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Immunology

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EDITED BY

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Erratum

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On page 28, the following line should be inserted between lines 12 and 13:
"P-K, PCA, and passive sensitization of leukocytes, which, therefore"

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PREFACE

It can safely be predicted that the seventies will be the decade of cellular immunology. Already the expansion is evident on all sides and many immunologists, previously involved in the antibody field, are turning to cellular work. To some extent this may be unfortunate because that most basic of problems, the mechanism of antibody variability, remains an enigma. Immunologists are still evenly divided on the issue of whether the germ line theory or a type of somatic model holds the explanation. Possibly the work at the cellular level might provide the answer. The *Advances* will participate actively in this timely movement and, as exemplified by this volume, will also continue to be involved in the currently less popular but no less important areas of immunology.

The article by Drs. John E. Hopper and Alfred Nisonoff concerns that very useful label of the immunoglobulins, their individual antigenic specificity or idiotypic specificity. The authors have utilized this property in superb fashion to trace the development of different antibody producing clones of cells in the primary and secondary response. It is abundantly clear that antigens related to the V regions and antibody combining sites are followed in these studies.

There are few areas where problems of nomenclature are more varied and confusing than in the field of allergic reactions. Dr. Elmer L. Becker treats this subject from all aspects, ranging from the initiating antigen, through the mediators produced, to the final cell involvement. A very reasonable classification of immediate-type allergic reactions has emerged that takes into account the many different phases of these reactions.

One of the exciting chapters in immunology has been the recent delineation of the IgE class of immunoglobulins and the demonstration of its significance for atopic allergic disorders. Just as in all other areas of immunoglobulin work, the discovery of a myeloma protein of the IgE type contributed enormously to the successful evolution of this work. Drs. Hans Bennich and S. Gunnar O. Johansson were responsible for this important aspect and they not only review this field but also present many observations that have not been published elsewhere. Because of the low concentration of IgE in most sera, its measurement has presented a special challenge. The ingenious procedures developed by the authors, as well as other methods, are discussed in useful detail.

Drs. J. L. Turk and A. D. M. Bryceson review the various different immunological reactions to the specific organisms in leprosy and

leishmaniasis. These authors have played a primary role in interpreting these reactions in terms of modern concepts of immunology. Defects in cellular immunity clearly play a major role in special forms of these disorders and many of the principles derived from these studies hold implications for a number of other diseases.

Dr. Barry R. Bloom, one of the leaders in the cellular immunity expansion, describes some of the forefronts of this field. The many mediators involved in lymphocyte reactions are considered in special detail. None of these factors has been isolated in pure form, which will be essential for their eventual understanding. However, an overall picture of the intricacies of cellular immunity is beginning to emerge which relates the various experimental models to *in vivo* events.

The cooperation and valuable assistance of the publishers in the production of Volume 13 are gratefully acknowledged.

H. G. KUNKEL
F. J. DIXON

July 1971

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Immunological Phenomena in Leprosy and Related Diseases

Nature and Classification of Immediate-Type Allergic Reactions

Structure and Function of Human Immunoglobulin E

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I. Introduction

Immunoglobulin E (IgE) represents a minor but distinct class of proteins present in serum of man and higher primates and possibly also in the serum of other species. In healthy individuals, the upper range of concentration is usually below 1 μg./ml. The detection and quantitation of IgE require very sensitive methods. Immunoglobulin E is elevated 4–30 times normal in various diseases, among which atopic disorders and parasitic infestations appear to be the most prominent. Pathological amounts of IgE have also been found in the serum of patients with γE myeloma.

The association of certain reaginic antibodies to a new class of im-

munoglobulin was postulated by K. Ishizaka and co-workers (1966a,b). The discovery that the myeloma protein ND and its normal counterpart share antigenic characteristics with reaginic antibodies and, in addition, carry skin-fixing structures, which appear similar to those of reagins, opened new possibilities to study the immunological and structural features of immediate hypersensitive reaction. The aim of this paper is to summarize our present knowledge of the biological and structural properties of IgE and its occurrence in various body fluids in health and disease. To this end, particular emphasis has been given to the methodology of identification and quantitation and also to the problem of isolation and characterization of IgE. References to the massive literature on reagins will be made only when found to be relevant for the understanding of a particular problem, and no attempts have been made to portray the long history of reagins, since this has been so masterly done in previous reviews by several authors (see K. Ishizaka and Ishizaka, 1968a; Sehon and Gyenes, 1965; Stanworth, 1963).

