

# Contents

<b>1</b>	<b>Thymus</b>	<b>1</b>
	Gail Pearse	
1.1	Immunobiology of the Thymus . . . . .	2
1.1.1	Structure of the Thymus. . . . .	2
1.1.2	Functional Overview and Potential Targets for Therapeutic Intervention . . . . .	4
1.1.3	T Cells and Their Function . . . . .	4
1.1.4	T Cell Development. . . . .	6
1.1.5	Self Tolerance . . . . .	8
1.1.6	Control of T Cell Migration in the Thymus. . . . .	9
1.1.7	Thymic Commitment and Lineage Decisions . . . . .	11
1.2	Organ-Specific Immunopathological Processes. . . . .	12
1.2.1	Changes in Thymic Cell Populations: Physiological Responses. . . . .	12
1.2.1.1	Development . . . . .	12
1.2.1.2	Ageing . . . . .	13
1.2.1.3	Reproductive Status. . . . .	13
1.2.2	Effect of Stress. . . . .	14
1.3	Immunotoxicity . . . . .	14
1.3.1	Chemotherapeutics. . . . .	17
1.3.2	Therapeutic Immunostimulation . . . . .	19
1.4	Proliferative Changes. . . . .	19
1.4.1	Lymphoid Hyperplasia. . . . .	19
1.4.2	Thymic Lymphoma . . . . .	20
1.4.3	Epithelial Hyperplasia . . . . .	21
1.4.4	Thymoma. . . . .	21
1.5	Organ Involvement in Generalized Immunopathological Processes . . . . .	22
1.5.1	Autoimmune Disease. . . . .	22
1.5.2	Dysfunction of T Cells (T-Cell Activation Defects) . . . . .	24

1.5.3	Transplant Rejection . . . . .	24
1.5.4	Graft Versus Host Disease (GVHD) . . . . .	25
1.5.5	Severe Combined Immunodeficiency (SCID) . . . . .	25
1.6	Animal Models of Thymic Immunopathological Processes . . . . .	26
1.6.1	Immunocompromised Animal Models . . . . .	26
1.6.2	SCID Mouse. . . . .	27
1.6.3	Athymic/Nude Mouse . . . . .	28
1.6.4	NSG (NOD.Cg-Prkdcscid Il2rgtm1Wjl/SzJ) Mouse . . . . .	28
1.6.5	The “Scurfy” Mouse . . . . .	30
	References. . . . .	31
<b>2</b>	<b>Spleen</b> . . . . .	<b>37</b>
	Tracey L. Papenfuss and Mark F. Cesta	
2.1	Introduction . . . . .	38
2.1.1	Development of the Spleen . . . . .	38
2.1.2	Structure and Function of the Spleen. . . . .	39
2.1.2.1	Red Pulp . . . . .	40
2.1.2.2	White Pulp. . . . .	42
2.1.2.3	Marginal Zone. . . . .	43
2.1.3	Species Differences in the Histology of the Spleen. . . . .	46
2.1.4	Splenectomy Effects on General Immune Functioning . . . . .	47
2.1.5	Stress Effects on General Immune Functioning . . . . .	47
2.1.6	Evaluation of the Spleen . . . . .	48
2.1.7	Species-Specific Background Findings in the Spleen . . . . .	51
2.2	Summary . . . . .	54
	References. . . . .	54
<b>3</b>	<b>Lymph Node</b> . . . . .	<b>59</b>
	Susan A. Elmore and Schantel A. Bouknight	
3.1	Lymph Node Development . . . . .	59
3.2	Lymph Node Structure and Function. . . . .	60
3.2.1	The Parenchyma (Lymphocytes) . . . . .	61
3.2.2	Dendritic Cells . . . . .	62
3.2.3	Stromal Cells . . . . .	62
3.3	Factors Affecting Lymph Node Morphology. . . . .	64
3.4	Histopathology of the Lymph Node. . . . .	66
3.4.1	Lymphoid Necrosis . . . . .	66
3.4.2	Vascular Lesions . . . . .	67
3.4.3	Lymphatic Sinus Ectasia . . . . .	67
3.4.4	Pigment . . . . .	69
3.4.5	Amyloidosis. . . . .	70
3.4.6	Lymphadenitis . . . . .	71
3.4.7	Lymphocyte Hyperplasia. . . . .	72
3.4.8	Plasma Cell Hyperplasia . . . . .	73

