Lecture IX

# Complement

# Hypersensitivity

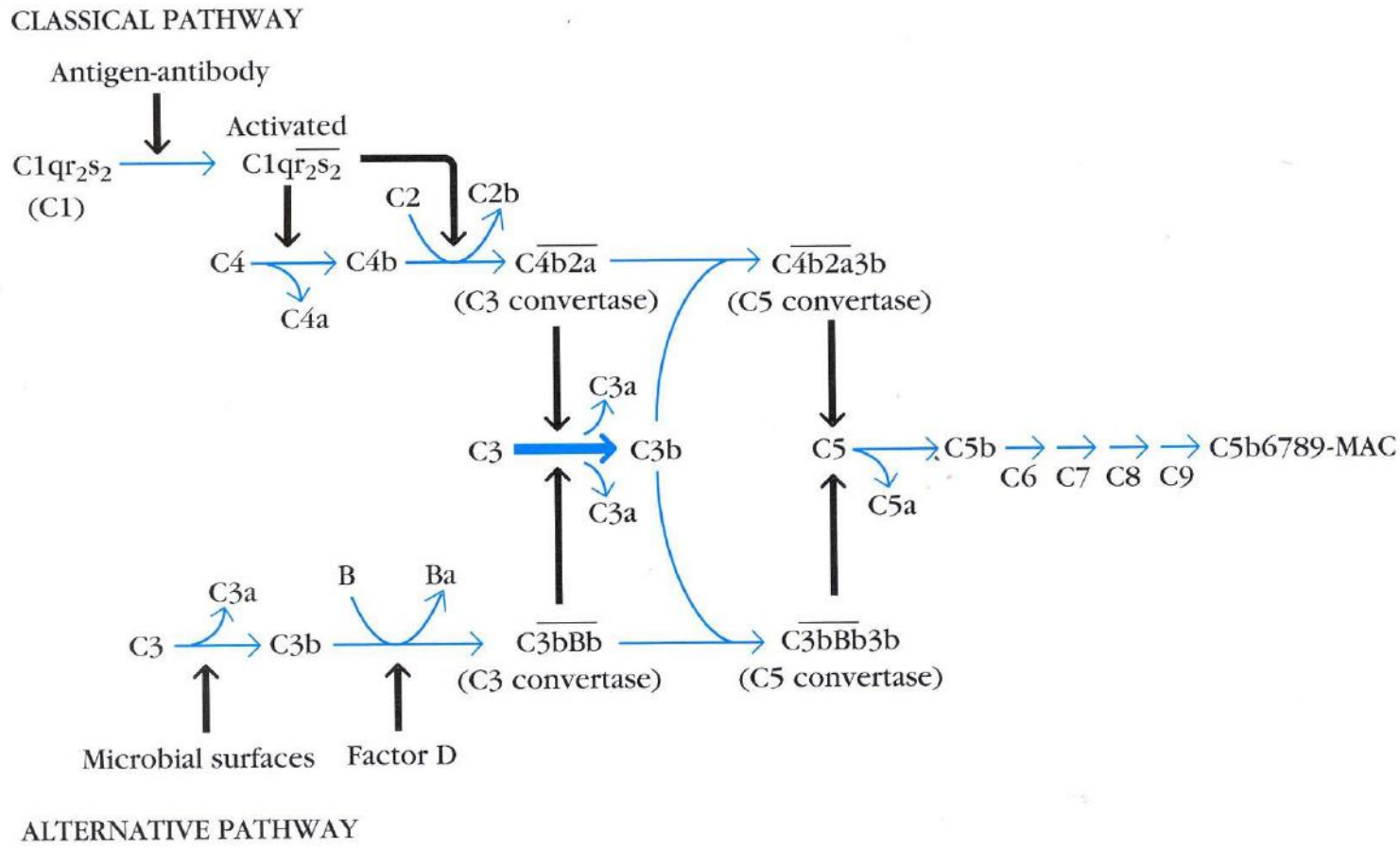



FIGURE 14-1

Overview of the complement activation pathways. The classical pathway is initiated by binding of C1 to antigen-antibody complexes. The alternative pathway is initiated by binding of C3b to activating surfaces such as microbial cell walls. Both pathways generate C3 and C5 convertases and bound C5b, which is converted into a membrane-attack complex (MAC) by a common sequence of terminal reactions. Hydrolysis of C3 is the major amplification step in both pathways, generating large amounts of C3b, which forms part of C5 convertase. C3b also can diffuse away from the activating surface and bind to immune complexes or cell surfaces, where it functions as an opsonin. Blue arrows indicate reaction steps; black arrows indicate enzymatic or activating activity.

