
CHAPTER 21

IMMEDIATE HYPERSENSITIVITY: ALLERGY

Allergies represent TYPE I reactions according to the *Gell and Coombs* classification. Most are caused by IgE ANTIBODIES which are capable of binding to Fc-receptors for IgE on tissue MAST CELLS. Cross-linking of these membrane-bound IgE's by specific antigen results in mast cell DEGRANULATION; this process releases HISTAMINE and a variety of other effector molecules, which in turn results in the myriad symptoms of allergy. (rash, hay fever, asthma *etc.*) Passive cutaneous anaphylaxis (PCA) in the guinea pig and the Prausnitz-Küstner (P-K) skin reaction in humans provide models for understanding the underlying mechanism of allergic reactions. Management of allergies begins with allergen avoidance, and includes the use of a variety of drugs and allergen-specific DESENSITIZATION.

One of the many manifestations of antibody, specifically antibody of the IgE isotype, is the mediation of **allergic reactions**. We are all familiar with such reactions, whether they appear as hay fever, asthma, sensitivity to penicillin or other drugs, or skin reactions due to substances in food or cosmetics. This class of humoral immune reactions is referred to as **immediate hypersensitivity**, since the time required for its development is much shorter than typically required for cellular immune reactions (**delayed-type hypersensitivity**) or other kinds of humoral reactions.

Any substance which can elicit an allergic response is referred to as an ALLERGEN. However, an allergen can only be effective in causing an allergic reaction if the recipient has been previously sensitized; that is, there must be present, in his tissues, antibodies of the IgE class directed against the allergen. An allergen can be a component of any number of microorganisms, plants or animals, or may be a synthetic compound. Allergic reactions may be elicited by exposure through the air (pollen), contact with the skin (cosmetics), ingestion (natural or artificial food products), or injection (drugs or insect bites).

GELL AND COOMBS CLASSIFICATION OF IMMUNE REACTIONS

Before describing the mechanisms involved in allergic reactions, we will review a general scheme of classification of immune reactions proposed almost fifty years ago by Gell and Coombs. While this scheme is quite dated in many respects, it remains widely used and can be helpful in understanding the relationships between different immune reactions,

Under this scheme, all immune reactions are classified into one of four headings known as Types I, II, III, and IV.

Type I reactions include all of **immediate hypersensitivity**, the allergic reactions we will cover in detail in this chapter. They are mostly IgE-mediated (although other Ig classes may sometimes participate), and their rapid onset, typically within minutes of exposure to antigen, is characteristic.

Type II reactions result from **antibody binding to membrane-bound Ag** resulting in complement-mediated cytotoxicity or opsonization/inflammation. This class of reactions may be typified by hemolytic anemia (resulting from auto-antibodies directed against red blood cells), hemolytic disease of the newborn (*HDN*, see Chapter 10), and certain drug reactions.

Type III reactions occur when Ab binds to *soluble* Ags to form **immune complexes**, which can cause any of several kinds of immune complex disease (see Chapter 5). While IgG, IgM and complement may be involved, as in Type II, the key difference is that *Type III reactions are the result of deposition of circulating antigen-antibody complexes in tissues, as opposed to the binding of antibodies to antigens which are an integral part of a target cell membrane.*

Type IV reactions include all **cell-mediated reactions** (Cell-Mediated Immunity or CMI). **Delayed-type hypersensitivity** (DTH) is a synonym for CMI, and alludes to the slower development of such reactions compared with antibody-mediated reactions. For example, the tuberculin skin test to PPD (Purified Protein Derivative) develops over a period of a few days, compared with a few minutes for Type I reactions and a few hours for Type III.

