Clinical Allergy and Immunology of the Eye

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Preface

Physicians and other scientific investigators have long recognized the ever increasing importance of allergy and other immune mechanisms in the causation of eye diseases. In fact, by 1914—8 years after the term "Allergie" was first used by von Pirquet—von Szily had already published an ophthalmic text entitled *Die Anaphylaxie in der Augenheilkunde*. This is not surprising, because even at that time the eye and its adnexae offered a unique opportunity to observe and study, both clinically and experimentally, most fundamental immune reactions to an extent not possible elsewhere in the body until a much later date.

Clinical Allergy and Immunology of the Eye attempts to present a balanced clinical and practical view of the current understanding of the eye problems caused by abnormalities of the immune system based on the authors' long-term interests in ocular allergy, immunology, microbiology, and therapeutics. Until recently, immunology has been viewed by the practicing clinician as a rather esoteric and somewhat intimidating laboratory science. In a very short space of time the science, in all its ramifications, has leaped center stage, from laboratory into the clinical arena, with important practical applications for the physician in areas of diagnosis and treatment.

This monograph has three parts. The first three chapters deal with the elaboration of basic immune mechanisms, pathological immune reactions, and principles of treatment based on manipulating the immune response. These chapters have been diagrammatically illustrated in detail in order to give greater understanding to inherently difficult material.

The second part represents the major portion of the book and is essentially clinical, offering an application of the science of immunology to those clinical problems that the ophthalmologist must confront in his daily practice. In preparing this portion, it was gratifying to note how the basic allergic classifications and the ocular allergic phenomena described and delineated in our previous contributions are still valid today and form the framework of much of the book.

The third part is a glossary of terms, to again allow a quick reference for understanding the new and extensive terminology of immune science.

A number of illustrations used in this text were first printed in Theodore and Schlossman's *Ocular Allergy* published by Williams & Wilkins, Baltimore, 1958. The authors wish to thank both Dr. Abraham Schlossman and the publishers for permission to do so. They also wish to express their appreciation to Carlos Lopez, Ph.D., of the Sloan-Kettering Institute, for his editorial help in the preparation of the first portion of the manual. We also wish to express our appreciation to the American Academy of Ophthalmology for the use of material previously published in the Academy manual *Allergy of the Eye* by Dr. Theodore.

F.H.T.
S.E.B.
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CHAPTER ONE

Basic Immune Mechanisms

Protection from disease results from the detection and subsequent elimination of substances recognized as foreign by the immune system. This active protection against "non-self" is called immunity. Historically, the word derives from the Latin "immunitas," meaning freedom from taxes, and it later came to be used to indicate freedom from disease. The ancients realized that, after recovering from a disease, an individual was less susceptible to a recurrence of that disease. Modern immunology is the study of those systems responsible for protection of the individual against external and internal assault.

Foreign substances which have the capacity to evoke immunological responses are referred to as antigens. Antigens generally come from the external environment and include microbial organisms such as bacteria, viruses, and fungi. Plant, food, and animal products may also give rise to an immune response. Vaccines, drugs, and chemicals (such as food additives, dyes, and metals) may stimulate an immune reaction if introduced into a competent host. All antigens share the common characteristic of being recognized as foreign.

The immune system may also be activated by foreign substances from the internal environment, e.g., modified self-components such as virally infected cells or transformed (cancer) cells. However, if an immune response occurs against the host's own tissues, it is referred to as an autoimmune reaction.

Antigens range in size from the simplest low molecular weight molecules to the most complex microbial agents. Many antigens occurring in nature are substances of high molecular weight and usually are proteins or carbohydrates. By definition, immunogens are capable of inducing an immune response and of binding to the antibody directed against antigenic structural determinants found on the immunogen. Some small molecules cannot induce an immune response but bear antigenic determinants capable of binding antibody. These low molecular weight molecules, known as haptens, require prior attachment to a carrier protein in order to be immunogenic. Antigenic determinants are three-dimensional structures on the surface of immunogens which bind specific antibody. Most of the complex antigens, such as bacteria and red blood cells, contain numerous antigenic determinants.

