Uveitis

Pathophysiology and Therapy

edited by
Ellen Kraus-Mackiw
and
G. Richard O'Connor

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with contributions by
William J. Dinning
Henry J. Kaplan
Ellen Kraus-Mackiw
H. Konrad Müller-Hermelink
Wolfgang Müller-Ruchholtz
G. Richard O'Connor
Hans G. Sonntag

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Contributors

William J. Dinning, FRCS, MRCP, DO
Uveitis Clinic
Moorfields Eye Hospital
London, England

Henry J. Kaplan, MD
Professor of Ophthalmology
Department of Ophthalmology
Emory University Clinic
Atlanta, Georgia

Ellen Kraus-Mackiw, MD
Professor of Ophthalmology
Director,
Department of Orthoptics,
Pleoptics, and Motility Disorders
University of Heidelberg
Heidelberg, Germany

H. Konrad Müller-Hermelink, MD
Professor of Pathology
Senior Physician, Institute of Pathology
University of Kiel
Kiel, Germany

Wolfgang Müller-Ruchholtz, MD, DDS
Professor of Immunology and Microbiology
Director, Department of Immunology
University of Kiel
Kiel, Germany

Preface

The world-wide community of ophthalmologists received a remarkable stimulus to analyze and study the causes of uveitis when Woods and Schlaegel published their respective classic monographs entitled "Endogenous Inflammations of the Uveal Tract" and "Essentials of Uveitis" in the 1960's. In the interval between that time and the present, several advances have been made in the fundamental biomedical sciences. In particular, developments that have been made in the field of immunology require the ophthalmologist of the present day to reconsider the pathophysiological processes that may be involved in uveal inflammations, as well as their consequences for therapy, in the light of new discoveries that have come forth in this area.

For the practicing ophthalmologist, as well as for physicians in related areas such as rheumatology and allergy, it is not easy to obtain an appropriate picture of a particular case of uveitis. The large amount of laboratory information that can be obtained on any given patient may indeed be confusing, and there may be considerable overlap in the terminology used by various physicians in their attempts to analyze a particular case.

The major objective of this book is to describe and correlate some of the numerous recent experimental and clinical observations that have been made in the field of uveitis in a practically oriented synopsis. Introductory as well as more highly advanced considerations of uveitis form an immunological, microbiological, and pathological point of view were included in this work in order to facilitate the understanding of pathophysiological relationships that exist in this group of diseases. In this way, we hope to provide the prerequisites for a meaningful utilization of the many diagnostic tests and treatments that are already available today.

We hope that interest will also be aroused in investigating the still unsolved problems concerned with the etiology of noninfectious endogenous and exogenous uveitis. At present we are often obliged to treat cases of unclarified etiology with non-specific anti-inflammatory therapy, aimed only at the immediate relief of the patient's symptoms. In severe, intractable

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uveitis we often resort to the use of cytotoxic substances whose influences on the immune system are not fully understood. Interdisciplinary collaboration among scientists who could contribute to our understanding of these matters is clearly important, and we hope that such collaboration may be stimulated by this book.

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Ellen Kraus-Mackiw
G. Richard O'Connor

G. Richard O'Connor, MD
Professor of Ophthalmology
Director, Francis I. Proctor Foundation
University of California
San Francisco, California

Hans-Günther Sonntag, MD
Professor of Immunology and Microbiology
Director, Institute of Hygiene
University of Heidelberg
Heidelberg, Germany

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1 Fundamentals of Immunology and Their Application to Uveitis

Wolfgang Müller-Ruchholtz

IMMUNOLOGISTS IN OPHTHALMOLOGY

It is always tempting to overestimate the importance of one's own field of interest in medicine. For an immunologist it may be especially tempting to stress the signficance of basic immunology for modern clinical ophthalmology. This line of thinking was reinforced by the recent statement of the US National Advisory Eye Council, "that immunologists should be encouraged to become better acquainted with ocular tissue and systems in order that these researchers may exploit the eye as an immunological model." Indeed, many years of interest have shown to me how fascinating the various immunologic models of the eye can be.

