Hypersensitivity

The term **hypersensitivity** is used to describe immune responses which are **damaging** rather than helpful to the host.

There are **4 types** of hypersensitivity reactions:

-- Type 1 hypersensitivity

-- Type 2 hypersensitivity

-- Type 3 hypersensitivity

-- Type 4 hypersensitivity

The **first 3** are mediated by **antibody**, the **fourth** by **T cells**.

Type I Hypersensitivity

-- It describes the **rapid (immediate) allergic** reaction.

-- **Eczema**, **asthma** and **urticaria** all result from type I hypersensitivity.

-- Type I Hypersensitivity is caused by contact of an antigen with a **pre-existing IgE** antibody.

-- IgE is present in very low levels in serum in most people (app. 50 ng per ml). Its' **half life in serum** is only **2-3 days**.

-- However, much of the IgE in the body is **bound to high affinity receptors (FcεRI)**; in the bound state the **half-life is ~3 weeks.**

-- These receptors are found on **mast cells** and **basophils**.

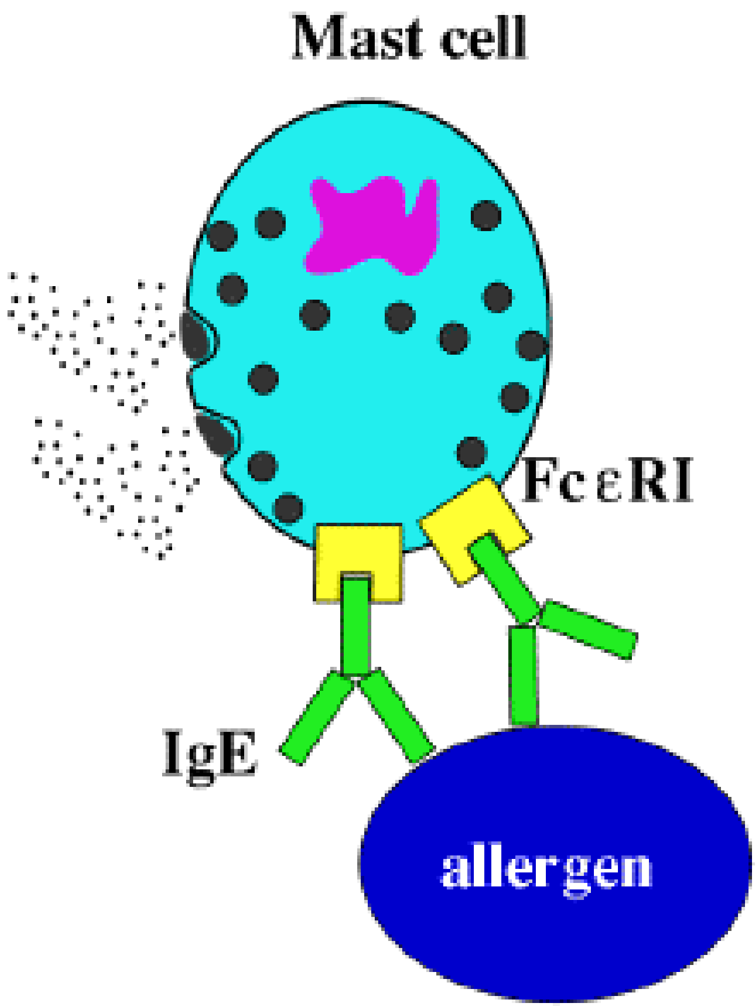
Mechanism

-- Each cell (**mast cells** and **basophils)** has a **high density** of these receptors **(40,000-250,000 per cell)** so that a wide range of antigens can be attached.

-- The cells are **activated** by the **cross-linking** of the FcεRI receptors via antigen binding to the bound IgE molecules.

-- Such cross-linking leads to **rapid degranulation** (60-300 secs) of the **mast cells/basophils** and the release of **primary inflammatory mediators** stored in the granules.

Type I hypersensitivity



-- These **primary** **mediators** such as histamine and serotonin cause all the normal consequences of an **acute inflammatory reaction** - increased vascular permeability, smooth muscle contraction, granulocyte chemotaxis and extravasation etc.

-- Mast cell activation via FcεRI also leads to the production of **two** other type of mediators.

These **secondary** **mediators**, unlike the stored granule contents, **must be synthesised *de novo*** and comprise **arachadonic acid metabolites** (prostaglandins and leukotrienes) and **proteins** (cytokines and enzymes).

