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Allergy in a Nutshell

A Handbook



Neeraj Gupta

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CHAPTER 2

Allergy Immunology

INTRODUCTION

Modern era of allergy started two centuries ago, in 1819, with classical description of hay fever (allergic rhinitis) by John Bostock. Charles Blackley performed first skin test on himself in 1869. The 20th century witnessed major advances in diagnosis and management of allergic disorders. The word "Anaphylaxis" was coined by Richet and Portier in 1902, for the "untoward and severe systemic reaction to a suspected allergen" with detrimental outcome including death, if not recognized and managed early. The term "Allergy" was first coined in 1906 by Clemens von Pirquet, a Viennese pediatrician, who defined it as "strange or untoward reactions to harmless substances". Prausnitz and Kustner, in 1921, suggested the presence of a transferable allergenic factor by demonstrating an "allergic hive" (P–K reaction) to the same specific antigen, at the transfer site of a recipient, when the recipient (nonsensitized person) has already received the serum from a sensitized individual. Ishizaka couple (in 1966) and Johansson group (in 1967) independently identified this transferable factor, which was named as IgE immunoglobulin by the World Health Organization (WHO) in 1968. This was the beginning of the immunological basis of allergic diseases.

The discovery of IgE was actually the begining of breakthro treatment options and research for these chronic diseases. Although allergy is an 'old disease', its understanding and acceptance even in the medical community is very 'recent'.

The term "allergy" has been loosely used by physicians and patients across the globe. Any reaction which is unexplainable with the present scientific knowledge has been called allergy. As the

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term is often misused, the need for its appropriate management was never felt.

We need to understand the basic pathophysiology in an allergic reaction to properly manage this upcoming epidemic. Nowadays, various in vitro and in vivo allergy tests are available which create a lot of confusion among healthcare providers and receivers. A revisit to allergy immunology will help in selecting the appropriate test for patients. This will help in deciding specific allergen immunotherapy early in life, which is the only disease-modifying therapy available for combating allergies.

DEFINITIONS

Allergology: It is the science related to allergic diseases, their pathophysiology, mechanisms, and differential diagnoses.

Sensitivity: Normal host response to a defined stimulus.

Hypersensitivity: It is the altered reactivity of the body to a particular allergen. It can be immunologically or nonimmunologically mediated. The commonly available allergy tests detect hypersensitivity to particular allergen, which might not be responsible for patient's symptoms.

Allergy: It is the clinical hypersensitivity usually diagnosed by correlation of clinical presentation and allergy tests. It is mostly mediated by immunoglobulin E (IgE) production, though non-IgE pathways are also known.

Atopy: It is the genetic definition of allergy with personal or familial tendency, in an individual, for development of hypersensitivity.

Sensitizer: Sensitizer is a protein which is able to instruct the immune system to start producing IgE antibodies.

Allergen: An allergen is a protein which is able to bind specific IgE antibodies. A complete or true allergen will be having both properties as able to instruct for IgE production and will bind to specific IgE molecules; whereas, a cross-reactive allergen will be

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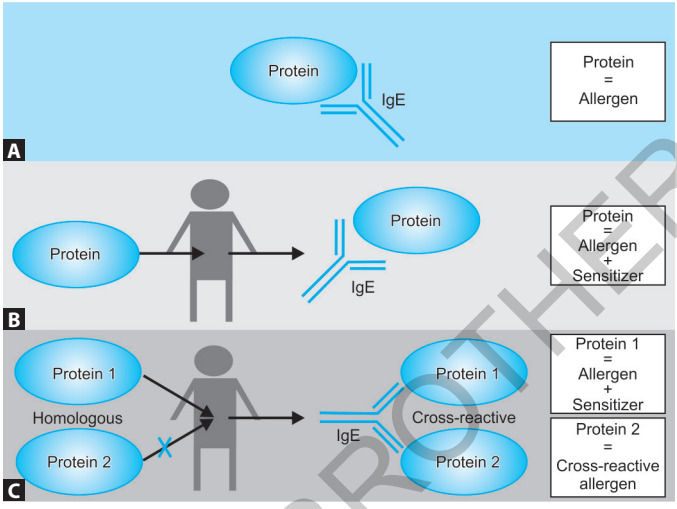

