

Week 6

Allergies

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Questions and Loose Ends

- Is it good for kids to be exposed to dirt?

The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

FEBRUARY 24, 2011

VOL. 364 NO. 8

Exposure to Environmental Microorganisms and Childhood Asthma

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ABSTRACT

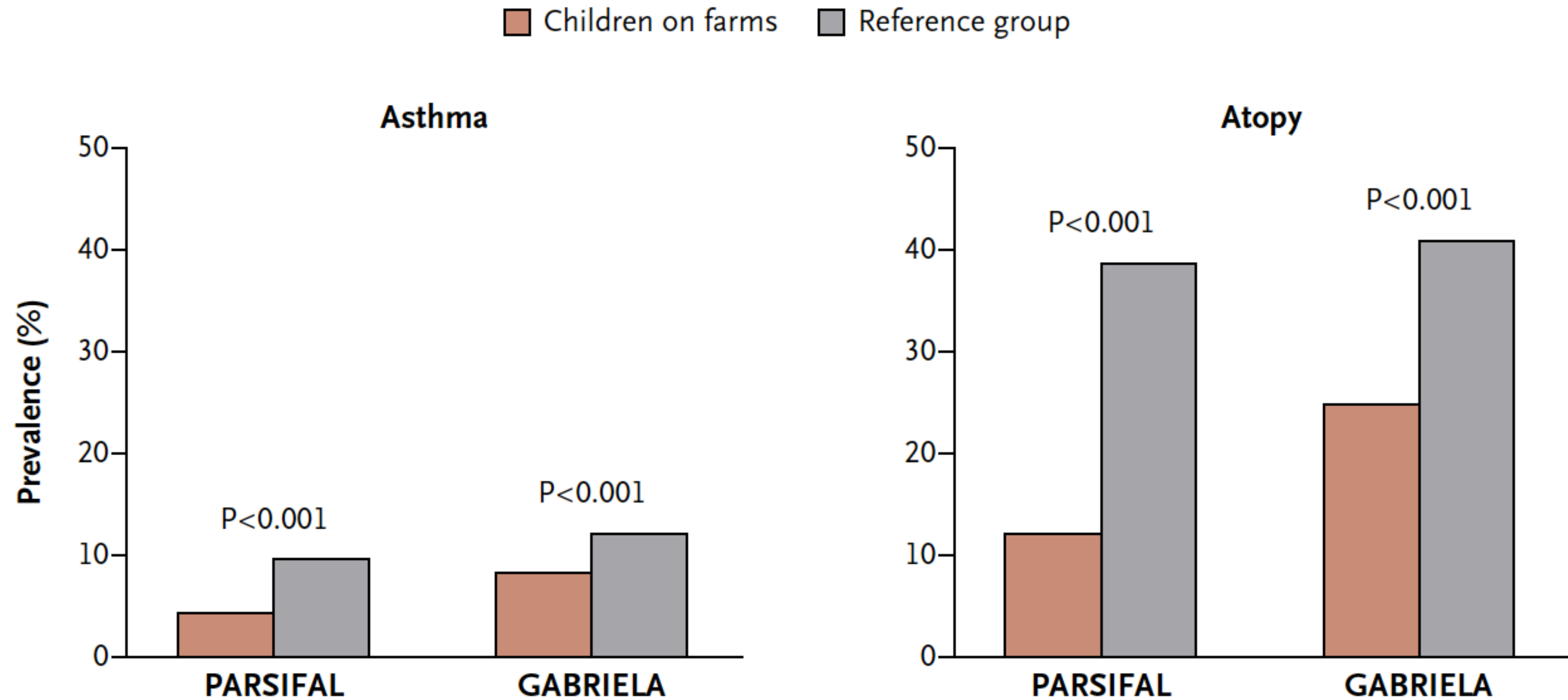


Figure 1. Prevalence of Asthma and Atopy among Children Living on Farms as Compared with Reference Groups. The PARSIFAL study population included 6843 school-age children 6 to 13 years of age, and the GABRIELA study population included 9668 children between 6 and 12 years of age. Calculations of prevalence in GABRIELA were weighted on the basis of the total number of children who were eligible for inclusion in the study (34,491 children).

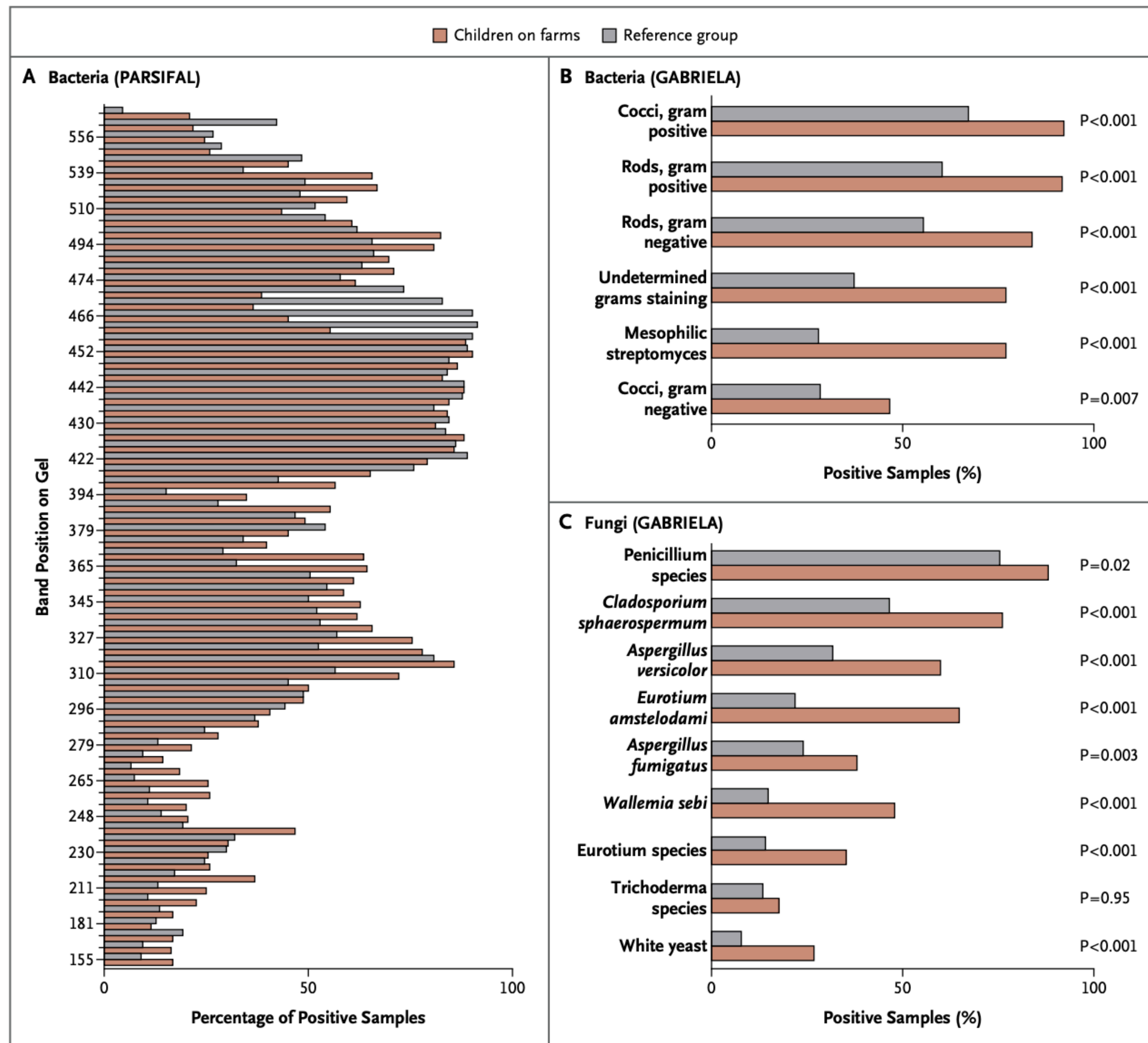


Figure 2. Detection of Environmental Microorganisms in Dust Samples in the PARSIFAL Study and GABRIELA.

In the PARSIFAL study (Panel A), samples of mattress dust were screened for bacterial origin with the use of single-strand conformation polymorphism (SSCP) analysis, with positive samples defined as those with detectable SSCP bands. In GABRIELA (Panels B and C), settled dust from children's rooms was evaluated for bacterial and fungal taxa with the use of culture techniques. The listed microbes were present in at least 10% of all samples.

Atopy

What atopy means?

Atopy: The genetic tendency to develop the **classic allergic diseases -- atopic dermatitis**, allergic rhinitis (hay fever), and asthma. Atopy involves the capacity to produce IgE in response to common environmental proteins such as house dustmite, grass pollen, and food allergens. Mar 29, 2021

[Medical Definition of Atopy - MedicineNet](https://www.medicinenet.com/atopy/definition.htm)

[https://www.medicinenet.com › atopy › definiti](https://www.medicinenet.com/atopy/definition.htm)

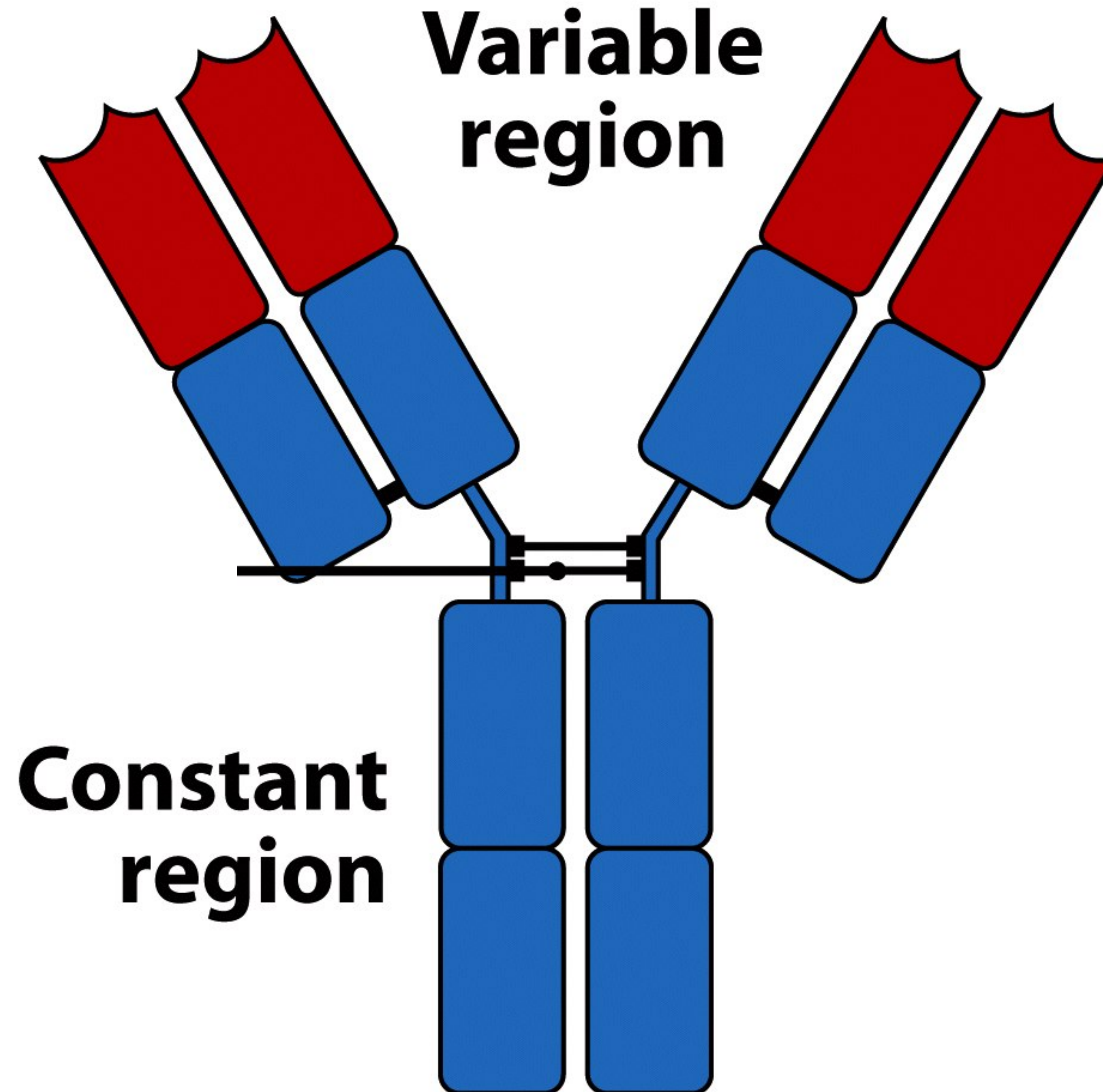
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Review

- Variations in Fc region of antibodies determine effector function (Fc receptors)
- Multiple Signals to Activate T cells:
 - First signal for T cell activation: peptide/MHC binding to TCR
 - Second signal: costimulation through binding of B7 to CD28 on T cell
 - Third signal: cytokines secreted by APC direct differentiation of Helper T cells

Antibody Structure (Immunoglobulin)



Constant Region

- Constant from antibody to antibody, but there are several different “classes” or “isotypes”
- IgM, IgG, IgA, IgE
- As B cell is activated, the secreted antibody may change class
- The class determines the Effector Mechanism, and is specific to a given species
- If you inject a mouse IgG antibody into a donkey, the donkey will make antibodies that bind to all mouse IgG antibodies; useful for research. Humans will also make antibodies against mouse IgG, neutralizing the therapeutic antibody, problematic for therapies
- Therapeutic antibodies are now “humanized” before being injected into people

Different Constant Regions (Isotypes)

