

basic & clinical immunology

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Preface

The past three decades have been marked by rapid advances in all medical and technologic fields pertaining to immunology, so that now this branch of medical science clearly ranks as a special discipline in its own right rather than a subdivision of microbiology or allergy.

With all this interest and activity has come inevitable expansion in the variety and bulk of the supporting literature. There are now a multitude of journals primarily devoted to immunologic topics, and almost all of the medical journals are soliciting or accepting articles on the immunologic features of disease, organ transplants, basic and applied research in immunology, tumor immunology, and immunotherapy.

There are many good books on the subject, and we hope we have not neglected to list any of them in the bibliography pages at the ends of the chapters. Observing that events seemed to have outrun our best competition, the editors decided that another book was justified. *Basic & Clinical Immunology* is already written as we prepare this Preface, and we note that the men and women who make the events happen are still not idle. The result is that as we examine page proof and prepare the Index we are already working on the Second Edition, due in 1978, and will continue to offer new editions biennially. *For these future publications, the reader's comments are urgently solicited.*

The book is divided into four sections, and the sequence of chapters is intended to be logical. The first section describes the fundamentals of immunochemistry and cellular immunology. The second section applies this knowledge to a discussion of immunobiology, an area that bridges basic and clinical immunology. The third section describes the immunologic laboratory tests that are available for evaluation of patients. The fourth section presents the immunologic aspects of a variety of human diseases.

The clinical chapters focus on primary immunologic diseases or on disorders with important immunopathologic characteristics. These discussions are not intended to serve as a manual of clinical treatment; where specific medications or drug dosages are mentioned, the physician should also consult more comprehensive medical texts.

It is hoped that this book will serve as a text for medical students, house officers, graduate students, practicing physicians, and others interested in learning more about the field. Immunologists from both basic and clinical disciplines should find it a comprehensive review.

The support provided by the staff of the publisher—particularly Drs Ransom and Lange—has been invaluable in this venture, and they have our deep appreciation. Much of the art work was done by the expert hand of Ms Laurel Schaubert, who has our thanks. Finally, we wish to express our gratitude to the contributing authors whose knowledge it is that represents whatever value this book may have; and to the institutions that have supported us during the long task of preparing this book.

—The Editors

Table of Contents

Preface	xv
Section I. Basic Immunology	1
1. The Historical Background of Immunology	3
<i>Pierre Grabar, DSc</i>	
Early Immunology 3	
"Cellular Immunity" Theory 4	
"Humoral" Theory 4	
Ehrlich's "Side-Chain" Theory 5	
Antitissue Immune Sera 9	
Immunochemistry 9	
Immunologic Tolerance 10	
Recent Period of Immunology 10	
Future Development 11	
Conclusion 12	
A Short Chronology of Important Achievements in Immunology 12	
2. The Structure of Immunoglobulins	15
<i>An-Chuan Wang, PhD</i>	
Basic Structure & Terminology 15	
Classes & Subclasses of Immunoglobulins 17	
Four-Chain Basic Unit 19	
Disulfide Bonds 21	
Domains 23	
Two Genes, One Polypeptide Chain 24	
Secretory Component & J Chain 25	
Carbohydrate Moieties of Immunoglobulins 27	
Evolution of Immunoglobulins 27	
3. Immunogenicity & Antigenic Specificity	32
<i>Joel W. Goodman, PhD</i>	
Immunogens 32	
Antigenic Determinants 33	
Immunogenic Determinants 39	
Thymus-Independent Antigens 39	
Concluding Remarks 40	
4. Antigen-Antibody Reactions	41
<i>Joseph L. Caldwell, MD</i>	
Antigen Binding 41	
Location of Antigen-Binding Regions 43	
Size of Antigen-Binding Region 45	
Detection of Antigen Binding 47	
Conformational Changes Resulting From Antigen Binding 50	
Overview 50	
5. Genetic Markers of Human Immunoglobulins	52
<i>Moses S. Schenfield, PhD</i>	
Genetic Markers on Antibodies 52	
Testing for Allotypes 54	
Gm Allotypes & Subclass Serum Levels 54	
Gm Allotypes & Levels of Other Immunoglobulins 55	
Role of Allotypes in Hypogammaglobulinemia 55	
Restrictions of Subclass & Allotype in Specific Antibodies 55	
Allotypes & Immune Response 55	
Allotypes & Disease 56	
Conclusion 57	

