ALLERGY AND IMMUNOLOGY OF THE EYE

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HARPER & ROW, PUBLISHERS
Hagerstown
Cambridge
New York
Philadelphia
San Francisco
London
Mexico City
Sao Paolo
Sydney
1817

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79 80 81 82 83 84 10 9 8 7 6 5 4 3 2 1

Library of Congress Cataloging in Publication Data
Friedlaender, Mitchell H
Allergy and immunology of the eye.
Includes bibliographies and index.
1. Eye—Diseases and defects—Immunological aspects. 2. Allergy. I. Title. [DNLM: 1. Eye diseases—Immunology. 2. Hypersensitivity.
WW140 F911a]
RE48.F74 617.7'1 79-9333
ISBN 0-06-140843-3

preface

In 1958, a time when modern-day immunology was still in its embryonic stages, Theodore and Schlossman's book OCULAR ALLERGY was published. During the past 21 years the field of immunology has veritably burgeoned, and today immunology touches every specialty within clinical medicine. New concepts have arisen which have begun to shed light on once-obscure diseases, many of which affect the visual system.

Immunologic mechanisms in ophthalmic disease have gained wide attention, and a book which updates immunologic concepts within ophthalmology has been greatly needed for many years. (Interest among ophthalmologists is long overdue, since for many decades the eye has been a site favored by immunologists for the study of immunologic phenomena.) In the future, immunologic study of ophthalmic disease will continue to expand, and a basic understanding of immunologic principles will become essential for those in training as well as for practicing clinicians. Basic scientists can also learn much about the clinical manifestations of immunologic processes by studying immunologic phenomena which occur in the eye.

ALLERGY AND IMMUNOLOGY OF THE EYE is intended to bring together an understanding of immunologic principles at work in conditions affecting the eye, and the varied clinical manifestations of these conditions. The first three chapters review the basic principles of general and ophthalmic immunology. Subsequent chapters cover the clinical entities in which these immunologic mechanisms are thought to play a significant role. It is intended that the reader will gain an understanding of the basic principles of immunology as well as a more specific understanding of the special and enlightening immunologic features of ocular tissues. If this goal is accomplished, this book will have served a useful purpose.

I wish to express my gratitude to several individuals who assisted me in researching, writing, and editing ALLERGY AND IMMUNOLOGY OF THE EYE. My outstanding teachers, Drs. Phillips Thygeson, H. Bruce Ostler, and G. Richard O'Connor provided great inspiration and many helpful suggestions for improving the clarity and the quality of this book. Drs. Joseph Michelson, Khalid Tabbara, Edward Howes, and Stewart Sell were kind enough to review chapters and to offer useful comments.

I would also like to thank Mrs. Lucy Lee and Mr. Richard Cyr for their valuable help with library work, Peggy Costa and Barbara Goldsmith for their proficient transcribing and typing, and the staff of the Medical Division of Harper and Row for their patience, hard work, and dedication.

M.H.F.

contents

ONE ONE ONE principles of general immunology

HISTORY OF THE CONCEPT OF IMMUNITY

Immunology is generally thought of as a modern-day discipline which has evolved only recently. The concept of immunity, however, dates back many centuries and its route is marked by several important milestones leading to our present-day understanding of immunology (Fig. 1-1). As far back as the eleventh century, Chinese physicians noted that inhalation of smallpox crusts prevented the occurrence of this dreaded disease. Variolation, the intradermal inoculation of powdered scabs, became widely used in the Middle East. During the eighteenth century the technique reached England, where Lady Mary Wortley Montagu popularized this primitive practice. In 1798, Edward Jenner, while still a medical student, greatly advanced the embryonic science of immunology when he discovered that milkmaids who contracted cowpox became resistant to smallpox infection.

Modern-day methods of preventive immunization against smallpox and other infectious diseases resulted largely from the efforts of Louis Pasteur. Pasteur developed the germ theory of disease, which led to the *in vitro* culture of microorganisms. Thus, material became available for the production of vaccines. Pasteur found that old cultures of cholera organisms, when given to fowl, produced no disease, yet the animals became resistant to subsequent infection with cholera. Inoculation with living attenuated organisms could thus produce resistance to infectious disease.

Robert Koch discovered the tubercle bacillus while investigating the bacterial etiology of infectious disease. In 1880, while attempting to develop a vaccine for tuberculosis, he observed the phenomenon of delayed hypersensitivity. Roux and Yersin, in 1885, showed that the diphtheria bacillus produces a potent exotoxin. Von Behring and Kitasato used this toxin to inoculate animals and to produce a toxin-neutralizing substance known as antitoxin. This antitoxin, when given to uninoculated animals, conferred protection against the harmful effects of the diphtheria bacillus. Thus, the important therapeutic technique of passive immunization was introduced.

