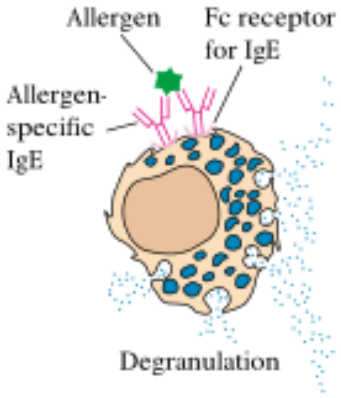
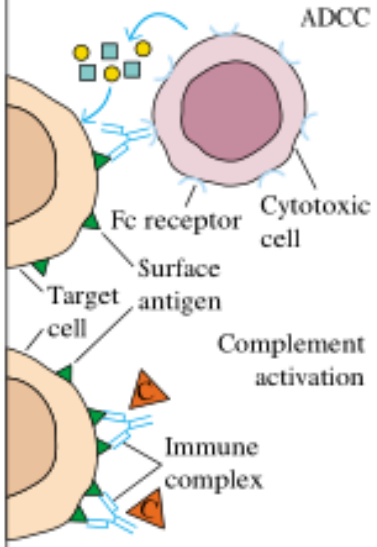
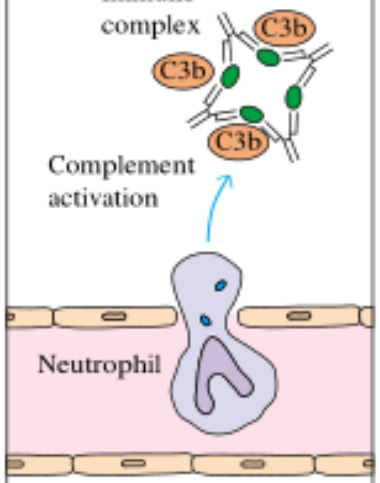
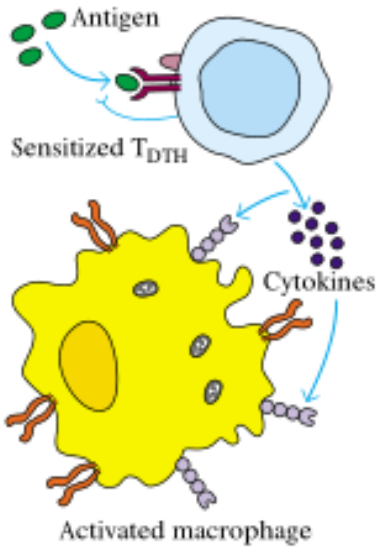
Hypersensitive reactions

For

B.Sc Life Sciences VI Sem
Paper Immunology
Teacher: Dr. Renu Solanki

 **Type I**	 **Type II**	 **Type III**	 **Type IV**
IgE-Mediated Hypersensitivity	IgG-Mediated Cytotoxic Hypersensitivity	Immune Complex-Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
Ag induces crosslinking of IgE bound to mast cells and basophils with release of vasoactive mediators	Ab directed against cell surface antigens meditates cell destruction via complement activation or ADCC	Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils	Sensitized T_H1 cells release cytokines that activate macrophages or T_C cells which mediate direct cellular damage
Typical manifestations include systemic anaphylaxis and localized anaphylaxis such as hay fever, asthma, hives, food allergies, and eczema	Typical manifestations include blood transfusion reactions, erythroblastosis fetalis, and autoimmune hemolytic anemia	Typical manifestations include localized Arthus reaction and generalized reactions such as serum sickness, necrotizing vasculitis, glomerulnephritis, rheumatoid arthritis, and systemic lupus erythematosus	Typical manifestations include contact dermatitis, tubercular lesions and graft rejection

