Pathophysiology of Ocular Allergy

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Disclosure Statement
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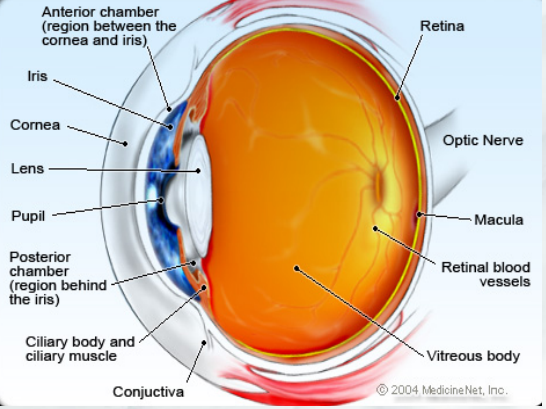
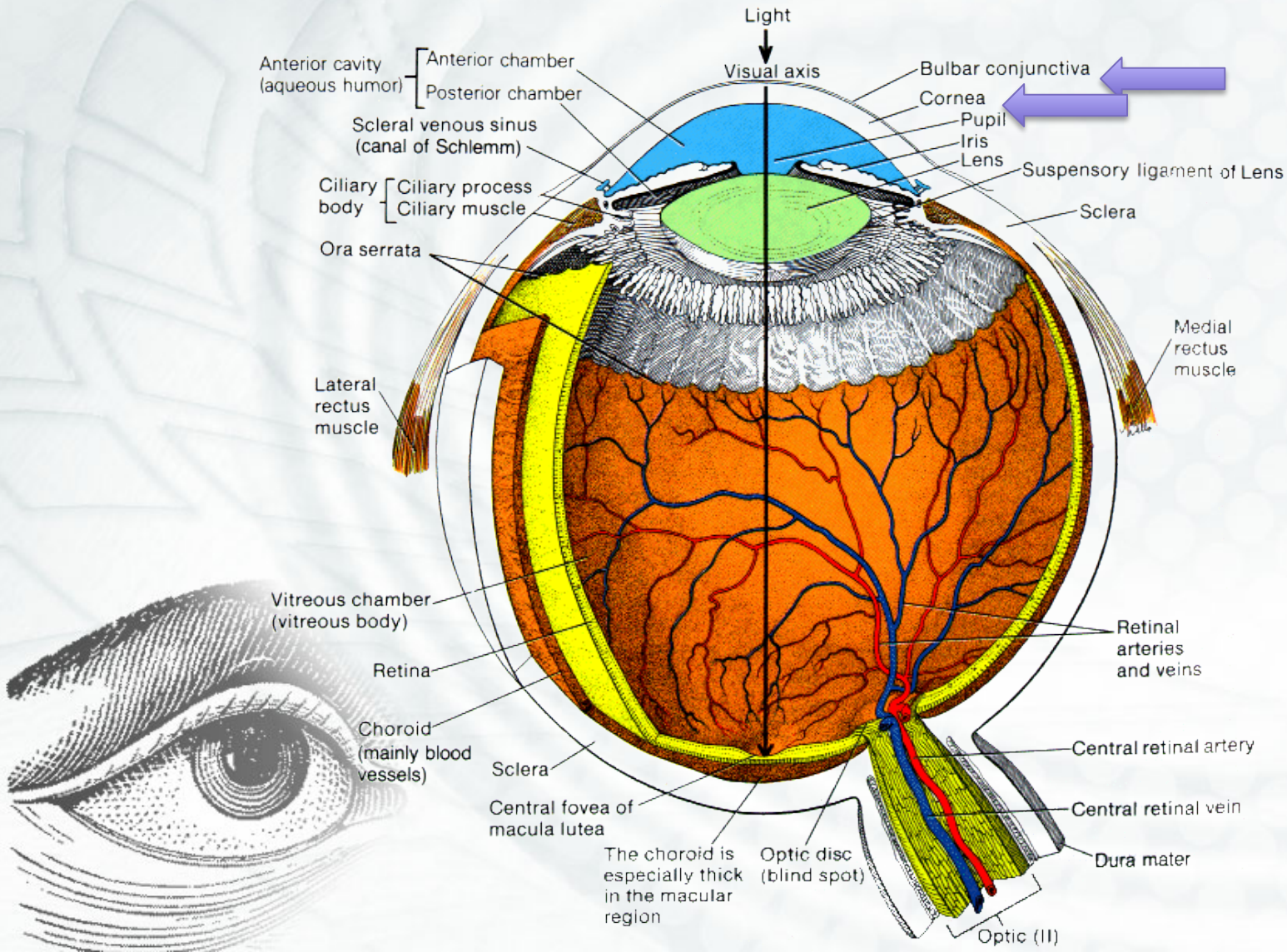


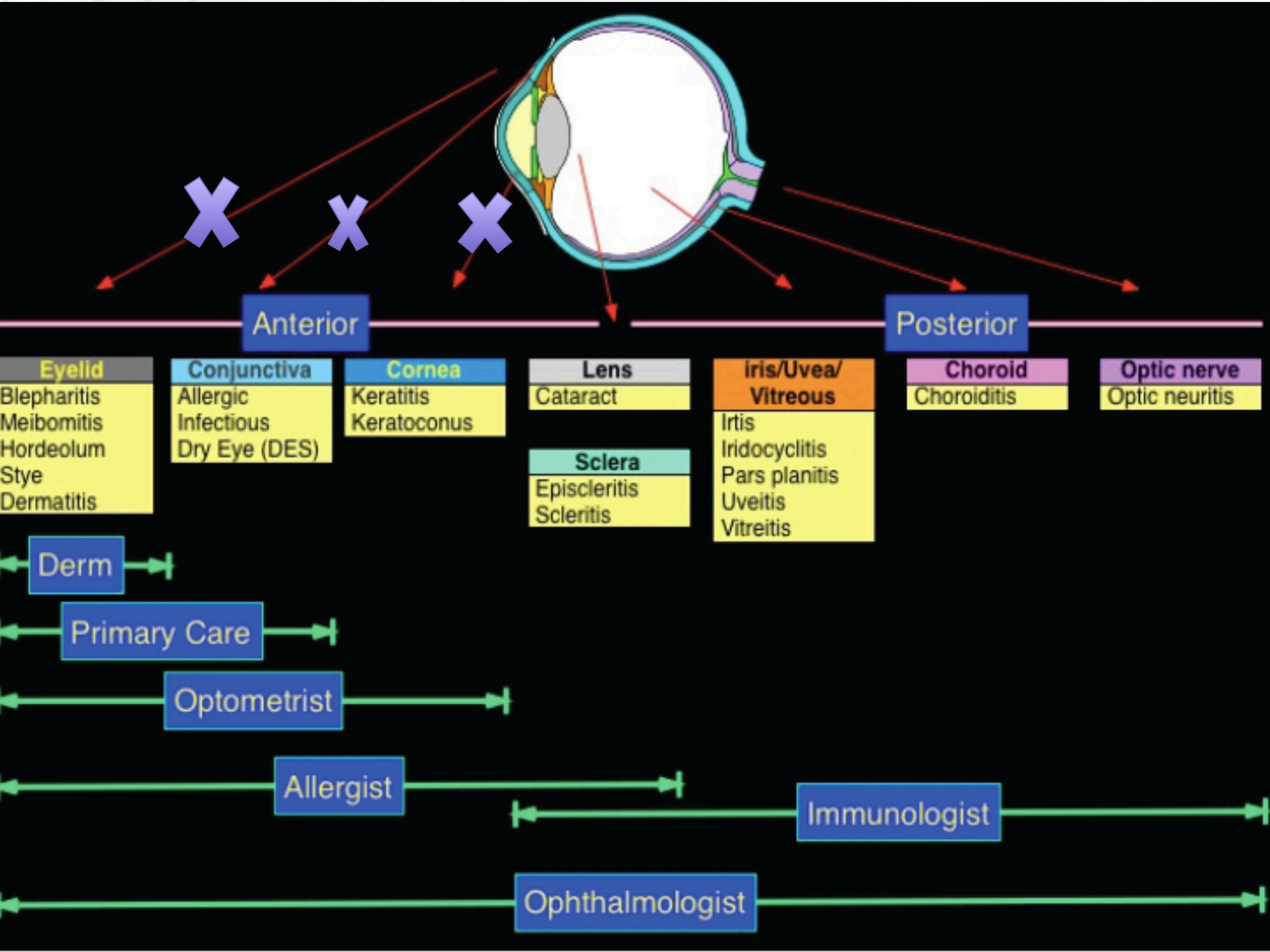
Learning Objectives

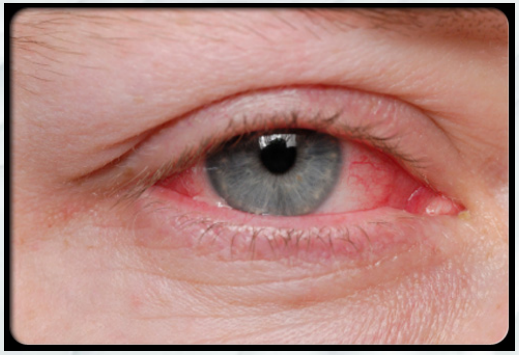
At the end of this lecture, the attendee should be able to :

- **List the 5 major types of ocular allergy**
- **Describe the major signs and symptoms for each major type of ocular allergy**
- **Discuss the differences in pathophysiology between the major types of ocular allergy**

Transverse view of L eyeball



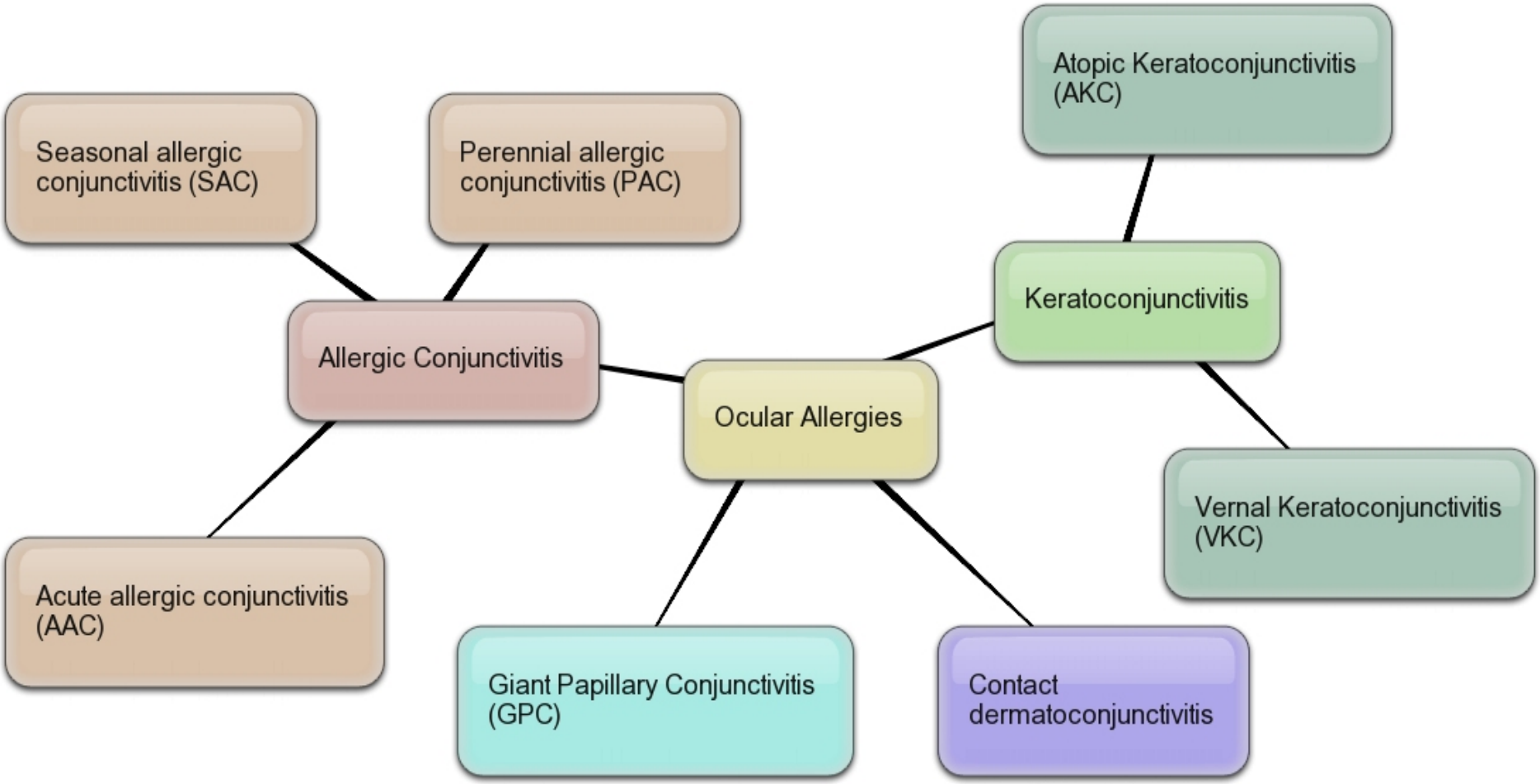

Anterior
Posterior
Eyelid
Blepharitis
Meibomitis
Hordeolum
Stye
Dermatitis
Conjunctiva
Allergic
Infectious
Dry Eye (DES)
Cornea
Keratitis
Keratoconus
Lens
Cataract
Sclera
Episcleritis
Scleritis
Iris/Uvea/ Vitreous
Irtis
Iridocyclitis
Pars planitis
Uveitis
Vitreitis
Choroid
Choroiditis
Optic nerve
Optic neuritis
Derm
Primary Care
Optometrist
Allergist
Immunologist
Ophthalmologist