At the turn of the century, two divergent immunologic theories were developing. The **humoral** theory, proposed by Paul Ehrlich, stressed the importance of the biochemical products, or **antibodies,** elaborated by certain cells. At about the same time, Metchnikoff developed the theory of **cellular immunity,** which emphasized the host's cellular response to foreign substances. Ehrlich proposed, in his side-chain theory, that receptors exist on cell surfaces and that when these receptors interact with toxins, excess receptors are shed into the circulation as antibody. Metchnikoff felt that wandering phagocytes are the body's primary defense system. We now recognize that phagocytic cells can respond nonspecifically to foreign substances but may also participate with lymphocytes in specific cellular immune reactions. The theories of both Metchnikoff and Ehrlich were essentially correct and both theories were laborated and interconnected over the next several decades. Although

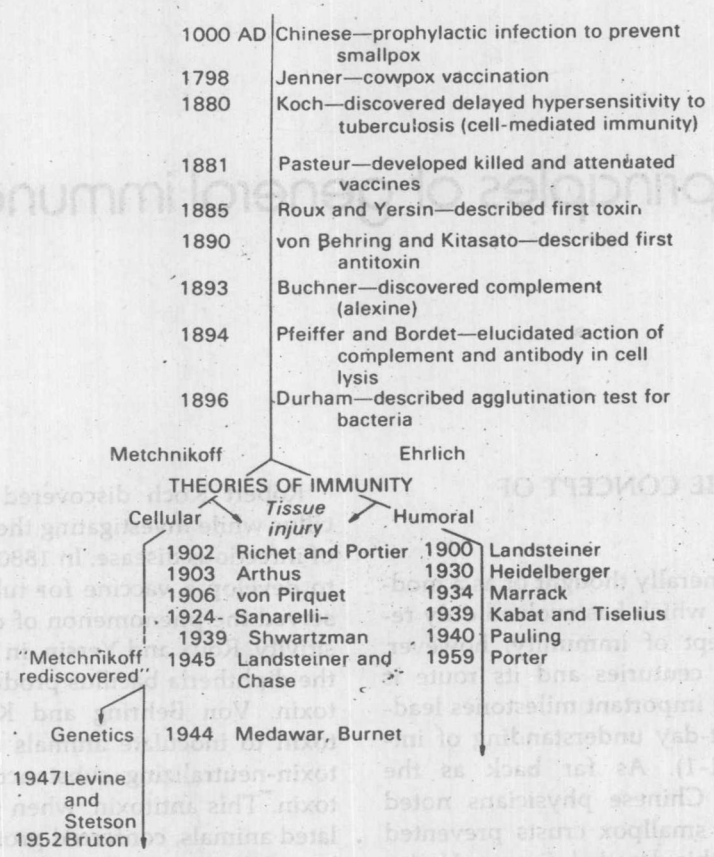

FIG. 1-1. Important milestones in the history of immunology. (Bellanti JA: Immunology, Philadelphia, WB Saunders, 1971, p 4)

today's concepts differ somewhat from those of Ehrlich and Metchnikoff, cellular and humoral immunity are now known to be the two major immunologic mechanisms by which the body maintains an adequate and proper defense system.

TYPES OF IMMUNITY

Immunology is the study of **immunity,** a term derived from the Latin *immunis,* meaning "free from burden." In one sense, immunity refers to the protection of the host from infection or reinfection by a microbial agent. The scope of immunity has been broadened, however, to include also the harmful or unpleasant effects resulting from interaction of a foreign substance with the host's defenses. To this type of response we apply the terms **allergy** and **hypersensitivity. Allergy** is the term coined by von Pirquet, who hypothesized that both the beneficial and harmful responses of the host to a foreign substance were manifestations of a common biologic mechanism. We now use the broader term **immunity** to denote a generalized reactivity of a host to a foreign substance as well as its protective status against these substances.

Immunity may be innate or acquired. **Innate immunity** refers to those immune properties which are genetically determined. **Acquired immunity** refers to immunity developed through some type of immunization process.

Protective immunization may be acquired by use of a **vaccine,** a substance which immunizes a host. It usually is a preparation of killed or attenuated microorganisms. Immunization may be spoken of as active or passive. In **active immunization,** exposure to an organism or administration of a vaccine causes the host to develop immunity, a process which

may take several weeks. This active form of protection, however, lasts for several months or even years. In **passive immunization,** serum from an immunized donor is passively transferred to a recipient and offers immediate but short-lived protection.

Immunity may also be considered as nonspecific or specific. **Nonspecific immunity** allows the host to differentiate between the host's own constituents and outside invaders, but this mechanism does not require the specific immunologic recognition of foreign substances. Nonspecific immunity includes the barrier functions of the skin, certain antimicrobial substances in the serum and external secretions, and nonspecific phagocytosis. **Specific immunity** depends on the immunologic recognition of foreign substances, known as antigens, and the reactions to these substances by humoral or cellular immune mechanisms, as will be discussed. **Specificity,** or specific recognition of a foreign substance is a key feature of the immune system.

LYMPHOID CELLS

In carrying out the function of the immune system, an extensive cell system, known as the **lymphoreticular system,** has evolved. Its cells are found throughout the body, with large collections located in the thymus, lymph nodes, and spleen (see Lymphoid Organs). An important component of this cell system is the lymphoid series of cells. This group includes both lymphocytes and plasma cells. The main function of the plasma cell is the production of **antibody,** a protein which reacts with a foreign substance, or **antigen.** The lymphocyte also has the ability to react specifically with an immunizing substance (antigen) and to elaborate certain cell products in consequence. Thus, two different types of **immune responses** may occur: one involving antigen and antibody, and another involving antigen and specifically sensitized lymphocytes.