3.4.9	Sinus Histiocytosis . . . . .	74
3.4.10	Extramedullary Hematopoiesis . . . . .	75
3.4.11	Neoplasia . . . . .	76
	References . . . . .	77
<b>4</b>	<b>Mucosa-Associated Lymphoid Tissues</b>	<b>81</b>
	Christine Frieke Kuper, Marcel V.W. Wijnands, and Serge A.L. Zander	
4.1	Introduction . . . . .	83
4.2	Immunobiology . . . . .	86
4.2.1	Development and Morphology of MALT . . . . .	86
4.2.1.1	Head Region and the Respiratory Tract . . . . .	91
4.2.1.2	Gastrointestinal Tract . . . . .	92
4.2.1.3	Non-mammalian Species . . . . .	96
4.2.2	Single Mucosal Lymphocytes (IELs and LPLs) . . . . .	97
4.2.3	Mucosal Mast Cells (MMC) . . . . .	99
4.2.4	Induction and Regulation of the Immune Response . . . . .	100
4.3	MALT Pathology . . . . .	104
4.3.1	Background Pathology . . . . .	104
4.3.2	Induced Pathology . . . . .	105
4.4	MALT Involvement in Generalized Immunopathological Processes . . . . .	106
4.4.1	Autoimmune Disease and Allergy . . . . .	106
4.4.2	Immunosuppression and Immunostimulation . . . . .	111
4.4.3	Sampling and Selection of MALT and IELs/LPLs . . . . .	113
4.5	Animal Models: MALT in Immunodeficient Animals . . . . .	114
	References . . . . .	115
<b>5</b>	<b>Immunopathology of the Nervous System</b>	<b>123</b>
	Amera K. Remick, Michelle L. Pershing, Tracey L. Papenfuss, Lisa G. Lanigan, Melissa J. Beck, and Jonathan D. Toot	
5.1	Immunobiology of the Nervous System . . . . .	124
5.1.1	Blood-Brain Barrier and Circumventricular Organs . . . . .	124
5.1.2	Glial Cells and Other Inflammatory Cells . . . . .	125
5.1.3	Inflammatory Reflex . . . . .	126
5.2	Selected Immune Conditions of the Nervous System . . . . .	126
5.2.1	Traumatic Brain Injury . . . . .	126
5.2.1.1	Neuropathology . . . . .	127
5.2.1.2	Pathogenesis of Immune Response . . . . .	128
5.2.1.3	Models of Traumatic Brain Injury . . . . .	129
5.2.1.4	Current State of Drug Development . . . . .	131
5.2.2	Infectious Diseases . . . . .	131
5.2.2.1	Pathogenesis of Immune Response . . . . .	132
5.2.2.2	Models of Infectious Disease . . . . .	134

