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Abstract
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This article concentrates on (i) the immunological basis, (ii) pathophysiological mechanisms, and (iii) control (theoretical and practical) of the immediate-type allergy.

Antigen-antibody reactions constitute an important group of defences, facilitating phagocytosis and blocking the toxic effects of parasitic poisons. The reaction confers 'immunity'. The combination of antigen and antibody is, however, not always beneficial. Pathological reactions as severe or more severe than the affect of the antigen alone arc sometimes noticed. Hypersensitivity or allergic reactions form major examples of such conditions. Allergy or hypersensitivity may be defined as a state in which the animal reacts in an excessive way to the introduction of an antigen or a hapten even though the antigen or hapten may be innocuous. Not all instances of hypersensitivity enjoy the identification of the exciting antigens, the mediating antibodies and the mechanisms of tissue damage.

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THE FIELD OF ALLERGY

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PART I — IMMUNOLOGICAL BASIS

Introduction

Antigen-antibody reactions constitute an important group of defences, facilitating phagocytosis and blocking the toxic effects of parasitic poisons. The reaction confers 'immunity'. The combination of antigen and antibody is, however, not always beneficial. Pathological reactions as severe or more severe than the effect of the antigen alone are sometimes noticed. Hypersensitivity or allergic reactions form major examples of such conditions. Allergy or hypersensitivity may be defined as a state in which the animal reacts in an excessive way to the introduction of an antigen or a hapten even though the antigen or hapten may be innocuous. Not all instances of hypersensitivity enjoy the identification of the exciting antigens, the mediating antibodies and the mechanisms of tissue damage.

Classification

Experimentally two types of hypersensitivity reactions can be demonstrated. They are: (a) the 'immediate type' and (b) the 'delayed type' reactions. Some of the main differences are summarised below.

	Immediate Type	*Delayed Type*
1. Speed of onset of reaction following antigen introduction	Immediate	Delayed 24-72 hours
2. Type of anti-bodies	γ - globulins	As yet Unidentified
3. Chemical medi-ators	Histamine 5 HT, SRS-A, ? Bradykinin. (Depending on species)	As yet Unidentified ? Bradykinin
4. Transfer from animal to animal	Possible with serum in many instances	Not possible with serum. Possible with cells in animals. In man extracts of cells are effective.
5. Types	Anaphylactic shock, Arthus reaction serum sickness, atrophy e.g. asthma, some drug sensitivity, Allergic rhinitis.	Bacterial allergy e.g. Tuberculin type reaction. Contact sensitivity to simple chemical, e.g. contact dermatitis.

Anaphylaxis

Portier and Richet (1902) found that whereas the first intravenous injection into dogs of an extract of sea anemones was relatively harmless, a second injection some 2 weeks later resulted in violent symptoms and often in the death of the dogs. Instead of 'phylaxis' (i.e. immunity), anaphylaxis developed. Soon Theobald, Smith, and Otto independently showed that the guinea pig could likewise be made hypersensitive even to non-poisonous extracts. To explain these facts two schools of thought developed. The first and now defunct theory was the 'anaphylatoxin hypothesis' led by Portier and Richet. The second and now widely accepted theory is the 'cellular hypothesis' supported by Dale. Briefly, this cellular theory maintained that the anaphylactic reaction was the result of union between antigen and antibody which had become 'fixed' to the living cell surface — Dale and Schultz independently showed that the phenomenon of anaphylaxis could be demonstrated in isolated tissues without the presence of blood. Dale showed that the uterus of a sensitised guinea pig (i.e. guinea pig which had received small injections of egg ovalbumin three weeks earlier), when suspended in a nutrient fluid at 37° C and oxygenated, would contract upon the addition to the bath of a small amount of the substance against which the guinea pig had been sensitised. The effect was quite specific since unrelated antigens gave no reaction. Furthermore, after the uterus had once responded by contraction to the antigen in question, a second addition of the same amount of the same antigen produced no effect. The tissue had thus become desensitised. Other workers have shown that other smooth muscle strips from sensitised guinea pigs behave in the same 'Schultz-Dale' manner as the myometrium. It is now possible to sensitise guinea pig tissues passively by soaking them in antibody solution (e.g. I^{133} labelled egg ovalbumin). There is ample evidence that antibody fixation to certain tissues is a necessary prerequisite for anaphylaxis.

