

Table of Contents

Preface *xix*

Volume I

1	Inflammation through the Ages: A Historical Perspective	1
	<i>Jean-Marc Cavaillon</i>	
1.1	Introduction	1
1.2	The First Treatments	1
1.3	The Definitions	3
1.4	Fever	3
1.5	Phagocytosis	4
1.6	Diapedesis	6
1.7	Chemotactism	7
1.8	Infection and Inflammation	8
1.9	Usefulness of Inflammation for Adaptive Immune Response	9
1.10	Mediators of Inflammation	10
	References	12

Part One Inducers and Sensors of Inflammation 17

2	Pathogen-associated Molecular Patterns	19
	<i>Jean-Marc Cavaillon</i>	
2.1	Definition	19
2.2	Endotoxin	20
	2.2.1 Brief Historical Background	20
	2.2.2 Biochemical Characteristics	21
	2.2.3 Detection	23
	2.2.4 Natural Ligands	24
	2.2.5 Cell Activation	25
	2.2.6 Tolerance	26
2.3	Other Bacterial PAMPs	26
	2.3.1 Lipoproteins	26
	2.3.2 Lipoteichoic Acid	27
	2.3.3 Flagellin	28

2.3.4	Peptidoglycan	28
2.3.5	Fimbriae	30
2.3.6	Glycogolipids	30
2.3.7	Heat Shock Proteins	30
2.3.8	Bacterial DNA	31
2.3.9	Bacterial RNA	32
2.4	Viral PAMPs	33
2.5	Parasitic PAMPs	35
2.6	Fungal PAMPs	36
2.7	Synergy	37
	References	38

3 Damage-associated Molecular Patterns 57

Jean-Marc Cavaillon

3.1	Definition	57
3.2	Necrosis versus Apoptosis	58
3.3	Receptors of Danger Signals	58
3.4	Main DAMPs	60
3.4.1	High-mobility Group Box 1	60
3.4.2	Heat Shock Protein	61
3.4.3	RNA and DNA	62
3.4.4	Mitochondria	62
3.4.5	Histones	62
3.4.6	Uric Acid Crystals	63
3.4.7	ATP	63
3.4.8	S100A8/S100A9	64
3.4.9	Interleukin-1 α and Interleukin-33	64
3.4.10	Heme	65
3.4.11	Hyaluronan	65
3.4.12	Biglycan	66
3.4.13	Heparan Sulfate	66
3.4.14	Eosinophil-derived Neurotoxin	66
3.4.15	Peroxiredoxins	67
	References	67

4 Bacterial Toxins 81

Marina de Bernard and Cesare Montecucco

4.1	Introduction	81
4.2	Toxins Modulating the Activity of Inflammatory Caspases and Inflammasomes	82
4.3	Toxins Modulating the Intracellular cAMP Levels	84
4.4	Toxins Modulating MAPK Signaling	85
4.4.1	Synergy between ET and LT	86
4.5	Toxins Affecting Host Cell Motility	87
4.6	Toxins Blocking Protein Synthesis or Protein Folding	88
4.7	Conclusions	89
	References	90

5	Venoms	99
	<i>Catarina Teixeira, Vanessa Moreira, and José María Gutiérrez</i>	
5.1	Introduction	99
5.2	Inflammation Induced by Snake Venoms	100
5.3	Inflammation Induced by Scorpion Venoms	105
5.4	Inflammation Induced by Spider Venoms	107
5.5	Inflammation Induced by Venoms of Bees, Vespids, and Ants	110
5.6	Conclusions	112
	References	113
6	Hypoxia as an Inducer of Inflammation	129
	<i>Ariel Brandwein and Clifford S. Deutschman</i>	
6.1	Introduction	129
6.2	Oxygen Sensing	130
6.3	Mitochondrial Oxygen Sensing	131
6.4	The Role of Transcription Factors	132
	6.4.1 Hypoxia-Inducible Factor	133
	6.4.2 Nuclear Factor κ B	135
6.5	The Warburg Effect	135
6.6	Acute versus Chronic Hypoxia	136
6.7	Inflammasome Activation	137
6.8	Summary and Conclusions	139
	References	139
7	Vaccine Adjuvants	143
	<i>Dennis M. Klinman and Hidekazu Shirota</i>	
7.1	Introduction	143
7.2	Adjuvants Approved for Human Use	144
7.3	Aluminum Compounds: The Gold Standard	144
7.4	AS04	145
7.5	Calcium Phosphate	145
7.6	Emulsions	146
	7.6.1 IFA and CFA	146
	7.6.2 MF59	146
	7.6.3 AS03	147
7.7	Nano/microparticles Including Liposomes and Virosomes	148
7.8	Immune Stimulating Complexes	148
7.9	Cytokines	149
	7.9.1 IL-12	149
	7.9.2 IL-2	149
	7.9.3 IL-15	150
	7.9.4 GM-CSF	150
7.10	Adjuvants that Target Toll-like Receptors	150
	7.10.1 Introduction	150
	7.10.2 TLR2	151
	7.10.2.1 Overview	151
	7.10.2.2 TLR2 ligands	151

