

Contents

1 Adverse Reactions to Drugs and Drug Allergy:	
Scope of This Book	1
1.1 Adverse Drug Reactions	1
1.1.1 Definition	1
1.1.2 Terminology: Classification of Adverse Drug Reactions and the terms Hypersensitivity, and Allergy	2
1.1.3 Usage of the Term “Allergy”	5
1.2 Drug Allergy	6
1.2.1 The Early Years	6
1.2.2 Drugs, Haptens, and Prior Exposure	6
1.2.3 Drug Allergies, Hypersensitivities, and Sensitivities (Intolerances)	7
1.2.4 Risk Factors for Drug Allergy	8
1.3 The Promise of Pharmacogenomics for understanding and managing Adverse Drug Reactions Including Drug Allergies	9
1.4 Improvements In Drug Delivery and the Allergenicity of Drugs	11
1.5 Scope of This Book	11
1.5.1 The Place of Drug Allergy in Immunology	11
1.5.2 The Need for a Single Text Book on Drug Allergy	12
Summary	12
Further Reading	13
2 Classification and Descriptions of Allergic Reactions to Drugs	15
2.1 Hypersensitivity: The Early Years—From Koch to Gell and Coombs	16
2.2 Classification of Hypersensitivity Reactions	16
2.2.1 Type I Hypersensitivity	16
2.2.2 Type II Hypersensitivity	23
2.2.3 Type III Hypersensitivity	23
2.2.4 Delayed-Type (Type IV) Hypersensitivity	24
Summary	34
Further Reading	35

3 Mechanisms of Hypersensitivity	37
3.1 Allergic Sensitization to Drugs and the Dogma of Previous Exposure	38
3.1.1 Immunogenicity of Free and Conjugated Drugs	38
3.1.2 Mediator Release by Free and Conjugated Drugs in Immediate Allergic Reactions	40
3.1.3 Immunological Recognition of Free, Unconjugated Drug Molecules.....	41
3.2 IgE Antibodies and IgE-Mediated Drug Hypersensitivities.....	42
3.2.1 Initiating Events in the Production of IgE Antibody	42
3.2.2 Allergic Release of Mediators of Hypersensitivity from Mast Cells	43
3.2.3 Amplification of IgE Antibody Production by Cellular Interaction.....	45
3.2.4 Low-Affinity IgE Receptor FcεRII (CD23)	45
3.2.5 Important Mediators of the Type I Immediate Allergic Response.....	46
3.2.6 Anaphylaxis	58
3.2.7 Other Mechanisms of Anaphylaxis: IgG, PAF, and Nitric Oxide	61
3.2.8 Drug-Induced Urticaria and Angioedema	62
3.3 The Allergen-Induced Late Phase Reaction	68
3.3.1 Early Studies: Implication of IgE Antibodies	69
3.3.2 Cellular Responses in the Late Phase Reaction and Comparison with the Delayed-Type Hypersensitivity Response.....	69
3.4 Drug-Induced Hypersensitivity and Immune Receptors	70
3.4.1 Background	70
3.4.2 Recognition and the Immune Response to Free, Unconjugated Drug	71
3.4.3 Abacavir and the MHC-Presented Altered Peptide Model of Drug Hypersensitivity.....	72
3.4.4 Carbamazepine and Other HLA-Drug Hypersensitivity Associations	73
3.4.5 The Question of Direct Drug Activation of T Cells Without Involvement of a Specific Peptide.....	74
3.5 Desensitization of Drug-Allergic Patients.....	75
3.6 Delayed-Type (Type IV) Hypersensitivity Drug Reactions.....	76
3.6.1 The Cellular Basis of Type IV Hypersensitivity Cutaneous Drug Reactions	76
3.6.2 T Helper Cell Responses and Th17	78
3.6.3 Delayed Cutaneous Adverse Drug Reactions.....	79
3.7 Type II Hypersensitivity Drug Reactions	84
3.8 Type III Hypersensitivity Drug Reactions.....	86
Summary	87
Further Reading	90

