THIRD EDITION

VOLUME I

Edited by

Elliott Middleton, Jr.

ALLERGY

Principles and Practice

Volume I

Third Edition

ALLERGY
PRINCIPLES AND PRACTICE

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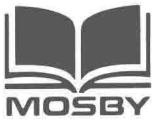
with 596 *illustrations*

THE C. V. MOSBY COMPANY
ST. LOUIS • WASHINGTON, D.C. • TORONTO 1988



A TRADITION OF PUBLISHING EXCELLENCE

Editor: Eugenia A. Klein
Developmental editor: Kathryn H. Falk
Assistant editor: Ellen Baker Geisel
Project manager: Lin A. Dempsey
Editing and production: Editing, Design & Production, Inc.
Design: Liz Fett

TWO VOLUMES

Third Edition

Printed in the United States of America

The C.V. Mosby Company
11830 Westline Industrial Drive, St. Louis, Missouri 63146

Library of Congress Cataloging-in-Publication Data

Allergy: principles and practice/edited by Elliott Middleton, Jr.
. . . [et al.]. —3rd ed.
p. cm.
Includes bibliographies and index.
ISBN 0-8016-3214-5
1. Allergy. I. Middleton, Elliott, 1925-
[DNLM: 1. Hypersensitivity. WD 300 A4345]
RC584.A44 1988
616.97—dc19

C/MV/MV 9 8 7 6 5 4 3 2 1

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To the clinical scientists who made this book possible,
to their patients who participated in valuable investigations,
and to our basic science colleagues whose studies
paved the way to new clinical insights.

PREFACE to third edition

The second edition of *Allergy: Principles and Practice,* published in 1983, turned out to be a great success. This achievement was, of course, entirely attributable to the talents and efforts of the 119 contributors to the second edition. Now it is a pleasure to record that in this new third edition we have what we believe to be an exceptionally fine, truly "state of the art" addition to the literature.

The contents of the second edition represented some rather significant changes from the first as new information was rapidly accumulated in the field. Appreciating the perhaps even more rapid growth of new knowledge taking place in allergy and immunology during the past 5 years or so, of importance to clinicians and laboratory scientists alike, the editors and publisher concluded that a third edition would be desirable. To this end meetings were initiated toward the end of 1985. An important decision was made, however, before we went to work, namely, to add two new editors to the original group of three in order to enhance the quality and coverage of material in the third edition and to help ensure the longevity of *Allergy: Principles and Practice* as a primary textbook and reference source. The three original editors selected N. Franklin Adkinson, M.D., of Johns Hopkins University and John W. Yunginger, M.D., of the Mayo Clinic to join in the effort as co-editors. It will be clear to all that their contributions have enhanced every aspect of the third edition.

In keeping with editorial policy from the beginning, some changes in authorship for various chapters has occurred in the preparation of the third edition. In this fashion new and different talents and fresh points of view are brought to bear. The valuable work of contributors to the first and second editions is not lessened in any way by these changes and their splendid efforts in assuring the success of the first two editions is acknowledged with great appreciation.

The third edition has 68 chapters contributed by 121 authors, 60 of whom are new to the book. Volume I continues as the source of basic information on the immunology, physiology, and pharmacologic aspects of allergic disease and Volume II remains the clinical science section; both are richly illustrated. Much new information has been included in Volume I reflecting the explosion of new fundamental understandings of the basic mechanisms involved in allergic disease, especially our knowledge of the nature, origins, and properties of proinflammatory chemical mediators that participate in the pathogenesis of allergic and inflammatory diseases and the biology of the cell types involved in allergic reactions. Volume II is thoroughly updated with regard to the essential clinical, diagnostic, and therapeutic aspects of allergic disease and should provide an authoritative source of information for practitioners in the specialty of Allergy and Immunology.

The editors gratefully acknowledge the time-consuming efforts of all contributors to the third edition, to their patient and tireless secretaries, and also to C.V. Mosby staff members Kathy Falk, Developmental Editor, and Ellen Baker Geisel, Assistant Editor, who did their best to keep us on schedule using their good humor and great organizational abilities.

As intended from the beginning, the third edition is an updated reference source as well as a thoroughly practical text. It is our hope that this book will be educational, and pleasing as well, to all who undertake its reading.

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Charles E. Reed
Elliot F. Ellis
N. Franklin Adkinson, Jr.
John W. Yunginger

PREFACE to first edition

Allergy, once a confusing subject for clinician and researcher alike, has emerged as a medical science in which immunology, physiology, and pharmacology interface uniquely. Our present state of knowledge is the culmination of the efforts of many workers over many decades of research in the clinic and laboratory. We want to acknowledge our incalculable debt to these investigators, both basic scientists and clinicians, who taught us not only fact but more importantly concepts and scientific method.

