


The Innate and Adaptive Immune System
Gone Wild!

Human Microbiome

- Human cells versus microbes
 - Microbes inhabit just about every part of the human body, living on the skin, in the gut, and up the nose
 - Microbes outnumbering 10:1 ratio (popular in a lot of papers and presentations)
 - 2016 1.3: 1 ration
 - Microorganisms make up only about 1 to 3 percent of the body's mass
 - 200-pound adult, that's 2 to 6 pounds of bacteria, but play a vital role in human health.
- Nearly everyone routinely carries pathogens, microorganisms known to cause illnesses
 - Healthy individuals these pathogens cause no disease
 - Simply coexist with their host and the rest of the human microbiome
 - Researchers must now figure out why some pathogens turn deadly and under what conditions, likely revising current concepts of how microorganisms cause disease.



7

Gut Microbiome


- Thousands of different species
- These include not only bacteria but fungi, parasites, and viruses.
- In a healthy person, these "bugs" coexist peacefully, with the largest numbers found in the small and large intestines but also throughout the body.
- The microbiome is even labeled a supporting organ because it plays so many key roles in promoting the smooth daily operations of the human body.
- Each person has an entirely unique network of microbiota
 - originally determined by one's DNA.
 - A person is first exposed to microorganisms as an infant, during delivery in the birth canal and through the mother's breast milk.
 - Exactly which microorganisms the infant is exposed to depends solely on the species found in the mother.
 - Later on, environmental exposures and diet can change one's microbiome to be either beneficial to health or place one at greater risk for disease.



8

Gut Microbiome

- Microbiota
 - Stimulate the immune system
 - Break down potentially toxic food compounds
 - Synthesize certain vitamins and amino acids
 - Including the B vitamins and vitamin K
 - As an example, the key enzymes needed to form vitamin B12 are only found in bacteria, not in plants and animals
- Gut bacteria also produce hundreds of neurochemicals that the brain uses to regulate basic physiological processes as well as mental processes such as learning, memory and mood.
- Gut bacteria manufacture about 95 percent of the body's supply of serotonin
 - Which influences both mood and GI activity.



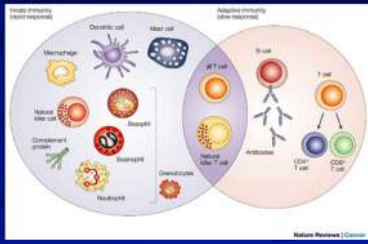
9

Immune System

- Luckily, we have a sophisticated biological system known as the immune system
- Immune system is the second most complex biological system known to us
 - The brain is number one
 - So sophisticated we are still learning about it.

10

Immune System - Innate and Adaptive

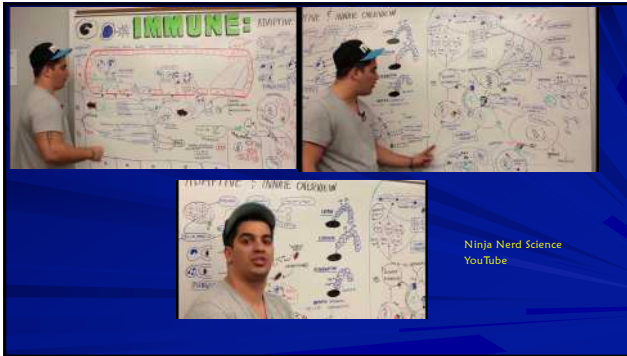


11

IMMUNITY

INNATE		ADAPTIVE	
NONSPECIFIC		SPECIFIC	
Fast response (0-4 hours)		Slow response (8-14 days)	
<ul style="list-style-type: none"> Macrophages Natural killer cell Neutrophils Granulocytes 	<ul style="list-style-type: none"> Dendritic cell Mast cell Natural killer cell Antibodies 	<ul style="list-style-type: none"> B cell T cell CD4+ T cell CD8+ T cell 	<ul style="list-style-type: none"> Humoral Cellular

12

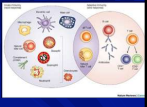


13

Ninja Nerd Science
 YouTube

Innate Immune System

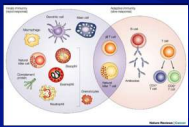
- ~ Ready when we are born
- ~ Neutrophils, macrophages, complement, and dendritic cells
 - * Our all-purpose weapons!
- ~ Innate immune system that has memorized the most common bacteria, viruses, and foreign invaders
- ~ Macrophage can eat 100 bacteria before exhausted
- ~ Neutrophils are suicide bombers kill invaders and self
- ~ Complement system – membrane attack complex
- ~ This is quick response.
- ~ Dendritic cells are intelligent officers- destroy the invaders rips them apart but places the proteins on the surface to enter the lymph system
 - * Dendritic cell all covered in protein is looking for a T helper cell