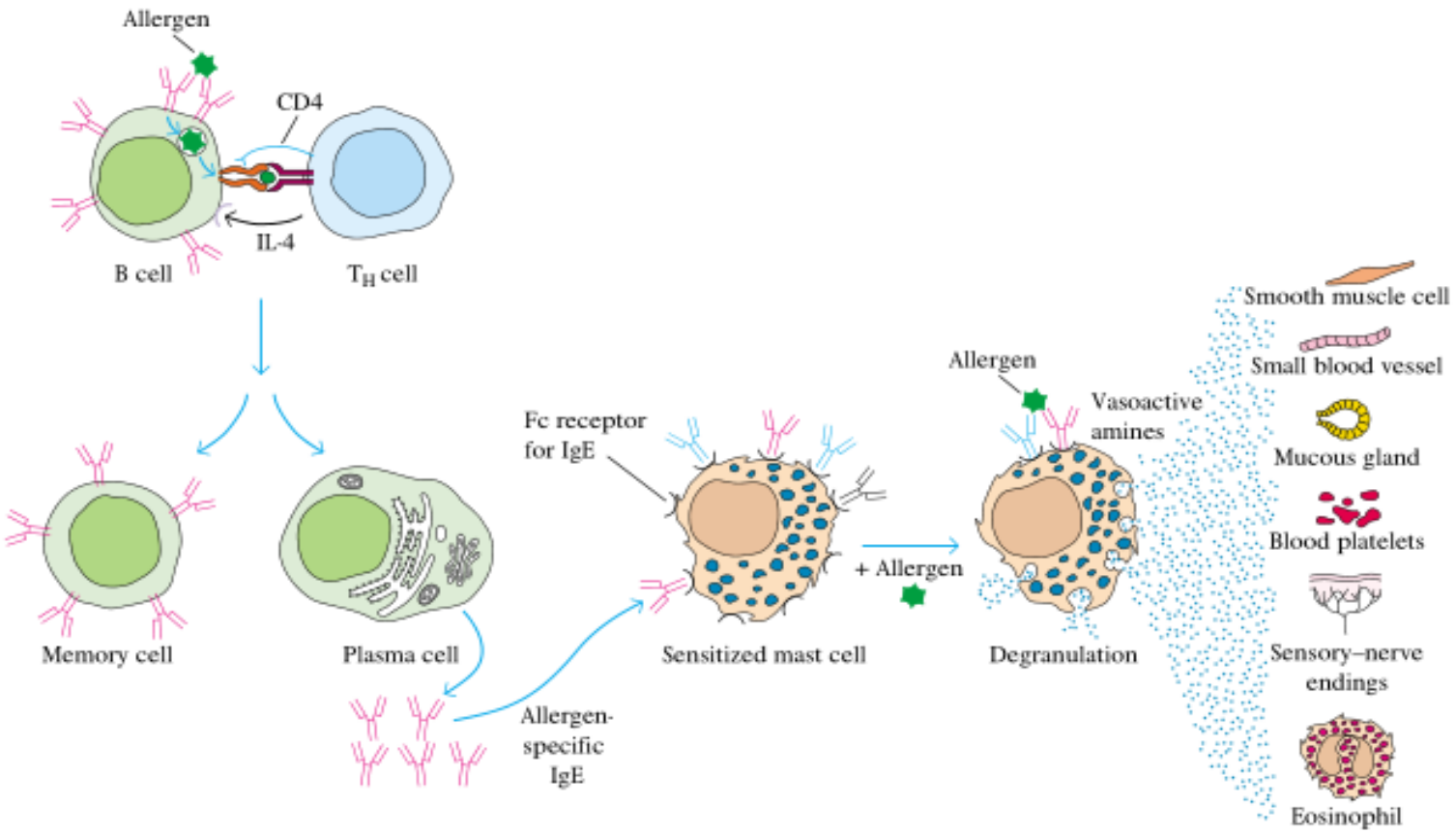


FIGURE 16-2 General mechanism underlying a type I hypersensitive reaction. Exposure to an allergen activates B cells to form IgE-secreting plasma cells. The secreted IgE molecules bind to IgE-specific Fc receptors on mast cells and blood basophils. (Many molecules of IgE with various specificities can bind to the IgE-Fc receptor.) Second exposure to the allergen leads to crosslinking of the bound IgE, triggering the release of pharmacologically active mediators, vasoactive amines, from mast cells and basophils. The mediators cause smooth-muscle contraction, increased vascular permeability, and vasodilation.

There Are Several Components of Type I Reactions

1. Allergens: The majority of humans mount significant IgE responses only as a defense against parasitic infections. After an individual has been exposed to a parasite, serum IgE levels increase and remain high until the parasite is successfully cleared from the body. The term allergen refers specifically to nonparasitic antigens capable of stimulating type I hypersensitive responses in allergic individuals.

TABLE 16-1 Common allergens associated with type I hypersensitivity

Proteins	Foods
Foreign serum	Nuts
Vaccines	Seafood
	Eggs
Plant pollens	Peas, beans
Rye grass	Milk
Ragweed	
Timothy grass	Insect products
Birch trees	Bee venom
	Wasp venom
Drugs	Ant venom
Penicillin	Cockroach calyx
Sulfonamides	Dust mites
Local anesthetics	
Salicylates	Mold spores
	Animal hair and dander

2. REAGINIC ANTIBODY (I_GE): Serum IgE levels in normal individuals fall within the range of 0.1–0.4 µg/ml; even the most severely allergic individuals rarely have IgE levels greater than 1 µg/ml.

IgE was found to be composed of two heavy and two light chains with a combined molecular weight of190,000.The higher molecular weight as compared with IgG (150,000) is due to the presence of an additional constant-region domain (see Figure 4-13). This additional domain (C H 4) contributes to an altered conformation of the Fc portion of the molecule that enables it to bind to glycoprotein receptors on the surface of basophils and mast cells.

Although the half-life of IgE in the serum is only 2–3 days, once IgE has been bound to its receptor on mast cells and basophils,it is stable in that state for a number of weeks.