Although immune responses generally result in elimination of foreign antigens without injury to the host, some antigens, referred to as allergens, may induce a hypersensitivity (allergic) reaction. The word allergy was coined in 1906 by von Pirquet to describe a state of altered reactivity. Today, the term is generally used to describe an acquired hypersensitivity which results in nonspecific damage to host tissue. In other words, allergy is a deleterious by-product of an immune response triggered by a foreign substance (allergen). Also implied is the fact that the allergen is usually innocuous, and its source is the external environment, e.g., pollens.

Occasionally, exposure to certain foreign antigenic determinants results in an unresponsive state referred to as immunological tolerance. Studies suggest that an active immune response mediated by suppressor T-cells may be responsible for this lack of reactivity. While a positive immune response results in elimination

of the foreign substance, a negative response may be required to protect the host from allergic or autoantigenic responses. The balance between positive and negative reactivities determines whether or not an immune response is detectable. Tolerance may also be attained through the elimination of a responsive clone of lymphocytes, i.e., clonal deletion.

IMMUNE RESPONSE

The immune response (Fig. 1.1) is a complex sequence of events in which the host recognizes that foreign molecules are invading the system (afferent arc) and then mobilizes a reaction against them (efferent arc). There are two types of responses which can occur, a nonspecific response and a specific response. The progression of these responses depends on the nature of the antigen and the genetic constitution of the host.

Nonspecific Response

The reticuloendothelial system (RES), a phylogenetically primitive system, mediates the host's nonspecific response. This system requires no prior experience with the foreign material and, therefore, expresses no immunological memory. The cells of the RES, macrophages, monocytes, and granulocytes effect inflammatory responses and the phagocytosis and clearing of foreign particles. Since this is a first encounter, there is no pre-existing antibody to facilitate engulfment of foreign particles. The RES effects removal of particulate substances such as certain bacteria and parasites.

The natural killer (NK) cell system (Fig. 1.2) is a newly described effector of resistance against virus-infected and tumor cells. The cells which mediate this response are marrow-dependent and, although not macrophages, appear to be re-

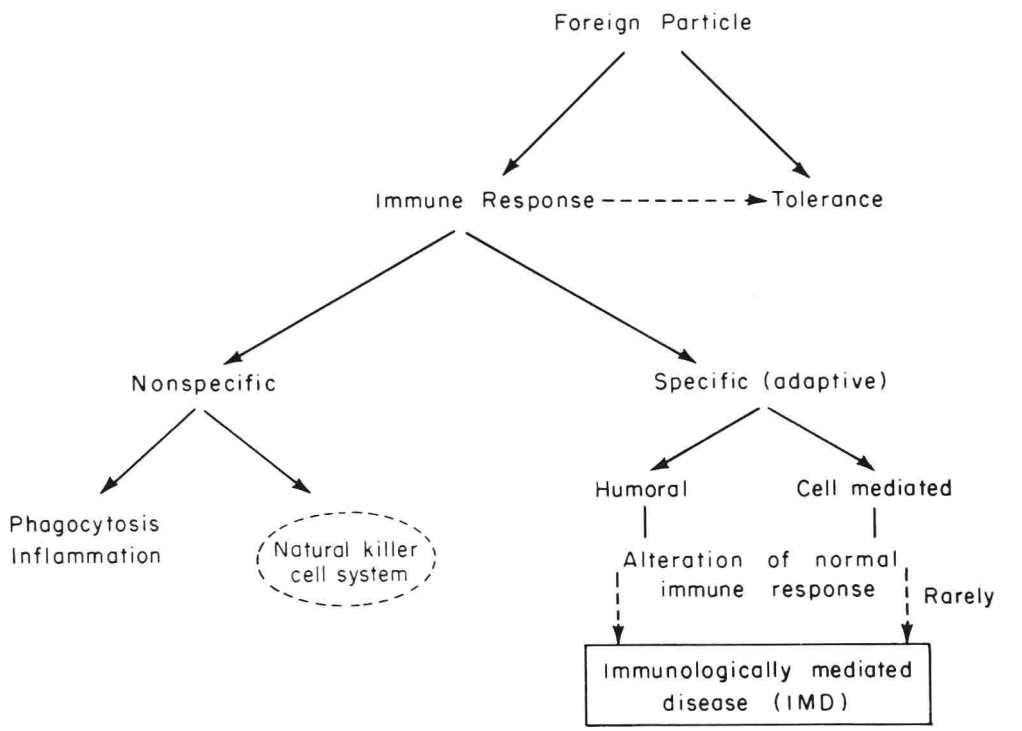

Figure 1.1 Possible reaction to foreign particle. Encounter with a foreign antigen (for example, a virus) could result in unresponsiveness to that antigen (tolerance) but, most likely, it would lead to both a non-specific and a specific (adaptive) immune response. Although the combination of humoral and cell-mediated immune responses would probably clear the antigen, it might persist and its stimulation of the immune response might result in immunologically mediated disease.

lated to the macrophage/neutrophil lineage of cells.