	7.10.2.3 Clinical Activity	151
	7.10.2.4 Safety	152
7.10.3	TLR3	152
	7.10.3.1 Overview	152
	7.10.3.2 TLR3 Ligands and Their Immunogenicity	152
	7.10.3.3 Safety	153
7.10.4	TLR4	153
	7.10.4.1 Overview	153
	7.10.4.2 TLR4 Ligands	153
	7.10.4.3 Clinical Activity	153
	7.10.4.4 Safety	154
7.10.5	TLR5	154
	7.10.5.1 Overview	154
7.10.6	TLR7/8	154
	7.10.6.1 Overview	154
	7.10.6.2 TLR7/8 Ligands and Their Preclinical Activity	155
	7.10.6.3 Clinical Activity	155
	7.10.6.4 Safety	155
7.10.7	TLR9	156
	7.10.7.1 Overview	156
	7.10.7.2 TLR9 Ligands	156
	7.10.7.3 Clinical Activity	156
	7.10.7.4 Safety	157
7.11	Adjuvant Combinations	157
7.12	Future Directions	157
	References	158
8	Pattern Recognition Receptors	175
	<i>Lauren Whitehead and Gordon D. Brown</i>	
8.1	Introduction	175
8.2	Toll-like Receptors	176
	8.2.1 Cell Surface-bound TLRs	177
	8.2.2 Endosomal TLRs	178
	8.2.3 TLR Signaling	179
	8.2.4 MyD88-dependent Signaling Pathway	179
	8.2.5 TRIF Signaling Pathway	179
8.3	C-type Lectin Receptors	181
	8.3.1 DC-SIGN	181
	8.3.2 Mannose Receptor	182
	8.3.3 Surfactant Protein D	182
8.4	Natural Killer Gene Complex-associated CLRs	183
	8.4.1 Activation Receptors	183
	8.4.2 Inhibitory Receptors	185
	8.4.3 CLR Signaling	186
8.5	RIG-1-like Receptors	187
	8.5.1 RLR Signaling	188

8.6	NOD-like Receptors	189
8.6.1	NOD1 and NOD2	191
8.6.2	NOD1 and NOD2 Signaling	192
8.6.3	NLRC4	192
8.6.4	NLRPs	192
8.7	DNA-sensing Molecules	193
8.7.1	Signaling Components of DNA-sensing Molecules	194
8.7.2	Cross-talk between PRRs	195
8.8	Conclusions	195
	Acknowledgments	196
	References	196

Part Two Inflammatory Cells 217

9	Monocytes and Macrophages	219
	<i>Irina N. Shalova, Shilpi Saha, and Subhra K. Biswas</i>	
9.1	Introduction	219
9.2	Origin and Differentiation	219
9.3	Activation and Polarization	221
9.4	Functions	222
9.4.1	Cytokine Production and Inflammation	223
9.4.2	Phagocytosis	224
9.4.3	Antigen Presentation	226
9.4.4	Migration	227
9.4.5	Immunoregulation	228
9.4.6	Vascular Functions	229
9.5	Molecular Pathways and Mechanisms Regulating Response	230
9.5.1	Signaling Pathways	230
9.5.2	Epigenetic Regulation	232
9.5.3	Micro-RNAs	234
9.6	Conclusions	235
	Acknowledgment	235
	References	236
10	Neutrophils	253
	<i>Salvatore Cuzzocrea</i>	
10.1	Characteristics	253
10.2	Hematopoiesis	254
10.3	Adhesion and Migration	255
10.3.1	Traffic and Margination	255
10.3.2	Adhesion to the Endothelial Wall	256
10.3.3	Transendothelial Migration	257
10.4	Phagocytosis and Degranulation	258
10.4.1	Phagocytosis	258
10.4.2	Degranulation	259

