Outline

Hypersensitivity reactions

- -Introduction
- –Type I
- –Type II
- –Type III
- –Type IV

Common Causes of Hypersensitivity Reactions

Mounting an immune response against innocent substances

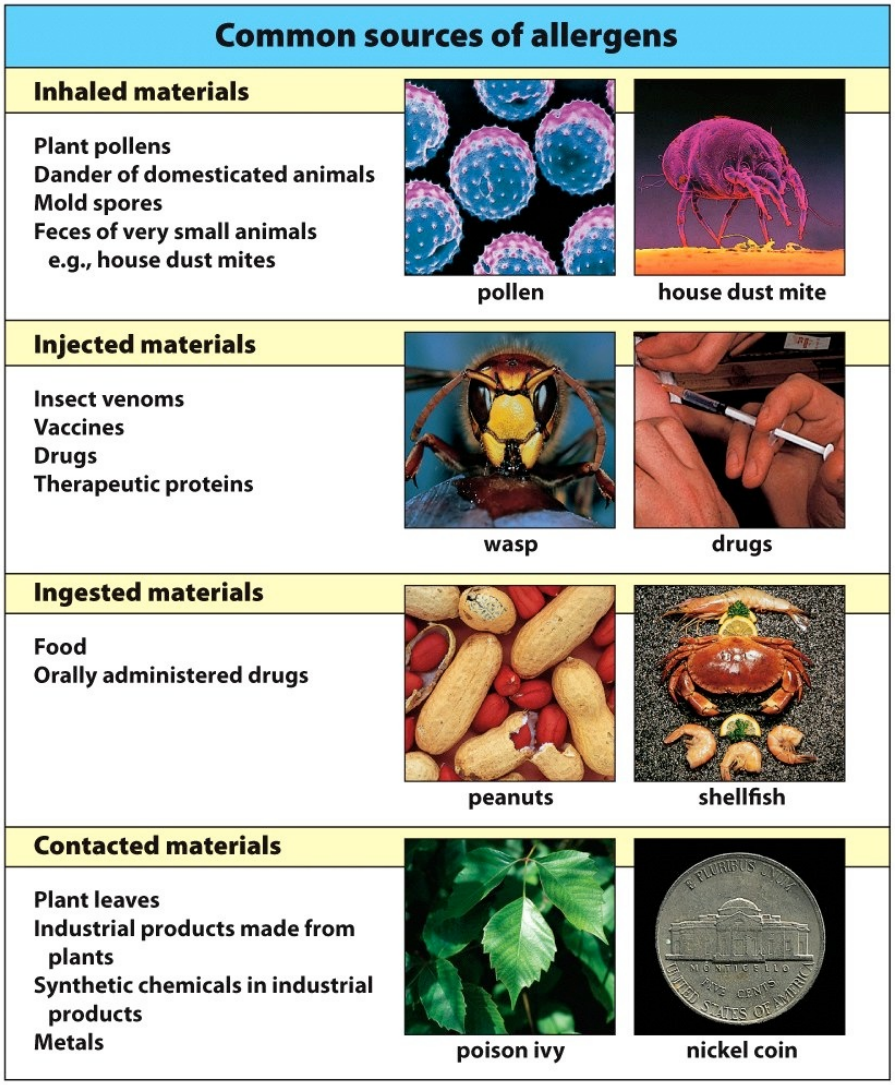


Figure 12.1 The Immune System, 3ed. (© Garland Science 2009)

Types of Hypersensitivity Reactions

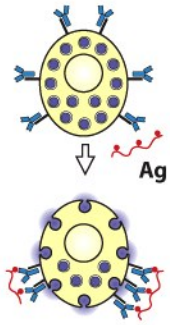
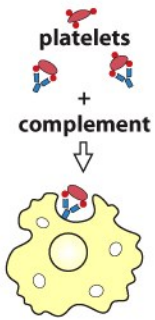
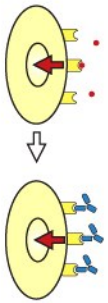
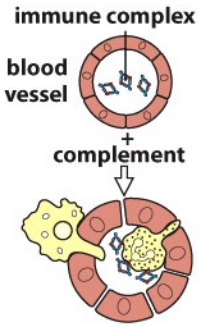
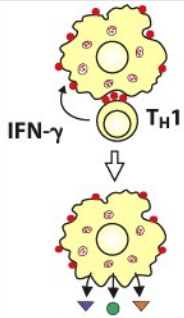
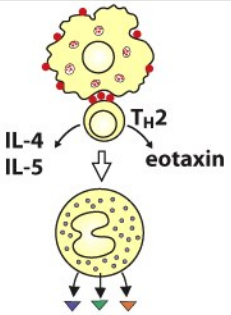
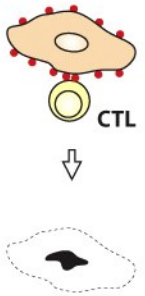
	Type I	Type II		Type III	Type IV		
Immune reactant	IgE	IgG		IgG	T_H1 cells	T_H2 cells	CTL
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Cell-surface receptor	Soluble antigen	Soluble antigen	Soluble antigen	Cell-associated antigen
Effector mechanism	Mast-cell activation	Complement, FcR^+ cells (phagocytes, NK cells)	Antibody alters signaling	Complement, phagocytes	Macrophage activation	IgE production, eosinophil activation, mastocytosis	Cytotoxicity
							
Example of hypersensitivity reaction	Allergic rhinitis, allergic asthma, atopic eczema, systemic anaphylaxis, some drug allergies	Some drug allergies (e.g. penicillin)	Chronic urticaria (antibody against FcεRI alpha chain)	Serum sickness, Arthus reaction	Allergic contact dermatitis, tuberculin reaction	Chronic asthma, chronic allergic rhinitis	Graft rejection, allergic contact dermatitis to poison ivy

Figure 14.1 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Sensitization to an Inhaled Allergen

Initial exposure to the antigen induces sensitization
Second exposure to the same antigen leads to allergy

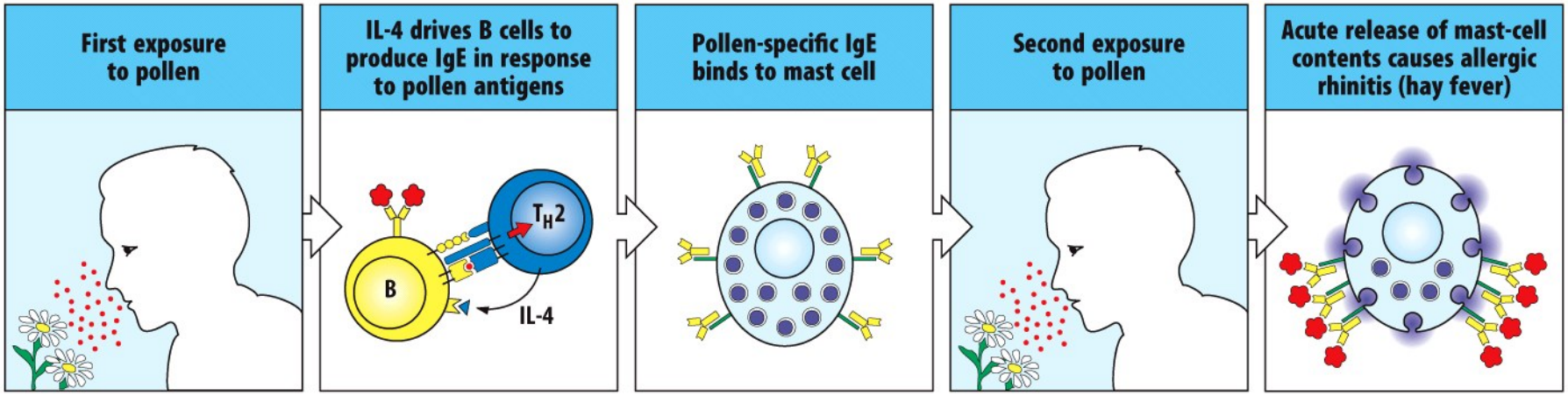


Figure 50.1 Case Studies in Immunology, 6ed. (© Garland Science 2012)

Properties of Inhaled Allergens

Features of airborne allergens that may promote the priming of T_H2 cells that drive IgE responses	
Protein, often with carbohydrate side chains	Only proteins induce T-cell responses
Low dose	Favors activation of IL-4-producing CD4 T cells
Low molecular weight	Allergen can diffuse out of particles into the mucosa
Highly soluble	Allergen can be readily eluted from particle
Stable	Allergen can survive in desiccated particle
Contains peptides that bind host MHC class II	Required for T-cell priming

Figure 14.5 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Small stable proteins

