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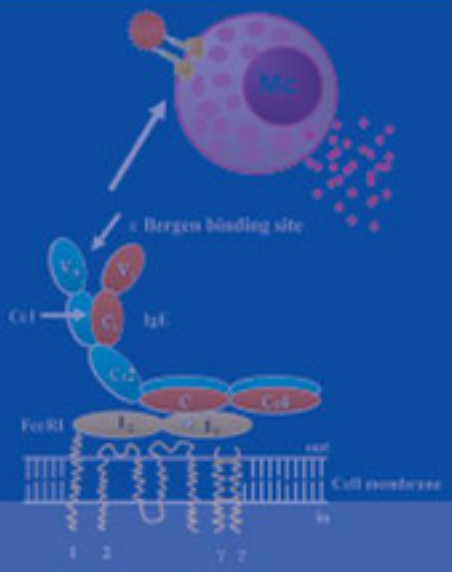

Allergy Frontiers:

Diagnosis and Health Economics

Volume 4

Springer

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Foreword

When I entered the field of allergy in the early 1970s, the standard textbook was a few hundred pages, and the specialty was so compact that texts were often authored entirely by a single individual and were never larger than one volume. Compare this with *Allergy Frontiers: Epigenetics, Allergens, and Risk Factors*, the present six-volume text with well over 150 contributors from throughout the world. This book captures the explosive growth of our specialty since the single-author textbooks referred to above.

The unprecedented format of this work lies in its meticulous attention to detail yet comprehensive scope. For example, great detail is seen in manuscripts dealing with topics such as "Exosomes, naturally occurring minimal antigen presenting units" and "Neuropeptide S receptor 1 (NPSR1), an asthma susceptibility gene." The scope is exemplified by the unique approach to disease entities normally dealt with in a single chapter in most texts. For example, anaphylaxis, a topic usually confined to one chapter in most textbooks, is given five chapters in *Allergy Frontiers*. This approach allows the text to employ multiple contributors for a single topic, giving the reader the advantage of being introduced to more than one viewpoint regarding a single disease.

This broad scope is further illustrated in the way this text deals with the more frequently encountered disorder, asthma. There are no fewer than 26 chapters dealing with various aspects of this disease. Previously, to obtain such a comprehensive approach to a single condition, one would have had to purchase a text devoted solely to that disease state.

In addition, the volume includes titles which to my knowledge have never been presented in an allergy text before. These include topics such as "NKT ligand conjugated immunotherapy," "Hypersensitivity reactions to nano medicines: causative factors and optimization," and "An environmental systems biology approach to the study of asthma."

It is not hard to see that this textbook is unique, offering the reader a means of obtaining a detailed review of a single highly focused subject, such as the neuropeptide S receptor, while also providing the ability to access a panoramic and remarkably in-depth view of a broader subject, such as asthma. Clearly it is intended primarily for the serious student of allergy and immunology, but can also serve as a resource text for those with an interest in medicine in general.

I find it most reassuring that even though we have surpassed the stage of the one-volume, single-author texts, because of the wonderful complexity of our specialty and its broadening scope that has evolved over the years, the reader can still obtain an all-inclusive and comprehensive review of allergy in a single source. It should become part of the canon of our specialty.

Phil Lieberman, M.D.

Foreword

When I started immunology under Professor Kimishige Ishizaka in the early 1950s, allergy was a mere group of odd syndromes of almost unknown etiology. An immunological origin was only suspected but not proven. The term "atopy," originally from the Greek word *à-topòs*, represents the oddness of allergic diseases. I would call this era "stage 1," or the primitive era of allergology.

Even in the 1950s, there was some doubt as to whether the antibody that causes an allergic reaction was really an antibody, and was thus called a "reagin," and allergens were known as peculiar substances that caused allergy, differentiating them from other known antigens.

It was only in 1965 that reagin was proven to be an antibody having a light chain and a unique heavy chain, which was designated as IgE in 1967 with international consensus. The discovery of IgE opened up an entirely new era in the field of allergology, and the mechanisms of the immediate type of allergic reaction was soon evaluated and described. At that point in time we believed that the nature of allergic diseases was a mere IgE-mediated inflammation, and that these could soon be cured by studying the IgE and the various mediators that induced the inflammation. This era I would like to call "stage 2," or the classic era.

The classic belief that allergic diseases would be explained by a mere allergen-IgE antibody reaction did not last long. People were dismayed by the complexity and diversity of allergic diseases that could not be explained by mere IgE-mediated inflammation. Scientists soon realized that the mechanisms involved in allergic diseases were far more complex and that they extended beyond the conventional idea of a pure IgE-mediated inflammation. A variety of cells and their products (cytokines/chemokines and other inflammatory molecules) have been found to interact in a more complex manner; they create a network of reactions via their receptors to produce various forms of inflammatory changes that could never be categorized as a single entity of inflammation. This opened a new era, which I would like to call the modern age of allergology or "stage 3."

