

IMMEDIATE HYPERSENSITIVITY

Modern Concepts and Developments

Edited by

MICHAEL K. BACH

Vol. 7

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Department of Hypersensitivity Diseases Research

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PREFACE

The appearance of this volume coincides with the end of the first decade since IgE was identified as a new class of immunoglobulins and since it was shown that this class of immunoglobulins is responsible for most if not all the atopic conditions in man. These last 10 years have been a period of intense research activity, not only in areas dealing with atopy but also in the entire field of immunology, and more broadly in all aspects of cellular biology. It is natural, therefore, that there should be a growing number of new recruits and converts to this area. For this reason it was felt that the time may be right for an attempt to present an anthology of some of the threads from which the fabric of research in atopy is being woven. It is my hope that such a compilation of position papers might be of help both to investigators already actively engaged in research in this field, and to those contemplating entrance into it.

In choosing the subjects to be covered, I naturally picked either those "threads" which seemed of particular relevance to me, or those which seemed to offer new and fruitful possibilities for hybridization to enrich the fabric of the better-established areas. The immunologic threads deal with aspects of the regulation of the immune response as it applies to IgE synthesis, the effector cells involved in atopy, and the pharmacologic mediators of anaphylaxis. Interwoven with these are aspects of endocrinology and pharmacology, protein chemistry and immunochemistry, and more than a little clinical immunology.

Our understanding of the regulation of the immune response has improved markedly. We recognize the major role played by genetic factors and by the complex interactions of the macrophages and of various sub-classes of B and T cells. While most of our understanding of these factors was gleaned from work with the more easily studied IgG antibodies, it will be seen from the chapters by Black and Marsh, by Tada, and by Ishizaka and his collaborators, that studies with IgE antibodies actually helped in the elucidation of the control mechanisms which are operating in the regulation of all immunoglobulin synthesis.

But anaphylactic or "anaphylactoid" reactions can be evoked by immunoglobulins other than IgE and, in certain situations, by agents which are not antibodies at all. Thus, the existence of heat-stable homocytotropic antibodies in animals is reviewed in the chapter by Stechschulte, while the evidence for similar antibodies in man is reviewed by Parish. Finally, generation of a neutral peptide with vascular permeability-enhancing properties is summarized by Wintroub, Goetzl and Austen.

Mast cells and basophils have long been associated with anaphylactic phenomena. However, immunologists have generally tended to name these two cells in the same breath and to implicitly equate them. Eosinophils are a hallmark of atopic reactions, but it is only in the last few years that we have begun to understand their role and the mechanisms responsible for their attraction to the sites of an anaphylactic reaction. The chapters by A. Dvorak, Padawer, and Zucker-Franklin present good reviews of the characteristics of these cells, their origin and function. The chapter by Kay, on eosinophil chemotactic factor of anaphylaxis, and the chapter by Ward on chemotaxis in general help explain how these cells are attracted to the site of reaction. Finally, it has become apparent in the last few years that, in addition to their role in immediate hypersensitivity, the mast cells and basophils appear to be critical reactants in many cell-mediated immune responses as well. This fact, which tends to tie immediate hypersensitivity to delayed hypersensitivity, is

explored by H. Dvorak in his chapter on Cutaneous Basophil Hypersensitivity (CBH) and is also touched on in several other contexts.

The immediate causes of anaphylactic reactions are the pharmacologic mediators of anaphylaxis which are released or produced by the effector cells upon appropriate stimulation. The chapters by Orange, Kay and Benveniste summarize our present knowledge of the nature of the better studied mediators. However, since compiling these chapters there has been a proliferation in the numbers of mediators which have been identified, and a discussion of these will have to await a future opus. The production or release of the mediators has turned out to be a very desirable model for the study of secretory phenomena in general. Activation involves membrane events and careful analysis has revealed that there may be several distinct initiation mechanisms. This is described by Morrison and Henson in their chapter. After activation, however, the release reaction is modulated by intracellular pharmacologic messengers, such as the prostaglandins and the cyclic nucleotides. And even though the effector cells do not have nerve synapses on their surface, adrenergic and cholinergic neurotransmitters appear to regulate the cyclic nucleotide levels and, thereby, the secretory function. These considerations are reviewed by Plaut and Lichtenstein. Finally, perhaps because of the explosive character of the secretory reaction, another family of pharmacologic antagonists, which can inhibit mediator release, has been recognized. Even though their detailed mode of action is still unknown, their ability to interfere with the calcium gating phenomenon which appears to be the release-initiating signal, seems to have been established. Johnson summarizes the large body of evidence which has been accumulated with these compounds.

An area of considerable interest to chemists is the nature of the substances which can elicit an atopic response. Needless to say, this is also of considerable medical relevance both in terms of efforts to develop modified derivatives of sensitizing drugs which might be used in the elicitation of blocking antibodies, and in the

development of modified drugs which are less likely than the present drugs to induce an anaphylactic, reagin-mediated response. Several aspects of this area are reviewed in chapters by Dineen, Strejan, Overell and by Warrington and his collaborators. The uniquely allergenic properties of helminths, and the possible role of atopy in the host defense against these pests is also elegantly considered in the first of these chapters.

The fact that IgE is a trace component of plasma, and that the target mast cells and basophils are a relatively rare cell type, requires that the interaction of IgE with its receptor on these cells must be a reaction of unusually high affinity. Thus studies on the nature of the IgE molecule and of its receptors have gained momentum as our knowledge of cell receptors, in general, has improved. The chapters by Bennich; Baenziger; Dorrington and Bennich; and by Metzger and Bach review certain aspects of this area.

As already mentioned above, interest in various aspects of immediate hypersensitivity is intimately connected to the problems which this form of the immune response poses for a considerable portion of the human population. While the application of our newly-gained knowledge to clinical medicine is still in its infancy, the available information on the role of IgE or the effects of IgE deficiency conditions has been summarized by Hong and by Ganguly and Waldman.

It must be apparent that the list of topics covered in this book is far short of exhausting the much larger list of subjects which touch on the experimental or clinical aspects of immediate hypersensitivity. Another editor, with a different set of biases, might well have chosen to stress quite different aspects of this field. It is hoped, however, that the reader will find a fabric of sufficiently varied texture to whet his or her appetite for further reading and experimentation in this field.

It is not possible to identify and acknowledge all the individuals who helped me in assembling this book. I'm thankful for the many friendships, around the world, which have developed as a

consequence of my contacts with those contributors whom I had not met before. But I am particularly indebted to four people. These are Dr. Robert P. Orange and Drs. Teruko and Kimishige Ishizaka, for their many constructive comments and suggestions and, above all, Dr. K. Frank Austen. Dr. Austen, by enabling me to experience a year in the exhilarating atmosphere of his laboratory, introduced me to this field of research back when the world was young (in 1969). He has remained a good friend and counselor ever since, and it is he who encouraged me to take on this task. Last but not least, special thanks are due to Mrs. Virginia Crawford, whose tireless and cheerful help in typing this book for publication has made publication possible.

Michael K. Bach

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