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Hypersensitivity

Altered state of immunoreactivity resulting in self-injury

Effector molecule that remove antigen can induce a localized inflammatory response that eliminates antigen without extensively damaging the host's tissue. Under certain circumstances, however, **this inflammatory response can have deleterious effects, resulting in significant tissue damage or even death.** This **inappropriate immune response** is termed **hypersensitivity or allergy.**

Hypersensitive reactions may develop in the course of **either humoral or cell-mediated responses.**

Within the humoral branch initiated by antibody or antigen-antibody complexes as **immediate hypersensitivity, because the symptoms are manifest within minutes or hours** after a sensitized recipient encounters antigen. **Delayed-type hypersensitivity (DTH) is so named in recognition of the delay of symptoms** until days after exposure.

Hypersensitive reactions are inflammatory reactions within the humoral or cell-mediated branches of the immune system that lead to extensive tissue damage or even death.

Gell and Coombs Classification

- In immediate hypersensitive reactions, different antibody isotypes induce **different immune effector molecules.**

- **IgE antibodies**, for example, induce **mast-cell degranulation with release of histamine and other biologically active molecules.**

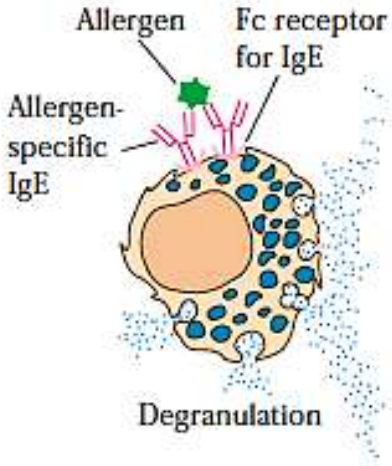
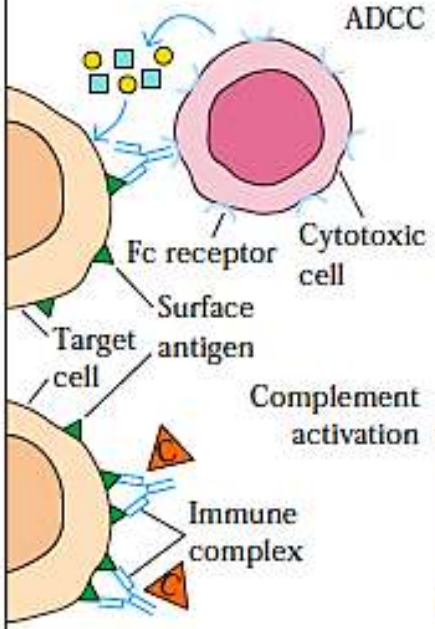
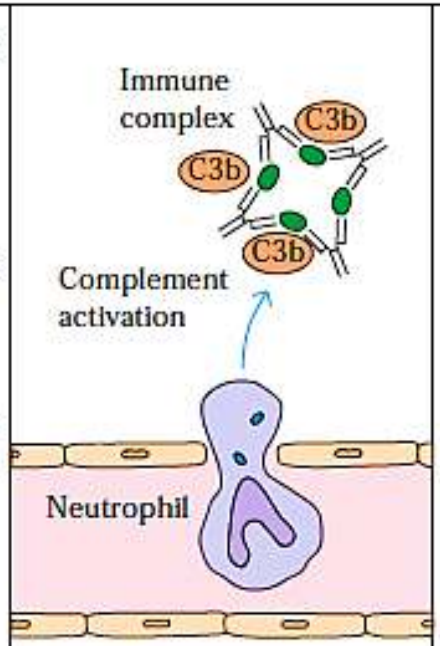
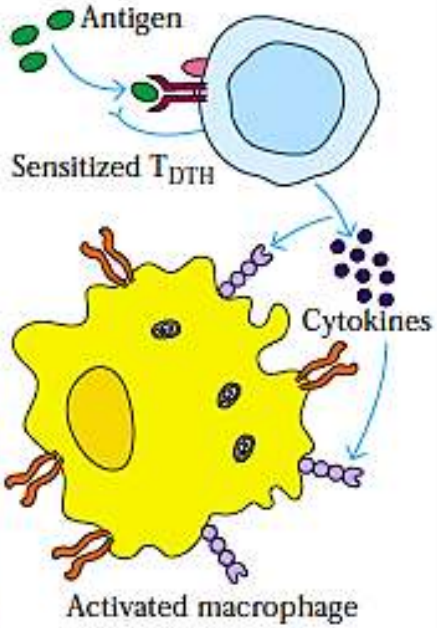
- **IgG and IgM** antibodies, on the other hand, induce hypersensitive reactions by **activating complement.** The effector molecules in the complement reactions are the membrane-attack complex and such complement **split products as C3a, C4a, and C5a.**

- In **delayed-type hypersensitivity** reactions, the **effector molecules are various cytokines secreted by activated T_H or T_C cells.**

- **P. G. H. Gell and R. R. A. Coombs** proposed a classification scheme in which hypersensitive reactions are divided into four types.

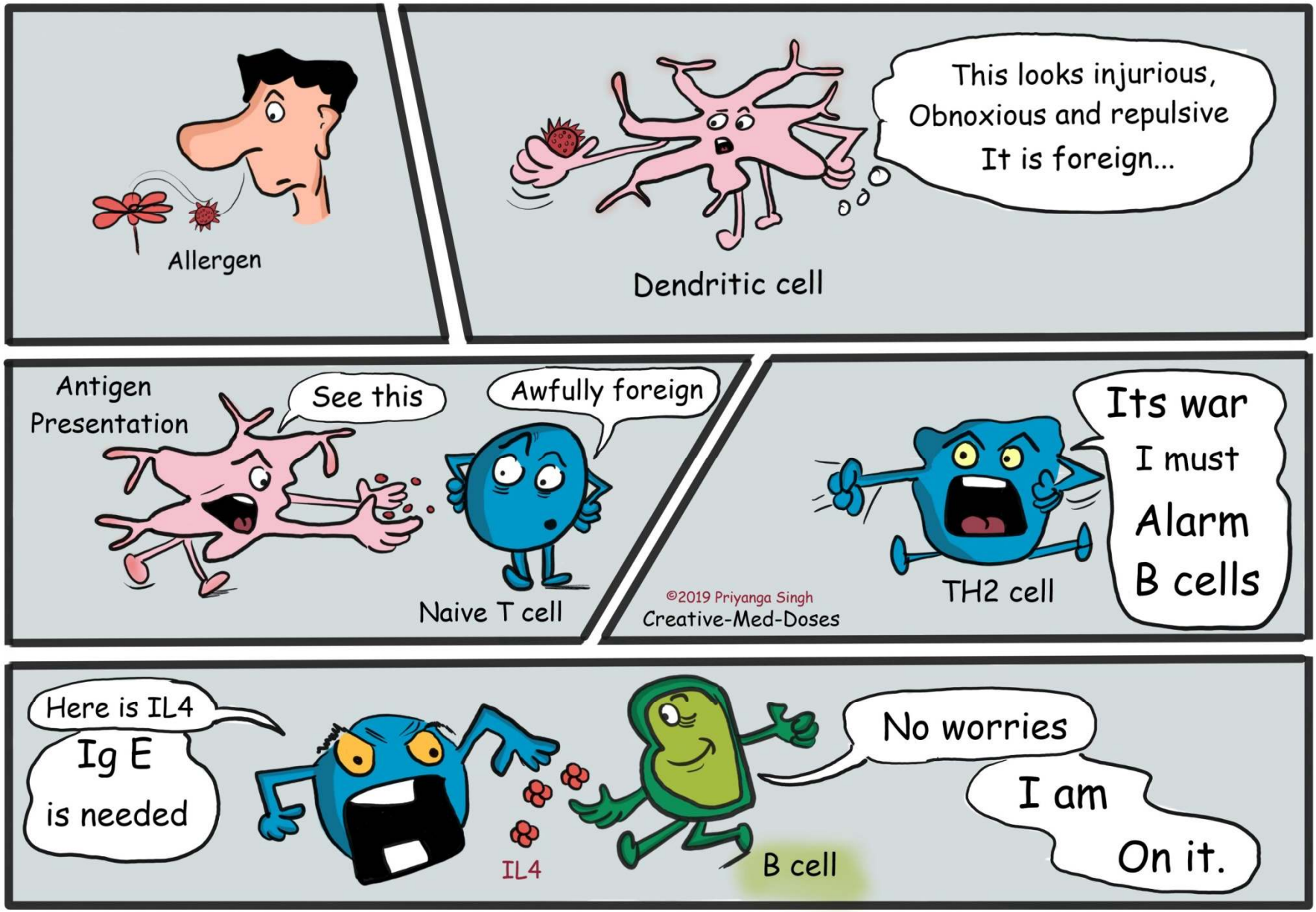
- **Three types of hypersensitivity occur within the humoral branch** and are mediated by antibody or antigen-antibody complexes**: IgE-mediated (type I), antibody-mediated (type II), and immune complex–mediated (type III).**

