ADVANCES IN IMMUNOLOGY

Volume 10

F. J. Dixon, Jr. &
Henry G. Kunkel

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Immunology

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PREFACE

Volume 10 of *Advances in Immunology* contains six reviews which reflect the ever-widening boundaries of immunology and its increasing depth of penetration into biomedical research. The continuing growth of the subject makes it desirable and essential for the reader to profit from periodic authoritative summations of knowledge on discrete subjects of immunology. When the summation expresses the perspective of a leader in his field, the contribution is doubly valuable. We are greatly indebted to the authors of this volume for taking the time to prepare such reviews.

The first chapter by Drs. Siskind and Benacerraf relates the essential features of the antibody response to the interaction of antigen with preformed, cell-bound, antibodylike receptors. The effect of this interaction on individual cells is determined by the affinity of the antigen cell-bound antibody combination and results in a recruitment or selection of cells and their activation. This process, describable in thermodynamic terms, is the central biological event which can explain or predict such features of the antibody response as the progressive increase in average binding affinity of antibody produced, the effect of antigen dose on amount and affinity of antibody, the mechanism of action of adjuvants, the essential role of specific cell proliferation stimulated by antigen, the interference of humoral antibody with antigenic selection of cells, the phenomenon of "original antigenic sin," and the induction of tolerance.

Dr. Grey, in the second chapter, offers a definitive review of the immunoglobulins of various species, a subject to which he has been an important contributor. These phylogenetic data are placed in perspective and used as a basis for understanding the development and present structure of the complex immunoglobulin systems of man and other vertebrate species.

One of the important and hitherto poorly understood mediators of anaphylaxis, slow reacting substance, is described in the third chapter by Drs. Orange and Austen who have contributed greatly to progress in this field. The events involved in the formation and release of this mediator as well as the current knowledge of its chemical and pharmacological characteristics are presented. The biological implications of slow reacting substance for the entire subject of acute immunologic reactions and their pharmacologic manipulations are discussed and provide an enticing preview to advances which may be expected in this field in the next few years.

Hemostasis is a complex process which is only recently attracting the attention of immunologists. The interesting parallels and, at times, direct interrelationships of hemostasis and serologic events initiated by antigen-antibody reactions are now becoming apparent. In the fourth chapter, Dr. Ratnoff discusses the interdependency of the blood clotting process, fibrinolytic phenomena, inflammation, and immunologic reactions. This review provides both the basis for a clear understanding of the many elements of hemostasis and a perspective which views the several defense mechanisms as a well-integrated continuum.

The contributions of immunology to the understanding of viral oncogenesis have and will continue to be of utmost importance. Fortunately, for the investigator and perhaps in some instances for the host himself, virus-induced tumors may bear the antigenic imprint of their inducers. The antigens of virus-induced tumors of animals and man are clearly and succinctly discussed in the fifth chapter by Dr. Habel who is one of the outstanding contributors to this field. The origin and characteristics of the various types of antigens in viral tumors and their participation in spontaneous or induced immunologic responses of the host are elucidated. The implications of such immunologic responses for prevention or therapy of virus-induced tumors are also considered.

While most fields of research grow in relationship to investigators' interests and available techniques, occasionally an important practical problem demanding immediate attention is thrust upon the scientific community regardless of its state of readiness. Such a situation exists with respect to the pressing need for effective tissue typing in man, necessitated by the technical feasibility of organ transplantation. In the last chapter, Dr. Amos writes a clear statement of our current knowledge of the genetics and immunology of human histocompatibility. In addition, he provides a first-hand view of the difficulties and limitations as well as the achievements of tissue typing as it is practiced today.

We wish to acknowledge the cooperation and assistance of the publishers who have done much to ensure the quality of this series of volumes.