These are called Isotypes, IgM, IgD, IgE, IgG, IgA, have different functions

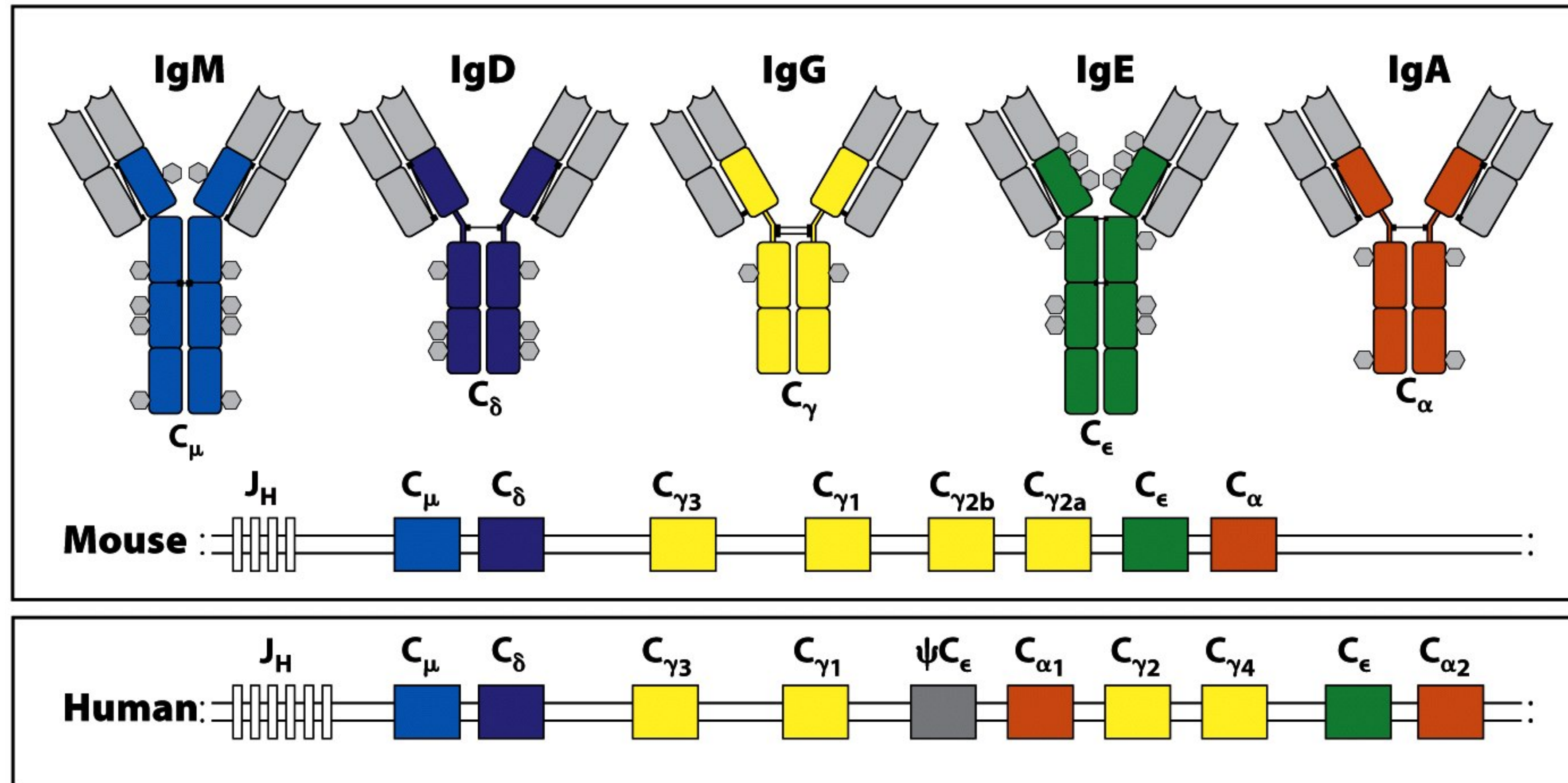
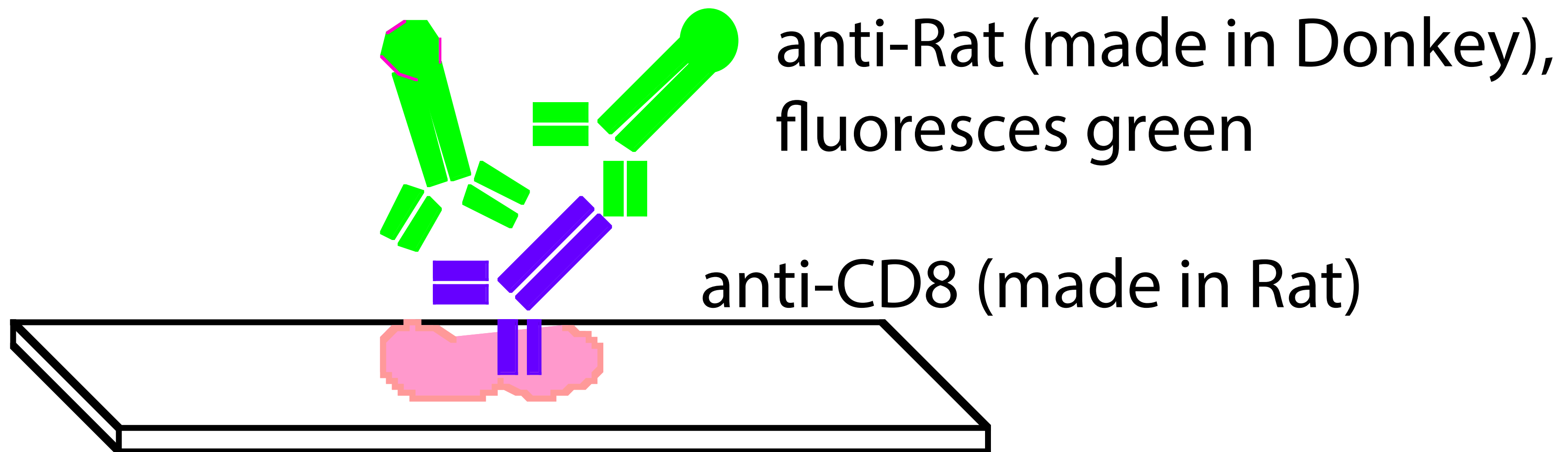
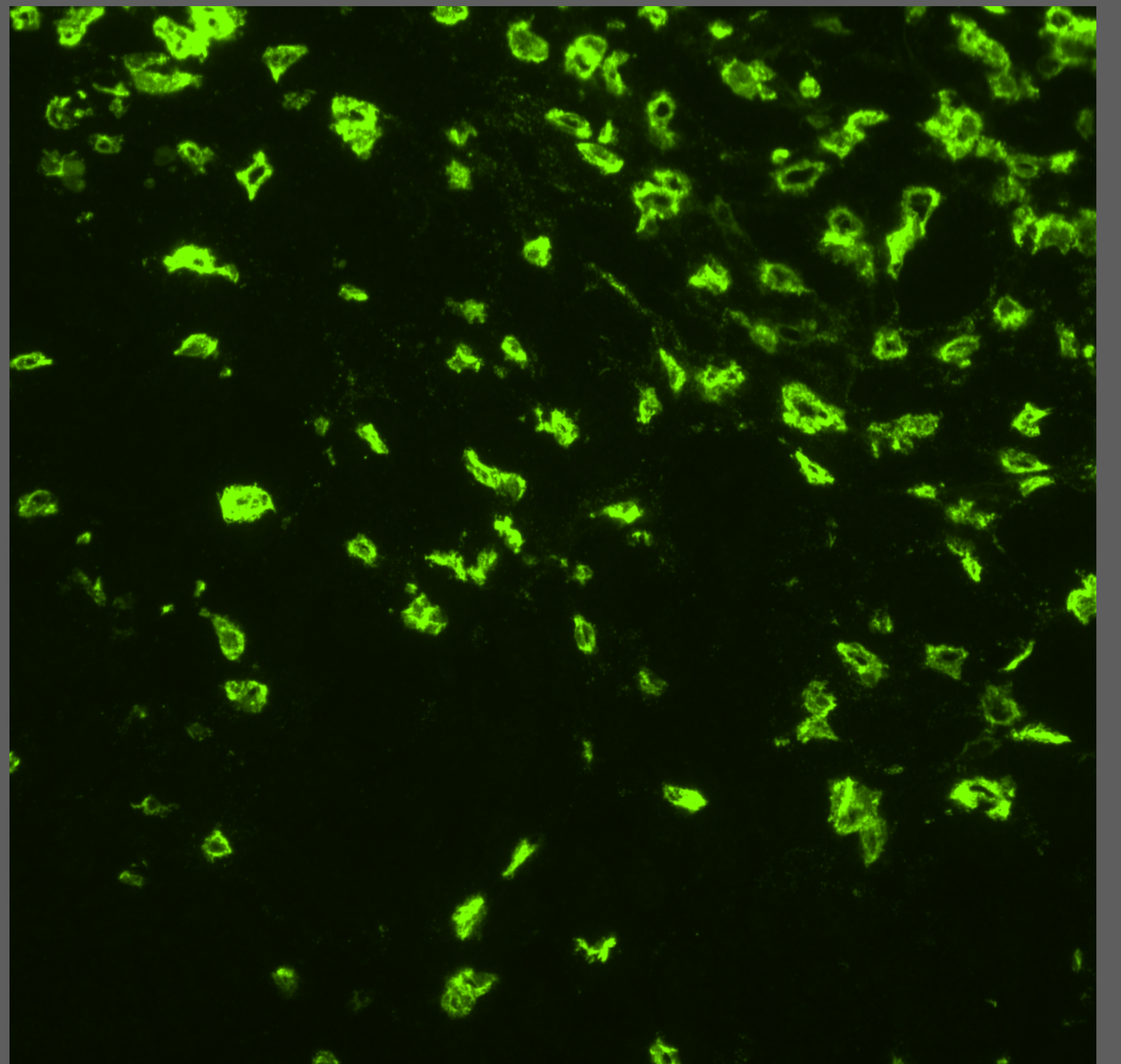
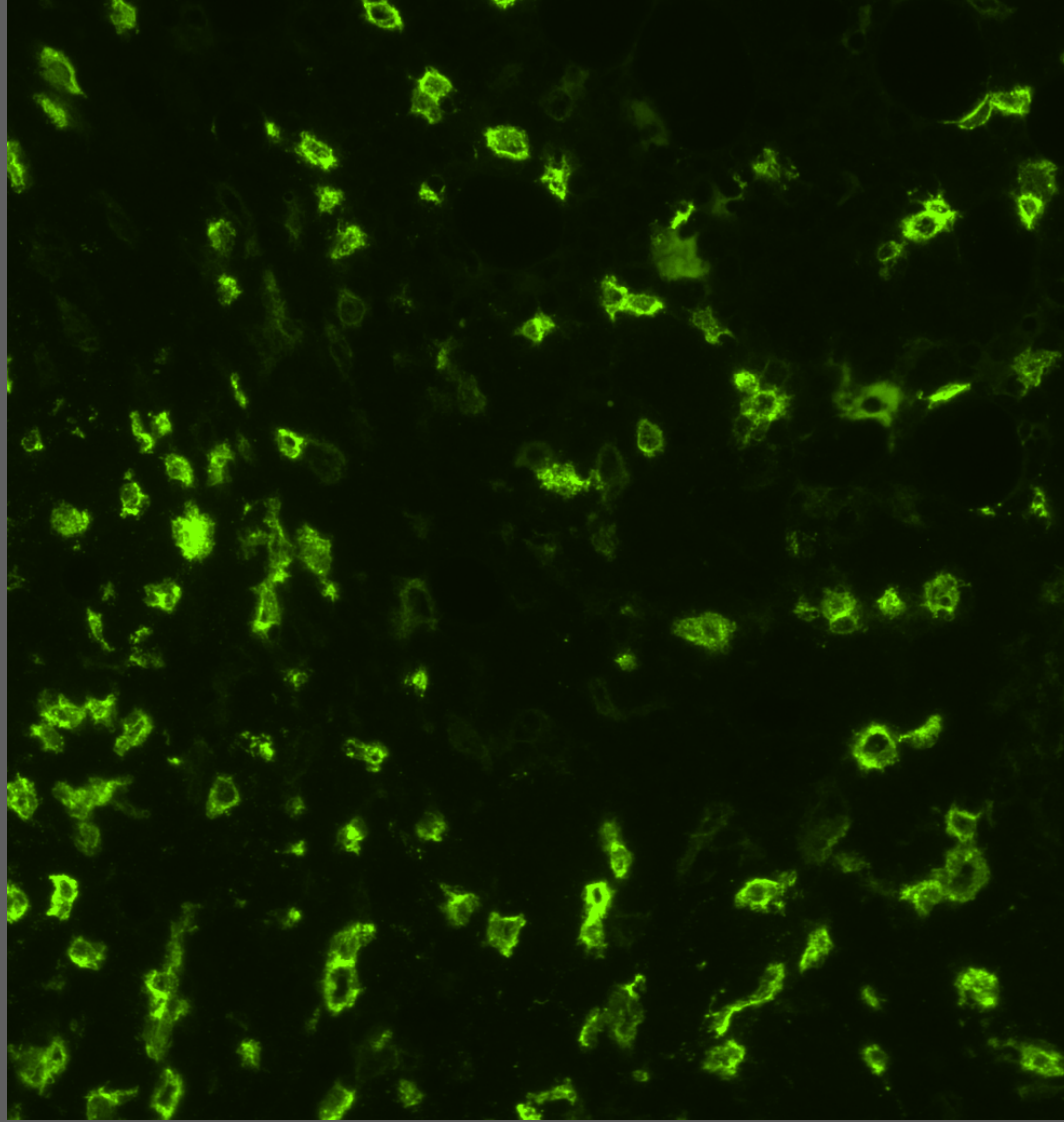


Figure 4-17 Immunobiology, 7ed. (© Garland Science 2008)





Costimulation

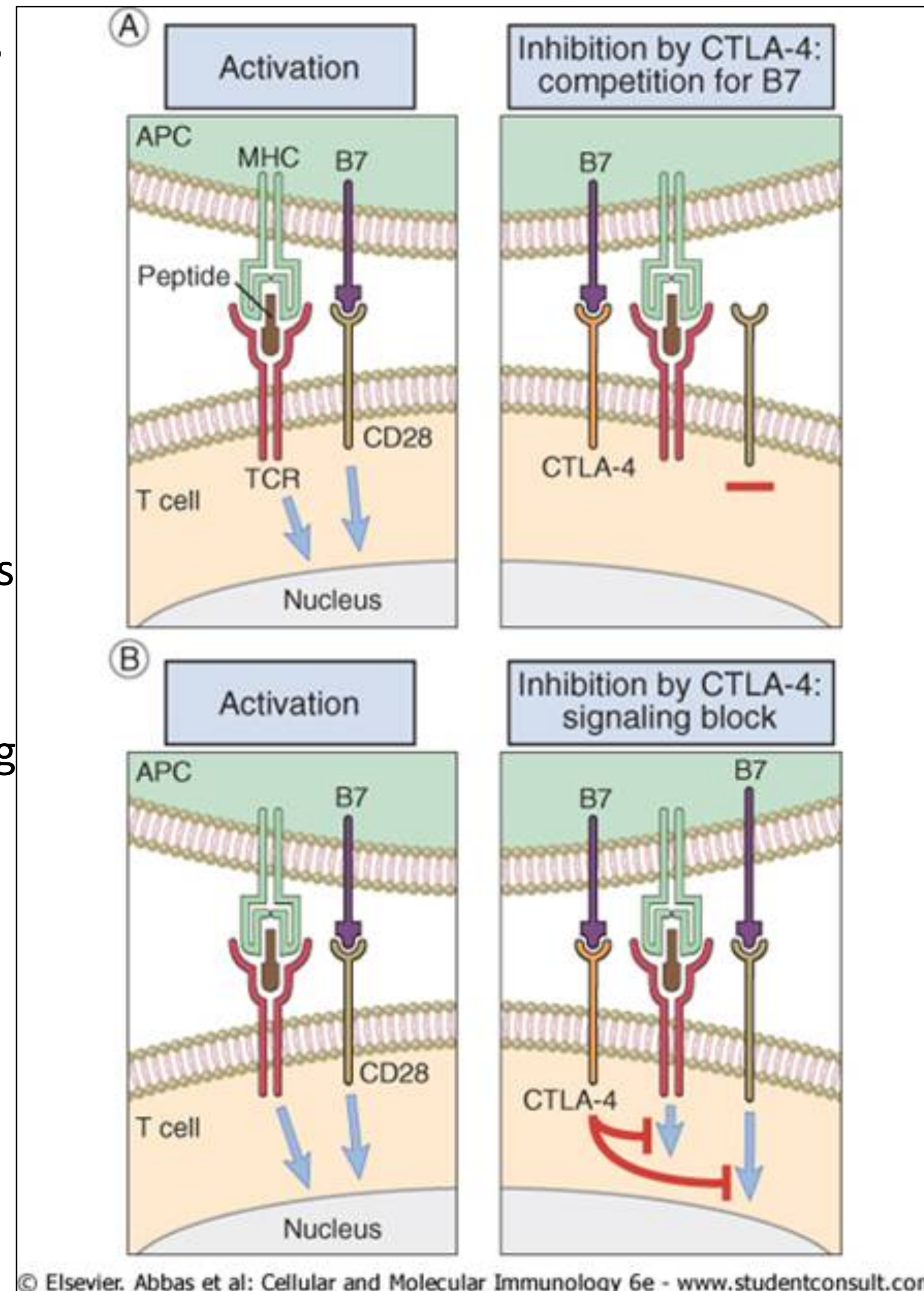
- Activation sets in motion mechanisms to end the T cell response: CD28 then CTLA-4

Engagement of CTLA-4 shuts down T cell activation

- A) Once activated T cells begin to express CTLA-4 which competitively prevents CD28 binding to B7.
- B) Following binding to B7, the **ITIM** motif of CTLA-4 associates with phosphatases resulting in **dephosphorylation** of the CD3 complex and subsequent inactivation of TCR-dependent signaling pathways.

This reduces T-cell receptor (TCR)-dependent activation of transcription factors NF- κ B, AP-1 and NF-AT.

