Allergy: Past, Present and Future

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It is true, as Lamartine wrote, "History teaches everything, even the future". The knowledge in allergy nowadays has a long history of development. Lucretius, a Latin philosopher who lived in the first century BC observed the food allergy and quoted as saying "what is one man's meat is another's poison".

The term asthma come from Greek, meaning a panting was recognized for a long time. Hippocrates "the Father of Medicine" (460-357 BC) recognized spasmodic nature of asthma and believed that it was caused by cold and moisture at least in children.

John Bostock, speaking to the Royal Medical Society of London in 1819, described his own "Periodic affection of the eyes and chest," the condition which he named "*Catarrhus aestivus*" or "Summer catarrh". This condition also obtained the popular name of "hay fever". Since he believed that it was produced by effluvium from new hay. Half a century later, Charles Blackley, a British allergy pioneer established that pollen plays an important role in the causation of hay fever. He used himself as a "guinea pig". He sampled pollens and rubbed them into a scratch on his arm and elicited a reaction measured 1.5 to 2.5 inches. He also provoked conjunctivitis, rhinitis and asthma. By microscopy of sticky slides he counted pollens in the air, and showed correlation between the count and his symptoms. Finally, he attached sticky glass slides to strings of kites and found a high count 500 meters above the ground level. This discovery explained to him why he suffered from hay fever in a large city, and this finding was the beginning the study of aerobiology.

In 1901, Charles Richet and Pual Portier studied the poison of sea anemones. They tried to make dogs immunized to the poison by injected the serum of sea anemone. Twenty-two days after the first injection he gave the second one, this time one tenth of the lethal dose. Within a few seconds the dog become extremely ill and died within a few minutes. They called this condition as anaphylaxis (opposite to prophylaxis).

In 1905, Clemens von Pirquet and Bela Schick reported that children who were given repeated injections of horse streptococcal antitoxin serum sometimes developed fever, swollen glands and rash as the characteristic of serum sickness. Von Pirquet proposed term "allergy" for the concept of change activity. He put together the Greek words "*allos*" which means different or change, and "*ergos*," work or action.

In 1919, Ramirez reported a case of man who had developed the first attack of asthma after received blood transfusion from an asthmatic donor. The patient was shown a positive skin reaction to horse dander. This was the first observation indicating that asthma can be mediated by a serum factor.

The phenomenon that allergy can be transferred by serum was confirmed in 1921 by Dr. Prausnitz and his allergic patient, Kustner. Serum from a fish allergic Kustner was injected to Prausnitz's arm. The next day, Prausnitz was injected with a fish extract in the same place and, for the first time in his life, he exhibited a positive skin reaction to fish. It was explained that Kustner's serum contain a factor that could mediated a positive skin test (or could passive transfer). The factor responsible for Prausnitz-Kustner reaction was subsequently named "reagin" by Coca and Cooke.

R.A. Cooke and A.E. Coca in 1923 proposed the term "Atopy" for those clinical forms of allergy manifested by hay fever and asthma, in which "the individuals as a group possess a peculiar capacity that makes them sensitive to a certain protein to which their environment and habit of life frequency expose them to". These, an inherited predisposition to become sensitized is a characteristic feature of atopy and presence of a factor called "reagin".

In 1967, Japanese team Ishizaka working in United States and SG0. Johansson and Hans Bennich working in Sweden, were able to demonstrate that reagin belongs to a new immunoglobulin class, IgE. Allergy then became a part of an exact discipline, clinical immunology.

In early 1970, Gell and Coombs classified allergic reaction into type I-IV, considering extreme complexity of immune response, namely anaphylactic, cytotoxic, immune complex and delayed reactions. This has been a useful oversimplification in the growing field of immunology.

