of the Microbe with Lesions of the Disease 139 The Second Postulate: Isolating the Bacterium in Pure Culture 140 The Third Postulate: Showing that the Isolated Bacterium Causes Disease Experimentally in Humans or Animals 141 The Fourth Postulate: Reisolating the Bacterium from the Intentionally Infected Animal 143  Modern Alternatives To Satisfy Koch's Postulates 143 Detecting the Presence of the Pathogen Only in Diseased Tissues 143 Eliminate the Pathogen and Prevent or Cure the Disease 144 Comparative Infectious Disease Causation 147 The Microbiota Shift Disease Problem 147 Koch's Postulates and Pathogenic Microbial Communities 147 Keystone Pathogens and Microbial Shift Diseases 149  Molecular Koch's Postulates 149	
History and Relevance of Koch's Postulates Early Germ Theory 136 Koch's Postulates: A Set of Criteria Used To Establish a Microbe-Disease Connection 137 Challenges to Satisfying Koch's Postulates 138 Easier Said than Done 138 The First Postulate: Association of the Microbe with Lesions of the Disease 139 The Second Postulate: Isolating the Bacterium in Pure Culture 140 The Third Postulate: Showing that the Isolated Bacterium Causes Disease Experimentally in Humans or Animals 141 The Fourth Postulate: Reisolating the Bacterium from the Intentionally Infected Animal 143 Modern Alternatives To Satisfy Koch's Postulates 143 Detecting the Presence of the Pathogen Only in Diseased Tissues 143 Eliminate the Pathogen and Prevent or Cure the Disease 144 Comparative Infectious Disease Causation 147 The Microbiota Shift Disease Problem 147 Koch's Postulates and Pathogenic Microbial Communities 147 Molecular Koch's Postulates 149 Concepts of Disease 150	
History and Relevance of Koch's Postulates 136 Early Germ Theory 136 Koch's Postulates: A Set of Criteria Used To Establish a Microbe-Disease Connection 137  Challenges to Satisfying Koch's Postulates 138 Easier Said than Done 138 The First Postulate: Association of the Microbe with Lesions of the Disease 139 The Second Postulate: Isolating the Bacterium in Pure Culture 140 The Third Postulate: Showing that the Isolated Bacterium Causes Disease Experimentally in Humans or Animals 141 The Fourth Postulate: Reisolating the Bacterium from the Intentionally Infected Animal 143  Modern Alternatives To Satisfy Koch's Postulates 143 Detecting the Presence of the Pathogen Only in Diseased Tissues 143 Eliminate the Pathogen and Prevent or Cure the Disease 144 Comparative Infectious Disease Causation 147  The Microbiota Shift Disease Problem 147 Koch's Postulates and Pathogenic Microbial Communities 147 Keystone Pathogens and Microbial Shift Diseases 149 Concepts of Disease 150 Varieties of Human-Microbe Interactions 150	
History and Relevance of Koch's Postulates 136 Early Germ Theory 136 Koch's Postulates: A Set of Criteria Used To Establish a Microbe-Disease Connection 137  Challenges to Satisfying Koch's Postulates 138 Easier Said than Done 138 The First Postulate: Association of the Microbe with Lesions of the Disease 139 The Second Postulate: Isolating the Bacterium in Pure Culture 140 The Third Postulate: Showing that the Isolated Bacterium Causes Disease Experimentally in Humans or Animals 141 The Fourth Postulate: Reisolating the Bacterium from the Intentionally Infected Animal 143  Modern Alternatives To Satisfy Koch's Postulates 143 Detecting the Presence of the Pathogen Only in Diseased Tissues 143 Eliminate the Pathogen and Prevent or Cure the Disease 144 Comparative Infectious Disease Causation 147  The Microbiota Shift Disease Problem 147 Koch's Postulates and Pathogenic Microbial Communities 147 Keystone Pathogens and Microbial Shift Diseases 149 Concepts of Disease 150 Varieties of Human-Microbe Interactions 150 Views of the Human-Microbe Interaction 150	
History and Relevance of Koch's Postulates Early Germ Theory 136 Koch's Postulates: A Set of Criteria Used To Establish a Microbe-Disease Connection 137  Challenges to Satisfying Koch's Postulates 138 Easier Said than Done 138 The First Postulate: Association of the Microbe with Lesions of the Disease 139 The Second Postulate: Isolating the Bacterium in Pure Culture 140 The Third Postulate: Showing that the Isolated Bacterium Causes Disease Experimentally in Humans or Animals 141 The Fourth Postulate: Reisolating the Bacterium from the Intentionally Infected Animal 143  Modern Alternatives To Satisfy Koch's Postulates 143 Detecting the Presence of the Pathogen Only in Diseased Tissues 143 Eliminate the Pathogen and Prevent or Cure the Disease 144 Comparative Infectious Disease Causation 147  The Microbiota Shift Disease Problem 147 Koch's Postulates and Pathogenic Microbial Communities 147  Molecular Koch's Postulates 149  Concepts of Disease 150  Varieties of Human-Microbe Interaction 150 Views of the Human-Microbe Interaction 150 Virulence as a Complex Phenomenon 152	
History and Relevance of Koch's Postulates Early Germ Theory 136 Koch's Postulates: A Set of Criteria Used To Establish a Microbe-Disease Connection 137  Challenges to Satisfying Koch's Postulates 138 Easier Said than Done 138 The First Postulate: Association of the Microbe with Lesions of the Disease 139 The Second Postulate: Isolating the Bacterium in Pure Culture 140 The Third Postulate: Showing that the Isolated Bacterium Causes Disease Experimentally in Humans or Animals 141 The Fourth Postulate: Reisolating the Bacterium from the Intentionally Infected Animal 143  Modern Alternatives To Satisfy Koch's Postulates 143 Detecting the Presence of the Pathogen Only in Diseased Tissues 144 Comparative Infectious Disease Causation 147  The Microbiota Shift Disease Problem 147 Koch's Postulates and Pathogenic Microbial Communities 147 Keystone Pathogens and Microbial Shift Diseases 149  Concepts of Disease 150 Varieties of Human-Microbe Interactions 150 Views of the Human-Microbe Interaction 150 Virulence as a Complex Phenomenon 152 Selected Readings 152	
History and Relevance of Koch's Postulates Early Germ Theory 136 Koch's Postulates: A Set of Criteria Used To Establish a Microbe-Disease Connection 137  Challenges to Satisfying Koch's Postulates 138 Easier Said than Done 138 The First Postulate: Association of the Microbe with Lesions of the Disease 139 The Second Postulate: Isolating the Bacterium in Pure Culture 140 The Third Postulate: Showing that the Isolated Bacterium Causes Disease Experimentally in Humans or Animals 141 The Fourth Postulate: Reisolating the Bacterium from the Intentionally Infected Animal 143  Modern Alternatives To Satisfy Koch's Postulates 143 Detecting the Presence of the Pathogen Only in Diseased Tissues 143 Eliminate the Pathogen and Prevent or Cure the Disease 144 Comparative Infectious Disease Causation 147  The Microbiota Shift Disease Problem 147 Koch's Postulates and Pathogenic Microbial Communities 147 Keystone Pathogens and Microbial Shift Diseases 149  Concepts of Disease 150 Varieties of Human-Microbe Interaction 150 Virulence as a Complex Phenomenon 152 Selected Readings 152	