Figs. 1A to C: (A) Allergen; (B) Sensitizer; (C) Protein 1 = complete or true allergen, Protein 2 = cross-reactive allergen.
(IgE: immunoglobulin E)
Source: Akdis CA, Agache I. Global Atlas of Allergy. EAACI. 2014.

able to only bind with IgE molecules but unable to trigger for IgE production (Figs. 1A to C).

Antibody or immunoglobulin: These are Y-shaped proteins that are produced by the immune system in response to an allergen or antigen exposure. These antibodies bind to harmful allergens and mediate their destruction. There are five types of antibodies among which IgE has been linked with most of allergic manifestations.

Anaphylaxis: It is severe, generalized, life-threatening allergic reaction simultaneously affecting multiple organ systems.

ALLERGY OR TOLERANCE DEVELOPMENT

Individuals are born with genetic predisposition for allergic disorders and depending upon the dose and timing of allergenic

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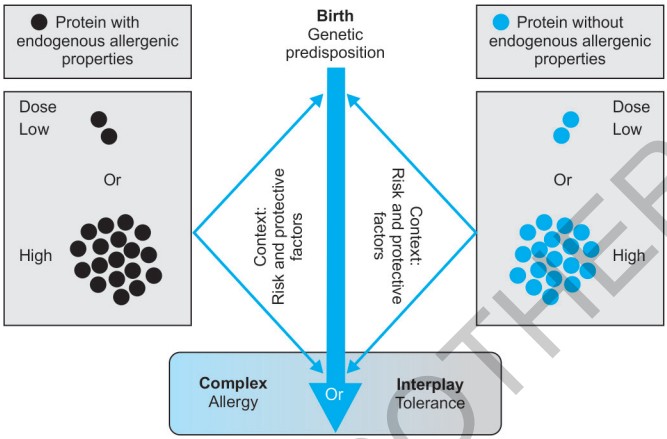

Fig. 2: Complex interplay of various factors determining onset of allergy.
Source: Akdis CA, Agache I. Global Atlas of Allergy. EAACI. 2014.

exposure, risk and protective factors later in life, either tolerance or hypersensitivity develops to that particular allergen (Fig. 2).

BASIC IMMUNOLOGY

The immune system has two components: (1) An adaptive immune system, and (2) An innate immune system. The adaptive immune system has the following advantages over the innate system:

- Specificity of antigen recognition
- Diversity of the antigen receptor repertoire
- Rapid clonal expansion
- Adaptiveness to the changing environment
- Immunological memory.

Lymphocytes are the primary cells of adaptive immunity; they include T cells, B cells, and natural killer cells.

Innate immune system: provides the first line of defense from infection in a non-specific manner. The innate responses

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are immediate, non-specific and lack memory. It comprises of epithelial, mucosal and enzymatic barriers. Innate immune system is found in all classes of plants and animals.

Host-Allergen Interaction

After exposure to a potentially allergenic protein, complex interaction happens at receptors on the cell surface via attachment of allergens either independently or with help of certain bacterial compounds (LPS: lipopolysaccharide, LTA: lipoteichoic acid), and the presentation to antigen-presenting cells or APCs (dendritic cells, B cells, monocytes/macrophages and their tissue counterparts) and triggering the immune response (Fig. 3).