14

Innate Immune System

- ~ Is ineffective against the billions of combinations or what we call a mutation
- ~ If there are billions of combinations, why aren't we dead?
- ~ This because we have an adaptive immune system!
- ~ The adaptive immune system call adapt to 1-10 billion protein combinations
- ~ We can adapt to those invaders



15

Adaptive Immune System

- ~ Slow to deploy but when it does it packs a huge punch
- ~ Slow because it takes time to find the T helper cell
- ~ Then done itself
- ~ These adapted T cell go to the infected sight and now active B-cells to produce antibodies
- ~ Takes time for the T cell to find the right B-cell, a day or two.
- ~ When it does it clones itself and can produce 2000 antibodies/second.
- ~ About 1 week later second line of defense is there in full force!
- ~ Adaptive is T-cells and B-cells (antibodies) super effective and deadly to our enemies!
- ~ Slow to deploy but when it does it's powerful
- ~ The adaptive immune system have a library of proteins
- ~ All organisms on earth are made up of the same basic parts - proteins

16

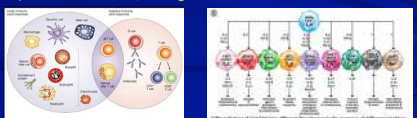
Memory and Continued Protection

- ~ The war is over the T cells self destroy except a few turn into T helper cells turn into memory cells.
- ~ Few B cells turn into B memory cells
- ~ Few B cells continue to make a low-grade antibody to make you immune maybe for life

17


T Helper 9

- ~ Helper T cell 9 is a **subgroup of CD4+T cells**
- ~ Differentiated from initial CD4+T cells induced by transforming growth factor β (TGF- β) and interleukin-4 (IL-4), and secretes IL-9 characteristically
- ~ Good -Th9 cells have been known to **provide immunity against helminth parasites**
- ~ **Good-** Play a vital role in vivo by providing antitumor immunity by secreting cytokines such as IL-9, IL-3, and IL-21
- ~ **Bad-** Dysregulated T helper cell (Th9) responses involved in the pathogenesis of multiple inflammatory diseases, including allergic airway inflammation, rheumatoid arthritis, and inflammatory bowel disease (IBD) among others



18

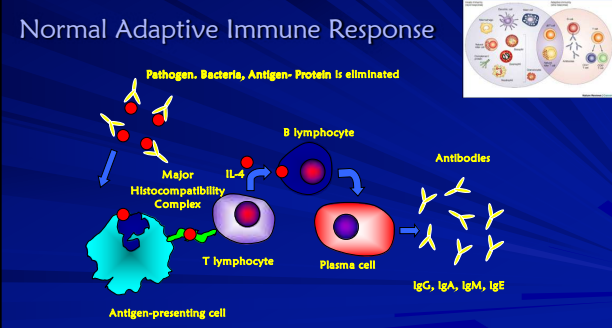
It's All About the Protein



- Proteins are the building blocks of life
- Proteins have billions of shapes, 3-D puzzle pieces
- Billions of combinations our enemies can use to construct their bodies
- Proteins are the language of the micro world (antigen/allergen)
- Cells don't have eyes or ears
- They touch them and have to recognize or decide if the protein is friend or part of an enemy
- Cells and cell membranes have countless amounts of receptors for these specific 3D protein puzzle pieces
- The reason why we deal with the flu each year, the proteins mutate/change

19

Normal Adaptive Immune Response



Pathogen. Bacteria, Antigen- Protein is eliminated

Antigen-presenting cell

Major Histocompatibility Complex

T lymphocyte

B lymphocyte

IL-4

Plasma cell

Antibodies

IgG, IgA, IgM, IgE

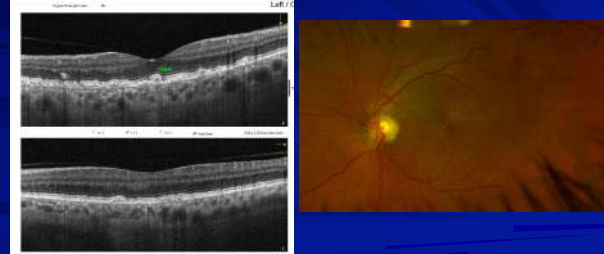
20

Hypersensitivity versus Immune Dysfunction

- Hypersensitivity reactions are **Immune responses that are exaggerated or inappropriate against an antigen or allergen**
- Immune dysfunction**
 - Up or down regulation of receptors
 - Gene mutations
 - Eye conditions from immune dysfunction
 - Dry eye
 - Thyroid eye disease
 - Drusen in macular degeneration