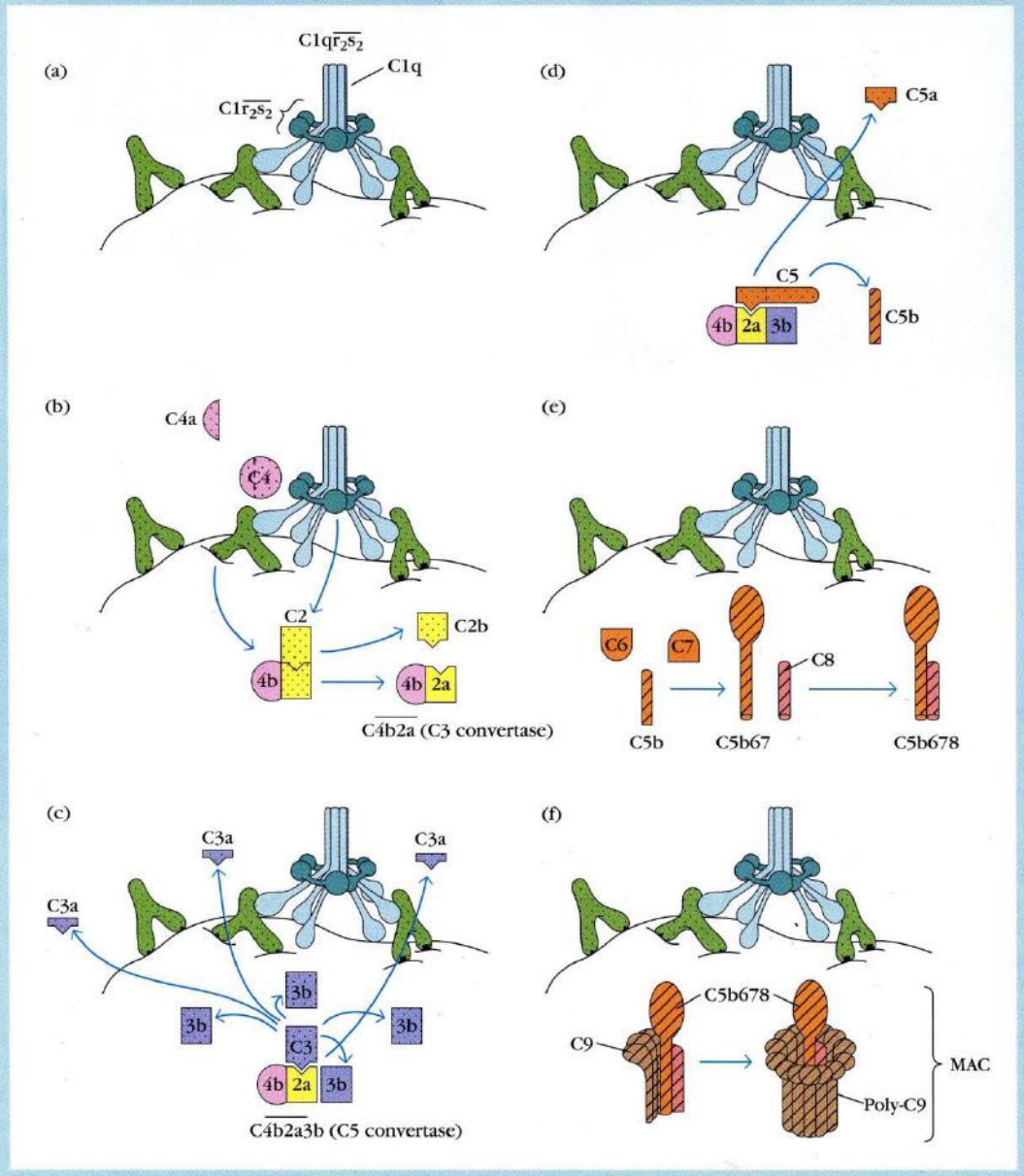



FIGURE 14-4

Schematic diagram of intermediates in the classical pathway of complement activation. Complement components, shown in solid colors, are bound to the antigenic surface but do not penetrate it; components that can insert into the cell membrane are marked with diagonal lines; and the freely diffusible components are stippled. The completed membrane-attack complex (MAC) forms a large pore in the membrane. See text for details.

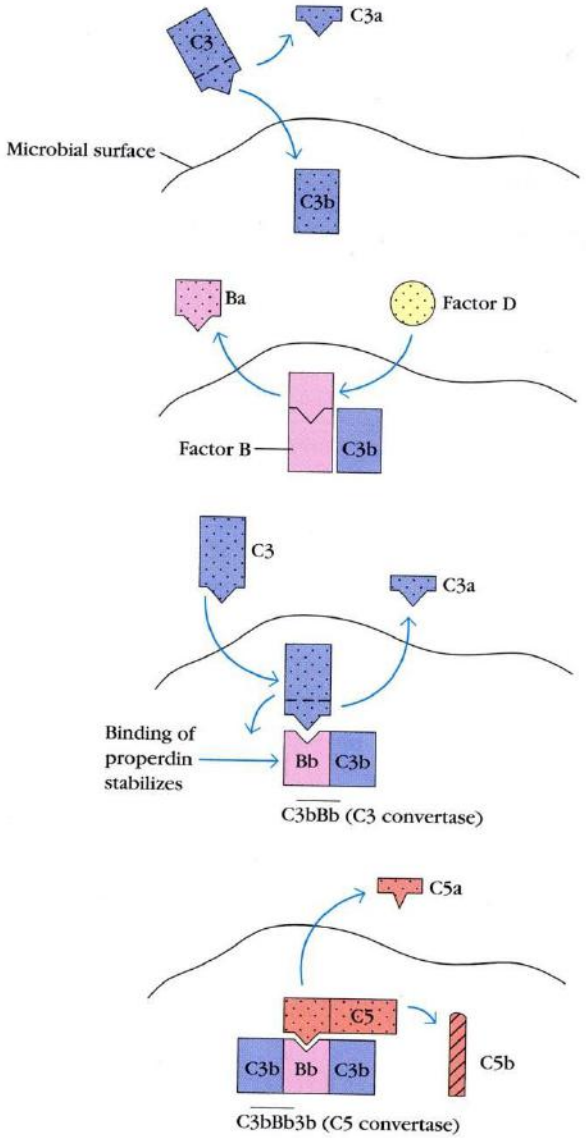
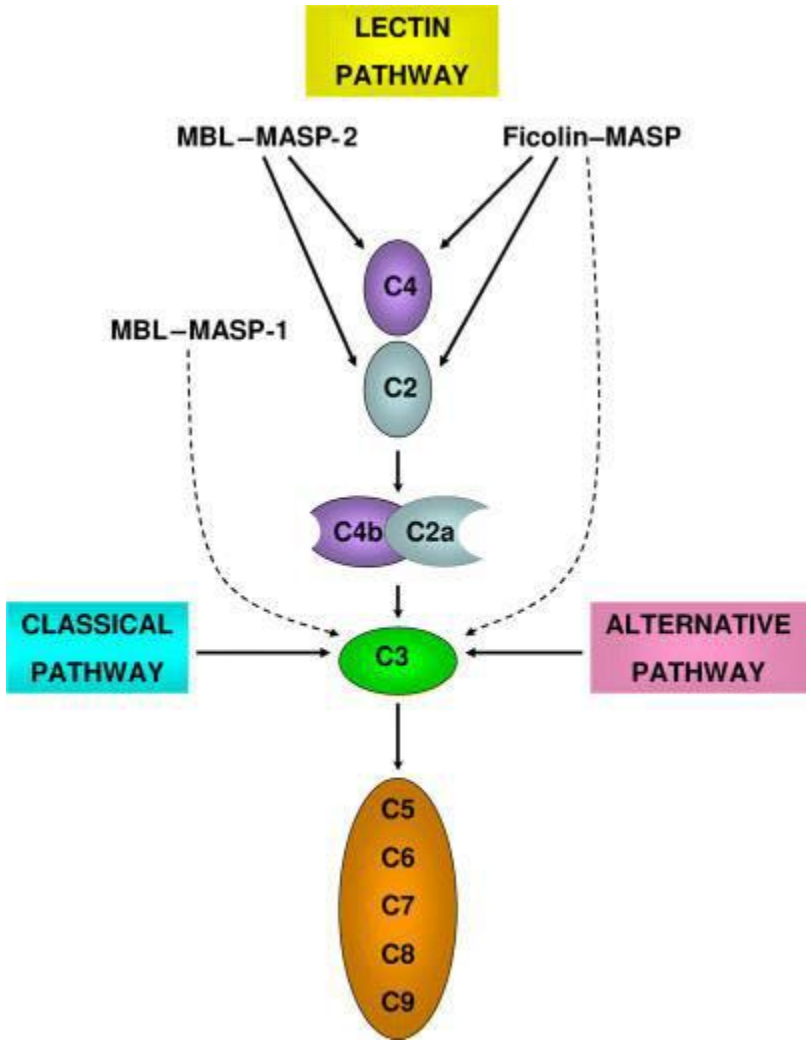



FIGURE 14-6

Schematic diagram of intermediates in formation of bound C5b by alternative pathway of complement activation. The $\overline{C3bBb}$ complex is stabilized by binding of properdin. Membrane-bound intermediates are shown in solid colors; components that can penetrate the cell membrane are marked with diagonal lines; freely diffusible components are stippled. Conversion of bound C5b to the membrane-attack complex occurs by the same sequence of reactions as in the classical pathway (see Figure 14-4e,f). See text for details.