Enzymes Targeting Tight Junctions Trigger Allergy

Der p1 is present in fecal pellets from the house dust mite

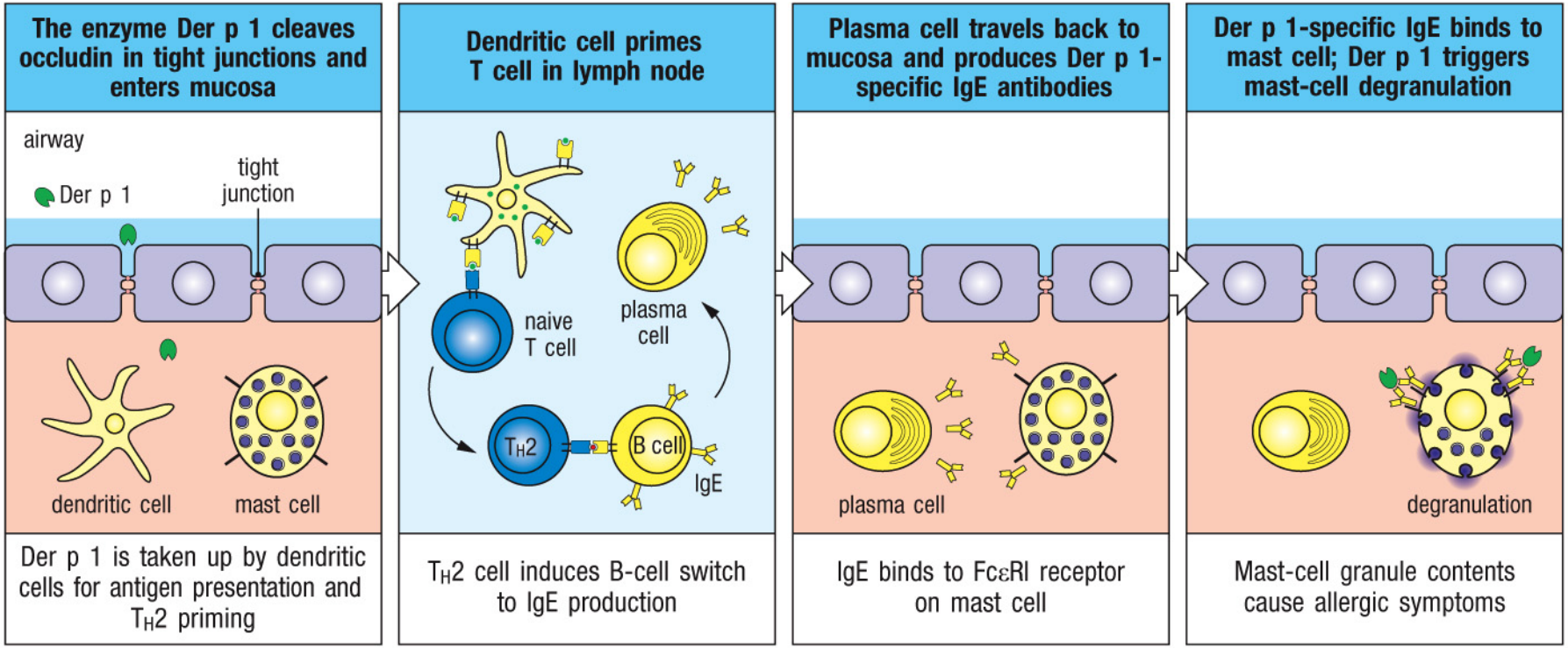


Figure 14.2 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

IgE Localizes to Tissues and Is Bound to Mast Cells

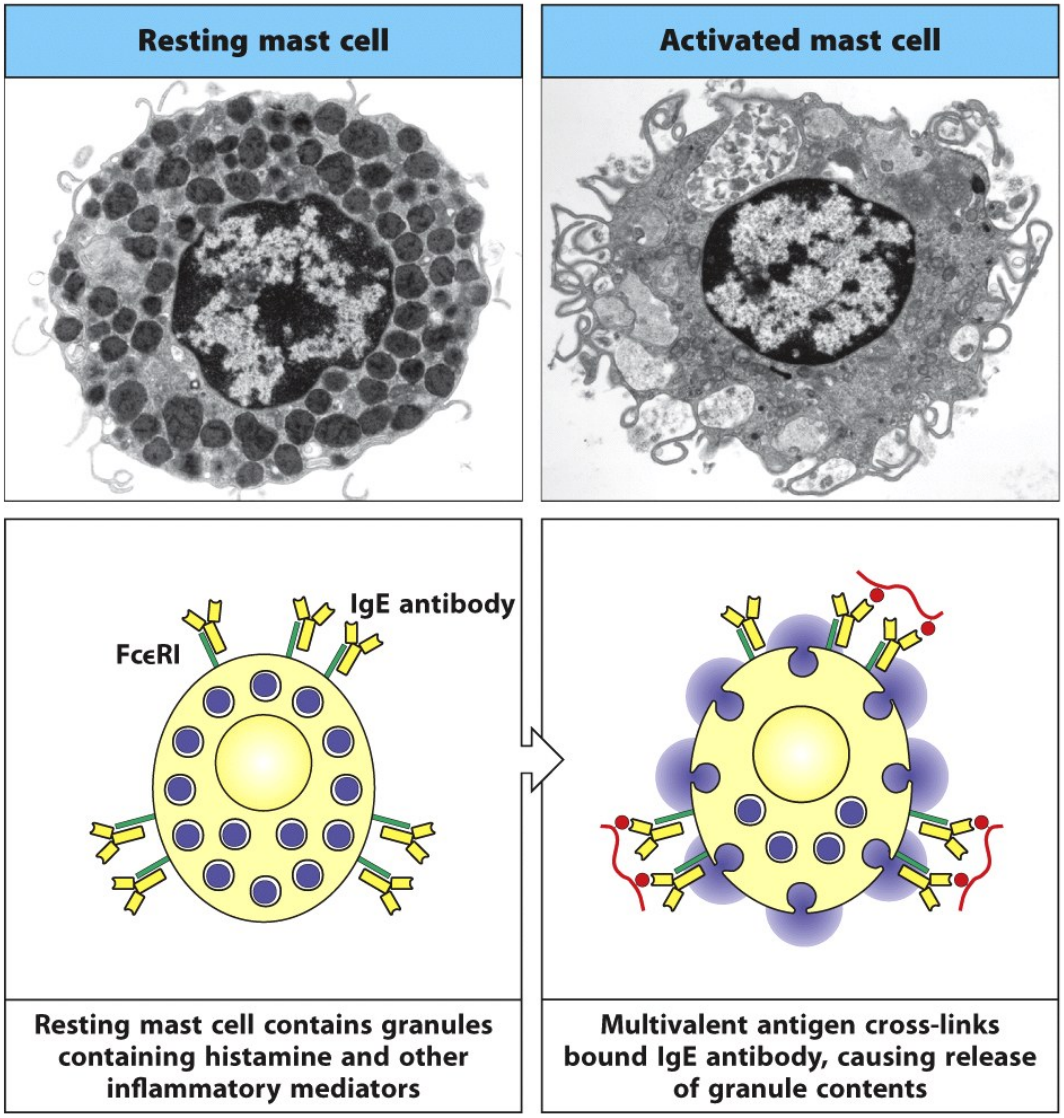


Figure 10.37 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Increase vesicular permeability

Antigen Binding to IgE on Mast Cells Amplifies IgE Production

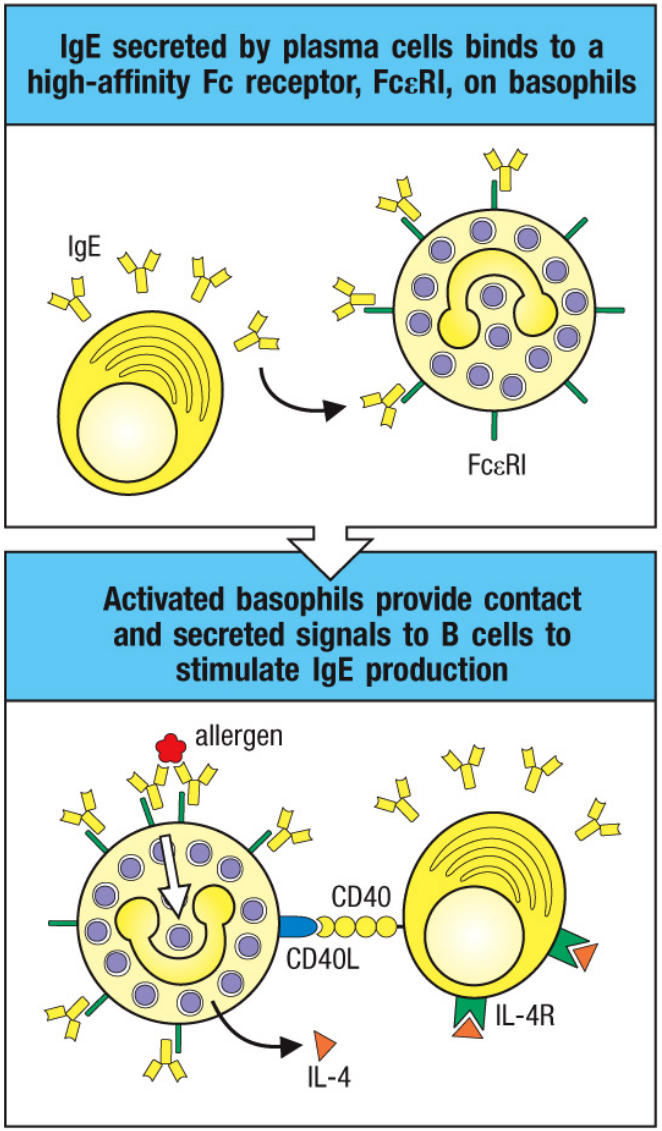


Figure 14.3 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Stimulation of class switch to IgE

Allergic Reactions Mediated by IgE

IgE-mediated allergic reactions			
Reaction or disease	**Common stimuli**	**Route of entry**	**Response**
Systemic anaphylaxis	Drugs Venoms Food, e.g., peanuts Serum	Intravenous (either directly or following absorption into the blood after oral intake)	Edema Increased vascular permeability Laryngeal edema Circulatory collapse Death
Acute urticaria (wheal-and-flare)	Post-viral Animal hair Bee stings Allergy testing	Through skin Systemic	Local increase in blood flow and vascular permeability Edema
Seasonal rhinoconjunctivitis (hay fever)	Pollens (ragweed, trees, grasses) Dust-mite feces	Contact with conjunctiva of eye and nasal mucosa	Edema of conjunctiva and nasal mucosa Sneezing
Asthma	Dander (cat) Pollens Dust-mite feces	Inhalation leading to contact with mucosal lining of lower airways	Bronchial constriction Increased mucus production Airway inflammation Bronchial hyperreactivity
Food allergy	Peanuts Tree nuts Shellfish Fish Milk Eggs Soy Wheat	Oral	Vomiting Diarrhea Pruritus (itching) Urticaria (hives) Anaphylaxis (rarely)

Figure 14.1 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Susceptibility of Allergy

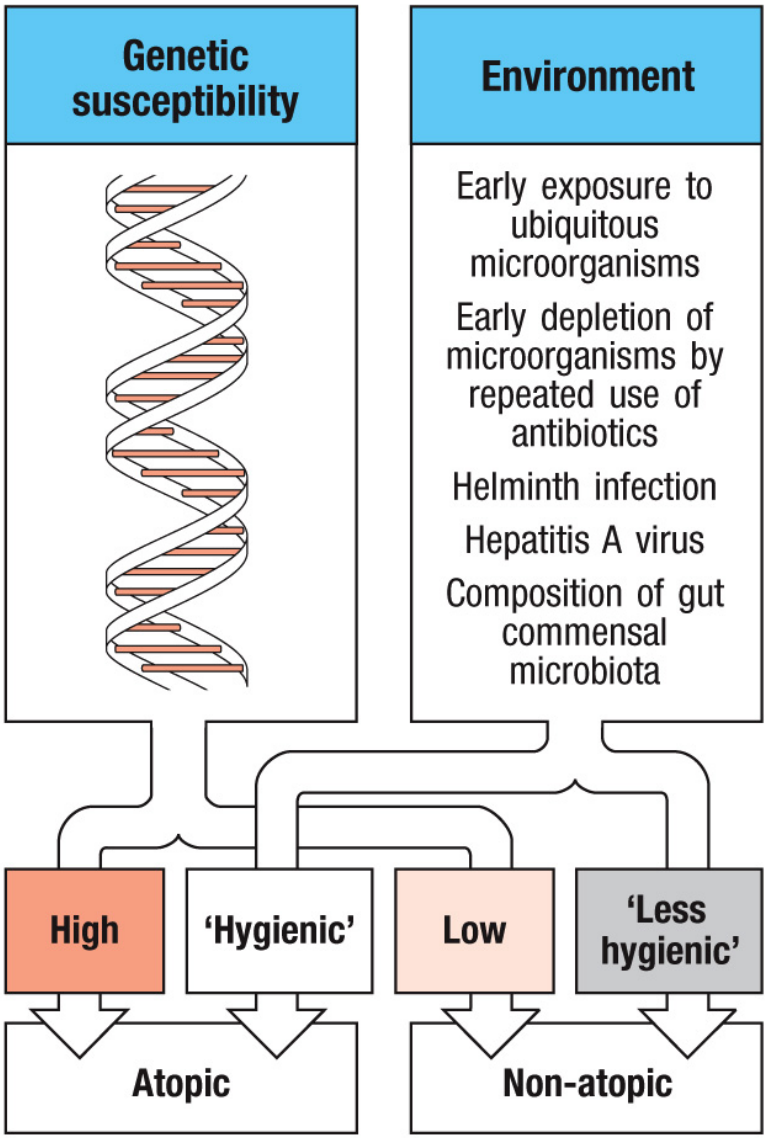


Figure 14.7 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Atopy: exaggerated tendency to mount IgE response to common environmental allergens (T_H2 response)

Hygiene hypothesis: exposure to some infectious agents in childhood drives the immune system toward T_H1 response and non-atopy

Counter-regulation hypothesis: exposure to infectious agents and microbiota in childhood drives the development of Treg

