INTRODUCTION

This lecture focuses on the diagnosis of IgE-mediated allergy. It is important to define and understand the terms:

- Atopy refers to IgE hypersensitivity or hyperresponsiveness and represents a predisposition to allergic diseases.
- Allergy, by contrast, refers to the clinical expression of atopic IgE-mediated disease (Fig 1).

Therefore atopic individuals may or may not have clinical symptoms (Fig 2). Some individuals are atopic whereas only a proportion has allergic diseases.

Allergic diseases peak at different ages (Fig 3). Food allergy and atopic eczema are predominant in early childhood (0-24 months) whereas asthma shows a biphasic peak, and rhinitis peaks in the 2 or third decade.

Allergic diseases are manifest as intestinal (GI) tract. This hyperresponsiveness may have both IgE-mediated and non-IgE-mediated components (Fig. 4). The situation is further complicated because allergen exposure in allergic subjects may increase target organ hyperresponsiveness, which results in exaggerated symptoms on exposure to nonspecific irritants (tobacco smoke, changes in temperature, etc.) in allergic subjects. Furthermore, increased nonspecific responsiveness lowers the threshold for symptoms on subsequent allergen exposure (Fig. 5).

Diagnosis of IgE-mediated allergy depends on the history and results of skin tests or radioallergosorbent (RAST) tests, which are occasionally supplemented by a therapeutic trial of avoidance of the suspected allergen or provocation testing in the target organ.

ALLERGY HISTORY

Before taking an allergy history, a professional but friendly manner, the early establishment of eye contact, and the avoidance of extraneous distractions should put patients at their ease. The history need not be time consuming although patients should be allowed to give their own accounts of symptoms followed by structured prompts or questions to cover points listed in Figure 6.

It has been showed that standardized questions put to the parents of children (aged 1-17 years) by a trained interviewer were highly predictive (Fig 7).
PATIENT'S ACCOUNT - The frequency and severity of symptoms, as well as the dominant symptom, should be established. For example, if nasal watery discharge is accompanied by nasal and palatal itching and associated eye symptoms, this is highly suggestive of allergy and a history of potential allergic triggers, e.g. pets, pollen, and house dust mites. Patients with mite-sensitivity may complain of immediate symptoms during activities such as bed-making, dusting, and vacuum cleaning. The symptoms are frequently worse on entering damp, older buildings, and better when the subject is outside, particularly in dry areas.

Are symptoms worse on exposure to pets? First, confusion may arise when there are several pets. Also the absence of known contact with pets does not exclude sensitization to animals or symptoms on exposure. It has been shown that high levels of the major allergens of cat and dog on the chairs and desks in schools but not on the floors. This suggested contamination from the clothes of children who owned pets.

Seasonal pollenosis is usually evident from the clinical history although it will vary according to geographic areas (Fig. 8). Within the US, tree pollen is predominant in March and April, and grass pollen peaks in June and July; weed pollens are most prevalent in late summer and fall, and molds during the late summer and fall months.

Allergic versus nonallergic triggers - Patients with inhalant allergies from whatever cause develop hyperresponsiveness in the target organ. Certain features in the history may point to either allergic or nonallergic triggers as the dominant causes of symptoms (Fig. 9). In general, allergen-induced symptoms require a period of sensitization (the latent interval). They may occur at very low allergen concentrations and affect only a proportion of exposed and sensitized individuals; symptoms may be ‘early’ (i.e. from minutes to 1-2 hours) or ‘late’(3-24 hours).

QUALITY OF LIFE - It is important to assess the impact of allergic symptoms on the patient's lifestyle, e.g. impairment of work, time off work (or school), interference with leisure activities (including sports and hobbies), and sleep disturbance.

FAMILY HISTORY - A personal and family history of asthma, rhinitis, eczema, or food allergy, or adverse reactions to drugs should be established in all cases. A history of allergens in the home should be obtained, including such details as pet ownership, presence of carpets, central heating, double glazing, and nature of soft furnishings in the bedroom and living areas (see Patient History Form, appendix A). Old, damp accommodation will favor the growth of house dust mite and molds. The effect of previous attempts at avoidance should be ascertained, bearing in mind that several months of vigorous environmental control or avoidance, or respiratory protection, may be required before any improvement may become apparent. Similarly, the response to pharmacological treatment including benefit and possible associated side-effects should be noted. Compliance with medication should be carefully assessed in every case, particularly where there has been an apparent poor response to treatment.

What is your main problem? It is often helpful to ask patients at the end of the interview to recap their main problem.
ALLERGY HISTORY - SPECIAL CASES

OCCUPATIONAL HISTORY - An occupational history should be obtained in all patients with asthma, rhinitis, and eczema (Fig 10). A knowledge of potential occupational causes is important. Symptoms tend to occur within the workplace or during the evening following work; they may improve at weekends and during holiday periods. The associated loss of self esteem, together with financial and social difficulties, may provoke symptoms of depressive illness and even suicidal tendencies. Moreover, symptoms may persist in up to 50% of cases for months or even years following termination of the occupational exposure. For these reasons an occupational cause should be established early and certainly not missed. A history of all occupations since leaving school should be obtained if a critical timing of exposure to a potential occupational sensitizer and onset of symptoms is not to be missed. Allergic contact eczema (Fig 11) may also result from common sensitizers in the home and workplace.