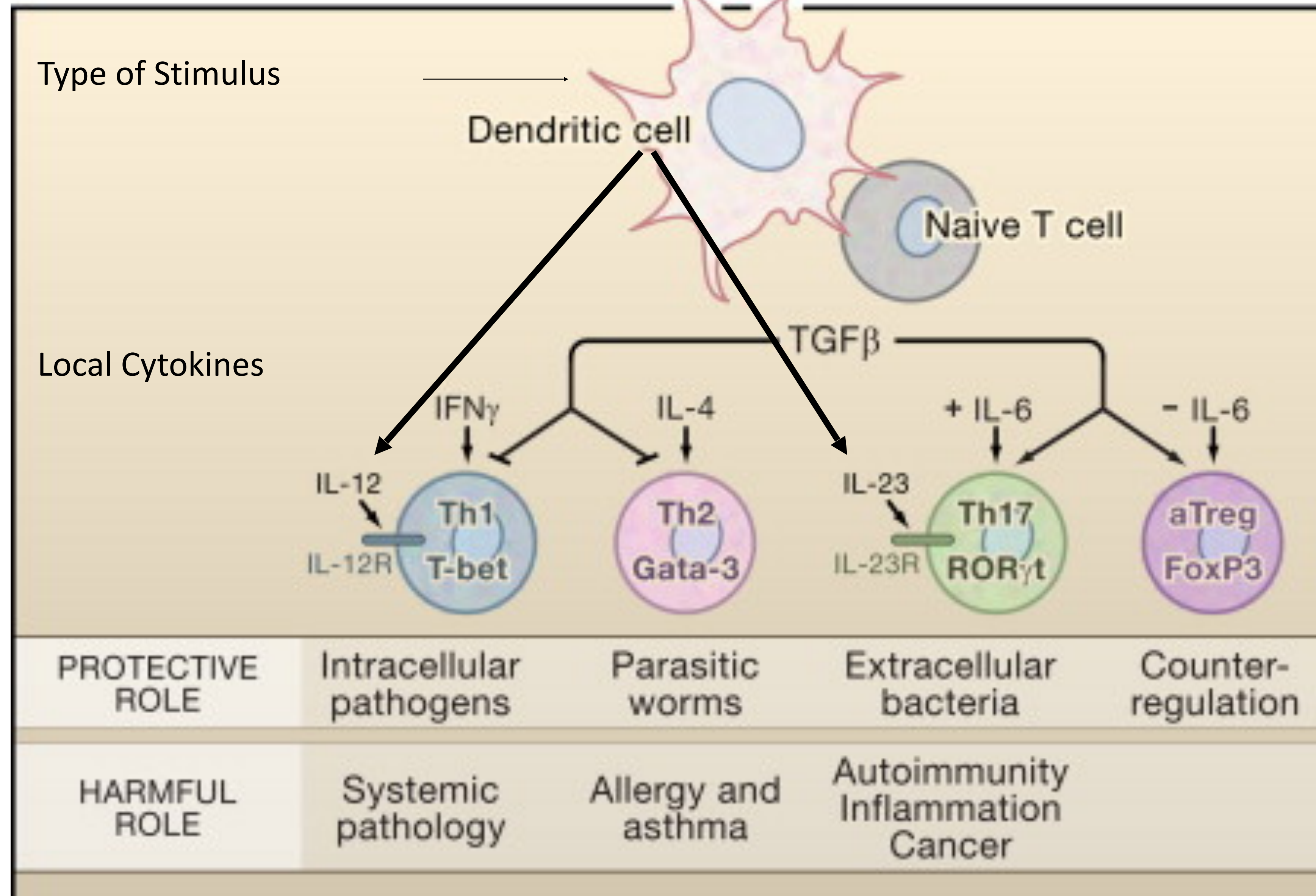
This results in decreased cytokine production by T cells and cell-cycle arrest.



Signal Three

Cytokines provide a Signal Three that prolongs survival (IL-12 for CD8+ T cells, and IL-1 for CD4+ T cells) and determines differentiation. Differentiation of CD4+ T cells goes in one of several different paths, suited to different pathogens.

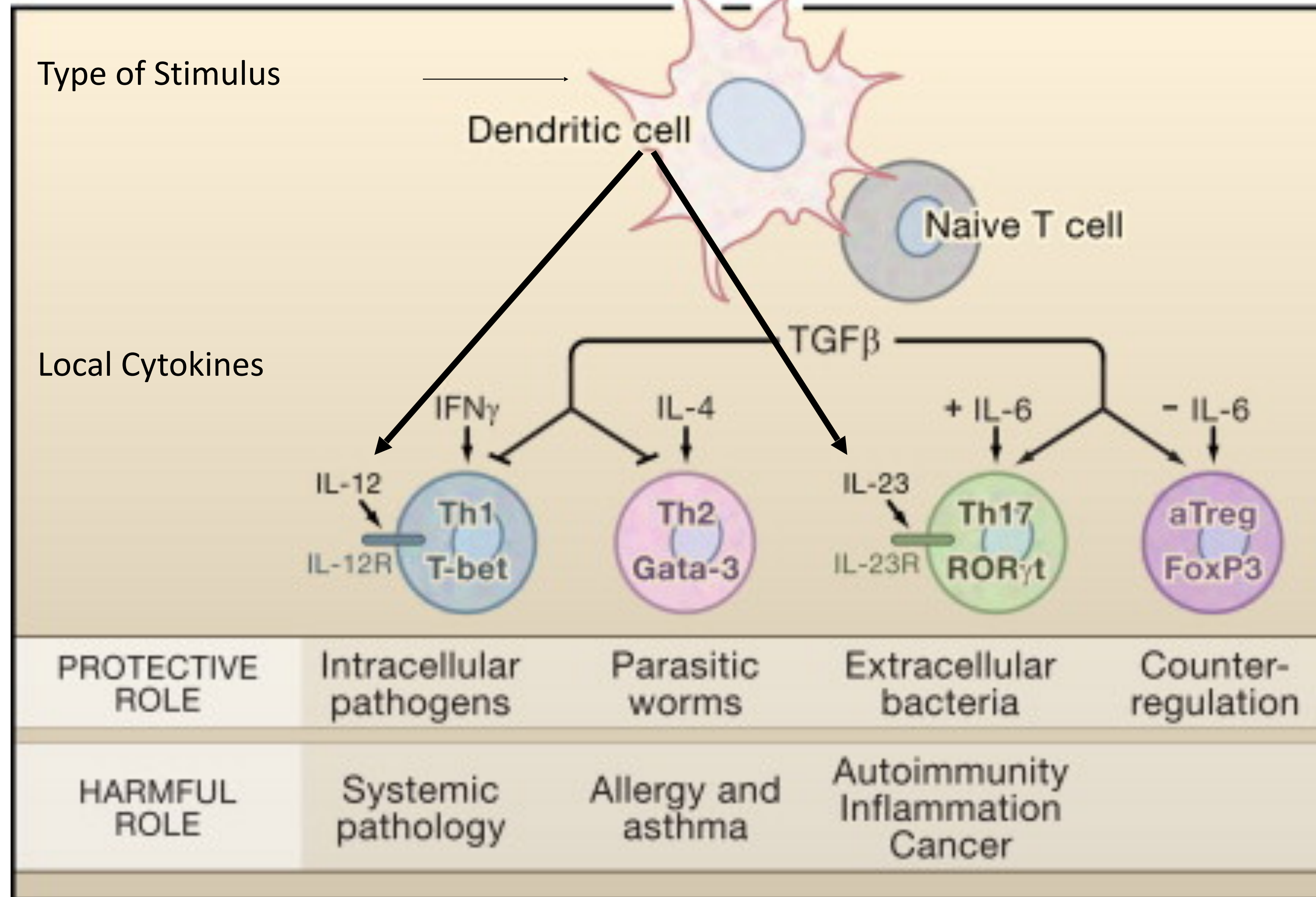
Differentiation to a particular T_H cell type is influenced by the DC type, innate immune sensing/response, and local cytokines (tissue type infected).



Allergies start with TH2 T cells acting on B cells

- IL-4 from APC promotes TH2 differentiation and IL-4 from TH2 cells promotes class switching of antibodies to IgE by B cells
- Proposed physiological function is defense against parasites like worms
- IgE allows triggering of mast cells by antigen
-

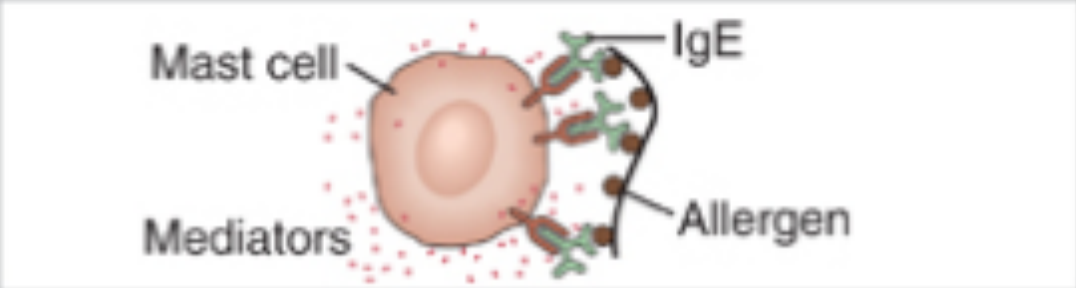
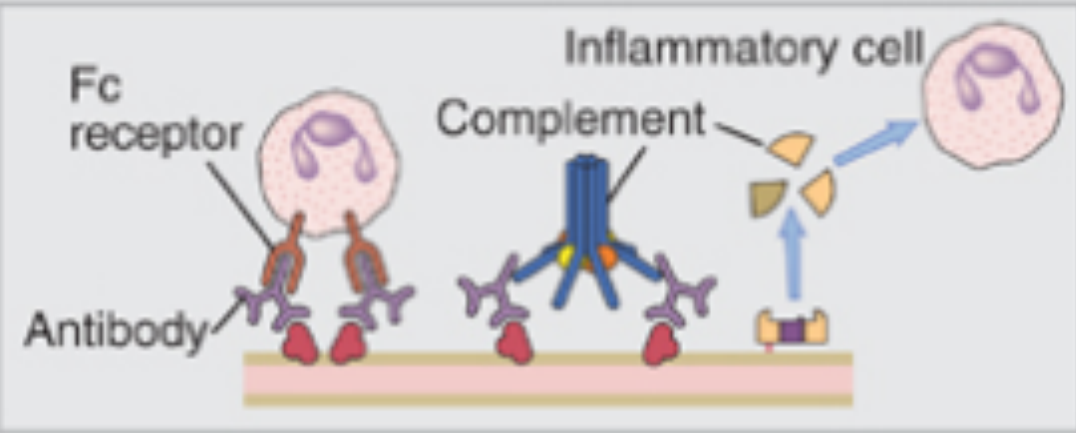
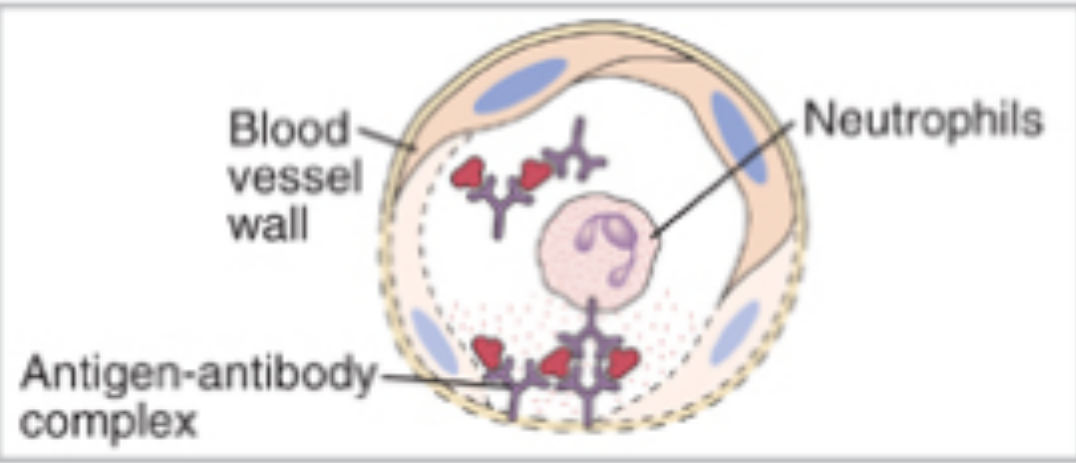
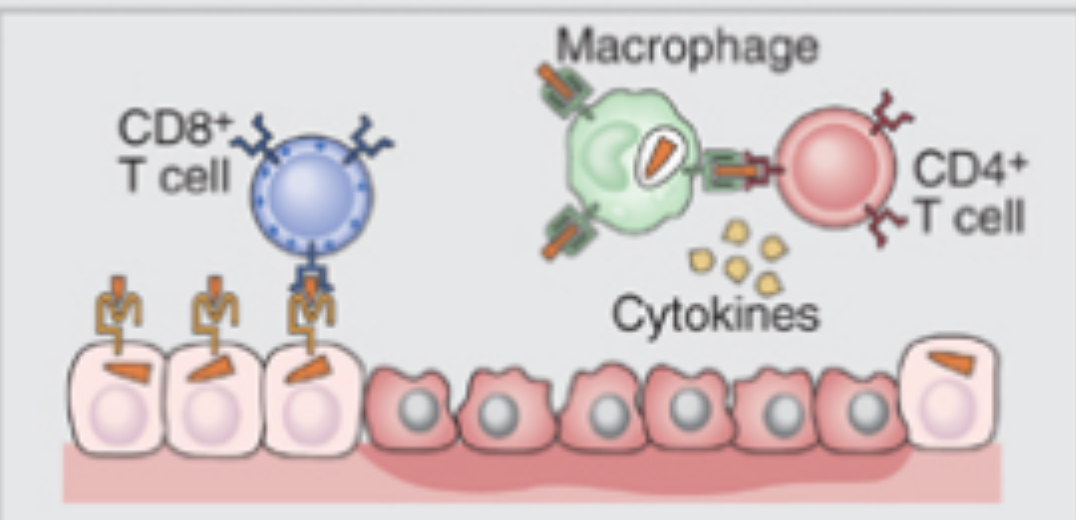
Differentiation to a particular T_H cell type is influenced by the DC type, innate immune sensing/response, and local cytokines (tissue type infected).



Allergies are a type of Hypersensitivity Reaction:

- Represent over-reactions of the immune system
- Can be directed against environmental, medically introduced, or even self antigens
- Most often refers to reactions against harmless environmental antigens (also called allergens)
- The term “Allergy” means ‘altered reactivity’

Classification of hypersensitivity reactions.

Type of hypersensitivity	Pathologic immune mechanisms	Mechanisms of tissue injury and disease
Immediate hypersensitivity (Type I)	<p>T_H2 cells, IgE antibody, mast cells, eosinophils</p> 	<p>Mast cell-derived mediators (vasoactive amines, lipid mediators, cytokines)</p> <p>Cytokine-mediated inflammation (eosinophils, neutrophils)</p>
Antibody-mediated diseases (Type II)	<p>IgM, IgG antibodies against cell surface or extracellular matrix antigens</p> 	<p>Complement and Fc receptor-mediated recruitment and activation of leukocytes (neutrophils, macrophages)</p> <p>Opsonization and phagocytosis of cells</p> <p>Abnormalities in cellular function, e.g. hormone receptor signaling</p>
Immune complex-mediated diseases (Type III)	<p>Immune complexes of circulating antigens and IgM or IgG antibodies deposited in vascular basement membrane</p> 	<p>Complement and Fc receptor-mediated recruitment and activation of leukocytes</p>
T cell-mediated diseases (Type IV)	<p>1. $CD4^+$ T cells (delayed type hypersensitivity) 2. $CD8^+$ CTLs (T cell-mediated cytotoxicity)</p> 	<p>1. Macrophage activation, cytokine-mediated inflammation</p> <p>2. Direct target cell lysis, cytokine-mediated inflammation</p>

Features of inhaled allergens that may promote the priming of T_H2 cells that drive IgE responses	
Molecular type	Proteins, because only they induce T-cell responses
Function	Allergens are often proteases
Low dose	Favors activation of IL-4-producing CD4 T cells
Low molecular weight	Allergen can diffuse out of particle into mucus
High solubility	Allergen is readily eluted from particle
High stability	Allergen can survive in desiccated particle
Contains peptides that bind host MHC class II	Required for T-cell priming