OPHTHALMOLOGISTS IN IMMUNOLOGY

Ophthalmologists should be encouraged to become better acquainted with the fundamentals of immunology in order to bridge the present gap between the knowledge thus far accumulated in this burgeoning science and its practical, clinical applications. Some understanding of immunobiologic mechanisms can enhance the ophthalmologist's appreciation of ocular pathophysiology and give him a more enlightened approach to treatment.

The foregoing is especially true for uveitis because the uveal tract, by virtue of its composition and function, is highly susceptible to inflammation. This inflammation is a result of interactions between endogenous (such as tissue-specific) or exogenous (such as microbial) antigens and immune effectors (such as antibodies or sensitized lymphocytes) in a variety of immune mechanisms.

INTERDISCIPLINARY NETWORK

Undoubtedly the fundamentals of immunology are closely related to all of the subsequent chapters in this monograph.

Microbiologic perspectives, as outlined basically by Sonntag and detailed clinically by O'Connor, are more readily understood when one considers that the interactions between the invading microorganism and the immune system, which are absolutely necessary for the protection of life, are also capable of progressive tissue destruction and even deadly immunopathologic consequences.

According to prevailing opinion, noninfectious uveitis often originates in immune (autoimmune) pathogenetic processes. However, as will be discussed in some detail, most immunologic processes are secondary, though important, events that determine progression and perpetuation. This topic is discussed at length in the chapters by O'Connor and Kraus-Mackiw.

Many therapeutic strategies aim at, or sometimes inadvertently imply, alterations of immunologic responsiveness. Immunosuppression, if effective, yields an at least locally immunocompromised host, with the consequence of potential pathogenicity of otherwise opportunistic microorganisms. Furthermore, we are just beginning to understand when and how so-called established immunosuppressive drugs may act as immunomodulators with immunostimulating potentials.

With regard to future trends it may simply be stated that the old saying that nothing is more practical than the right theory will also hold for uveitis and its immunophysiologic/pathologic mechanisms—as far as they can be demonstrated.

The following brief presentation can only represent a simplified view of the present state of the art.

GENERAL IMMUNOBIOLOGY

Definition of the immune system

This system serves the vital maintenance of biologic integrity and individuality of the most differentiated macroorganisms in evolution, i.e., vertebrates, especially birds and mammals. It does so by reacting against structures (*antigenic determinants*) that are recognized as *foreign*. A complex cellular network undergoes a series of interactions leading to a new state of equilibrium, functionally described either as *sensitization* (i.e., increased state of reactivity) or as *immunotolerance* (i.e., reduced/abolished reactivity against the antigen in question).

The alterations of the state of reactivity may be characterized by three features: They are (1) acquired by contact; (2) deal specifically with a certain

antigen; and (3) are expressed by certain *lymphocyte* subsets and by humoral *antibodies* (their presence or absence).

The *morphologic substrate* of this functional system is widely distributed in the organism: bone marrow, thymus, Peyer's patches, spleen, lymph nodes, recirculating lymphocytes, and secondarily tissue-tropic lymphocytes (as can be found in uveitis).

Antigens

Structures that initiate the aforementioned interactions are mostly of exogenous origin (mainly invading microorganisms), but may also be endogenous (autoantigens). Smaller molecules, such as many drugs that are in the order of several hundred daltons, may be unable to elicit an immune response unless coupled to a larger carrier molecule; they are designated as *haptens* and are capable of reacting *per se* with antibodies once these have been formed.

The *chemical composition* of antigens may vary greatly, from the most common natural substances (i.e., proteins and polysaccharides) to synthetic compounds (e.g., PVP). A few substances are not antigenic, e.g., pure lipids. The size of an individual antigenic determinant has been found in well-studied polypeptides or polysaccharides to be as small as 3 to 6 amino acid or sugar sequences. Thus, larger molecules and, to a greater extent, molecular compounds, such as cell surfaces, exhibit many different antigenic determinants (show *polyspecificity*), each in multitude (polyvalency) (Fig. 1-1).