Two different populations of small lymphocytes are known to exist (Fig. 1-2). Both are derived from bone marrow stem cells. **T lymphocytes** are lymphocytes that have been processed by the thymus or are in some way dependent upon the thymus. The thymus is responsible for specific **cellular** (or **cell-mediated) immune responses** which are mediated by **T lymphocytes,** and if a thymectomy is performed on an animal during the neonatal period, these cell-mediated responses fail to develop. **B lymphocytes** are dependent on the

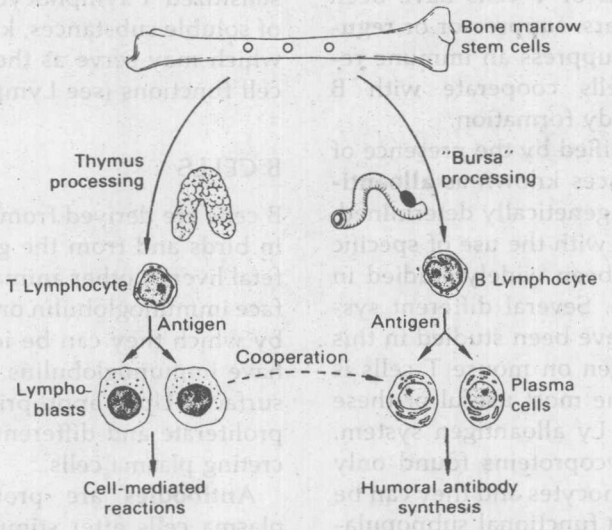

FIG. 1-2. Processing of bone marrow stem cells by the thymus to form T lymphocytes and by the bursa or "bursal equivalent" to form B cells. (Roitt IM: Essential Immunology, Oxford, Blackwell, 1974, p 48)

bursa of Fabricius, a gut-associated lymphoid organ in birds, and on the so-called "bursal equivalent" in man. The location of the bursal equivalent in man is not known; however, it is in the fetal liver that immunoglobulin-producing cells are recognized earliest. The bursa, or its equivalent, appears to be responsible for **humoral immunity** (*i.e.*, immune responses mediated by antibodies). Both populations of lymphocytes, when appropriately stimulated, undergo morphologic changes and divide. The T lymphocytes undergo transformation to a blast form after which they are **sensitized,** that is, capable of recognizing a specific antigen; B lymphocytes differentiate into plasma cells which form antibody.

T CELLS

T cells (Fig. 1-2), the lymphocytes which are processed by the thymus, occupy the thymus-dependent areas of lymphoid tissue. The use of antithymus serum, cytotoxicity tests, and other techniques allows T cells to be identified.

T cells are capable of mediating many diverse types of immunologic reactions. These include immunity to many viruses, bacteria, and fungi; contact allergy; graft and tumor rejection; and certain types of autoimmune disorders. Subpopulations of T cells have been identified in recent years: **suppressor** or **regulator** T cells actively suppress an immune response; **helper** T cells cooperate with B lymphocytes in antibody formation.

T cells may be identified by the presence of markers on their surfaces known as **alloantigens.** Alloantigens are genetically determined. They can be identified with the use of specific antiserums, and have been widely studied in inbred strains of mice. Several different systems of alloantigens have been studied in this manner. The thy antigen on mouse T cells is an example. One of the most useful of these markers has been the Ly alloantigen system. These markers are glycoproteins found only on the surface of lymphocytes and they can be used to identify certain functional subpopulations of T lymphocytes. Five different Ly alloantigens have been identified, each with two different antigenic specificities, or alleles. Ly-1 is determined by a gene on chromosome 19 of the mouse, and Ly-2 and Ly-3 by genes on chromosome 6. In the peripheral blood of mice, 50% of T lymphocytes possess Ly-1, 2, and 3; 30% have Ly-1 only, and 7% have Ly-2 and 3. It appears that cells possessing only Ly-1 express helper functions with respect to antibody formation and delayed hypersensitivity while cells with Ly-2 and 3 suppress immune responses and may also be cytotoxic. Cells possessing Ly-1, 2, and 3 seem to be precursors of the other cell types and are not functionally committed cells. T cells of different Ly types appear to interact and cooperate with one another in a variety of immunologic activities, including antibody formation, cytotoxicity, immunosuppression, delayed hypersensitivity, and killing of microorganisms by macrophages.

Certain thymus-derived factors seem to be associated with T cell maturation and these factors may restore T cell responses in neonatally thymectomized animals. One of these factors, known as thymopoietin, causes bone marrow cells to develop into T lymphocytes.

After stimulation by a sensitizing antigen, the T lymphocyte undergoes transformation into a blast cell. These cells are pyroninophilic and actively synthesize new DNA, as evidenced by uptake of tritiated thymidine. The sensitized T lymphocyte elaborates a number of soluble substances, known as **lymphokines,** which may serve as the mediators of some T cell functions (see Lymphokines, Ch. 2).

