Allergic rhinitis, asthma and atopic eczema are among the commonest causes of chronic ill health, and there is enough evidence that these diseases are increasing in prevalence.

The term Allergy was introduced to medical practice in 1906 by Clemens Von Pirquet the Austrian pediatrician, to describe the strange non-disease related symptoms that some diphtheria patients developed when treated with horse serum antitoxin. The word comes from the Greek work “alol” meaning “change in the original state” Indeed an allergic reaction is the result of body’s change when it adversely responds to a harmless substance.

Von Pirquet defined allergy as “the ability of animals and humans to develop altered responses to foreign substances after repeated exposure” It was his intent that the term should apply to the “uncommitted” biologic response - which may lead either to immunity (a beneficial effect) or allergic disease (harmful effect). With the passage of time the word has become corrupted and is now used synonymously with IgE mediated allergic disease.

An important step in our understanding of allergy was the paper by Prausnitz and Kustner (1921) describing that cod fish allergy of the former could be passively transferred to the later by injection of serum. They called the unknown agent in the serum as “Reagin”. Almost half a century later Ishizaka in USA and Johanssen in Sweden discovered the role of IgE class antibodies as the principal mediator in the allergic reaction. In response to exposure to an allergen such as pollen, the allergic individual produces IgE antibodies. The mechanism by which IgE plays a central role depends on its binding to high affinity receptors on mast cells and basophils. On exposure to a specific allergen, allergen molecules crosslink adjacent Fab components of IgE on the cell surface, activating intracellular signal transduction, leading to synthesis and release of chemicals including leukotrienes in addition to release of preformed mediators like histamine. IgE is present in normal people also, but in those with allergic diseases it is present in increased amount and more importantly, it is directed against specific allergens.

The next concept that needs to be clarified is “atopy” (from Greek word atopos meaning out of place). It can be defined as a state of hereditary disordered immunity in which the predominant T helper lymphocyte type 2 immune mechanisms drive the production of IgE on exposure to common environmental antigen or allergens. What does IgE do in normal individuals? It is interesting to know sloughing of epithelium, mucus hyper secretion and smooth contraction are useful to expel worms from the intestine - and eosinophilic proteins have the capacity of breach the integument of parasites.

The central question about atopy is why some individuals mount vigorous Th2 driven response and produce IgE after a seemingly innocuous challenge of a minute dose exposure to an allergen? Complex genetic and environmental factors are thought to be responsible, principally through enhancing Th2 in opposition to Th1 immune mechanism.

In utero, T cells of the fetus are primed by common environmental allergens, that cross the placenta, the
immune response of virtually all newborns is dominated by Th2 cells. It has been proposed that during subsequent development the normal (i.e. nonatopic) infant’s immune system shift, in favor of a Th-1 mediated response to inhaled allergens (a process termed “immune deviation”)6, whereas in potentially atopic infant there is a further increase in Th2 cells that were primed in utero.

Microbes are probably the chief stimuli of protective Th1 mediated immunity. Macrophages that engulf microbes secrete interleukin-12, which induces Th1 cells and natural killer cells to produce interferon-gamma thereby shifting the immune system into “allergy protective”, Th1 mediated response.7

The marked increase in the prevalence of atopic disease in Western Europe, USA and Australia during recent years, has stimulated research mainly centering on environmental influences. Publication of the paper Hay giver, Hygiene and House hold size by David P Strachan in 1989 started a debate on influence of better hygiene on development of allergic illnesses, but, the hypothesis is far from being proved convincingly. Similarly in a paper from Caracas, Venezuela- it was suggested that treating children with anthelmenties lowered the total IgE level but increased skin sensitivity to house dust mite (HDM) and leaving them untreated increased total IgE but HDM sensitization dropped.9

Pharmacotherapy of allergy started with discovery of antihistaminic drug in 1937 and corticosteroids in 1948. The ground work for the development of antihistamines was made in the first half of the twentieth century by Swiss - Italian Pharmacologist Daniel Bovet (1907 - 1972). Bovet’s work led to production of antihistamines for allergy relief and earned him a Nobel prize in 1957. But a real exciting discovery was the identification of leukotrienes (trienes from leukocytes ) for which Prof. Bengt Samuelson received the Noble prize in Medicine / Physiology in 1982, as the elusive “Slow Reacting Substance of anaphylaxis”. Within a short period we had allergy controlling drugs like Leukotriene receptor antagonists (Zafirlukast, Montelukast) and biosynthesis inhibitor (Zileuton).

If it is IgE, that is creating all the problems and if IgE is not really serving any vital function in our system, people started thinking of a way to get rid of IgE altogether. The initial attempt was to develop an antibody to the part of IgE molecule that serves as a receptor for the allergen to cross link, (Fab components), but this was not found to be effective as the antibody itself was causing release of mediators from inflammatory cells, The next step was to prepare an antibody to the part of IgE molecule that attaches to the surface of mast cells. This antibody could not do anything about the IgE already sitting on the mast cell, but prevented the circulating IgE from attaching itself to the receptors on the mast cells. The circulating complexes of anti IgE antibody and IgE molecules get eventually removed from the circulation by the reticuloendothelial system.

Humanized versions of these murine monoclonal anti-IgE antibody was developed by grafting the variable immunoglobulin region of murine origin on to a “backbone” of the constant region of human IgG.11

The first two large clinical trail of humanized IgE antibody was published in 1997 and 1999. While the precise role of this product is still somewhat uncertain - it is generally accepted to be used in moderate to severe persistent asthma in adults as an add-on therapy, and certainly not a “cure” for the disease. Anti IgE therapy is the only currently licensed antibody therapy; data suggests it can reduce exacerbation rates by 50% and may reduce steroid requirement. It can only be used if total IgE is between 30 and 700 IU/ml.

Cytokines or their antagonists for the treatment of Asthma are being investigated, but unfortunately there is no concrete evidence yet for such treatment to be effective.14

REFERENCES