A
Manual
of
CLINICAL
ALLERGY

SHELDON · LOVELL · MATHEWS

A Manual of

CLINICAL ALLERGY

ILLUSTRATED

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Foreword

THE PRACTICE of allergy is a challenge to the physician's ingenuity and medical ability. Also it is a great deal of fun. An interest which brings great personal satisfaction and diversion, allergy presents a wide variety of cases. The relief which treatment provides for many patients may be complete and sometimes is quite dramatic. Not unlike a detective, the allergist must track down the offending agent which bothers his patient. Often the search is extended into such fields as otolaryngology, psychiatry, dermatology, neurology, chemistry, botany, and even into other realms which may have little direct relationship to medicine. The identification and elimination of the allergenic factor, or where this is impossible, building up of the patient's tolerance to this environmental allergen is the main activity which keeps an allergist at work.

There is need for more physicians who practice a good quality of allergy based on a sound medical background. It is hoped that the following pages will stimulate some of the doctors and students who read them to afford their allergic patients the thorough etiologic management which they deserve.

THE AUTHORS

Preface

This book is prepared primarily for the physician interested in devoting part of his time to the treatment of allergy patients, or in establishing an allergy practice. Since there is no field of medicine or surgery in which patients do not at times present themselves with allergic complaints, the book will perhaps be of interest to any physician or student of medicine.

There are a number of excellent text books and several journals on the subject of allergy. This manual does not attempt to replace or supplant such texts and periodicals but rather should be used in conjunction with them. An effort has been made to present the subject in a manner found practical at the allergy clinics of the University of Michigan Hospital and the University of Michigan Health Service. This work is an outgrowth of the training program provided for medical students and the post-graduate courses in allergy at the University Hospital.

In a manual of this type, it has been necessary to delete lengthy discussion of differential diagnosis, immunologic theory and controversial matters. Naturally these important points should not be ignored, and other texts and periodicals can be referred to for that information which is not covered here. On the other hand, undue emphasis purposely has been placed on certain aspects of allergy practice which often are not very thoroughly covered in the standard texts. This is exemplified by the sections on pollen and mold identification, the preparation of testing and treatment extracts, pulmonary function tests, allergy to plastics, and equipment for the allergist's office. In recent years, endocrine factors in allergic disease, drug allergy, collagen diseases, and vascular allergy have been recognized as being more important than was appreciated in the past, so relatively more space has been devoted to these matters than has been customary in standard texts.

By placing emphasis on the practical features of doing a sound allergy work-up and treating patients in a safe and medically acceptable fashion, this manual attempts to show how a physician can conduct the management of allergic patients in a way which will be of service not only to patients but also to medical colleagues in the community. As a larger number of doctors become interested in and capable of the proper handling of allergic diseases, a greater portion of the vast atopic population will receive the best type of medical care.

Ann Arbor, Michigan January, 1953 J. M. S. R. G. L. K. P. M.

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The shadowgraph of ragweed pollen on the book cover was made from a photograph by the Westinghouse Research Laboratory electron microscope which has a capacity of $50,000 \times \text{magnification}$. The authors are indebted to Westinghouse Electric Corporation for permission to use the

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The resident physicians and instructors in training at the University Hospital who contributed to the preparation of the manual have our

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Ann Arbor, Michigan

K. P. M.

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Immunochemical Aspects of Allergy

ROSS B. PRINGLE, PH.D.*

THE STATE of our present knowledge of the fundamental principles of allergy is reflected by the definitions we use. An antigen, for example, is defined according to what it does rather than what it is. It is any substance which when introduced parenterally into the animal tissues stimulates the production of an antibody, and which when mixed with that antibody reacts specifically with it in some observable way. This definition would be fairly satisfactory except that we can define an antibody only as any substance which makes its appearance in the blood serum or body fluids of an animal in response to the stimulus provided by the introduction of an antigen into the tissues, and which reacts specifically with that antigen in some observable way. Although such a cyclic definition is embarrassing from a theoretical standpoint, it is satisfactory for everyday purposes. In practice, the allergic reaction is regarded as analogous to an antigen-antibody reaction. Here the term allergen corresponds to antigen and reagin to antibody. Atopy is a term first used by Coca to refer to spontaneously occurring allergic disease in man in which there is a familial background of hypersensitivity. Although Coca originally regarded only hay fever, bronchial asthma, and atopic dermatitis as atopic diseases, the term today often is used in a somewhat broader sense to differentiate all familial human allergic disease from artificially induced hypersensitivity states. The following is an outline of some of the more important aspects of the chemistry of antigens and antibodies as they pertain to allergy. One may find the individual topics discussed in detail in the standard works of immunology and protein chemistry.1-4

^{*} From the Montgomery Allergy Research Laboratory, University of Michigan.

^{1.} Boyd, W. C.: Fundamentals of Immunology, ed. 2. Interscience Publishers, Inc.,

New York, 1947.
2. Topley, W. W. C., and Wilson, G. S.: The Principles of Bacteriology and Immunity, ed. 3. William Wood & Co., Baltimore, 1946.

^{3.} Landsteiner, K.: The Specificity of Serological Reactions, revised ed. Harvard University Press, Cambridge, Mass., 1945.