21

Immune Dysfunction - Drusen



22



23

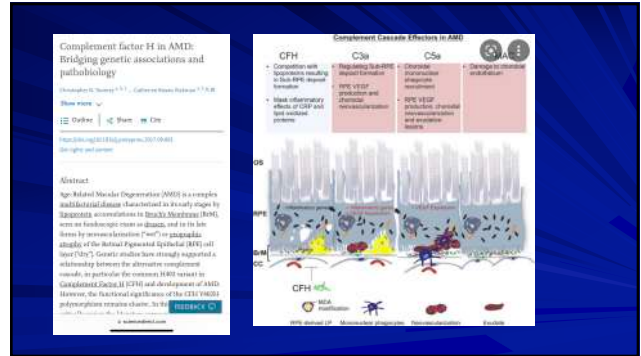


Ninja Nerd Science
 YouTube

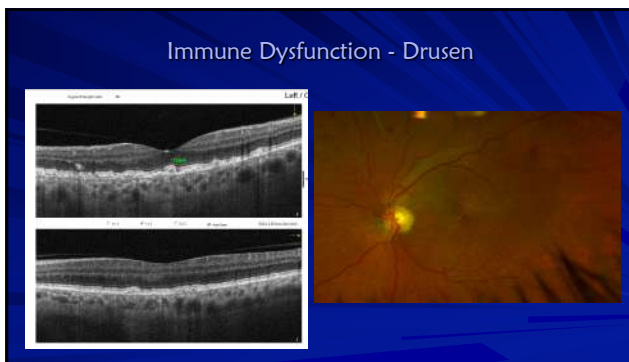
24



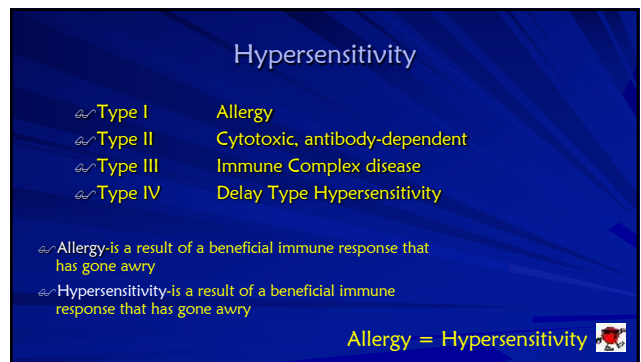
25



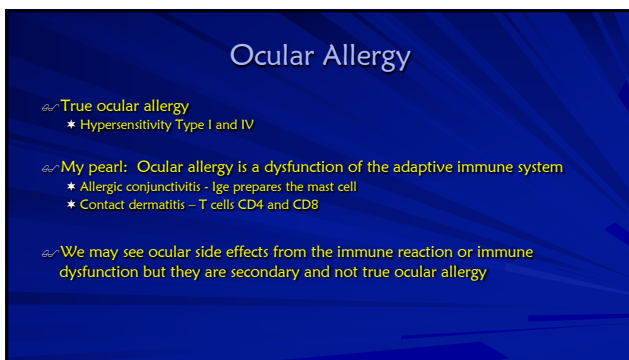
26



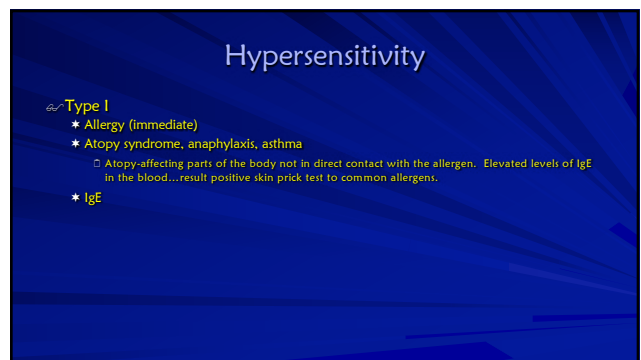
27



28



29

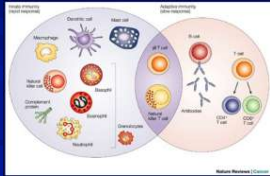


30

Hypersensitivity

Delayed and Not antibody driven

- Type IV- Delayed type hypersensitivity
 - Regulated by T-cells
 - Sub-categories:
 - Contact
 - Mediated by Langerhan's cells and keratinocytes
 - Tuberculin
 - Granulomatous
 - IE. Contact Dermatitis



37

It's Still About the Protein

- Haptens are small molecules that elicit an immune response only when attached to a large carrier such as a protein
- Well-known example of a hapten is **urushiol, which is the toxin found in poison ivy**
 - Absorbed through the skin from a poison ivy plant
 - Urushiol undergoes oxidation in the skin cells to generate the actual hapten.
 - Reactive quinone-type molecule
 - Then reacts with skin proteins to form hapten adducts