The past two decades saw an explosion of knowledge of cell biology, immunochemistry, etc, have led to understand the mechanism of allergic disease and provided a tremendous impact on the diagnosis and treatment of allergic diseases. Now we understand two phases of IgE mediated allergic response. The early phase reaction occurs within a minutes after the exposure to an allergen in sensitized individuals leading to degranulation of mast cells releasing of histamine, leukotriene, cytokines and protease. The reactions usually subside within 30-90 minutes. The clinical responses include wheal and flare reaction on the skin, sneezing, watery rhinorrhea and blockage in the nose or itching and redness in the eyes. These symptoms can be inhibited by H1-antihistamines. Whereas in the bronchi, the early response is caused by smooth muscle contraction which can be prevented and reversed by inhaled beta 2-agonists.

The late phase reactions cause tissue inflammation. It begins two to four hours after the exposure to allergens and it lasts for 24 hours. The mechanism of the late responses includes T-cell activation, up regulations of adhesion molecules (initiated earlier), and eosinophil

accumulation, activation and secretion. The clinical responses include diffusely demarcated indurations on the skin, intermittent sneezing and persistent blockage in the nose, and show biphasic curve of late and early response in the bronchi. Glucocorticoids efficiently block the development of the late responses in all tissues.

In the past decades variety of aspects in allergy have been changed, especially the prevalence of atopic diseases, pathogenesis of diseases, causative allergens and medications that are used in allergic diseases. Only some aspects of new discoveries are reviewed below.

Increasing the prevalence of atopic diseases

Recently, the International Study of Asthma and Allergies in Childhood (ISAAC) has developed a standardized questionnaire to study the prevalence of allergic diseases and can compare geographically. The studies of ISAAC indicated that prevalence of atopic dermatitis, allergic rhinitis and asthma has increased worldwide including Thailand. There are a number of possible causes but none of them are satisfactory. Increased awareness of allergic diseases, reduced breast feeding in modern society, increased mite exposure, role of air pollution and decreased chronic recurrent infections could switch Th 1 to Th 2 cells (hygiene hypothesis) all these lead to increased development of allergic diseases.

House dust mite

In 1922, Robert A. Cooke described house dust as an important cause of bronchial asthma and allergic rhinitis. However, not until 1967 that Voorhorst and Spieksma proved that the major allergen in the house dust was house dust mite. House dust mites are the most common indoor source of allergen. *Dermatophagoides pteronyssinus* and *D. Farinae* are the most common spices of house dust mites. There are many mites in bedding and mattress and also in stuffed furniture and carpets. Mites are frequent in warm and humid areas, but they are rare in dry areas and at high altitudes.

Beside house dust mites and pet danders, cockroaches are also main sources of indoor allergens in urban dwellings, especially in low socioeconomic communities.

Medications used in allergic diseases

Asthma

There are two types of asthma medications, namely: anti-inflammatory drugs as "controller" and bronchodilators as "reliever".

Bronchodilators

Beta 2-Adrenergic Agonist

Previously, bronchodilators were widely used alone as first-line daily therapy. Adrenaline was introduced by injection in 1903, and ephedrine by oral was discovered and widely used in Japan for treatment of asthma in 1917 and introduced into the United States in 1923. Both medications are not only effective on beta receptor (bronchodilator) but they also act on alpha - receptor (cardiovascular effects).

Subsequently, inhaled medication has been proved of advantages over oral route because of its action is more rapid with higher drug concentration in the target tissue and lower risk of systemic adverse effects. Isoproterenol was the first inhale bronchodilator, it causes prompt bronchodilatation, but it has short duration of action (1-2 hours) and may cause tachycardia and arrhythmia. So it was replaced by new short-acting beta 2-selective agonists as salbutamol and terbutaline which are more potent and safe with minimal systemic effects.

Long-acting selective beta 2-adrenergic agonists, salmeterol and formoterol, have been recently marketed, both are potent and long acting bronchodilators (12 hours). They are particularly effective in the prevention of nocturnal asthma and reduction of the need of short-acting inhalers.