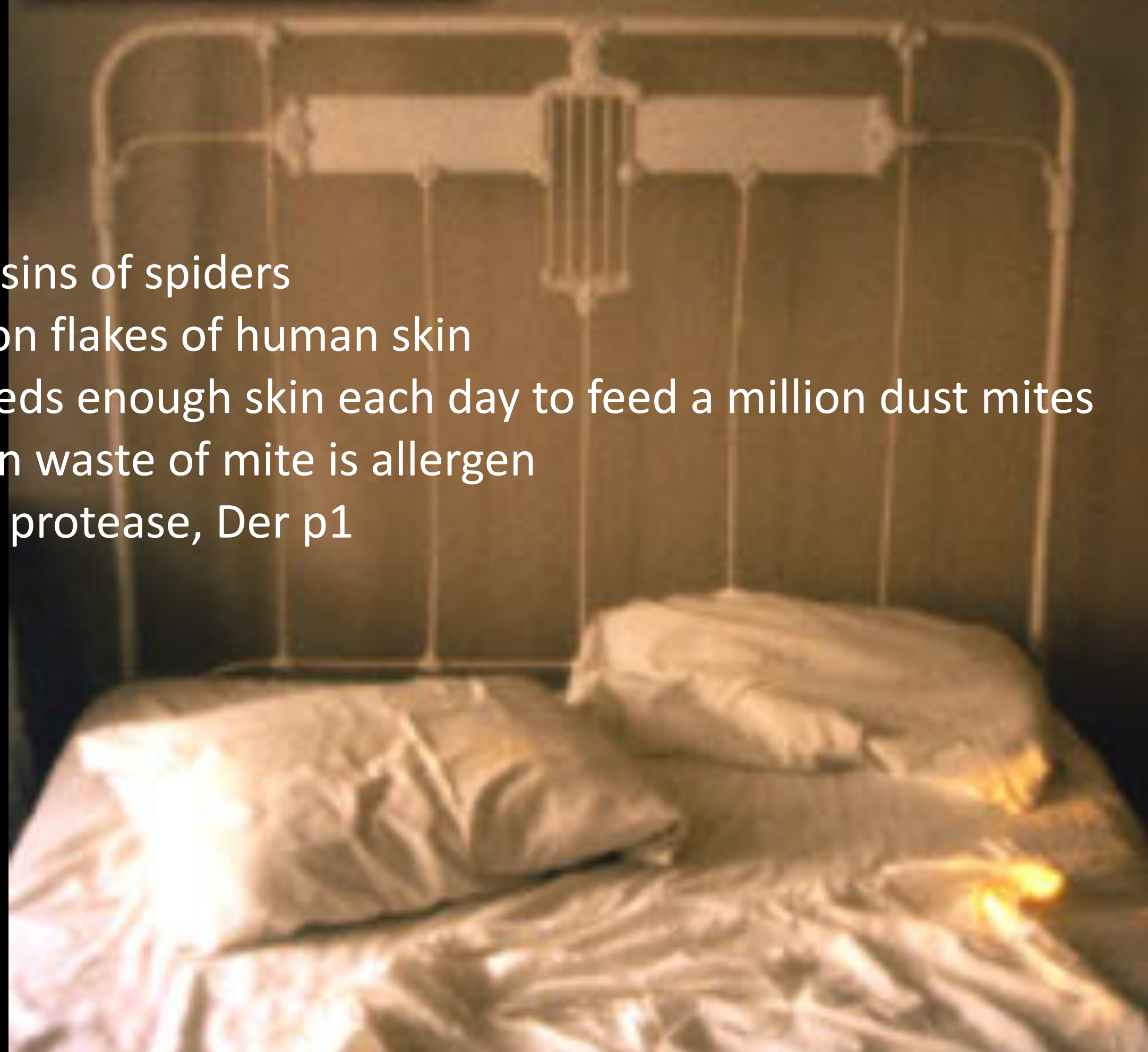
Figure 12.13 The Immune System, 3ed. (© Garland Science 2009)

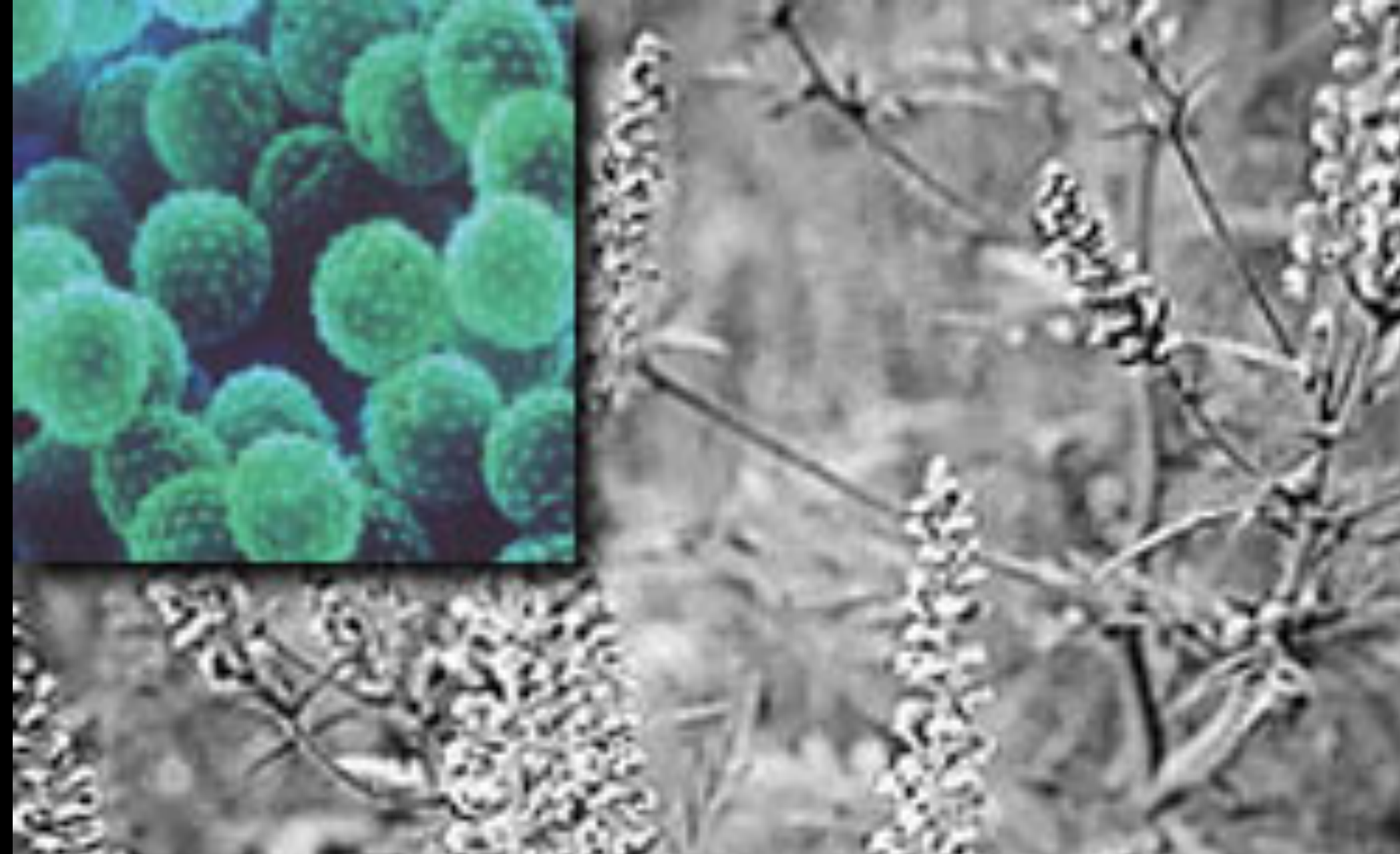
Autosomal-dominant Compelling Helio-Ophthalmic Outburst syndrome, or, of course, ACHOO.



Dust Mites

- Ugly cousins of spiders
- Survive on flakes of human skin
- Adult sheds enough skin each day to feed a million dust mites
- Protein in waste of mite is allergen
- Cysteine protease, Der p1

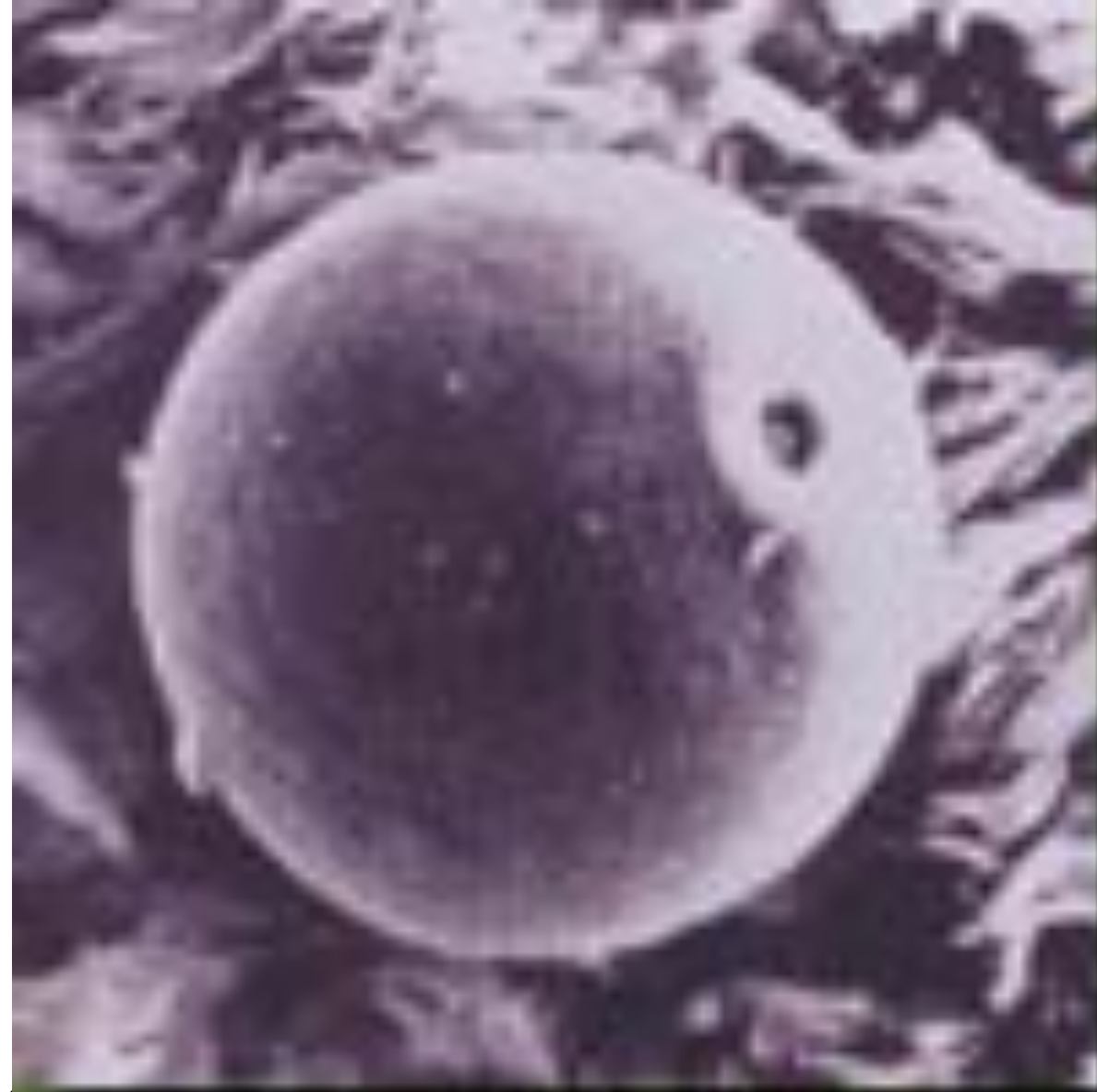




Ragweed

- Named for the ragged shape of its leaves
- Most common plant allergen
- A single plant can produce a million grains of pollen in a single day
- A billion grains during its growing season





Grass Pollen

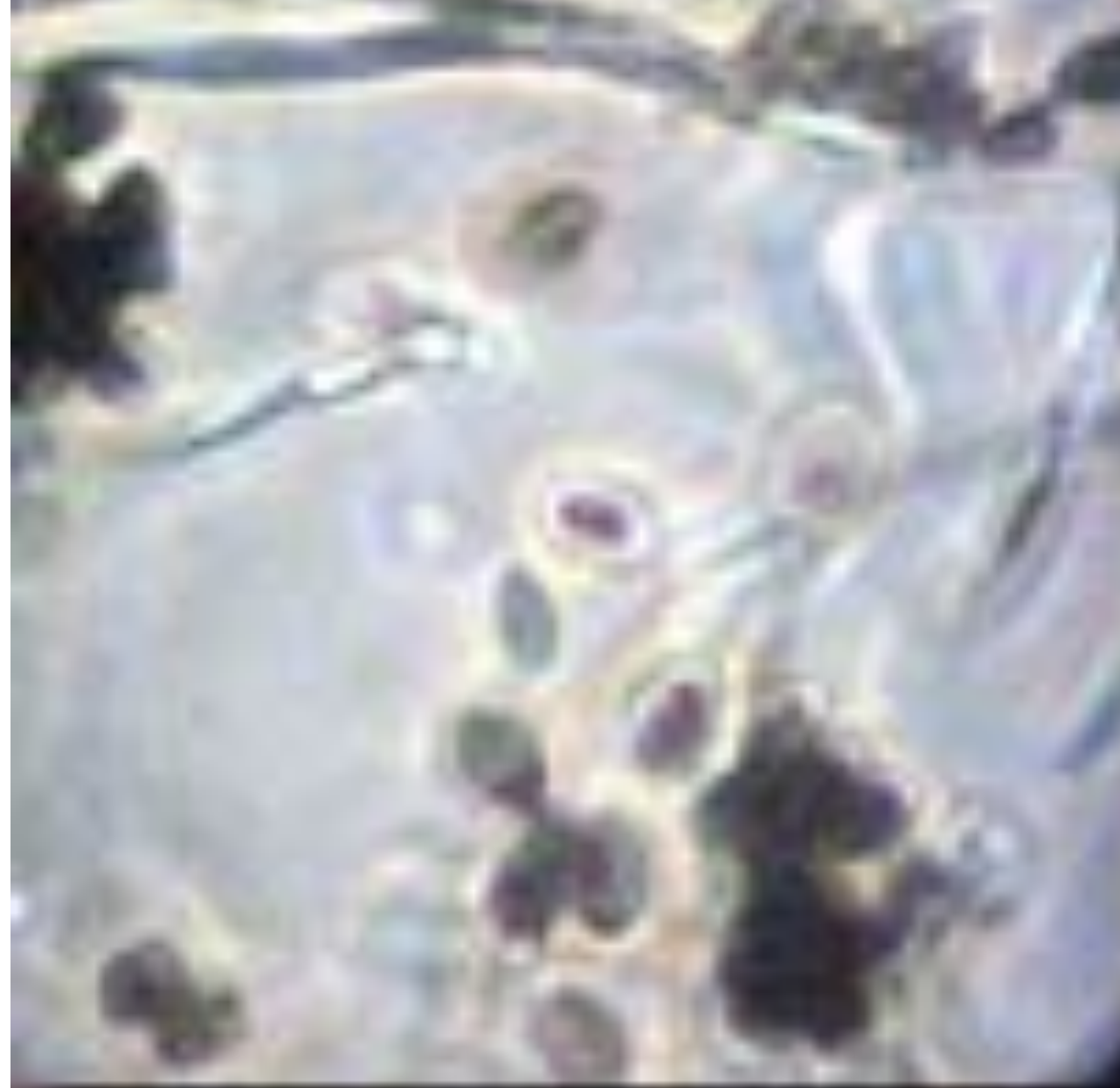
- Grasses rely on the wind to spread their pollen
- Of the 1,200 or so species of grass in North America, only about 20 cause allergic reactions