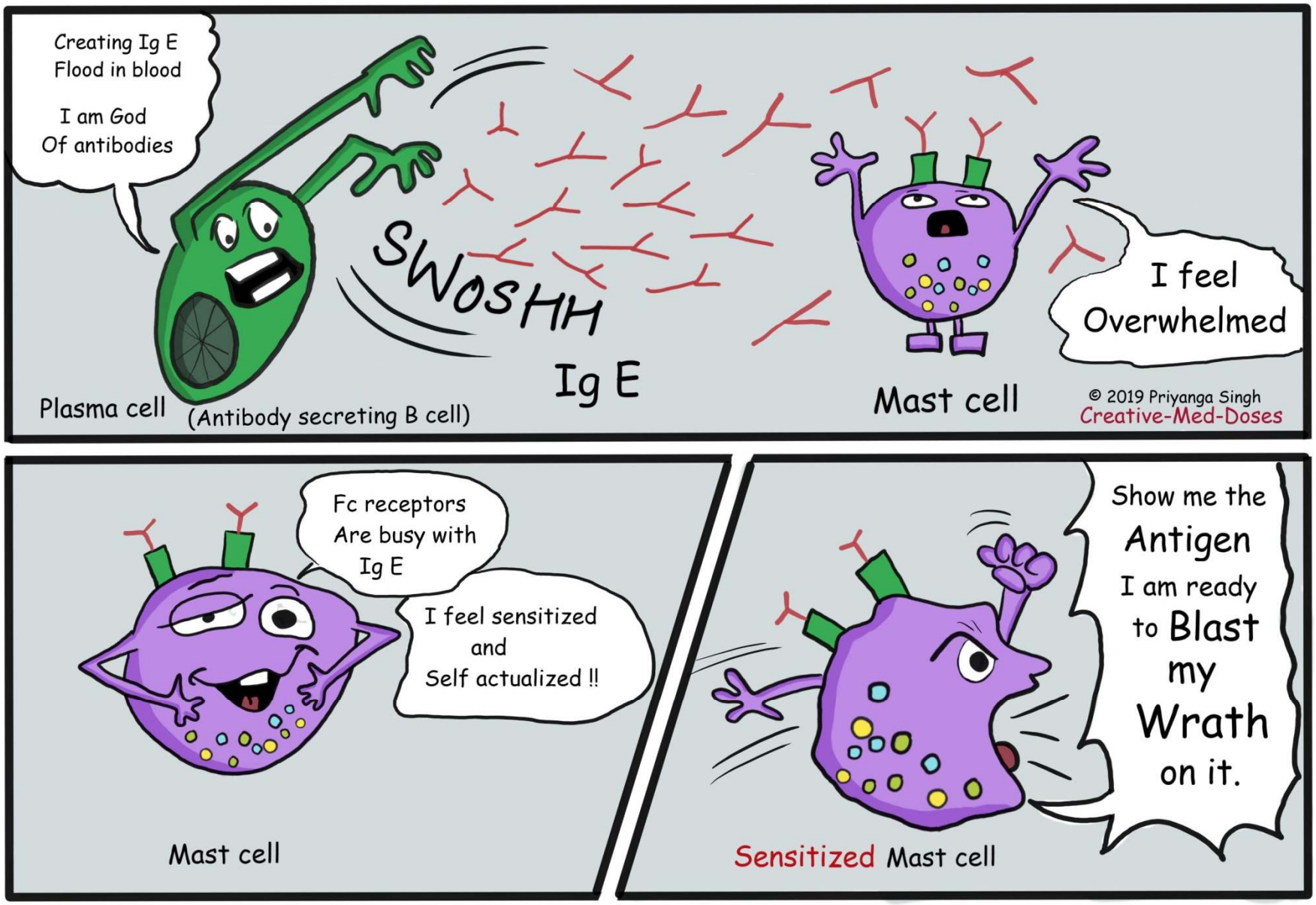
- A **fourth type** of hypersensitivity depends on reactions within the cell-mediated branch, and **is termed delayed-type hypersensitivity, or DTH (type IV).**

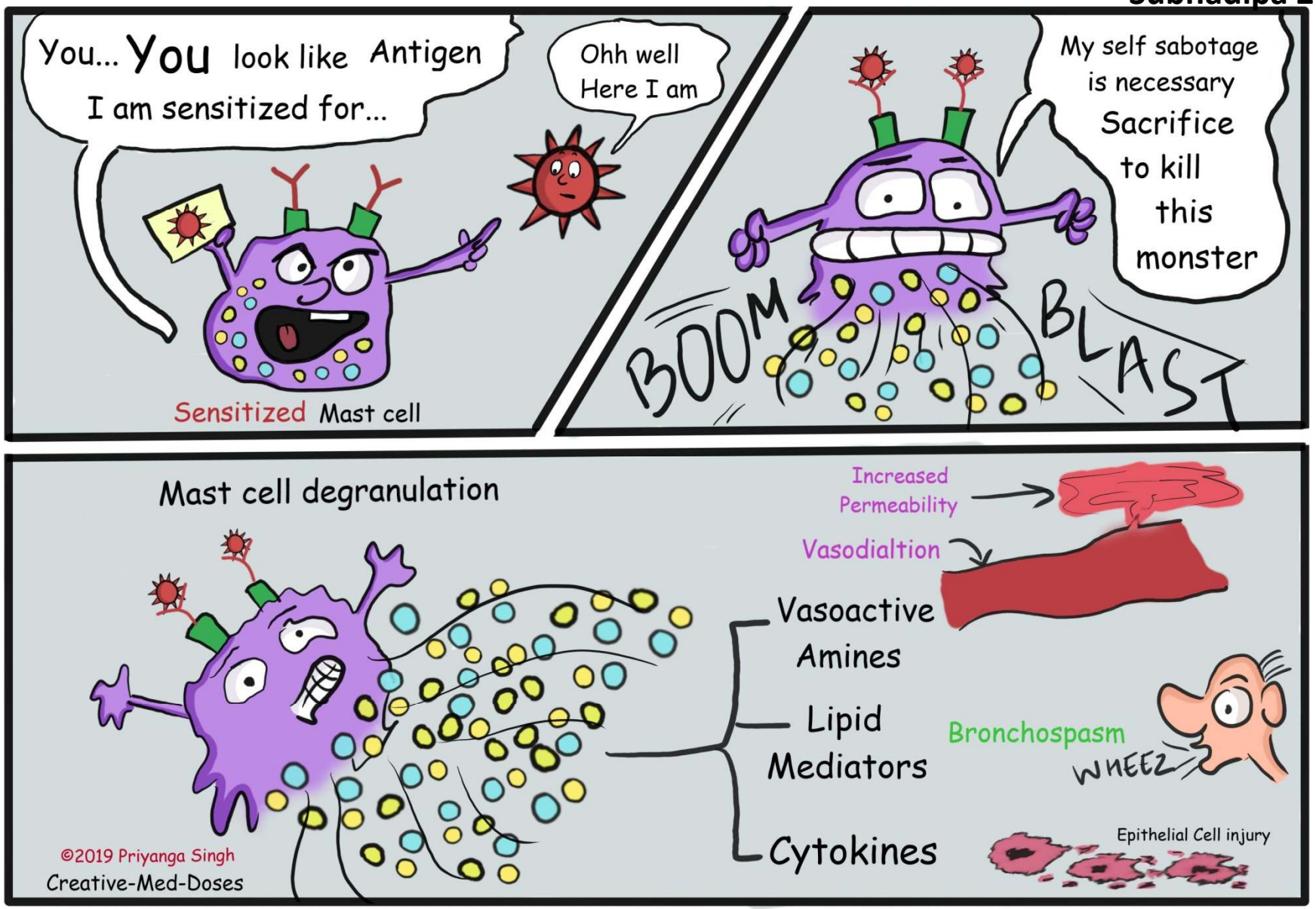
 **Type I**	 **Type II**	 **Type III**	 **Type IV**
IgE-Mediated Hypersensitivity	IgG-Mediated Cytotoxic Hypersensitivity	Immune Complex-Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
Ag induces crosslinking of IgE bound to mast cells and basophils with release of vasoactive mediators	Ab directed 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

"I've discovered that I'm homework intolerant."

Type I Hypersensitivity




Creating Ig E
Flood in blood
I am God
Of antibodies
SWOSHH
Ig E
Plasma cell
(Antibody secreting B cell)
Mast cell
I feel
Overwhelmed
© 2019 Priyanga Singh
Creative-Med-Doses
Fc receptors
Are busy with
Ig E
I feel sensitized
and
Self actualized !!
Mast cell
Show me the
Antigen
I am ready
to Blast
my
Wrath
on it.
Sensitized Mast cell

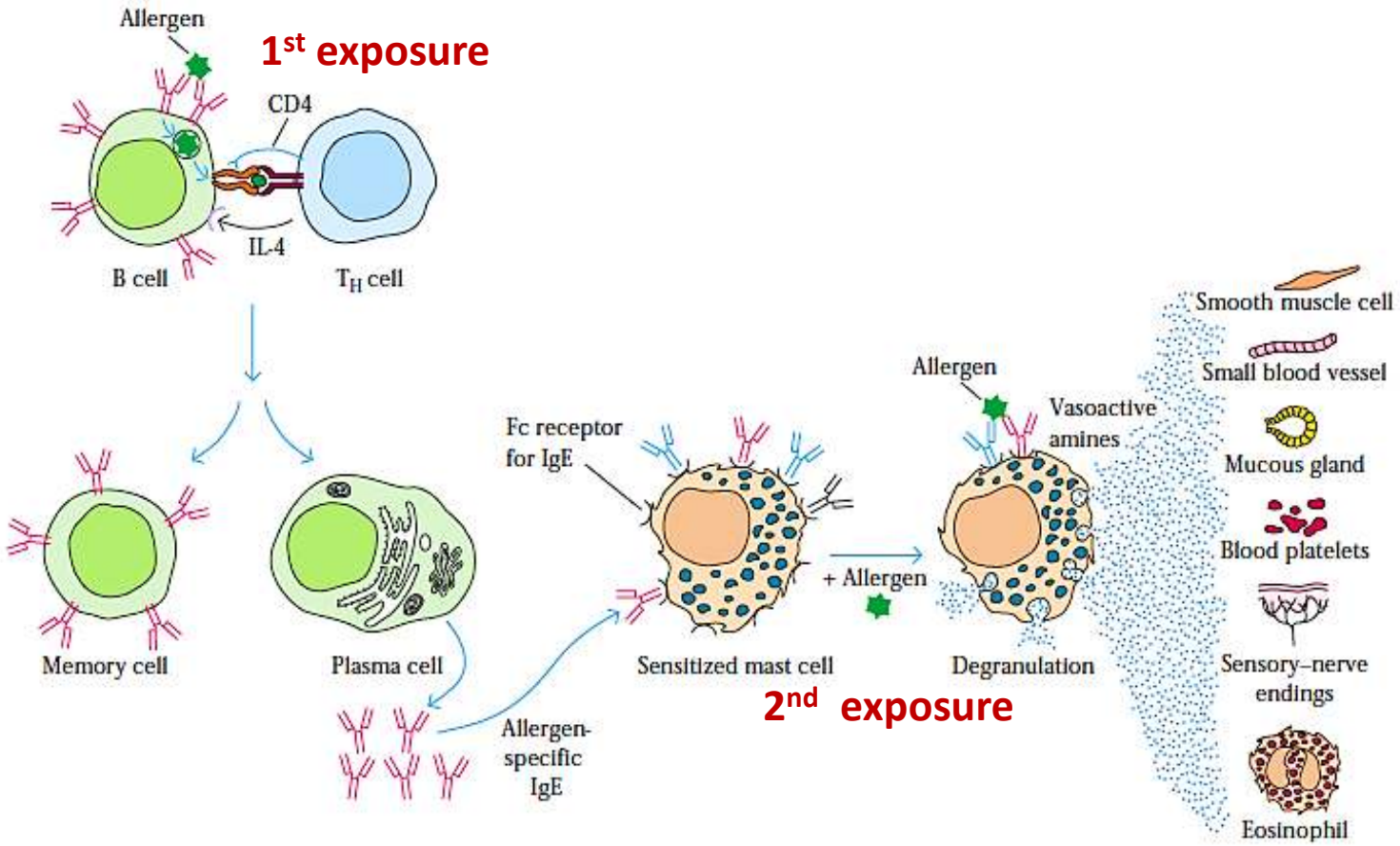

You... You look like Antigen I am sensitized for...
Ohh well Here I am
Sensitized Mast cell
My self sabotage is necessary Sacrifice to kill this monster
BOOM
BLAST
Mast cell degranulation
Increased Permeability
Vasodialtion
Vasoactive Amines
Lipid Mediators
Cytokines
Bronchospasm
WHEEZ
Epithelial Cell injury
©2019 Priyanga Singh
Creative-Med-Doses