LECTIN
PATHWAY
MBL–MASP-2
Ficolin–MASP
C4
MBL–MASP-1
C2
C4b
C2a
CLASSICAL
PATHWAY
C3
ALTERNATIVE
PATHWAY
C5
C6
C7
C8
C9

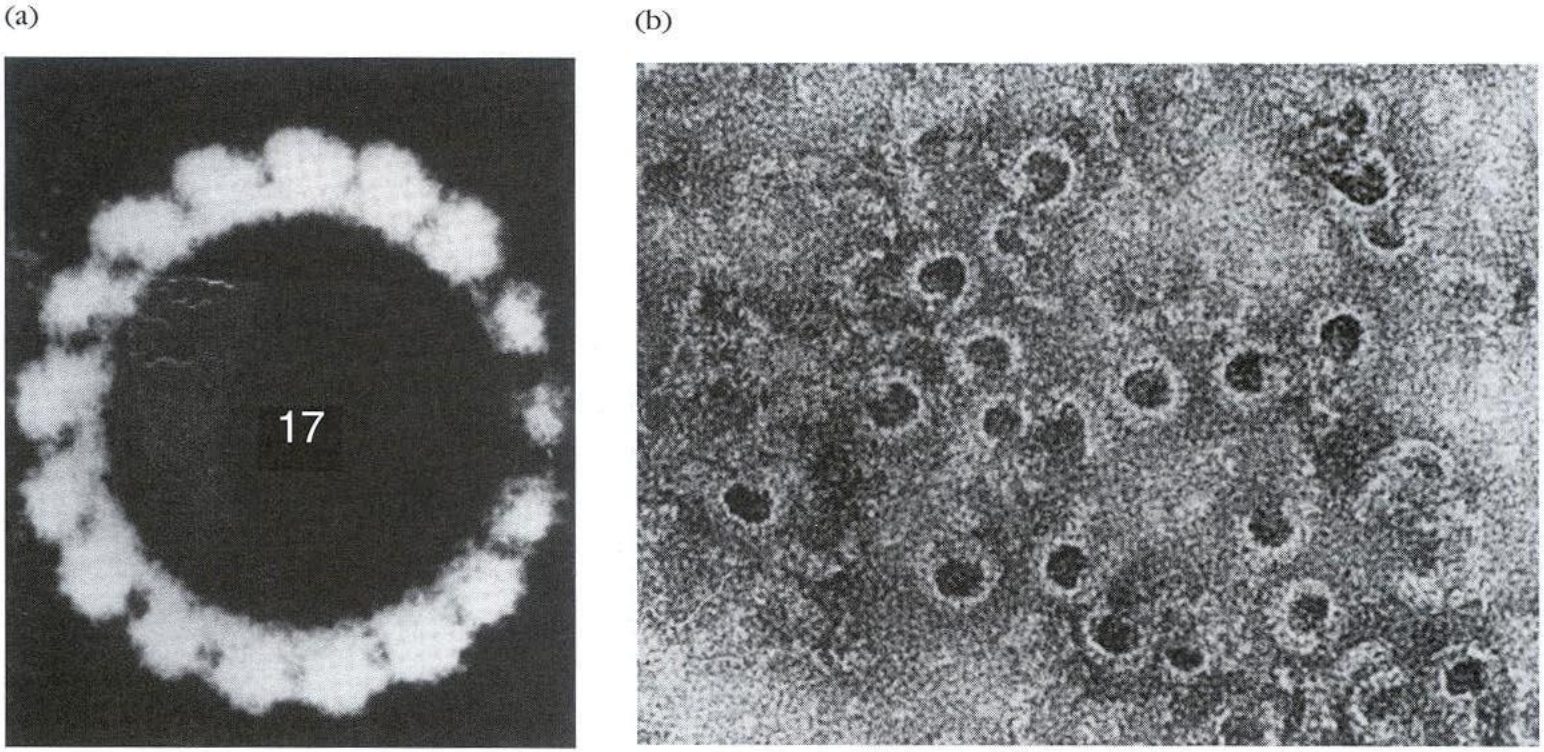
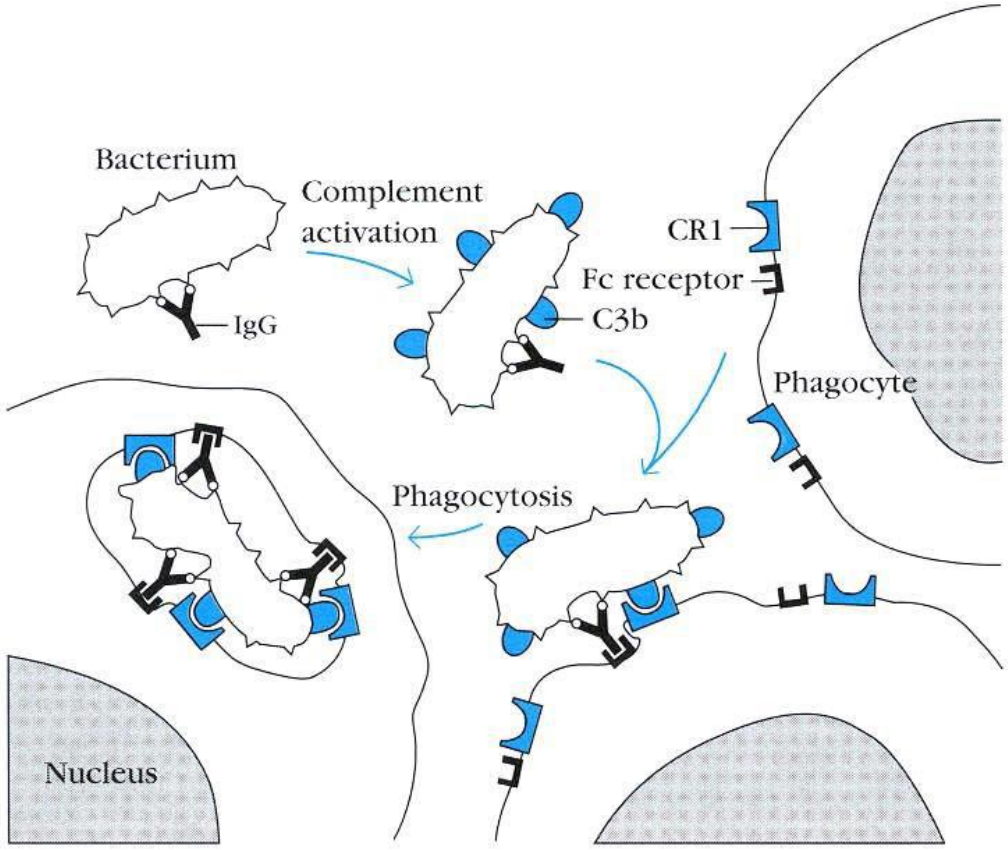



FIGURE 14-7

(a) Photomicrograph of poly-C9 complex formed by in vitro polymerization of C9. (b) Photomicrograph of complement-induced lesions on the membrane of a red blood cell. These lesions result from formation of membrane-attack complexes. [Part (a) from E. R. Podack, 1986, in *Immunobiology of the Complement System*, Academic Press; part (b) from J. Humphrey and R. Dourmashkin, 1969, *Adv. Immunol.* **11**:75.]