B CELLS

B cells are derived from the bursa of Fabricius in birds and from the gastrointestinal tract or fetal liver in other animals. B cells possess surface immunoglobulin on their cell membranes, by which they can be identified. Most B cells have immunoglobulins IgM and IgD on their surfaces. Upon appropriate stimulation, B cells proliferate and differentiate into antibody-secreting plasma cells.

Antibodies are proteins synthesized by plasma cells after stimulation by an antigen. Antibodies have the capability of reacting specifically and uniquely with the configuration that was responsible for their formation. In the

human, antibody is associated with five major classes of proteins known as **immunoglobulins,** designated IgG, IgA, IgM, IgD, and IgE. Each has a distinct chemical nature and a specific biologic role. IgG is the most abundant of the immunoglobulins and provides the bulk of immunity against infectious agents which have a blood-borne dissemination, including bacteria, viruses, parasites, and fungi. Antibodies and immunoglobulins are discussed in detail later in this chapter.

HUMAN T AND B CELLS

For differentiating human T and B cells, the rosetting test with sheep erythrocytes is a useful technique. Some 80%–100% of human T cells will form rosettes with normal sheep erythrocytes. Each of these rosettes appears as a central lymphocyte with four or more red blood cells attached to its surface (Fig. 1-3). B cells will not form rosettes with normal sheep erythrocytes. If, however, the red cells are first coated with antibody and if complement is then added, rosetting of B cells, but not T cells, will take place.

T cells comprise 60%–75% of all lymphocytes in the peripheral blood, spleen, and lymph nodes; B cells account for 20%–30%. In lymphoblastic leukemia most of the leukemic cells are T cells, while in chronic lymphatic leukemia most are B cells. Lymphomas may contain either B or T cells. T cells are decreased in patients with cancer, lepromatous leprosy, and certain other diseases.

A third population of lymphocytes exists, which do not have B or T cell markers. These lymphocytes are known as **null cells.** Null cells may simply be immature T cells that have not yet been exposed to thymus tissue. Null cells may play a role in various rheumatoid diseases. A cell which may be identical to the null cell is the **killer** cell or **K** cell which appears to be responsible for certain forms of cell-mediated cytotoxicity.

LYMPHOID ORGANS

Lymphocytes are found in the lymph nodes, spleen, thymus, and gastrointestinal tract. All lymphoid organs have a similar structure. The organs are encapsulated and divided into lobules by connective tissue strands. Blood is supplied by a single artery and drained by veins and lymphatics. The parenchyma consists of a cortex, or peripheral zone, and a medulla, or central zone.

Lymph nodes (Fig. 1-4) serve as filters for the lymphatic drainage. The cortical region of

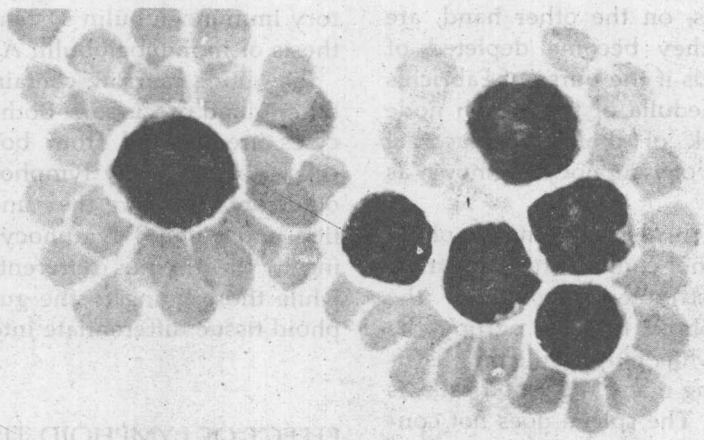

FIG. 1-3. Rosettes formed by sheep erythrocytes surrounding T lymphocytes. (Courtesy of Dr. S. Barrett).

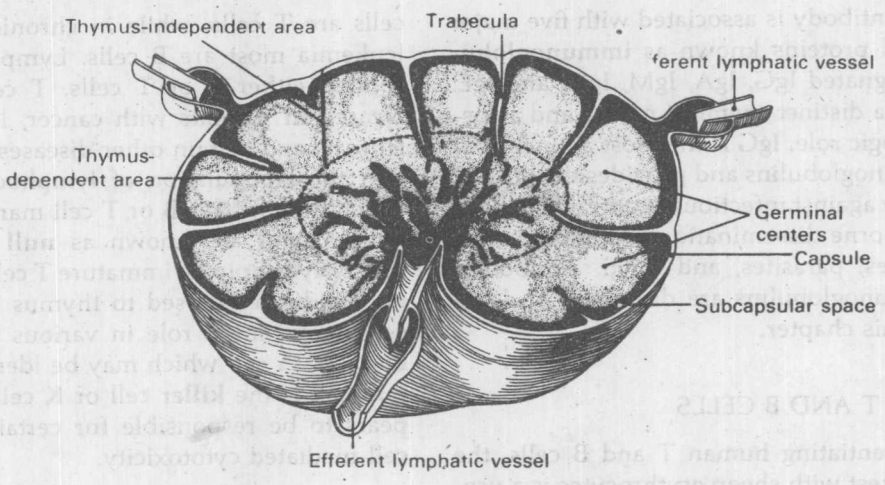

FIG. 1-4. Structure of lymph node showing thymus-dependent and bursa-dependent areas. (Bellanti JA: Immunology, Philadelphia, WB Saunders, 1971, p 33)