5.2.2.3	Current State of Drug Development . . . . .	134
5.2.3	Autoimmune Diseases . . . . .	135
5.2.3.1	Multiple Sclerosis . . . . .	135
5.2.4	Neurodegenerative Disorders . . . . .	140
5.2.4.1	Parkinson's Disease . . . . .	141
5.2.4.2	Alzheimer's Disease . . . . .	146
5.2.5	Neurodevelopmental Disorders . . . . .	153
5.2.5.1	Attention Deficit Hyperactivity Disorder . . . . .	153
5.2.5.2	Autism Spectrum Disorder . . . . .	159
5.2.6	Common Mental Disorders . . . . .	165
5.2.6.1	Anxiety . . . . .	165
5.2.6.2	Depression . . . . .	170
5.2.6.3	Schizophrenia . . . . .	173
5.2.7	Neoplasia . . . . .	181
5.2.7.1	Pathogenesis of Immune Response . . . . .	182
5.2.7.2	Models of Neoplasia . . . . .	182
5.2.7.3	Current State of Drug Development . . . . .	184
	References . . . . .	185
<b>6</b>	<b>Immunopathology of the Urinary System</b>	<b>221</b>
	Catherine A. Picut	
6.1	Introduction . . . . .	221
6.2	Anatomy of the Glomerulus . . . . .	224
6.3	Immune Cells of the Kidney in Health and Disease . . . . .	227
6.4	Immune-Mediated Glomerulonephritis . . . . .	235
6.4.1	Type I Hypersensitivity-Acute or Th2-Mediated Hypersensitivity . . . . .	236
6.4.2	Type II Hypersensitivity: Anti-glomerular Basement Membrane Nephritis; Membranous Nephropathy (MN); Antenatal Membranous Nephropathy . . . . .	244
6.4.3	Type III Hypersensitivity: Immune Complex Glomerulonephritis; Lupus Nephritis; IgA Nephropathy . . . . .	249
6.4.4	Type IV Hypersensitivity: Delayed-Type Hypersensitivity . . . . .	260
6.4.5	Type V Hypersensitivity: Loss of Regulatory T Cells . . . . .	263
6.5	Immune-Mediated Tubulo-Interstitial Nephritis . . . . .	264
6.6	Pathogenesis of Glomerular Injury in Immune Mediated Glomerulonephritis . . . . .	265
6.7	Acute Kidney Injury (AKI) . . . . .	279
6.8	Immune Deficiency Associated with Chronic Renal Disease . . . . .	285
6.9	Spontaneous Disease in Rats . . . . .	287
6.10	Immune Defense of the Lower Urinary Tract . . . . .	301
6.11	Summarized Points . . . . .	305
	References . . . . .	306

<b>7 Immunopathology of the Hepatobiliary System</b>	<b>329</b>
Danielle L. Brown	
7.1 Immunobiology of the Hepatobiliary System . . . . .	330
7.1.1 Macroscopic and Microscopic Structure . . . . .	330
7.1.2 Cell Types Involved in Immunobiology . . . . .	333
7.1.2.1 Kupffer Cells . . . . .	333
7.1.2.2 Dendritic Cells . . . . .	335
7.1.2.3 Sinusoidal Endothelial Cells . . . . .	336
7.1.2.4 Lymphocytes . . . . .	338
7.1.2.5 Stellate Cells . . . . .	342
7.1.2.6 Hepatocytes . . . . .	344
7.1.2.7 Biliary Epithelial Cells. . . . .	345
7.1.3 Innate (Nonspecific) Immunity . . . . .	345
7.1.3.1 Production of Acute-Phase Proteins . . . . .	347
7.1.3.2 Nonspecific Phagocytosis of Particles and Nonspecific Pinocytosis of Molecules . . . . .	348
7.1.3.3 Nonspecific Cell Killing . . . . .	349
7.1.3.4 Disposal of Waste Molecules of Inflammation and Nonspecific Immunity . . . . .	349
7.1.4 Adaptive (Acquired or Specific) Immunity . . . . .	350
7.1.4.1 Deletion of Activated T Cells . . . . .	350
7.1.4.2 Induction of Tolerance to Ingested and Self-Antigens. . . . .	352
7.1.4.3 Extrathymic Proliferation of T Cells . . . . .	354
7.1.4.4 Disposal of Waste Molecules of Specific Immunity . . . . .	355
7.2 Organ-Specific Immunopathological Processes. . . . .	355
7.2.1 Hepatic Inflammation . . . . .	355
7.2.2 Hepatic Fibrosis . . . . .	358
7.2.3 Chronic Liver Failure (Cirrhosis) . . . . .	362
7.2.4 Drug-Induced Liver Injury. . . . .	363
7.2.5 Autoimmune Liver Disease . . . . .	367
7.2.6 Viral Hepatitis . . . . .	369
7.2.7 Alcoholic Liver Disease. . . . .	372
7.2.8 Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis . . . . .	374
7.2.9 Ischemia-Reperfusion Injury . . . . .	376
7.2.10 Hepatic Neoplasia . . . . .	378
7.3 Organ Involvement in Generalized Immunopathological Processes . . . . .	379
7.3.1 Widespread Acute Inflammation (Septicemia/Endotoxemia). . . . .	379
7.3.2 Age-Related Changes . . . . .	380
7.3.3 Systemic Autoimmune Disease . . . . .	383