Specific Adaptive Immune Response

During the primary encounter with antigen, macrophages process and present antigen to other cells of the immune system. The latter then mediate the specific or adaptive immune response (Fig. 1.3). This system is phylogenetically more recently developed than nonspecific immunity and also differs in expressing specificity and memory. The two major responses elicited in the adaptive immune response are humoral and cell-mediated immunity. These two responses are primarily mediated by different subpopulations of lymphocytes. The cell-mediated immune response is mediated by thymus-derived cells (T-cells). The humoral immune response is mediated by B-cells (bursa-derived in chickens, or its bone marrow equivalent in humans), but it also requires some T-cell participation.

Recent studies suggest that the macrophage plays a central role in various aspects of the adaptive immune response.[1-3] Macrophages process antigen and present it (in conjunction with cellular determinants) to the appropriate lymphocyte populations and are also capable of modulating these responses by the production and secretion of helper and suppressor factors.

Nonspecific and adaptive immunity are complemented and enhanced by the Biological Amplification System: the coagulation-kinin sequence and the complement cascade. All of these could be included as part of the nonspecific response, while activation of complement by the classical pathway (by antigen-antibody complexes) could be included as part of the adaptive immune response.

HUMORAL IMMUNITY

Three cell populations, macrophages, T-cells, and B-cells, must interact in order for antigen stimulation to result in an antibody response to most naturally occurring antigens (Fig. 1.4). The antigen is processed by the macrophages and then presented as part of its cell surface in association with self-determinants to the lymphoid cells. The presentation of antigen to the B-cells in conjunction with T-cell help (probably by way of a helper factor induced by interaction of helper T-cell with antigen) results in the transformation of B-cells into a large, metaboli-

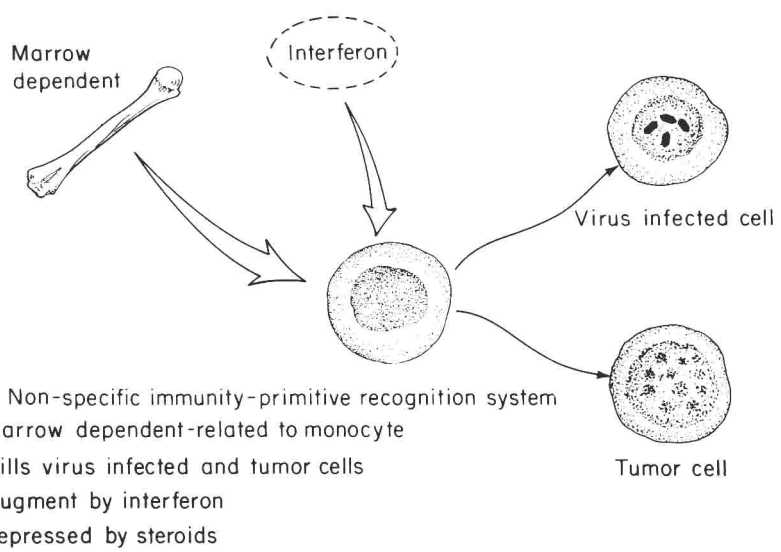

Figure 1.2 Natural killer (NK) cell system. The NK cell system is thought to play an important role in resistance to syngeneic tumors and virus infections. The effector cell is dependent on the bone marrow for maturation and appears to be related to the macrophage/neutrophil lineage. Interferon augments NK cell function and may be required for NK cell activity.