CHAPTER 7 Mechanisms of Genetic Modification and Exchange: Role in
Pathogen Evolution 15
Adapt or Perish 158 Acquiring New Virulence Traits by Horizontal Gene Transfer 158
Mechanisms of Genetic Change and Diversification 158 Spontaneous Mutation 158 Phase Variation 159 Antigenic Variation 161
Horizontal Gene Transfer: Mobile Genetic Elements  Natural Transformation 162  Conjugation: Plasmids and Transposons 165  Phage Transduction 171
Control of Horizontal Gene Transfer 171  Toxin-Antitoxin Systems—Retaining the Goods 171  Restriction-Modification Systems—Bacterial Innate Immunity from Foreign DNA 173  CRISPR-Cas Systems—Bacterial Adaptive Immunity from Foreign DNA 173  Type 6 Secretion Systems—Bacterial Defense Against Conjugation 174
Pathogenicity Islands and Pathogen Evolution Properties of Pathogenicity Islands Pathogen Evolution in Quantum Leaps 174 Pathogen Evolution in Quantum Leaps 177
Selected Readings 178
Questions 179
Solving Problems in Bacterial Pathogenesis 179
CHAPTER 8 Identification of Virulence Factors: Measuring Infectivity and Virulence 18
How Does One Experimentally Measure Virulence and Satisfy Koch's Postulates? 183
Animal Models of Infection 184  Human Volunteers 184  Nonhuman Animal Models 186
Measuring Bacterial Infection in Animal Models188Ethical Considerations188Animal Model Basics188Survival Curve Analysis and Biophotonic Imaging189ID <sub>50</sub> and LD <sub>50</sub> Values190Competition Assays191
Tissue Culture and Organ Culture Models 192 Tissue Culture Models 192 Gentamicin Protection Assay for Cell Adhesion and Invasion 193 Plaque Assay for Intracellular Survival and Cell-to-Cell Spread 195 Fluorescence Microscopy Techniques for Assessing Effects of Pathogens on Host Cells 196 Organ Culture Models 196
The Continuing Need for Reliable and Plentiful Information about Disease Pathology 197
Selected Readings 198
Questions 199
Solving Problems in Bacterial Pathogenesis 200
CHAPTER 9 Identification of Virulence Factors: Molecular Approaches for Bacterial Factors 20
Finding a Needle in a Haystack 204
Biochemical Approaches 204 Isolation and Purification of Toxic Factors 204
Molecular Genetic Approaches 208
Screening Using Recombinant Genes 208 Reporter Fusions 208

