INTRODUCTION
The term ‘allergy’, coined by von Pirquet, is used to define the series of events which occurs when an antigen, which is not harmful in itself, causes an immune response, leading to symptoms and disease in genetically predisposed individuals. An antigen that induces the allergic response is called an allergen.

Atopy, described by Coca & Cooke, as understood today is the increased genetic predisposition to allergic reactions, recognized by skin prick tests, elevated total IgE levels and specific IgE levels against common allergens.

GENETICS
Allergy and asthma are a spectrum of diseases based on various genetic and physiologic mechanisms. Cookson et al noted the linkage of a specific chromosome region to allergic phenotype - the 11q13 gene locus. Cytokine gene cluster at 5q is a large genetic region spanning a gamut of DNA and contains numerous genes influencing the atopy phenotype. Researchers have analyzed a mouse chromosomal segment homologous to human chromosome 5 locus exhibiting a T cell and Airway phenotype regulator (Tapr).

A joint US and UK consortium of researchers have identified a gene associated with airway remodeling in asthma, which offers a potential new target for developing drugs that can prevent changes in lung tissue that result in hyper-responsiveness. The gene-ADAM33 (a disintegrin and metalloprotease 33)-located on chromosome 20p13 was found to be significantly associated with asthma. ADAM33 codes for a protein that has four functions, one of which is to act as a protease that is likely to have a role in the tissue changes seen in airway remodeling. Current treatments for asthma target the allergic component of asthma or dilate constricted airways, but it may be possible to develop therapies targeted at ADAM33 and its products to prevent the onset of airways remodeling even if the allergic component of asthma is present. The protease function of the protein coded for by ADAM33 offers a particularly good target for drug development, with the discovery of a similar gene in mice providing a useful animal model.

The incidence of atopy is now estimated to be a whopping 50% in western countries. The incidence in India has been found to be 25.3% according to a randomized survey of the Indian population.

The various manifestations of atopy and allergy are allergic rhinitis, allergic asthma, allergic conjunctivitis, allergic dermatitis, drug allergies, bee stings and urticaria/angioedema. Nasobronchial allergies i.e. asthma or rhinitis alone or asthma with rhinitis are the commonest allergic manifestations with 75.4% of patients belonging to this group.

The 10 commonest allergens in the Indian environment are house dust mite (D. farinae), Aspergillus fumigatus, dog danders, cat epithelia, coconut, fish, cockroach, housefly, mosquito and pollen from Parthenium hysterophorus (congress grass).

THE ALLERGIC CASCADE
The allergic response manifested on exposure to a harmless allergen is the result of a complex orchestrated interaction of various immune cells and immunoglobulins.

Participants of the allergic cascade
The various components of the allergic cascade (Fig. 1) include the antigen presenting cells, T cells, B cells, mast cells, eosinophils, macrophages, neutrophils and a host of chemical compounds-cytokines, adhesion molecules and cellular receptors acting in cohort to produce an allergic response.

1. Antigen presenting cells: Dendritic cells & Langerhans cells are derived from the myeloid/lymphoid lineages of the bone marrow. The specific cellular marker of these cells is the CD83 molecule. These cells express specific MHC-Class II proteins and stimulate allergen specific T and B cell lineage proliferation.

2. Monocyte /Macrophage cells: Arising from precursor cells within bone marrow, monocytes circulate in the blood and migrate to the tissues to transform into tissue macrophages. They mediate the allergic response by secreting cytokines (IL-1, IL-6, IL-12, TNF-α) and producing allergen specific activation of T and B-lymphocytes.

3. T- cells: The pool of effector T cells is established in thymus early in life. This is maintained by new T cell production in the thymus as well as antigen driven expansion of virgin peripheral T cells into Memory cells.

4. B cells: Mature B cells comprise 10-15% of peripheral lymphocytes. They exhibit on their surface IgG molecules. Primary antigenic exposure leads to the production of memory B cells (allergen specific). These memory B cells, on secondary antigenic stimulation give rise to clonal
proliferation of plasma cells which produce allergen specific IgE.

5. Neutrophils, Basophils and Eosinophils: Granulocytes are amplifiers and effectors of innate immune system as well as acquired immune system. Neutrophils express receptors for IgG (CD16) and for activated complement components. Upon activation, azurophilic granules containing myeloperoxidase, lysozyme, elastase and specific granules containing lactoferrin and collagenase and superoxide radicals are generated at the neutrophil surface. Eosinophils express Fc receptors for IgG (CD32). Eosinophils contain various cytokines and compounds such as major basic protein, eosinophilic cationic protein, eosinophil derived neurotoxin and eosinophil peroxidase, which are directly capable of damaging tissues. Basophils have high affinity receptors for IgE. These IgE molecules bound to the surface of basophils upon exposure to an antigen undergo cross-linking to release histamine, eosinophil chemotactic factor of anaphylaxis and neutral proteases. Basophils also contain surface receptors for activated complement components (C3a, C5a).