Desensitisation

Guinea pigs sensitised to anaphylactic shock can be desensitised by repeated small injections of antigen. It has been shown that during the process of desensitisation a very high titre of circulating antibody is produced, and if antigen is administered to such an immune animal, anaphylactic reaction does not develop because the amount of circulating antibody is sufficient to neutralise all the injected antigen. Serum from such an immune animal is capable of inducing 'passive' sensitisation to anaphylaxis, thus demonstrating that the antibodies involved are of the same type.

Species variation

There is considerable species variation in the manifestations of generalised anaphylaxis. In the guinea pig there is severe bronchospasm leading to asphyxia and death. In the rabbit death is ascribed to corpulmonale. In the dog, death is due to hepatic congestion and peripheral circulatory failure. Man resembles the guinea pig in that there is acute respiratory distress of asthmatic type and generalised oedema. Anaphylactic reaction in man is in fact rare but when it does occur, it usually follows repeated injections of therapeutic serum (e.g. ATS), or certain drugs (e.g. penicillin and neoarsphenamine).

There is experimental evidence that cot deaths, which are responsible for about 2,000 infant deaths per year, may be due to hypersensitivity to cow's milk protein.

The disturbances in generalised anaphylaxis are fundamentally the same in all species. The main effects are: (a) spasm of smooth muscle, and (b) damage to endothelium of blood vessels and an increase in permeability, giving rise to generalised oedema.

Anaphylaxis has been used as an experimental model in the study of allergy. The basic mechanisms are not fundamentally different from other types of immediate hypersensitivity.

Atopy, Food, Dust and Drug Sensitivity

This group of allergies occur after the ingestion of certain foods and drugs, the inhalation of antigens like pollen, and the injection of drugs. There is considerable variation in symptomatology which seems to be dependent upon the route of absorption and the nature of the antigen or hapten.

Examples:

(a) Inhalation antigens, e.g. pollen, gives rise to respiratory symptoms such as allergic rhinitis, hay fever and asthma.

(b) Ingested substances, e.g. mushrooms, shellfish, give rise to gastro-intestinal symptoms and rashes. There is possibly absorption of

whole protein from the gut, so providing an antigen.

(c) Injected drugs, e.g. streptomycin and penicillin, usually give rise to skin rashes.

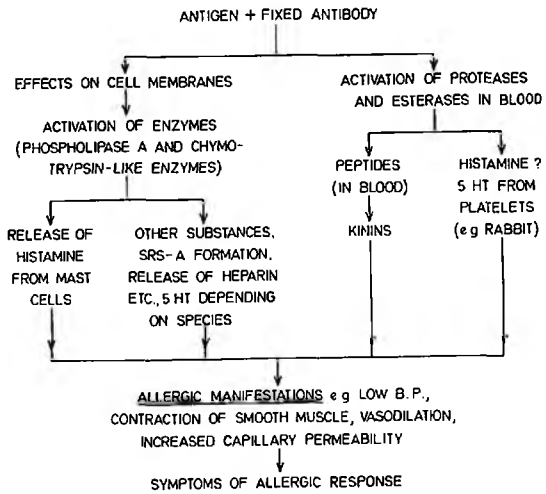
There seems to be a genetic basis in these types of allergy — hence the name atopy.

Miscellaneous Examples

Other examples of immediate hypersensitivity are Arthus reaction and serum sickness, but these conditions seem to be dependent on antigen-antibody complexes.

Many diseases have been labelled allergic although their pathogeneses are by no means clear. Examples are Type I nephritis, rheumatic fever and polyarteritis nodosa. A number of drug 'diseases' have also been documented as being allergic, and chlorpromazine obstructive jaundice is a well known example of this group.

PART II — MECHANISMS



The mechanism by which antigen-antibody combination brings about the release of pharmacological agents is far from being well understood. Briefly — antigen combines with fixed antibody. This 'reaction' is believed to lead to activation of tissue enzyme systems which include chymotrypsin-like enzymes and phospholipase A (Austen and Brocklehurst, 1961, etc.). Complement may or may not play a part at this stage.