Hypersensitivity Susceptibility Loci

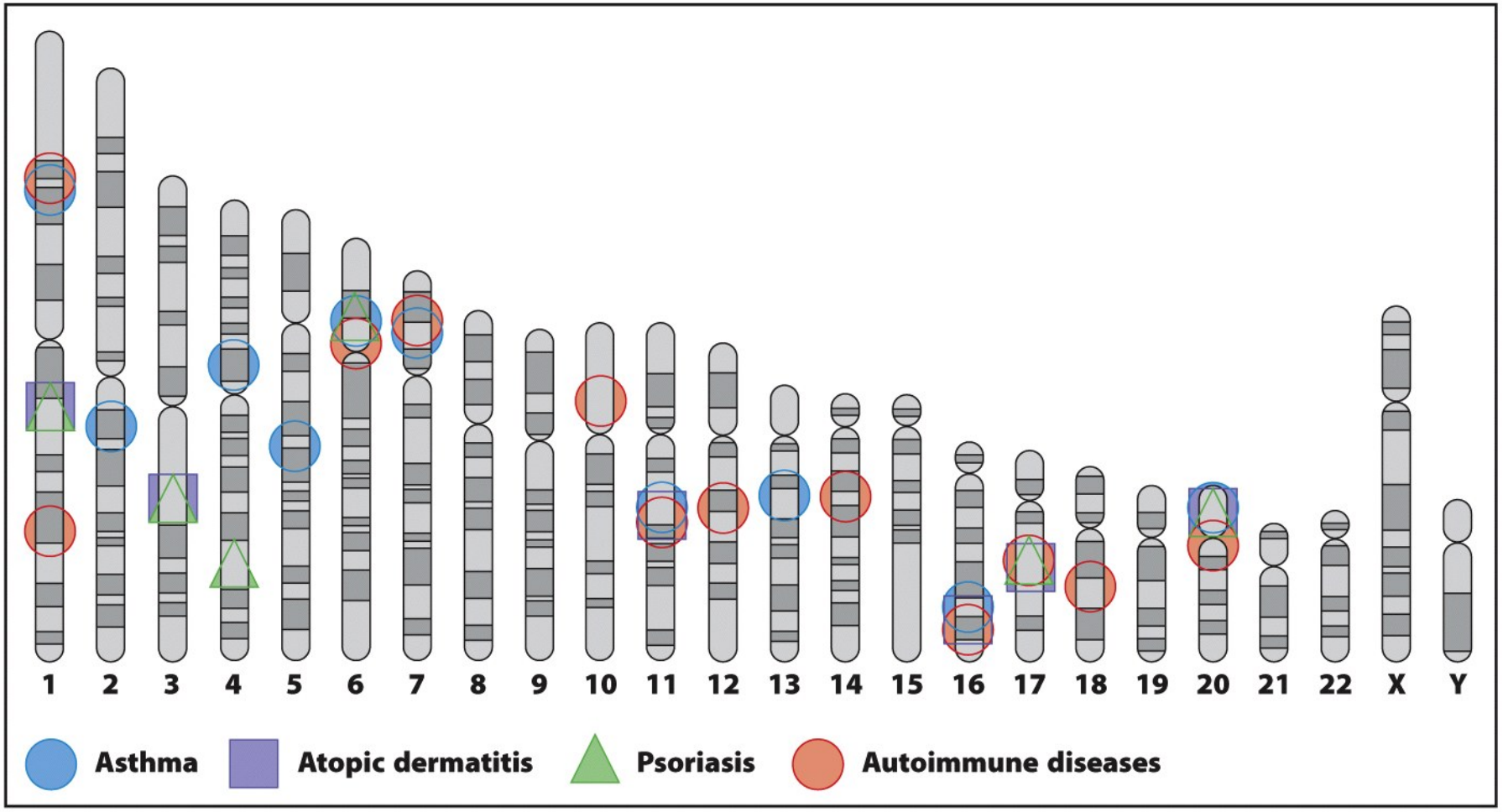


Figure 14.7 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Susceptibility Genes for Asthma

Asthma susceptibility loci
Genes expressed in airway epithelial cells
Chemokines: *CCL5*, *CCL11*, *CCL24*, *CCL26*
Antimicrobial peptides: *DEFB1*
Secretoglobin family: *SCGB1A1*
Epithelial barrier protein: *FLG*
Genes regulating CD4 T-cell and ILC2 differentiation and function
Transcription factors: *GATA3*, *TBX21*, *RORA*, *STAT3*, *PHF11*, *IKZF4*
Cytokines: *IL4*, *IL5*, *IL10*, *IL13*, *IL25*, *IL33*, *TGFβ1*
Cytokine receptors: *IL2RB*, *IL4RA*, *IL5RA*, *IL6R*, *IL18R*, *IL1RL1*, *FCER1B*
Pattern recognition receptors: *CD14*, *TLR2*, *TLR4*, *TLR6*, *TLR10*, *NOD1*, *NOD2*
Antigen presentation: *HLA-DRB1*, *HLA-DRB3*, *HLA-DQA*, *HLA-DQB*, *HLA-DPA*, *HLA-DPB*, *HLA-G*
Prostaglandin receptors: *PDFER2*, *PTGDR*
Genes with other functions
Proteinase or proteinase inhibitor: *ADAM33*, *USP38*, *SPINK5*
Signaling proteins: *IRAKM*, *SMAD3*, *PYHIN1*, *NOTCH4*, *GAB1*, *TNIP1*
Receptors: *ADRB2*, *P2X7*
Other: *DPP10*, *GPRA*, *COL29A1*, *ORMDL3*, *GSDMB*, *WDR36*, *DENND1B*, *RAD50*, *PBX2*, *LRRC32*, *AGER*, *CDK2*

Figure 14.6 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Outline

Hypersensitivity reactions

- -Introduction
- –Type I
- –Type II
- –Type III
- –Type IV

Types of Hypersensitivity Reactions

Immune complex

	Type I	Type II		Type III	Type IV		
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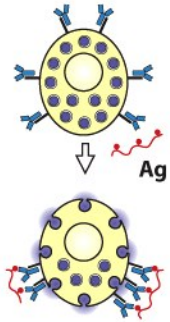
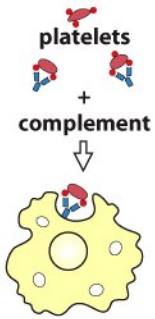
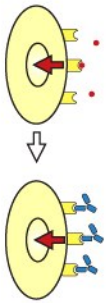
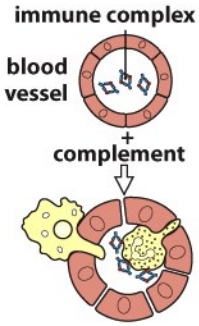
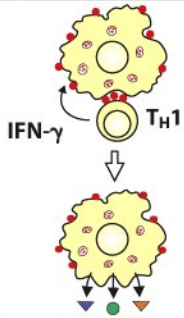
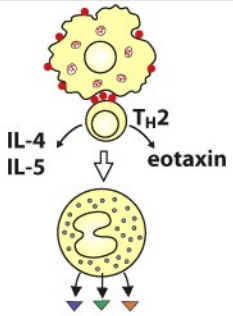
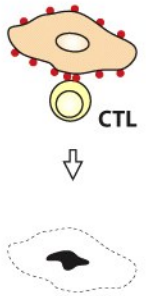
							
Example of hypersensitivity reaction	Allergic rhinitis, allergic asthma, atopic eczema, systemic anaphylaxis, some drug allergies	Some drug allergies (e.g. penicillin)	Chronic urticaria (antibody against FcεRI alpha chain)	Serum sickness, Arthus reaction	Allergic contact dermatitis, tuberculin reaction	Chronic asthma, chronic allergic rhinitis	Graft rejection, allergic contact dermatitis to poison ivy

Figure 14.1 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Effects of Mast Cell Activation on Different Tissues

Mast cells are residing near mucosal surfaces and the connecting tissue around blood vessel.

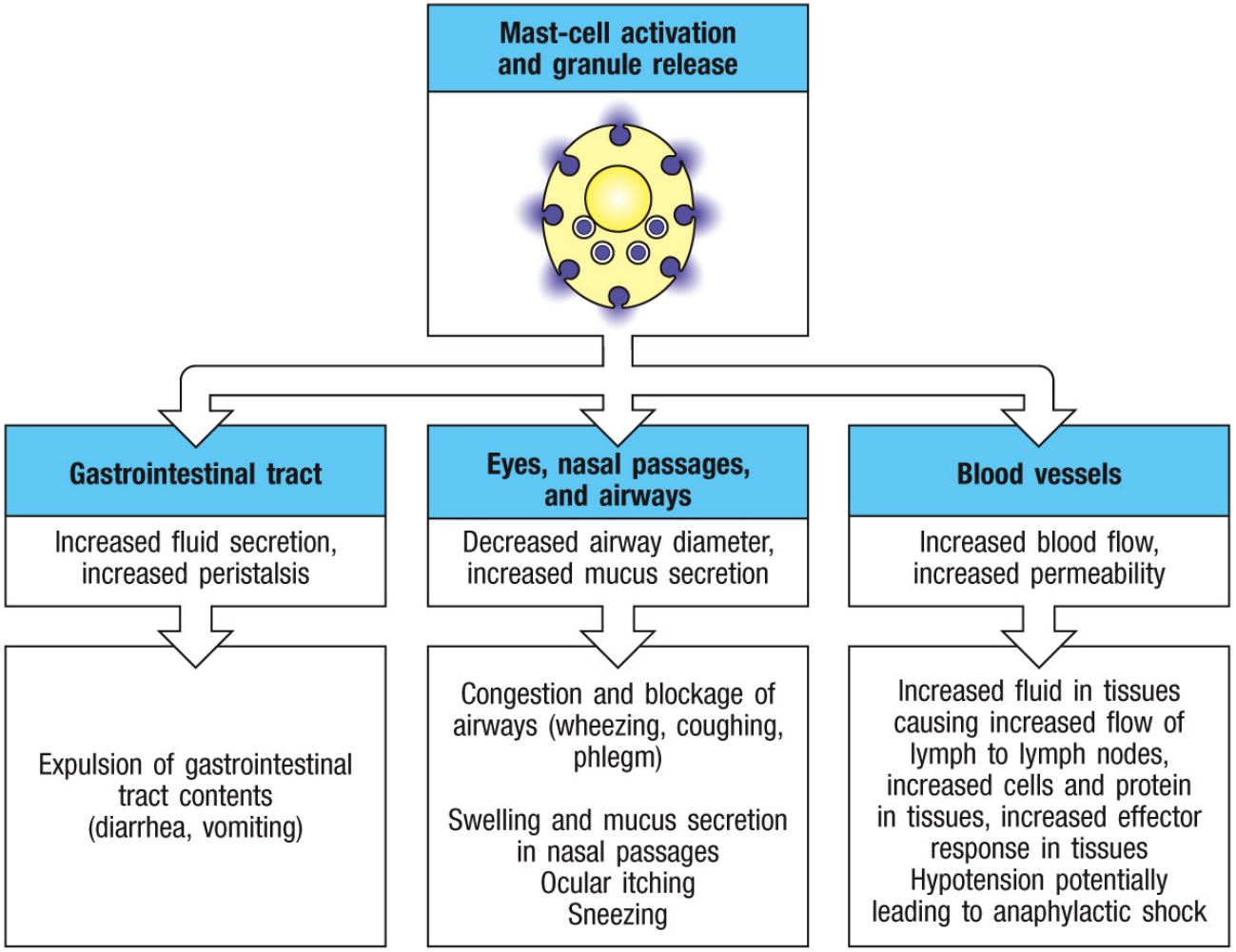


Figure 14.8 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Molecules Released by Mast Cells

	Class of product	Examples	Biological effects
Stored in granules	Enzyme	Tryptase, chymase, cathepsin G, carboxypeptidase	Remodel connective tissue matrix
Stored in granules	Toxic mediator	Histamine, heparin	Toxic to parasites Increase vascular permeability Cause smooth muscle contraction Anticoagulation
Stored in granules	Cytokine	IL-4, IL-13, IL-33	Stimulate and amplify T_H2-cell response
Stored in granules	Cytokine	IL-3, IL-5, GM-CSF	Promote eosinophil production and activation
Synthesized in response to stimulation	Cytokine	TNF-α (some stored preformed in granules)	Promotes inflammation, stimulates cytokine production by many cell types, activates endothelium
Synthesized in response to stimulation	Chemokine	CCL3	Attracts monocytes, macrophages, and neutrophils
Synthesized in response to stimulation	Lipid mediator	Prostaglandins D_2, E_2 Leukotrienes C4, D4, E4	Smooth muscle contraction Chemotaxis of eosinophils, basophils, and T_H2 cells Increase vascular permeability Stimulate mucus secretion Bronchoconstriction
Synthesized in response to stimulation	Lipid mediator	Platelet-activating factor	Attracts leukocytes Amplifies production of lipid mediators Activates neutrophils, eosinophils, and platelets

Figure 14.9 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Eosinophils Cause Inflammation and Tissue Damage During Allergic Reactions

