ABC OF ALLERGOLOGY

INTRODUCTION TO ALLERGY

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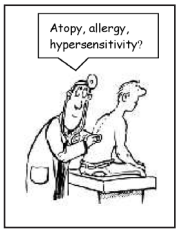
This is the first in a series of articles on the Basics of Allergology. *Current Allergy and Clinical Immunology* readers expressed a wish to see more basic clinical allergy articles geared specifically towards primary care physicians. We plan to include an ABC article on allergology in each subsequent issue. These two-page articles will explore the basics of allergy diagnosis and practical allergy management.

Dr Adrian Morris, a primary care allergist will write the articles under the supervision of an organ-based expert for each field of allergy covered. Future articles will include basics of allergy diagnosis and typical allergic diseases such as allergic rhinitis, eczema, asthma, urticaria, venom allergy, drug allergy, food allergy and anaphylaxis.



This initial article will cover allergy terms, nomenclature and give an overview of the primary immune responses in allergology.

The exact definition of allergy has for many years been a contentious issue and thankfully the task force of the European Academy for Allergy and Clinical Immunology (EAACI) expertly revised the allergy nomenclature in 2001.[1]

Clemens von Pirquet (1874-1929), an Austrian paediatrician, was the first person to use the term 'allergy' in 1906 for the 'adverse' symptoms he saw developing in some patients given a horse-serum-based diphtheria antitoxin. With the discovery of the immunoglobulin E (IgE) antibody in 1968 by Johansson and Ishizaka, allergy became synonymous with IgE and immediate hypersensitivity reactions. Other Gell and Coombes type II to IV reactions were considered, but felt to be of limited importance in allergy. If the reaction did not emulate a typical immediate IgE immune reaction, then it was usually considered idiosyncratic or pseudo-allergic. With the realisation that delayed hypersensitivity reactions involving IgG and T-cells also play a role, researchers came to the conclusion that allergy was not exclusive to IgE.

ALLSA has therefore adopted the new EAACI allergy nomenclature which far more suitably explains the adverse reactions we see in allergology, some of which are not IgE mediated. Hypersensitivity has therefore become the 'umbrella' term to cover all reproducible adverse reactions that we see in clinical 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 hyper-reactivity which is an exaggerated normal response to a defined stimulus.

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

Allergy is an acquired potential to develop hypersensitivity reactions to a normally innocuous substance and is mediated by *immunological* mechanisms (but not exclusively IgE).

Allergy can either be antibody or cell mediated. **IgE-mediated allergy** is mediated by IgE as in pollen allergic rhinitis, while **non-IgE mediated allergy** may be *IgG mediated* as in allergic alveolitis or *cell-mediated* as in allergic contact 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 'classic' allergic diseases such as asthma, rhinoconjunctivitis or eczemal dermatitis.* To help illustrate this, IgE responses to pollen and cat dander are more frequent in atopic families, whereas IgE responses to bee venom and drugs are not more frequent in atopic families. Hence pollinosis is referred to as an atopic disease whereas venom anaphylaxis is not an atopic disease.

Atopy phenotype is the (genetic) predisposition to a *predominance of T-helper 2 (TH2)* (IgE-producing) T-lymphocyte lineage type immune responses and development of classic IgE allergies. This seems to be coded on chromosome 5 (interleukin 4 & 5-induced IgE synthesis) and chromosome 11 (IgE Fc receptor production).

The allergic march is the chronological progression from one allergic manifestation to the next as an atopic child grows up. We see mainly food allergy and atopic eczema in infancy, while asthma develops in the middle childhood years and allergic rhinitis manifests in the teens.

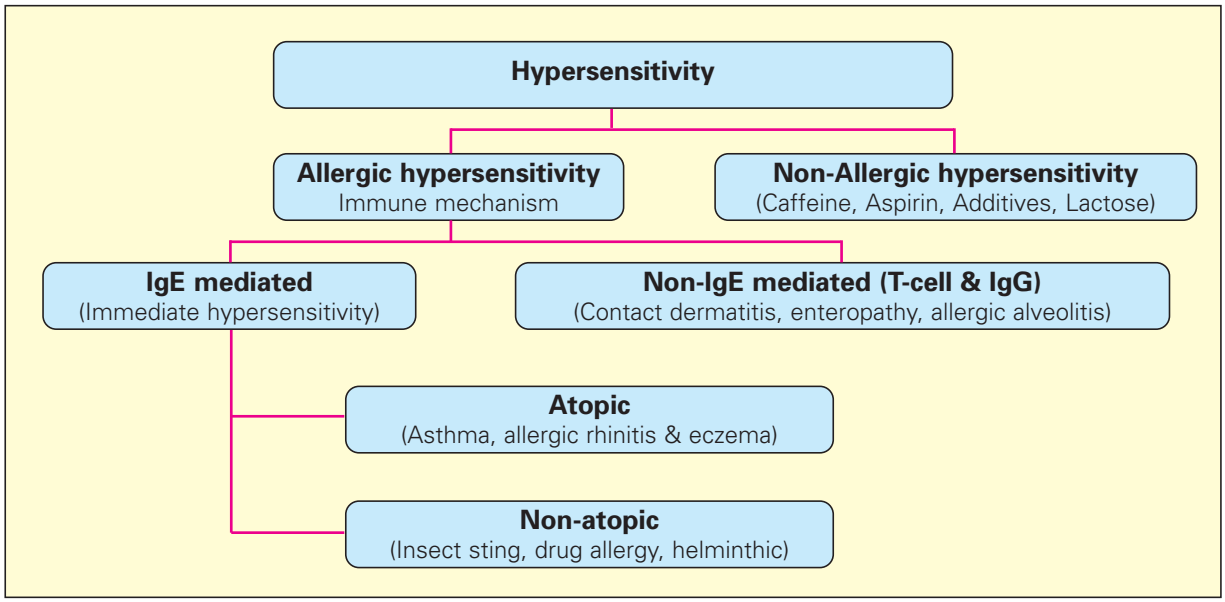
Allergens are usually specific protein antigens (peptides) that stimulate immune hypersensitivity by reacting with IgE or IgG antibodies and T-cells. In certain circumstances low-molecular-weight sugars, metals and isocyanates act as haptens by attaching to other proteins, and so induce an immune response. Allergens enter the body via inhalation, ingestion, skin contact or injection (drugs and venom).