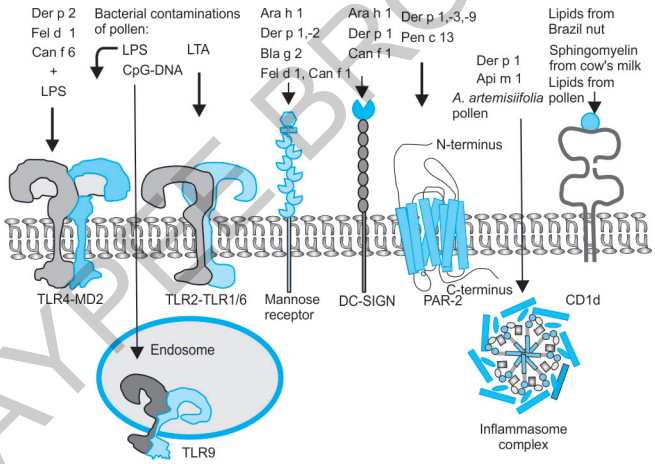

Fig. 3: Allergens acting at various receptors via several mechanisms.

(TLR: toll-like receptors; LPS: lipopolysaccharides; LTA: lipoteichoic acid; PAR: protease-activated receptor)

Various allergens viz. Der p 1, 2, -3, -9 (house-dust mite), Fel d 1 (cat), Can f 1, 6 (dog), Bla g 2 (cockroach), Ara h 1 (peanut), Pen c 13 (mold).

Source: Akdis CA, Agache I. Global Atlas of Allergy. EAACI. 2014.

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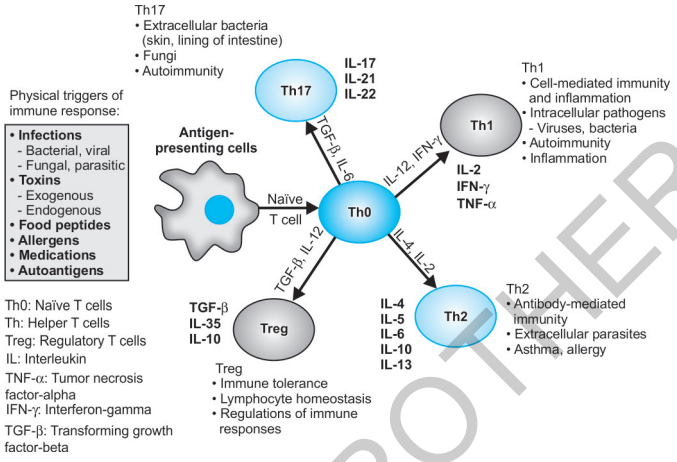

Fig. 4: CD4+ T helper cell differentiation.

Source: Modified from Zhu J, Paul WE. CD4 cells: fates, functions and faults. Blood. 2008;112:1557-69.

Selection of Allergenic Pathway

Antigen-presenting cells like dendritic cells present allergens to CD4+ T helper (Th) cells. These naïve CD4+ Th cells can differentiate into various effector helper cells with distinct capacities, viz. Th1 (induction of cellular immune responses), Th2 (antibody production and allergic response), Th17 (inflammatory responses), and Treg (regulation) cells. Depending upon the various genetic and environmental factors, either Th1 or Th2 response is decided. Th2 cells are induced by IL-4 and further produce various cytokines, which stimulates clonal proliferation of B cells producing plasma cells, leading to IgE production (Fig. 4).

TYPES OF HYPERSENSITIVITY REACTIONS

Hypersensitivity reactions can be grouped into four types depending upon mechanism involved (Fig. 5).

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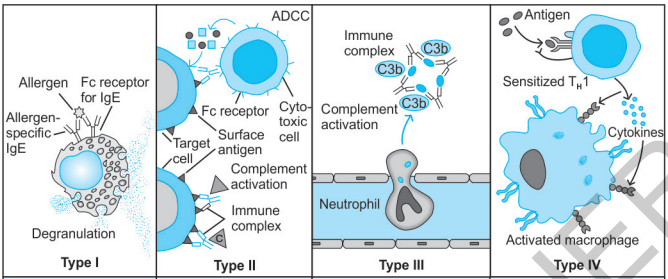