6. The Complement System	58
<i>Neil R. Cooper, MD</i>	
Mechanism of Action of the Complement System 58	Control Mechanisms of the Complement System 63
The Classical Complement Pathway 58	Methods of Detection & Quantitation of Complement Components 64
The Alternative Complement Pathway 62	Biologic Consequences of Complement Activation 66
The Reaction of C5-C9: The Membrane Attack Mechanism 63	Biologic Significance of the Complement System 68
7. Cells Involved in Immune Responses	70
<i>Steven D. Douglas, MD</i>	
Histologic Organization of the Lymphoreticular System 70	Mononuclear Phagocytes (Monocyte-Macrophages) 81
Lymphoid Cells 72	Other Cell Types Involved in Immunologic Phenomena 83
8. Cell Cooperation in Immune Responses	88
<i>John J. Marchalonis, PhD</i>	
T & B Cell Cooperation 88	Transformation of T & B Cells 90
Thymus Dependence of Antigens & Immunoglobulins 88	Cooperation Between T & B Cells 91
Specific Recognition of Antigen by T & B Cells 88	Conclusions 96
9. Biosynthesis of Antibodies	97
<i>J. Vivian Wells, MD</i>	
Technics for Study of Antibody Biosynthesis 97	Immunoglobulin Biosynthesis 98
Control of Antibody Biosynthesis 98	Assembly & Secretion of Immunoglobulins 99
	Secreted & Membrane Immunoglobulin 101
10. Mediators of Cellular Immunity	102
<i>Ross E. Rocklin, MD</i>	
Factors Affecting Macrophages 103	In Vivo Significance of Mediators 110
Factors Which Affect Polymorphonuclear Leukocytes 107	Cell Types Producing Mediators 111
Mediators Affecting Lymphocytes 108	Pharmacologic Modulation of Mediator Production 112
Mediators Affecting Other Cell Types 108	Clinical Significance 112
	Biologic Significance 112
Section II. Immunobiology	115
11. Phylogeny & Ontogeny of the Immune Response	117
<i>Daniel P. Stites, MD, & Joseph L. Caldwell, MD</i>	
Phylogeny of Immunity in Animals 117	B Cells 123
Immunity in Invertebrates 117	Thymic Humoral Factors 127
Immunity in Vertebrates 120	Human Fetal Complement Development 128
Ontogeny of Immunity in Vertebrates 121	Development of Immunoglobulins in Human Serum 129
Lymphoid Cell Development 121	
T Cells 121	
12. Genetic Regulation of Immune Responses	130
<i>Joseph L. Caldwell, MD</i>	
Guinea Pig Immune Response Genes Linked to the Major Histocompatibility Complex 130	Murine Immune Response Genes Linked to the Major Histocompatibility Locus 133
	Human Immune Response Genes Linked to the Major Histocompatibility Locus 137
13. Specific Immunologic Unresponsiveness	140
<i>William D. Linscott, PhD</i>	
Immunologic Tolerance 140	Immunologic Enhancement 147

14. Autoimmunity	151
<i>Norman Talal, MD, Ken Fye, MD, & Haralampos Moutsopoulos, MD</i>	
Immunologic Tolerance 152	Other Animal Models for Autoimmune Diseases 157
The Role of Viruses in Autoimmunity 154	Conclusion 158
Animal Models for Human Autoimmune Disease: NZB Mouse Disease 155	
15. Transplantation Immunology	160
<i>Herbert A. Perkins, MD</i>	
The Major Human Histocompatibility Loci 181	Kidney Transplantation 165
The HLA Genes & Their Allelic Products 181	Other Solid Organ Transplants 166
Haplotypes & Their Inheritance 183	Marrow Transplants 168
Frequency & Distribution of HLA Antigens 184	Blood Transfusion 167
Typing HLA Antigens 185	Platelet Transfusions 167
Indications for Histocompatibility Testing 185	Granulocyte Transfusions 167
	Current Research Efforts 167
	Conclusion 168
16. The Secretory Immune System	170
<i>Stephen P. Hauptman, DO, & Thomas B. Tomasi, Jr., MD, PhD</i>	
17. Immunity & Infection	182
<i>David J. Drutz, MD</i>	
Host Defenses at Body Surfaces 182	The Mononuclear Phagocyte System & Its Function 189
Systemic Immunity to Infection 184	Special Aspects of Viral Immunity 191
Polymorphonuclear Neutrophil Leukocyte Function 185	Fever 183
18. Metabolism of Immunoglobulins	195
<i>J. Vivian Wells, MD</i>	
Principles of Metabolic Turnover Studies 195	Factors Controlling Immunoglobulin Metabolism 200
Technics of Metabolic Studies 196	Immunoglobulin Metabolism in Various Disorders 201
Metabolism of Immunoglobulins 197	
19. Immediate Hypersensitivity	204
<i>Oscar L. Frick, MD</i>	
Anaphylaxis 204	Cell Receptors & Allergic Reactions 215
Allergy & Atopy 207	The Balance Theory of Regulation Controls 219
Target Cells of IgE-Mediated Allergic Reactions 212	The β -Adrenergic Blockade Theory of Asthma 221
Mediators of Allergic Reactions 212	Approaches to the Treatment of Allergy Based Upon the Mechanism of the Reaction 223
20. Immune Mechanisms in Tissue Damage	225
<i>J. Vivian Wells, MD</i>	
Type I Reactions 225	Type III Reactions 231
Type II Reactions 228	Arthus Reaction 232
Complement-Dependent Antibody Lysis 229	Serum Sickness 232
Antibody-Dependent Cell-Mediated Cytotoxicity 231	Immune Complex Disorders 232
	Type IV Reactions 236
	Cell-Mediated Cytotoxicity 238
	Humoral Amplification Systems 238
	Drug Reactions 240
21. Tumor Immunology	242
<i>Vera S. Byers, PhD, & Alan S. Levin, MD</i>	
Historical Aspects of Tumor Immunology 242	Role of the Immune System in Growing Tumors 250
Etiologic Factors in Tumorigenesis 242	Clinical Correlates 254
Host Response to Tumors 248	Immunotherapy 256
Mechanisms of Cell-Mediated Cytotoxicity 248	Conclusion 258