GELL AND COOMBS CLASSIFICATION OF IMMUNE REACTIONS

Reaction	Description	Participating Antibody	Skin Reaction Example (Cellular Infiltrate)	Typical Time of Onset
TYPE I	Immediate hypersensitivity (e.g. allergy)	IgE (plus Mast Cell)	Allergy skin test (eosinophils & PMNs, <i>late phase</i> only)	1-20 min
TYPE II	Ab to cell-associated antigens (e.g., hemolytic anemia)	IgG/IgM	----	---
TYPE III	Ab to soluble Ags, immune complexes (e.g., serum sickness)	IgG(IgM)	Arthus reaction (neutrophils [PMNs])	7-10 hrs
TYPE IV	Delayed-type hypersensitivity (DTH); Cell-mediated immunity (CMI) (e.g. graft rejection)	---	Tuberculin test (mononuclear cells, <i>i.e.</i> lymphocytes and macrophages)	1-3 days

These distinct kinds of immune reactions can be distinguished not only by the *time course* of their development, but also by the nature of the *cellular infiltrate* present in the sites of a typical reaction. We have seen (Chapter 5) that one of the consequences of complement fixation is the release of factors which are chemotactic for PMN's; thus we typically find these cells in Type III reactions (Arthus reaction). As we will see later in this chapter, one of

the mediators of allergic reactions is a factor which is chemotactic for eosinophils--thus the characteristic infiltrate of the *late phase* of Type I reactions (e.g. allergy skin test). The mechanisms of cell-mediated immunity have been discussed in Chapter 12, and we have seen that lymphocytes and macrophages are both effector cells of such reactions, and that macrophage-chemotactic factors are known mediators. Thus, *mononuclear* cells (a term encompassing macrophages and lymphocytes) characterize the inflammation at the site of a tuberculin skin test (Type IV reaction). We can therefore see a clear connection between the nature of the cellular infiltrate identified by the pathologist, and what is known of the cellular and molecular mechanisms of immune reactions.

IgE: REAGINIC ANTIBODY

IgE antibodies are also known as **reagins** or **reaginic antibody**. They have several features which distinguish them from other classes of Ig:

Low serum levels IgE serum concentrations are lower than any other class of Ig, typically in the range of nanograms per ml. (But remember that only *IgE which is bound to mast-cells* can initiate allergic reactions.)

Heat labile IgE is very sensitive to heat, and can be inactivated by moderate heating which has little effect on other Ig classes (for instance, heating at 56C for 30 minutes, typically carried out to inactivate complement).

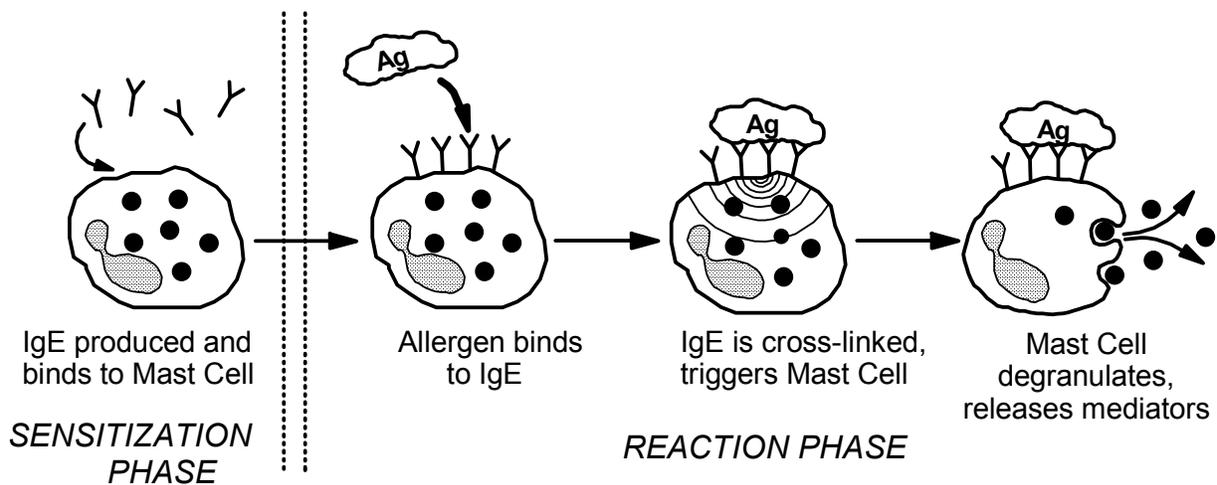
"Homocytotropic" This refers to the ability of an animal's Ig to bind to its *own* mast cells and initiate allergic reaction. IgE is the major mediator of allergy, although in humans IgG4 can also carry out this function with lower efficiency. [This term exists only to distinguish IgE from *"heterocytotropic"* antibody, which can initiate allergic reactions only in a species other than the one from which the antibody was obtained. Rabbit IgG, for instance, can cause allergic responses when transferred to guinea pigs, although it does not do so in the rabbit. Heterocytotropic antibodies are mostly of experimental interest.]

