Otolaryngologic Allergy

Hueston C. King, M.D. Editor

Otolaryngologic Allergy

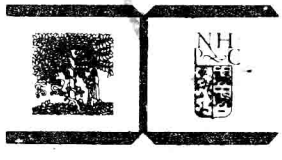
Hueston C. King, M.D. Editor

Clinical Associate Professor
Department of Otolaryngology
University of Miami School of Medicine
Miami, Florida

Published by

Symposia Specialists Inc.
MEDICAL BOOKS

Distributed by



ELSEVIER/NORTH-HOLLAND
NEW YORK • AMSTERDAM • OXFORD

Published by:

Symposia Specialists, Inc.
1470 N.E. 129th Street, Miami, Florida 33161

Distributed by:

Elsevier North Holland, Inc.
52 Vanderbilt Avenue, New York, New York 10017

Sole distributors outside U.S.A. and Canada:

Elsevier Science Publishers B.V.
P.O. Box 211
1000 AE Amsterdam
The Netherlands

Library of Congress Catalog Card Number 80-54734
International Standard Book Number 0-444-00592-7

Manufactured in the United States of America

Foreword

The Otolaryngologist in Allergy

It has been estimated that fully half of the problems faced by otolaryngologists are the direct result of allergy. In view of this, it is not surprising that otolaryngologists have involved themselves with allergy care in increasing numbers for nearly half a century. Starting with the methods employed by the general allergist and driven by the impatience of the surgeon, the otolaryngologist began early to attempt to refine and improve upon the general allergist's established techniques, with a view toward obtaining more rapid and complete clinical relief. The early experiments were crystallized by the work of Dr. Herbert Rinkel and his co-workers in the early 1960s, and these methods, appropriately refined and updated, remain the tools of the otolaryngologic allergist today. It should be stressed that at no time did the otolaryngologic allergist differ in principle from the general allergist in his approach to patient care; he merely felt that it should be possible to improve upon a relatively cumbersome and time-consuming patient care program. A steadily increasing number of physicians employing Rinkel's modalities and a progressively increasing patient load have tended to give credence to his convictions.

The unique needs of the otolaryngologist dictated the formation of a national organization to teach allergy as it applied to otolaryngology, invoking the principles of regional specialization* dear to the hearts of otolaryngologists. Not only did a majority of otolaryngologic allergists feel that the traditional techniques could be improved upon, but the percentage of a general allergy teaching program or workshop directly applicable to otolaryngology was small enough to discourage the otolaryngologist's participation. Had he wanted to be a general allergist, he would have taken his background

*No one can be all things to all people, especially in medicine. One studies either a single technique to apply to the entire body or one area of the body in which to employ all available techniques.

training in pediatrics or internal medicine. The otolaryngologist's national organization, The American Society of Ophthalmologic and Otolaryngologic Allergy, was formed in 1941. The Society is approved by the AMA for providing CME credits, and is represented on the American Board of Otolaryngology and the American Academy of Otolaryngology, as well as the Council on Medical Specialities of the AMA. It annually sponsors four to six national workshops in otolaryngologic allergy. It is from the experienced faculty of these workshops that the authors of this book have been drawn. Most have been teaching the material described for many years. The format of the book is based on that of the established workshops, and it is designed to provide a reference source available to all.

This book will be controversial. The principles it presents are not new, although their appearances in print have been conspicuous by their scarcity. All material, of course, is fully updated — as far as it is possible to update a field that is changing almost hour by hour. Some of the material presented is not at the present time supported by detailed immunologic studies. It must be borne in mind that until quite recently all aspects of allergy care were on an empirical and clinical basis, and that it may be some years before the laboratory is able to verify and explain all of the actions of the immune system. The general allergists of internal medicine and pediatric background may not like this book. The regional specialists, the otolaryngologists practicing allergy, need it. It is to them that the book is directed, with the hope that it may improve their performance in a critical facet of their specialty. It is hoped that it may also dispel some of the myths of the "Rinkel school" by clarifying the otolaryngologist's conviction over many years as a different route to a similar goal. Practitioners other than otolaryngologists may learn from the material presented.

Some years ago, a friend of mine, a professor whose work appears in this book, asked me philosophically which approach to allergy care I thought the medical establishment of the country would accept "twenty years from now." I told him that I devoutly hoped neither current approach would be accepted unchanged. If it is, we will have learned nothing in two decades. Let us hope that will not be the case.

Hueston C. King, M.D.

Contents

Nasal Allergy

David A. Dolowitz, M.D.