Ocular Allergy

- Allergic Conjunctivitis
  - Season Allergic Conjunctivitis
  - Perennial Allergic Conjunctivitis
- Vernal Keratoconjunctivitis
- Atopic Keratoconjunctivitis
- Giant Papillary Conjunctivitis
- Contact Ocular Dermatitis

Ocular Allergy Classification



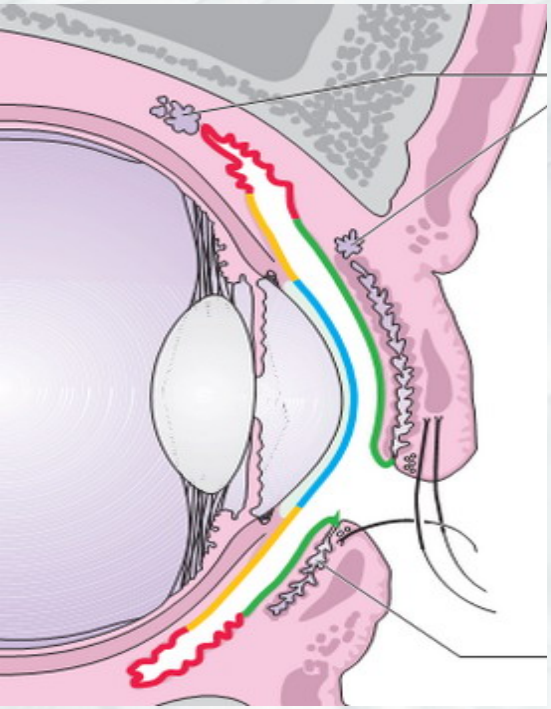
Ocular Allergy & Pathophysiology

- Ocular Allergy Mechanisms

  - **<u>Adaptive immunity</u>**
    - IgE-mast cell-mediated
    - T-lymphocyte-mediated
      - T cell-mediated cytotoxicity
      - Th1: IFN-gamma recruits/ activates macrophages *(contact dermatitis)*
      - Th2: IL-5 recruits/activates eosinophils *(most important in most ocular allergy)*

Ocular Allergy & Pathophysiology

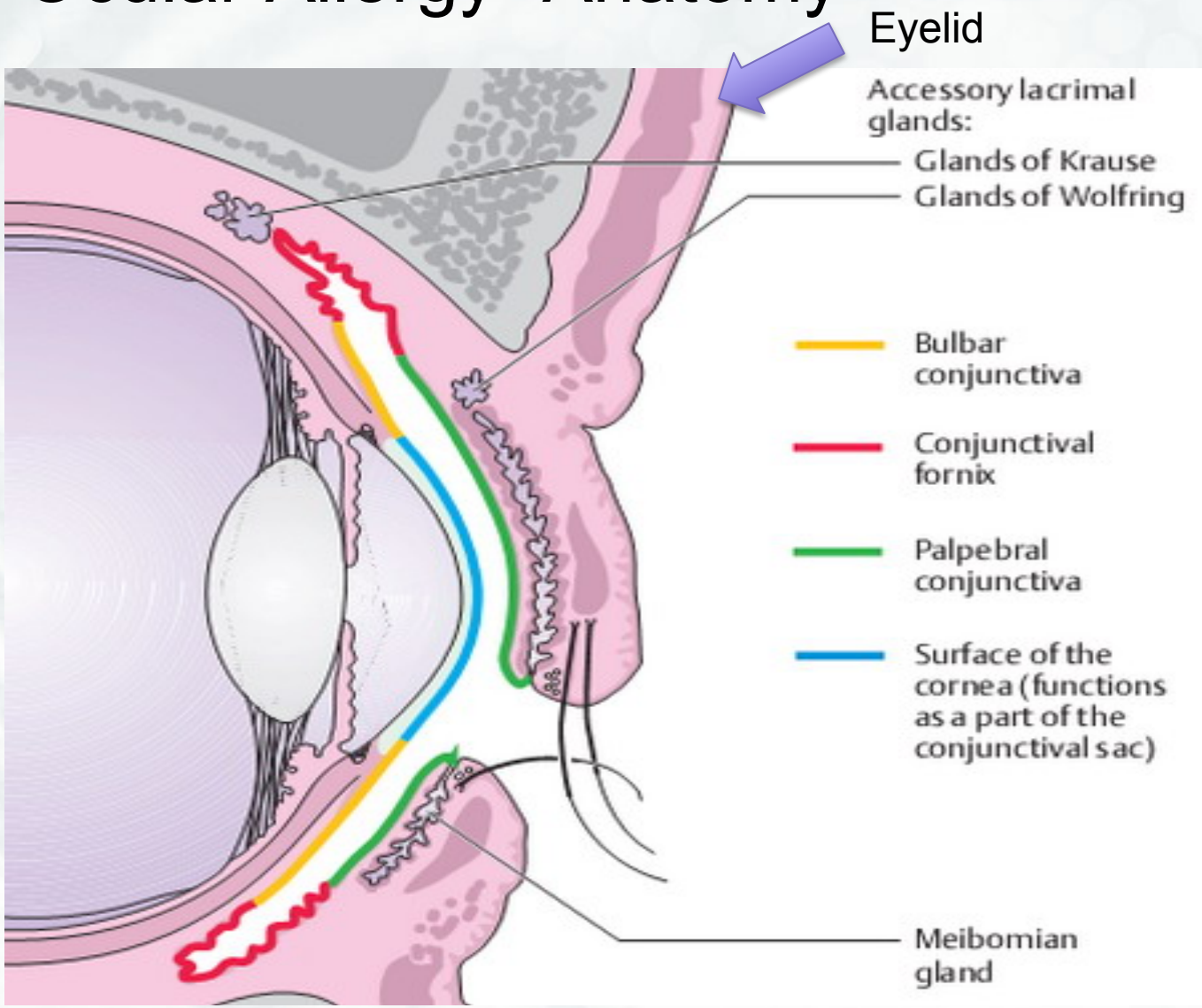
- Ocular Allergy Mechanisms
  - **Innate immunity** (new research)
    - New evidence of innate/adaptive cross-talk in ocular allergy
    - Toll like receptor expression found in cornea and conjunctiva
    - Commensal flora which helps to maintain epithelial mucosal homeostasis may help protect against allergy
- Ocular allergy (all types) may differ **more in quantity than quality** of cytokines in tears, with **both Th1 and Th2 profiles**

