Hypersensitivity Reactions

Introduction

Under some circumstances, immunity, rather than providing protection, produces damaging and sometimes fatal results. Such harmful reactions are known collectively as **Hypersensitivity** or **allergic** reactions**.**

Hypersensitivity reactions differ from protective immunity only in that they are **exaggerated or inappropriate and damaging** to the host.

The cellular and molecular mechanisms of the two types of reaction are virtually identical. Hypersensitivity reactions are of four classes, designated type I, II, III and V1, Table 9.

	Type I	**Type II**	**Type III**	**Type IV**	
Immune reactant	IgE, TH2 cells	IgG	IgG	T cells	
Antigen	Soluble antigen	Cell surface antigen	Soluble antigen	Soluble antigen	Cell associated antigen
Effector mechanism	Mast-cell activation	Complement FcR cells (phagocytes, NK cells)	Complement Phagocytes	Macrophage activation	Cytotoxicity
Example	Allergic rhinitis, asthma, systemic anaphylaxis	Some drug allergies (e.g. penicillin) transfusion reaction	Serum sickness, Systemic lupus erythematosus	Contact dermatitis, graft rejection, rheumatoid arthritis	Contact dermatitis graft rejection diabetes mellitus

Table 9: The four types of hypersensitivity reaction.

Type I: Immediate or anaphylactic reaction

Allergens are antigens that induce IgE mediated reactions in susceptible individuals who also referred to as **atopic** individuals, while **atopy** "i.e., uncommon" is frequently used to referred to conditions which manifest type I hypersensitivity such as bronchial asthma and eczema.

Mechanism

All normal individuals can make IgE antibody specific for a variety of antigens but only few of them develops clinical symptoms.

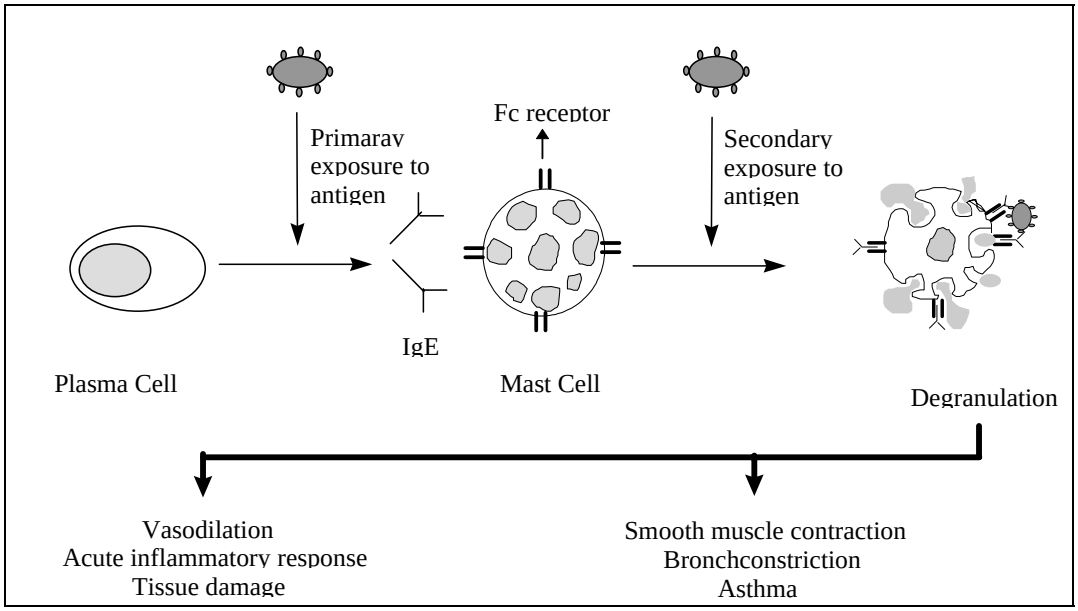

Figure 40: Mechanism of type I hypersensitivity reaction.