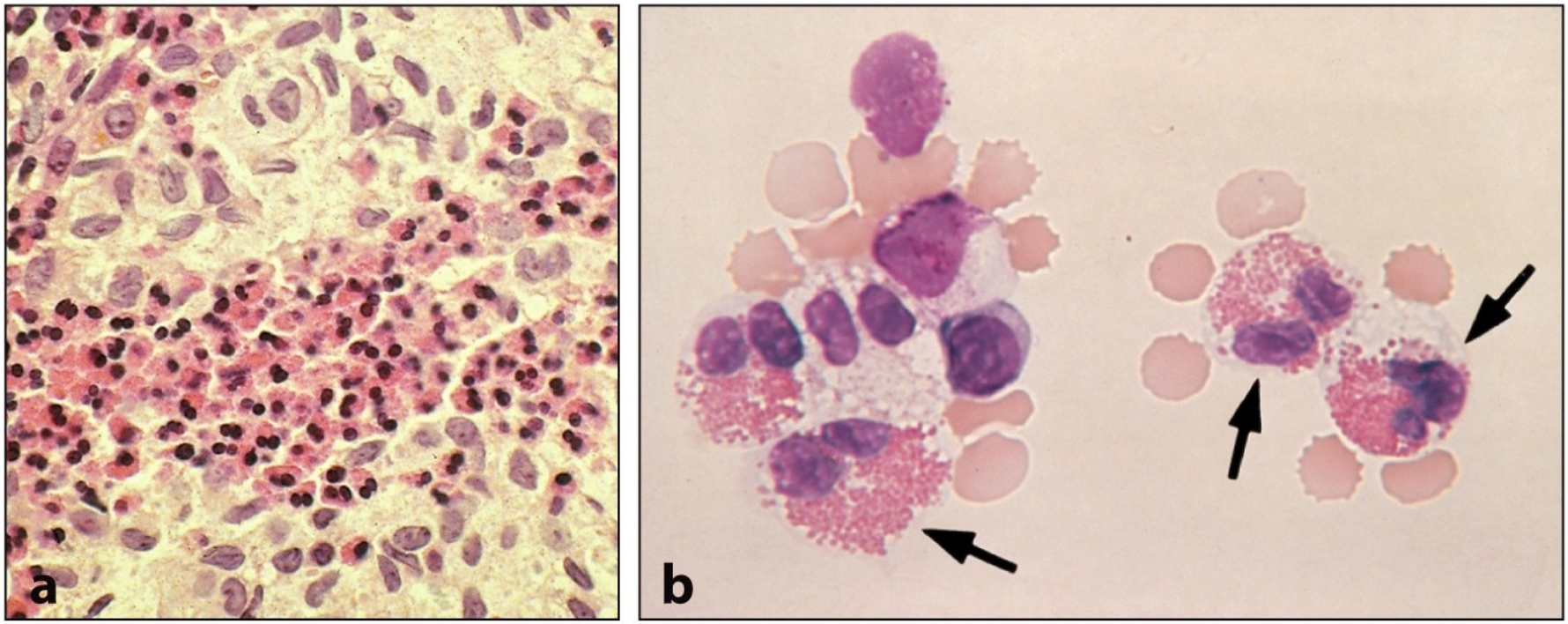


Figure 12.8 The Immune System, 3ed. (© Garland Science 2009)

Eosinophil Granules Contain Toxic Proteins

Class of product	Examples	Biological effects
Enzyme	Eosinophil peroxidase	Toxic to targets by catalyzing halogenation Triggers histamine release from mast cells
	Eosinophil collagenase	Remodels connective tissue matrix
	Matrix metalloproteinase-9	Matrix protein degradation
Toxic protein	Major basic protein	Toxic to parasites and mammalian cells Triggers histamine release from mast cells
	Eosinophil cationic protein	Ribonuclease Toxic to parasites Neurotoxin
	Eosinophil-derived neurotoxin	Neurotoxin
Cytokine	IL-3, IL-5, GM-CSF	Amplify eosinophil production by bone marrow Eosinophil activation
	TGF-α, TGF-β	Epithelial proliferation, myofibroblast formation
Chemokine	CXCL8 (IL-8)	Promotes influx of leukocytes
Lipid mediator	Leukotrienes C4, D4, E4	Smooth muscle contraction Increase vascular permeability Increase mucus secretion Bronchoconstriction
	Platelet-activating factor	Attracts leukocytes Amplifies production of lipid mediators Activates neutrophils, eosinophils, and platelets

Figure 14.10 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Allergic Reactions Have Immediate and Late-Phase Responses

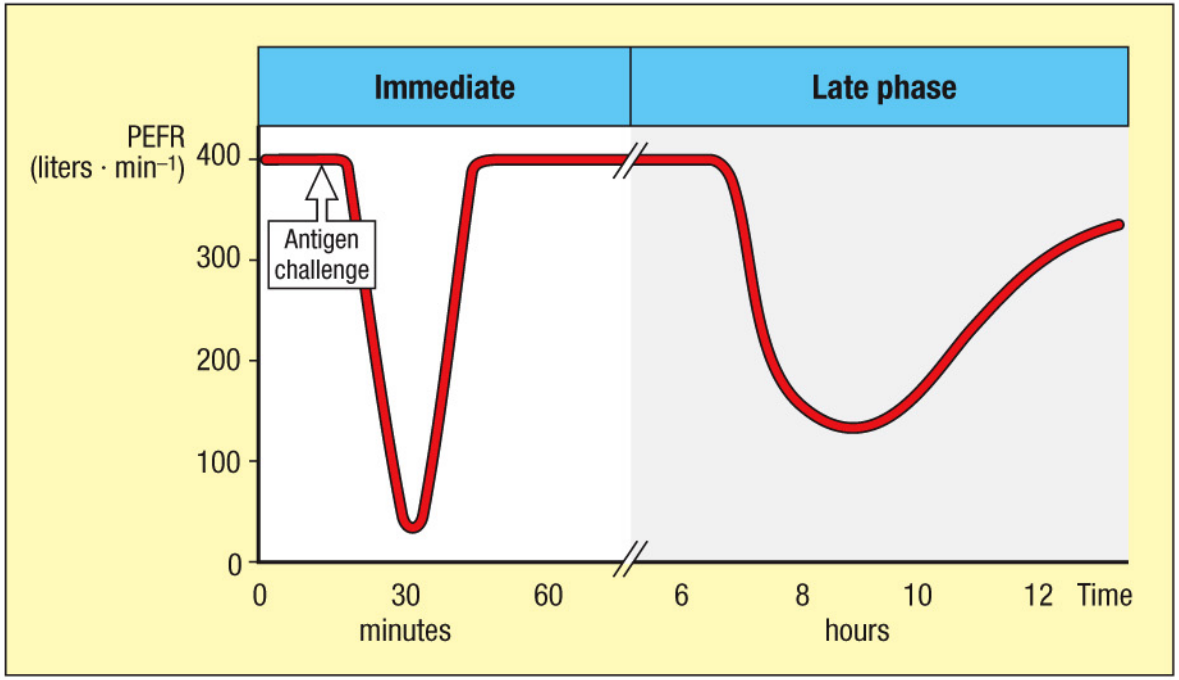
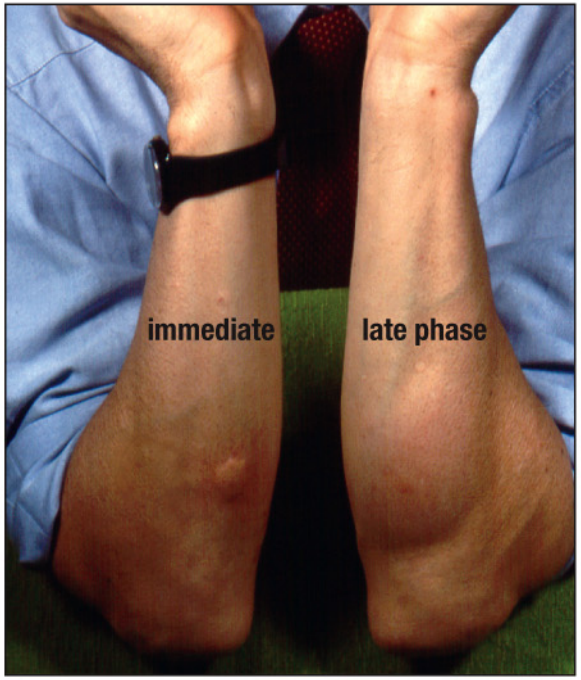


Figure 14.11 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)



Increase in vascular permeability and muscle contraction

Induced synthesis and release of mediators (cytokines, etc.)

Occurs in 50% of individuals after immediate response

Allergy Tests- Immediate Responses

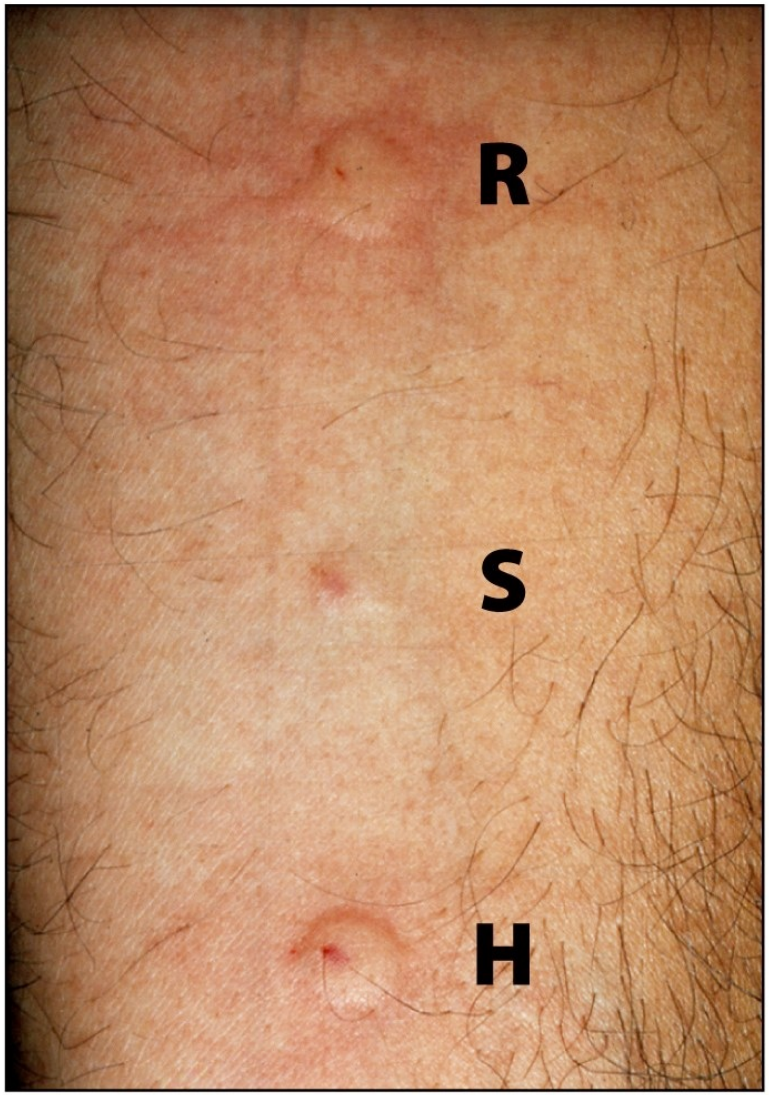


Figure 12.24 part 2 of 2 The Immune System, 3ed. (© Garland Science 2009)

