

Contents

Preface xiii

Acknowledgments xvii

1 Infection of a Susceptible Host 2

Introduction 3

A Brief History of Viral Pathogenesis 3

Microbes as Infectious Agents 3

The First Human Viruses 4

The Golden Age of Viral Pathogenesis 5

The New Millennium and Viral Pathogenesis 6

Infection Basics 6

A Series of Unfortunate Events 6

Initiating an Infection 6

Viral Entry 9

Successful Infections Must Modulate or Bypass Host Defenses 14

Viral Spread 16

Organ Invasion 21

Tropism 23

Perspectives 26

References 26

2 Infection of Populations 28

Introduction 29

Principles of Viral Pathogenesis 29

Statistics 30

Epidemiology 31

Shedding of Virions 34

Transmission of Viral Infection	36
Geography and Season	37
Viral Virulence	40
Host Susceptibility to Viral Disease	48
Other Determinants of Susceptibility	48

Perspectives 50

References 51

3 Virus Offense Meets Host Defense: Early Actions 52

Introduction 53

Primary Physical and Chemical Defenses	54
The First Critical Moments of Infection	54

Intrinsic Cellular Defenses 55

How Do Individual Cells Detect Foreign Invaders?	55
Receptor-Mediated Recognition of Pathogen-Associated Molecules	55
Cytokines, the Primary Output of Intrinsic Cell Defense	59
Interferons, Cytokines of Early Warning and Action	61
Apoptosis (Programmed Cell Death)	72

The Hostile Cytoplasm: Other Intrinsic Defenses 78

Autophagy	78
Epigenetic Silencing	78
RNA Silencing	78
Cytosine Deamination (ApoBec, [Apolipoprotein B Editing Complex])	79
Trim (Tripartite Interaction Motif) Proteins	79

Perspectives 80

References 82

4 Immune Defenses 86

Introduction 87

Innate and Adaptive Immune Defenses	87
-------------------------------------	----

The Innate Immune Response 89

General Features	89
Sentinel Cells	89
Natural Killer Cells	91
Complement	93
The Inflammatory Response	97

The Adaptive Immune Response 99

General Features	99
Cells of the Adaptive Immune System	101
Adaptive Immunity: the Action of Lymphocytes That Carry Distinct Antigen Receptors	102
Antigen Presentation and Activation of Immune Cells	107
The Cell-Mediated Adaptive Response	110
The Antibody Response	116
The Immune System and the Brain	120

Immunopathology: Too Much of a Good Thing 121

Immunopathological Lesions	121
Viral Infection-Induced Immunosuppression	124
Systemic Inflammatory Response Syndrome	124

- Autoimmune Diseases 124
- Heterologous T-Cell Immunity 125
- Superantigens “Short-Circuit” the Immune System 126
- Mechanisms Mediated by Free Radicals 127

Perspectives 127**References 131****5 Patterns of Infection 134****Introduction 135****Life Cycles and Host Defenses 135****Mathematics of Growth Correlate with Patterns of Infection 136****Acute Infections 138**

- Definition and Requirements 138
- Acute Infections Tend To Be Efficiently Contained and Cleared 138
- Antigenic Variation Provides a Selective Advantage in Acute Infections 140
- Acute Infections Present Common Public Health Problems 141

Persistent Infections 142

- Definition and Requirements 142
- An Ineffective Intrinsic or Innate Immune Response Can Promote a Persistent Infection 143
- Modulation of the Adaptive Immune Response Perpetuates a Persistent Infection 143
- Persistent Infections May Be Established in Tissues with Reduced Immune Surveillance 147
- Persistent Infections May Occur When Cells of the Immune System Are Infected 147

Two Viruses That Cause Persistent Infections 148

- Measles Virus 148
- Lymphocytic Choriomeningitis Virus 149

Latent Infections 150

- General Properties 150
- Herpes Simplex Virus 150
- Epstein-Barr Virus 156

Slow Infections: Sigurdsson’s Legacy 160**Abortive Infections 160****Transforming Infections 161****Perspectives 161****References 162****6 Human Immunodeficiency Virus Pathogenesis 164****Introduction 165**

- Worldwide Scope of the Problem 165

HIV Is a Lentivirus 166

- Discovery and Characterization 166
- Distinctive Features of the HIV Replication Cycle and the Roles of Auxiliary Proteins 169