6. Mast cells: Mast cells are distributed at cutaneous and mucosal surfaces and are characterized by the presence of vesicles, granules containing preformed mediators of immediate type hypersensitivity. These granules contain mediators like histamine, tryptase and carboxypeptidase. Tryptase forms kallikrien, which is another immediate acting mediator of allergy. Mast cells contain lipid precursors that within 4-6 hours give rise to prostaglandins and leukotrienes like LTD-4, LTE-4, LTB-4 and PGD-2. Prostaglandin (PG) D2, the major cyclooxygenase metabolite generated from immunologically stimulated mast cells, is thought to contribute to the pathogenesis of allergic diseases due to its various inflammatory effects.

7. Cytokines: Cytokines are soluble proteins produced by various cells in the body. They are involved in the regulation of growth, development and activation of immune system and mediation of inflammatory response. They can be classified as:
   a. Immunomodulatory cytokines: Involved in activation, growth and differentiation of lymphocytes/monocytes. e.g. IL-2, IL-4, IL-10, TGF-β.
   b. Proinflammatory cytokines: produced by mononuclear phagocytes. e.g. IL-1, TNF-α, IL-6, MCP-1, MCP-2, MCP-3, RANTES.
   c. Cytokines that regulate immature leukocyte growth and differentiation. e.g. IL-3, IL-7, GM-CSF.

The induction of allergic disease requires sensitization of an atopic individual to a specific allergen. An allergen on entering...
Based on the cytokine response, the T lymphocytes can either preferentially differentiate into Th-1 subtype (inflammatory) or the Th-2 subtype (allergic). Th-2 response is associated with activation of specific B cells subsets that transform into plasma cells. For B-cells to switch from IgM to IgE-bearing cells and mature into IgE-producing plasma cells (isotype switching), they require two signals. The IL-4 secreted by Th-2 cells provides the first signal required for B-cells to differentiate into IgE-secreting plasma cells. When it binds to the IL-4 receptor on the B-cell surface, it stimulates transcription of a gene encoding the constant region domains of the IgE heavy chain. The second signal is provided by the interaction of the CD40 ligand on the surface of T-cells with the CD40 receptor on the B-cell.\(^\text{10,12}\)

IL-5 uniquely promotes the development and differentiation of eosinophils. IL-5, a product of Th-2 cells, also plays an important role in the mobilization of eosinophils from the bone marrow and into the bloodstream.\(^\text{11}\) Atopic individuals have a relative skewing of T cell proliferation towards Th-2 subtype. It is this defect in the regulation of T helper cells (favoring Th-2 cells over Th-1 cells) and the resultant overproduction of IgE antibodies in response to environmental allergens that are largely responsible for allergic reactions.

The presence of an allergen causes bridging of 2 IgE receptors triggering degranulation of vesicles/granules of mast cells. Immediate preformed mediators like histamine, proteoglycans, tryptase, carboxypeptidases, and platelet activating factor cause triggering degranulation of vesicles/granules of mast cells. For B-cells to switch from IgM to IgE-bearing cells and mature into IgE-producing plasma cells (isotype switching), they require two signals. The IL-4 secreted by Th-2 cells provides the first signal required for B-cells to differentiate into IgE-secreting plasma cells. When it binds to the IL-4 receptor on the B-cell surface, it stimulates transcription of a gene encoding the constant region domains of the IgE heavy chain. The second signal is provided by the interaction of the CD40 ligand on the surface of T-cells with the CD40 receptor on the B-cell.\(^\text{10,12}\)

In addition late mediators like leukotrienes LTC 4, LTD 4, LTB 4, PGD 2 and cytokines released by mast cells help in sustaining inflammation via direct effect and by causing chemotaxis-attraction of neutrophils and eosinophils to the site of insult. Eosinophils are important cells present at the site of allergic response. The bright red granules of eosinophils contain Major basic protein, eosinophilic cationic protein, eosinophilic peroxidase and eosinophil derived neurotoxin. Eosinophils become activated when adhesion molecules are present in an inflamed tissue. Adhesion molecules are grouped into selectins family (E, P and L), superimmunoglobulin family (ICAM-1, ICAM-2, ICAM-3, VCAM-1) and integrins (LFA-1, MAC-1). Cytokines in inflammatory areas upregulate these adhesion molecules and facilitate attachment, adhesion, sticking and transendothelial migration of eosinophils to the tissue site of inflammation.\(^\text{14}\) Eosinophils exhibit CCR3 receptor on their cell surface. After activation, these receptors signal the apoptosis (programmed cell death) of the eosinophil. Eosinophils may contribute to tissue remodeling processes in asthma by regulating the deposition of extra cellular matrix proteins in bronchial sub epithelial basement membrane. The traditional viewpoint that inflammation is the cause of asthma has meant that airway remodeling, the other major histological feature of the disease, has received considerably less attention, and its relevance to disease pathogenesis is still controversial. Yet, changes involving epithelial goblet cell hyperplasia and metaplasia, collagen deposition and thickening of the lamina reticularis, smooth muscle hyperplasia, and proliferation of airway blood vessels and nerves are consistently observed in ongoing disease, as well as in postmortem asthmatic airways.\(^\text{11}\) IL-4 and IL-13, but not IL-5, are critical for the development of sustained airway hyperreactivity and airway remodeling after allergen exposure.\(^\text{15,16}\) Recent advances have shown that IL-17 levels are increased in asthmatic Airways, which enhance the production of several profibrotic cytokines and inflammatory mediators.\(^\text{17}\)