IgE Crosslinkage Initiates Degranulation

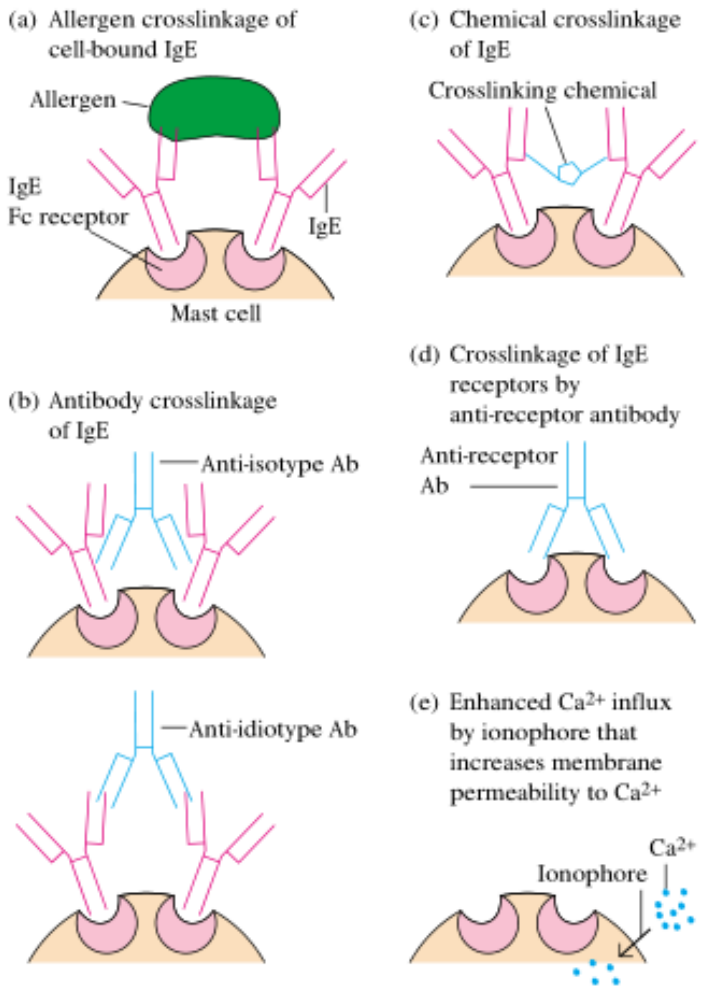


FIGURE 16-5 Schematic diagrams of mechanisms that can trigger degranulation of mast cells. Note that mechanisms (b) and (c) do not require allergen; mechanisms (d) and (e) require neither allergen nor IgE; and mechanism (e) does not even require receptor crosslinkage.

TABLE 16-3 Principal mediators involved in type I hypersensitivity

Mediator	Effects
	PRIMARY
Histamine, heparin	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-α	Systemic anaphylaxis; increased expression of CAMs on venular endothelial cells
IL-2, IL-3, IL-4, IL-5, IL-6, TGF-β, and GM-CSF	Various effects (see Table 12-1)

Type I Reactions Can Be Systemic or Localized

SYSTEMIC ANAPHYLAXIS

LOCALIZED ANAPHYLAXIS (ATOPY)

-ALLERGIC RHINITIS: ALLERGIC RHINITIS: Results from the reaction of airborne allergens with sensitized mast cells in the conjunctivae and nasal mucosa to induce the release of pharmacologically active mediators from mast cells; these mediators then cause localized vasodilation and increased capillary perme-
ability.

- ASTHMA: In some cases, airborne or blood-borne allergens, such as pollens, dust, fumes, insect products, or viral antigens, trigger an asthmatic attack (allergic asthma); in other cases, an asthmatic attack can be induced by exercise or cold, apparently independently of allergen stimulation (intrinsic asthma). Like hay fever, asthma is triggered by degranulation of mast cells with release of mediators, but instead of occurring in the nasal mucosa, the reaction develops in the lower respiratory tract. The resulting contraction of the bronchial smooth muscles leads to bronchoconstriction.

-FOOD ALLERGIES

Various foods also can induce localized anaphylaxis in allergic individuals. Allergen crosslinking of IgE on mast cells along the upper or lower gastrointestinal tract can induce localized smooth-muscle contraction and vasodilation and thus such symptoms as vomiting or diarrhea.

-ATOPIC DERMATITIS

Atopic dermatitis (allergic eczema) is an inflammatory disease of skin. The allergic individual develops skin eruptions that are erythematous and filled with pus.

Several Methods Are Used to Detect Type I Hypersensitivity Reactions

The advantage of skin testing is that it is relatively inexpensive and allows screening of a large number of allergens at one time. The disadvantage of skin testing is that it sometimes sensitizes the allergic individual to new allergens.

