

CONTENTS

PRINCIPLES AND METHODS FOR ASSESSING ALLERGIC HYPERSENSITIZATION ASSOCIATED WITH EXPOSURE TO CHEMICALS

PREAMBLE	xvi
ABBREVIATIONS	xxvii
PREFACE	xxviii
1. THE IMMUNE SYSTEM	1
1.1 Introduction	1
1.1.1 Evolution and function of the adaptive immune system	1
1.1.2 Immunosuppression, immunodeficiency and autoimmunity	5
1.1.3 Allergy and allergic diseases	6
1.1.4 Conclusion	8
1.2 Physiology and components of the immune system	8
1.2.1 T-cells	9
1.2.1.1 Balancing the immune response	10
1.2.2 B-cells	16
1.2.3 Macrophages	18
1.2.4 Antigen-presenting cells	19
1.2.4.1 Co-stimulatory molecules in T-cell activation	20
1.2.5 Adhesion molecules	22
1.2.6 Fc receptors	23
1.2.7 Polymorphonuclear leukocytes	27
1.2.8 Cytotoxic lymphocytes	27
1.2.9 Mast cells	30
1.2.10 Basophils	31
1.2.11 Eosinophils	31
1.2.12 Complement components	32
1.2.13 Immunoglobulins	32
1.2.13.1 IgG	32
1.2.13.2 IgA	36

	1.2.13.3 IgM	38
	1.2.13.4 IgD	39
	1.2.13.5 IgE	39
1.3	Immunotoxicology	40
1.4	Immunosuppression/immunodeficiency	41
	1.4.1 Biological basis of immunosuppression/ immunodeficiency	41
	1.4.2 Consequences of immunosuppression/ immunodeficiency	42
1.5	Immunological tolerance	43
	1.5.1 T-cell tolerance to self-antigens	43
	1.5.2 B-cell tolerance to self antigens	45
	1.5.3 Tolerance to non-self antigens	46
	1.5.3.1 Scope	46
	1.5.3.2 Mucosal defence against exogenous toxic pressures	46
	1.5.3.3 Induction of oral tolerance	49
	1.5.3.4 Factors determining the development of oral tolerance	50
	1.5.3.5 Orally induced flare-up reactions and desensitization	51
	1.5.3.6 Mechanisms of tolerance	52
	1.5.3.7 Conclusions	55
2.	HYPERSENSITIVITY AND AUTOIMMUNITY — OVERVIEW OF MECHANISMS	56
2.1	Classification of immune reactions	57
	2.1.1 Type I hypersensitivity	57
	2.1.1.1 Anaphylaxis	60
	2.1.2 Type II hypersensitivity	60
	2.1.3 Type III hypersensitivity — immune complex reaction	61
	2.1.3.1 Arthus reaction	62
	2.1.4 Type IV — delayed-type hypersensitivity	62
	2.1.4.1 Mechanisms of allergic contact dermatitis	64
	2.1.4.2 T-cell responses in chemically induced pulmonary diseases	68
	2.1.5 Type V stimulatory hypersensitivity	69

2.2	Regulation of hypersensitivity	69
2.2.1	Regulation of IgE synthesis by IL-4 and IFN γ	73
2.2.2	Eosinophilia and IL-5	74
2.2.3	The relationship between Th2 cells and type I hypersensitivity	75
2.2.4	IL-12 drives the immune response towards Th1	75
2.2.5	IL-13, an interleukin-4-like cytokine	75
2.3	Autoimmune reactions	76
2.4	Possible mechanisms of autoimmune reactions	80
2.4.1	Release of anatomically sequestered antigens	80
2.4.2	The "cryptic self" hypothesis	81
2.4.3	The self-ignorance hypothesis	82
2.4.4	The molecular mimicry hypothesis	82
2.4.5	The "modified self" hypothesis	83
2.4.5.1	Hapten-induced antibody responses to "modified self"	83
2.4.5.2	Hapten-induced autoantibodies that recognize "self" proteins	83
2.4.6	Immunoregulatory disturbances	86
2.4.6.1	Errors in central or peripheral tolerance	86
2.4.6.2	Polyclonal activators	87
2.5	Type I hypersensitivity diseases and allied disorders	88
2.5.1	Asthma	91
2.5.1.1	Definition	91
2.5.1.2	Airways inflammation and asthma	93
2.5.2	Occupational asthma	94
2.5.2.1	Occupational asthma and allergy	95
2.5.3	Atmospheric pollutants and asthma	97
2.5.4	Rhinitis	100
2.5.5	Atopic eczema	101
2.5.6	Urticaria	103
2.5.7	Gastrointestinal tract diseases: mechanisms of food-induced symptoms	104
2.5.7.1	Non IgE-mediated food-sensitive enteropathy	104