FOOD ALLERGY AND INTOLERANCE - The accurate diagnosis of food allergy is critically dependent on a good history. Up to 20% of the population may perceive food as a cause of their symptoms, whereas the prevalence of true food allergy is around 1-3%; food allergy tends to occur in highly atopic subjects with a strong personal and family history of allergies. A clear association between ingestion (or contact) with the food and symptoms may be elicited. Foods that commonly provoke symptoms: in children are eggs, milk, and peanuts; in adults they are fish, shellfish, fruit, peanuts, tree nuts, etc. (Fig. 12). Frequently, more than one organ system is involved; i.e. true food allergy is a rare cause of isolated asthma in adults, although severe food induced allergy may provoke asthma associated with other typical organ involvement, e.g. lip tingling, angioedema, nettle rash, nausea, and vomiting.

This is in contrast to the typical patient presenting with non-IgE-mediated food intolerance; the symptoms tend to be nonspecific or confined to one organ. There is often no clear history of provoking foods. Alternatively, atypical foods, such as yeast and wheat, are perceived to be involved, with no clear association between ingestion and exposure or delayed symptoms following ingestion. Such patients are either nonatopic or the symptoms occur independently of their atopic status; the latter patients, unlike those with typical food allergy, are unlikely to be highly atopic on the basis of their personal or family history, or via the detection of allergen-specific IgE on skin prick testing or RAST testing.

Non-IgE-mediated food-induced reactions may occur following the ingestion of preservatives such as salicylates, benzoates, and tartrazine. Common products containing preservatives include meat pies, sausages, cooked ham and salami, colored fruit drinks, confectionery, and wine (Fig. 13). No diagnostic tests are available and diagnosis depends upon the history and observation of the effect of exclusion diets and, where necessary, blinded food challenges.

Several clinically relevant cross-reactions may occur between certain inhalant allergens and foods (Fig. 14). A common example is oral allergy syndrome in patients with springtime hayfever (i.e. sensitivity to birch pollen) and oral itching and lip swelling on eating apples (particularly green apples), hazelnuts, and stone fruits (peaches, plums, etc.). Such reactions tend not to be severe and cooked fruits are well tolerated, indicating the
labile nature of the allergens responsible.

ANAPHYLAXIS - Anaphylaxis by definition (Fig. 15) may be life threatening. The differential diagnosis depends upon the history of provoking factors and, where possible, an eyewitness account should always be obtained. The differential diagnosis includes anaphylactoid reactions, syncope, and psychogenic reactions, as well as other medical conditions such as myocardial infarction, epilepsy, and metabolic or other causes of loss of consciousness. Also, airway obstruction due to a foreign body could be the cause.

EXAMINATION

SKIN - When rash is the presenting symptom, the entire skin, including hair and nails, should be examined. Individual lesions of urticaria may coalesce, are intensely itchy and, characteristically, last several hours (generally less than 24 hours).

Urticarial lesions that remain fixed, persist for longer than 24 to 48 hours, or leave a residual bruise, should raise the possibility of an underlying vasculitic cause. Dermographism is a common accompaniment of urticaria or it may be the only manifestation, and may confound the interpretation of skin prick tests. Urticaria is evident as raised irregular wheals usually on a red base; there may be associated subcutaneous swellings (angioedema). In view of the episodic nature of urticaria, examination results may be entirely normal.

NOSE - External examination of the nose may reveal a transverse skin crease, which is rare. Internal inspection of the nasal mucosa may reveal the typical appearance of a pale, watery swollen bluish mucosa in allergic patients but only if symptomatic at the time of examination. Structural causes of obstruction should be excluded. The larynx should be examined in cases where there is associated hoarseness.

Examination - Physical examination is required for all patients, although the extent will be guided by the history (Fig. 16).

SKIN PRICK TESTS

Skin prick tests (SPTs) provide important objective information, although they must always be interpreted in the light of the clinical history. SPTs (or RAST tests) using an appropriate number of common allergens (for example, cat, dog, house dust mite, grass pollen, etc) may confirm or exclude atopy (Fig. 17, 18, 19).

SPTs, in general, tend to be more sensitive, whereas allergen-specific IgE measurements may be more specific. The reliability of skin test extracts will depend on their containing adequate concentrations of all major allergenic determinants. Extracts should be biologically standardized in order to avoid batch-to-batch variation, and manufacturers' advice on shelf life and storage (generally at +4°C) should be observed.

For routine clinical use the skin wheal is recorded as the mean of the
longest diameter and the orthogonal diameter, i.e. the diameter at 90° to the midpoint of the longest diameter, excluding pseudopodia. Results are compared with the negative control (allergen diluent). A positive test is 2 mm or more greater than the negative control. However, as mentioned above, a skin wheal 6 mm or more across is more likely to be clinically relevant, although this may not always be the case.

