

ADVANCES IN  
**Immunology**

EDITED BY

F. J. DIXON

HENRY G. KUNKEL

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# ADVANCES IN **Immunology**

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## PREFACE

Despite our very considerable information about antibodies and the immune process a number of striking gaps in our knowledge certainly remain. Perhaps foremost among these is the mechanism by which the diversity of antibodies is achieved. Immunologists remain divided into two highly divergent camps on this issue and those espousing the germ line theory appear almost as numerous as the so-called somatocists. The very significant developments regarding the structure of antibodies have failed to resolve the dispute. Many workers in the field now feel that the answer will come only through concerted studies at the cellular level. An understanding of the different types of lymphocytes and their differentiation appears essential. Volume 15 is replete with new information in this area.

In the first chapter Dr. David Katz and Dr. Baruj Benacerraf have summarized in a superb fashion the many lines of evidence concerning the interaction of B and T cells in the immune response. The regulatory effect of the T cells on B cell activity has clearly emerged as a dominant principle. The cooperative interaction between specific B and T cells and antigen is discussed at length and the evidence for distinct factors secreted by T cells which are capable of affecting B cell function is presented. The advantages of such a two-cell mechanism in terms of host defense mechanisms become apparent.

In the second chapter Dr. Emil Unanue deals with the other important cell involved in the immune response, the macrophage. He has contributed very significantly to our understanding of the role of this cell in the removal, processing, and presentation of antigen to the responding lymphoid cell. Various *in vitro* systems for studying the immune response are considered in detail and the significant role of the macrophage in most of these is apparent. Variations and contradictions of past studies, primarily because of the widely different antigens employed, are brought together so that a coherent picture emerges.

The chapter by Dr. Joseph Feldman covers a most timely subject, immunological enhancement. It is a phenomenon that has long been known but which has suddenly come to the fore with the appreciation that it has broad immunological significance ranging from effects on tumor growth to the privileged position of the fetus in the maternal environment. Dr. Feldman prefers the term "immunological blockade" in this broader setting and has given it specific meaning in terms of known

antibodies and their effects on lymphocytes. Although considerable gaps remain in our knowledge of the exact types of antibodies involved and their specificity, the author has done much to dispel the mysterious aura that for so long has surrounded the enhancement phenomenon.

The fourth contribution, by Dr. David Gasser and Dr. Willys Silvers, presents in detail the subject of sex-linked or presumed sex-linked antigens. The intriguing transplantation phenomenon of specific rejection of certain male to female skin receives special consideration. Evidence is cited which supports the concept that this Y antigen is determined by a gene on the Y chromosome. However, it has not reached the status of the more numerous X-linked antigens which are also discussed. The authors avoid the intricate language that characterizes many reviews in transplantation immunology; this chapter should prove broadly enlightening.

In the final chapter Dr. Edward Franklin and Dr. Dorothea Zucker-Franklin present a very thorough review of the problem of amyloid and the recent exciting developments concerning the nature of the deposits. This very considerable clinical problem has intrigued immunologists for many years but always proved uniquely resistant to the many investigative efforts. It now appears that there are two distinct types of deposit. One of these clearly involves the variable region of immunoglobulin light chains. The other type is less well defined but appears to involve a totally different protein. Much of the controversy and confusion that have troubled most outside observers is resolved in this very timely review.

The constant cooperation and assistance of the publishers in the production of Volume 15 are most gratefully acknowledged.

HENRY C. KUNKEL  
FRANK J. DIXON

## CONTENTS

LIST OF CONTRIBUTORS . . . . .	vii
PREFACE . . . . .	ix
CONTENTS OF PREVIOUS VOLUMES . . . . .	xi

### The Regulatory Influence of Activated T Cells on B Cell Responses to Antigen

DAVID H. KATZ AND BARUJ BENACERRAF

I. Introduction . . . . .	2
II. Specific Cells of the Immune System . . . . .	3
III. Requirement of Two Distinct Lymphoid Cell Types in the Development of Humoral Immune Responses . . . . .	4
IV. Nature of the Regulatory Influence of Activated T Cells on Antibody Responses by B Cells . . . . .	23
V. Immunological Specificity and Properties of T and B Cells Concerned with Cooperation Phenomena . . . . .	28
VI. Mechanism of Regulation of B Cell Function by T Cells . . . . .	42
VII. Suppressive Effects of T Cells on Antibody Synthesis . . . . .	62
VIII. Functions of T and B Lymphocytes in Various Immunological Phenomena . . . . .	67
IX. Biological and Pathophysiological Significance of the Regulatory Influence of T Cells on Antibody Production . . . . .	82
References . . . . .	85