4	Diagnosis of Allergic Reactions to Drugs	91
4.1	Case History	92
4.2	Skin Testing	93
4.2.1	General Aspects of Skin Testing for Drug Hypersensitivity.....	93
4.2.2	Skin Prick Test Method	94
4.2.3	Intradermal Testing.....	95
4.2.4	Patch Tests	97
4.3	Serum Immunoglobulin E Antibody Tests	100
4.3.1	In Vitro Detection of Drug-Reactive IgE Antibodies.....	101
4.3.2	Tests for the Clinic and Research	103
4.3.3	Quantitation, Interpretation and Reporting of Results	104
4.4	Drug Challenge (Provocation) Testing.....	105
4.5	Detection and Measurement of Released Mediators/Markers of Hypersensitivity	107
4.5.1	Tryptase	107
4.5.2	Histamine	109
4.5.3	Cysteinyl Leukotrienes.....	111
4.6	Basophil Activation Test.....	113
4.6.1	Basophils and Background to the Basophil Activation Test (BAT)	113
4.6.2	Basophil Activation Markers.....	114
4.6.3	Some Technical Aspects	115
4.6.4	Controls	116
4.6.5	Evaluation of Results	116
4.6.6	Application to Drug Allergies.....	117
4.6.7	Analysis by Flow Cytometry of Intracellular Histamine and Its Release by Activated Basophils at the Single Cell Level	117
4.6.8	Future Research and Conclusions	118
4.7	Tests for Delayed Type Drug Hypersensitivity Reactions.....	118
4.7.1	Lymphocyte Transformation Test.....	120
4.7.2	The Local Lymph Node Assay	121
4.7.3	Toward Nonproliferation-Based In Vitro Assays: Cell Surface Activation Markers, Cytokines, Chemokines, and Skin-Homing Receptors	121
4.8	And Finally: Is the Patient Allergic to the Drug?	124
	Summary	125
	Further Reading.....	127
5	β-Lactam Antibiotics	129
5.1	Penicillins	131
5.1.1	Incidence of Penicillin Hypersensitivity and Clinical Aspects	131
5.1.2	Penicillin Antigens and Allergenic Determinants	132
5.1.3	Heterogeneity of IgE Antibody Responses to Penicillins and the Spectrum of Penicillin Allergenic Determinants.....	141

5.1.4	Risk Factors for Immediate (Type I) Reactions to Penicillins	147
5.1.5	Skin Testing Today for Immediate Hypersensitivity to Penicillin	148
5.1.6	In Vitro Tests for Immediate Hypersensitivity to Penicillins	151
5.1.7	Challenge (Provocation) Testing for Penicillin Hypersensitivity	153
5.1.8	Penicillin Desensitization	154
5.1.9	Delayed-Type Hypersensitivity Reactions to Penicillins	156
5.1.10	The Genetic Basis of Penicillin-Induced Liver Injury	159
5.2	Cephalosporins	159
5.2.1	Incidence of Cephalosporin Hypersensitivity and Clinical Aspects	160
5.2.2	Clinical Aspects of Cross-Reactivity of Cephalosporins and Penicillins	160
5.2.3	Structures and Classification of Cephalosporin Drugs	161
5.2.4	Cephalosporin Antigens and Allergenic Determinants	161
5.2.5	Skin Testing with Cephalosporins	173
5.2.6	Delayed Reactions to Cephalosporins	174
5.3	Monobactams	175
5.4	Carbapenems	176
5.5	Clavams	177
	Summary	178
	Further Reading	180
6	Other Antimicrobial Drugs	183
6.1	Antibiotics	184
6.1.1	Macrolides	184
6.1.2	Tetracyclines	186
6.1.3	Rifamycins	187
6.1.4	Vancomycin and Teicoplanin	188
6.1.5	Antibiotics Used Topically with Emphasis on Neomycin and Bacitracin	193
6.1.6	Ribostamycin	197
6.1.7	Chloramphenicol	198
6.1.8	Clindamycin	198
6.1.9	Pristinamycin	200
6.1.10	Fosfomycin	200
6.2	Antimicrobials Other than Antibiotics	200
6.2.1	Sulfonamides	200
6.2.2	Trimethoprim	213
6.2.3	Quinolones	218
6.2.4	Chlorhexidine	225
6.2.5	Povidone-Iodine	230
	Summary	231
	Further Reading	232