22. Immunosuppression & Immunopotentialiation	260
<i>David R. Webb, Jr., PhD</i>	
Immunosuppression 260	Conclusions 266
Immunopotentialiation 263	
23. Aging & the Decline of Immune Responsiveness	267
<i>Marguerite M. B. Kay, MD</i>	
Age-Related Changes in Immune Functions 267	Mechanisms Responsible for Diseases Associated With Declining Immune Functions 273
Mechanisms for the Age-Related Decline in Normal Immune Functions 269	
Section III. Immunologic Laboratory Tests	279
24. Laboratory Methods for Detection of Antigens & Antibodies	281
<i>Daniel P. Stites, MD</i>	
Immunodiffusion 281	Radioimmunoassay (RIA) 300
Methodology & Interpretation 282	Radioimmunoassay Methodology & Interpretation 300
Application: Serum Immunoglobulin Levels in Health & Disease 284	Solid Phase Radioimmunoassay Systems 302
Electrophoresis 286	Immunoradiometry 302
Zone Electrophoresis 287	Applications of Radioimmunoassay 302
Immunoelectrophoresis (IEP) 287	Immunohistochemical Technics 303
Radioimmuno-electrophoresis 290	Immunofluorescence 303
Electroimmunodiffusion 293	Other Immunohistochemical Technics 308
Immunochemical & Physicochemical Methods 294	Agglutination 308
Ultracentrifugation 294	Agglutination Technics 309
Column Chromatography 296	Hemagglutination Inhibition 310
Serum Viscosity 297	Clinically Applicable Tests Which Employ Agglutination Reactions 310
Cryoglobulins 298	Complement Function 311
Pyroglobulins 299	Hemolytic Assay 312
Detection of Immune Complexes 299	Measurement of Individual Complement Components 312
	Complement Fixation 314
25. Laboratory Methods of Detecting Cellular Immune Function	316
<i>Daniel P. Stites, MD</i>	
Introduction 316	Clinical Application of B & T Cell Assays 324
Delayed Hypersensitivity Skin Tests 316	Neutrophil Function 325
Lymphocyte Activation 317	Tests for Motility 326
Methods & Interpretations 318	Tests for Recognition 326
Assays for Human T & B Lymphocytes 319	Tests for Ingestion 326
T Lymphocyte Assays 322	Tests for Degranulation 327
B Lymphocyte Assays 323	Tests for Intracellular Killing 327
Section IV. Clinical Immunology	331
26. Immunodeficiency Diseases	333
<i>Arthur J. Ammann, MD, & H. Hugh Fudenberg, MD</i>	
Antibody (B Cell) Immunodeficiency Disorders 334	Cellular (T Cell) Immunodeficiency Disorders 342
X-linked Infantile Hypogammaglobulinemia 335	Congenital Thymic Aplasia (DiGeorge Syndrome, Immunodeficiency With Hypoparathyroidism) 343
Transient Hypogammaglobulinemia of Infancy 337	Chronic Mucocutaneous Candidiasis (With & Without Endocrinopathy) 344
Common, Variable, Unclassifiable Immunodeficiency (Acquired Hypogammaglobulinemia) 338	Combined Antibody-Mediated (B Cell) & Cell-Mediated (T Cell) Immunodeficiency Diseases 346
X-linked Immunodeficiency With Hyper-IgM 339	Severe Combined Immunodeficiency Disease 346
Selective IgA Deficiency 340	Cellular Immunodeficiency With Abnormal Immunoglobulin Synthesis (Nezelof's Syndrome) 348
Selective IgM Deficiency 342	
Selective Deficiency of IgG Subclasses 342	

26. Immunodeficiency Diseases (cont'd)

- Immunodeficiency With Ataxia-Telangiectasia 349
- Immunodeficiency With Thrombocytopenia, Eczema, & Recurrent Infection (Wiskott-Aldrich Syndrome) 350
- Immunodeficiency With Thymoma 351
- Immunodeficiency With Short-Limbed Dwarfism 352
- Immunodeficiency With Enzyme Deficiency 352
- Episodic Lymphocytopenia With Lymphotoxin 353
- Graft-Versus-Host (GVH) Disease 353
- Phagocytic Dysfunction Diseases 353
- Chronic Granulomatous Disease 354
- Glucose-6-Phosphate Dehydrogenase Deficiency 355
- Myeloperoxidase Deficiency 355
- Chédiak-Higashi Syndrome 355
- Job's Syndrome 356
- Tuftsian Deficiency 356
- Lazy Leukocyte Syndrome 356
- Elevated IgE, Defective Chemotaxis, Eczema, & Recurrent Infection 356
- Complement Abnormalities & Immunodeficiency Diseases 356
- C1q Deficiency 357
- C1r & C1s Deficiency 357
- C2 Deficiency 357
- C3 Deficiency 357
- Familial C5 Dysfunction 357