SEQUENCE OF EVENTS IN ALLERGIC RESPONSES

Allergic immune responses can be separated into two components, a period of *sensitization* followed by the allergic *reaction* itself.

Sensitization Phase

- 1) Exposure of the immune system to the immunogenic allergen results in the **induction of IgE antibody**, with the participation of T-cells, B-cells and macrophages. This induction of Ig synthesis must precede the allergic reaction itself, which is outlined in Figure 18-1.
- 2) **IgE antibody binds to tissue mast cells** through its Fc piece (see Figure 18-1). Mast cells have Fc receptors on their surface with an extremely high affinity for IgE antibodies. The stage is now set for the initiation of an allergic response.



IgE AND ALLERGIC REACTIONS

Figure 21-1

Reaction Phase

- 1) Re-exposure to the allergen results in the **binding of the allergen to mast-cell-bound IgE antibody**. Cross-linking of IgE molecules on the mast cell surface by multivalent antigen is required for the subsequent reactions.
- 2) The large, basophilic granules present in the mast cells are released into the tissues; this process of **degranulation** releases a variety of pharmacologically active compounds; some directly from the granules (e.g. histamine and heparin), others newly synthesized by the cell soon afterwards (see below).

Mediator	Effect
Histamine , heparin, proteases	Contraction of the smooth muscle of bronchi, gut and venules; capillary dilation & vascular permeability; increased mucus secretion
Prostaglandins, leukotrienes,	Bronchoconstriction; asthma; increased mucus secretion and venule permeability.
Kinins	Vasodilation, histamine-like activity
Cytokines, chemokines, interleukins (IL-4,8)	Inflammation, tissue remodeling
ECF-A (<i>Eosinophil Chemotactic Factor of Anaphylaxis</i>)	Eosinophilia

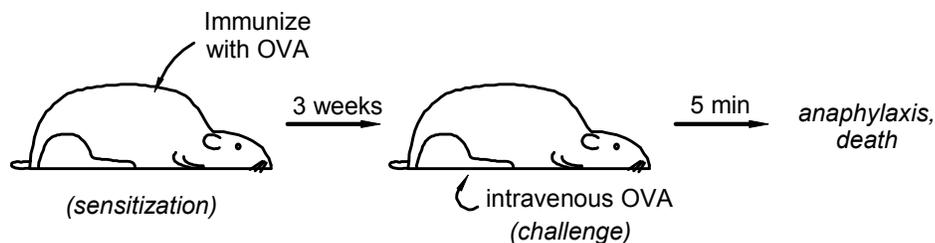
These and other active compounds can lead to such conditions as **asthma** and **rhinitis**, generally in response to allergens in pollen, dust or animal dander. Allergens in cosmetics can lead to **rashes**, and allergens in food, drugs or injected animal poisons may result in rashes or in **vascular** or **gastrointestinal anaphylaxis**. These conditions may range from very mild to severe, and are potentially fatal (for instance, in the case of severe asthma or vascular anaphylaxis).

The nature and severity of allergic reactions depends on the route of exposure and the degree of sensitization, it varies considerably from one species to another, and within humans may vary tremendously between different individuals; there are clearly very significant genetic factors which are not understood, but they include at least some HLA- linked components.