Type I	Type II	Type III	Type IV
IgE-mediated hypersensitivity	IgE-or IgM-mediated cytotoxic hypersensitivity	Immune complex-mediated hypersensitivity	Cell-mediated hypersensitivity
Ag induces cross-linking of IgE bound to mast cells and basophils with release of vasoactive mediators.	Ab directed against cell surface antigens mediates cell destruction via complement activation or ADCC.	Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils.	Sensitized T_H1 cells shown above release cytokines that activate macrophages or T_c cell that mediate direct cellular damage. T_H2 cells and CTLs mediate similar responses.
Typical manifestations include systemic anaphylaxis and localized anaphylaxis such as hay fever, asthma, hives, food allergies, and eczema.	Typical manifestations include blood transfusion reactions, erythroblastosis fetalis, and autoimmune hemolytic anemia.	Typical manifestations include localized Arthus reaction and generalized reactions such as serum sickness, necrotizing vasculitis, glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus.	Typical manifestations include contact dermatitis, tubercular lesions, and graft rejection.

Fig. 5: Types of hypersensitivity reactions.
(ADCC: antibody-dependent cellular cytotoxicity; IgE: immunoglobulin E)
Source: Kuby Immunology, Sixth edition copyright 2007 W.H. Freeman and Company.

Type I (Immediate Type or IgE Mediated)

There are 2 phases in allergy reaction:

1st phase (Sensitization): This happens during the initial exposure of the antigen. The antigen is specially prepared for presentation to the T cell by the Antigen Presnting Cell (APC). The APC will splice up the antigen into small fragments, which then combine with special proteins called Major Histocompatibility Complex (MHC) type 2 (genetic material which helps to distinguish between self and non self). This combined complex, called Epitope, will become visible to the T lymphocyte which recognizes the antigen as 'foreign'. The T cell get activated and become an Effector T cell and produces cytokines namely Interleukin (IL) 4 and IL 13.

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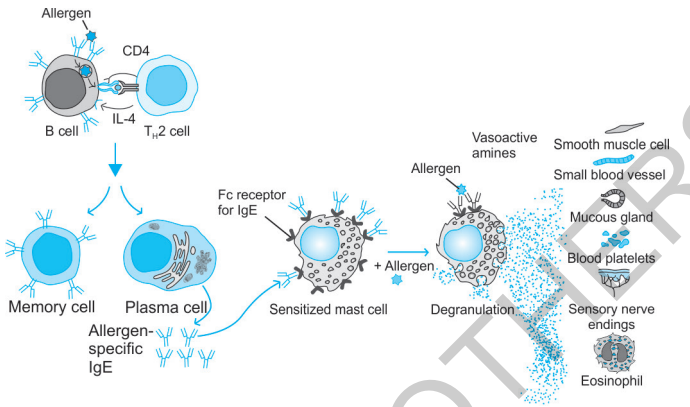

Fig. 6: Type I hypersensitivity reaction.
(IgE: immunoglobulin E)
Source: Kuby Immunology, Sixth edition copyright 2007 W.H. Freeman and Company.

IL 4 and IL 13 will stimulate the neighboring B lymphocytes to produce IgE antibodies thro class switching. The IgE antibodies are released into the circulation as free IgE and also gets bound to the high affinity IgE receptor (F Cepsilon R1) on the surface of the mast cell and basophil. This results in the mast cell being 'armed' and ready to release the mediators if coupled with the specific antigen. This is the state of 'sensitization' (Fig. 6).

2nd phase (Re-exposure): The antigen on re-exposure will be picked up thro coupling reaction by specific IgE antibodies bound on the surface of the mast cells. This reaction generally occurs with the mast cells at the site of entry of the antigen (nose, lungs, skin, eyes, GI tract) where the concentration of the mast cells are highest. The ligation of the cell bound specific IgE antibody by the specific antigen triggers the release of inflammatory lipid mediators, cytokines and chemokines to cause the allergic inflammation at the site of entry.