This late phase of allergic response, carrying it to over 6-8 hours is characterized by increased concentrations of Th-2 subtype cells and eosinophils, basophils, neutrophils which release cytokines and other proteins. This is manifested by nasal blockade, nasobronchial hyper reactivity, and chronic wheeze.\(^\text{13}\) Th-2 cytokines induce mastocytosis, eosinophilia, IgE synthesis, and mucus production. Each element of this response protects against some worms; however, different worms are protected against by different elements of the total response. These considerations suggest that Th-2 cytokine antagonists may increase the risk and severity of worm infections and Th-1 cytokine-mediated inflammatory disorders. Such therapy should be relatively safe if it is restricted to areas in which worm infections are rare and commonsense precautions are taken to minimize the risk of inducing Th-1 cytokine-related inflammatory disease.\(^\text{18}\)

Chronic inflammation is caused by repeated allergen exposure, which lowers the threshold for subsequent stimuli. Allergic individuals react more strongly to:
- Low levels of primary allergen.
- Other allergens to which they are mildly sensitive.
- Non-specific triggers such as cold air, cigarette smoke, strong chemical odor.\(^\text{13}\)

In upper airway allergy, a mild inflammation has been demonstrated in the tissues even in the absence of any symptoms, which is termed as "minimal persistent inflammation". This experimental evidence suggests a long-term treatment with anti-inflammatory drugs.\(^\text{13}\)

## BRONCHIAL ASTHMA

Asthma is defined as a chronic inflammatory disease of airways characterized by airway hyper responsiveness to a multiplicity of stimuli, reversible airflow limitation and chronic eosinophilic infiltration of airways.\(^\text{19}\)

The conventional therapy of asthma evolved around controlling the last step of bronchial airway constriction and administering steroids, which decreases the inflammatory response.

1. **Short acting Beta agonists:** **Salbutamol, Terbutaline.**

These act via stimulating β-2 receptors in the smooth muscles of the airways thereby causing bronchodilation. The
action on β−2 receptors may also inhibit release of chemical mediators from mast cells, enhance mucociliary function and decrease microvascular permeability.

2. Long acting Beta 2 agonists: **Salmeterol, Formoterol**

   Their effect lasts for at least 12 hours enabling better patient compliance. Formoterol has an advantage of having dual action. Its onset of action is very fast (within 1 minute) hence enabling it to be used as a rescue medication. When used for as needed medication Formoterol has also been shown to be better than terbutaline in improving the quality of life in asthma. The combination of Formoterol and Budesonide has been shown to have synergistic action in ameliorating the acute and chronic symptoms of asthma. Formoterol by dry powder inhalation is better tolerated and more effective than theophylline in the treatment of COPD. Salmeterol has an onset of action at 17 minutes and cannot therefore be used as rescue medication. Salmeterol has been reported to cause gingivitis, probably due to decreased salivary flow and due to decreased concentration of immunoglobulin A in saliva. Salmeterol has also been known to cause sudden respiratory arrests. **Bambuterol** is a novel β−2 agonist, a pro-drug of terbutaline, designed for once daily usage.

3. Anti cholinergic agents: The prototype being **Ipratropium bromide**, these agents act as antagonists on muscarinic receptors M-1, M-2 and M-3. Activation of M-1 and M-3 receptors stimulates bronchodilation by antagonizing these receptors. However due to its non-selective action on all the receptor subtypes it has a few side effects. **Tiotropium bromide** is designed for once daily usage. It acts initially by blocking all the receptor subtypes but later releases M-2 receptor thereby minimizing the side effects. These agents are the drugs of choice in COPD.

4. Methyl Xanthines: One of the most widely used anti asthma drugs. Action is due to inhibition of phosphodiesterase enzyme, leading to accumulation of cAMP and subsequent bronchodilation. In addition theophylline and its congeners are known to have immunomodulatory effect on T cells-favoring retention of T lymphocytes in circulation and their reduction in airways. They also cause relaxation of bronchial smooth muscle. In addition theophylline and its congeners are the drugs of choice in COPD. **Doxofylline** (7-(1,3-dioxalan-2-ylmethyl) theophylline) is a novel xanthine bronchodilator, which differs from theophylline in that it contains a dioxalan group in position 7. Similarly to theophylline, its mechanism of action is related to the inhibition of phosphodiesterase activities, but in contrast it appears to have decreased affinities towards adenosine A1 and A2 receptors, which may account for its better safety profile.