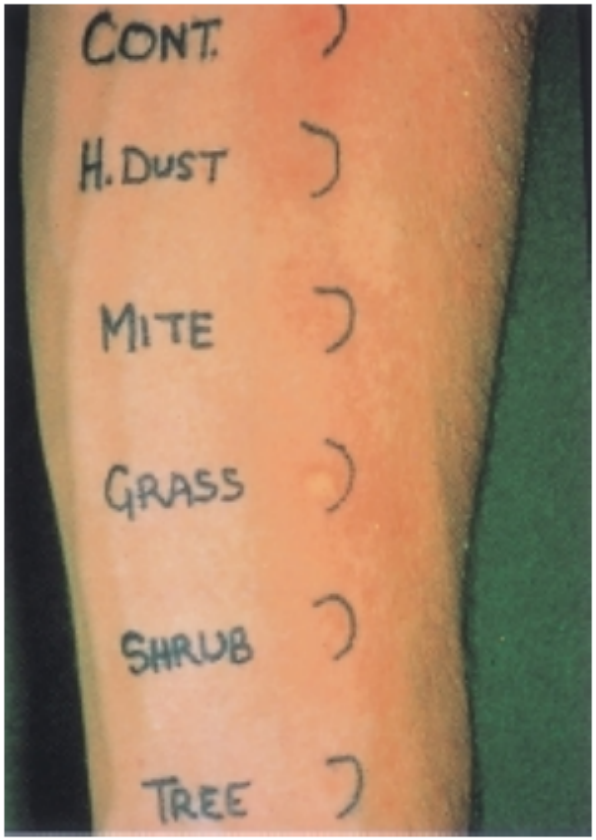
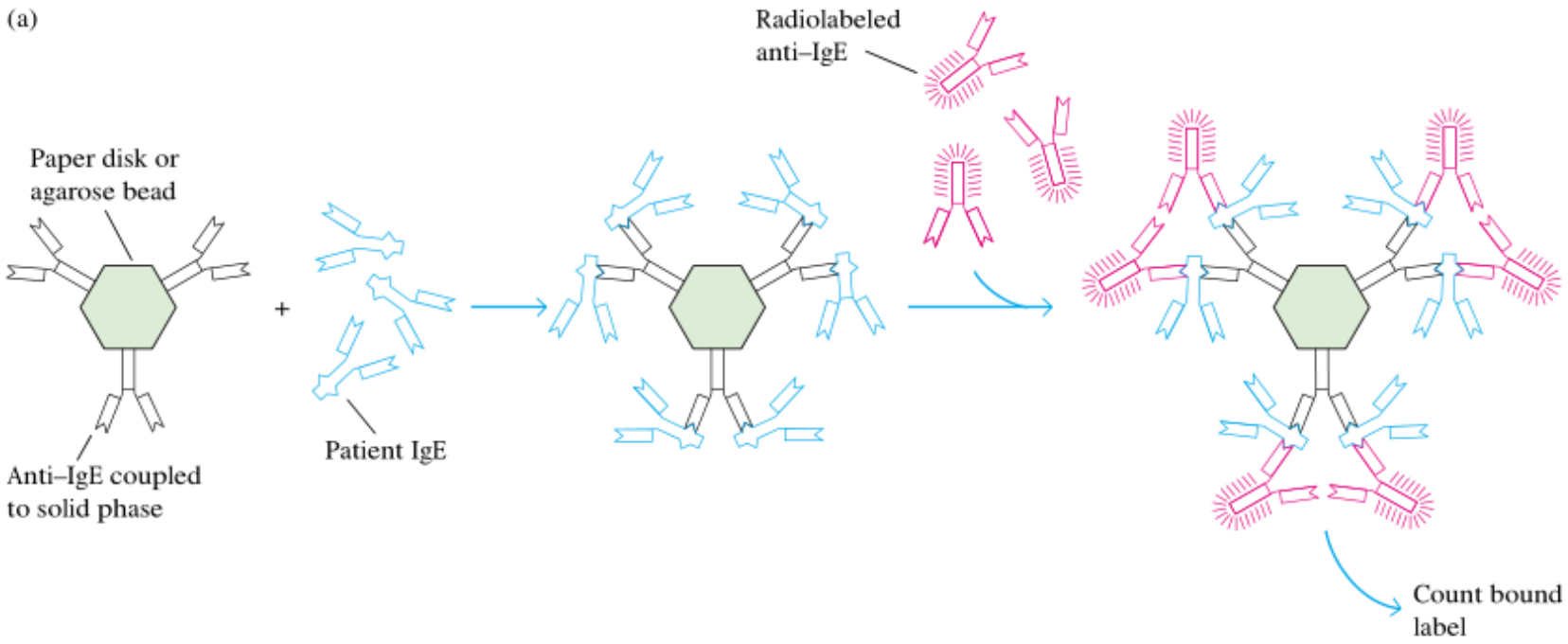
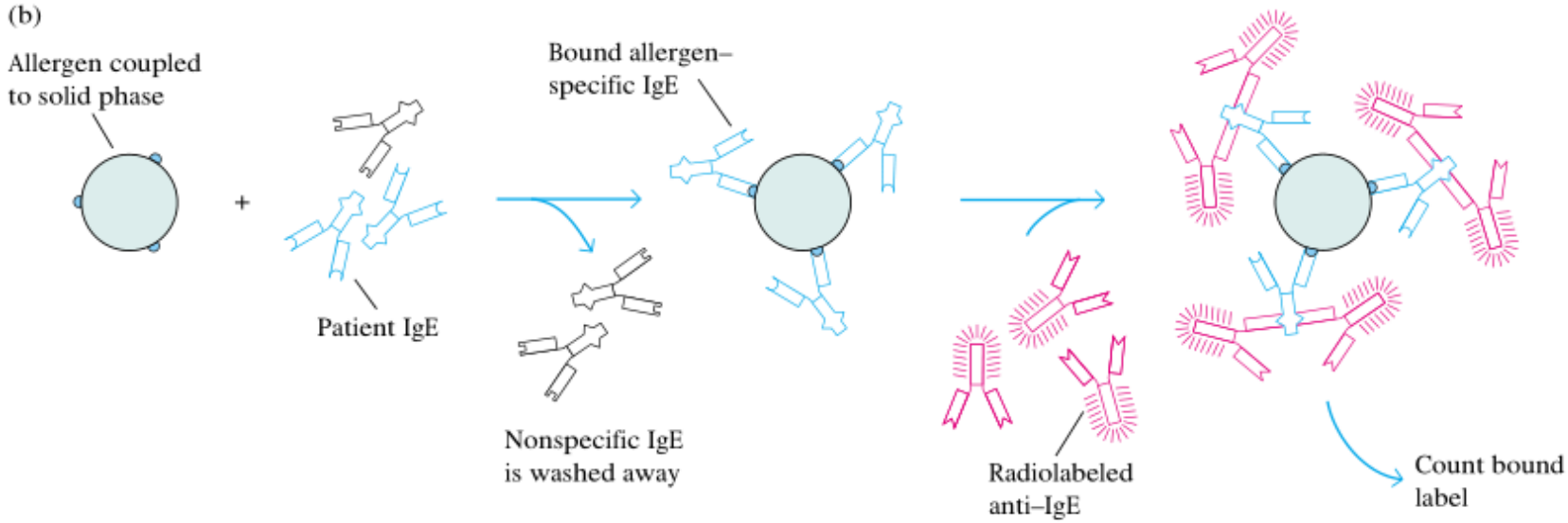


