Immunology

Edited by

JEAN-FRANCOIS BACH

Immunology

Edited by

JEAN-FRANÇOIS BACH, M.D., D.Sc.

Professeur Agrégé of Clinical Immunology
Hôpital Necker, Paris

American edition with the assistance of:

R. S. SWENSON, M.D.
Stanford University School of Medicine

Foreword by:

ROBERT S. SCHWARTZ, M.D.
Tufts University School of Medicine

A Wiley Medical Publication
John Wiley & Sons
New York · Chichester · Brisbane · Toronto

Original French edition published in 1976 by
Flammarion under the title *Immunologie*

ISBN 2-257-10236-3

Library of Congress Cataloging in Publication Data:

Main entry under title:
Immunology.
(A Wiley medical publication)
Translation of Immunologie.
Includes bibliographies and index.
1. Immunology. I. Bach, Jean-François.
[DNLM: 1. Immunology. QW504 B118i]
QR181.I4213 599'.02'9 77-12139
ISBN 0-471-01760-4

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

CONTRIBUTORS

Stratis Avrameas Directeur de Recherches au CNRS, Unité d'Immunocytologie, Institut Pasteur, Paris

Jean-François Bach Professeur Agrégé d'Immunologie clinique, INSERM, U 25, Clinique néphrologique, Hôpital Necker, Paris

Marie-Anne Bach Chargé de Recherches à l'INSERM, U 25, Clinique néphrologique, Hôpital Necker, Paris

Jacques Benveniste Chargé de Recherches à l'INSERM, U 25, Clinique néphrologique, Hôpital Necker, Paris

André Capron Professeur d'Immunologie, Service d'Immunologie et de Biologie parasitaire, Institut Pasteur, Paris

Claude de Préval Chargé de Recherches au CNRS, Centre d'Immunologie, INSERM and CNRS, Marseille

Robert M. Fauve Professeur à l'Institut Pasteur, Unité d'Immunophysiologie cellulaire, Institut Pasteur, Paris

Claude Griscelli Professeur Agrégé de Pédiatrie, INSERM, U 132, Unité d'Immunohématologie, Hôpital des Enfants Malades, Paris

Philippe H. Lagrange Chef de Laboratoire à l'Institut Pasteur, Laboratoire de la Tuberculose, Institut Pasteur, Paris

Jean-Paul Lévy Professeur Agrégé d'Hématologie, INSERM, U 152, Laboratoire d'Hématologie, Hôpital Cochin, Paris

Martine Papiernik Chargé de Recherches à l'INSERM, U 25, Clinique néphrologique, Hôpital Necker, Paris

André P. Peltier Maître de Recherches à l'INSERM, U 18, Clinique rhumatologique, Hôpital Lariboisière, Paris

Jean-Louis Preud'homme Maître de Recherches à l'INSERM, U 108, Institut de Recherches sur les Maladies du sang, Hôpital Saint-Louis, Paris

Jean-Pierre Revillard Professeur Agrégé d'Immunologie clinique INSERM, U 80, Département de Néphrologie, Hôpital Édouard Herriot, Lyon

Félix Reyes Chef de Clinique—Assistant des Hôpitaux, INSERM, U 91, Clinique hématologique, Hôpital Henri Mondor, Créteil

Charles Salmon Professeur d'Immunologie, Centre national de Transfusion sanguine, INSERM, U 76, Hôpital Saint-Antoine, Paris

FOREWORD

This text was originally published in French by Flammarion. Its general excellence, and in particular its thoroughness and clarity of exposition, immediately marked it as a book worthy of wide distribution. Therefore, this English translation will be greatly appreciated.

As Professor Bach himself notes in the Introduction to the French edition, there is already available a good selection of texts in immunology. In fact, so many are now offered to readers of English that teachers often have difficulty in choosing among them. In the past I have usually recommended two, and sometimes three, different texts because I felt that no one of them satisfied all the needs and questions of my students. I believe that Professor Bach's volume is *the* general text in immunology that will meet the requirements of even the most demanding students and teachers.