5. Cromones: **Disodium Cromoglycate** and **Nedocromil sodium**.

   Disodium Chromoglycate is the prototype of cromones discovered by Altounyan. Cromones are anti-inflammatory agents acting via stabilization of mast cells and preventing the release of chemical mediators such as histamine. Long-term administration reduces bronchial hyper responsiveness, acting as prophylactic agents. Their therapeutic benefits are very limited possibly in children and exercise-induced asthma. Ketotifen is a mast cell and basophil stabilizer as well as an H1 receptor antagonist. Ketotifen again has very limited therapeutic benefits and in fact has significant side effects such as sedation and weight gain.

6. Anti Leukotriene agents: These agents inhibit the formation, release and peripheral action of leukotrienes. **Zileuton** is a 5-lipo-oxygenase inhibitor. Zafirlukast, Montelukast and Pranlukast are antagonists at receptor sites. (Cysteinyl leucotriene receptor 1 antagonists). Despite their promising mechanism of action, these drugs have not been able to significantly alter the disease process. The cells have been found to have two forms of leukotriene receptors—Cysteinyl LT1 and Cysteinyl LT2 receptors. Studies have revealed that Cyst LT2 mRNA is abundantly expressed on activated eosinophils. This has raised the possibility that Cyst LT2 antagonists would be more effective in ameliorating the LT’s response explaining the relative failure of the existing Cyst LT1 antagonists. Moreover these drugs are known to cause side effects like Churg Strauss disease. Despite their minor cytokine modulating action, leukotriene receptor antagonists are much inferior to inhaled glucocorticoids in adults with mild to moderate asthma.

7. Steroids: The mainstay of chronic asthma, steroids have been proven to improve airway inflammation and airway hyper responsiveness. Oral steroids are nowadays not recommended due to significant side effects. Inhaled corticosteroids such as Budesonide, Belomethasone, Flunisolide, Fluticasone and Mometasone have minimal side effects and have excellent efficacy in reducing airway inflammation. The side effects of long-term inhalational steroids are suppression of hypothalamus pituitary adrenal axis. With repeated dosing across a dose range of 250-1000 micrograms twice daily, fluticasone propionate produced significantly greater adrenal suppression than budesonide for both plasma and urinary cortisol. Factors contributing to the systemic adverse activity profile of fluticasone comprise enhanced receptor potency, prolonged receptor residency time, greater tissue retention, and a longer elimination half-life. Children receiving high dose inhaled steroids may present with symptomatic hypoglycemia secondary to adrenal suppression. Within months, not only adrenocortical insufficiency but also myopathy may develop in children receiving high-dose fluticasone. These disorders can masquerade as incapacitating fatigue or difficult breathing.

   Long term once daily inhalational budesonide is effective in the treatment of children with persistent asthma. Studies have however shown that long term Budesonide have no effect on the adrenal function in children. Incidentally budesonide has been moved up from category C to category B as regards usage in pregnancy making its use relatively safe in pregnant women. Budesonide drug delivery has also been tried in the form of encapsulated stealth liposomes. This
mode of drug delivery ensures once weekly administration and has the potential to improve compliance.\textsuperscript{31}
Adjustable maintenance dosage with budesonide / formoterol combination provides more effective by reducing exacerbations and reliever medication usage compared with fixed dose salmeterol/fluticasone. \textsuperscript{42}
Newer steroids are classified as:\textsuperscript{43}
a. On site activated steroids: eg. Ciclesonide,\textsuperscript{44} Rolleponide (under study).
b. Soft steroids: They have improved local, topical selectivity and have much less steroid effect outside target area. e.g. Lactone GCS conjugate, Loteprednol etabonate.

8. Phosphodiesterase 4 inhibitors: The beneficial effects of phosphodiesterase 4 (PDE4) inhibitors in allergic asthma have been shown in previous preclinical and clinical studies. Because allergic rhinitis and asthma share several epidemiologic and pathophysiologic factors, PDE4 inhibitors might also be effective in allergic rhinitis. A study shows that a PDE4 inhibitor, rolfluimilast, effectively controls symptoms of allergic rhinitis.\textsuperscript{45} Thus PDE4 inhibitors might be a future treatment option not only in allergic asthma but also in allergic rhinitis or the combination of the 2 diseases. Cilomilast is an oral selective phosphodiesterase-4 (PDE 4) inhibitor being developed for treatment of chronic obstructive pulmonary disease (COPD).\textsuperscript{46}