### The Regulatory Role of Macrophages in Antigenic Stimulation

E. R. UNANUE

I. Introduction . . . . .	95
II. Association of Macrophage-Bound Antigen with Immunogenicity . . . . .	97
III. Handling of Antigen by Macrophages . . . . .	128
IV. Macrophage-Lymphocyte Contact . . . . .	147
V. Macrophages and Adjuvants . . . . .	149
VI. Summary . . . . .	151
References . . . . .	157

### Immunological Enhancement: A Study of Blocking Antibodies

JOSEPH D. FELDMAN

I. History . . . . .	167
II. Definitions . . . . .	169

III. Components . . . . .	170
IV. Immunological Enhancement . . . . .	177
V. Fetus as Homograft . . . . .	188
VI. Tolerance . . . . .	190
VII. Theories . . . . .	191
VIII. Prospects . . . . .	204
References . . . . .	205

### Genetics and Immunology of Sex-Linked Antigens

DAVID L. GASSER AND WILLYS K. SILVERS

I. Introduction . . . . .	215
II. The Y Antigen in Mice . . . . .	216
III. The Xg Blood Group Locus in Man . . . . .	236
IV. Other Sex-Limited and Sex-Linked Antigens . . . . .	238
V. Summary . . . . .	242
References . . . . .	243

### Current Concepts of Amyloid

EDWARD C. FRANKLIN AND DOROTHEA ZUCKER-FRANKLIN

I. Introduction . . . . .	249
II. General Approaches to the Study of Amyloid . . . . .	253
III. Morphological Studies in Sectioned Tissues . . . . .	255
IV. Morphological, Biochemical, Physicochemical, and Antigenic Properties of Amyloid Fibrils . . . . .	264
V. Speculations on the Pathogenesis of Amyloid . . . . .	294
References . . . . .	299
AUTHOR INDEX . . . . .	305
SUBJECT INDEX . . . . .	327

## LIST OF CONTRIBUTORS

Numbers in parentheses indicate the pages on which the authors' contributions begin.

- BARUJ BENACERRAF, *Department of Pathology, Harvard Medical School, Boston, Massachusetts* (1)
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## Contents of Previous Volumes

### Volume 1

Transplantation Immunity and Tolerance

M. HAŠEK, A. LENGEROVÁ, AND T. HRABA

Immunological Tolerance of Nonliving Antigens

RICHARD T. SMITH

Functions of the Complement System

ABRAHAM G. OSLER

*In Vitro* Studies of the Antibody Response

ABRAM B. STAVITSKY

Duration of Immunity in Virus Diseases

J. H. HALE

Fate and Biological Action of Antigen-Antibody Complexes

WILLIAM O. WEIGLE

Delayed Hypersensitivity to Simple Protein Antigens

P. G. H. GELL AND B. BENACERRAF

The Antigenic Structure of Tumors

P. A. GORER

AUTHOR INDEX—SUBJECT INDEX

### Volume 2

Immunologic Specificity and Molecular Structure

FRED KARUSH

Heterogeneity of  $\gamma$ -Globulins

JOHN L. FAHEY

The Immunological Significance of the Thymus

J. F. A. P. MILLER, A. H. E. MARSHALL, AND R. G. WHITE

Cellular Genetics of Immune Responses

G. J. V. NOSSAL

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CHARLES G. COCHRANE AND FRANK J. DIXON