the lymph node contains tightly packed nodules of lymphocytes, known as primary follicles, and more loosely packed nodules surrounded by a rim of tightly packed lymphoid cells, known as secondary follicles. Each primary follicle has a central zone of immature cells known as the **germinal center.** The paracortical areas are strips of lymphoid tissue lying between the follicles. These paracortical areas are considered to be thymus-dependent areas; thymectomy in neonatal animals leads to depletion of lymphoid cells in these areas. The follicular areas, on the other hand, are bursa-dependent: they become depleted of lymphocytes in birds if the bursa of Fabricius is removed. The medulla of the lymph node contains a network of draining sinusoidal channels, and rows of lymphocytes known as **medullary cords.**

The spleen (Fig. 1-5) also contains lymphoid follicles. These are not confined to the cortical areas but are distributed throughout the parenchyma. Lymphoid follicles occupy the area known as the white pulp, while the vascular region, containing many red blood cells, is known as red pulp. The spleen does not contain lymphatic vessels, but, rather, has an extensive arterial and venous drainage.

The thymus (Fig. 1-6) contains a cortical area and a medulla; however, it has no lymphoid follicles. Rather, the cortex consists of packed lymphocytes. The thymus processes T lymphocytes, which, as was said, are the mediators of cellular immunity.

The gastrointestinal system contains lymphoid tissue in the Peyer's patches, appendix, and tonsillar areas. Lymphocytes in these areas are arranged as follicles, and some thymus-dependent follicles are present in these tissues. The tonsils form a ring of lymphoid tissue around the oral cavity (Waldeyer's ring). The gastrointestinal lymphoid tissues are important in the development of the secretory immunoglobulin system, and in the synthesis of immunoglobulin A.

The bone marrow contains stem cells and other blood precursors. Both B and T lymphocytes are derived from bone marrow stem cells. Bone marrow lymphocytes circulate to other organs where they undergo differentiation into B and T lymphocytes: those migrating to the thymus differentiate into T cells, while those going to the gut-associated lymphoid tissue differentiate into B cells.

EFFECT OF LYMPHOID TISSUE STIMULATION

An immune response is the specific recognition of a foreign substance by the body's immune system and the formation of antibody or

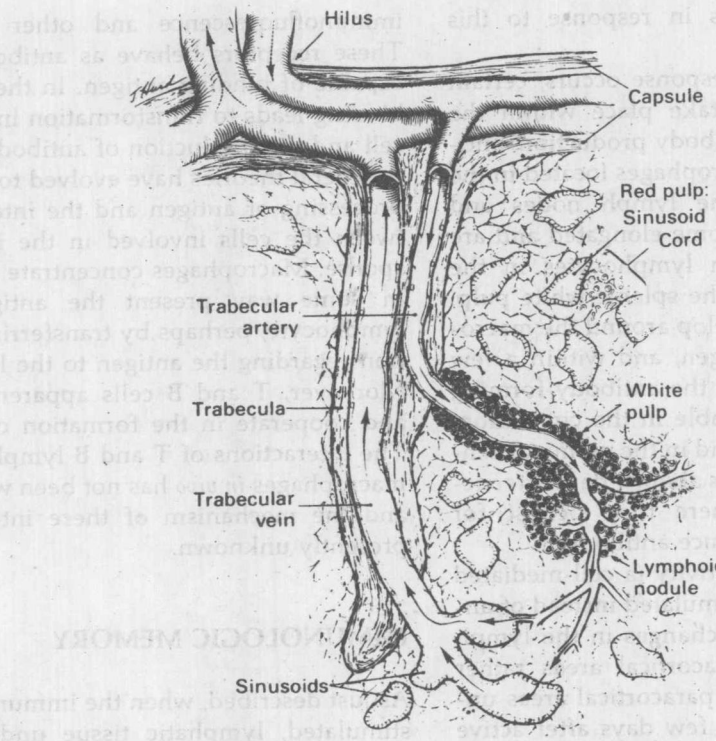

FIG. 1-5. Schematic drawing of spleen. (Bellanti JA: Immunology, Philadelphia, WB Saunders, 1971, p 35)