^{4.} Haurowitz, F.: Chemistry and Biology of Proteins. Academic Press, Inc., New York, 1950.

ANTIGENS

Although no antigens have been completely defined in a chemical sense, it is known that they usually belong to the high molecular weight class of compounds known as proteins. Most animal and bacterial proteins are antigenic, whereas, generally speaking, other substances are not antigenic. A protein is deprived of its antigenicity when broken down by acid hydrolysis or by the action of proteolytic enzymes such as those present in the gastrointestinal tract. Thus, in immunologic experiments, it usually is necessary to inject an antigen parenterally to produce antibodies. The condition of food allergy appears to be an exception to this statement. Apparently the minute quantities of undigested food which are absorbed from the gastrointestinal tract are sufficient at times to result in reagin formation and subsequent allergic symptoms.

The outstanding characteristic of antigens is their exquisite specificity of action. An antibody will react only with that antigen which was responsible for its formation. In any exceptional cases the test antigen is very similar to the injected antigen. It was found by Landsteiner³ that the specificity of antigens is not due to the protein molecule as a whole but is associated only with certain groups of the molecule. This was proved by coupling different proteins to the same chemical group and showing that they would cross react. These added chemical groups in the free state may combine with the antibody formed against the coupled protein but are not able to induce the formation of antibodies by themselves. Because these groups are bound to the antibody, they are called haptens (Greek, haptein, to bind). Furthermore, a hapten by itself may compete with an antigen containing the same hapten for the corresponding antibody and thus inhibit the normal reaction. Sometimes haptens even give precipitates with the corresponding antibody.

Proteins owe their specific characteristics to differences in physical attributes, such as size, shape, distribution of charges, and other factors. These variations are reflections of differences in chemical structure. The structure of proteins depends on the order and arrangement of their constituent amino acids. Although differences in the amino acid composition of proteins are slight, the number of these building blocks in a single protein molecule is so large that permutations and varying combinations make the number of possible arrangements infinite. From theoretical considerations, it is evident that the exposed amino acids, i.e., those appearing at the end of the peptide chains, will be most important in determining the character of the protein. Sanger⁵ has shown that horse and donkey hemoglobin cross react immunologically because each has the same terminal α -amino residues. On the other hand, human and beef hemoglobin, containing different amino acids at the end of their peptide chains, do not cross react with horse hemoglobin.

^{5.} Porter, R. R., and Sanger, F.: The Free Amino Groups of Haemoglobins, Biochem. J. 42:287–294, 1948.

ALLERGENS

Allergens are the environmental agents which cause the diseases of allergy, but they include some substances which do not satisfy the classical definition of antigens. After all, this definition was formulated to fit the needs of the experimental science of immunology and not for clinical purposes. Allergens may be classified according to the route through which they produce their effects as inhalants, ingestants, contactants, injectants, and physical allergens. Examples are pollen, house dust, danders, foods and drugs, poison ivy, formaldehyde, arsphenamine, bacteria, fungi, and apparently such agents as heat, cold, and sunlight. In practice, the allergen is identified by its ability to produce an allergic reaction. For use in skin testing, fractions generally regarded as protein in nature (except for contactants) have been prepared from plant and animal materials known to produce allergies, as well as from house dust. The protein nature of the active agents in pollens is in doubt since preparations have been made which resist enzymatic digestion. Moreover, physical measurements by electrophoresis, ultracentrifugation, and diffusion indicate the molecular weight of active components to be about 5000, much less than that of proteins. Since at present skin reactivity is the only method of estimating allergenic potency and since unexplained reactivity to some miscellaneous compounds such as nucleic acids, nucleotides, purines, and amino acids is seen in some individuals hypersensitive to ragweed, some reservations must be retained in evaluating data obtained from skin testing.

It has been realized for a long time that when certain small molecules such as iodine, picryl chloride, and other nitro compounds are injected parenterally, they are able to cause a condition of allergy due to the formation of antibodies against derivatives of the substances injected. All these substances are reactive chemically and combine readily with proteins in vitro. It may be assumed that they also combine with proteins at the site of injection and that the conjugated proteins thus formed are the true antigens. Recently, Weissberger and associates have shown that the allergenic potency of p-amino-N-dialkylanilines (used as developers in the color photographic process) is related to their reducing action as measured by the polarograph. The stronger the reducing action, the more readily the compounds become oxidized to semiquinones and quinones, which may form antigens by condensation or combination with body proteins.

ANTIBODIES

Antibodies are specific, thermolabile proteins found usually in the globulin fraction of the blood plasma. In the electrophoresis apparatus they migrate with the γ -globulins or with a mobility between that of β - and

^{6.} Bent, R. L., Dessloch, J. C., Duennebier, F. C., Fassett, D. W., Glass, D. B., James, T. H., Julian, D. B., Ruby, W. R., Snell, J. M., Sterner, J. H., Thirtle, J. R., Vittum, P. W., and Weissberger, A.: Chemical Constitution, Electrochemical, Photographic and Allergenic Properties of p-Amino-N-dialkylanilines, J. Am. Chem. Soc. 73:3100, 1951.