	2.5.7.2	IgE-mediated food allergy	105
	2.5.7.3	Role of gastrointestinal tract physiology in food allergy	106
2.6		Type II hypersensitivity diseases	107
	2.6.1	Drug-induced Type II reactivity	107
	2.6.2	Transfusion reactions	109
	2.6.3	Autoimmune haemolytic anaemia	110
	2.6.4	Autoimmune thrombocytopenic purpura	113
	2.6.5	Pemphigus and pemphigoid	114
	2.6.6	Myasthenia gravis	115
2.7		Type III hypersensitivity diseases	117
	2.7.1	Immune complex disease	117
	2.7.2	Serum sickness	118
	2.7.3	Allergic bronchopulmonary aspergillosis	119
	2.7.4	Extrinsic allergic alveolitis	120
		2.7.4.1 Farmer's lung	121
		2.7.4.2 Bird-fancier's lung	121
2.8		Type IV hypersensitivity diseases	121
	2.8.1	Chronic beryllium disease	123
	2.8.2	Systemic autoimmune diseases	125
		2.8.2.1 Systemic lupus erythematosus	125
		2.8.2.2 Rheumatoid arthritis	126
		2.8.2.3 Scleroderma	126
		2.8.2.4 Sjögren's syndrome	127
		2.8.2.5 Hashimoto's disease	128
3.		FACTORS INFLUENCING ALLERGENICITY	130
	3.1	Introduction	130
	3.2	Inherent allergenicity	130
		3.2.1 Inherent properties of chemicals inducing autoimmunity	132
	3.3	Exogenous factors affecting sensitization	134
		3.3.1 Exposure	134
		3.3.1.1 Magnitude of exposure	134
		3.3.1.2 Frequency of exposure	135
		3.3.1.3 Route of exposure	137
		3.3.2 Atmospheric pollution	138
		3.3.2.1 Tobacco smoke	140
		3.3.2.2 Geographical factors	141
		3.3.3 Metals	141

3.3.4	Detergents	142
3.4	Endogenous factors affecting sensitization	142
3.4.1	Genetic influence	142
3.4.1.1	Contact sensitization	142
3.4.1.2	IgE-related allergy	143
3.4.1.3	Other genetic factors	145
3.4.2	Tolerance	145
3.4.2.1	Orally induced flare-up reactions and desensitization	146
3.4.2.2	Non-specific and specific mechanisms of unresponsiveness	147
3.4.3	Underlying disease	149
3.4.4	Age	150
3.4.5	Diet	151
3.4.6	Gender	151
4.	CLINICAL ASPECTS OF THE MOST IMPORTANT ALLERGIC DISEASES	152
4.1	Clinical aspects of allergic contact dermatitis	152
4.1.1	Introduction	152
4.1.2	Regional dermatitis	153
4.1.2.1	Hand eczema	153
4.1.2.2	Facial dermatitis	155
4.1.2.3	Other types of dermatitis	156
4.1.3	Special types of allergic contact reactions	156
4.1.3.1	Systemic contact dermatitis	156
4.1.3.2	Allergic photo-contact dermatitis	157
4.1.3.3	Non-eczematous reactions	157
4.1.3.4	Allergic contact urticaria	157
4.1.4	Allergic contact dermatitis as an occupational disease	158
4.1.5	Diagnostic methods	160
4.1.5.1	Patch testing	160
4.1.5.2	<i>In vitro</i> testing	163
4.1.6	Assessment of exposure	163
4.1.7	Treatment and prevention of allergic contact dermatitis	165
4.1.7.1	Primary prevention	165
4.1.7.2	Secondary prevention	167

