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Ocular Mucosal Immunity

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I. INTRODUCTION

The secretory immune system of the eye defends the ocular surface against antigenic challenge (Franklin, 1989; Friedman, 1990; Sullivan, 1990). This immunological role is mediated primarily through secretory IgA (SIgA) antibodies, which are known to inhibit viral adhesion and internalization; prevent bacterial attachment, colonization, and activity; interfere with parasitic infestation; and reduce antigen-related damage in mucosal sites (Underdown and Schiff, 1986; Brandtzaeg, 1985; Mestecky, 1987; Mestecky and McGhee, 1987; Brown and Kloppel, 1989; Childers *et al.*, 1989; McGhee *et al.*, 1989; MacDonald *et al.*, 1990). Thus, the ocular secretory immune system appears to protect the eye against allergic, inflammatory, and infectious disease, thereby promoting conjunctival and corneal integrity and preserving visual acuity.

This chapter reviews the immunological architecture and regulation of the secretory immune system of the eye, and explores the impact of ocular infection and autoimmune disease on the structure and function of this system. For information on nonmucosal aspects of ocular immunity, for example, anterior chamber-associated immune deviation and retinal immunology, the reader is referred to several excellent reports (Gery *et al.*, 1986; Streilein, 1987; Usui *et al.*, 1990).

II. ARCHITECTURE OF THE SECRETORY IMMUNE SYSTEM OF THE EYE

A. Tissues Involved in Ocular Mucosal Immunity

The principal tissues involved in immunological protection of the ocular surface are the lacrimal gland and the conjunctiva. The lacrimal gland, which serves as the predominant source of tear SIgA antibodies (Sullivan and Allansmith, 1984; Peppard and Montgomery, 1987), is the primary effector tissue in the secretory immune defense of the eye (Franklin, 1989; Friedman, 1990; Sullivan, 1990). This gland contains a diverse array of lymphocytes, including plasma cells, T cells, B cells, dendritic cells, and macrophages (Table I; Figure 1). In humans, plasma cells represent the most numerous lymphocytic population, accounting for more than 50% of all mononuclear cells in lacrimal tissue (Weiczorek *et al.*, 1988). The vast majority of these plasma cells are IgA positive (Franklin *et al.*, 1973; Allansmith *et al.*, 1976a,1985; Brandtzaeg *et al.*, 1979,1987; Gillette *et al.*, 1980; Crago *et al.*, 1984; Damato *et al.*, 1984; Brandtzaeg, 1985; Kett *et al.*, 1986; Weiczorek *et al.*, 1988) and express an IgA1/IgA2 subclass distribution that is either different from (Kett *et al.*, 1986) or similar to (Crago *et al.*, 1984; Allansmith *et al.*, 1985) that of other mucosal tissues. In addition, a high percentage of lacrimal IgA plasma cells, which are located in the gland's interstitium, synthesizes both J chain and polymeric IgA (pIgA; Brandtzaeg, 1985) that may bind secretory component (SC; Brandtzaeg, 1983). These cells are complemented by limited numbers of IgG, IgM, IgE, and IgD plasma cells (Franklin *et al.*, 1973; Allansmith *et al.*, 1976; Brandtzaeg *et al.*, 1979,1987; Gillete *et al.*, 1980; Damato *et al.*, 1984; Wieczorek *et al.*, 1988), although the IgD-containing subset may increase during IgA deficiency (Brandtzaeg *et al.*, 1979). The second most frequent lymphocyte population in human lacrimal tissue consists of T cells, which are situated between acinar and ductal epithelial cells, throughout glandular interstitial regions, and within small periductular lymphoid aggregates (Weiczorek *et al.*, 1988; Pepose *et al.*, 1990). The distribution of T cells appears to vary topographically according to specific subclasses, including suppressor/cytotoxic and helper T cells (Weiczorek *et al.*, 1988; Pepose *et al.*, 1990), and presents with an overall helper : suppressor ratio of approximately 0.56 (Weiczorek *et al.*, 1988). Minor or rare populations of lacrimal lymphocytes include surface Ig-bearing B cells, Langerhans-type dendritic cells, monocyte–macrophages, and activated IL-2^+ T cells, which occur almost exclusively in periductular lymphocyte foci (Weiczorek *et al.*, 1988; Pepose *et al.*, 1990). These latter lymphoid aggregates, when present, typically appear as primary follicles without germinal center formation and, theoreticaly, may be involved in antigen processing (Weiczorek *et al.*, 1988).

The human lacrimal gland also

1. produces lysozyme (Gillette *et al.*, 1980,1981), and SC (Franklin *et al.*, 1973; Allansmith and Gillette, 1980; Gillette *et al.*, 1980), the pIgA antibody receptor (Underdown and Schiff, 1986; Brandtzaeg *et al.*, 1987; Brown and Kloppel, 1989) in acinar and ductal epithelium
2. synthesizes lactoferrin (Gillette and Allansmith, 1980; Gillette *et al.*, 1980) and convertase decay-accelerating factor, which protects against autologous complement activation (Lass *et al.*, 1990), in acinar cells
3. expresses HLA-DR antigens on B cells, dendritic cells,

Table I Lymphocyte Populations Identified in Lacrimal Glands of Various Species

Species	References
Human	
IgA (predominant; both IgA1 and IgA2), IgG, IgM, IgD, and IgE plasma cells Suppressor/cytotoxic (predominant), helper, and activated ($IL2^+$) T cells Surface IgM- (predominant), IgD-, IgG-, or IgA-bearing B cells Macrophages and dendritic cells	Franklin *et al.* (1973); Allansmith *et al.* (1976a,1985); Brandtzaeg *et al.* (1979,1987); Gillette *et al.* (1980); Crago *et al.* (1984); Damato *et al.* (1984); Brandtzaeg (1985); Kett *et al.* (1986); Wieczorek *et al.* (1988)
Rabbit	
IgA (predominant) and IgG plasma cells	Shimada and Silverstein (1974); Franklin *et al.* (1979); Jackson and Mestecky (1981)
Rat	
IgA (predominant), IgG, IgG1, IgG2a, IgG2b, IgG2c, and IgM plasma cells Immature, suppressor/cytotoxic, and helper T cells Surface IgM-, IgA-, and IgG-bearing B cells Macrophages and mast cells (rare)	Gudmundsson *et al.* (1984,1985a,1988); Sullivan *et al.* (1986,1990a, 1990/91); Allansmith *et al.* (1987); Hann *et al.* (1988); Pappo *et al.* (1988); Montgomery *et al.* (1989,1990); Sullivan and Hann (1989a)
Mouse	
IgA (predominant), IgG, and IgM plasma cells Surface IgA-, IgG-, or IgM-bearing B cells	McGee and Franklin (1984); Montgomery *et al.* (1985)

ductule epithelium (Weiczorek *et al.*, 1988) and certain acini (Mircheff *et al.*, 1991)

4. contains lymphatic channels that drain into local cervical and preauricular lymph nodes (Iwamoto and Jakobiec, 1989)

With respect to human accessory lacrimal tissue, its immunological characteristics appear to be identical to those of the major lacrimal gland (Gillette *et al.*, 1980,1981; Sacks *et al.*, 1986).

Lacrimal tissues of rats, rabbits, cows, and mice also seem to share the immune features of the human gland (Table I). Thus, rat lacrimal glands contain a pronounced population of IgA plasma cells (Gudmundsson *et al.*, 1985a; Sullivan *et al.*, 1986,1990a,1990/91; Allansmith *et al.*, 1987; Hann *et al.*, 1988; Sullivan and Hann, 1989), which undergo a striking age-related increase in density from infancy to adulthood (Hann *et al.*, 1988; Sullivan *et al.*, 1990a). These cells are accompanied by IgG and IgM plasma cells (Gudmundsson *et al.*, 1985a; Allansmith *et al.*, 1987; Hann *et al.*, 1988; Sullivan *et al.*, 1990a), immature suppressor/cytotoxic and helper T cells (Gudmundsson *et al.*, 1988; Pappo *et al.*, 1988; Montgomery *et al.*, 1989,1990), surface Ig-bearing B cells (Pappo *et al.*, 1988; Montgomery *et al.*, 1989,1990) that proliferate in response to mitogen exposure (Pappo *et al.*, 1988), phagocytic macrophages that express Fc receptors and Ia antigens (Pappo *et al.*, 1988), and rare mast cells (Gudmundsson *et al.*, 1984). Moreover, acinar cells from rat lacrimal tissue synthesize and secrete SC (Sullivan *et al.*, 1984b,1990b; Gudmundsson *et al.*, 1985a; Hann *et al.*, 1989, 1991; Kelleher *et al.*, 1991; Lambert *et al.*, 1993) which appears to transport pIgA into tears against an apparent concentration gradient (Allansmith *et al.*, 1987; Sullivan and Allansmith, 1988; Sullivan and Hann, 1989b). Similarly, lacrimal glands of cows (Butler *et al.*, 1972), rabbits (Shimada and Silverstein, 1975; Franklin *et al.*, 1979), and mice (McGee and Franklin, 1984) either produce IgA or harbor plasma cell populations that are predominantly IgA positive and, at least in rabbits, contain acinar and ductal cells that produce SC (Franklin *et al.*, 1979). However, periductular lymphoid aggregates appear to be very uncommon in lacrimal tissues of these species, except under pathological conditions (e.g., autoimmune disorders; Kessler, 1968; Mizejewski, 1978; Hoffman *et al.*, 1984; Jabs *et al.*, 1985; Liu *et al.*, 1987; Jabs and Prendergast, 1988; Ariga *et al.*, 1989; Liu, 1989; Vendramini *et al.*, 1991; Sato *et al.*, 1991).

The primary origin of IgA-containing lymphocytes and T cells in the lacrimal gland remains to be determined, but may, in part, be local cervical (Brandtzaeg *et al.*, 1979; Ebersole *et al.*, 1983), distant peripheral (Montgomery *et al.*, 1985; O'Sullivan and Montgomery, 1990), and gut-associated lymphoid tissue (Montgomery *et al.*, 1983; O'Sullivan and Montgomery, 1990), as well as the thoracic duct (O'Sullivan and Montgomery, 1990), spleen (McGee and Franklin, 1984), and mammary gland (Montgomery *et al.*, 1985). The migration of lymphocytes into the lacrimal gland appears to be random (McGee and Franklin, 1984), yet the selective retention and heterogeneous distribution of IgA-containing cells within lacrimal tissue is not random (Sullivan *et al.*, 1990/91) and may be stimulated by antigenic challenge (Jackson and Mestecky, 1981; Allansmith *et al.*, 1987) and regulated by microenvironmental (Franklin, 1981; Pockley and Montgomery, 1990/91a), endocrine (Sullivan *et al.*, 1986; Hann *et al.*, 1988; Sullivan and Hann, 1989a), neural (Walcott *et al.*, 1986; Franklin *et al.*, 1988,1989; Oeschger *et al.*, 1989; Sullivan *et al.*, 1990/91), T-cell (Franklin *et al.*, 1985; Franklin, 1989; Franklin and Shepard, 1990/91), or acinar epithelial-cell (Franklin *et al.*, 1985) signals. The lymphocytic accumulation