Ragweed pollen

Saline, negative control

Histamine, positive control

Dose and Route of Allergen Entry Determines the Type of IgE Mediated Reaction

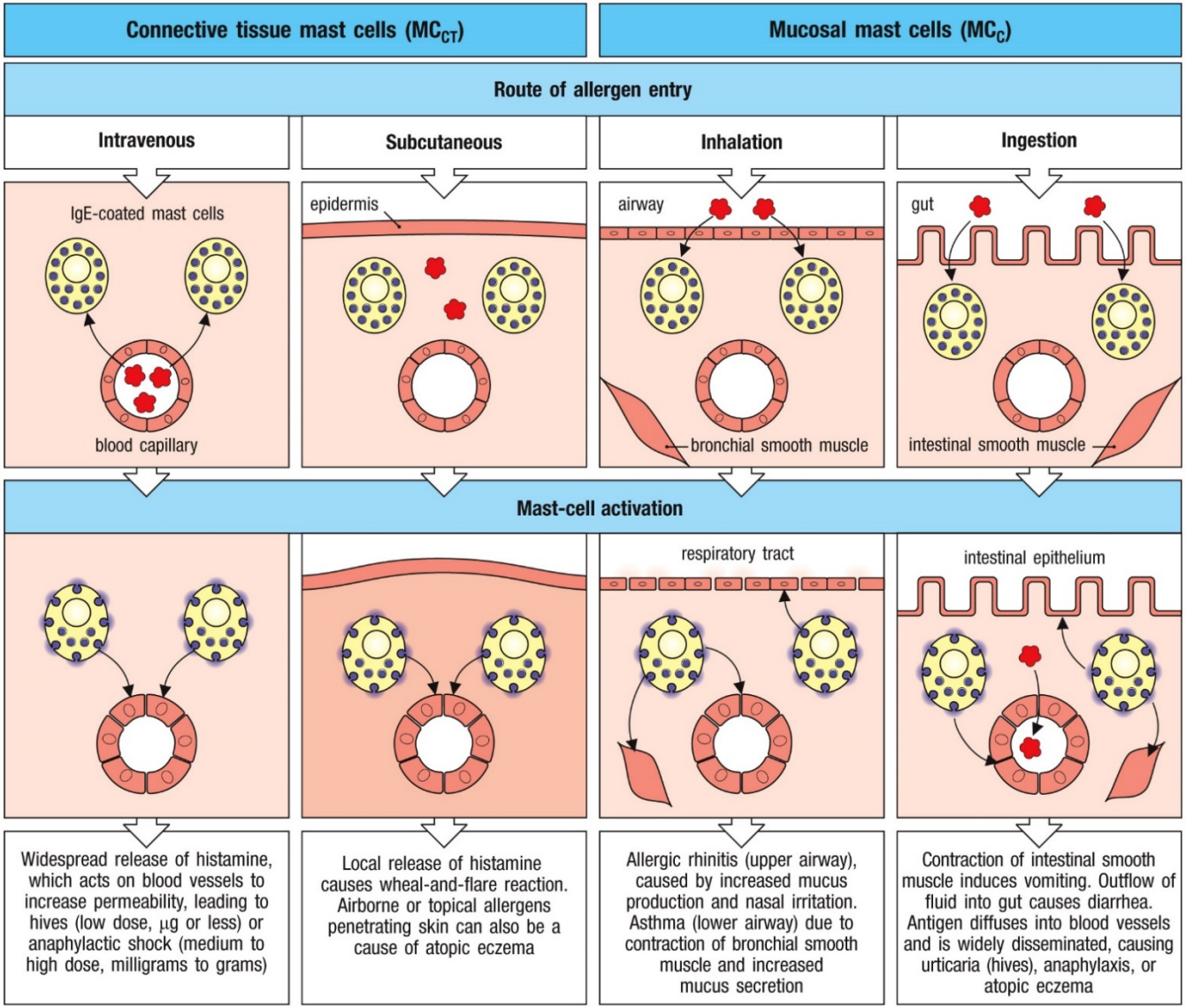


Figure 14.12 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Allergic Asthma

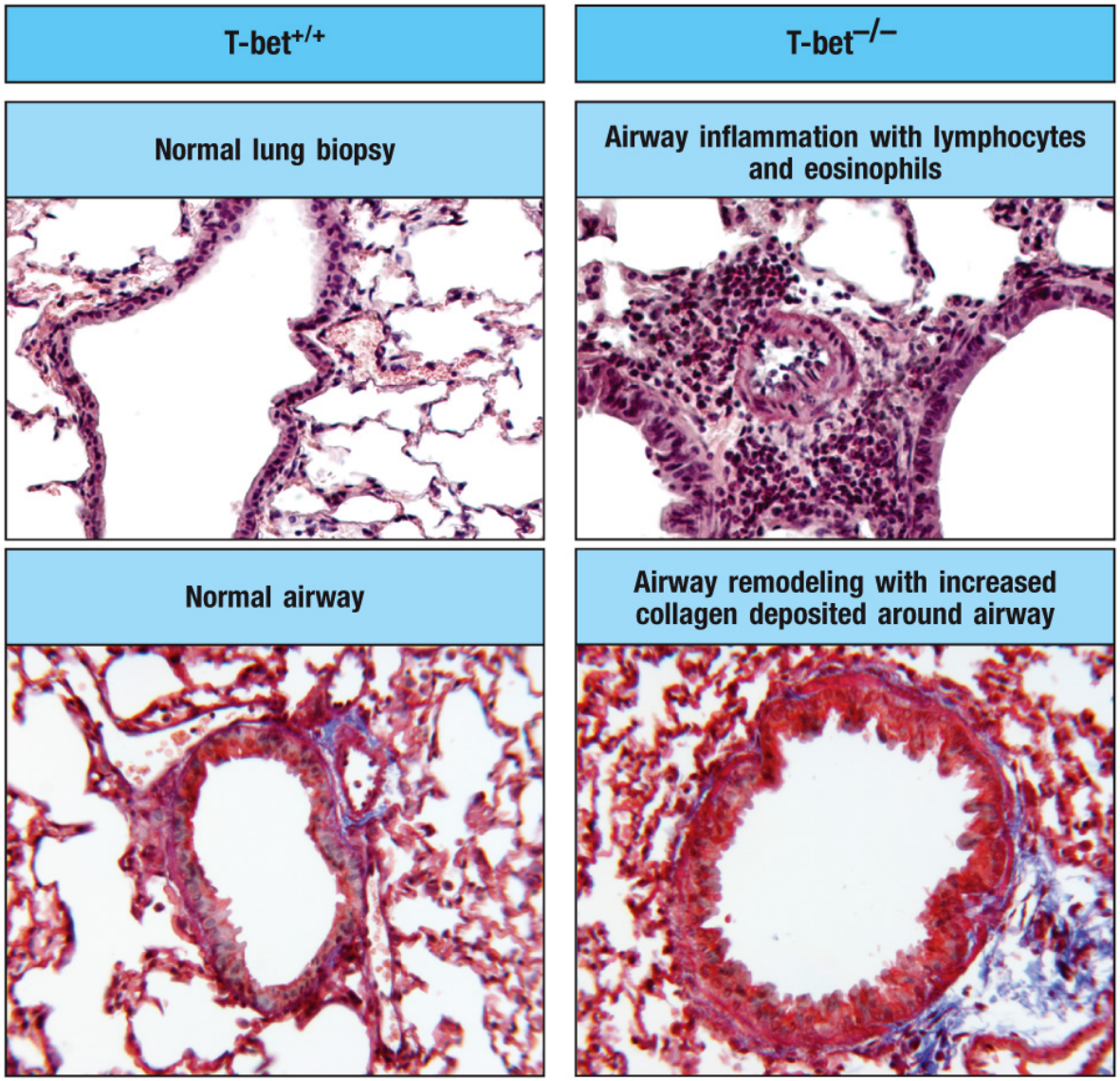


Figure 14.14 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Ingested Allergen Can Cause Vomiting, Diarrhea, Urticaria and Anaphylactic Reactions

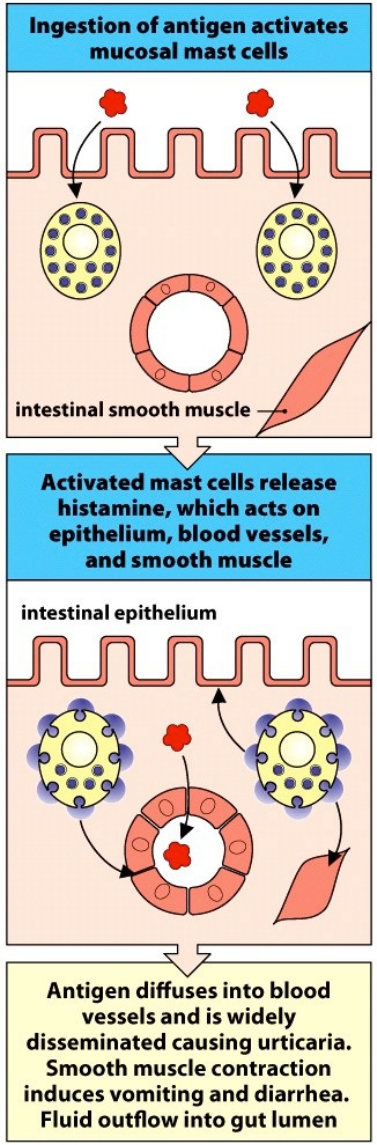


Figure 12.25 The Immune System, 3ed. (© Garland Science 2009)

Urticaria/Hive

Urticaria (skin rash) is caused by antigen that enters blood vessels and is carried to the skin, including food

Approaches to Treat Allergy

Treatments for allergic disease		
Target	**Mechanism of treatment**	**Specific approach**
In clinical use		
Mediator action	Inhibit effects of mediators on specific receptors Inhibit synthesis of specific mediators	Antihistamines, β-agonists Leukotriene receptor blockers Lipoxygenase inhibitors
Chronic inflammatory reactions	General anti-inflammatory effects	Corticosteroids
T_H2 response	Induction of regulatory T cells	Desensitization therapy by injections of specific antigen
IgE binding to mast cell	Bind to IgE Fc region and prevent IgE binding to Fc receptors on mast cells	Anti-IgE antibodies (omalizumab)
Proposed or under investigation		
T_H2 activation	Induction of regulatory T cells	Injection of specific antigen peptides Administration of cytokines, e.g., IFN-γ, IL-10, IL-12, TGF-β Use of adjuvants such as CpG oligodeoxynucleotides to stimulate T_H1 response
Activation of B cell to produce IgE	Block co-stimulation Inhibit T_H2 cytokines	Inhibit CD40L Inhibit IL-4 or IL-13
Mast-cell activation	Inhibit effects of IgE binding to mast cell	Blockade of IgE receptor
Eosinophil-dependent inflammation	Block cytokine and chemokine receptors that mediate eosinophil recruitment and activation	Inhibit IL-5 Block CCR3

Figure 14.16 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Mild conditions

serious conditions

Allergy shots

Outline

Hypersensitivity reactions

- -Introduction
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- –Type III
- –Type IV

Types of Hypersensitivity Reactions

Type II: IgG binds to cell surface protein or receptor

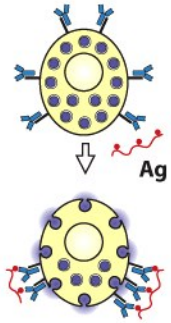
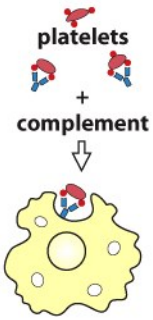
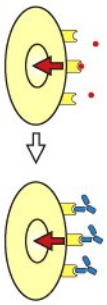
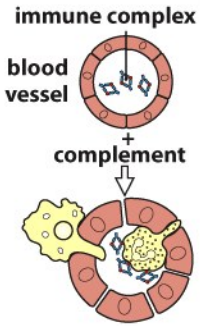
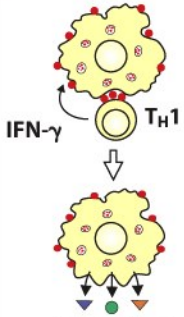
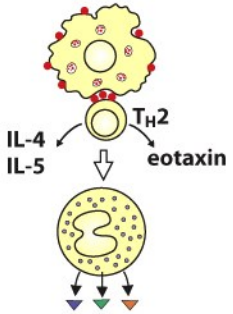
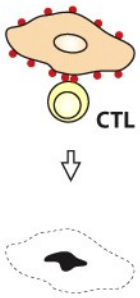
	Type I	Type II		Type III	Type IV		
Immune reactant	IgE	IgG		IgG	T_H1 cells	T_H2 cells	CTL
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Cell-surface receptor	Soluble antigen	Soluble antigen	Soluble antigen	Cell-associated antigen
Effector mechanism	Mast-cell activation	Complement, FcR^+ cells (phagocytes, NK cells)	Antibody alters signaling	Complement, phagocytes	Macrophage activation	IgE production, eosinophil activation, mastocytosis	Cytotoxicity
							
Example of hypersensitivity reaction	Allergic rhinitis, allergic asthma, atopic eczema, systemic anaphylaxis, some drug allergies	Some drug allergies (e.g. penicillin)	Chronic urticaria (antibody against FcεRI alpha chain)	Serum sickness, Arthus reaction	Allergic contact dermatitis, tuberculin reaction	Chronic asthma, chronic allergic rhinitis	Graft rejection, allergic contact dermatitis to poison ivy