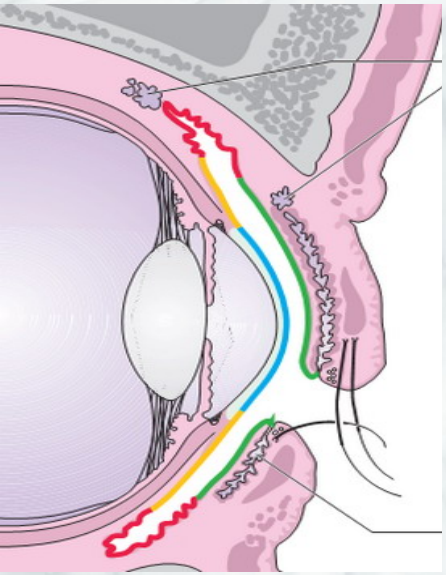


Ocular Allergy & Pathophysiology

- Eye structures involved
  - Conjunctiva
  - Cornea
  - Limbus
  - Eyelid

Ocular Allergy- Anatomy

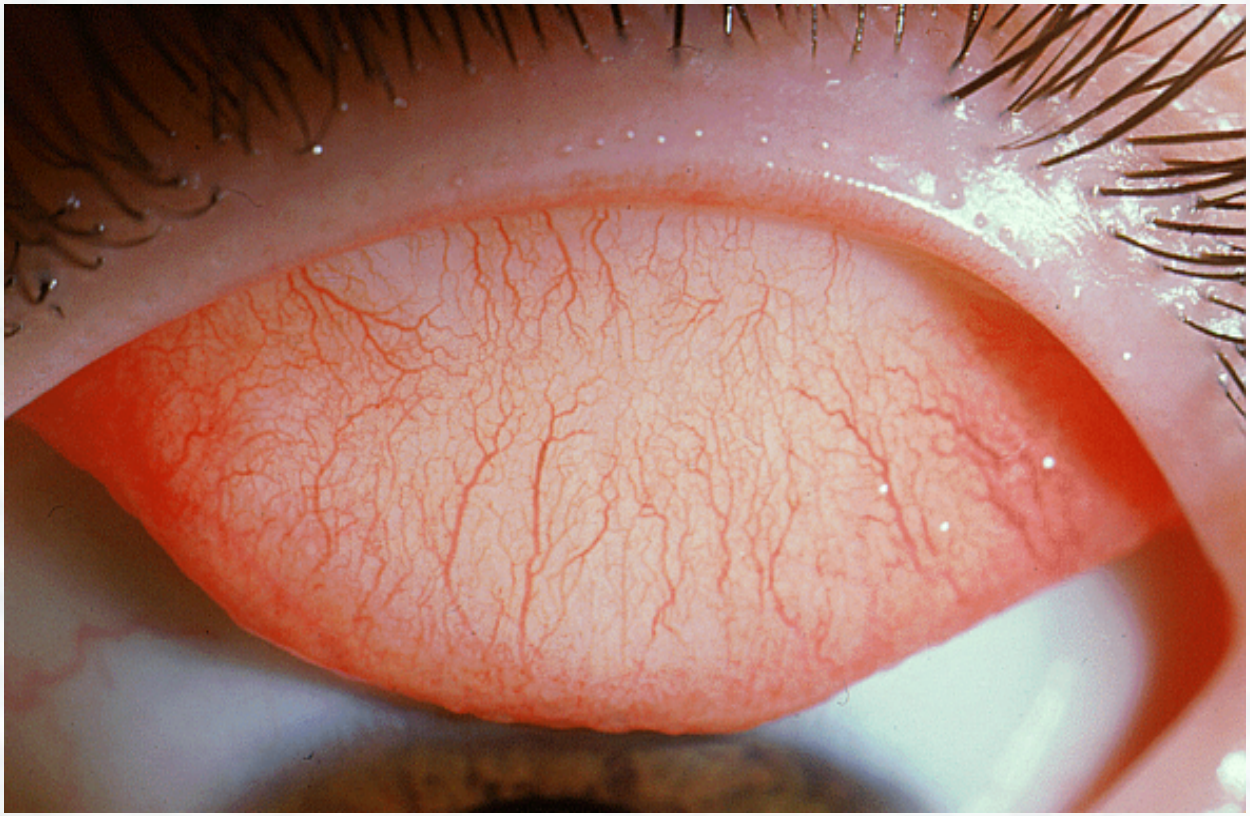




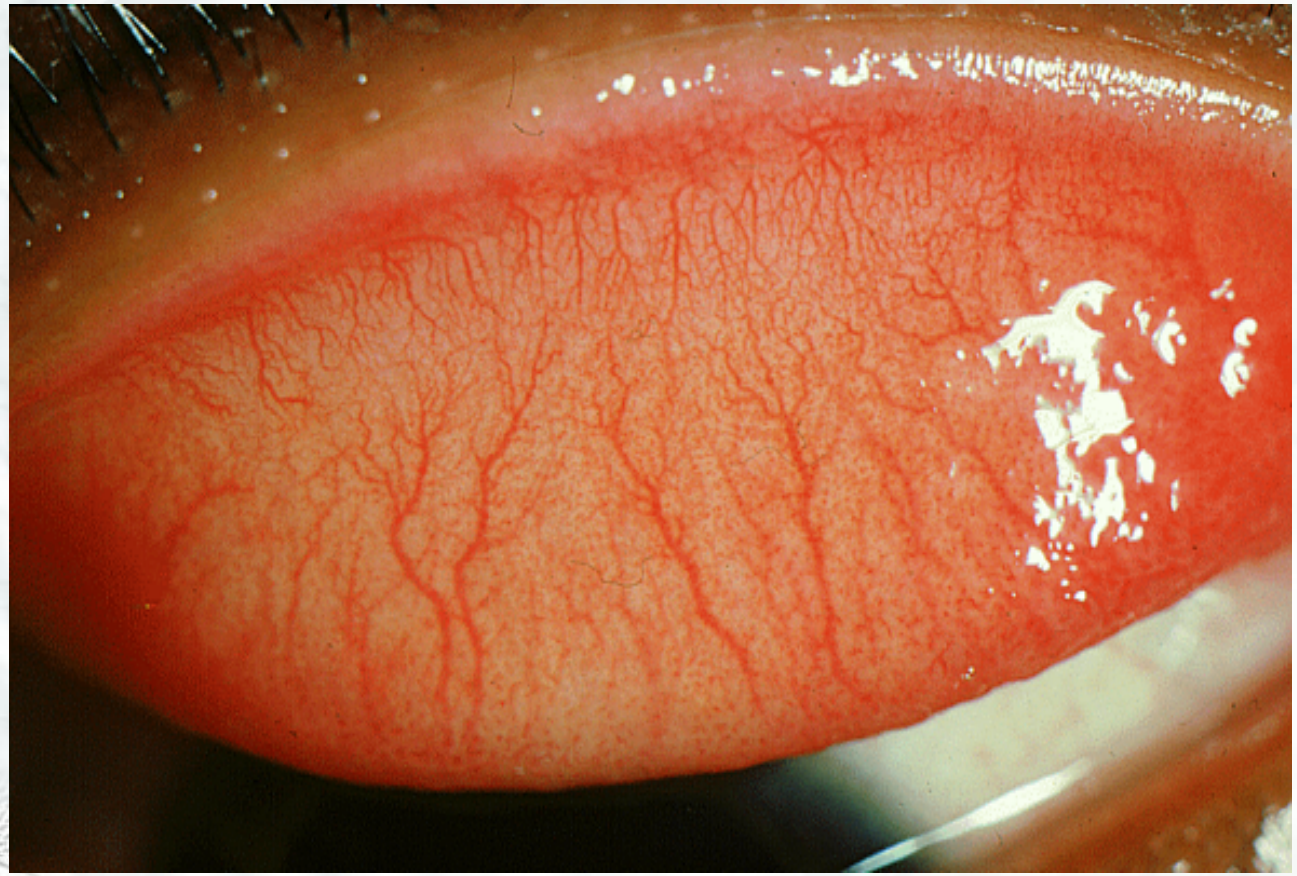
Ocular Allergy & Pathophysiology

- Eye structures involved
  - Conjunctiva
  - Cornea
  - Limbus
  - Eyelid
- Cells & mediators responsible
  - B lymphocytes
  - T lymphocytes
  - Cytokines
  - Chemokines
  - Allergen presenting cells

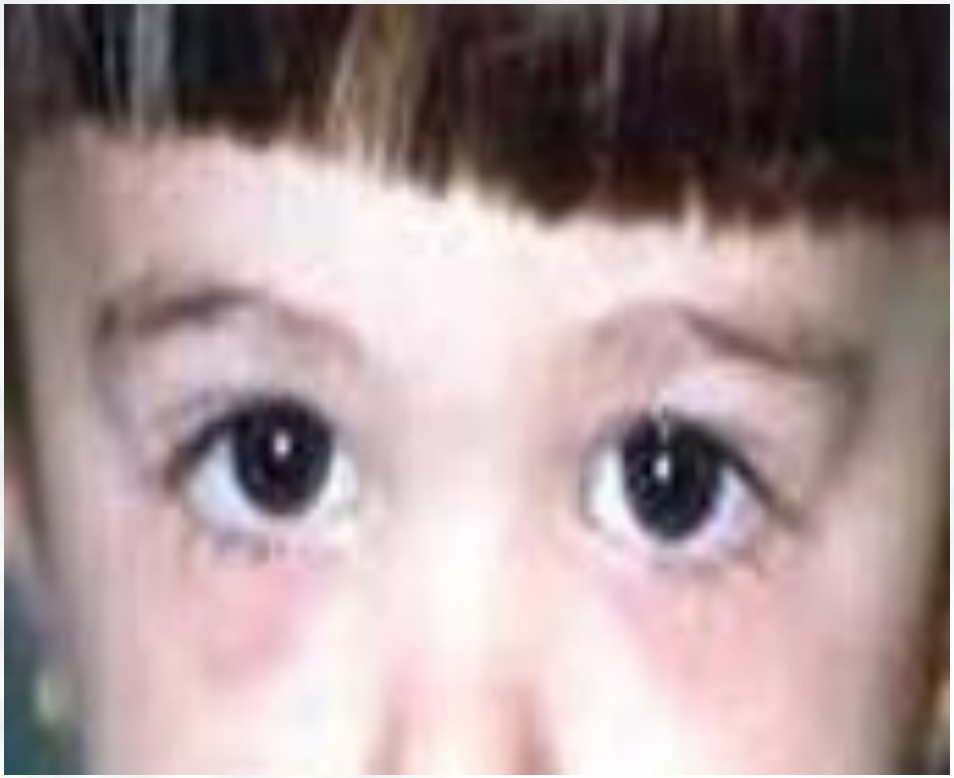
Seasonal allergic conjunctivitis with moderate injection



Persistent intermittent allergic conjunctivitis



Allergic Shiners



Allergic Conjunctivitis

Affects approximately 20% population

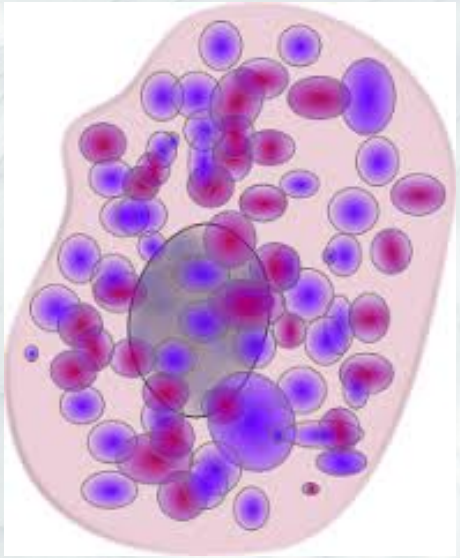
Symptoms

- Red, itchy, burning, watery
- Dryness/irritation
- Discomfort
- Mucoid discharge

Signs

- Bulbar conjunctival hyperemia and edema
- Eyelid chemosis and edema
- Mild watery discharge
- Papillary hypertrophy of upper palpebral conjunctiva
- Cornea rarely involved

Chemosis



MAST CELL

Allergic Conjunctivitis Pathophysiology

- Mast cell-IgE immediate reaction (major immunological process)
- Eosinophil-Th2 delayed reaction (relatively minor immunological process)
- Cell-mediated cytotoxicity (if prolonged and severe)
- H1 is main mediator
- Mast cells are of mucosal type (TC_T)
- Conjunctiva is main affected tissue
- sIgE elevated serum/tears
- **Mast cell** in main cell in this disease

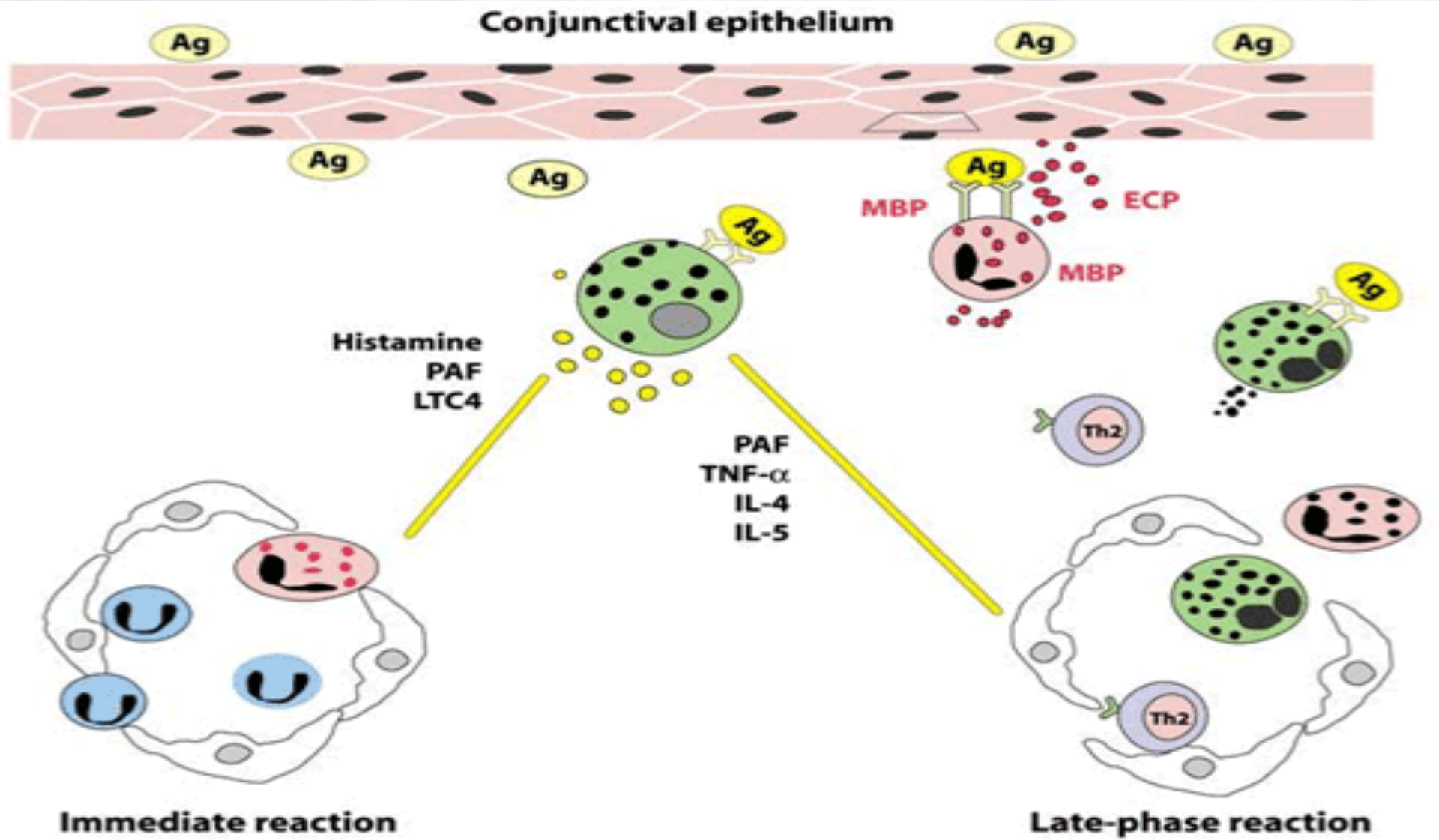
Allergic Conjunctivitis Pathophysiology

- ↑ Mast cells
- H1 & H2 lymphocytic receptors important
- ↑ Eosinophils (esp. in substantia propria)
- Tears have
  - ↑ Histamine
  - ↑ Tryptase
  - ↑ Leukotriene C4
  - ↑ Eosinophilic peroxidase
  - ↑ Cationic protein
  - ↑ IgE