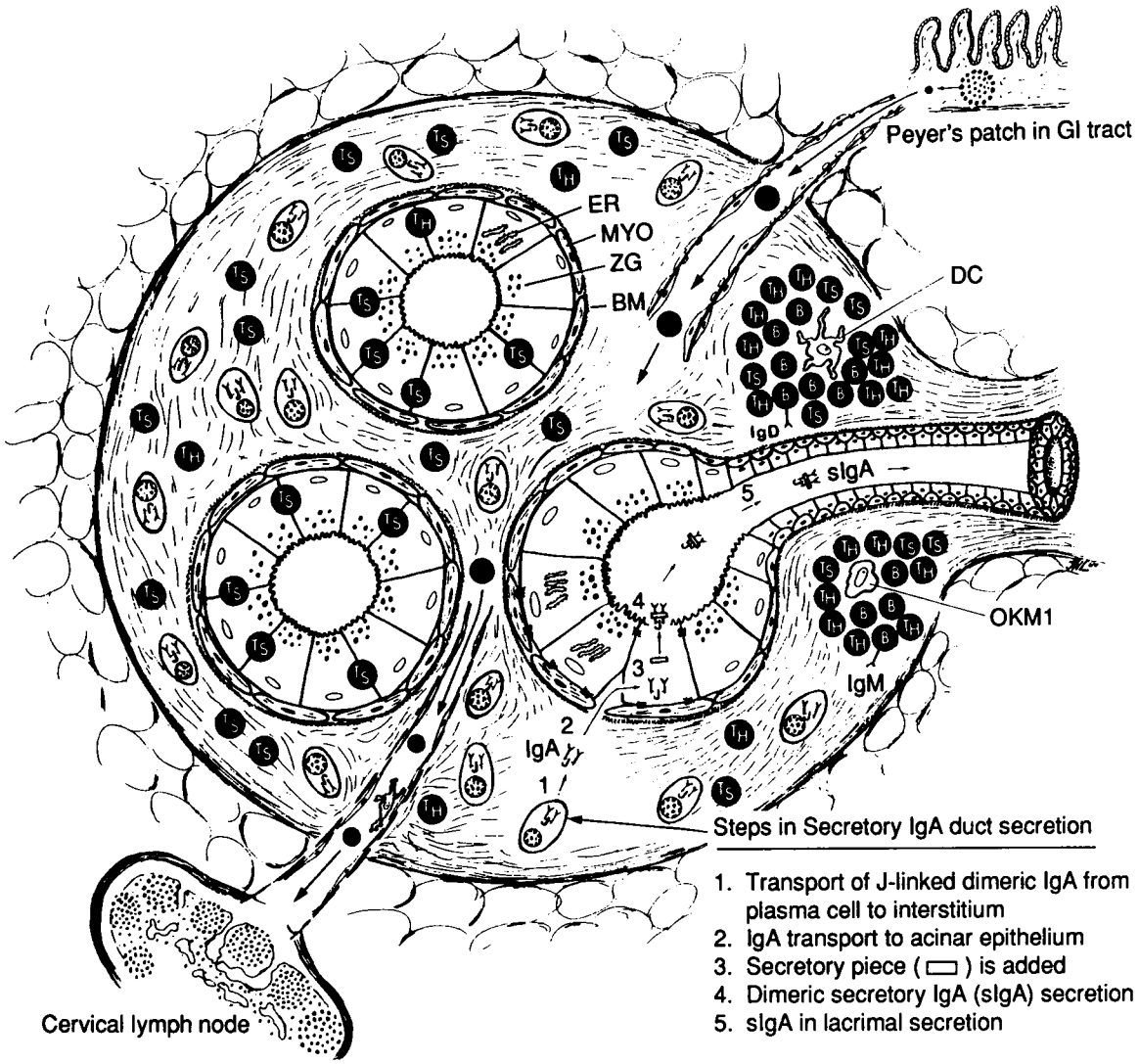

Figure 1 Schematic representation of the secretory immune system of the human lacrimal gland. Topographical features include acinar cells, which contain endoplasmic reticulum (ER) and lysozyme- and lactoferrin-positive zymogen granules (ZG), and synthesize and secrete SC (termed secretory piece); myoepithelial cells, which are adjacent to acinar cells and surrounded by a basement membrane (BM); interstitial plasma cells, which are the primary lymphoid cell and produce principally IgA, but also some IgG, IgM, or IgD; T helper (Th) and suppressor (T_S) cells, which are distributed throughout the interstitium, the intercellular spaces between acinar or ductal cells, and the periductular lymphoid aggregates; B cells (B), $OKT6^+$ Langerhans-type dendritic cells (DC), and $OKM1^+$ monocyte-macrophages, predominantly located in periductular lymphoid aggregates, which most often appear as primary follicles without germinal center formation and may be active in antigen processing; and unlabeled darkened cells, which refer to circulating T or B lymphocytes, which may originate in other mucosal tissues (e.g., intestinal Peyer's patch) and, if not retained locally, possibly exit the lacrimal gland through lymphatic channels to regional cervical ro preauricular lymph nodes. Immunoglobulin A is secreted by plasma cells (1), bound by SC on the acinar cell basolateral membrane (2,3), transported in distinct vesicles (4), and released at the apical surface as SIgA into tear-containing lumina (5). [This figure has been reproduced and published, courtesy of *Ophthalmology* (1988). 95:100–109.]

in, or adherence to, lacrimal tissue appears to require calcium as well as functional oxidative phosphorylation and contractile microfilament systems, and to depend on cell-surface protein and carbohydrate determinants (O'Sullivan and Montgomery, 1990).

In addition to the lacrimal gland, the conjunctiva has been postulated to play an active role in both inductive and effector actions of the ocular secretory immune system (Chandler and Gillette, 1983; Franklin and Remus, 1984; Franklin, 1989; Tagawa *et al.*, 1989; Allansmith and Ross, 1991). In support of this hypothesis, the rabbit conjunctiva contains a substantial number of IgA, and occasional IgG and IgM, plasma cells in the substantia propria and numerous T and B cells in specialized lymphoid follicles (Shimada and Silverstein, 1975;

Franklin *et al.*, 1979; Franklin and Remus, 1984). Moreover, rabbit conjunctival B cells may be induced to differentiate into IgA-positive cells by mitogen stimulation (Franklin and Remus, 1984) and the rabbit conjunctival epithelium produces SC (Franklin *et al.*, 1979; Liu *et al.*, 1981). Since investigators also have reported the presence of plasma cells (Allansmith *et al.*, 1976a; Bhan *et al.*, 1982; Tagawa *et al.*, 1989); T cells (Bhan *et al.*, 1982; Sacks *et al.*, 1986; Tagawa *et al.*, 1989); HLA-DR-positive epithelial, stromal (Lee *et al.*, 1990/91), and Langerhans cells; interdigitating dendritic cells; macrophages; neutrophils (Sacks *et al.*, 1986); mast cells (Allensmith *et al.*, 1978a; Allansmith and Ross, 1991); and lymphatic channels (Srinivasan *et al.*, 1990) in human conjunctival tissue, these findings might indicate that the conjunctiva is involved in antigen processing, lymphocyte migration, and ocular secretory immune defense (Chandler and Gillette, 1983). However, this conclusion is somewhat controversial and perhaps not entirely correct.

1. The evidence for plasma cell existence in normal human conjunctiva appears tenuous: plasma cell identification by light microscopy could not be verified by immunofluorescent staining for cell-associated IgA, IgG, IgM, IgD, or IgE (Allensmith *et al.*, 1976b) and plasma cell enumeration in another study was performed with an antibody that cross-reacted with T cells (Bhan *et al.*, 1982). In contrast, more recent investigations have demonstrated a complete absence of plasma cells in conjunctival tissue of humans (Sacks *et al.*, 1986) and rats (Gudmundsson *et al.*, 1985a). Instead, the majority of lymphocytes in human conjunctiva appears to be primarily suppressor/cytotoxic T cells, with a smaller population of helper T cells that are distributed in a subclass-dependent manner throughout the epithelium and substantia propria of the forniceal, tarsal, and epibulbar conjunctiva (Sacks *et al.*, 1986.
2. B cells (Bhan *et al.*, 1982; Sacks *et al.*, 1986) and activated T cells (Sacks *et al.*, 1986) rarely are observed in human conjunctiva.
3. SC is not synthesized or expressed in either human (Allansmith and Gillette, 1980) or rat (Sullivan *et al.*, 1984b; Gudmundsson *et al.*, 1985a) conjunctival epithelium. Although one study has reported SC, as well as IgA and IgG, synthesis in human conjunctival biopsies (Lai *et al.*, 1973), tissue samples may have contained accessory lacrimal tissue.
4. The conjunctival epithelium in humans (Sacks *et al.*, 1986) and rats (Setzer *et al.*, 1987) does not possess specialized cells for antigen sampling, as found in the intestine (Owen, 1977), or lung (Bienenstock, 1985), and appears to limit severely the passage of most antigens because of structural size and molecular weight restrictions (Huang *et al.*, 1989; Kahn *et al.*, 1990). Therefore, the normal human or rat conjunctiva seems unlikely to synthesize IgA, transport IgA antibodies to the ocular surface, or play a direct and significant role in B-cell maturation or migration.

Nevertheless, the conjunctiva does contain the immunological capacity for antigen processing, cell-mediated immunity, and hypersensitivity responses (e.g., Allansmith *et al.*, 1981,1983; Chandler and Gillette, 1983; Hann *et al.*, 1985; Cornell-Bell *et al.*, 1986; Sacks *et al.*, 1986; Abelson and Smith, 1991).

As concerns the cornea, this tissue does not actively provide immune protection for the anterior surface of the eye. The cornea possesses interstitial IgA, IgG, IgM, IgD, and IgE (Allansmith *et al.*, 1978b), which appear to originate from serum, diffuse from the limbal to central regions, and require extended time periods (months) for complete turnover (Verhagen *et al.*, 1990). However, lymphocytes (Allansmith *et al.*, 1978b) and differentiated Langerhans cells (Seto *et al.*, 1987) are essentially absent from, and SC is not produced by (Allansmith and Gillette, 1980), the avascular corneal epithelium and stroma. The cornea, though, is certainly susceptible to viral (e.g., Sabbaga *et al.*, 1988; Bale *et al.*, 1990; Pavan-Langston, 1990), bacterial (e.g., Hazlett *et al.*, 1981a; Snyder and Hyndiuk, 1988) or other antigenic (e.g., graft; Smolin and O'Connor, 1981) challenge, and the possible ensuing vascularization or inflammation may impair corneal function and vision significantly (Smolin and O'Connor, 1981; Theodore *et al.*, 1983).

Other tissues, organisms, and factors involved in mucosal defense of the eye (Smolin, 1985) include:

1. the orbital skeletal structure, which minimizes potential trauma
2. the eyelid architecture, which is relatively impermeable to macromolecules
3. the eyelid blink reflex and ciliary movement, which rapidly clear foreign objects from the ocular surface
4. the resident conjunctival populations of nonpathogenic bacteria, consisting of aerobes and facultative and obligate anaerobes, which may curtail the ability of invasive bacteria to attach and colonize (McNatt *et al.*, 1978
5. the continuous tear flow and reflex tearing, which act to remove microorganisms and cellular debris through hydrokinetics and eventual drainage into the nasolacrimal duct

B. Role of the Tear Film in Ocular Surface Defense

The preocular tear film plays a critical role in the defense of the eye against microbial and antigenic exposure, as well as in the maintenance of corneal clarity and visual ability (Holly, 1987). These functions are extremely dependent on the stability, tonicity, and composition of the tear film structure, which includes an underlying mucin foundation, a considerable middle aqueous component, and an overlying lipid layer (Holly, 1987; Whitcher, 1987). Alteration, deficiency, or loss of the tear film may increase significantly the susceptibility to ocular surface desiccation and infection, corneal ulceration and perforation, and marked visual impairment and blindness (Lamberts, 1983; Whitcher, 1987; Lubniewski and Nelson, 1990).