Figure 14.1 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Types of Hypersensitivity Reactions

Type III: IgG immune complex

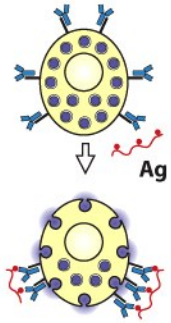
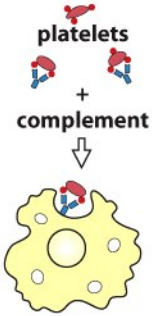
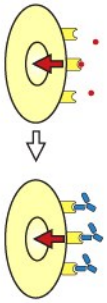
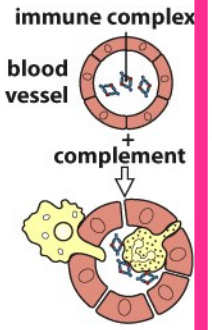
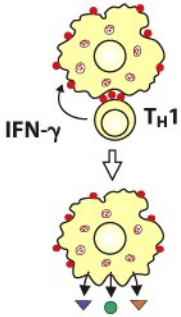
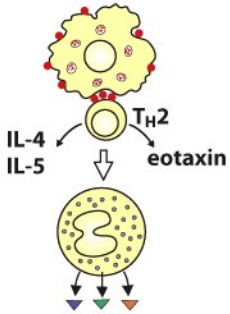
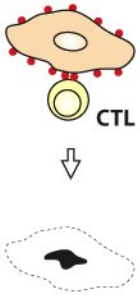
	Type I	Type II		Type III	Type IV		
Immune reactant	IgE	IgG		IgG	T_H1 cells	T_H2 cells	CTL
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Cell-surface receptor	Soluble antigen	Soluble antigen	Soluble antigen	Cell-associated antigen
Effector mechanism	Mast-cell activation	Complement, FcR^+ cells (phagocytes, NK cells)	Antibody alters signaling	Complement, phagocytes	Macrophage activation	IgE production, eosinophil activation, mastocytosis	Cytotoxicity
							
Example of hypersensitivity reaction	Allergic rhinitis, allergic asthma, atopic eczema, systemic anaphylaxis, some drug allergies	Some drug allergies (e.g. penicillin)	Chronic urticaria (antibody against FcεRI alpha chain)	Serum sickness, Arthus reaction	Allergic contact dermatitis, tuberculin reaction	Chronic asthma, chronic allergic rhinitis	Graft rejection, allergic contact dermatitis to poison ivy

Figure 14.1 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Deposition of Immune Complexes in Tissues Causes a Local Inflammatory Response (Arthus Reaction)

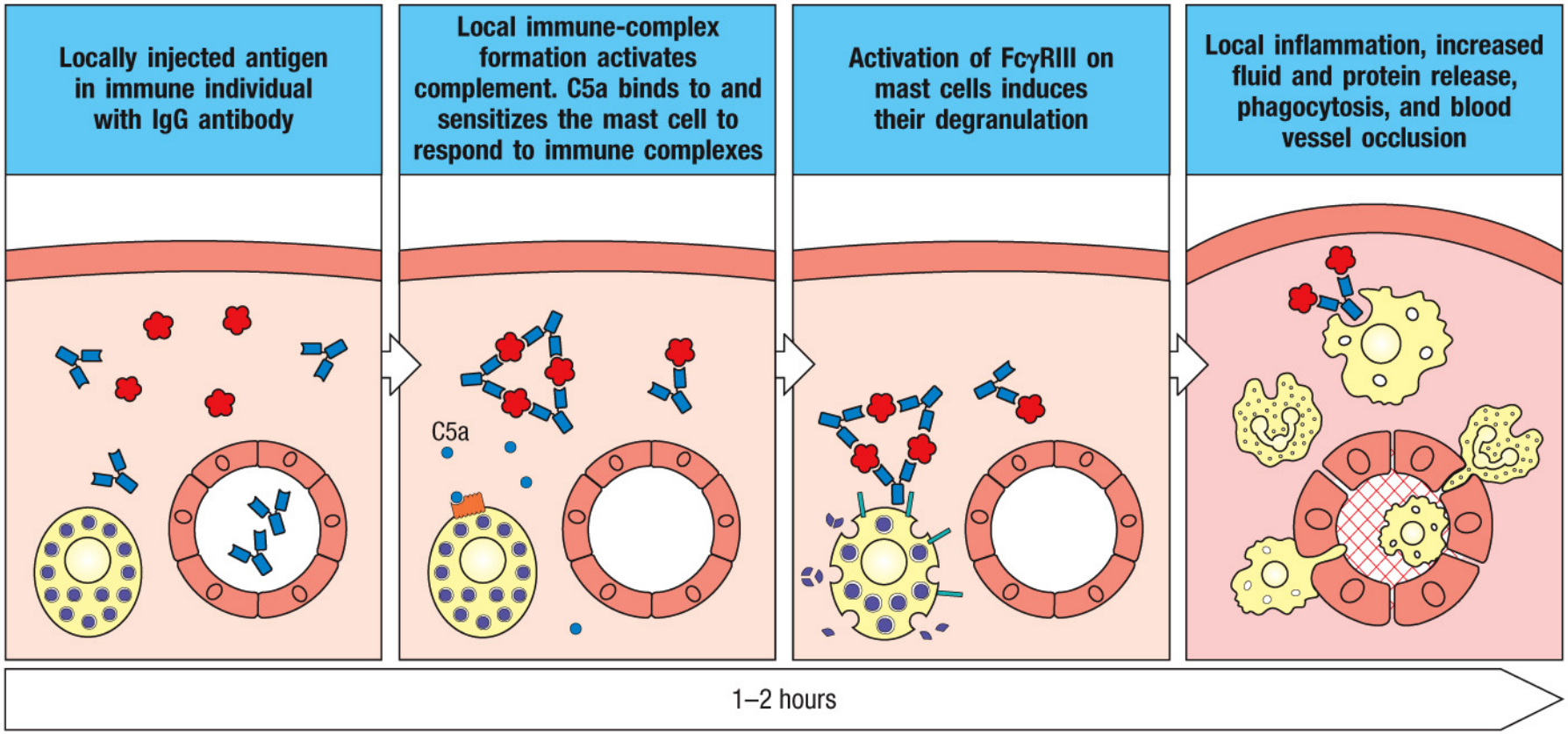


Figure 14.17 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Immune Complexes Are Formed During an Immune Response

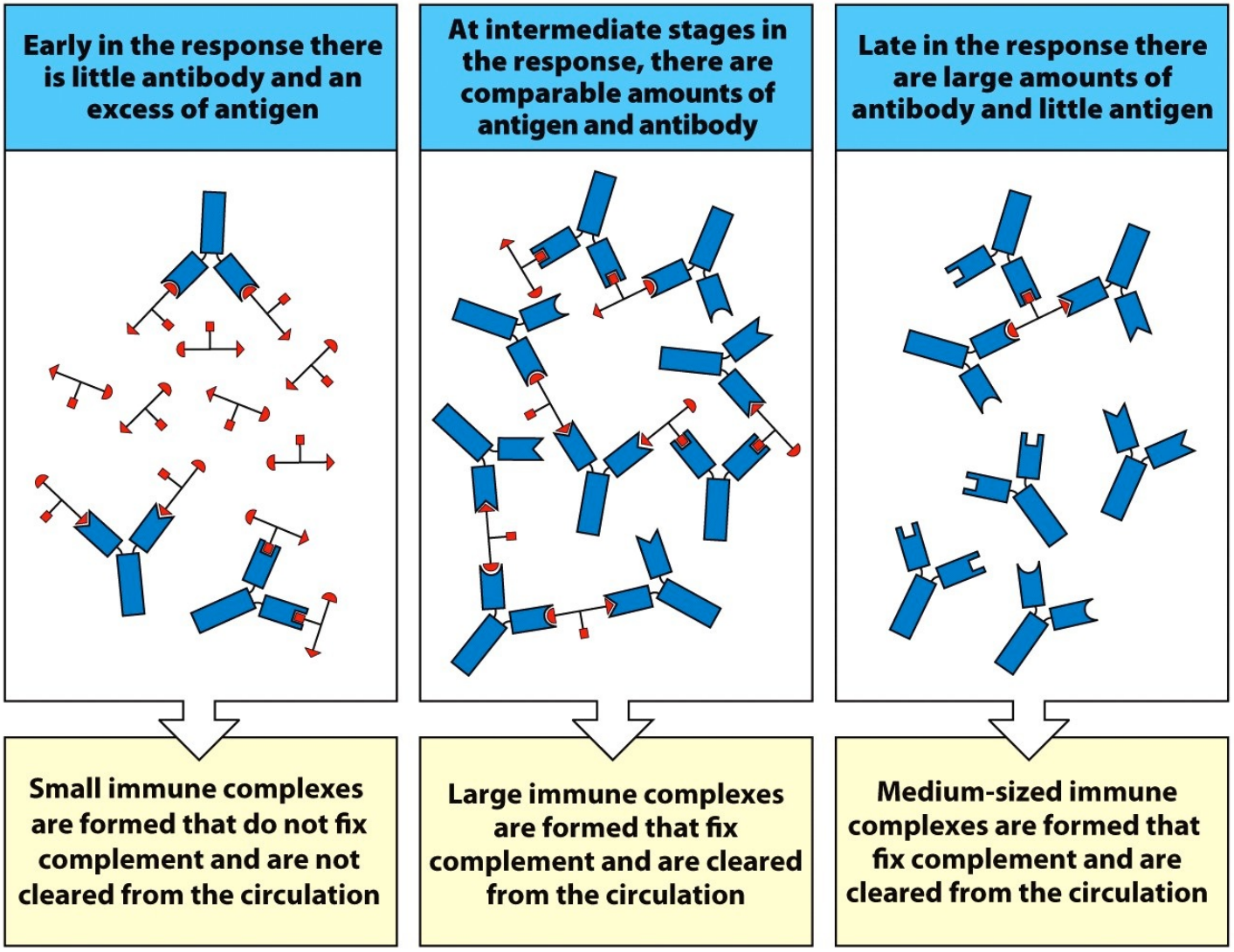


Figure 12.31 The Immune System, 3ed. (© Garland Science 2009)