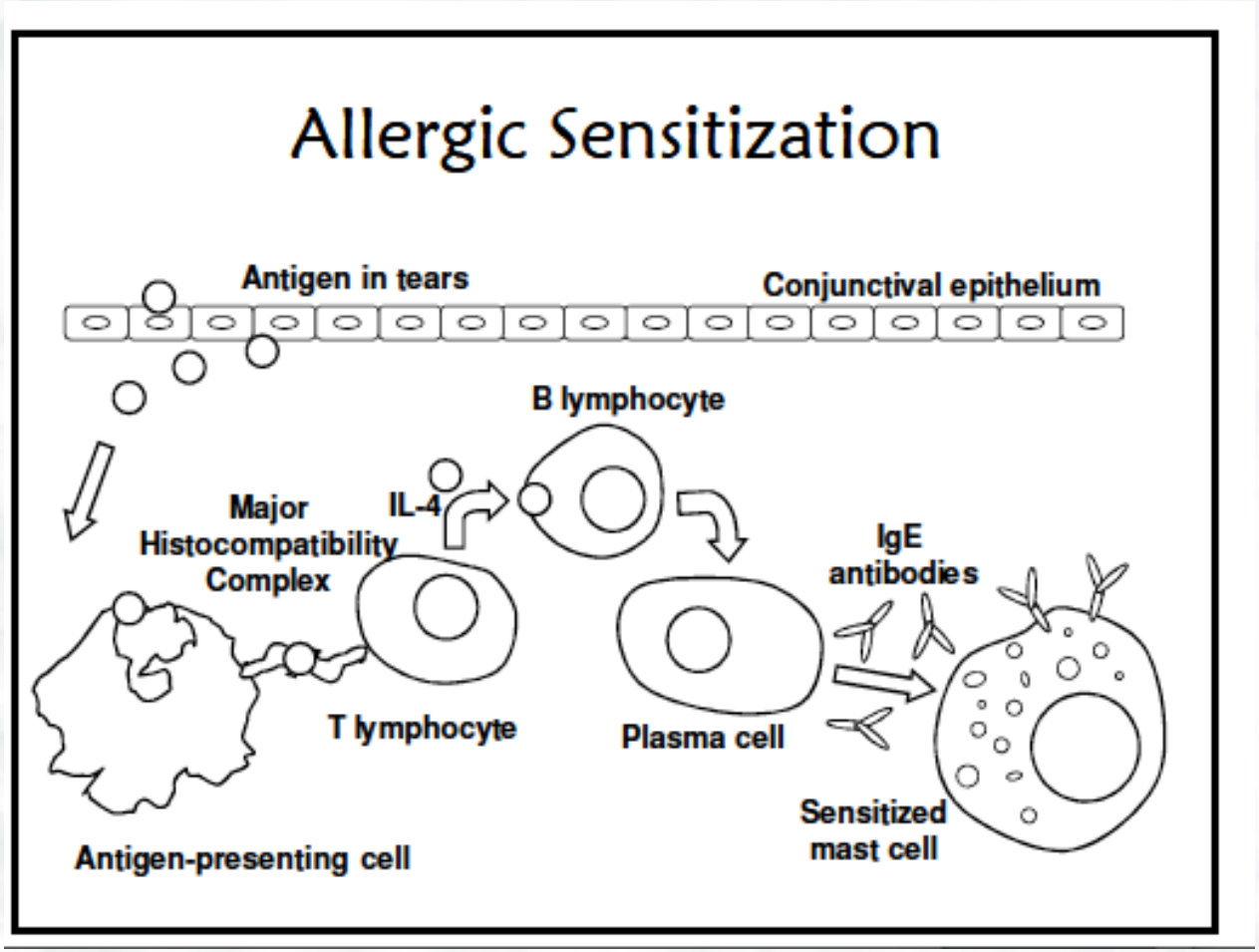
Mediators of IgE-related reactions producing Allergic Conjunctivitis symptoms

- **Histamine:** Itching, redness, edema
- **Prostaglandins:** Sensitized nerves, enhanced pain, edema, redness
- **Leukotrienes**: Chemotaxis, edema, & vascular permeability
- **Chemotactic factors:** Recruitment of eosinophils and neutrophils leading to tissue destruction

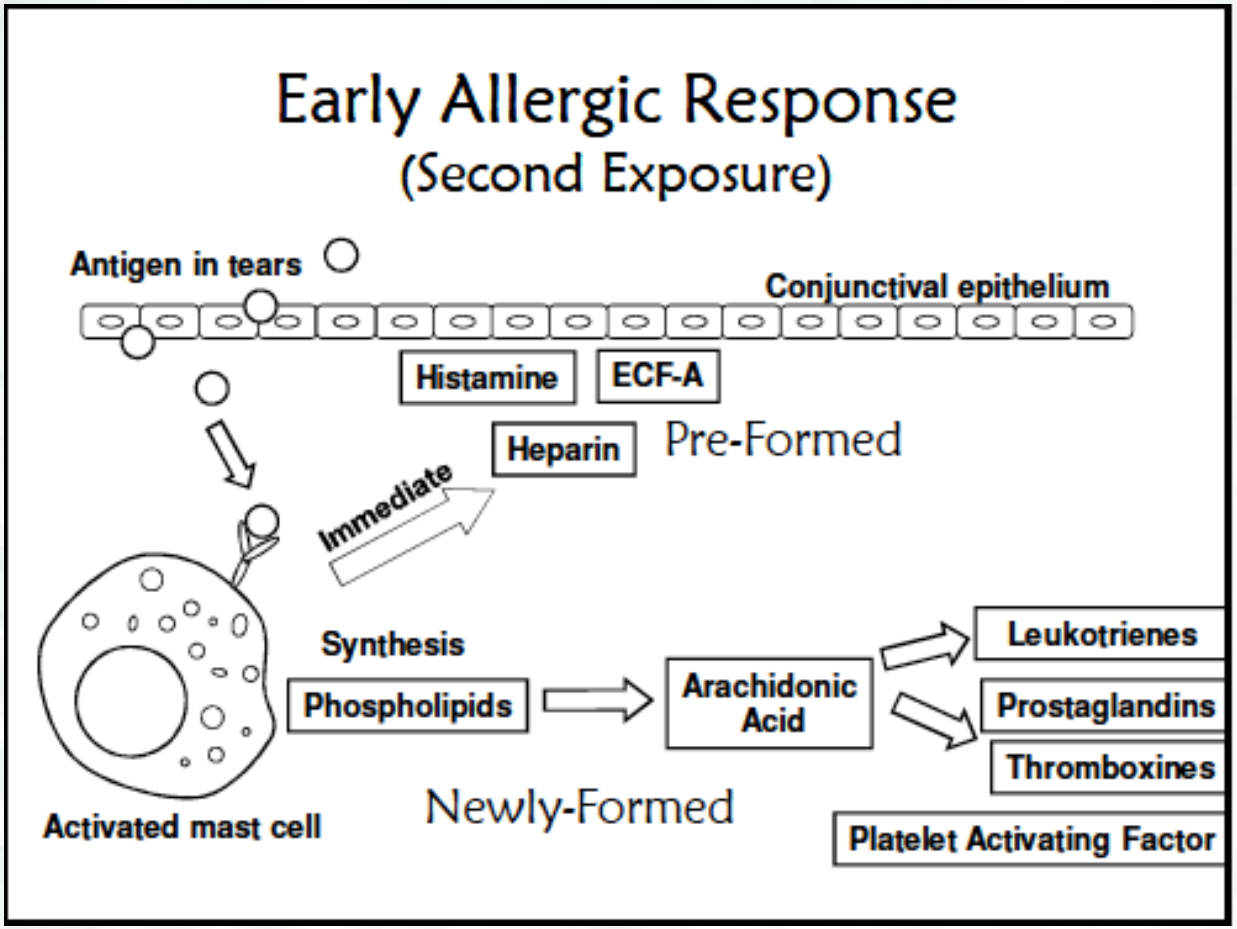
Conjunctival Epithelium



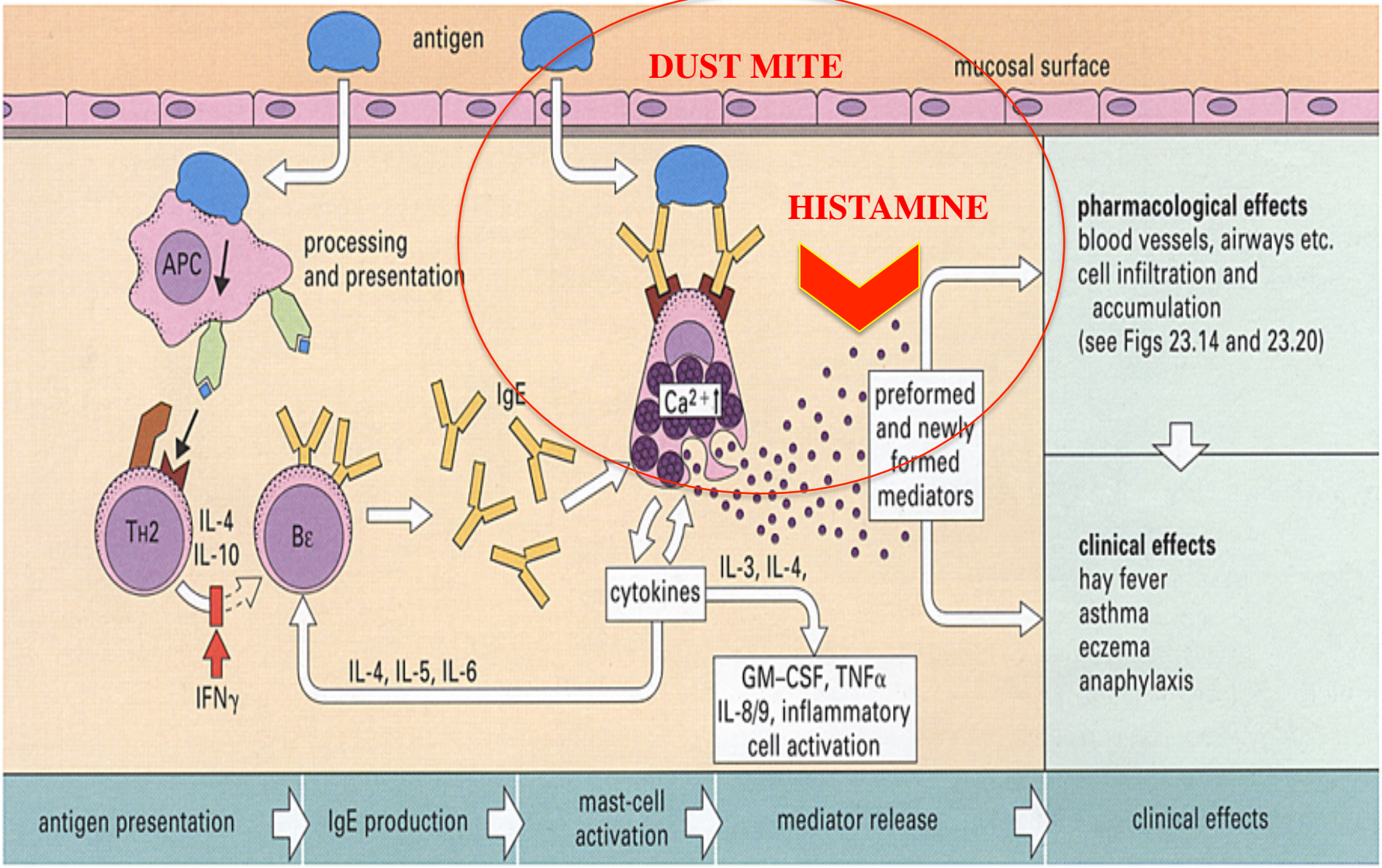
IgE Allergic Sensitization
First exposure to allergen