Phagocytosis

DERRICK ROWLEY

**Antigen-Antibody Reactions in Helminth Infections**

E. J. L. SOULSBY

**Embryological Development of Antigens**

REED A. FLICKINGER

**AUTHOR INDEX-SUBJECT INDEX****Volume 3*****In Vitro* Studies of the Mechanism of Anaphylaxis**

K. FRANK AUSTEN AND JOHN H. HUMPHREY

**The Role of Humoral Antibody in the Homograft Reaction**

CHANDLER A. STETSON

**Immune Adherence**

D. S. NELSON

**Reaginic Antibodies**

D. R. STANWORTH

**Nature of Retained Antigen and Its Role in Immune Mechanisms**

DAN H. CAMPBELL AND JUSTINE S. GARVEY

**Blood Groups in Animals Other Than Man**

W. H. STONE AND M. R. IRWIN

**Heterophile Antigens and Their Significance in the  
Host-Parasite Relationship**

C. R. JENKIN

**AUTHOR INDEX-SUBJECT INDEX****Volume 4****Ontogeny and Phylogeny of Adaptive Immunity**

ROBERT A. GOOD AND BEN W. PAPERMASTER

**Cellular Reactions in Infection**

EMANUEL SUTER AND HANSRUEDY RAMSEIER

**Ultrastructure of Immunologic Processes**

JOSEPH D. FELDMAN

**Cell Wall Antigens of Gram-Positive Bacteria**

MACLYN McCARTY AND STEPHEN I. MORSE

**Structure and Biological Activity of Immunoglobulins**

SYDNEY COHEN AND RODNEY R. PORTER

**Autoantibodies and Disease**

H. G. KUNKEL AND E. M. TAN

**Effect of Bacteria and Bacterial Products on Antibody Response**

J. MUNOZ

**AUTHOR INDEX-SUBJECT INDEX****Volume 5****Natural Antibodies and the Immune Response**

STEPHEN V. BOYDEN

**Immunological Studies with Synthetic Polypeptides**

MICHAEL SELA

**Experimental Allergic Encephalomyelitis and Autoimmune Disease**

PHILIP Y. PATERSON

**The Immunology of Insulin**

C. G. POPE

**Tissue-Specific Antigens**

D. C. DUMONDE

**AUTHOR INDEX-SUBJECT INDEX****Volume 6****Experimental Glomerulonephritis: Immunological Events  
and Pathogenetic Mechanisms**

EMIL R. UNANUE AND FRANK J. DIXON

**Chemical Suppression of Adaptive Immunity**

ANN E. GABRIELSON AND ROBERT A. GOOD

**Nucleic Acids as Antigens**

OTTO J. PLESCIA AND WERNER BRAUN

***In Vitro* Studies of Immunological Responses of Lymphoid Cells**

RICHARD W. DUTTON

**Developmental Aspects of Immunity**

JAROSLAV ŠTERZL AND ARTHUR M. SILVERSTEIN

**Anti-antibodies**

PHILIP G. H. GELL AND ANDREW S. KELUS

**Conglutinin and Immunoconglutinins**

P. J. LACHMANN

**AUTHOR INDEX-SUBJECT INDEX**

**Volume 7****Structure and Biological Properties of Immunoglobulins**

SYDNEY COHEN AND CESAR MILSTEIN

**Genetics of Immunoglobulins in the Mouse**

MICHAEL POTTER AND ROSE LIEBERMAN

**Mimetic Relationships between Group A Streptococci and Mammalian Tissues**

JOHN B. ZABRISKIE

**Lymphocytes and Transplantation Immunity**

DARCY B. WILSON AND R. E. BILLINGHAM

**Human Tissue Transplantation**

JOHN P. MERRILL

**AUTHOR INDEX-SUBJECT INDEX****Volume 8****Chemistry and Reaction Mechanisms of Complement**

HANS J. MÜLLER-EBERHARD

**Regulatory Effect of Antibody on the Immune Response**

JONATHAN W. UHR AND GÖRAN MÖLLER

**The Mechanism of Immunological Paralysis**

D. W. DRESSER AND N. A. MITCHISON

***In Vitro* Studies of Human Reaginic Allergy**

ABRAHAM G. OSLER, LAWRENCE M. LICHTENSTEIN, AND DAVID A. LEVY

**AUTHOR INDEX-SUBJECT INDEX****Volume 9****Secretory Immunoglobulins**

THOMAS B. TOMASI, JR., AND JOHN BIENENSTOCK

**Immunologic Tissue Injury Mediated by Neutrophilic Leukocytes**

CHARLES G. COCHRANE

**The Structure and Function of Monocytes and Macrophages**

ZANVIL A. COHN

**The Immunology and Pathology of NZB Mice**

J. B. HOWIE AND B. J. HELYER

**AUTHOR INDEX-SUBJECT INDEX**

**Volume 10**

Cell Selection by Antigen in the Immune Response

GREGORY W. SISKIND AND BARUJ BENACERRAF

Phylogeny of Immunoglobulins

HOWARD M. GREY

Slow Reacting Substance of Anaphylaxis

ROBERT P. ORANGE AND K. FRANK AUSTEN

Some Relationships among Hemostasis, Fibrinolytic Phenomena,  
Immunity, and the Inflammatory Response