Management of steroid-resistant asthma\textsuperscript{47-49}
Steroids are the mainstay in the treatment of allergic asthma. However, increased incidence of steroid resistance has emerged among various subjects.
Steroid resistance is defined as the failure to respond to high doses of oral glucocorticoids i.e. 2 weeks course of 40 mg prednisolone/day.
The efficacy of steroid treatment is documented by monitoring the morning Forced Expiratory Volume at 1 second (FEV 1) prior to treatment with bronchodilators. During the 2 weeks of steroid treatment, the pre bronchodilator morning FEV 1 of a steroid resistant patient will not improve by more than 15%.
Other indicators of steroid resistance include the need to raise the steroid doses to achieve the same level of clinical benefit, overuse of inhaled β agonists, high frequency of hospitalization and emergency visits.
There is no known association between steroid resistance and age. However there is a definite linkage between severity of disease and steroid resistance.
Other conditions that could masquerade steroid resistant asthma are poor compliance, drug interaction with glucocorticoids, abnormal glucocorticoid absorption or elimination.
Steroid resistance is divided into 2 types:
Type I: Vast majority (90%) show this type of resistance characterized by decreased binding affinity of glucocorticoids to T cell receptors due to prolonged steroid use.
Type II: Primary inactivity of steroid receptor or abnormally low number of glucocorticoid receptor binding sites.
The management of steroid resistant patients:
After determining the adequacy of dosages and the correct mode of administration of steroids, patients labeled as resistant are tried on alternative drugs.
1. Methotrexate: Methotrexate causes inhibition of T cell proliferation through inhibition of enzyme Amidophosphoribosyl transferase. Concomitant weekly methotrexate therapy allowed progressive clinically significant reduction in oral prednisolone doses between weeks12-28 from 15mg/day to 5mg/day. Methotrexate therapy also increases peripheral blood T cell sensitivity to prednisolone inhibition.\textsuperscript{49}
2. Cyclosporine: Cyclosporine markedly and selectively inhibits T lymphocyte proliferation, IL-2 and other cytokine production and response of inducer T cells to IL-1. It is used as a second line immunomodulator drug in steroid resistant asthma.
3. Leflunomide: Basically a disease modifying agent for rheumatic diseases, it also causes selective suppression of Th cytokine expression. They have a steroid sparing effect.
4. Rapamycin: It inhibits T cell proliferation by blocking cytokine production, but toxicity has limited its use to investigational role in steroid resistant asthma.
5. IV immunoglobulins: Steroid-sparing effect appears to be present but is not used, as it is prohibitively expensive.
6. Gold: it has been used in Japan, and isolated studies in Europe and America have shown decreased use of steroids, improved symptoms but no change in FEV 1.

ALLERGIC RHINITIS
Allergic rhinitis is the most commonly allergy encountered in clinical practice and constitutes about 55 % of allergies seen in India. Rhinitis is a condition manifested by: \textsuperscript{13}
- Nasal blockade
- Running nose (rhinnorhoea)
- Sneezing
To diagnose rhinitis any 2 of the 3 symptoms must be present for more than 1 hour everyday for more than 2 weeks.
Histamine released from mast cells and basophils leads to nasal discharge and nasal congestion. Kinins (bradykinin) generated by mast cell tryptase and plasma kallikriens stimulate afferent neuron to cause watery rhinnorhoea by inducing vasodilation, edema and plasma exudation.
The mainstay of treatment for allergic rhinitis has been the use of topical corticosteroids, nasal sprays and new generation non-sedating antihistamines.

1. **Topical corticosteroids**: The commonly topical agents used are Budesonide, Beclomethasone, Fluticasone and Flunisolone. Fluticasone has been proposed to be an effective topical agent; however the incidence of HPA axis suppression is seen with Fluticasone even at low doses. A Meta analysis on Fluticasone concludes that systemic side effects of Fluticasone are equivalent to oral prednisolone. Budesonide is a molecule effective in rhinitis which has a novel mechanism of action (Fig. 2). Inhaled Budesonide conjugates in the bronchial mucosa with a lipid to form a conjugate. Conjugated Budesonide is unable to bind to the glucocorticoid receptor, but is retained within the cells. As the concentration of unconjugated budesonide decreases, budesonide is slowly released from the conjugates through the action of intracellular lipases, and thus becoming available to bind to the receptor. These studies suggest that this mechanism of action of budesonide results in a prolonged duration of action with minimal side effects.

**Rolflponide palmitate** is an esterified glucocorticosteroid pro-drug with a promising pre-clinical profile designed to deliver topical airway treatment for allergic rhinitis and asthma. Topical treatment with aqueous solutions of rolflponide palmitate attenuates nasal symptoms and improves nasal PIF in allergic rhinitis. The overall efficacy of 400 µg of rolflponide palmitate is similar to that of 128 µg of budesonide in the pollen-season.

2. **Systemic corticosteroids**: Short courses may be needed for severe symptoms, especially when nasal blockage is so severe that nasal sprays are ineffective.

3. **Mast cell stabilizers**: Sodium chromoglycate and Nedocromil sodium are not found to be much effective in the treatment as proposed initially.