EXPERIMENTAL MODELS OF ANAPHYLAXIS

Vascular Anaphylaxis in the Guinea Pig

The *guinea pig* is extremely sensitive to the development of severe allergic reactions, and was for many years the system of choice for studying allergic responses and the physiology of IgE.



Vascular Anaphylaxis in the Guinea Pig

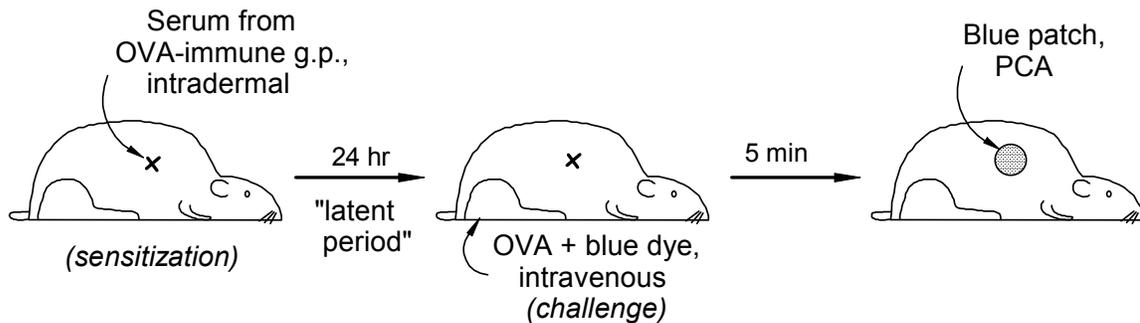
Figure 21-2

A guinea pig can be sensitized by intramuscular injection of an antigen, say OVA (ovalbumin). Its immune system responds by producing antibody to OVA, including (but not exclusively) IgE. Some of this circulating IgE will be fixed onto mast cells in various tissues, including the vasculature and respiratory tract. Three weeks later, the same animal can be challenged either with an intravenous dose of OVA or by exposure to an aerosol containing OVA. Following IV injection, the animal will rapidly develop severe vascular shock and die within a few minutes (the combination of *venule constriction* and *capillary dilation* results in *pooling* of blood in the peripheral circulation and a drastic drop in blood pressure). If exposed to the aerosol, it will equally rapidly die from bronchial constriction, an experimental model for human asthma.

Passive Cutaneous Anaphylaxis (PCA)

The ability to carry out an anaphylactic reaction can be transferred from a sensitive animal to a normal one by transferring serum (this defines it as a humoral immune response). This can

be done in such a way as to cause a local rather than systemic reaction, as illustrated by PCA (Figure 18-3). Serum is collected from a guinea pig sensitized to OVA (as described above), and a small amount is injected intradermally into a normal recipient.



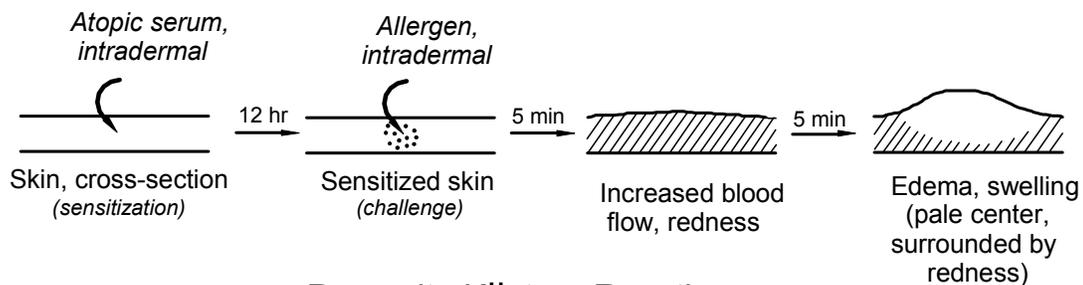
Passive Cutaneous Anaphylaxis in the Guinea Pig

Figure 21-3

After 24 hours (the **latent period** required for the IgE antibodies to bind to the surface of local mast cells), OVA together with the dye Evans Blue is injected intravenously. Within minutes, a blue patch becomes visible on the animal's skin where the immune serum had been injected. This is because local degranulation of the mast cells has resulted in capillary dilation, and the leakage of fluids from blood into the intercellular spaces of the skin is readily visible due to the presence of blue dye.