Immune Complex is Removed

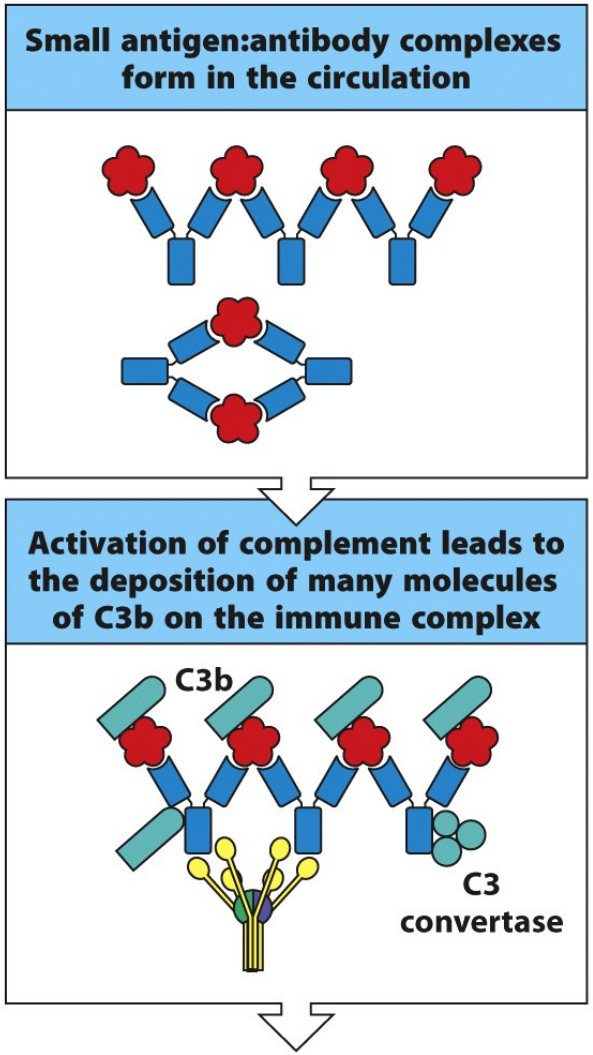


Figure 10.31 part 2 of 4 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

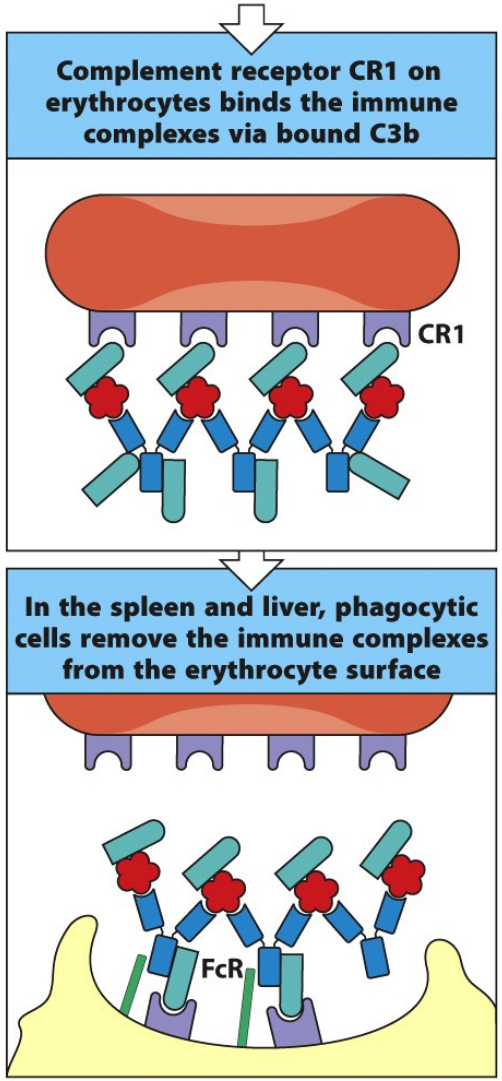


Figure 10.31 part 4 of 4 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Serum Sickness Is an Example of Immune Complex Mediated Syndrome

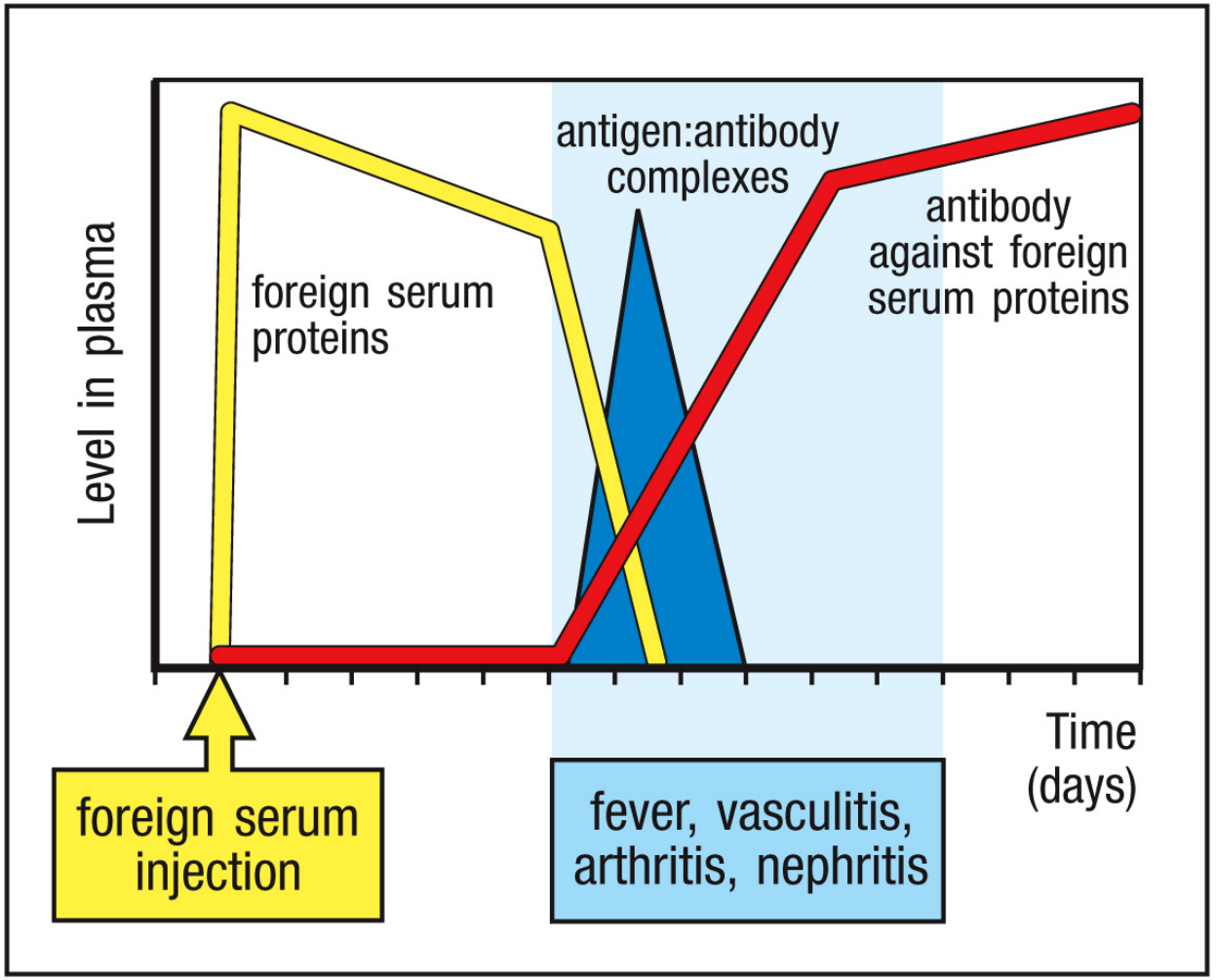


Figure 14.18 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Large amount of antigens deposited in the blood vessel, joints and kidney
-persistent infection or antidote

Serum Sickness

Figure 52.4 Case Studies in Immunology, 6ed. (© Garland Science 2012)

Types of Hypersensitivity Reactions

Type IV: cell mediated; delayed-type

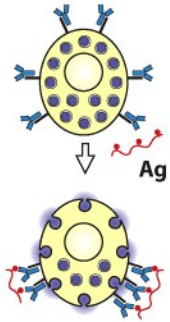
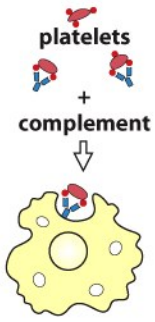
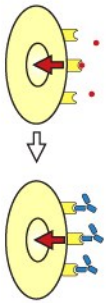
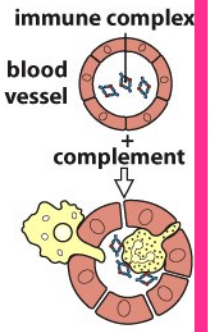
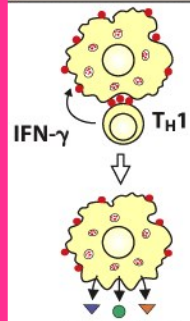
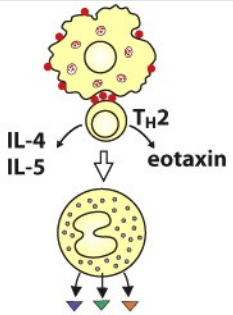
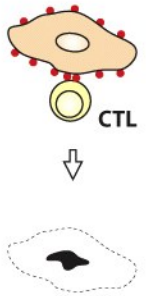
	Type I	Type II		Type III	Type IV		
Immune reactant	IgE	IgG		IgG	T_H1 cells	T_H2 cells	CTL
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Cell-surface receptor	Soluble antigen	Soluble antigen	Soluble antigen	Cell-associated antigen
Effector mechanism	Mast-cell activation	Complement, FcR^+ cells (phagocytes, NK cells)	Antibody alters signaling	Complement, phagocytes	Macrophage activation	IgE production, eosinophil activation, mastocytosis	Cytotoxicity
							
Example of hypersensitivity reaction	Allergic rhinitis, allergic asthma, atopic eczema, systemic anaphylaxis, some drug allergies	Some drug allergies (e.g. penicillin)	Chronic urticaria (antibody against FcεRI alpha chain)	Serum sickness, Arthus reaction	Allergic contact dermatitis, tuberculin reaction	Chronic asthma, chronic allergic rhinitis	Graft rejection, allergic contact dermatitis to poison ivy

Figure 14.1 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

T-Cell Mediated Hypersensitivity Responses

Cellular hypersensitivity reactions are mediated by antigen-specific effector T cells		
Syndrome	**Antigen**	**Consequence**
Delayed-type hypersensitivity	Proteins: Insect venom Mycobacterial proteins (tuberculin, lepromin)	Local skin swelling: Erythema Induration Cellular infiltrate Dermatitis
Contact hypersensitivity	Haptens: Pentadecacatechol (poison ivy) DNFB Small metal ions: Nickel Chromate	Local epidermal reaction: Erythema Cellular infiltrate Vesicles Intraepidermal abscesses
Gluten-sensitive enteropathy (celiac disease)	Gliadin	Villous atrophy in small bowel Malabsorption

Figure 14.19 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Stages of the Delayed Type Hypersensitivity

Tuberculin skin test: action of previously primed Th1 cells/memory cells

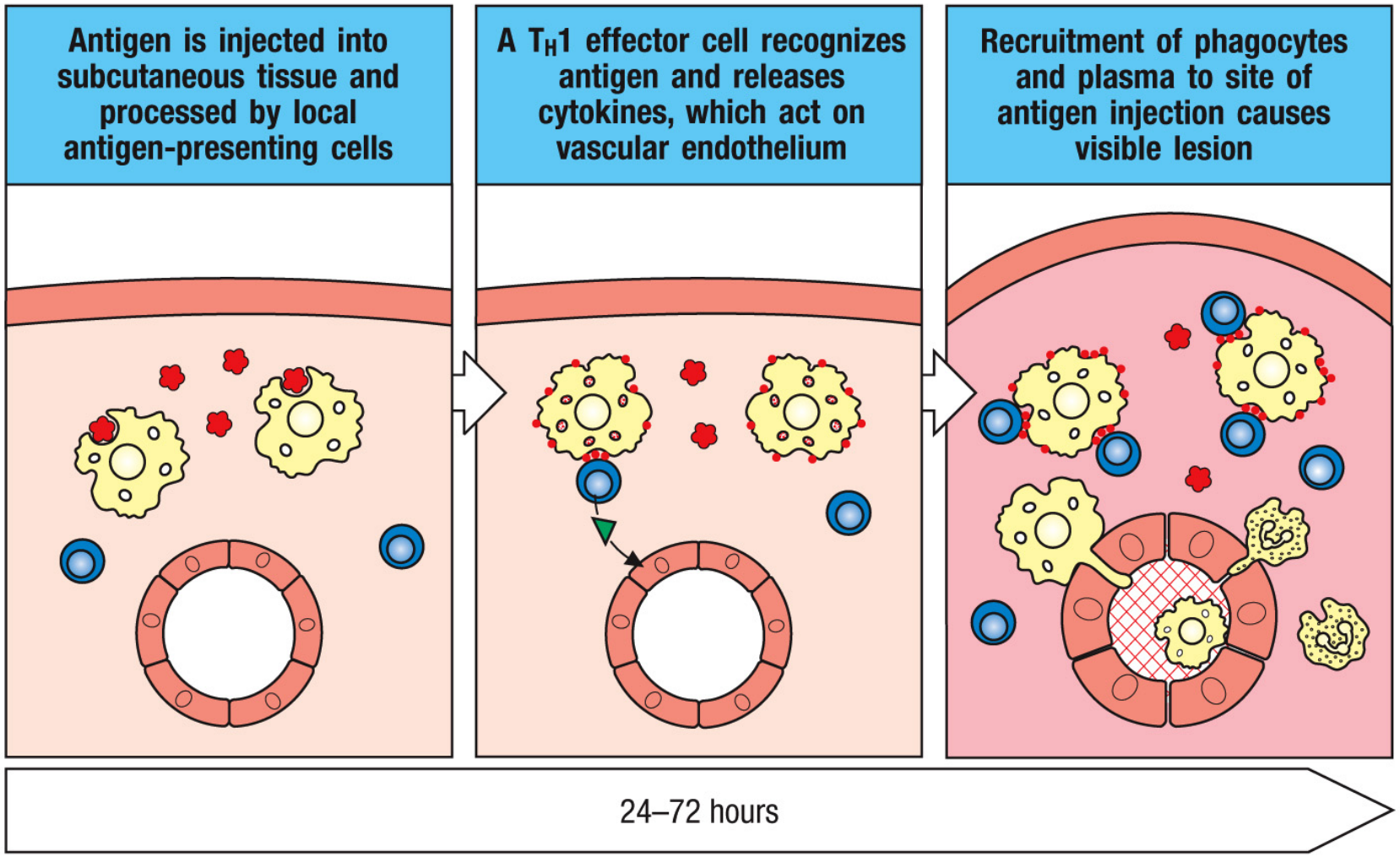


Figure 14.20 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Poison Ivy Contact Dermatitis