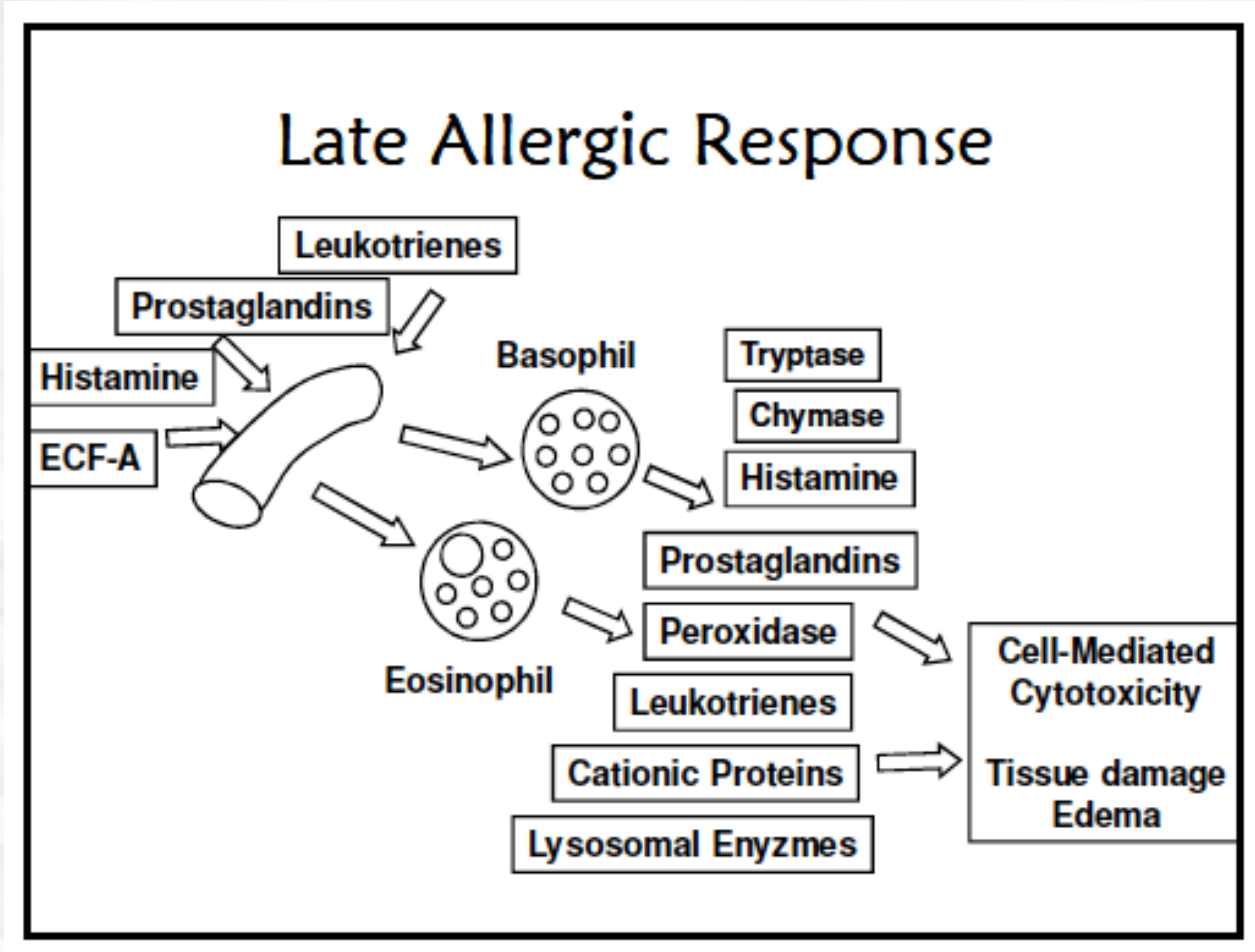
Mast cell-IgE Immediate Reaction



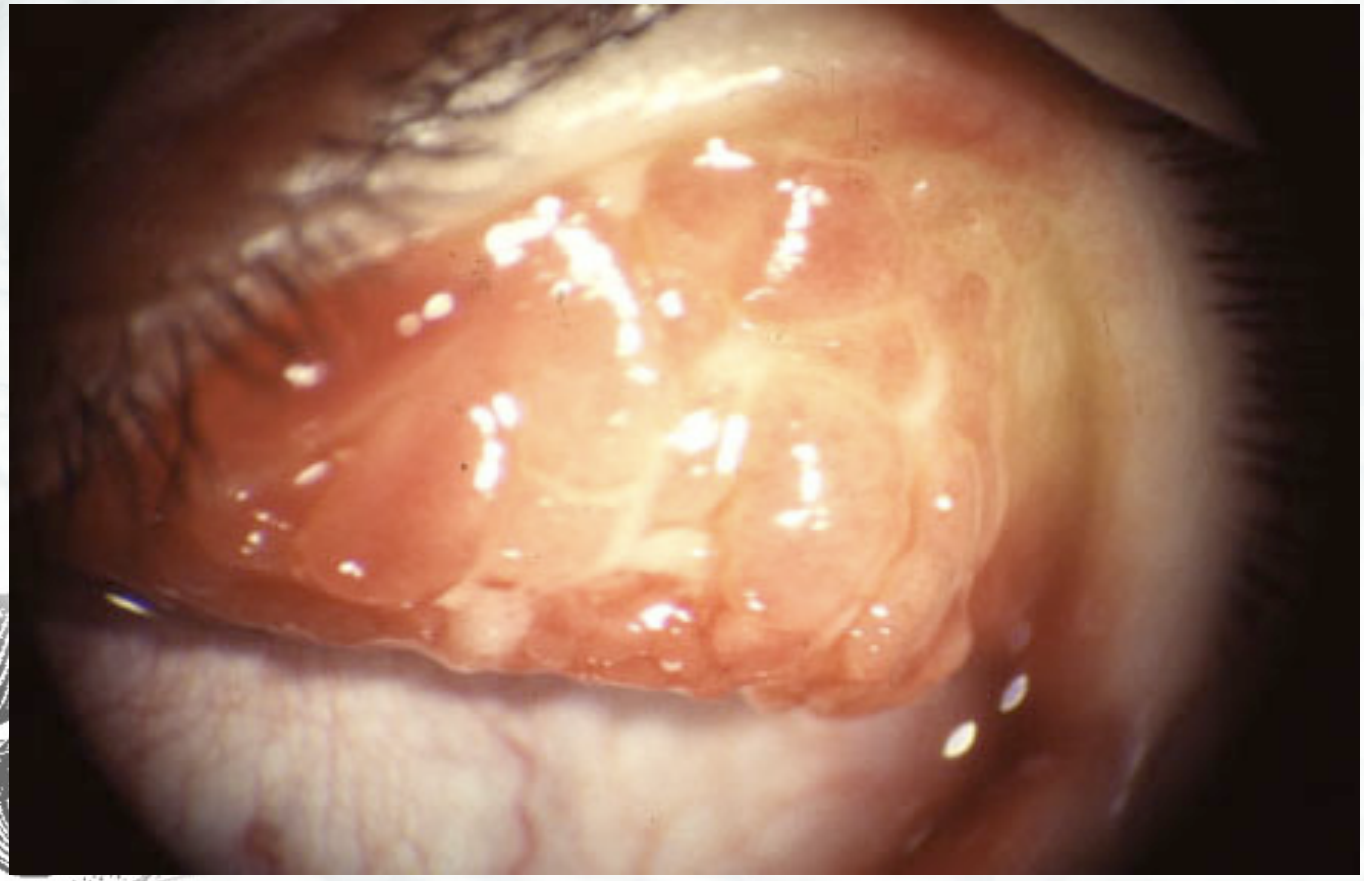
Pathophysiology of an immediate allergic reaction