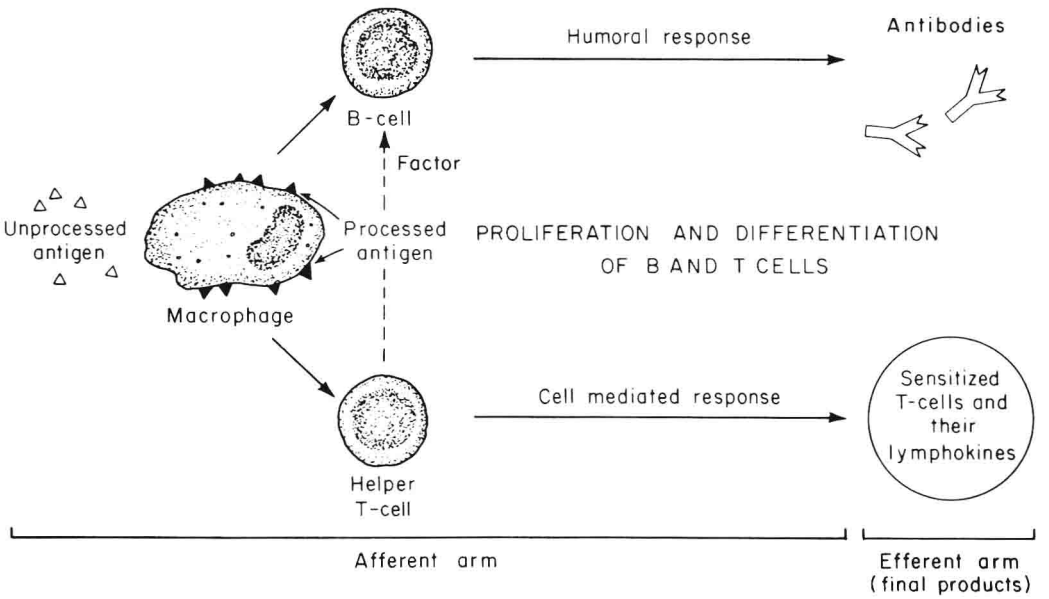

Figure 1.3 Basic organization of adaptive immunity. Macrophages, B-cells, and T-cells interact in the generation of an adaptive immune response. Antigen is processed by the macrophage and presented to the T-cells and B-cells, with the help of a factor made by T-cells, producing antibodies, the effector molecules of the humoral immune response. T-cell subpopulations interact to produce sensitized lymphocytes which effect cell-mediated immunity.

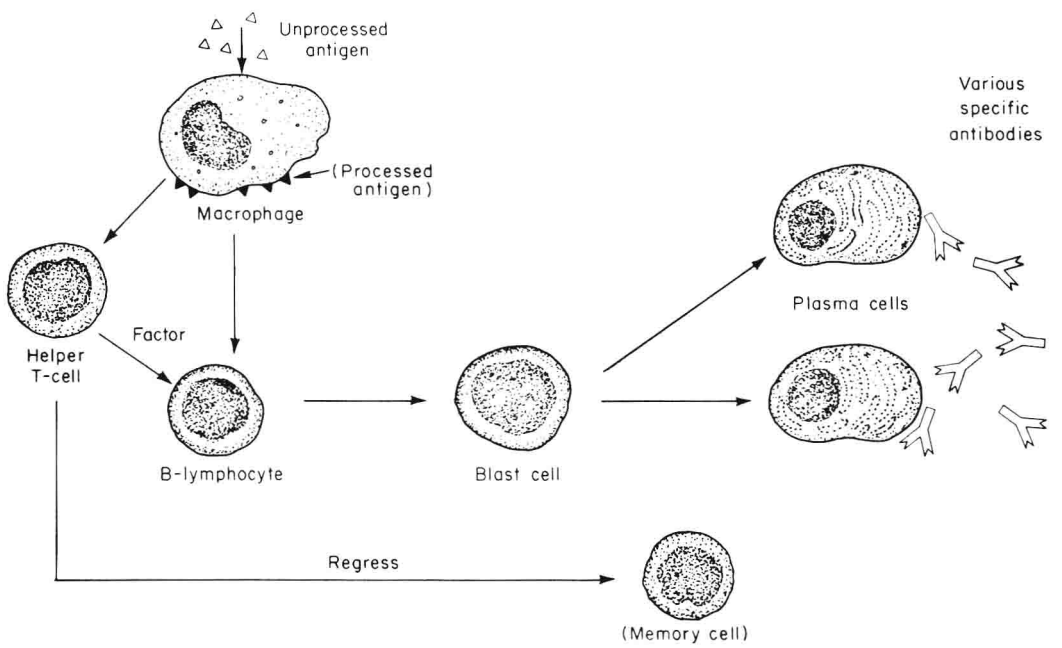

Figure 1.4 Humoral immune response. The humoral immune response requires the presentation of processed antigen by the macrophage to the B-cells. Macrophages present antigen in the context of self antigen to T-cells which then produce a factor which helps B-cells differentiate to produce antibody.