(a)




(b)

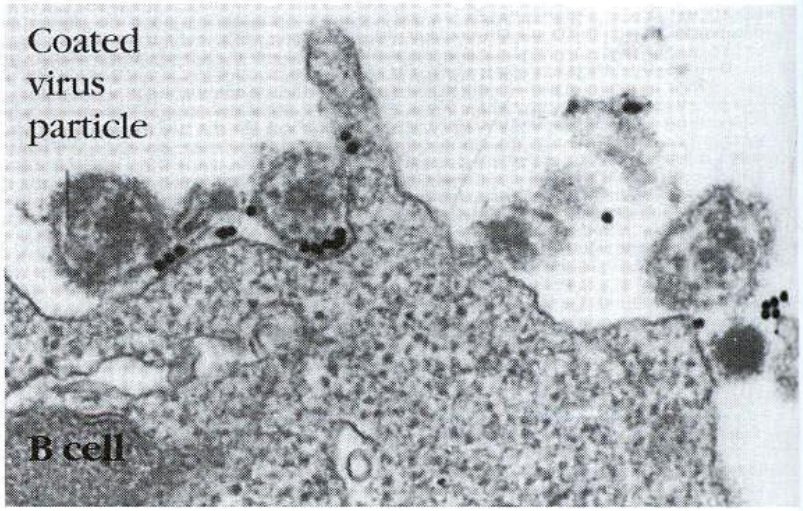



FIGURE 14-11

(a) Schematic representation of the role of C3b in opsonization. (b) Electron micrograph of Epstein-Barr virus coated with antibody and C3b and bound to the C3b receptors (CR1) on a B lymphocyte. [From N. R. Cooper and G. R. Nemerow, 1986, in *Immunobiology of the Complement System*, Academic Press.]

# COMPLEMENT COMPONENTS IN THE FORMATION OF C3 AND C5 CONVERTASES

| | CLASSICAL PATHWAY | ALTERNATIVE PATHWAY |
|---|---|---|
| Precursor proteins | C4 + C2 | C3 + factor B |
| Activating protease | $C\overline{1s}$ | Factor D |
| C3 convertase | $\overline{C4b2a}$ | $\overline{C3bBb}$ |
| C5 convertase | $\overline{C4b2a3b}$ | $\overline{C3bBb3b}$ |
| C5-binding component | C3b | C3b |

## COMPLEMENT-BINDING RECEPTORS

| RECEPTOR | MAJOR LIGANDS | ACTIVITY | CELLULAR DISTRIBUTION |
|---|---|---|---|
| CR1 (CD35) | C3b, C4b | Blocks formation of C3 convertase; binds immune complexes to cells | Erythrocytes, neutrophils, monocytes, macrophages, eosinophils, follicular dendritic cells, B cells, some T cells |
| CR2 (CD21) | C3d, C3dg,* C3bi | Part of B-cell coreceptor; binds Epstein-Barr virus | B cells, some T cells |
| CR3 (CD11b/18)<br>CR4 (CD11c/18) | C3bi | Bind cell-adhesion molecules on neutrophils, facilitating their extravasation; bind immune complexes, enhancing their phagocytosis | Monocytes, macrophages, neutrophils, natural killer cells, some T cells |
| C3a/C4a receptor | C3a, C4a | Induces degranulation of mast cells and basophils | Mast cells, basophils, granulocytes |
| C5a receptor | C5a | Induces degranulation of mast cells and basophils | Mast cells, basophils, granulocytes, monocytes, macrophages, platelets, endothelial cells |

* Cleavage of C3dg by serum proteases generates C3d and C3g.

## SUMMARY OF BIOLOGICAL EFFECTS MEDIATED BY COMPLEMENT PRODUCTS

| EFFECT | COMPLEMENT PRODUCT MEDIATING * |
|---|---|
| Cell lysis | C5b–9, the membrane-attack complex (MAC) |
| Inflammatory Response: | |
| Degranulation of mast cells and basophils † | C3a, C4a, and C5a (anaphylatoxins) |
| Degranulation of eosinophils | C3a, C5a |
| Extravasation and chemotaxis of leukocytes at inflammatory site | C3a, **C5a**, C5b67 |
| Aggregation of platelets | C3a, C5a |
| Inhibition of monocyte/macrophage migration and induction of their spreading | Bb |
| Release of neutrophils from bone marrow | C3c |
| Release of hydrolytic enzymes from neutrophils | C5a |
| Increased expression of complement receptors type 1 and 3 (CR1 and CR3) on neutrophils | C5a |
| Opsonization of particulate antigens, increasing their phagocytosis | **C3b**, C4b, C3bi |
| Viral neutralization | C3b, C5b–9 (MAC) |
| Solubilization and clearance of immune complexes | C3b |

* Boldfaced component is most important in mediating indicated effect.

† Degranulation leads to release of histamine and other mediators that induce contraction of smooth muscle and increased permeability of vessels.

## MICROBIAL EVASION OF COMPLEMENT-MEDIATED DAMAGE

| MICROBIAL COMPONENT | MECHANISM OF EVASION | EXAMPLES |
|---|---|---|
| | **GRAM-NEGATIVE BACTERIA** | |
| Long polysaccharide chains in cell-wall LPS | Side chains prevent insertion of MAC in bacterial membrane | Resistant strains of *E. coli* and *Salmonella* sp. |
| Outer membrane protein | MAC interacts with membrane protein and fails to insert into bacterial membrane | Resistant strains of *Neisseria gonorrhoeae* |
| Elastase | Anaphylotoxins C3a and C5a are inactivated by microbial elastase | *Pseudomonas aeruginosa* |
| | **GRAM-POSITIVE BACTERIA** | |
| Peptidoglycan layer of cell wall | Insertion of MAC into bacterial membrane is prevented by thick layer of peptidoglycan | *Streptococcus* sp. |
| Bacterial capsule | Capsule provides physical barrier between C3b deposited on bacterial membrane and CR 1 on phagocytic cells | *Streptococcus pneumoniae* |
| | **OTHER MICROBES** | |
| Proteins that mimic complement regulatory proteins | Proteins present in various bacteria, viruses, fungi, and protozoans inhibit the complement cascade | Vaccinia virus, herpes simplex, Epstein-Barr virus, *Trypanosoma cruzi, Candida albicans* |

KEY: CR 1 = type 1 complement receptor; LPS = lipopolysaccharide; MAC = membrane-attack complex (C5b–9).

