Contents

Preface xvii
Acknowledgements xxi
About the Authors xxiii

1 Infections of Populations: History and Epidemiology  2

Introduction to Viral Pathogenesis  3

A Brief History of Viral Pathogenesis  4
The Relationships between Microbes and the Diseases They Cause  4
The First Human Viruses Identified and the Role of Serendipity  4
New Techniques Led to the Study of Viruses as Causes of Disease  7

Viral Epidemics in History  8
Epidemics Shaped History: the 1793 Yellow Fever Epidemic in Philadelphia  8
Tracking Epidemics by Sequencing: West Nile Virus Spread to the Western Hemisphere  9
The Economic Toll of Viral Epidemics in Agricultural Organisms  9
Population Density and World Travel as Accelerators of Viral Transmission  10
Zoonotic Infections and Viral Epidemics  10

Epidemiology  10
Fundamental Concepts  11
Tools of Epidemiology  13
Surveillance  15

Parameters That Govern the Ability of a Virus To Infect a Population  16
Environment  16
Host Factors  19

Perspectives  22
References  23
2 Barriers to Infection 24

Introduction 25

An Overview of Infection and Immunity 25
  A Game of Chess Played by Age-Old Masters 25
  Initiating an Infection 27

Successful Infections Must Modulate or Bypass Host Defenses 29
  Skin 29
  Respiratory Tract 31
  Alimentary Tract 33
  Urogenital Tract 35
  Eyes 35

Viral Tropism 36
  Accessibility of Viral Receptors 36
  Host Cell Proteins That Regulate the Infectious Cycle 36

Spread throughout the Host 39
  Hematogenous Spread 40
  Neural Spread 42

Organ Invasion 45
  Entry into Organs with Sinusoids 45
  Entry into Organs That Lack Sinusoids 46
  Organs with Dense Basement Membranes 46
  Skin 47
  The Fetus 47

Shedding of Virus Particles 47
  Respiratory Secretions 48
  Saliva 48
  Feces 49
  Blood 49
  Urine 49
  Semen 49
  Milk 49
  Skin Lesions 49

Perspectives 50

References 50

3 The Early Host Response: Cell-Autonomous and Innate Immunity 52

Introduction 53

The First Critical Moments of Infection: How Do Individual Cells Detect a Virus Infection? 54
  Cell Signaling Induced by Receptor Engagement 55
  Receptor-Mediated Recognition of Microbe-Associated Molecular Patterns 55
  Cellular Changes That Occur Following Viral Infection 60
Adaptive Immunity and the Establishment of Memory  98

Introduction  99

Attributes of the Host Response  99
  Speed  99
  Diversity and Specificity  100
  Memory  100
  Self-Control  100

Lymphocyte Development, Diversity, and Activation  100
  All Blood Cells Derive from a Common Hematopoietic Stem Cell  100
  The Two Arms of Adaptive Immunity  101
  The Major Effectors of the Adaptive Response: B Cells and T Cells  101
  Diverse Receptors Impart Antigen Specificity to B and T Cells  107

Events at the Site of Infection Set the Stage for the Adaptive Response  108
  Acquisition of Viral Proteins by Professional Antigen-Presenting Cells Enables Production of Proinflammatory Cytokines and Establishment of Inflammation  108
  Antigen-Presenting Cells Leave the Site of Infection and Migrate to Lymph Nodes  111

Antigen Processing and Presentation  114
  Professional Antigen-Presenting Cells Induce Activation via Costimulation  114
  Presentation of Antigens by Class I and Class II MHC Proteins  115
  Lymphocyte Activation Triggers Massive Cell Proliferation  119

The Cell-Mediated Response  119
  CTLs Lyse Virus-Infected Cells  119
  Control of CTL Proliferation  122
  Noncytolytic Control of Infection by T Cells  122
  Rashes and Poxes  122
The Humoral (Antibody) Response 122
  Antibodies Are Made by Plasma Cells 122
  Types and Functions of Antibodies 125
  Virus Neutralization by Antibodies 125
  Antibody-Dependent Cell-Mediated Cytotoxicity:
    Specific Killing by Nonspecific Cells 127

Immunological Memory 128
Perspectives 130
References 130

5 Mechanisms of Pathogenesis 134

Introduction 135
Animal Models of Human Diseases 135
Patterns of Infection 136
  Incubation Periods 137
  Mathematics of Growth Correlate with Patterns of Infection 138
  Acute Infections 139
  Persistent Infections 143
  Latent Infections 150
  “Slow” Infections 157
  Abortive Infections 157
  Transforming Infections 157

Viral Virulence 158
  Measuring Viral Virulence 158
  Alteration of Viral Virulence 159
  Viral Virulence Genes 160