7.4	Animal Models of Organ-Specific Immunopathological Processes . . . . .	383
7.4.1	Mouse Models of Acute Hepatitis Using Concanavalin A . . . . .	383
7.4.2	Mouse Model of Endotoxin-Induced Liver Injury. . . . .	384
7.4.3	Mice Injected with $\alpha$ -Galactosylceramide. . . . .	384
7.4.4	Animal Models of Idiosyncratic Drug-Induced Liver Injury (IDILI). . . . .	385
7.4.4.1	LPS-RAN Model. . . . .	385
7.4.4.2	LPS-DCLF Model. . . . .	385
7.4.4.3	Halothane Injection . . . . .	386
7.4.5	Animal Models of Autoimmune Liver Disease . . . . .	386
7.4.5.1	Immunization/Injection Models . . . . .	386
7.4.5.2	Inbred Models . . . . .	388
7.4.5.3	Transgenic and Knockout Mice. . . . .	389
7.4.6	Animal Models of Viral Hepatitis . . . . .	390
7.4.7	Animal Models of NAFLD . . . . .	391
	References. . . . .	392
<b>8</b>	<b>Immunopathology of the Respiratory System</b>	<b>419</b>
	Melanie A. Greeley	
8.1	Introduction . . . . .	419
8.2	Anatomical Structures . . . . .	420
8.2.1	Nose . . . . .	420
8.2.2	Larynx . . . . .	421
8.2.3	Trachea. . . . .	423
8.2.4	Lung. . . . .	423
8.3	Mucociliary Apparatus. . . . .	425
8.3.1	Normal Mucociliary Apparatus . . . . .	425
8.3.2	Mucociliary Apparatus and Toxicity . . . . .	432
8.4	Inflammatory Cells and Molecules of Innate Immunity . . . . .	433
8.4.1	Molecules. . . . .	438
8.5	Acquired Immunity . . . . .	441
8.5.1	Normal Respiratory Tract . . . . .	441
8.5.2	Acquired Immunity and Toxicology . . . . .	441
8.6	Pharmaceuticals and Immunopathology . . . . .	444
8.7	Development and Immunopathology. . . . .	446
	References. . . . .	447
<b>9</b>	<b>Immunopathology of the Cardiovascular System</b>	<b>455</b>
	Molly H. Boyle	
9.1	Introduction: Immune Responses and Inflammation in the Cardiovascular System. . . . .	457
9.1.1	Cholesterol Metabolism and the Immune System. . . . .	462

9.1.2	Interplay Between Cardiovascular Pathology and Immune Dysfunction . . . . .	465
9.1.2.1	Chagas Disease Cardiomyopathy: Immunopathology and Genetics. . . . .	466
9.1.2.2	Cardiac Pathology Associated with <i>Streptococcus</i> spp. Infections . . . . .	467
9.1.3	Therapeutics. . . . .	468
9.1.3.1	Monoclonal Antibodies and Potential Immunotoxicity . . . . .	468
9.1.3.2	Marketed Cardiovascular Therapies and Potential Immunotoxicity . . . . .	469
9.1.3.3	Immunomodulatory Therapies with Cardiovascular Implications. . . . .	470
9.1.3.4	Immune-Based Cardiotoxicity of Noncardioactive Agents . . . . .	471
9.1.4	Nonclinical Species Background Cardiovascular Pathology with Immune-Mediated Associations and Routine Animal Models . . . . .	471
9.1.4.1	Spontaneous Polyarteritis and Other Vascular Lesions. . . . .	471
9.1.4.2	Spontaneous Murine Lupus-Like Syndromes . . . . .	473
9.1.4.3	Spontaneous “Cardiomyopathy” in the Mouse . . . . .	474
9.1.5	Translational Challenges . . . . .	474
	References. . . . .	476
<b>10</b>	<b>Immunopathology of the Male Reproductive Tract</b>	<b>479</b>
	Catherine A. Picut, Eveline P.C.T. de Rijk, and Darlene Dixon	
10.1	Introduction . . . . .	480
10.2	Histologic Anatomy . . . . .	481
10.2.1	Overview . . . . .	481
10.2.2	Testis . . . . .	482
10.2.3	Excurrent Duct System . . . . .	487
10.2.4	Accessory Sex Glands . . . . .	491
10.3	Immunologic Privilege and Immunosuppression of the Testis . . . . .	491
10.3.1	Immune Privilege in General. . . . .	491
10.3.2	Blood Testis Barrier . . . . .	492
10.3.3	Immune Cells of the Testis . . . . .	495
10.4	Immune Privilege and Immunosuppression of the Excurrent Duct System . . . . .	505
10.4.1	Common Mucosal Immunity. . . . .	505
10.4.2	Immune cells of the Excurrent Duct System. . . . .	506