Tree Pollen

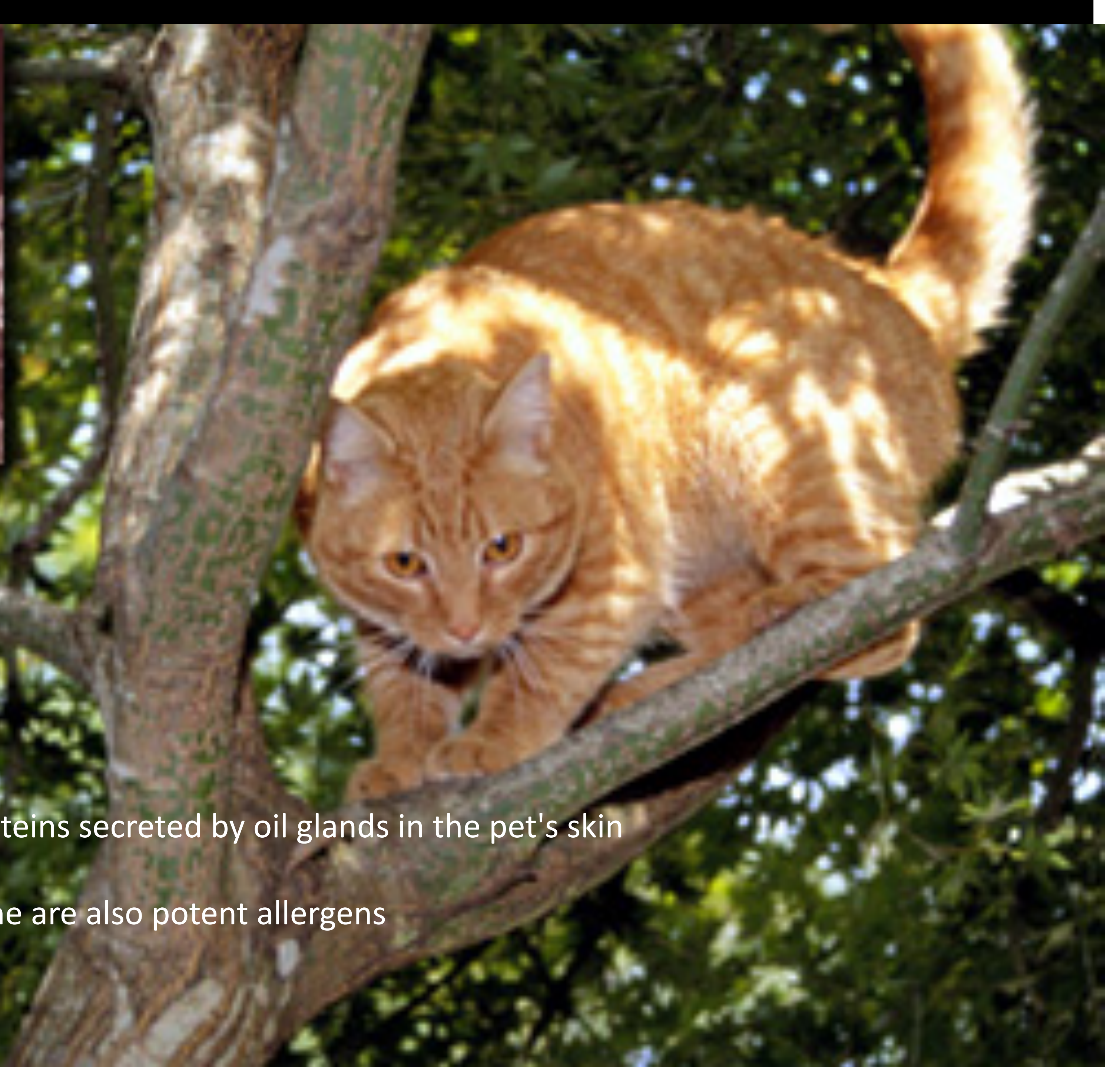
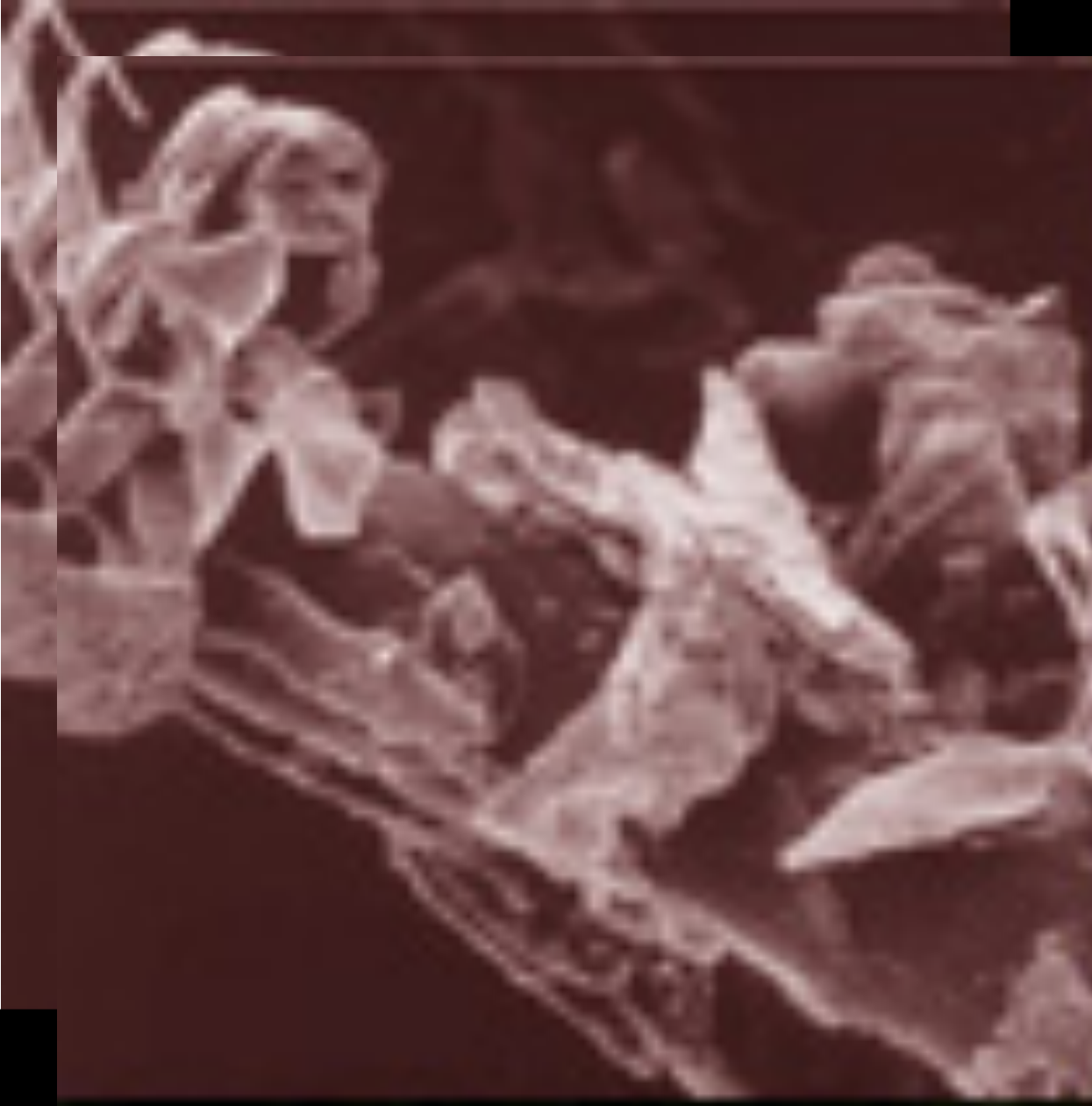
- Of the 650 trees native to the U.S., the pollens of about 100 are allergens





Mold

- Like mildew, are fungi; reproduce by releasing spores into atmosphere
- Allergies to mold are most common in midsummer to fall, triggered by molds that grow on rotting logs, falling leaves and composts piles
- However, mold allergy symptoms can occur year-round due to molds that grow inside bathrooms, kitchens and basements



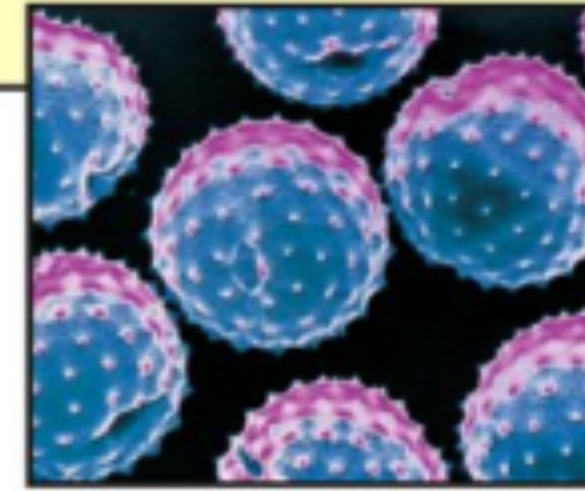
Animal Dander

- Allergens are actually proteins secreted by oil glands in the pet's skin and shed in its dander
- Proteins in saliva and urine are also potent allergens

Common sources of allergens

Inhaled materials

Plant pollens
Dander of domesticated animals
Mold spores
Feces of very small animals
e.g., house dust mites



pollen



house dust mite

0.25 mm long

Injected materials

Insect venoms
Vaccines
Drugs
Therapeutic proteins



wasp



drugs

Ingested materials

Food
Orally administered drugs

6% of children
2% of adults



peanuts



shellfish

Contacted materials

Plant leaves
Industrial products made from plants
Synthetic chemicals in industrial products
Metals



poison ivy



nickel coin

Peptide sequences are known

Figure 10-1 The Immune System, 2/e (© Garland Science 2005)

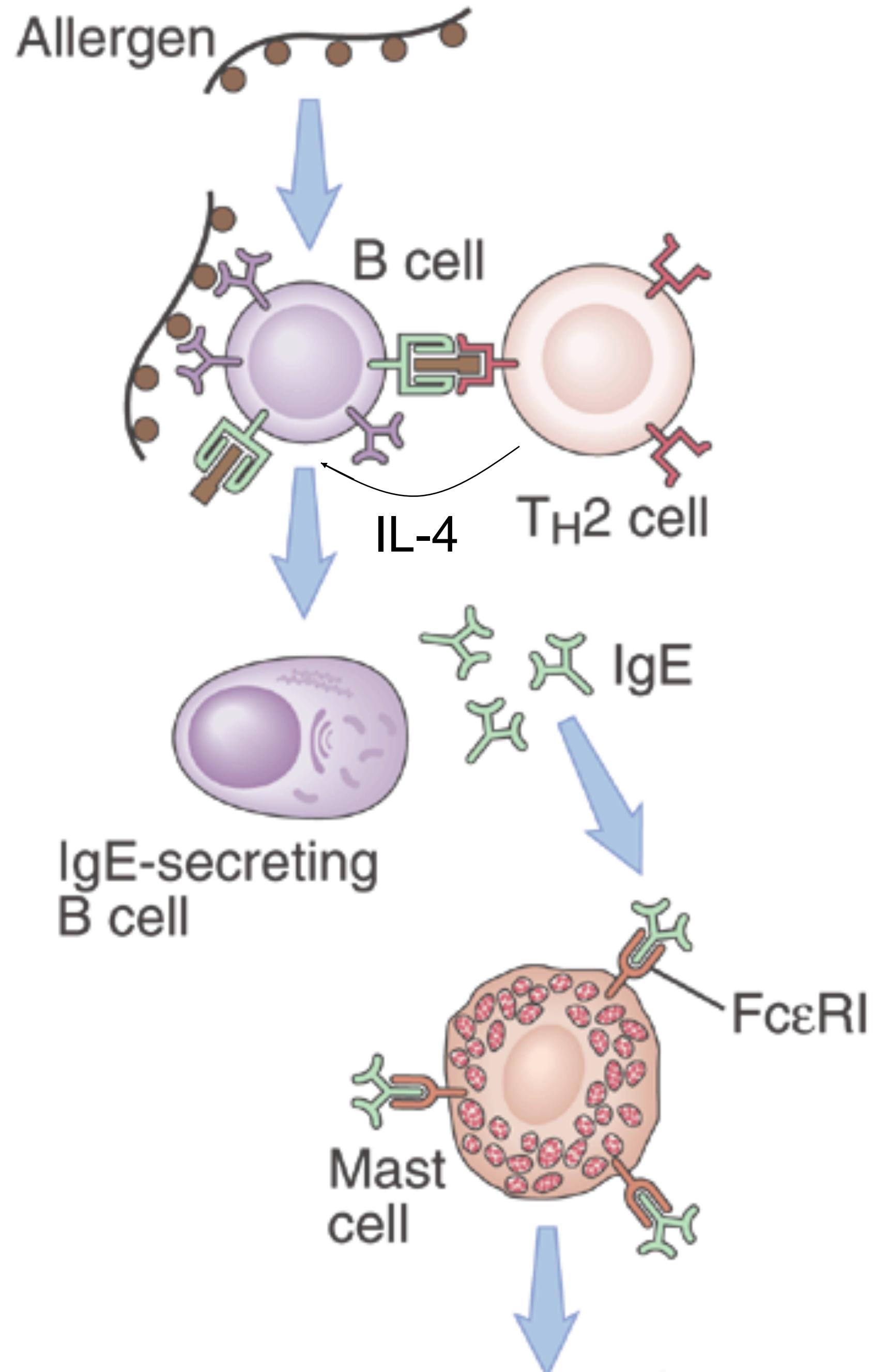
Sensitization stage of immediate hypersensitivity reaction

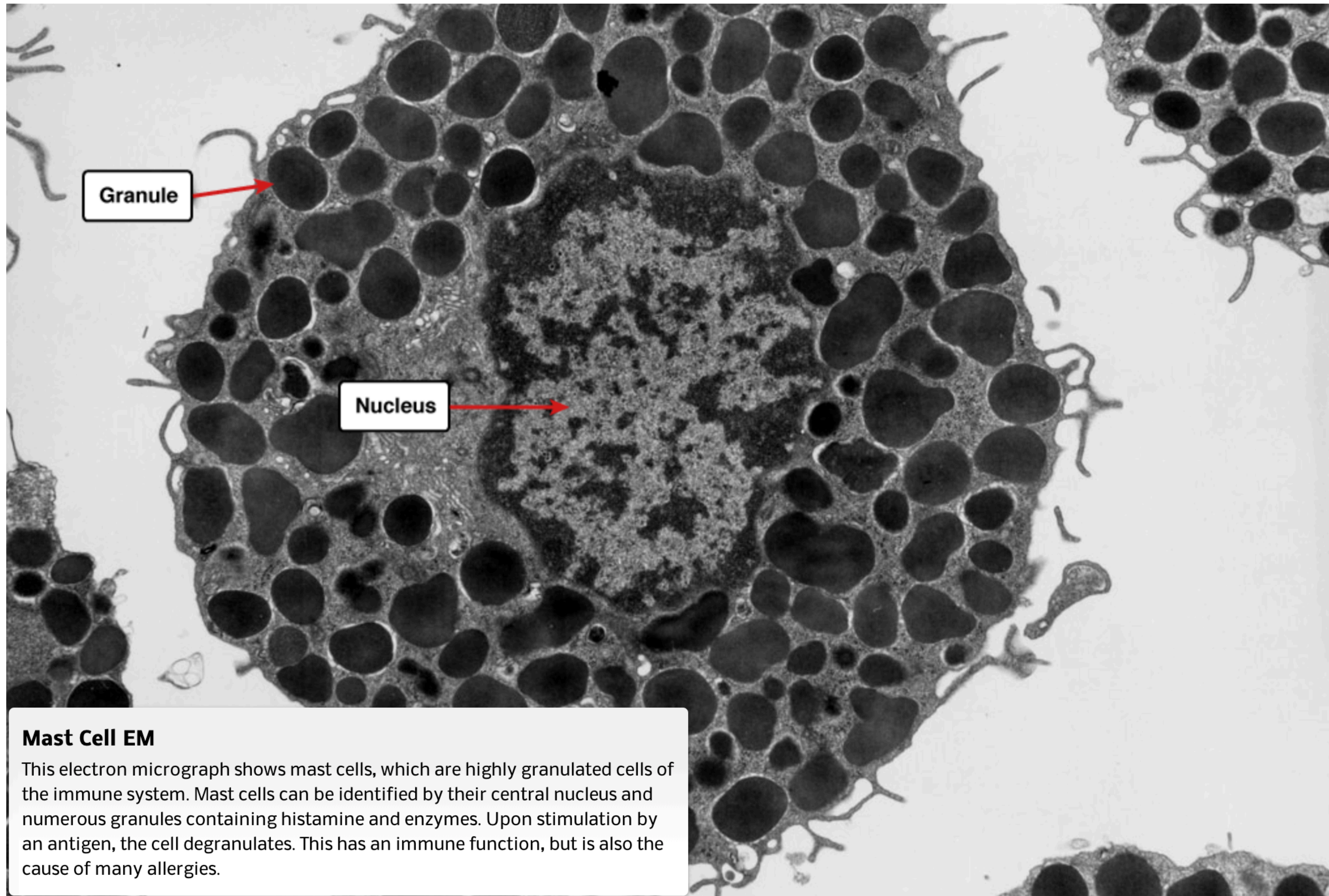
First exposure to allergen

Antigen activation of T_H2 cells and stimulation of IgE class switching in B cells

Production of IgE

Binding of IgE to $Fc\epsilon R1$ on mast cells





Mast Cell EM

This electron micrograph shows mast cells, which are highly granulated cells of the immune system. Mast cells can be identified by their central nucleus and numerous granules containing histamine and enzymes. Upon stimulation by an antigen, the cell degranulates. This has an immune function, but is also the cause of many allergies.