cally active "blast cells," which then differentiate into plasma cells that produce antibody. Burnet's clonal selection theory proposes that antigen reacts with pre-existing receptors on B-lymphocytes, leading to proliferation and activation of those cells.

On first stimulation with antigen, the host produces IgM antibodies while a second exposure to antigen or continued exposure, as in a virus infection, results in an IgG antibody response. The response to a second exposure to antigen, referred to as an anamnestic response, is faster and stronger than the first response. This is a function of memory T-cells. They are a subpopulation of sensitized T-cells which regress to small lymphocytes. These memory cells then proliferate and promote both the strong secondary response and the conversion to IgG production.

The mechanisms which result in the great diversity of specificities of antibody capable of binding with the very large number of different antigenic determinants are being defined at the molecular level. Briefly, this great diversity is generated by the rearrangement of a number of genes which code for the various portions of the immunoglobulin molecules. The choice of the genetic regions (from among many), as well as the way in which they are spliced together, results in the many possible antigen binding sites.

The humoral immune response to certain linear antigens such as pneumococcal polysaccharide and endotoxin is T-cell independent. This response also appears to be independent of macrophage processing and presentation and probably depends on a stimulatory effect of this type of antigen on B-cells.

Antibody: Structure and Function

Antibodies are found in the globulin fraction of the serum and are referred to as immunoglobulins (Ig). The basic Ig molecule is made up of two light polypeptide chains (L) and two heavy chains (H) held together by disulfide bridges (Fig. 1.5).

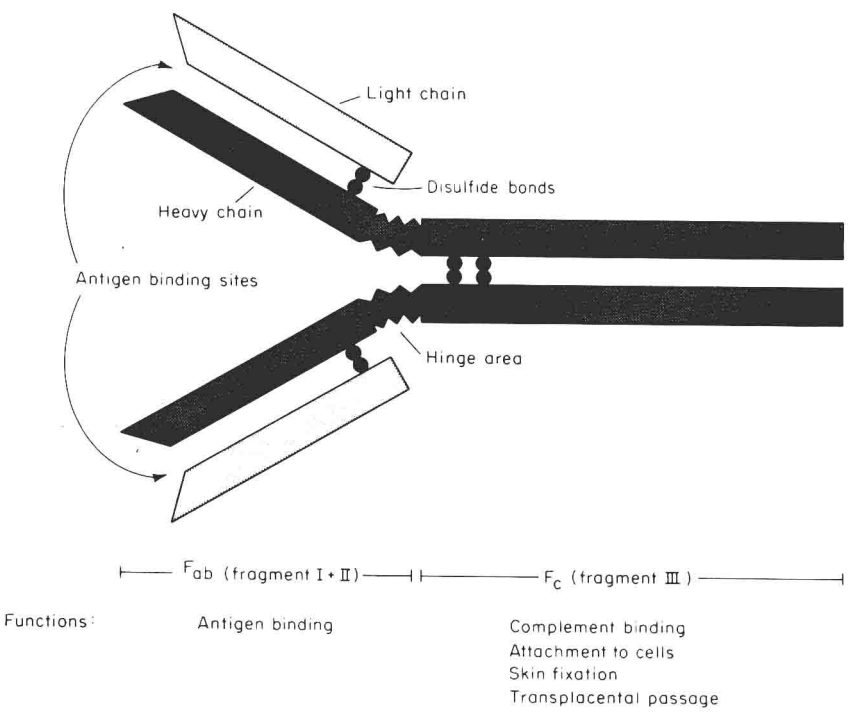

Figure 1.5 Schematic representation of basic antibody molecule consisting of two light chains and two heavy chains held together by disulfide bonds. The two Fab fragments contain the antigen binding sites. The Fc fragment is responsible for binding complement, attaching to cells, fixing to skin, and transplacental passage.