Cellular Targets 176

Routes of Transmission 177

Sources of Virus Infection 177

Modes of Transmission 177

Mechanics of Spread 179

The Course of Infection 180

Patterns of Virus Appearance and Immune Cell

Indicators of Infection 180

Variability of Response to Infection 181

Origins of Cellular Immune Dysfunction 182

CD4⁺ T Lymphocytes 182

Cytotoxic T Lymphocytes 182

Monocytes and Macrophages 182

B Cells 183

Natural Killer Cells 183

Autoimmunity 183

Immune Responses to HIV 184

Humoral Responses 184

The Cellular Immune Response 186

Summary: the Critical Balance 186

Dynamics of HIV-1 Replication in AIDS Patients 186

Effects of HIV on Different Tissues and Organ Systems 188

Lymphoid Organs 188

The Nervous System 188

The Gastrointestinal System 190

Other Organ Systems 190

HIV and Cancer 191

Kaposi's Sarcoma 191

B-Cell Lymphomas 193

Anogenital Carcinomas 194

Prospects for Treatment and Prevention 194

Antiviral Drugs and Therapies 194

Highly Active Antiretroviral Therapy 194

Prophylactic Vaccine Development To Prevent Infection 195

Perspectives 196

References 197

7 Transformation and Oncogenesis 200

Introduction 201

Properties of Transformed Cells 202

Control of Cell Proliferation 204

Oncogenic Viruses 207

Discovery of Oncogenic Viruses 208

Viral Genetic Information in Transformed Cells 212

The Origin and Nature of Viral Transforming Genes 217

Functions of Viral Transforming Proteins 218

Activation of Cellular Signal Transduction Pathways by Viral Oncogene Products 221

Viral Mimics of Cellular Signaling Molecules 221

Alteration of the Production or Activity of Cellular Signal Transduction

Proteins 224

Disruption of Cell Cycle Control Pathways by Viral Oncogene Products 230

Abrogation of Restriction Point Control Exerted by the Rb Protein 230

Production of Virus-Specific Cyclins 233

Inactivation of Cyclin-Dependent Kinase Inhibitors 233

Transformed Cells Must Also Grow and Survive 234

Integration of Mitogenic and Growth-Promoting Signals 234

Mechanisms That Permit Survival of Transformed Cells 234

Tumorigenesis Requires Additional Changes in the Properties of Transformed Cells 239

Inhibition of Immune Defenses 240

Other Mechanisms of Transformation and Oncogenesis by Human Tumor Viruses 241

Nontransducing, Complex Oncogenic Retroviruses:

Tumorigenesis with Very Long Latency 241

Oncogenesis by Hepatitis Viruses 242

Perspectives 246**References 247****8 Vaccines 250****Introduction 251****The Historical Origins of Vaccination 251**

Smallpox: a Historical Perspective 251

Large-Scale Vaccination Programs Can Be Dramatically Effective 253

Vaccine Basics 256

Immunization Can Be Active or Passive 256

Active Vaccines Stimulate Immune Memory 256

The Fundamental Challenge 260

The Science and Art of Making Vaccines 261

Basic Approaches 261

Vaccine Technology 271

Most Killed and Subunit Vaccines Rely on Adjuvants To Stimulate an Immune Response 271

Delivery 272

Immunotherapy 273

The Quest for an AIDS Vaccine 274

Formidable Challenges 274

The Central Issues 275

Perspectives 275**References 276****9 Antiviral Drugs 278****Introduction 279**

Paradox? So Much Knowledge, So Few Antivirals 279

Historical Perspective 281

Discovering Antiviral Compounds 281

The New Lexicon of Antiviral Discovery 281

Screening for Antiviral Compounds 282

Designer Antivirals and Computer-Based Searching 285

- The Difference between "R" and "D" 287
- Examples of Some Approved Antiviral Drugs 289
- The Search for New Antiviral Targets 293
- Antiviral Gene Therapy and Transdominant Inhibitors 295
- Resistance to Antiviral Drugs 298

Human Immunodeficiency Virus and AIDS 299

- Examples of Anti-HIV Drugs 299
- The Combined Problems of Treating a Persistent Infection and Emergence of Drug Resistance 303
- Combination Therapy 305
- Strategic Treatment Interruption 307
- Challenges and Lessons Learned 307

Perspectives 307

References 308

10 Evolution and Emergence 310

Virus Evolution 311

- The Classic Theory of Host-Parasite Interactions 311
- How Do Viral Populations Evolve? 312
- The Origin of Viruses 321
- The Fundamental Properties of Viruses Constrain and Drive Evolution 330

Emerging Viruses 333

- The Spectrum of Host-Virus Interactions 333
- Encountering New Hosts: Fundamental Problems in Ecology 339
- Expanding Viral Niches: Snapshots of Selected Emerging Viruses 341
- Host Range Can Be Expanded by Mutation, Recombination, or Reassortment 345
- Some Emergent Viruses Are Truly Novel 349
- A Revolution in Diagnostic Virology 350

Perceptions and Possibilities 350

- Infectious Agents and Public Perceptions 350
- What Next? 351

Perspectives 353

References 354

APPENDIX A Diseases, Epidemiology, and Disease Mechanisms of Selected Animal Viruses Discussed in This Book 357

APPENDIX B Unusual Infectious Agents 385

Glossary 393

Index 399