The development of type I anaphylactic sensitivity can be divided into several phases: (1) **the sensitization phase**, during which IgE antibody is produced in response to an antigen and binds to specific receptor on mast cells and basophil, Figure 40; (2) the **activation phase,** during which re-exposure to the same antigen triggers the mast cells and basophil to respond by release of the contents of their granules; and (3) the **effector phase,** during which a complex response (anaphylaxis) as a result of the many pharmacologically active agents released by the mast cells and basophils.

1	2	3	4	5
First exposure to pollen	IL-4 drives B cells to produce IgE	Pollen-specific IgE binds to mast cell	Second exposure to pollen	Acute release of mast cell contents causes allergic rhinitis (hay fever)

Table 10: The stages of type I hypersensitivity reaction in hay fever.

Pharmacologically active substances for hypersensitivity

The initial response to IgE triggering of mast cells is immediate release of **performed** mast cell granule contents, particularly vosoactive amine histamine and various enzymes. Later on, arachidoic acid metabolism in the mast cells generates **leukotrienes** which are also pro-inflammatory, causing a more sustained increase in blood flow and vascular permeability.

Examples of the diseases caused by type I hypersensitivity

All IgE mediated responses involve mast cell degranulation, but the symptoms of the experienced by the patient can be very different depending on whether the allergen is injected, inhaled or eaten and depending on the dose of the allergen, table.

IgE-mediated allergic reactions			
Syndrome	**Common allergens**	**Route of entry**	**Response**
Systemic anaphylaxis	Drugs Serum Venom	Intravenous	Edema, vasodilatation Tracheal occlusion collapse, death
Wheel and flare	Insect bites Allergy testing	Subcutaneous	Local vasodilatation Local edema
Allergic rhinitis (hay fever)	Pollens Dust mite faces	Inhaled	Edema of nasal mucosa irritation of nasal mucosa
Bronchial asthma	Pollens Dust mite feces	Inhaled	Bronchial constriction Increased mucus production
Food allergy	Shellfish, Milk, Eggs, Fish, Wheat	Oral	Vomiting, diarrhea, itching, urticaria

Table 11: IgE mediated reactions to allergens.

Why some individuals develop allergy?

We do not yet understand what causes some individuals to become allergic to a substance while others do not. Some of the important factors include:

1- The MHC genotype plays a role in determining susceptibility to allergy,

2- Differences in mucosal permeability may restrict the effect of allergens lodging on the mucosal surface,

3- Allergic sensitization in a susceptible individual may result from failure of IgE Control mechanisms.

Immune therapy

Allergists use carefully controlled and repeated exposure to the allergen to **desensitize** the patients, which is believed to gradually divert the response to one dominated by production of IgG and IgA antibodies specific for the allergen.

Type II: Cytolytic or Cytotoxic Reactions

Mechanism

Binding of the specific Ab directly to an antigen on the surface of a cell produces damage to that cell through **two major pathways**. In the first pathway, antibody (usually IgM, but also IgG) activates the entire complete complement sequence and eventual lysis of the cell. In the second pathway (usually IgG) serve to engage receptors on phagocytic cells for Fc and C3b. These lead to phagocytosis and destruction of the cell by macrophages and neutrophils, Figure 41. These reactions occur within hours of re-exposure.