## GELL AND COOMBS CLASSIFICATION OF HYPERSENSITIVE REACTIONS

| TYPE | DESCRIPTIVE NAME | INITIATION TIME | MECHANISM | TYPICAL MANIFESTATIONS |
|---|---|---|---|---|
| | | | IMMEDIATE REACTIONS | |
| Type 1 | IgE-mediated hypersensitivity | 2–30 min | Ag induces cross-linkage of IgE bound to mast cells and basophils with release of vasoactive mediators | Systemic anaphylaxis<br>Localized anaphylaxis:<br>Hay fever<br>Asthma<br>Hives<br>Food allergies<br>Eczema |
| Type II | Antibody-mediated cytotoxic hypersensitivity | 5–8 h | Ab directed against cell-surface antigens mediates cell destruction via complement activation or ADCC | Blood-transfusion reactions<br>Erythroblastosis fetalis<br>Autoimmune hemolytic anemia |
| Type III | Immune complex–mediated hypersensitivity | 2–8 h | Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response | Localized Arthus reaction<br>Generalized reactions:<br>Serum sickness<br>Glomerulonephritis<br>Rheumatoid arthritis<br>Systemic lupus erythematosus |
| | | | DELAYED REACTIONS | |
| Type IV | Cell-mediated hypersensitivity | 24–72 h | Sensitized $T_{DTH}$ cells release cytokines that activate macrophages or $T_C$ cells, which mediate direct cellular damage | Contact dermatitis<br>Tubercular lesions<br>Graft rejection |

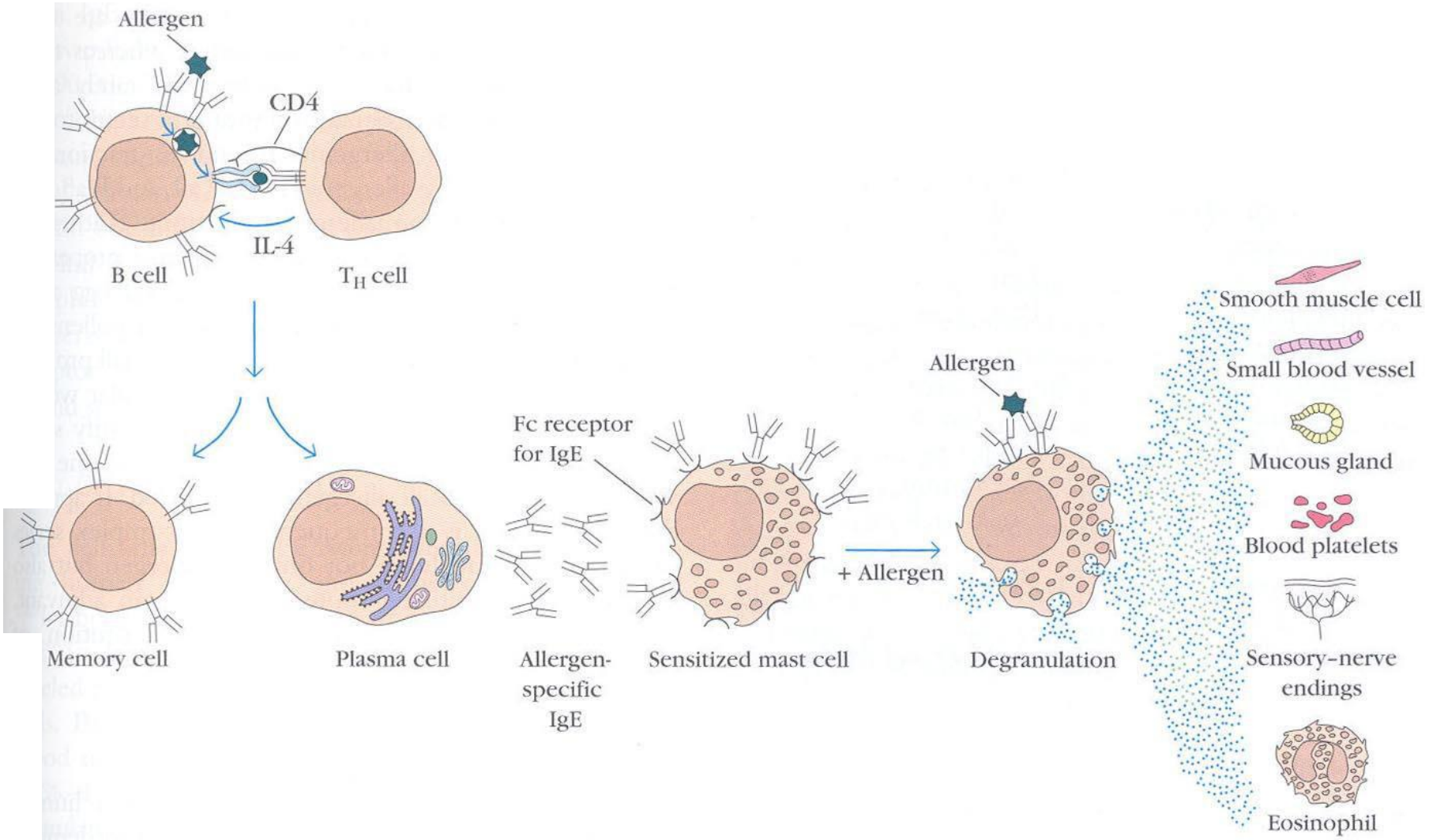



FIGURE 17-1

General mechanism underlying a type I hypersensitive reaction. Exposure to an allergen activates B cells to form IgE-secreting plasma cells. The secreted IgE molecules bind to IgE-specific Fc receptors on mast cells and blood basophils. Second exposure to the allergen leads to cross-linking of the bound IgE, triggering the release of pharmacologically active mediators from mast cells and basophils. The mediators cause smooth-muscle contraction, increased vascular permeability, and vasodilation.