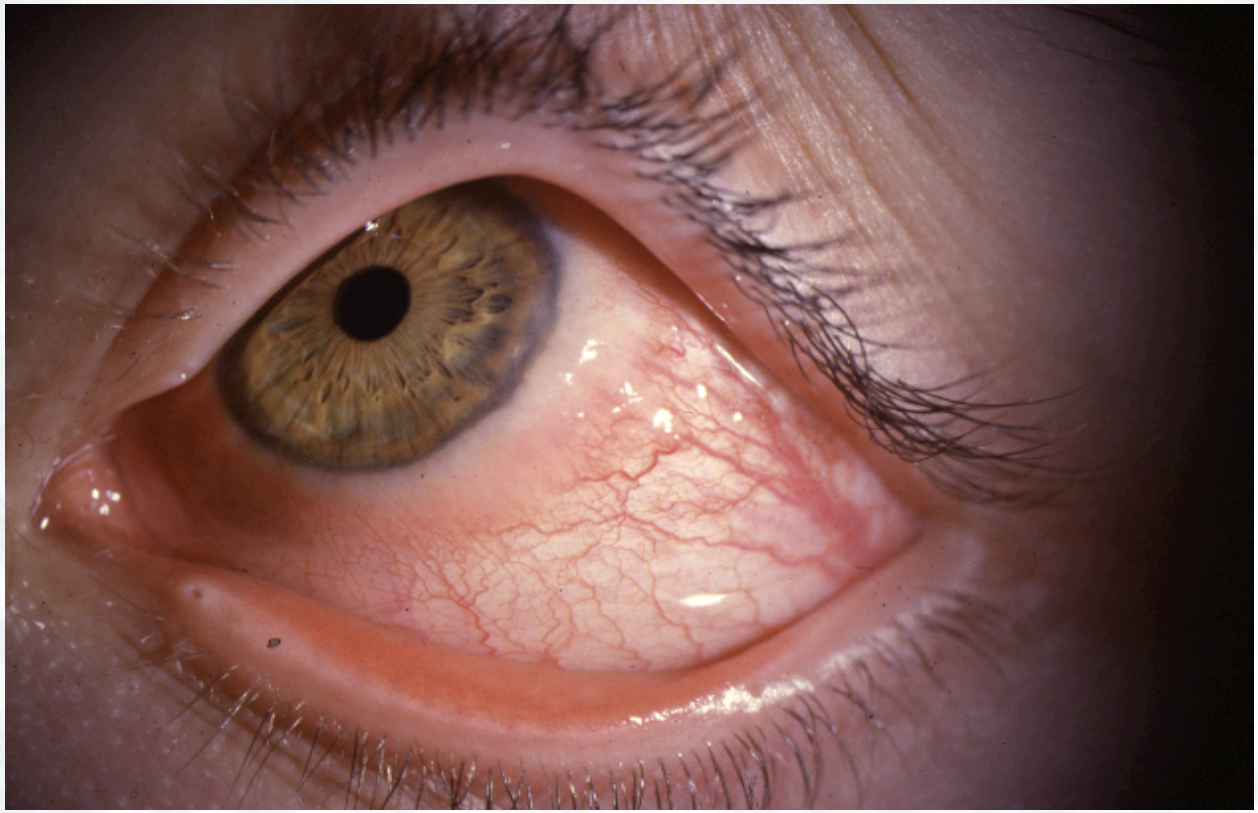
Eosinophil-Th2 Delayed Reaction



Tarsal vernal keratoconjunctivitis



Limbal Vernal conjunctivitis



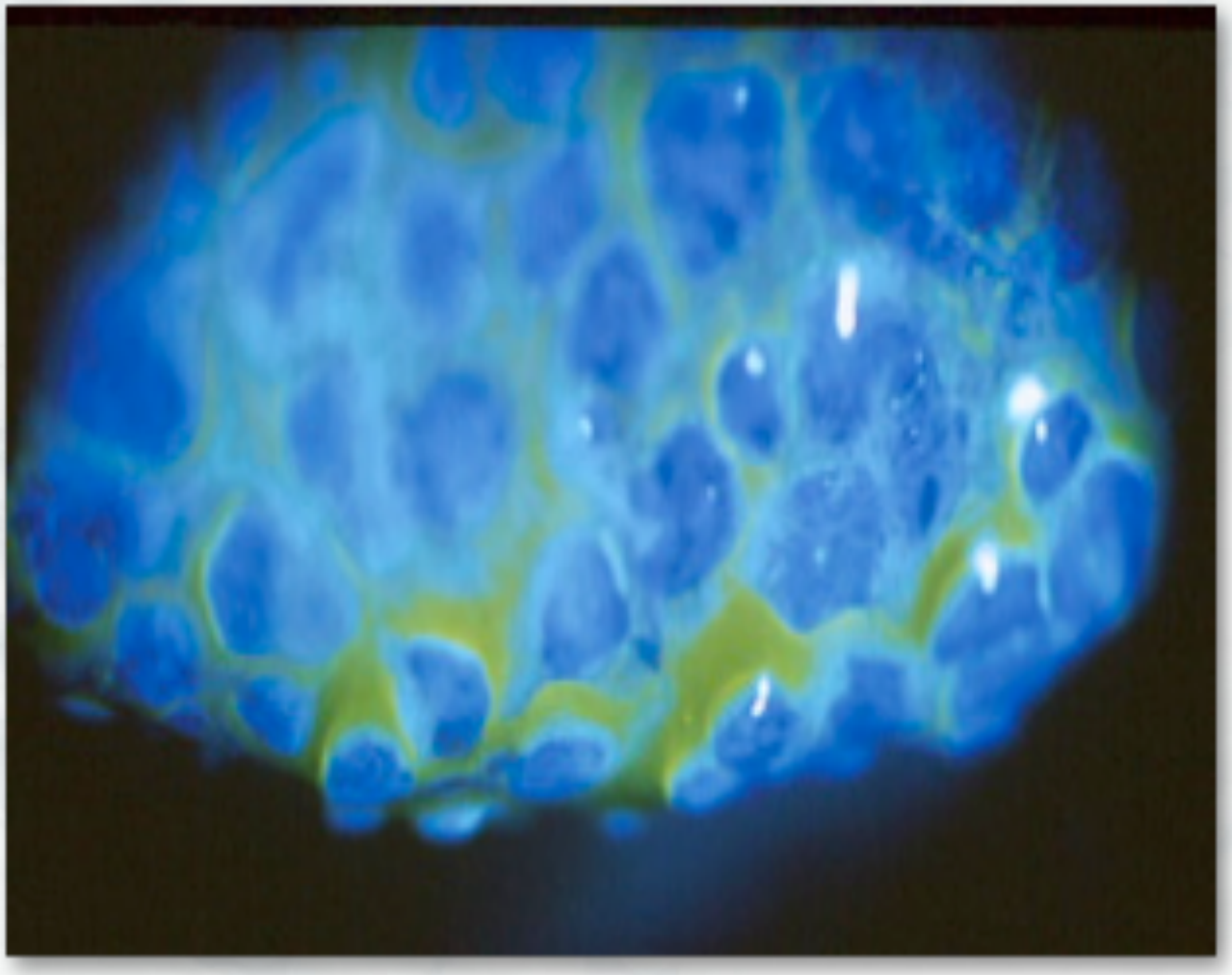
Vernal Keratoconjunctivitis

- In US and temperate climates peaks in childhood 11-13 y/o (3-25yr)
- Lasts 4-11 yrs
- Males > females
- Worse spring and summer
- sIgE to pollen and perennial allergens in most patients
- Some patients lack sIgE
- Elevated serum/tear total and sIgE
- Cornea, limbus, conjunctiva involved

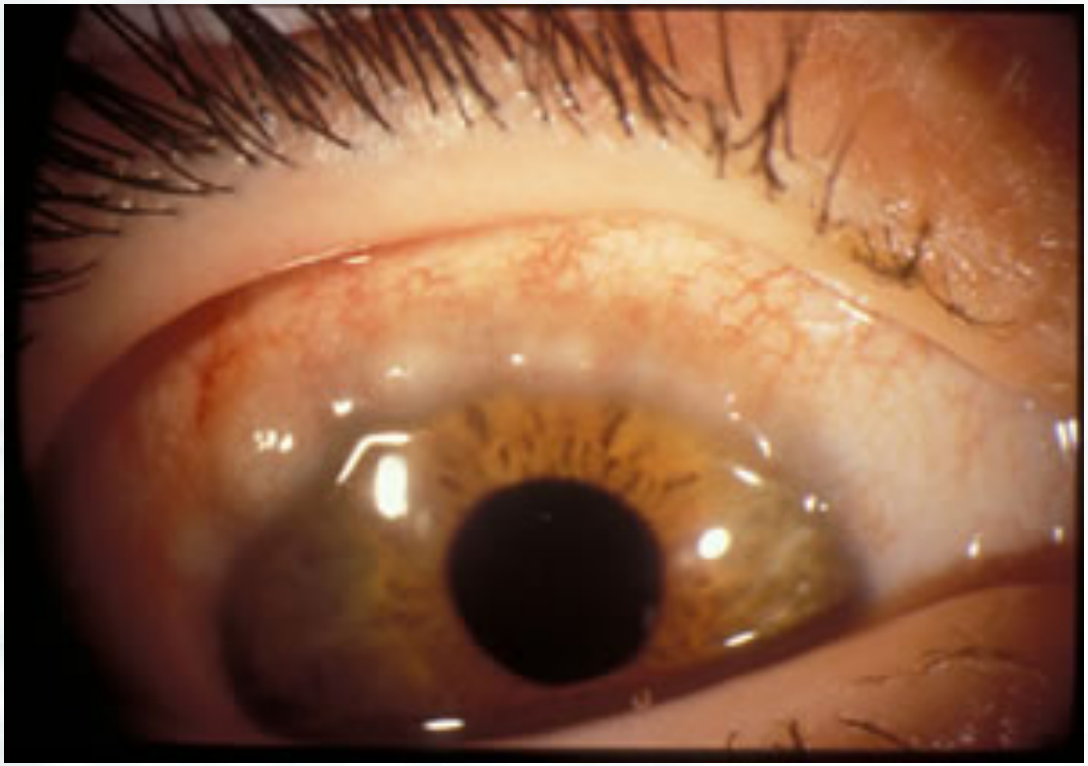
Vernal Keratoconjunctivitis

SYMPTOMS	SIGNS
Intense itching	Giant papillae
Intense tearing	Horner-Trantas dots
Severe photophobia	Shield Ulcers (corneal plaque)
Intense foreign body sensation	Epithelial plaques
Thick ropy discharge	Corneal ulceration
Ocular pain (cornea is involved)	Superficial punctate keratitis

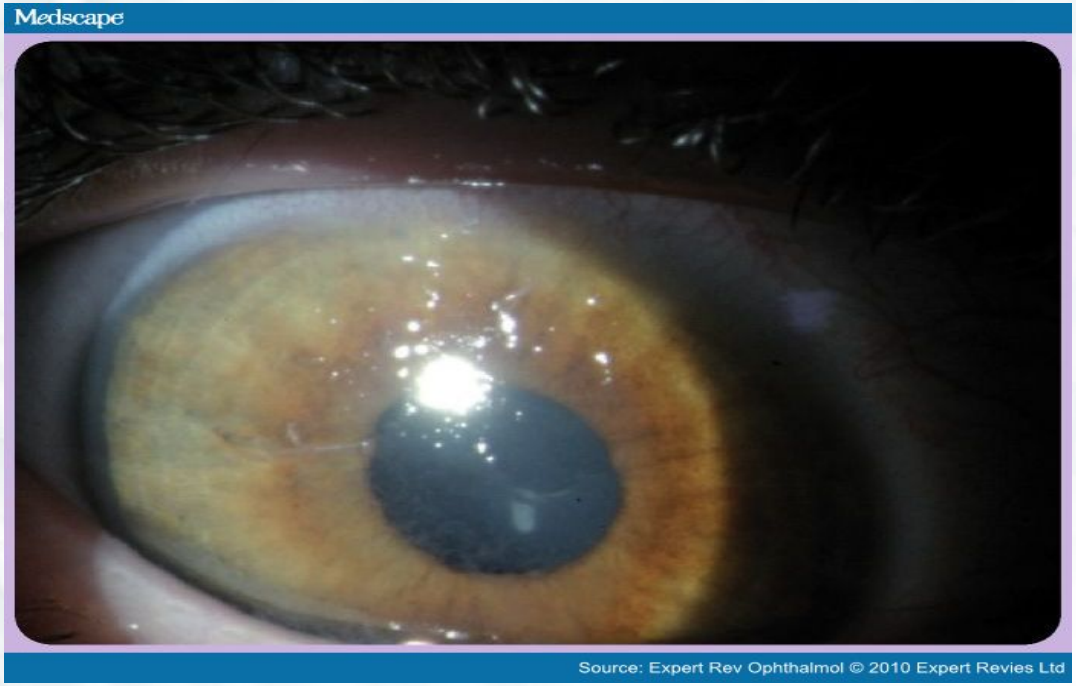
Fluorescein staining of the papillary conjunctivitis