38

Allergic Contact Dermatitis

- One of the most frequent inflammatory skin diseases, and is characterized by redness, papule and vesicles, followed by scaling and dryness
- Elicited upon skin contact with nonprotein chemicals, haptens, and corresponds to a cutaneous delayed type hypersensitivity reaction, mediated by hapten-specific T-cells
- During the sensitization phase, both CD4(+) and CD8(+) T-cell precursors are activated in the draining lymph nodes by presentation of haptenedated peptides by skin dendritic cells
- Subsequent hapten painting on a remote skin site induces the recruitment and activation of specific T-cells at the site of challenge
- This leads to apoptosis of keratinocytes, recruitment of inflammatory cells and development of clinical symptoms

39

IMMUNITY

INNATE
NONSPECIFIC
fast response (0-4 hours)

ADAPTIVE
SPECIFIC
slow response (4-14 days)

40

Allergic Contact Dermatitis

- Experimental studies have demonstrated that, in normal contact hypersensitivity responses to strong haptens, CD8(+) type 1 T-cells are effector cells of contact hypersensitivity through cytotoxicity and interferon-gamma production
- While CD4(+) T-cells are endowed with downregulatory functions. The latter may correspond to the recently described CD4(+)CD25(+) regulatory T-cell population
- In some instances, especially when there is a deficient CD8(+) T-cell pool, CD4(+) T-cells can be effector cells of contact hypersensitivity
 - In human allergic contact dermatitis
 - imilar to that reported for strong haptens.

41

Classification of Ocular Allergy

- Allergic conjunctivitis
 - Seasonal
 - Perennial
- Atopic keratoconjunctivitis
- Vernal keratoconjunctivitis
- Giant papillary conjunctivitis
- Contact dermatitis

42

32-year-old man

- My eyes itch so bad I want to claw them out
- I went golfing today (May)
- Rubbing them feels good but I think it makes it worse
- Vision and externals are normal

43

Seasonal Allergic Conjunctivitis

- Happened the last 2 years but not this bad



44

Allergic Conjunctivitis

- Seasonal**
- Occurs in spring, fall or both
 - Grass, tree pollen or ragweed



- Perennial**
- Year round with periods that are more pronounced
 - Animal dander, dust mites, mold, grass
 - History of other atopic diseases



45

Signs and Symptoms of Allergic Conjunctivitis

- | Seasonal | Perennial |
|--|---|
| <ul style="list-style-type: none">ItchingRednessBurningExcessive tearingStringy white mucusRhinitis | <ul style="list-style-type: none">Similar to seasonal allergic conjunctivitisMilder than seasonal allergic conjunctivitisMore constant than seasonal allergic conjunctivitisSeasonal exacerbations |

46

Non-pharmacologic Interventions

- Allergen avoidance**
 - Pet control
 - Use air conditioning, HEPA filters
 - Avoid outdoor activities during high pollen periods
- Cold compresses**
- Lubricating eye drops**
- Wash your hair before going to bed**

47

Pharmacologic Interventions

- Topical eye drops**
 - Vasoconstrictors
 - Antihistamines
 - Antihistamine/vasoconstrictor combination
 - Antihistamine/mast cell stabilizer combination
 - Mast cell stabilizers
 - Nonsteroidal anti-inflammatory drugs (NSAIDs)
 - Corticosteroids
- Oral antihistamines**
- Allergen immunotherapy**

48

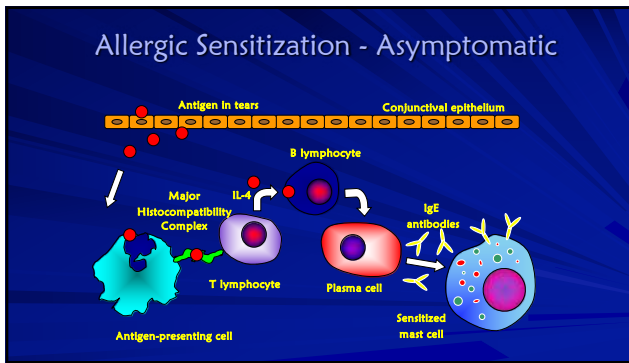
What is happening?
 It will help with diagnosis, management, treatment, and how pharmaceuticals work?

49

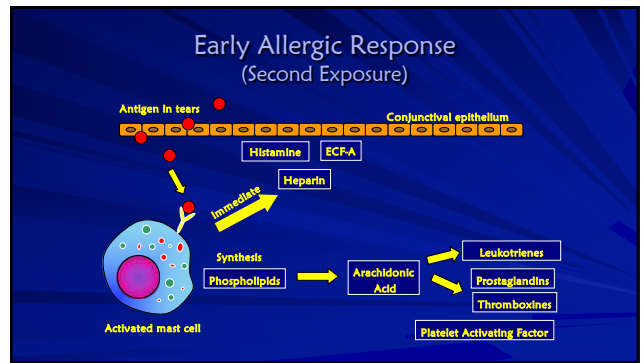
Ocular Allergy is Mainly Type I Hypersensitivity