FIGURE 16-10 Skin testing by intradermal injection of allergens into the forearm. In this individual, a weal and flare response developed within a few minutes at the site where grass was injected, indicating that the individual is allergic to grass. *[From L. M. Lichtenstein, 1993,* Sci. Am. ***269****(2):117. Used with permission.]*

Another method of assessing type I hypersensitivity is to determine the serum level of total IgE antibody by the **radioimmunosorbent test (RIST).**This highly sensitive technique, based on the radioimmunoassay.



Radioallergosorbent test (RAST) detects the serum level of IgE specific for a given allergen



Antibody-Mediated Cytotoxic (Type II) Hypersensitivity

Type II hypersensitive reactions involve antibody-mediated destruction of cells. Antibody can activate the complement system, creating pores in the membrane of a foreign cell or it can mediate cell destruction by antibody-dependent cell-mediated cytotoxicity (ADCC).

-Transfusion Reactions Are Type II Reactions

-Hemolytic Disease of the Newborn Is Caused by Type II Reactions:

Hemolytic disease of the newborn develops when maternal IgG antibodies specific for fetal blood-group antigens cross the placenta and destroy fetal red blood cells. The consequences of such transfer can be minor, serious, or lethal. Severe hemolytic disease of the newborn, called erythroblastosis fetalis, most commonly develops when an Rh + fetus expresses an Rh antigen on its blood cells that the Rh – mother does not express.

-Drug-Induced Hemolytic Anemia Is a Type II Response

Certain antibiotics (e.g.,penicillin, cephalosporin, and streptomycin) can adsorb nonspecifically to proteins on RBC membranes, forming a complex similar to a hapten-carrier complex. In some patients, such drug-protein complexes induce formation of antibodies, which then bind to the adsorbed drug on red blood cells, inducing complement-mediated lysis and thus progressive anemia. When the drug is withdrawn, the hemolytic anemia disappears