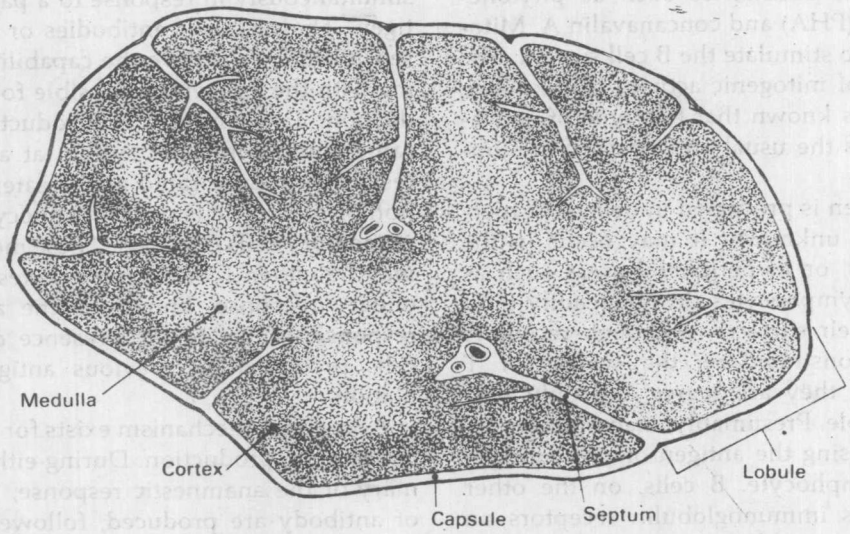

FIG. 1-6. Schematic drawing of thymus gland. (Bellanti JA: Immunology, Philadelphia, WB Saunders, 1971, p 36)

sensitized lymphocytes in response to this recognition.

When an immune response occurs, certain morphologic changes take place within the lymphoid tissue. In antibody production, antigen is taken up by macrophages located in the medullary areas of the lymph nodes and spleen. These cells become elongated and are closely associated with lymphocytes in the lymph node cortex or the splenic white pulp. Lymphoid follicles develop around the macrophages containing antigen, and within a few days the progenitors of the antibody-forming plasma cells are detectable in the circulation. Plasma cells can be found in the germinal centers and medullary cords about 7 days after active immunization. There they persist for several weeks and produce antibodies.

If delayed hypersensitivity (a cell-mediated immune response) is stimulated instead of antibody production, the changes in the lymph node occur in the paracortical areas rather than in the cortex. The paracortical areas undergo expansion, and a few days after active immunization, large pyroninophilic blast cells appear in the paracortical regions. These cells undergo division and small lymphocytes (T cells) are released into the draining lymph (see also Lymphocyte Transformation, Ch. 2).

Blast transformation of T cells can also be induced by certain agents known as **mitogens.** These include substances such as phytohemagglutinin (PHA) and concanavalin A. Mitogens may also stimulate the B cell system. The mechanism of mitogenic activity is unknown; however, it is known that this type of activation bypasses the usual antigen-specific stimulation.

How antigen is processed in delayed hypersensitivity is unknown. It may occur in the lymph nodes, or in peripheral areas such as the skin. T lymphocytes do not readily bind antigen to their surfaces. Although receptors can be demonstrated on the surface of T lymphocytes, they are scarce and only partially accessible. Presumably, macrophages assist in processing the antigen or presenting it to the T lymphocyte. B cells, on the other hand, possess immunoglobulin receptors on their cell surfaces which are detectable by immunofluorescence and other techniques. These receptors behave as antibody and are capable of binding antigen. In the B cell, this binding leads to transformation into a plasma cell and the production of antibody.

Several theories have evolved to explain the processing of antigen and the interaction between the cells involved in the immune response. Macrophages concentrate antigen and in some way present the antigen to the lymphocyte, perhaps by transferring information regarding the antigen to the lymphocyte. Moreover, T and B cells apparently interact and cooperate in the formation of antibody. The interactions of T and B lymphocytes and macrophages *in vivo* has not been well defined, and the mechanism of these interactions is presently unknown.

IMMUNOLOGIC MEMORY

As just described, when the immune system is stimulated, lymphatic tissue undergoes differentiation and proliferation. This may result in **humoral immunity,** with proliferation of plasma cells and production of antibody, or **cellular immunity,** with proliferation of specifically sensitized T lymphocytes (*i.e.*, lymphocytes capable of specific recognition). Both types of immunity may also be produced simultaneously in response to a particular antigen. The resultant antibodies or specifically sensitized T cells have the capability of reacting with the antigen responsible for their production. Furthermore, reintroduction of the same antigen into the system at a later time results in a more rapid and greater proliferation of plasma cells or of lymphocytes known as **memory cells** (Fig. 1-7). These memory cells may be either T or B lymphocytes. This secondary response, known as the **anamnestic response,** is due to the presence of memory cells produced by previous antigenic stimulation.