Several textbooks on allergy are already in existence. Why another one? We pondered this question for some time before embarking on what turned out to be, expectedly, a rather formidable task. It was our opinion that a truly comprehensive book about allergy should focus strongly not only on the exciting developments of the past decade or two in immunology but also provide in-depth coverage of equally pertinent new information on physiology and pharmacology, two areas of critical importance to the student of allergy. We have made no attempt to cover all of the subject matter considered to fall under the general rubric of clinical immunology and so do not include sections dealing with rheumatology, other connective tissue disorders, immunohematology, or tumor immunology, for example, since these subjects are well covered elsewhere.

The chapters dealing with immunology, pharmacology, and physiology appear at the beginning in the basic science section of the book to provide the necessary conceptual framework for the clinical science section, which deals with the variety of clinical states that fall within the purview of allergy and the allergist. The value of the clinical descriptions is vastly enhanced by a careful reading of the earlier chapters.

We were most fortunate in securing a truly outstanding "star-studded" cast of contributors who managed to find time in their already overcrowded schedules to help us write the book. We thank them all for their efforts and are grateful for the patient indulgence of a few who put up with some predictable editorial fussing meant to achieve proper balance and avoid excessive overlap.

Most of the chapters can be read as free-standing articles or monographs on that particular subject. This has led to a certain irreducible amount of duplication. By and large, there is consistency among chapters in which comparable material has been presented by different authors, but the reader will find occasional areas of controversy, a natural state of affairs in a rapidly growing field.

It is our opinion that some chapters in this book represent the most comprehensive summaries of the subject matter to be found in print. Thus *Allergy: Principles and Practice* serves not only as a textbook but as a reference book. Indeed, this was our intent, but original estimates for the length of the book were necessarily revised upward as it became clear that much excellent material could not properly be left out. The final product then turns out to be a book we hope will be useful to all students of allergy: practitioners, clinical investigators, other researchers, allergy trainees, and medical students.

The generous and unstinting help of many people in addition to the contributors made this book possible. Without the competent and devoted secretarial assistance of Marci Dame, Evelyn Beimers, Bonnie Barcy, Carol Sperry, and Candace Anderson, the task could not have been accomplished. We thank our wives and families for their forbearance while we were sequestered away from home for day and night weekend sessions during the planning and editing phases. From the beginning their support has been essential to the successful completion of our job. A number of colleagues, too numerous to name, provide help in critical reading of manuscripts. To these and others who were helpful in a variety of ways, we offer thanks.

We are saddened that two contributors died during the preparation of the book. Jane Harnett is the senior author of the chapter dealing with aspirin idiosyncrasy. Dr. Harnett compiled much of the information for the chapter and worked on the manuscript under extremely difficult circumstances up to within only a few days of her untimely death. She is remembered fondly and with respect by all those with whom she worked. Robert P. Orange, one of the most brilliant and creative investigators of his generation, died suddenly during the preparation of the book. No one can guess what additional important discoveries Dr. Orange would have made had he not died so prematurely.

We would like to record here our personal sorrow at the loss of these fine physicians. We hope that their representation in this textbook will help keep memories of them alive.

Elliott Middleton, Jr.
Charles E. Reed
Elliot F. Ellis

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BASIC SCIENCE

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THE IMMUNE SYSTEM: AN OVERVIEW

J. John Cohen

SELF AND NONSELF

All living things have systems for distinguishing themselves from the rest of their universe, and between themselves and others of their species. Humans, for example, can distinguish one another by sight or sound or feel; many animals can do so by smell. The immune system, also a sense organ, allows individuals to differentiate between self and nonself on a cellular and molecular basis. This ability is desirable in that microscopic foreign invaders are recognized and dealt with appropriately. A more subtle point is that deviations from normal in the body's own constituents might also be recognized as foreign (nonself) and the same mechanisms for inactivation or destruction brought to bear. This idea, called *immune surveillance,* suggests that the immune system is constantly examining body molecules and cell surfaces; should some structure be detected that is not part of what the system has learned to recognize as self, it will be dealt with as if it were a foreign invader.[1] It is difficult at this stage of our knowledge to tell which imperative—recognition of foreignness or immune surveillance—has been the stronger driving force in the evolution of immunity. The immune system may well be evolving faster than the rest of the organism, because its adaptations are driven by entities (microorganisms and tumors) that have their own genomes and that, reciprocally, evolve in response to immunologic pressures.

The chief agents of immune recognition are *lymphocytes,* cells that in their resting state are so undistinguished that until 1960 they were generally assumed to be the burnt-out remains of something more interesting. Lymphocytes have on their surfaces receptors for the antigenic determinants, or epitopes, of foreign molecules or antigens. Each lymphocyte has many copies of a single receptor of very restricted specificity, so that to safely recognize most possible antigens the body requires millions of different lymphocytes, each with its own particular receptor variant. When an antigen enters the body, it will eventually encounter those lymphocytes whose receptors fit its antigenic determinants well. Here "fit" means that the three-dimensional charge distributions of antigenic determinant and receptor are complementary enough to produce binding above a certain energy threshhold. When this occurs, the cell receives an internal signal and initiates an activation process. The nature of the activating signal is just beginning to be unraveled; it involves calcium flux and protein kinase activation in a manner similar to that seen with some other receptor-ligand interactions.[2]

Activation of a lymphocyte involves both *proliferation* and *differentiation*. The proliferative phase produces a clone of cells with receptors identical to those of the parent; since lymphocytes can divide every 12 hours or so, in 6 days one cell could produce about 4000 descendants.