Pathogenesis 164
  Infected Cell Lysis 164
  Immunopathology 164
  Immunosuppression Induced by Viral Infection 168
  Oncogenesis 169
  Molecular Mimicry 170

Perspectives 172
References 172

6 Cellular Transformation and Oncogenesis 174

Introduction 175
  Properties of Transformed Cells 175
  Control of Cell Proliferation 178

Oncogenic Viruses 182
  Discovery of Oncogenic Viruses 182
  Viral Genetic Information in Transformed Cells 187
  The Origin and Nature of Viral Transforming Genes 189
  Functions of Viral Transforming Proteins 192
Activation of Cellular Signal Transduction Pathways by Viral Transforming Proteins 192
Viral Signaling Molecules Acquired from the Cell 192
Alteration of the Production or Activity of Cellular Signal Transduction Proteins 195

Disruption of Cell Cycle Control Pathways by Viral Transforming Proteins 201
Abrogation of Restriction Point Control Exerted by the Rb Protein 201
Production of Virus-Specific Cyclins 204
Inactivation of Cyclin-Dependent Kinase Inhibitors 204

Transformed Cells Must Grow and Survive 206
Mechanisms That Permit Survival of Transformed Cells 206

Tumorigenesis Requires Additional Changes in the Properties of Transformed Cells 209
Inhibition of Immune Defenses 210

Other Mechanisms of Transformation and Oncogenesis by Human Tumor Viruses 210
Nontransducing Oncogenic Retroviruses: Tumorigenesis with Very Long Latency 210
Oncogenesis by Hepatitis Viruses 213

Perspectives 214
References 214

Human Immunodeficiency Virus Pathogenesis 218
Introduction 219
Worldwide Impact of AIDS 219

HIV is a Lentivirus 219
Discovery and Characterization 219
Distinctive Features of the HIV Reproduction Cycle and the Functions of Auxiliary Proteins 222
The Viral Capsid Counters Intrinsic Defense Mechanisms 230

Cellular Targets 230
Routes of Transmission 231
Modes of Transmission 231
Mechanics of Spread 233

The Course of Infection 234
The Acute Phase 234
The Asymptomatic Phase 235
The Symptomatic Phase and AIDS 236
Variability of Response to Infection 236

Origins of Cellular Immune Dysfunction 237
CD4+ T Lymphocytes 237
Cytotoxic T Lymphocytes 238
Monocytes and Macrophages 238
B Cells 238
Natural Killer Cells 238
Autoimmunity 238

Immune Responses to HIV 238
Innate Response 238
The Cell-Mediated Response 238
Humoral Responses 239
Summary: the Critical Balance 240

Dynamics of HIV-1 Reproduction in AIDS Patients 241

Effects of HIV on Different Tissues and Organ Systems 242
Lymphoid Organs 242
The Nervous System 244
The Gastrointestinal System 245
Other Organs and Tissues 246

HIV and Cancer 246
Kaposi's Sarcoma 246
B Cell Lymphomas 248
Anogenital Carcinomas 248

Prospects for Treatment and Prevention 248
Antiviral Drugs 248
Confronting the Problems of Persistence and Latency 249
Gene Therapy Approaches 249
Immune System-Based Therapies 250
Antiviral Drug Prophylaxis 250

Perspectives 250
References 252

Vaccines 254
Introduction 255

The Origins of Vaccination 255
Smallpox: a Historical Perspective 255
Large-Scale Vaccination Programs Can Be Dramatically Effective 257

Vaccine Basics 260
Immunization Can Be Active or Passive 260
Active Vaccination Strategies Stimulate Immune Memory 261
The Fundamental Challenge 264

The Science and Art of Making Vaccines 265
Inactivated or "Killed" Virus Vaccines 265
Attenuated Virus Vaccines 269
Subunit Vaccines 270
Recombinant DNA Approaches to Subunit Vaccines 272
Virus-Like Particles 272
DNA Vaccines 273
Attenuated Viral Vectors and Foreign Gene Expression 274
Vaccine Technology: Delivery and Improving Antigenicity  275
  Adjuvants Stimulate an Immune Response  275
  Delivery and Formulation  276
  Immunotherapy  276

The Quest for an AIDS Vaccine  277
  Formidable Challenges and Promising Leads  277

Perspectives  279
References  279

9 Antiviral Drugs  282

Introduction  283
  Historical Perspective  283

Discovering Antiviral Compounds  284
  The Lexicon of Antiviral Discovery  284
  Screening for Antiviral Compounds  285
  Computational Approaches to Drug Discovery  287
  The Difference between “R” and “D”  288