The L-chains for all Ig molecules are of two kinds—lambda and kappa—while the H-chains of each immunoglobulin class are different and determine the Ig class. The basic Ig molecule assumes a Y shape: the upper arms are each composed of an L-chain and part of an H-chain, and the tail is made up of the rest of the two H-chains. The fragments which contain the antibody binding sites (Fab) are in the small arms; each Ig molecule contains two Fabs. The tail, referred to as the Fc portion because it is the crystallizable fragment, is responsible for many of the other properties of the Ig molecules, such as complement activation and binding to phagocytes.

Analysis of the structure of the Fab portion of the Ig molecule indicates that both the L-chain and the H-chain have amino acid sequences which are the same from one molecule to the next (constant regions), while certain sequences are variable. When the Ig molecule folds into its normal three-dimensional configuration, hypervariable segments form the antigen binding site. The variability of amino acid sequences results in variable three-dimensional binding sites which conform to the antigen and thus result in the specificity of the antibody for antigen.

Immunoglobulin G (IgG)

IgG is the most abundant Ig in the serum and the predominant Ig in the eye. It has a molecular weight (M.W.) of 150,000 and is the only Ig to cross the placenta. There are four subclasses of IgG determined by different H-chains. The different H-chains bestow slightly different biological properties to each subclass, e.g., the capacity to bind complement or the ability to block IgE binding.

During a nonspecific response, macrophages and neutrophils phagocytose foreign particles such as bacteria which adhere weakly to nonspecific sites on the surface of the phagocytes. This activity is greatly enhanced during the adaptive immune response due to the cytophilic nature of IgG. The exposed Fab sites of IgG antibodies or opsonins combine with the antigen (bacteria), and the Fc portions of the antibodies adhere to Fc receptors on the surface of phagocytic cells, thereby enhancing phagocytosis. Both opsonization and a second phenomenon, immune adherence, facilitate clearing of antigen by phagocytic cells (Fig. 1.6). Immune adherence results from the activation of complement by the interaction of antigen with IgG or IgM. One complement component bound to the antigen-antibody complexes, C3b, increases binding to phagocytes through their C3b receptors; this results in increased phagocytosis.

Immunoglobulin A (IgA)

IgA is the dominant Ig found in external secretions and is thus referred to as the secretory Ig. It is also found in the serum, where it is the second most abundant Ig. In serum, IgA is present as a monomer of M.W. 160,000, similar to IgG, but in secretions it is found as a dimer linked by a small polypeptide chain and a secretory component (SC). The SC is produced by epithelial cells and is attached to IgA as it is transported across the mucous membrane (Fig. 1.7). The SC appears to protect the IgA molecule from enzymatic degradation and also helps fix it to the mucosa. The lacrimal gland has IgA-producing plasma cells in it, SC-producing epithelial cells in its acini, ducts and tubules, and secretory IgA in the tears bathing its mucosal surface.[4] SC has also been found in conjunctival epithelium.[5] IgA plays an important role in defense against infection of mucous membranes, coating microorganisms to prevent their adherence to mucosal cells. IgA also has the ability to activate complement by the alternative pathway.

Immunoglobulin M (IgM)

IgM (M.W. 900,000) is the largest of the immunoglobulins and is made up of five monomers held together by a small polypeptide and disulfide bridges (Fig. 1.8). On primary exposure to an antigen, IgM antibodies are the first to be made. Biologically, IgM antibodies fix complement and agglutinate particulate antigen with a higher degree of efficiency than do other Ig's.

Immunoglobulin D (IgD)