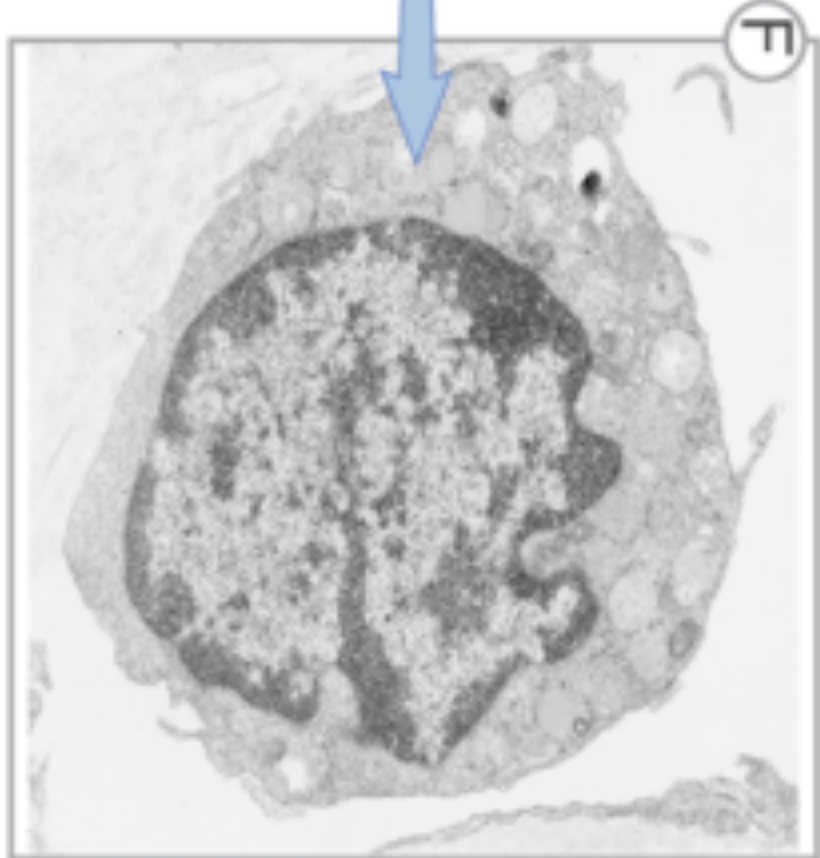
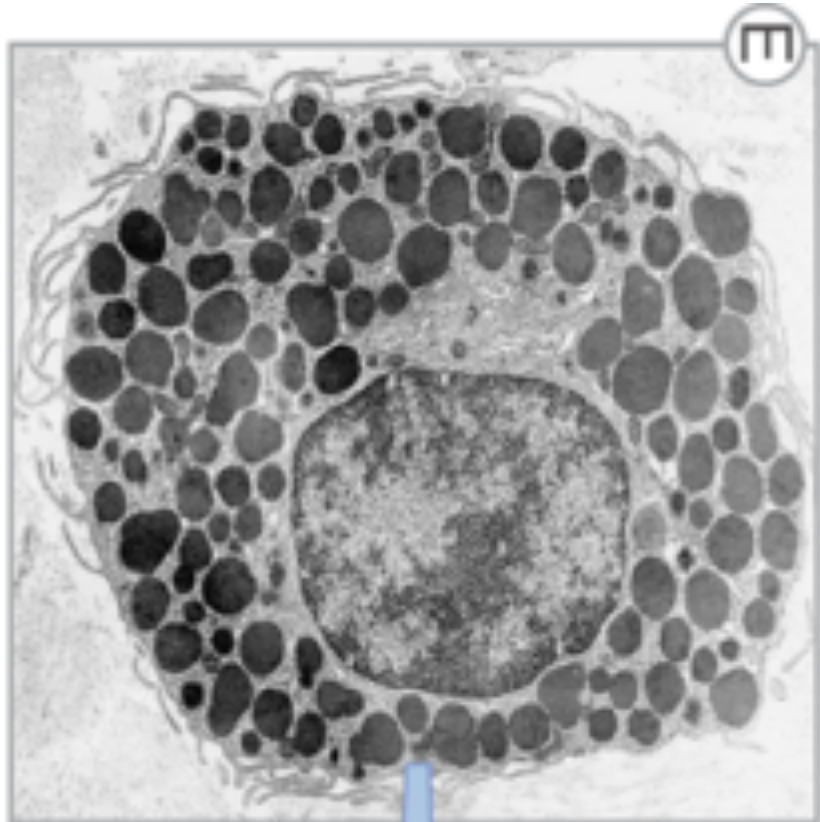
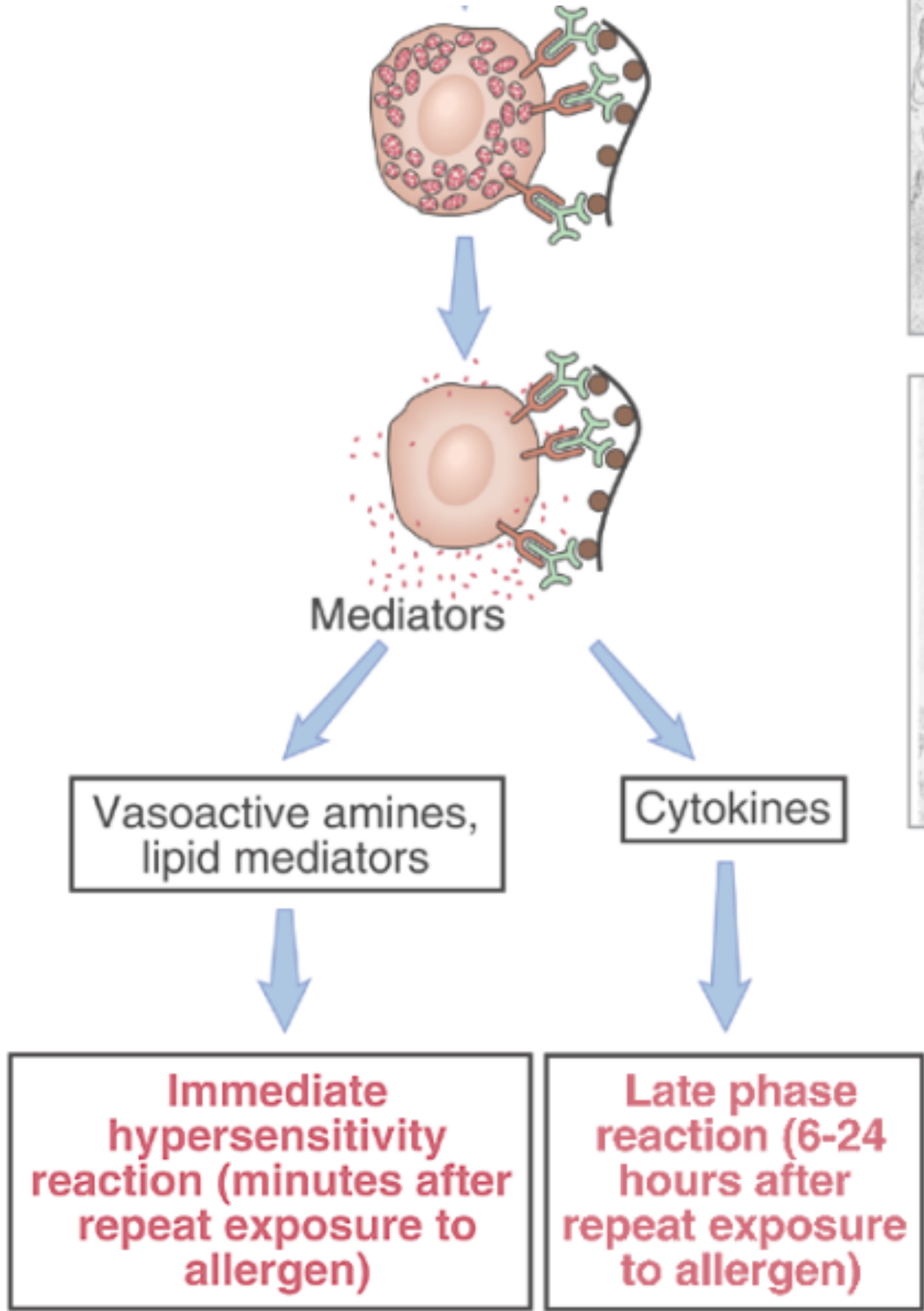
Mast Cell Granules

contain

- histamine
- serotonin
- Tumor Necrosis Factor
- Lipid mediators like prostaglandins and leukotrienes

Repeat exposure to allergen

Activation of mast cell: release of mediators



The effects of mast cell degranulation depend upon the tissue that has been exposed to allergen.

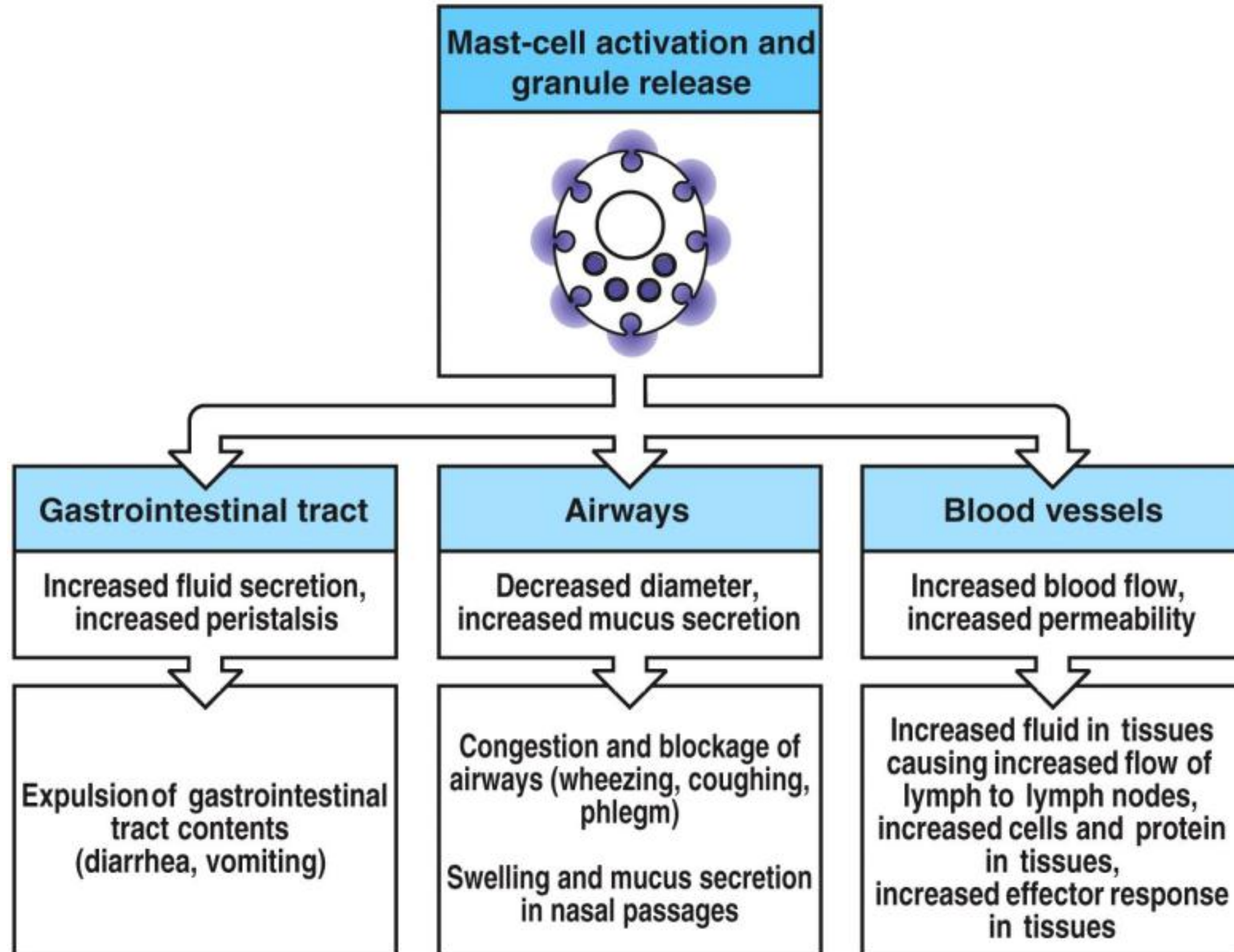


Figure 12-11 Immunobiology, 6/e. (© Garland Science 2005)

Sneezing increases ciliary beat frequency

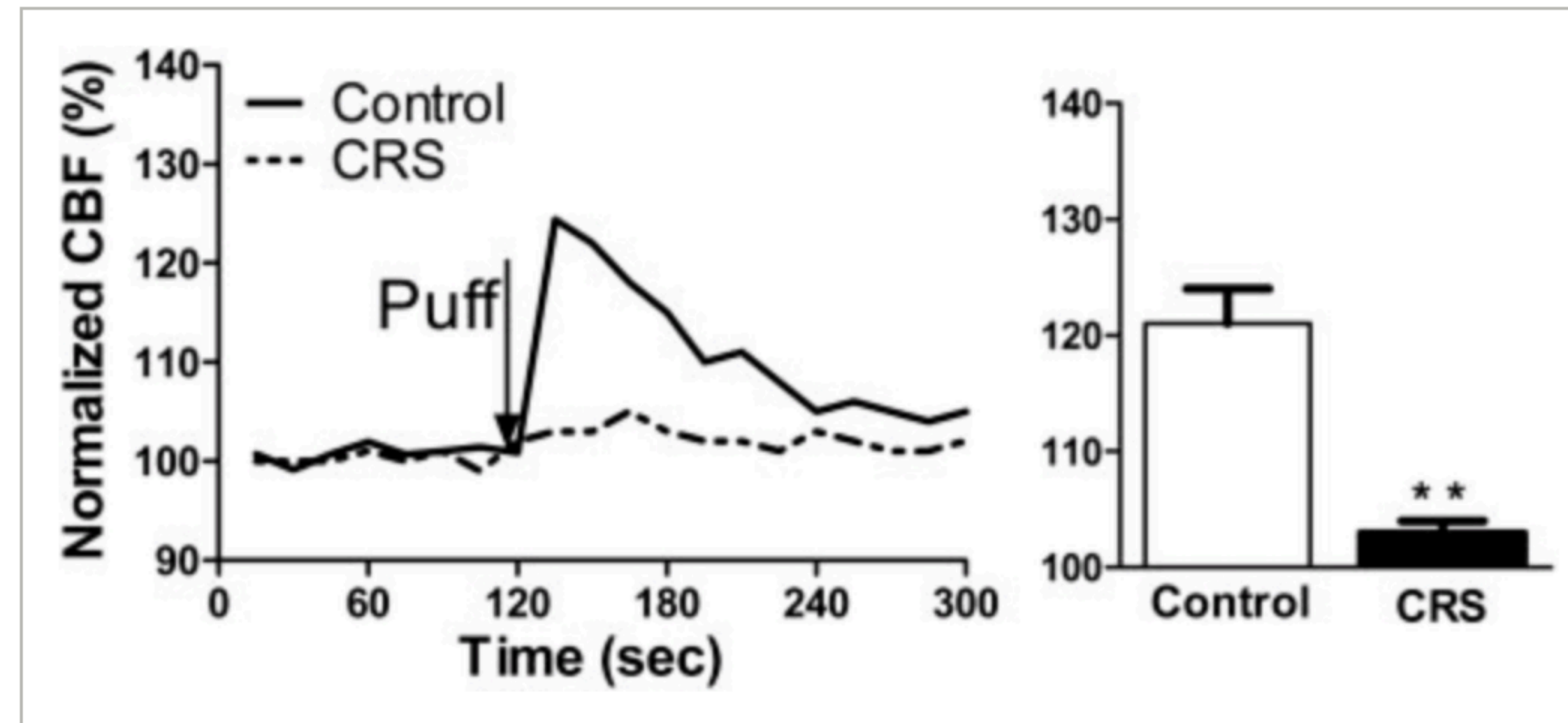


Figure 9

[Open in figure viewer](#)

Blunted CBF in chronic rhinosinusitis (CRS) compared with control. Left panel: representative CBF tracing in sinonasal mucosa from a patient with CRS and a control patient before and after the air puff. Right panel: Sinonasal mucosa from patients with CRS evince a blunted ciliary response following sneeze stimulus ($103.00 \pm 1.00\%$; $n=7$) compared to mucosa from control patients ($121.00 \pm 3.00\%$; $n=6$). Results are means \pm SE. $**P < 0.01$ vs. vehicle.