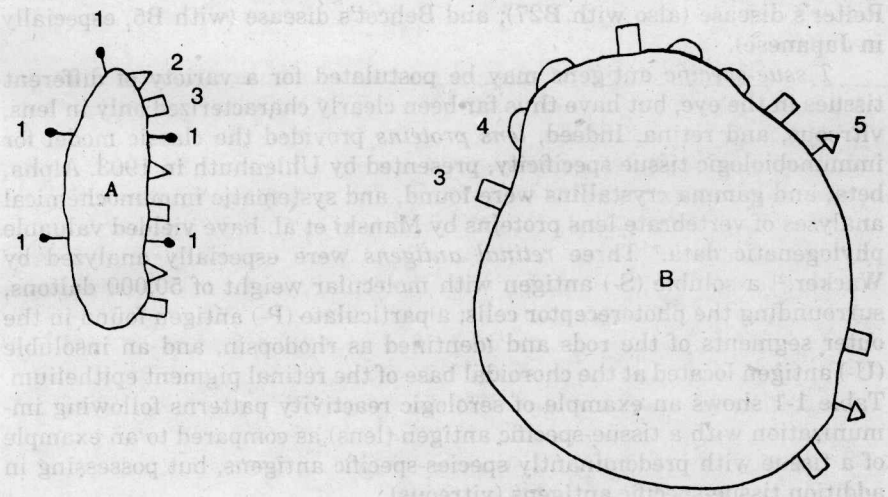

Figure 1-1 Schematic demonstration of polyvalency, polyspecificity, and sharing of antigenic determinants (structural component No. 3 is common to structural compositions A and B).

Nature's economy and its evolutionary traits are reflected in the appearance of certain antigenic determinants in many different combinations. Different cells within an individual share antigens (*individual-specific antigens,* such as HLA, the so-called *h*uman *l*eukocyte *a*ntigens, which represent the major histocompatibility antigens). Also, a certain type of cell or tissue may express *tissue-specific antigens,* which are common to these cells even across species barriers. Furthermore, seemingly arbitrary distributions again and again provide surprises, an old example being the appearance of blood group substances A and B on bacterial cell surfaces (e.g., on *E. coli*). This sharing of the same or a similar structural component makes it possible to explain the many so often misinterpreted immunologic *cross-reactions* without violating the dogma of specificity of immunologic reactions (see Fig. 1-1).

HLA structures are determined by the most polymorphic cell surface structure-encoding genetic system known in man, the MHC (major histocompatibility complex) region of chrosome VI. Their biologic role certainly does not consist in hampering man-made tissue transplantation (e.g., cornea), but rather in regulating cell-cell interactions and controlling immune responsiveness to a variety of foreign structures. The main interest of the clinician in HLA is based on the *association of HLA types with the genetic predisposition to a number of diseases* featuring (1) unknown etiology, (2) the tendency to chronicity, and often (3) correlation with immunologic abnormalities. These associations are still poorly understood, but are expected to increase in diagnostic and prognostic value for an increasing number of diseases within the near future. In this chapter we shall restrict ourselves to mentioning some uveitis-associated diseases: ankylosing spondylitis (associated with HLA-B27, especially in Caucasians, less often in Blacks); Reiter's disease (also with B27); and Behcet's disease (with B5, especially in Japanese).

