

Allergy explained: the new definitive terminology

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INTRODUCTION

The study of allergic diseases has been plagued with controversy over the years. This has partly been due to the various media and medical organisations perceiving allergy in vastly different ways. The general public will often regard any adverse reaction to a food or medication as an allergy, even if this is a recognised side-effect or toxic reaction.

Medical doctors and nurses insist allergy is an Immediate IgE-mediated immune reaction and any other non-IgE responses are not considered to be an allergy. To further complicate the issue, complementary therapists will attribute diverse symptoms such as bloating, weight gain, fatigue and body aches to allergy or so called 'food intolerances'.



This article will explain allergy terminology and give an overview of the primary immune responses seen in the common allergic diseases such as hay fever, asthma and eczema.

DEFINING ALLERGY

The exact definition of allergy has for many years been a contentious issue. However, the European Academy for Allergy and Clinical Immunology's (EAACI) task force expertly devised the new allergy nomenclature in 2001 (Johansson 2001).

Clemens von Pirquet (1874-1929), a celebrated Austrian paediatrician, was the first person to coin the term allergy in 1906 for the adverse symptoms he saw develop in patients given a horse-serum-based diphtheria antitoxin. With the discovery of the Immunoglobulin E (IgE) antibody in 1968, IgE became synonymous with allergy and the Immediate Type I Hypersensitivity Reaction. Other non-IgE mechanisms were not considered to be allergy, and were deemed to be of limited importance in the hypersensitivity response. If the reaction did not strictly conform to the immediate IgE immune reaction, then it was usually considered idiosyncratic or pseudo-allergic. Patients would usually be told that they were not allergic.

With the realisation that delayed allergic hypersensitivity reactions also play a role, researchers came to the conclusion that allergy was not exclusively IgE mediated and all that was IgE was not always allergy. Hypersensitivity is a more universally accepted term used to describe both adverse immune reactions and responses where no immune

mechanism can be demonstrated. Hypersensitivity has therefore become the umbrella term to cover all reproducible adverse reactions seen in clinical medical practice.

Hypersensitivity causes objectively reproducible symptoms or signs, initiated by exposure to a defined stimulus at a dose tolerated by normal subjects. This must be distinguished from clinical hyper-reactivity which is an exaggerated normal response to a defined stimulus.

Allergic hypersensitivity is the term used when an immunologic mechanism is evident; while when no immune mechanism can be proven we use the term *non-allergic hypersensitivity* (this term embraces many different and diverse disorders including so called intolerances and adverse drug reactions).

Allergy is an acquired potential to develop hypersensitive reactions to normally innocuous substances and is mediated by immunologic mechanisms (but not exclusively IgE). Allergy can either be antibody or cell-mediated, IgE-mediated allergy being mediated by IgE antibodies (as in pollen allergic rhinitis), while non-IgE mediated allergy may be IgG mediated (as in allergic alveolitis - Farmers Lung) or cell-mediated (as in allergic contact dermatitis - nickel dermatitis).

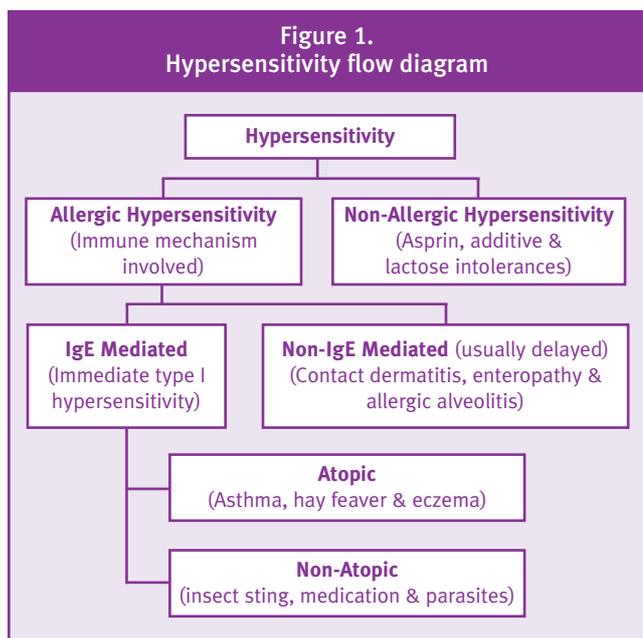
Atopy is a personal or familial (genetic) tendency to produce IgE antibodies in response to low doses of allergens, usually proteins, and to develop classical allergic diseases such as asthma, rhinoconjunctivitis or eczema-dermatitis. To better illustrate this, IgE responses to pollen and cat dander are more frequent in atopic families, whereas IgE responses to wasp venom and medication are not; hence hay fever is referred to as an atopic disease whereas venom anaphylaxis is not.

The allergic march is the chronological progression of one allergic manifestation to the next as an atopic child grows up. Mainly food allergy and atopic eczema are seen in infancy; as these settle, asthma then develops in the middle childhood years and finally hay fever manifests in the teenage years. Asthma may then recur and become problematic again in middle age.

Allergens are usually innocuous protein molecules (also called antigens, allergens or peptides) that stimulate immune hypersensitivity by reacting with IgE or IgG antibodies and T-cells. In certain circumstances, non-protein low molecular weight molecules such as

metals and isocyanates attach to other carrier proteins and so 'fool' the immune system into producing an immune reaction. Allergens enter the body by many routes including inhalation, ingestion, skin contact or injection (medication and venom).