Objectives

This paper is a review of nasal allergy. Its historic development, including a brief summary of the known immunologic mechanisms involved, is discussed. Clinically, diagnosis using history, physical examination and laboratory tests — including in vitro methods — is explored. Since ENT allergy is closely allied to infection, x-ray examination is considered, with emphasis on a surgical approach to relief of infection. Types of allergy: pollen atopy, fungi, bacteria, dusts, animal danders and foods, are examined; and our method of treatment is presented. The concept that there is much to be learned by an examination of the marked similarity between the learning process and the immune reaction is briefly mentioned.

Introduction

One of the areas of poorest results in otolaryngologic treatment of the past was the relief of nasal obstruction and concomitant sinus infections. While unobstructed breathing usually followed intranasal surgery for the removal of hard anatomic obstacles, removal of soft-tissue obstructions often yielded only temporary relief. Gradually it was realized that such mucosal swelling had many causes. It could follow infection, vasomotor rhinitis or allergy. This discussion will be limited to a discussion of the last area.

From its inception, the concept of allergy has been controversial. It was postulated in an era when faith was giving way to the scientific method that anything, to be believed, had to be measurable and reproducible in more than just an

David A. Dolowitz, M.D., The Allergy, Ear, Nose and Throat Clinic, The University of Utah Medical School, Salt Lake City.

occasional individual. Thus, the intuitive guesses of geniuses like Von Pirquet [1, 2], Erlich [3], Kahn [4], Schick [2, 5], Coca [6], etc. that allergy was a hyperimmune response were ignored. It is only recently that the accumulation of sufficient background knowledge, collected by many workers, has reached a level where everyone can understand the concepts. The entire field of immunology, the concept of dynamic cellular microbiology, much of the mechanism of inflammation with its dependence for explanation on enzyme systems, hormonal messengers and toxic mediators were all unknown. So to the skeptics, the concept of allergy was suspect.

Basically the hyperimmune response is postulated as an overshoot of the defense mechanism of inflammation which attempts to remove foreign protein from a host. Thus, it is a quantitative fault in a dynamic physiologic process existing in a specific genetic group of people [7] rather than a pathologic disease demonstrable by Koch's postulates.

Concept of Allergy

The start of clinical allergic literature occurred in 1819, when John Bostock described a recurrent seasonal syndrome of "summer catarrh" consisting of excessive sneezing, nasal congestion accompanied by a watery discharge and occular itching and tearing. After nine years of work he associated these symptoms with the presence of hay and coined the term "hay fever."

Three years later, Elliotson reported that grass pollens were the causative agent in hay fever.

In 1873, Blakely showed the presence of pollen in the air by trapping it on glycerine-covered glass slides. The chief constituent found was grass pollen. He found a relationship between the amount of pollen present and the intensity of the "pollen catarrh." His final demonstration was the production of symptoms when he placed grass pollen granules on his skin.

There the concept remained until 1911, when Noon [8] started relieving symptoms by desensitization effected by giving subcutaneous injections of a causative hay fever pollen extract.

From this point the study of allergy split into two paths, clinical and laboratory. The students of the latter [7, 9-12] worked on obscure details of the alterations of reactions, slowly

fitting the findings into a picture which eventually became the field of immunology. It is only in the last decade that the picture is beginning to emerge. It is still very complex and one hopes that the next ten years will pull still more facts together to establish a simpler pattern.

The clinical studies were carried on mainly by physicians who themselves or whose families suffered from allergies. Since they found they could be helped, they ignored the controversy and gradually developed an empiric therapy.

In inhalant and pollen allergy they developed the scratch and later the intradermal diagnostic testing. This was accomplished in the early days by placing the antigens on abraded skin [8]. Later measured amounts were used in intradermal injections [13, 14] and diagnosis was established by the size of the resulting wheal or erythema. Still later a passive transfer test was developed. This used Prausnitz-Küstner's [15] finding that serum from an allergic individual would react with wheal and erythema formation to an antigen when both were transferred by injection into a nonallergic host's skin.

Once the allergic antigens were diagnosed, extracts of them were injected into the patient's skin and it was found they would desensitize him to these allergens. It was felt that these extracts produced blocking antibodies in the host which effected the protection. Therefore, in an effort to increase the blocking effect, larger and larger doses of extract were used. Eventually massive dosages, while relieving some of the allergic symptoms, produced side effects that reproduced and passed in severity the signs and symptoms of the allergic problems.

About this time Hansel [16] noticed that he obtained a better desensitization if he kept to a lower dosage rather than continue to build up the antigen to larger dosages. Rinkel [17], using this lower dosage, felt there should be an optimal dose for each patient and evolved a skin titration test to arrive at a quantitative methodology.