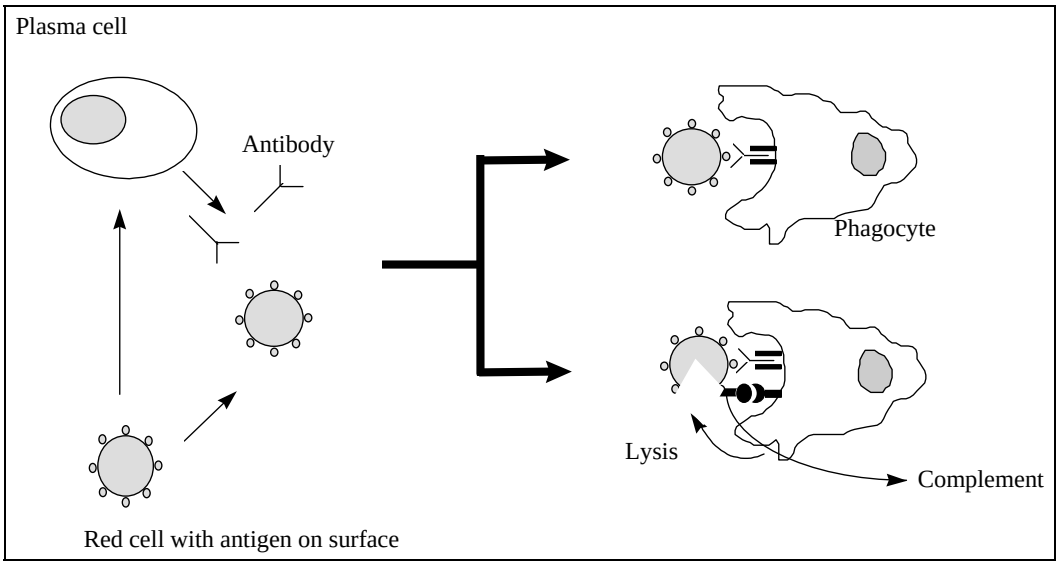

Figure 41: Mechanism of type II cytolytic or cytotoxic hypersensitivity reaction.

Examples of diseases caused by type II hypersensitivity

Transfusion reactions:

The simplest form of cytotoxic reactions is seen after transfusion of ABO incompatible blood. As an example people with type O blood have in their circulation naturally occurring IgM anti A and anti B which react with the A and B blood group substances. If such persons were to be transfused with a unit of

type A red cell, the antibodies can cause complement dependent lysis or phagocytosis of the transfused cell.

Rh incompatibility reactions:

Antibodies against Rh antigens can be damaging to new-born babies. In brief, a Rhesus negative (Rh^-) mother may be immunized by the transplacental passage of red cells from the baby and may make antibodies against Rh^+ cells of her (usually first) baby who has inherited the Rh antigen (or factor) from his father. Any subsequent Rh+ babies she might have may be damaged by these antibodies which can cross the placenta, bind to the baby's erythrocytes, activate complement and lyse the cells causing anemia.

Fortunately, this hemolytic disease of the new-born is now understood, and is controllable and can be largely avoided by preventing sensitization of the mother in the first place.

This is done by a process known as passive immunization. Immediately after the birth of her first child, the mother is injected with anti-rhesus antibodies. These bind to any fetal erythrocytes that have entered her blood stream around the time of birth when the placenta was breaking down and bring about their destruction without them sensitizing her immunologically. The next baby to be conceived develops in an environment free of these damaging antibodies.

Autoimmune reaction:

As a consequence of certain infectious diseases or for other, still unknown reactions, some people produce Ab against their own red cells. This antibody, on binding to the red cells, destroy them by lysis or phagocytosis via receptors for Fc and C3b. This may lead to progress anemia.

Type III: Immune Complex Reactions

Mechanism

Immune complexes are generated in every antibody response. The pathogenic potential of immune complexes is determined in part by their **size**. Larger aggregates fix complement and are readily removed by phagocytes, while the small complexes that form at antigen excess tend to deposit in blood vessel walls of certain tissue sites, and it is here that they cause tissue damage or immunocomplex disease.

Immune complexes can activate platelets and basophils via Fc receptors to release vasoactive amines which cause endothelial cell retraction and increased vascular permeability leading to complex deposition, Figure 42: The mechanisms of immune complex hypersensitivity. Figure 42.