Anaphylaxis is a severe life-threatening, generalised hypersensitivity reaction. The reaction develops over a short period of time (within minutes) and starts with itching of the throat, palms and soles. There is usually associated urticaria (hives), initially patchy and then becoming generalised. This progresses to multiple organ involvement with asthma, shock and circulatory collapse. We term allergic anaphylaxis where an immunologic component is evident. This may be IgE mediated from specific IgE antibodies or non-IgE mediated when IgG immune complex, complement-related or cell-mediated mechanisms are involved. If no immune mechanism is evident, we then term this non-allergic anaphylaxis (previously referred to as an anaphylactoid reaction).



THE MOST EXTENSIVELY STUDIED IMMUNE RESPONSE IS THAT MEDIATED BY IgE

The IgE mediated allergic response comprises three stages, as seen in typical IgE mediated allergic diseases such as asthma, hay fever and anaphylaxis (Warner 2000).

Initial allergic sensitisation

On first exposure, Antigen Presenting Cells (APC) found in the skin and mucus membranes of the lung, nose and bowel capture and present the allergenic protein to T-cells which then induce B-lymphocytes to produce specific IgE antibodies. These IgE antibody molecules bind to tissue mast cell and basophils in the mucous membranes. They remain there ready to trigger an allergic reaction when re-exposure to that specific allergen occurs.

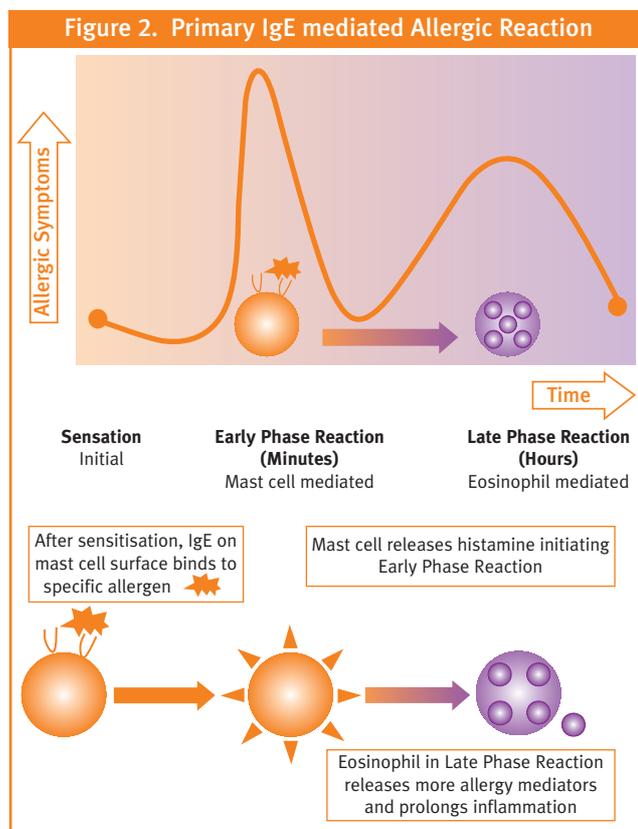
Early phase (Immediate Type I Hypersensitivity) Reaction (lasting up to 2 hours)

Re-exposure to a specific allergen such as grass pollen then induces these mast cells and basophils to rupture releasing preformed inflammatory mediators (histamine, tryptase and heparin) along with newly synthesised mediators (leukotrienes and cytokines). Histamine is the best known of these mediators. It induces smooth muscle constriction (bronchospasm), vascular permeability (swelling), mucus secretion (phlegm) and sensory nerve stimulation (itch).

Late phase reaction (lasting from 2 to 24 hours after allergen exposure)

Further allergy mediator production (leukotrienes, cytokines, histamine) then occurs with associated tissue infiltration of

inflammatory cells (eosinophils). T-lymphocytes of the T Helper₂ subset also release cytokines that further stimulate IgE production, attract eosinophils to the site of inflammation and increase tissue mast cell numbers. This rapid spiral of events is called the Allergic Inflammatory Cascade.



BASICS OF ALLERGIC DISEASE MANAGEMENT

Prevention of allergic disease by avoiding or minimising exposure to the offending allergens.

- **primary prevention** - preventing initial allergic sensitisation by avoiding any exposure to allergen in infancy
- **secondary prevention** - preventing expression of the allergic disease by removing allergen after initial exposure and sensitisation.
- **tertiary prevention** - targets the effective control of allergen exposure, so modifying established disease

Appropriate medication to control symptoms in established disease by dampening immune responses and the subsequent cascade of pro-inflammatory mediators. Examples include preventer and reliever medications in asthma, eczema and rhinitis.

Allergen immunotherapy to induce immune tolerance to specific allergens and effectively "cure" the allergy in established disease that is not controlled with conventional medication (antihistamines, low dose inhaled steroids etc). Immunotherapy received adverse publicity in 1986 when the Committee for Safety in Medicine advised against it, mainly because injudicious use in asthma had led to a number of asthma deaths. The procedure is much safer these days and regaining mainstream medical acceptance as the most effective manner to treat allergies. It should only be performed on appropriate patients in hospital with full resuscitation equipment readily available.

FURTHER READING

1. Johansson SGO et al (2001) A revised nomenclature for allergy, European Academy for Allergology Clinical Immunology Position Paper: Allergy 2001;56; 813-824. <http://www.eaaci.org> Last accessed 10.2.04
2. Warner J et al (2000) The Allergy Report Vol.1. American Academy Allergy Asthma and Immunology Position Paper (2000) <http://www.aaaai.org> Last accessed 10.2.04