With respect to immune protection, the tear film contains numerous components (Gachon *et al.*, 1979; van Haeringen, 1981; Bron and Seal, 1986; Smolin, 1987) that combine to

provide both specific and nonspecific immunological activity (Tables II and III). Specific immunity is mediated primarily through the action of IgA antibodies, which are the predominant immunoglobulin in tears of humans (Josephson and Weiner, 1968; Table III) and experimental animals (Butler *et al.*, 1972; Hazlett *et al.*, 1981b; Sullivan and Allansmith, 1985,1987; Gudmundsson *et al.*, 1985; Wells and Hazlett, 1985; Sullivan and Hann, 1989a; Sullivan *et al.*, 1992a), occur almost entirely in polymeric form (Delacroix *et al.*, 1982; Delacroix and Vaerman, 1983; Gudmundsson *et al.*, 1985a; Allansmith *et al.*, 1985; Coyle *et al.*, 1987,1989), and originate from local production in lacrimal gland plasma cells (Butler *et al.*, 1972; Chao *et al.*, 1980; Janssen and van Bijisterveld, 1983; Sullivan and Allansmith, 1984; Peppard and Montgomery, 1987). In humans, tear IgA is distributed almost equally among IgA1 and IgA2 subclasses (Delacroix *et al.*, 1982; Fullard and Snyder, 1990; Fullard and Tucker, 1991). Most tear IgA appears to be transported by and bound to SC, which is synthesized and secreted by lacrimal epithelial cells (Franklin *et al.*, 1973; Allansmith and Gillette, 1980; Gillette *et al.*, 1980; Sullivan *et al.*, 1984b; Gudmundsson *et al.*, 1985a; Hann *et al.*, 1989,1991; Sullivan *et al.*, 1990b; Kelleher *et al.*, 1991; Lambert *et al.*, 1993) and is present in the tear film as an SIgA conjugate or as free SC (Gachon *et al.*, 1979; Delacroix and Vaerman, 1983; Sullivan *et al.*, 1984a; Sullivan and Allansmith, 1984,1987,1988; Gudmundsson *et al.*, 1985a; Watson *et al.*, 1985; Sullivan *et al.*, 1988; Coyle *et al.*, 1989; Sullivan and Hann, 1989a). The high concentrations of SIgA coexist with low levels of IgG and very limited quantities of IgM and IgE (Table III; Sullivan and Hann, 1989a; Sullivan *et al.*, 1990c). Tear IgG may be derived, in part, from lacrimal tissue synthesis (Butler *et al.*, 1972; Chao *et al.*, 1980; Janssen and van Bijsterveld, 1983), after which it moves down a steep concentration gradient into tears (Sullivan and Allansmith, 1988; Sullivan and Hann, 1989a; Sullivan *et al.*, 1990c), as well as from serum, after deposition in and passage through the conjunctival or lacrimal gland interstitium (McGill *et al.*, 1984; Fullard and Snyder, 1990; Fullard and Tucker, 1991; D. A. Sullivan, unpublished data). The source of tear IgM may be lacrimal tissue (Fullard and Snyder, 1990; Fullard and Tucker, 1991), whereas the origin of IgE in normal tears has yet to be determined. No IgD has been detected in the tear film (McClellan *et al.*, 1973; Bluestone *et al.*, 1975; Sen *et al.*, 1976,1978). It is important to note that the concentration of tear immunoglobulins, as shown in Table III, may be influenced significantly by the method of tear collection, the extent of tear stimulation, and the procedures that involve processing of tear samples (van Haeringen, 1981; Stuchell *et al.*, 1984; Fullard, 1988; Tuft and Dart, 1989; Fullard and Snyder, 1990; Fullard and Tucker, 1991; Kuizenga *et al.*, 1991). In addition, although tear Ig levels do not appear to display diurnal rhythms (Horwitz *et al.*, 1978), IgA concentrations may be exceedingly high after prolonged closure of the eyelids (Sack *et al.*, 1991).

Table II Specific and Nonspecific Immunological Factors in Tears of Individuals without Ocular Pathology

Secretory immunoglobulin A	Ceruloplasmin
Monomeric immunoglobulin A	Prostaglandin E_2
Immunoglobulin G	Tear-specific prealbumin
Immunoglobulin M	Histamine
Immunlglobulin E	Properdin factor B
Secretory component	Leukotrienes
Lysozyme	Complement (C3, C3 activator)
Lactoferrin	Anti-complement factor
β-Lysin	Complement decay-accelerating factor
Peroxidase	Superoxide radical producing system
Transferrin	Anti-chlamydial factor
Plasminogen activator	Lysosomal enzymes
α1-Antitrypsin	Antibiotic-producing bacteria
β2-Macroglobulin	T cells
α1-Antichymotrypsin	B cells
Inter-α-trypsin inhibitor	Macrophages
α2-Macroglobulin	Polymorphonuclear leukocytes

Additional specific and nonspecific agents in human tears that support ocular mucosal immunity follow.

1. Lysozyme and lactoferrin, which are secreted by the lacrimal gland (Gillette and Allansmith, 1980; Gillette *et al.*, 1980,1981), represent major tear components (van Haeringen, 1981; Gachon, 1982/83) and possess antibacterial activity (Smolin, 1987). Lactoferrin also may prevent activation of the classical complement pathway through inhibition of C3 convertase and may modulate ocular inflammatory reactions (Kijlstra, 1990/91).
2. β-Lysin may rupture bacterial cell membranes (Ford *et al.*, 1976). The presence of this substance in human tears is controversial (Selsted and Rafael, 1982; Janssen *et al.*, 1984).
3. Complement factors C3 and C3 activator, properdin and properdin factor B (Chandler *et al.*, 1974; Bluestone *et al.*, 1975; Yamamoto and Allansmith, 1979; Liotet *et al.*, 1982; Ballow *et al.*, 1985; Smolin, 1987), as well as anti-complement (Kijlstra and Veerhuis, 1981) and convertase decay-accelerating (Medof *et al.*, 1987; Lass *et al.*, 1990) factors are present. In certain eye diseases, tear IgA appears to fix complement (Barnett, 1968).
4. Nonlysozyme antibacterial factor (NLAF), which inhibits growth of staphylococci (Thompson and Gallardo, 1941) actually may be β-lysin (Ford *et al.*, 1976); its presence is controversial (van Haeringen, 1981; Selsted and Rafael, 1982; Janssen *et al.*, 1984).
5. Anti-chlamydial factor is a heat-stable substance that reduces *Chlamydia* attachment (Elbagir *et al.*, 1989).
6. Peroxidase (van Haeringen *et al.*, 1979; Fullard and Snyder, 1990; Fullard and Tucker, 1991) may exert bactericidal, viricidal, and fungicidal activity, as observed in other secretions, given appropriate levels of H_2O_2 and oxidizable cofactors (De *et al.*, 1987). Such peroxidase functions, however, may not operate

Table III Immunlglobulin Concentrations in Tears of Individuals without Ocular Pathology

Reference		Number of samples	Tear concentration (μg/ml)						
			IgA	SIgA	mIgA	IgG	IgM	IgE	IgD
Chordiker and Tomasi	(1963)	7	70			trace			
Douglas *et al.*	(1967)	4	118						
Bracciolini	(1968)	40	850			trace	0		
Little *et al.*	(1969)	10	212			trace	0		
Bazzi *et al.*	(1970)	9	230			790	0		
Knopf *et al.*	(1970)	7	125			36			
Brauninger and Centifanto	(1971)	24	88–500					detectable	
McClellan *et al.*	(1973)	74	170			140	0/trace	0.25	0
Chandler *et al.*	(1974)	3	230–300				0–12		
Bluestone *et al.*	(1975)	5		70.6		trace	0		0
Allansmith *et al.*	(1976b)	10						0.061	
Sen *et al.*	(1976)	50	246			trace	~0		0
Sen *et al.*	(1978)	220	307			<10	~0		0
Zavaro *et al.*	(1980)	26	199			31	<6.0		
Delacroix *et al.*	(1982)	6	124						
Donshik and Ballow	(1983)	10	123			10	0/trace	2.1[a]	
Gachon *et al.*	(1982/83)	38–101	411			32			
Gupta and Sarin	(1983)	5–35	233			trace	18		
Mackie and Seal	(1984)	54	<100			400–600			
Mannucci *et al.*	(1984)	17	113			32	0	<5.0[a]	
McGill *et al.*	(1984)	55	410–630			7–65			
Samra *et al.*	(1984)	54						0.82[a]	
Aalders-Deenstra *et al.*	(1985)	16						0.058[a]	
Coyle and Sibony	(1986)	20	186			6.7	5.6		
Sand *et al.*	(1986)	25		795					
Coyle *et al.*	(1987a)	23	198						
Coyle and Sibony	(1987)	12	200			2.0	4.9		
Vinding *et al.*	(1987)	42		2420					
Fullard	(1988)	6	398	542		0.54	0.31		
Lue *et al.*	(1988)	3	83			2.1	1.2		
Coyle	(1989)	19		374					
Hoebeke *et al.*	(1989)	8							0
Yuasa *et al.*	(1989)	8							0
Fullard and Snyder	(1990)	30		793	12.15	1.50	2.94		
Lal *et al.*	(1990)	15	350			110	120		
Mavra	(1990)	5				18.5			
Fullard and Tucker	(1991)	6		1930	13.21	3.66	18.3		
Temel *et al.*	(1991)	22	80			70	9		

[a] International Units/ml.

through the thiocyanate–H_2O_2 system, because tear thiocyanate concentrations are suboptimal (van Haeringen *et al.*, 1979).
7. Plasminogen activator (van Haeringen, 1981) is chemotactic for leukocytes (Bron, 1988).
8. Histamine, prostaglandins, and leukotrienes most likely derive from conjunctival mast cell production (van Haeringen, 1981; Gluud *et al.*, 1985; Abelson and Smith, 1991; Allansmith and Ross, 1991).
9. Antiproteases (e.g., α1-antitrypsin) are found (Zirm *et al.*, 1976; van Haeringen, 1981; Liotet *et al.*, 1982).
10. Lysosomal enzymes are present (Yamaguchi *et al.*, 1989).
11. Specific tear prealbumin and transferrin may have antibacterial actions (van Haeringen, 1981; Selsted and Rafael, 1982).
12. Ceruloplasmin may reduce viral infectivity and also may act as a superoxide dismutase (Bron and Seal, 1986).
13. Antibiotic-producing bacteria, primarily staphylococci, apparently occur frequently among ocular flora (Halbert and Swick, 1952).
14. A superoxide radical-producing system, which exhibits bactericidal activity, is situated within conjunctival mucus threads (Proctor *et al.*, 1977)
15. A low density of T and B lymphocytes, plasma cells, macrophages, and polymorphonuclear leukocytes has been identified in the normal tear film (Coyle and Bulbank, 1989).