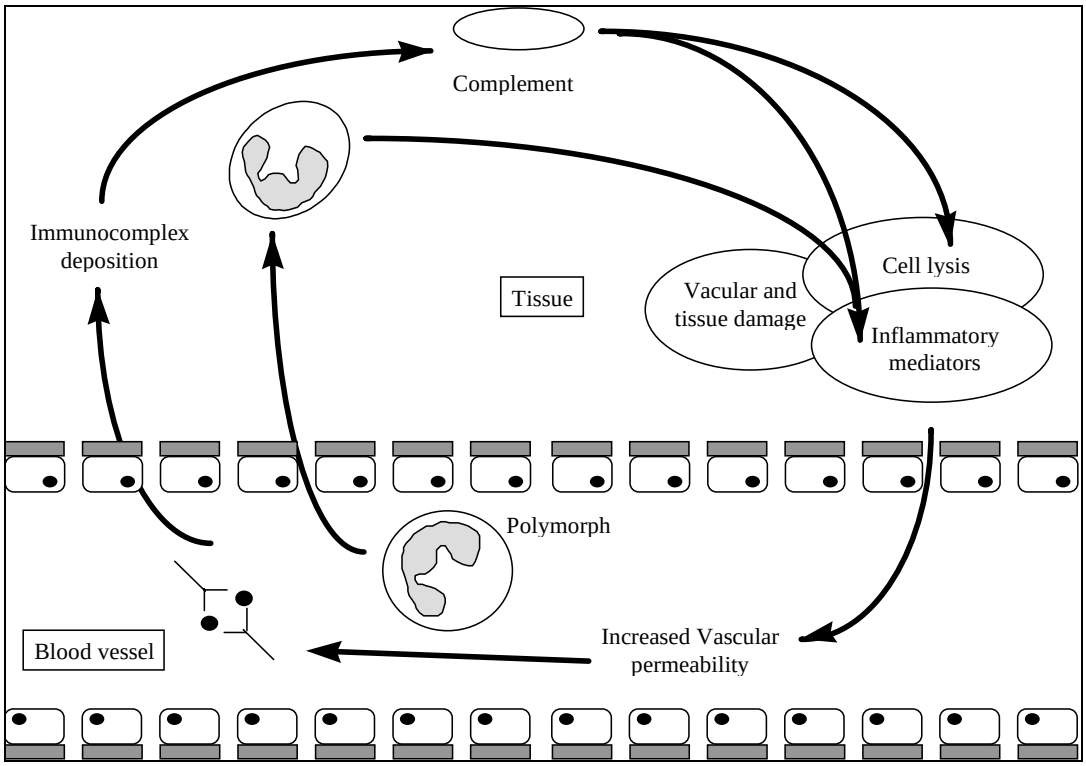

Figure 42: The mechanisms of immune complex hypersensitivity.

Examples of type III hypersensitivity reactions

Arthus reaction:

It is a skin reaction seen as an area of redness and swelling which is maximal 6 hours after intradermal injection of antigen. It is caused by IgG When a sensitized individual has IgG antibodies directed against an antigen immune complexes can be generated locally by injection of the antigen into the skin, IgG antibody that has diffused into the tissues forms immune complexes locally. The immune complexes creates a local inflammatory response by type III hypersensitivity reaction. This is called an **Arthur reaction**, Fig (12.5).

Serum sickness:

In the pre-antibiotic era, immune horse serum was often used to treat pneumococcal pneumonia. Specific antibodies in the horse serum would help the patient to clear the infection. However, such treatments also stimulate the immune system to make IgG antibody to the foreign serum proteins and after a period of time immune complexes form throughout the body, Figure 43.

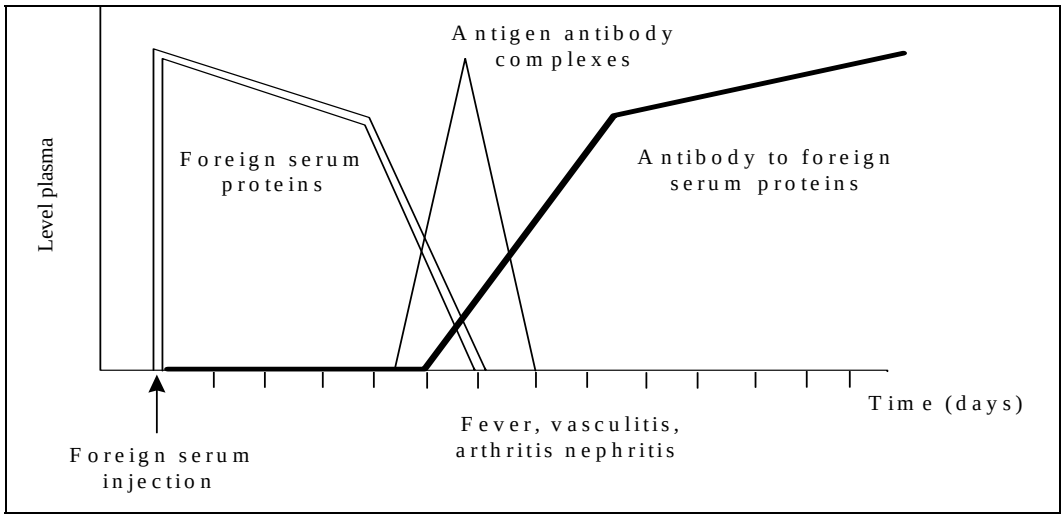

Figure 43: The relation ship between circulating antigen antibody complexes and the serum sickness.