A feedback mechanism exists for the control of antibody production. During either the primary or the anamnestic response, high levels of antibody are produced, followed by a tapering off of antibody levels. Such regulatory

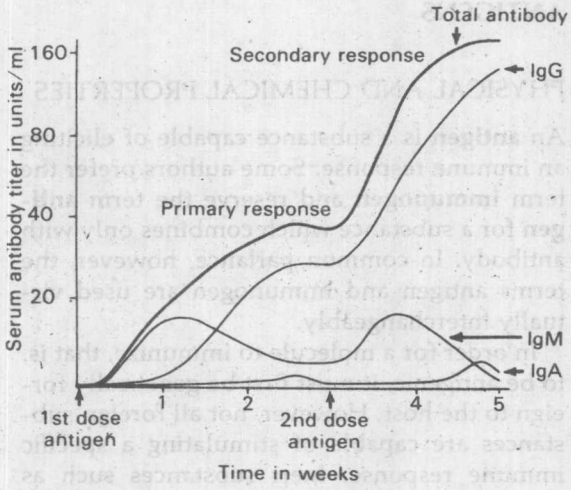

FIG. 1-7. Primary and secondary (anamnestic) antibody response. Note shorter latency period and higher concentration of antibody during secondary response. (Kongshavn PAL, Hawkins D, Shuster J: The biology of the immune response. In Freedman SO, Gold P (eds): Clinical Immunology, Hagerstown, Harper & Row, 1976, p 35)

mechanisms are important in controlling the immune system when continued antigenic stimulation takes place. The mechanism by which feedback takes place is unknown, but it may be related to suppressor cells or to inhibition by specific antibody.

EFFECTOR MECHANISMS

Two types of effector mechanisms exist which mediate the several kinds of immune responses. One, known as **humoral immunity,** is mediated by antibody. The second, known as **cell-mediated** or **cellular immunity,** is mediated by specifically sensitized T lymphocytes. A third response, a state of nonreactivity known as **immune tolerance,** may also develop after immune stimulation of B or T lymphocytes (Fig. 1-8).

HUMORAL IMMUNITY

Antibodies may interact with antigens under a variety of circumstances. These interactions occur within the blood stream, on mucosal surfaces, or within various tissues of the body. The effects of such interactions may be beneficial or harmful to the host; in the latter situation we say that a state of **allergy** or **immediate hypersensitivity** exists. Humoral immunity accounts for the body's responses to a variety of microorganisms as well as for the production of many allergic conditions and disease entities. The humoral immune system is closely linked embryologically with lymphoid tissue commonly known as gut-associated lymphoid tissue (GALT). In birds, the bursa of Fabricius is responsible for processing the cells involved in humoral immunity. In man the analogous lymphoid tissue may be located in the bone marrow, fetal liver or GI tract.

CELL-MEDIATED (CELLULAR) IMMUNITY

The second major effector mechanism which participates in the immune response involves specifically sensitized lymphocytes directed against foreign antigens. Cellular immunity is monitored by the thymus, and responses are mediated by the thymus-dependent T lymphocytes. The term **delayed hypersensitivity** had also been used as a synonym for

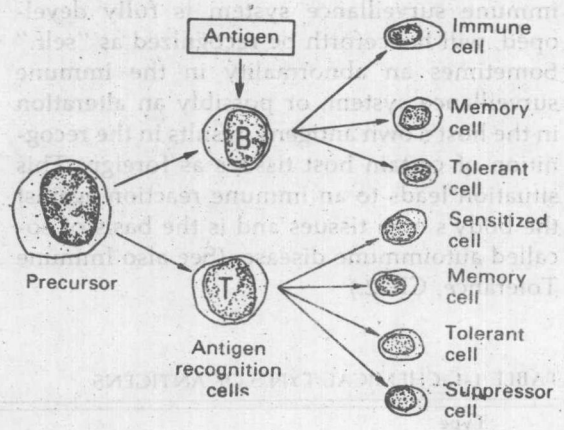

FIG. 1-8. Response of B and T cells to antigen. B and T lymphocytes may respond immunologically in several ways. B lymphocytes may develop into antibody-producing plasma cells, B memory cells or tolerant B cells. T lymphocytes may become sensitized, memory, tolerant, or suppressor T cells. (Sell S: Immunology, Immunopathology, and Immunity, Hagerstown, Harper & Row, 1975, p 117)

cellular immunity, and this mechanism is discussed under that heading in Chapter 2. However, some authors feel that this term should be restricted to the undesirable or tissue-damaging responses induced by T cells. Cell-mediated immunity encompasses other important biologic responses, including recovery from many infectious diseases, surveillance against neoplasia, and rejection of foreign grafts and malignant cells.

IMMUNE TOLERANCE

A state of unresponsiveness to a specific antigen may be induced under certain circumstances. This phenomenon, known as immune tolerance, prevents the host from responding to a foreign substance with antibody or sensitized T cells. Again, this response is specific. It may be produced by presenting the host with an antigen that is not easily catabolized, such as pneumococcal polysaccharide. It may also be induced with unusually high or low doses of antigen, and may at times be induced by administration of antigen by the oral or intravenous route. A host also maintains nonreactivity to his own bodily tissues because of immune tolerance: presumably, antigens that the host encounters *in utero* or at birth, before the immune surveillance system is fully developed, will henceforth be recognized as "self." Sometimes an abnormality in the immune surveillance system, or possibly an alteration in the host's own antigens, results in the recognition of certain host tissues as foreign. This situation leads to an immune reaction against the body's own tissues and is the basis of so-called autoimmune disease. (See also Immune Tolerance, Ch. 2.)