Despite the fact that allergy was not accepted by many physicians, the allergists split into two schools and spent their energy debating which was correct. This caused a further lessening in confidence in much of the medical profession.

In the past three decades, Shambaugh [18, 19], Hansel [20], Sanders [21] and Williams [22] spent a great deal of

effort presenting the concept of a quantitative evaluation in a reasonable manner, but so far have been unable to convince the "large-dosers" who prefer their qualitative methods. Their efforts may soon be accepted, since their quantitative methods are being confirmed by the work of the immunologists.

Immunology

The earliest immunologists working in the laboratory studied the methods by which hosts resisted infections. As knowledge of these functions expanded, their interests broadened until now immunology may be considered the study of a host's alteration of its responses to repeated contacts with an invading substance.

It has long been known that when a foreign material enters a cell or organism, it must be extruded, disrupted and/or absorbed, or the host cell dies. This is accomplished by a series of microbiologic reactions. These work frequently as biologic antagonists with feedback mechanisms, such as production vs. inhibition loops, permitting a vernier-like control of the reactions.

When cells are invaded, the first step necessary for the host's protection is the recognition that the invader is foreign. This material (the antigen), after activation, must be capable of provoking a response in an immunologically competent host. The second step is the production of a plasma protein, an antibody, which has a specific reaction with the provoking antigen. Third, there must be either a humoral or a cellular union between the antigen and antibody. This union may involve complement. It will also trigger the release of inflammatory mediators causing the destruction of the invaders alone or with complement's help. Fourth, enough energy must be made available to effect these processes and their subsequent actions. Finally, in a small genetic group there is an overshoot in the resulting vasoamine release liberated by the mediators which, being excessive, causes an allergic response of the shock tissues instead of the destruction of the antigen-antibody complex.

In summary, the invading molecule is seized by macrophages soon after entering the body. It is then identified as

foreign or self. Heparin and a specialized thymic lymphocyte, producing and liberating macrophage-aggegating factor and macrophage-spread-inhibiting factor, play a role in activating the macrophages that is not yet understood. If the invader is deemed foreign, the macrophage marks it as such, probably by altering its RNA, and escorts it to the lymphatic system. This lymphocytic system is one of the most important elements, if not the keystone, of immunologic protection. It begins in the embryo as cells in the yolk sac. These cells then migrate to the fetal liver, then to the bone marrow, there becoming the lymphocyte stem cell by birth.

The lymphocyte has developed both a cellular and humoral mechanism of protection. Both of these use antibodies to act and react differently to protect the host.

Cellular Immunity

The antigen-macrophage entity is conducted to the thymus. Here it meets thymosin, a recently discovered family of polypeptide hormones [23] controlling feedback loops, which regulate major components of the cellular and humoral immune system. Each polypeptide acts separately or in series to alter T-cell subpopulations both developmentally and in modifying their functions. Thus, thymosin affects T cells, which in turn can enhance or suppress antibody production [24] through their influence on specific B-cell precursors of the antibody-producing cells. Other of these polypeptides mediate the migration-inhibition factor, the macrophage-aggregating and the macrophage-spread-inhibiting factors, a skin reactive factor, products of antigen recognition, lymphotoxins, a chemotactic factor, a blastogenic factor, transfer factor, interferons, cytophilic antibodies and direct lymphocyte target-cell cytotoxic factors, to name some of them.

Returning to our antigen-macrophage combination at the thymus, the foreign body is attached to the properly activated T lymphocyte. This new combination, from which the macrophage has detached itself, migrates to the external zone (cortex) of a lymph gland. Here it is joined by a specific antibody formed by a specific lymphocyte. The antigen-antibody lymphocyte complex creates a cellular controlled immunity of a slower type.

Should this type of specific antigen again enter the host, the same specific lymphocyte and its descendants will again form the same antigen-antibody lymphocyte complex. The second and subsequent invasions will, however, produce much greater activity in the formation of antibodies and of the many antigen-antibody lymphocyte complexes.

Humoral Immunity

The macrophage does not always conduct the invading antigen to the thymus. It may take it to the bursa equivalent. B cells in birds develop from the bursa of Fabricius, a lower intestinal pouch containing large numbers of lymphocytes. This bursa is not present in man and so an equivalent of this bursa has been postulated since B cells are easily found. Why and how the route to the thymus or bursa is selected is still unknown. On reaching the bursa equivalent the macrophage similarly releases the antigen to a large lymphocyte, but here it is of the B variety. Again it proliferates and/or clones, with these antibody-producing cells remaining specific to this antigen only, for all subsequent invasions of any antigens.