4. **Anti-histamines**: Anti-histamines are particularly effective in ameliorating the symptoms of rhinitis viz. sneezing, itching and watery rhinnorhoea.

A major problem with anti-histamines was sedation. However the newer generation antihistamines are relatively non-sedating. **Fexofenadine** is a widely prescribed, non-sedating anti-histamine. It has been shown to suppress IL-8, which is responsible for neutrophilic chemotactic activity. Fexofenadine thus suppresses both the early and late phases of allergic response and besides in view of ICAM-1 suppression, is able to inhibit eosinophil chemotaxis.

**Desloratidine** (metabolite of loratidine) a non-sedating anti-histamine and **Levocabitizine** (levosoiomer of cetirizine) are molecules with rapid onset and long duration of action. Levocetirizine however, displays the same degree of sedation as its parent compound, cetirizine.

**Azelastine** is a unique topical antihistamine, which is effective and virtually free of side effects.

**TAK-427** is a long acting antihistamine under trial, which suppresses acute phase allergic reactions.

**Inverse Agonism**: Current models of histamine-receptor activity are changing. Histamine receptors are G-protein coupled receptors and have traditionally been reviewed as existing in either an activated or inactivated state. It is now thought that they exist in equilibrium between their active and inactive states. In this two state model, agonists stimulate the active conformation and inverse agonists stabilize the inactive one. Histamine receptors have recently been shown to have constitutive activity i.e. in the absence of histamine they exist in a partially activated state. Inverse agonists down regulate this constitutive activity. With these new studies, our understanding of the molecular mechanisms by which anti-histamines produce beneficial effects in allergic disease continues to increase.

5. **Decongestants**: systemic decongestants are of doubtful value in allergic rhinitis. However they are useful when used intermittently, particularly during initiation of therapy.

6. **Ipratopium bromide**: This is a locally acting anticholinergic drug, which mainly helps patients with watery rhinnorhoea.

7. **Botox**: In selected cases, injection of 40 units of Botox-A into the turbinates, as a single agent, may help the symptomatic control of AR for up to 8 weeks.

8. **Ramatroban**: Nasal obstruction is currently thought to be closely related to the presence and abundance of lipid mediators, such as leukotriene and thromboxane (TX) A2. The novel drug ramatroban, a TXA2 receptor antagonist, has been demonstrated, in clinical trials, to improve nasal obstruction in the treatment of patients with allergic rhinitis and it has recently become commercially available.

9. **Anti-Leukotriene agents**: These agents were used in seasonal allergic rhinitis. However numerous studies have proven that anti-leukotriene agents do not have clinical benefits and have an effect equal to placebo for the control of the symptoms of allergic rhinitis.

**ALLERGIC CONJUNCTIVITIS**

Allergic conjunctivitis is a common manifestation seen in India and is usually associated with rhinitis. Treatment options include oral anti histamines and recently topical anti histamines - Azelastine eye drops.

Newer drugs in the management of this condition are:

**Lodoxamide** (0.1%) is a newly introduced mast cell stabilizer, which is several hundred times more potent than chromolyn sodium. It is used in the treatment of vernal, atopic and giant papillary conjunctivitis.

**Emedastine difumarate** is a potent H1 antagonist and has been found to give good relief. It inhibits H1 induced IL-6, IL-8 and GM-CSF secretions.

**Olpatadine** a dual acting drug, is a long acting H-1 selective antagonist active in a concentration dependant manner and also has a mast cell stabilizing action.

**Loteprednol etabonate** (0.2%) is a new topical steroid used on a long-term basis for the treatment of seasonal and perennial conjunctivitis with a remarkably low incidence of side effects.
SKIN ALLERGIES

Atopic dermatitis

It is the cutaneous expression of the atopic state. Based on the increasing knowledge of T-cell-mediated pathogenesis in atopic dermatitis (AD), systemic immunosuppressive drugs are increasingly applied. The chronic, relapsing course of severe AD necessitates a drug, both efficacious and safe in long-term application.

Diagnostic criteria for atopic dermatitis: 66

- Pruritus and scratching
- Course marked by exacerbation and remission
- Lesions typical of eczematous dermatitis
- Personal or family history of atopy
- Clinical course lasting longer than 6 weeks

Clinical features include perioral pallor, Denny Morgan folds (extra fold of skin beneath lower eyelids), increased palmar markings, and increased incidence of cutaneous infections—particularly Staphylococcus aureus. They have elevated levels of IgE. Plasma IL-18 levels were also found to be elevated in these patients. As the clinical severity of atopic dermatitis increases, the plasma IL-18 level also tends to increase. These findings suggest that IL-18 may be associated with the severity of atopic dermatitis. 67

Management includes avoidance of cutaneous irritants, adequate cutaneous hydration and use of low to mid potency topical glucocorticoids. Side effects of long-term topical steroids include cutaneous atrophy and immunosuppression. Treatment with systemic steroids should be limited to severe exacerbations, unresponsive to topical therapy. Antihistamines are an important component of treatment. Fexofenadine 180 mg/day is an effective non-sedating antihistamine.