- Consists of three phases
 - Sensitization phase- patient unaware
 - Activation phase (early allergic response)
 - Late allergic response

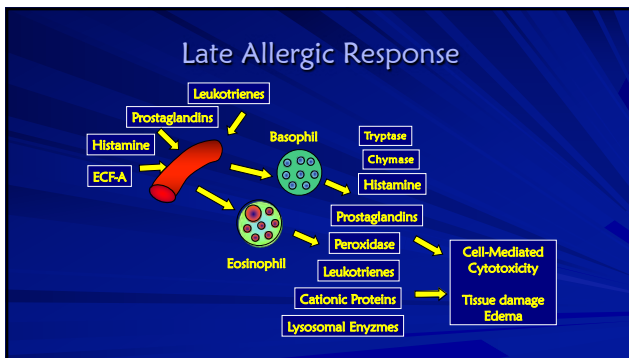
50



51



52

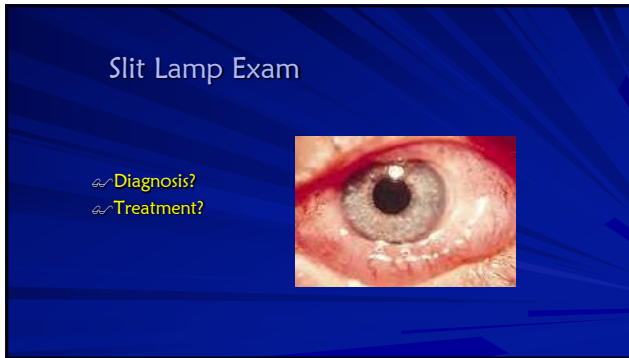


53

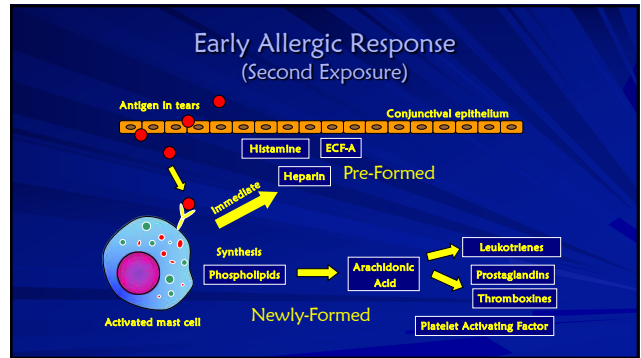
28-year-old man

- Flew to Myrtle Beach, SC to golf
- His eyes became itchy, he rubbed them, and within one hour it became very swollen
- He was there last year around the same time and nothing like this happened

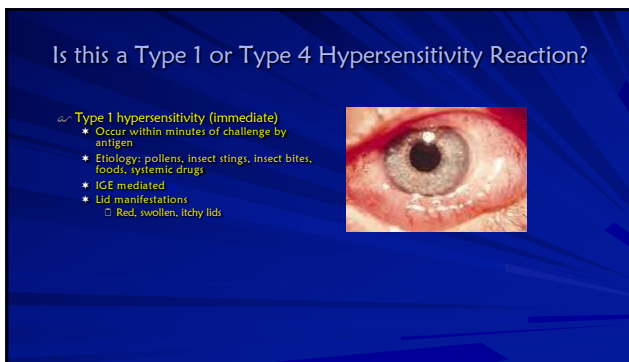
54



55



56



57

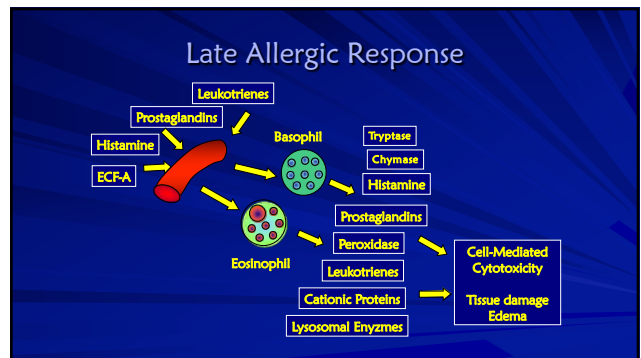
6-year-old boy

- ~ Eyes are red and itchy again since the beginning of April, now May 10th
- ~ "He rubs them all the time"
- ~ He is already using Pataday 1 gt qd OU, Rxed by pediatrician
 - * Uses it everyday
- ~ Used to get mucous and discharge from the eye but has not since on Pataday
- ~ Let's take a look

58



59



60

Vernal Conjunctivitis

- ~ Ages 3-25, peak incidence 11-13y/o, lasts 4-11 yrs
- ~ males > females
- ~ Thick ropy discharge, severe itching and corneal involvement Worse spring and summer
 - * Important clinical signs:
 - Large papillae, Horner-Trantas dots
 - SPK
 - Well demarcated sterile ulcer (shield ulcer)
- ~ Type I hypersensitivity
 - * With early and late phases
- ~ Children generally will outgrow this allergy
 - * Their super-immune system slows down