Type I Hypersensitivity

A type I hypersensitive reaction is mediated by IgE antibodies, whose Fc region binds to receptors on mast cells or blood basophils. Cross-linkage of the fixed IgE by allergen leads to mast cell or basophil degranulation with release of pharmacologically active mediators. The principal effects of these mediators are smooth-muscle contraction and vasodilation. Clinical manifestations of type I reactions include potentially life-threatening systemic anaphylaxis and localized responses such as hay fever and asthma.

Type I Hypersensitivity

First 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 (degranulation), vasoactive amines,** from mast cells and basophils. The mediators cause **smooth-muscle contraction (may be either systemic or localized, depending on the extent of mediator release), increased vascular permeability, and vasodilation.**



Components of Type I hypersensitivity

Allergens

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

Some persons, however, may have an abnormality called **atopy, a hereditary predisposition to the development of immediate hypersensitivity reactions against common environmental antigens.** The IgE regulatory defects suffered by atopic individuals allow **nonparasitic antigens to stimulate inappropriate IgE production, leading to tissue damaging type I hypersensitivity.**

- Abnormally **high levels of circulating IgE and also more than normal numbers of circulating eosinophils.** These individuals are more susceptible to allergies such as **hay fever, eczema, and asthma.**
- The genetic propensity to atopic responses has been mapped to several candidate loci. One locus, on **chromosome 5q, is linked to a region that encodes a variety of cytokines, including IL-3, IL-4, IL-5, IL-9, IL-13, and GM-CSF**. A second locus, on **chromosome 11q, is linked to a region that encodes the β chain of the high-affinity IgE receptor.**

Reaginic antibody (IgE)

The local wheal and flare response that occurs when an allergen is injected into a sensitized individual is called the P-K reaction. Because the serum components responsible for the P-K reaction displayed specificity for allergen, they were assumed to be antibodies, but the nature of these **P-K antibodies, or reagins,** was not demonstrated for many years.

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.**

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.

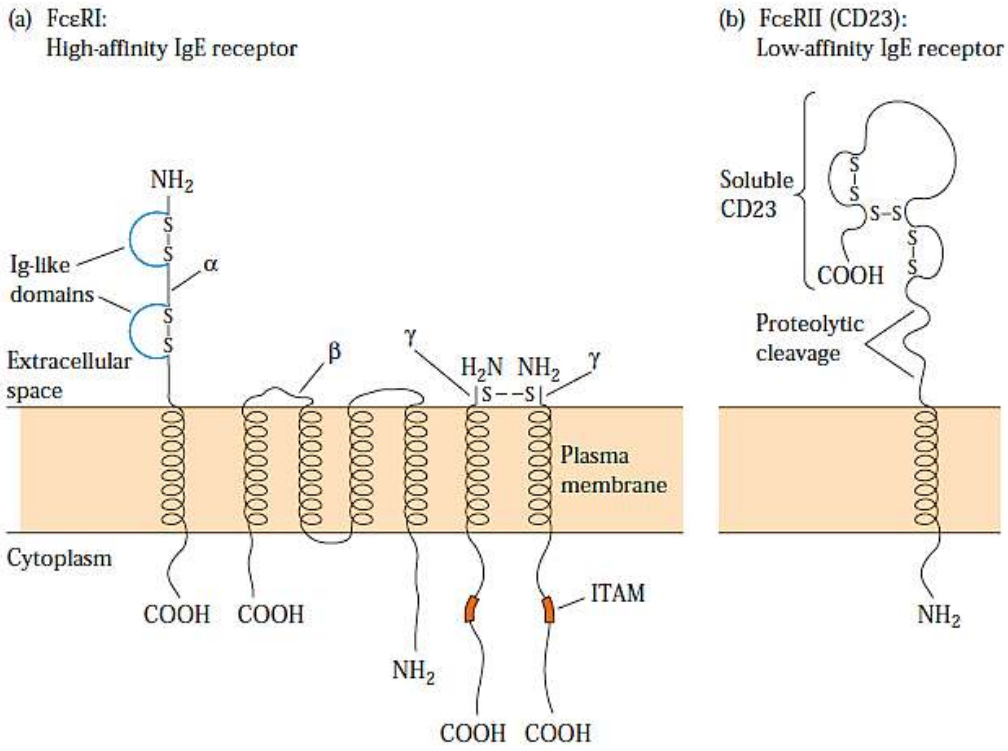
Basophils and mast cells

Basophils are granulocytes that circulate in the blood of most vertebrates; in humans, they account for 0.5%–1.0% of the circulating white blood cells. I has electron-dense membrane-bound granules scattered throughout the cytoplasm that contain pharmacologically active mediators.

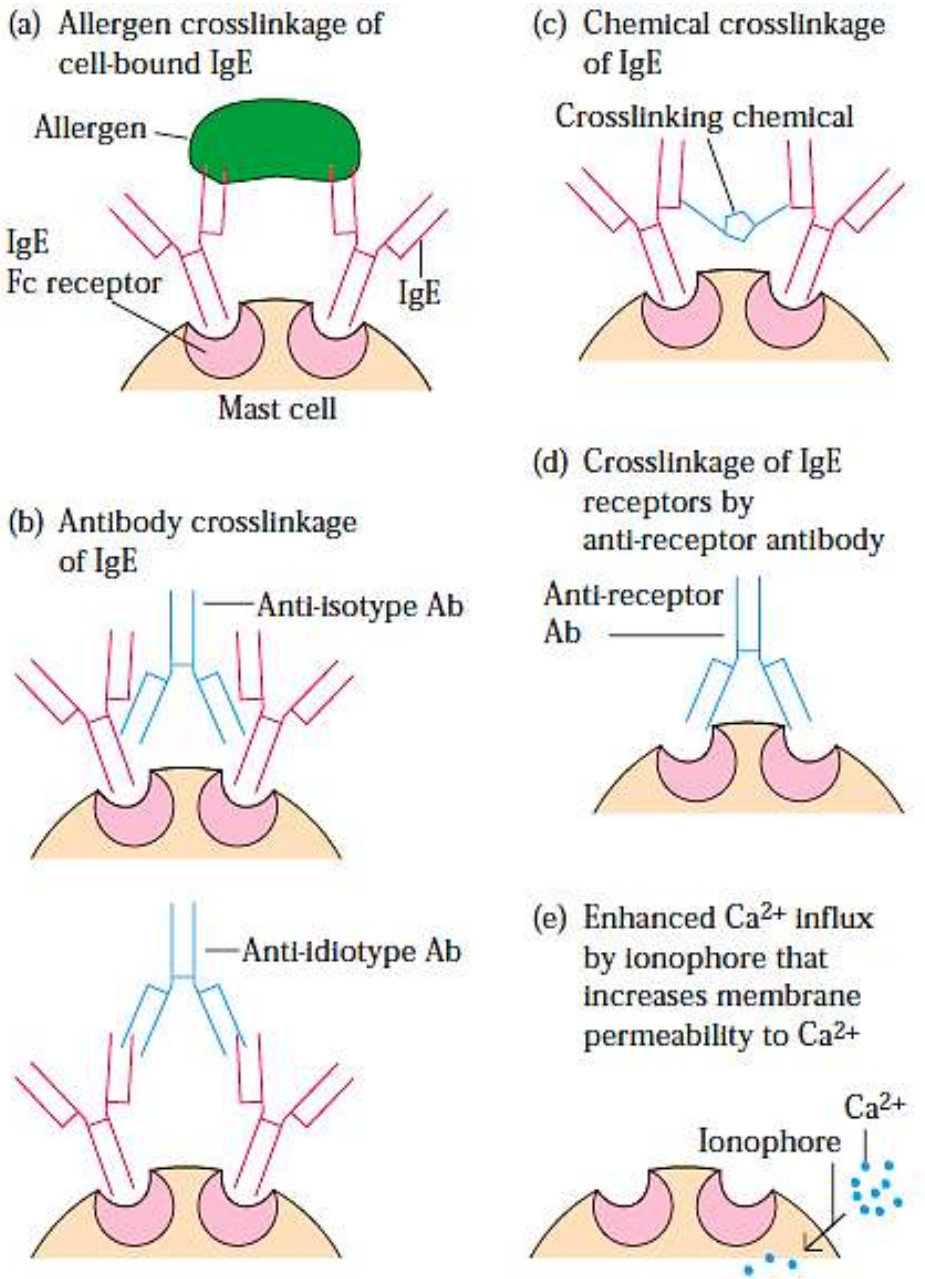
Mast-cell precursors are formed in the bone marrow during hematopoiesis and are carried to virtually all vascularized peripheral tissues, where they differentiate into mature cells. Mast cells are found throughout connective tissue, particularly near blood and lymphatic vessels. Some tissues, including the skin and mucous membrane surfaces of the respiratory and gastrointestinal tracts, contain high concentrations of mast cells

Mast cells reveal numerous membrane-bounded granules distributed throughout the cytoplasm, which, like those in basophils, contain pharmacologically active mediators. After activation, these mediators are released from the granules, resulting in the clinical manifestations of the type I hypersensitive reaction. Mast cells also secrete a large variety of cytokines that affect a broad spectrum of physiologic, immunologic, and pathologic processes.