The vast and complex subject of immunology is taken up in six sections: the organization and structure of cells relevant to immunity, immunochemistry, types of immune responses, cellular immunology, immunogenetics, and immunopathology. Numerous tables, diagrams, and illustrations enhance the text and imprint upon the reader concepts that often elude words. A good example of the blending of diagrams and words may be seen in the section on the complement system. This is often a very difficult subject for students, but Dr. Peltier has handled the matter skillfully. Another example is the beautifully illustrated chapter on antibody formation at the cellular level. Indeed, Professor Bach has chosen his collaborators well: all of them have made a valuable contribution.

Who should read (and study) this book? Medical students, to be sure. It might be argued that this book is too long or too detailed for many medical students, but of course it is the teacher's responsibility to indicate priorities in the learning process. Graduate students in immunology will find this text invaluable, especially because it deals so competently with topics of medical interest. Physicians in medical and surgical subspecialty training (e.g., hematology, rheumatology, or transplantation surgery) will also find much to interest them. And teachers of immunology will be enlightened by the organization and lucidity of the text. In short, this book should appeal both to beginners and to experienced practitioners of immunology.

I congratulate Professor Bach and his colleagues for their fine addition to the literature.

Boston, Massachusetts ROBERT S. SCHWARTZ, M.D.

PREFACE

Immunology is now considered a major biomedical discipline, on a level with bacteriology or hematology, a branch of which it has been for a long time. Such recognition is justified by the considerable development of immunologic research in the last twenty years.

Several Immunology textbooks have been published in the last decade including the excellent works of Roitt; Weiser; Bellanti; Eisen; Hobart and McConnell; Humphrey and White; and in French, that of Fougereau. However, to our knowledge, no book has simultaneously dealt with immunochemical bases, recent developments in cellular immunology, and modern aspects of immunopathology. This is an ambitious endeavor if one considers the numerous uncertainties persisting in each of these fields, particularly in cellular immunology. While the present knowledge of immunoglobulin structure includes many definitive elements, this is not the case with lymphocyte receptors, theories of B- and T-cell interactions, or tumor rejection. In all these fields data now available may be completely modified in the future. We feel, however, that cellular immunology has reached a stage deserving detailed presentation. It is, in addition, a topic of considerable research, presently even more active than immunochemistry (at least judging by the volume of publications). Clinical immunology has also achieved a certain degree of autonomy, and the time has come to consider it a major clinical discipline based on highly specialized laboratory investigations. We wanted to include clinical immunology in a textbook dealing with basic principles, since it appears more and more that only an excellent knowledge of the theories and techniques of basic immunology will permit immunopathologists to broaden their field of investigation. Conversely, clinical immunology can provide invaluable assistance to basic immunology, as it has already done, for example, with myelomatous immunoglobulins and suppressor T cells.

This book is intended for several types of readers: immunologists, immunology students, nephrologists, hematologists, rheumatologists, immunopathologists, research scientists, and many others who are working in immunology or in related fields.

JEAN-FRANÇOIS BACH, M.D., D.SC.

ACKNOWLEDGMENTS

I would like to thank Professor Jean Hamburger, who gave me the idea for this book and to whom I owe much. I would also like to thank all those who made the writing of this book possible. First of all the contributors, my wife, and R. S. Swenson, who played a major role in the English version. The many friends who agreed to read, reread, and criticize the manuscript deserve many thanks, in particular A. M. Staub, J. Berger, G. Biozzi, J. P. Cartron, L. Degos, M. Fellous, and Necker colleagues C. Carnaud, J. Charreire, M. Dardenne, M. Digeon, C. Fournier, L. Halbwachs, J. Leibowitch, J. London, K. Pyke, and N. Rothfield. I am also grateful for the friendly and efficient collaboration of C. Ollivier and C. Slama for secretarial assistance, M. Netter and M. Lillie for the illustrations, and John Wiley & Sons for the publication of this book.

JEAN-FRANÇOIS BACH, M.D., D.SC.

CONTENTS

Chapter 1

INTRODUCTION

Jean-François Bach

Immunology is now a major scientific discipline, but its history is not very old, less than 100 years if one refers to the studies of vaccines by Pasteur, and even less if one considers cellular immunology, which did not really begin until 1950 (Fig. 1.1).

I. A FEW DEFINITIONS

The term "immunity" (from the Latin *immunis,* "free of") initially referred to the resistance of individuals to microbial infection. Immunology was then the study of immunity against bacteria. This definition has been widened today to include analogous reactions, specific or nonspecific, to a given antigen which tend to eliminate foreign substances. Immune reactions do not always have favorable effects, as can be seen in hypersensitivity reactions, such as anaphylaxis.