Activated enzyme systems cause changes in the cells, such as mast cells which release pharmacologically active substances notably histamine, heparin, SRS-A, 5 HT, and bradykinin. The pattern of release is to some extent dependent on the species. The activation of tissue proteases and esterases may act on substrates such as peptides in the blood to release vasoactive substances such as kinins.

The symptoms of hypersensitivity result from the actions of these pharmacological agents. A summary of the evidence supporting the above statements is made below.

Enzymic Participation

The influence here stems from indirect evidence in which the effects were observed of pH change, temperature change, calcium lack and specific enzyme inhibitors on certain standard tests, e.g. Schultz-Dale type of test. Mongar and Schild concluded (1962) that the enzymes were calcium requiring and heat labile.

Role of Histamine

As Schachter states "Ever since that time that the similarity between the symptoms of histamine intoxication and acute anaphylactic shock was pointed out by Dale and Laidlaw (1910) an impressive body of evidence implicating histamine in anaphylaxis has accumulated." Many workers have demonstrated the release of histamine from sensitised organs both *in vitro* and *in situ* by specific antigen. Histamine liberators, e.g. 48/80, are able to reproduce many of the symptoms of anaphylactic shock when administered to animals. Schayer, and others, using radioactive histidine, have concluded that not only do mast cells store histamine, but also form histamine from histidine. Extrusion of mast cell granules, which are thought to contain histamine-heparin complexes, have been observed during antigen-antibody reaction. The evidence for the release of histamine in anaphylaxis is overwhelming and the release of this substance has been assumed to occur also in other immediate-type allergic reactions.

Slow Reacting Substances of Anaphylaxis (SRS-A)

Kellaway and Trethewie (1940), reported the occurrence of a slow reacting substance from a sensitised tissue following a challenge

with an antigen. The perfusate from guinea pig lung was assayed on guinea pig ileum and these workers recognised that the contraction differed from that caused by histamine in that the gut was slower to relax.

Brocklehurst (1952) noticed that high concentrations of antihistamines were unable to abolish SRS-A response. SRS-A does not appear to exist in preformed state, but is generated by events set in motion by antigen-antibody 'reaction' (Brocklehurst). In the tissues of sensitised guinea pigs and in human asthmatic lungs challenged with the appropriate antigens SRS-A is released along with histamine, but the peak release of SRS-A occurs later than that of histamine and moreover the release of SRS-A continues longer. SRS-A can cause a strong and well-maintained contraction in isolated human bronchioles and it is presumed to play an important role in asthma and so to be as least part of the cause of therapeutic failures of antihistamines in this condition. Herxheimer and Stressman (1961) have shown that whereas impure SRS-A aerosol decreased the vital capacity in asthmatic patients, it had only a small effect in normal subjects.

Other Substances

5 HT has been shown to be important in some species (rabbit and mouse) but not in man.

Bradykinin is present in the blood during anaphylaxis in several species of animals and can mimic some of the changes which are not abolished by antihistamines and presumably cannot be attributed to histamine. An enzyme capable of forming bradykinin in plasma, from dog plasma pseudoglobulin and from Mawer Fraction C is rapidly released from sensitised guinea pig lung or skin when these blood-free tissues are challenged with specific antigens (Brocklehurst).

Some of the inflammatory changes accompanying antigen-antibody 'interaction' might be due to bradykinin generated locally.

PART III — CONTROL OF ALLERGY

Theoretically the allergic reaction can be prevented in a number of ways:—

(a) The first anti-allergic step, often impractical, is the avoidance of contact with known antigens.

(b) By preventing antibody synthesis, e.g. by total body irradiation, antimetabolites and corticosteroids. The obvious disadvantages here far out-weigh any possible therapeutic advantages.

(c) By preventing antibody fixation to tissues. (This has not been possible.)

(d) By inhibiting enzymes involved in the allergic process. Little is known about these cellular enzymes, although it is possible they have normal physiological functions, and so it follows that inhibition of these enzymes may interfere with some vital metabolic processes (Brocklehurst, 1962).