Both acute and a chronic responses contribute to asthma

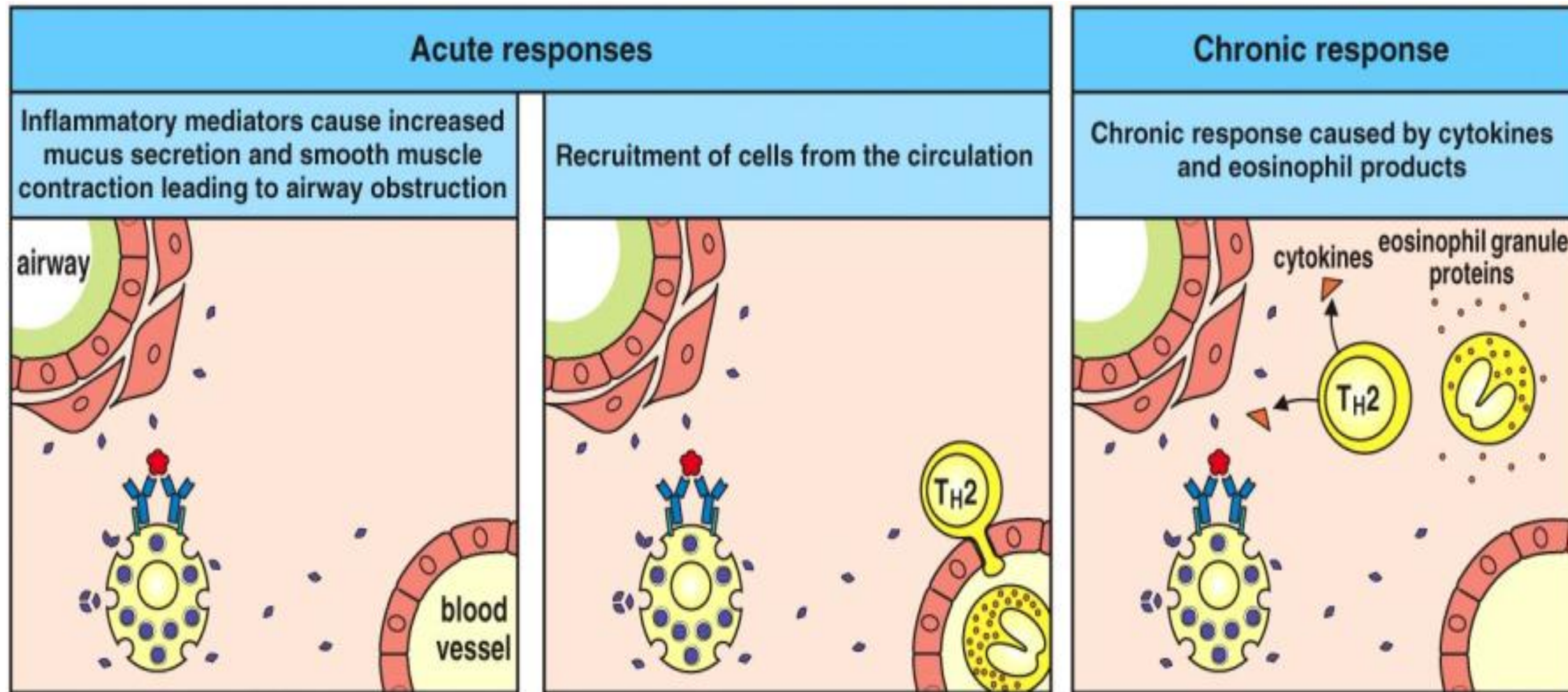


Figure 12-18 Immunobiology, 6/e. (© Garland Science 2005)

Bronchial constriction in lower airways traps air which makes expiration of air difficult (trapped air).

Asthma is a chronic condition with lung damage

Asthma is dominated by presence of T cells (Th2 type).

Circulating Antigen: Anaphylaxis

- Injected, insect bites, high levels of antigen via other routes
- Systemic response of IgE cross linking receptors on connective tissue mast cells and circulating basophils
- Systemic antigen, like bee sting

Anaphylaxis is a life-threatening allergic reaction that affects more than one organ system.

Allergens that can set off anaphylaxis

FOOD



- Peanuts
- Tree nuts: almonds, pecans, cashews, walnuts
- Shellfish
- Cow's milk products
- Hen's eggs
- Fish
- Soy
- Wheat

VENOM



- Yellow jackets
- Wasps and hornets
- Honeybees
- Fire ants
- Spiders

LATEX



- Balloons
- Rubber gloves
- Condoms
- Elastic bands (i.e., physical therapy bands/rubber bands)
- Dental dams

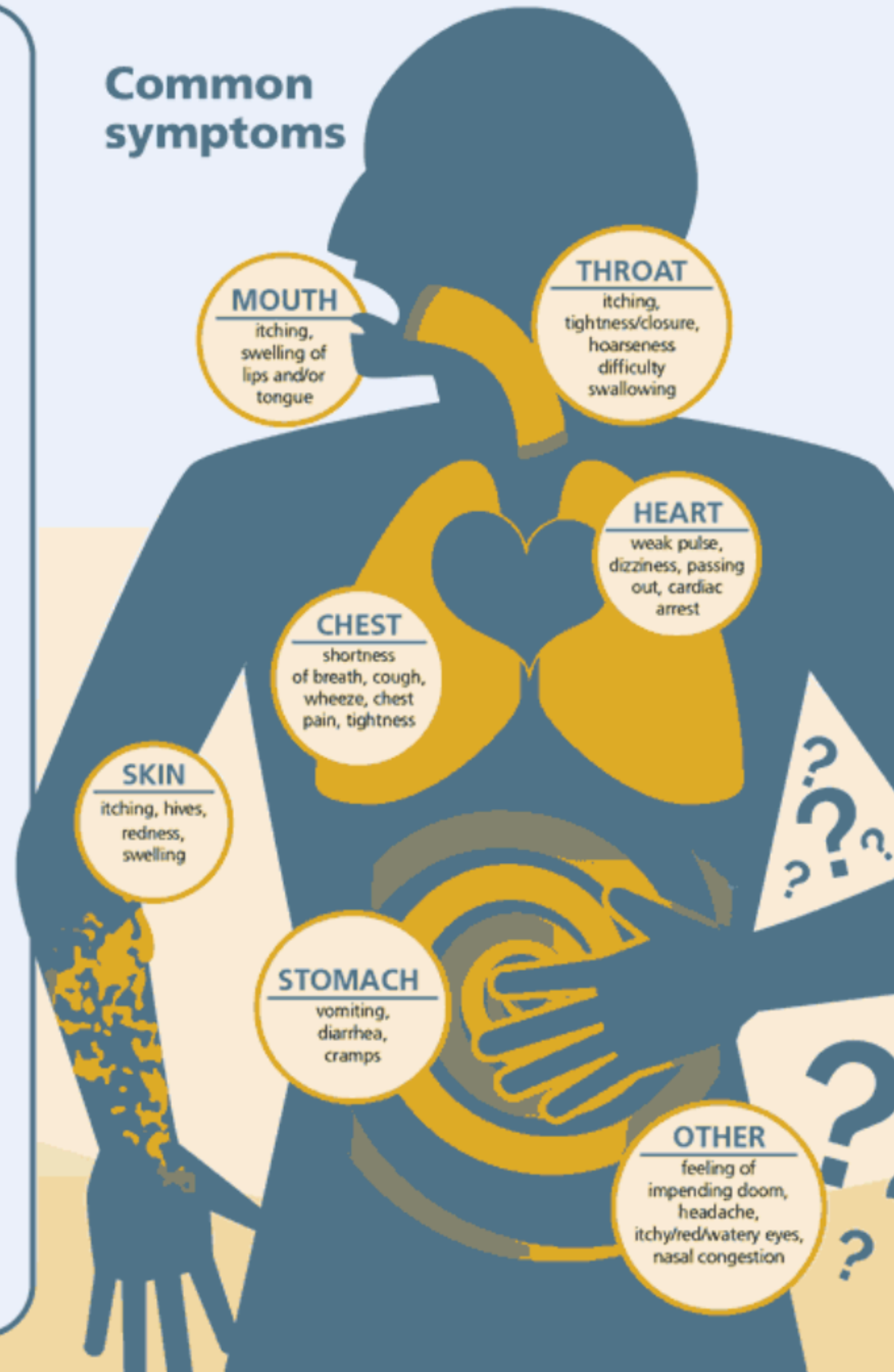
Foods with cross-reactive proteins to natural rubber: banana, avocado, chestnut and kiwi

MEDICATION



- Penicillin
- Aspirin, ibuprofen and other NSAID pain relievers

Common symptoms



MOUTH

itching, swelling of lips and/or tongue

THROAT

itching, tightness/closure, hoarseness, difficulty swallowing

HEART

weak pulse, dizziness, passing out, cardiac arrest

CHEST

shortness of breath, cough, wheeze, chest pain, tightness

SKIN

itching, hives, redness, swelling

STOMACH

vomiting, diarrhea, cramps

OTHER

feeling of impending doom, headache, itchy/red/watery eyes, nasal congestion

Epi Everywhere! Every Day! Right Away!

RECOGNIZE THE SEVERITY



Anaphylaxis is life-threatening, unpredictable, presents in multiple ways and can progress quickly. If symptoms appear refer to your Emergency Care/Action Plan.

USE EPINEPHRINE IMMEDIATELY



Epinephrine is the **first line** of treatment to stop the progression of anaphylaxis. Use your epinephrine auto-injector at the **first sign of symptoms** – don't wait to see what happens!

[anaphylaxis-overview-chart](#)



Always call for emergency medical assistance and go to the emergency room for follow-up observation and treatment.

CARRY TWO AUTO-INJECTORS



Keep two epinephrine auto-injectors on hand, in case symptoms recur before emergency medical assistance is available. Up to 35% of people will require more than one dose.

FOLLOW UP



Consult a board-certified allergist for accurate diagnosis and prevention/treatment plan.

Treatment of Allergy

Syndrome	Therapy	Mechanism of action
Anaphylaxis	Epinephrine	Causes vascular smooth muscle contraction; increases cardiac output (to counter shock); inhibits further mast cell degranulation
Bronchial asthma	Corticosteroids Phosphodiesterase inhibitors	Reduce inflammation Relax bronchial smooth muscles Inhibit leukotriene synthesis
Most allergic diseases	"Desensitization" (repeated administration of low doses of allergens) Anti-IgE antibody (in clinical trials) Antihistamines Cromolyn	Unknown; may inhibit IgE production and increase production of other Ig isotypes; may induce T cell tolerance Neutralize and eliminate IgE Block actions of histamine on vessels and smooth muscles Inhibits mast cell degranulation

Anaphylactic reactions are treated with epinephrine

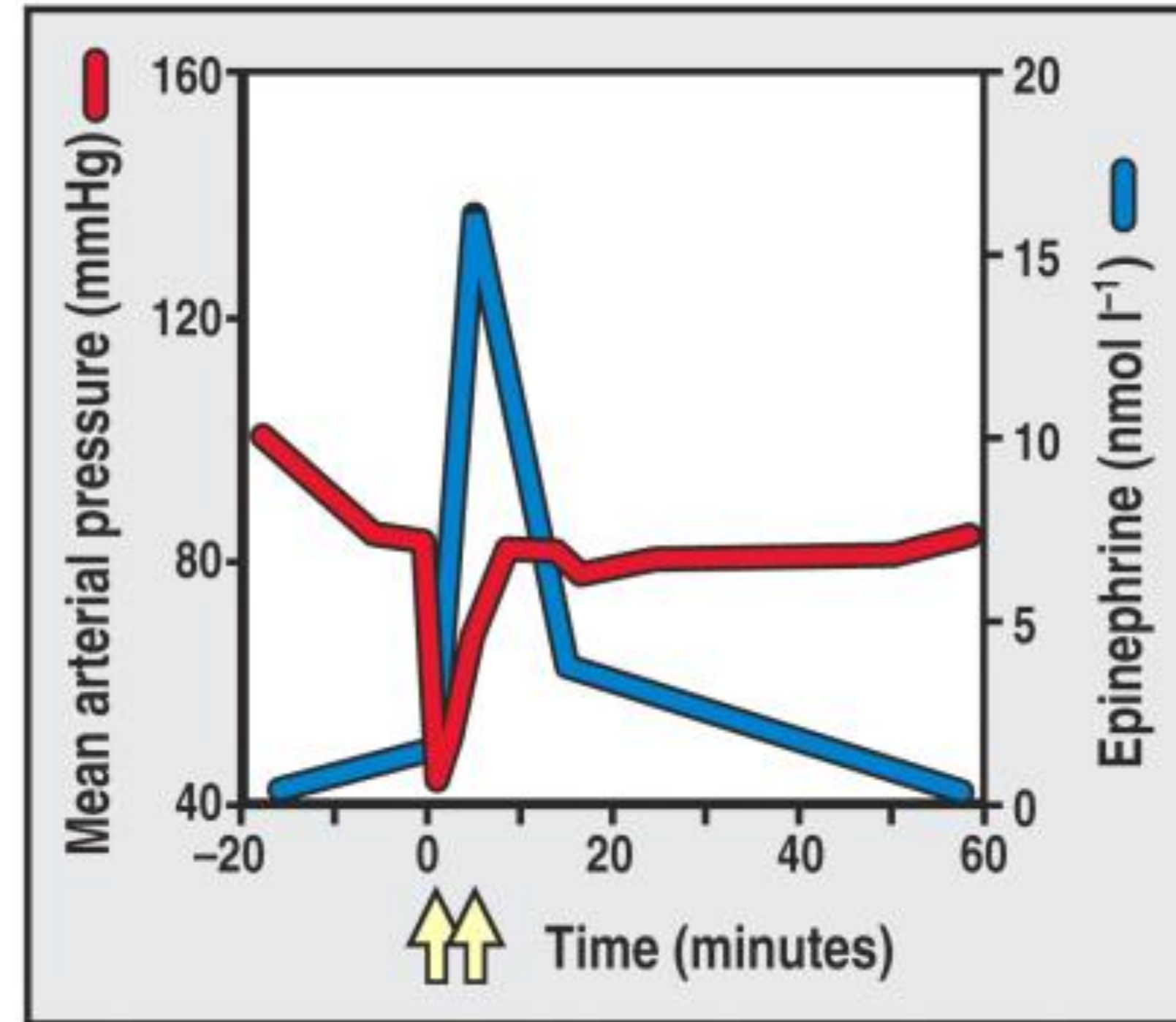


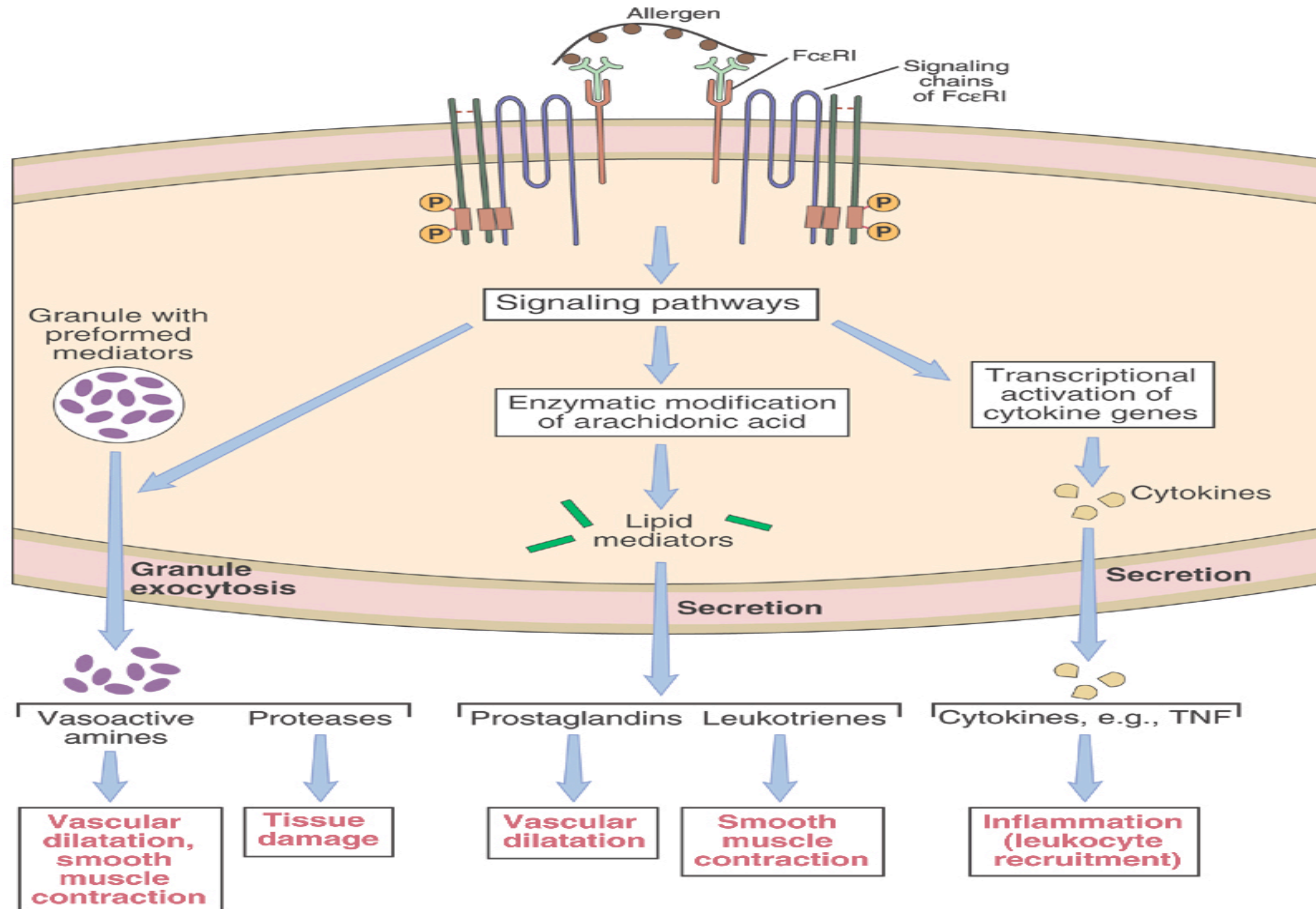
Figure 10-20 The Immune System, 2/e (© Garland Science 2005)