The modern era stage 3 coincided with the discovery that similar kinds of cytokines and cells are involved in the regulation of IgE production. When immunologists investigated the cell types and cytokines that regulate IgE production, they found that two types of helper T cells, distinguishable by the profile of

cytokines they produce, play important regulatory roles in not only IgE production but also in regulating allergic inflammation. The advancement of modern molecular technologies has enabled detailed analyses of molecules and genes involved in this extremely complex regulatory mechanism. Hence, there are a number of important discoveries in this area, which are still of major interest to allergologists, as can be seen in the six volumes of this book.

We realize that allergology has rapidly progressed during the last century, but mechanisms of allergic diseases are far more complex than we had expected. New discoveries have created new questions, and new facts have reminded us of old concepts. For example, the genetic disposition of allergic diseases was suspected even in the earlier, primitive era but is still only partially proven on a molecular basis. Even the molecular mechanisms of allergic inflammation continue to be a matter of debate and there is no single answer to explain the phenomenon. There is little doubt that the etiology of allergic diseases is far more varied and complex than we had expected. An immunological origin is not the only mechanism, and there are more unknown origins of similar reactions. Although therapeutic means have also progressed, we remain far from our goal to cure and prevent allergic diseases.

We have to admit that while we have more knowledge of the many intricate mechanisms that are involved in the various forms of allergic disease, we are still at the primitive stage of allergology in this respect. We are undoubtedly proceeding into a new stage, stage 4, that may be called the postmodern age of allergology and hope this era will bring us closer to finding a true solution for the enigma of allergy and allergic diseases.

We are happy that at this turning point the editors, Ruby Pawankar, Stephen Holgate, and Lanny Rosenwasser, are able to bring out such a comprehensive book which summarizes the most current knowledge on allergic diseases, from epidemiology to mechanisms, the impact of environmental and genetic factors on allergy and asthma, clinical aspects, recent therapeutic and preventive strategies, as well as future perspectives. This comprehensive knowledge is a valuable resource and will give young investigators and clinicians new insights into modern allergology which is an ever-growing field.

Tomio Tada, M.D., Ph.D., D.Med.Sci.

Foreword

Allergic diseases represent one of the major health problems in most modern societies. The increase in prevalence over the last decades is dramatic. The reasons for this increase are only partly known. While in former times allergy was regarded as a disease of the rich industrialized countries only, it has become clear that all over the world, even in marginal societies and in all geographic areas—north and south of the equator—allergy is a major global health problem.

The complexity and the interdisciplinary character of allergology, being the science of allergic diseases, needs a concert of clinical disciplines (internal medicine, dermatology, pediatrics, pulmonology, otolaryngology, occupational medicine, etc.), basic sciences (immunology, molecular biology, botany, zoology, ecology), epidemiology, economics and social sciences, and psychology and psychosomatics, just to name a few. It is obvious that an undertaking like this book series must involve a multitude of authors; indeed, the wide spectrum of disciplines relevant to allergy is reflected by the excellent group of experts serving as authors who come from all over the world and from various fields of medicine and other sciences in a pooling of geographic, scientific, theoretical, and practical clinical diversity.

The first volume concentrates on the basics of etiology, namely, the causes of the many allergic diseases with epigenetics, allergens and risk factors. Here, the reader will find up-to-date information on the nature, distribution, and chemical structure of allergenic molecules, the genetic and epigenetic phenomena underlying the susceptibility of certain individuals to develop allergic diseases, and the manifold risk factors from the environment playing the role of modulators, both in enhancing and preventing the development of allergic reactions.

In times when economics plays an increasing role in medicine, it is important to reflect on this aspect and gather the available data which—as I modestly assume—may be yet rather scarce. The big effort needed to undertake well-controlled studies to establish the socio-economic burden of the various allergic diseases is still mainly ahead of us. The Global Allergy and Asthma European Network (GA2LEN), a group of centers of excellence in the European Union, will start an initiative regarding this topic this year.

In volume 2, the pathomechanisms of various allergic diseases and their classification are given, including such important special aspects as allergy and the bone marrow, allergy and the nervous system, and allergy and mucosal immunology.

Volume 3 deals with manifold clinical manifestations, from allergic rhinitis to drug allergy and allergic bronchopulmonary aspergillosis, as well as including other allergic reactions such as lactose and fructose intolerances.

Volume 4 deals with the practical aspects of diagnosis and differential diagnosis of allergic diseases and also reflects educational programs on asthma.

Volume 5 deals with therapy and prevention of allergies, including pharmacotherapy, as well as allergen-specific immunotherapy with novel aspects and special considerations for different groups such as children, the elderly, and pregnant women.

Volume 6 concludes the series with future perspectives, presenting a whole spectrum of exciting new approaches in allergy research possibly leading to new strategies in diagnosis, therapy, and prevention of allergic diseases.