Cyclosporine and phototherapy are of proven value in treating atopic dermatitis.

Leflunomide is a pyrimidine de novo synthesis-inhibiting immunosuppressant exhibiting an extremely long in vivo half-life of its active metabolite. Leflunomide was efficient in the long-term treatment of recalcitrant AD. 68

Tacrolimus is a non-steroidal topical agent which affects a broad spectrum of inflammatory mediators. It has good cutaneous permeability and has no potential for cutaneous atrophy. Another congener of tacrolimus, Pimecrolimus is also available for use. These agents suppress T lymphocyte responses by inhibiting Calcineurin. 6

Pimecrolimus a less potent drug as compared to Tacrolimus, is approved for short term and long term treatment of atopic dermatitis in children over 3 months of age.

Mycophenolate mofetil is a highly effective drug for treating moderate-severe AD, with no serious adverse effects occurring in any patients. Thus, mycophenolate might develop into a promising alternative in the therapy of moderate-severe AD. 70

Specific Immunotherapy

Allergen immunotherapy, also called Specific Immunotherapy, is the only recognized treatment of allergic disease that can ameliorate symptoms and alter the natural course of the disease. Other synonyms for this treatment are desensitization, hyposensitization, allergy shots, allergy vaccines and allergen injection therapy. This form of therapy was discovered by Leonard Noon at St. Mary’s Hospital in London in 1911. 62

Mechanisms of specific immunotherapy. 72

1. Induction of T cell tolerance or functional silencing (anergy).
2. Altered balance of cytokines so that there is decreased Th-2 response and increased Th-1 (non-allergenic) response.
3. Increased production of immunosuppressive cytokines - IL-10, TGF-beta by T regulatory cells (Fig. 3). Successful immunotherapy involves a switch to Th0 cells and suppression of IgE with an increase in IgG4 and IgA through the interaction of IL-2, IL-12, IFN-gamma and IL-15. IL-10 controls IgG4 whereas TGF-beta controls IgA. On the other hand, unsuccessful immunotherapy involves increase in IgE production through IL-4, IL-5 and IL-13.
4. Induction of IgG blocking antibodies, which antagonize the action of allergen IgE antibody. e.g. IgG4 antibodies.

Urticaria

Leukotriene antagonists have been found to be ineffective in the treatment of idiopathic urticaria. 71

Contact dermatitis (Cartact dermatitis) (not characterized by high IgE levels) is a manifestation of delayed type hypersensitivity mediated by T-lymphocytes in the skin. The allergic reaction is marked by erythema, vesiculation and severe pruritus. A high potency fluorinated topical glucocorticoid is used to treat allergic cutaneous dermatitis. In India, the commonest causes of contact dermatitis are Nickel sulfate (artificial jewellery) and Parthenium hysterophorus, a wild weed which was accidentally introduced into India through the PL-480 wheat aid programme of the USA. 8

Fig. 3 : Specific immunotherapy
SIT involves the subcutaneous injection of allergen extracts in increasing concentrations and decreasing frequency, starting about twice a week to once a week and later once in 2 weeks. The aim of SIT is to induce a state of “hypo sensitization” with diminished clinical response on natural re exposure of allergen.62 Incidentally, specific immunotherapy has been reported to be safe during pregnancy. Specific immunotherapy affects levels of cytokines like IL-2 and IL-1β in patients with allergic asthma and rhinitis.73 Since most allergen sources can be reconstructed with recombinant allergens it would also be possible to replace allergen-extract-based immunotherapy with recombinant allergen-based strategies.

Allergen peptides are active components of an individual allergen. These peptides when presented without co stimulatory signals downregulate T cell response. Studies are underway with peptides from several common allergens.

