ADVANCES IN
Immunology

EDITED BY

F. J. DIXON HENRY G. KUNKEL

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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 G. KUNKEL
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The Regulatory Influence of Activated T Cells on B Cell Responses to Antigen

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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-