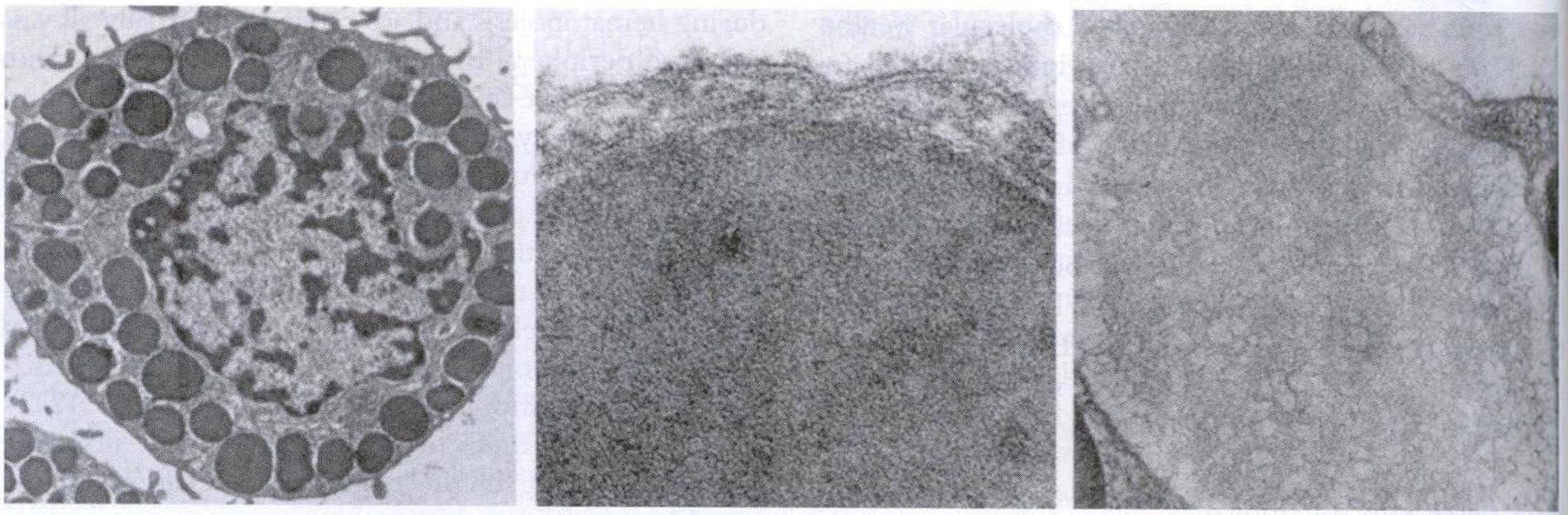



FIGURE 17-2

(a) Electron micrograph of a typical mast cell reveals numerous electron-dense membrane-bounded granules prior to degranulation. (b) Close-up of intact granule underlying the plasma membrane of a mast cell. (c) Granule releasing its contents during degranulation. [From S. Burwen and B. Satir, 1977, *J. Cell Biol.* **73**:662.]

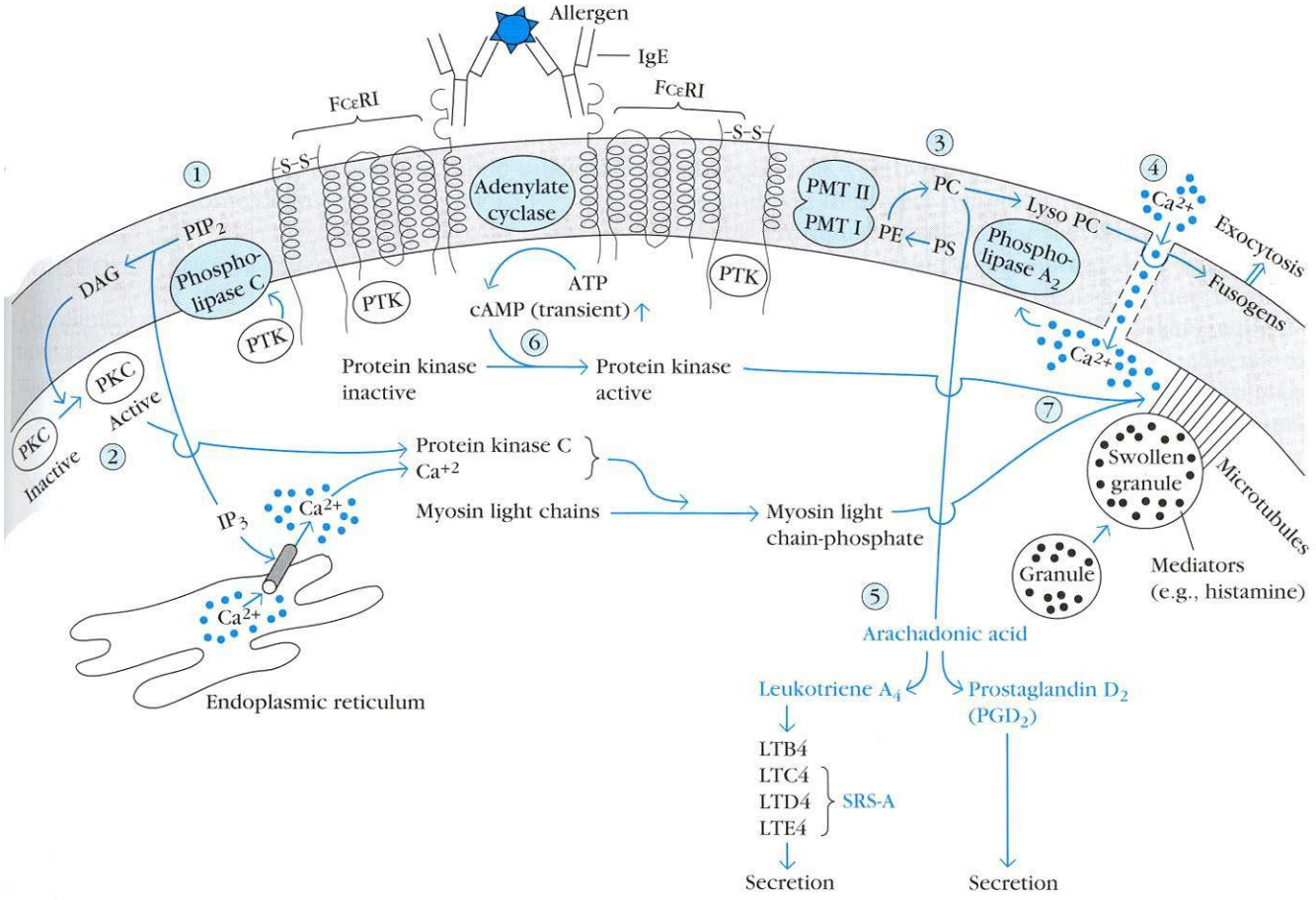



FIGURE 17-5

Diagrammatic overview of biochemical events in mast cell activation and degranulation. Allergen cross-linkage of bound IgE results in FcεRI aggregation and activation of protein tyrosine kinase (PTK). (1) PTK then phosphorylates phospholipase C, which converts phosphatidylinositol-4,5 bisphosphate ($PIP_2$) into diacylglycerol (DAG) and inositol triphosphate ($IP_3$). (2) DAG activates protein kinase C (PKC), which phosphorylates myosin light chains necessary for microtubular assembly and the fusion of the granules with the plasma membrane. $IP_3$ is a potent mobilizer of intracellular $Ca^{2+}$ stores. Cross-linkage of FcεRI also activates an enzyme that converts phosphatidylserine (PS) into phosphatidylethanolamine (PE). (3) Eventually PE is methylated to form phosphatidylcholine (PC) by two phospholipid methyl transferase enzymes I and II (PMT I and II). (4) The accumulation of PC on the exterior surface of the plasma membrane causes an increase in membrane fluidity and facilitates the formation of $Ca^{2+}$ channels. The resulting influx of $Ca^{2+}$ activates phospholipase $A_2$, which promotes the breakdown of PC to form lysophosphatidylcholine (lyso PC) and arachidonic acid. (5) Arachidonic acid is converted into potent mediators: the leukotrienes and prostaglandin $D_2$. (6) FcεRI cross-linkage also activates the membrane adenylate cyclase leading to a transient increase of cAMP within 15 s. A later drop in cAMP levels is mediated by protein kinase and is required for degranulation to proceed. (7) cAMP-dependent protein kinases are thought to phosphorylate the granule-membrane proteins, thereby changing the granules' permeability to water and $Ca^{2+}$. The consequent swelling of the granules facilitates fusion with the plasma membrane and release of the mediators.