IgE-binding Fc receptors



IgE Crosslinkage Initiates Degranulation



Intracellular Events Also Regulate Mast-Cell Degranulation

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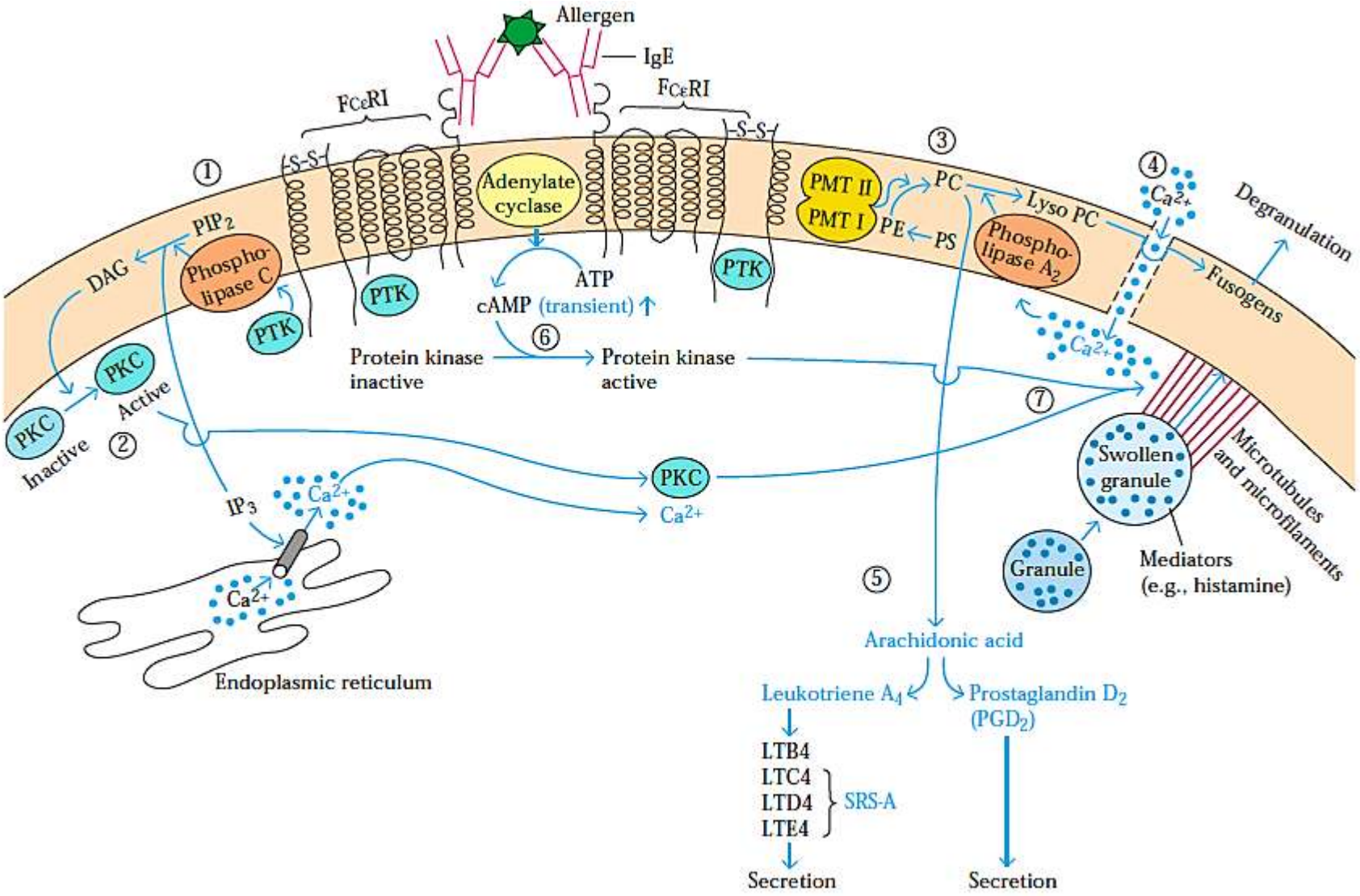
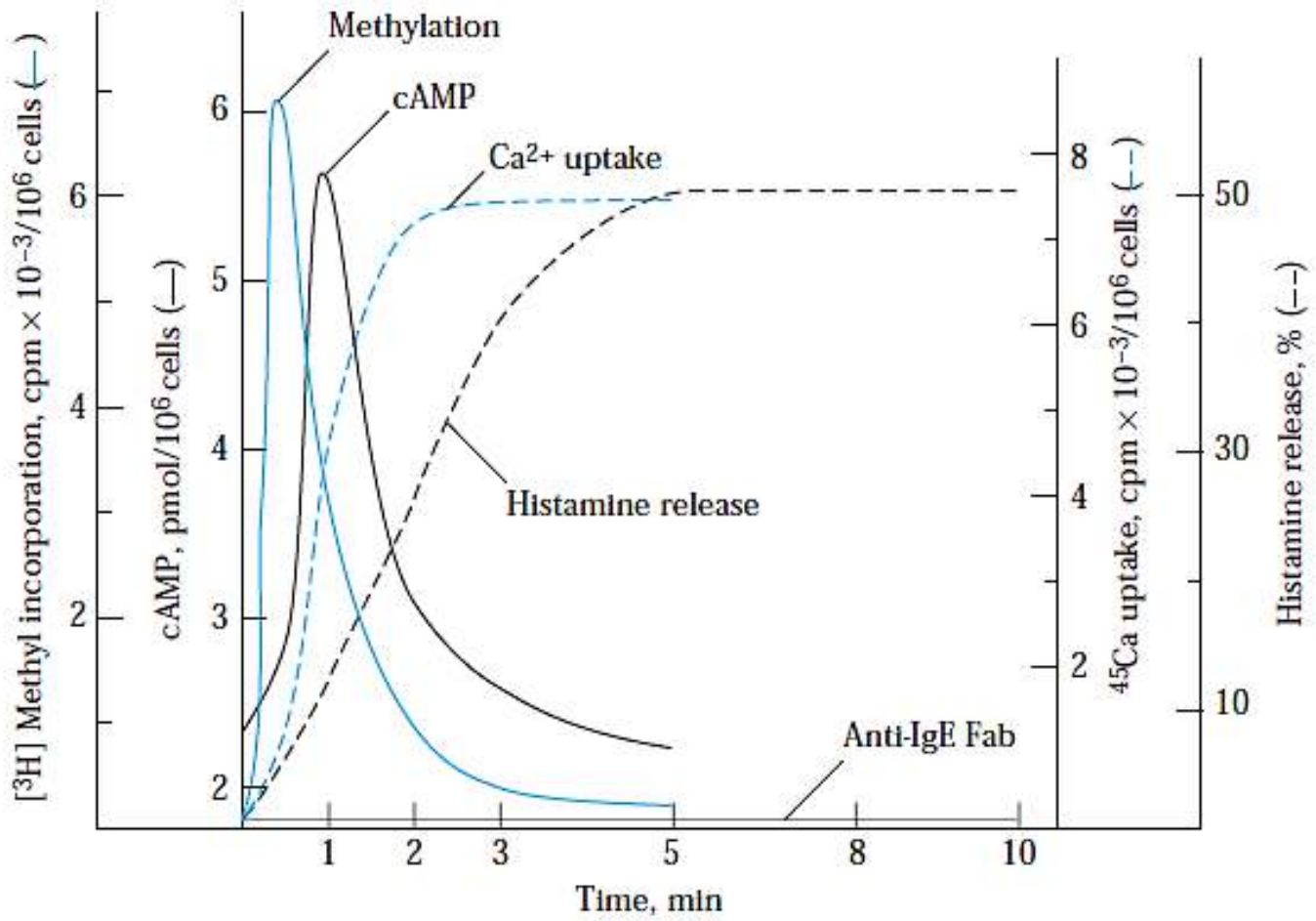


Several Pharmacologic Agents Mediate Type I Reactions



Principal mediators involved in type I hypersensitivity

The **primary mediators** are **produced before degranulation and are stored in the granules.** The **secondary mediators** either are synthesized **after target-cell activation or are released by the breakdown of membrane phospholipids during the degranulation process.**