(e) By desensitisation. This method has been tried, but the results are often disappointing even when the existing antigen has been indentified.

(f) The last, and at present most simple method of controlling the allergic symptoms is the inhibition or destruction of the pharmacological substances released during antigen-antibody 'reaction'.

There is no satisfactory way of antagonising SRS-A although it has been reported that homochlorcyclizine is a useful therapeutic agent in several allergic conditions including asthma. This drug has multiple actions — anti 5HT, antihistamine, antiacetylcholine and weakly anti-SRS-A. It is therefore difficult to predict which action is responsible for the clinical improvement.

Theoretically there are three ways in which a drug can oppose the actions of histamine:

(i) by physiological antagonism — e.g. adrenaline which has many of its pharmacological actions opposite to those of histamine.

(ii) the drug might destroy histamine, e.g. formaldehyde, nitrates and the enzyme diamine oxidase. These drugs are of very limited therapeutic value.

(iii) by preventing histamine from reaching its site of action, e.g. by competition — the antihistamines. The last measure has proved to be the best therapeutic method of controlling the allergic reaction at present.

Antihistamines

These drugs oppose all the effects of injected histamine except that on gastric secretion. The use of antihistamines in allergy, however, has certain serious disadvantages. I shall summarise these under three short paragraphs.

Disadvantages of the drugs. These include multiple actions of these antihistamines. All of them depress and sometimes stimulate the C.N.S. About 20% of people on antihistamines complain of minor and moderately severe side effects. Few complain of serious side effects such as blood dyscrasias, the paradoxical occurrence of hypersensitivity reactions.

Therapeutic uses of antihistamines. The best therapeutic results have been obtained in acute uticaria and seasonal hay fever. In perennial vasomotor rhinitis, chronic urticaria, angioneurotic oedema and allergic reactions to various allergens including drugs, the results of antihistamines are less gratifying. In serum sickness they are of symptomatic value.

For acute anaphylactic reactions the antihistamines are not as effective as adrenaline or the corticosteroids. Antihistamines have failed to benefit patients with bronchial asthma in spite of the undoubted allergic basis of the condition. Again these drugs have not been shown to be of any therapeutic value in the so-called allergic diseases like polyarteritis nodosa, acute rheumatic fever and type I nephritis.

Possible interference with a physiological role of histamine. Histamine is widely distributed in the organism. It is stored in a readily releasable form. Again, Schayer has shown recently that histamine is readily formed evern from tissue free of mast cells in response to stress. He has postulated a microcirculation regulator role for 'inducable' histamine (which is perhaps stretching conclusions too far). Kahlson (1962) has also shown increased production of 'nascent' histamine in rapidly growing tissues, e.g. granulation tissue, tumour cells and rat embryos. Many other observations have forced Kahlson to conclude that 'nascent' histamine formation is an integral part of the metabolism of certain rapidly growing tissues. I find it hard to believe that the presence of histamine in the complicated and homeostatically balanced organism is simply to cause pathological changes. A physiological role for histamine is a very distinct possibility and has to be studied. Blocking the actions of histamine in certain clinical situations may have other dangers and possibly what one gains on the roundabout is lost on the swings.

PART IV — CONCLUDING REMARKS

The immunological basis of the allergic process is undoubtedly proved, but the reaction sequence after antigen-antibody combination is still not clear. Progress has been made in the study of the pharmacological agents thought to be responsible for the allergic symptoms, but here too, there are gaps. Why should the protective action of antigen and antibody combination result in detrimental reactions in certain individuals? Is this due to an inborn error? If so, what is the basic biochemical abnormality that is involved? What is the agent responsible for the propagation of the allergic process once started? The fertile soil of the delayed-type hypersensitivity has not yet been cultivated.

It is estimated that about one person in ten in Great Britain suffers from one kind of allergy. It is also thought that in spite of individual susceptibility anyone is liable to develop a type of hypersensitivity reaction if exposed to the antigen for a certain time. Allergic reactions to drugs and antitoxins pose more problems in therapeutics. Many of these considerations given above make a thorough understanding of the allergic process highly desirable.

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