10.5	Cytokine Synthesis	260
10.5.1	TNF- α	260
10.5.2	IL-1 and IL-1 Receptor Antagonist	260
10.5.3	IL-8 as a Model of Chemokines	261
10.5.4	Modulation of Cytokine Expression and Production by Neutrophils	261
10.6	Neutrophil Apoptosis	261
10.7	Neutrophils in Pathology	262
10.7.1	Bacterial Infection	263
10.7.2	Tissue Injury-induced Inflammation: Ischemia-reperfusion Injury	263
10.7.3	Crystal-induced Inflammation	263
10.7.4	Cytokine-induced Inflammation: Rheumatoid Arthritis	263
10.7.5	Autoimmunity Against Neutrophil Components: Antineutrophil Cytoplasmic Antibodies and Vasculitis	264
10.7.6	Genetic Disorders of Neutrophil Regulations: Hereditary Periodic Fever Syndromes	264
10.7.7	Cystic Fibrosis: Neutrophil-mediated Tissue Damage and Concomitant Persistence of Infection	265
10.8	Conclusions	265
	References	266
11	Mast Cells: Master Drivers of Immune Responses against Pathogens	273
	<i>W.X. Gladys Ang and Soman N. Abraham</i>	
11.1	Introduction	273
11.2	Biology of Mast Cells	273
11.3	Role of Mast Cells in Immune Surveillance	275
11.3.1	Strategic Peripheral Location	275
11.3.2	Direct Recognition of Pathogens	275
11.3.3	Indirect Recognition of Pathogens	276
11.3.4	Activation by Endogenous Danger Signals	276
11.3.5	Degranulation and Secretory Responses to Pathogens	277
11.4	Mast Cells in Innate Immunity	278
11.4.1	Direct Bactericidal Activity of Mast Cells	278
11.4.2	Resistance to Exo- and Endotoxins	278
11.4.3	Induction of Immune Cell Trafficking to Sites of Infection	279
11.5	Mast Cells in Adaptive Immunity	279
11.5.1	Mast Cells as Effectors of Adaptive Immunity	279
11.5.2	Recruitment of DCs and Effector T Cells to Sites of Infection	280
11.5.3	Recruitment of Dendritic Cells and T Cells to Draining Lymph Nodes	280
11.5.4	Antigen Presentation	280
11.6	Enhancement of Immunity by Boosting Mast Cell Activity	281
11.6.1	Mast Cell Activators as Novel Vaccine Adjuvants	281
11.6.2	Synthetic Mast Cell Granules	281

11.7	Potentially Detrimental Roles of Mast Cell Activation during Immune Responses	282
11.7.1	Overactivation of Mast Cells	282
11.7.2	Negative Modulation of Immunity by Mast Cells	283
11.8	Concluding Remarks	283
	Acknowledgments	284
	References	284

12	Dendritic Cells in Inflammatory Disease	289
	<i>Bart N. Lambrecht, Martin Guillems, and Hamida Hammad</i>	
12.1	What Defines a Dendritic Cell?	289
12.2	Dendritic Cell Subsets	290
12.3	Dendritic Cells and T-cell Polarization	291
12.4	Dendritic Cells in Allergic Inflammation	292
12.4.1	Dendritic Cells are Necessary and Sufficient for Induction of Th2 Immunity	292
12.4.2	Different Subtypes of DCs Induce Th2 Immunity	293
12.4.3	Dendritic Cells are Also Required for Effector Th2 Immune Responses to Allergens	294
12.4.4	DCs Get Activated Directly after Exposure to Allergen	295
12.4.5	Lung DCs Activated Indirectly by Epithelial Cells	296
12.5	Inflammatory DCs' Role in Human Allergy	298
12.6	Dendritic Cells in Autoimmune Inflammatory Disease	298
12.7	Conclusions	299
	References	300