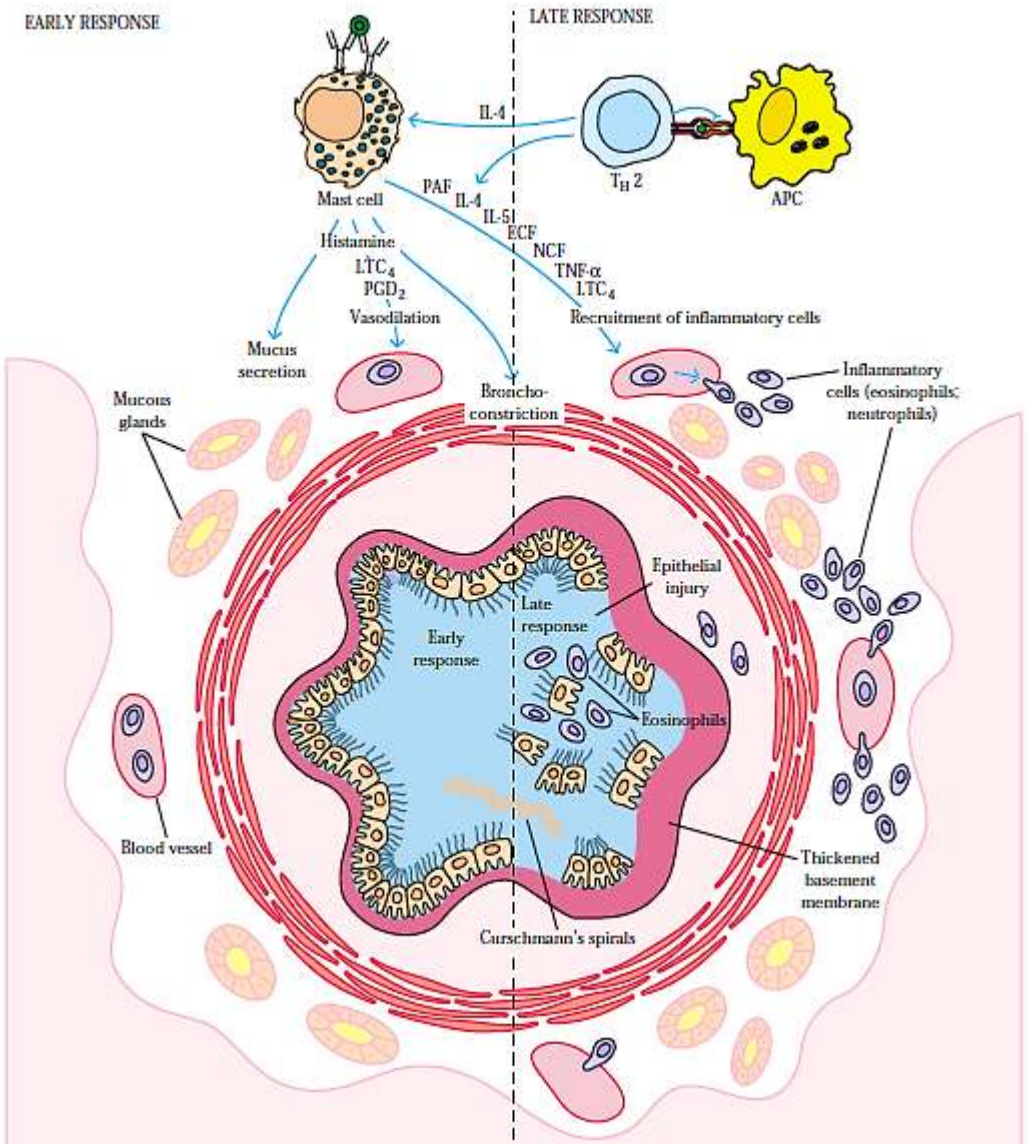
Mediator	Effects
	PRIMARY
Histamine, heparin	Increased vascular permeability; smooth-muscle contraction
Serotonin	Increased vascular permeability; smooth-muscle contraction
Eosinophil chemotactic factor (ECF-A)	Eosinophil chemotaxis
Neutrophil chemotactic factor (NCF-A)	Neutrophil chemotaxis
Proteases	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 is a **shock-like and often fatal state whose onset occurs within minutes** of a type I hypersensitive reaction.
- Systemic anaphylaxis in humans is characterized by a similar sequence of events. A wide range of antigens have been shown to trigger this reaction in susceptible humans, including the **venom from bee, wasp, hornet, and ant stings; drugs, such as penicillin, insulin, and antitoxins; and seafood and nuts.**
- If not treated quickly, these **reactions can be fatal.**
- **Epinephrine is the drug** of choice for systemic anaphylactic reactions.
- In **localized anaphylaxis**, the reaction is limited to a **specific target tissue or organ, often involving epithelial surfaces at the site of allergen entry.**
- The **tendency to manifest** localized anaphylactic **reactions is inherited and is called *atopy.***
- Atopic allergies, which afflict at least 20% of the population in developed countries, include a wide range of IgE-mediated disorders, including **allergic rhinitis (hay fever), asthma, atopic dermatitis (eczema), and food allergies.**

Late-Phase Reactions Induce Localized Inflammatory Reactions

EARLY RESPONSE (minutes)	
Histamine	Vasodilation
PGD_2	Bronchoconstriction
LTC_4	Mucus secretion



LATE RESPONSE (hours)	
IL-4, TNF-α, LTC_4	Increased endothelial cell adhesion
PAF, IL-5, ECF	Leukocyte migration
IL-4, IL-5	Leukocyte activation

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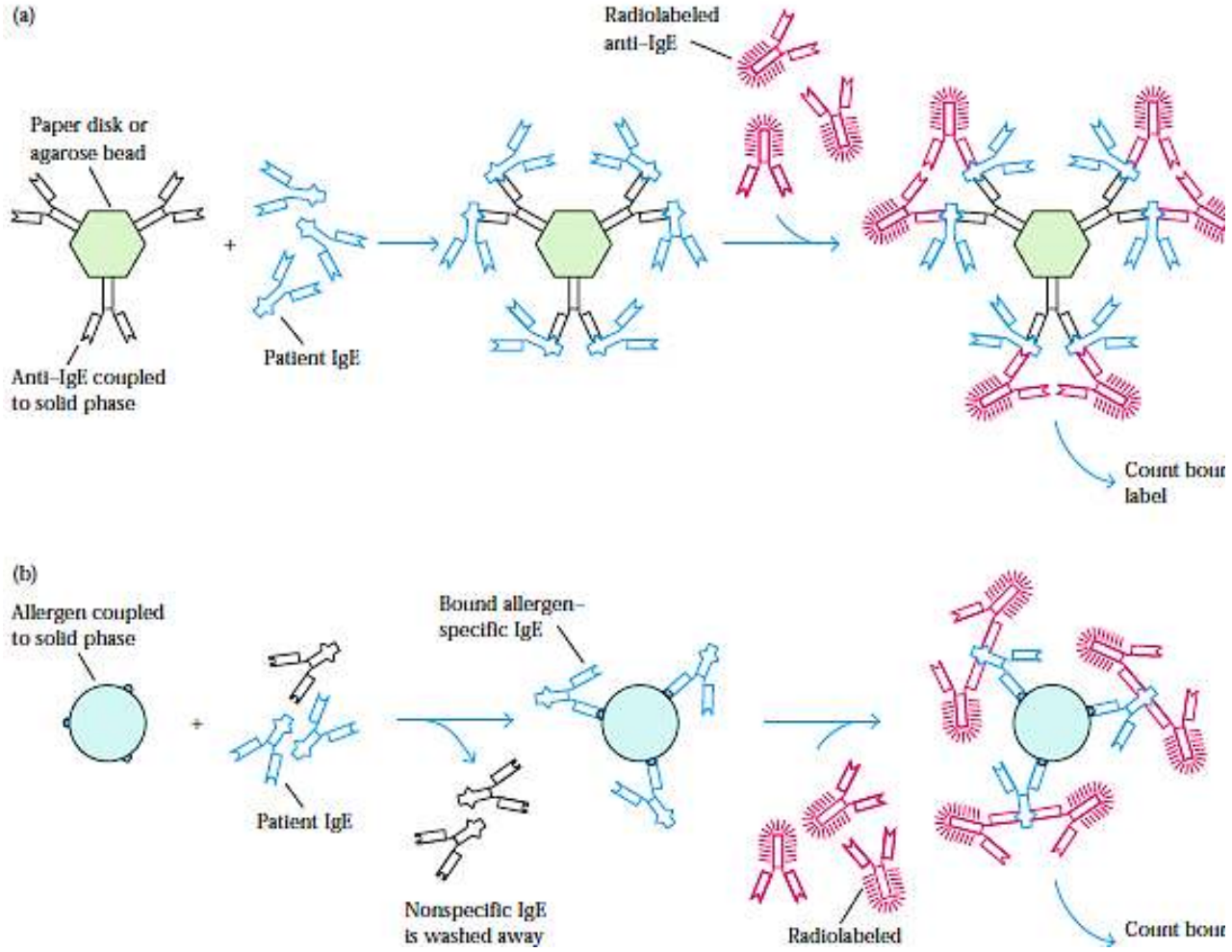
Several Methods Are Used to Detect Type I Hypersensitivity Reactions

Skin testing by intradermal injection of allergens into the forearm



Radioimmunosorbent test (RIST)

Mechanism of action of some drugs used to treat type I hypersensitivity

Often the removal of house pets, dust-control measures, or avoidance of offending foods can eliminate a type I response.

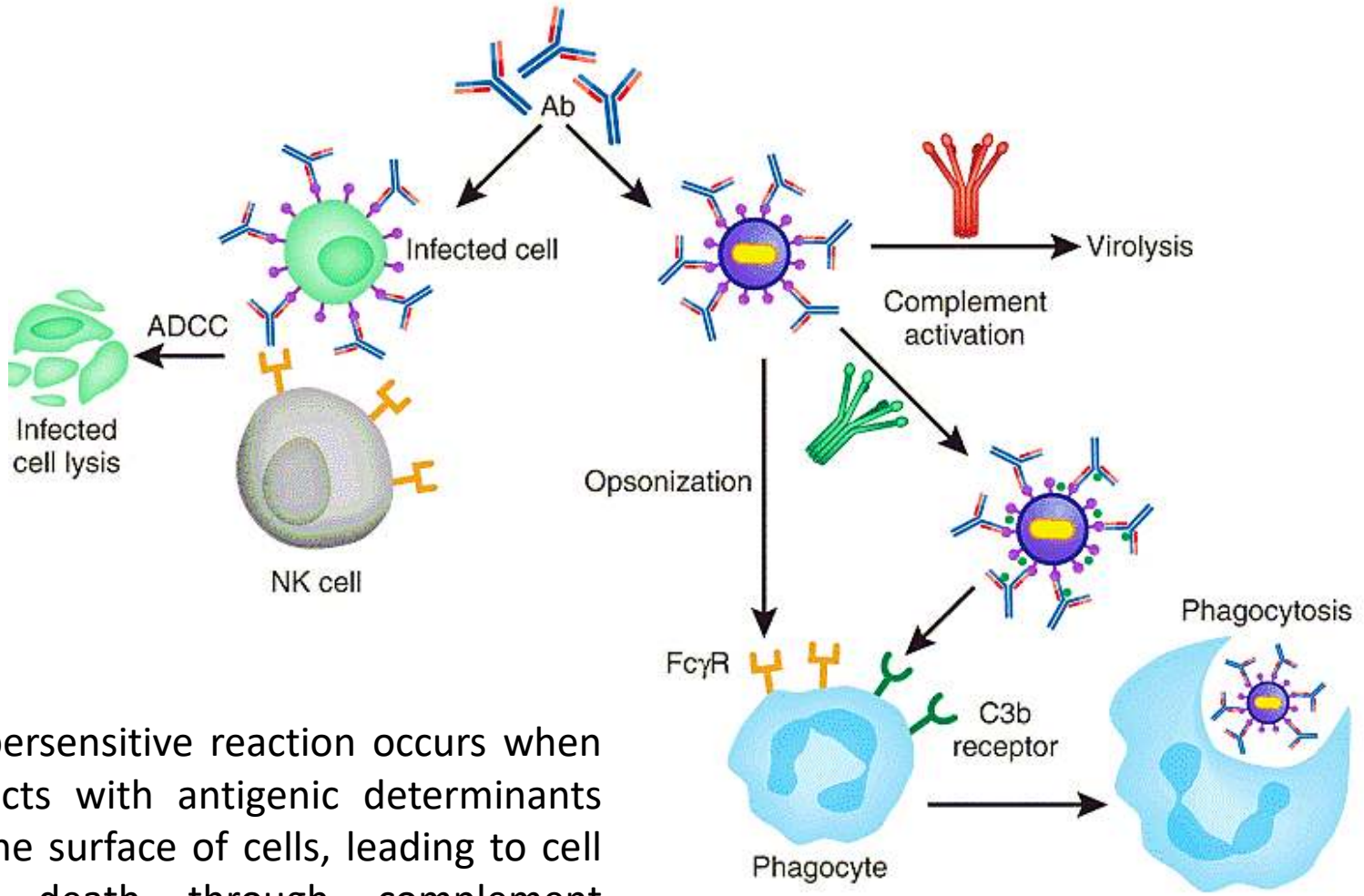
Immunotherapy with repeated injections of increasing doses of allergens **(hyposensitization)** has been known for some time to reduce the severity of type I reactions. Such repeated introduction of allergen by subcutaneous injections appears to cause a shift toward IgG production or to induce T-cell– mediated suppression (possibly by a shift to the TH1 subset and IFN- production) that turns off the IgE response. In this situation, the IgG antibody is referred to as ***blocking antibody*** because it competes for the allergen, binds to it, and forms a complex that can be removed by phagocytosis;
as a result, the allergen is not available to crosslink the fixed IgE on the mast-cell membranes, and allergic symptoms decrease.