The antigen-B cell (bursa equivalent-derived) combination migrates to the inner layer (germinal center) of a lymph gland. There the B cell may change to a plasma cell, a small lymphocyte or remain an immature cell. Like plasmocytes, these form antibodies specific to the antigen. Then humorally released, these antibodies unite with the antigens, in turn releasing inflammatory mediators.

Immunoglobulins

Resistance to infection was the earliest topic interesting the first workers in immunology. As knowledge increased, attention shifted to the study of the altered response of the body to the infectious agents and their toxins. The measurement of immunologic competence to specific substances and how the body maintains its integrity became the focus of attention. The importance of B cells in antibody production has been mentioned. It was found that if the bursa of Fabricius, a pouch in bird intestine containing lymphocytes, was removed in young chickens, severe reduction of antibody production resulted.

Nature produced a similar experiment in humans, agammaglobulinemia. Electrophoretic blood studies showed the γ-globulins were the ones chiefly reduced. Hence, the antibodies were first named γ-globulins and later immunoglobulins. They are the antibodies released from B lymphocytes.

There are five groups of immunoglobulins. There are three major groups: IgG, IgA, and IgM. Two, IgD and IgE, are minor. Recent studies led to the chemical isolation of an isotype, a subtype present in all people, and an allotype found in only a small genetic group. While proof has not yet been found, speculation suggests the allotype may be a precipitator in allergy.

Eighty-five to ninety percent of antibodies in man are composed of IgG and IgM. They protect the host against bacterial and viral infections by combining with surface antigens in these invaders. In diphtheria, tetanus, anthrax and gas gangrene it is due to the IgG and IgM that antitoxins can combine with the bacterial toxins to help in protection. With different T-cell stimulation these immunoglobulins can promote opsonization, activate phagocytes to devour certain bacteria (e.g. pneumococci), cause precipitation or agglutination of the invaders and stimulate complement fixation or hemolysis. Thus, the classic antibody reactions are due to varied thymic T-cell stimulation of the B cells producing IgG and IgM, which react differently — frequently in combination with complement, depending on the type and location of the stimulation.

The γ-globulin IgA has been called secretory because it is found mostly in the secretions of mucous membranes. These range from tears, nasal mucus, saliva, bronchial mucus, secretions from the small intestine to prostatic and vaginal secretions. A role in the passive immunity of the human fetus and early newborn is suggested by the presence of IgA in amniotic fluid and colostrum. IgA, as well as IgM and IgG, frequently combines with complement to produce increased antimicrobial activity. This will be discussed later.

IgD remains a mystery. It has been found in patients with rheumatoid disease, disseminated lupus, diphtheria toxoid reactions and Hashimoto thyroiditis in combination with other immunoglobulins, all reacting to the same antigen. In a few milk-sensitive patients there is a sensitivity to both the serum

albumins and γ-globulins, including IgD. There has been unconfirmed work suggesting that IgD acts to regulate the activity of the other immunoglobulins.

Although found in amounts of less than 1%, IgE controls atopic (immediate allergic) reactions. IgE is found in skin and to a lesser extent in the blood of patients with allergic rhinitis, allergic asthma, atopic dermatitis and, interestingly, in parasitic infestations. The amount of IgE in human serum is so small that it may explain the poor response to γ-globulin treatment in patients with sinopulmonary infection.

IgE antigen combinations cause the release of toxic amines from mast cells, basophils and neutrophils. Low levels of the combination produce degranulation of the cells with mild histamine release. High levels cause cytotoxic destruction of the cells with total release of the toxic amines.

The first exposure of the host to a given antigen prepares the organism to produce antibodies to combine with the antigen and so destroy it. Subsequent invasions of this antigen trigger immunologic memory, enabling the host to respond with a markedly increased production of the antibodies and permitting a much greater level of destruction of the antigen.

Energy Needs

All these processes necessary for the protection of the host are dependent on energy for their completion. This energy is derived from the oxidation of foods with glucose as one of the major sources. The foods can be directly oxidized and thus aerobically change to lactic acid or may be reduced to pyruvic acid in order to convert chemical to electrical energy. In man, reduction through pyruvic acid (the Krebs cycle) is found to be nature's chief method [25].

In the Krebs cycle, intermediary steps convert inorganic phosphorus into adenosine triphosphate (ATP). This compound serves as an energy storage mechanism, a type of battery, holding energy to be delivered when needed. At that time, the ATP breaks down to adenosine monophosphate (AMP) and adenosine diphosphate (ADP). This decomposition releases electrons supplying the quantums of energy needed to supply the carrying out of the basic biologic processes. This includes the immune protective phenomena from the recognition of an