Molecule	Effects
Primary mediators	
Histamine	Vascular permeability, sm contraction
Serotonin	vascular permeability, sm contraction
ECF-A	eosinophil chaemotaxis
NCF-A	neutrophil chaemotaxis
proteases	mucus secretion, connective tissue degradation
Secondary mediators	
Leukotrienes	vascular permeability, sm contraction
Prostaglandin	vasodilation, sm contraction, platelet activation
Bradykinin	vascular permeability, sm contraction
Cytokines	numerous effects inc. activation of vascular endothelium, eosinophil recruitment and activation

Time line

-- The **type I response** has an **early** and a **late** component.

-- A **very rapid early response** occurs **within a few minutes** and maximal after about 20 minutes. It is caused by **primary mediators.**

-- If the challenge is **cutaneous** it produces the so-called **'wheal and flare'** - raised patch surrounded by a pink effusion.

-- The **late response** seen after some hours produced by **secondary mediators** is characterized by **cellular infiltrate** which gives a **hard but barely pigmented nodule** in the case of skin.


Immediate and late skin reactions
late response
(at 5 hours)
immediate response
(at 20 minutes)
1:10
1:100
1:1000
1:10000

Incidence and genetic susceptibility

-- Some **20-30%** of the population exhibit **type I hypersensitivity** or **atopic allergy** to common environmental substances.

-- If **both parents** exhibit susceptibility, **offspring** is more than **2** × more likely to have similar susceptibility.

-- Some individuals have **multiple** and **severe** allergies.

-- These individuals are termed **atopic** and frequently have raised total serum IgE levels (10 -100 × normal).

-- The antigens causing **type I hypersensitivity** are called **allergens**.

Common antigens which cause Type I hypersensitivity reactions

Pollens
Birch Tree
Ragweed
Oil Seed Rape

Food
Nuts (eg peanuts)
Eggs
Seafood

Drugs
Penicillin
Salicylates (asprin)

Insect products
Bee venom
House Dust Mite

Animal hair
Cat hair and dander

Anaphylaxis

-- Consequences of a **localised** type I reaction are **unpleasant and annoying**.

-- But the consequences of a **generalised** reaction are **potentially fatal**.

-- Ingestion of nuts or seafood, insect bites (venom), and drug injection may all cause **life-threatening reactions** in highly sensitized individuals.

-- Death in such cases is due to **systemic release** of **vasoactive mediators.**

-- It leads to **general vasodilation** and **smooth muscle contraction** resulting in **sudden loss of blood pressure**, **massive oedema** and **severe bronchiole constriction (systemic anaphylaxis).**

Atopy

-- **Atopy** refers to the genetic tendency to develop allergic diseases.

Atopic disorders such as **asthma** and **eczema** are **immediate-hypersensitivity reactions** with strong **familial predisposition** and are associated with **elevated IgE levels**.

-- **Atopic hypersensitivity** is **antibody-mediated** so it is transferable by serum but not by lymphoid cells.

Other causes include:

-- Failure of **regulation** at T-cell level (e.g., **increased production of IL-4**)

-- **Enhanced uptake** and presentation of **environmental antigens** by APCs.

-- **Hyperreactivity of target tissues** which often contain large numbers of **Th2 cells** which play a major role in atopy.

- -- The incidence of atopy is **higher in developed countries** because of **low** level of **parasitic infections** which makes IgE **surplus** to cause these reactions.

- -- In developing countries, **parasitic and intestinal infections** are **common** and **IgE remains engaged in fighting them.**

-- The causing antigens are typically found in environment, e.g., **pollens** released by plants, **mite feces** in carpets or foods such as **shellfish**, **eggs** etc.

-- Many sufferers give **immediate type reaction** to skin tests containing the offending antigen.

- -- There is evidence that **proteases** in allergens cleave fibrinogen resulting in **activation** of Toll-like receptors (**TLR-4**) on the surface of **macrophages** and **airway-lining** cells to activate the atopic response.

- -- Mutations in gene encoding **alpha chain of IL-4** receptor strongly increase susceptibility.

- -- These mutations make **IL-4 hyperactive** and as a result **B cells increase IgE synthesis.**

Drug hypersensitivity

-- Drugs particularly **antimicrobial agents** such as **penicillin** are the commonest cause of hypersensitivity.

-- Usually the culprit is **not intact drug** but a metabolic product which acts as a hapten and binds to a body protein evoking immune response.

-- The resulting **IgE antibody** react with the hapten or intact drug to give rise to type-1 hypersensitivity.

Desensitization

-- To **prevent** acute life-threatening reactions such as anaphylaxis, **desensitization** can be done.

-- **Acute desensitization** involves the administration of antigen at **15 minute** intervals.

-- Antigen-IgE complexes form on a **small scale** and not enough mediators are released to produce a major reaction.

-- This permits the administration of a **drug or foreign protein** to a hypersensitive person.

-- **Chronic desensitization** involves the **long-term** weekly administration of the antigen to which the person is hypersensitive.