Another form of immunotherapy is the use of **humanized monoclonal anti-IgE.**

Drug	Action
Antihistamines	Block H_1 and H_2 receptors on target cells
Cromolyn sodium	Blocks Ca^{2+} influx into mast cells
Theophylline	Prolongs high cAMP levels in mast cells by inhibiting phosphodiesterase, which cleaves cAMP to 5′-AMP*
Epinephrine (adrenalin)	Stimulates cAMP production by binding to β-adrenergic receptors on mast cells*
Cortisone	Reduces histamine levels by blocking conversion of histidine to histamine and stimulates mast-cell production of cAMP*

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

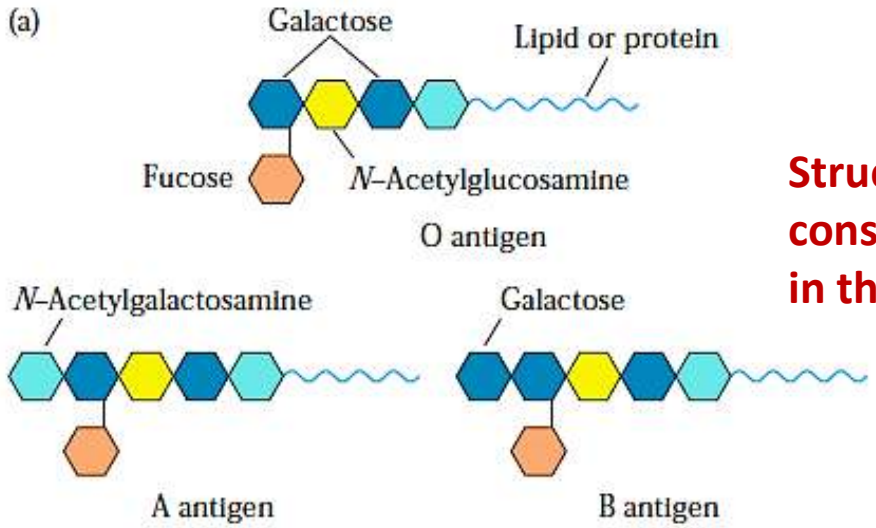
Type II hypersensitivity



A type II hypersensitive reaction occurs when antibody reacts with antigenic determinants present on the surface of cells, leading to cell damage or death through complement mediated lysis or antibody-dependent cell-mediated cytotoxicity (ADCC).
Transfusion reactions and hemolytic disease of the newborn are type II reactions.

Antibody-Mediated Cytotoxic (Type II) Hypersensitivity

Transfusion Reactions Are Type II Reactions



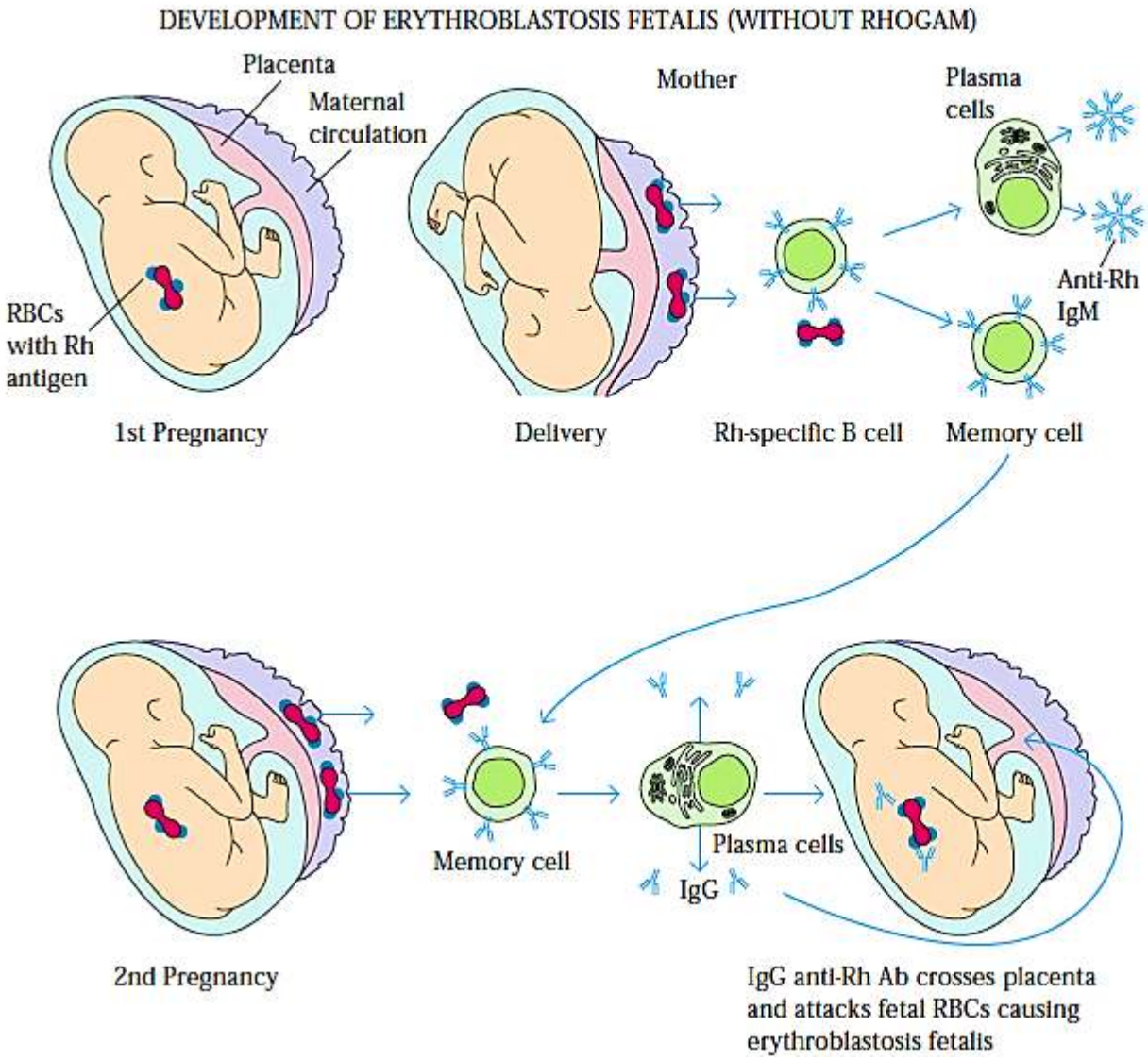
Structure of terminal sugars, which constitute the distinguishing epitopes, in the A, B, and O blood antigens

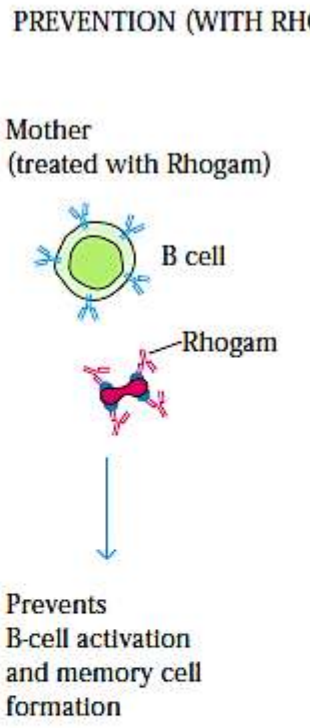
(b)

Genotype	Blood-group phenotype	Antigens on erythrocytes (*agglutinins*)	Serum antibodies (*isohemagglutinins*)
AA or AO	A	A	Anti-B
BB or BO	B	B	Anti-A
AB	AB	A and B	None
OO	O	None	Anti-A and anti-B

ABO genotypes and corresponding phenotypes, agglutinins, and isohemagglutinins.

Hemolytic Disease of the Newborn Is Caused by Type II Reactions





Within **24–48 h** after the first delivery.