II. Isolation and Physicochemical Characteristics of Immunoglobulin E

As a result of the obvious difficulties encountered in the isolation of reasonably homogeneous samples of a protein, which, like IgE, represents only a minor serum constituent, the physicochemical characteristics given in this paper will refer mainly to the first described E myeloma protein, ND. However, there is sufficient experimental evidence now available to support the belief that the ND protein has its major biological, immunological, and physicochemical characteristics in common with the IgE present in normal serum (Bennich *et al.*, 1968).

A. Identification of Myeloma Protein ND

Our first attempt in 1965 to isolate the atypical myeloma protein ND was done by zone electrophoresis (Johansson and Bennich, 1967a). The M component migrated in the fast γ region. The isolated fraction, containing 93% of the M component contaminated mainly with IgG, was used for the first immunization experiments in rabbits and for carbohydrate analysis. The latter indicated that the M-component contained about 10% of total carbohydrate—a result suggesting a possible relationship of ND to IgA or IgM. Gel filtration experiments on serum ND on calibrated columns of Sephadex G-150 gave results in the same direction; indications that the M component distributed within the same elution volume as monomeric or 7 S IgA initiated a direct comparison of a monomeric A myeloma protein and protein ND. Both proteins were isolated from serum by precipitation with sodium sulfate and subsequently purified by recycling chromatography on Sephadex G-150 to

eliminate contaminating IgG. The purified A and ND proteins were added to a solution of monomeric normal IgG and the mixture was analyzed on a calibrated column of Sephadex G-200. The distribution of IgA and protein ND coincided completely as determined by quantitative immunological analysis, and the elution volume was significantly smaller than that of IgG. In contrast to these results, ultracentrifugal analyses indicated a significantly difference for IgA and protein ND, the sedimentation constant values ($s^{\circ}_{20,w}$) were 6.5 and 7.9, respectively.

Molecular weight determinations gave a value of about 139,000 for IgA and 196,000 for protein ND using a partial specific volume of 0.713 for both proteins. By reduction of protein ND with mercaptan followed by dissociation in acid, about 20% of the protein moiety could be recovered as λ chains. The remaining 80% constituted a single carbohydrate-containing component with a characteristic electrophoretic mobility in starch gel electrophoresis in acid urea. This major constituent was regarded as representing the heavy chain of an atypical immunoglobulin.

The problem of preparing class-specific antisera to IgE(ND) was not solved until fragments of ND protein were isolated (see Section III,B). Hereby it also became possible to develop the radioimmunosorbent test (RIST) described in Section IV and the radioallergosorbent test (RAST) described in Section VII. By using the RIST, a counterpart to ND was found in normal serum. The concentration in healthy individuals are usually found to be extremely low as will be further discussed in Section V. However, by chance the serum from one of the apparently healthy blood donors included in the first series of experiments was found to contain a significantly higher level of IgE(ND) than the main level of the test group. The donor was subsequently found to have a previously clinically undiagnosed hypersensitivity to dog dander, a finding which initiated a study of the level of IgE(ND) in patients suffering from asthma and hay fever, as will be further discussed in Section VI. The significantly higher level of IgE(ND) found in cases of extrinsic asthma strongly suggested a relation to reaginic antibodies as did the presence of allergen antibodies of IgE class in these patients.

In 1966, K. Ishizaka *et al.* (1966a), from their studies on antiragweed antibodies in reagin-containing fractions of atopic sera, suggested the presence of a unique immunoglobulin as a carrier of reaginic activity. The specific activity was found in the γ_1 region by radioimmunoelectrophoresis and the protein was tentatively designated γE-globulin. An exchange of antisera between Denver and Uppsala was made in March 1967 and, by comparatively antigenic analyses of myeloma protein ND and γE-globulin, direct immunological evidence was obtained that