Tissue-specific antigens may be postulated for a variety of different tissues in the eye, but have thus far been clearly characterized only in lens, vitreous, and retina. Indeed, *lens proteins* provided the classic model for immunobiologic tissue specificity, presented by Uhlenhuth in 1903. Alpha, beta, and gamma crystallins were found, and systematic immunochemical analyses of vertebrate lens proteins by Manski et al. have yielded valuable phylogenetic data.[7] Three *retinal antigens* were especially analyzed by Wacker:[21] a soluble (S-) antigen with molecular weight of 50,000 daltons, surrounding the photoreceptor cells; a particulate (P-) antigen found in the outer segments of the rods and identified as rhodopsin, and an insoluble (U-) antigen located at the choroidal base of the retinal pigment epithelium. Table 1-1 shows an example of serologic reactivity patterns following immunization with a tissue-specific antigen (lens) as compared to an example of a tissue with predominantly species-specific antigens, but possessing in addition tissue-specific antigens (vitreous).

The in-vivo *immunobiologic relevance* of an antigenic determinant is governed mainly by two factors: its accessibility and its immunogenicity.

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TABLE 1-1 Serologic Reactivity Patterns of Rabbit Antisera Produced by Immunization with Bovine Lens or Vitreous

Entirely Tissue-Specific Reactions Following Immunization with Lens

Species Tested	Tissue Tested		
	Lens	Vitreous	Other Tissues
Cattle	+ + +	–	–
Rat	+ +	–	–
Man	+ +	–	–
Antibody-prod. rabbit	+	–	–

Predominantly Species-Specific Reactions Following Immunization with Vitreous

Antiserum	Species Tested	Tissue Tested		
		Vitreous	Kidney	Liver
Native	Cattle	+ + +	+ +	+ +
	Rat	–	–	–
	Man	–	–	–
Absorbed	Cattle	(+)	–	–

The requirement of *accessibility* holds at various levels: (1) At the *molecular level,* it is easily understandable that only the exposed end and side chains can be recognized, i.e., become capable of inducing an immune reaction and acting as a target once reactivity has been elicited. (2) At the *cellular level,* as should be clear from the foregoing, only surface structures are accessible, unless a cell has been damaged in some manner. Though easily understandable, this feature must be stressed, because it is overlooked repeatedly. (3) At the *histologic level,* much discussion has arisen about the so-called immunologically *privileged site,* especially in the eye, i.e., cornea and anterior chamber. The best controlled studies on the *cornea* were performed by Gronemeyer,[4] who allografted corneas between inbred rats: He showed that "immunologic privilege" is by no means an all-or-none phenomenon, but depends on grade of donor/recipient histoincompatibility, grade of recipient presensitization, temporary protection against the inflammatory response to the grafting procedure, and especially the distance between graft and limbal vascular network. With regard to the anterior chamber and alien tissues, Kaplan has shown that the size of the graft, its histologic nature, and—if it is an endocrine tissue—the endocrine status of the host are also restrictive factors that appear to determine the type of response.[5] Under these circumstances antibody-mediated immunity is promoted, whereas cell-mediated responsiveness is at least transiently suppressed.

The latter remark also applies to *immunogenicity,* which is determined by several features. Among others, the extent of *structural foreignness,* the *physical state* (particulate vs. soluble), the so-called *antigenic competition* with concomitantly exposed structures, and the provision of additional functional signals (initiating adequate antigen processing) may be mentioned. The metabolic activity of various cells has long been known to provide a *second (non-specific) signal* for eliciting immune responses against the surface antigens of a foreign cell. And the so-called *adjuvants* (be they lipopolysac-

charides from gram-negative rods or the mycobacterial cell wall substances of Freund's adjuvants) make it possible to initiate or intensify an immune response to the admixed antigens, in essence, via signal effects.

Sensitization

The present views of cellular network interactions are of still growing complexity and are overlaid with much confusion. In earlier times everything appeared to be much simpler: The second half of the last century was dominated by Metchnikof's view that immunity to microorganisms was effected by cells, named macrophages and microphages (now called granulocytes). Several years later, the opposing view of v.Behring and Pfeiffer—that humoral antibodies played a decisive role—was generally adopted. Not until 1942 was the important role played by immunocytes (cell-mediated immunity) discovered by Landsteiner and Chase. In the 1960s the importance of distinguishing B lymphocytes (which differentiate into antibody-secreting plasma cells) from T lymphocytes was realized. Since then, the T subset family has seemed to grow steadily. Thus, only a general, simplified view may be given here, as schematically outlined in Figure 1-2.