Several strategies for reducing the allergic activity of vaccines have been studied in great detail and have been evaluated in clinical trials. Three fundamental principles have been applied: The first approach using allergen-derived short T cell epitope-containing peptides is thought to induce T cell tolerance without causing release of inflammatory mediators because of the lack of immunoglobulin E binding epitopes. This approach has yielded controversial results when applied earlier for cat and venom allergy.73 The second approach focuses on the use of allergen-derived B cell epitope-derived peptides. In contrast to the T cell peptide approach, this strategy selects surface-exposed allergen-derived peptides which are longer than the T cell peptides (>25 amino acids) in order to induce blocking immunoglobulin G antibodies. Based on the three-dimensional structure of an allergen or on data obtained by experimental epitope mapping, it is possible to select peptides which lack immunoglobulin E binding but can induce immunoglobulin G responses inhibiting immunoglobulin E binding. The third and most developed approach is the engineering of recombinant allergen derivatives with reduced allergenic activity. For this purpose various strategies have been applied. It has been found that immunoglobulin E recognition of respiratory allergens strongly depends on the presence of conformational immunoglobulin E epitopes. Therefore, most strategies for reducing allergic activity and immunoglobulin E binding capacity focus on the altering or abolishment of the structural fold of allergens.74 CpG-based immunotherapy significantly reversed both acute and chronic markers of inflammation as well as airway hyper responsiveness. CpG DNA may provide the basis for a novel form of immunotherapy of allergic asthma. Both antigen-specific and, to a lesser extent, antigen-nonspecific responses to mucosal administration of CpG DNA are seen.73 Sublingual immunotherapy (SLIT) has been postulated as a newer modality of sensitizing an individual. SLIT involves topical administration of allergens leading to the hyposensitization / desensitization of the individual. Predictably the side effects of SLIT are much less as compared to conventional subcutaneous injections of allergens. It would also decrease the cost of immunotherapy.76 Uncertainties about the use of SLIT is the optimal maintenance dose to be administered, as there is no evidence of a defined dose response relationship. Major clinical trials are underway to prove the efficacy of SLIT. A study undertaken by Khinchi et al showed that subcutaneous immunotherapy (SCIT) was more effective for asthma. This aspect was counterbalanced by superior safety profile of SLIT.77 In another study on mite induced allergic subjects, it was found that SCIT was more effective in controlling asthma whereas SLIT well controlled the rhinitis symptoms.78

Newer drugs in asthma control

**Altrakincept**: IL-4 receptor antagonist.79,80 IL-4 mediates important proinflammatory function in asthma including induction of IgE isotype expression via stimulation of B cells, expression of VCAM-1, mucin production and switching of Th-2 response. Soluble recombinant IL-4 receptor which acts as an antagonist in vivo inactivates naturally occurring IL-4 without mediating cellular activation. Nebulized form of IL-4R has a serum half-life of 1 week. Single dose of IL-4 R, 1500 mcg per week, appears safe and effective in moderate asthma.

**Omalizumab**: anti IgE antibody.81-83 It is available as human monoclonal, chimeric, anti-IgE antibody. It binds to FcERI receptor binding site on IgE and reduces the amount of free IgE available to mast cells, basophils and other cells. The doses of omalizumab are 150-375 mg intradermal or subcutaneous every 2-4 weeks. Subcutaneous administration of omalizumab is indicated for adults and adolescents (age greater than or equal to 12 years) with allergic asthma that is moderate to severe and inadequately controlled with inhaled corticosteroids. In placebo-controlled trials, omalizumab reduces asthma exacerbations and the need for inhaled steroids in this group. There are however problems with Omalizumab. For instance, in India we do require IgE for it’s anti-parasitic activity and one wonders whether we will be swamped with parasites if we allow Omalizumab to bring down IgE levels to 15 to 20% of normal levels. Also, IgE has an important role in tumour surveillance. Will the incidence of malignancies go up if we prescribe Omalizumab. Finally, the cost of all monoclonal antibodies is substantial and Omalizumab is no exception.

**Suplatast tosilate**: IPD 1151T. It is a Dimethyl sulphonium compound.62,86-88 It selectively inhibits Th-2 cytokines, primarily IL-4, IL-5 without any effect on IFN γ from Th-1 cells. There is a notable drop in the average number of infiltrating eosinophils, IgE-2+ cells, CD25 and CD4+ cells. It inhibits IL-13 release from basophils. The dosage is 100 mg 3 times a day.

**Efalizumab**:89 It is a humanized IgG1 mAb against the lymphocyte function antigen-1 (LFA-1) alpha chain, CD11a. Blocking of LFA-1/intercellular adhesion molecule interactions could inhibit asthmatic inflammation by blocking adhesion and activation of LFA-1-positive leukocytes.
Blocking of LFA-1/intercellular adhesion module interactions by efalizumab inhibits the development of allergen-induced cellular inflammatory responses measured in induced sputum and might attenuate the late asthmatic response.

**Resiquimod.** Resiquimod is a new immune response modifier from the family of imidazoquinolineamines. It inhibits allergen induced Th-2 response, airway inflammation and airway reactivity. It is a potent modulator of IgE production in vitro in normal but also in allergic donors. Antiviral activity has been demonstrated against a variety of viruses, and clinical efficacy has been demonstrated against genital warts, herpes genitalis and molluscum contagiosum. Resiquimod can be administered topically but also exists as an oral formulation.

**IDEC-152.** A recent study has investigated the safety, clinical activity, and pharmacokinetic profile of IDEC-152, an IgG1 anti-CD23 antibody, in patients with mild-to-moderate persistent allergic asthma. These data suggest that IDEC-152 is safe and has the potential for clinical activity in allergic asthma.

Finally, the eosinophil plays a crucial role in the allergic immune response, especially during the late phase. The eosinophil expresses the CCR3 receptor on its surface which could become a potential target for blockade, which would effectively block off the late reaction.

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