27. Rheumatoid Diseases

Ken Fye, MD, Haralampos Moutopoulos, MD, & Norman Talal, MD

360

- Systemic Lupus Erythematosus (SLE) 360
- Rheumatoid Arthritis (RA) 365
- Juvenile Rheumatoid Arthritis (JRA) 370
- Sjögren's Syndrome, 372
- Progressive Systemic Sclerosis 374
- Polymyositis-Dermatomyositis 377
- Polyarteritis Nodosa, Wegener's Granulomatosis, & Other Vasculitides 379
- Serum Sickness 383
- Behçet's Disease 383
- Ankylosing Spondylitis 384
- Reiter's Syndrome 384
- Psoriatic Arthritis 385
- Relapsing Polychondritis 386
- Relapsing Panniculitis (Weber-Christian Disease) 386
- Hereditary Complement Deficiencies & Collagen Vascular Diseases 386
- Hypogammaglobulinemia & Rheumatoid Arthritis 387

28. Hematologic Diseases

J. Vivian Wells, MD, & Curt A. Ries, MD

390

- I. White Blood Cell Disorders 390
 - Leukemias 390
 - Acute Leukemia 390
 - Chronic Leukemia 392
 - 1. Chronic Myelogenous Leukemia 392
 - 2. Chronic Lymphocytic Leukemia 393
 - 3. Leukemic Reticuloendotheliosis 393
 - Lymphoreticular Disorders 395
 - Paraproteinemias 395
 - 1. Multiple Myeloma 397
 - 2. Waldenström's Macroglobulinemia 399
 - 3. Solitary Plasmacytoma 400
 - 4. Amyloidosis 400
 - 5. H Chain Diseases 401
 - 6. Benign Monoclonal Gammopathy 401
 - 7. Plasma Cell Leukemia 402
 - 8. Cryoglobulinemia 402
 - Biclonal Gammopathy 403
 - Malignant Lymphomas 403
 - Infectious Mononucleosis 407
 - Leukocytopenia 409
 - Chronic Autoimmune Neutropenia 409
 - Drug-Induced Autoimmune Neutropenia 409
- II. Red Cell Disorders 409
 - Immune Hemolytic Anemias 409
 - 1. Autoimmune Hemolytic Anemia 411
 - 2. Cold Agglutinin Syndromes 412
 - 3. Drug-Induced Immune Hemolytic Anemia 412
 - 4. Paroxysmal Cold Hemoglobinuria 413
 - Paroxysmal Nocturnal Hemoglobinuria 414
 - Pure Red Cell Aplasia 414
- III. Platelet Disorders 414
 - Idiopathic Thrombocytopenic Purpura 415
 - Drug-Associated Thrombocytopenic Purpura 416
 - Isoimmune Thrombocytopenic Purpura 417
- IV. Bone Marrow Transplantation 417
 - Donor Selection for Bone Marrow Transplantation 417
 - Technics of Bone Marrow Transplantation 417
 - Clinical Management 418
 - Specific Diseases in Which Bone Marrow Transplantation May Be Indicated 418
 - Complications of Bone Marrow Transplantation 419
 - Conclusion 420
- V. Hemostatic Disorders 420
 - Vascular Phase 420
 - Platelet Phase 421
 - Coagulation Phase 421
- VI. Blood Replacement Therapy 422
 - Blood Groups 422
 - Hemolytic Disease of the Newborn 424
 - Blood Transfusion 425
 - Blood Transfusion Reactions 425
 - Blood Fractionation Products 426

29. Allergic Diseases 430

Abba I. Terr, MD

- | | |
|---|--|
| Atopy 430 | Stinging Insect Hypersensitivity 440 |
| Skin Testing for Immediate Hypersensitivity 431 | Urticaria & Angioedema 441 |
| Immunotherapy (Hyposensitization) 432 | Hereditary Angioedema (Hereditary Angioneurotic Edema) 442 |
| Allergic Rhinitis (Hay Fever) 433 | Drug Allergy 442 |
| Asthma 435 | Penicillin Allergy 444 |
| Atopic Dermatitis 438 | Food Allergy 445 |
| Anaphylaxis 439 | |

30. Gastrointestinal & Liver Diseases 449

Keith B. Taylor, MD

- | | |
|--|--|
| Structural & Functional Components of the Immune System Peculiar to the Gastrointestinal Tract 449 | 2. Sjögren's Syndrome 454 |
| Immunoglobulins in the Intestinal Tract 450 | 3. Chronic Atrophic Gastritis & Pernicious Anemia 454 |
| The Gastrointestinal Tract as a Site of Immunologic Reactions 450 | Gluten-Sensitive Enteropathy (Celiac Sprue) 456 |
| Acute Gastrointestinal Allergy 451 | Crohn's Disease (Intestinal Granulomatous Disease) 458 |
| Chronic or Relapsing Inflammatory Diseases of the Gastrointestinal Tract 453 | Nonspecific Chronic Ulcerative Colitis 460 |
| 1. Aphthous Ulceration of the Buccal Cavity 453 | Hepatitis 461 |
| | 1. Acute Viral Hepatitis 461 |
| | 2. Chronic Hepatitis 463 |
| | Primary Biliary Cirrhosis 464 |

