Chapter 14

Allergy & Hypersensitivity
過敏反應

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Learning objectives

- Understand how IgE is produced during allergic reactions.
- Understand the effector mechanisms of allergic reaction.
- Understand the mechanisms underlying other hypersensitivity diseases.

Hypersensitivity

- an immune reaction to innocuous antigens that results in tissue injury and/or disease
  - directed against foreign antigens and damage is a consequence of inflammation
- Classified into 4 types (by Coombs and Gell)
- Distinguished based on
  - immune mechanisms involved, and
  - types of antigen recognized

Allergen

- Definition:
  - An antigen capable of causing allergy
- Can you define the following terms?
  - Immunogen 免疫原
  - Antigen 抗原
  - Allergen 過敏原

Hypersensitivity types I-III

Fig 14-1

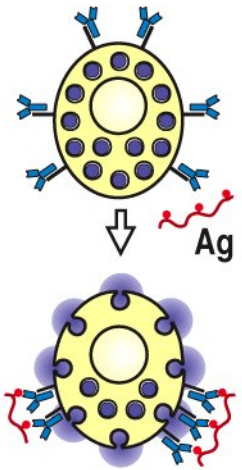
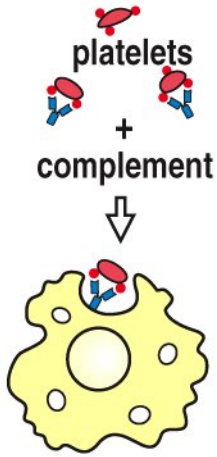
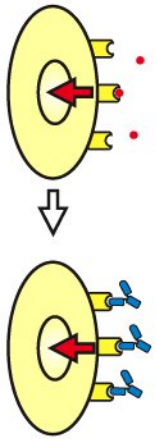
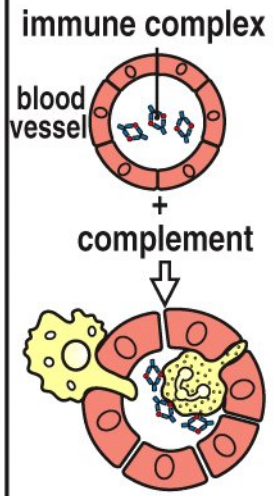
	Type I	Type II		Type III
Immune reactant	IgE	IgG		IgG
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Cell-surface receptor	Soluble antigen
Effector mechanism	Mast-cell activation	Complement, FcR^+ cells (phagocytes, NK cells)	Antibody alters signaling	Complement, Phagocytes
				
Example of hypersensitivity reaction	Allergic rhinitis, asthma, systemic anaphylaxis	Some drug allergies (eg, penicillin)	Chronic urticaria (antibody against FCεR1α)	Serum sickness, Arthus reaction

Figure 12-2 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Urticaria

Hypersensitivity type IV

Fig 14-1

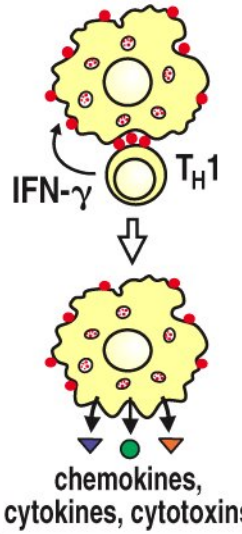
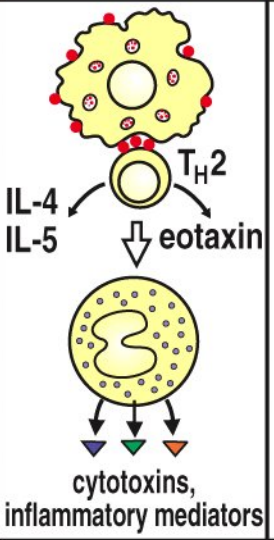
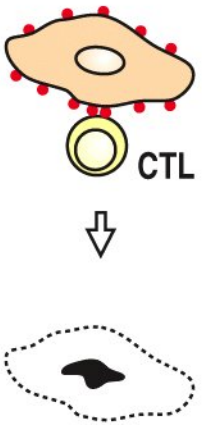
	Type IV		
Immune reactant	T_H1 cells	T_H2 cells	CTL
Antigen	Soluble antigen	Soluble antigen	Cell-associated antigen
Effector mechanism	Macrophage activation	IgE production, Eosinophil activation, Mastocytosis	Cytotoxicity
			
Example of hypersensitivity reaction	Contact dermatitis, tuberculin reaction	Chronic asthma, chronic allergic rhinitis	Contact dermatitis

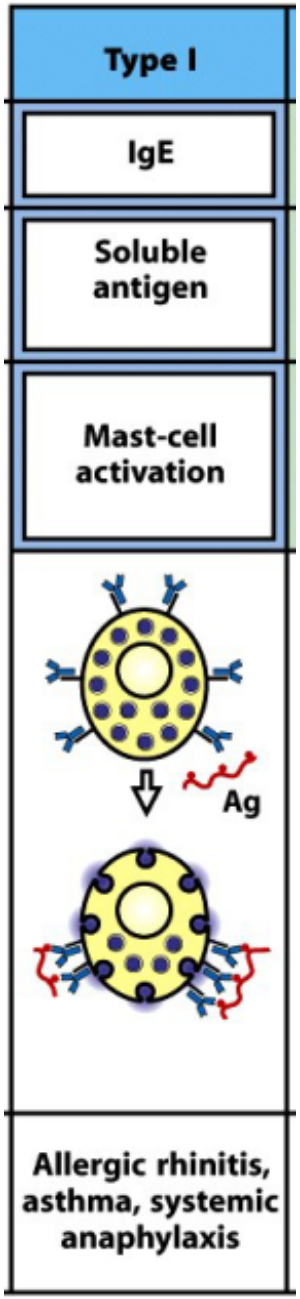
Figure 12-2 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Contact dermatitis

Alternative names of hypersensitivity types

- Type I
  - Immediate/Atopic/Anaphylactic
- Type II
  - Cytotoxic/Cytolytic
- Type III
  - Immune complex/Arthus
- Type IV
  - Delayed type/T-cell mediated

Type I Hypersensitivity



IgE-mediated reactions to extrinsic antigens

IgE-mediated allergic reactions			
Syndrome	**Common allergens**	**Route of entry**	**Response**
Systemic anaphylaxis	Drugs Serum Venoms Peanuts	Intravenous (either directly or following oral absorption into the blood)	Edema Increased vascular permeability Tracheal occlusion Circulatory collapse Death
Acute urticaria (wheal-and-flare)	Animal hair Insect bites Allergy testing	Through skin	Local increase in blood flow and vascular permeability
Allergic rhinitis (hay fever)	Pollens (ragweed, timothy, birch) Dust-mite feces	Inhalation	Edema of nasal mucosa Irritation of nasal mucosa
Asthma	Danders (cat) Pollens Dust-mite feces	Inhalation	Bronchial constriction Increased mucus production Airway inflammation
Food allergy	Tree nuts Peanuts Shellfish Milk Eggs Fish	Oral	Vomiting Diarrhea Pruritis (itching) Urticaria (hives) Anaphylaxis (rarely)

Figure 12-1 Immunobiology, 6/e. (© Garland Science 2005)

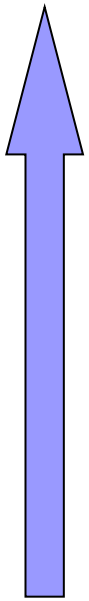
All IgE-mediated responses involve mast-cell degranulation!!

Fig 14-2

Allergens

1. Ags delivered (often) via mucosa surface, and at low dose.
2. Can selectively evoke Th2 cells that drive an IgE response

More potent allergens



- protein
- polypeptide
- polysaccharide
- nucleic acid
- low M.W. chemicals

Less potent allergens

Common allergens

- Pollen
- House dust mite
  - e.g. protease Der p1 in the feces
- Animal dander
- Microorganisms
- Serum protein/Animal protein
- Antibiotics (penicillin, streptomycin)
  - e.g. some patients develop anti-penicillin IgE
- Insect poison

Characteristics of inhaled allergen

- Generally low in M.W.
  - < 40 kD
- Water soluble
- Generally stable

Fig 14-5

It is not fully understood how or why, but these type of antigens tend to stimulate **IL-4 production**;

1. IL-4 production tends to lead to more IL-4 production (autocrine).

2. And IL-4 favors Ig class switching to IgE.

Features of inhaled 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
Enzymatically active	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
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

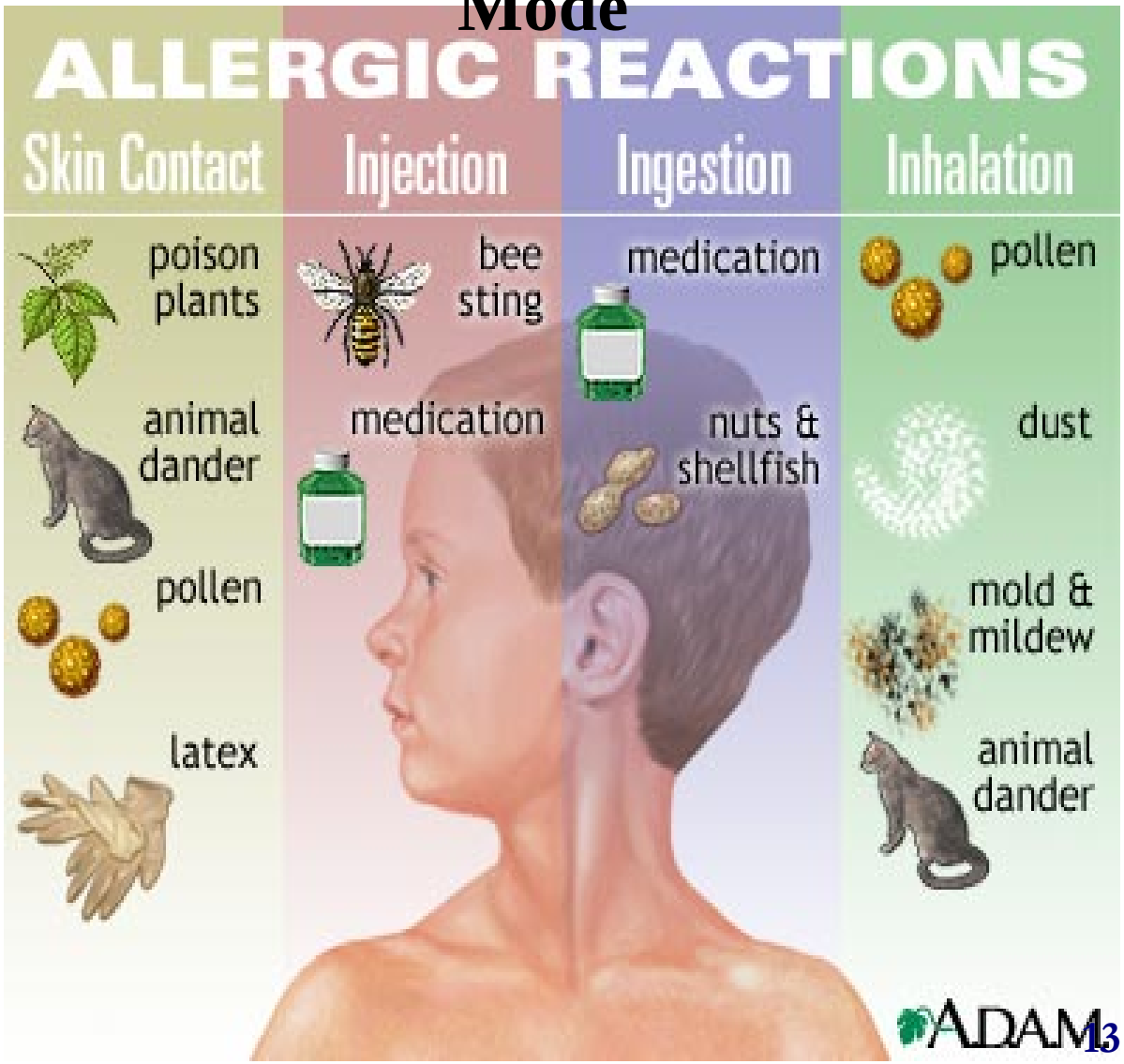
Figure 13-3 Immunobiology, 7ed. (© Garland Science 2008)

Route of allergen entry

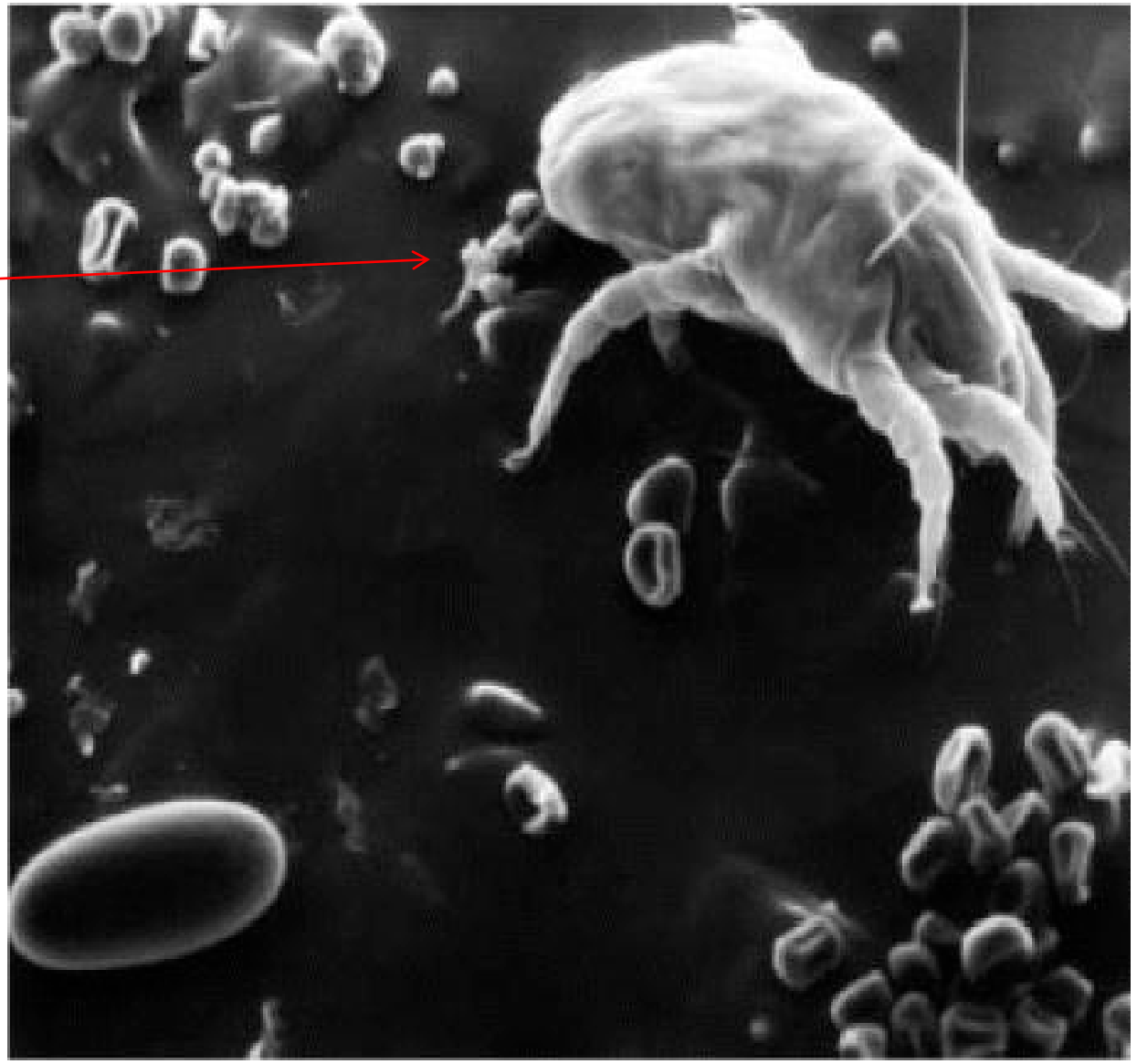
Portal of entry

- Skin
- Blood
- GI tract (gut)
- Respiratory tract
- Eye (rare)

Mode



Dust mite (*Dermatophagoides pteronyssimus*)



Sensitization to an inhaled allergen (Der p1)

Fig 14-3

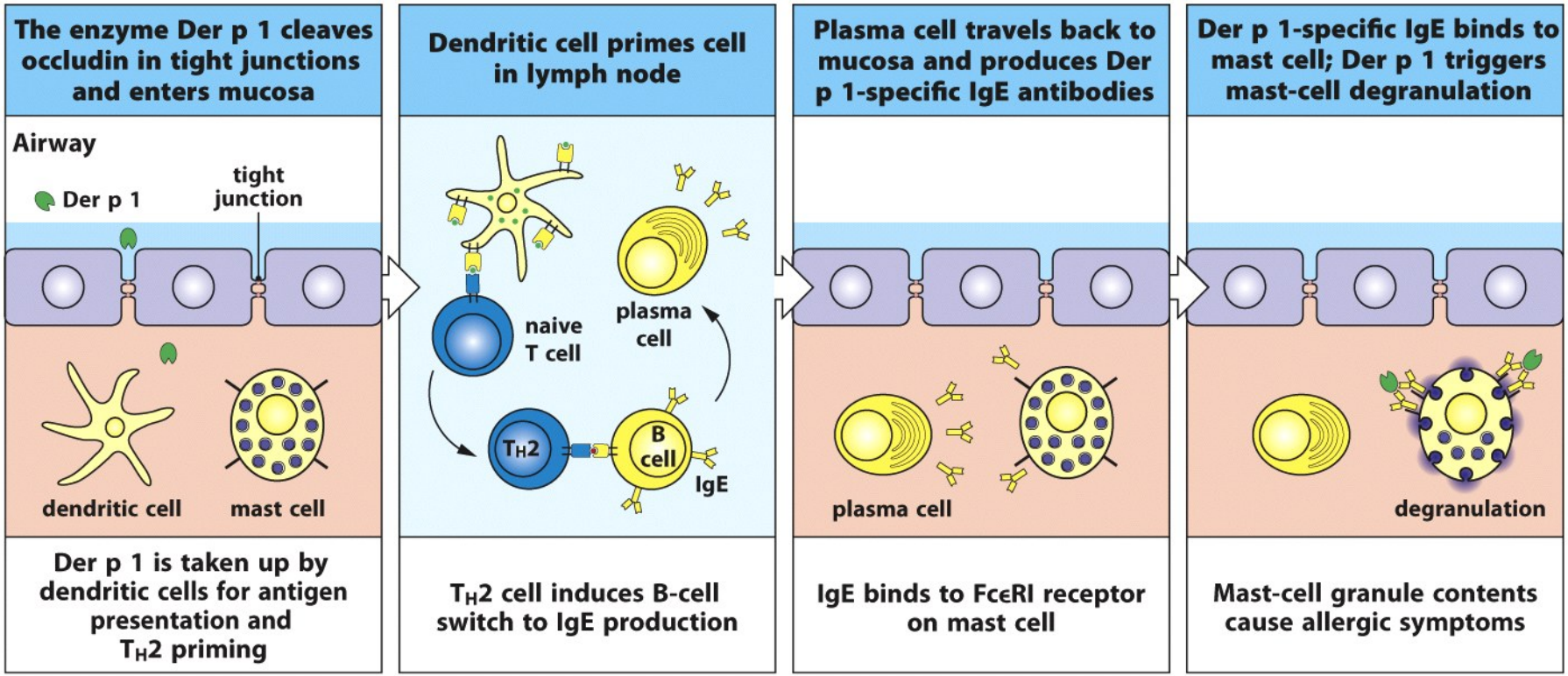
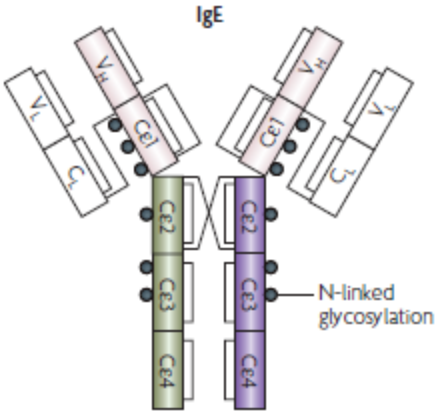


Figure 14.3 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Der p1 can cleave tight junction protein (e.g. occludin), allowing itself enter through the epithelial barrier to encounter APCs (DCs) down below → Th2 responses is activated.

Characteristics of IgE



- Located predominantly in tissues
  - Important for defense against muticellular parasites
- 2 known receptors
  - FcεRI (mast cells, basophils, activated eosinophils)
  - FcεRII/CD23 (B, DCs) → (-) regulator of IgE
- Heat labile
  - Fc binding destroyed by heating at 56°C for 30 min
  - antigen binding is not lost
- Short half-life
  - serum half-life is 2.5 days (c.f. IgG is 21 days)
  - when bound on mast cell → 12 weeks

IgE and parasitic infection

- Eosinophils and IgE are important in the defense against helminth parasitic infection
  - Skin
  - Epithelial surface of the airways (MALT)
  - GI tract (GALT)

- Cells at the above anatomical sites are specialized to secrete predominantly cytokines driving TH2 responses

Two sets of specific signals for IgE production

1. Signals promoting Th0 → Th2 differentiation
   - **IL-10 (major)**
   - IL-4, 5, 9, 13 (minor)
   - IL-2 (T-cell growth factor)
2. Signals promoting Ig class switch on B cells
   a. 1st signal
      - **IL-4 (major)**
      - IL-5, 9, 10, 13 (minor)

   b. 2nd signal
      - **co-stimulatory signals (CD40L)**
        - from either DCs or mast cells

Events leading to IgE class switching and massive IgE production

(1) IL-4/13 induce activation of JAK tyrosine kinases

Fig. 6-30 (7th ed.)

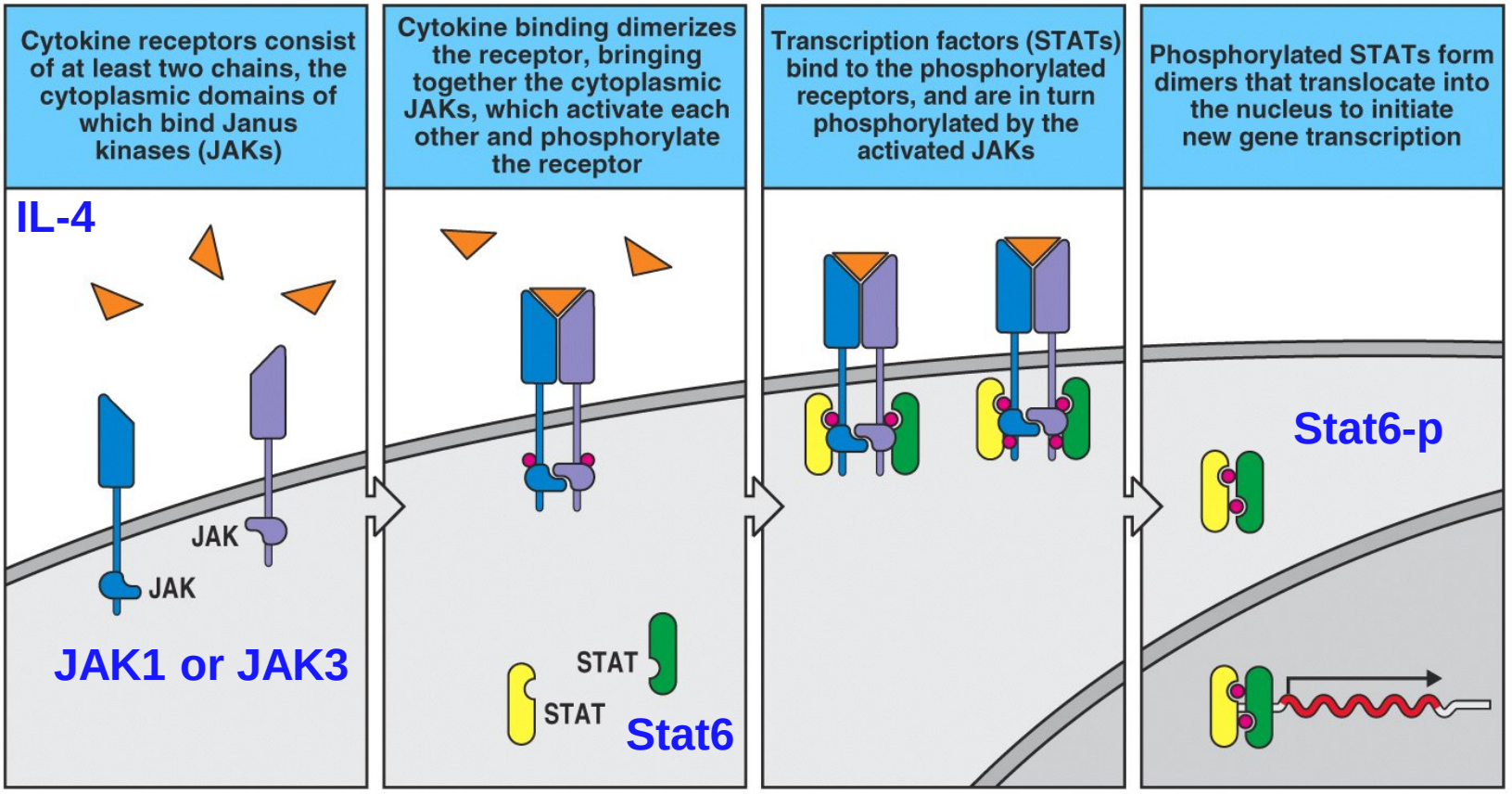


Figure 6-23 Immunobiology, 6/e. (© Garland Science 2005)

Ig switched to IgE

Events leading to IgE class switching and massive IgE production

(2) Mast cell activation causes amplification of IgE synthesis

Fig 14-4

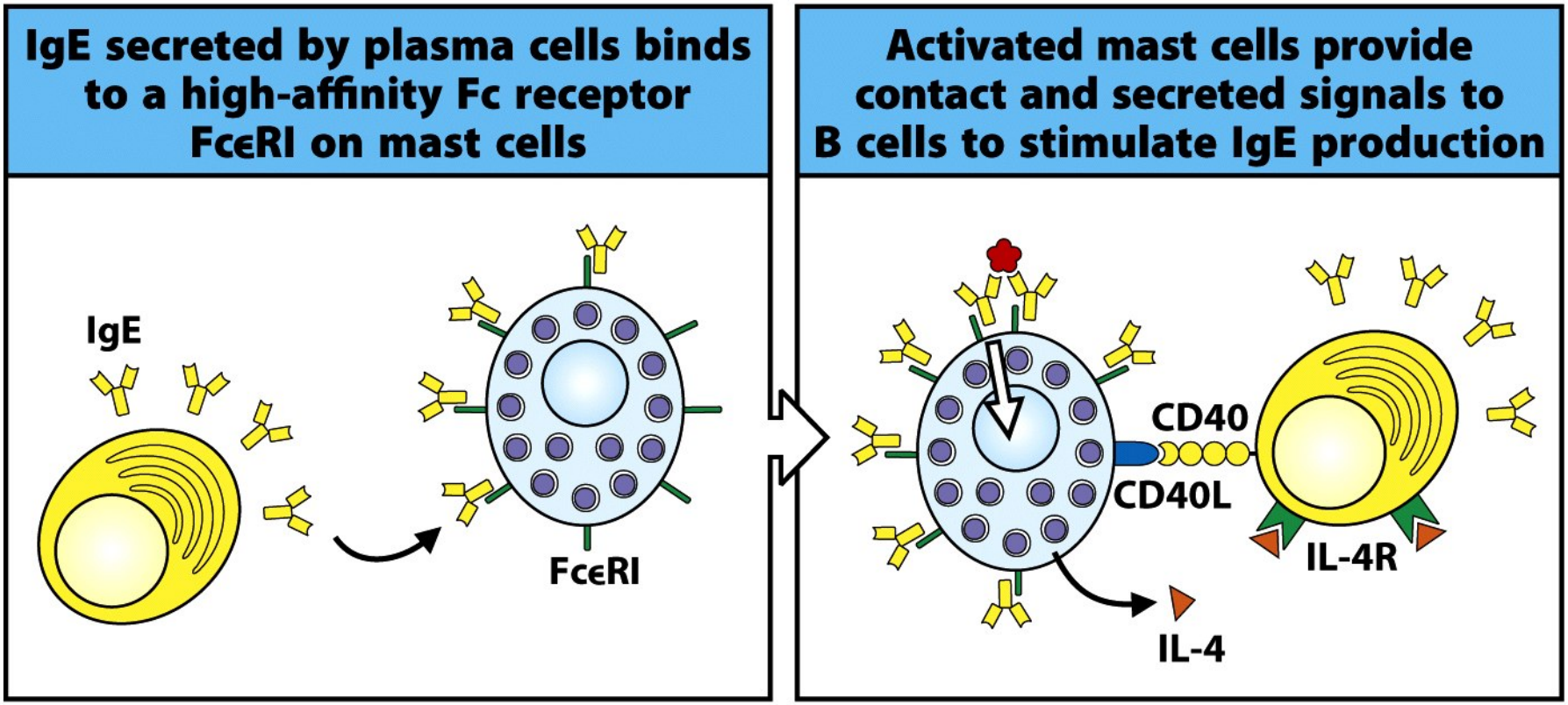


Figure 13-6 Immunobiology, 7ed. (© Garland Science 2008)

Mast cell degranulation by antigen (allergen) cross-linking of FcεR-bound IgE

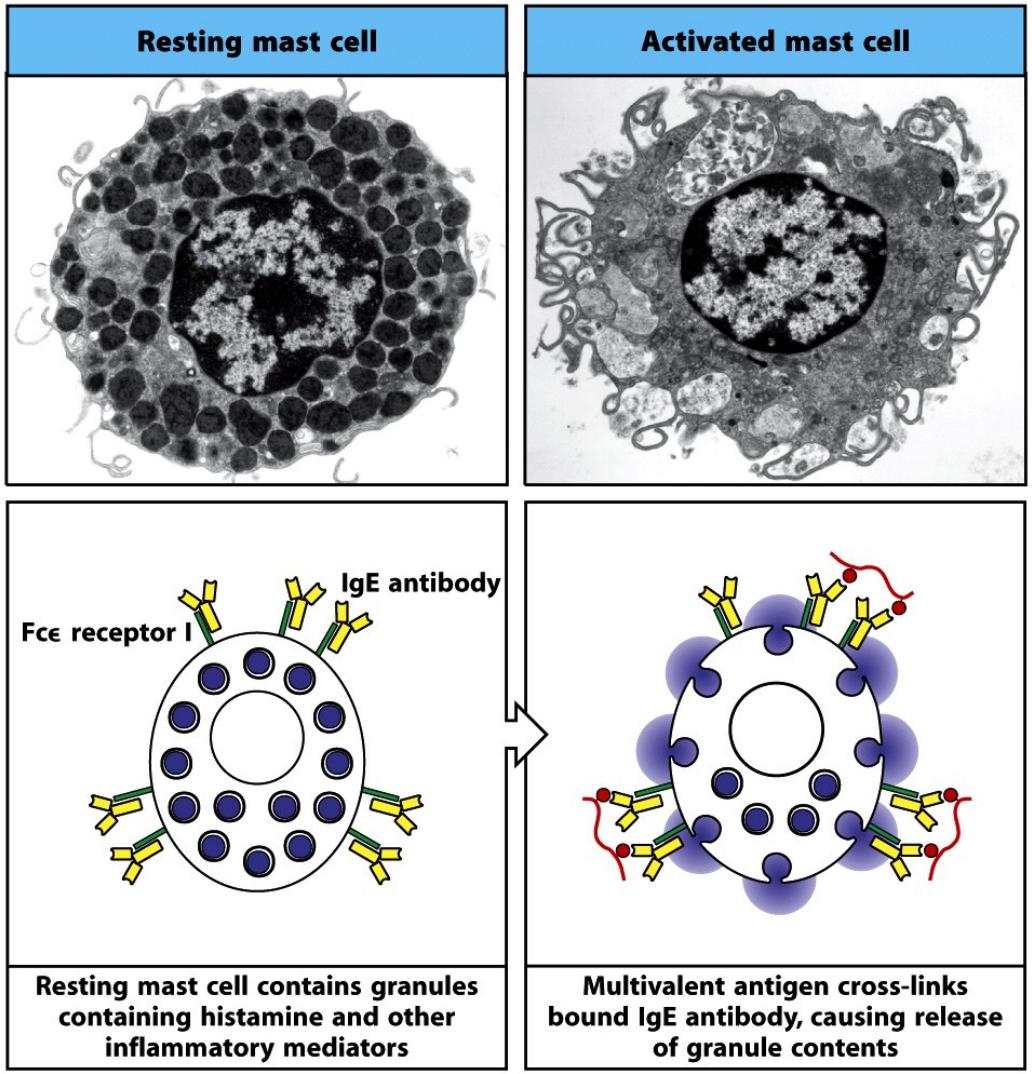


Figure 9-35 Immunobiology, 7ed. (© Garland Science 2008)

1. **Sensitization phase**

   - Occurs when body first encounter allergen

   - IgE produced and bound to mast cell

2. **Activation phase**

   - Occurs when the same allergen encountered IgE-bound mast cell

   - Cross-linking

   - Degranulation

Type I Hypersensitivity

Eosinophils and basophils may also participate

Atopy (特異性體質)

- Definition:
  - The increased trend seen in some individuals (atopics) to show exaggerated tendency to mount IgE responses to wide variety of innocuous substances
- Strong hereditary linkages
- Influenced by several genetic loci (Fig. 13-7)
- Mediated by a serum factor formally termed "reagin"
  - Now known as IgE

Atopics (具特異性體質者)

- Individuals exhibiting predisposition to type I hypersensitivity
- Characteristics
  - Family history (genetically linked)
  - Raised seral IgE levels
  - Skin prick test (+)
  - However, not all atopics exhibit clinical diseases

5q31-33
. IL-3,4,5,9,13; GM-CSF genes
. TIM proteins
(Tim3/Tim-2 proteins inhibit Th1/Th2 cells, respectively)
. IL-12 p40 subunit (promotes Th1 responses)

Fig 14-7

6p21
. MHC-II genes

11q12-13
. FcεRI β subunit

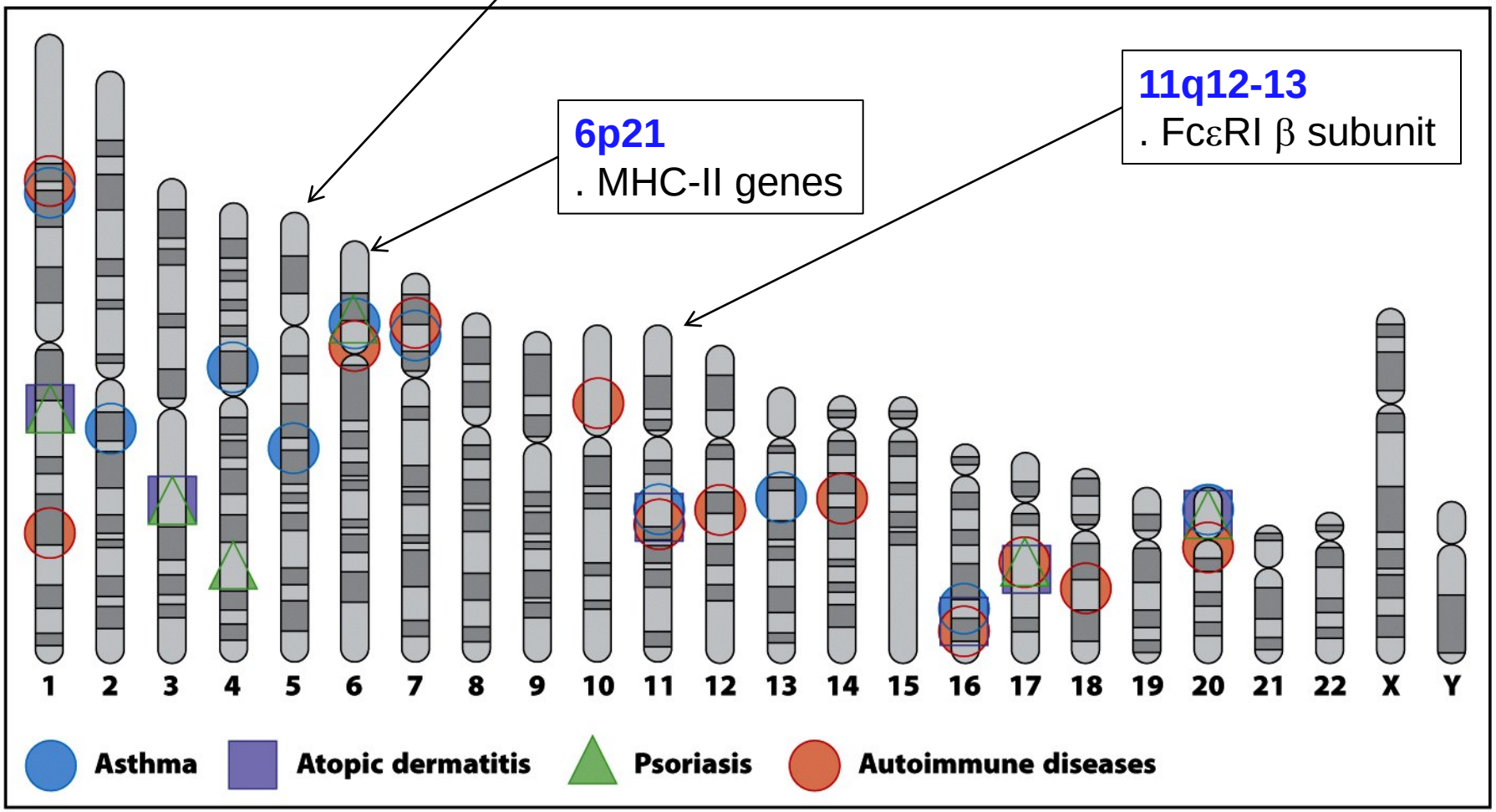


Figure 13-7 Immunobiology, 7ed. (© Garland Science 2008)

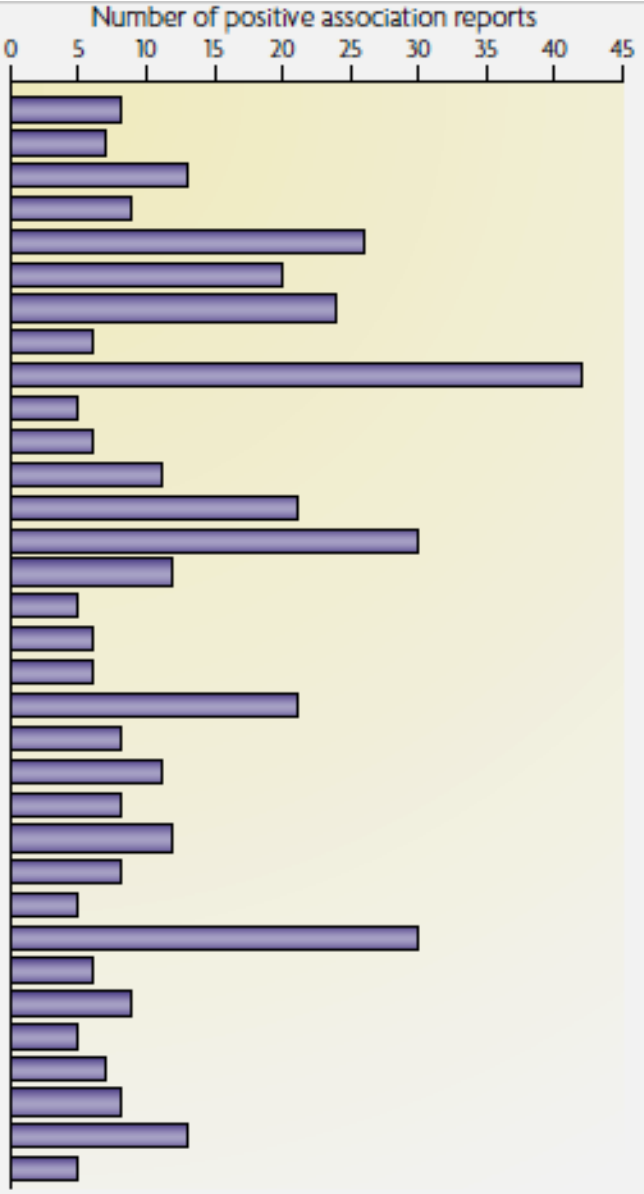
Candidate susceptibility genes for asthma

Fig 14-8

Asthma susceptibility genes	
Genes triggering the immune response or directing CD4 T_H cell differentiation	Pattern recognition receptors: *CD14, TLR2, TLR4, TLR6, TLR10, NOD1, NOD2*
	Immunoregulatory cytokines: *IL-10, TGFβ1*
	Transcription factors: *STAT3*
	Antigen presentation: *HLA-DR, HLA-DQ, HLA-DP* alleles
	Prostaglandin receptor: *PDGER2*
Genes regulating T_H2 cell differentiation and effector afunction	*GATA3, TBX21, IL-4, IL-13, IL4RA, FCER1B, IL-5, IL5RA, IL12B*
Genes expressed in epithelial cells	Chemokines: *CCL5, CCL11, CCL24, CCL26*
	Antimicrobial peptides: *DEFB1*
	CC16
	Epithelial cell barrier: *SPINK5, FLG*
Genes identified by positional cloning	*ADAM33, DPP10, PHF11, GPRA, HLA-G, IRAKM, COL29A1*

Figure 14.8 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Gene	Chromosome	Function and pathway	Common variants
GSTM1	1p13.3	Environmental and oxidative stress — detoxification	+/null
FLG	1q21.3	Epithelial barrier integrity	Arg510X, 2282del4
IL10	1q31-q32	Immunoregulation	–1082A/G, –571C/A
CTLA4	2q33	T-cell-response inhibition and immunoregulation	–318C/T, 49A/G
IL13	5q31	T_H2 effector functions	–1112C/T, Arg130Gln
IL4	5q31.1	T_H2 differentiation and IgE induction	–589C/T, +33C/T
CD14	5q31.1	Innate immunity — microbial recognition	–1721G/A, –260C/T
SPINK5	5q32	Epithelial serine protease inhibitor	Glu420Lys
ADRB2	5q31-q32	Bronchial smooth-muscle relaxation	Arg16Gly, Gln27Glu
HAVCR1	5q33.2	T-cell-response regulation — HAV receptor	5383_5397del
LTC4S	5q35	Cysteinyl leukotriene biosynthesis — inflammation	–444A/C
LTA	6p21.3	Inflammation	NcoI (intron 1)
TNF	6p21.3	Inflammation	–308G/A, –857C/T
HLA-DRB1	6p21	Antigen presentation	Multi-SNP alleles
HLA-DQB1	6p21	Antigen presentation	Multi-SNP alleles
HLA-DPB1	6p21	Antigen presentation	Multi-SNP alleles
GPRA	7p14.3	Regulation of cell growth and neural mechanisms	Haplotypes
NAT2	8p22	Detoxification of drugs and carcinogens	Slow acetylation SNPs
FCERIB	11q13	High-affinity Fc receptor for IgE	Ile181Leu, Gly237Glu
CC16	11q12.3-q13.1	Epithelium-derived anti-inflammatory protein	38A/G
GSTP1	11q13	Environmental and oxidative stress — detoxification	Ile105Val
IL18	11q22.2-q22.3	Induction of IFNγ and TNF	–656T/G, –137G/C
STAT6	12q13	IL-4 and IL-13 signalling	2964G/A, (GT)n exon 1
NOS1	12q24.2-q24.31	Nitric oxide synthesis — cell–cell communication	3391C/T, 5266C/T
CMA1	14q11.2	Mast-cell chymotryptic serine protease	*Bst*X1, –1903G/A
IL4R	16p12.1-p12.2	α-chain of the IL-4 and IL-13 receptors	Ile50Val, Glu551Arg
CCL11	17q21.1-q21.2	Epithelium-derived eosinophil chemoattractant	Ala23Thr, –1328G/A
CCL5	17q11.2-q12	Monocyte, T-cell and eosinophil chemoattractant	–403A/G, –28C/G
ACE	17q23.3	Inactivation of inflammatory mediators	In/del
TBXA2R	19p13.3	Smooth-muscle contraction, inflammation	924T/C, 795T/C
TGFB1	19q13.1	Immunoregulation, cell proliferation	–509C/T
ADAM33	20p13	Cell–cell and cell–matrix interactions	Multiple SNPs
GSTT1	22q11.23	Environmental and oxidative stress — detoxification	A/null



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Nature Reviews Immunology 2008. 8(3)

Fig 14-9

"Hygiene hypothesis"

- **Both** inherited and environmental factors contribute to the likelihood of developing allergic diseases

- Th1 responsiveness (non-atopic)
  - Fewer in susceptible genes
  - More exposures to some infectious agents during in childhood
    - In a more unhygienic environment

- Th2 responsiveness (atopic)
  - More in susceptible genes
  - Less exposures to infectious agent in childhood
    - In a more hygienic environment

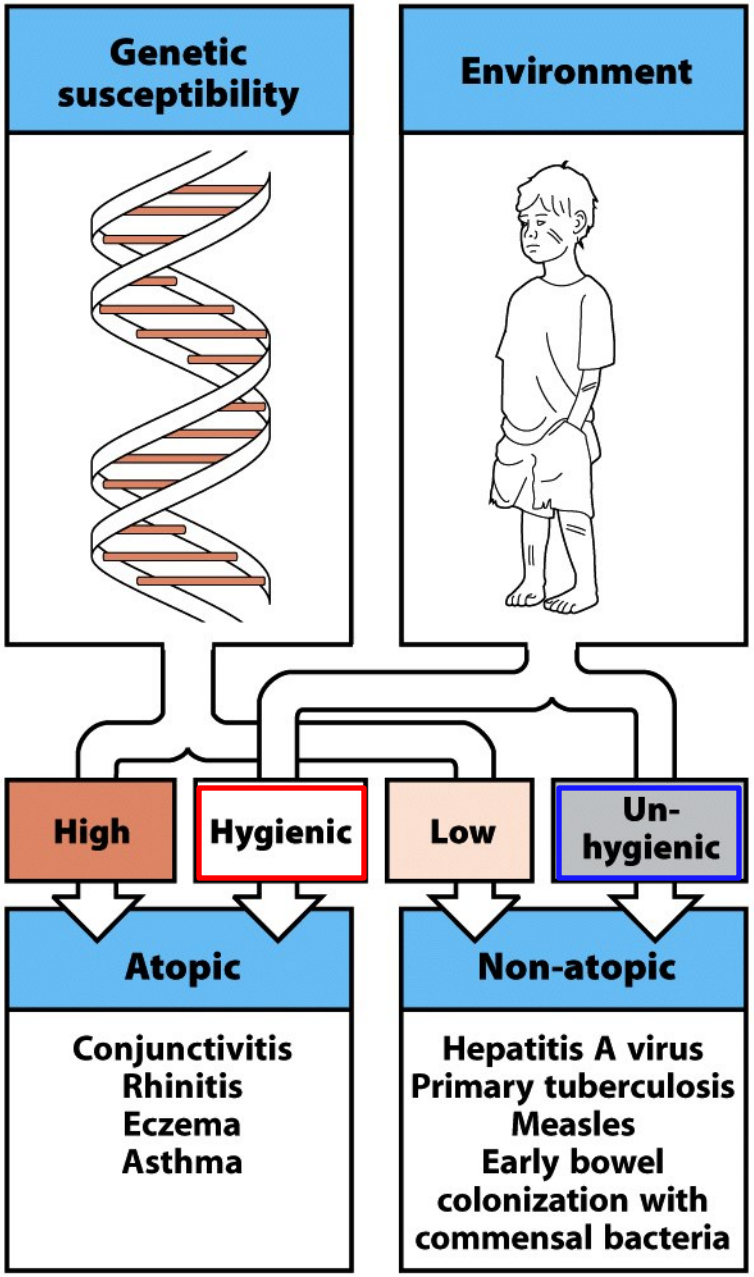


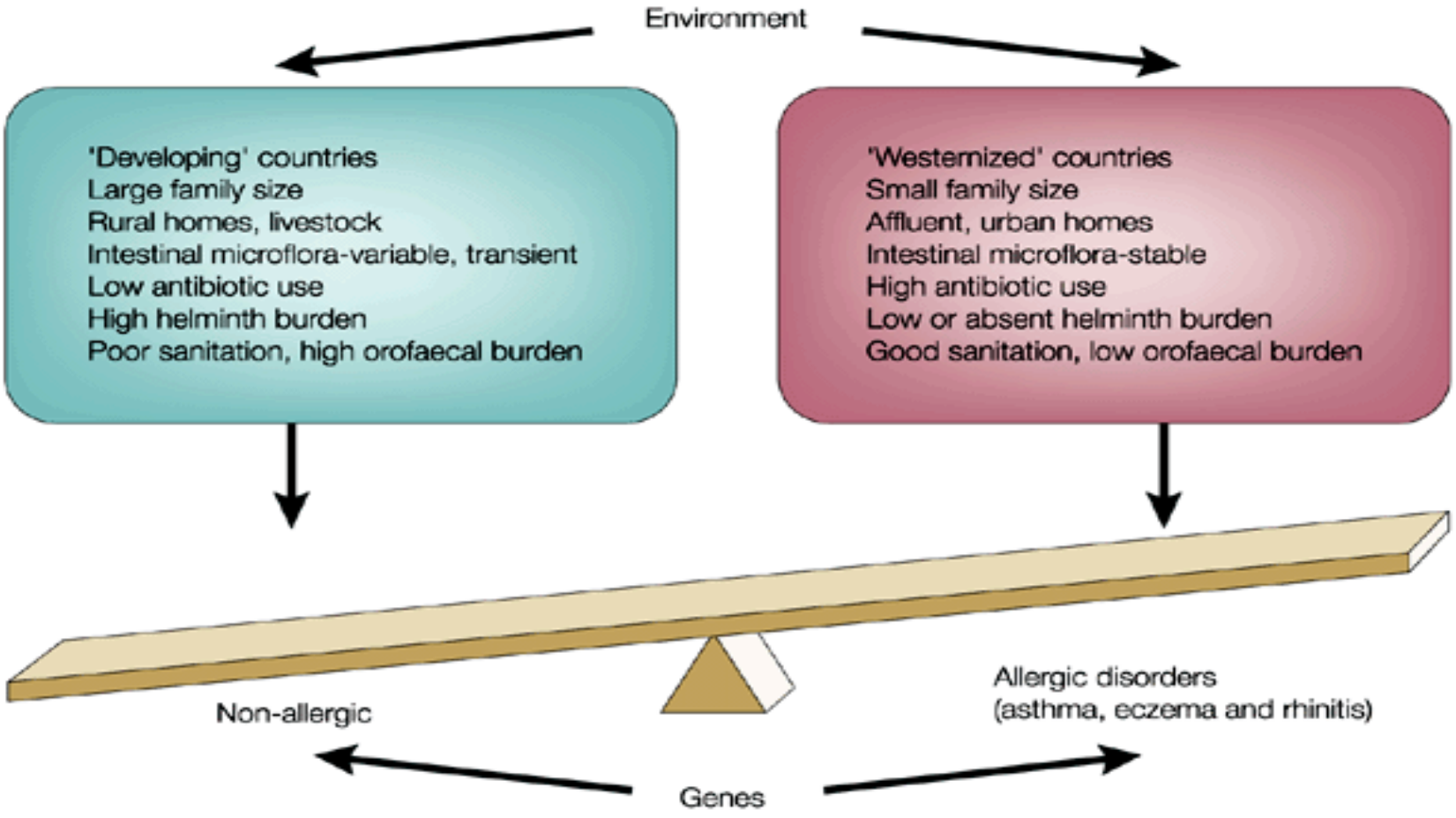
Figure 13-9 Immunobiology, 7ed. (© Garland Science 2008)

Environmental factors determining tendency for atopic allergic diseases

Fig 14-9

- Early exposure to ubiquitous microorganisms
- Helminth infection
- Hepatitis A virus infection
- Composition of gut commensal microbiota

Both genetic and environmental factors contribute to the development of IgE-mediated allergy



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Effector mechanisms in allergic reaction

Mast-cell activation has many effects

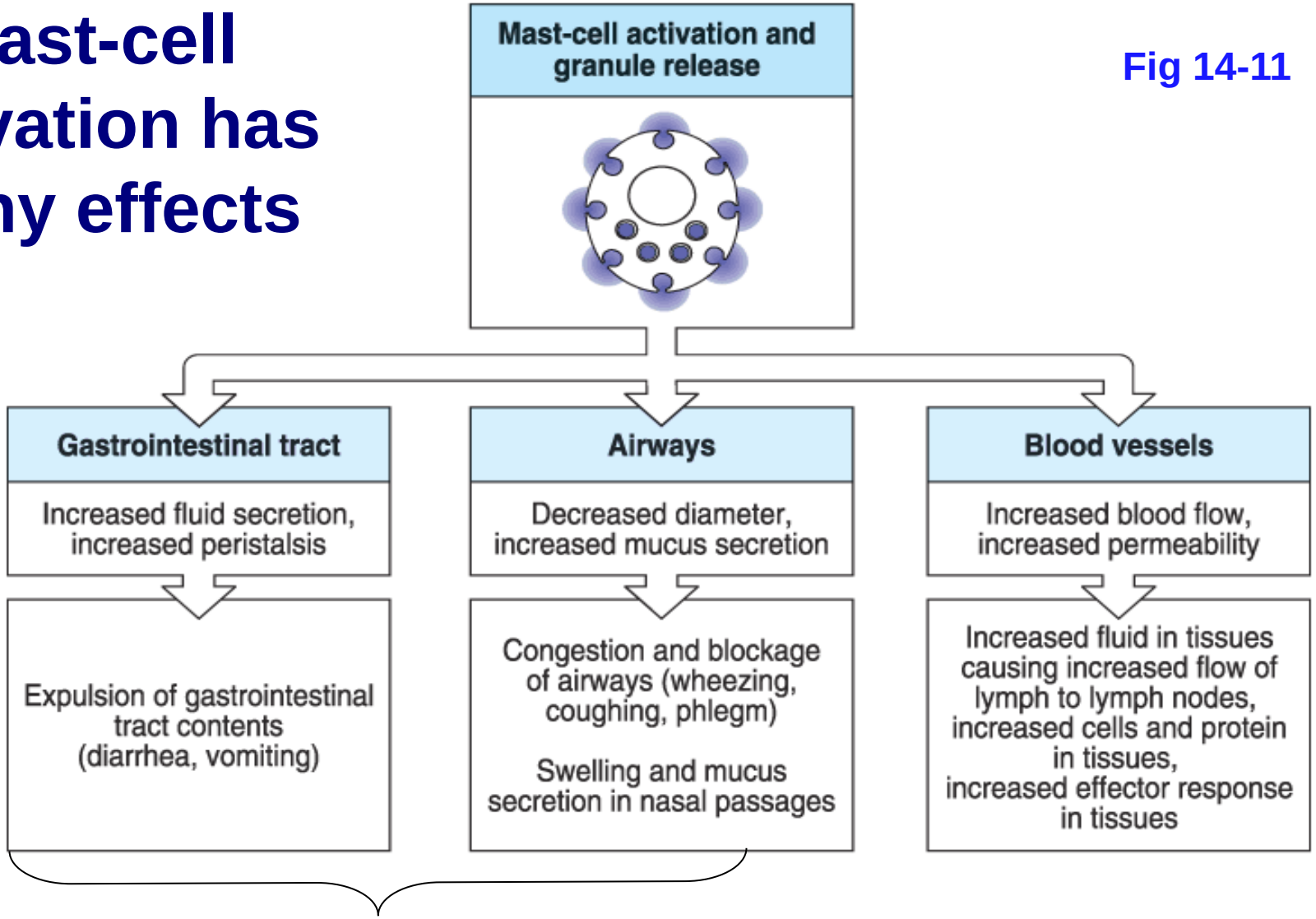


Fig 14-11

Why? Normally IgE responses are associated with worm infestations. These responses help evacuate the places where the worms often live.

Molecules released by activated mast cells

Fig 14-11

Pre-formed and stored in granules

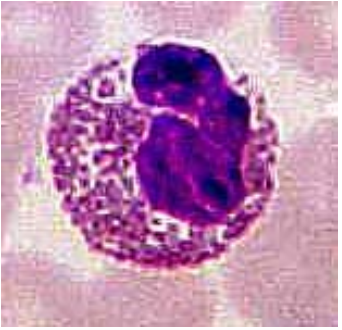
Class of product	Examples	Biological effects
Enzyme	Tryptase, chymase, cathepsin G, carboxypeptidase	Remodel connective tissue matrix
Toxic mediator	Histamine, heparin	Toxic to parasites Increase vascular permeability Cause smooth muscle contraction

Molecules released by activated mast cells

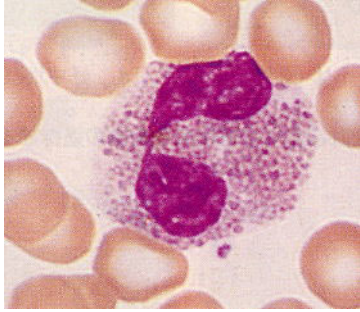
Fig 14-11

Newly synthesized upon m activation

Cytokine	IL-4, IL-13	Stimulate and amplify T_H2-cell response
	IL-3, IL-5, GM-CSF	Promote eosinophil production and activation
	TNF-α (some stored preformed in granules)	Promotes inflammation, stimulates cytokine production by many cell types, activates endothelium
Chemokine	CCL3	Attracts monocytes, macrophages, and neutrophils
Lipid mediator	Prostaglandins D_2, E_2 Leukotrienes B4, C4	Cause smooth muscle contraction Increase vascular permeability Stimulate mucus secretion
	Platelet-activating factor	Attracts leukocytes Amplifies production of lipid mediators Activates neutrophils, eosinophils, and platelets



Eosinophils



- Granulocytic leukocytes
  - Granules harbor arginine-rich basic proteins
    - easily stained with acidic dye eosin
- Most are found in tissues (connective tissues, interconnection with IgE)
  - Respiratory tract
  - GI tract
- Will express FcεRI receptor when activated

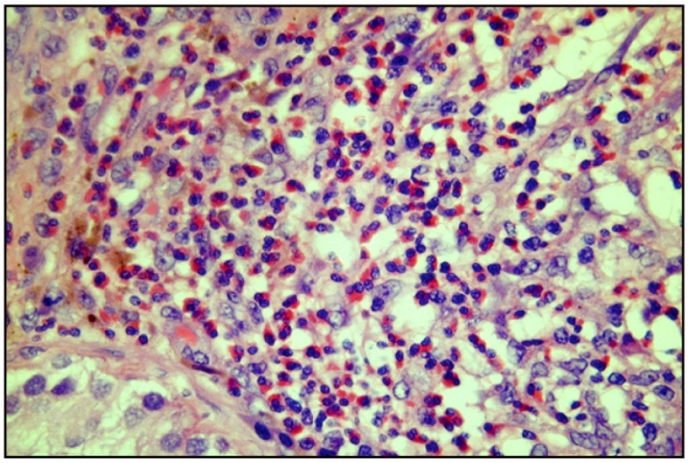


Figure 12-13 Immunobiology, 6/e. (© Garland Science 2005)

Molecules released by activated eosinophils

Pre-formed mediators

Fig 14-12

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
Toxic protein	Major basic protein	Toxic to parasites and mammalian cells Triggers histamine release from mast cells
	Eosinophil cationic protein	Toxic to parasites Neurotoxin
	Eosinophil-derived neurotoxin	Neurotoxin

Figure 12-14 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Molecules released by activated eosinophils

Newly-synthesized mediators

Fig 14-12

Class of product	Examples	Biological effects
Cytokine	IL-3, IL-5, GM-CSF	Amplify eosinophil production by bone marrow Cause eosinophil activation
Chemokine	CXCL8 (IL-8)	Promotes influx of leukocytes
Lipid mediator	Leukotrienes C4, D4, E4	Cause smooth muscle contraction Increase vascular permeability Increase mucus secretion
	Platelet-activating factor	Attracts leukocytes Amplifies production of lipid mediators Activates neutrophils, eosinophils, and platelets

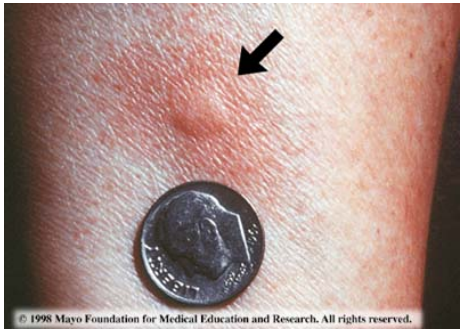
Figure 12-14 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Chemical mediator release

- Immediate phase → 2-3 min. ~ 6 hr
  - Histamine, prostaglandins
  - Eosinophil chemotactic facter (ECF)
  - Neutrophil chemotactic factor (NCF) etc.

- Late phase → > 6-24 hr
  - SRS-A (e.g. Leukotrienes)
  - Platelet-activating factor (PAF)
  - Chemokines/Cytokines (e.g. IL-3, IL-5, GM-CSF)

Fig 14-13



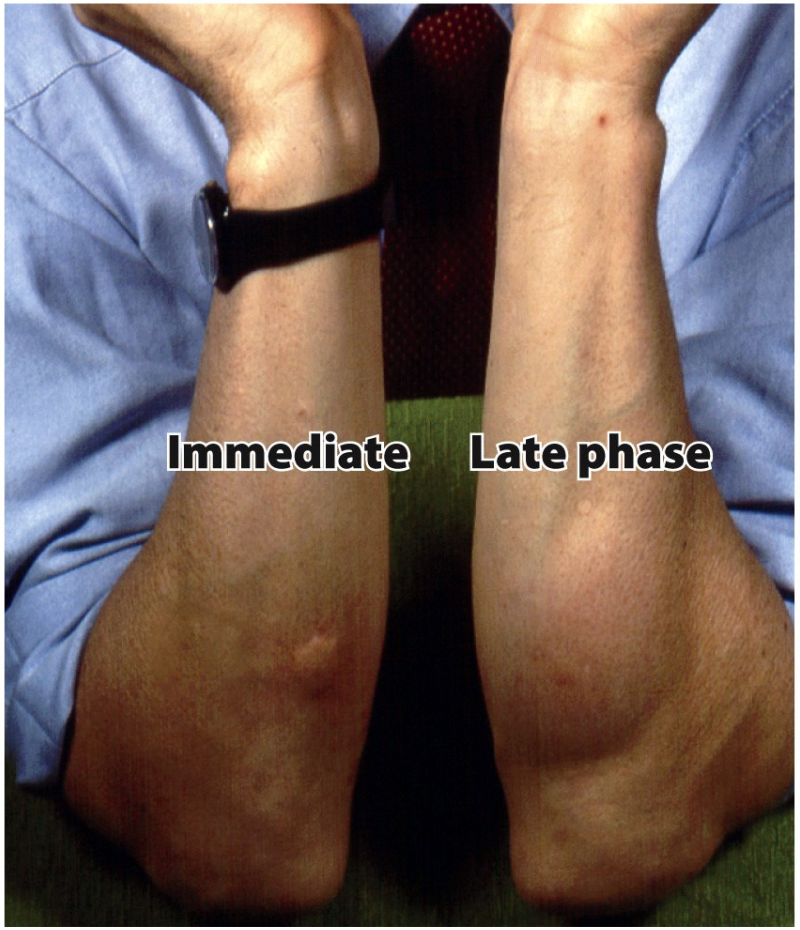


Figure 13-14 part 2 of 2 Immunobiology, 7ed. (© Garland Science 2008)

Immediate phase

-Wheal-and-flare (喇叭狀局部膨疹)
-Mediators released
-1st contraction of smooth muscle

Late phase

-Induction of more mediators
-Recruitment of eosino./Th2 cells
-2nd contraction of smooth muscle
-Edema (due to vasodilation)
-Smooth muscle hypertrophy/hyperplasia

Immediate vs late-phase reaction

Fig 14-13

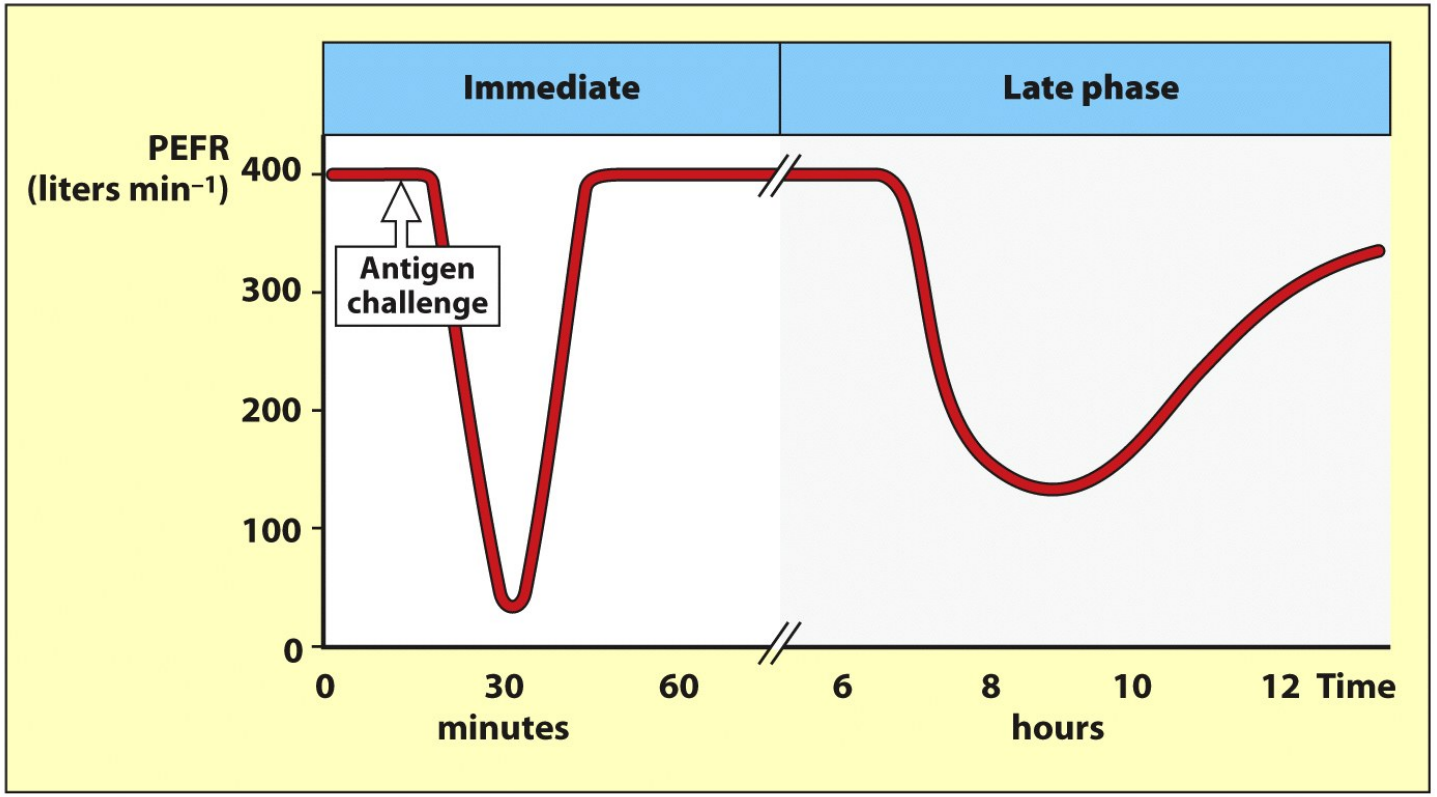


Figure 14.13 part 1 of 2 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Peak expiratory flow rate (用力呼氣尖峰流速)

-可以客觀地評估氣喘患者氣流阻塞程度

- 以**尖峰吐氣流量計(AsthmaMentor)**測量之

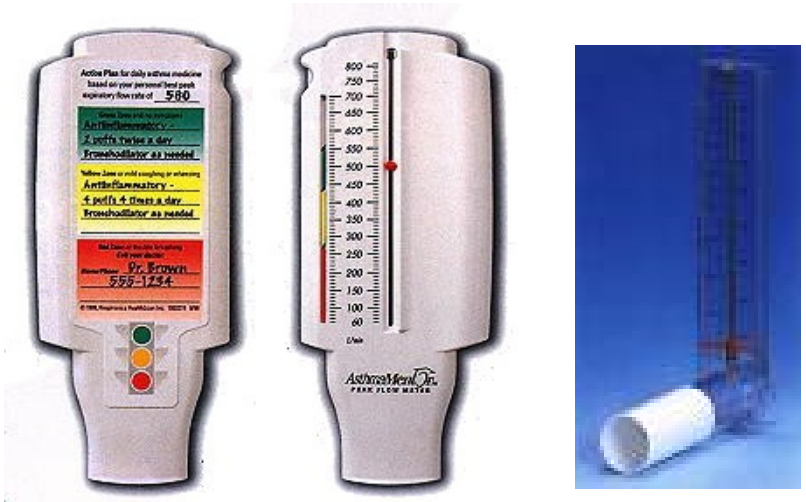
PEFR
Normal values

尖峰吐氣流量計(AsthmaMentor)

$$\text{尖峰呼氣流速每日變異度} = \frac{\text{PEFR(晚)} - \text{PEFR(早)}}{1/2\,[\text{PEFR(晚)} + \text{PEFR(早)}]} \times 100\%$$

- 兒童的尖峰呼氣流速每日變異度若<u>大於20%</u>，即可診斷為氣喘。

(給同學們參考用)



Target organs affected by mast-cell activation

- Smooth muscle
  - Contraction
- Blood vessels
  - Increased vascular permeability → Dilation (擴張)
- Mucosal gland
  - Increased mucus secretion
- Leukocytes
  - Increased influx into surrounding tissues
    - Termed 'infiltration'

Examples of diseases

- Allergic rhinitis 過敏性鼻炎
  - Hay fever
- Urticaria 蕁麻疹;風疹塊
  - Hives, disseminated wheal-and-flare
- Eczema 溼疹
  - Atopic dermatitis
- Food allergy 食物過敏
- Bronchial asthma 氣喘
- Anaphylactic shock (anaphylaxis) 系統性休克

Factors determining consequences of IgE-mediated reactions

- Dose of allergen
- Route of allergen entry
- Quantity of IgE present

The site of mast cell activation determines the clinical effects

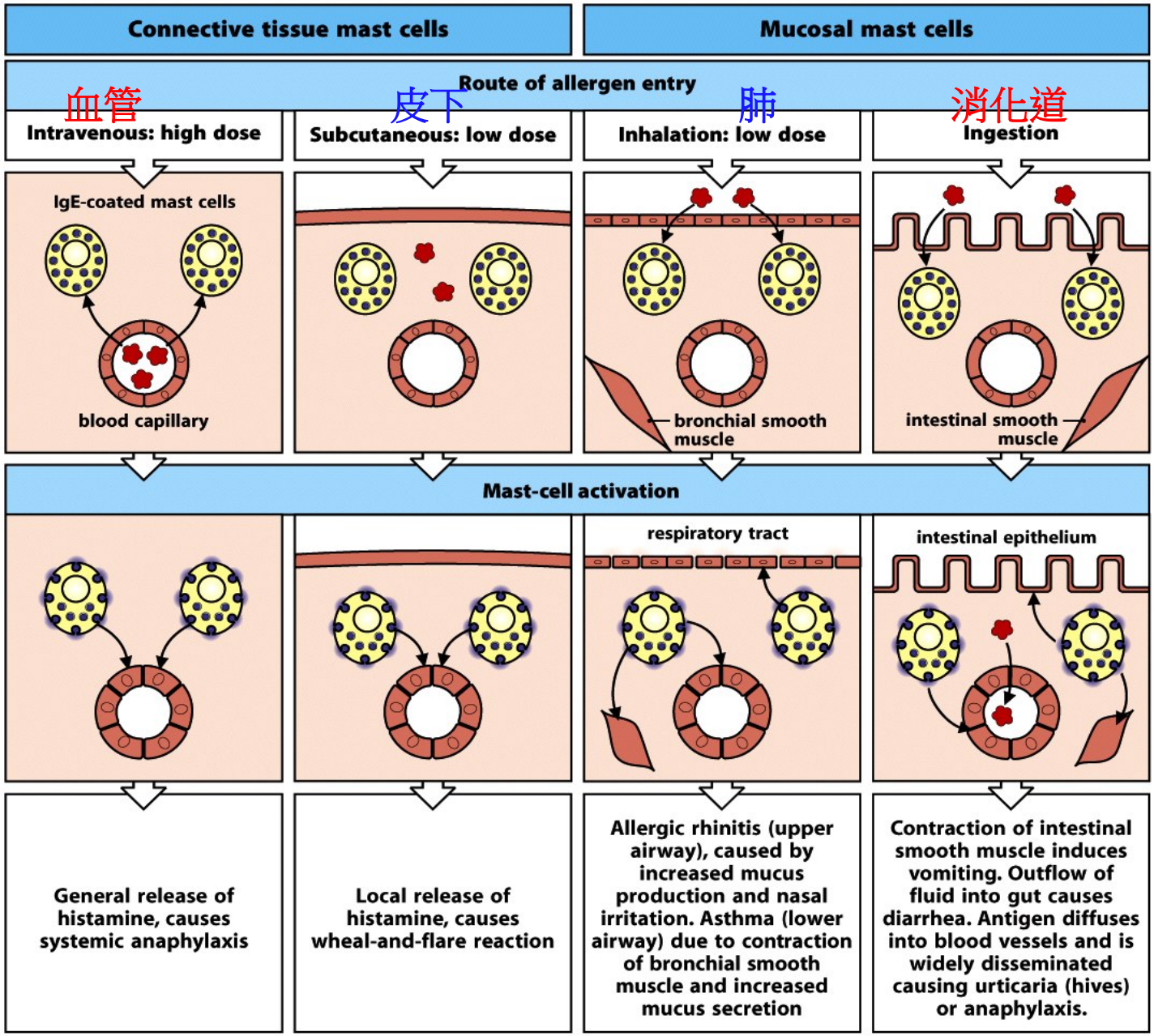


Figure 13-15 Immunobiology, 7ed. (© Garland Science 2008)

Fig 14-14

1. Doses of Ag
2. Routes of Ag entry
3. Amount of Ag-specific IgE present

Local:
- subcutaneous
- inhalation

Systemic:
- intravenous
- ingestion

Fig 13-15

Acute response in allergic asthma can lead to chronic inflammation of the airways Fig 14-15

T_H2-mediated chronic airway obstruction

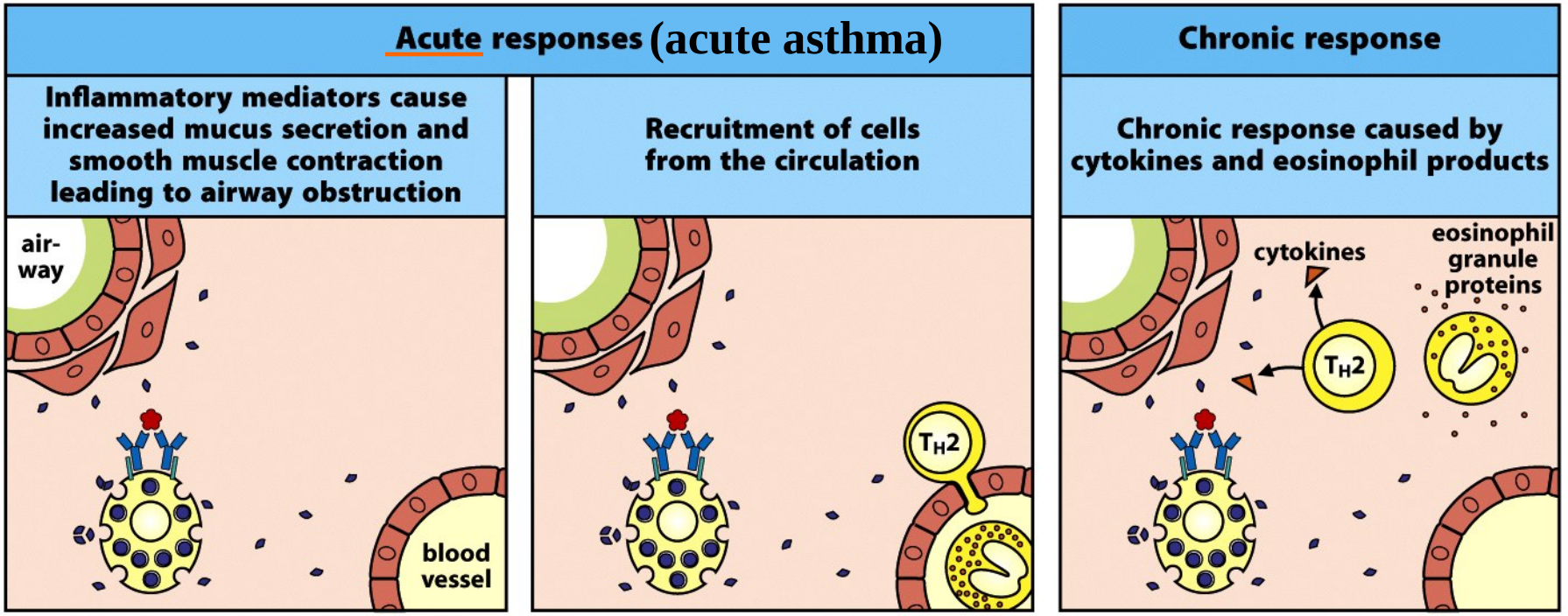


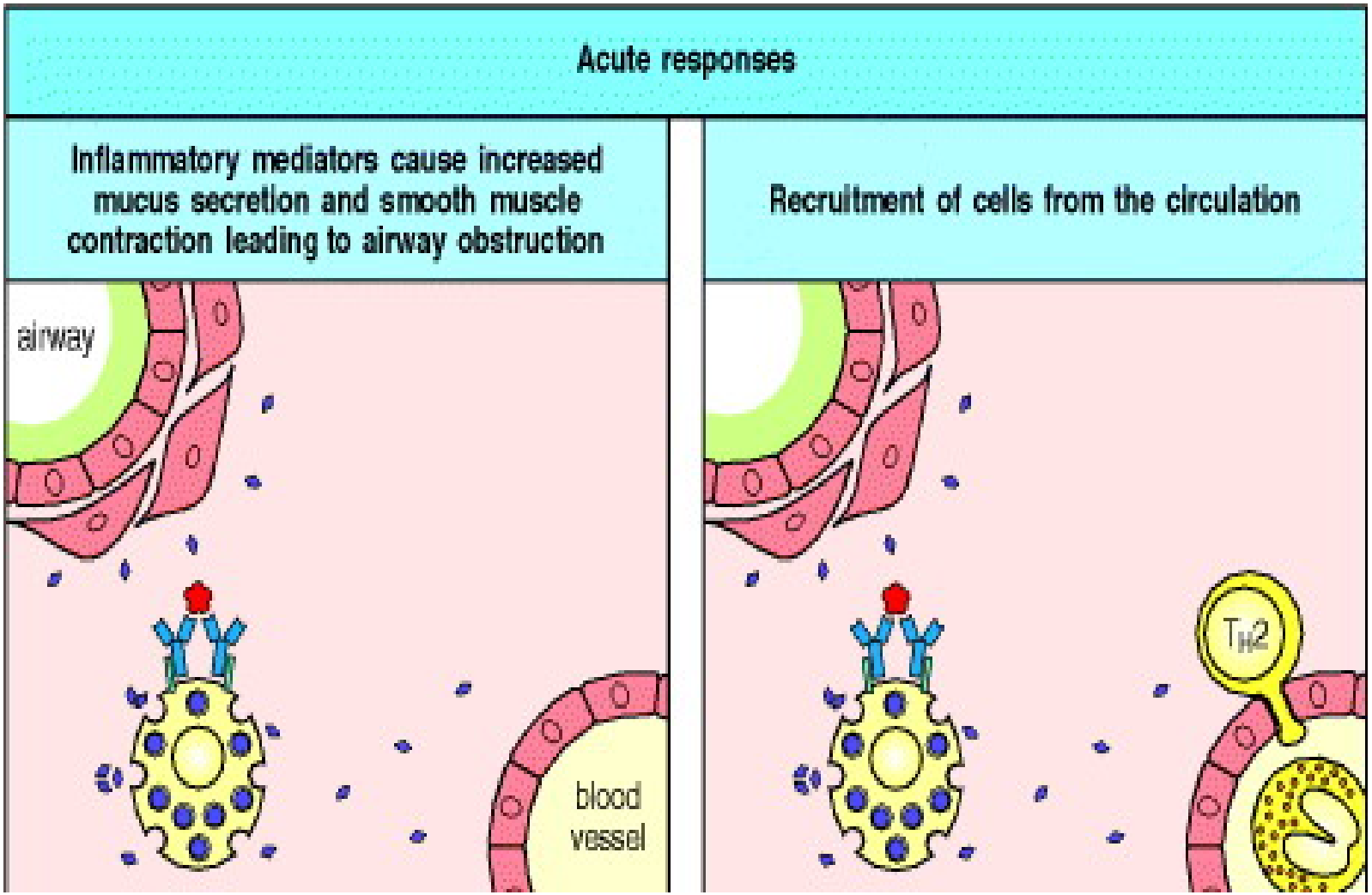
Figure 13-16 Immunobiology, 7ed. (© Garland Science 2008)

Type I hypersensitivity because IgE-mediated → Type IV hypersensitivity because T_H2 involvement

Acute asthma

Fig 14-15

(activation of submucosal mast cells in the airways)



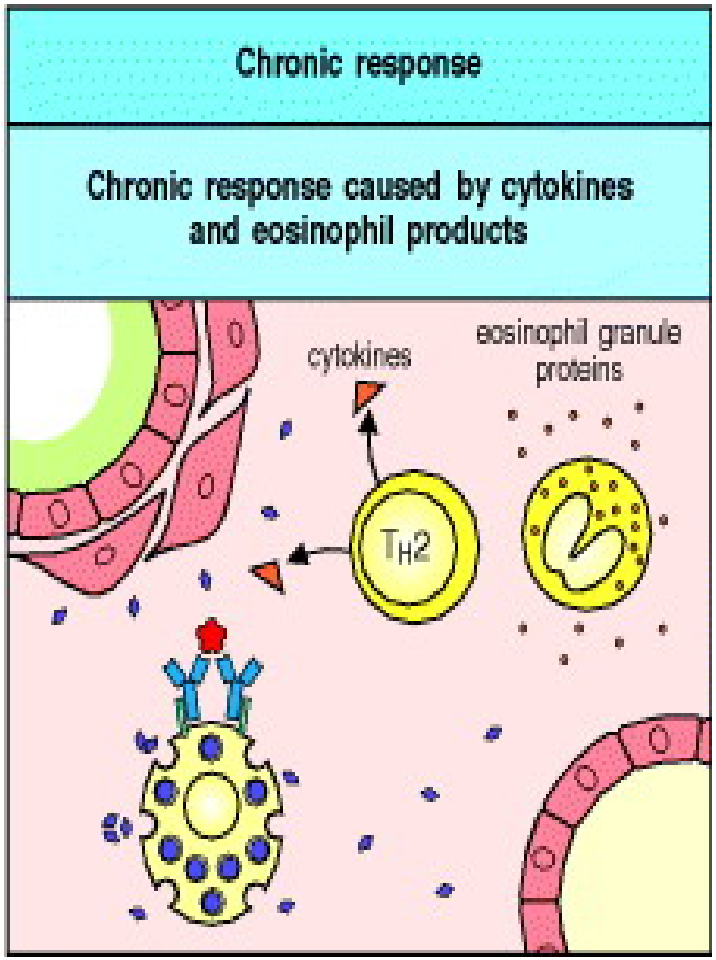
Massive cytokine release and tissue damage lead to chronic asthma!!

Chronic asthma

(continuous inflammation of the airways)

Fig 14-16

Fig 14-15



Complete airway obstruction

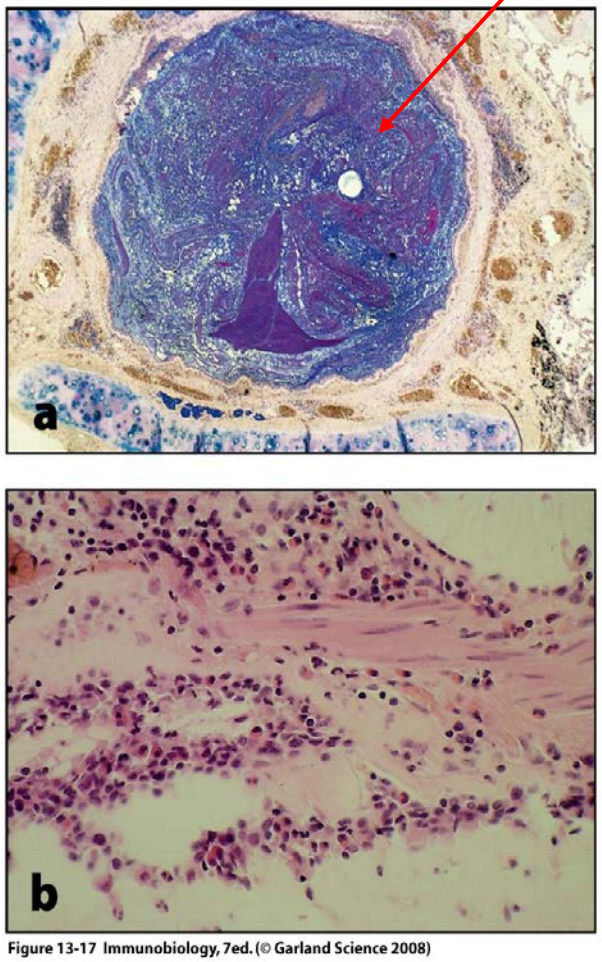


Figure 13-17 Immunobiology, 7ed. (© Garland Science 2008)

- Blockade of airway due to mucosal secretion
- Infiltrates of TH2 lymphocytes, eosinophils, neutrophils,…etc.

Fig 13-17

Risk factors for development of food allergy

Fig 14-18

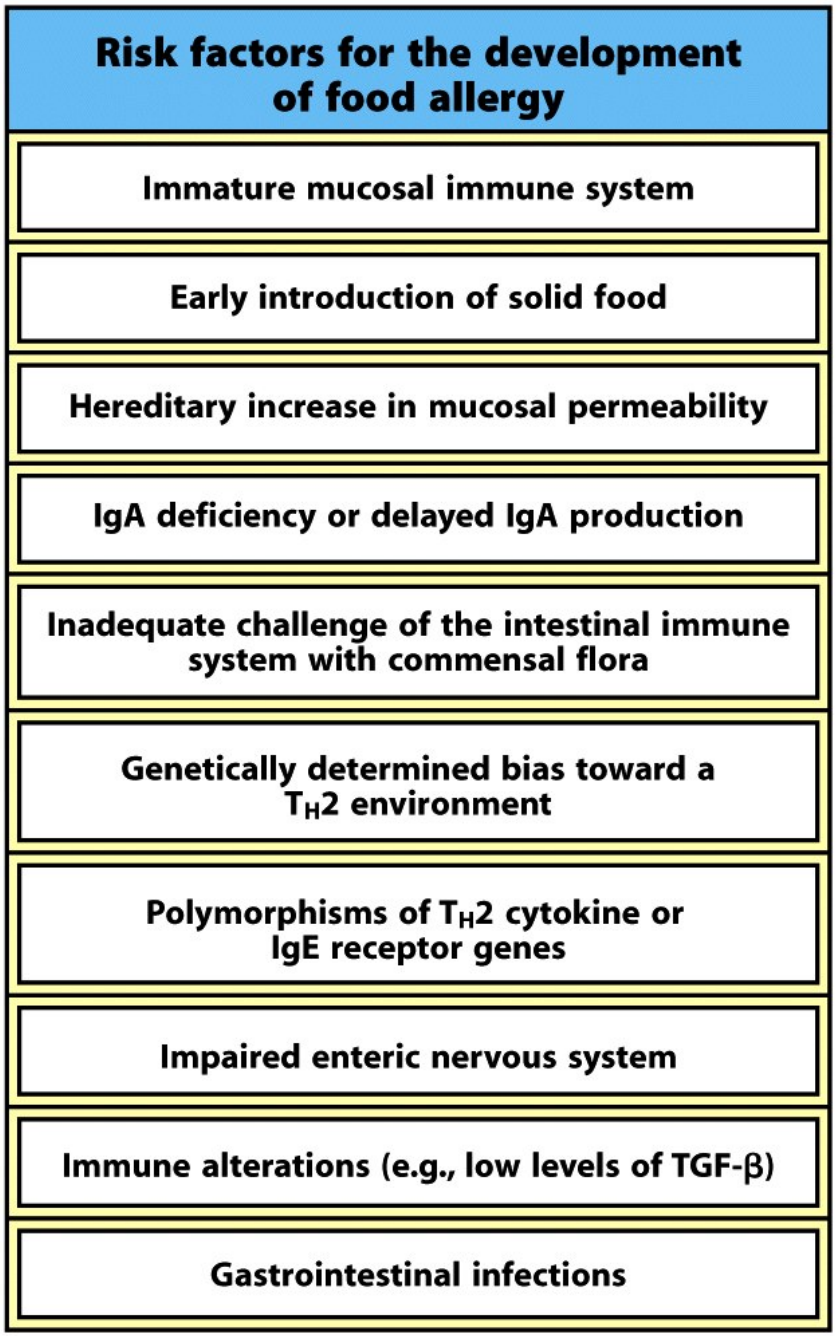


Figure 13-20 Immunobiology, 7ed. (© Garland Science 2008)

How can allergic diseases be treated?

Fig 14-19

Treatments for allergic disease		
Target step	**Mechanism of treatment**	**Specific approach**
In clinical use		
Mediator action	Inhibit effects of mediators on specific receptors Inhibit synthesis of specific mediators	Antihistamines, β-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)

Figure 14.19 part 1 of 2 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

How can allergic diseases be treated?

Fig 14-19

Treatments for allergic disease		
Target step	**Mechanism of treatment**	**Specific approach**
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

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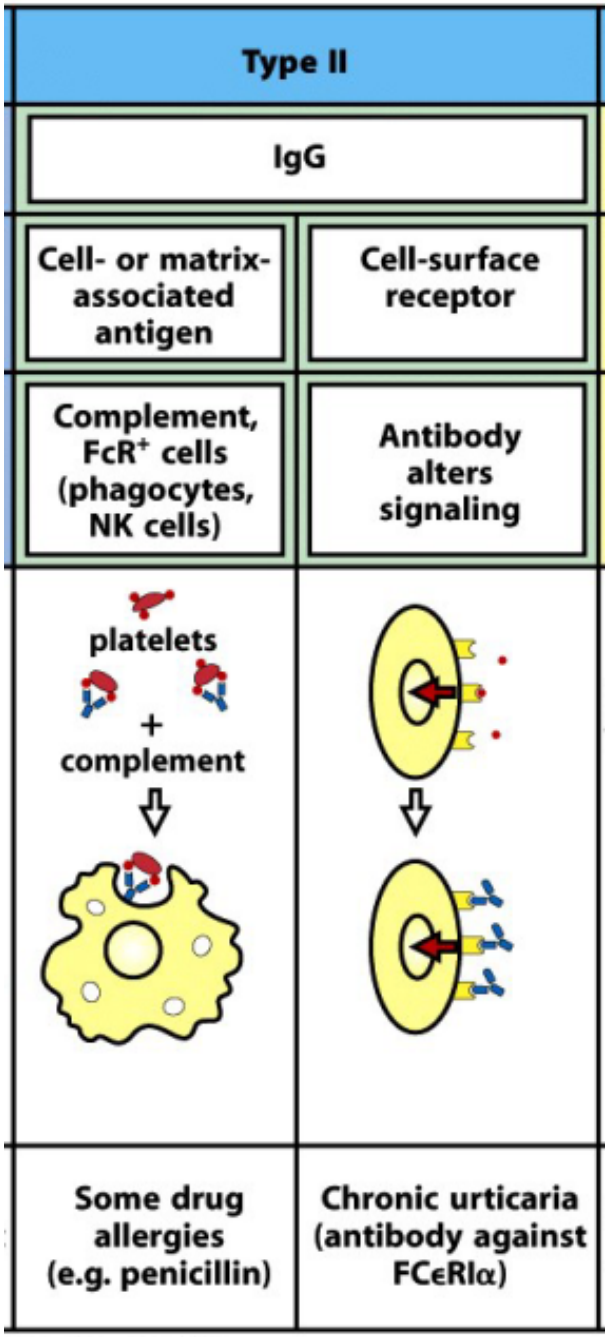
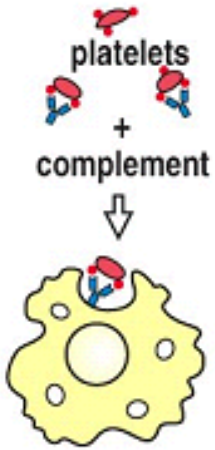
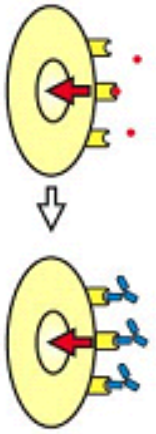
Type II Hypersensitivity



	Type II	
Immune reactant	IgG	
Antigen	Cell- or matrix-associated antigen	Cell-surface receptor
Effector mechanism	Complement, FcR⁺ cells (phagocytes, NK cells)	Antibody alters signaling
		
Example of hypersensitivity reaction	Some drug allergies (eg, penicillin)	Chronic urticaria (antibody against FCεR1α)

arland Science 2005)

Type II hypersensitivity

1. Rare
2. **IgG-mediated** anti-cell-associated antigen response

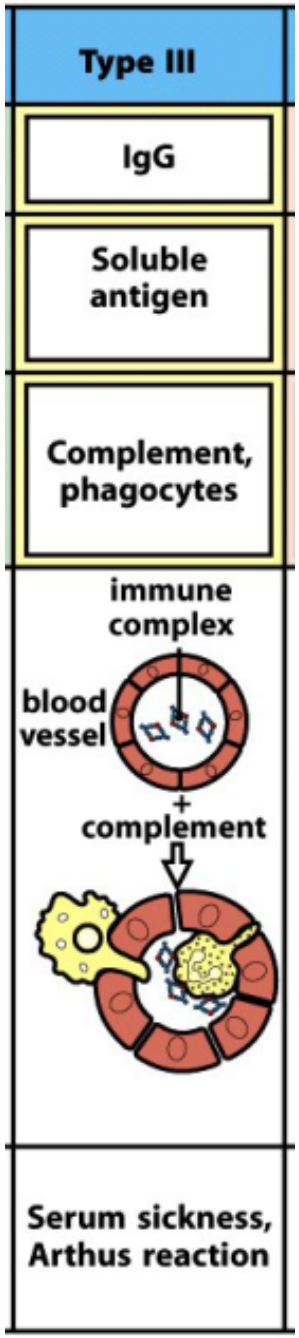
Immune response to certain drugs (e.g., penicillin) where drug binds to cell surface and antibody causes removal of the cells (usually by macrophages).

Type II Hypersensitivity (blood transfusion)

Type II hypersensitivity

- Mediated by binding of IgG to cell or tissue matrix Ag
- Occurs when
  - foreign cells (such as blood) are transfused, or
  - following administration of drugs such as penicillin which bind to self-proteins on RBCs or platelets
    - Penicillin acts as hapten (to change the antigenic structure of cells)
    - Causes hemolytic anemia or thrombocytopenia
- Mechanisms of the clearance of the cells
  - complement-mediated destruction, or
  - FcγR-mediated clearance by phagocytic cells

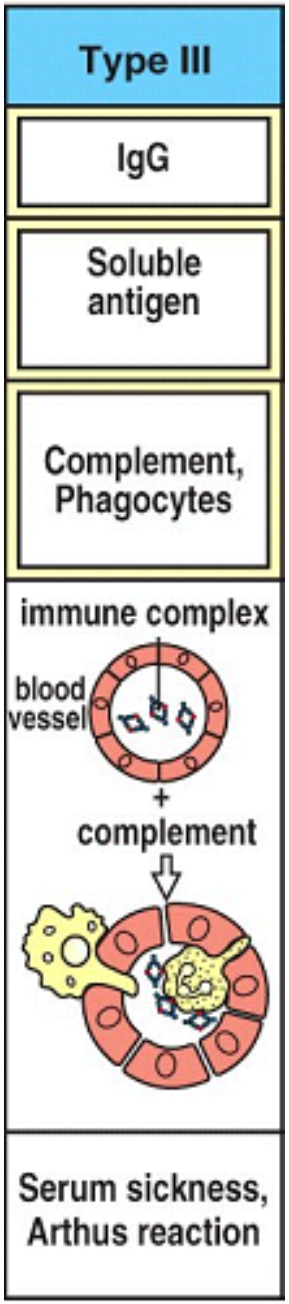
Type III Hypersensitivity



Type III Hypersensitivity

- Arises with soluble Ags
- Deposition of Ab:Ag aggregates (immune complexes; ICs) leads to tissue damage
- Two types
  - local (subcutaneous), and
  - systemic (injection, via blood stream)
- A local reaction can occur following subcutaneous injection or inhalation of antigens to which the individual already has IgG antibodies

Type III hypersensitivity



Arthus Reaction (local type) : **Fig 14-20**

acute IgG-mediated hypersensitivity to soluble Ag

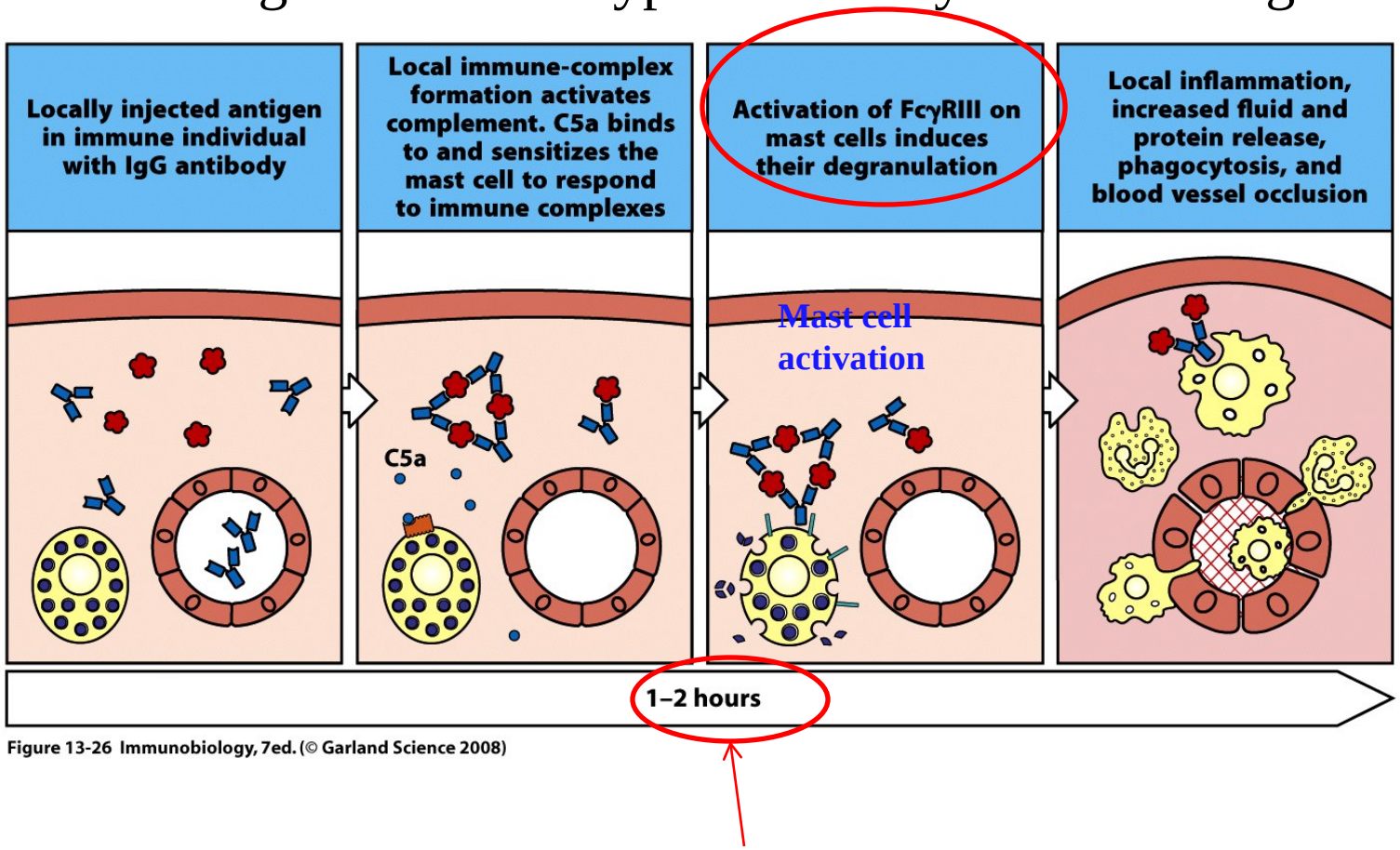


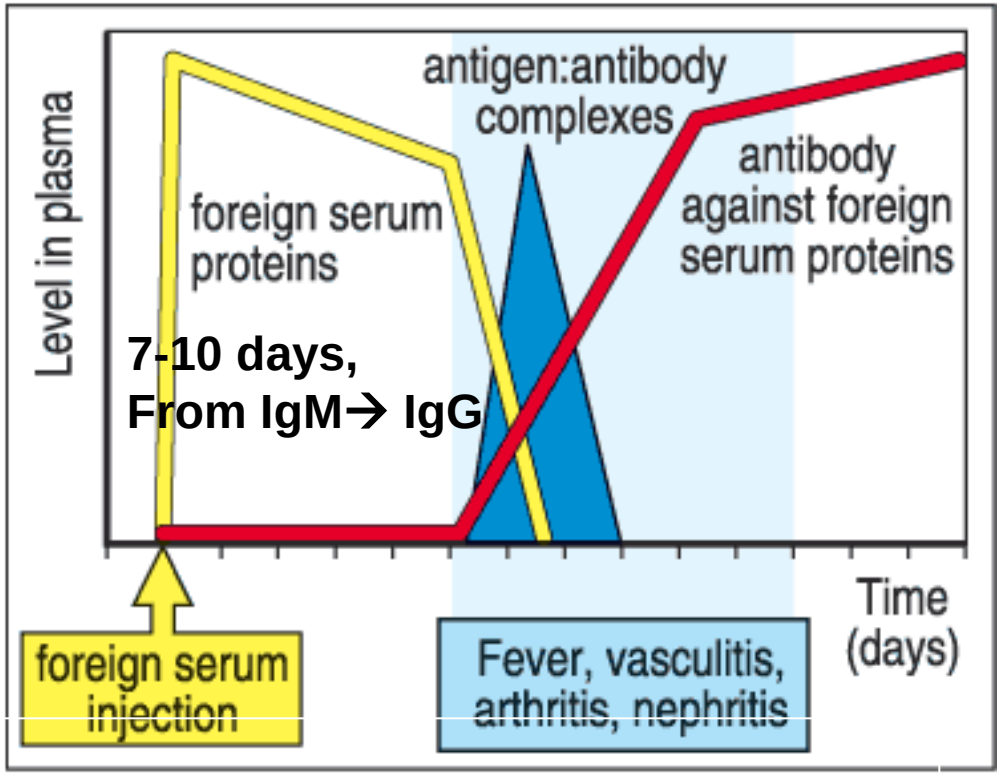
Figure 13-26 Immunobiology, 7ed. (© Garland Science 2008)

So, Type I, II, III are Immediate-type hypersensitivity

Serum sickness
(IgG immune complexes in the blood)

Fig 14-21

(Type III hypersensitivity – systematic type)



1. Symptoms are delayed while a primary immune response develops.

2. Symptoms arise from the **activation of complement (mainly)** and activation of other cells (e.g. mast cells).

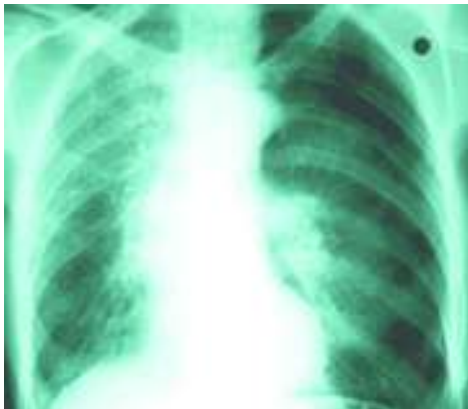
3. Symptoms include fever, rash, arthritis and glomerulonephritis.

4. Usually, serum sickness is self-limiting.

Type III Hypersensitivity (Systemic, IC deposition)

Farmer's lung

- Repeated exposure to high concentrations of inhaled hay dust or mold spores can lead to IgG antibody production
- Immune complexes can form in alveolar wall of lung
- Accumulation of fluid, protein, and cells can impair gas exchange

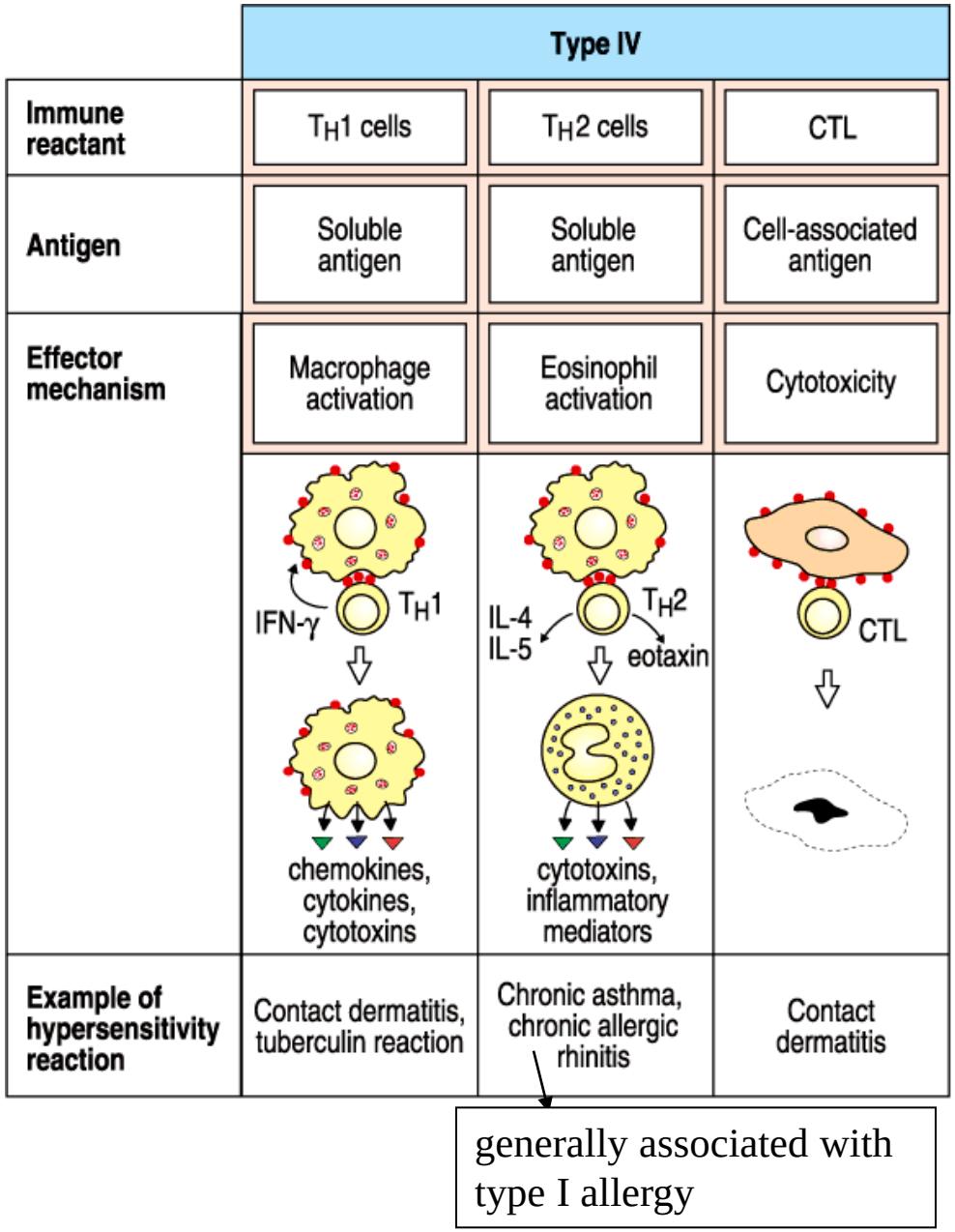


Duration of symptoms depends on the ability of the system to clear the Ag

- In serum sickness
  - the symptoms are self-limited due to clearance of the antigen
- Chronic 'serum sickness'
  - some chronic bacterial infection
    - e.g. sub-acute bacterial endocarditis (infection of heart valve)
  - Chronic viral infections (e.g. HBV)
  - Persistent presence of foreign Ags, but system fails to clear them out efficiently!!
- In chronic HBV infection, ICs can lead to a chronic vasculitis
  - To cause renal disease and nerve damage

Type IV Hypersensitivity
or
Delayed type hypersensitivity (DTH)

Type IV hypersensitivity (“delayed type hypersensitivity”)



Unlike the previous three hypersensitivity types (Ab-mediated), type IV hypersensitivity is mediated by **Ag-specific effector T cells**

Delayed-type hypersensitivity is mediated by antigen-specific T cells

Fig 14-22

Type IV hypersensitivity reactions are mediated by antigen-specific effector T cells		
Syndrome	**Antigen**	**Consequence**
(1) Delayed-type hypersensitivity Th1	Proteins: Insect venom Mycobacterial proteins (tuberculin, lepromin)	Local skin swelling: Erythema Induration Cellular infiltrate Dermatitis
(2) Contact hypersensitivity Th1, M, CTL	Haptens: Pentadecacatechol (poison ivy) DNFB Small metal ions: Nickel Chromate	Local epidermal reaction: Erythema Cellular infiltrate Vesicles Intraepidermal abscesses
Gluten-sensitiveenteropathy (celiac disease)	Gliadin	Villous atrophy in small bowel Malabsorption

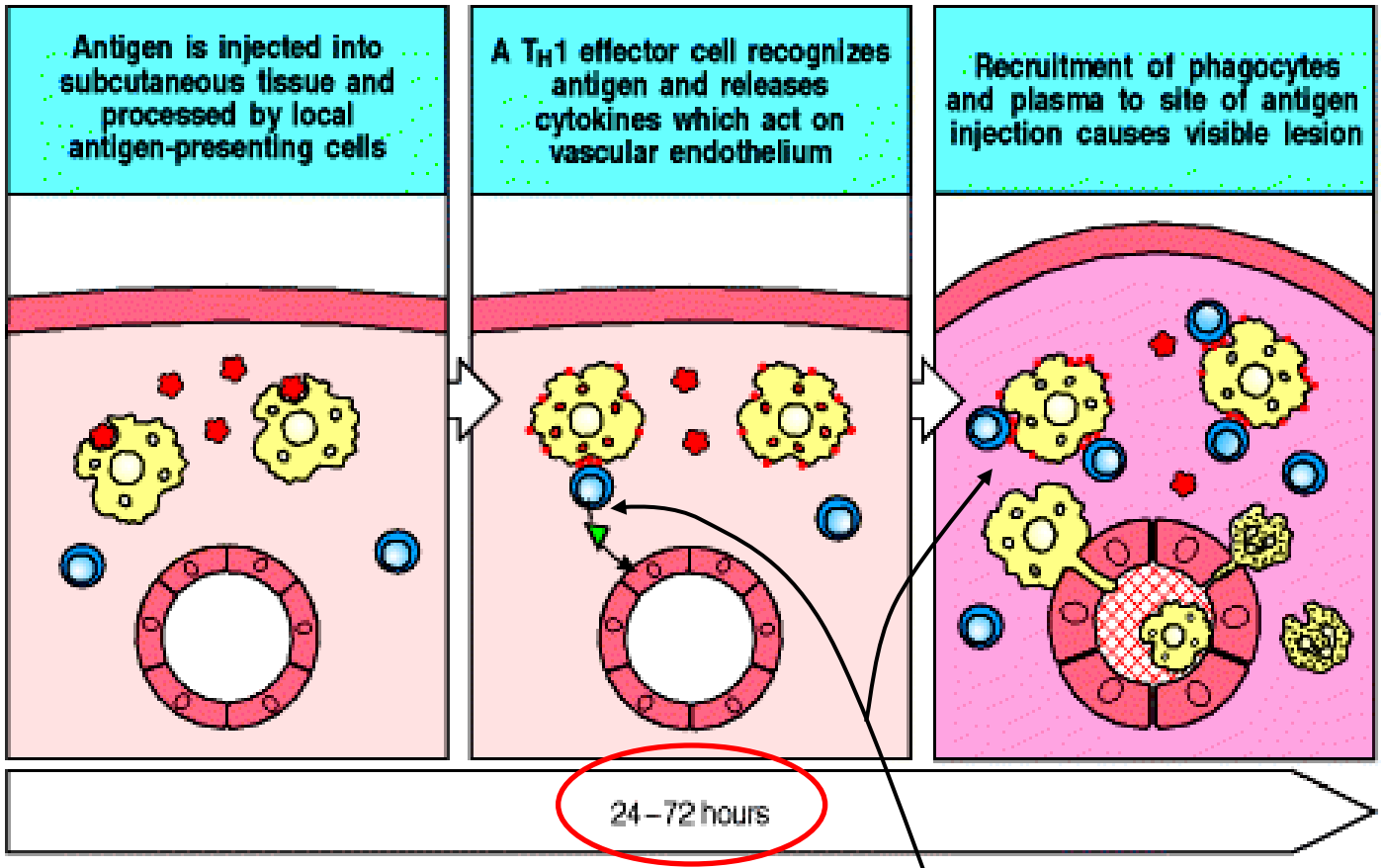
Figure 12-24 Immunobiology, 6/e. (© Garland Science 2005)

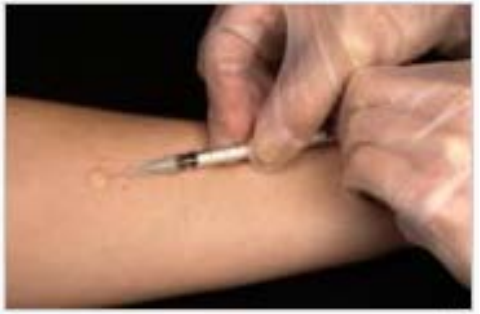
Tuberculin test

- Prototypic delayed type hypersensitivity (DTH) reaction
- Performed to determine whether an individual has been previously infected with *Mycobacterium tuberculosis*
- Small amount of tuberculin (mixture of peptides and carbohydrates derived from *M. tuberculosis*) injected subcutaneously
- Individuals previously exposed or immunized with BCG (attenuated form of *M. tuberculosis*) develop local Th1-mediated inflammatory reaction in 24-72 hrs

Delayed type hypersensitivity (DTH)

Fig 14-23





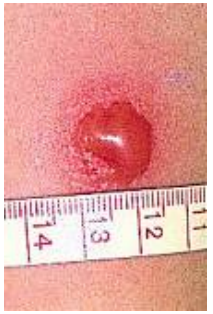
The Mantoux skin test consists of an intradermal injection of exactly one tenth of a milliliter (mL) of PPD tuberculin.

The size of induration is measured 48-72 hours later.

T_H1 from a previous illness or immunization (memory)

Mantoux test (USA); Heaf test (UK)

DTH animation



Chemokines and cytokines released by T_H1 cells in DTH

Fig 14-24

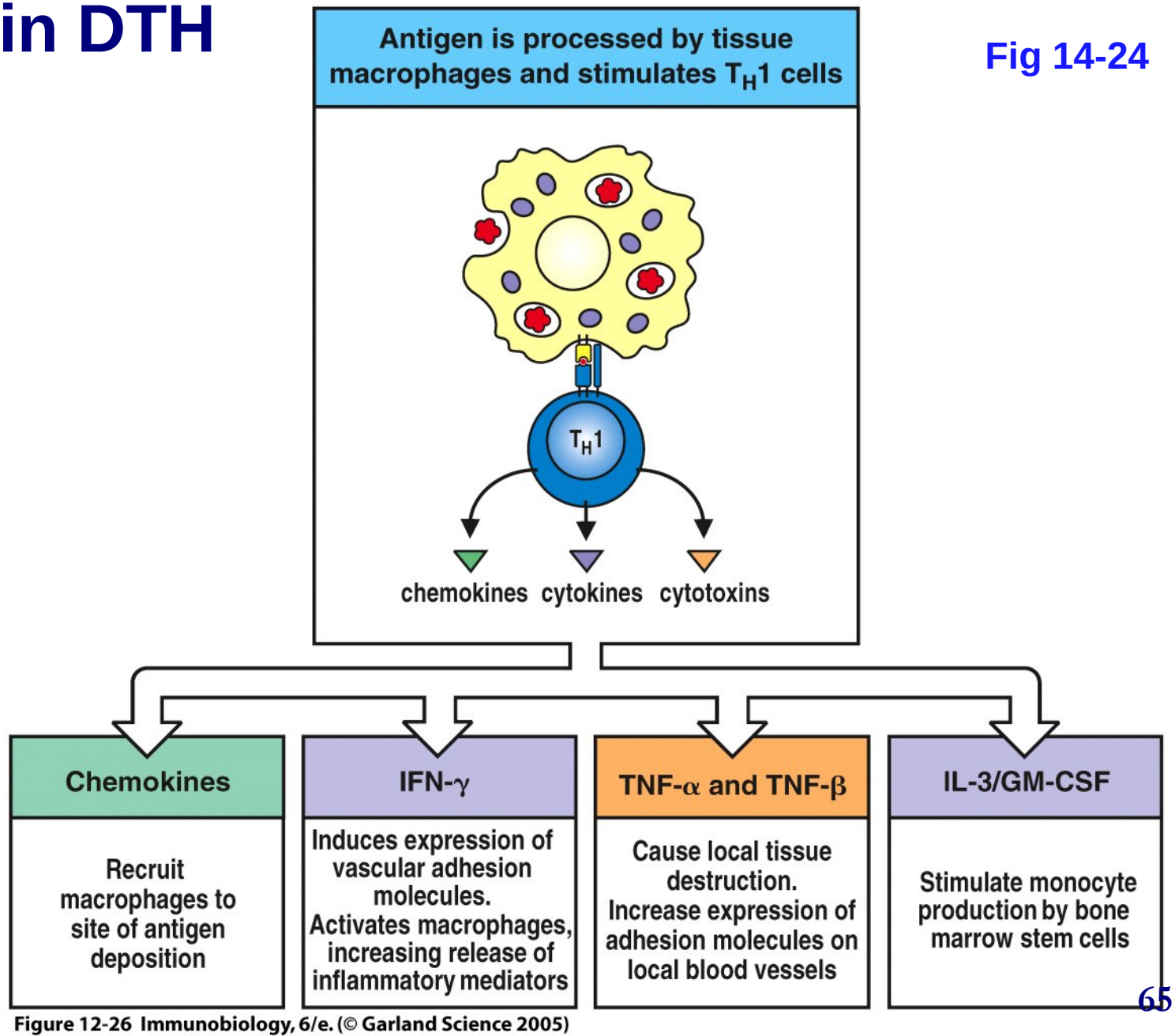
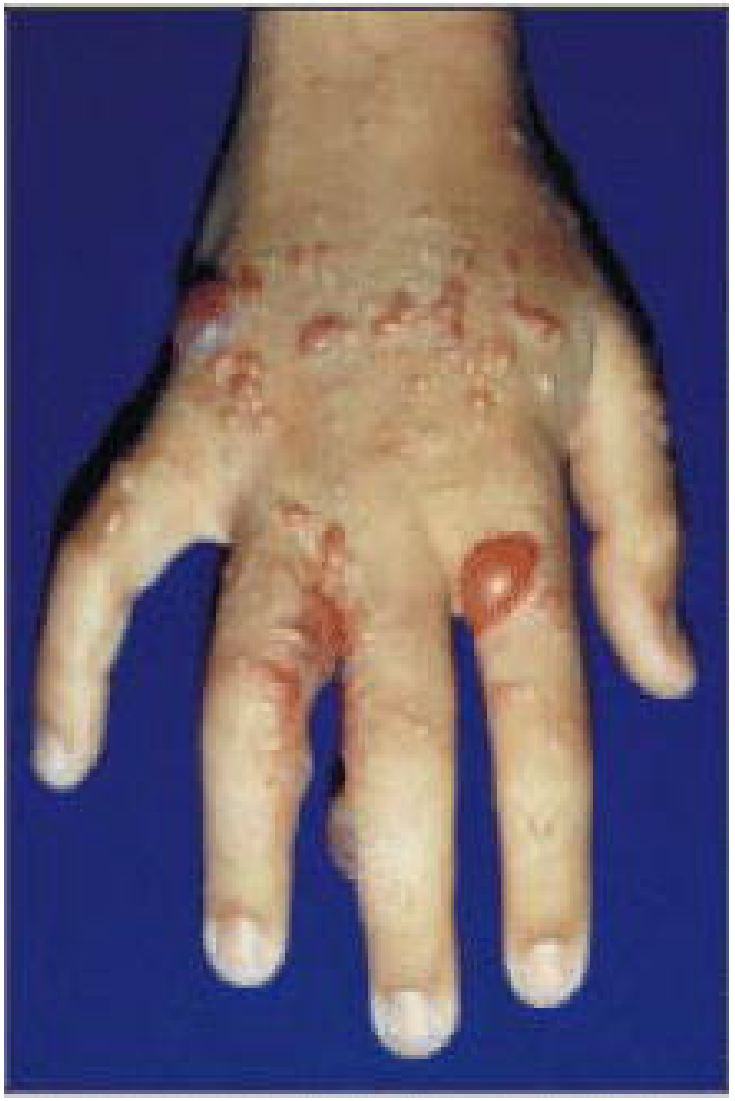


Figure 12-26 Immunobiology, 6/e. (© Garland Science 2005)

Contact sensitivity

- Reactions triggered by self proteins modified by small organic molecules or metal ions
- Damage mediated by
  - T_H1 cells and macrophages they activate; or
  - direct action of antigen-specific cytotoxic $CD8^+$ T cells
- Require initial sensitizing exposure and re-exposure
- Most frequent reaction is poison ivy (毒長春藤)

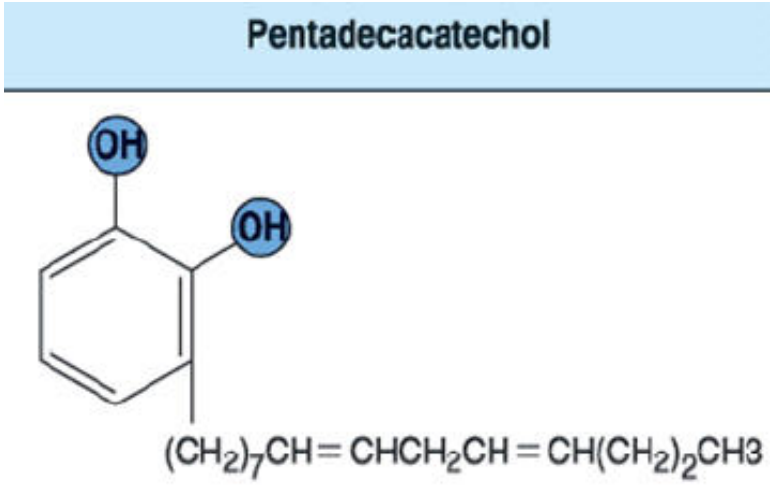
Fig 14-26



Type IV Hypersensitivity (poison ivy contact)

Poison ivy

- T cell response to pentadecacatechol in the leaf
  - small, highly reactive chemical
- Penetrates outer layers of skin and binds to proteins on the surface of skin cells
  - Ag can persist in the skin for days
- First contact the individual becomes sensitized
- Upon second exposure, DTH manifests!!



Chemical formula of causative agent from poison ivy

Mechanism of poison ivy contact sensitivity

Fig 14-25

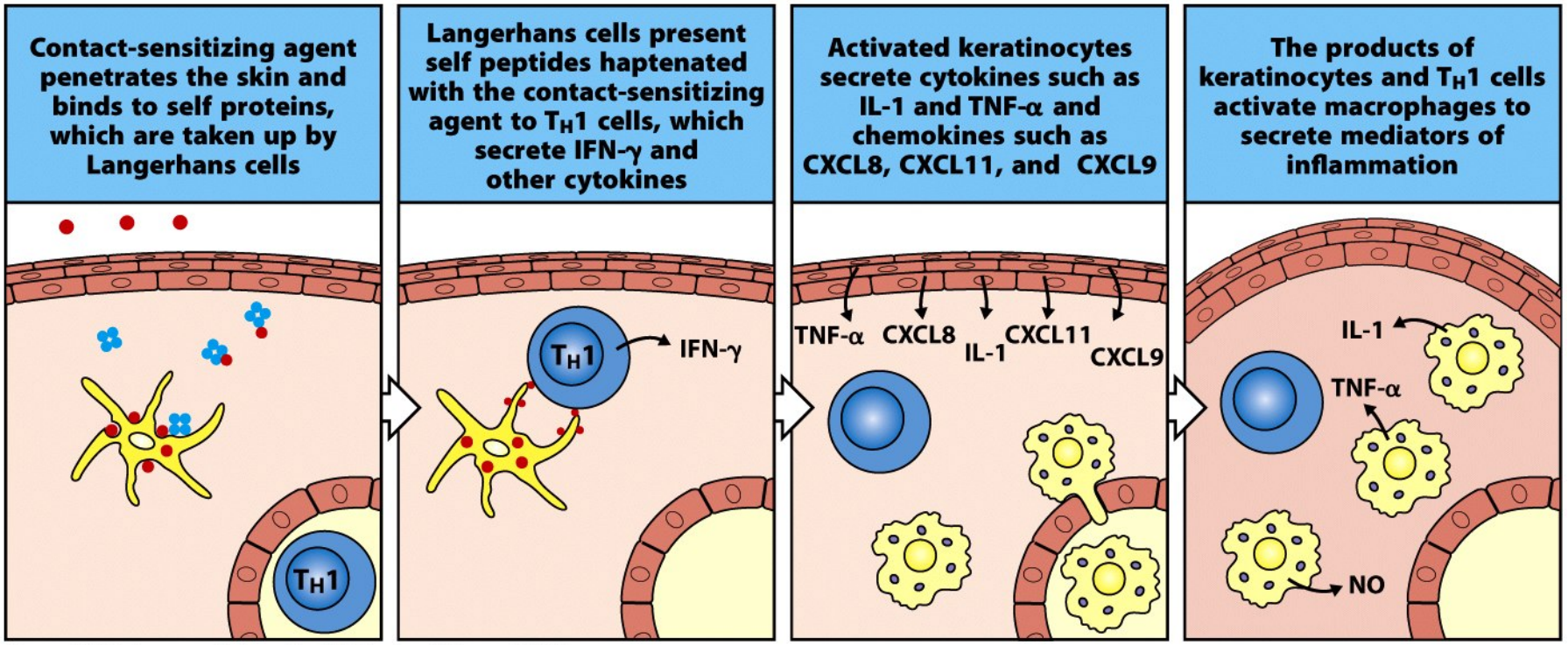
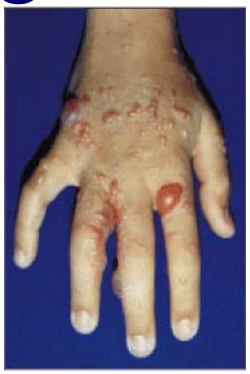


Figure 13-31 Immunobiology, 7ed. (© Garland Science 2008)

A contact-sensitizing agent is usually a small molecule that can:

1. penetrates the skin, and
2. binds to self-proteins, making them "look" like foreign; then
3. be recognized by underlying APCs (e.g. Langerhans cells)

Contact sensitivity – immune mechanisms leading to tissue damage



- Tissue damage mediated by
  - **cytokines** and **direct cell-cell interactions**
- Enzymes released by activated Th1 cells degrade the proteins of the extracellular matrix that hold the skin together leading to blistering
- Lipid-like haptens can diffuse through the plasma membrane of cells into the cytosol and bind to intracellular proteins eliciting a CD8+ T cell response
- CD8+ T cells can directly lyse target cells

Treatment for contact sensitivity

- Corticosteroids (steroids) 腎上腺皮質醣類固醇
  - Inhibit the inflammatory response by inhibiting production of cytokines and chemokines

- Sensitivity is life-long once acquired and contact should be avoided

美研究：過敏的人較不易得癌症

中廣新聞網 更新日期：2010/05/24 14:05

美國一項研究發現，有過敏症狀的人比較不容易得癌症。

德州科技大學研究發現，有氣喘症狀的婦女得卵巢癌的比例比一般婦女少三成。對空氣裡懸浮物質過敏的孩子得血癌的比例則比一般孩子少四成。

哈佛大學的船就也發現，氣喘、濕疹、花粉症等過敏症狀的患者比較不會得腦瘤。德州科大傳染病學家穆拉說，過敏可以啟動體內免疫系統，增強對疾病的抵抗力，所以，過敏的人反倒不容易得癌症。

Summary

- Hypersensitivity can be classified into 4 categories.
- Most allergies involve the production of IgE antibody against common environmental allergens.
- IgG and antigen-specific effector T cells also contribute to hypersensitivity to other antigens.

End of Chapter