OSCAR D. RATNOFF

Antigens of Virus-Induced Tumors

KARL HABEL

Genetic and Antigenetic Aspects of Human Histocompatibility Systems

D. BERNARD AMOS

AUTHOR INDEX-SUBJECT INDEX

**Volume 11**

Electron Microscopy of the Immunoglobulins

N. MICHAEL GREEN

Genetic Control of Specific Immune Responses

HUGH O. McDEVITT AND BARUJ BENACERRAF

The Lesions in Cell Membranes Caused by Complement

JOHN H. HUMPHREY AND ROBERT R. DOORMASHKIN

Cytotoxic Effects of Lymphoid Cells *In Vitro*

PETER PERLMANN AND GÖRAN HOLM

Transfer Factor

H. S. LAWRENCE

Immunological Aspects of Malaria Infection

IVOR N. BROWN

AUTHOR INDEX-SUBJECT INDEX

**Volume 12**

The Search for Antibodies with Molecular Uniformity

RICHARD M. KRAUSE

Structure and Function of  $\gamma$ M Macroglobulins

HENRY METZGER

**Transplantation Antigens**

R. A. REISFELD AND B. D. KAHAN

**The Role of Bone Marrow in the Immune Response**

NABIH I. ABDON AND MAXWELL RICHTER

**Cell Interaction in Antibody Synthesis**

D. W. TALMAGE, J. RADOVICH, AND H. HEMMINGSEN

**The Role of Lysosomes in Immune Responses**

GERALD WEISSMANN AND PETER DUKOR

**Molecular Size and Conformation of Immunoglobulins**

KEITH J. DORRINGTON AND CHARLES TANFORD

**AUTHOR INDEX—SUBJECT INDEX****Volume 13****Structure and Function of Human Immunoglobulin E**

HANS BENNICH AND S. GUNNAR O. JOHANSSON

**Individual Antigenic Specificity of Immunoglobulins**

JOHN E. HOPPER AND ALFRED NISONOFF

***In Vitro* Approaches to the Mechanism of Cell-Mediated Immune Reactions**

BARRY R. BLOOM

**Immunological Phenomena in Leprosy and Related Diseases**

J. L. TURK AND A. D. M. BRYCESON

**Nature and Classification of Immediate-Type Allergic Reactions**

ELMER L. BECKER

**AUTHOR INDEX—SUBJECT INDEX****Volume 14****Immunobiology of Mammalian Reproduction**

ALAN E. BEER AND R. E. BILLINGHAM

**Thyroid Antigens and Autoimmunity**

SIDNEY SHULMAN

**Immunological Aspects of Burkitt's Lymphoma**

GEORGE KLEIN

**Genetic Aspects of the Complement System**

CHESTER A. ALPER AND FRED S. ROSEN

**The Immune System: A Model for Differentiation in Higher Organisms**

L. HOOD AND J. PRAHL

**AUTHOR INDEX—SUBJECT INDEX**

# The Regulatory Influence of Activated T Cells on B Cell Responses to Antigen

DAVID H. KATZ AND BARUJ BENACERRAF

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I. Introduction . . . . .	2
II. Specific Cells of the Immune System . . . . .	3
III. Requirement of Two Distinct Lymphoid Cell Types in the Development of Humoral Immune Responses . . . . .	4
A. Response to Foreign Erythrocyte and Protein Antigens . . . . .	4
B. "Carrier Effect" and Cooperative Interactions Specific for Different Determinants on the Same Antigen . . . . .	14
IV. Nature of the Regulatory Influence of Activated T Cells on Antibody Responses by B Cells . . . . .	23
A. Stimulation of B Cells in the Absence of T-Cell Regulation . . . . .	23
B. Effect of T-Cell Activity on the Class of Immunoglobulin Synthesized . . . . .	25
C. Role of T-Cell Regulation in the Selective Pressure by Antigen on B Cells . . . . .	26
V. Immunological Specificity and Properties of T and B Cells Concerned with Cooperation Phenomena . . . . .	28
A. Immunological Specificity of T and B Cells . . . . .	28
B. Antigen Receptors on T and B Cells . . . . .	32
C. Recognition of Hapten and Carrier Determinants by T and B Cells . . . . .	33
D. Sensitivity and Resistance of T and B Cell Function to X-Irradiation and Corticosteroids . . . . .	37
VI. Mechanism of Regulation of B Cell Function by T Cells . . . . .	42
A. Transfer of Genetic Information . . . . .	42
B. Antigen Presentation and Concentration . . . . .	43
C. Regulation of B Cell Function in Antibody Production by Mediators Produced and Secreted by T Cells . . . . .	47
VII. Suppressive Effects of T Cells on Antibody Synthesis . . . . .	62
A. Enhancement of Immune Responses by Depletion of T Cells . . . . .	62
B. Suppression of Antibody Responses by the Administration of More Than One Antigen (Antigenic Competition) . . . . .	65
VIII. Functions of T and B Lymphocytes in Various Immunological Phenomena . . . . .	67
A. Immunological Tolerance . . . . .	67
B. Immunological Memory . . . . .	75
C. Immunological Adjuvants . . . . .	79
D. Cell-Mediated Immunity . . . . .	81
IX. Biological and Pathophysiological Significance of the Regulatory In- fluence of T Cells on Antibody Production . . . . .	82
References . . . . .	85