IgD (M.W. 185,000) is found in very low concentrations in the serum. Because it

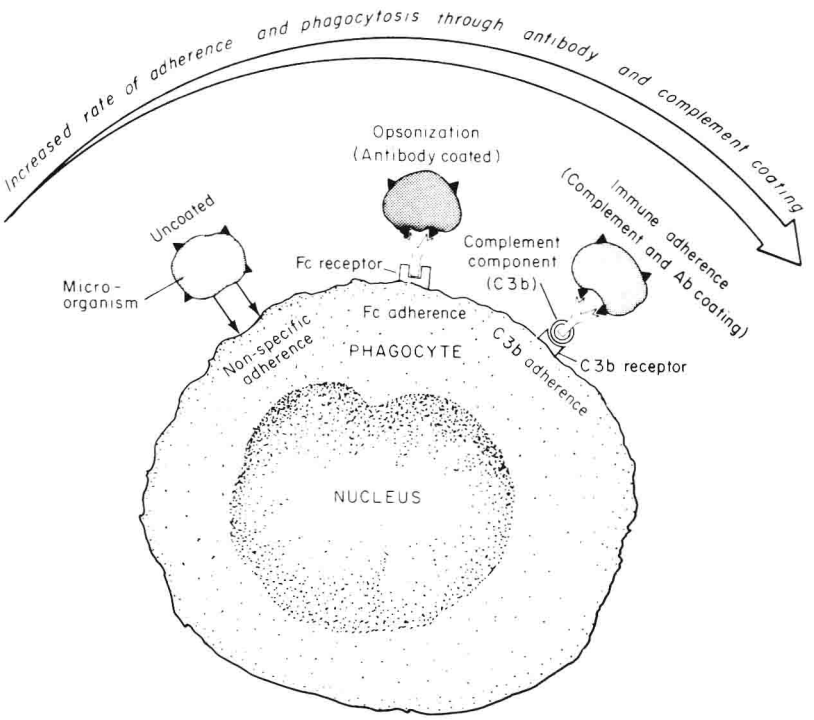

Figure 1.6 Antibody (opsonin) and complement facilitate phagocytosis of particles by enhancing their adherence to phagocytic cells. Immunoglobulin G attaches via an Fc receptor or complement C3b, fixed to an antibody molecule, attaches via the C3 receptor. Opsonization and immune adherence increase phagocytosis.

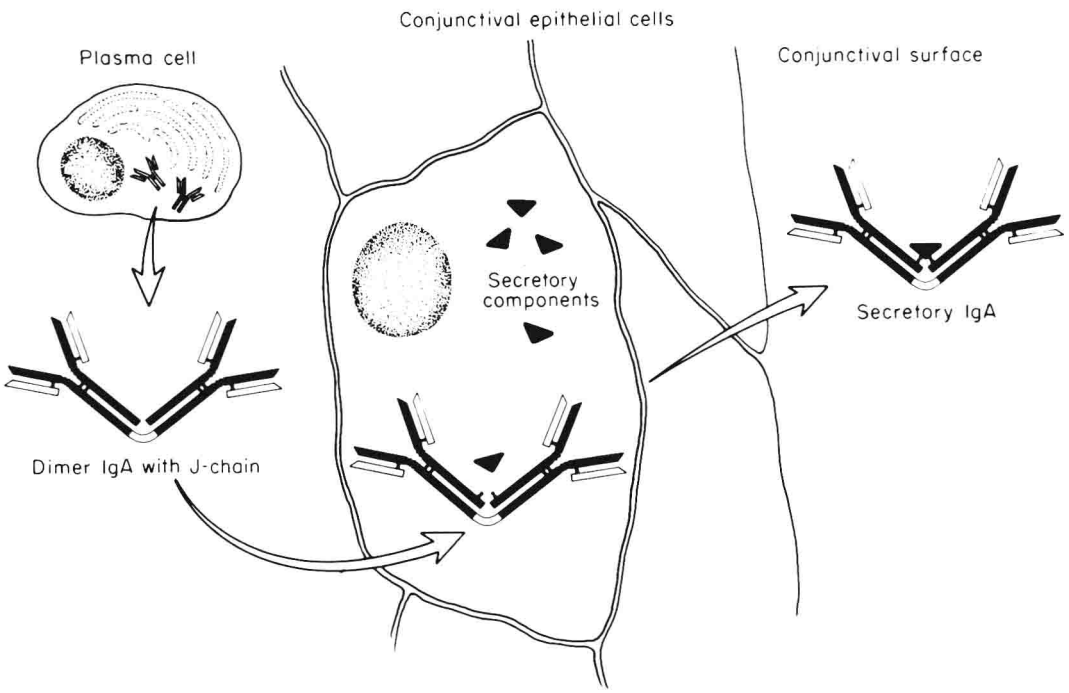

Figure 1.7 The secretory component (SC) is added to the IgA molecule as it is transported across mucous membranes, including the lacrimal gland and conjunctival epithelium.

