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**IMMUNOLOGY,
PART II
Regulation**

**Edited by
EDWARD S. GOLUB**

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IMMUNOLOGY, PART II Regulation

Edited by

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SERIES EDITOR'S FOREWORD

Microbiology has been the source of several related sciences that either took their origin in the concepts devised by microbiologists or in the methods developed by microbiologists. One may suppose this arose initially when procaryotes were regarded as the simplest cells, but continued long after it was clear that there were fundamental differences between procaryotic and eucaryotic cells. One such subject, immune reactions, while always dependent upon the eucaryotic cell for response, was part of microbiology at its start as a science, and indeed Jenner's cow-pox vaccination even preceded scientific microbiology by almost a century. Its role in the development of treatment of infectious disease played a clearly beneficial part in the development of microbiology. In spite of the developing profession of immunology, the subject was always a somewhat minor part of the knowledge expected of a microbiologist. During the 1950s a change in concept began the present independent growth of the subject. This change in concept was the development of the clonal selection theory. During the next decade, the importance of "B" and "T" cells in the development of cell mediated response and in the development of circulating antibody became evident. In the past decade these developments have so broadened immunology that today it constitutes an independent science and, as Dr. Golub argues, is indeed entitled to its own series—Benchmark Papers in Immunology.

From another point of view, the function of this Benchmark series in microbiology is to provide the seminal and significant papers in a convenient form to persons engaged in the study of the science of microbiology, which has now become so broad that no person can be a real expert in all its areas. As such, it is to microbiologists who ought to know the fundamentals of immunology that these volumes are addressed, rather than to practicing immunologists who are presumably completely familiar with the papers included. While there is always a choice made among those available (and indeed some papers are simply not available due to copyright restrictions) we trust that professional immunologists will find these volumes convenient and useful. Eventually these might lead to a Benchmark Series in Immunology but at present we will retain them as part of microbiology just as are volumes on microbial genetics and molecular biology.

Series Editor's Foreword

In the meantime, however, here are the important papers especially on cellular immunity and these provide the sound and solid basis upon which the present really important developments are based.

WAYNE W. UMBREIT

PREFACE

When I first agreed to edit a Benchmark volume on Immunology, I realized that the selection of papers would be difficult and that some would consider my choices at worst stupid and at best idiosyncratic. Economic constraints that I had not considered at the outset have played a greater role in making selections than I could have anticipated. The cost seems to rise exponentially as additional pages beyond 400 are added to a volume. The publisher allowed me to go to two volumes (I suggested three or four), but even so I have had to eliminate papers that I had originally selected. Furthermore, some journals charge near prohibitive fees for the right to reproduce papers. We tend to forget that it is the journals who hold the copyright to our work (which was financed with public funds) and have the legal right to charge what they choose for reproduction rights. This expense forced me to eliminate many articles that appeared in the most widely read journal in which immunology papers appear. Not being able to use the work of a scientist because of pecuniary constraints was odious to me and almost led me to abandon the entire enterprise, but I felt that the potential benefit to students, scholars, and scientists outweighed my chagrin. I therefore will stand by my choices of papers but plead extenuating circumstances. I hope the papers give a balanced, certainly not a thorough, view of the tide of cellular immunology over the past two decades.

I want to thank the authors of the papers for their cooperation. My special thanks to Mrs. Beth Brumit who took such care in organizing the correspondence required for this work and in typing the manuscript.

EDWARD S. GOLUB

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INTRODUCTION

Part I of *Immunology* develops the ideas of clonal selection and cell interactions in the immune response. Part II deals with the regulation of the response. The thrust of the work of the decade of the 1970s has been to begin to untangle the interconnected web of reactions that allow the subpopulations of specifically programmed lymphocytes to recognize the antigens with which they react. Part I described the critical role of the gene products of the major histocompatibility complex in cell interaction. Part II presents the work done to elucidate the mechanisms involved in the recognition of antigen. Therefore, this volume will explore papers that served as benchmarks for studies of surface receptors for antigen on B-cells and T-cells and immune tolerance. Great advances in unlocking the structure of the immunoglobulin molecule in the 1960s culminated in two Nobel prizes. During the 1970s a greater understanding of the organization of these genes developed because of advances in molecular biology that has now led to a better understanding of the most fundamental of immunological problems, the generation of diversity. Accordingly, benchmark papers in immunoglobulin structure and generation of diversity are also included in this volume.