## I. Introduction

The clonal selection theory of Burnet and his postulate that antigen-reactive precursors of antibody-secreting cells bear antibody receptors of unique specificity (1-3) have been largely substantiated in the past decade (4-8). Another major advance in immunobiology has been the recognition of two pathways for the differentiation of antigen-reactive cells. It is generally accepted that a class of bone marrow lymphocytes migrates to the thymus where the cells develop the ability to respond to antigen. These thymus-derived lymphocytes, generally referred to as T cells, are responsible for the various phenomena of cell-mediated immunity: delayed sensitivity, homograft, and graft-versus-host reactions. The second lymphocyte cell type arises also in the bone marrow and settles ultimately in distinct anatomical sites in peripheral lymphoid tissues where these cells give rise to the precursors of antibody-secreting cells, B cells (9-11).

The most recent discoveries in immunobiology concern the realization that the differentiation of antigen-stimulated specific B cells into antibody-secreting cells depends, for most antigens, on the concomitant activity of specifically stimulated T cells. The original observations established the requirements of specifically activated T cells for the antibody response by B cells to antigen *in vivo* and *in vitro* in various systems and clarified the relationship between hapten determinants and carrier function originally introduced by Landsteiner (12). It was later recognized that the effect of stimulated T cells on the response of B cells to antigen is more complex and affects also (a) the switch from the production of IgM to IgG antibodies and (b) the rate of selection of specific cells by antigen in the immune response as reflected in the change in affinity of humoral antibody with time. It was further shown that the activity of histocompatibility-linked, specific, immune response (Ir) genes in T cells is essential for all these phenomena triggered by antigen. More recently, it is becoming apparent also that regulatory effects of activated T cells on antibody responses by B cells may be suppressive under certain conditions, whereas under other conditions, as stated above, they are stimulatory, which may explain the well-known phenomenon of antigenic competition. In fact, what appeared at first as an important and essential cooperation phenomenon between two specific cell types and antigen to trigger effective antibody responses is now more appropriately interpreted as the expression of a fundamental regulatory function of activated T cells on B cell responses.

The present review first describes the experimental data on which these statements are based and relates how insight into these fundamen-



tal and fascinating phenomena was achieved. The topics discussed also include intimate mechanisms of the regulation of antibody responses by T cells, the significance of these phenomena for the regulatory processes of the immune system, and their possible implication for the pathogenesis of various immunopathological states.

## II. Specific Cells of the Immune System

The immunocompetent lymphocytes can be divided into two general types on the basis of functional differences: (1) T cells—small lymphocytes that have adapted to certain specific immune functions by virtue of some as yet undefined influence of the thymus (thymus-derived); and (2) B cells—small lymphocytes that have not been directly influenced by the thymus and which are the progenitors of mature antibody-producing plasma cells.

Experimental evidence weighs heavily in favor of the concept that unipotential cells which populate the various hematopoietic tissues of fully developed individuals are derived from common pluripotential stem cells (for review, see 9). Ontogenically, stem cells originate in the embryonic yolk sac and primitive blood islands, migrating later to hematopoietic colonies in fetal liver and bone marrow. Further migration occurs via the bloodstream to various tissues of the hematopoietic system where further differentiation occurs (13, 14). Differentiation to unipotential progenitor cells of either lymphoid or myeloid lines is signaled by inductive factors, presumably existing in the microenvironment of the different hematopoietic organs of the individual (15). We shall limit our considerations here to the lymphoid cell lines.

Stem cells differentiate into unipotential progenitor lymphoid cells under the microenvironmental influences of the primary lymphoid organs (14). Avian lymphoid systems have been shown to consist of two distinct primary lymphoid organs—the bursa of Fabricius and the thymus—the influence of which on the differentiation of the stem cells that have migrated to them is clearly distinguishable on the basis of the functional differences of such cells in the immune system (16–20). Surgical extirpation of the bursa from a newly hatched chick results in depression of serum immunoglobulin levels and marked diminution in the capacity to develop humoral antibody responses to antigen stimulation, but has little effect on the ability to reject tissue allografts (20–22); in contrast, early removal of the thymus diminishes the capacity to develop delayed hypersensitivity and impairs allograft rejection (20–25). In mammals, it is now also clearly established that there exists two distinct lymphoid systems responsible for differentiation of immunocompetent cells. One is clearly thymus-influenced, but the other is not. Hence, neonatal thymec-