	4.1.7.3	Ways of preventing contact sensitization	167
	4.1.8	Information needed for a preventative programme	168
4.2		Atopic eczema (atopic dermatitis)	169
	4.2.1	Definition	169
	4.2.2	Epidemiology of atopic eczema	170
	4.2.3	Clinical manifestations and diagnostic criteria	172
	4.2.3.1	Age-dependent clinical manifestations	172
	4.2.3.2	Diagnosis of atopic eczema	172
	4.2.3.3	Stigmata of the atopic constitution	173
	4.2.3.4	Prognosis	173
	4.2.4	Etiology	173
	4.2.4.1	Genetic influence	173
	4.2.5	Environmental provocation factors	174
	4.2.6	Pathophysiology	175
	4.2.6.1	Dry skin	175
	4.2.6.2	Autonomic dysregulation	175
	4.2.6.3	Cellular immunodeficiency	175
	4.2.6.4	Increased IgE production	176
	4.2.6.5	Psychosomatic aspects	176
	4.2.7	Diagnostic approach	177
	4.2.7.1	Medical history	177
	4.2.7.2	Skin tests	177
	4.2.7.3	Laboratory tests	178
	4.2.7.4	Provocation tests	179
	4.2.8.	Therapeutic considerations	179
	4.2.8.1	Avoidance of provocation factors	179
	4.2.8.2	Basic dermatological therapy	180
	4.2.8.3	Anti-inflammatory therapy	181
	4.2.9	Conclusion	181
4.3		Allergic rhinitis and conjunctivitis	181
	4.3.1	Introduction	181
	4.3.2	Definition	182
	4.3.3	Clinical manifestations	182
	4.3.3.1	Seasonal allergic rhinitis and conjunctivitis (hay fever, pollinosis)	182

	4.3.3.2	Perennial allergic rhinitis and conjunctivitis	183
	4.3.3.3	Prognosis	183
4.3.4		Etiology	183
	4.3.4.1	Allergic rhinitis and conjunctivitis caused by contact with chemicals	184
4.3.5		Pathophysiology	185
4.3.6		Diagnostic techniques	186
	4.3.6.1	Medical history	186
	4.3.6.2	Clinical examination	186
	4.3.6.3	Allergy testing	187
4.3.7		Therapeutic considerations	187
4.4		Clinical aspects of allergic asthma caused by contact with chemicals	188
	4.4.1	Introduction	188
	4.4.2	Importance of occupational asthma	188
	4.4.3	Chemical causes of occupational asthma	189
	4.4.3.1	Isocyanates	189
	4.4.3.2	Acid anhydrides	192
	4.4.3.3	Complex platinum salts	193
4.4.4		Diagnosis of occupational asthma	194
	4.4.4.1	Investigation of causes of occupational asthma	195
	4.4.4.2	Serial peak expiratory flow (PEF) rate measurements	195
	4.4.4.3	Immunological investigations	196
	4.4.4.4	Inhalation challenge tests	196
4.4.5		Outcome of occupational asthma	198
4.4.6		Management and prevention of occupational asthma	199
4.5		Food allergy	201
	4.5.1	Definitions	201
	4.5.2	IgE-mediated food allergy	202
	4.5.2.1	Oral allergy syndrome	203
	4.5.2.2	Allergic reactions after ingestion of food	203
	4.5.2.3	Allergic reactions following skin contact with food	205
4.5.3		Non-IgE-mediated immune reactions	205
	4.5.3.1	Gluten-sensitive enteropathy (coeliac disease)	205

4.5.4	Diagnosis of adverse food reactions	206
4.5.4.1	Case history and elimination diet	206
4.5.4.2	Skin tests	206
4.5.4.3	Specific serum IgE	207
4.5.4.4	IgG determination	207
4.5.4.5	Other <i>in vitro</i> tests	208
4.5.4.6	Oral challenge tests	208
4.5.5	Therapeutic considerations	209
4.5.6	Prevalence	209
4.5.6.1	Introduction	209
4.5.6.2	Children	209
4.5.6.3	Adults	210
4.5.6.4	Conclusions	212
4.6	Autoimmune diseases associated with drugs, chemicals and environmental factors	213
4.6.1	Introduction	213
4.6.2	Systemic lupus erythematosus	213
4.6.3	Scleroderma: environmental and drug exposure	218
4.6.4	Silicone breast implants	218
4.6.5	Toxic oil syndrome	220
4.6.6	Eosinophilia-myalgia syndrome	221
4.6.7	Vinyl chloride disease (occupational acro-osteolysis)	222
4.6.8	Systemic vasculitis: environmental factors and drugs	222
4.6.9	Conclusion	223
5.	EPIDEMIOLOGY OF ASTHMA AND ALLERGIC DISEASE	224
5.1	Introduction	224
5.2	Definition and measurement of allergic disease	224
5.2.1	Asthma	224
5.2.1.1	Definition	224
5.2.1.2	Assessment	224
5.2.2	Rhinitis	226
5.2.3	Atopic dermatitis	226
5.2.3.1	Definition	226
5.2.3.2	Assessment	227
5.2.4	Skin-prick test and serum IgE	227