61

6-year-old boy

- ~ Take a shower and wash hair before going to bed
- ~ NP AT
- ~ Cont Pataday
- ~ Add steroid treatment



62

25-year-old man

- ~ My eyes are red and itchy all year round
 - * At times of the year they are worse, like today
- ~ I do cold compresses, artificial tears and Pataday
 - * This seems to help but my eyes are really never white, clear and have some itch
 - * "I thought allergies occurred in the spring and summer"
- ~ I work with the public and my clients always ask about my eyes
- ~ Patient has eczema and avoids many detergents and perfumes
- ~ Patient also suffers from asthma and uses inhalers
- ~ Let's take a look

63



64

Atopic Keratoconjunctivitis

- ~ Atopic keratoconjunctivitis (AKC) is the result of a condition called "Atopy"
- ~ Atopy is a genetic condition whereby the immune system produces higher than normal antibodies in response to a given allergen
- ~ There is usually a family history of multiple allergies
- ~ Although AKC is a perennial disease, symptoms tend to worsen in the winter (dryness)
- ~ Atopic dermatitis which is generally seen early in childhood
 - * Atopic keratoconjunctivitis appears during late adolescence
 - * Men are more commonly affected than women.

65

64-year-old woman

- ~ Diagnosed with bacterial conjunctivitis 8 days ago OD
- ~ Used Tobramycin qid OD, appeared to be worsening, was told to use q2 hours
- ~ In today for second opinion

66

Discussion



Diagnosis: contact dermatitis Treatment

6 days later

67

Type 4 Hypersensitivity

- ⤿ Delayed/ cell mediated
 - * Occur in hours, days to months after antigen challenge
 - * T cell mediated
 - * Etiology: contact dermatitis, topical medications, jewelry, nail polish
 - * Manifestations:
 - Itching
 - Red lids
 - Superficial skin changes

68

Contact Dermatitis

- ⤿ Causes:
 - * Topical Medications
 - Alpha agonists, B-blocker, Pilocarpine, Atropine
 - * Contact lens solutions
 - * Cosmetics
 - * Fingernail polish
 - * Pet dander
 - * Molds
 - * Detergents
 - * Latex
 - * Hair dye
 - * Metals: nickel



69

73-year-old man

- ⤿ In today because his "pink eye" that he contracted from his granddaughter will not clear up
- ⤿ Started 3 weeks ago, worsened for 2 weeks, now stable


70

Discussion

Conjunctivitis?

- ⤿ Glaucoma patient using
 - * ½ Betimol qd OU AM
 - * Alphagan-P 0.15% bid OU
 - * Travatan Z qd OU PM


Which is most likely the offending agent?



71

Is this a Type 1 or Type 4 Hypersensitivity Reaction?

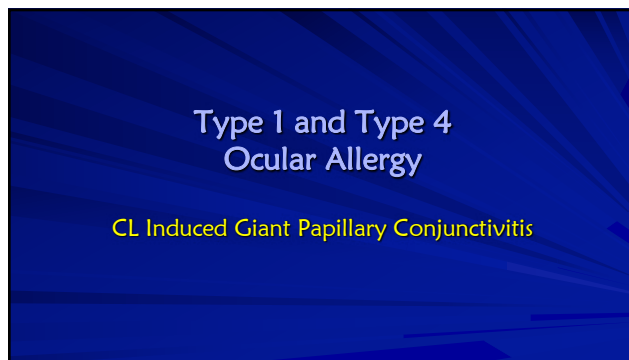
- ⤿ Type 4 hypersensitivity (delayed/ cell mediated)
 - * Occur in hours, days to months after antigen challenge
 - * Etiology: contact dermatitis, topical medications, jewelry, nail polish
 - * Manifestations:
 - Itching
 - Red lids
 - Superficial skin changes
- ⤿ Patient has been using Alphagan-P 0.15% for 9 months
- ⤿ Contact Dermatitis