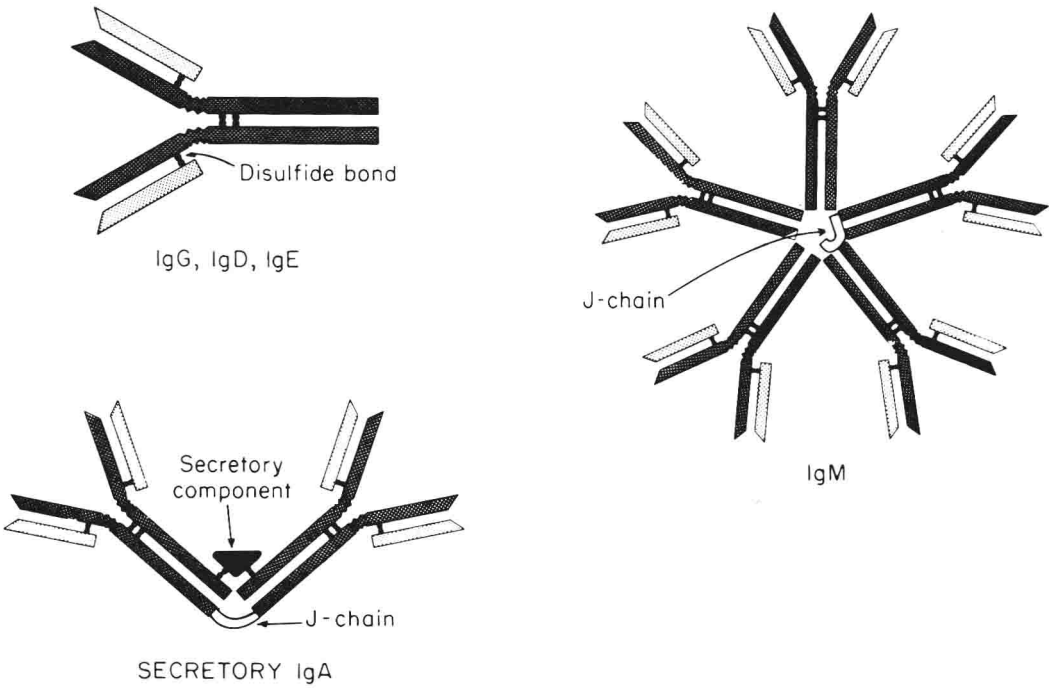

Figure 1.8 IgG, IgD, IgE, and serum IgA are all similar in structure: They are made up of the basic four-chain structure described for IgG. IgA in secretions is a dimer held together by a small J-piece. IgM is a pentamer held together by a J-piece and disulfide bonds.

has been found bound to the membrane of lymphocytes, it is thought that it may serve as a receptor for antigens.

Immunoglobulin E (IgE)

IgE (M.W. 200,000) is present in serum in minute concentrations. Levels of IgE are markedly elevated in patients with atopic allergy. The combination of IgE and allergen, while the IgE is bound to mast cells or basophils, causes degranulation and release of vasoamines which are responsible for allergic reactions (Fig. 1.9). IgE may also play a role in defense against certain parasitic infections.

Immunoglobulins have been found in all structures of the eye except the lens.[6] The highest concentrations were found in the cornea, choroid, and conjunctiva. All five immunoglobulins and albumin were present in the immunoglobulin-containing tissues except for the cornea, which did not routinely contain IgM centrally. Although the concentration of IgG and IgA appears to be uniform throughout the cornea, significantly less IgM is found in the central than in the peripheral cornea, probably because the large size of IgM restricts its diffusion into the cornea from the limbus.[7] Immunoglobulins in the human cornea are probably derived from the limbal vessels. The ocular surface epithelium is usually free of immunoglobulins and albumin.

The immunoglobulin with the highest concentration in tears is IgA followed by IgG.[8] The relative concentration of IgG increases in the tears with inflammation of the external eye probably from transudation of serum proteins from vessels of the external eye.

CELL-MEDIATED IMMUNE RESPONSE

As the name implies, the cell-mediated immune (CMI) response is mediated by cells, not by humoral factors. In experimental animals the capacity to produce a CMI response can be transferred by lymphoid cells, but not by serum. CMI responses are T-cell functions which do not require B-cells or antibody to be expressed (Fig. 1.10).

The CMI response mediates delayed-type hypersensitivity (DTH) reactions,