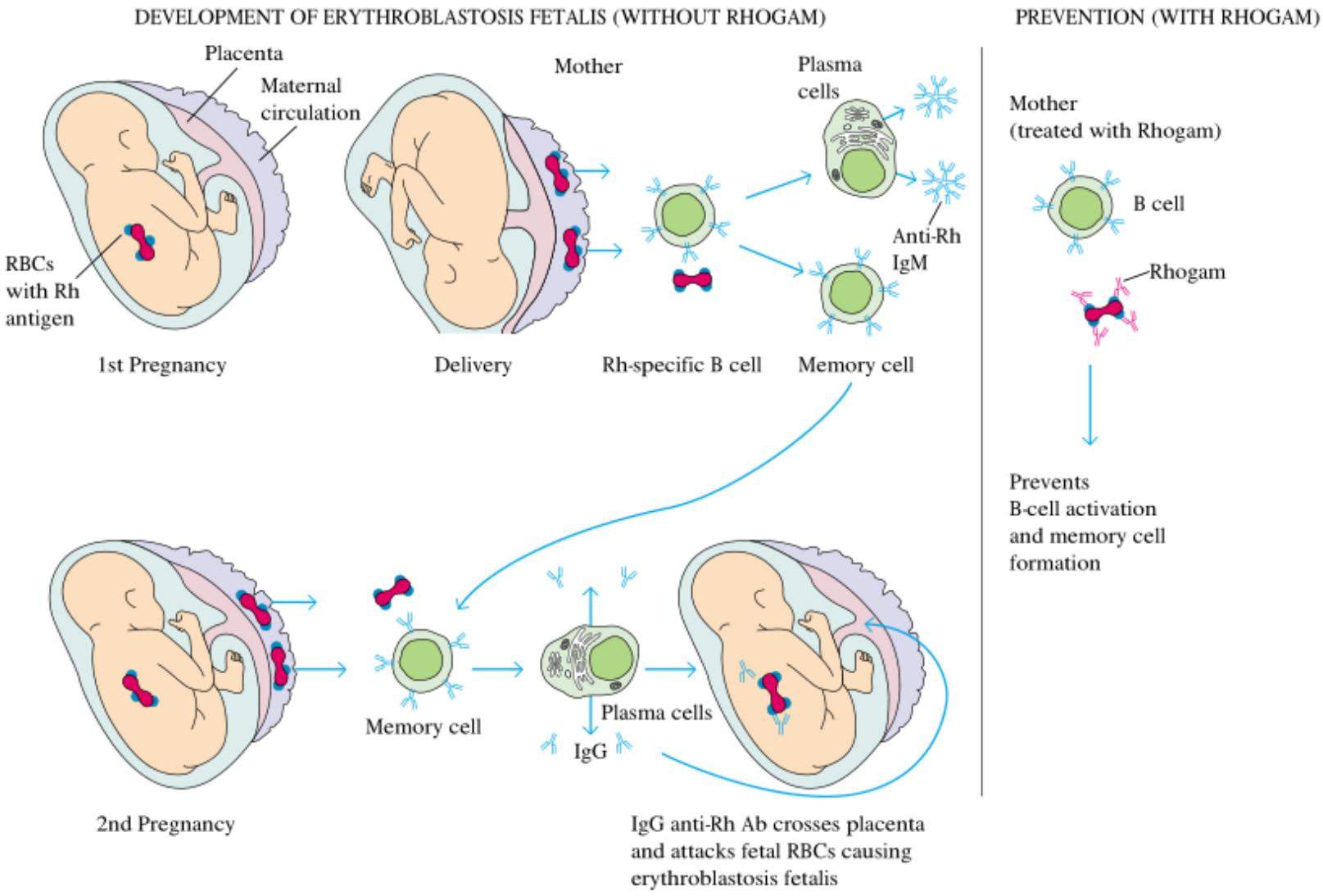


FIGURE 16-14 Development of erythroblastosis fetalis (hemolytic disease of the newborn) caused when an Rh^- mother carries an Rh^+ fetus (*left*), and effect of treatment with anti-Rh antibody, or Rhogam (*right*).

Immune Complex–Mediated (Type III) Hypersensitivity

Much of the tissue damage in type III reactions stems from release of lytic enzymes by neutrophils as they attempt to phagocytose immune complexes.

As the reaction develops, localized tissue and vascular damage results in an accumulation of fluid (edema) and red blood cells (erythema) at the site. The severity of the reaction can vary from mild swelling and redness to tissue necrosis.