10.4.3	Blood-Epididymis Barrier (BEB) . . . . .	506
10.4.4	Immunosuppressive Proteins of the Excurrent Duct System. . . . .	507
10.5	Endocrine-Immune System Interaction . . . . .	507
10.5.1	Hormones That Suppress the Immune Response . . . . .	508
10.5.2	Role of Inflammatory Mediators in Spermatogenesis . . . . .	509
10.5.3	Endocrine Function of Immune Cells . . . . .	510
10.6	Inflammatory Disease . . . . .	511
10.6.1	How Inflammation Affects Spermatogenesis. . . . .	512
10.6.2	Autoimmune Infertility . . . . .	514
10.6.3	Autoimmune Orchitis . . . . .	515
10.6.4	Experimental Models of Testicular Inflammation and Autoimmune Orchitis . . . . .	516
10.7	Spontaneous Disease Associated with Immune Disruption. . . . .	518
10.8	Implications for Toxicologic Pathology. . . . .	527
10.9	Summarized Points . . . . .	528
	References. . . . .	528
<b>11</b>	<b>Immunopathology of the Female Reproductive Tract and Mammary Gland</b> . . . . .	<b>541</b>
	Catherine A. Picut, Darlene Dixon, and Eveline P.C.T. de Rijk	
11.1	Introduction . . . . .	542
11.2	Non-Pregnant State . . . . .	543
11.2.1	Immunological Regulation in the Ovary . . . . .	543
11.2.1.1	Immunological Protection of the Oocyte. . . . .	543
11.2.1.2	Ovarian Macrophages. . . . .	545
11.2.2	Modified Mucosal Immunity of FRT in the Non-pregnant State . . . . .	550
11.2.2.1	Role of Epithelial Cells in Mucosal Immunity. . . . .	551
11.2.2.2	Leukocytes of the Non-pregnant FRT. . . . .	555
11.2.2.3	Immune Function of Seminal Fluid . . . . .	558
11.2.3	Reproductive Disease of the Non-pregnant State . . . . .	559
11.2.3.1	Premature Ovarian Failure (POF). . . . .	559
11.2.3.2	Endometriosis . . . . .	561
11.2.3.3	Polycystic Ovary Syndrome (PCOS) . . . . .	561
11.3	Pregnant State . . . . .	562
11.3.1	Anatomy of the Placenta . . . . .	562
11.3.2	General Features of Immunology of Pregnancy . . . . .	567
11.3.3	Immune Cells of the Placenta . . . . .	569
11.3.3.1	Uterine Natural Killer (uNK) Cells. . . . .	569
11.3.3.2	Placental (or Decidual) Macrophages. . . . .	573



11.3.3.3	Dendritic Cells . . . . .	574
11.3.3.4	T Cell Subpopulations. . . . .	575
11.3.4	Suppression of Fetus Rejection during Pregnancy . . . . .	576
11.3.4.1	Production of Immunosuppressive Molecules . . . . .	577
11.3.4.2	Inhibitory co-stimulatory Proteins on Trophoblasts and Macrophages . . . . .	580
11.3.4.3	Complement-Activating Regulatory Proteins on Trophoblasts. . . . .	581
11.3.4.4	Modified MHC-Class I Expression. . . . .	582
11.3.4.5	Pro-apoptotic Mechanisms (Fas–Fas L) and Microvesicles as Decoys . . . . .	583
11.3.4.6	Multinucleated Cell Transformation. . . . .	586
11.3.5	Enhancement of Systemic Innate Immune Response During Pregnancy . . . . .	586
11.3.6	Increased Susceptibility to Infection During Pregnancy. . . . .	589
11.3.7	Pregnancy Problems Associated with Immune Dysregulation. . . . .	590
11.3.7.1	Pre-eclampsia . . . . .	590
11.3.7.2	Recurrent Miscarriages. . . . .	595
11.4	Mammary Gland . . . . .	596
11.4.1	General Immune Components of Mammary Gland Tissue . . . . .	597
11.4.2	Immune Components of Colostrum/Milk . . . . .	598
11.4.3	Process of Mammary Gland Involution. . . . .	601
11.5	Summarized Points . . . . .	602
	References. . . . .	602
<b>12</b>	<b>Immunopathology of the Musculoskeletal System</b>	<b>615</b>
	Brad Bolon and Jairo Nunes	
12.1	Introduction . . . . .	616
12.1.1	Immune Cells and Signals in Musculoskeletal Tissues During Health and Disease . . . . .	617
12.1.1.1	Bones and Joints (including Tendons and Ligaments) . . . . .	617
12.1.1.2	Skeletal Muscle. . . . .	624
12.1.2	Immune-Mediated Musculoskeletal Diseases . . . . .	625
12.1.2.1	Arthritis. . . . .	625
12.1.2.2	Myositis. . . . .	636
12.1.2.3	Osteitis . . . . .	637
12.1.3	Summarized Points . . . . .	638
	References. . . . .	639