13	Roles for NK Cells and ILC1 in Inflammation and Infection	315
	<i>Christian A.J. Vosshenrich and James P. Di Santo</i>	
13.1	Introduction	315
13.2	Distinguishing Group 1 ILC and NK Cells	316
13.3	NK Cell and ILC1 Activating and Inhibitory Receptors	317
13.3.1	Natural Cytotoxicity Receptors	317
13.3.2	NKG2D	318
13.3.3	DNAX Accessory Molecule-1 (DNAM-1, CD226)	318
13.3.4	MHC Class I-specific Receptors and NK Cell "Education"	318
13.3.5	Are ILC1s "Educated" Similar to Conventional NK Cells?	319
13.4	Evidence for Distinct Subsets of NK Cells and ILC1	319
13.5	Effector Functions of NK Cells and ILC1	320
13.6	NK Cells and Group 1 ILCs in Inflammation and Infection	322
13.6.1	Mouse Cytomegalovirus	322
13.6.2	Influenza Virus	323
13.6.3	NK Cells and Other Viral Infections	324
13.6.4	Salmonella	324
13.6.5	Listeria monocytogenes	325
13.6.6	Mycobacteria and Other Bacteria	325

13.7	NK Cell and ILC1 Memory	326
13.8	Concluding Remarks: NK and ILC1 as Partners in a Type 1 Network	327
	References	329
14	Group 2 and 3 Innate Lymphoid Cells: New Actors in Immunity and Inflammation	341
	<i>Nicolas Serafini and James P. Di Santo</i>	
14.1	ILCs: A New Family of Innate Effector Cells	341
14.2	ILC2 and ILC3 Heterogeneity and Homeostasis	342
14.3	ILC2 in Acute and Chronic Inflammation	345
14.4	ILC3 in Acute and Chronic Inflammation	348
14.5	Therapeutically Harnessing ILC2 and ILC3	351
14.6	Concluding Remarks	352
	References	353
15	Th9 Cells: From the Bench to the Bedside and Back Again	365
	<i>Benjamin J. Ulrich, Matthew M. Hufford, and Mark H. Kaplan</i>	
15.1	The History of T Helper Cells	365
15.2	Introduction to Th9 Cells	367
15.2.1	Development	367
15.2.2	Additional Th9-inducing Cytokines	368
15.2.3	Th9-inducing Cell Surface Ligands	369
15.2.4	The Function of Th9 Cells	369
15.3	Th9 Cells in Disease: The Helpful and Unhelpful	371
15.3.1	Tumor Immunity	372
15.3.2	Helminth Immunity	372
15.3.3	Inflammatory Bowel Disease	373
15.3.4	Allergic Inflammation	374
15.3.5	Dermatitis	376
15.3.6	Food Allergy	377
15.4	Targeting Th9 Cells Therapeutically	377
15.4.1	Th9 Differentiation	377
15.4.1.1	Cytokines and Costimulators Required for Differentiation	377
15.4.1.2	Transcription Factors for Differentiation	379
15.4.1.3	Factors Required for Promotion of Th9 Biology	380
15.4.2	Th9-associated Effector Molecules	381
15.5	Summary and Future Directions	382
	References	382
16	Th17 Cells	395
	<i>Mélissa Noack and Pierre Miossec</i>	
16.1	Introduction	395
16.2	Differentiation of Th17 Cells	396
16.2.1	Th17 Cell Differentiation in Mice	396
16.2.2	Th17 Cell Differentiation in Humans	397

16.2.3	Pathogenic Th17 Cells	398
16.2.4	Circulating versus Tissue Phenotypes	398
16.3	Cytokines and Chemokines Related to Th17 Cells	399
16.3.1	Major Cytokines and Chemokines Produced by Th17 Cells	399
16.3.1.1	IL-17A (IL-17)/IL-17F	399
16.3.1.2	IL-21	400
16.3.1.3	IL-22	400
16.3.1.4	CCL20	400
16.3.2	Major Cytokines Acting on Th17 Cells	401
16.3.2.1	IL-23	401
16.3.2.2	IL-27	401
16.4	Th17 and Inflammatory Diseases	401
16.4.1	Psoriasis	402
16.4.2	Arthritic Diseases	402
16.4.3	Multiple Sclerosis	403
16.4.4	Inflammatory Bowel Diseases	403
16.5	Mechanisms in Chronic Inflammation	403
16.5.1	Differentiation, Recruitment, and Maintenance of Th17 Phenotype during Chronic Inflammation	403
16.5.2	Secretion of IL-17 and its Activity	404
16.6	Plasticity of Th17 Cells	405
16.7	Clinical Targeting of Th17 Cells	407
16.8	Conclusions	408
	Acknowledgment	408
	References	408