-- This **stimulates** the production of **IgA- and IgG-blocking antibodies** which can **prevent** subsequent antigen from **reaching IgE on mast cells** thus preventing a reaction.

-- It also induces **regulatory T cells** to produce **IL-10** which **reduces** the synthesis of IgE.

Treatment and prevention

Treatment of anaphylactic reactions includes:

-- Drugs to **counteract** the action of mediators

-- Maintenance of an **airway**

-- Support of **respiratory** and **cardiac** functions

-- A**ntihistamines** should be given singly or in combination.

-- For **asthma** patients, inhaled **bronchodilators** such as **albuterol** are used.

-- In severe cases, a **monoclonal anti- IgE** antibody is indicated.

-- Treatment of **allergic rhinitis** typically involves **antihistamines** along with **nasal decongestants**.

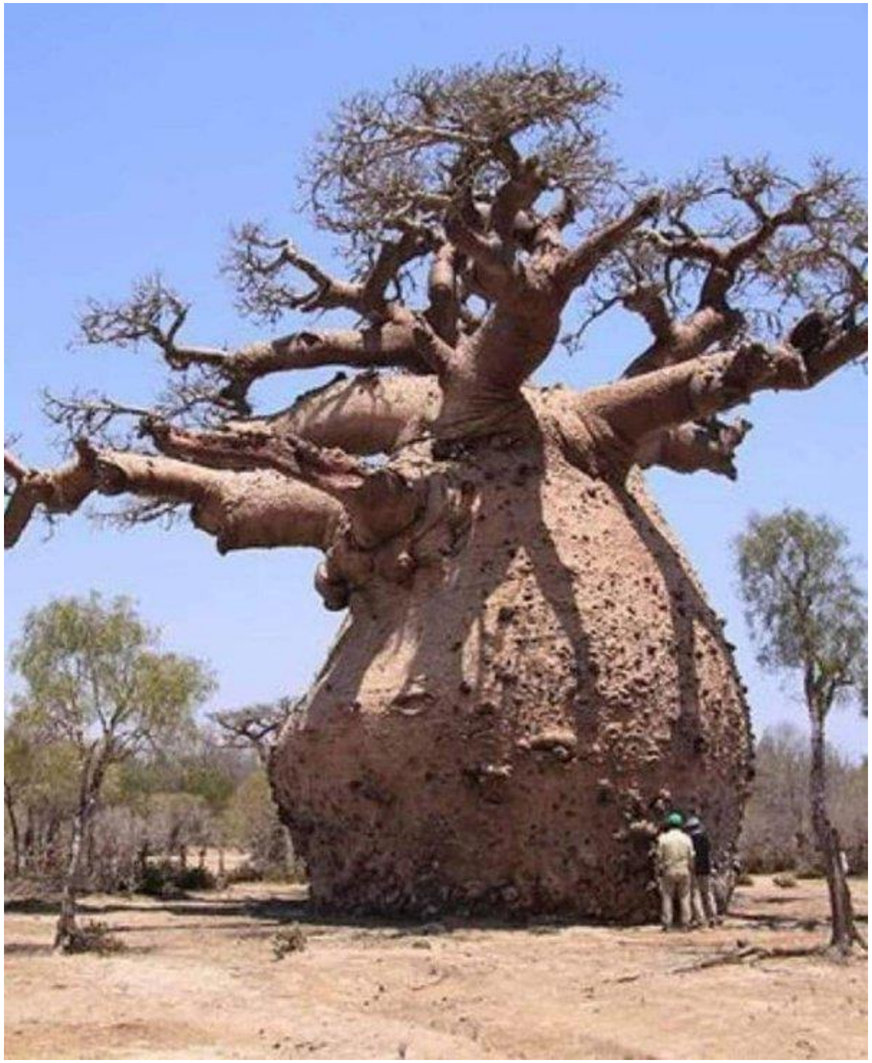
کردار

ایک دفعہ ایک شخص حضرت امام جعفر الصادقؑ
کے پاس آیا اور اس نے سوال کیا 'میں دین کی تبلیغ
کیلئے جارہا ہوں کوئی ایسا عمل بتادیں جو دین کی
تبلیغ میں بہت مدد گار ثابت ہو'

امام جعفر صادقؑ نے جو جواب دیا میں سمجھتا ہوں
کہ اس جواب میں پورا دین بیان کر دیا.......

آپ نے فرمایا

*"کوشش کرنا کہ دین کی تبلیغ کیلئے تمھیں
اپنی زبان استعمال نہ کرنی پڑے"*.



The **Baobab** tree can hold up to 32,000 gallons of water


In Wedding
Bride's Sisters
Bride's Brothers
/ dontgetserious


Thank You!