This is an unusual type of allergy; because serum proteins (the allergen) are given in large amounts and are long-lived, the sensitization and the allergic reaction both take place after only one dose of allergen.

Infection associated immune complex disease:

In a number of infectious diseases such as malaria, leprosy, viral hepatitis and bacterial endocarditis, there may be times during the course of the infection when large amounts of antigen and antibodies exist simultaneously and cause the formation of immune aggregates that are deposited in various locations. Thus some of the symptoms of these diseases may include a component attributable to a type III hypersensitivity.

Type IV: Cell Mediated Hypersensitivity Reactions

Nomenclature

The nomenclature of this type of hypersensitivity response has varied over the years, according to historic usage. Originally the response was termed the **tuberculin reaction**. Subsequently, the delayed nature of the onset of these responses, has led to their collective designation as delayed-type hypersensitivity (DTH) reactions. With the discovery that all these reactions are mediated by T cells, they are now classified **as T cell-mediated** or simply **cell-mediated immunity**.

Mechanism

Delayed type hypersensitivity (DTH) reactions are mediated by inflammatory CD4 T cells (Th1) that activate local inflammatory responses and by cytotoxic CD8 T cells that can kill tissue cells directly. Unlike immediate type hypersensitivity, DTH reactions appear 18-24 hours after antigenic challenge of a sensitized individual. As in other types of sensitivity reactions, DTH hypersensitivity consists of two main stages, namely, the sensitization stage and the challenge stage, which leads to the reaction. These are shown diagramatically in Figure 44.

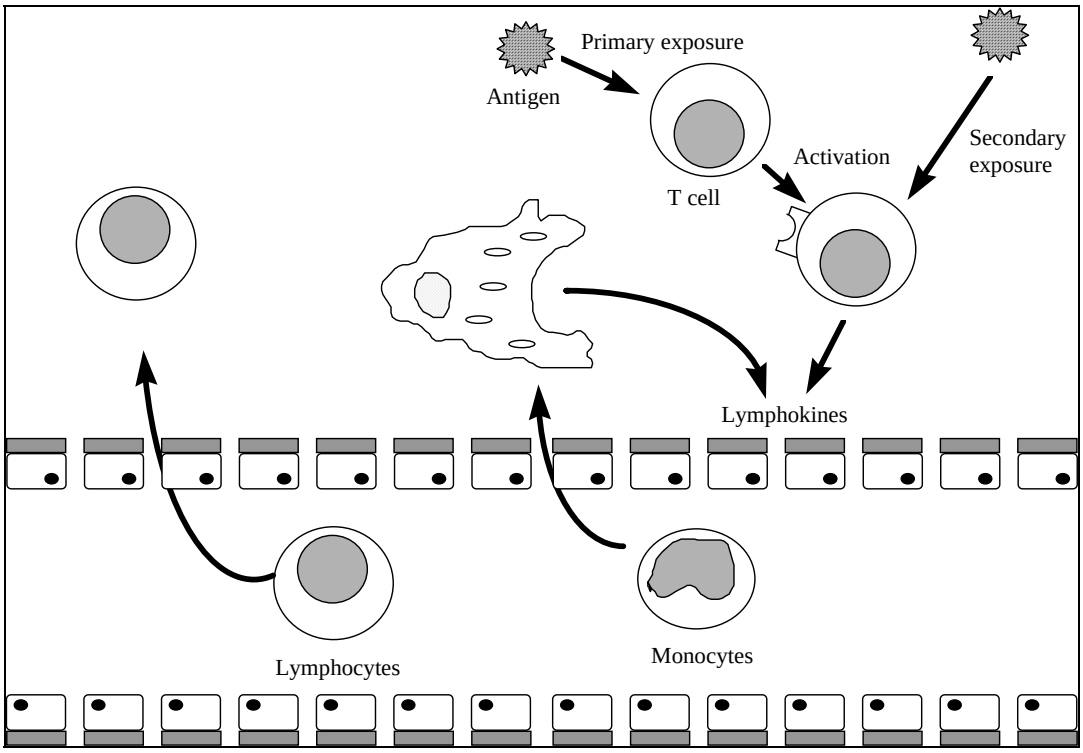

Figure 44: Mechanism of type IV delayed type hypersensitivity reaction.