31. Cardiac & Pulmonary Diseases 467

Joseph L. Caldwell, MD

- | | |
|--|---|
| Postpericardiotomy Syndrome 467 | Idiopathic Interstitial Fibrosis (Hamman-Rich Syndrome) 476 |
| Acute Rheumatic Fever 468 | Goodpasture's Syndrome 477 |
| Hypersensitivity Pneumonitis (Extrinsic Allergic Alveolitis) 472 | Pulmonary Reactions to Leukoagglutinins 477 |
| Sarcoidosis 474 | |

32. Renal Diseases 479

Curtis B. Wilson, MD, Wayne A. Border, MD, & David H. Lehman, MD

- | | |
|--|---|
| Glomerulonephritis 479 | Tubulo-interstitial Nephritis 490 |
| 1. Anti-Glomerular Basement Membrane Antibody-Induced Glomerulonephritis 480 | 1. Tubulo-interstitial Injury in Glomerulonephritis 490 |
| 2. Immune Complex Glomerulonephritis 482 | 2. Drug-Induced Interstitial Nephritis 492 |
| Hypocomplementemia & Glomerulonephritis 488 | 3. Hypergammaglobulinemic Renal Tubular Acidosis 493 |
| | Renal Diseases of Unproved Immunopathogenesis 493 |

33. Dermatologic Diseases 497

Thomas T. Provost, MD

- | | |
|--------------------------------------|---|
| Allergic Contact Dermatitis 497 | Benign Mucous Membrane Pemphigoid 505 |
| Photoallergic Contact Dermatitis 499 | Herpes Gestationis 505 |
| Atopic Dermatitis 499 | Dermatitis Herpetiformis 506 |
| Dermatophytosis 500 | Vasculitides 506 |
| Mucocutaneous Candidiasis 501 | Discoid Lupus Erythematosus 507 |
| Bullous Diseases 502 | Cutaneous Manifestations of Complement Deficiencies 508 |
| Pemphigus Vulgaris 502 | Conclusions 508 |
| Bullous Pemphigoid 503 | |

34. Infectious Diseases 511

David J. Drutz, MD, & John Richard Graybill, MD

- | | |
|---|--|
| Extracellular Infections in Which Opsonins & Polymorphonuclear Neutrophils Are Decisive in Recovery 511 | 2. Meningococcal Infection 513 |
| 1. Pneumococcal Infection 511 | 3. <i>Haemophilus influenzae</i> Infection 515 |
| | 4. Gonorrhea 516 |
| | 5. <i>Streptococcus pyogenes</i> Infection 518 |

34. Infectious Diseases (cont'd)

- 6. *Staphylococcus aureus* Infection 518
- 7. *Klebsiella pneumoniae* Infection 519
- 8. *Pseudomonas aeruginosa* Infection 519
- 9. Plague 519
- 10. Anthrax 519
- Infections in Which Antibody May Be Decisive in Prevention or in Recovery Through a Mechanism Other Than Opsonization 523
 - 1. Diseases Resulting From Exotoxin Production 523
- 2. Infections in Which Epithelial Cell Attachment Is the Critical First Step in Establishment of Infection 523
- 3. Complement-Mediated Bacteriolysis 523
- 4. Viral Neutralization 523
- Infections in Which Humoral & Cellular Immunity Collaborate in Host Defense 523
 - 1. Cryptococcosis 524
 - 2. Syphilis 526
- 3. Salmonellosis 528
- 4. Candidiasis 529
- 5. Listeriosis 530
- Intracellular Infections in Which Lymphocytes & Macrophages Are Decisive in Recovery & Humoral Immune Mechanisms Play No Protective Role 530
 - 1. Tuberculosis 531
 - 2. Leprosy 533
 - 3. "Atypical Mycobacteria" 534
 - 4. Histoplasmosis 535
 - 5. Coccidioidomycosis 538
 - 6. Brucellosis 542
 - 7. Tularemia 542
- Infectious Diseases Characterized by Unique Host-Parasite Relationships 543
- Infections Complicated by Deposition of Circulating Immune Complexes 546
- The Spectrum of Host-Virus Immunologic Relationships 548
- Opportunistic Infections 550

35. Endocrine Diseases 554

Noel R. Rose, MD, PhD

- Chronic Thyroiditis 554
- Primary Hypothyroidism (Adult Myxedema) 561
- Hyperthyroidism 561
- Thyrogastic Disease 563
- Chronic Adrenocortical Insufficiency 564
- Ovarian Failure 565
- Diabetes Mellitus 565
- Idiopathic Hypoparathyroidism 568
- Infertility 566

36. Neurologic Disease: 569

Paul M. Hoffman, MD

- Demyelinating Diseases 569
 - Acute Disseminated Encephalomyelitis (ADEM) 569
 - Multiple Sclerosis 570
 - Acute Idiopathic Polyneuritis (Guillain-Barré Syndrome) 573
 - Myasthenia Gravis 574
- Immunologic Abnormalities in Some Uncommon Neurologic Diseases 575
- Myotonia Dysrthica 575
- Chronic Polyneuropathies & Motor Neuron Diseases 576
- Slow, Chronic, & Latent Viral Infections of the Nervous System 576