III. IMMUNE RESPONSE OF THE OCULAR SECRETORY IMMUNE SYSTEM TO ANTIGENIC CHALLENGE

A. Organisms and Naturally Occurring or Induced Antibodies in Human Tears

In human tears, a diverse array of bacterial and viral organisms has been identified, including *Staphylococcus epidermidis, Corynebacterium* (Gregory and Allansmith, 1986,1987), *Staphylococcus aureus, Pneumococcus, Pseudomonas pyocyanea, Streptococcus viridans, Streptococcus pyogenes, Proteus vulgaris, Klebsiella pneumoniae, Escherichia coli,* α-hemolytic streptococci (Sen and Sarin, 1982), HTLV-III (Ablashi *et al.*, 1987), hepatitis B virus (Gastaud *et al.*, 1989), coxsackievirus (Langford *et al.*, 1980), herpesvirus 1 (Shani *et al.*, 1985; Fox *et al.*, 1986; Wilhelmus *et al.*, 1986), and cytomegalovirus (Cox *et al.*, 1975). Moreover, lacrimal tissue of healthy adults may contain both cytomegalovirus and Epstein–Barr virus (Pepose *et al.*, 1990; Pflugfelder *et al.*, 1990a,b). Perhaps in response to these and other microbial exposures, tears may harbor a variety of naturally occurring or induced IgG or SIgA antibodies against numerous antigens, including herpes simplex virus 1 (Little *et al.*, 1969; Norrild *et al.*, 1982; Pedersen *et al.*, 1982; Fox *et al.*, 1986; Coyle and Sibony, 1988), Epstein–Barr virus, varicella zoster virus, rubella, mumps, cytomegalovirus (Coyle and Sibony, 1988), measles (Coyle and Sibony, 1988; Friedman *et al.*, 1989), adenovirus (Nordbo *et al.*, 1986), influenza virus (Waldman and Bergman, 1987), rhinovirus (Douglas *et al.*, 1967), human immunodeficiency virus (HIV; Liotet *et al.*, 1987), *S. epidermidis, Streptococcus mutans* serotypes c and d, a *Corynebacterium* species (Burns *et al.*, 1982; Gregory *et al.*, 1984; Gregory and Allansmith, 1986,1987), *Chlamydia trachomatis* (Treharne *et al.*, 1978; Herrmann *et al.*, 1991), and other allergens (Ballow *et al.*, 1983; Kari *et al.*, 1985). These antibodies, although sometimes expressed in quiescent eyes (Waldman and Bergman, 1987; Coyle and Sibony, 1988), may increase in concentration significantly during active infection (refer to Table VI). The levels of natural tear IgA antibodies against bacterial organisms have been suggested to be either dependent on (Gregory and Allansmith, 1987) or independent of (Burns *et al.*, 1982) local antigenic stimulation.

B. Ocular Immune Response to Defined Antigens

Antigenic challenge to the surface of the eye may result in a marked accumulation of specific SIgA, IgG, and IgM antibodies in tears (Table IV); an accelerated and enhanced anamnestic response after secondary exposure (Mestecky *et al.*, 1978; Gregory *et al.*, 1984; MacDonald *et al.*, 1984; Gregory and Filler, 1987; Levenson *et al.*, 1988); and the generation of immune resistance to, and protection against, antigen reapplication (Table V; also Malaty *et al.*, 1988). In addition, definitive ocular immune responses, as well as the possible accumulation of Ig-containing cells in lacrimal tissue (Jackson and Mestecky, 1981; Allansmith *et al.*, 1987), may be stimulated by antigenic challenge to other sites, including subconjunctival, intracorneal, intravitreal, oral, intrabronchial, gastric, intraduodenal, intravenous, subcutaneous, intradermal, or intramuscular sites (Table IV). The nature (e.g., antibody isotype), extent, and kinetics of these immune reactions appear to be very dependent on the form (e.g., live versus inactivated microorganisms; strain), concentration, route, duration, and frequency of antigen administration: potential immune responses may be augmented, intermittent, suppressed, or absent (Banyard and Morris, 1980; Montgomery *et al.*, 1983,1984a,b; Mondino *et al.*, 1987a, 1991; Peppard *et al.*, 1988; Centifanto *et al.*, 1989; Hall and Pribnow, 1989). Moreover, the magnitude of induced ocular immunity may be altered by the use of adjuvants (e.g., Peppard *et al.*, 1988; Peppard and Montgomery, 1990) and may be influenced by the concurrent state of systemic immunity (Waldman and Bergmann, 1987; Bergmann *et al.*, 1987).

The mechanism by which antigenic exposure to the surface of the eye stimulates a local (e.g., IgA) immune response remains to be elucidated. Direct antigen transfer across the conjunctival epithelium (Huang *et al.*, 1989; Kahn *et al.*, 1990) or countercurrent passage through the lacrimal duct (Sullivan *et al.*, 1990c) appears to be restricted severely. Further, the immunological architecture of healthy lacrimal tissue appears to be limited in its capacity to process and present antigen effectively (Weiczorek *et al.*, 1988). Conse-

Table IV Ocular Secretory Immune Response to Defined Antigenic Challenge

Species	Antigen	Route[a,b]	Ocular response	Reference
Rat	Dinitrophenylated type III pneumococcal vaccine	Intravenous	Infrequent tear IgA antibodies	Montgomery *et al.* (1983,1984a)
		Subcutaneous	↑ Tear IgA, IgG, and IgM antibodies	
		Gastric	↑ Tear IgA antibodies	
		Ocular	↑ Tear IgA antibodies	
Rat	Cholera toxin	Ocular/Ocular	↑ Conjunctival antitoxin-containing cells	Pu *et al.* (1983)
		—/Ocular	No cellular response	
		Intraduodenal/—	No cellular response	
		Intraduodenal/intraduodenal	No cellular response	
		Intraduodenal/ocular	↑ Conjunctival antitoxin-containing cells	
		Intragastric/ocular	↑ Conjunctival antitoxin-containing cells	
Rat	Dinitrophenylated type III pneumococcal vaccine	Ocular	↑ Tear IgA antibodies	Montgomery *et al.* (1984b)
		Ocular/gastric	↑ Tear IgA antibodies	
		Gastric	↑ Tear IgA antibodies	
		Gastric/ocular	↑ Tear IgA antibodies	
Rat	Dinitrophenylated *Pneumococcus* (inactivated)	Ocular	↑ Tear IgA antibodies	Peppard *et al.* (1988)
		Gastric	↑ Tear IgA antibodies	
Rat	Dinitrophenylated *Streptococcus pneumoniae* (inactivated)	Gastric/ocular	↑ Tear IgA antibodies	Peppard and Montgomery (1990)
Guinea pig	Live guinea pig inclusion conjunctivitis organisms	Ocular	↑ Tear SIgA antibodies	Murray *et al.* (1973)
	Inactivated guinea pig inclusion conjunctivitis organisms	Intraperitoneal	No tear SIgA antibodies	
Guinea pig	Live guinea pig inclusion conjunctivitis organisms	Ocular	↑ Tear SIgA antibodies	Watson *et al.* (1977)
Guinea pig	Live guinea pig inclusion conjunctivitis organisms	Ocular	↑ Tear IgA and IgG antibodies	Malaty *et al.* (1981)
	Inactivated guinea pig inclusion conjunctivitis organisms	Ocular	No tear IgA or IgG antibodies	
Guinea pig	Live guinea pig inclusion conjunctivitis organisms	Ocular	↑ Tear SIgA antibodies	Finney and Bushell (1986)
Guinea pig	*Shigella* ribosomal vaccine	Subcutaneous	↑ Tear IgA 'O' antibodies	Levenson *et al.* (1988)
	Lipopolysaccharide	Subcutaneous	↑ Tear IgA 'O' antibodies	
Rabbit	Human serum albumin	Oral and intravenous	↑ Lacrimal gland IgA antibody-producing cells	Jackson and Mestecky (1981)
Rabbit	Herpes simplex virus 1	Ocular	↑ Tear IgG, no IgA or IgM antibodies	Willey *et al.* (1985)
Rabbit	Peptidoglycan–ribitol teichoic acid (from *Staphylococcus aureus*)	Intradermal with CFA	↑ Tear IgG and SIgA antibodies	Mondino *et al.* (1987a,b)
		Subconjunctival with CFA	↑ Tear IgG and SIgA antibodies	
	Live *S. aureus*	Ocular	↑ Tear IgG and SIgA antibodies	
		Ocular	↑ Tear IgG and SIgA antibodies	
Rabbit	Herpes simplex virus 1	Scarified cornea	↑ Tear IgA, IgM, and IgG antibodies	Centifanto *et al.* (1989)

(*continues*)

Table IV (*continued*)

Species	Antigen	Route[a,b]	Ocular response	Reference
Rabbit	Ovalbumin	Ocular	↑ Tear IgG, infrequent IgA antibodies; ↑ IgG and IgM antibody-producing cells in conjunctiva but not in lacrimal gland	Hall and Pribnow (1989)
		Intravitreous	↑ Tear IgG antibodies	
		Intravenous	No IgG or IgA antibodies	
Rabbit	Peptidoglycan-ribitol teichoic acid (from *S. aureus*)	Intradermal with CFA	↑ Tear IgG and SIgA antibodies	Mondino *et al.* (1991)
		Subconjunctival with CFA	↑ Tear IgG and SIgA antibodies	
		Intradermal with CFA/ocular	↑ Tear IgG and SIgA antibodies	
		Subconjunctival with CFA/ocular	↑ Tear IgG and SIgA antibodies	
	Live *S. aureus*	Ocular	↑ Tear IgG and SIgA antibodies	
Cattle	Keyhole limpet hemocyanin	Subconjunctival with IFA	↑ Tear antibodies	Banyard and Morris (1980)
		Intramuscular with IFA	↑ Tear antibodies	
		Ocular (3 months)	↑ Tear antibodies	
		Ocular (3 days)	No tear antibody response	
Calves	Live rotavirus	Oral	↑ Tear IgA and IgM antibodies	van Zaane *et al.* (1987)
		Oral/oral	No tear antibodies	
		Oral/oral/ocular	↑ Tear IgA antibodies	
		Oral(2)/ocular/intrabronchial	↑ Tear IgA and IgM antibodies	
		Intrabronchial	↑ Tear IgA and IgM antibodies	
		Intrabronchial/oral	↑ Tear IgA and IgM antibodies	
Horse	*Leptospira interrogans*	Intramuscular	↑ Tear antibodies	Parma *et al.* (1987)
Monkey	Inactivated *Chlamydia trachomatis*	Ocular	↑ Tear antibodies	MacDonald *et al.* (1984)
	Inactivated *C. trachomatis*/ Live *C. trachomatis*	Ocular	↑ Tear antibodies	
Monkey	*C. trachomatis*	Ocular	↑ Conjunctival suppressor/cytotoxic and helper T cells; ↑ lymphoid follicles containing IgM-positive B cells, some IgG- and IgA-positive B cells	Whittum-Hudson *et al.* (1986)
Monkey	Inactivated *C. trachomatis*	Oral	No IgA, IgG, IgM antibodies	Taylor *et al.* (1987)
	Live C. trachomatis	Ocular	↑ Tear IgA, IgG and IgM antibodies	
		Oral	No IgA antibodies	
		Rectal	No IgA antibodies	
		Rectal/oral/intramuscular	↑ Tear IgA and IgG antibodies	
		Rectal/oral/intramuscular/ocular	↑ Tear IgA, IgG and IgM antibodies	
Monkey	*C. trachomatis* lipopolysaccaride expressed in recombinant *Escherichia coli*	Oral	No IgA, IgG, IgM antibodies	Taylor and Prendergast (1987)