Methylxanthine

For decades, theophylline was used as bronchodilator for a relief of an acute asthmatic attack. However, it has a very narrow therapeutic index (10-15 μg/ml). Blood level above 20 μg/ml can cause serious side effects as seizure. Currently, theophylline has no longer been used in acute asthmatic attacks. Only the sustain-released theophylline has shown to be useful as supplement drug in the control of nocturnal asthma.

Anti-inflammatory drugs

Corticosteroids.

Philip Hench, et al. identified chemical structure of cortisone in 1941. Carryer and co-workess in 1950, were first group demonstrated of dramatic response of *status asthmaticus* by cortisone but almost immediately side-effects. The first attempt of inhaled hydrocortisone acetate was made by Gelfand in 1951 with favorable response. Beclomethasone dipropionate, was found to be 5,000 times as potent as hydrocortisone, and it has become available as inhalation in asthma and intranasal spray in allergic rhinitis in 1972. It separates anti-inflammatory and unwanted systemic activities by its high affinity for glucocorticoid receptor. Advances in development of steroid chemistry, other steroid compounds as budesonide and fluticasone are available for inhalation in treatment of asthma. At the present time, inhaled steroid is the first-line daily therapy for bronchial asthma based on the following reason: asthma is a chronic inflammatory disease that contributes to airway hyperresponsiveness which can be inhibited by inhaled steroid. Early intervention of inhaled steroid can inhibit the development of irreversible reduced lung functions. Furthermore, it increases the risk of asthma death in patients who rely heavily on the use of beta-2 inhalers.

The discovery in the last decade that the addition of a long-acting beta-2 agonist to low doses of inhaled corticosteroids provides more effective asthma control than a higher dose of inhaled corticosteroid alone has been a major step forward for asthma therapy and has become more popular at the present time.

The other advances in used of inhaled medication: Chloroflurocarbon (CFC) is used to propel many meter-dose inhaler (MDI) of both inhaled corticosteroid and inhaled beta-2 agonist. This substance depletes the ozone layer which affects the ecology and increased incidence of skin cancer. Many countries worldwide have aimed for its complete elimination and replace it with non-ozone depleting chemicals called hydrofluroalkane (HFA) in the near future.

Leukotriene receptor antagonists and synthesis inhilitors

Leukotriene receptor antagonists and synthesis inhibitors are the newest controller drugs. These drugs are taken orally which is a definite advantage. Montelukast and pranlukast can be given once daily and easy-to-take pediatric dose formulations. The onset of action can be shown to be within a few hours to a day. It can be used alone in

milder asthma or in combination with inhaled corticosteroid and can decrease the dose of steroid to control the patient's asthma.

Other drugs

Cromoglycate and Nedocromil

In 1967, Altounyan discovered sodium cromoglycate as an antiasthmatic drug. It still has unclear mode of action. It is virtually not absorbed through mucosal surfaces; it is, therefore, inhaled in powder from, a MDI, or as a nebulized solution. It is usually clinically effective in young allergic patients with mild to moderate asthma. It can be used either occasionally before allergen exposure and exercise or on a regular basis four times daily. A new compound, nedocromil sodium, also seems to be effective in asthma. Due to its low efficacy, high price and no immediate effect cause, it is not popular at the present time.

Allergic rhinitis

Two major drugs are now popular for the treatment of allergic rhinitis, antihistamine and intranasal corticosteroids.

Antihistamines

H1-antihistamines were discovered by Bovet and Staueb at the Pasteur Institute in 1937. At the beginning, the compound was too weak and too toxic for clinical use. In 1942, phenbenzamine, the first antihistamine was used in the treatment of allergic disease. Within a few years, other H1-antiantihistamines were made available, e.g., pyrilamime maleate, dephenhydramine, hydroxyzine, chlorpheniramine, etc. They have overall unfavorable risk/benefit ratios, since they show poor selectivity, short duration of action, sedative and anticholinergic effects. For over 20 years, advances in pharmacological researches have produced several compounds with high potency, a longer duration of action and minimal sedative effects. They are so-called new or second-generation H1-antiantihistamines, e.g., cetirizine, fexofenadine, loratadine. They are now more popular for treatment of allergic diseases.