37. Eye Diseases 579

G. Richard O'Connor, MD

- Antibody-Mediated Diseases 579
 - Hay Fever Conjunctivitis 579
 - Vernal Conjunctivitis & Atopic Keratoconjunctivitis 580
 - Rheumatoid Diseases Affecting the Eye 581
 - Other Antibody-Mediated Eye Diseases 583
- Cell-Mediated Diseases 583
 - Ocular Sarcoidosis 584
 - Sympathetic Ophthalmia & Vogt-Koyanagi-Harada Syndrome 584
 - Other Diseases of Cell-Mediated Immunity 585

38. Parasitic Diseases 587

Theodosia M. Welch, PhD

- The Immune Response to Protozoa 587
 - Malaria 587
 - Amebiasis 588
 - Leishmaniasis 588
 - 1. Cutaneous Leishmaniasis 588
 - 2. Visceral Leishmaniasis 589
 - 3. American Leishmaniasis 589
 - Toxoplasmosis 589
 - Trypanosomiasis 590
 - 1. African Trypanosomiasis 590
 - 2. American Trypanosomiasis 591
- The Immune Response to Helminths 591
 - Trematodes 592
 - 1. Schistosomiasis 592
 - 2. Cercarial Dermatitis (Swimmer's Itch) 593
 - Cestodes 593
 - 1. Echinococcosis 593
 - Nematodes 593
 - 1. Trichinosis 594
 - 2. Ascariasis 594
 - 3. Toxocara Infections 594

39. Immunization	<i>Stephen N. Cohen, MD</i>	596
Immunization Against Infectious Diseases		596
Immunization Against Noninfectious Diseases		605
40. Experimental Aspects of Immunotherapy	<i>Joseph Wybran, MD</i>	606
Bacillus Calmette-Guérin (BCG)		606
Subfractions of BCG		608
Purified Protein Derivative (PPD)		608
Dinitrochlorobenzene (DNCB)		608
<i>Corynebacterium parvum</i>		608
Levamisole		609
Thymus Factors		609
Immune Ribonucleic Acid		609
Dialyzable Transfer Factor (TFd)		609
Appendix		613
Glossary of Terms Commonly Used in Immunology		615
Acronyms & Abbreviations Commonly Used in Immunology		624
Index		627

Section I

***Basic
Immunology***

1 . . .

The Historical Background of Immunology

Pierre Grabar, DSc

Immunology is a relatively young branch of medical science. Many observations of importance to immunology were made by microbiologists around the turn of this century, usually in the course of active research in bacteriology and infectious diseases. For many years immunology was studied as part of microbiology, and progress in the field consisted mainly of application of what had been learned about immunologic phenomena to the problems of the diagnosis and control of bacterial infections. Some of the most important advances were made possible by the introduction of chemical techniques in the elucidation of the nature of antigens and antibodies.

The explosive increase in fundamental information has made immunology an independent branch of science. *Zeitschrift für Immunitätsforschung* began publication in 1909 and the *Journal of Immunology* in 1916. There are now 25 national member societies in the International Union of Immunological Societies. This chapter will outline some of the contributions by pioneers in immunology which have led to the current state of the art. Where appropriate, reference is made to relevant chapters in this book.

The term *immune* derives from Latin *immunis*, ie, exempt from "charges" (taxes, expenses). However, for nearly a century the term immunity has denoted resistance to possible attack by an infectious agent. Resistance to second attacks of certain diseases had been observed even in ancient times. Attempts to protect against variola (smallpox) were made in ancient China and western Asia by inoculation (variolation) using vesicle fluid from persons with mild forms of smallpox, or by purposely seeking out contact with diseased individuals. Lady Mary Wortley Montagu (1721) introduced into England from Turkey the process of *variolation*, or inoculation with unmodified smallpox virus. It was quite dangerous since disease and death often resulted. Similarly, an ancient Greek king of Pontus, Mithridates VI, tried to protect himself against the effects of poison by administering small

amounts of poisonous substances on multiple occasions—a procedure that came to be called *mithridatism*.

EARLY IMMUNOLOGY

The first effective—though still empirical—immunization was performed by Edward Jenner, an English physician (1749–1823), who observed that persons who got well after infection with cowpox were protected against smallpox. Jenner introduced vaccination with cowpox in 1796 as a means of protecting against smallpox. The term *vaccination* (L *vacca* cow) was introduced to replace the term *variolation*.

The scientific approach was not applied to the study of immunologic phenomena until almost a century later as a consequence of work on microbes by Louis Pasteur (1822–1895) and his collaborators. They investigated the possibility of protecting against infection by vaccinations with attenuated strains of microorganisms. Their first observation (1878–1880) was that a culture of *Pasteurella aviseptica* (then called chicken cholera) which had been left in the laboratory during vacation lost its virulence for chickens, and that animals inoculated with this culture were protected against the virulent strain. Pasteur concluded that this culture contained attenuated microbes and, to honor the work of Jenner (nearly 100 years before), extended the term *vaccination* to denote conferring immunity by injection of attenuated strains of organisms. The idea of using attenuated strains of microorganisms was confirmed by Pasteur when he studied vaccination against anthrax (1881). Research on the mechanisms of protective effects led Richet and Héricourt to the conclusion (1888) that the blood of an animal immunized with staphylococci conferred partial protection against subsequent inoculation with these microorganisms. The next year, Charrin and Roger observed that the serum of an animal immunized with *Pseudomonas aeruginosa* (then called *Bacterium aeruginosum* among other names) agglutinated a suspension of this microbe.