<b>13 Immunopathology of the Endocrine System</b>	<b>649</b>
Thomas J. Rosol and Brent E. Walling	
13.1 Introduction	649
13.2 Autoimmune Diseases of Endocrine Glands	651
13.2.1 Molecules and Signaling Pathways of Endocrine Autoimmunity	651
13.2.1.1 HLA Family	651
13.2.1.2 CTLA-4/PTPN22	654
13.2.1.3 FOXP3/IL-2R/CD25	654
13.2.1.4 IDDM2	654
13.2.1.5 CD40	655
13.2.1.6 TSHR	655
13.2.1.7 FCRL3	655
13.2.1.8 AIRE	655
13.2.1.9 Others	656
13.2.2 Organ Involvement in Endocrine Autoimmunity	656
13.2.2.1 Pituitary Gland	656
13.2.2.2 Thyroid Gland	658
13.2.2.3 Animal Models for Autoimmune Thyroid Disease	660
13.2.2.4 Adrenal Gland	661
13.2.2.5 Pancreas and Type 1 Diabetes Mellitus (T1D)	662
13.2.2.6 NOD Mouse and Type 1 Diabetes Mellitus	665
13.2.2.7 BioBreeding (BB) Rat and Type 1 Diabetes Mellitus	665
13.2.2.8 Insulin Autoimmune Syndrome	666
13.2.2.9 Parathyroid Gland	667
13.2.2.10 Polyendocrine Syndromes	668
13.2.2.11 Celiac Disease	669
13.3 Drug-Induced Endocrine Autoimmunity (DIEA)	670
13.3.1 Interferon- $\alpha$	671
13.3.2 Interleukin-2 (IL-2) and Autoimmune Thyroiditis	671
13.3.3 Anti-CTLA4 Antibody (Ipilimumab)	671
13.3.4 Amiodarone	672
13.3.5 Insulin Autoimmune Syndrome (IAS, Hirata's Syndrome) and Sulfhydryl Compounds	672
13.4 Innate Immunity in Endocrine Diseases	672
13.4.1 Type II Diabetes Mellitus	673
13.4.2 Metabolic Syndrome	673
13.5 Cytokines and Endocrine Organs	674
13.5.1 Interleukin-1 (IL-1)	675
13.5.2 Interleukin-2 (IL-2)	676
13.5.3 Interleukin-6 (IL-6)	676