Sensitization of induction stage

This stage lasts one or two weeks. Contact of T cells with antigens on an antigen presenting cell results in antigen recognition, proliferation, and activation of T cells. The key cells are the inflammatory Th1 CD4 cells. Cytokine released by these cells activates macrophages. A small number of $CD8^+$ cytotoxic T cells also appear during T cell expansion.

Elicitation of the DTH reaction

A second exposure to antigen (i.e. antigenic challenge) causes the delayed type reaction. The antigen presented by APC, interacts with the sensitized (i.e. primed) Th1 or T inflammatory cells resulting in release of cytokines that have a variety of biological effects. These include activation of local endothelial cells, attraction of macrophages to the reaction site, **activation of macrophages**, and the release of additional cytokines. It takes approximately 18-24 or even 48

hours from time of antigenic challenge to recruit and activate these cells, fig (12.8).

Consequences of DTH

Many of the effector functions in CMI are performed by **activated macrophages**. In most favorable circumstances, CMI results in destruction of the organism that elicited the response in the first place. This destruction is carried out by **ingestion** and **degradation** by **lysozomal enzymes** of the **activated macrophages** as well as by peroxide and superoxide radicals.

In circumstances where the antigen is readily eliminated, the lesion resolve with little tissue damage. In some circumstances however, the antigen is persistent. For example, schistosoma; eggs and intracellular mycobacteria. In these cases, the response can be prolonged and destructive to the host continuos accumulation of macrophages lead to granuloma formation. The disease process may then be attributable to the host immune response. In viral diseases, additional destruction by cytotoxic T cells occurs.

Variants of DTH

Several known variants of classical DTH or tuberculin reactions have the same basic mechanisms but have additional features, which are described below:

Delayed-type hypersensitivity reaction (tuberculin test):

This is used to determine whether an individual has previously been infected or immunized with *Mycobacterium tuberculosis*. When small amounts of a protein from *M. tuberculosis* are injected into subcutaneous tissue, a T-cell mediated local inflammatory reaction evolves over 24-72 hours in individuals who have previously responded to this pathogen. The response is mediated by inflammatory T cells (Th1) that enter the site of antigen injection, recognize peptide: MHC class II complex on antigen-presenting cells, and release inflammatory cytokines that increase local blood vessel permeability, bringing

fluid and protein into the tissue and recruiting accessory cells to the site. Each of these phases takes several hours and so the mature response appears only 24-48 hours after challenge.

Contact dermatitis

Very similar reactions are observed in several allergic responses. For instance, the rash produced by poison ivy is caused by a T-cell response to a chemical in the poison. This compound binds covalently to host proteins. Modified self peptides may bind to self MHC class II molecules. When specifically sensitized T cells recognize them they produce extensive inflammation by type IV hypersensitivity mechanism. Because the chemical is delivered by contact with the skin, this is called **a contact hypersensitivity reaction**.

Granulomatous reactions:

It develops where there is a persistent stimulus which macrophages can not eliminate. Persistent pathogens such as mycobacteria and Schistosoma species induce immunological granulomas. The lesion consists of a palisade of epithelioid cells and macrophages surrounding the infectious agent.

Cell mediated immunity

Effective specific immune protection against organisms such as mycobacteria (TB) which remain largely hidden from the immune system depends upon T-amplifier cells rather than upon antibody. These recognize bacterially-derived antigen which is expressed on the macrophage membrane in a recognition which is guided by the Major Histocompatibility Complex (as are most other aspects of T cell activity). The amplifier cells produce lymphokines that activate macrophages in a way that makes them better able to destroy the bacteria within them.