In 1889, Pfeiffer, a pupil of Koch, used cross-immunization of guinea pigs with 2 similar microbes

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(*Vibrio cholerae* and *V. metchnikovii*) to show that it was possible to distinguish them immunologically, since immunization against one did not protect against the other. The specificity of the protective effects of immunization had already been observed, but this example showed how extremely fine the specificity could be in some cases (Chapters 2 and 3).

"CELLULAR IMMUNITY" THEORY

In 1882 in Messina the Russian zoologist Elie Metchnikoff (1845–1916) studied the role of motile cells of a transparent starfish larva in protection against foreign intruders. He introduced a rose thorn into these larvae and noted that a few hours later the thorn was surrounded by motile cells. This experiment can be considered the starting point of cellular immunology. It had already been established by Koch and Neisser that bacteria can be found in leukocytes, but it was thought that this was the result of bacterial invasion of the leukocytes. Metchnikoff showed that the leukocytes had in fact engulfed the microorganisms. In 1883, Metchnikoff observed that *Daphnia*, a tiny transparent metazoan animal, can be killed by spores of the fungus *Monospora bicuspidata* and that in some instances these spores are attacked by blood cells and can be destroyed in these cells, thereby protecting the animal against the invaders. In 1884, he extended these observations to the leukocytes of rabbits and humans, using various bacteria. He noted that the engulfment of microorganisms by leukocytes, which he called *phagocytosis*, is greatly enhanced in animals recovering from an infection or after vaccination with a preparation of these microorganisms. He therefore concluded that phagocytosis was the main defense mechanism of an organism. He later showed the existence of 2 types of circulating cells capable of phagocytosis—the polymorphonuclear leukocytes and the macrophages—as well as certain fixed cells capable of phagocytosis, and proposed the general term *phagocytes* for all of these cells (Chapter 7).

The *cellular immunity* theory of Metchnikoff, who worked at the Pasteur Institute in Paris from 1887, was accepted with enthusiasm by some but was criticized by several other pathologists. The inflammatory reaction had been described by Celsus as early as the first century AD, but before Metchnikoff it had been studied only in mammals. Pathologists such as Virchow (1871) agreed that inflammation was due to changes in the connective tissue cells induced by various agents, particularly by abnormal deposits of metabolic products. Cohnheim (1873) and his collaborator Arnold (1875) considered inflammation to be a local vascular lesion due to a noxious agent which allowed blood cells to penetrate into tissues. Metchnikoff, who had observed the same accumulation of motile cells in lower animals with no circulatory vessels, asserted that diapedesis in higher animals was a process of active

penetration of these cells through the walls of the vessels (1892). In his opinion, inflammation resulted in an enzymatic digestion process due to ingestion of the noxious agent by the motile phagocytes.

Metchnikoff's theory came under severe criticism somewhat later by those who observed immunity in the absence of cells. Fodor in 1886 was apparently the first to observe a direct action of an immune serum on microbes during the course of his studies on anthrax bacilli. Behring* and Kitasato (1890) demonstrated the neutralizing antitoxic activity of sera from animals immunized with diphtheria or tetanus toxin, which was considered the first proof of humoral immunity. In 1894, Calmette observed the same neutralizing activity of snake venom antiserum. The preparation of large amounts of diphtheria toxin antiserum in horses for human use started almost immediately in the Behring Institute in Marburg (Germany) in 1893; at the Pasteur Institute in Paris (Roux and Martin, 1894); in the USA; and also at the Lister Institute in London (1895). This was the beginning of serum therapy, a form of treatment which developed remarkably over the next 50 years.

"HUMORAL" THEORY

An important humoral defense mechanism described by Pfeiffer and Isaëff (1894) has come to be called the *Pfeiffer phenomenon*. Cholera vibrios injected into the peritoneum of previously immunized guinea pigs lose mobility, are clumped, are no longer stainable, and are later phagocytosed by leukocytes, but they are also lysed in the absence of cells.

A theory of immunity due to humoral factors provoked intense debate between Metchnikoff and the supporters of this new theory, mainly from the laboratory of Robert Koch (1843–1910). At the time of Pfeiffer's discovery, a young Belgian, Jules Bordet (1870–1961), was engaged in the study of agglutination reactions in Metchnikoff's laboratory at the Pasteur Institute. He became interested in the Pfeiffer phenomenon and in 1895 showed that both bacteriolysis and lysis of red cells (which he described in 1898) required 2 factors: one, which he called *sensitizer*, was thermostable and specific; the other, which he called *alexine*, was thermolabile and nonspecific. The factor designated alexine by Bordet came to be called *cytase* by Metchnikoff and *complement* by Ehrlich (Chapter 6). Bordet believed that his "alexine" possessed enzymatic activity and that it consisted of several components.