A common feature of the major immune responses is their specificity for antigen. Antigens are substances that react specifically with antibodies or cellular receptors, and are capable of stimulating antibody production or cellular reactions. Substances that react with antibodies but are not able by themselves to stimulate antibody production are haptens. The capacity of antigens to provoke an immune response defines their immunogenicity. Antibodies are defined as substances whose production is elicited by administering antigens or haptens coupled to carriers and that are capable of binding specifically to antigens or haptens. One notes the mutual dependence of antigen and antibody definition. The antigen specificity mentioned above is, indeed, the original element of the immune response. This point becomes obvious after a second stimulation with the same antigen; antibodies or cellular reactions are then produced at higher intensity than during the primary response, whereas a second stimulation by another antigen gives rise to a primary-type immune response. One foresees here the concept of "immunologic memory." Before examining the main types of immune reactions, a brief historical survey should permit a better grasp of the various fields of immunology.

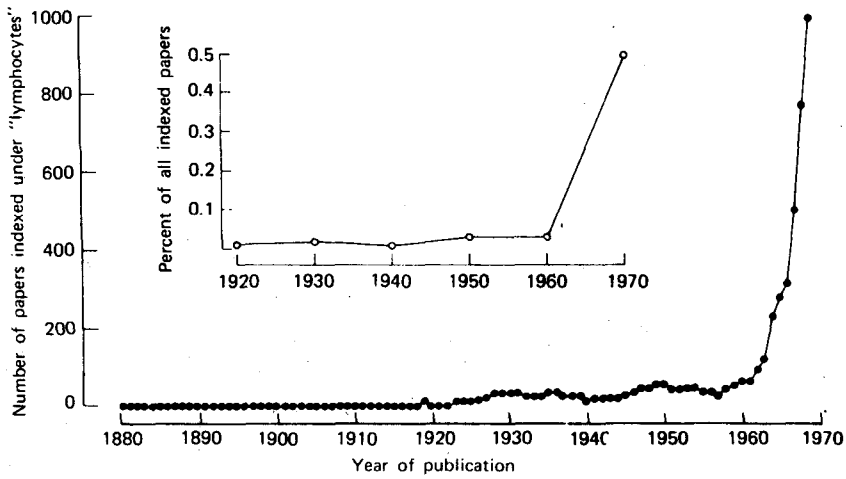

Fig. 1.1. Historical evolution of the literature on lymphocytes. (From R. A. Good, in Advances in the biosciences, New York, 1972, Pergamon Press, p. 125.)

II. HISTORICAL SURVEY

The history of immunology may be divided into four main periods. Initially, immunity was the main preoccupation; this was the time of the first vaccines. Next, serology became the main object of investigation after the discovery of antibodies and complement. The third period, contemporary with development of molecular biology, was that of studies of immunoglobulin structure. The present period examines cellular immunology, a discipline begun by Metchnikoff and Ehrlich at the beginning of this century but studied in depth only since 1950. This classification of immunology into four periods is obviously artificial, and it is clear that each of the above topics elicits very important contributions, even today, including the development of new vaccines, purification of vaccine antigens, homograft and tumor immunity, interferon, phagocytosis, defense against infectious agents, immunoglobulin genetics, and improvement of serologic techniques. This classification is also made artificial by the increasing interdependence of the various branches of immunology: for example, both immunochemists and cellular immunologists are interested in the structure of antigen-binding receptors on the lymphocyte surface.

IMMUNITY AGAINST INFECTIOUS DISEASES

It has long been known that numerous infectious diseases develop only once in a given individual, but only at the beginning of the eighteenth century was the first vaccination achieved. Vaccination from man to man was introduced in 1721 in England by Lady Montagu, wife of the British Ambassador to Turkey, where vaccination was already commonly performed. However, the method was too direct and included risks of severe reactions and transmission of infections, such as leprosy and syphilis. The method was rationalized by Jenner, who, in 1796,

proposed vaccination by a cow-produced vaccine. Vaccination, in the broader sense, was then rapidly developed against diseases other than measles and smallpox. Great progress was achieved under the aegis of Pasteur, who prepared the first antibacterial vaccine by attenuating cholera bacilli after prolonged in vitro culture.