Much has been learned from the "mouse immunology," i.e., analytic studies in experimental models, largely with the many different mouse inbred strains. In spite of several objections, mainly from human pathologists, it may be said that in functional immunobiologic terms, all mammals have been proven to be remarkably similar.

Pluripotent *hemopoietic stem cells* have self renewal potential and give rise to various differentiation lineages, such as *lymphoid precursors,* which differentiate further along two pathways into B or T lymphocytes. *B lymphocytes* start to synthesize immunoglobulins (Ig) in their cytoplasm. Their next differentiation state is indicated by the demonstrability of Ig of certain classes (q.v.) as cell surface components. Finally, plasma cells secrete Ig into the humoral phase. Among additional *B lymphocyte surface markers* are F_c (antibody) and C3 (complement) receptors and various mitogen receptors.

T lymphocytes require the thymus for their normal pathway of timely maturation. They may be functionally classified into two groups: *T effector cells,* effecting cell-mediated immunity after adequate antigen-induced proliferation and further differentiation, and *T regulator cells.* The latter are responsible for *stimulation (help) and suppression* of B- and T-determined responsiveness and therefore appear to play a central role in the immunoregulatory network. This holds especially for *antigen-specific response regulation* and is, at least in part, effected by T_H or T_S-cell-released *immunoregulatory molecules.* In addition, however, nonspecific help or suppression is observed (and unfortunately contributes to the confusion). It should be pointed out that these interrelations imply T cell dependency of most, though not all, B cell and antibody responses (to "*T-dependent antigens*").

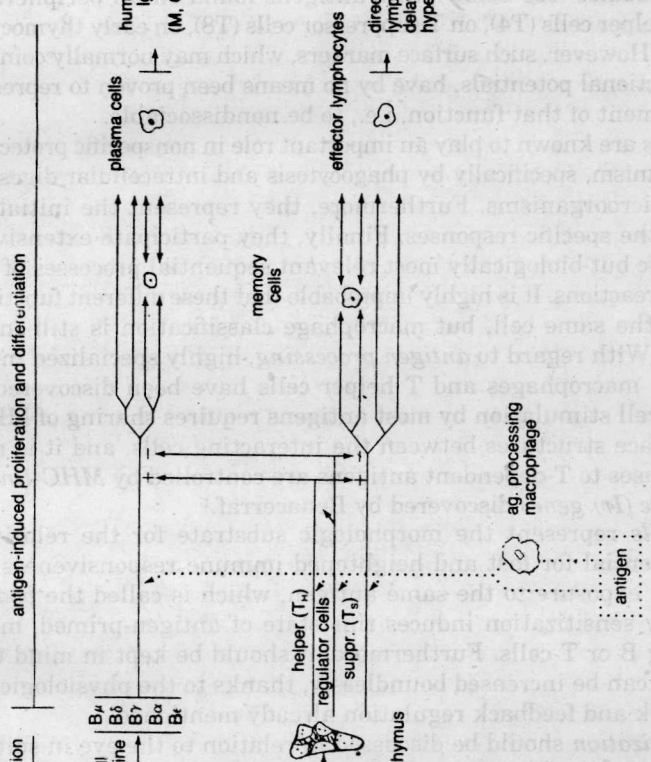

Figure 1-2 Simplified schematic outline of cell maturation, interaction, and differentiation in sensitization.

Because of this remarkable and important variety of T cell functions, it has been of interest to learn of *T-cell markers* which allow their identification and quantification also in man. A sheep erythrocyte receptor (allowing rosette formation of human T cells with sheep erythrocytes), T-specific mitogen responsiveness (e.g., with concanavallin A), and *T-specific cell surface antigens* have been found. The latter have recently been classified, with the help of monoclonal antibodies (see below), into antigens found on all peripheral T cells (T3), on T helper cells (T4), on T suppressor cells (T8), on early thymocytes (T10), and so on. However, such surface markers, which may normally coincide with certain functional potentials, have by no means been proven to represent a structural element of that function, i.e., to be nondissociable.