**General practice**
Whether or not skin prick testing should be performed routinely in general practice (Primary Care Physicians Office, PCP’s) remains a matter of debate. A study evaluated skin prick testing in children and adults in 320 patients in 16 general practices. The study involved two days' training in allergy, combined with instruction in skin prick testing with four common allergens (and positive and negative controls) followed by reinforcement on a further training day, including the interpretation of results. Participating nurses found that the technique was simple, relatively easy to incorporate into their routine assessment of new referrals to the asthma clinic, and acceptable to both adults and children. The procedure undoubtedly increased the nurses’ awareness of the role of allergy in patients’ asthma. An important finding was the value of negative results of SPTs, which excluded atopy in these patients and enabled the investigators to advise patients against inappropriate allergen avoidance measures. The nurses also found the visual illustration provided by positive results helpful to reinforce advice. At this time very few PCP’s perform SPT’s, however the trend is changing in favor of PCP’s performing SPT’s.

**IN-VITRO TESTS**

**Total IgE**
The concentration of total serum IgE is approximately 10,000 times less than that of serum IgG and therefore requires sensitive tests for its determination. About half of IgE allergic patients will have a total IgE within the normal range, and therefore the predictive value of the test is rather limited. However, as higher serum IgE levels are often seen in hyperreactivity diseases in which large parts of skin and mucosa are involved, an elevated total IgE should stimulate further investigations of allergen-specific IgE.

**Allergen-specific IgE**

*Immuoassays*
Determination of allergen-specific IgE in serum is made by radioimmunoassays (RIA), enzyme-linked immunosorbent assays (ELISA), or chemiluminescence methods, usually by specialized immunology or clinical chemistry laboratories. The best known test for allergen-specific IgE is the radioallergosorbent test (RAST) (Fig. 20). In this test, individual allergen extracts are chemically bound to plastic tubes or wells in a multi well plate. Any number or variety of allergens can be requested. A small aliquot of the patient's serum is added and any IgE specific for that particular allergen binds to the tube or plate. After
thorough washing, radiolabelled anti-IgE is added and, after a predetermined period of incubation, further washed and the radioactivity counted. In an ELISA, the anti-IgE is labelled with an enzyme capable of causing a quantitative colorimetric reaction with an added substrate. In chemiluminescence assays, the anti-IgE is labelled with a substance, such as luciferase, capable of emitting photons. The result is semiquantitative and expressed on an arbitrary scale with reference to a standard. The sensitivity of these techniques varies with the different extract systems, a high quality allergen extract and an optimal detection system being necessary to achieve high sensitivity and specificity.

For inhalant allergies, the sensitivity of the RAST system is 80% - 90% and the specificity is higher than that of the SPTs, often is greater than 90%. The advantages of RAST compared to SPTs are compared in Figure 1.24.

APPROACH

Allergy diagnosis it does not depend primarily on the clinical history and physical examination. In fact greater than 50% of patients that have been seen by PCP’s for allergies have been misdiagnosed. Patient history and physical examination, aided by objective tests of IgE sensitivity (either skin tests or serum IgE measurements), should be mandatory to answer the following questions:

- Is the patient atopic?
- Does allergy contribute to the patients symptoms?
- What are the clinically relevant allergens?

A diagnostic approach is presented in Fig 21. There should be a high index of suspicion for allergy in patients presenting with symptoms of asthma, rhinitis, or eczema, particularly if there is an associated personal or family history of other atopic disease. Whether or not allergy is suspected on the basis of the initial history, the clinical literature view is that a number of SPTs, and/or RAST, to common aero allergens (indoor and outdoor allergens) should be performed in the majority of patients to confirm or exclude atopy; a physical examination should also be included. When both the clinical history and results of SPTs or/and RAST are negative, one can exclude allergy with a high degree of confidence and no specific treatment for allergy is indicated. Similarly, when the history and tests are both positive, then allergen avoidance measures, and in selected cases immunotherapy, should be carefully considered for each individual patient.

Therapeutic trial of potentially time consuming and expensive avoidance measures (or the removal of a family pet) will depend on factors such as the disease severity, the requirement for pharmacotherapy, and the likelihood of successful intervention with either allergen-specific avoidance or immunotherapy. The importance of allergy educated and trained nurse in the clinic cannot be overemphasized (Fig. 22).
Fig 23

Diagnostic Approach to Allergy

- Asthma
- Gastrointestinal symptoms
- Eczema/urticaria
- Rhinitis

Positive
- Allergy history

Negative
- Allergy history

SPT/RAST

Positive
- Further SPT/RAST
- Target organ provocation
- Trial of diagnostic allergy avoidance
- Consider

Negative
- Tertiary referral
- Allergy diagnosis
- Review/repeat above
- Allergy excluded

Consider
- Allergen avoidance
- Immunotherapy

No allergy-specific treatment

Fig 22

The Specialist Nurse in the Allergy Clinic

- Skin prick testing
- Asthma education, self-management plans
- Spirometry and peak expiratory flow recording
- Checking inhaler technique, correct use of nasal sprays, and drops
- Advice on avoidance of allergens
- Instruction on self-administration of epinephrine
- Liaison with parents, school nurses, pharmacists, etc.
- Involvement in allergen injection immunotherapy