Genome-wide Sequencing Approaches for Identifying Virulence Genes Tn-Seq Technology to Identify In Vivo-Expressed Genes 214 RNA-Seq Technology to Identify In Vivo-Expressed Genes 216 Comparative Genomic Sequence Analysis for Identifying Virulence Genes 217	
Proteomics Approaches for Identifying Virulence Factors  Protein Microarrays (Proteoarrays) 218  In Vivo-Induced Antigen Technology (IVIAT) 218	
The Importance of Understanding Bacterial Physiology 219	
Selected Readings 222	
Questions 223	
Solving Problems in Bacterial Pathogenesis 223	
HAPTER 10 Identification of Virulence Factors: Molecular Approaches for Host Factors	226
Comparative Approaches to Identify Host Factors Required for Infection  Transgenic Animal Models 228  In vivo Imaging of Animals during Infection 231  Systems Genetics: Comparative Genomics of the Host Response 231	
Screening Approaches to Identify Host Factors Required for Infection 235  Genome-Wide Screening 235	
Host Response Profiling to Identify Host Factors Required for Infection  Transcriptomics 240  Proteomics 243  Metabolomics 246	
The Promise and the Caution 247	
Selected Readings 248	
Questions 249	
Solving Problems in Bacterial Pathogenesis 249	
HAPTER 11 Bacterial Strategies for Colonization and Survival in the Host	254
HAPTER 11 Bacterial Strategies for Colonization and Survival in the Host What Does Not Kill You Makes You Stronger—Or, a Better Pathogen 255	254
What Does Not Kill You Makes You Stronger—Or, a Better Pathogen  255  Preinfection 258  Survival in the External Environment 258  Biofilms 258	254
What Does Not Kill You Makes You Stronger—Or, a Better Pathogen  Preinfection 258  Survival in the External Environment 258  Biofilms 258  Motility and Chemotaxis 260	254
What Does Not Kill You Makes You Stronger—Or, a Better Pathogen  Preinfection 258  Survival in the External Environment 258  Biofilms 258  Motility and Chemotaxis 260	254
What Does Not Kill You Makes You Stronger—Or, a Better Pathogen  258  Survival in the External Environment 258  Biofilms 258  Motility and Chemotaxis 260  Colonization of Host Surfaces 263  Penetrating Intact Skin 263  Penetrating the Mucin Layer 263  Evading the Host's Innate Immunity 264  Nutrient and Iron Acquisition Mechanisms 265	254
What Does Not Kill You Makes You Stronger—Or, a Better Pathogen  Preinfection 258 Survival in the External Environment 258 Biofilms 258 Motility and Chemotaxis 260  Colonization of Host Surfaces 263 Penetrating Intact Skin 263 Penetrating the Mucin Layer 263 Evading the Host's Innate Immunity 264 Nutrient and Iron Acquisition Mechanisms 265 Adherence 268  Evading the Host Immune Response 275 Avoiding Complement and Phagocytosis 277 Invasion and Uptake by Host Cells 280 Surviving Phagocytosis 281 Cell-to-Cell Spread 286 Tissue Penetration and Dissemination 288	254
What Does Not Kill You Makes You Stronger—Or, a Better Pathogen  258  Survival in the External Environment 258  Biofilms 258  Motility and Chemotaxis 260  Colonization of Host Surfaces 263  Penetrating Intact Skin 263  Penetrating the Mucin Layer 263  Evading the Host's Innate Immunity 264  Nutrient and Iron Acquisition Mechanisms 265  Adherence 268  Evading the Host Immune Response 275  Avoiding Complement and Phagocytosis 277  Invasion and Uptake by Host Cells 280  Surviving Phagocytosis 281  Cell-to-Cell Spread 286  Tissue Penetration and Dissemination 288  Beyond Virulence Factors 288	254
What Does Not Kill You Makes You Stronger—Or, a Better Pathogen  Preinfection 258  Survival in the External Environment 258  Biofilms 258  Motility and Chemotaxis 260  Colonization of Host Surfaces 263  Penetrating Intact Skin 263  Penetrating the Mucin Layer 263  Evading the Host's Innate Immunity 264  Nutrient and Iron Acquisition Mechanisms 265  Adherence 268  Evading the Host Immune Response 275  Avoiding Complement and Phagocytosis 277  Invasion and Uptake by Host Cells 280  Surviving Phagocytosis 281  Cell-to-Cell Spread 286  Tissue Penetration and Dissemination 288  Beyond Virulence Factors 288  Selected Readings 289	254