Prausnitz-Küstner (P-K) Reaction

This is a human version of passive cutaneous anaphylaxis, and is primarily of experimental rather than routine clinical interest. Serum from an "atopic" (allergic) patient is injected intradermally into a non-allergic recipient. Twelve hours later (this is the **latent period**) a small amount of the allergen is injected into the same region. Within minutes the allergic reaction becomes visible as a **wheal and flare**. The "wheal" is a region of swelling resulting from the leakage of fluid into the extracellular space (edema), the red "flare" surrounding it is the result of increased blood flow.



Prausnitz-Küstner Reaction

Figure 21-4

EARLY-PHASE *VERSUS* LATE-PHASE ALLERGIC REACTIONS

Allergic reactions are referred to as “Immediate Hypersensitivity” because of their typically rapid onset. However, there are often important long-term consequences of the immediate reaction which are collectively referred to as the *Late-Phase Reaction*. In the case of an allergic skin reaction (Prausnitz-Küstner, for example) the early or immediate phase occurs within a few minutes. However, over the course of subsequent hours and days a cellular infiltrate dominated by eosinophils will develop, which also includes neutrophils, macrophages and TH2 cells (keep in mind that we have only mentioned a few of the many inflammatory and chemotactic factors released by mast cells during degranulation).

In the case of asthmatic reactions, the late-phase response may be manifested by a chronic inflammation and hypersensitivity of the bronchi, with important diagnostic and therapeutic implications. Cromolyn sodium, mentioned below, can be given prophylactically to inhibit mast-cell degranulation and prevent the initial reaction. In the presence of an ongoing chronic late-phase reaction, however, administration of steroids may be indicated for their anti-inflammatory properties.

EVALUATION OF THE ALLERGIC STATE

In managing allergic patients, it would be useful to have a simple and accurate laboratory test to determine the specificity and severity of any allergy. While no ideal test exists, one can monitor IgE levels in such patients, as well as skin sensitivity to defined antigens, with varying degrees of usefulness.

Determination of serum IgE levels in allergic patients can be carried out by several assays. One of them, the RadioImmunoSorbent Test (RIST), measures total *serum IgE*; however, these levels correlate very poorly with the degree of clinical allergy. Somewhat better is the RadioAllergoSorbent Test (RAST), which measures the levels of circulating IgE *antibody* directed against a particular allergen; still, the correlation is not good.

The reasons why these tests are less than satisfactory are not fully clear, but reflect the fact that there exists a high degree of variability among different people, not only in the levels of IgE (relative to other isotypes) in humoral immune responses, but also in the efficiency of its fixation to tissue mast cells, the sensitivity of mast cells to degranulation, and the sensitivity of various tissues to the effector molecules and the inflammatory response.

Skin testing can be very useful in determining to which allergens a particular patient is sensitive. This involves injecting small amounts of various purified antigens intradermally, and measuring the severity of the *wheal and flare* reaction over a period of about half an hour. (This is an *active* rather than a passive cutaneous anaphylaxis reaction).

Test diets are also very helpful in identifying food allergies. The patient is placed on a diet free of the most common sources of allergens (wheat and related grains, dairy products, eggs, *etc.*), and various foods are added one at a time over a period of weeks or months to determine which may be responsible for the allergic response.