Type I hypersensitivity is most commonly responsible for clinically relevant allergies. Free IgE release is the basis of total

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or specific serum IgE testing; whereas bound IgE is responsible for skin prick test or oral and nasal challenge tests.

Common clinical effects of immediate hypersensitivity on various organs will be as:

- Lung—wheezing, dyspnea, and tachypnea
- Nose and eyes—runny nose, redness, and itching of eyes
- Skin—pruritic, vesicular or bullous lesions
- Gastrointestinal tract—vomiting and diarrhea
- Systemic—shock, hypotension, and wheezing
- Brain—behavioral disorders postulated.

Common examples include anaphylaxis, allergic rhinitis, allergic asthma, and atopic dermatitis.

Type II (Antibody-mediated Cytotoxic or Cytolytic)

Antibody reacts directly with the antigen that is bound to the cell membrane to induce cell lysis through complement activation. Hemolytic anemia, hemolytic disease of newborn, blood transfusion reactions, myasthenia gravis, and Goodpasture syndrome are the common examples.

Type III (Immune Complex Mediated)

Antigen and antibodies (IgM and IgG) bind to each other to form antigen-antibody immune complexes which get deposited in blood vessels or other tissues. This deposition causes complement activation and massive infiltration of neutrophils. Arthus reaction, serum sickness, leprosy, glomerulonephritis, necrotizing vasculitis, rheumatoid arthritis, and systemic lupus erythematosus are some of the examples of type III hypersensitivity.

Type IV (Cell-mediated or Delayed Hypersensitivity)

Initiated by T lymphocytes and mediated by Effector T cells and macrophages. The response involves the interaction of the antigens with the surface of the lymphocytes. Sensitized lymphocytes after contact with antigen, release cytokines after 48–72 hours. These cytokines are biologically active and cause inflammation. Common

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examples include contact dermatitis, fungal infection, tubercular lesions and graft rejection.

PHASES OF TYPE 1 ALLERGIC REACTION

Immediate Phase Reaction

Onset within minutes to initial to 2 hours due to preformed or rapidly synthesized mediators (Fig. 7). Vascular permeability and smooth muscle contraction are the most common effects noticed during this phase. The preformed mediators are:

- Histamine
- Neutral proteases (tryptase, chymase, cathepsin G, and carboxypeptidase)
- Proteoglycans (heparin and chondroitin sulfates)
- Chemotactic and activating factors [eosinophil chemotactic factor (ECF)-A and neutrophil chemotactic factor (NCF)].

Late-phase Reaction

After the chemical mediators of the acute response subside, late-phase responses can often occur (Figs. 8A to C). This is due to the migration of other leukocytes such as neutrophils, lymphocytes, eosinophils, and macrophages to the initial site. The reaction is usually seen 4–6 hours after the initial reaction. Cytokines from

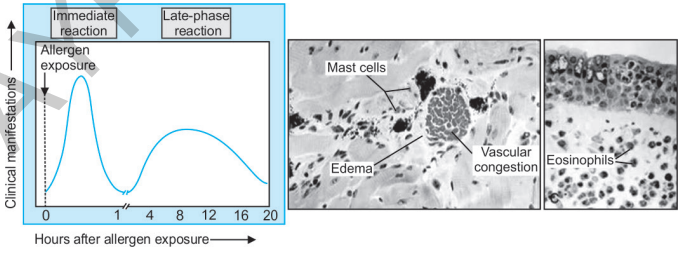

Fig. 7: Time course of allergic reaction.