CHAPTER 12 Toxins and Other Toxic Virulence Factors	294
Bacterial Toxins 295 Transparent Mechanisms, Exciting Applications, Mysterious Purposes 295 Toxin Characteristics and Nomenclature 300 Nonprotein Toxins 302 Peptide and Protein Exotoxins 304 Toxic Effector Proteins of Specialized Secretion Systems 312	
Examples of Toxin-Mediated Diseases 313  Diphtheria Toxin 313  Clostridial Neurotoxins 319  Cholera Toxin 323	
Toxin-Based Therapeutics and Research Tools 327 Immunotoxins 327	
Selected Readings 329	
Questions 330	
Solving Problems in Bacterial Pathogenesis 331	
CHAPTER 13 Delivery of Virulence Factors	334
Bacterial Secretion Systems and Virulence 335	
Common Secretory Systems 336  The General Secretory (Sec) System 336  The Accessory Secretory (Sec) System 336  The Cotranslational Signal-Recognition Particle (SRP) System 336  The Twin-Arginine Transport (TAT) System 337	
Secretion Systems Specific to Gram-Negative Bacteria 338 Sec-Dependent Secretion Systems 338 Sec-Independent Secretion Systems 341	
Specialized Secretion Systems Specific to Gram-Positive Bacteria 350 General Secretory Transporter Systems in Gram-Positive Bacteria 350 Cytolysin-Mediated Translocation (CMT) in <i>S. pyogenes</i> (Group A Strep) 351 Type 7 Secretion System (T7SS) 352	
Selected Readings 353	
Questions 354	
Solving Problems in Bacterial Pathogenesis 355	
borving riobicino in bacteriai ratinogenesis obo	
CHAPTER 14 Virulence Regulation	360
Virulence Gene Regulation 361	
Mechanisms of Regulation 361  Operons, Regulons, and Global Regulators 362 Activators and Repressors 362 Two-Component Regulatory Systems 364 Sigma Factors 368 Transcriptional Terminators and Antiterminators 369 Regulation of Translation Initiation 372 Regulatory Small RNAs 372 Bacterial Chromatin 375	
Responding to Environmental Signals 376  Phase Variation and Bistable Switches 376  Hypermutability, Intragenomic Recombination, and Positive Selection 377  Coordinate Virulence Regulation 377  Quorum Sensing 378  Chemotaxis 387  Selected Readings 389  Questions 389	
Questions 389	

Special Global Perspective Problems: Integrating Concepts in Pathogenesis 39	5
HAPTER 15 Antimicrobial Compounds and Their Targets	400
Antimicrobial Compounds: The Safety Net of Modern Medicine The Importance of Antimicrobial Compounds 401 Avoiding, Reducing, and Preventing Exposure 402 Killing versus Inhibiting Growth 404 Tests Used To Assess Antibiotics 404	
Antiseptics and Disinfectants 405	
Antibiotics 407	
Characteristics of Antibiotics 407 The Process of Antibiotic Discovery 409 The Economics of Antibiotic Discovery 413	
Mechanisms of Antibiotic Action 416 Targets of Antibiotic Action 416 Cell Wall Synthesis Inhibitors 417 Protein Synthesis Inhibitors 422 Antibiotics That Target DNA and RNA Synthesis 425 Inhibitors of Tetrahydrofolate Biosynthesis 429 The Newest Antibiotics 429 The Newest Antibiotic Targets 430 Strategies for Enhancing Antibiotic Efficacy 431	
The Continuing Challenge 432	
Selected Readings 433	
Questions 434	
Solving Problems in Bacterial Pathogenesis 435	
HAPTER 16 Antibiotic Resistance	436
	430
How Did We Get to Where We Are? 438	
And Now the Really Scary Part 440  Emergence and Challenge of Multidrug Resistance (MDR) 440  Multiple Resistance and Genetic Linkage 441  Next-Generation MDR Pathogens: The "Superbugs"! 441	
Mechanisms of Antibiotic Resistance 444  Overview of Resistance Mechanisms 444  Resistance to Antiseptics and Disinfectants 444  Limiting Access of the Antibiotic 445  Enzymatic Inactivation of the Antibiotic 446  Modification or Protection of the Antibiotic Target 451	
Failure to Activate an Antibiotic 453 Regulation of Resistance Genes 454  Antibiotic Toloropeo and Possister Colla 457	
Antibiotic Tolerance and Persister Cells Antibiotic Tolerance 457 Persistence 459 Toxin-Antitoxin Systems 459	
Horizontal Gene Transfer (HGT) of Resistance Genes 461	
Propagating and Maintaining Antibiotic Resistance through Selective Pressure and Fitness 463	Changes in
Will We Return to the Pre-Antibiotic Era? 464 Returning to Status Quo or Moving Forward? 464 The Hunt for Alternative Approaches to Antibiotics 466	