This simple clonal expansion seems to be an adequate explanation for immunologic memory; the next time the organism encounters the same antigen, the number of cells that recognize it is much greater than in the native state, and the immune response begins more quickly and reaches higher levels faster. In addition, true memory cells may exist whose sensitivity to being triggered by antigen is greater than that of naive cells.

Proliferation explains memory; differentiation explains the immune response. Lymphocytes when activated begin to synthesize new RNA, get larger, and secrete proteins. These proteins—lymphokines and antibodies—account for most of the phenomena that we associate with immunity. Since they are made under different circumstances by different lymphocytes, they will be discussed in more detail after we consider lymphocyte subpopulations.

THE CLONALITY OF LYMPHOCYTES

The most interesting question in immunology has been, How does the immune system recognize the millions of possible foreign molecular conformations? Consider receptors as locks and antigens as keys. There are two basic ways to ensure that we have a lock for every possible key: we can carefully measure each new key we come upon and custom make a lock to fit it, or we can first fabricate millions of locks of all possible random shapes and hope that one of them will accept any new key, no matter how unfamiliar its shape might be. This latter approach, which seems laborious and wasteful, is the approach taken by the immune system. By birth the human has millions of lymphocytes, each bearing a unique receptor, generated by apparently random recombination of segments of DNA (see Chapter 2). Most of these will never be used in a person's lifetime, but their presence assures that the likelihood of a new pathogen devastating the individual or the species is remote, unless that pathogen (like the AIDS virus) has evolved some trick other than foreignness to elude the immune response.

When antigen enters the body, it selects the cells with the best-fitting receptors by binding to and activating them as outlined above, inducing clonal expansion; this process, which is called *clonal selection,* is a cellular example of darwinism. Since fit is a relative physicochemical concept, it is not surprising that sometimes two quite distinct antigens might have antigenic determinants that fit the same receptor, resulting in *cross-reaction*. A lymphocyte, after all, is not designed to be the cell that reacts with *Treponema pallidum;* it simply bears a receptor with a shape that happens to fit a particular structure on that organism, and the fact that extracts of heart have a similar structure (probably a phosphate ester) is a chance cross-reaction, of which diagnostic advantage was taken many decades ago. More sinister cross-reactions can be imagined, for example, between human heart and certain streptococci.

ORGANIZATION AND DEVELOPMENT OF THE IMMUNE SYSTEM

The organs of the immune system can be thought of as central or peripheral. The primary function of the central organs is the generation of new lymphocytes to populate and repopulate the peripheral organs, in which immune responses actually take place. Here the immune system is intimately connected with the reticuloendothelial system, which resists definition in modern terms but can generally be considered as the aggregate of fixed phagocytic cells and their associated reticular fibers and cells. This arrangement is advantageous in that it brings together cells specialized for trapping, phagocytosis, and degradation with cells whose function is recognition.

In fetal development lymphoid precursors first appear in the blood islands of the yolk sac, later move to the liver, and finally to the bone marrow.[3] By birth the main central lymphocyte-producing organs are the bone marrow and the thymus, and this situation is maintained throughout most of life, although the thymus exports relatively few cells after puberty. The development of lymphocytes has been reasonably well worked out. As part of the blood system they derive from a pluripotential hematopoietic stem cell (Fig. 1-1). This cell upon division gives rise to precursors of all the cells of the blood: erythroid, myeloid, and lymphoid. Although there is no direct evidence for it yet, it seems reasonable that a lymphoid stem cell is derived from the pluripotential stem cell, and it in turn gives rise to two types of precursors, pre–B and pre–T cells.

The pre–B cell is distinguishable in bone marrow because it contains cytoplasmic polypeptide chains similar to those of the antibody it will eventually secrete. It matures into a B cell, with antibody inserted into its plasma membrane; it uses the antibody as its antigen receptor. There is evidence that at the earliest stages of a B cell's life, it will be tolerized (functionally inactivated) rather than immunized if its receptors encounter its cognate antigen. This is an attractive idea when one realizes that the most ubiquitous "antigens" that a lymphocyte would be exposed to are self components (serum proteins, common cell surface molecules, etc.). If the process of generating receptor diversity is random, as the evidence indicates, then a proportion of cells must display anti–self receptors and will have to be eliminated lest they cause autoimmunity. The automatic elimination of any antigen-binding early B cell (a process called *clonal abortion*) provides one mechanism by which such self-reactive clones might be removed from the repertoire.[4] Clones reactive only to foreign antigens would, for the most part, escape clonal abortion. Any cell surviving this transient abortable stage will mature into an inducible B cell. Such B cells are exported from the bone marrow and populate characteristic areas of the peripheral organs (Figs. 1-2 and 1-3).

In birds, B cell precursors leave the bone marrow and