(*continues*)

Table IV (*continued*)

Species	Antigen	Route[a,b]	Ocular response	Reference
Monkey	*C. trachomatis* major outer membrane protein/[live *C. trachomatis*][c,d]	Ocular/[ocular]	↑ Tear IgA antibodies	Taylor *et al.* (1988)
		Intraperitoneal/oral/[ocular]	Rare antibodies	
		Intraperitoneal/oral/ocular/[ocular]	↑ Tear IgA antibodies	
		[ocular]/[ocular]	↑ Tear IgA antibodies	
		—/[ocular]	↑ Tear IgA antibodies	
Monkey	*C. trachomatis*/chlamydial antigen extract	Ocular	↑ *Chlamydia*-specific lymphocytes in conjunctiva	Pal *et al.* (1990/91)
Human	Live rhinovirus	Intranasal	↑ Tear IgA neutralizing antibodies	Douglas *et al.* (1967)
Human	Live rhinovirus	Intranasal	↑ Tear IgA and IgG antibodies	Knopf *et al.* (1970)
	Inactivated rhinovirus	Intranasal	↑ Tear IgA antibodies	
Human	Inactivated *streptococcus mutans*	Oral	↑ Tear IgA antibodies	Mestecky *et al.* (1978)
Human	Inactivated *S. mutans* type c whole cells	Oral	↑ Tear IgA antibodies	Gregory *et al.* (1984)
Human	Influenza virus vaccine	Oral	↑ IgA antibodies	Bergmann *et al.* (1986)
Human	Influenza virus vaccine	Oral	↑ Tear IgA antibodies	Bergmann *et al.* (1987)
Human	Inactivated *S. mutans* whole cells	Oral	↑ Tear IgA antibodies	Gregory and Filler (1987)
Human	Inactivated *S. mutans* type c	Oral	↑ Tear IgA, IgG and IgM antibodies	Czerkinsky *et al.* (1987)
Human	Influenza virus vaccine	Oral	↑ Tear IgA antibodies	Waldman and Bergmann (1987)
		Intramuscular	↑ Tear IgA antibodies	
Human	Pneumococcal vaccine	Subcutaneous	↑ Tear IgA, IgG, and IgM antibodies	Lue *et al.* (1988)

[a] The route of antigen exposure does not convey information about the frequency of antigen application, that is, antigens may have been administered once or multiple times via the specific route. If different routes were used, the sequence of use is given and the routes are separated by a slash. In addition, if primary and secondary immunizations by one route yielded different responses, a distinction is made between these challenges.

[b] Abbreviations: CFA, complete Freund's adjuvant; IFA, incomplete Freund's adjuvant.

[c] The use of sequential antigen administration at different times is designated by a slash.

[d] Note, oral doses given with cholera toxin.

quently, the ocular secretory immune response to infectious or toxic substances may require antigenic clearance through the nasolacrimal duct and stimulation of gut-associated lymphoid tissue. Consistent with this hypothesis are the following observations:

1. Topical application of noninvasive antigens to the rat ocular surface appears to result in passage through the nasolacrimal canal into the gastrointestinal tract, and not retrograde transfer to the lacrimal gland or lymphatic drainage into local lymph nodes (Sullivan *et al.*, 1990a).
2. Intranasal, oral, or gastric administration of bacteria, viruses, or other antigens may induce the accumulation of specific tear IgA antibodies and the generation of ocular surface protection (Mestecky *et al.*, 1978; Nichols *et al.*, 1978; Montgomery *et al.*, 1983,1984a,b; Gregory *et al.*, 1984; Bergmann *et al.*, 1986,1987; Czerkinsky *et al.*, 1987; van Zaane *et al.*, 1987; Waldman and Bergman, 1987; Peppard *et al.*, 1988; Peppard and Montgomery, 1990).

This remote-site stimulation most likely would involve IgA lymphoblast migration from mesenteric and peripheral lymph nodes, spleen, and thoracic duct lymph to the lacrimal gland (Montgomery *et al.*, 1983,1985; McGee and Franklin, 1984; O'Sullivan and Montgomery, 1990), followed by local antibody production and transport to the ocular surface. In contrast, the contribution of serum IgA antibodies to ocular surface defense appears to be minimal or nonexistent (Sullivan and Allansmith, 1984; Montgomery *et al.*, 1984a,b; Bergmann *et al.*, 1987; Czerkinsky *et al.*, 1987; Peppard and Mont-

Table V Influence of Prior Immunization on Subsequent Ocular Response to Infectious Organisms

Species	Immunogen[a]	Immunization route[b]	Clinical response to ocular challenge	Reference
Guinea pig	Live GPIC	Ocular	↑ Resistance to GPIC infection	Murray *et al.* (1973)
	Inactivated GPIC	Intraperitoneal	No resistance to GPIC infection	
Guinea pig	Live GPIC	Oral	↑ Resistance to GPIC infection	Nichols *et al.* (1978)
Guinea pig	Live GPIC	Ocular	↑ Resistance to GPIC infection	Malaty *et al.* (1981)
	Inactivated GPIC	Ocular	No resistance to GPIC infection	
Guinea pig	Live GPIC	Ocular	↑ Resistance to GPIC infection	Finney and Bushell (1986)
Guinea pig	*Shigella* ribosomal vaccine	Subcutaneous	↑ Resistance to *Shigella sonnei* infection	Levenson *et al.* (1988)
Guinea pig	SOMP	Subcutaneous with CFA[c]	↑ Resistance to *Shigella* infection	Adamus *et al.* (1980)
Rabbit	SOMP	Subcutaneous with CFA	↑ Resistance to *Shigella* infection	Adamus *et al.* (1980)
	Rabbit antiserum to SOMP	Intravenous	↑ Resistance to *Shigella* infection	
Calves	Modified live bovine rhinotracheitis virus vaccine	Ocular	↓ Resistance to *Moraxella bovis* infection	George *et al.* (1988)
		Intranasal	↓ Resistance to *M. bovis* infection	
Monkey	Inactivated *Chlamydia trachomatis*	Ocular	↓ Resistance to *C. trachomatis* infection	MacDonald *et al.* (1984)
Monkey	Inactivated *C. trachomatis*	Oral	No resistance to *C. trachomatis* infection	Taylor *et al.* (1987)
	Live *C. trachomatis*	Ocular	↑ Resistance to *C. trachomatis* infection	
		Oral	Mild or no resistance to *C. trachomatis* infection	
		Rectal/oral/intramuscular	↑ Resistance to *C. trachomatis* infection	
Monkey	Lipopolysaccaride from *C. trachomatis* expressed in recombinant *Escherichia coli*	Oral	No resistance to *C. trachomatis* infection	Taylor and Prendergast (1987)
Monkey	*C. trachomatis* major, outer membrane protein[d]	Ocular	Partial resistance to *C. trachomatis* infection	Taylor *et al.* (1988)
		Intraperitoneal/oral	Partial resistance to *C. trachomatis* infection	
		Intraperitoneal/oral/ocular	Partial resistance to *C. trachomatis* infection	

[a] GPIC, Guinea pig inclusion conjunctivitis organisms; SOMP, *Shigella* outer membrane protein.

[b] The route of antigen exposure does not convey information about the frequency of antigen application, that is, antigens may have been administered once or multiple times via the specific route. If different routes were used, the sequence of use is given and the routes are separated by a slash.

[c] CFA, Complete Freund's adjuvant.

[d] Note, oral doses are given with cholera toxin.

gomery, 1987; Lue *et al.*, 1988). IgG antibodies from serum, however, may play a significant role in certain inflammatory disorders of the eye (Chandler *et al.*, 1974; Mackie and Seal, 1984; Seal, 1985; Wilhelmus *et al.*, 1986; Gupta and Sarin, 1983). Overall, ocular immune protection may be conferred by both local and distant antigenic exposure; lacrimal tissue acts at least as a recipient of committed IgA-containing cells that elaborate antigen-specific antibodies. However, the development of an optimal strategy to promote secretory immunity in the eye has yet to be established.

C. Influence of Ocular or Systemic Disease or Contact Lens Wear on the Secretory Immune System of the Eye

As demonstrated in Table VI, various ocular and systemic diseases, as well as contact lens wear, may influence secretory immune expression in the human eye significantly. Thus, bacterial, viral, and fungal infections of the ocular surface; exposure to allergens; endocrine abnormalities; or graft-versus-host disorders may increase levels of specific antibodies, total immunoglobulins, complement proteins, and nonspecific immune factors significantly or may induce changes in the lymphocytic profile of the conjunctiva. Interestingly, if pathological alterations are evident in only one eye, immune responses may (Krichevskaya *et al.*, 1980; Shani *et al.*, 1985) or may not (Centifanto *et al.*, 1970; Hall and O'Connor, 1970) occur in the contralateral unaffected eye. With respect to contact lenses, these may bind (Gudmundsson *et al.*, 1985b) and also cause modifications in the concentrations of (Table VI) immune components in the tear film; the precise immunological effects may depend on the composition of lens material, the efficacy of cleaning regimens, and the length of wear (Manucci *et al.*, 1984; Vinding *et al.*, 1987; Temel *et al.*, 1991).

In contrast, such conditions as IgA deficiency, intrauterine infection, ocular surgery, keratoconjunctivitis sicca, malnutrition, and autoimmune disease often may suppress ocular mucosal immunity (Table VI). For example, severe malnutrition may lead to a significant decrease in tear IgA and SC concentrations, a diminished number of IgA-containing cells in lacrimal tissue, and a blunted SIgA antibody response to infectious challenge (McMurray *et al.*, 1977; Watson *et al.*, 1977,1985; Sullivan *et al.*, 1990d; Sullivan *et al.*, 1993). Similarly, autoimmune disorders such as multiple sclerosis or Sjögren's syndrome may alter or disrupt immune function in the eye significantly. Multiple sclerosis, an autoimmune disease of possible viral origin, is associated with heightened levels of monomeric IgA and lymphocytes, and reduced amounts of SC, in tears of afflicted individuals (Coyle and Sibony, 1987; Coyle, 1989; Coyle and Bulbank, 1989). Sjögren's syndrome, an autoimmune disease that occurs almost exclusively in females, is characterized by a progressive lymphocytic infiltration into the lacrimal gland, an immune-mediated destruction of lacrimal acinar and ductal epithelial cells, decreased tear IgA content, and keratoconjunctivitis, sicca (Tabbara, 1983; Boukes *et al.*, 1987; Moutsopoulos and Talal, 1987; Talal and Moutsopoulos, 1987; Kincaid, 1987). Further, in experimental models of this complex disorder, generation of autoantibodies to (Ohashi *et al.*, 1985) and deposition of IgG, IgA, and complement in ductal epithelial cells of (DeLuise *et al.*, 1982) lacrimal tissue may accompany the striking glandular inflammation (Kessler, 1968; Hoffman *et al.*, 1984; Jabs *et al.*, 1985; Jabs and Prendergast, 1988; Ariga *et al.*, 1989; Vendramini *et al.*, 1991; Sato *et al.*, 1992). The etiology of Sjögren's syndrome may involve the endocrine system (Ahmed *et al.*, 1985,1989; Raveche and Steinberg, 1986; Nelson and Steinberg, 1987; Talal and Ahmed, 1987; Ahmed and Talal, 1990; Carlsten *et al.*, 1990), but also may be the result of primary infection with and reactivation of Epstein–Barr virus, cytomegalovirus, herpes virus-6, or retroviruses. These viruses have been identified in lacrimal or salivary tissues of Sjögren's syndrome patients (Burns, 1983; Fox *et al.*, 1986; Fox, 1988; Garry *et al.*, 1990; Krueger *et al.*, 1990; Prepose *et al.*, 1990; Pflugfelder *et al.*, 1990a,b; Mariette *et al.*, 1991) and may stimulate the inappropriate epithelial-cell HLA-DR expression, T helper/inducer-cell activation, B-cell hyperactivity, and autoantibody production evident in these affected tissues (Maini, 1987; Moutsopoulos and Talal, 1987; Fox, 1988; Venables, 1989). In support of this possibility, certain viral infections in experimental animals exert a striking impact on the lacrimal gland and induce a periductular infiltration of plasma cells, lymphocytes, and macrophages; distinct nonsuppurative periductular inflammation; significant interstitial edema; widespread necrosis of the acinar and ductal epithelium; degenerative and atrophic alterations in epithelial cells; diminished tear flow; and keratoconjunctivitis sicca (Jacoby *et al.*, 1975; Lai *et al.*, 1976; Percy *et al.*, 1984,1990; Green *et al.*, 1989). Moreover, research has demonstrated that herpes viruses (e.g., cytomegalovirus) and coronaviruses (e.g., sialodacryoadenitis virus) may invade and replicate in rat lacrimal gland acinar cells (Huang *et al.*, 1993, Wickham *et al.*, 1992); Epstein–Barr virus may bind to specific receptors in ductal epithelium of the human lacrimal gland (Levine *et al.*, 1990/91); and HIV infection may predispose patients to keratoconjunctivitis sicca (Couderc *et al.*, 1987; Ulirsch and Jaffe, 1987; deClerck *et al.*, 1988; Lucca *et al.*, 1990). However, the precise role of viruses in the induction of autoimmune disease, as well as the mechanism by which viral infection may interfere with lacrimal gland function and immune expression, remains to be determined.