## PRINCIPAL MEDIATORS INVOLVED IN TYPE I HYPERSENSITIVITY

| MEDIATOR | EFFECTS |
|---|---|
| | **PRIMARY** |
| Histamine | Increased vascular permeability; smooth-muscle contraction |
| Serotonin | Increased vascular permeability; smooth-muscle contraction |
| Eosinophil chemotactic factor (ECF-A) | Eosinophil chemotaxis |
| Neutrophil chemotactic factor (NCF-A) | Neutrophil chemotaxis |
| Proteases | Bronchial mucus secretion; degradation of blood-vessel basement membrane; generation of complement split products |
| | **SECONDARY** |
| 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 |
| Cytokines | |
| IL-1 and TNF-$\alpha$ | Systemic anaphylaxis; increased expression of CAMs on venular endothelial cells |
| IL-2, IL-3, IL-4, IL-5, IL-6, TGF-$\beta$, and GM-CSF | Various effects (see Table 13-1) |

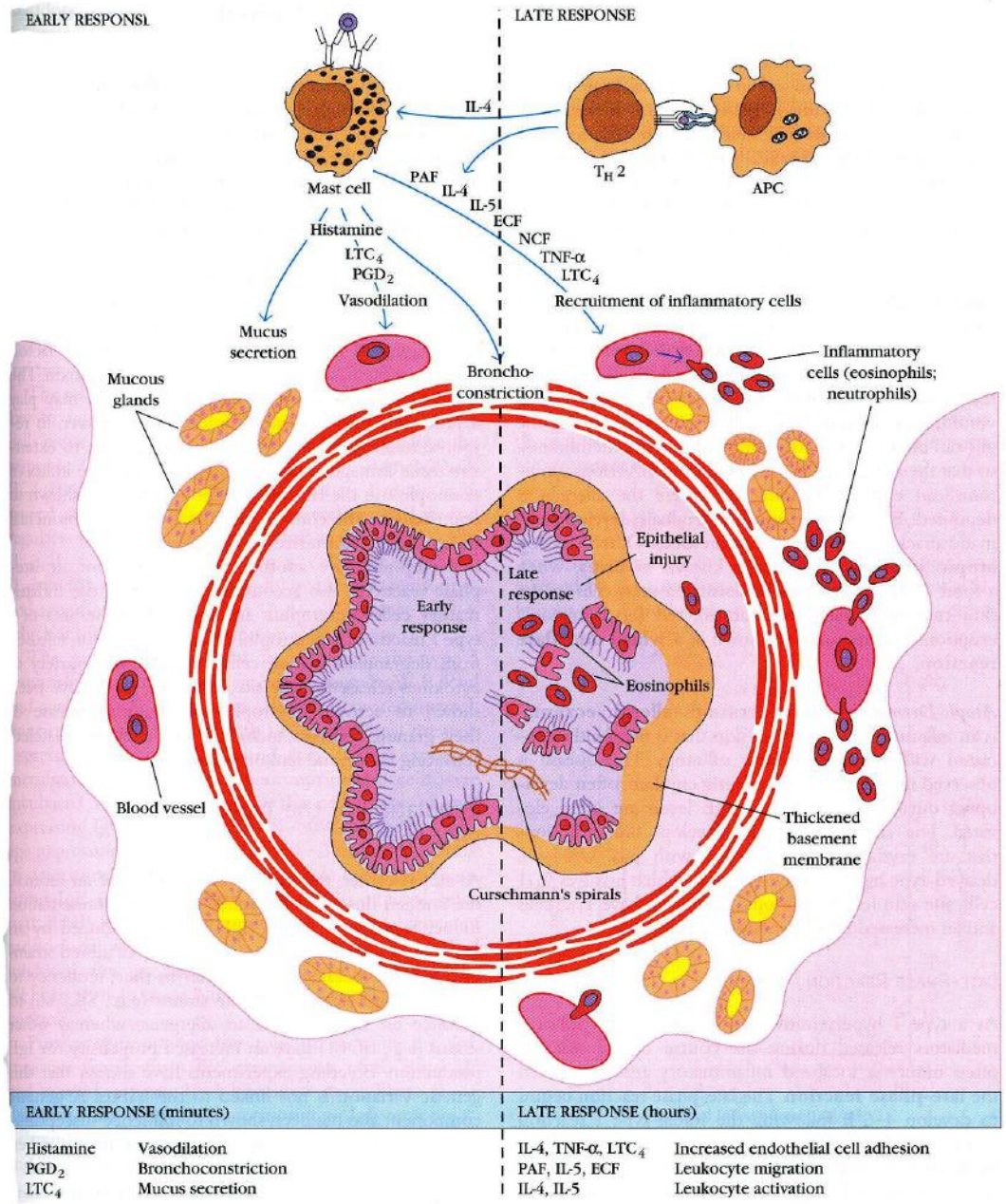



FIGURE 17-7

The early and late inflammatory response in asthma. The immune cells involved in the early and late response are represented at the top. The effects of various mediators on an airway, represented in cross-section, are illustrated in the center. See text for explanation.