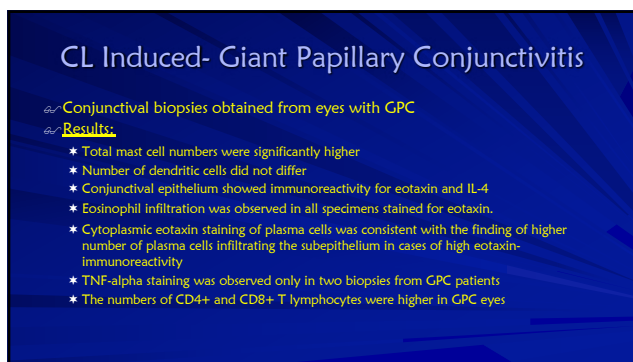
72



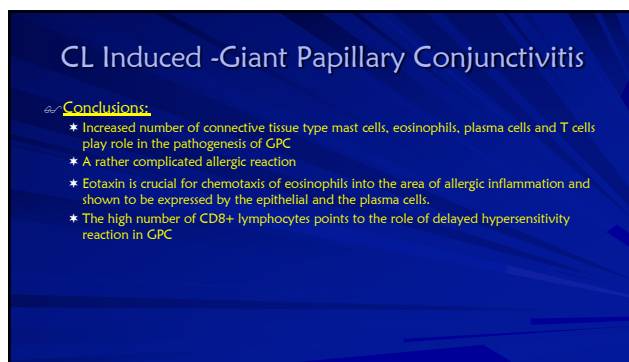
73



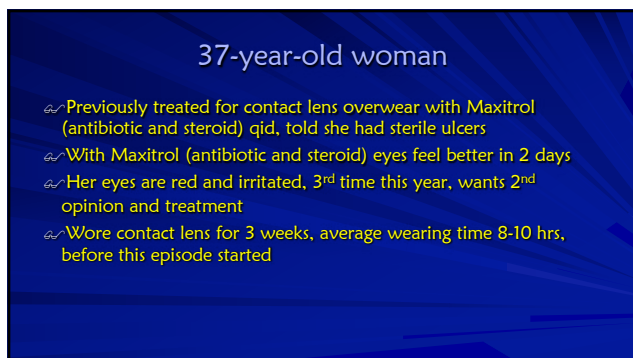
74



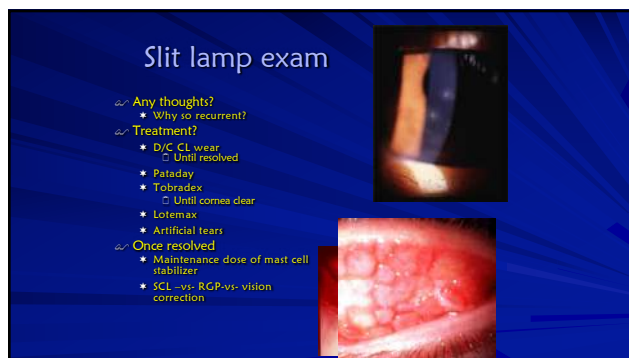
75



76



77



78

Giant Papillary Conjunctivitis

- Condition characterized by formation of large papillae (>0.3mm) on the superior palpebral conjunctiva
- No seasonal variation
- Etiology
 - Contact lens wear
 - Exposed sutures (conjunctiva or cornea)
 - Prosthesis
- Pathophysiology
 - Mechanical trauma induces inflammatory cascade and mast cell degranulation
 - No increase in histamine levels
 - Plasma cells, mast cells, eosinophils and basophils are found in cytologic scrapings. (Type I & IV)
 - Over-reaction of body's immune system
 - Arachidonic acid cycle main component

79

Giant Papillary Conjunctivitis

- Treatment
 - Stop CL wearing time until resolved
 - Change to disposable soft CL's, Dailies SCL, RGP
 - Mast cell stabilizers
 - Topical steroids (short term)

80

Hypersensitivity, Immune Dysfunction, Ocular Microbiome Dysfunction

All the above?

81

14-year-old boy

- My eye is red, watery and very painful
- Started about 10 days ago
- Tried artificial tears without help
- Child is healthy
- Does not wear contact lens
- Let's look at the photo

82

Diagnosis and Treatment?



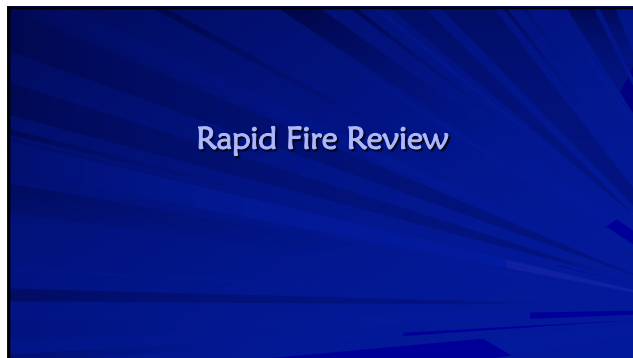
83

Phlyctenulosis

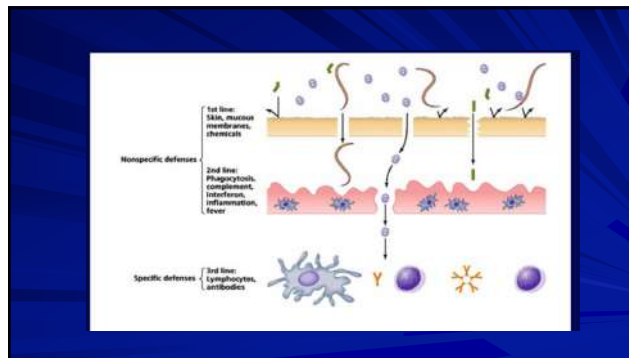
- Focal nodule of inflammatory tissue
- Two forms
 - Conjunctival
 - Corneal
- Focal nodule can migrate from conjunctiva to cornea
- Etiology
 - Staphylococcus (most common)
 - Rosacea
 - Tuberculosis
- Treatment
 - Rule out tuberculosis if suspicious
 - Chest X-ray and PPD
 - Combination antibiotic/steroid
 - Treat underlying lid disease
 - Blepharitis
 - Rosacea