FRANK J. DIXON
HENRY G. KUNKEL

July, 1969

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Cell Selection by Antigen in the Immune Response

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I. Introduction

We shall describe here certain basic phenomena characteristic of the immune response and analyze their mechanism at both the cellular and the molecular levels. Among the characteristics of the immune response

with which we shall deal in this paper are (*a*) the change in average binding affinity of antibody for the antigenic determinant which occurs with time after immunization; (*b*) the effect of antigen dose on the concentration and average binding affinity of serum antibody; (*c*) the effect of adjuvants upon the concentration and affinity of circulating antibody; (*d*) the commitment of individual plasma cells and lymphocytes to the synthesis of antibody of a single class, allotype, specificity, and affinity; (*e*) the crucial role of specific cell proliferation, resulting from antigenic stimulation, upon the process of selection of populations of immune cells producing antibodies of progressively higher affinity for the immunizing antigen; (*f*) the effect of humoral antibody upon the process by which antigen selects cells synthesizing antibodies of progressively higher affinity; (*g*) the phenomenon of "original antigenic sin," that is, the selective effect of previous immunization on the population of cells which become available for stimulation by a structurally related antigen; (*h*) the specificity of tolerance induction as related to the energetics of the antigen–antibody interaction and the relationship of specific unresponsiveness to immunological selection and to the process of immune cell proliferation.

These various phenomena will be explored in an attempt to formulate a unified concept of the immune response as an antigen-driven proliferation and selection of specific cells that are committed to the synthesis of specific immunoglobulin molecules prior to contact with antigen. An attempt will be made to define the conditions governing the selection aspect of this process.

We have assumed a strictly clonal theory of antibody synthesis such as originally proposed by Burnet (*1–3*), in which cells become committed to the production of a specific antibody molecule in a random fashion prior to antigen exposure, presumably by a process of somatic mutation. We would suggest that such precommitted cells bear representations of antibody molecules having binding properties identical to those of the antibody synthesized by the particular cell, or its progeny, upon antigenic stimulation. Such antibody present on committed cells shall be referred to as "cell-associated antibody." We would suggest that cells are specifically stimulated to proliferate and/or secrete antibody as a result of the interaction of cell-associated antibody with specific antigen (possibly in a "processed" form). A single cell so stimulated would be expected to produce a homogeneous antibody product. The heterogeneity of serum antibody would thus reflect a heterogeneity of the antibody-synthesizing cell population. In such a system, cells can be viewed as competing for available antigen. Thus, cells bearing antibody molecules of highest bind-

ing affinity for the antigen would stand a better chance of binding antigen and, thus, of being stimulated to proliferate and/or secrete antibody. We view antigen (or processed antigen) as acting continuously, throughout the course of the immune response, to select those cells of highest antigen-binding affinity from a proliferating immune cell population. We have here an essentially evolutionary view of the immune response, in which availability of antigen serves as the crucial selective pressure. Thus, we suggest that one step in the pathway leading to antibody synthesis involves the interaction of antigen (or processed antigen) with preexisting antibody molecules presumably located on the surface of the cell that synthesized them. This selective step in the immune response can be considered in simple energetic terms, that is, antigen molecules would be most likely bound by those cells bearing antibody molecules of highest affinity for that antigen. Based upon such a theory the results of a wide variety of different experimental situations may be predicted.

In summary, we shall review the evidence that one step, in some as yet undefined sequence of steps leading to antibody synthesis, behaves as if it involves the interaction of antigen with pre-existing antibody molecules in a manner predictable by simple energetic considerations. Based upon this interaction of antigen with cell-associated antibody, populations of antibody-forming cells can continuously be selected by antigen in a predictable fashion. The importance of the interaction of antigen with "cell-associated antibody" has been discussed by a number of workers including Eisen (*95a*), Steiner and Eisen (*48*), Jerne (*3a*), Mitchison (*3b*), Talmage (*3c*), Lenox and Cohn (*3d*), and by Fazekas de St. Groth and Webster (*139*).

II. Antibody-Binding Affinity

A. Definitions and Concepts

The term affinity refers to the "strength" of the interaction between the antibody molecule and the antigenic determinant. With a high-affinity antibody, a strong bond is formed between the antibody and the homologous antigenic determinant. In essence this means that it would require a large amount of energy to pull apart the antibody–antigen complex. Affinity can be viewed as the measurement of antibody specificity (in the sense of conformational correspondence to the homologous determinant; not in the sense of a lack of cross reactivity, since the degree of cross reactivity is often greater with higher-affinity antibody), and as such may be expressed either as the equilibrium constant (K) for the antibody–antigen interaction or as the standard free energy change (ΔF°) for the reaction. For the general reaction: