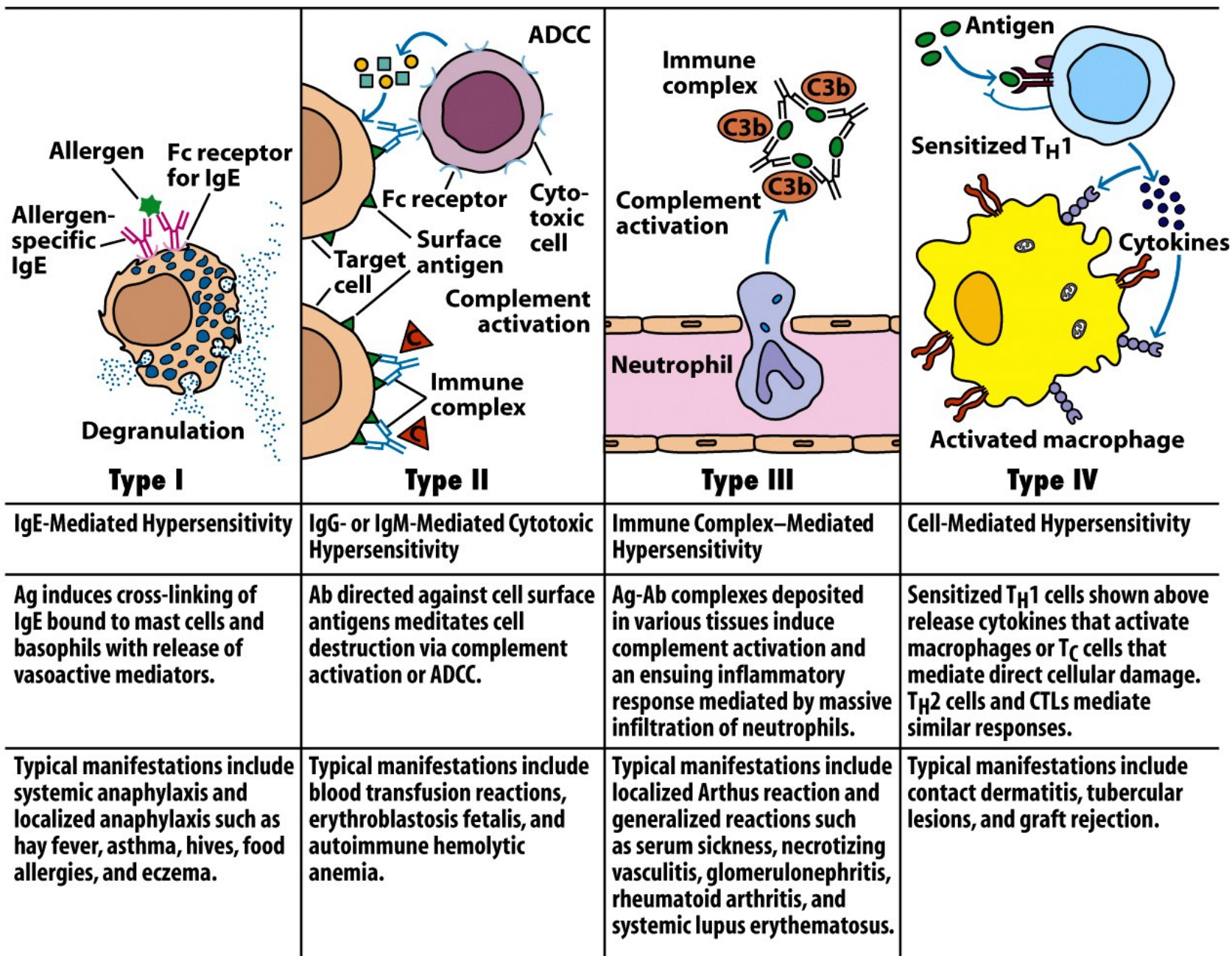


# Hypersensitivity Reactions (Types I, II, III, IV)

April 15, 2009

Inflammatory response - local, eliminates antigen without extensively damaging the host's tissue.

*Hypersensitivity* - immune & inflammatory responses that are harmful to the host (von Pirquet, 1906)



**Figure 15-1**  
*Kuby IMMUNOLOGY, Sixth Edition*  
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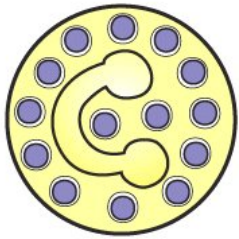
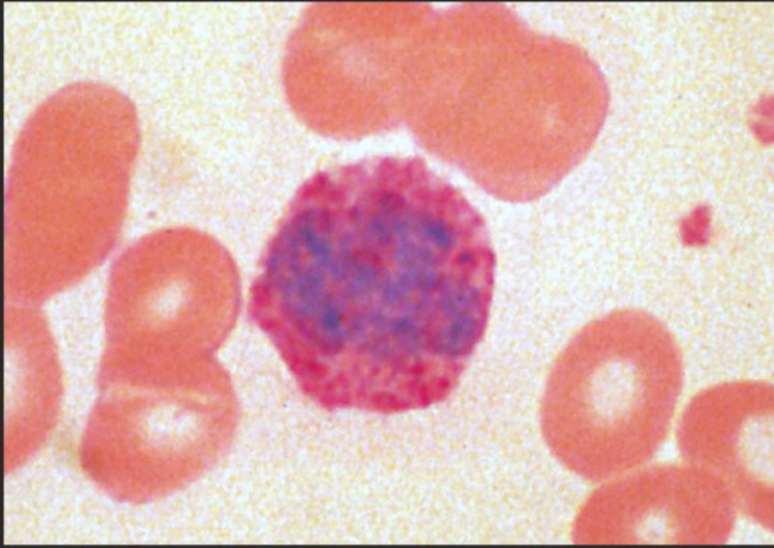
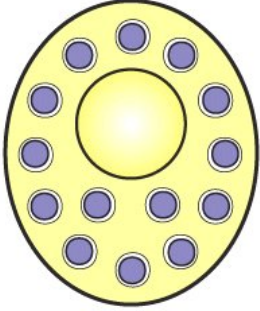
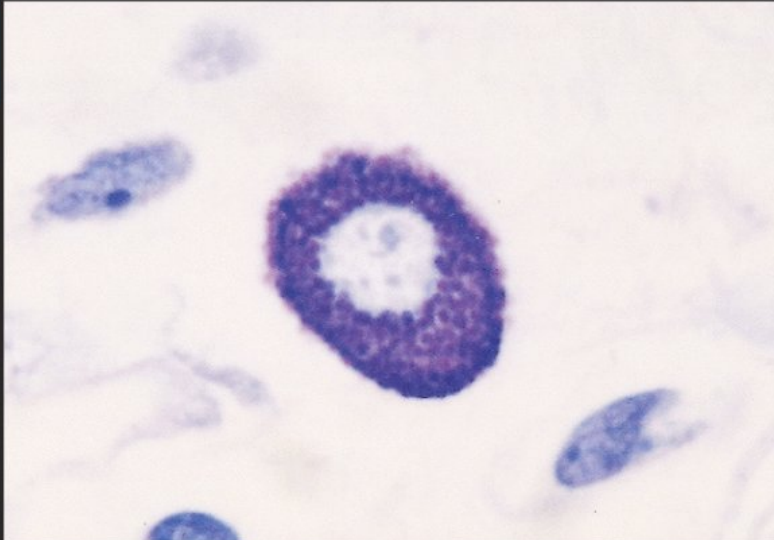
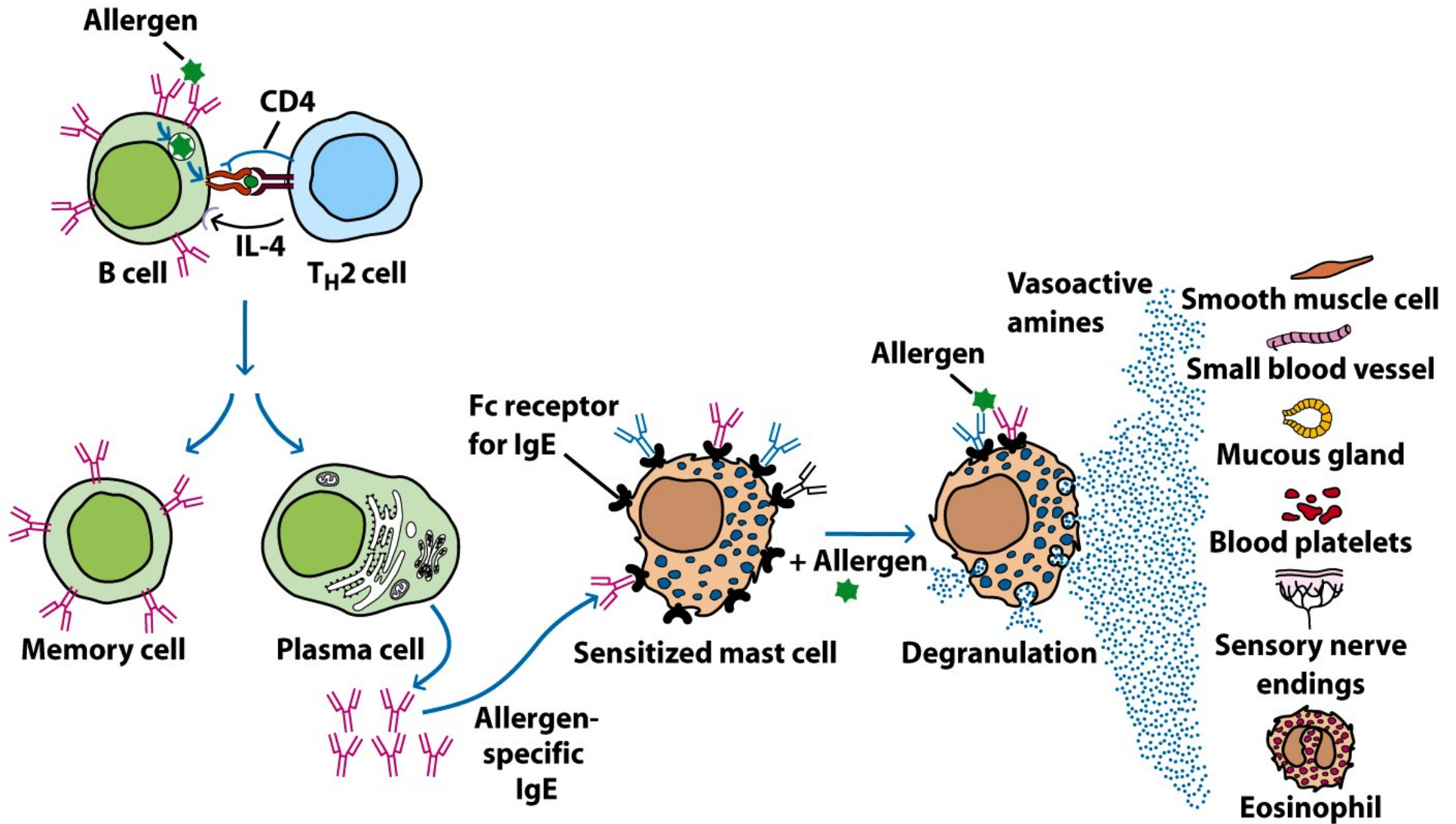
Cell - Type I		Activated function
<p><b>Basophil</b></p> 		<p>Produce effector molecules</p> <p>Capable of ingesting foreign Particles</p> <p>Association with parasite infection</p>
<p><b>Mast cell</b></p> 		<p>Release of granules containing histamine and other active agents</p>

Figure 1-4 part 3 of 3 Immunobiology, 6/e. (© Garland Science 2005)

<b>Characteristic</b>	<b>Mast cells</b>
Origin of precursor	CD34 <sup>+</sup> hematopoietic progenitor cells
Major site of maturation	Connective tissue
Cells in circulation	No
Mature cells recruited into tissues from circulation	No
Mature cells residing in connective tissue	Yes
Proliferative ability of mature cells	Yes
Life span	Weeks to months
Major development factor (cytokine)	Stem cell factor
Expression of FcεRI	High levels
Major granule contents	Histamine, heparin and/or chondroitin sulfate, proteases

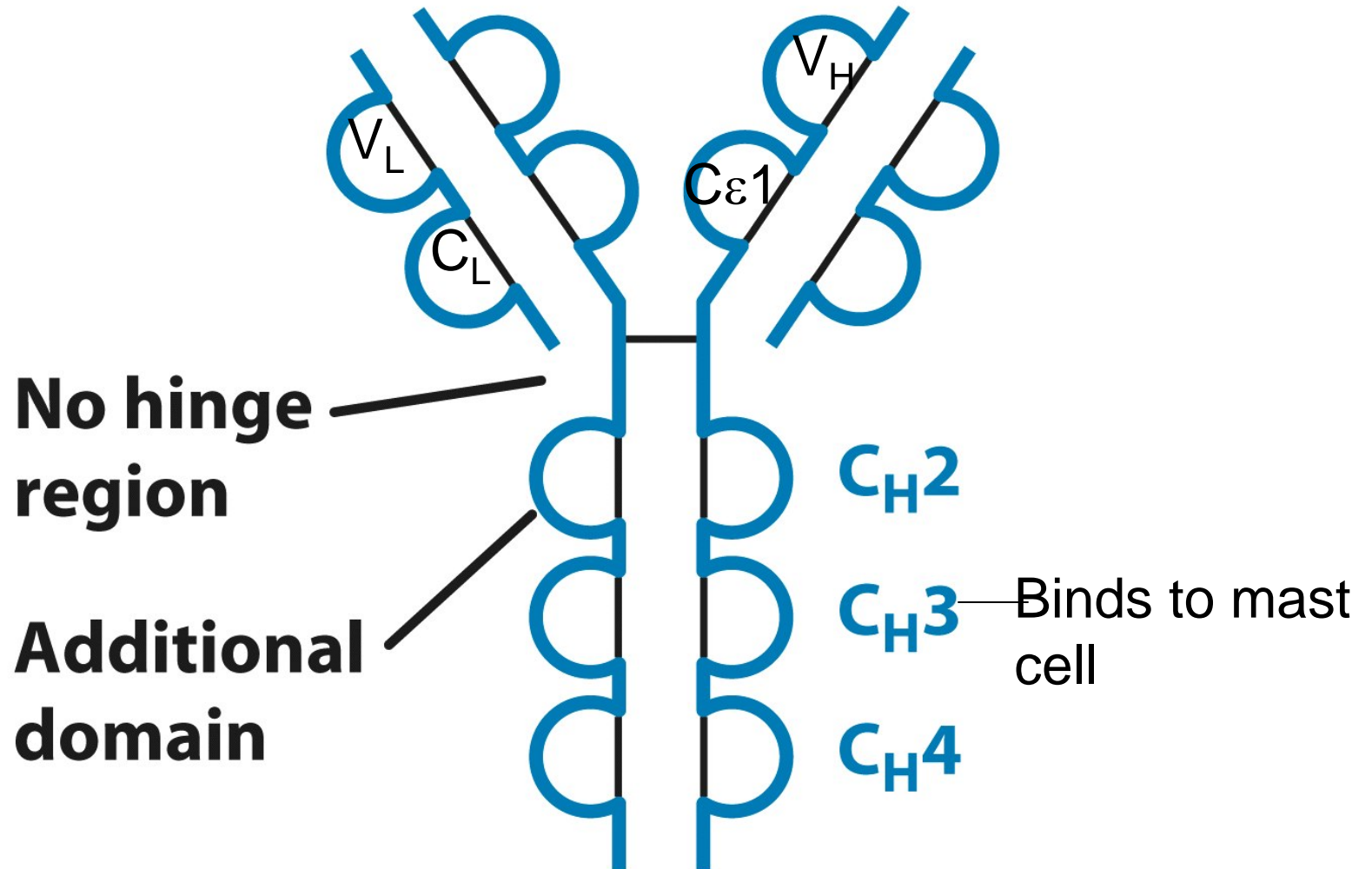
Modified from  
Abbas, Lichtman &  
Pillai, Table 19-1

# Type I hypersensitivity response



**Figure 15-2**  
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# IgE



Normal serum level = 0.0003 mg/ml

# FcεRI: High-affinity IgE receptor

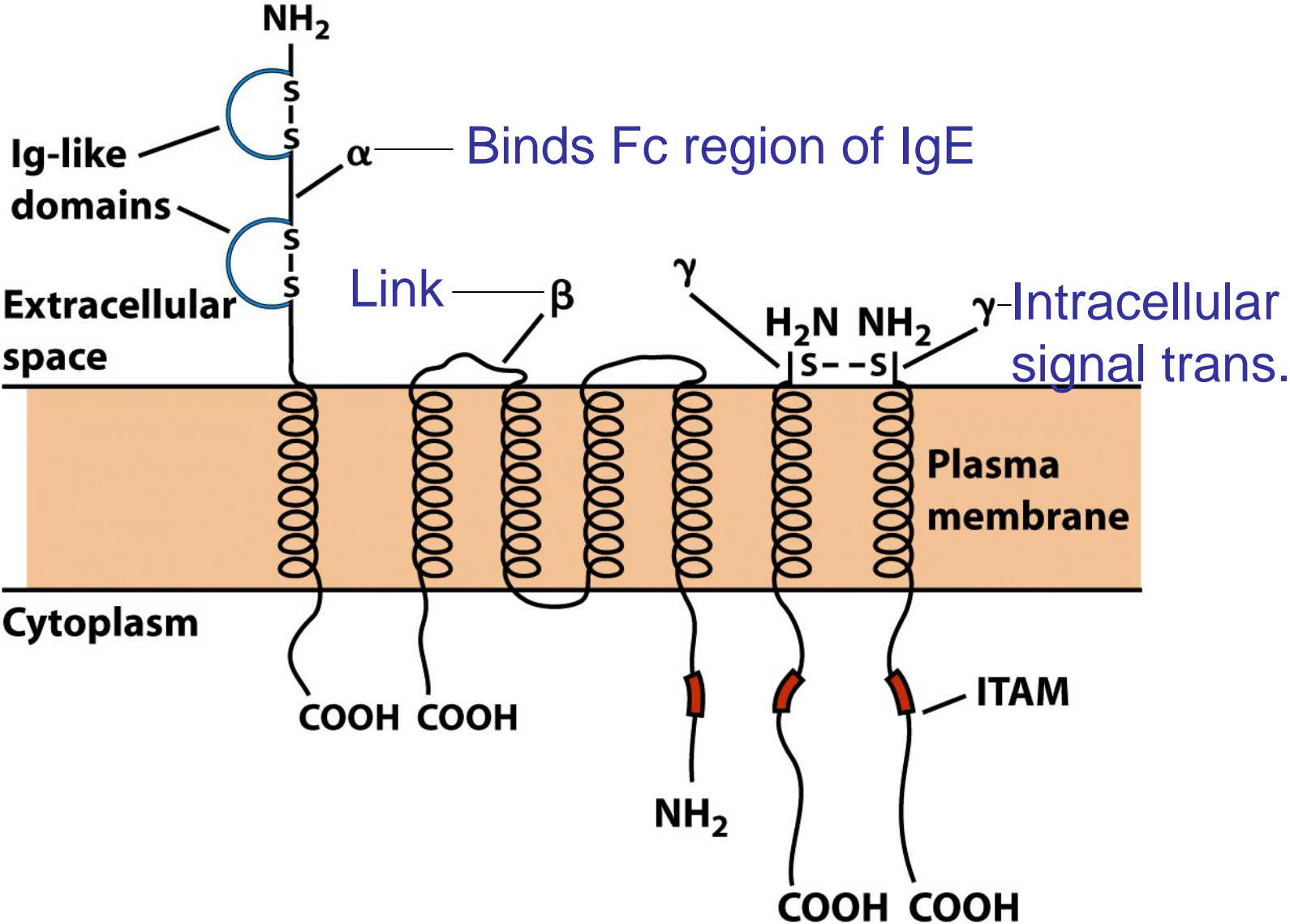


Figure 15-4a  
 Kuby IMMUNOLOGY, Sixth Edition  
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# Initiation of degranulation

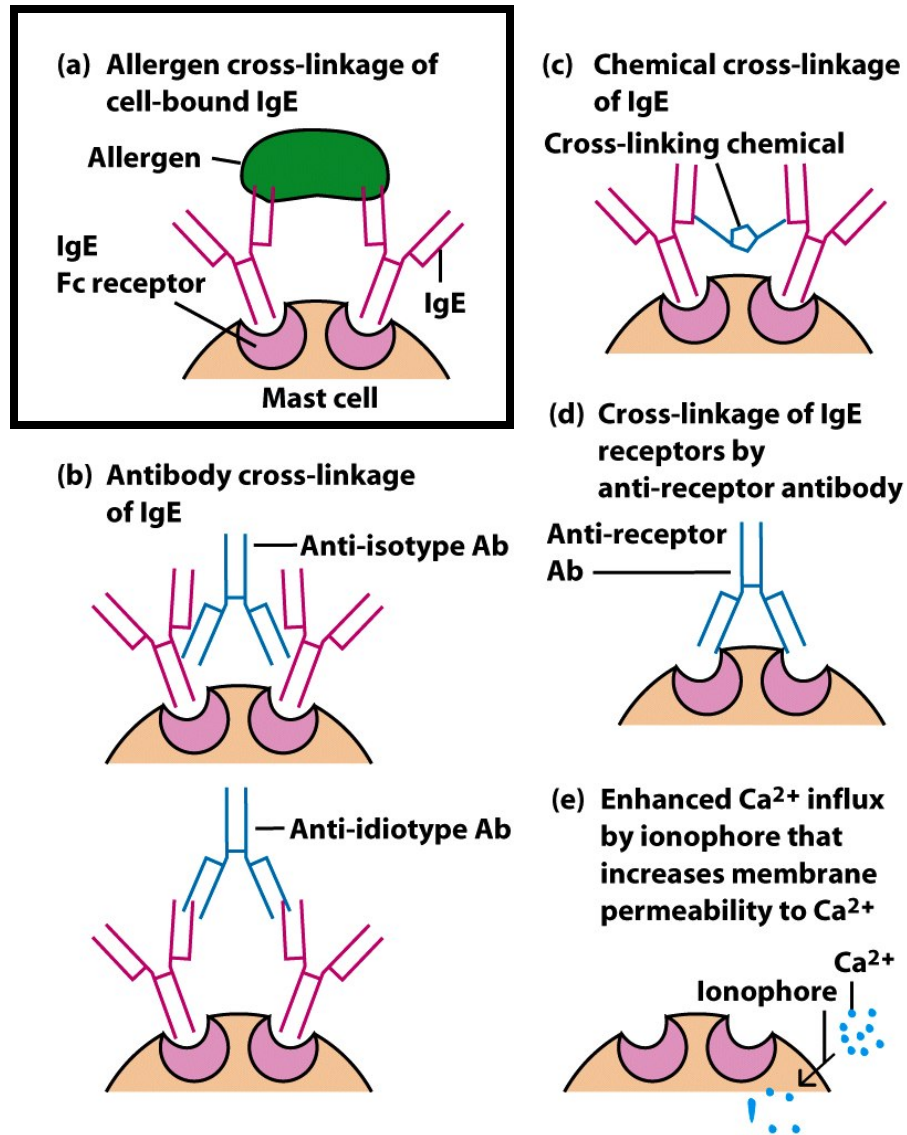
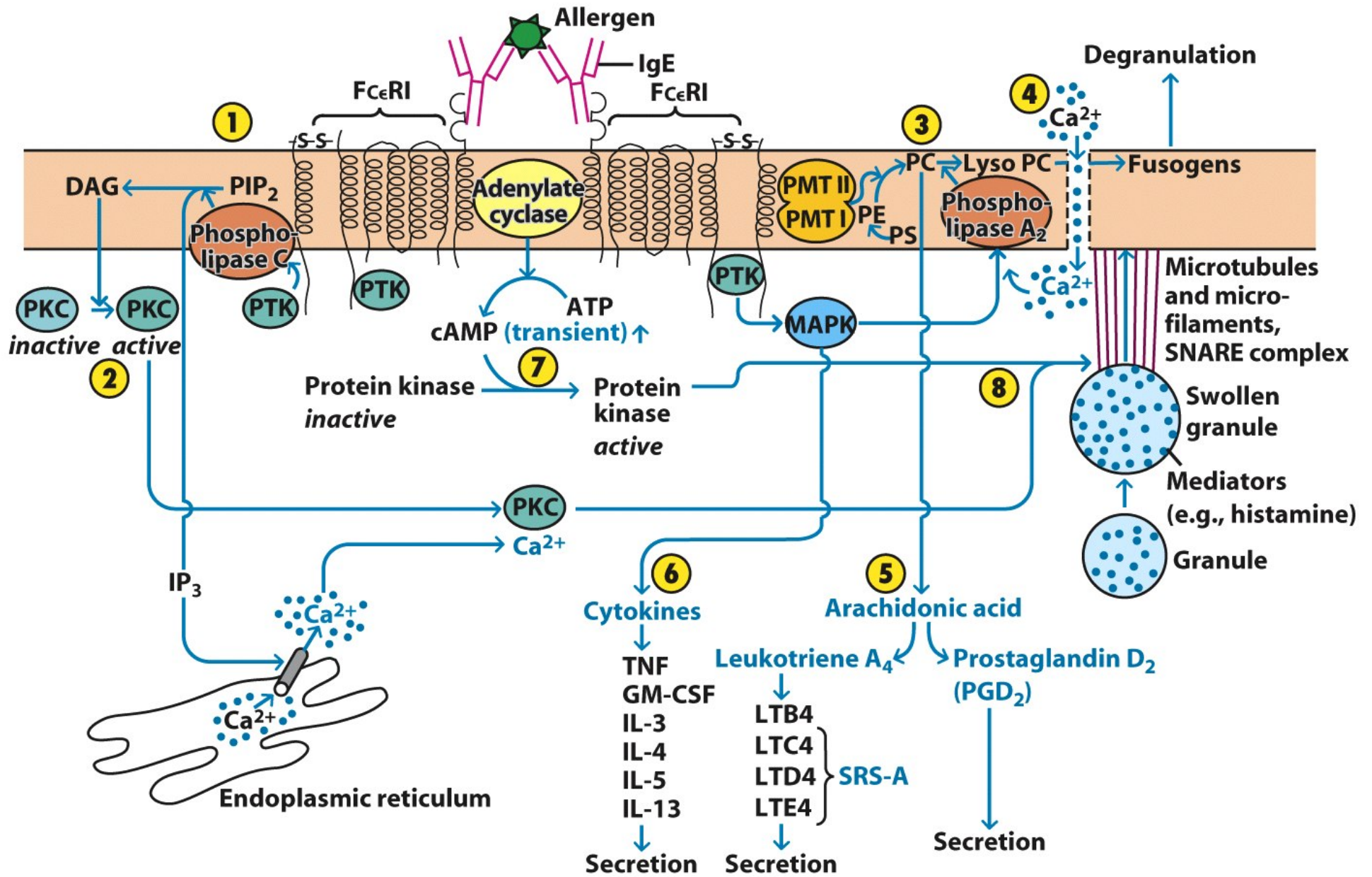
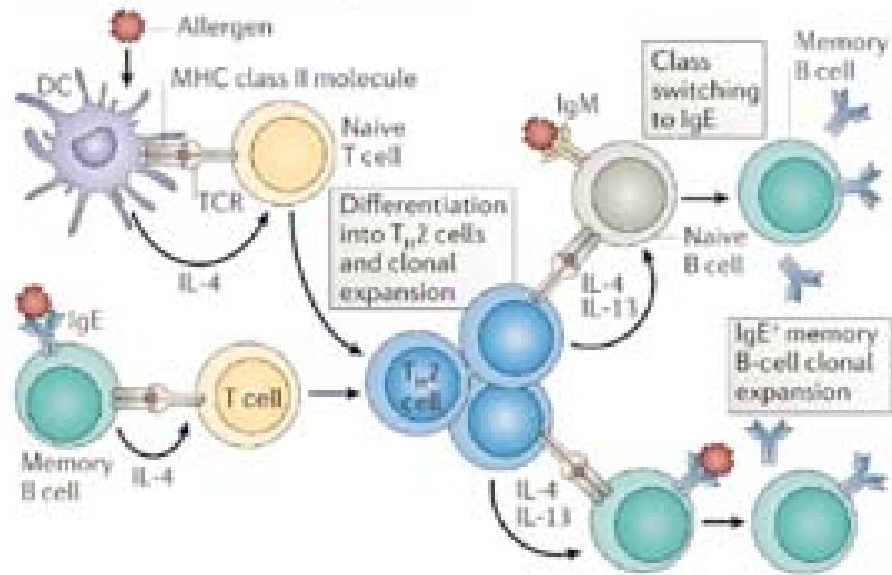


Figure 15-5  
Kuby IMMUNOLOGY, Sixth Edition  
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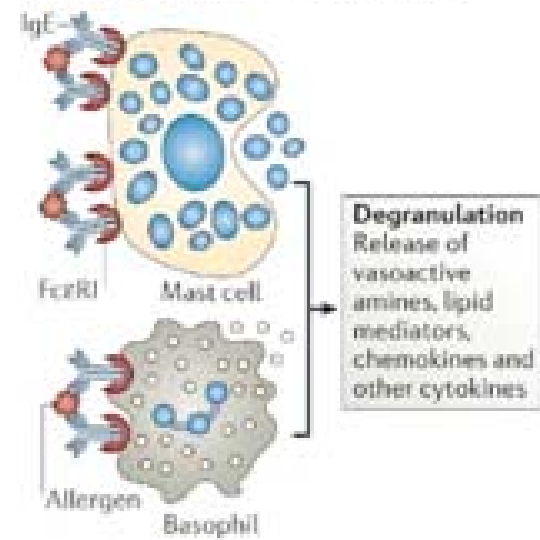


**Figure 15-6**  
 Kuby IMMUNOLOGY, Sixth Edition  
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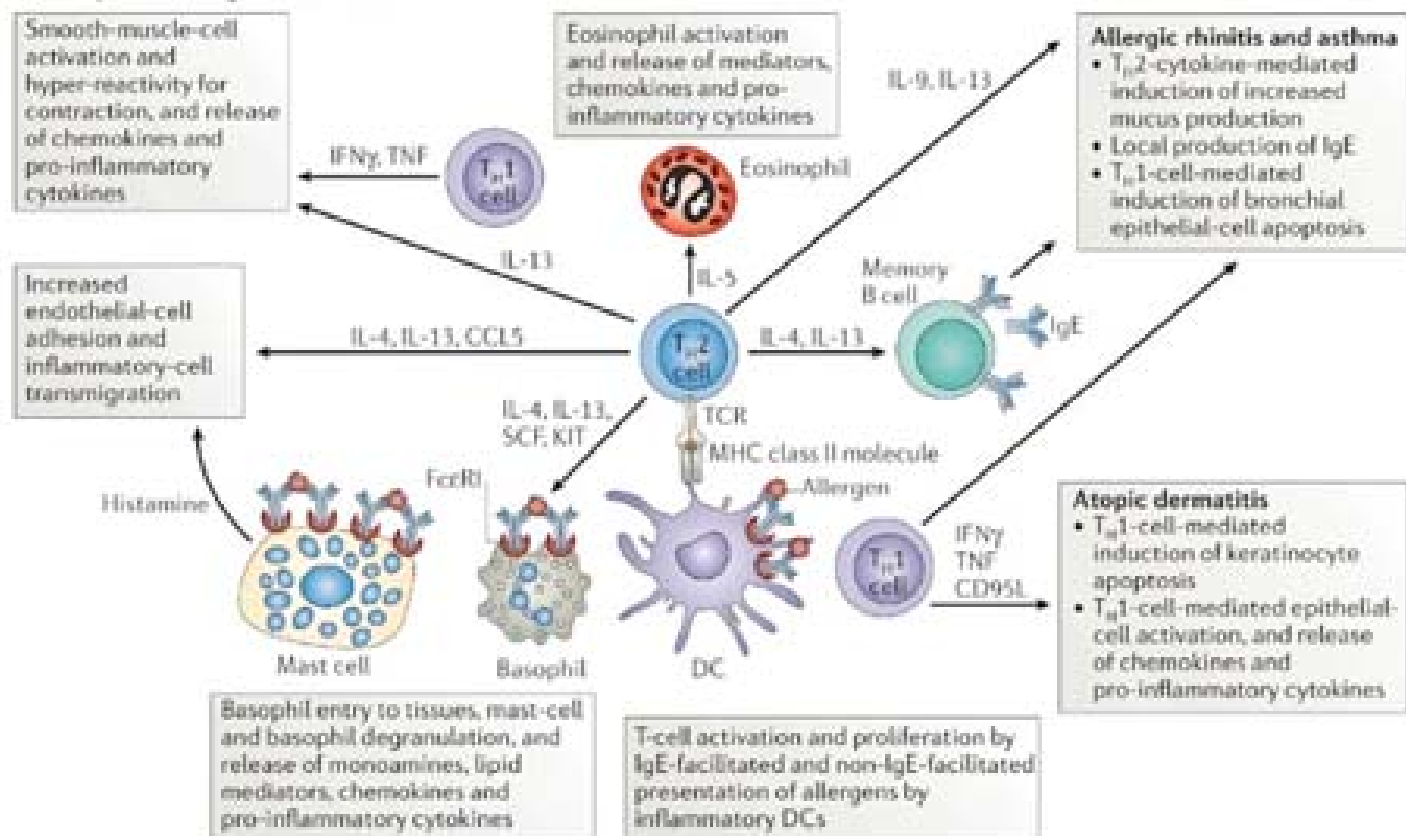
**a Sensitization and memory induction**



**b Immediate phase: type 1 reaction**



**c Late phase: allergic inflammation**



Larche et al. Nat. Rev. Immunol 6:761-771, 2006

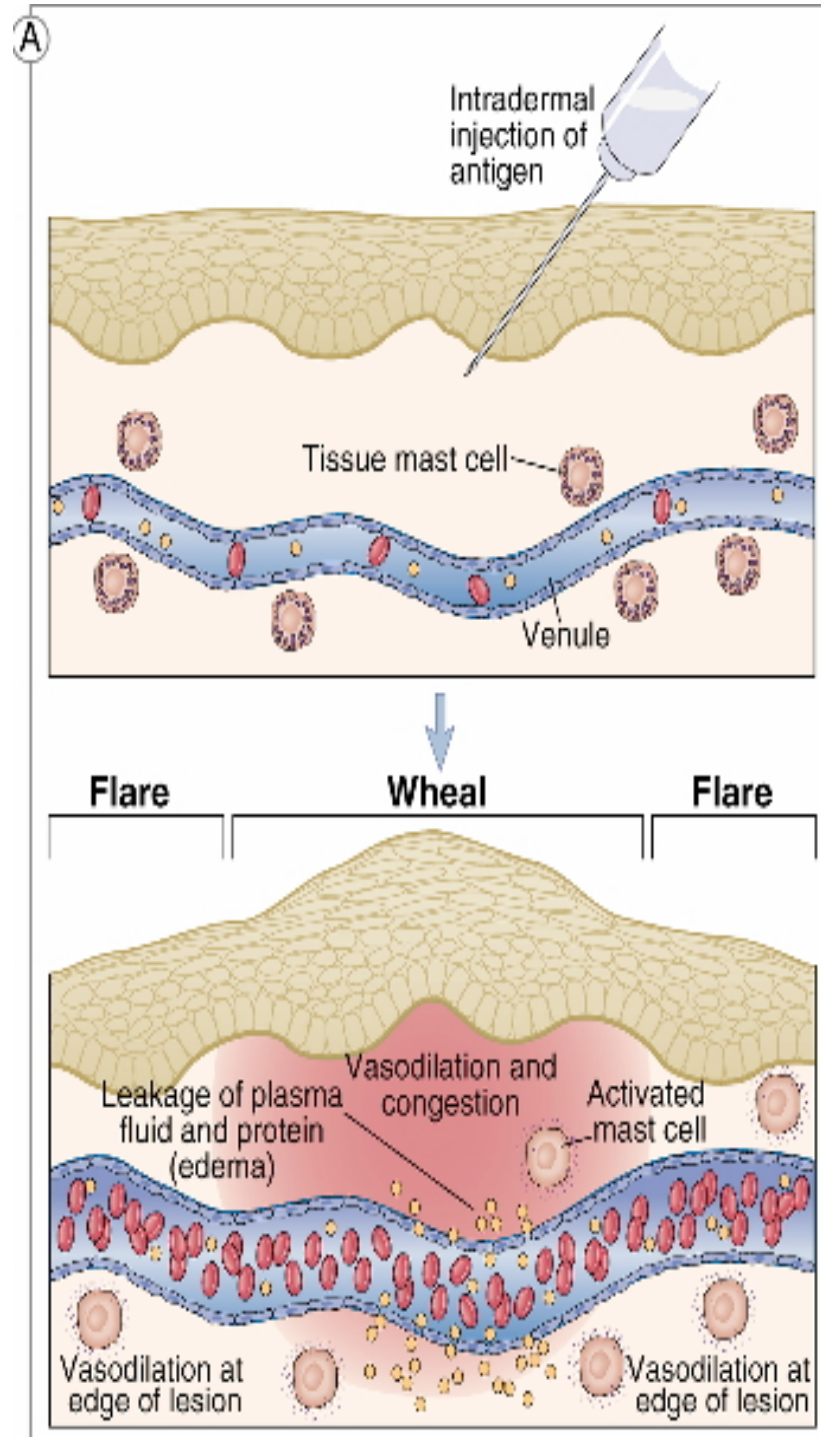
Copyright © 2006 Nature Publishing Group  
Nature Reviews | Immunology

<b>TABLE 15-3 Principal mediators involved in type I hypersensitivity</b>	
<b>Mediator</b>	<b>Effects</b>
<b>PRIMARY</b>	
Histamine, heparin	Increased vascular permeability; smooth muscle contraction
Serotonin (rodents)	Increased vascular permeability; smooth muscle contraction
Eosinophil chemotactic factor (ECF-A)	Eosinophil chemotaxis
Neutrophil chemotactic factor (NCF-A)	Neutrophil chemotaxis
Proteases (tryptase, chymase)	Bronchial mucus secretion; degradation of blood vessel basement membrane; generation of complement split products
<b>SECONDARY</b>	
Platelet-activating factor	Platelet aggregation and degranulation; contraction of pulmonary smooth muscles
Leukotrienes (slow reactive substance of anaphylaxis, SRS-A)	Increased vascular permeability; contraction of pulmonary smooth muscles
Prostaglandins	Vasodilation; contraction of pulmonary smooth muscles; platelet aggregation
Bradykinin	Increased vascular permeability; smooth muscle contraction
<b>Cytokines</b>	
IL-1 and TNF- $\alpha$	Systemic anaphylaxis; increased expression of CAMs on venular endothelial cells
IL-4 and IL-13	Increased IgE production
IL-3, IL-5, IL-6, IL-10, TGF- $\beta$ , and GM-CSF	Various effects (see Table 12-1)

Table 15-3

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Abbas, Lichtman & Pillai, 19-8



**Figure 15-10**  
*Kuby IMMUNOLOGY, Sixth Edition*  
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# Factors in the development of allergic diseases

- Geographical distribution
- Environmental factors - climate, air pollution, socioeconomic status
- Genetic risk factors
- “Hygiene hypothesis”
  - Older siblings, day care
  - Exposure to certain foods, farm animals
  - Exposure to antibiotics during infancy
- Cytokine milieu



**TABLE 15-1****Common allergens associated with type I hypersensitivity****Proteins**

**Foreign serum**  
**Vaccines**

**Plant pollens**

**Rye grass**  
**Ragweed**  
**Timothy grass**  
**Birch trees**

**Drugs**

**Penicillin**  
**Sulfonamides**  
**Local anesthetics**  
**Salicylates**

**Foods**

**Nuts**  
**Seafood**  
**Eggs**  
**Peas, beans**  
**Milk**

**Insect products**

**Bee venom**  
**Wasp venom**  
**Ant venom**  
**Cockroach calyx**  
**Dust mites**

**Mold spores**

**Animal hair and dander**  
**Latex**

Table 15-1

*Kuby IMMUNOLOGY, Sixth Edition*

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# IgE-mediated diseases in humans

- Systemic (anaphylactic shock)
- Asthma
  - Classification by immunopathological phenotype can be used to determine management strategies
- Hay fever (allergic rhinitis)
- Allergic conjunctivitis
- Skin reactions
- Food allergies

# Diseases in Humans (I)

- **Systemic anaphylaxis** - potentially fatal - due to food ingestion (eggs, shellfish, peanuts, drug reactions) and insect stings - characterized by airway obstruction and a sudden fall in blood pressure.

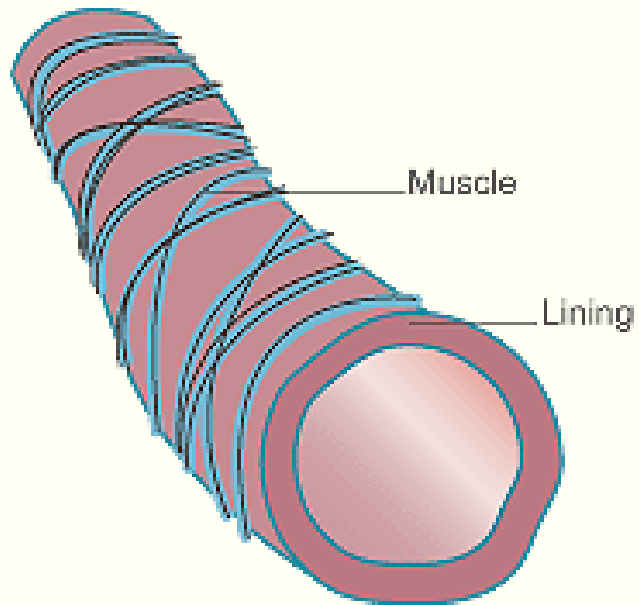
# Diseases in Humans (II)

## **Bronchial asthma**

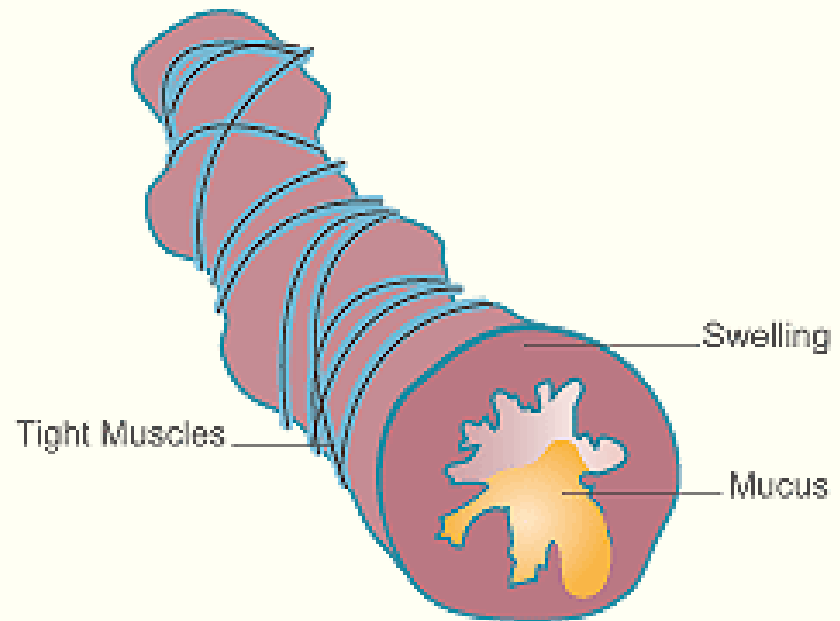
- Chronic inflammation
  - Intermittent & reversible airway obstruction
  - Chronic bronchial inflammation with eosinophil infiltration
  - Bronchial smooth muscle hypertrophy and hyperreactivity
- Dominated by the presence of eosinophils, CD4+ T lymphocytes (Th2), and a large proportion of CD4+ NKT cells expressing an invariant T cell receptor that recognizes glycolipid antigens.

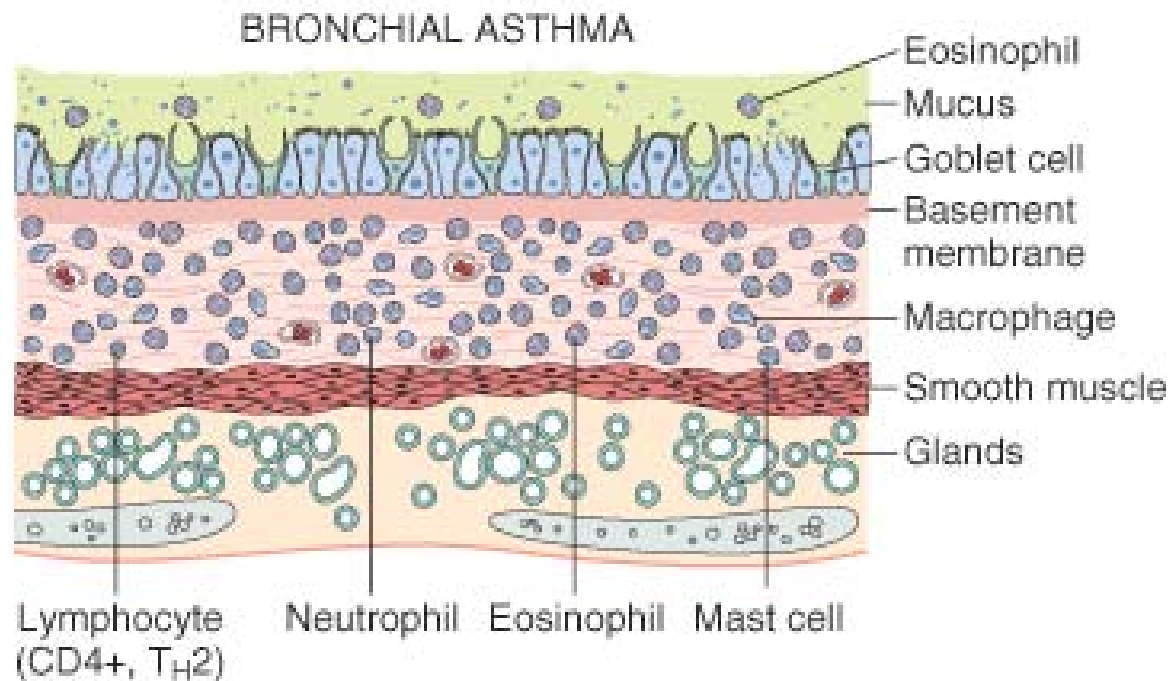
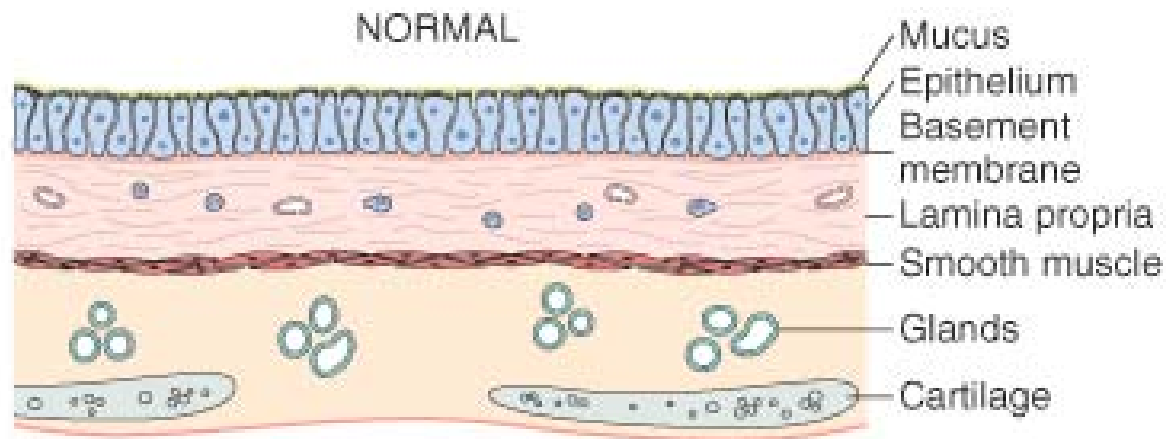
## Asthma

Normal Airway

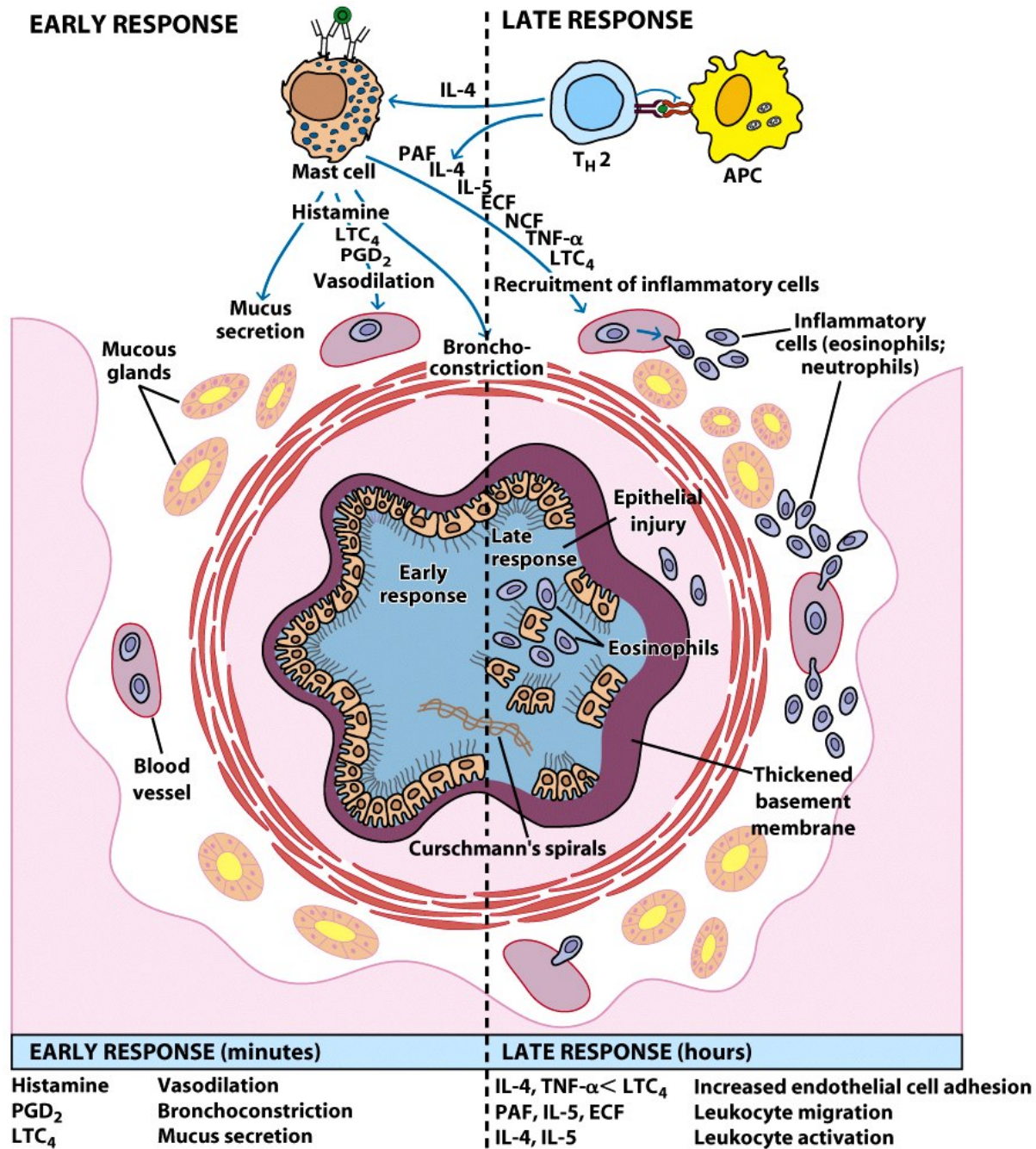


Airway in Person with Asthma



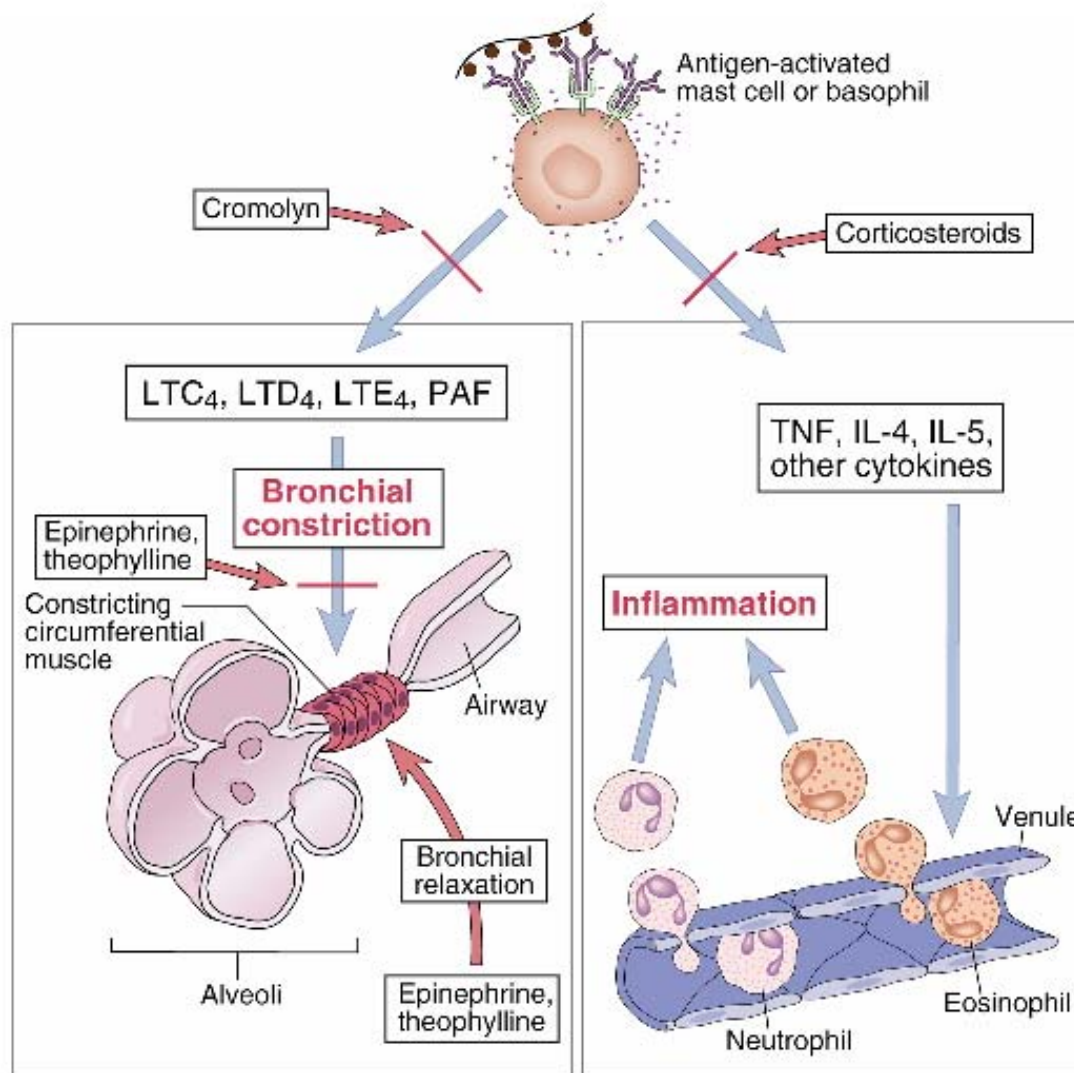


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**Figure 15-8**  
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# Mediators and treatment of asthma



Anti-IL-13 -  
reduce mucus  
overproduction  
and eosinophilia

Anti-chemokine  
receptors:  
CCR3, CCR4,  
CCR8 on Th2  
cells.

Anti-RANTES or  
-eotaxin abs to  
prevent  
recruitment of  
eosinophils



**TABLE 15-4****Mechanism of action of some drugs used to treat type I hypersensitivity**

<b>Drug</b>	<b>Action</b>
<b>Antihistamines</b>	<b>Block H<sub>1</sub> and H<sub>2</sub> receptors on target cells</b>
<b>Cromolyn sodium</b>	<b>Blocks Ca<sup>2+</sup> influx into mast cells</b>
<b>Theophylline</b>	<b>Prolongs high cAMP levels in mast cells by inhibiting phosphodiesterase, which cleaves cAMP to 5'-AMP*</b>
<b>Epinephrine (adrenaline)</b>	<b>Stimulates cAMP production by binding to β-adrenergic receptors on mast cells*</b>
<b>Cortisone</b>	<b>Reduces histamine levels by blocking conversion of histidine to histamine and stimulates mast-cell production of cAMP*</b>

**\* Although cAMP rises transiently during mast-cell activation, degranulation is prevented if cAMP levels remain high.**

# Diseases in Humans (III)

- **Upper respiratory tract**
  - Allergic rhinitis (hay fever) - reactions to plant pollen or house dust mites in the upper respiratory tract - mucosal edema, mucus secretion, coughing, sneezing, difficult in breathing - also associated with allergic conjunctivitis. Some evidence that asthma can develop in patients who have allergic rhinitis. Treatment - antihistamines
- **Gastrointestinal tract**
  - Result from release of mediators from intestinal mucosal and submucosal mast cells following sensitization through the g.i. route of exposure - enhanced peristalsis, increased fluid secretion from intestinal cells, vomiting, and diarrhea. This is not the same as an anaphylactic response. Reactions usually begin in childhood - often remit in late childhood or in adulthood.
- **Skin**
  - Urticaria (wheal and flare) - mediated by histamine.
  - Eczema - late-phase reaction to allergen in the skin - inflammation - can be treated with steroids.

# Urticaria



Copyright Slice of Life & Suzanne S. Stensaas - obtained from PEIR, Dept. of Pathology, UAB

# Atopic Eczema



Copyright Slice of Life & Suzanne S. Stensaas - obtained from PEIR, Dept. of Pathology, UAB

# Radioallergosorbent Test (RAST)

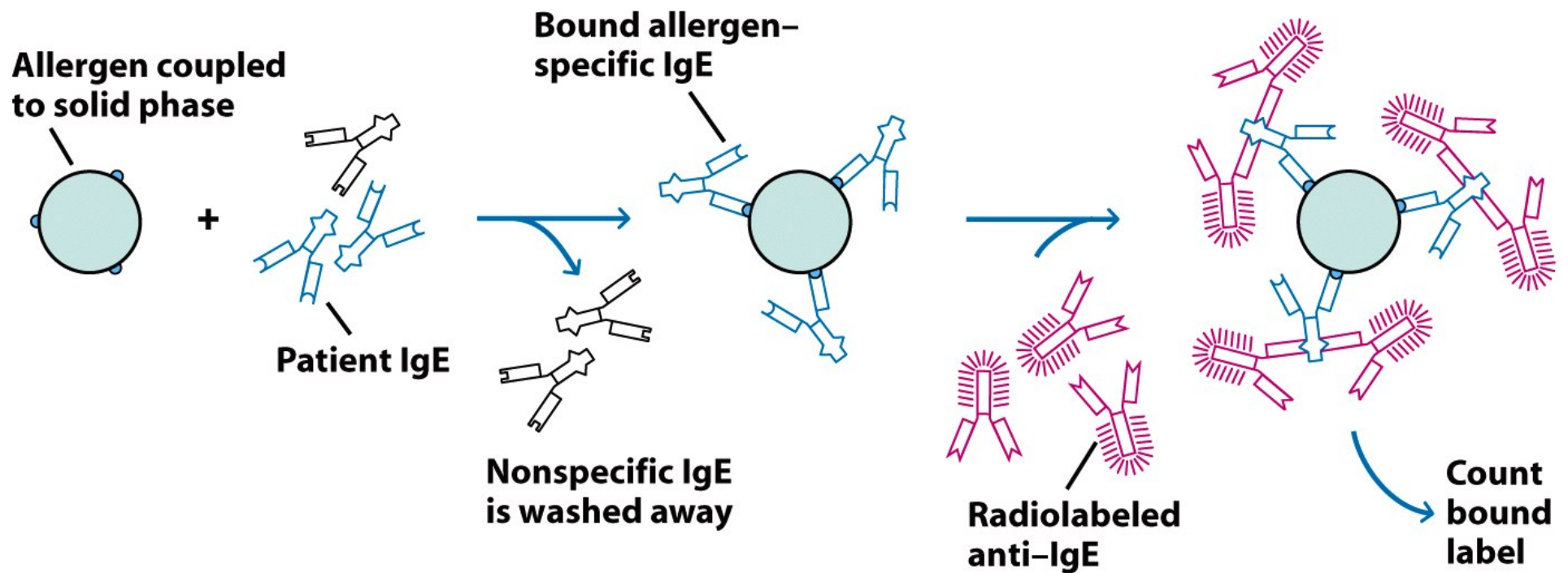


Figure 15-11b  
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1st study of allergen-specific immunotherapy:

Noon, L. Prophylactic inoculation against hay fever

Lancet I, 1572-1573 (**1911**)

## Desensitization/Allergen-Specific Immunotherapy

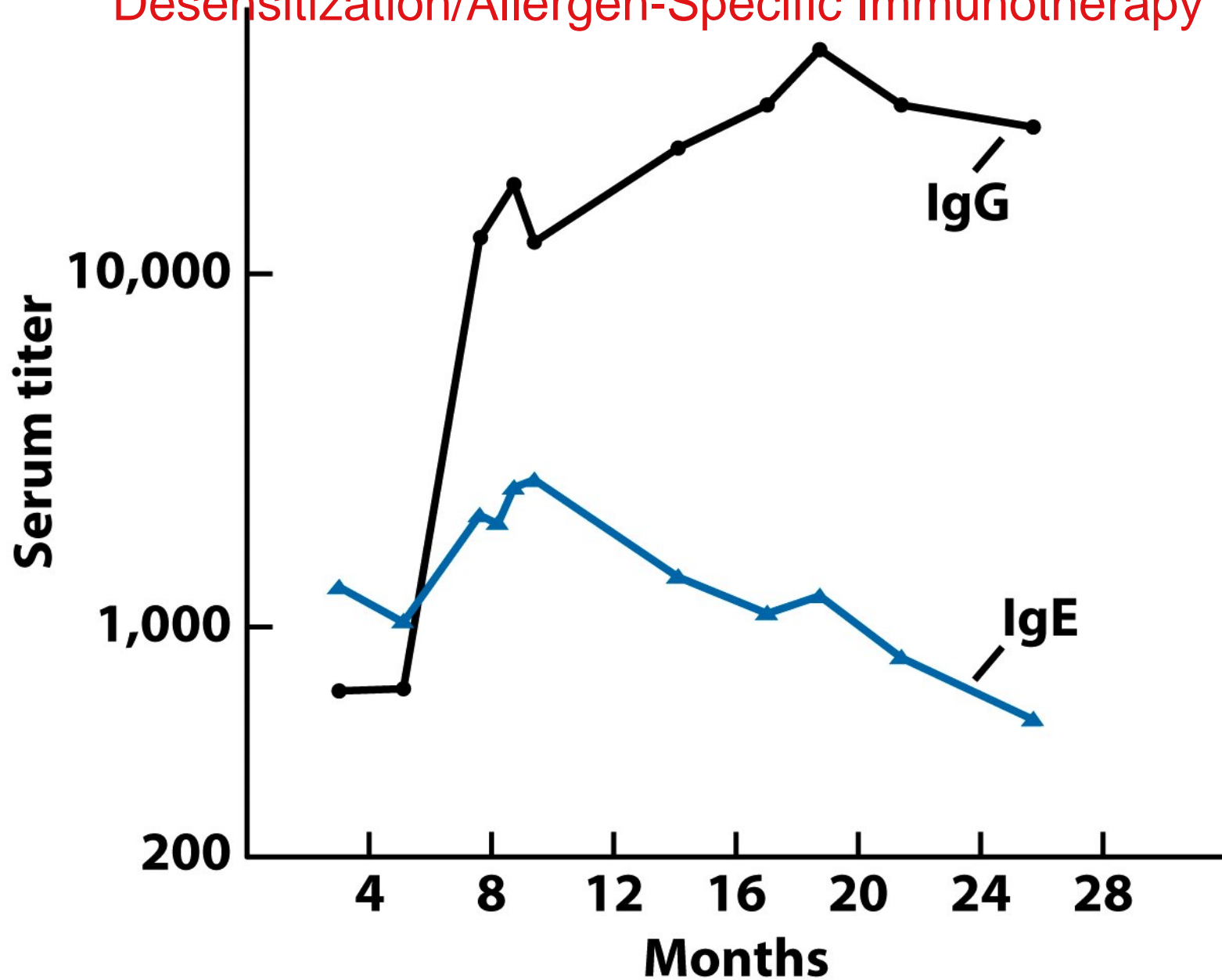


Figure 15-12  
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*Subcutaneous or sublingual administration*

# Peanut Flour May Ease Peanut Allergy

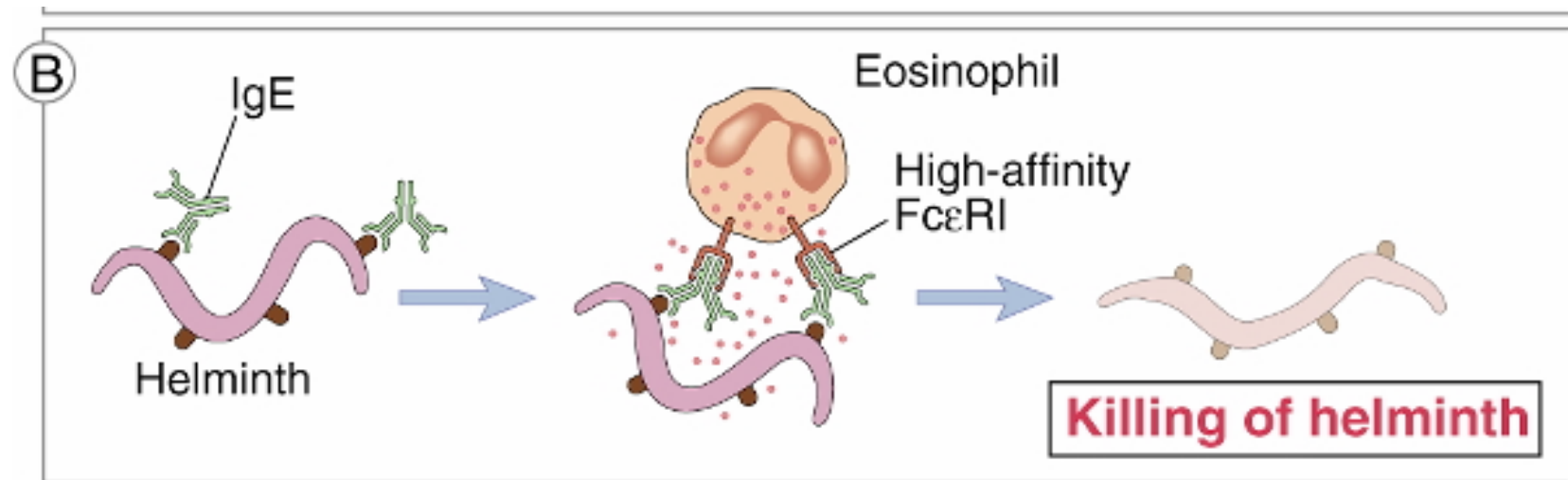
from [WebMD](#) — a health information Web site for patients

February 24, 2009. Eating a tiny bit of peanut flour every day may increase peanut tolerance in children who are allergic to peanuts, a new study shows.

Each child went home with instructions to eat 5 mg of peanut flour mixed with yogurt each day, gradually adding more peanut flour over the next six weeks.



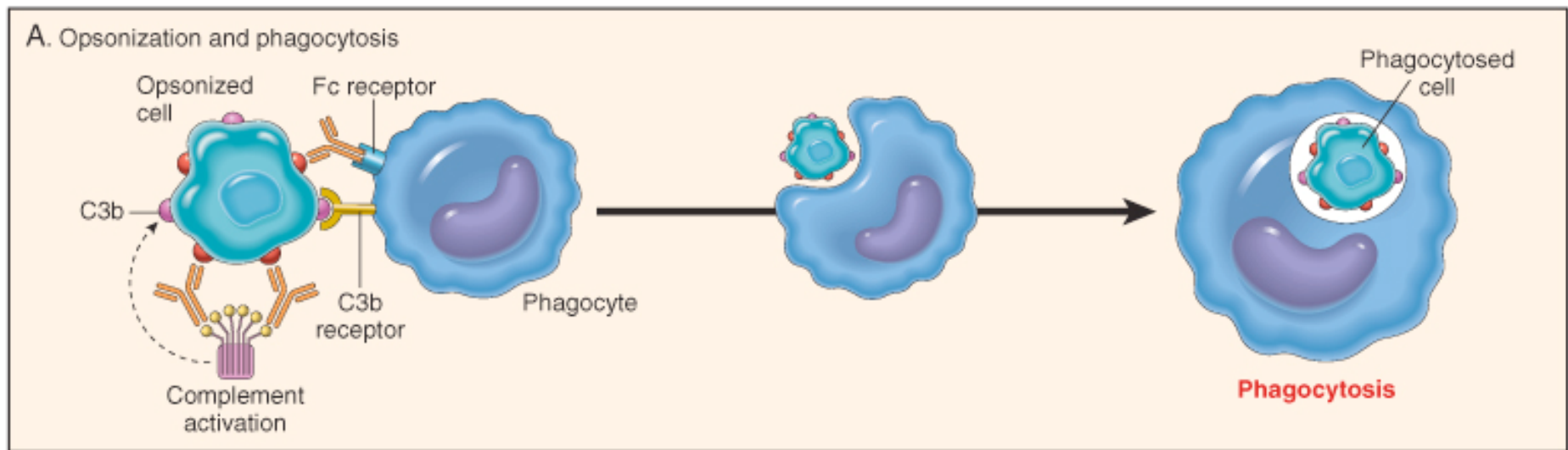
# Protective role of IgE



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# Type II hypersensitivity

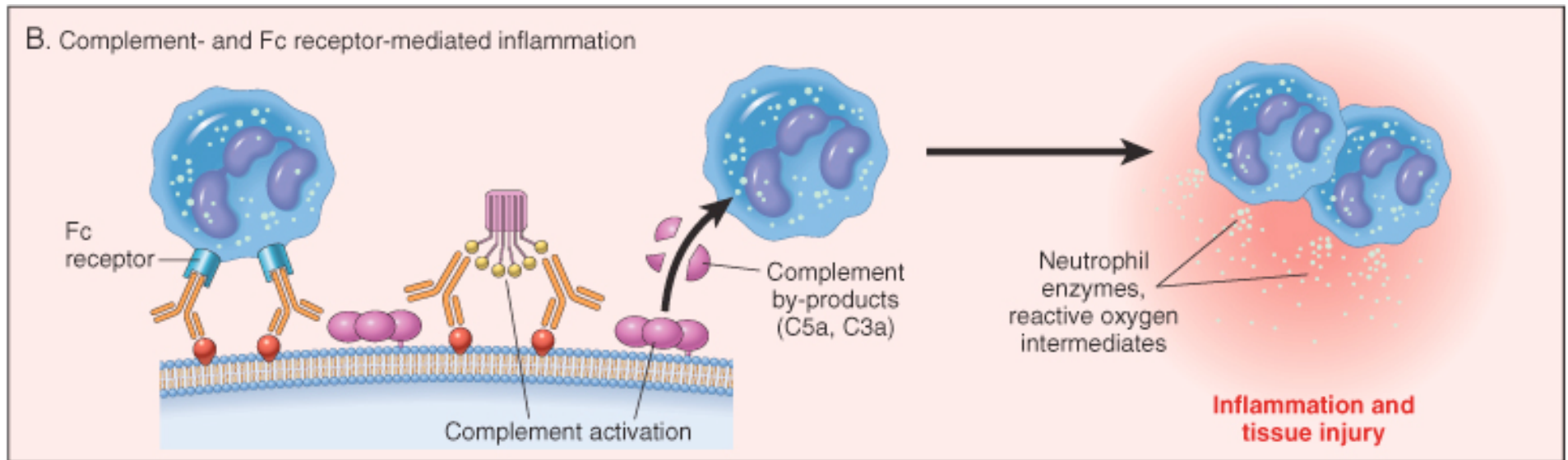
- Mediated by abs directed towards antigens present on cell surfaces or the extracellular matrix (type IIA) or abs with agonistic/antagonistic properties (type IIB).
- Mechanisms of damage:
  - Opsonization and complement- and Fc receptor-mediated phagocytosis
  - Complement- and Fc receptor-mediated inflammation
  - Antibody-mediated cellular dysfunction



© Elsevier 2005

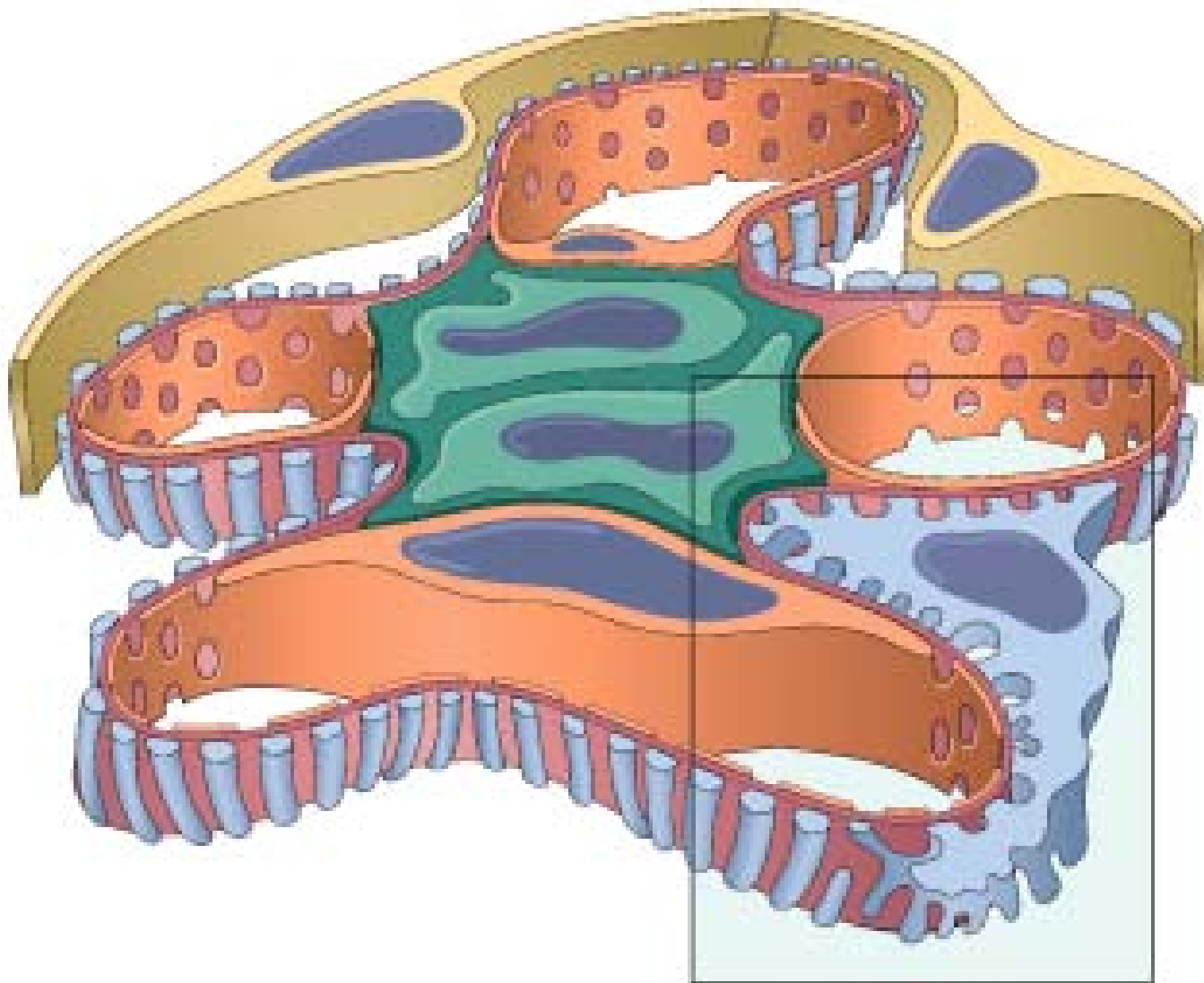
Examples: autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura

Kumar et al. Robbins and Cotran Pathologic Basis of Disease



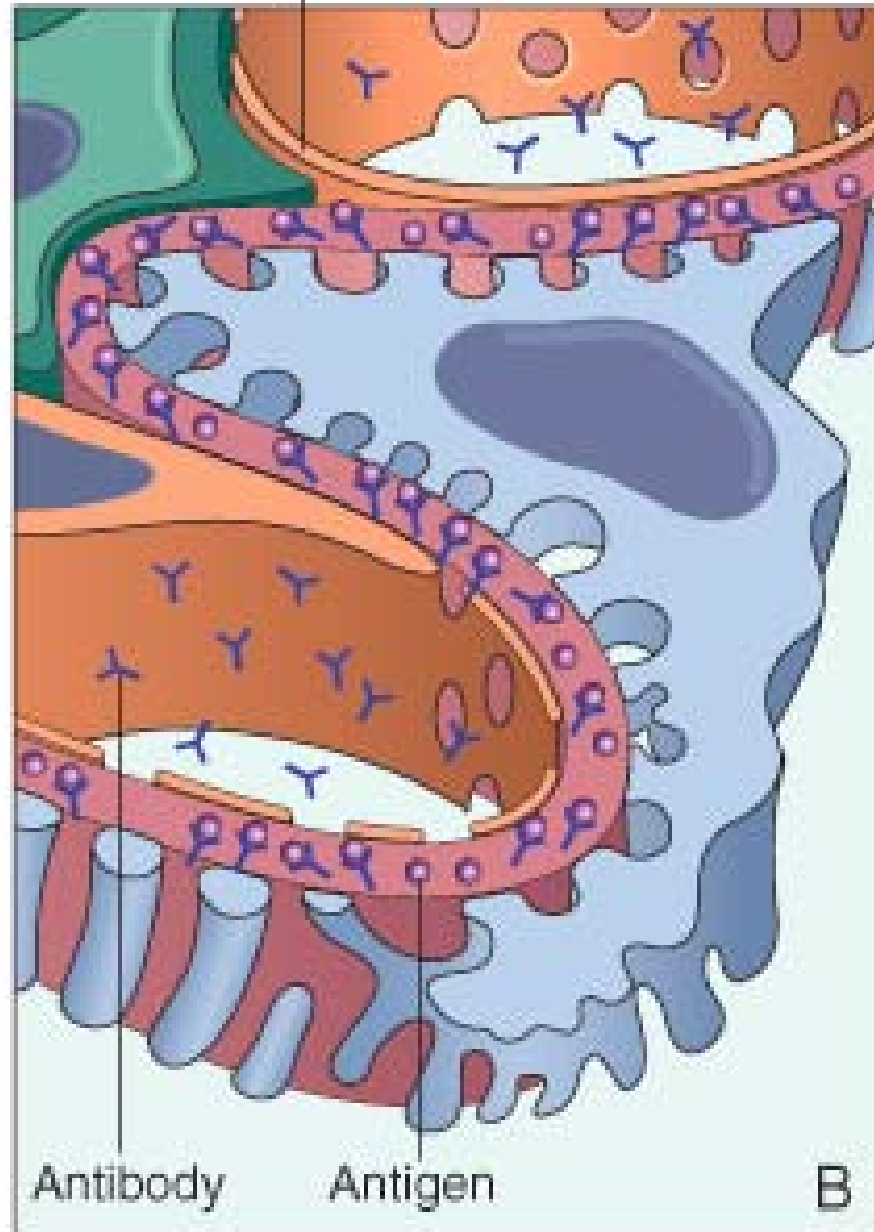
© Elsevier 2005

Examples: pemphigus vulgaris, Goodpasture syndrome

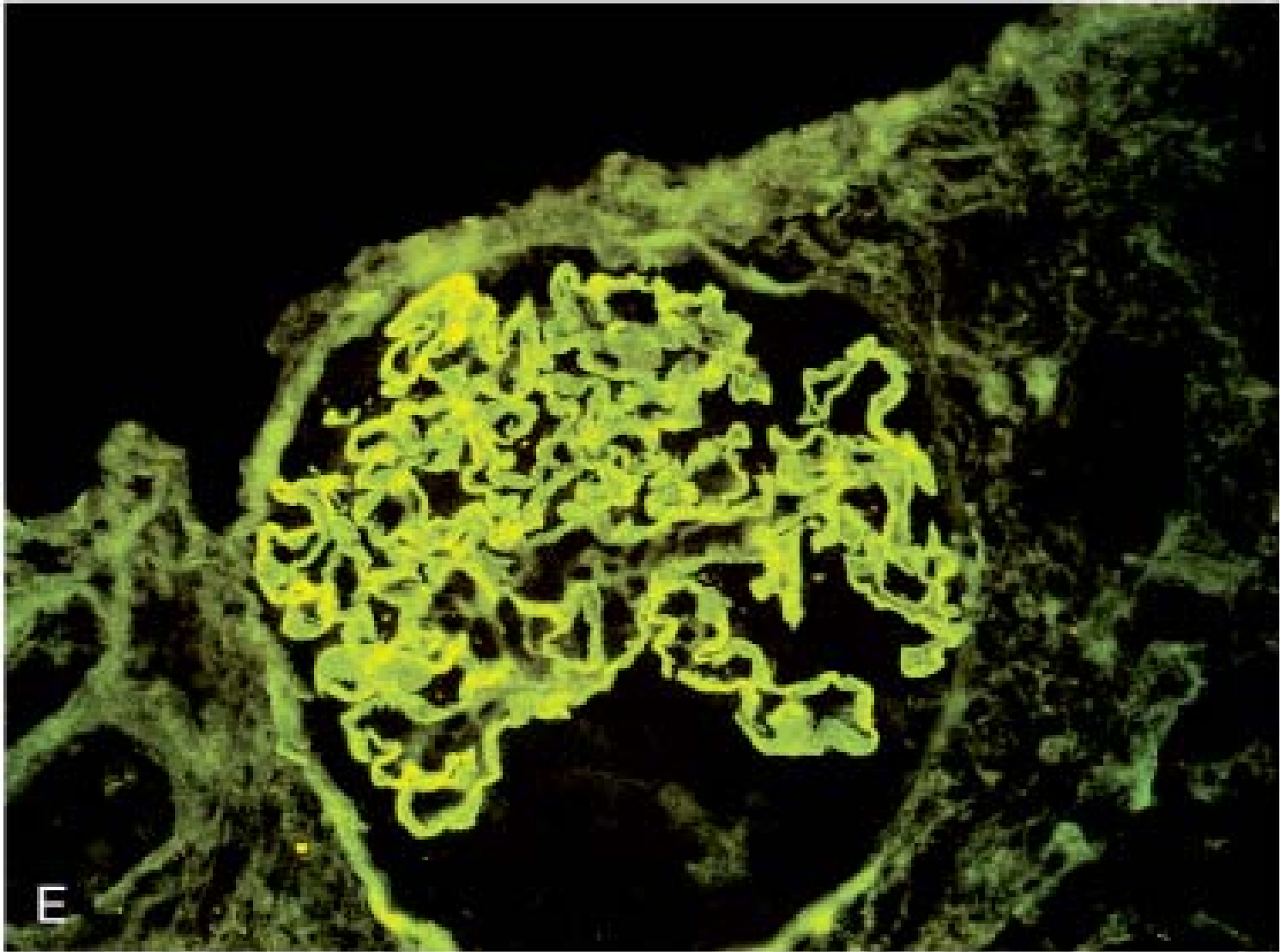


# ANTI-GBM

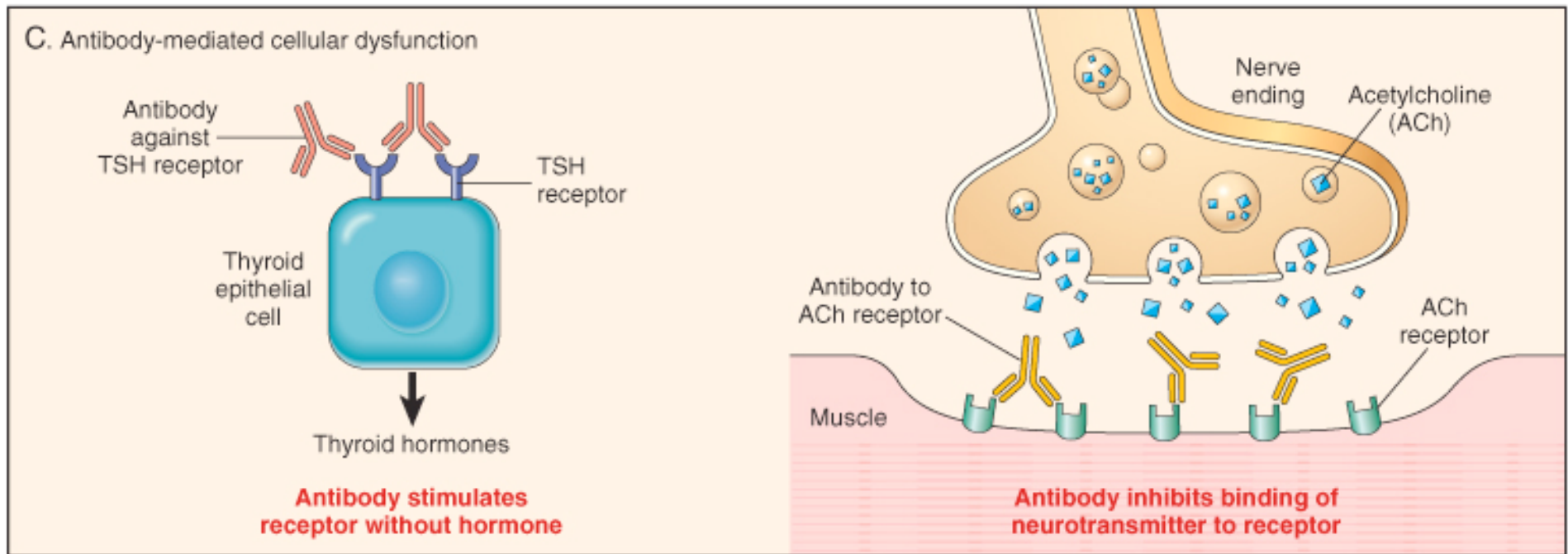
Endothelium



Kumar et al. Robbins and Cotran  
Pathologic Basis of Disease. Elsevier  
2005



Kumar et al. Robbins and Cotran Pathologic Basis of Disease. Elsevier 2005.



© Elsevier 2005

Examples: Graves disease (hyperthyroidism), myasthenia gravis

Kumar et al. Robbins and Cotran Pathologic Basis of Disease

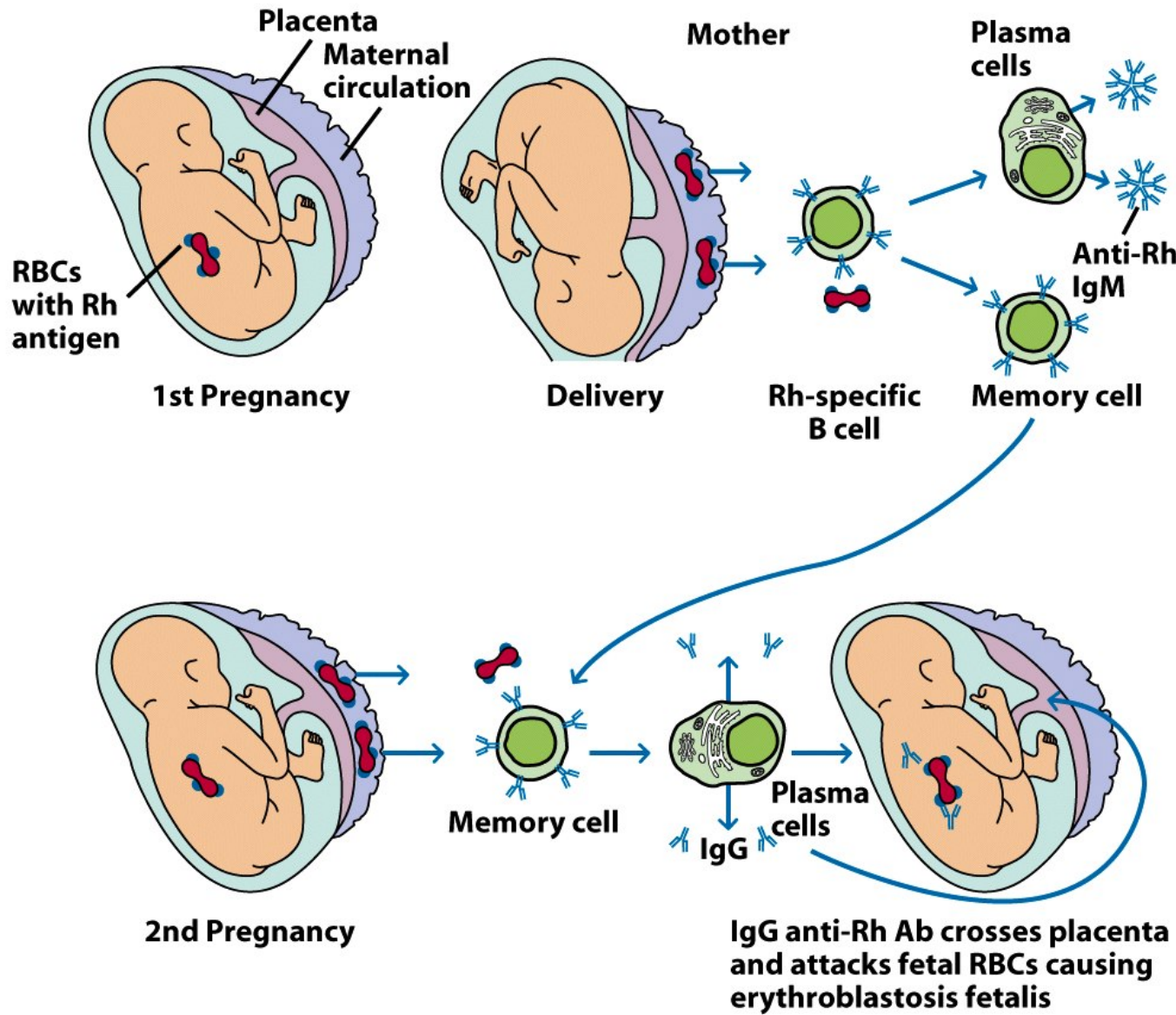


# Non-autoimmune type II reactions

- Transfusion reactions (ABO incompatibility)
- Hemolytic disease of the newborn (erythroblastosis fetalis)



## DEVELOPMENT OF ERYTHROBLASTOSIS FETALIS (WITHOUT RHOGAM)



## PREVENTION (WITH RHOGAM)

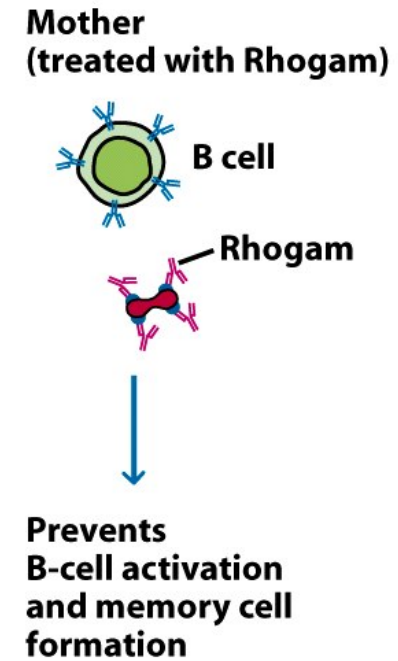
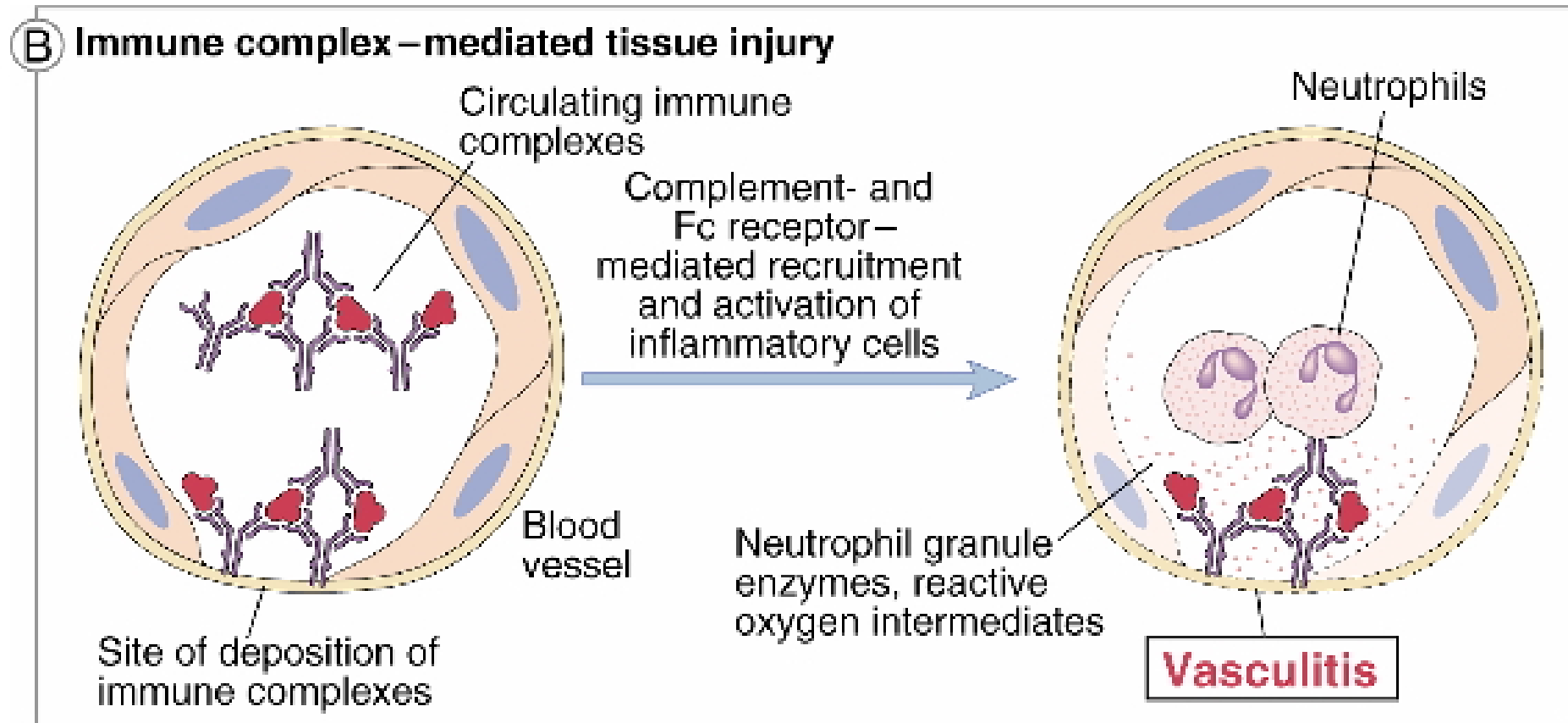


Figure 15-14  
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# Type III hypersensitivity (immune complex disease)

Mechanisms of  
Ab deposition

Effector mechanisms  
of tissue injury



# Serum sickness - a transient immune complex-mediated syndrome

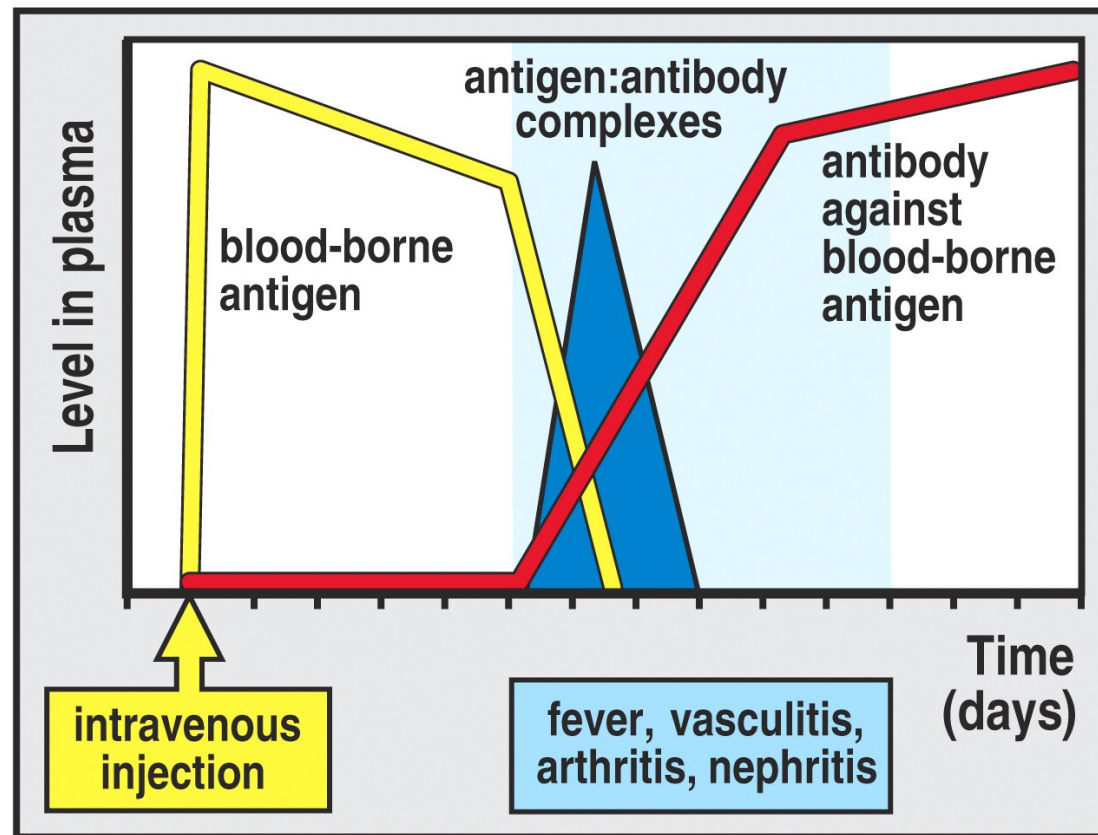


Figure 10-32 The Immune System, 2/e (© Garland Science 2005)

# Arthus reaction

Peaks @ 4-8 hours  
 Visible edema  
 Severe hemorrhage  
 Can be followed by ulceration

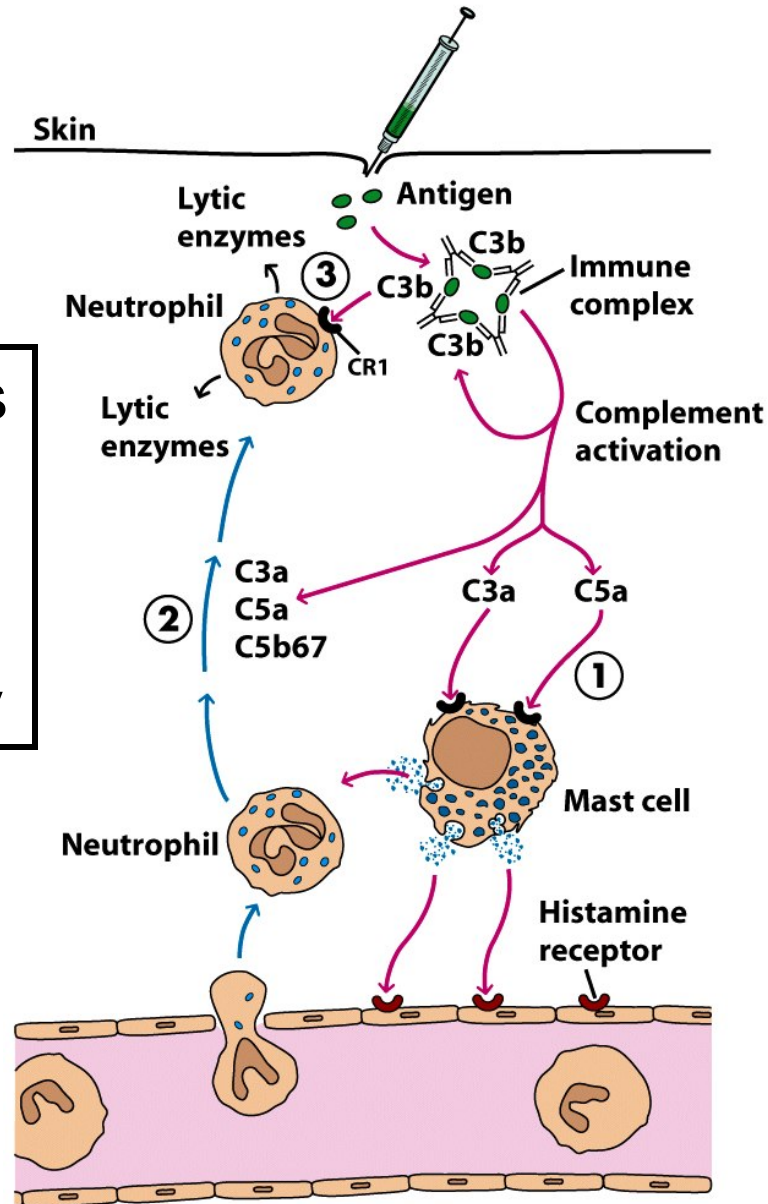
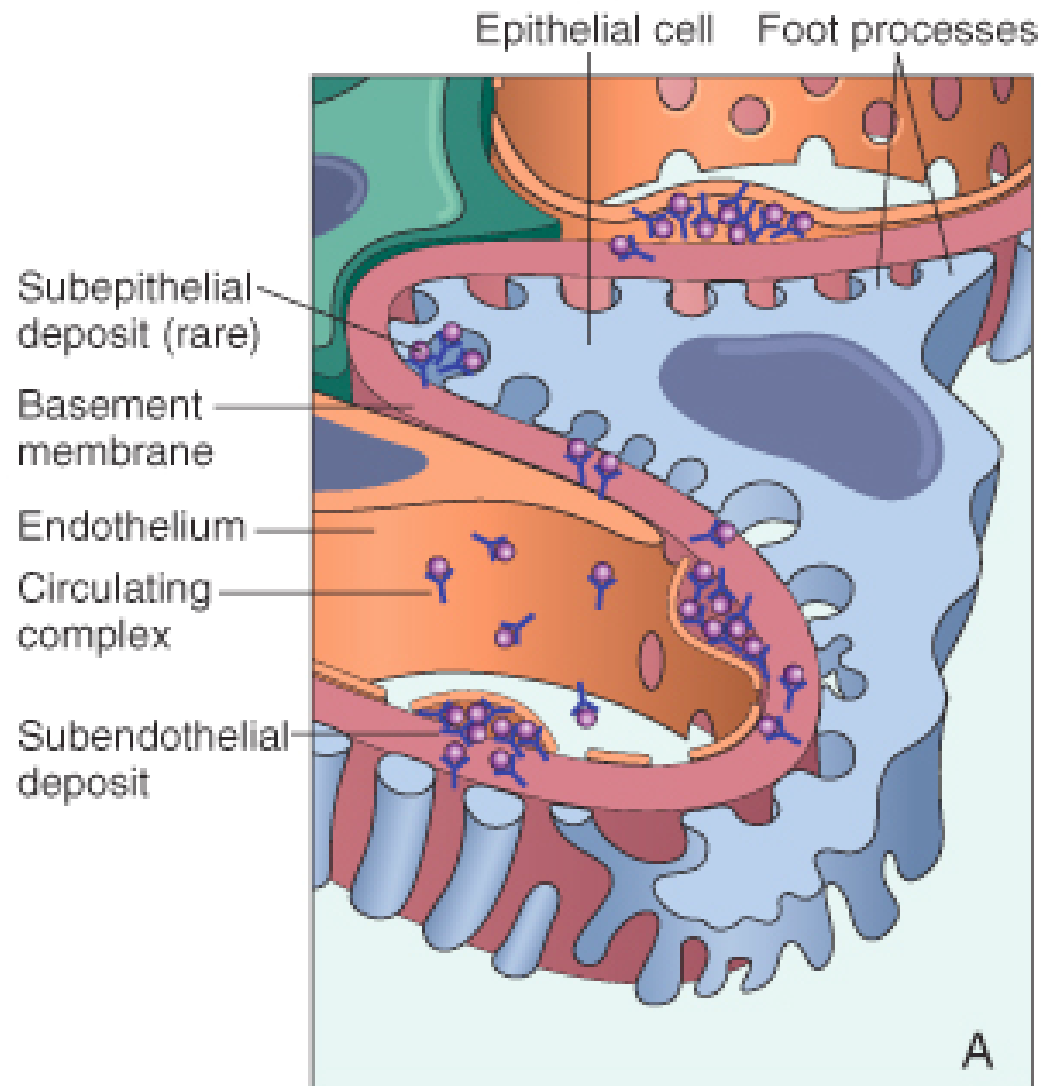


Figure 15-15  
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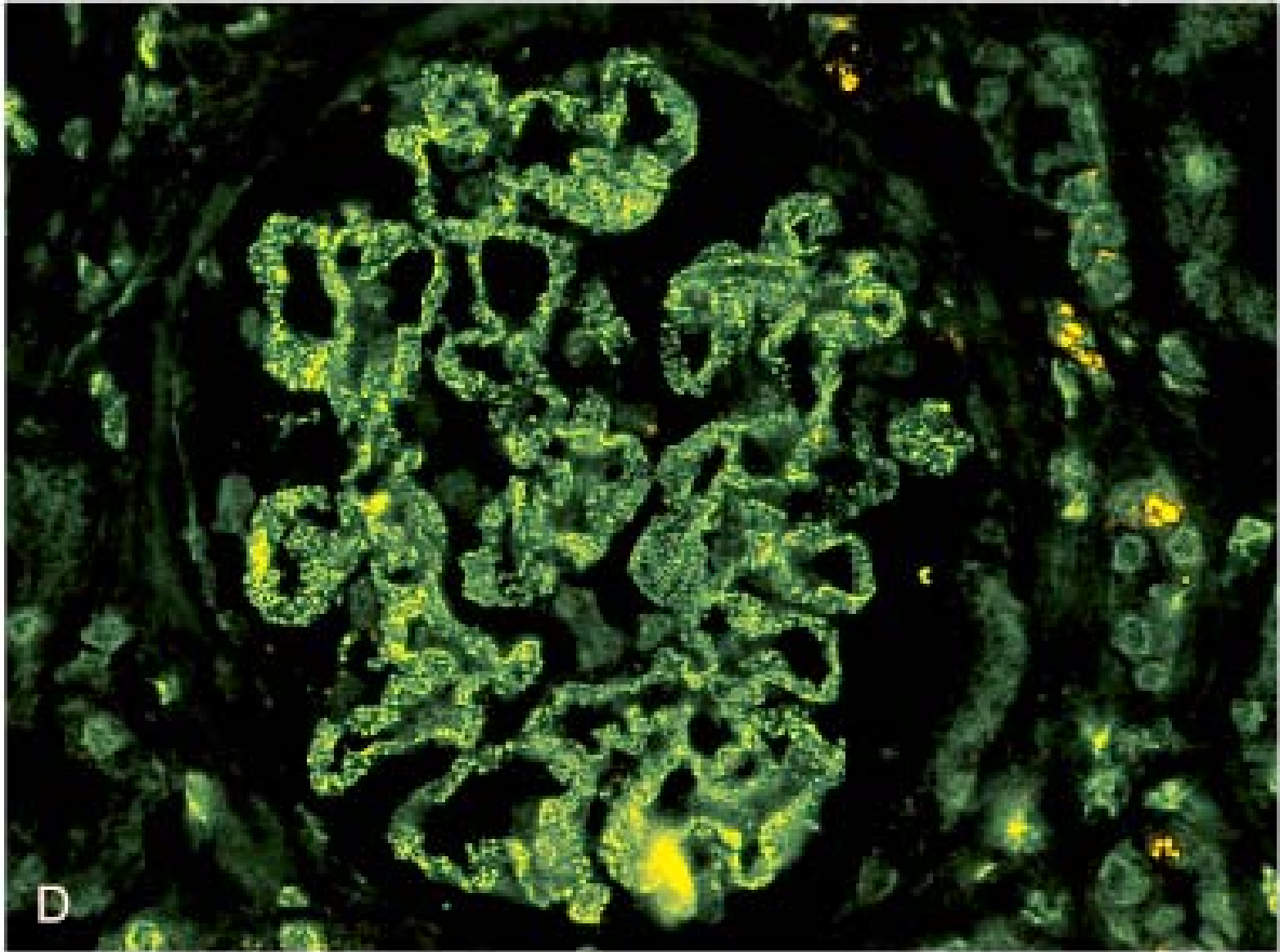
# Formation of circulating immune complexes contributes to the pathogenesis of:

- Autoimmune diseases
  - SLE (lupus nephritis), rheumatoid arthritis
- Drug reactions
  - Allergies to penicillin and sulfonamides
- Infectious diseases
  - Poststreptococcal glomerulonephritis, meningitis, hepatitis, mononucleosis, malaria, trypanosomiasis

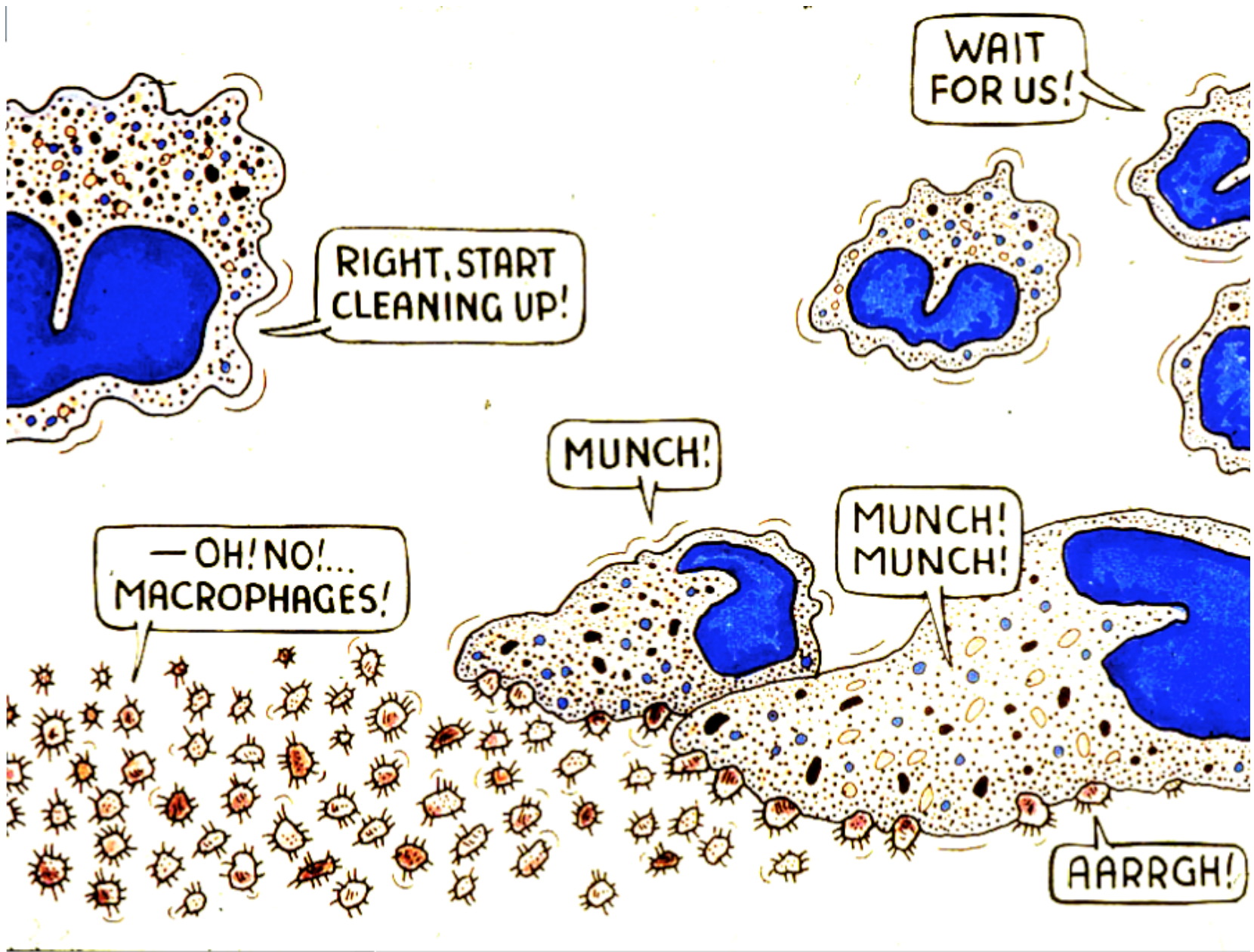
## IMMUNE COMPLEX DEPOSITION



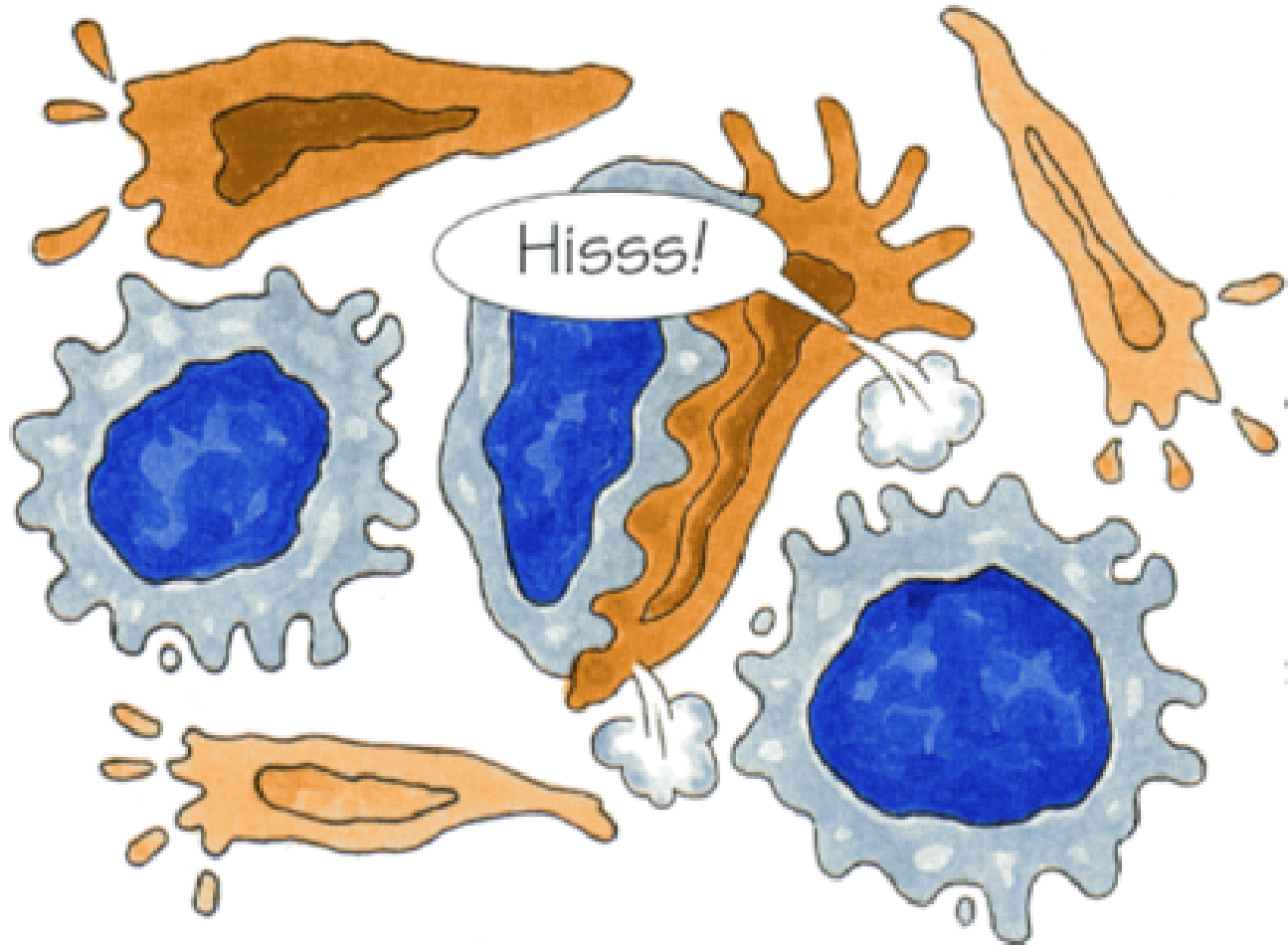




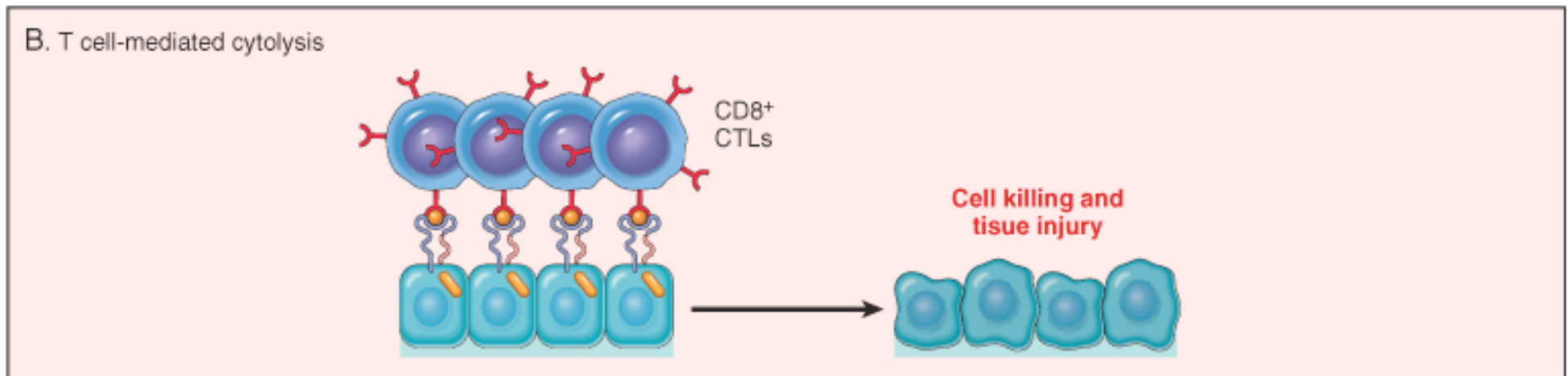
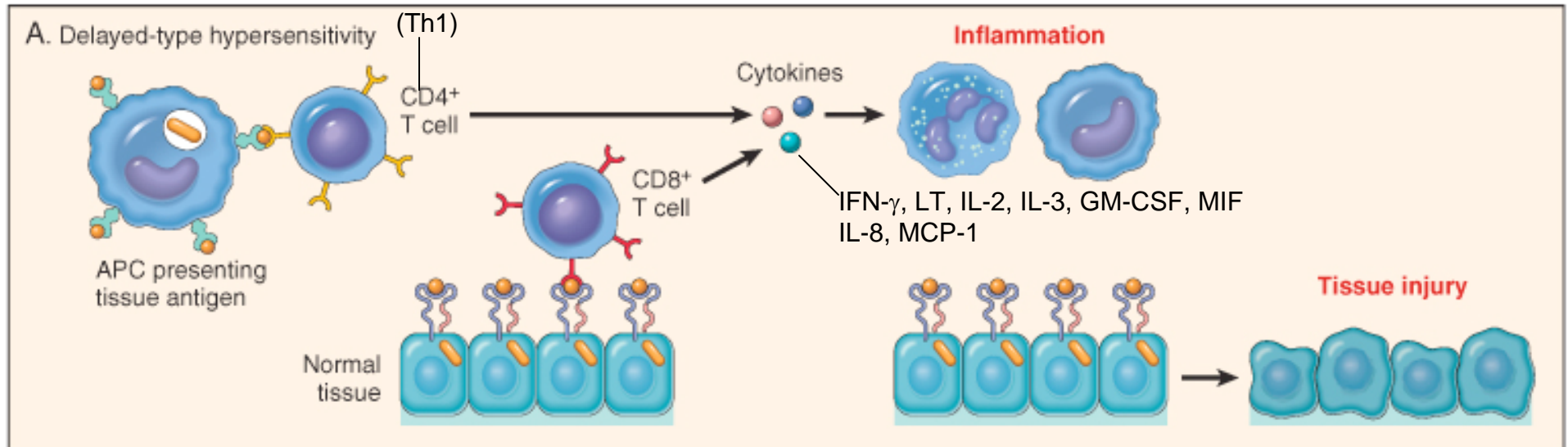
Kumar et al. Robbins and Cotran Pathologic Basis of Disease. Elsevier 2005.



# Killer T lymphocytes



# Type IV hypersensitivity (DTH)



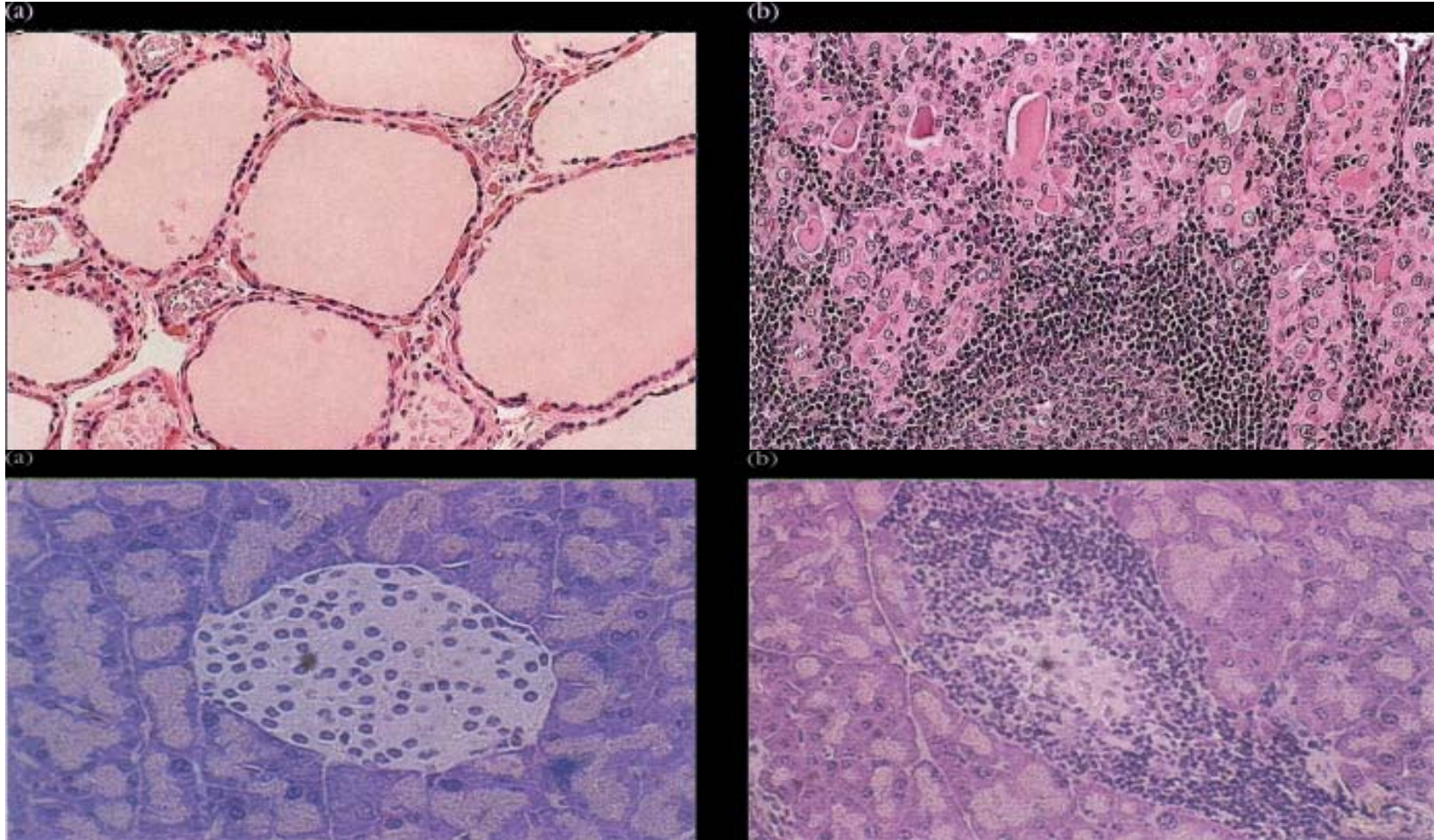
**TABLE 15-6****Intracellular pathogens and contact antigens that induce delayed-type (type IV) hypersensitivity****Intracellular bacteria***Mycobacterium tuberculosis***virus***Mycobacterium leprae**Listeria monocytogenes**Brucella abortus***Intracellular fungi***Pneumocystis carinii**Candida albicans**Histoplasma capsulatum**Cryptococcus neoformans***Intracellular parasites***Leishmania sp.***Intracellular viruses****Herpes simplex****Variola (smallpox)****Measles virus****Contact antigens****Picrylchloride****Hair dyes****Nickel salts****Poison ivy****Poison oak**

Table 15-6

Kuby IMMUNOLOGY, Sixth Edition

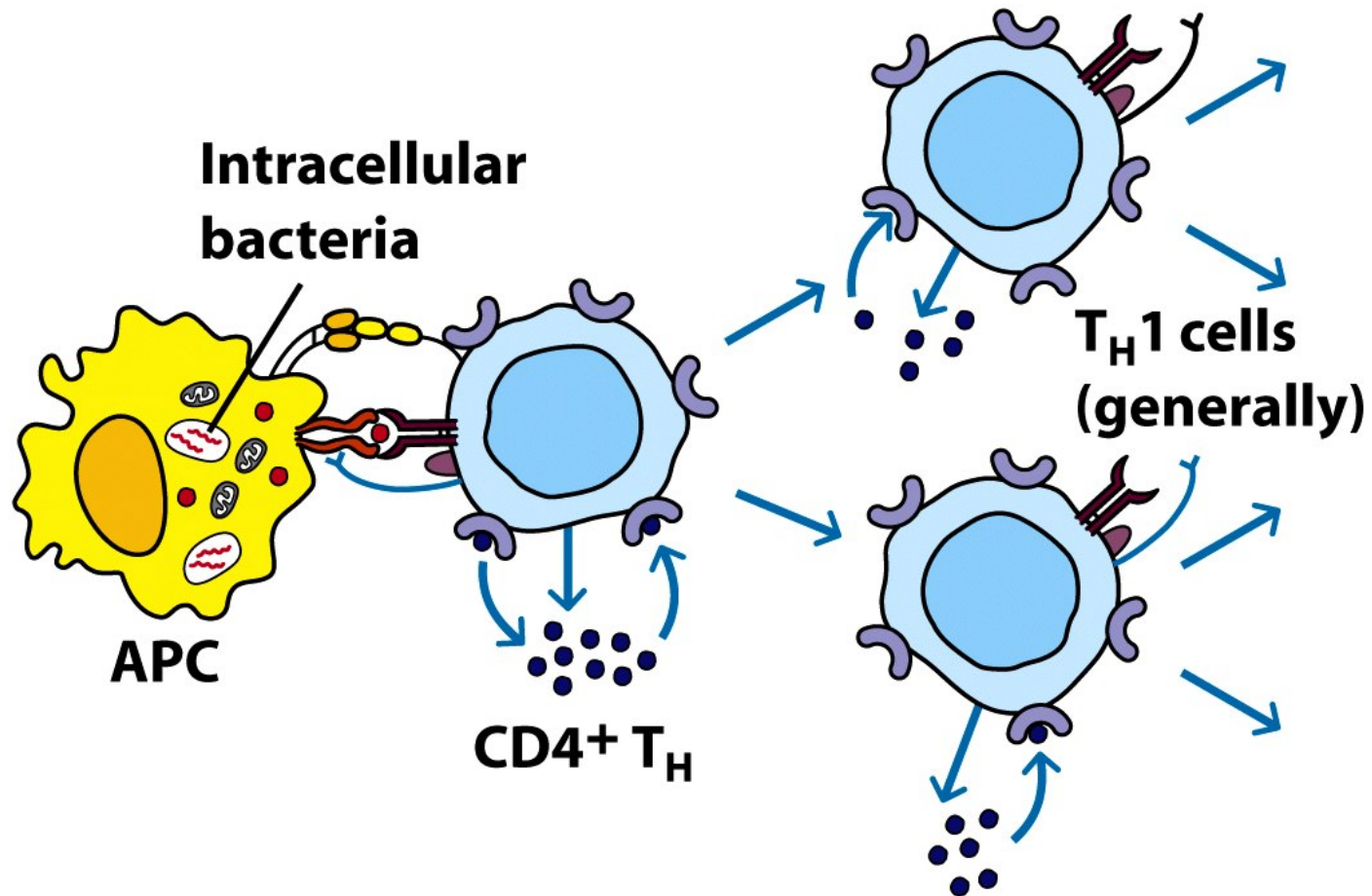
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# Autoimmune diseases mediated by direct cellular damage



Top - Goldsby et al, Figure 20-1- Hashimoto's thyroiditis  
Bottom - Goldsby et al, Figure 20-3 - Type I diabetes

# Sensitization phase

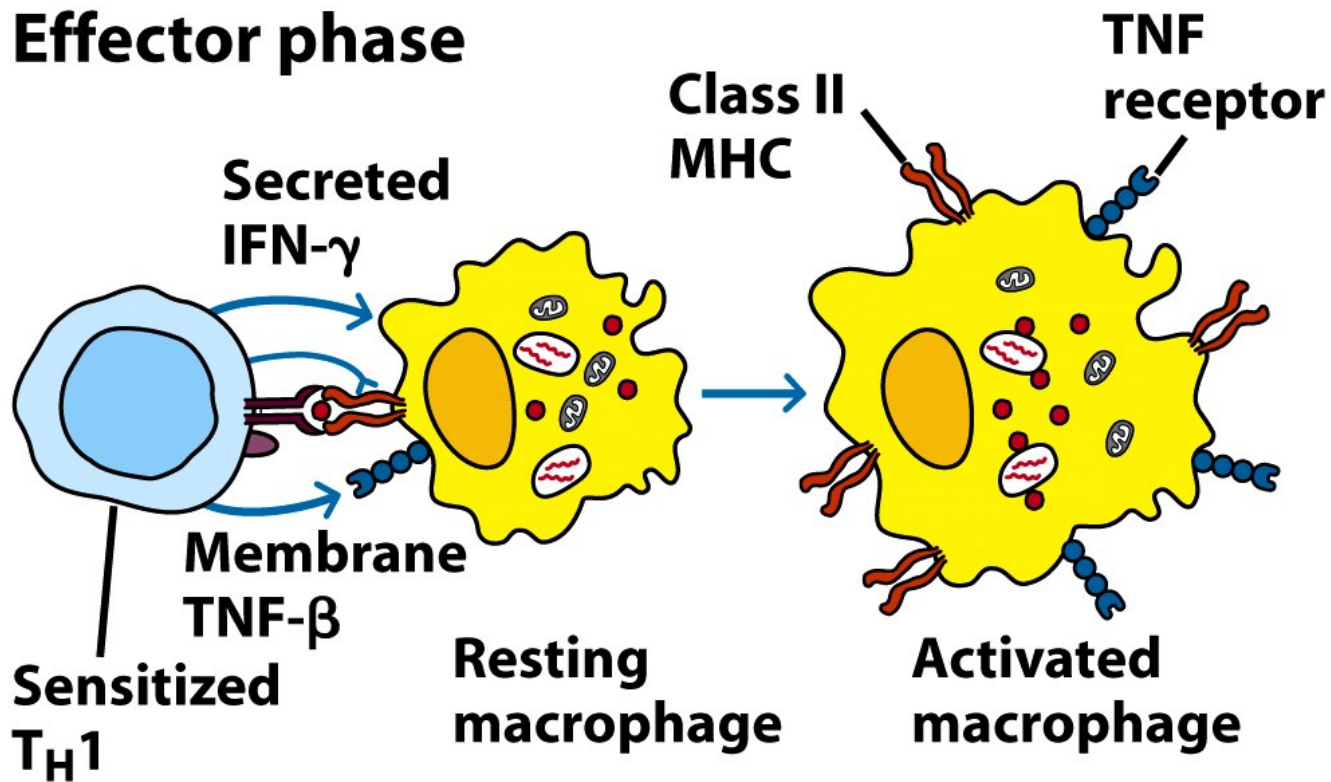


**Antigen-presenting  
cells: Macrophages  
Langerhans cells**

**DTH-mediating cells:  
T<sub>H</sub>1 cells generally  
CD8 cells occasionally**

Figure 15-17a  
*Kuby IMMUNOLOGY, Sixth Edition*  
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## Effector phase



### $T_H1$ secretions:

**Cytokines:**  $IFN-\gamma$ ,  $TNF-\beta$ ,  
IL-2,  
IL-3, GM-CSF, MIF  
**Chemokines:** IL-8/CXCL8,  
MCP-1/CCL2

### Effects of macrophage activation:

↑ **Class II MHC molecules**  
↑ **TNF receptors**  
↑ **Oxygen radicals**  
↑ **Nitric oxide**

Figure 15-17b

Kuby *IMMUNOLOGY*, Sixth Edition

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## Pentadecacatechol

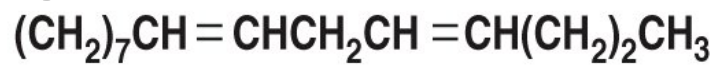
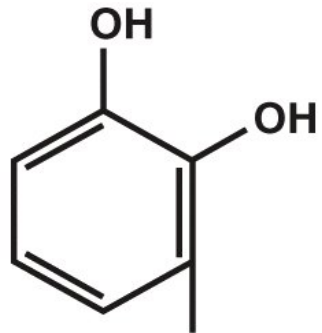
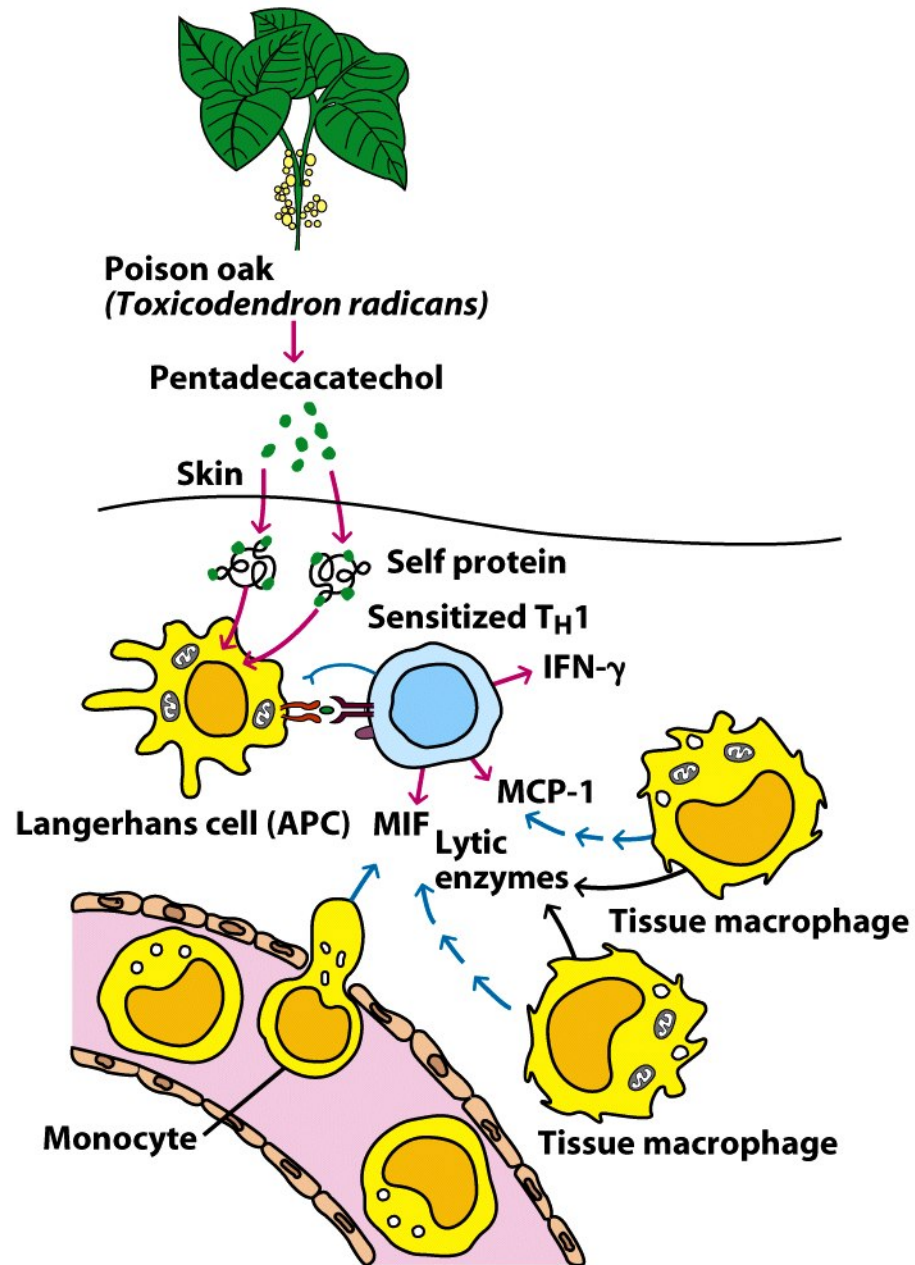


Figure 10-36 The Immune System, 2/e (© Garland Science 2005)

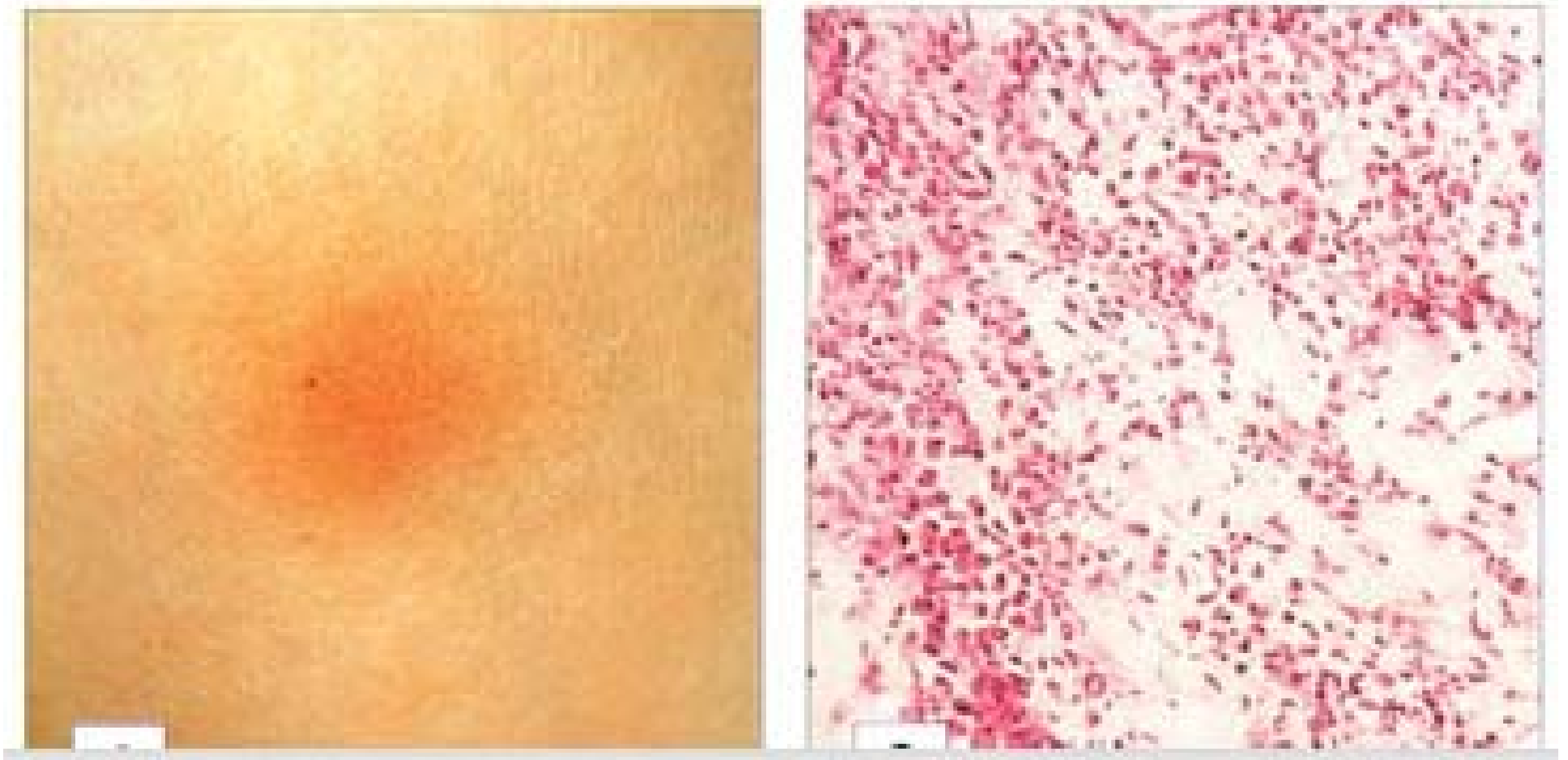


**Figure 15-20**  
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## Clinical and patch test appearances of contact hypersensitivity

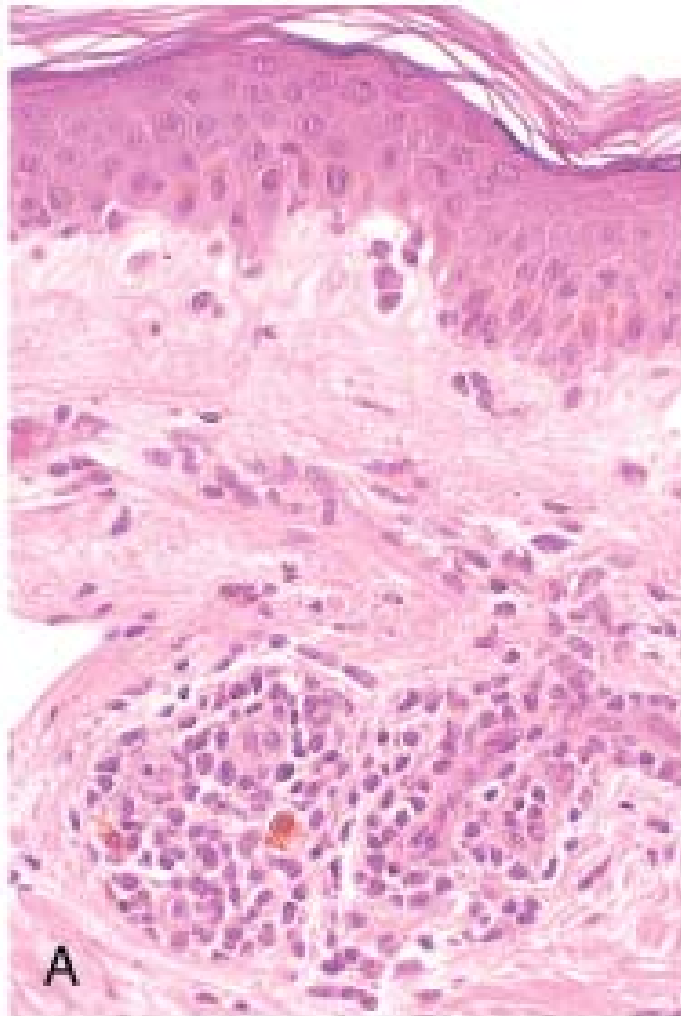


# Tuberculin-type hypersensitivity reaction

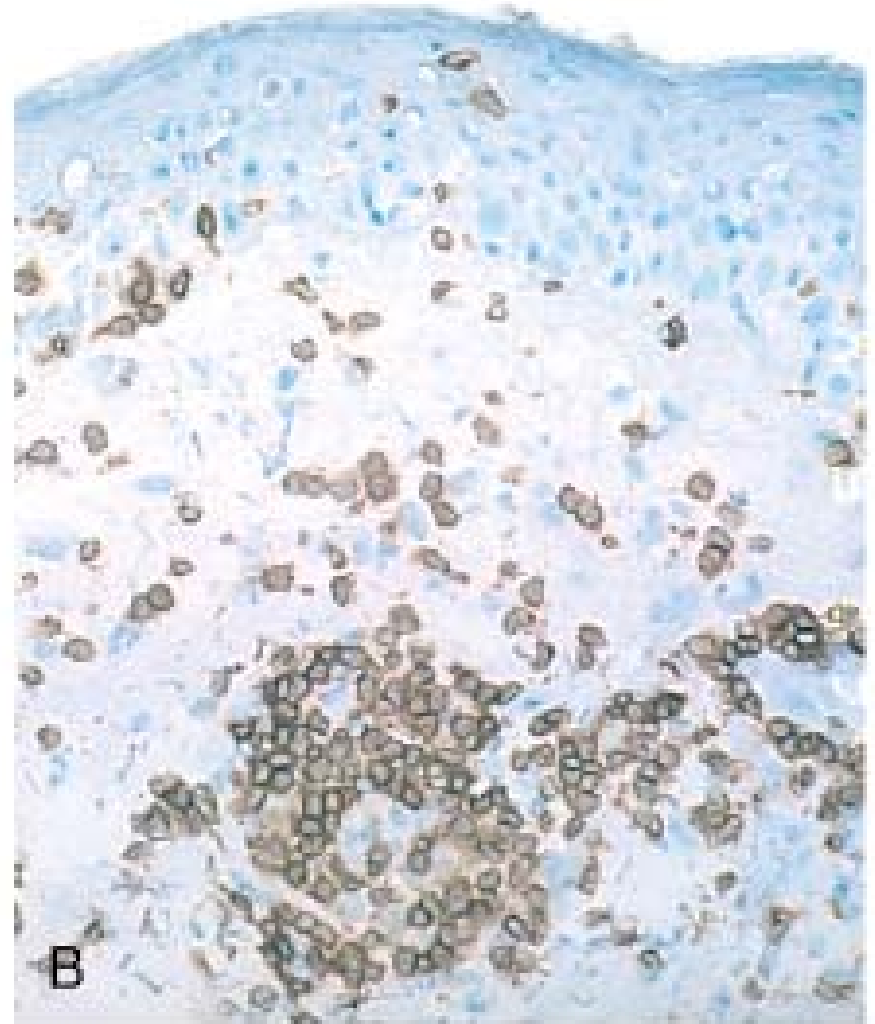


Roitt 24.8

# DTH in the skin



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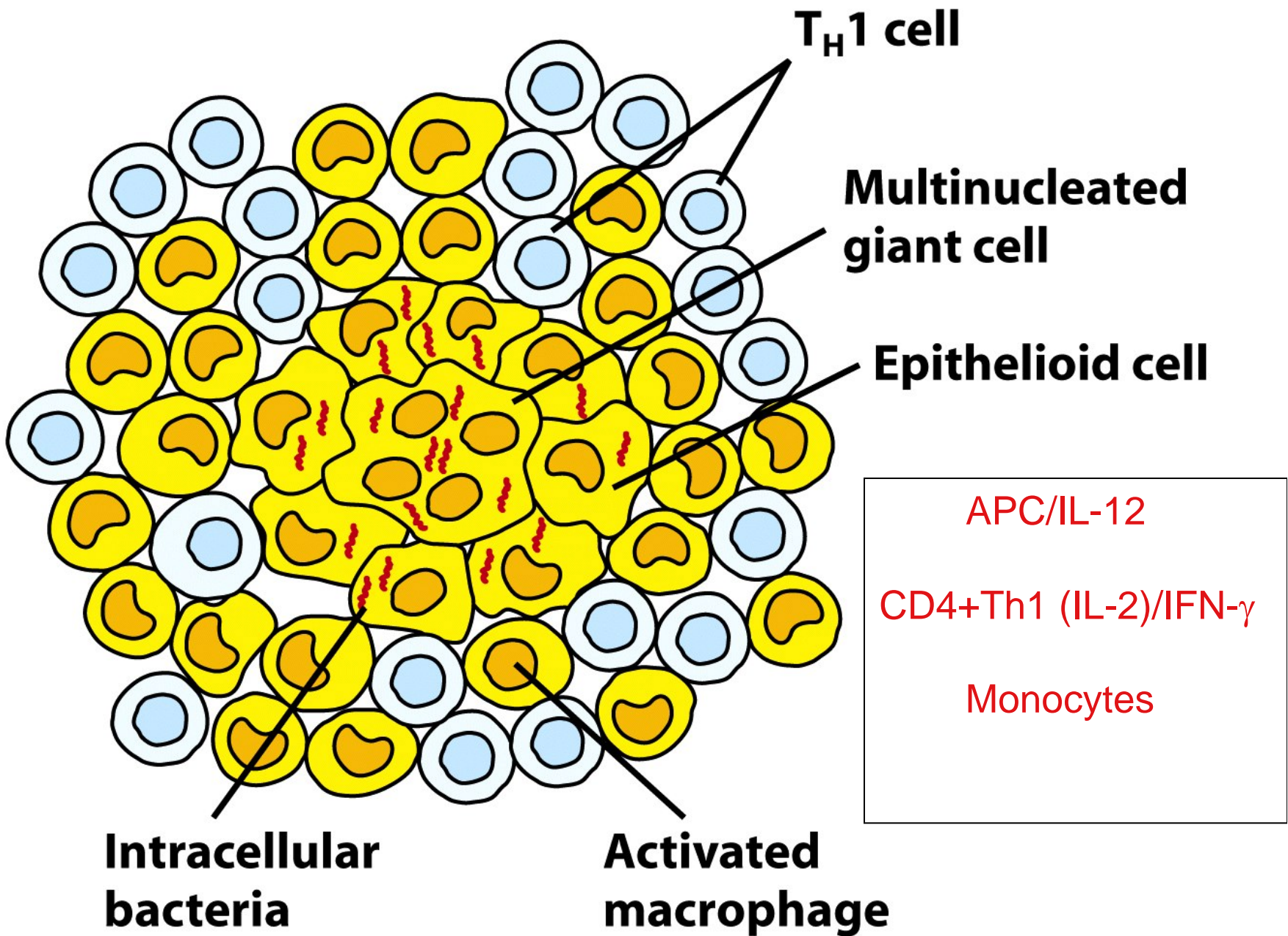


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# Uses of tuberculin-type reactions

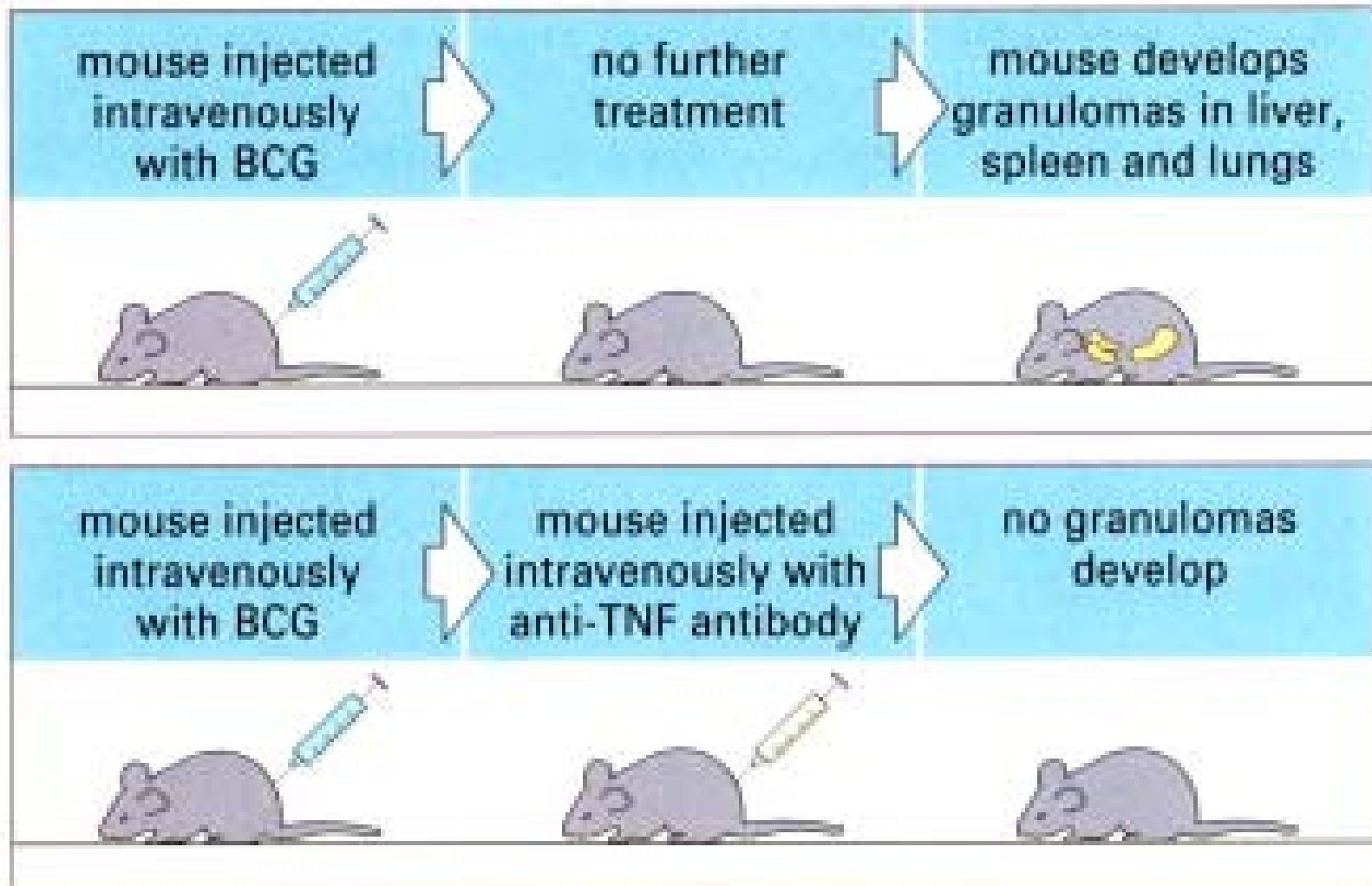
Demonstration of past infection with a microorganism.

Assessment of cell-mediated immunity.



**Figure 15-18**  
*Kuby IMMUNOLOGY, Sixth Edition*  
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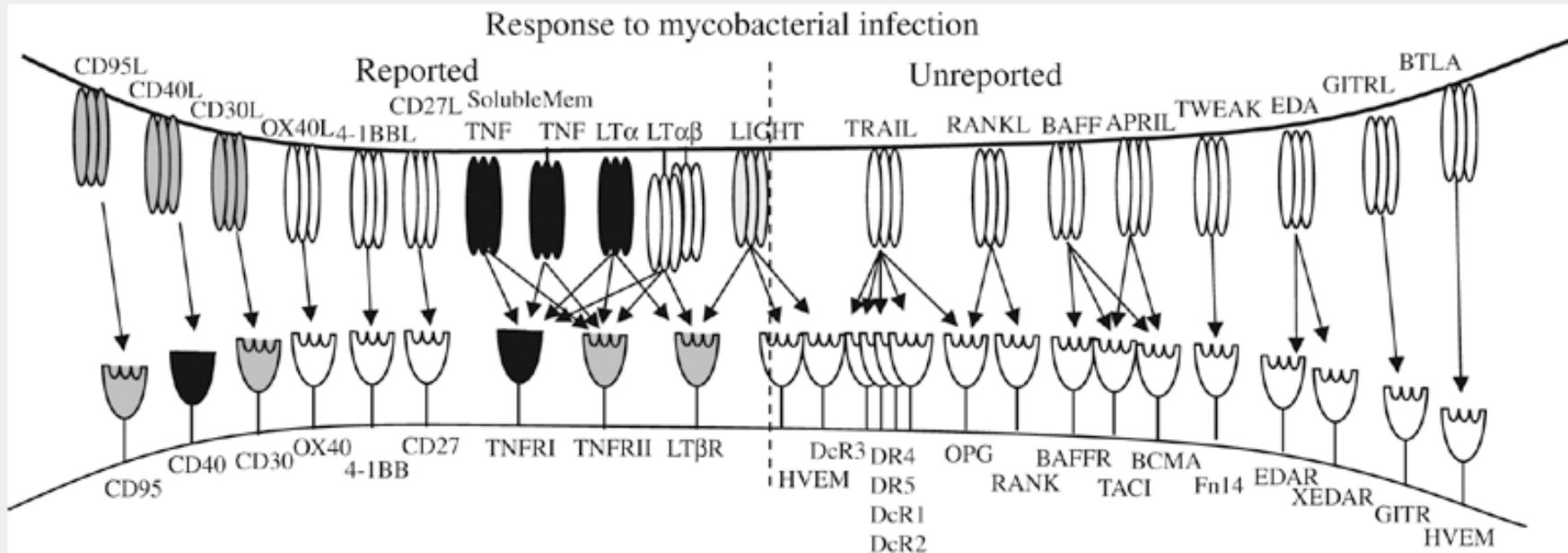
# The importance of TNF- $\alpha$ in the formation of granulomas





# Diseases associated with granuloma formation:

- Leprosy
- Tuberculosis
- Schistosomiasis
- Sarcoidosis
- Crohn's disease

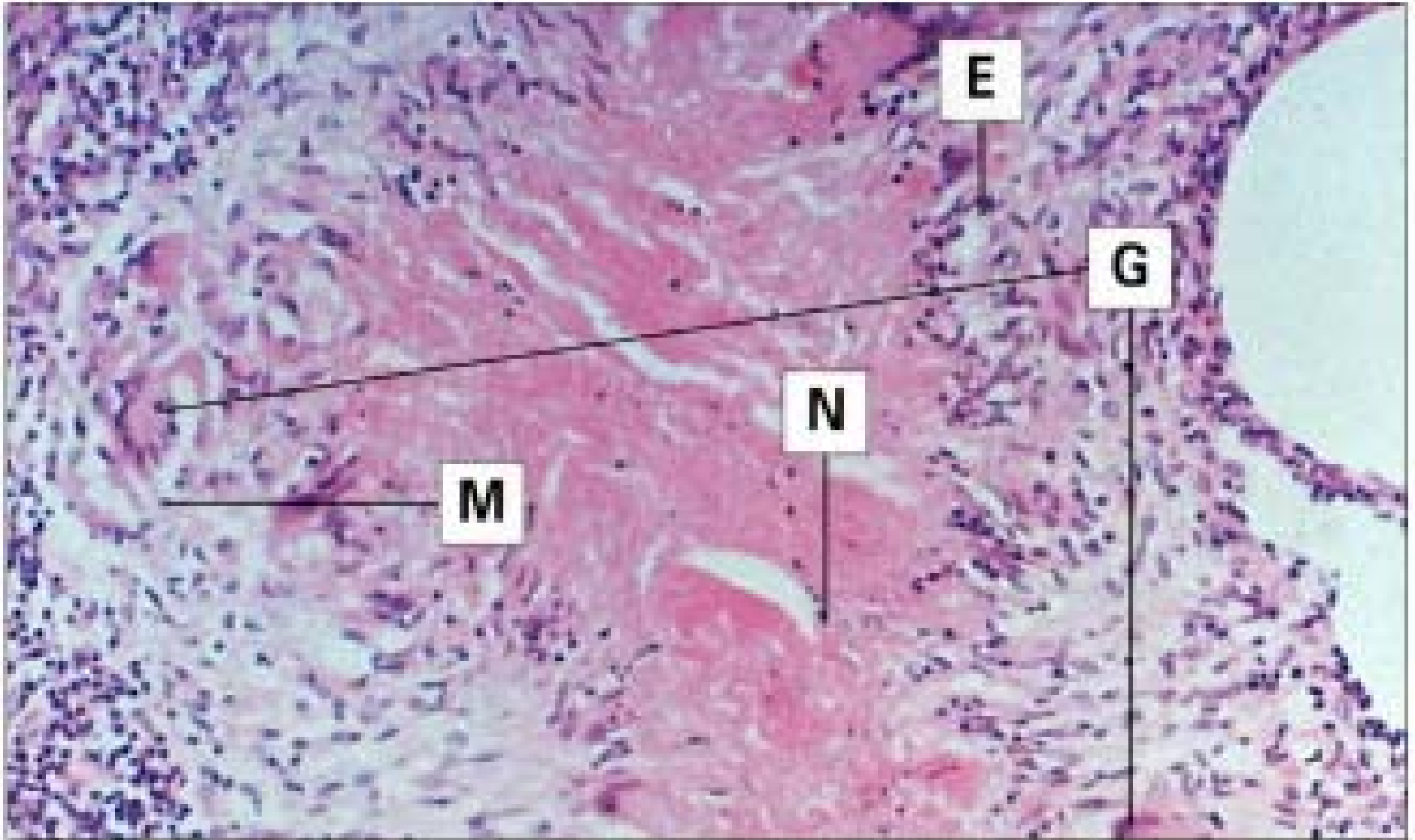


TNF superfamily involvement in granuloma formation and resistance to mycobacterial infection. Reported: Dark gray ligands and receptors are essential for normal granuloma formation and sustained resistance to mycobacterial infection. Pale gray ligands and receptors are required for optimal protective immunity to mycobacterial infection. Unfilled ligands and receptors were not required for normal granuloma formation and expression of protective immunity to mycobacterial infection. Unreported: Ligands and receptors whose function in granuloma formation and resistance to mycobacterial infection has not yet been reported.

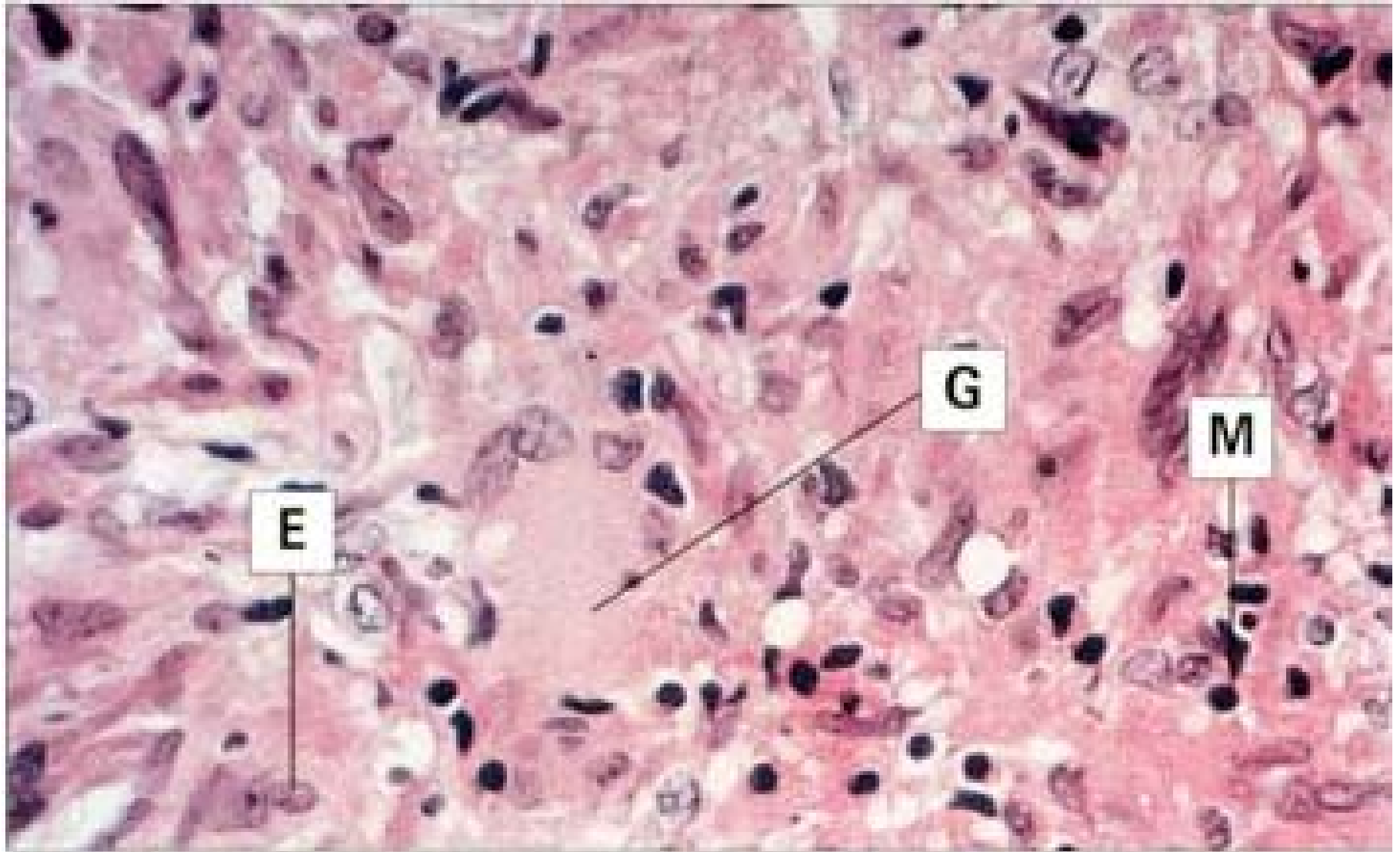
# Chemokine expression in tissues from *M. tuberculosis*-infected individuals

<b><i>In vivo/ex vivo sample</i></b>	<b><i>Chemokines</i></b>
Pleura	MIP-1 $\alpha$ , MIP-1 $\beta$ Mig, RANTES IP-10, MCP-1 MCP-1, MIP-1 $\alpha$ , MIP-1 $\beta$
BALF	IP-10, IL-8 MCP-1, MCP-3, MCP-4 RANTES MIP-1 $\alpha$ Exotaxin
Lung	MCP-1, MCP-3, MCP-4, IP-10 Eotaxin
Alveolar macrophages	CCR5 RANTES MIP-1 $\alpha$ MCP-1
Plasma	IL-8, IP-10
	MCP-1, RANTES MIP-1 $\alpha$ , MIP-1 $\beta$ RANTES MCP-1
PBMC	MIP-1 $\alpha$ RANTES
	MCP-1 IL-8
Cerebral spinal fluid	MCP-1, IL-8, MIP-1 $\alpha$

# Tuberculosis



## Sarcoidosis (lymph node)



# Skin Reactions

Immediate

Arthus

DTH