Rhogam **binds to any fetal red blood cells** that enter the mother's circulation at the time of delivery and **facilitate their clearance before B-cell activation and ensuing memory-cell production can take place.**

Treatment in case of severe reaction

If hemolytic disease caused by Rh incompatibility is detected during pregnancy, the treatment depends on the severity of the reaction. For a severe reaction, the **fetus can be given an intrauterine blood-exchange transfusion to replace fetal Rh^+ red blood cells with Rh^- cells. These transfusions are given every 10–21 days until delivery.**

The mother can also be treated during the pregnancy by **plasmapheresis.** In this procedure, a cell separation machine is used to separate the mother's blood into two fractions, **cells and plasma**. **The plasma containing the anti-Rh antibody is discarded, and the cells are reinfused into the mother in an albumin or fresh-plasma solution.**

Drug-Induced Hemolytic Anemia Is a Type II Response

TABLE 16-5 Penicillin-induced hypersensitive reactions

Type of reaction	Antibody or lymphocytes induced	Clinical manifestations
I	IgE	Urticaria, systemic anaphylaxis
II	IgM, IgG	Hemolytic anemia
III	IgG	Serum sickness, glomerulonephritis
IV	T_{DTH} cells	Contact dermatitis

Immune Complex–Mediated (Type III) Hypersensitivity

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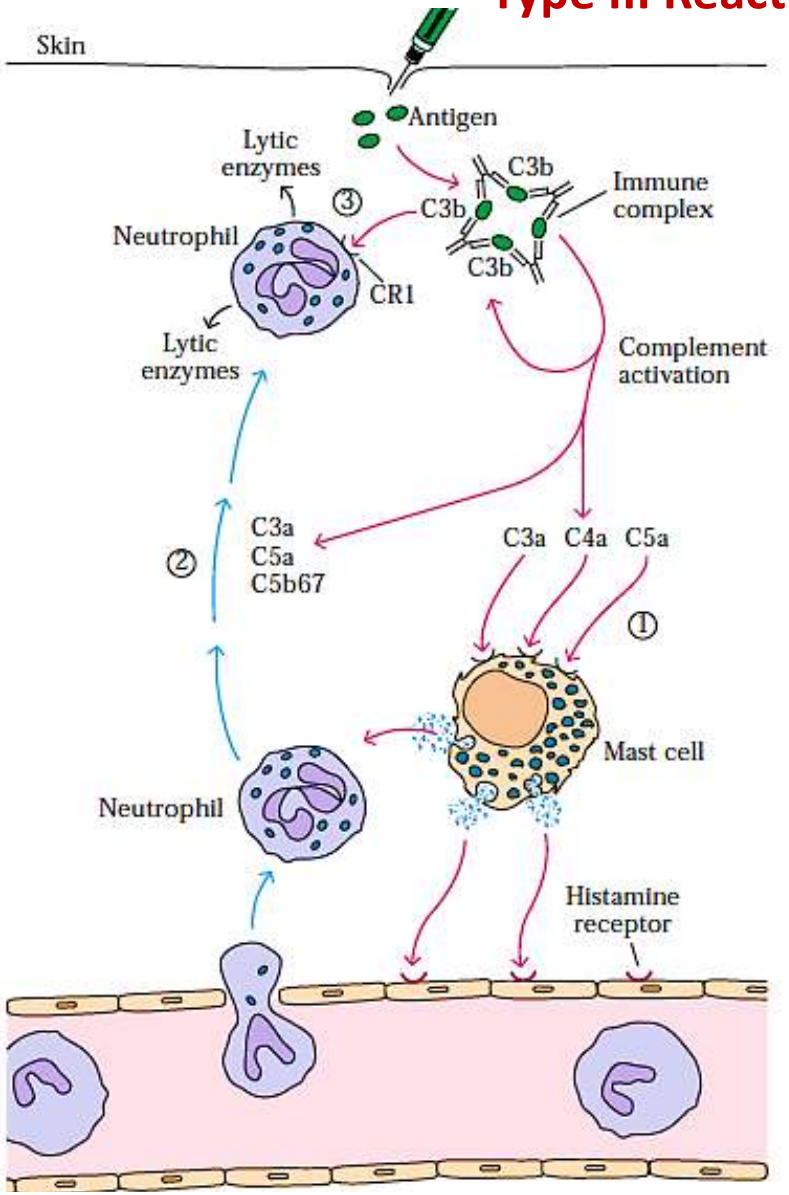
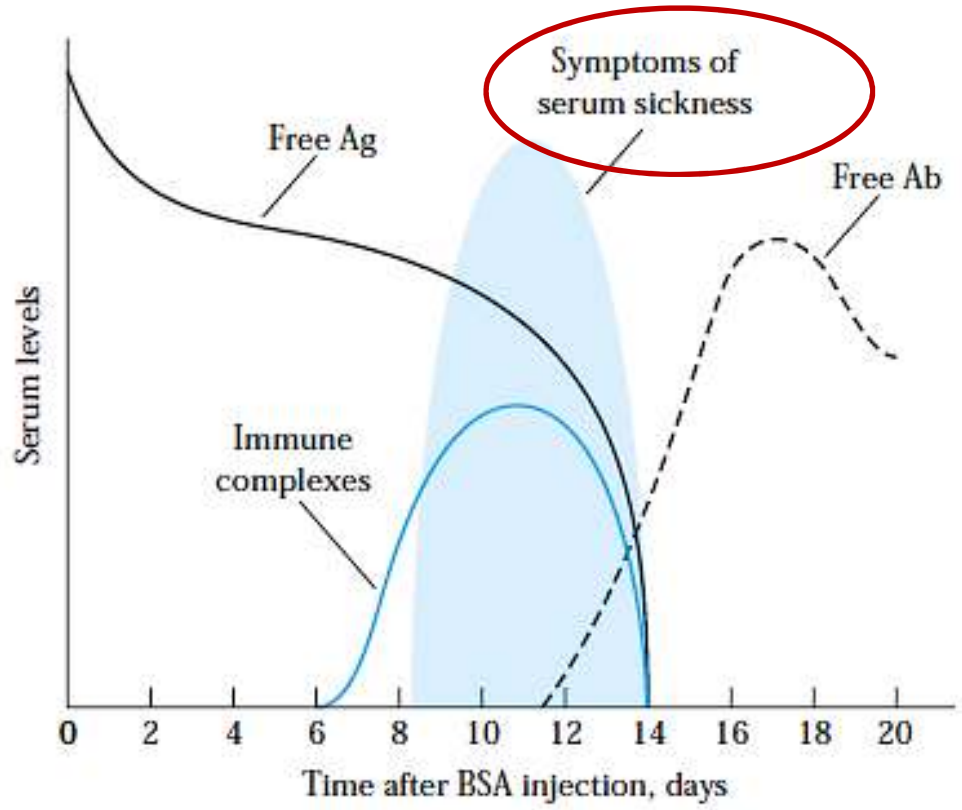
Type III Reactions Can Be Localized



A type III hypersensitive reaction is mediated by the formation of immune complexes and the ensuing activation of complement. Complement split products serve as immune effector molecules that elicit localized vasodilation and chemotactically attract neutrophils. Large amounts of immune complexes can lead to tissue-damaging type III hypersensitive reactions.

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.

Type III reactions can also be generalized



- **Autoimmune Diseases**

Systemic lupus erythematosus
Rheumatoid arthritis
Goodpasture's syndrome

- **Drug Reactions**

Allergies to penicillin and sulfonamides

- **Infectious Diseases**

Poststreptococcal glomerulonephritis
Meningitis
Hepatitis
Mononucleosis
Malaria
Trypanosomiasis

A large dose of **antigen (BSA) was injected** into a rabbit at day 0. **As antibody formed, it complexed with the antigen and was deposited in the kidneys, joints, and capillaries.** The symptoms of serum sickness (light blue area) corresponded to the peak in immune-complex formation. As the **immune complexes were cleared**, **free circulating antibody (dashed black curve) was detected** and the symptoms of serum sickness subsided.

Type IV or Delayed-Type Hypersensitivity (DTH)

A type IV hypersensitive reaction involves the cell-mediated branch of the immune system. Antigen activation of sensitized T_H1 cells induces release of various cytokines that cause macrophages to accumulate and become activated. The net effect of the activation of macrophages is to release lytic enzymes that cause localized tissue damage. **The reaction is characterized by large influxes of nonspecific inflammatory cells, in particular, macrophages.**

Intracellular pathogens and contact antigens that induce delayed-type (type IV) hypersensitivity

Intracellular bacteria	Intracellular viruses
Mycobacterium tuberculosis	Herpes simplex virus
Mycobacterium leprae	Variola (smallpox)
Listeria monocytogenes	Measles virus
Brucella abortus	
Intracellular fungi	Contact antigens
Pneumocystis carinii	Picrylchloride
Candida albicans	Hair dyes
Histoplasma capsulatum	Nickel salts
Cryptococcus neoformans	Poison ivy
Intracellular parasites	Poison oak
Leishmania sp.	