Macrophages are known to play an important role in nonspecific protection of the macroorganism, specifically by phagocytosis and intracellular digestion of pathogenic microorganisms. Furthermore, they represent the initiatory cell for most of the specific responses. Finally, they participate extensively in the nonspecific but biologically most relevant sequential processes of the specific immune reactions. It is highly improbable that these different functions are effected by the same cell, but macrophage classification is still in its very beginning. With regard to *antigen processing,* highly specialized interactions between macrophages and T helper cells have been discovered in recent years. T-cell stimulation by most antigens requires sharing of MHC-determined surface structures between the interacting cells, and it is now clear that responses to T-dependent antigens are controlled by *MHC-linked immune response (Ir) genes* discovered by Benacerraf.[1]

Memory cells represent the morphologic substrate for the relatively long-lasting potential for fast and heightened immune responsiveness following repeated exposure to the same antigen, which is called the *booster effect.* Not every sensitization induces this state of antigen-primed, metabolically resting B or T cells. Furthermore, it should be kept in mind that no sensitization can be increased boundlessly, thanks to the physiologically required network and feedback regulation already mentioned.

Local sensitization should be discussed in relation to the eye in spite of the general statement that sensitization is not a localized event. With reference to the mucosae, the so-called *secretory immune system* may be mentioned. The principal immunoglobulin is *IgA*, produced locally by plasma cells whose precursors have originated elsewhere (in Peyer's patches?) and have migrated to the given location via the vascular system. It represents a first line of defense against invasion and colonization of potential pathogens and a barrier against penetration of the eye's *mucosal surfaces* by foreign substances.

Intraocular sensitization, as a local event, appears feasible on cytologic grounds since macrophages, lymphocytes, and plasma cells can be found in the interstitial tissue of the uveal tract. This may allow local antibody formation and cell-mediated immunity independent of pre-organized lymphoid tissue. The latter, being the usual end of the afferent limb of sensitization, is represented by the spleen for the anterior region of the eye (because of

drainage through Schlemm's canal) and by the local lymph nodes draining the orbits for the posterior region (because of recently described bulk flow passing through the sclera). However, relevant immunomorphologic studies are still lacking.

Primarily *nonspecific inflammatory processes*, be they of traumatic, toxic, microbial, or other origin, may well allow the homing of additionally *immigrating* specifically reactive lymphocytes of other origin. Silverstein has provided impressive evidence for three ensuing events:[17] (1) Establishment of long-lasting *local immunologic memory*, leading to uveitis in an eye, into which an antigen had been introduced many months before, after intravitreal reintroduction of small amounts of the same antigen, but not in the other eye. (2) Appearance of similar uveitis following *systemic* (e.g., intravenous) *readministration* of the antigen. (3) Appearance of cells forming antibodies against a variety of antigens that the animal had been exposed to, but that had not entered the eye—obviously as a consequence of nonspecific chemotactic inflammatory processes.

Local antibody production in the eye has been studied most convincingly by Witmer and Martenet in their extensive measurements of the ratio of aqueous humor activity to serum antibody activity.[24] They have shown a ratio equal to or higher than 1.0 in a large number of paired aqueous humor and serum antibody tests, dealing with uveitis patients with tuberculosis, streptococcal diseases, toxoplasmosis, viral diseases, and lens-induced uveitis.

Cell-mediated immunity (CMI)

T effector lymphocytes, as mentioned previously and schematically outlined in Figure 1-1, represent CMI *sensu stricto*. An *antigen-combining cell surface structure* enables them to interact as specifically with an antigenic determinant as an immunoglobulin does. This structure appears to be related to the combining site of antibodies (q.v.) or, more precisely, to its *H chain variable region* (V_H). However, it is still unclear whether the same set of V_H genes determines both the T and the B cell (product) antigen combining site.