It is of interest that Bordet's studies of humoral factors were performed in Metchnikoff's laboratory and were in contradiction to the master's theories. Later, both theories gained general acceptance and it

*The particle von was added later to Behring's name after he became famous—about the time he received the Nobel Prize.

was established that humoral factors originated from lymphoid cells.

During this period, the term *antigen* was introduced to designate any substance (then mainly microbes or cells) capable of inducing a reaction against itself and the illogical term *antibody* (both being "anti-") to designate the factor present in the serum possessing this activity. At first, various special names were used to indicate each observed antibody activity, such as *agglutinins*, *precipitins*, *sensitizers*, and *opsonins* (Chapters 4 and 16). The first observation of agglutination is described above. The precipitin reaction was described later—in 1897 by Kraus with microbial culture supernates and the serum of immunized animals, and in 1899 by Tschistovitch with serum protein antigens and by Bordet with milk antigens and serum of animals injected with these fluids. The precipitin reaction was introduced by Wassermann and Uhlenhuth into forensic medicine for the identification of blood or meat.

Complement & Immunologic Diagnosis

The term *sensitizer* was used by Bordet to denote the thermostable serum component reacting in the lysis of bacteria. Ehrlich called it *amboceptor*. In 1900, Bordet established the reaction which he designated *alexine* (*complement*) *fixation or deviation*, using cholera vibrios, a corresponding immune serum, and complement (fresh normal serum). As a control of fixation of the latter, he added red cells sensitized by the homologous antiserum; the absence of hemolysis proved that the complement had been absorbed by the first reaction (Chapter 6). This system allowed him to make quantitative estimations. In 1901, he described (with Gengou) this general principle, which is still valid and useful and which was first applied by Wassermann, Neisser, and Bruck in 1906 in the diagnosis of syphilis using tissues from syphilitic patients as antigen. Various modifications of this method have been subsequently introduced, eg, the use of an alcoholic extract of guinea pig heart (reagin) as antigen (Landsteiner) and, particularly, the use of lipids (see Chapter 34).

The classical method of diagnosis of typhoid fever by salmonella agglutination reactions was established independently in 1896 by Widal in France and by Durham. The latter worked at that time in Germany in Gruber's laboratory, where agglutination reactions had been under study for several years. A method of diagnosing pneumonia proposed in 1902 by Neufeld consisted of observing the swelling (*Quellung*) of the capsules of pneumococci when the microorganisms were exposed to patient serum containing antipneumococcal antibodies (see Chapter 34).

Resolution of Conflicting Theories

In 1895, Denys and Leclef observed the fixation of antibodies present in an antistreptococcus serum by these organisms and called them *bacteriotropins*. Neufeld and Rimpau had also demonstrated similar in vitro fixation. In 1903, Wright and Douglas, after a careful study of Metchnikoff's observation that phago-

cytosis of microbes is facilitated by the serum of an immunized animal, used washed cells to demonstrate that the immune serum contained an active factor they called *opsonin*. They proposed the term *opsonization* for the activity, and this phenomenon acted as a "bridge" between the apparently contradictory humoral and cellular theories.

During this same period, Paul Ehrlich (1854–1915) studied the neutralization of toxins by immune serum, using the highly toxic vegetable poisons abrin and ricin, which could be extracted easily in sufficient quantity. These studies enabled him to establish a technic for the evaluation of the antitoxic activity of diphtheria antiserum (1897).

EHRLICH'S "SIDE-CHAIN" THEORY

Ehrlich was interested in the theoretic aspects of immunologic phenomena and in 1896 elaborated his *side-chain theory* to explain the appearance of antibodies in the circulation. He considered it an "enhancement" of a normal mechanism and suggested that cells capable of forming antibodies possessed on their surface membrane specific side chains which were receptors for antigens. He proposed that binding of antigen to the side chains provoked new synthesis of these side chains, which were liberated into serum as antibodies. He expressed the specificity of the reaction of antigens and antibodies as a "key [antigen] in a lock [antibody]" and thought that this reaction was of a chemical nature. During the next few years, he tried to substantiate his theory with various arguments, but the theory was not generally accepted. It was criticized by Bordet, who felt that the antigen-antibody reaction was of colloid nature; by Gruber; and particularly by Arrhenius and Madsen, who insisted on the reversibility of the reaction and on different proportions of reactants in specific precipitates. Nevertheless, Ehrlich's general theory, with modifications and additions, has been taken into consideration by many authors, and his hypothesis on the existence of specific receptors on immunocompetent cells has recently been completely vindicated (Chapter 8).

The transmission of antibodies across the placenta or through the mammary gland in milk from maternal mice to their offspring was observed by Ehrlich in 1892. In 1893, Klemperer demonstrated the existence of antibodies in the eggs of poultry and therefore transmission of antibodies to newborn chicks.

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In 1875, L. Landois published his monograph *Blood Transfusion*. He noted the effects of blood transfusions between members of different species and observed it was preferable to work within a single species. He also stated, however, that there were differences within a single species since a recipient's own cells could be hemolyzed by serum from a nonidentical donor of the same species.