5.2.5	Allergic contact dermatitis	228
5.3	Asthma and atopy: prevalence rates and time trends in prevalence rates	228
5.3.1	Europe	228
	5.3.1.1 Prevalences	228
	5.3.1.2 Time trends	230
5.3.2	Oceania	231
	5.3.2.1 Prevalences	231
	5.3.2.2 Time trends	232
5.3.3	Eastern Mediterranean	232
5.3.4	Africa	233
5.3.5	Asia	233
	5.3.5.1 Prevalences	233
	5.3.5.2 Time trends	233
5.3.6	North America	234
	5.3.6.1 Prevalences	234
	5.3.6.2 Time trends	234
5.3.7	The International Study of Asthma and Allergies in Childhood	235
5.3.8	Conclusion	236
5.4	Age and gender distribution	239
5.5	Migration	239
5.6	Viral infection	240
5.7	Socioeconomic status	241
5.8	Occupational exposure	243
5.8.1	Chemicals with low relative molecular mass	246
	5.8.1.1 Diisocyanates	246
	5.8.1.2 Acrylates	247
	5.8.1.3 Anhydrides	247
	5.8.1.4 Solder flux	247
5.8.2	Metals	248
	5.8.2.1 Cobalt	248
	5.8.2.2 Metal-polishing industry	248
	5.8.2.3 Aluminium	249
	5.8.2.4 Platinum salts	249
5.8.3	Natural rubber latex	249
5.8.4	Flour	251
5.8.5	Animals	251
5.8.6	Other agents	252

5.9	Allergic contact dermatitis	252
5.9.1	Epidemiology of allergic contact dermatitis	252
5.9.1.1	Nickel	253
5.9.1.2	Chromates	253
5.9.1.3	Fragrances	253
5.9.1.4	Preservatives	254
5.9.1.5	Medicines	254
5.9.1.6	Plants and woods	254
5.9.2	Lack of a relationship between atopy and allergic contact sensitization	255
5.10	Diet	256
5.10.1	Breast feeding	257
5.10.2	Sodium	258
5.10.3	Selenium	259
5.10.4	Vitamins and antioxidants	260
5.11	Number of siblings and crowding	261
5.12	Indoor environment	261
5.12.1	Tobacco smoke	262
5.12.2	Pets	263
5.12.3	Biocontaminants	263
5.12.3.1	House dust mites and insects	263
5.12.3.2	Moulds	264
5.12.4	Other indoor factors	265
5.13	Indoor and outdoor environmental factors	265
5.13.1	Nitrogen dioxide	265
5.13.2	Sulfur dioxide, acid aerosols and particulate matter	265
5.13.3	Volatile organic compounds, formaldehyde and other chemicals	266
5.14	Outdoor air pollution	267
5.14.1	Pollen and dust	268
5.14.2	Ozone	269
5.14.3	Motor vehicle emissions	269
5.15	Conclusions	270
6.	HAZARD IDENTIFICATION: DEMONSTRATION OF ALLERGENICITY	272
6.1	Hazard and risk; allergy and toxicity	272

6.1.1	Testing allergic potential and toxicity testing	273
6.1.2	Databases and prior experience	274
6.2	Validation and quality assurance	274
6.3	Structure-activity relationships	275
6.3.1	Case-Multicase system	276
6.3.2	DEREK skin sensitization rulebase	276
6.3.3	SAR for respiratory hypersensitivity	277
6.4	Predictive testing <i>in vivo</i>	278
6.4.1	Testing for skin allergy	278
6.4.1.1	Testing in guinea-pigs	278
6.4.1.2	Testing in mice	280
6.4.1.3	Predictive testing for skin allergy in humans	281
6.4.2	Testing for respiratory allergy	282
6.4.2.1	Guinea-pig model	282
6.4.2.2	Mouse IgE model	285
6.4.2.3	Rat model	286
6.4.2.4	Predictive testing for respiratory allergy in humans	287
6.4.2.5	Cytokine fingerprinting	287
6.5	Testing for food allergy	287
6.6	<i>In vitro</i> approaches	289
6.7	Testing for autoimmunity	290
6.7.1	Popliteal lymph node assay	290
6.7.2	Animal models of autoimmune disease	291
6.8	Clues from general toxicity tests	294
7.	RISK ASSESSMENT	296
7.1	Introduction	296
7.2	Risk assessment of allergy	296
7.3	Factors in risk assessment of allergy	297
7.4	Information aspects	299
7.4.1	No information about hazard	299
7.4.2	Scanty or no information about exposure	300
7.4.3	Unreliable or scanty information about risk	301
7.5	Conclusions	304
8.	TERMINOLOGY	305

9. CONCLUSIONS	319
10. RECOMMENDATIONS FOR PROTECTION OF HUMAN HEALTH	321
11. FURTHER RESEARCH	324
REFERENCES	326
CONCLUSIONS	392
CONCLUSIONES	396