A number of effects are to be distinguished (Fig. 1-3), but it is still unknown to what extent they are effected by different T effector cell subsets. These effects are discussed below.

1. *Direct cytotoxicity* is expressed by destruction of cells with foreign cell surface antigens as a consequence of direct cell contact without complement being required. This *T killer cell effect* is currently studied in vitro by quantifying the destruction of cell monolayers following the addition of lymphocytes or by measuring the release of ^{51}Cr from ^{51}Cr-labeled target cells.

2. *Release of lymphokines.* A number of soluble factors are released which are, thus far, mainly characterized by mediator functions. They may be looked at as the connecting link between antigen-specific CMI, as an initiating event, and a large variety of nonspecific sequences, influencing

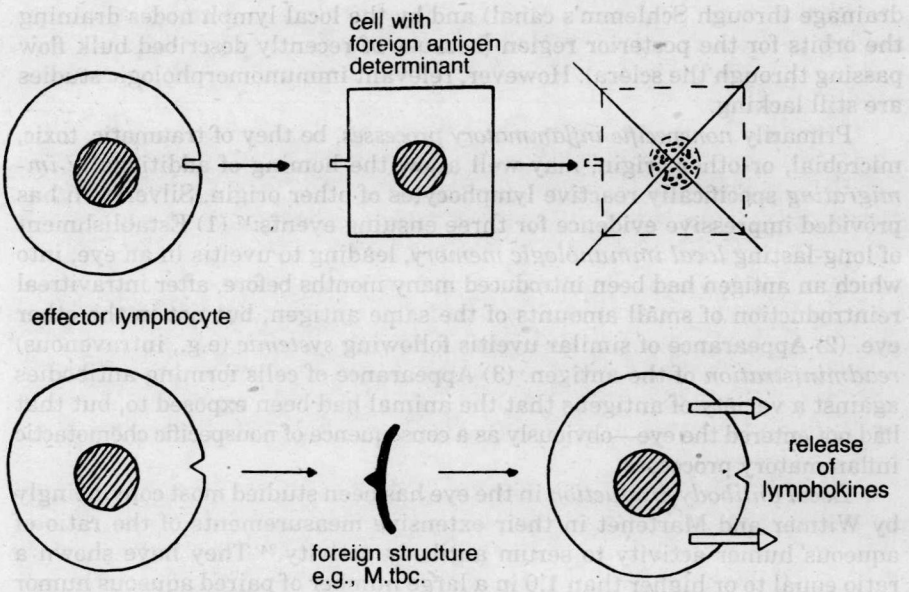

Figure 1-3 T effector lymphocytes and their reactivity.

the activity of macrophages (e.g., migration inhibitory, MIF; macrophage metabolism-activating, MAF), neutrophilic leukocytes (e.g., chemotactic factor), basophils, eosinophils and other cells. Among the other biologically active molecules, immune interferon must be mentioned.

3. *Delayed hypersensitivity* has been discussed as being effected by a specialized T cell subset, T_{DH}. However, the effects are classically described at the histologic rather than the cellular level: perivascular cuffing with lymphocytes, followed by a granulomatous response consisting of a nidus of macrophages, many of them swollen by ingested antigenic material and designated epithelioid cells, surrounded by lymphocytes. This appearance may well be understood as the in vivo histologic expression of a poorly defined sum of those mediator functions analyzed in vitro (already discussed), which are of biologic relevance. A more detailed discussion appears in the section entitled Allergic Mechanism IV.

Two additional types of cells may be mentioned briefly here, though they are clearly not capable of antigen-specific (i.e., immune) reactions in the proper sense.

One type has been named *K (killer) cell* because it is responsible for an *antibody-dependent cellular cytotoxicity* effect. These cells, which are possibly lymphoid, but not B or T cells, express complement receptors and receptors for the Fc of IgG on their surfaces. Therefore, they are capable of binding

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