Intranasal corticosteroids

In 1972, becomethasone dipropionate was introduced as a nasal spray for seasonal allergic rhinitis. Subsequently other new intranasal corticosteroids have been developed. They include budesonide, flunisolide, fluticasone propionate, momethasone furoate and triamcinolone acetonide. The effect of intranasal glucocorticoids is based on their local activity. They are currently considered as first-line therapy for adults in moderate to severe cases of allergic and non-allergic rhinitis.

Allergen immunotherapy

In 1911, Noon and Freeman introduced allergen immunotherapy for the treatment of asthma and allergic rhinitis. At the beginning, the mechanism of action and its efficacy are due to increase in allergen-specific IgG (blocking antibody) and decrease in allergen-specific IgE. Until recent studies indicated that immunologic changes during immunotherapy are complex. Successful immunotherapy is often associated with a shift from Th2 to Th1 $CD4^+$ lymphocyte immune response to allergen. It is also associated with immunologic tolerance while the relationship between immunotherapy efficacy and the levels of specific IgE antibody are usually variable and increases in allergen-specific Ig G blocking titer are not predictive of the duration and degree of efficacy of immunotherapy.

Immunotherapy has been proved effective in the treatment of pollen, fungi, animal danders, dust mites, cockroaches and hymenoptera sensitivity. It is also effective in the treatment of allergic rhinitis, asthma and stinging insect hypersensitivity. It may also prevent the development of asthma in children with allergic rhinitis.

Future trends in immunotherapy are developing, various routes of drug administration such as oral, sublingual-swallow, nasal route or rapid rush immunotherapy are still under investigation. Their clinical applications are to be determined.

Atopic dermatitis

Atopic dermatitis is one of the common atopic diseases. It often in the first manifestation of allergic disease, and frequently accompanied by allergic respiratory diseases as asthma and allergic rhinitis. The effective management of allergic dermatitis includes some combination of trigger avoidance, measure to restore skin barrier function and anti-inflammatory medications. There are multiple anti-inflammatory medication options available for treating atopic dermatitis. Topical corticosteroids are appropriate for the vast majority of patients, and potency of the corticosteroid agent chosen should be individualized base on severity of dermatitis, the location and surface area of the affected skin, and the age of patients. Long-term use of topical corticosteraid may cause side effects including skin atrophy. The new class of topical calcineurin inhibitors (tacrolimus and pimecrolimus) that have been recently introduced with a safe and effective option for the long-term control of atopic dermatitis.

Allergy In Thailand

Allergy was introduced to Thailand only 50 years ago. At the beginning few doctors were interested allergic disease, and few research works on allergic diseases were published in medical journals. Fifteen years later, many Thai allergists and immunologists who finished their studies from the United States, Europe and Australia formed allergy and immunology group to exchange knowledge among the members. A society was officially formed on April 4, 1984 under the name of "The Allergy and Immunology Society of Thailand." Then the society launched an international medical journal of "Asian Pacific Journal of Allergy and Immunology" on June 1983 and was distributed worldwide. The society also hosted "The First Asian Pacific Congress of Allergology and Immunology" on November 22-26, 1992 with more than 1,100 participants from 30 countries attended. Now there are more than 700 members of our society. At the present time, most medical schools in Thailand have arranged a formal 2-year training program on allergy and immunology for certification of Thai Board of Allergy and Immunology under Thai Medical Council. The number of certified allergists has been tremendously increased. Allergy centers in medical schools are active in teaching, researching and providing care for allergic patients. In 2007, the society will host of "The World Allergy Congress" in Bangkok.

SUMMARY

Allergic diseases have been recognized for a long time. Stepping stones in understanding in etiology, basic mechanism of diseases, diagnosis and treatment were

discovered by thousands of scientists and physicians. The field of allergy will be rapidly growing in both basic

and clinical sciences to improve the care of allergic patients in the future.

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