ANTIGENS

PHYSICAL AND CHEMICAL PROPERTIES

An **antigen** is a substance capable of eliciting an immune response. Some authors prefer the term **immunogen** and reserve the term **antigen** for a substance which combines only with antibody. In common parlance, however, the terms antigen and immunogen are used virtually interchangeably.

In order for a molecule to immunize, that is, to be antigenic, it must first be genetically foreign to the host. However, not all foreign substances are capable of stimulating a specific immune response. Inert substances such as carbon, for example, will only induce a nonspecific phagocytic response. Antigens tend to be large molecules, with molecular weights of 10,000 or more. Still, some smaller molecules with molecular weights in the range of 1000 have been shown to be antigenic. While there is a lower limit of molecular weight below which substances are unlikely to be antigenic, there seems to be no upper limit in size. Usually antigens are proteins but they may also be polysaccharides or combinations of proteins and polysaccharides (Table 1-1). Normally, lipids and nucleic acids are not antigenic; however, they may become antigenic if combined with proteins or polysaccharides.

Haptens are small molecules which induce an immune response only after combining with a protein. The hapten–protein complex may then function as a complete antigen, and a specific immune response will be directed against the hapten or the hapten and carrier protein.

Insoluble particles such as red blood cells

TABLE 1-1. CHEMICAL TYPES OF ANTIGENS

Type	Source
Protein	Serum proteins, microbial products (toxins), enzymes
Lipoprotein	Serum lipoproteins; cell membranes
Polysaccharides	Capsules of bacteria (pneumococcus)
Lipopolysaccharides	Cell walls of gram-negative bacteria (endotoxins)
Glycoproteins	Blood group substances A and B
Polypeptides	Hormones (insulin, growth hormone), synthetic compounds
Nucleic acids	Nucleoproteins, single-stranded DNA

(Bellanti JA: Immunology. Philadelphia, Saunders, 1971, p 98)

may possess many different antigenic groups, which are known as **antigenic determinants.** (These antigenic determinants may be found in soluble as well as in particulate antigens.) Those determinants which are most readily accessible to antibody or lymphocytes tend to be closer to the outer surface of the molecule. In very complex macromolecules, certain amino acids or groups of amino acids are antigenically more potent than others. Further, a higher degree of variability in amino acid composition tends to confer a greater antigenicity upon a molecule.

A variety of factors influence the immunogenicity of an antigen. These include solubility, molecular configuration, charge, and accessibility of the determinant groups. A substance which can be degraded and phagocytized by the host is more likely to elicit an immune response. (If the antigen is eliminated, the immune response has been beneficial. If the antigen persists, the mechanisms of immunity may lead to immunologic tissue injury.) Chemical properties are also important. Most organic substances, with the exception of lipids, can be immunogenic. The vast majority of immunogens are protein in nature; often these proteins are combined with carbohydrates, lipids, or nucleic acids. Polysaccharides, such as the capsular components of the pneumococcal bacteria, or lipopolysaccharides, such as endotoxins, are biologically important antigens. Glycoproteins can be antigenic; these include the blood group antigens A and B, associated with transfusion reactions. For many years nucleic acids were considered nonimmunogenic; however, in certain diseases such as systemic lupus erythematosus, an immune response to the patient's own nucleic acids may develop and lead to tissue damage.

BIOLOGIC PROPERTIES

It is well known that live, attenuated, vaccines confer greater protection than killed or inactivated preparations; this may be due to the removal of important determinant groups during the preparation of a killed vaccine. Also, an immune response to a particular antigen may vary from one species to the next. Thus, the mouse develops a good immune response to the isolated pneumococcal polysaccharide capsule while the rabbit does not. Even within a species there may be variations in the immunologic response to a given antigen. The dose and route of introduction of an antigen are also important factors. A very low dose or a very high dose of an antigen may actually produce tolerance. Similarly, antigens given by the oral or intravenous route may lead to immunologic unresponsiveness. On the other hand, parenteral administration of the same antigen may produce a potent immune response. Ordinarily, however, the immunogenicity of an antigen can be assessed by the antigen's ability to stimulate an immune response. The type of immune response which develops depends on the nature of the antigen. Specific antibody may be produced in response to one type of antigen while specifically sensitized T lymphocytes develop in response to a different antigen. Some antigens can elicit both a humoral and a cellular immune response.

EXOGENOUS ANTIGENS

The antigens which confront the host in the environment are varied in nature. They include, for example, microorganisms, drugs, airborne pollens, and pollutants. These **exogenous antigens** under certain conditions may cause an infectious or allergic disease (Table 1-2). Bacterial cell walls, for instance, are known to contain a number of antigenic substances. The exterior structure of virus particles can also serve as a rich source of exogenous antigens.

ENDOGENOUS ANTIGENS

Antigens found within the host are known as **endogenous antigens.** They may be subdivided into heterologous, homologous, and autologous antigens (Table 1-2).

Heterologous Antigens

Those antigens which are shared by phylogenetically unrelated species are known as **heterologous** antigens. These antigens, also known as **heterogeneic** or **heterophilic,** reflect