390

Solving Problems in Bacterial Pathogenesis

	Selected Readings 468	
	Questions 469	
	Solving Problems in Bacterial Pathogenesis 470	
	Special Global Perspective Problems: Integrating Concepts in Pathogenesis 470	
CI	HAPTER 17 Vaccination: A Critical Component of the Modern Medical Armamentarium	476
	Vaccines: A Major Health Care Bargain 477	
	What Makes an Ideal Vaccine? 479	
	Immunization Programs480Barriers to Implementation and Success of Immunization Programs483The Antivaccination Movement484	
	Vaccine Success Stories 485 Subunit Vaccines 485 Conjugate Vaccines 490	
	Vaccine "Less-than-Success" Stories 492	
	A New Age of Vaccine Development: Making Vaccines Better Approaches to Enhancing Immunogenicity 494 Adjuvants 494 Programming Adaptive Immunity 496 Targeting Mucosal Immunity 500	
	Storage of Vaccines—Strategies to Increase Shelf Life 504	
	Passive Immunization 504	
	Selected Readings 505	
	Questions 505	
	Solving Problems in Bacterial Pathogenesis 508	
	Special Global Perspective Problems: Integrating Concepts in Pathogenesis 510	
CI	HAPTER 18 The Gram-Positive Opportunistic Pathogens	514
	What Is an Opportunist? 515 Characteristics of Gram-Positive Opportunists 516	
	Notable Gram-Positive Opportunists 516  Staphylococcus aureus—Commensal Ready for a Fight 516  Staphylococcus epidermidis—Accidental Pathogen 524  Streptococcus pneumoniae—"Captain of All the Men of Death" 527  Clostridium difficile—True Opportunist 534	
	Other Gram-Positive Opportunists 542	
	Selected Readings 543	
	Questions 544	
	Solving Problems in Bacterial Pathogenesis 544	
Ch	HAPTER 19 The Gram-Negative Opportunistic Pathogens	548
	Jumping Over the (Cell) Wall: Gram-Negative Bacteria Can Be Opportunistic Pathogens Too! 549 Common Traits of Gram-Negative Opportunists 549	
	The Dark Side of Some Residents of the Human Body The Ever-Changing Face of <i>E. coli</i> 550 Klebsiella pneumoniae Nosocomial Infections 554 Bacteroides fragilis—The Bad Sheep of the Family 555 Porphyromonas gingivalis—A Keystone Pathogen 557	
	Environmental Inhabitants Weigh in as Opportunists 558  Pseudomonas aeruginosa—A Versatile Opportunist of the Highest Order 558  Burkholderia cepacia Complex—P. aeruginosa's Evil Twin 565	

574

Acinetobacter baumannii—A Deadly Threat Emerges from the Iraq War 565

Don't Forget the Arthropods! 567

Ehrlichia spp. 567

Selected Readings 568

Questions 569

Solving Problems in Bacterial Pathogenesis 569

Special Global Perspective Problems: Integrating Concepts in Pathogenesis 570

## CHAPTER 20 The Changing Roles of Microbiologists in an Age of Bioterrorism and Emerging Diseases

When Microbiologists Are Called to the Front Line 575

Tracking Down a Bioterrorist 576

Unintentional or Deliberate? 577

Timing 579

Tracing the Source 579

Lessons Learned 579

The "Top Four" Bioterror Agents 582

Bacillus anthracis Spores 582

Smallpox 583

Yersinia pestis 583

Botulinum Neurotoxin 584

What If Bioterrorists Hit Us with Something Completely New? 585

Biosecurity in a Complex, Dynamic, and Ever-Changing World 585

Food Safety and Biosecurity 586

The Case for Food Irradiation 587

The Future of Biosecurity 589

Selected Readings 589

Questions 590

Solving Problems in Bacterial Pathogenesis 591

Glossary 593 Index 661