Source: Downloaded from http://geoffreye-reedlife.blogspot.com/2011/02/hypersensitivity-reactions.html

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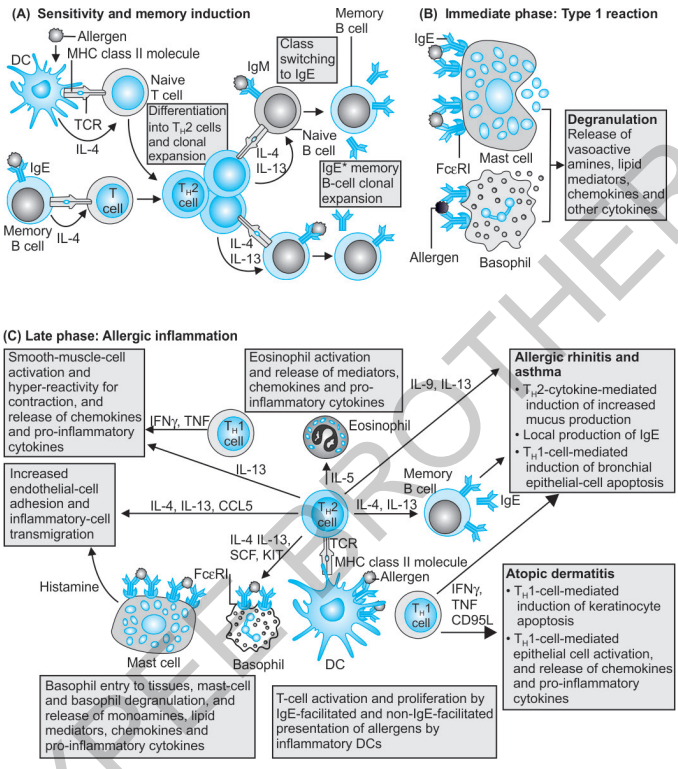

Figs. 8A to C: Various phases of allergic reaction.

(CCL: chemokine ligand; DC: dendritic cell; Ig: immunoglobulin; IL: interleukin; IFN: interferon; TNF: tumor necrosis factor; MHC: major histocompatibility complex; SCF: stem cell factor)

Source: Larche M, Akdis CA, Valenta R. Immunological mechanisms of allergen specific immunotherapy. Nature Reviews Immunol. 2006;6:761-71.

mast cells may play a role in the persistence of long-term effects. Late-phase responses seen in asthma are slightly different from those seen in other allergic responses, although they are still caused by release of mediators from eosinophils and are still dependent on activity of Th2 cells.

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There are 2 types of mediators involved:

1. *Preformed*: Tryptase, Chymase, Cathepsin G, Carboxypeptidase, Histamine and Heparin.
2. *Synthesized*: Cytokines (IL 4, IL 13, IL 3, IL 5, GM-CSF, TNF-alpha), Leukotrienes (C4, D4, E4), platelet activating factor (PAF), Chemokine (MIP-1 alpha).

The early phase mediators cause acute inflammation of the allergic reaction with redness, swelling and exudation causing acute symptoms.

The late phase reactions are caused by mediators which are much more potent and cause cell infiltration, vasodilatation, tissue damage causing long term results of tissue damage, ensuing repair and continued cycle of similar events. This results in the so called 'tissue remodelling' characteristic of asthma and related conditions.

Chronic Phase

It occurs due to repetitive or persistent allergen exposure. Innate immune cells (eosinophils, basophils, neutrophils, and monocyte or macrophages) and adaptive immune cells (Th2 cells, other T cells, and B cells) take up residence in the tissues.

PRINCIPAL MEDIATORS INVOLVED IN TYPE I HYPERSENSITIVITY

Primary Mediators and Their Effects

- Histamine, heparin—increased vascular permeability, smooth muscle contraction
- Serotonin—increased vascular permeability, smooth muscle contraction
- Eosinophil chemotactic factor-A—eosinophil chemotaxis
- Neutrophil chemotactic factor-A—neutrophil chemotaxis
- Proteases—bronchial mucus secretion, degradation of blood-vessel basement membrane, generation of complement, and split products.

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- Exclusive chapter on bursting the common myths and questions raised in outpatient department (OPD) by patients
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- Useful for practicing allergists, pediatricians, physicians, and residents.

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