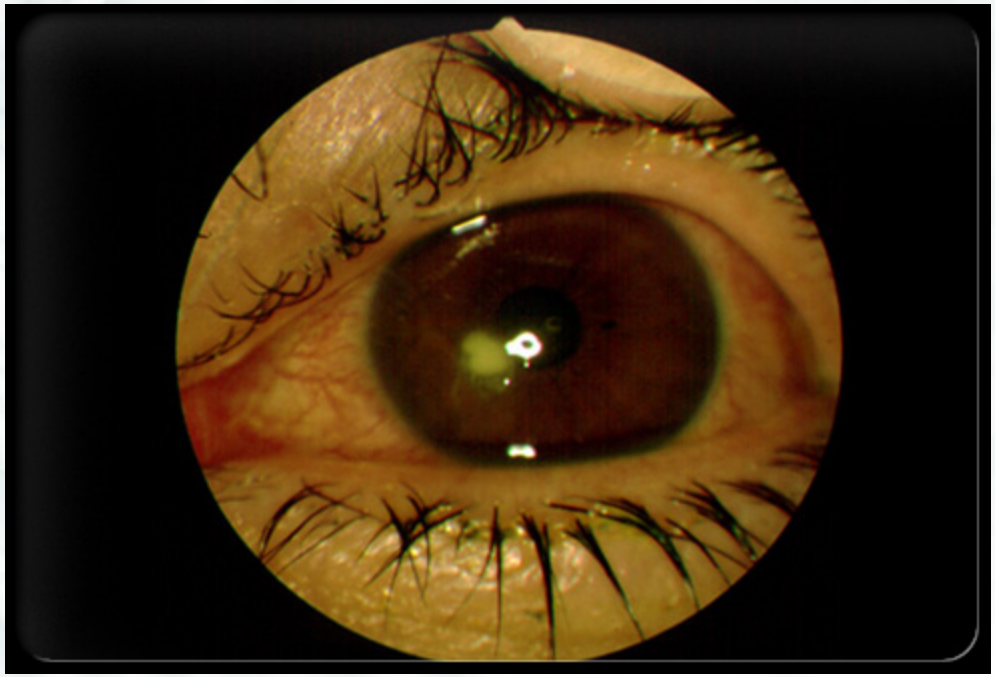
Horner-Trantas dots



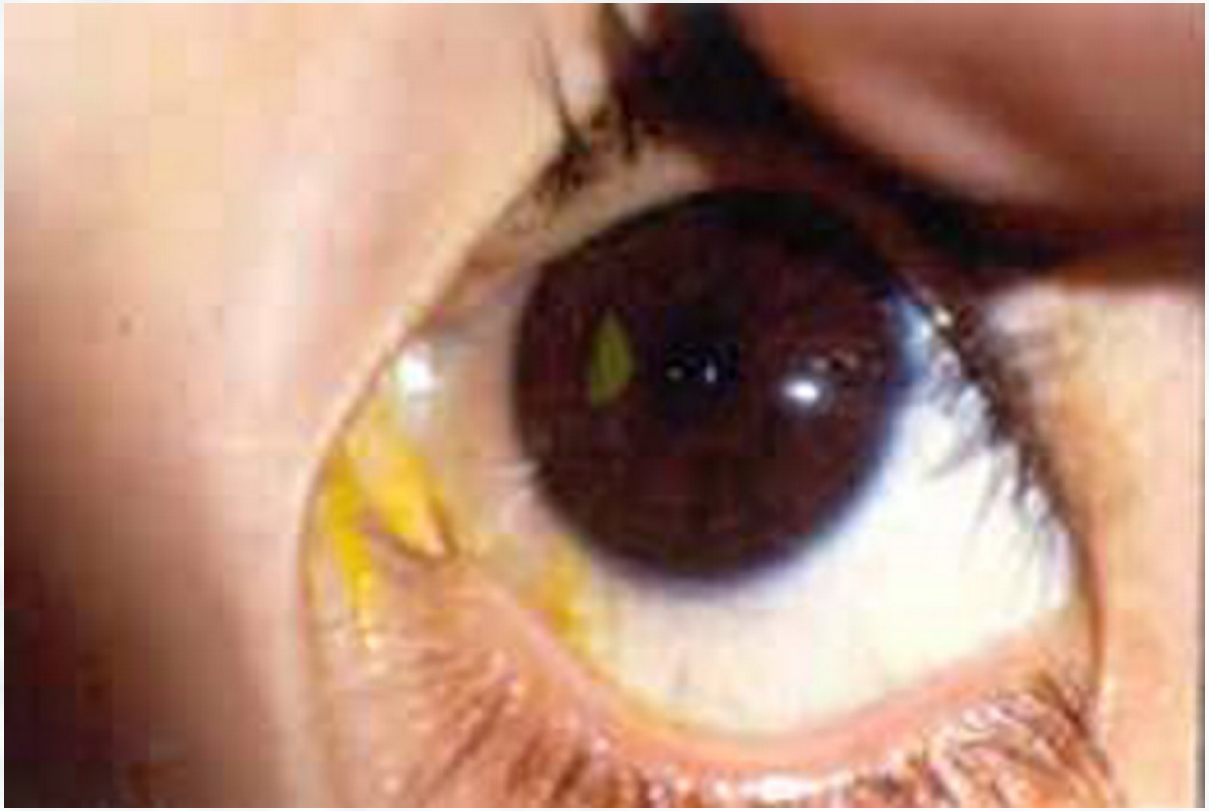
Shield Ulcer



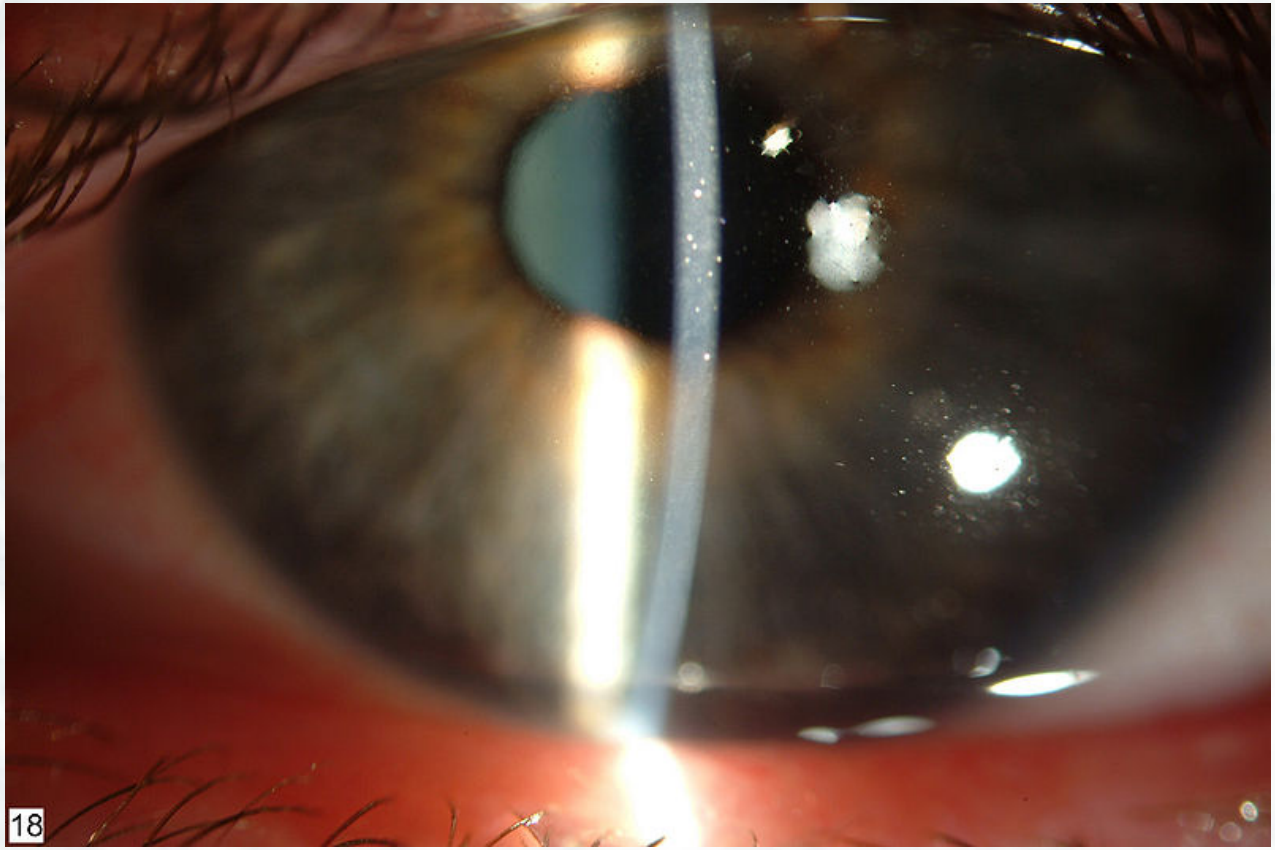
Corneal Ulcer



Corneal ulcer staining with fluorescein



Superficial Punctate Keratitis

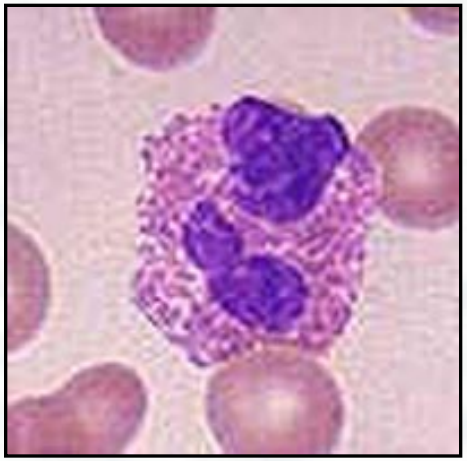


Vernal Keratoconjunctivitis

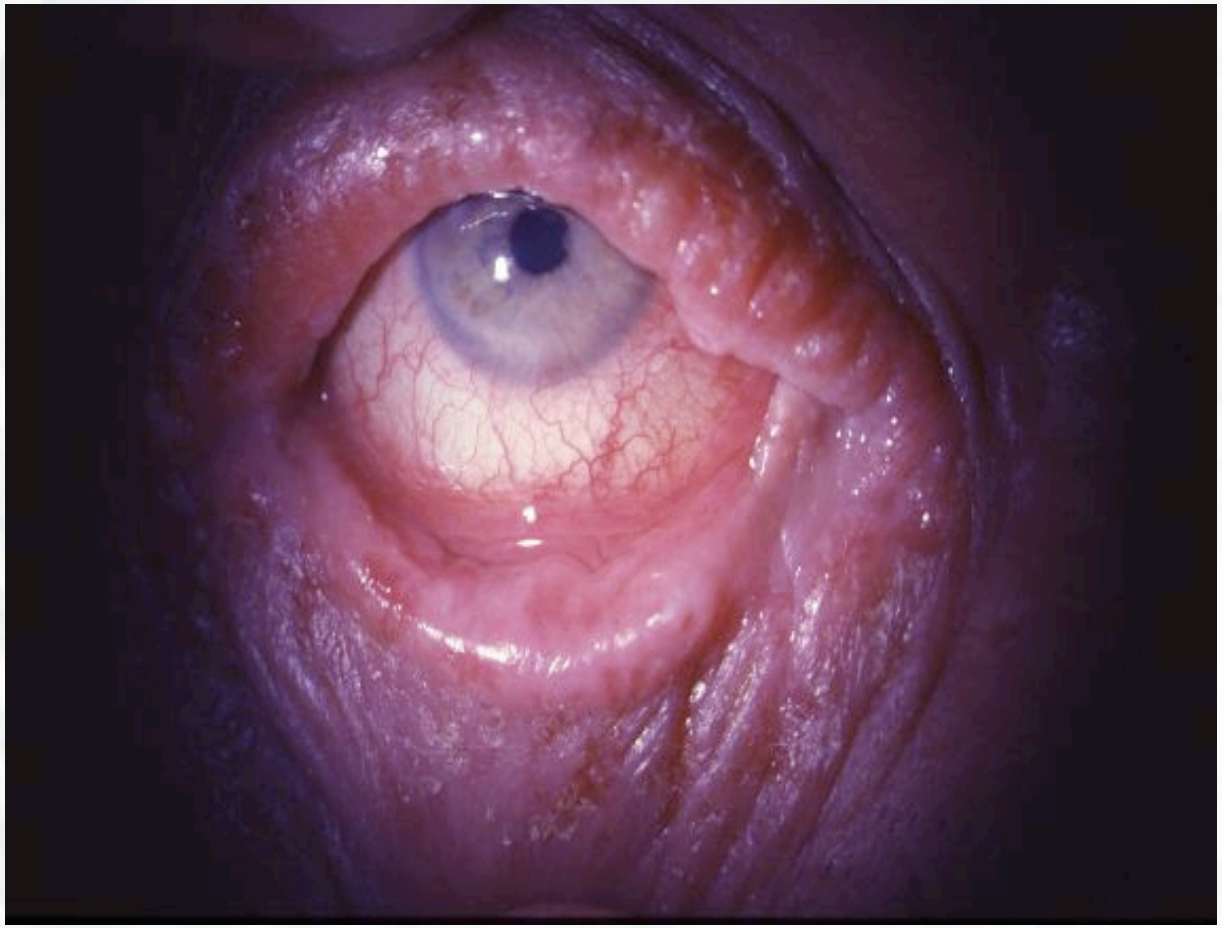
- May represent over-expression of chromosome 5q which regulates:
  - IL-3, IL-4, IL-5, and GM-CSF
- ↑ Nerve growth factor, Substance P, IL-9 IL-13, eotaxin
- 2 major forms
  - Giant Papillae- upper tarsal conj.
  - Limbal- gelatinous infiltrates

Vernal Keratoconjunctivitis

- Late phase eosinophil-Th2 response is major immune response
- IgE-mast cell response is minor Mast cells are TC $_{TC}$ (connective tissue type)
- Corneal fibroblasts play key role in ↑eotaxin
- Eosinophil is main cell in this disease



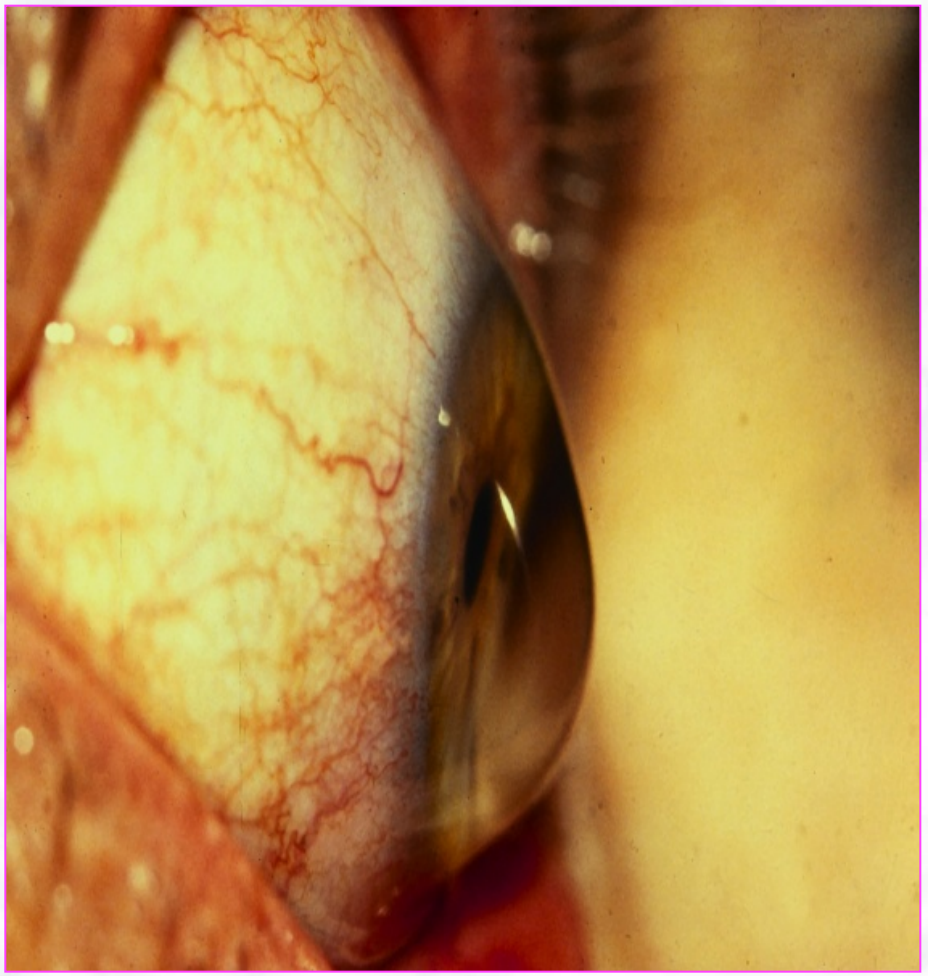
Atopic keratoconjunctivitis

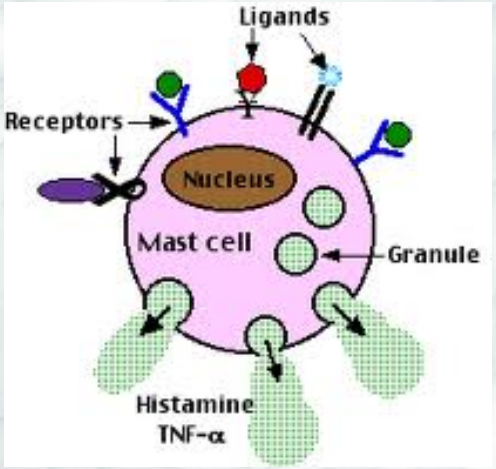


Atopic Keratoconjunctivitis

- Presents in atopic individuals in late adolescents/young adults
- Males> females
- Childhood hx of atopic dermatitis
- Perennial symptoms but worse in winter/ dryer climates
- Conjunctiva, eyelids, periorbital area, cornea, limbus involved
- Severe patients may develop keratoconus