IV. ENDOCRINE, NEURAL, AND IMMUNE MODULATION OF THE OCULAR SECRETORY IMMUNE SYSTEM

During the past three decades, scientists have recognized increasingly that the endocrine and nervous systems regulate multiple aspects of cellular and humoral immunity. The exact nature of this hormonal and neural control—which influences significantly such parameters as lymphocyte maturation, antigen presentation, lymphokine production, and antibody synthesis—critically depends on the specific signal, target cell, and local microenvironment (Besedovsky and Sorkin, 1977; Comsa *et al.*, 1982; Grossman, 1984; Munck *et al.*, 1984; Payan *et al.*, 1984; Ahmed *et al.*, 1985; Besedovsky *et al.*, 1985; Berczi, 1986; Berczi and Kovacs, 1987; Felten *et al.*, 1987; Jancovik *et al.*, 1987; Weigent and Blalock, 1987; Freier, 1989; Hadden *et al.*, 1989; Talal and Ahmed, 1987; Ahmed and Talal, 1990; Ader *et al.*, 1991). Moreover, this neuroendocrine–immune interrelationship is bidirectional, that is, antigenic exposure also may induce the lymphocytic secretion of lymphokines, hormones, and neuropeptides that directly modulate endocrine and neural function (Besedovsky and Sorkin, 1977; Besdovsky *et al.*, 1985; Cotman *et al.*,

Table VI Impact of Ocular or Systemic Disease or Contact Lens Wear on the Secretory System of the Human Eye

Disease	Ocular immune response in the tear film[a]	Reference
Acute adenovirus conjunctivitis	~IgA, ↑ IgG, ~IgM	Gupta and Sarin (1983)
Acute bacterial conjunctivitis	~Lysozyme, ↑ IgA	Sen and Sarin (1979,1982)
Acute bacterial corneal ulcer	~IgA	Sen and Sarin (1979)
Acute endogenous uveitis	~IgA	Sen and Sarin (1979)
Acute follicular conjunctivitis	↑ IgA, ↑ IgG, ↑ IgM	McClellan *et al.* (1973)
	↑ SIgA and ↑ IgG antibodies to herpes simplex virus	Fox *et al.* (1986)
Acute hemorrhagic conjunctivitis	↑ Neutralizing activity to enterovirus and coxsackie virus; ↑ fibroblast interferon	Langford *et al.* (1985)
Acute keratoconjunctivitis	↑ IgA	Sen and Sarin (1979)
Allergic conjunctivitis	~IgG, ~IgE	Donshik and Ballow (1983)
	↑ IgE	Hoebeke *et al.* (1989)
	↑ IgE	Yuasa *et al.* (1989)
	↑ IgE	Kari *et al.* (1985)
	~Complement C3, factor B, and C3 des Arg	Ballow *et al.* (1985)
contact lens	No IgE	Hoebeke *et al.* (1989)
Atopic asthma without conjunctivitis	↑ IgE	Aalders-Deenstra *et al.* (1985)
Atopic conjunctivitis		
chronic	↑ IgE	Aalders-Deenstra *et al.* (1985)
seasonal	↑ IgE	Aalders-Deenstra *et al.* (1985)
Bacterial corneal ulcer	↑ IgA, ~IgG, ~IgM	Lal *et al.* (1990)
Blepharoconjunctivitis	~IgA, ~IgG	McClellan *et al.* (1973)
	↑ IgA	Sen and Sarin (1979)
	~IgA, ↑ IgG, ↑ IgM	Zavaro *et al.* (1980)
Bronchopneumonia	~IgA, ~lysozyme	Bhaskaram *et al.* (1986)
Chronic conjunctivitis	~IgA, ~lactoferrin, ~lysozyme	Boukes *et al.* (1987)
Chronic graft versus host disease	↑ IgG	Heitman *et al.* (1988)
	↑ T cells in conjunctiva	Bhan *et al.* (1982)
Chronic irritative conjunctivitis	↓ Lysozyme	Sen and Sarin (1982)
Chronic nonulcerative blepharitis and meibomianitis	~IgA, ~IgG, ~lysozyme, ~lactoferrin	Seal (1985)
Contact lens wear	↓ IgA	Suttorp-Shelton *et al.* (1989)
	~Complement C3, factor B, and C3 des Arg	Ballow *et al.* (1985)
extended wear	↓ IgA, ~lysozyme	Vinding *et al.* (1987)
	↑ IgA, ~IgG, ~IgM, ~IgE	Mannucci *et al.* (1984)
rigid	↑ IgA, ~IgG, ~IgM	Temel *et al.* (1991)
soft	~IgA, ~IgG, ~IgM	Temel *et al.* (1991)
	~lactoferrin	Ballow *et al.* (1987)
Corneal dendritic ulcers	↑ SIgA and ↑ IgG antibodies to herpes simplex virus	Fox *et al.* (1986)
Corneal graft reaction	↑ IgA	Sen and Sarin (1979)
Follicular conjunctivitis (+/-trachoma)	IgA and IgG plasma cells in conjunctiva	Tagawa *et al.* (1989)
	↑ IgA, ↑ IgG, ↑ IgM	Zavaro *et al.* (1980)
Fungal corneal ulcer	↑ IgA, ~IgG, ~IgM	Lal *et al.* (1990)
Fungal ulcer—active	↑ IgG	Chandler *et al.* (1974)
Giant papillary conjunctivitis	~IgA, ↑ IgG, ↑ IgM, ↑ IgE	Donshik and Ballow (1983)
	↓ Lactoferrin	Ballow *et al.* (1987)
	↓ IgA	Suttorp-Shelton *et al.* (1989)
	↑ Complement C3, factor B, and C3 des Arg	Ballow *et al.* (1985)
Grave's ophthalmopathy	↑ SIgA	Khalil *et al.* (1989)
Herpes simplex virus keratitis	~IgA, ↑ IgG	McClellan *et al.* (1973)
	↑ Antibodies to HSV	Krichevskaya *et al.* (1980)
	↑ IgA antibodies	Shani *et al.* (1985)

(*continues*)

Table VI (*continued*)

Disease	Ocular immune response in the tear film[a]	Reference
active	↑ SIgA and ↑ IgG antibodies to HSV, ↑ serum albumin	Pedersen *et al.* (1982)
	↑ SIgA antibodies to HSV	Fox *et al.* (1986)
dendritic	↑ IgG antibodies to HSV, ~IgA antibodies	Wilhelmus *et al.* (1986)
Herpetic keratoconjunctivitis	~IgA, IgA HSV neutralizing antibodies present	Little *et al.* (1969)
HIV-1 infection	↑ Incidence of keratoconjunctivitis sicca	Lucca *et al.* (1990)
Idiopathic dry eye	↓ IgA, ↓ lactoferrin, ↓ lysozyme	Boukes *et al.* (1987)
IgA deficiency	Recurrent or chronic conjunctivitis	South *et al.* (1968)
IgG multiple myeloma	↑ Oligoclonal IgG	Mavra *et al.* (1990)
Keratoconjunctivitis sicca	↓ Lysozyme	Scharf *et al.* (1982)
	↓ IgA, ↑ IgG, ↓ lysozyme, ↓ lactoferrin	Seal (1985)
	↑ Superoxide	Bron (1988)
	↑ IgA, ↑ IgG, ↑ IgM	Zavaro *et al.* (1980)
Keratomalacia	↑ IgA	Sen and Sarin (1979)
Malnutrition—severe	↓ IgA, ↓ free secretory component (FSC), ↓ lysozyme	Watson *et al.* (1985)
	↓ IgA, ↑ IgG	McMurray *et al.* (1977)
Malnutrition with epithelial xerosis	↓ Lysozyme	Sen and Sarin (1982)
Measles	↓ SIgA, ↓ lysozyme, ↑ bacterial pathogens	Bhaskaram *et al.* (1986)
	↑ SIgA and ↑ IgA antibodies to measles	Friedman *et al.* (1989)
Mooren's ulcer	↑ IgG	Chandler *et al.* (1974)
Multiple sclerosis	No oligoclonal IgG	Mavra *et al.* (1990)
	↑ Monomeric IgA	Coyle *et al.* (1987a)
	↑ Monomeric IgA, ↓ secretory component	Coyle (1989)
	↑ Oligoclonal IgG	Coyle *et al.* (1987b)
	↑ Total lymphocytes, ↑ T cells, null cells	Coyle and Bulbank (1989)
	↑ SIgA and ↑ IgG antibodies to measles, herpes simplex virus, and rubella virus	Coyle and Sibony (1987)
Myotonic muscular dystrophy	↓ Lactoferrin	Tsung *et al.* (1983)
Neurosarcoidosis	↑ Oligoclonal IgG	Mavra *et al.* (1990)
Nonatopic conjunctivitis	~IgE	Aalders-Deenstra *et al.* (1985)
Ocular pemphigoid	↑ T cells in conjunctiva	Bhan *et al.* (1982)
mild	↑ IgA, ~lysozyme, ~lactoferrin	Seal (1985)
severe	↑ IgG, ~lysozyme, ~lactoferrin	Seal (1985)
dry eye	↓ IgA, ↑ IgG, ↓ lysozyme, ↓ lactoferrin	Seal (1985)
Ocular cicatricial pemphigoid	↑ IgG or ↑ IgA in conjunctival basement membrane	Furey *et al.* (1975)
Orofacial herpetic vesicles	↑ SIgA and ↑ IgG antibodies to herpes simplex virus	Fox *et al.* (1986)
Pemphigus	↓ IgA, ↑ IgG, ↓ lysozyme, ↓ lactoferrin	Seal (1985)
Perrenial conjunctivitis (dry eye)	~IgG, ~IgE	Donshik and Ballow (1983)
Phlyctenular conjunctivitis	~IgA, ~lysozyme	Sen and Sarin (1979,1982)
Picornavirus epidemic conjunctivitis	Human fibroblast interferon	Langford *et al.* (1980)
Postintrauterine infection (infant)	↓ IgA, ↓ IgG	McMurray and Rey (1981)
Postoperative cataract surgery	↓ IgA	Sand *et al.* (1986)
	↓ Lactoferrin, ↑ neutrophils	Jensen *et al.* (1985)
	↑ PGE_2	Gluud *et al.* (1985)
	↑ Superoxide	Bron (1988)
Rheumatoid arthritis and keratoconjunctivitis sicca	↓ Lysozyme	Sharf *et al.* (1982)
Sicca syndrome	↓ Lactoferrin	Mackie and Seal (1984)
	↓ Antimicrobial properties	Liotet *et al.* (1980)
Sjögren's syndrome	↓ IgA, ↓ lactoferrin, ↓ lysozyme	Boukes *et al.* (1987)
	↓ Globulins	Suarez (1987)
	↑ B and ↑ T cell infiltration into lacrimal tissue	Pepose *et al.* (1990)