Pasteur also produced a vaccine against rabies by injecting the spinal extract of rabid animals obtained after drying for several days at room temperature. The first and famous vaccination of a young man (Joseph Meister) was performed on July 6, 1885. Pasteur Institutes were founded in Paris and in various European cities for vaccine production.

Several years later, in 1902, the French investigators Portier and Richet discovered a new aspect of the immune response, anaphylaxis. In immunizing dogs with sea anemone toxin, Portier and Richet showed that small amounts of the toxin injected into already sensitized animals induced a lethal syndrome characterized by convulsions and collapse. It was the first demonstration of a noxious effect of the immune response, quite different from the favorable effects already known and exemplified by serotherapeutic successes. About the same time, Metchnikoff discovered macrophage functions, and, under the leadership of Pfeiffer and Von Behring, immunity was shown to be borne by substances present in the serum of hyperimmunized animals. Ehrlich proposed a prophetic theory of the cellular mechanisms of antigen recognition and antibody production. This theory was rapidly forgotten before being reintroduced with little modification 50 years later.

SEROLOGY

In parallel with the development of vaccinations, the first approaches to the cellular and humoral bases of immunity, initiated by Metchnikoff and Von Behring, became the subject of passionate discourse between supporters of "humoral" and "cellular" theories. However, for many years the humoral aspect was exclusively considered. Agglutination (Gruber, Widal), complement (Bordet), and precipitation (Oudin, Outcherlony) were successively discovered. In 1942, Coons described immunofluorescence, and in 1945 the use of antiglobulins for hemagglutination was discovered by Coombs.

IMMUNOCHEMISTRY

The biochemical nature of antigens and antibodies was progressively explored between 1922 and 1960. Haptens were discovered in 1921 by Landsteiner. Evidence that low-molecular-weight substances could react with antibodies gave a decided impetus to the biochemical study of antigens. Landsteiner later became famous with his discoveries, at 25-year intervals, of the ABO and rhesus blood groups, which made blood transfusion possible. At about the same time, Heidelberger described the biochemical basis of the structure of polysaccharide antigens by means of quantitative precipitation. Kabat, a pupil of Heidelberger, showed soon afterward that antibodies migrate in electrophoresis concurrent with γ-globulins. Then began the biochemical characterization of immunoglobulins, which reached its definitive form with Porter and Edelman's work in the 1960s. By

use of enzymatic degradation, Porter showed the existence of four polypeptide chains in the immunoglobulin molecule, and Edelman presented the first amino acid sequence of an immunoglobulin light chain. The discovery of IgE and its role in allergy by Ishizaka, Bennich, and Johansson permitted a new approach to the phenomenon of allergy previously described by Prausnitz and Kustner.

CELLULAR IMMUNOLOGY

The discovery of delayed hypersensitivity is not a recent one. At the end of the last century, Koch first described tuberculin allergy, which is now known to exclusively involve lymphoid cells and not serum antibodies. In fact, however, direct evidence of the major role of lymphocytes in all types of immune responses was not forthcoming until the 1960s, when Gowans showed that it was possible to transfer immunocompetence and immunologic memory to irradiated animals by use of pure lymphocyte preparations. The role of the thymus was discovered in 1962 by J. Miller, a French-born Australian. At the same time, R. A. Good's group established the role of the bursa of Fabricius of the chicken in the differentiation of antibody-producing cells. Numerous experiments were then performed to dissect lymphocyte populations, in particular at the Walter and Eliza Hall Institute in Melbourne, Australia, under G. Nossal's direction and in Mill Hill Institute in London with J. Humphrey and N. A. Mitchison. The demonstration of the existence of two lymphocyte categories, B and T cells, cooperating in the production of antibodies rapidly followed. The nature of the cells implicated in cellular immunity, in particular cytotoxic cells, was determined by taking advantage of newly developed cell cultures that allowed nearly complete in vitro reproduction of the various types of in vivo immune responses. All of these data permitted a reconsideration of theories of antibody formation; the clonal hypothesis of Burnet and Jerne became the subject of passionate controversy. The immunologic tolerance phenomenon was extensively studied after the pioneering work of Medawar.

III. CLASSIFICATION OF IMMUNE RESPONSES

The polymorphism of immune responses is striking. It is now known that there are multiple cell types that support various immune responses. These cells interact, either synergistically or antagonistically, as, for example, in immune rejection of grafts and tumors. In most cases, a given antigen simultaneously initiates several types of immune responses.