Epinephrine acts at β_2 -adrenergic receptors to stimulate vascular smooth muscle contraction which raises blood pressure. Also relaxes constricted bronchial smooth muscle and stimulates the heart. Patients prone to these reactions carry an “Epi-Pen” Albuterol, also a B2-adrenergic reagent can be inhaled Epinephrine also used to treat “anaphylactoid” reactions caused by non-immune mediated mast cell activation (certain drugs/chemicals)

Immediate Hypersensitivity

- Involves a sensitization stage in which IgE is generated against the antigen (allergen)
- IgE binds to the receptor FcεR1 expressed by mast cells and activated eosinophils
- Binding of antigen to IgE causes cross-linking of associated FcεR1 which triggers release of inflammatory mediators from granules.
- Reaction is immediate and often widespread as mast cells are resident in mucosal and epithelial surfaces lining the body.
- This reaction exists to mediate host defense against helminth (worm) infections

Mast Cell Activation

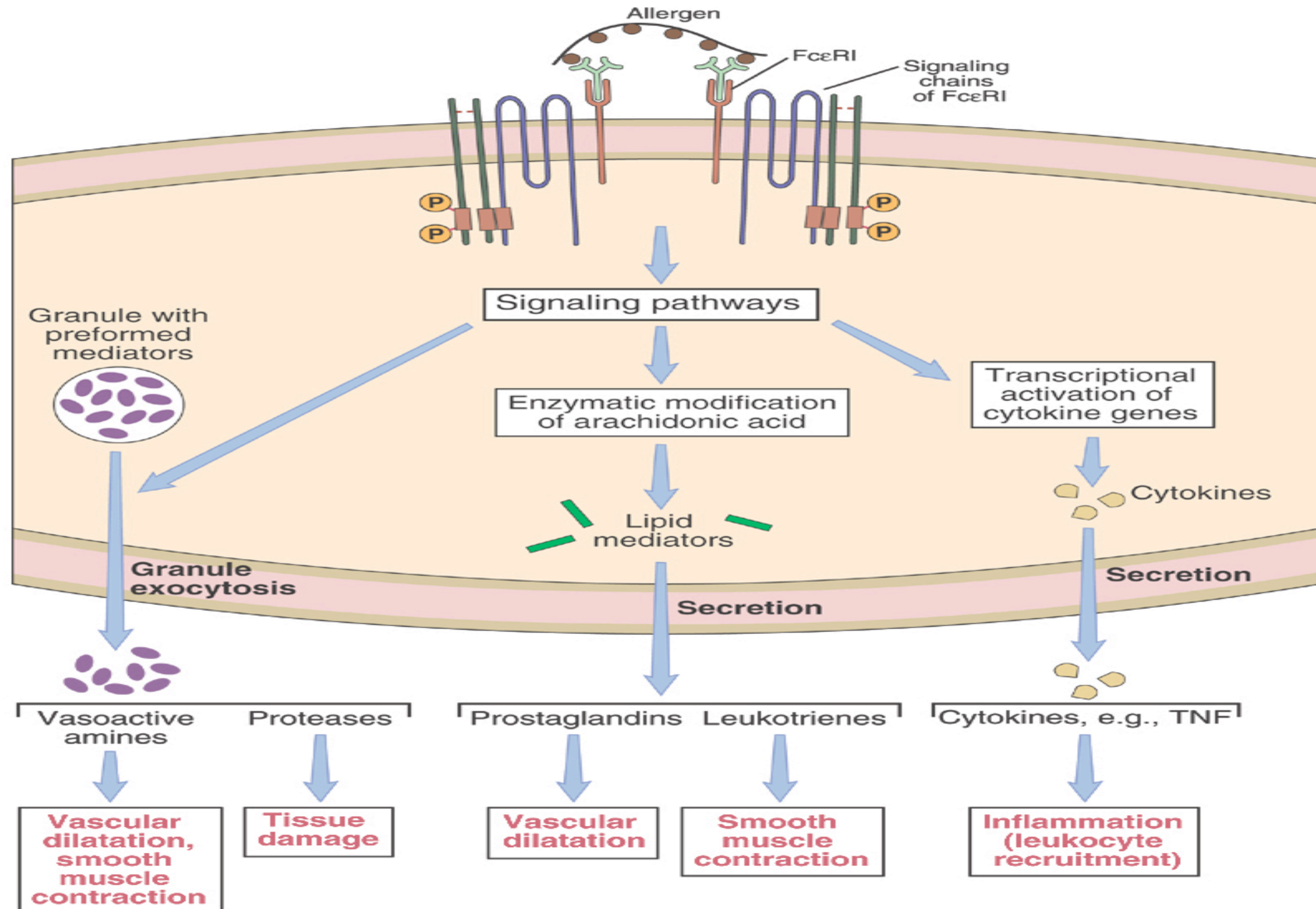


Clinical and pathologic presentation of allergy

Clinical syndrome	Clinical and pathologic manifestations
Allergic rhinitis, sinusitis (hay fever)	Increased mucus secretion; inflammation of upper airways, sinuses
Food allergies	Increased peristalsis due to contraction of intestinal muscles
Bronchial asthma	Bronchial hyper-responsiveness caused by smooth muscle contraction; inflammation and tissue injury caused by late phase reaction
Anaphylaxis (may be caused by drugs, bee sting, food)	Fall in blood pressure (shock) caused by vascular dilatation; airway obstruction due to laryngeal edema

and bronchial smooth muscle contraction

Mast Cell Activation



Food allergy

- 6% of children, 2% of US adults
- Leading cause of anaphylaxis outside of hospitals, 30,000 ER cases per year
- May lead to IgE or cell mediated responses, and be expressed at any of atopic sites (gut, skin, bronchi, systemic)
- Gut largest immunologic organ

Restaurant owner jailed for six years after killing customer with peanut allergy 'threw away his success for profits'

MOHAMMED Zaman was jailed for the death of Paul Wilson after he served him a takeaway containing peanuts despite his request for "no nuts".



By **Tom Wilkinson**
17:33, 23 MAY 2016

NEWS

Food Allergy

- **Maybe** inflated danger claims: Food Allergy and Anaphylaxis Network (supported by maker of EpiPen adrenaline injector) claims food allergy kills 150-200 people per year in US, but CDC number for confirmed cases is 10-20



Ingested Antigen

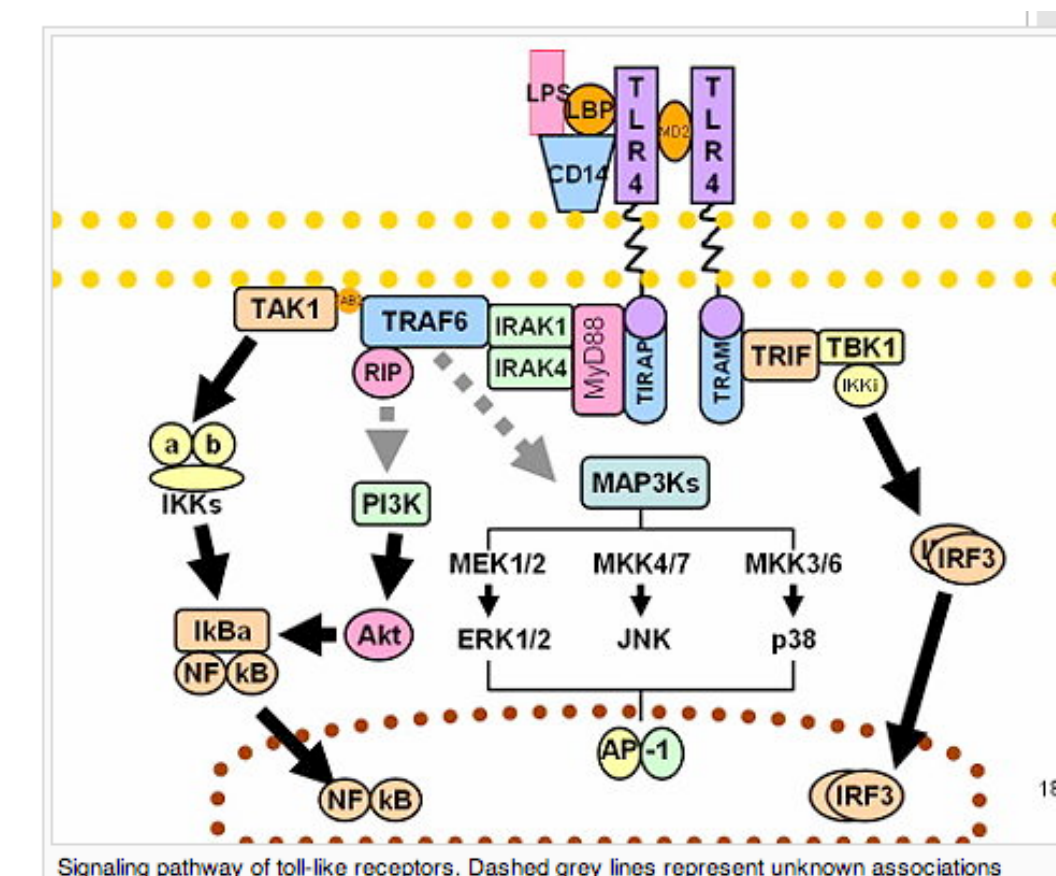
- Food allergy (there are non-allergy food intolerances, such as lactose intolerance)
- Local or systemic responses (antigen absorbed and distributed by circulation) can produce skin responses

IgE-mediated allergic reactions			
Syndrome	Common allergens	Route of entry	Response
Systemic anaphylaxis	Drugs Serum Venoms Peanuts	Intravenous (either directly or after rapid absorption)	Edema Increased vascular permeability Tracheal occlusion Circulatory collapse Death
Wheal and flare	Insect bites Allergy testing	Subcutaneous	Local increase in blood flow and vascular permeability
Allergic rhinitis (hay fever)	Pollens (ragweed, timothy, birch) Dust-mite feces	Inhaled	Edema of nasal mucosa Irritation of nasal mucosa
Bronchial asthma	Pollens Dust-mite feces	Inhaled	Bronchial constriction Increased mucus production Airway inflammation
Food allergy	Shellfish Milk Eggs Fish Wheat	Oral	Vomiting Diarrhea Pruritis (itching) Urticaria (hives) Anaphylaxis

Figure 12.12 The Immune System, 3ed. (© Garland Science 2009)

Gene-Environment Interactions

- Twin studies support genetic role (monozygotic twins compared to dizygotic twins), as do SNPs via 23 and Me
- E.g., one environmental factor is endotoxin (LPS) exposure (related to hygiene hypothesis)
- Endotoxin acts via TLR-4 and CD14 (binds LPS and LPS binding protein)
- Polymorphisms in promoter for CD14 gene related to asthma



> [J Interferon Cytokine Res.](#) 2021 Sep 30. doi: 10.1089/jir.2021.0136. Online ahead of print.

Ir Journal of interferon & cytokine research : the
official journal of the International Society for
Interferon and Cytokine Research

G/A Gene Polymorphism and Susceptibility to Bronchial Asthma in Children: A Single-Center Study

[Hanaa M El Maghraby](#)¹, [Nagwan A Ismail](#)², [Samia Hussein](#)³, [Norhan A Sabbah](#)³,
[Alshimaa L Abdallah](#)¹

Affiliations + expand

PMID: 34591718 DOI: [10.1089/jir.2021.0136](#)

...Gene-Environment Interactions

- CD14 promoter polymorphism T: houses with low endotoxin, polymorphism is protective for asthma
- But, in houses with high endotoxin levels, this polymorphism is associated with higher asthma incidence

Allergy Therapies

- Symptomatic: antihistamine, adrenaline, corticosteroid, anti-leukotriene, cromolyn (stabilizes mast cell granules)
- Desensitization with protein or peptide antigens, with or without adjuvant (adjuvant may shift to Th1).
Desensitization may also generate IgG antibodies that prevent allergic antigen from reaching IgE coated mast cells
- Anti-IgE antibodies

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Most allergic diseases	"Desensitization" (repeated administration of low doses of allergens) Anti-IgE antibody (in clinical trials) Antihistamines Cromolyn	Unknown; may inhibit IgE production and increase production of other Ig isotypes; may induce T cell tolerance Neutralize and eliminate IgE Block actions of histamine on vessels and smooth muscles Inhibits mast cell degranulation

Maternal factors

- Transplacental and lactating exchange of antibodies
- Mice: maternal exposure of peanut allergic moms to low dose peanut reduced response of offspring to peanut and altered IgG_{2a} to IgG₁
- Airborne exposure of mom to allergen (OVA) who nursed pups reduced allergic airway responses in offspring
- Exposure of mom mice to bacteria isolated from cowsheds reduced allergic responses in offspring and induced DCs with Th1 biasing properties

Inhaled Antigen

- Allergic rhinitis for upper respiratory tract
- Asthma for lower respiratory tract
- Chronic response leads to destruction of epithelium and nonspecific inflammation to other irritants

Desensitization and Redirection

- Low doses of allergic peptides
- Traditionally s.c., but recent trials with sublingual route to employ mechanisms of oral tolerance
 - Grazax in Europe for grass hay fever
- New adjuvants like CpG DNA (TLR9 ligand) promote TH1 response
- Induces Tregs and IgG secreting B cells r/t IgE
- Treatment with helminths may shift helper T cell phenotype

'Hypoallergenic cats' go on sale

What are claimed to be the world's first specially bred hypoallergenic cats have gone on sale in the US.



At just three weeks old these kittens have already been reserved

US biotech firm Allerca says it has managed to selectively breed them by reducing a certain type of protein that triggers allergic reactions.

iture

VIDEO AND AUDIO NEWS

Joshua, the first hypo-allergenic cat

[▶ WATCH](#)

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'Cat allergies 'could be blocked'

27 Mar 05 | Health

'Pets 'could lower allergy risk'

27 Aug 02 | Health

'Keeping pets 'prevents allergies'

Fel d 1 by RNAi

Yet Allerca's promises were apparently hollow. In 2013, an ABC report [found](#) that a kitten Allerca tried to sell reporters was an ordinary cat from a local pet breeder. (Allerca did not respond to attempts at contact.)

aka Lifestyle Pets

- claiming to use gene silencing, RNAi, to reduce expression of Fel d 1, main cat allergen protein
- Time Magazine Invention of the Year for 2006
- prices ranged from \$7,000 to \$29,000
- ABC News did expose, stated Allerca cats no less allergenic than ordinary cats