TREATMENT OF THE ALLERGIC STATE

- 1) **Avoidance** of allergens is the single most important and effective element in managing allergic states. This may include eliminating known allergens from one's diet (nuts, milk, eggs, for instance), removing them from one's home (wool carpets, feather pillows, pets and plants, for instance), and, of course, avoiding drugs to which one is sensitive (penicillin and its derivatives, for instance). Eliminating the major known allergens from one's environment can not only avoid reactions to those substances, but can also reduce overall sensitivity to other allergens.
- 2) **Desensitization** may be quite effective, but not in all cases. This involves deliberate immunization with small but increasing amounts of a particular purified allergen over a period of months or years. It is thought that the effectiveness of this procedure results from the induction of high levels of IgG antibodies, which can prevent allergic reactions by competing for the allergen and preventing it from reaching mast-cell bound IgE.

Desensitization has been useful for pollen and dust allergens as well as for some animal danders, but its effectiveness is unpredictable and varies between individuals. It is not generally useful for food or drug allergies (although a protocol has recently been introduced for penicillin allergies). Desensitization also carries with it a certain degree of risk, as each injection may itself induce a more or less severe allergic reaction. The procedure must be carried out under careful supervision.

- 3) **Drugs** can be useful in both preventing and treating allergic reactions.

Antihistamines inhibit binding of histamine to its receptors (but will not effect the target tissue response once histamine is bound).

Corticosteroids are anti-inflammatory (useful for the late-phase response), and can also inhibit histamine synthesis.

Cromolyn sodium is widely used as a prophylaxis for exercise and allergy-induced asthma, although its mechanism of action is unclear. While it is known to stabilize mast cells, this is probably not the basis for its efficacy.

Isoproterenol, salbutamol and epinephrine can be used to counteract the effects of various of the mediators released by mast cells; *unlike the drugs mentioned above, they can be effective in controlling an ongoing allergic reaction.* Prompt treatment of a systemic anaphylactic reaction (to a food, drug or insect bite, for example) can be life-saving.

PENICILLIN SENSITIVITY: SELF-PROTEINS MAY ACT AS CARRIERS

Type I allergic reactions to penicillin are not uncommon, and can be life-threatening. The mechanism of generation of such reactions is of interest. The beta-lactam ring of this antibiotic is chemically highly reactive, and can spontaneously and covalently bind to serum proteins. The result is, in effect, the production of a hapten-carrier complex which may be immunogenic (despite the fact that the carrier molecules are "self"); they are capable of

generating a humoral antibody response (including IgE) to the penicillin hapten, and of triggering an allergic reaction once IgE is present. (Penicillin bound to red blood cells may also serve as a target for antibody-dependent cell destruction and hemolytic anemia, an example of a "Type II" immune reaction.)

Other drugs and chemicals can also bind to "self" proteins, and *give rise to allergic reactions (humoral immunity) in addition to delayed type hypersensitivity (cell-mediated immunity)* to small molecules which would not by themselves be immunogenic. DTH skin reactions to metals such as nickel in jewelry are generated in this manner, producing *Contact Dermatitis*.

WHY IgE?

While the dangers and discomfort associated with IgE-mediated reactions are well known, the physiological benefits derived from IgE are less clear; surely the evolution of the IgE system did not occur in order for us to enjoy the benefits of hay fever and asthma. One important clue seems to be the association of extraordinarily high levels of IgE (thirty or more times normal levels) with certain helminthic infections, and IgE-mediated contraction of the smooth muscle of the gut may obviously promote expulsion of large numbers of the parasites.

It has also been shown that eosinophils can cause damage to some of these parasitic worms, but the situation remains puzzling. Most of the excess IgE is not specific for the parasites, and the eosinophilia associated with such infections affords only a limited level of protection. In short, the damaging effects of the IgE system are still understood far better than the positive role it must have had in mammalian evolution.

CHAPTER 21, STUDY QUESTIONS:

1. Is the IgE antibody bound to a particular mast cell monospecific? Is it monoclonal?
2. Would heating an antiserum at 56C for 30 minutes affect its ability to transfer an ARTHUS reaction? A PRAUSNITZ-KÜSTNER REACTION? CONTACT DERMATITIS?
3. What is the rationale for allergy DESENSITIZATION?