7	Drugs and Other Agents Used in Anesthesia and Surgery.....	235
7.1	Drug-Induced Reactions During Anesthesia.....	235
7.2	Incidences of Drug- and Other Agent-Induced Anaphylaxis During Anesthesia.....	237
7.3	Clinical Features of Anaphylactic and Anaphylactoid Reactions During Anesthesia.....	238
7.4	Anaphylaxis to Neuromuscular Blocking Drugs.....	239
7.4.1	Some Epidemiological Background.....	239
7.4.2	Mechanisms Underlying Anaphylaxis to Neuromuscular Blocking Drugs.....	240
7.4.3	Diagnosis of Anaphylaxis to Neuromuscular Blocking Drugs.....	246
7.4.4	Cross-Reactions Between Neuromuscular Blocking Drugs.....	256
7.4.5	The NMBD–IgE Conundrum: The Origin of IgE Antibodies to Neuromuscular Blocking Drugs.....	263
7.4.6	Sugammadex and Anaphylaxis to Rocuronium.....	267
7.4.7	Antigenic Similarity Between α -Bungarotoxin and Neuromuscular Blocking Drugs.....	272
7.5	Anaphylaxis to Hypnotic Drugs Used in Anesthesia.....	273
7.5.1	Thiopentone.....	273
7.5.2	Propofol.....	276
7.6	Anaphylaxis to Colloids.....	278
7.6.1	Hydroxyethyl Starch.....	278
7.6.2	Gelatin.....	279
7.6.3	Dextrans.....	279
7.7	Local Anesthetics.....	281
7.7.1	Chemistry.....	281
7.7.2	Adverse Reactions to Local Anesthetics.....	281
7.7.3	Diagnosis of Reactions to Local Anesthetics.....	284
7.8	Polypeptides.....	284
7.8.1	Protamine.....	284
7.8.2	Aprotinin.....	286
7.8.3	Latex.....	287
7.9	Heparin.....	289
7.9.1	Adverse Reactions to Heparin.....	289
7.9.2	Diagnostic Methods.....	289
7.9.3	Danaparoid and Hirudins.....	290
7.9.4	Fondaparinux.....	290
7.10	Patent Blue V, Isosulfan Blue, and Methylene Blue.....	291
	Summary.....	293
	Further Reading.....	294
8	Opioid Analgesic Drugs.....	295
8.1	Terminology.....	296
8.2	Structure–Activity Relationships.....	296
8.3	Classification of Opioid Drugs.....	301
8.4	Opioids and Histamine Release.....	303
8.4.1	Histamine Receptors.....	303

8.4.2	Early Studies on Opioid Drug-Induced Release of Histamine.....	304
8.4.3	Summary of Morphine-Induced Hemodynamic and Cutaneous Changes in Humans	305
8.5	Allergenicity of Opioid Analgesic Drugs	308
8.5.1	Naturally Occurring and Semisynthetic Opioid Drugs	308
8.5.2	Synthetic Opioid Drugs	311
8.6	Resolving the Histamine-Releasing and Allergic Effects in Diagnosing Reactions to Opioid Drugs	313
8.7	Why Are Opioid Analgesic Drugs So Poorly Allergenic?.....	315
8.8	Some Important Clinical Implications Related to the Use of Opioid Analgesic Drugs.....	316
	Summary	317
	Further Reading	317
9	Nonsteroidal Anti-Inflammatory Drugs.....	319
9.1	Therapeutic Applications of NSAIDs.....	320
9.2	Patient Usage.....	320
9.3	Classification of NSAIDs	321
9.3.1	Salicylates.....	321
9.3.2	Propionic Acid Derivatives	321
9.3.3	Aryl and Heteroaryl Acetic Acids.....	321
9.3.4	Anthranilates (Fenamic Acid Derivatives)	323
9.3.5	Oxicams (Enolic Acid Derivatives).....	323
9.3.6	Phenylpyrazolones.....	323
9.3.7	Anilides.....	323
9.3.8	COX-2 Selective Inhibitors	323
9.4	Mechanism of Action of NSAIDs	324
9.4.1	Biosynthesis of the Prostanoids.....	324
9.4.2	The Cyclooxygenase Isoforms COX-1 and COX-2	324
9.4.3	Classification of NSAIDs by COX Isoenzyme Selectivity.....	326
9.4.4	The So-Called COX-3 Isoform	327
9.5	Sensitivities to NSAIDs	328
9.5.1	Definition and Epidemiology	329
9.5.2	Clinical Classification of Sensitivities to NSAIDs	330
9.5.3	IgE Antibodies to Aspirin.....	339
9.5.4	NSAID Sensitivities and BAT.....	340
9.5.5	Genetic Mechanisms of Aspirin-Induced Sensitivities	340
	Summary	341
	Further Reading.....	342
10	Contrast Media.....	343
10.1	Iodinated Contrast Media	344
10.2	Usage and Safety of Contrast Media.....	346
10.3	Adverse Reactions	347
10.3.1	Classification and Symptoms.....	347