Examples of Some Antiviral Drugs  293
  Approved Inhibitors of Viral Nucleic Acid Synthesis  293
  Approved Drugs That Are Not Inhibitors of Nucleic Acid Synthesis  298

Expanding Target Options for Antiviral Drug Development  300
  Entry and Uncoating Inhibitors  300
  Viral Regulatory Proteins  300
  Regulatory RNA Molecules  300
  Proteases and Nucleic Acid Synthesis and Processing Enzymes  301

Two Success Stories: Human Immunodeficiency and Hepatitis C Viruses  301
  Inhibitors of Human Immunodeficiency Virus and Hepatitis C Virus Polymerses  303
  Human Immunodeficiency Virus and Hepatitis C Virus Protease Inhibitors  306
  Human Immunodeficiency Virus Integrate Inhibitors  306
  Hepatitis C Virus Multifunctional Protein NS5A  308
  Inhibitors of Human Immunodeficiency Virus Fusion and Entry  309

Drug Resistance  309
  Combination Therapy  310
  Challenges Remaining  312

Perspectives  312
References  314

10 Evolution  316

Virus Evolution  317
Classic Theory of Host-Parasite Interactions  317
How Do Virus Populations Evolve? 318
Two General Survival Strategies Can Be Distinguished 319
Large Numbers of Viral Progeny and Mutants Are Produced in Infected Cells 319
The Quasispecies Concept 321
Sequence Conservation in Changing Genomes 321
Genetic Shift and Genetic Drift 324
Fundamental Properties of Viruses That Constrain and Drive Evolution 326
The Origin of Viruses 327
Host-Virus Relationships Drive Evolution 333
DNA Virus Relationships 333
RNA Virus Relationships 333
The Protopvirus Hypothesis for Retroviruses 335
Lessons from Paleovirology 335
Endogenous Retroviruses 336
DNA Fossils Derived from Other RNA Viral Genomes 337
Endogenous Sequences from DNA Viruses 337
The Host-Virus “Arms Race” 337
Perspectives 339
References 340
Emergence 342
The Spectrum of Host-Virus Interactions 343
Stable Interactions 344
The Evolving Host-Virus Interaction 345
The Dead-End Interaction 345
Common Sources of Animal-to-Human Transmission 347
The Resistant Host 348
Encountering New Hosts: Ecological Parameters 348
Successful Encounters Require Access to Susceptible and Permissive Cells 349
Population Density, Age, and Health Are Important Factors 350
Experimental Analysis of Host-Virus Interactions 350
Learning from Accidental Infections 351
Expanding Viral Niches: Some Well-Documented Examples 351
Poliomyelitis: Unexpected Consequences of Modern Sanitation 351
Smallpox and Measles: Exploration and Colonization 352
Notable Zoonoses 352
Hantavirus Pulmonary Syndrome: Changing Climate and Animal Populations 352
Severe Acute and Middle East Respiratory Syndromes (SARS and MERS): Two New Zoonotic Coronavirus Infections 352
Acquired Immunodeficiency Syndrome (AIDS): Pandemic from a Zoonotic Infection 353
Host Range Can Be Expanded by Mutation, Recombination, or Reassortment 354
Canine Parvoviruses: Cat-to-Dog Host Range Change by Two Mutations 354
Influenza Epidemics and Pandemics: Escaping the Immune Response by Reassortment 354
New Technologies Uncover Hitherto Unrecognized Viruses 355
Hepatitis Viruses in the Human Blood Supply 357
A Revolution in Virus Discovery 357
Perceptions and Possibilities 358
Virus Names Can Be Misleading 359
All Viruses Are Important 359
What Next? 359
Can We Predict the Next Viral Pandemic? 359
Emerging Viral Infections Illuminate Immediate Problems and Issues 360
Humans Constantly Provide New Venues for Infection 360
Preventing Emerging Virus Infections 361
Perspectives 361
References 362

12 Unusual Infectious Agents 364
Introduction 365
Viroids 365
Replication 365
Sequence Diversity 366
Movement 366
Pathogenesis 368
Satellites 368
Replication 369
Pathogenesis 369
Virophages or Satellites? 369
Hepatitis Delta Satellite Virus 370
Prions and Transmissible Spongiform Encephalopathies 371
Scrapie 371
Physical Nature of the Scrapie Agent 371
Human TSEs 371
Hallmarks of TSE Pathogenesis 372
Prions and the prnp Gene 372
Prion Strains 374
Bovine Spongiform Encephalopathy 374
Chronic Wasting Disease 376
Treatment of Prion Diseases 377
Perspectives 377
References 378

APPENDIX  Diseases, Epidemiology, and Disease Mechanisms of Selected Animal Viruses Discussed in This Book 379
Glossary 407
Index 413