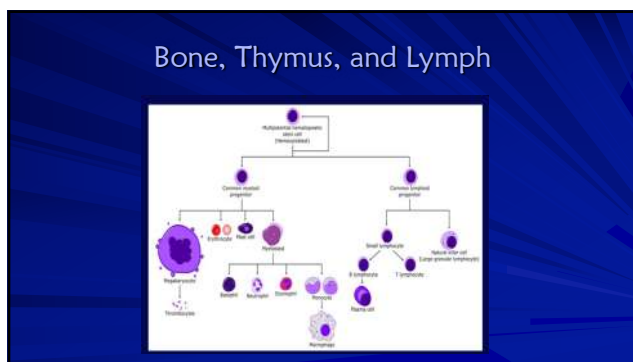
84



85



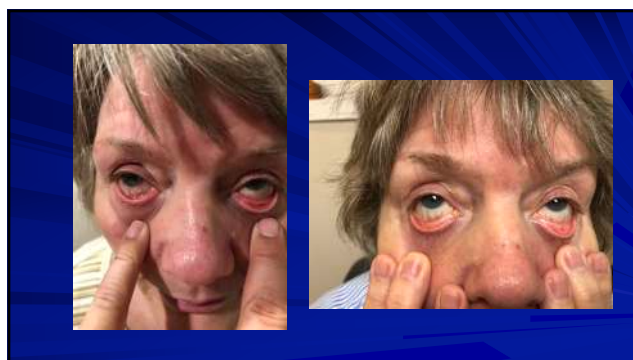
86



87



88



89

A slide with text and three stacked photographs of a woman's eyes. The text reads: "I have been working in my yard for the last 2 weeks and my eyes are red and irritated", "Early phase", "* Histamine", "Late phase", "* Eosinophils and basophils". The photos show the progression of eye irritation from normal to red and swollen.

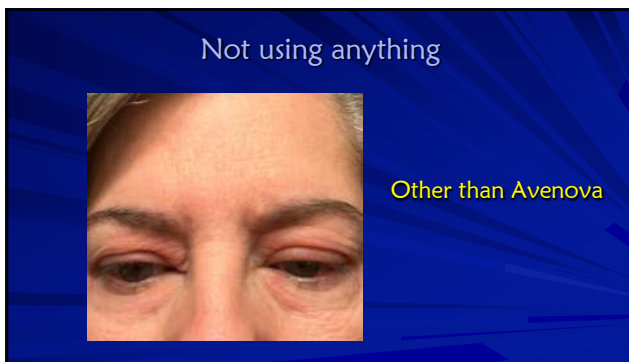
90



91



92



93



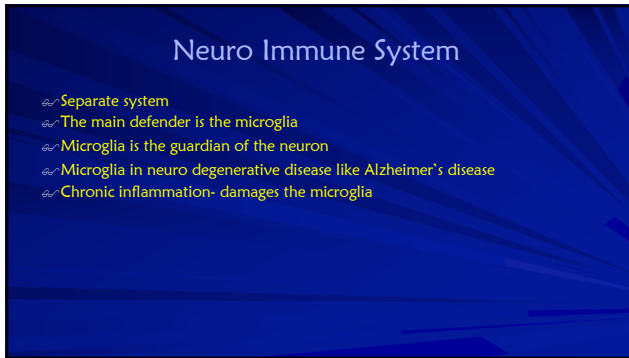
94



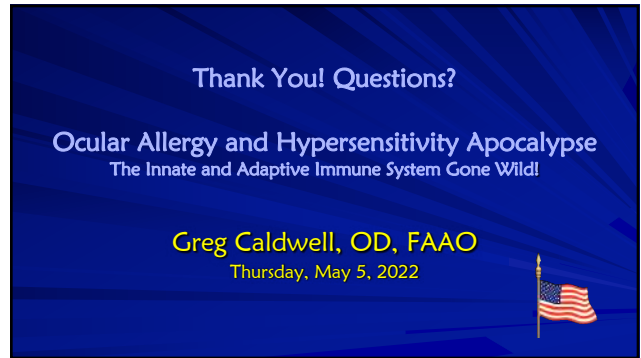
95



96



97



98