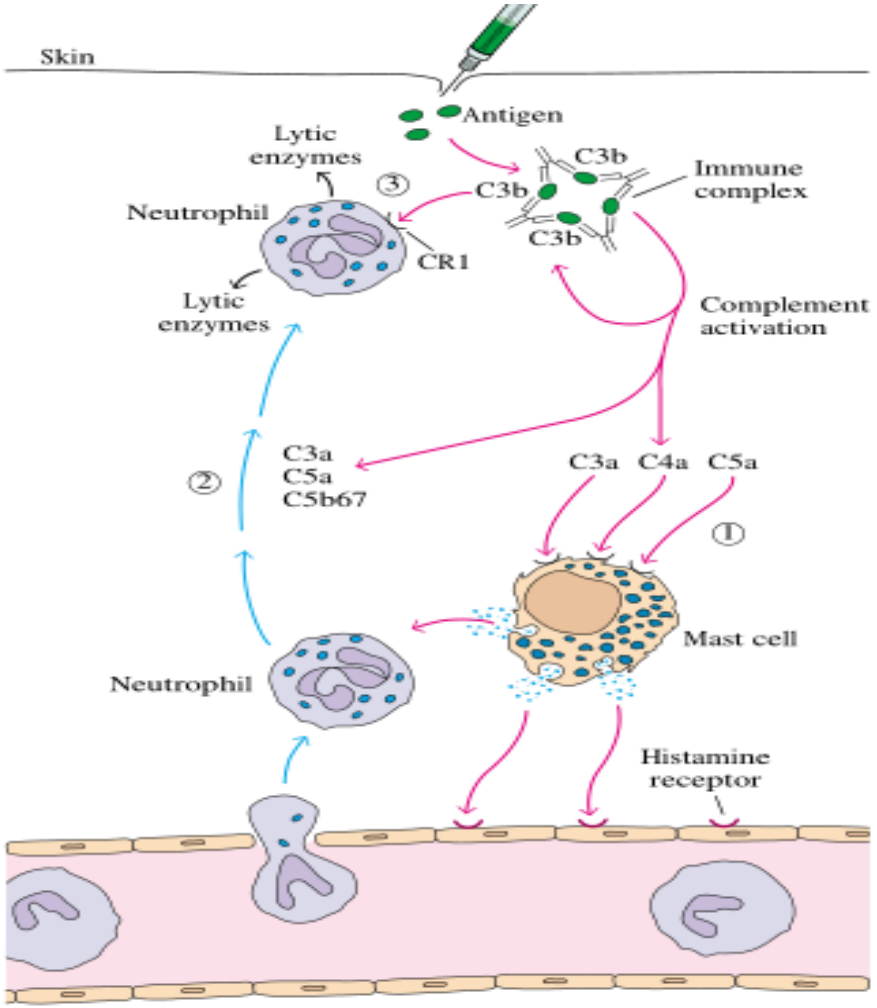


FIGURE 16-15 Development of a localized Arthus reaction (type III hypersensitive reaction). Complement activation initiated by immune complexes (classical pathway) produces complement intermediates that (1) mediate mast-cell degranulation, (2) chemotactically attract neutrophils, and (3) stimulate release of lytic enzymes from neutrophils trying to phagocytose C_3b-coated immune complexes.

Generalized type III reactions were often observed after the administration of antitoxins containing foreign serum, such as horse antitetanus or antidiphtheria serum. In such cases, the recipient of a foreign antiserum develops antibodies specific for the foreign serum proteins; these antibodies then form circulating immune complexes with the foreign serum antigens. Typically, within days or weeks after exposure to foreign serum antigens, an individual begins to manifest a combination of symptoms that are called serum sickness . These symptoms include fever, weakness, generalized vasculitis (rashes) with edema and erythema, lymphadenopathy, arthritis, and sometimes glomerulonephritis.

Type IV or Delayed-Type Hypersensitivity (DTH)

When some subpopulations of activated T_H cells encounter certain types of antigens, they secrete cytokines that induce a localized inflammatory reaction called delayed-type hypersensitivity (DTH). The reaction is characterized by large influxes of nonspecific inflammatory cells, in particular, macrophages.

This type of reaction was first described in 1890 by Robert Koch, who observed that individuals infected with Mycobacterium tuberculosis developed a localized inflammatory response when injected intradermally with a filtrate derived from a mycobacterial culture. He called this localized skin reaction a “tuberculin reaction.”

The hallmarks of a type IV reaction are the delay in time required for the reaction to develop and the recruitment of macrophages as opposed to neutrophils, as found in a type III reaction. Macrophages are the major component of the infiltrate that surrounds the site of inflammation.