Anaphylaxis is a severe life-threatening, generalised or systemic hypersensitivity reaction. The reaction develops over a short period of time (within minutes) and starts with itching of the gums/throat, palms and soles. There is usually associated urticaria, initially localised which then becomes generalised. This progresses to multiple-organ involvement with asthma, hypotension and circulatory collapse. We use the term ***allergic anaphylaxis*** where an immunological component is evident, and ***IgE mediated*** with IgE or ***non-IgE mediated*** when IgG immune complex, complement-related or immune cell-mediated mechanisms are evident. If no immune mechanism is evident, we term this ***non-allergic anaphylaxis*** (previously referred to as *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, allergic rhinoconjunctivitis and anaphylaxis.

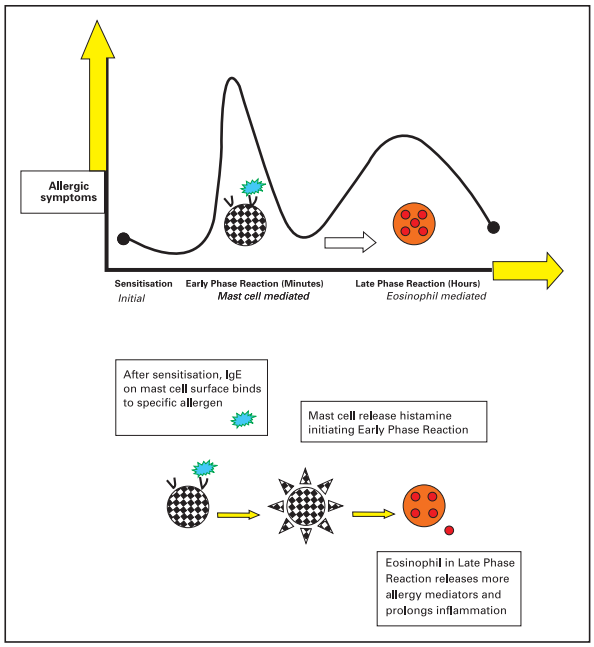
- **Initial allergic sensitisation.** On initial exposure,



Hypersensitivity responses (adapted from EAACI position paper)[1]

antigen-presenting cells (APC) present the allergen peptide to T-cells (TH2 cells) which then induce B-lymphocytes to produce antigen-specific IgE. These bind to mast cell and basophil high-affinity IgE receptors. (This process can take up to 6 weeks to develop allergen-specific IgE.)

- **Early-phase (immediate hypersensitivity) reaction (up to 2 hours).** Re-exposure to the allergen then induces mast cells and basophils to degranulate, releasing preformed inflammatory mediators (histamine, tryptase and heparin) along with newly synthesised mediators (leukotrienes and cytokines). Histamine is the best studied of these mediators. It induces smooth-muscle constriction (bronchospasm), vascular permeability (swelling), mucus secretion (mucorrhoea) and sensory nerve stimulation (itch).
- **Late phase reaction (2-24 hours after allergen exposure).** Further mediator production (leukotrienes, cytokines, histamine) then occurs with infiltration of inflammatory cells (eosinophils releasing major basic protein, eosinophil cationic protein and more leukotrienes). TH2 lymphocytes also release cytokines that further stimulate IgE production, eosinophil chemo-attraction and increase mucosal mast cell numbers.



Immediate and late allergic hypersensitivity reactions (reproduced from The Allergy Report. American Academy for Allergy, Asthma and Immunology, 2000).[2]

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BASICS OF ALLERGIC DISEASE MANAGEMENT

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

- **Primary prevention** – preventing 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 in established disease.

Appropriate medication to control symptoms in established disease by dampening immune responses and 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 steroids, etc.).

REFERENCES

1. A revised nomenclature for allergy, European Academy for Allergology and Clinical Immunology Position Paper. *Allergy* 2001: **56**: 813-824. (Available on EAACI website *http://www.eaaci.org)*
2. American Academy Allergy Asthma and Immunology Position Paper. *The Allergy Report* Vol.1, 2000. (Available on AAAAI website *http://www.aaaai.org)*