13.5.4	Tumor Necrosis Factor- $\alpha$ (TNF- $\alpha$ ) . . . . .	676
13.5.5	Euthyroid Sick Syndrome (ESS) or Nonthyroidal Illness Syndrome (NTIS). . . . .	677
13.6	Effects of Hormones on the Immune System . . . . .	678
13.6.1	Glucocorticoids . . . . .	678
13.6.2	Prolactin . . . . .	679
13.6.3	Parathyroid Hormone. . . . .	679
	References. . . . .	680
<b>14</b>	<b>Ocular Immunopathology</b> . . . . .	<b>695</b>
	Meg Ferrell Ramos, Leandro Teixeira, Curtis R. Brandt, and Diana Auyeung-Kim	
14.1	Introduction . . . . .	696
14.2	Ocular Immunology . . . . .	697
14.2.1	Innate Immune Systems. . . . .	698
	14.2.1.1 Effector Functions Resulting from Innate Sensing. . . . .	700
14.2.2	Adaptive Immune Responses. . . . .	701
14.2.3	Immune Privilege in the Eye . . . . .	705
	14.2.3.1 Anterior Chamber Associated Immune Deviation (ACAID) . . . . .	706
14.3	Immunopathology of the Eye. . . . .	708
14.3.1	Terminology. . . . .	708
14.3.2	Innate Immune Responses . . . . .	709
14.3.3	Adaptive Immune Responses. . . . .	712
14.3.4	Immunopathology Outcomes. . . . .	717
14.4	Ocular Anatomy. . . . .	720
14.4.1	Introduction . . . . .	720
14.4.2	Eyelids . . . . .	721
14.4.3	Conjunctiva . . . . .	722
14.4.4	Cornea . . . . .	723
14.4.5	Ocular Glands and the Pre-corneal Tear Film . . . . .	724
14.4.6	Sclera . . . . .	725
14.4.7	Uveal Tract and Filtration Angle . . . . .	726
14.4.8	Lens . . . . .	730
14.4.9	Vitreous . . . . .	730
14.4.10	Retina . . . . .	732
14.4.11	Retinal Pigmented Epithelium . . . . .	737
14.4.12	Optic Nerve . . . . .	738
14.4.13	Ocular Blood Supply . . . . .	739
14.4.14	Lymphatics and Draining Lymph Nodes . . . . .	740
14.5	Regulatory Aspects of Ocular Drug Development. . . . .	741
14.5.1	Preclinical Development of Ocular Drugs. . . . .	741
14.5.2	New Molecular/Biological Entities . . . . .	744
14.5.3	Ocular Pharmacology. . . . .	744

14.5.4	Ocular Pharmacokinetics . . . . .	745
14.5.5	Ocular Toxicity Studies . . . . .	746
14.5.6	Systemic Toxicity . . . . .	749
14.5.7	Reformulation and/or New Route of Exposure . . . . .	750
14.5.8	Combination Products . . . . .	750
14.5.9	Other Considerations . . . . .	751
14.5.9.1	Impurities . . . . .	751
14.5.9.2	Endotoxin in Devices . . . . .	752
14.5.9.3	Ocular Irritation . . . . .	753
14.5.9.4	Safety Margins . . . . .	753
	References . . . . .	754
<b>15</b>	<b>Immunopathology of Drug and Toxin-Related Skin Reactions</b>	<b>763</b>
	Rony Shreberk-Hassidim and Yuval Ramot	
15.1	Skin Anatomy and Immunobiology . . . . .	763
15.1.1	Keratinocytes . . . . .	765
15.1.2	Dendritic Cells . . . . .	766
15.1.3	Langerhans Cells . . . . .	766
15.1.4	Dermal Dendritic Cells . . . . .	769
15.1.5	Other Components Involved in the Dermatological Immune Response . . . . .	770
15.2	Specific Immunopathological Processes of the Skin: Contact Exposure to Drugs and Toxins . . . . .	771
15.2.1	Epidemiology and Types . . . . .	771
15.2.2	Pathogenesis of ACD . . . . .	771
15.2.3	The Aryl Hydrocarbon Receptor . . . . .	777
15.3	Skin Involvement in Generalized Immunopathological Processes: Systemic Exposure to Drugs and Toxins . . . . .	778
15.3.1	Epidemiology and Types . . . . .	778
15.3.2	Pathogenesis of SJS and TEN . . . . .	780
15.4	Animal Models . . . . .	782
15.4.1	Atopic Dermatitis . . . . .	783
15.4.2	Psoriasis . . . . .	784
15.4.3	Acne . . . . .	785
15.4.4	Phototoxicity . . . . .	785
15.4.5	General Considerations . . . . .	786
	References . . . . .	787
	<b>Index . . . . .</b>	<b>799</b>

Immunopathology in Toxicology and Drug Development

Volume 2, Organ Systems

Parker, G. (Ed.)

2017, XXII, 826 p. 255 illus., 250 illus. in color.,

Hardcover

ISBN: 978-3-319-47384-0

A product of Humana Press