10.3.2	Incidence of Reactions.....	349
10.3.3	Risk Factors	350
10.3.4	Biphasic Reactions.....	350
10.4	Mechanisms of Adverse Reactions to Iodinated Contrast Media	351
10.4.1	Anaphylactoid and Anaphylactic Reactions	352
10.4.2	Delayed Reactions	355
10.5	Tests for the Diagnosis and Study of Adverse Reactions to Contrast Media	356
10.5.1	Skin Tests	356
10.5.2	IgE Antibody Tests.....	357
10.5.3	Tests to Detect the Release of Mediators.....	358
10.5.4	Challenge Tests	359
10.6	Premedication for the Prevention of Anaphylactoid/ Anaphylactic Reactions to Iodinated Contrast Media.....	360
10.7	Gadolinium-Based Contrast Agents	361
10.7.1	Molecular Structures of Gadolinium-Based Contrast Agents	361
10.7.2	Nephrogenic Systemic Fibrosis	361
10.7.3	Other Adverse Reactions	361
	Summary	365
	Further Reading.....	366
11	Biologics	369
11.1	Monoclonal Antibodies for Therapy.....	370
11.1.1	Nomenclature.....	370
11.1.2	Monoclonal Antibodies Approved for Therapy	370
11.1.3	Immune Reactions to Monoclonal Antibodies.....	371
11.2	Etanercept.....	379
11.3	Interferons.....	380
11.4	Interleukin 2.....	380
11.5	Denileukin Difitox and Aflibercept	381
11.6	Anakinra	381
11.7	Anti-thymocyte Globulin.....	382
11.8	Epoetins	382
11.9	Human Insulin	383
	Summary	384
	Further Reading.....	385
12	Corticosteroids	387
12.1	Introduction, Incidence of Allergy, and Sensitization	387
12.2	Corticosteroid Haptens: Metabolism and Degradation	388
12.3	Delayed Reactions.....	390
12.3.1	Clinical Presentation.....	390
12.3.2	Diagnosis of Corticosteroid Hypersensitivity.....	390
12.3.3	Structure–Activity Relationships of Corticosteroid Cross-Reactions.....	393
12.4	Immediate Reactions to Corticosteroids.....	394
12.4.1	Incidence, Sensitization, Clinical Presentation, and Risk Factors	394

12.4.2	Immediate reactions: Important/Interesting Findings and Observations Reported so Far	394
12.4.3	Identifying and Understanding Cross-Reactions: Finding a Safe Alternative Corticosteroid	396
12.4.4	Diagnostic Methods	396
	Summary	397
	Further Reading	397
13	Drugs Used for Chemotherapy	399
13.1	Taxanes	400
13.1.1	Premedication for Taxanes	404
13.1.2	Desensitization for Hypersensitivity Reactions to Taxanes	405
13.2	Organoplatinum Chemotherapeutic Drugs	405
13.2.1	Symptoms of Hypersensitivity to Platinum Drugs	405
13.2.2	Incidences of, and Risk Factors for, Hypersensitivity Reactions to Platinum Drugs	407
13.2.3	Mechanisms and Diagnosis of Platinum Drug-Induced Hypersensitivity Reactions	407
13.2.4	Desensitization	408
13.3	Tyrosine Kinase Inhibitors	409
13.3.1	The Philadelphia Chromosome and Tyrosine Kinases	409
13.3.2	Imatinib Mesylate	410
13.3.3	Gefitinib and Erlotinib	411
13.4	Proteasome Inhibitors	412
13.4.1	The Proteasome	412
13.4.2	Bortezomib	412
13.4.3	Second Generation Proteasome Inhibitors	415
13.5	Cytokine-release and tumor lysis syndromes	415
	Summary	415
	Further Reading	417
14	Proton Pump Inhibitors	419
14.1	Chemistry	419
14.2	Mechanism of Action	420
14.3	Hypersensitivity Reactions to Proton Pump Inhibitors	420
14.4	Diagnosis of Hypersensitivity to Proton Pump Inhibitors	422
14.5	Proton Pump Inhibitors, Gastroesophageal Reflux Disease, and Asthma	423
14.6	Other Safety Concerns with Proton Pump Inhibitors	423
	Summary	423
	Further Reading	424
	Postface—Concluding Remarks	425
	Index	429