CELLULAR AND HUMORAL IMMUNITY

The basic and rather ancient differentiation between cellular and humoral immunity remains valid and has recently been confirmed by numerous experimental findings.

Schematically, humoral immunity is mediated by antigen-specific molecules, namely, antibodies, produced at a distance from their site of action. Humoral

immunity is easily transferred by serum and less well by cells. Humoral immunity is completely suppressed by neonatal bursectomy in birds and is influenced little by neonatal thymectomy.

Cell-mediated immunity is borne by specifically sensitized cells that come in contact with target tissue and then release locally nonantigen-specific mediators. Cell-mediated immunity is easily transferable by cells but not by serum. It is suppressed by neonatal thymectomy and not by bursectomy. We shall see later that this dichotomy between humoral and cell-mediated immunity is contingent on the differences between B and T lymphocytes.

GELL AND COOMBS' CLASSIFICATION

Gell and Coombs proposed a simple classification of immune responses into four types. The classification is obviously arbitrary but remains essentially valid, particularly in terms of immunopathology, and for type-I, -III, and -IV reactions, type-II reactions being very heterogeneous and somewhat artifically grouped.

Type-I responses are reactions in which antigens react with antibodies passively bound to cell surfaces. Their interaction releases pharmacologically active mediators from the passively sensitized cells; anaphylaxis is one example.

Type-II responses correspond to cytotoxicity reactions induced by antibodies in the presence of complement. Hemolysis by antierythrocyte antibodies illustrates this mechanism.

Type-III responses correspond to the lesions induced by immune complexes, soluble or insoluble. Serum sickness and Arthus reactions are the classic examples of this type of hypersensitivity.

Type-IV responses are delayed hypersensitivity reactions, such as tuberculin allergy and graft or tumor rejection.

Type-I reactions (anaphylactic)

Type I are anaphylactic reactions. Anaphylaxis is acute and often lethal, developing within minutes after injection of an antigen to which the host has already been sensitized. One should note, however, that the term anaphylaxis is sometimes incorrectly applied to type-II or -III reactions. Thus, one speaks of reverse passive anaphylaxis for local or general type-II responses observed after local or systemic injection of anti-Forssman antiserum to guinea pigs. Also, the term aggregate anaphylaxis is applied to type-III Arthus reactions observed in the skin of rabbits or humans subjected to repeated local injections of antigens.

The understanding of the mechanisms of type-I reactions has been considerably enhanced by the knowledge of the nature of anaphylactic antibodies and by the dissection of the events that follow contact between antigen and sensitized cells (as will be examined in detail in Chap. 11). Let us mention, however, that anaphylactic antibodies (reagins) have a strong tendency to bind passively to cells ("cytotropic" antibodies), with considerable species specificity (reagins from one species do not bind well to cells from other species). For a long time, reaginic antibodies have been evaluated by the Prausnitz-Kustner phenomenon, which is a passive cutaneous anaphylactic (PCA) reaction. This reaction does not, however, detect only anaphylactic antibodies. In fact, intradermal injection of fairly large

amounts of precipitating antibodies followed by intravenous injection of the corresponding antigen causes an inflammatory reaction within a few hours; this reaction is not, however, type I but rather an Arthus phenomenon (see below). An essential difference between Arthus's and anaphylactic reactions is the requirement (in the latter) for a lag time during which reaginic antibodies bind to cells.

In man, reaginic antibodies belong to the immunoglobulin E (IgE) class and in the guinea pig to the IgG1 class. The mechanism of anaphylactic reactions is relatively monomorphous. Reaginic antibodies bind to tissue mast cells and to basophils in the peripheral blood. The antigen is bound by the antibodies and causes release of various mediators, including histamine, which produces local edema and contraction of the smooth muscle (hence, asthma in anaphylactic shock). Nonreaginic antibodies may also be cytophilic, but they do not seem able to induce release of vasoactive hormones by mast cells.