RECEPTORS AND SIGNALS

Editor's Comments on Papers 1 Through 9

- 1 **KENNEDY et al.**
A Transplantation Assay for Mouse Cells Responsive to Antigenic Stimulation by Sheep Erythrocytes
- 2 **RAFF, STERNBERG, and TAYLOR**
Immunoglobulin Determinants on the Surface of Mouse Lymphoid Cells
- 3 **TAYLOR et al.**
Redistribution and Pinocytosis of Lymphocyte Surface Immunoglobulin Molecules Induced by Anti-Immunoglobulin Antibody
- 4 **GREY et al.**
Immunoglobulins on the Surface of Lymphocytes. V. Quantitative Studies on the Question of Whether Immunoglobulins Are Associated with T Cells in the Mouse
- 5 **MARCHALONIS, CONE and VON BOEHMER**
Surface Immunoglobulins of Peripheral Thymus-Derived Lymphocytes
- 6 **BINZ, LINDENMANN, and WIGZELL**
Inhibition of Local Graft-versus-Host Reaction by Anti-Alloantibodies
- 7 **JERNE**
Towards a Network Theory of the Immune System
- 8 **ZINKERNAGEL and DOHERTY**
Restriction of in vitro T Cell-Mediated Cytotoxicity in Lymphocytic Choriomeningitis Within a Syngeneic or Semiallogeneic System
- 9 **SHEARER**
Cell-Mediated Cytotoxicity to Trinitrophenyl-Modified Syngeneic Lymphocytes

If one accepts the notion of clonal selection as the underlying paradigm in the immune response (Jerne 1955, Burnet 1957) then one must make two predictions. The first is that antigen induces proliferation of cells, and the second is that the responsive cell has a receptor for specific antigen. The first prediction was shown to be true by Baney, Vazquez, and Dixon (1962). The papers in this section show that the second prediction (i.e., that there are antigen-specific receptors) is also true.

Just as the pluripotent hematopoietic stem cell was assayed in a transplantation assay (Till and McCulloch 1961), the same group devised an assay that allowed the cell responsive to antigen to be quantitated. It thus became possible to quantitate the “antigen-sensitive cell” (Paper 1).

The discovery by Raff (Paper 2) that some lymphocytes had readily demonstrable immunoglobulin (Ig) on their surfaces led to the conjecture that this Ig could serve as receptor for antigen. Important insight that grew out of this was the discovery by Taylor et al. (Paper 3) that Ig (and other molecules) could move in the plane of the membrane. This led to the realization that the membrane of cells was fluid with floating islands of protein molecules (Singer and Nicolson 1972). It soon became clear that Ig-positive cells were θ negative (θ 's now called Thy-1). A controversy arose over the presence of Ig on T-cells. Since it was generally agreed that Ig on B-cells could act as receptor for antigen, one would predict that the T-cell receptor would be similar. Immunoglobulin was found to be present on T-cells by some workers (Paper 4) but not by others (Paper 5).

It now appears that the T-cell receptor is coded by Ig genes and shares idiotypic determinants with the B-cell Ig (Cold Spring Harbor Laboratory 1976). The direction of this work derives to a great extent from the work of Binz, Wigzell, and colleagues (Paper 6). It appears that the T-cell receptor is an H-chain variable region (Cold Spring Harbor Laboratory 1976).

It will be recalled that the clonal selection theory of Burnet derived from the natural selection theory of Jerne. This theory led to the experiments and great advances of the 1960s and 1970s. Another theory by Jerne, the network theory (Paper 7), postulated that responses by an animal to its own receptors could modulate the immune response. This theory predicts autoantiidiotypic responses, and these responses have in fact been demonstrated (Binz and Wigzell 1976) indicating that responses to “self” are possible.

Not only is recognition and response to self possible but it may also be mandatory for a response to antigen. Independent work by Zinkernagel and Doherty (Paper 8) and Shearer (Paper 9) has shown that the response to a foreign antigen (antigen X) is made only if