(*continues*)

Table VI (*continued*)

Disease	Ocular immune response in the tear film[a]	Reference
Specific granule deficiency	~Lactoferrin	Raphael *et al.* (1989)
Steven's Johnson syndrome	~IgA, ↑ IgG, ~IgM	Zavaro *et al.* (1980)
Subacute sclerosing panencephalitis	↑ Oligoclonal IgG	Mavra *et al.* (1990)
Systemic lupus erythematosus	↑ Oligoclonal IgG	Mavra *et al.* (1990)
Thygeson's conjunctivitis	No IgE	Hoebeke *et al.* (1989)
Trachoma	↓ Lysozyme	Sen and Sarin (1982)
	↑ Histamine, ↑ PGF_2	Bron (1988)
	↑ Serotype-specific antibodies	Treharne *et al.* (1978)
Trachoma-induced conjunctivitis	↑ IgA antibodies to *Chlamydia trachomatis*	Herrmann *et al.* (1991)
Vernal conjunctivitis	~IgA, ~lysozyme	Sen and Sarin (1979,1982)
	~IgA, ↑ IgG	McClellan *et al.* (1973)
	~IgE	Allansmith *et al.* (1976b)
	↓ Lactoferrin	Ballow *et al.* (1987)
	↑ Antibodies to pollen, ↑ IgG, ↑ IgM, ~IgA	Ballow *et al.* (1983)
	↑ Histamine, ↑ PGF_2	Bron (1988)
	↑ IgA, ↑ IgD, ↑ IgE conjunctival plasma cells	Allansmith *et al.* (1976)
	↑ IgE, ~IgA	Brauninger and Centifanto (1971)
	↑ IgG, ↑ IgE	Donshik and Ballow (1983)
	↑ Major basic protein	Udell *et al.* (1981)
	↑ T cells in conjunctiva	Bhan *et al.* (1982)
	↑ Complement C3, factor B, and C3 des Arg	Ballow *et al.* (1985)
	↑ IgA, ↑ IgG, ↑ IgM	Zavaro *et al.* (1980)
Vernal keratoconjunctivitis	↑ IgE	Yuasa *et al.* (1989)
	↑ IgE	Samra *et al.* (1984)
	↑ IgE	Aalders-Deenstra *et al.* (1985)
Viral corneal ulcer	↑ IgA, ↑ IgG, ↑ IgM	Lal *et al.* (1990)
Viral meningitis	↑ Oligoclonal IgG	Mavra *et al.* (1990)

[a] Symbols: ↑: increase; ↓: decrease; ~: no detectable change.

1987; Weigent and Blalock, 1987; Raine, 1988; Freier, 1989; Hadden *et al.*, 1989; Ader *et al.*, 1990,1991; D'Orisio and Panerai, 1990). In fact, researchers have proposed that the immune system serves as a sensory organ, providing input to the endocrine and nervous compartments in response to noncognitive stimuli such as infection (Blalock, 1984). Consequently, an extensive triangular association appears to exist between the endocrine, nervous, and immune systems that acts to promote and maintain homeostasis.

In the secretory immune system, diverse hormones and neural agonists are known to exert a tissue-selective influence that may augment, antagonize, or curtail immunological processes (Stead *et al.*, 1987,1991; Sullivan, 1990; Kelleher *et al.*, 1991; Lambert *et al.*, 1993). Thus, depending on the precise agent and the specific mucosal site, neuroendocrine interactions may significantly modify

1. the accumulation, proliferation, retention, or function of IgA- and IgG-positive cells, T cells, mast cells, eosinophils, basophils, natural killer cells, polymorphonuclear leukocytes, and/or macrophages
2. the synthesis or secretion of IgA and IgG antibodies and cytokines, the expression of major histocompatibility complex (MHC) Class II antigens, the elaboration and release of SC, and the uptake and transport of pIgA into luminal secretions
3. the adherence and presentation of microorganisms to mucosal cells, the magnitude of neurogenic inflammation, and the extent of local immune protection against infectious agents

In addition, antigen-induced immune responses may alter mucosal neuroendocrine structure, sensitivity, or function significantly (Rowson *et al.*, 1953; Baker and Plotkin, 1978; Botta, 1979; Forslin *et al.*, 1979; Stead *et al.*, 1987,1991; Weisz-Carrington, 1987; Sullivan, 1990; Ader *et al.*, 1991; Kelleher *et al.*, 1991; Bienenstock, 1992; Lambert *et al.*, 1993; McKay *et al.*, 1992; Wira and Prabhala, 1992; Wood, 1992).

With respect to the ocular secretory immune system, endocrine and neural factors appear to exert a dramatic effect on immunological expression and activity (Table VII). However, although this neuroendocrine–immune interrelationship has been shown definitively in eyes of experimental animals, it has yet to be evaluated in humans. In rats, androgens elicit a marked increase in the production and secretion

Table VII Neural, Endocrine, and Immune Regulation of IgA and Secretory Component Levels in the Rat Ocular Secretory Immune System[a]

Treatment	Lacrimal gland		Tears		Reference
	IgA	SC	IgA	SC	
Neural					
Vasoactive intestinal peptide		↑			Kelleher *et al.* (1991)
Calcitonin gene-related peptide		—			Kelleher *et al.* (1991)
Cholinergic agonist (carbachol)		↓			Kelleher *et al.* (1991); Lanbert *et al.* (1993)
β-Adrenergic agonist (isoproterenol)		↑			Kelleher *et al.* (1991)
α-Adrenergic agonist (phenylephrine)		—			Kelleher *et al.* (1991)
α-Endorphin		—			Kelleher *et al.* (1991)
β-Endorphin		—			Kelleher *et al.* (1991)
Leucine-enkephalin		—			Kelleher *et al.* (1991)
Methionine-enkephalin		—			Kelleher *et al.* (1991)
Neuropeptide Y		—			Kelleher *et al.* (1991)
Somatostatin		—			Kelleher *et al.* (1991)
Substance P		—			Kelleher *et al.* (1991)
Endocrine					
Testosterone	↑	↑	↑	↑	Sullivan *et al.* (1984a,b;1988,1990b); Sullivan and Allansmith (1985,1987); Sullivan (1988); Sullivan and Hann (1989a)
Dihydrotestosterone		↑		↑	Sullivan *et al.* (1984a,1990b); Hann *et al.* (1991); Kelleher *et al.* (1991); Lambert *et al.* (1993)
Dihydrotestosterone/carbachol		↑[b]			Kelleher *et al.* (1991); Lambert *et al.* (1993)
Cyproterone acetate		—			Lambert *et al.* (1992)
Dihydrotestosterone/cyproterone acetate		—			Lambert *et al.* (1993)
Dihydrotestosterone/actinomycin D		—			Lambert *et al.* (1993)
4-Estren-7α-methyl-17β-ol-3-one	↑		↑	↑	Sullivan *et al.* (1988); Sullivan and Hann (1989a)
5α-Androstan-17β-ol			—	↑	Sullivan *et al.* (1988)
Danazol			—	—	Sillivan *et al.* (1988)
Estradiol		—	—	—	Sullivan *et al.* (1984a,1990b); Sullivan and Allansmith (1985)
Testosterone/estradiol			↑	↑	Sullivan and Allansmith (1987)
Progesterone		—	—	—	Sullivan *et al.* (1984a,1990b); Sullivan and Allansmith (1987)
Testosterone/progesterone			↑	↑	Sullivan and Allansmith (1987)
Cortisol			—	—	Sullivan *et al.* (1984a); Sullivan and Allansmith (1985)
Dexamethasone[c]		—	—	—	Sullivan and Hann (1989b); Sullivan *et al.* (1990b)
Aldosterone		—			Sullivan *et al.* (1990b)
Prolactin		—	—	—	Sullivan *et al.* (1988); Kelleher *et al.* (1991)
Growth hormone		—	—	—	Sullivan *et al.* (1988); Kelleher *et al.* (1991)
α-Melanocyte stimulating hormone		—	—		Sullivan *et al.* (1988); Kelleher *et al.* (1991)
Adrenocorticotrophic hormone		—			Kelleher *et al.* (1991)
Arginine vasopressin		—			Kelleher *et al.* (1991)
Oxytocin		—			Kelleher *et al.* (1991)
Insulin[d]	↑	↑	↑	↑	Sullivan and Hann (1989a); Hann *et al.* (1991)
Melatonin		—			Kelleher *et al.* (1991)
Human chorionic gonadotropin		—			Kelleher *et al.* (1991)
Bovine pituitary extract		—			Kelleher *et al.* (1991)
Rat hypothalamic extract		—			Kelleher *et al.* (1991)
Cyclic adenosine monophosphate		↑			Kelleher *et al.* (1991); R. W. Lambert *et al.* (1993)
cAMP Inducer (cholera toxin)		↑			Hann *et al.* (1991); Kelleher *et al.* (1991); Lambert *et al.* 1993
Cholera toxin/carbachol		↑			Lambert *et al.* (1993)
Cyclic guanosine monophosphate		—			Kelleher *et al.* (1991)
Phosphodiesterase inhibitor (IBMX)		↑			Kelleher *et al.* (1991)
Prostaglandin E_2		↑			Kelleher *et al.* (1991)

(*continues*)

Table VII (*continued*)

Treatment	Lacrimal gland IgA	Lacrimal gland SC	Tears IgA	Tears SC	Reference
Immune					
γ-Interferon		—			Kelleher *et al.* (1991)
Interleukin 1α		↑			Kelleher *et al.* (1991)
Interleukin 1β		↑			Kelleher *et al.* (1991)
Interleukin 5	↑				Pockley and Montgomery (1990/91b)
Interleukin 6	↑	—			Pockley and Montgomery (1990/91b); Kelleher *et al.* (1991)
Tumor necrosis factor α		↑			Kelleher *et al.* (1991)

[a] Symbols: ↑: increase; ↓: decrease; —: no change; blank: not determined.
[b] The stimulatory effects of dihydrotestosterone and cholera toxin were reduced significantly by the presence of carbachol.
[c] Low concentrations of glucocorticoid are required for optimal acinar cell production of SC *in vitro* (Hann *et al.*, 1991).
[d] Insulin's influence has been observed *in vitro* or inferred from studies with diabetic rats (Sullivan and Hann, 1989a; Hann *et al.*, 1991).