17 Platelets 419

Jack Levin

17.1	Introduction	419
17.2	Expression of Toll-like Receptors	422
17.3	Interactions between Platelets and Bacteria	422
17.4	Interactions between Platelets and White Blood Cells	423
17.5	Platelet Integrins	424
17.6	Role of Platelets in Immune Responses	425
17.7	Platelets and Inflammatory Disorders	425
17.8	Malaria	426
17.9	Systemic Lupus Erythematosus	426
17.10	Conclusions	426
	References	427

18 Epithelial Cells 437

Jill M. Hoffman and Charalabos Pothoulakis

18.1	Introduction	437
18.2	The Intestinal Epithelium: An Archetypal Epithelial Barrier	438
18.3	Choosing a Cell Fate: The Absorptive Lineage	438
18.4	Choosing a Cell Fate: The Secretory Lineage	439

- 18.4.1 Goblet Cells 439
- 18.4.2 Paneth Cells 441
- 18.4.3 Enteroendocrine Cells 441
- 18.5 The Epithelium: The Sum is Greater than its Parts 442
- 18.6 Epithelial Homeostasis: Maintaining the Balance 443
 - 18.6.1 Wnt Signaling 443
 - 18.6.2 Notch Signaling 444
 - 18.6.3 Inflammation-induced Alterations in Epithelial Cells 445
- 18.7 Concluding Remarks 447
- References 447

- 19 Inflammation: The Role of Endothelial Cells 457
 - J. Steven Alexander, D. Neil Granger, and Norman R. Harris*
 - 19.1 Introduction 457
 - 19.2 Vasomotor Dysfunction 458
 - 19.2.1 Mechanism of Vascular Smooth Muscle Contraction/relaxation 459
 - 19.2.2 Endothelial Cell-dependent Vasoactivity 459
 - 19.2.3 Endothelium-dependent Vasoactivity in IBD 460
 - 19.2.3.1 Leukocyte– and Platelet–endothelial Cell Adhesion 461
 - 19.2.3.2 Enhanced Thrombosis 463
 - 19.2.3.3 Angiogenesis/vasculogenesis 465
 - 19.2.3.4 Junctional and Vascular Permeability 468
 - 19.3 Conclusions 470
 - References 471

Volume II

Part Three Inflammatory Mediators 477

- 20 IL-1 Superfamily and Inflammasome 479
 - Charles A. Dinarello*
- 21 TNF Superfamily 529
 - Salvatore Cuzzocrea*
- 22 Interleukin-17 A-E 549
 - Giovanni Monteleone, Irene Marafini, and Edoardo Troncone*
- 23 IL-6 Superfamily 573
 - Toshio Tanaka, Masashi Narazaki, and Tadamistu Kishimoto*
- 24 Type I and II Cytokine Superfamilies in Inflammatory Responses 587
 - William F. Carson IV and Steven L. Kunkel*

- 25 **Chemokines and Chemotaxis** 619
Osamu Yoshie and Kouji Matsushima
- 26 **Lipid Mediators in Inflammation** 651
Shuh Narumiya, Takehiko Yokomizo, and Junken Aoki
- 27 **Free Radicals in Inflammation** 695
Andrew Cumpstey and Martin Feelisch
- 28 **Proteases** 727
Celine Deraison, Chrystelle Bonnart, and Nathalie Vergnolle
- 29 **Psychiatric Disorders and Inflammation** 767
Robert Dantzer
- 30 **Complement System** 785
Peter A. Ward and Claudia Kemper
- 31 **Heat Shock Proteins** 813
Willem van Eden, Femke Broere, and Ruurd van der Zee

Volume III

Part Four Inflammation and Host Response 831

- 32 **Inflammation and Coagulation** 833
Marcel Levi
- 33 **Fever: Mediators and Mechanisms** 861
Joachim Roth
- 34 **Pain** 891
Christoph Stein
- 35 **Inflammation, Hormones, and Metabolism** 915
Muska Khpal and Mervyn Singer
- 36 **Microenvironmental Regulation of Innate Immune
Cell Function** 947
Emily R. Watts, Eilise Ryan, Sarah R. Walmsley, and Moira K.B. Whyte
- 37 **Epigenetics of Inflammation** 971
Vidula Vachharajani and Charles E. McCall

