

ADVANCES IN
Immunology

VOLUME 16

ADVANCES IN **Immunology**

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PREFACE

Immunologic research covers a broad field ranging from the molecular structures of Ig molecules and their genetic implications to the nature of immunologic diseases of man and animals. These varied studies are interdependent in that what is being learned about Ig molecules at the molecular level is being translated into mechanisms of immunologic responses and reactions in experimental situations, and the results of these studies serve as a basis for our developing understanding of the pathogenesis of clinical immunologic diseases. The reviews included in Volume 16 cover this broad spectrum of investigation and illustrate well the cohesiveness of immunologic research.

In the first contribution, Drs. Natvig and Kunkel present in detail the antigenic and biochemical basis for the classification of Ig molecules. Antigenic analyses of Ig molecules from different individuals have provided a long list of genetic markers of the Ig genes, the behavior of which appears to be controlled by regular Mendelian laws. The distribution of Ig classes and subclasses in normal serum and the selective nature of Ig classes in certain antibodies are discussed, along with the characterization of Ig molecules on the surfaces of normal lymphocytes, leukemic lymphocytes, and myeloma plasma cells. Myeloma proteins and related homogeneous Igs are compared, and their biological activities and structurally abnormal forms are described. Finally, the idiotypic antigens of the variable portions of light and heavy chains of myeloma proteins and specific antibodies are discussed and their use in the study of the variable regions in different Ig molecules is described.

The second article, by Dr. Weigle, is an authoritative discussion of immunologic unresponsiveness. Certainly, therapeutic manipulation of the immune response to achieve specific unresponsiveness in a variety of immunologic diseases is a prime goal, and recent advances in our understanding of this phenomenon bring us closer to its realization. As Dr. Weigle explains, the induction and termination of unresponsiveness can now be described in terms of B and T lymphocytes, their antigen receptors, serum antibody, and antigenic structure and dose. Finally, the implications of these mechanisms of induction and termination of unresponsiveness for autoimmune and neoplastic diseases are placed in good perspective by the author.

In the third contribution, Drs. Wheelock and Toy describe the complex interrelationship between lymphocytes and infecting viruses. Lym-

phocytes may play a variety of roles in viral infections—from acting as primary targets of infection to providing an immunologic barrier against infection and, finally, to mediating the destructive changes in a virus-induced immunopathologic disease. Infection of lymphocytes in both acute and chronic viral infections is common and may be evidenced by both morphologic and functional abnormalities of the lymphocytes. The basis of the inadequacy of the lymphoid system in immunodeficiency states and after immunosuppression which predisposes to viral infections and to activation of latent viruses is discussed, along with the ways in which lymphocytes may normally act to terminate viral infections. Finally, the means by which lymphocytes contribute to viral disease—by harboring virus and allowing replication, by themselves undergoing malignant transformation, and by inducing allergic inflammation—are considered in detail.

Drs. Cochrane and Koffler provide, in the fourth article, a complete and critical statement of our knowledge of immune complex diseases. There can be little doubt of the frequency of immune complex diseases caused by circulating antigen-antibody complexes. Many of the mechanisms by which these complexes cause disease are recognized, and the authors define them clearly in molecular and cellular terms. The missing element in most clinical immune complex diseases is identification of the antigen or etiologic agent. However, the description of the presently known etiologic agents and their roles in pathogenesis which is presented here will certainly contribute to an intensified search for other agents and an improved understanding of this important pathogenic mechanism.

In the final contribution, Dr. Zvaifler describes immunopathologic events contributing to joint disease in rheumatoid arthritis. The peculiar anatomy of the joint which permits or encourages the production of chronic inflammation is considered. The phlogogenic events, including the accumulation and precipitation of immunoglobulins presumably as antibody-antigen complexes, the activation of complement, kinins, and clotting factors, and the participation of polymorphonuclear and mononuclear leukocytes in the inflammation, are critically discussed and integrated. As the author points out, our understanding of the pathogenesis of rheumatoid arthritis is reasonably clear but we still await identification of the etiologic agent and/or antigens involved.

The cooperation and assistance of the publishers in the production of Volume 16 are gratefully acknowledged.

FRANK J. DIXON
HENRY G. KUNKEL

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Human Immunoglobulins: Classes, Subclasses, Genetic Variants, and Idiotypes

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I. Immunoglobulin Classes and Subclasses

A. INTRODUCTION

The immunoglobulin classes and subclasses represent a group of structurally related proteins, and in all instances consist of two pairs of polypeptide chains held together by disulfide bridges and noncovalent forces. Each chain has an N-terminal part of about 107 to 115 amino acids, which contains the variable areas and is primarily involved in the specific interaction with the antigen, and a constant portion of about

107 to 110 amino acids for the light chain and about 310 to 330 amino acids for the heavy chain. The constant part, particularly of the heavy chains, carries the sites for many of the other important biological activities, such as complement fixation, interaction with rheumatoid factors, interaction with receptors on cell membranes, transplacental transfer, and passive cutaneous anaphylaxis (PCA). The heavy chains (about 450 amino acids) are distinctly different in biochemical and antigenic structure for each of the immunoglobulin classes and subclasses (see Killander, 1967; Cairns, 1967; Edelman *et al.*, 1969; Bearn, and Kunkel, 1968). These differences form the basis for the classification of the immunoglobulins into five main classes and into four IgG and two IgA subclasses (Grey and Kunkel, 1964; Terry and Fahey, 1964; Kunkel and Prendergast, 1966; Feinstein and Franklin, 1966; Vaerman and Heremans, 1966). At present it is not known whether there are subclasses within the three other immunoglobulin classes, IgM, IgD, and IgE. The previously reported subclasses of IgM were probably related to variable region subgroups of IgM proteins. Each chain can interact with any type of light chain (κ or λ) and any light-chain subgroup to make an immunoglobulin molecule.

The light chains (about 214 amino acids) are common to all immunoglobulin classes although the ratio of κ to λ is not always the same. Table I shows the distribution of light-chain types within the various IgG subclasses.

The accumulated evidence indicates that the synthesis of the variable and the constant region (Hilschmann and Craig, 1965) of the chains is governed by different genes, one variable (V) and one constant (C) (Hood and Prahl, 1971). There appear to be three main groups of the V-region genes: those for κ light chains, those for λ light chains, and those for all the heavy chains. Each of the variable groups consists of a number of subgroups (Milstein, 1967; Solomon *et al.*, 1965; Tischendorf *et al.*,

TABLE I
RATIO OF κ TO λ PROTEINS IN IMMUNOGLOBULIN G SUBCLASSES

Protein	IgG1		IgG2		IgG3		IgG4	
	1 ^a	2 ^b	1 ^a	2 ^b	1 ^a	2 ^b	1 ^a	2 ^b
κ	104	155	11	30	9	15	5	14
λ	43	109	10	31	8	12	1	2
Ratio κ/λ	2.41	1.42	1.10	0.96	1.12	1.25	5.0	7.0

^a (1) Data of Terry *et al.* (1965).

^b (2) Data of Schur *et al.* (see Schur, 1972).