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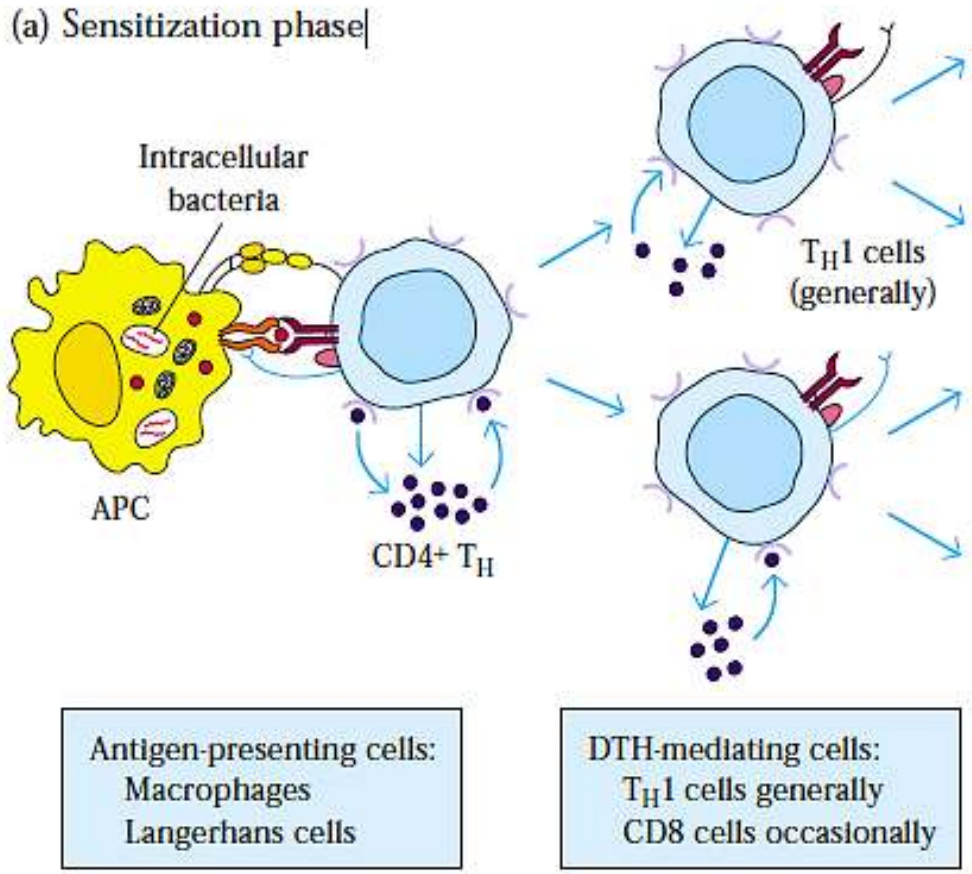
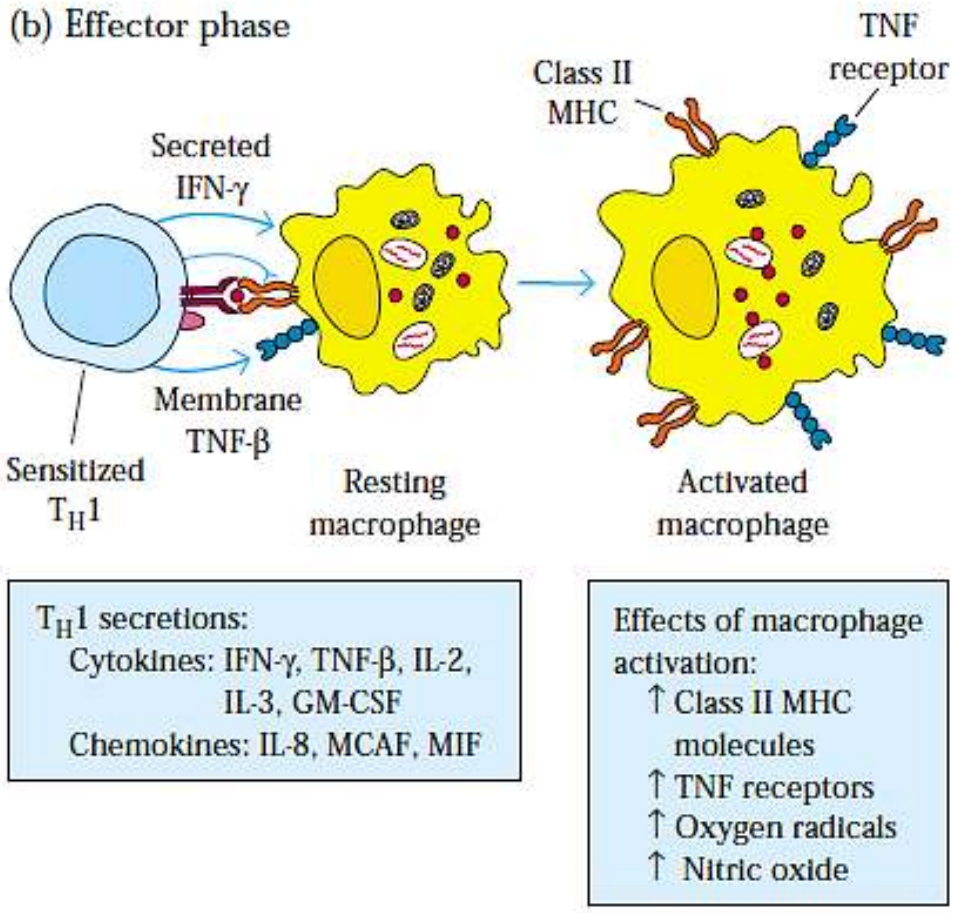
There are several phases of the DTH response

Sensitization Phase



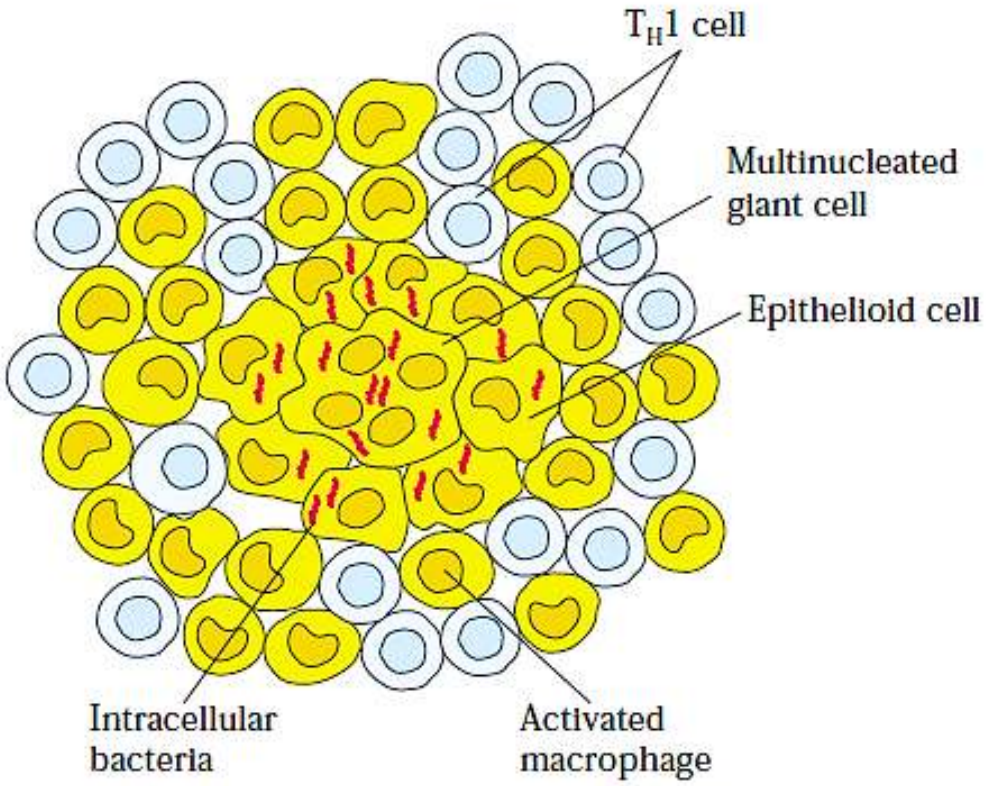
In the sensitization phase, after initial contact with antigen (e.g., peptides derived from intracellular bacteria), **T_H cells proliferate and differentiate into T_H1 cells.**

Effector phase

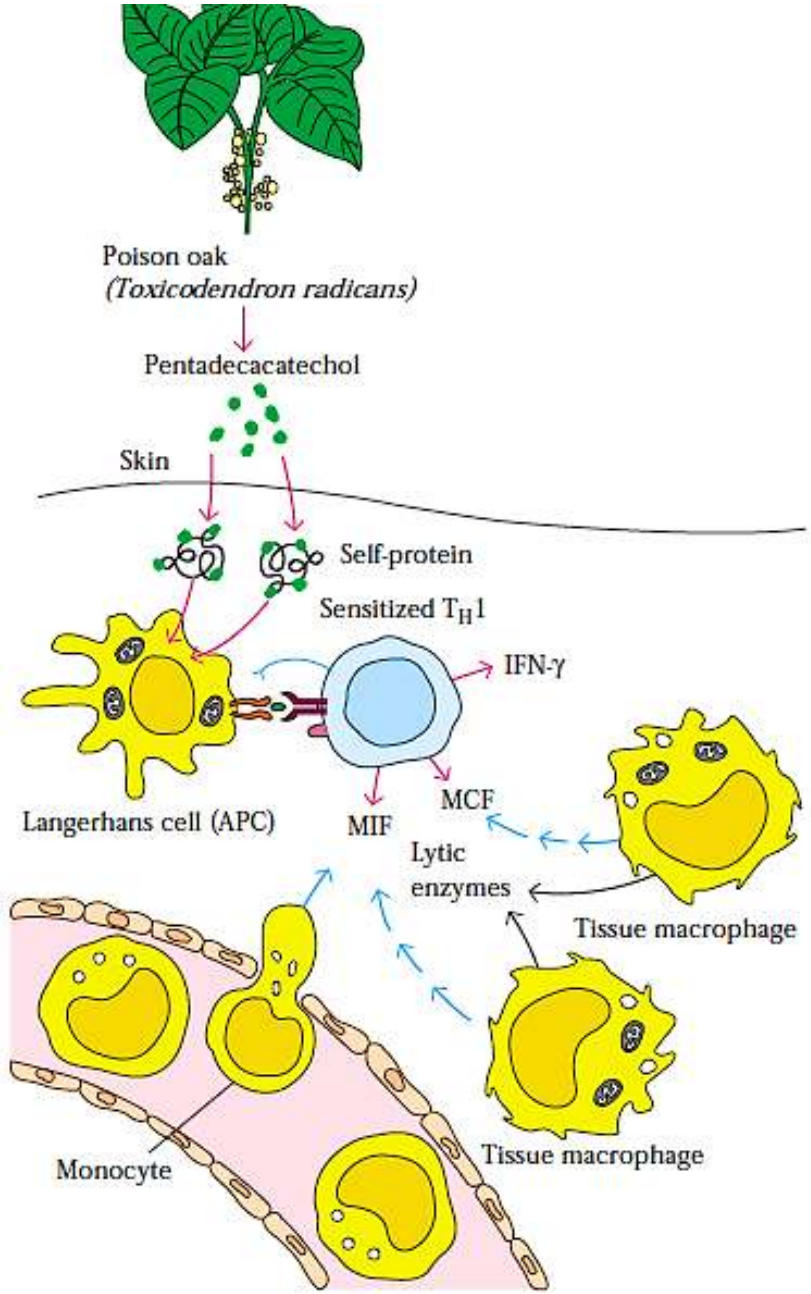


In the effector phase after **subsequent exposure of sensitized T_H1 cells to antigen, the T_H1 cells secrete a variety of cytokines and chemokines.** These factors **attract and activate macrophages and other nonspecific inflammatory cells**. Activated macrophages are more effective in presenting antigen, thus perpetuating the DTH response, and function as the primary effector cells in this reaction.

A prolonged DTH response can lead to formation of a granuloma, a nodule-like mass. Lytic enzymes released from activated macrophages in a granuloma can cause extensive tissue damage.



Contact Dermatitis is a type of DTH response



Development of delayed-type hypersensitivity reaction after a second exposure to poison oak. Cytokines such as IFN-, 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.