The editors have accomplished an enormous task to first select and then motivate the many prominent authors. They and the authors have to be congratulated. The editors are masters in the field and come from different disciplines. Ruby Pawankar, from Asia, is one of the leaders in allergy who has contributed to the understanding of the cellular and immune mechanisms of allergic airway disease, in particular upper airway disease. Stephen Holgate, from the United Kingdom, has contributed enormously to the understanding of the pathophysiology of allergic airway reactions beyond the mere immune deviation, and focuses on the function of the epithelial barrier. He and Lanny Rosenwasser, who is from the United States, have contributed immensely to the elucidation of genetic factors in the susceptibility to allergy. All three editors are members of the Collegium Internationale Allergologicum (CIA) and serve on the Board of Directors of the World Allergy Organization (WAO).

I have had the pleasure of knowing them for many years and have cooperated with them at various levels in the endeavor to promote and advance clinical care, research, and education in allergy. Together with Lanny Rosenwasser as co-editor-in-chief, we have just started the new *WAO Journal* (electronic only), where the global representation in allergy research and education will be reflected on a continuous basis.

Finally, Springer, the publisher, has to be congratulated on their courage and enthusiasm with which they have launched this endeavor. Springer has a lot of experience in allergy—I think back to the series *New Trends in Allergy*, started in 1985, as well as to my own book *Allergy in Practice,* to the *Handbook of Atopic Eczema* and many other excellent publications.

I wish this book and the whole series of *Allergy Frontiers* complete success! It should be on the shelves of every physician or researcher who is interested in allergy, clinical immunology, or related fields.

Johannes Ring, M.D., Ph.D.

Preface

Allergic diseases are increasing in prevalence worldwide, in industrialized as well as industrializing countries, affecting from 10%–50% of the global population with a marked impact on the quality of life of patients and with substantial costs. Thus, allergy can be rightfully considered an epidemic of the twenty-first century, a global public health problem, and a socioeconomic burden. With the projected increase in the world's population, especially in the rapidly growing economies, it is predicted to worsen as this century moves forward.

Allergies are also becoming more complex. Patients frequently have multiple allergic disorders that involve multiple allergens and a combination of organs through which allergic diseases manifest. Thus exposure to aeroallergens or ingested allergens frequently gives rise to a combination of upper and lower airways disease, whereas direct contact or ingestion leads to atopic dermatitis with or without food allergy. Food allergy, allergic drug responses and anaphylaxis are often severe and can be life-threatening. However, even the less severe allergic diseases can have a major adverse effect on the health of hundreds of millions of patients and diminish quality of life and work productivity. The need of the hour to combat these issues is to promote a better understanding of the science of allergy and clinical immunology through research, training and dissemination of information and evidence-based better practice parameters.

Allergy Frontiers is a comprehensive series comprising six volumes, with each volume dedicated to a specific aspect of allergic disease to reflect the multidisciplinary character of the field and to capture the explosive growth of this specialty. The series summarizes the latest information about allergic diseases, ranging from epidemiology to the mechanisms and environmental and genetic factors that influence the development of allergy; clinical aspects of allergic diseases; recent therapeutic and preventive strategies; and future perspectives. The chapters of individual volumes in the series highlight the roles of eosinophils, mast cells, lymphocytes, dendritic cells, epithelial cells, neutrophils and T cells, adhesion molecules, and cytokines/chemokines in the pathomechanisms of allergic diseases. Some specific new features are the impact of infection and innate immunity on allergy, and mucosal immunology of the various target organs and allergies, and the impact of the nervous system on allergies. The most recent, emerging therapeutic strategies are discussed, including allergen-specific immunotherapy and anti-IgE treatment,

while also covering future perspectives from immunostimulatory DNA-based therapies to probiotics and nanomedicine.

A unique feature of the series is that a single topic is addressed by multiple contributors from various fields and regions of the world, giving the reader the advantage of being introduced to more than one point of view and being provided with comprehensive knowledge about a single disease. The reader thus obtains a detailed review of a single, highly focused topic and at the same time has access to a panoramic, in-depth view of a broader subject such as asthma.

The chapters attest to the multidisciplinary character of component parts of the series: environmental, genetics, molecular, and cellular biology; allergy; otolaryngology; pulmonology; dermatology; and others. Representing a collection of state-of-the-art reviews by world-renowned scientists from the United Kingdom and other parts of Europe, North America, South America, Australia, Japan, and South Africa, the volumes in this comprehensive, up-to-date series contain more than 150 chapters covering virtually all aspects of basic and clinical allergy. The publication of this extensive collection of reviews is being brought out within a span of two years and with the greatest precision to keep it as updated as possible. This six-volume series will be followed up by yearly updates on the cutting-edge advances in any specific aspect of allergy.

The editors would like to sincerely thank all the authors for having agreed to contribute and who, despite their busy schedules, contributed to this monumental work. We also thank the editorial staff of Springer Japan for their assistance in the preparation of this series. We hope that the series will serve as a valuable information tool for scientists and as a practical guide for clinicians and residents working and/or interested in the field of allergy, asthma, and immunology.

Ruby Pawankar, Stephen Holgate, and Lanny Rosenwasser

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