Urushiol oil (modifies intracellular proteins) induces CD8 T cell response

Figure 14.23 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Celiac Disease

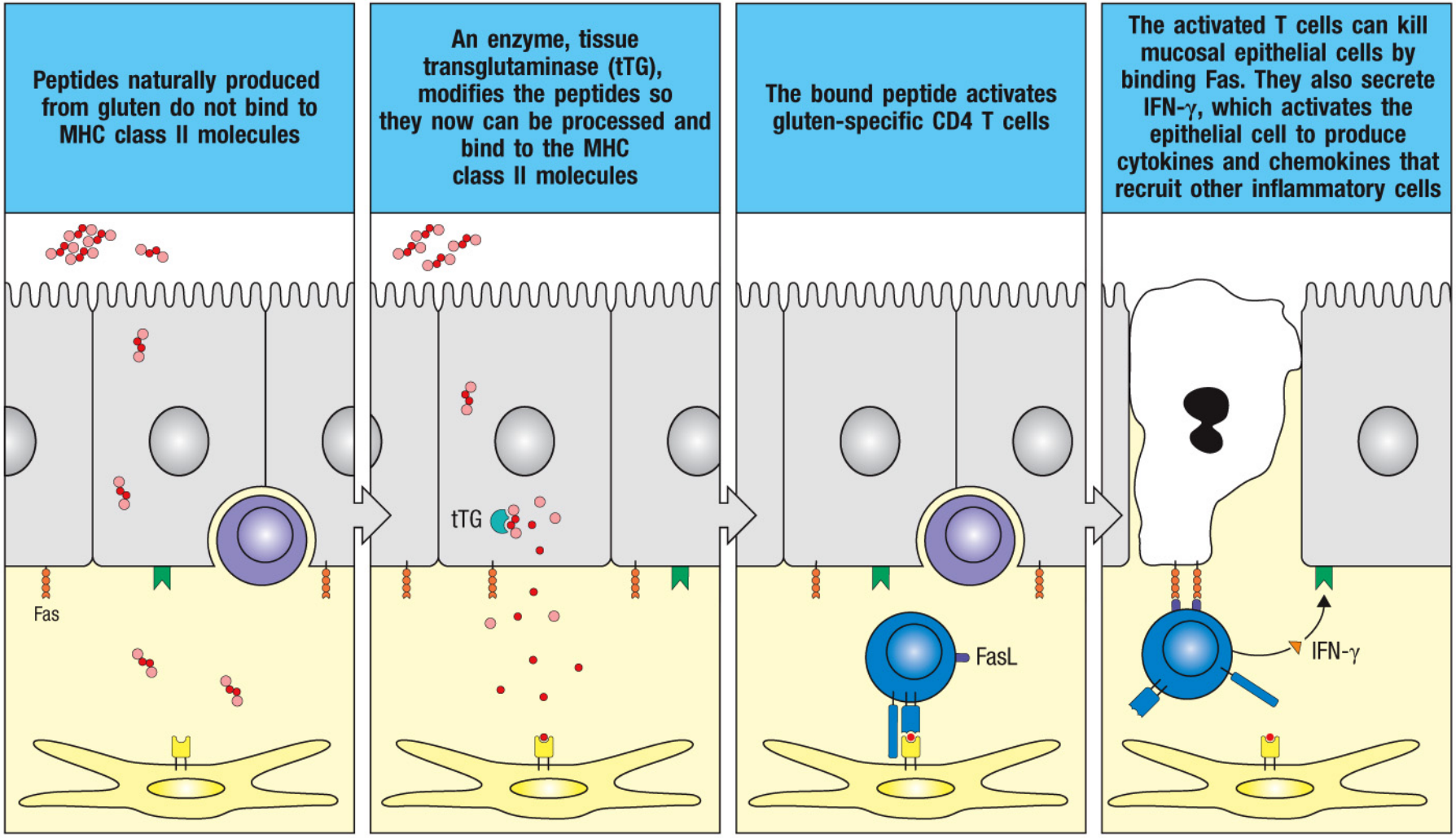


Figure 14.25 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Celiac Disease

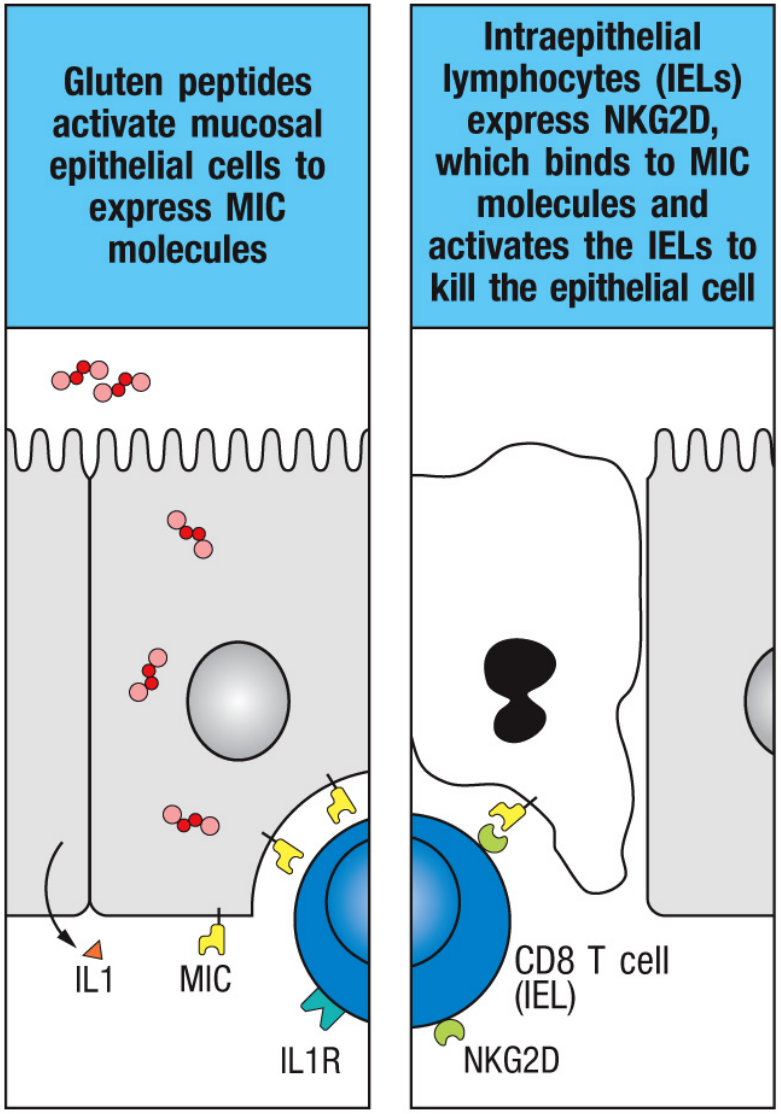


Figure 14.27 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Destruction of Gastrointestinal Villi in Celiac Disease

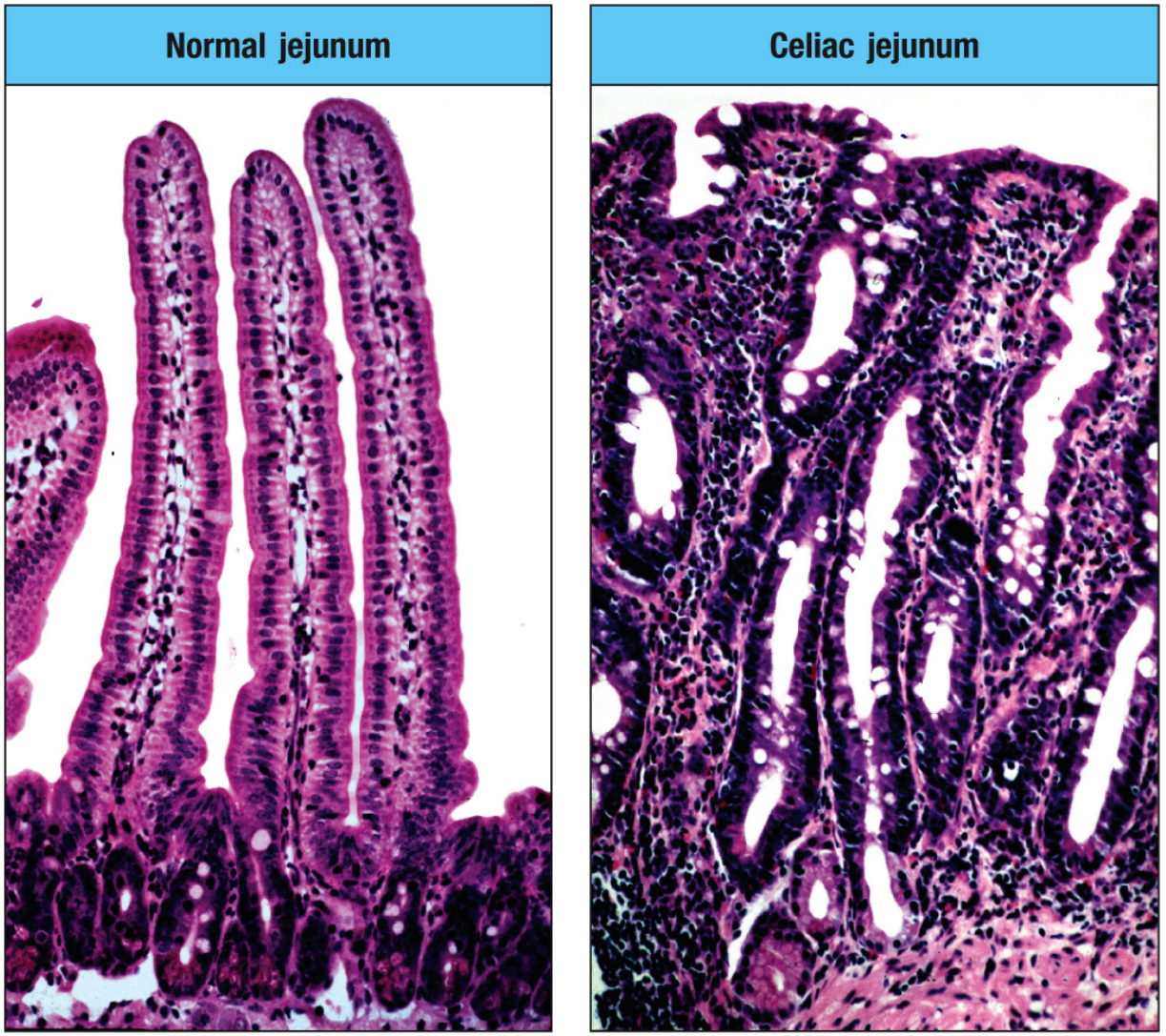


Figure 14.24 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Question

- True or false:
- Sensitization is required for the development of all types of allergy.

- A) True
- B) False

Question

- What determines the result of an allergic reaction?
- A) type of antigen
- B) dose
- C) route of exposure
- D) genetics
- E) all of the above