Part Five Inflammation and Diseases 993

- 38 Allergy and Inflammation 995**
Milena Sokołowska, Anna Głobińska, and Cezmi A. Akdis
- 39 Sepsis 1031**
Manu Shankar-Hari and Mervyn Singer
- 40 Autoimmunity and Inflammation 1053**
Shrikant Ramesh Mulay, Onkar P. Kulkarni, Khader Rupanagudi, and Hans-Joachim Anders
- 41 Psoriasis and Other Skin Inflammatory Diseases 1091**
Jaehwan Kim and James G. Krueger
- 42 Rheumatoid Arthritis and Other Inflammatory Articular Diseases 1105**
Rogier M. Thurlings, Sander W. Tas, and Paul Peter Tak
- 43 Missing Heritability of Crohn's Disease and Implications for Therapeutic Targeting and Improved Care 1141**
Matthias Chamaillard
- 44 Inflammation and Transplantation 1147**
William M. Baldwin, III and Robert L. Fairchild
- 45 Inflammatory Mechanisms in Chronic Obstructive Pulmonary Disease 1173**
Peter J. Barnes
- 46 Obesity: A Complex Disease with Immune Components 1199**
Yuejun Liu and Karine Clément
- 47 Inflammation and Type 2 Diabetes 1225**
Marleen M.J. van Greevenbroek, Casper G. Schalkwijk, and Coen D.A. Stehouwer
- 48 Inflammation-Mediated Neurodegeneration: Models, Mechanisms, and Therapeutic Interventions for Neurodegenerative Diseases 1255**
Hui-Ming Gao, Yun Gao, Dezhen Tu, Yue Liu, Hui Zhou, and Jau-Shyong Hong
- 49 Inflammation in Atherosclerosis 1279**
Mario A.R. Lauterbach, Larisa I. Labzin, and Eicke Latz

- 50 Acute Kidney Injury 1301**
Johan Mårtensson and Rinaldo Bellomo
- 51 Ischemia–Reperfusion Syndrome 1313**
Christophe Adrie, Sally A. Shin, and Mehran Monchi
- 52 Single-Nucleotide Polymorphisms and Inflammation 1329**
Evangelos J. Giamarellos-Bourboulis

Volume IV

Part Six Resolution of Inflammation and Tissue Repair 1347

- 53 Pentraxins in the Orchestration of Defense and Tissue Repair during the Acute Phase Response 1349**
Alberto Mantovani, Cecilia Garlanda, and Barbara Bottazzi
- 54 Anti-Inflammatory Cytokines, Soluble Receptors, and Natural Antagonists 1363**
Willem Joost Wiersinga and Tom van der Poll
- 55 Regulatory T Cells 1377**
Luciana Berod, Katharina Lahl, Matthias Lochner, Christian T. Mayer, and Tim Sparwasser
- 56 Leukocyte Reprogramming 1423**
Jean-Marc Cavaillon
- 57 Roles of Specialized Proresolving Lipid Mediators in Inflammation Resolution and Tissue Repair 1447**
Matthew Spite and Charles N. Serhan
- 58 Glucocorticoids 1467**
Heming Nicholas and Annane Djillali
- 59 The Neuroimmune Communicatome in Inflammation 1485**
Peder S. Olofsson, Christine N. Metz, and Valentin A. Pavlov
- 60 The Inflammatory Response in Tissue Repair 1517**
Nikolaos G. Frangogiannis

Part Seven Detection and Treatments 1539

- 61 Biomarkers in Inflammation 1541**
Andreas Kortgen and Michael Bauer

62	<i>In Vivo</i> Imaging of Inflammation	1567
	<i>Anne Roivainen and Antti Saraste</i>	
63	Novel Targets for Drug Development	1583
	<i>Alan S. Cross and Steven M. Opal</i>	
64	Inflammation and Microbiota and Gut Reconditioning	1609
	<i>Stig Bengmark</i>	
65	Natural Products as Source of Anti-Inflammatory Drugs	1661
	<i>Shivaprasad H. Venkatesha, Bodhraj Acharya, and Kamal D. Moudgil</i>	