Keratoconus





Atopic Keratoconjunctivitis

- Late phase Type 1 IgE-mast cell mediated immune response if <u>most</u> important
- T-lymphocyte-mediated hypersensitivity
  - Th2 eosinophil triggered is <u>moderately</u> important
  - Th1 cell-mediated is involved

· ↑ Eosinophils in serum and tears

· ↑↑↑ IgE in serum

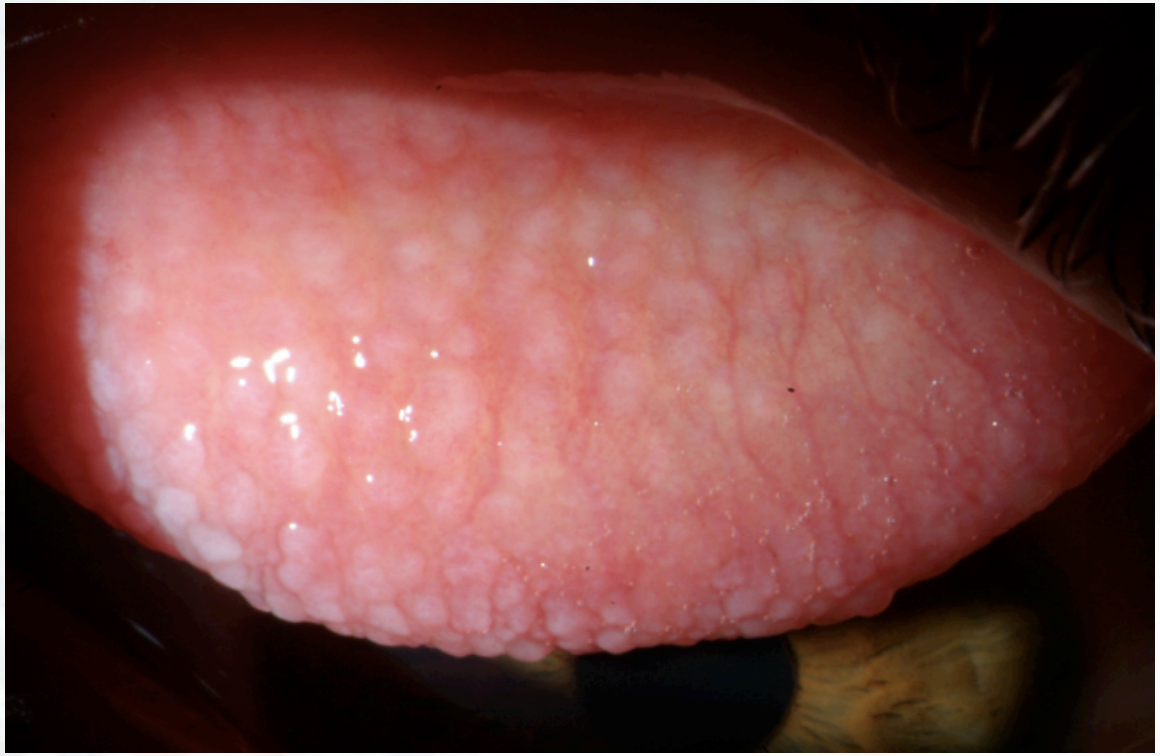
· ↑ TNF-α, IL-4, IL-13 in tears

· ↑ IFN_{γ} , a TH1 cytokine

Atopic Keratoconjunctivitis

SYMPTOMS	SIGNS
Intense itching of eyes, lids, periorbital area	Tylosis
Intense tearing	Swollen eyelids
Severe photophobia	Scaly, indurated lids
Blurred vision	Hyperemic conjunctiva
Stringy, rope-like mucous	Edematous conjunctiva
Burning	Tarsal conjunctival papillae
Dry sebsation	Meibomian gland dysfunction
	Dry eye
	Keratoconus

Giant Papillary Conjunctivitis



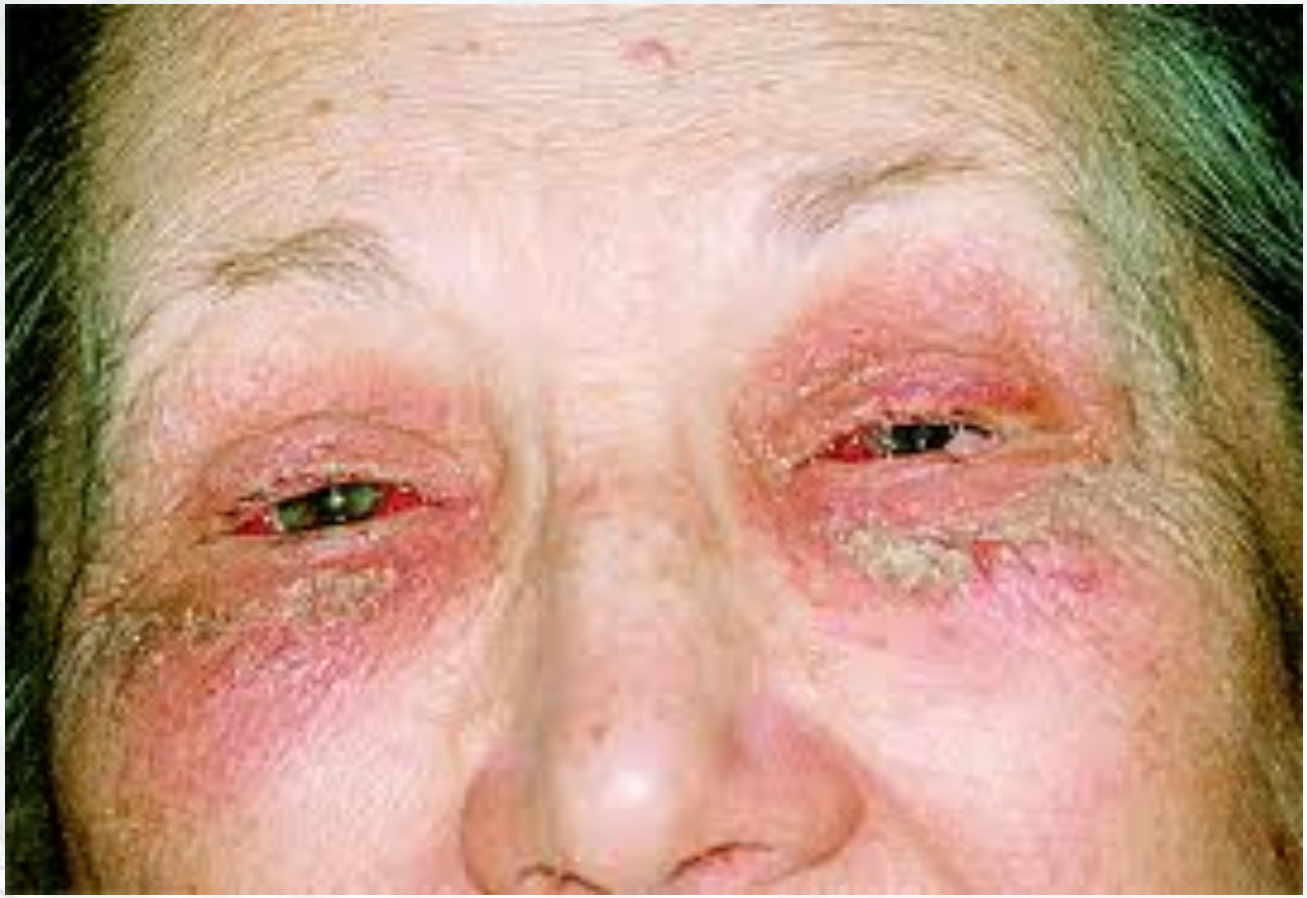
Giant Papillary Conjunctivitis

- Pathogenesis involves **mechanical** and **immunologic** mechanisms
- Combination of **Type 1 and Type 4** (Gell and Coombs) immune response
- Response to foreign substance, e.g. contact lens surface debris, exposed sutures, prosthesis
- Mechanical trauma can provide port of entry of allergens or irritants
- Characteristic large papillae (>.3mm) on the superior palpebral conjunctiva
- Usually resolves when **contact lens are removed**

Giant Papillary Conjunctivitis

- Increased lymphocytes
- Increased numbers of mast cells, eosinophils, and basophils but lower than in other forms of ocular allergy
- Tears have increased IgE, IgG, IgM (made to contact lens allergenic materials/contaminants)
- ↑ Leukotriene C4, IL-4, IL-6, eotaxin, CD4 T cells, mucosal-associated M cells
- Papillary formation, fibroblast proliferation, and collagen production is noted

Ocular Contact Dermatitis

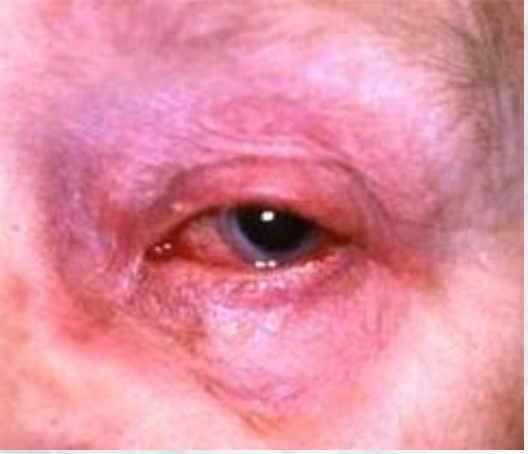


Contact Ocular Dermatitis

Reactions noted almost exclusively at site of exposure of the putative antigen

- Direct contact
- Indirect contact with hands
- Aerogenic exposure

- Small molecular weight molecules/haptens conjugate with proteins in skin to become immunogenic
- Atopic contact dermatitis causes > 50% eyelid dermatitis
- Responsible for 5% of all contact dermatitis
- 25% develop secondary irritant dermatitis



Ocular Contact Dermatitis

- Contact dermatitis can be from allergens or irritants
- Involves eyelids, periocular skin, ocular surface
- Erythema, itching, edema, vesciculation, and scaling
- Initial sensitization following allergen exposure takes 10-14 days
- Upon subsequent exposure, symptoms starts hours to days after exposure to the allergen

8 Main causative agents in eyelid Contact Dermatitis

- 1) Gold sodium thiosulfaate (8.2%)
- 2) Fragrance mix (7.1%)
- 3) Balsam of Peru (6.3%)
- 4) Nickel sulfate (6%)
- 5) neomycin (3.3%)
- 6) methyldibromoglutaronitrile (3%)
- 7) Quaternium-15 (3%
- 8) Methylchloroisothiazolinone/ methylisothiazolinone (2.2%).

Ocular Contact Dermatitis Pathophysiology

- Th1 lymphocyte mediated delayed hypersensitivity
- Allergens and irritants can bind to the Langerhan cells (allergen presenting cell) found within the suprabasilar layer of the epidermis
- Langerhan cells migrate to the regional lymph nodes to complete the sensitization process
- Allergens (not irritants) induce CD1a+ CD83 + Langerhans cell migration

Ocular Contact Dermatitis Pathophysiology

- Increase in basophils, eosinophils, Th1 lymphocytes, dendritic cells
- Increase of IL-1, IL-6, IL-8, GM-CSF, RANTES, Interferon-inducible protein 10
- IL-8 seems to be present only in allergic contact dermatitis
- CD4+ CCR10+ memory cells remain in the dermis
- Filaggrin barrier defects likely predispose to allergic contact dermatitis