of SC by lacrimal gland acinar cells (Sullivan *et al.*, 1984b,1990b; Kelleher *et al.*, 1991; Hann *et al.*, 1991), enhance the concentration of IgA in lacrimal tissue (Sullivan and Hann, 1989a), and stimulate the transfer and accumulation of SC and IgA, but not IgG, in tears (Sullivan *et al.*, 1984a; Sullivan and Allansmith, 1985; Sullivan and Hann, 1989a). These hormone actions, which may be induced by various andogenic compounds (Sullivan *et al.*, 1988), are not duplicated by estrogen, progestin, glucocorticoid, or mineralocorticoid treatment (Sullivan *et al.*, 1984a,1990b; Sullivan and Allansmith, 1985). Morevoer, the immunological effects of androgens appear to be unique to the eye, because androgen administration does not seem to influence IgA or SC levels in salivary, respiratory, intestinal, uterine, or bladder tissues (Sullivan *et al.*, 1988) and actually suppresses mucosal immunity in the mammary gland (Weisz-Carrington *et al.*, 1978). The mechanism by which androgens regulate ocular SC dynamics may involve hormone association with specific nuclear receptors in lacrimal gland acinar cells, binding of these androgen–receptor complexes to genomic acceptor sites, and promotion of SC mRNA transcription and translation. In support of this hypothesis:

1. saturable, high-affinity, and androgen-specific receptors, which adhere to DNA, have been identified in lacrimal tissue (Ota *et al.*, 1985; Edwards *et al.*, 1990; Rocha *et al.*, 1993)
2. androgens increase mRNA levels in lacrimal glands and stimulate lacrimal glycoprotein synthesis (Quintarelli and Dellovo, 1965; Shaw *et al.*, 1983; Gubits *et al.*, 1984)
3. androgen-induced SC production by acinar cells may be inhibited by androgen receptor (cyproterone acetate), transcription (actinomycin D), or translation (cycloheximide) antagonists (Sullivan *et al.*, 1984b; Lambert *et al.*, 1993). In contrast, the processes underlying androgen action on IgA in the rat eye, as well as hormone enhancement of tear IgA levels in the mouse (Sullivan *et al.*, 1992a) remain to be determined.

Androgen activity also may explain the pronounced gender-related differences in the rat ocular secretory immune system. The number of IgA-containing cells (Sullivan *et al.*, 1986; Hann *et al.*, 1988) and the IgA and SC output (Sullivan *et al.*, 1984b; Sullivan and Allansmith, 1985,1988) are significantly greater in adult male lacrimal tissue than in that of adult females. This sexual dimorphism also extends to tears in which, from puberty to senescence, free SC and IgA but not IgG occur at considerably higher levels in male rats (Sullivan *et al.*, 1984a,1990c; Sullivan and Allansmith, 1985,1988). Indeed, androgen influence may be involved in the distinct gender-associated differences in the structural appearance, histochemistry, biochemistry, immunology, and molecular biological expression of the lacrimal gland in a variety of species, including mice, hamsters, guinea pigs, rats, rabbits, and humans (e.g., Tier, 1944; Martinazzi and Baroni, 1963; Cavallero, 1967; Shaw *et al.*, 1983; Cornell-Bell *et al.*, 1985; Mhatre *et al.*, 1988; Pangerl *et al.*, 1989; Warren *et al.*, 1990; Sullivan and Sato, 1992a). With respect to humans, gender appears to influence (1) the degree of lymphocyte accumulation in the lacrimal gland (Waterhouse, 1963); (2) the IgA concentrations in tear of adults (Sen *et al.*, 1978), but not elderly (Sand *et al.*, 1986); and (3) the frequency of Sjögren's syndrome-related lacrimal gland imjunopathology (Tabbara, 1983; Moutsopoulos and Talal, 1987; Kincaid, 1987). Interestingly, androgen administration to animal models of Sjögren's syndrome (i.e., MRL/Mp-lpr/lpr and NZB/NZW F1 female mice) results in an almost complete suppression of autoimmune sequelae in lacrimal tissue (Ariga *et al.*, 1989; Vendramini *et al.*, 1991; Sato *et al.*, 1991,1992; Sullivan and Sato, 1992a); and an increased output of IgA (Sullivan *et al.*, 1992b).

In addition to androgens, the hypothalamic–pituitary axis appears to play an important role in the expression of the rat ocular secretory immune system. Disruption of this axis by hypophysectomy or extirpation of the anterior pituitary significantly reduces the number of IgA plasma cells in lacrimal tissue, diminishes the acinar cell production of SC, causes a striking decrease in the levels of tear IgA and SC,

and almost completely curtails androgen action on ocular mucosal immunity (Sullivan and Allansmith, 1987; Sullivan, 1988; Sullivan and Hann, 1989a). Moreover, this endocrine disturbance has a marked effect on lacrimal gland structure and function, leading to both acinar cell atrophy (Martinazzi, 1962) and diminished tear output (Sullivan and Allansmith, 1986). The physiological mechanisms responsible for hypothalamic–pituitary involvement in the ocular secretory immune system remain to be elucidated, but may include numerous neuroendocrine and immunological pathways: the hypothalamus and pituitary regulate multiple endocrine circuits, directly influence neural innervation in the lacrimal gland, and clearly modulate immune activity (Hosoya *et al.*, 1983; Wilson and Foster, 1985; Berczi, 1990; Berczi and Nagy, 1990). Further, the hypothalamic–pituitary axis is known to control many hormones, neurotransmitters, and lymphokines that modify androgen and acinar cell function and control mucosal immunity (Mooradian *et al.*, 1987; Sullivan, 1990).

Other studies in experimental animals also have demonstrated that (1) sex steroids may alter the development of allergic conjunctivitis in rabbits significantly (Saruya, 1968) and (2) diabetes may diminish significantly the expression of the secretory immune system of the eye. Thus, in diabetic rats, the density of IgA-containing cells in lacrimal tissue and the concentrations of IgA and SC in tears are reduced significantly (Sullivan and Hann, 1989a). These diabetic effects most likely relate to the absence of insulin, which is essential for optimal SC synthesis by acinar (Hann *et al.*, 1991) as well as intestinal (Buts *et al.*, 1988) cells, and apparently is required for maximal androgen action on target tissues (Jackson and Hutson, 1984). Similarly, both the thyroid and the adrenal glands are necessary to achieve the full magnitude of androgen-induced effects on the secretory immune system of the eye (Sullivan and Allansmith, 1987).

From the perspective of neural regulation, the stromal, periductal, perivascular, and acinar areas of lacrimal tissue are innervated by many parasympathetic, sympathetic, and peptidergic fibers that harbor numerous immunoactive transmitters, including vasoactive intestinal peptide (VIP), substance P, methionine enkephalin, leucine enkephalin, calcitonin gene-related peptide, and adrenergic and cholinergic agents (Ruskell, 1971,1975; Uddman *et al.*, 1980; Nikkinen *et al.*, 1984,1985; Lehtosalo *et al.*, 1987; Uusitalo *et al.*, 1990; Walcott, 1990). These neural agonists are known to control lymphocyte retention or function at other mucosal sites (Ottoway, 1984; Stanisz *et al.*, 1986; Walcott *et al.*, 1986; Freier *et al.*, 1987; Scicchitano *et al.*, 1988; Hart *et al.*, 1990) and their release may influence the adherence, distribution, or activity of IgA plasma cells or T cells in the lacrimal gland (Franklin *et al.*, 1988,1989; Oeschger *et al.*, 1989; Sullivan *et al.*, 1990/91). Consistent with this possibility, VIP appears to augment T-cell attachment to murine lacrimal tissue (Oeschger *et al.*, 1989) and systemic administration of the β-adrenergic blocker practolol suppresses human tear IgA levels (Wright, 1975; Garner and Rahi, 1976). However, the nature of the sympathetic–immune interaction requires further clarification, because ocular application of the β-blocker timolol to humans (Coakes *et al.*, 1981) and sympathetic denervation in rats (Sullivan *et al.*, 1990/91) have no apparent effect on tear IgA content.

VIP and the β-adrenergic agent isoproterenol have been demonstrated to increase, whereas the cholinergic agonist carbamyl choline has been shown to decrease, basal and androgen-stimulated SC production by rat acinar cells (Kelleher *et al.*, 1991). This neural regulation of SC synthesis may be mediated through the modulation of intracellular adenylate cyclase and cAMP activity. In support of this hypothesis, VIP and adrenergic agents are known to enhance (Mauduit *et al.*, 1984; Dartt, 1989), and cholinergic agents possibly suppress (Jumblatt *et al.*, 1990), the generation of cellular cAMP. Further, exposure of lacrimal gland acinar cells to cAMP analogs, cAMP inducers (i.e., PGE_2 and cholera toxin), or phosphodiesterase inhibitors may elevate SC production (Kelleher *et al.*, 1991). This cAMP influence on SC elaboration, although pronounced in the lacrimal gland, is not necessarily reproduced in other mucosal epithelial cells (Lambert *et al.*, 1993).

Additionally, neural pathways are extremely important in the spread of herpes virus infection in the eye (Shimeld *et al.*, 1987) and ocular viral transmission and activity may be modulated by neuropeptides (Herbort *et al.*, 1989). Moreover, although the optic nerve does not appear to regulate the ocular secretory immune system (Sullivan *et al.*, 1990/91), light does seem to control anterior chamber-associated immune deviation (Ferguson *et al.*, 1988), herpes virus-related retinitis (Hayashi *et al.*, 1988), and various parameters of systemic immunity (Maestroni *et al.*, 1987).

The secretory immune system of the eye in experimental animals also may be regulated by lymphokines. For example, interleukins (IL) 1α and 1β and tumor necrosis factor α (TNFα), but not IL-6 or interferon γ (IFNγ), stimulate the acinar cell synthesis and secretion of SC (Kelleher *et al.*, 1991). The regulatory effect of TNFα on acinar cell SC production is similar to that found in colonic cell lines, in which TNFα increases the production, surface expression, and release of SC (Kvale *et al.*, 1988a,b). However, the absence of IFNγ effect on SC output by acinar cells is notable because this lymphokine regulates SC dynamics in both intestinal (Sollid *et al.*, 1987; Kvale *et al.*, 1988a) and uterine (Wira and Prabhala, 1992) epithelial cells. Although IL-6 appears to have no influence on lacrimal SC production (Kelleher *et al.*, 1991), both IL-6 and IL-5 stimulate the synthesis of IgA in lacrimal tissue explants (Pockley and Montgomery, 1990/91b) and, in combination, augment the secondary tear IgA antibody response to pneumococcal antigen (Pockley and Montgomery, 1991) and suppress IgG and IgM synthesis in lacrimal tissue (Pockley and Montgomery, 1990/91a). As a further consideration, androgens, VIP, and IL-1 all share the capacity to increase IgA production in specific tissues (Drew and Shearman, 1985; Stanisz *et al.*, 1986; Crowdery *et al.*, 1988; Sullivan and Hann, 1989a); pIgA, in turn, may heighten the monocytic output of TNFα (Deviere *et al.*, 1991). If analogous activity occurs in the lacrimal gland, then various neuroimmunoendocrine factors may control the synthesis of both IgA antibodies and the IgA receptor, leading to enhanced antibody transfer to tears and improved ocular surface defense.

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