Type-I reactions in man include generalized anaphylactic shock, characterized by asthma, widespread urticaria, and vascular collapse, which occur after introduction of an allergen into the circulation of individuals previously sensitized to this allergen. The rupture of hydatic cysts, drug intake (particularly penicillin), and unsuccessful desensitization by, for example, pollen extracts or an insect sting, may cause such shocks. Less commonly, the antigen is introduced by inhalations. Local antigen administration to the lung or skin more often induces local anaphylactic reactions, such as hay fever, allergic asthma, or urticaria.

Type-II reactions (cytotoxic)

Type-II reactions are mediated by antibodies directed against cellular antigenic determinants or against antigens or haptens intimately linked to cell membranes. The antibody is generally of the IgG or IgM class and is activated after fixation of complement, which is the effector mechanism for cytotoxic lesions.

Examples of type-II reactions are numerous; post-transfusion hemolysis after administration of incompatible red blood cells is a type-II reaction (however, urticaria or bronchospasm, sometimes observed simultaneously, is a type-I reaction). Type-II reactions against cellular antigens include newborn hemolytic disease, autoimmune experimental orchitis, Masugi's nephritis, and hyperacute homograft rejection. One may also classify as type-II the blastic transformation of lymphocytes that react with anti-Ig or antilymphocyte serum. Lastly, type-II reactions include those in which antibodies are directed against antigens or haptens passively absorbed onto cells. Allergies to some drugs (e.g., Sedormid, quinine or quinidine) are examples of this phenomenon: the drug (antigen) is bound to red blood cells or leukocytes. In fact one may note that type-II reactions include very heterogeneous phenomena, to which one could also add the effects of cytotoxic T cells or K cells (see below).

Type-III reactions (immune complexes)

Antigen-antibody complexes formed with a slight excess of antigen in the presence of complement deposit in various tissues with toxic consequences.

Complexes may be formed in the presence of excess antigen when large amounts of antigen circulate and small amounts of antibodies are produced (e.g., serum sickness) or after antibody injection into tissues that contain local high antigen concentrations. Such is the case for Arthus phenomenon that develops after several hours (hence, the alternative term semidelayed hypersensitivity). Arthus phenomenon can be produced passively by injecting antibodies intravenously and antigen locally.

The experimental and practical rationale for differentiating between type-I and -III reactions is supported by the therapeutic efficacy of administering antihistamine drugs in type-I reactions, which is not true for those classified as type III (with the exception of reduction in edema), and by suppression of type-III reactions after elimination of platelets or polymorphs or by heparin therapy, all of which have no effect on type-I reactions. Lastly, the intensity of type-III reactions is directly proportional to the titer of precipitating antibodies, which are not involved in type-I reactions.

Examples of type-III reactions are numerous in immunopathology. They include the experimental model of serum sickness disease, acute glomerulonephritis, systemic lupus erythematosus, some drug allergies, and interstitial pneumonia, farmers' lung, or pigeon breeders' disease.

Type-IV reactions (delayed hypersensitivity)

Type-IV reactions are represented by the model of delayed hypersensitivity observed in tuberculin allergy. The "delay" refers to the time required for expression of the reaction induced by the second stimulation and not the induction of hypersensitivity, which has a time duration of the same order of magnitude as that of other immune responses. Delayed hypersensitivity reactions provoke hypertrophy of paracortical areas of lymph nodes, which contrasts with the cortical hypertrophy and the development of germinal centers observed in types-I, -II, and -III reactions: The use of adjuvants (particularly Freund's) favors the development of delayed hypersensitivity. Delayed hypersensitivity skin reactions develop in several stages. Locally injected antigens may immediately induce a slight nonantigen-specific inflammatory reaction similar to that observed with any high-molecular-weight molecule. It is only after several hours that a mononucleated cell infiltrate develops, essentially originating from the blood. Sensitized cells then release various mediators. One should, however, note that specifically sensitized cells comprise a minority of cells present in the infiltrate. Nonsensitized cells are attracted to the infiltrate by chemotactic mediators. It is important to note that type-IV reactions are only transferable by cell transfusion, which is at variance with types-II and -III reactions, both transferable by serum.

All efforts to isolate from lymphoid cells a humoral mediator that bears antigen-specific information have failed, except perhaps for the work on transfer factor by Lawrence.

Examples of type-IV phenomena in man include skin reactions to tuberculin and to numerous bacterial and fungal antigens. They are also incriminated in the immune rejection of allografts and tumors and in certain autoimmune diseases. It is clear that type-IV reactions should no longer be called "hypersensitivity