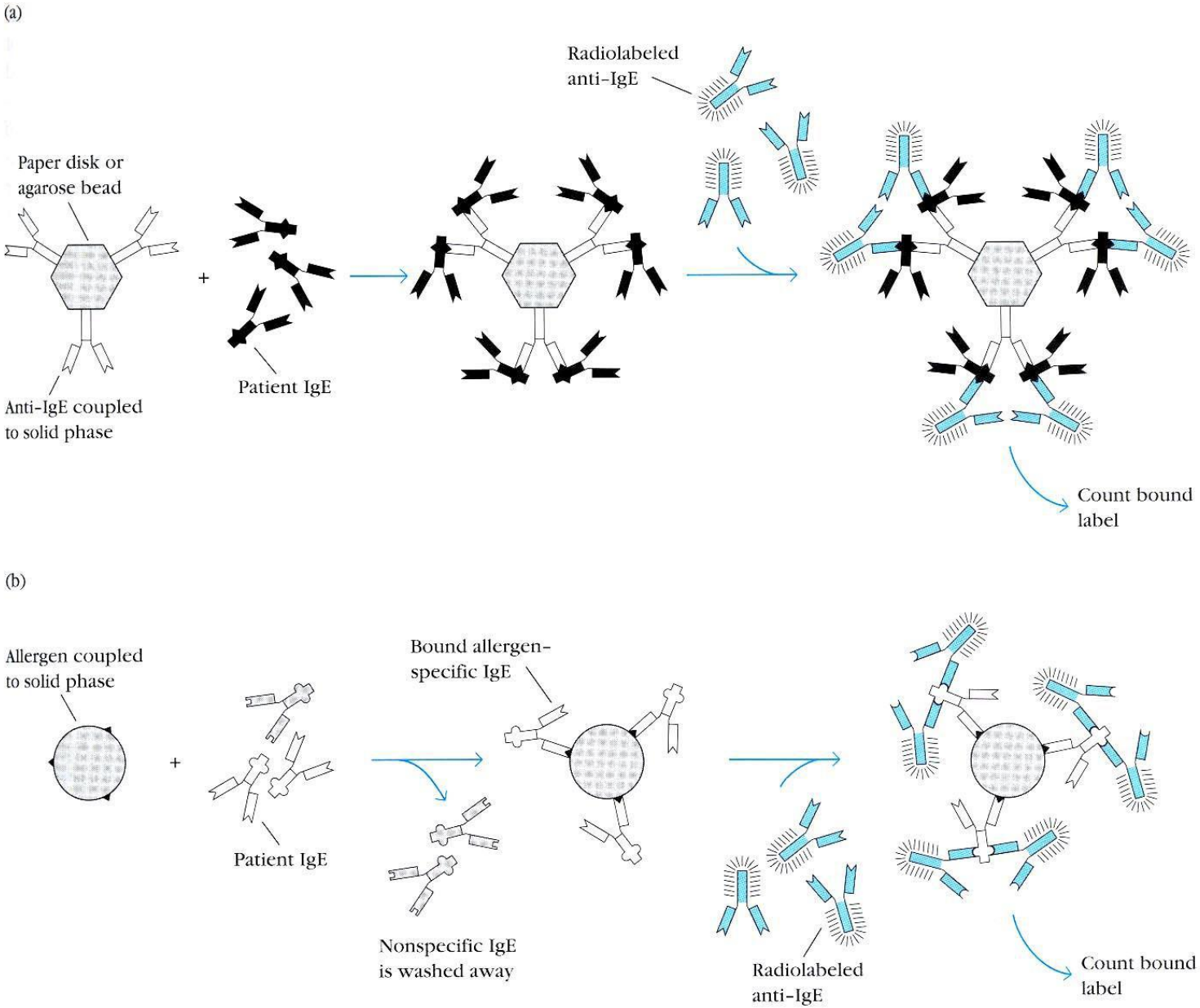



FIGURE 17-10

Procedures for assessing type I hypersensitivity. (a) Radioimmunosorbent test (RIST) can quantify nanogram amounts of total serum IgE. (b) Radioallergosorbent test (RAST) can quantify nanogram amounts of serum IgE specific for a particular allergen.

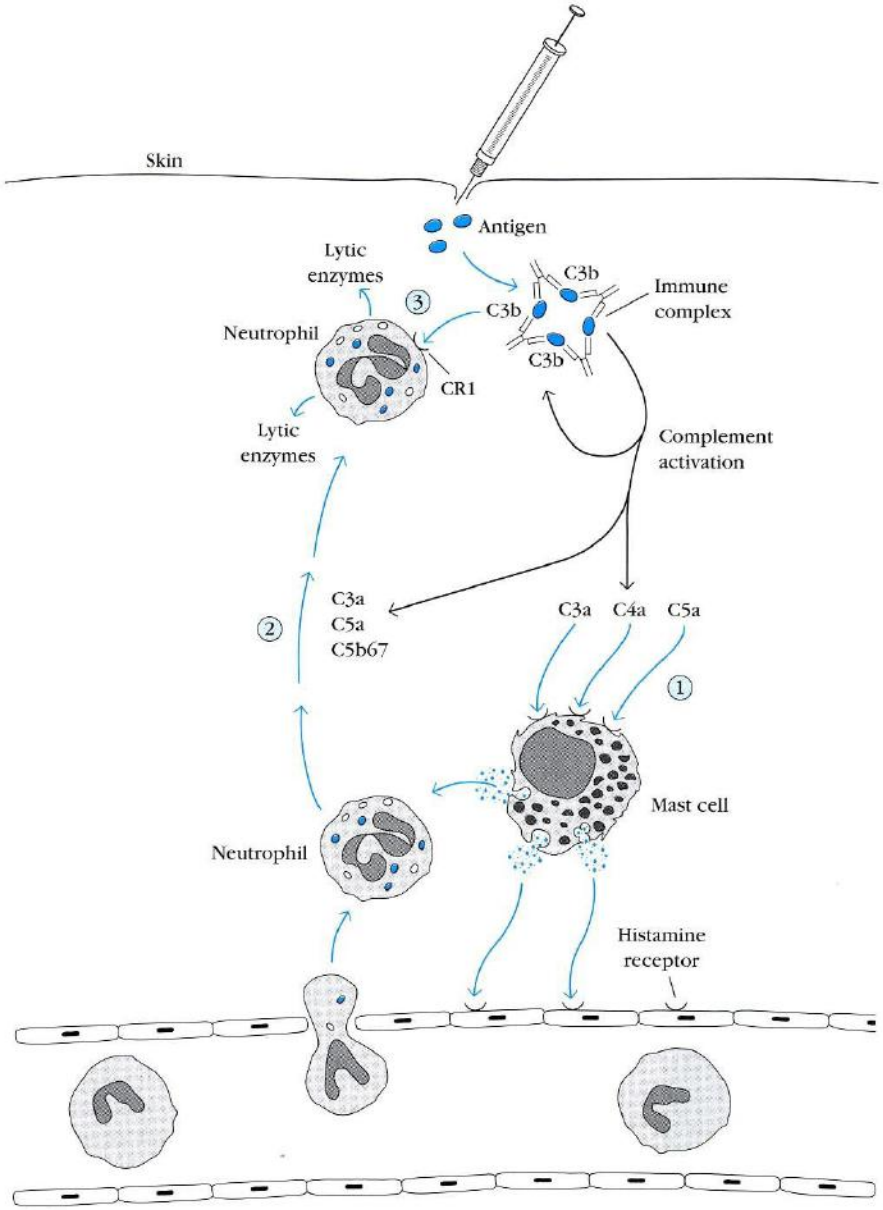



FIGURE 17-14

Development of a localized Arthus reaction (type III hypersensitive reaction). Complement activation initiated by immune complexes (classical pathway) produces complement intermediates that (1) mediate mast cell degranulation, (2) chemotactically attract neutrophils, and (3) stimulate release of lytic enzymes from neutrophils trying to phagocytose C3b-coated immune complexes. See text for further discussion.