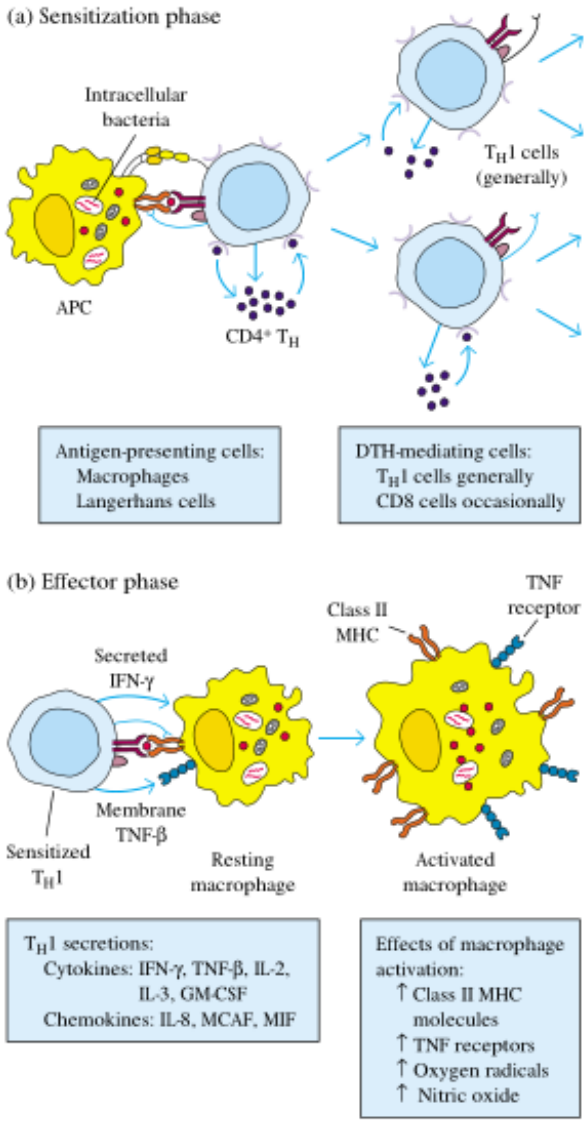


FIGURE 16-17 Overview of the DTH response. (a) In the sensitization phase after initial contact with antigen (e.g., peptides derived from intracellular bacteria), T_H cells proliferate and differentiate into T_H1 cells. Cytokines secreted by these T cells are indicated by the dark blue balls. (b) In the effector phase after subsequent exposure of sensitized T_H1 cells to antigen, the T_H1 cells secrete a variety of cytokines and chemokines. These factors attract and activate macrophages and other nonspecific inflammatory cells. Activated macrophages are more effective in presenting antigen, thus perpetuating the DTH response, and function as the primary effector cells in this reaction.

Many contact-dermatitis reactions, including the responses to formaldehyde, trinitrophenol, nickel, turpentine, and active agents in various cosmetics and hair dyes, poison oak, and poison ivy, are mediated by T_H 1 cells. Most of these substances are small molecules that can complex with skin proteins.

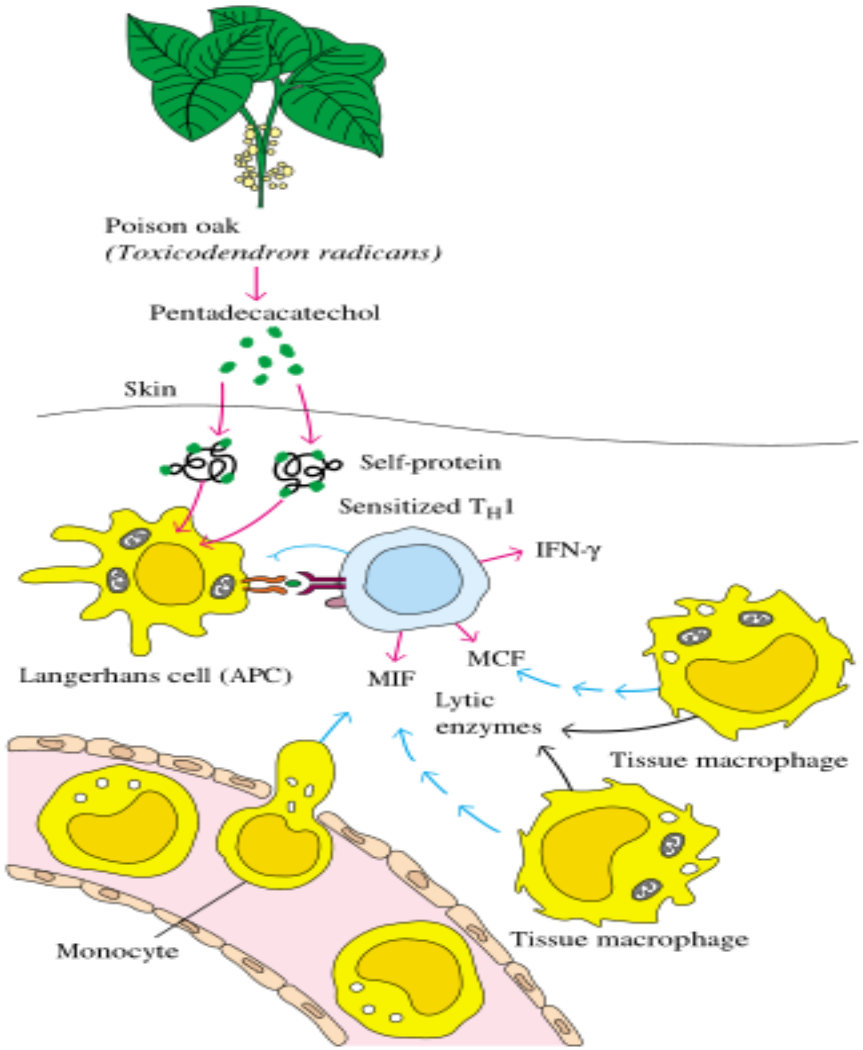


FIGURE 16-20 Development of delayed-type hypersensitivity reaction after a second exposure to poison oak. Cytokines such as IFN-γ, macrophage-chemotactic factor (MCF), and migration-inhibition factor (MIF) released from sensitized T_H1 cells mediate this reaction. Tissue damage results from lytic enzymes released from activated macrophages.

Reference:

- Kindt, T. J., Goldsby, R.A., Osborne, B. A. and Kuby, J. (2006). Immunology, VIEdition, W.H. Freeman and Company.