Hay fever

A REPORT OF THE ROYAL COLLEGE OF PHYSICIANS

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‘I am suffering from my old complaint the hay fever (as it is called). My fear is perishing by deliquescence. I melt away in nasal and lachrymal profluvia’.

Sidney Smith, 1835.

Hay fever means seasonal rhinitis—and in some cases conjunctivitis—due to pollen allergy. What a patient means by hay fever may however be different—that is, any form of rhinitis or conjunctivitis, whether seasonal or not.

The pollens which are responsible are all capable of eliciting an immunoglobulin E (IgE) antibody response. While grass pollens are the major cause, symptoms can also be provoked by tree, flower and shrub pollen. The type of pollen differs in different parts of the world. Ragweed and birch pollens are the main causes of seasonal allergy in the United States and Scandinavia respectively, but olive trees cause problems in Southern Europe, the prosopis tree in the Middle East, and Bermuda grass in many other areas.

Symptoms can be florid, with pronounced sneezing, tickling of the nose, watery rhinorrhoea or nasal blockage, and itchy watery eyes. There may be an associated pollen asthma. The condition usually begins in childhood or in early adult life but it can sometimes appear in older people. There is often an improvement or a complete remission in middle life but symptoms can disappear at any time. While grass pollen provokes symptoms mainly in June and July, patients who are sensitive to tree pollens start to complain in April, and shrub and flower pollens cause problems which can continue from summer to autumn.

The symptoms of perennial rhinitis are similar, but this condition occurs throughout the year and is more often associated with nasal obstruction. It may either be allergic (usually due to house dust mite or household animals) or non-allergic (often called vasomotor rhinitis).

Hay fever is common. Estimates of prevalence and incidence vary [1], but figures from the United States suggest a prevalence of childhood allergic rhinitis, both seasonal and perennial, of between 3.1 and 9% [1]. Of the population served by a London general practice, 2.2% regarded themselves as sufferers [2] but the accumulative frequency (those who have or have had hay fever) is probably nearer 10%. A prevalence of 15% was found in Danish medical students [3].

Between 1970 and 1981, the number of consultations for hay fever in general practice in England and Wales doubled from about 10 to 20 per 1,000 population [4]. Although this may in part reflect the improved prospects (or expectations) of treatment, there is some evidence to suggest that there may have been a true increase in prevalence in recent years.

Factors influencing the development of allergy

Hay fever is the commonest manifestation of the atopic state—atopy being defined as the development of specific IgE antibodies to inhaled allergens. In the UK, those allergens are most commonly grass pollen, house dust mite (Dermatophagoides pteronyssinus) and animal danders, usually cat or dog. As judged by a positive skin prick test or radioallergosorbent test (RAST) to one or more of these allergens, about a third of the population is atopic, but no more than one third of these subjects develop clinical allergic diseases such as rhinitis, conjunctivitis or asthma. Other factors must therefore influence the clinical expression of atopy. In keeping with this, the clinical features of hay fever can disappear without any loss of specific IgE. Symptoms also tend to become less severe with age.

The familial occurrence of both atopy and allergic disorders is well known. Of those with one atopic parent, about one in three develop allergy; this figure rises to about two in three if both parents are atopic.

Raised total IgE levels at birth appear to have a predictive value for development of allergies in later life [5]. Follow-up studies in Sweden have shown that neonatal exposure to allergen is also important, since the risk of developing allergy appears to be related to the month of birth, for example children born just before the birch pollen season and exposed to birch pollen in their early months are more likely to develop this sensitivity [6,7]. Seasonal influences on neonatal sensitisation have been confirmed in the UK for house dust mite and grass pollen allergy but these are not the only factors. Exposure to airborne pollutants in industrial areas and to cigarette smoke in the home also influence the development of allergic symptoms in babies and young children, and so does respiratory infection. This may be because damage to the respiratory epithelium allows greater access of inhaled allergens to the IgE producing plasma cells, but it
Pathogenesis of hay fever

Hay fever is an example of an immediate hypersensitivity (type I) reaction. Those who are affected produce IgE antibodies to pollen which attach through their cell binding (Fc) piece to receptors on the surface of mast cells. When pollen interacts with the antibody binding (Fab) portions of specific IgE antibodies which are sufficiently close together on the surface of the mast cell, the cell is activated and releases a variety of inflammatory mediators, which are either stored in granules in the mast cell or newly synthesised by the cell. Pre-formed stored mediators include histamine and chemotactic factors which attract neutrophils and eosinophils. In addition, platelet activating factor is newly synthesised, and through the metabolism of arachidonic acid in the cell membrane both cyclo-oxygenase products (prostaglandins) and lipooxygenase products (leukotrienes) are synthesised.

When an allergen such as pollen extract is insufflated into the nose of a patient with allergic rhinitis, the clinical response involves sneezing, a rapid increase in nasal secretions, and the development of congestion or obstruction, which can be measured as an increased nasal airway resistance. If the nasal secretions are collected and analysed, an immediate increase in the histamine level can be demonstrated [11] over and above the high baseline histamine levels which many of these patients show. Prostaglandin D2 [11] and leukotrienes B4, C4, D4, and E4 [12,13] are generated, and as a marker of the allergenic response there is a rise in kinin levels and a rise in tosyl-L-arginine methyl ester (TAME) esterase activity [11].

The release of inflammatory mediators produces a variety of effects. Histamine causes increased vascular permeability, capillary dilatation, increased secretions and smooth muscle contraction. Prostaglandin D2 also increases vascular permeability and contracts smooth muscle, as do leukotrienes C4, D4, and E4 (the slow-reacting substance of anaphylaxis) in a slower time scale. The leukotrienes also decrease peripheral blood flow and increase mucus production, and leukotriene C4 induces pronounced and prolonged nasal obstruction [13]. Leukotriene B4, which is produced in smaller amounts, has a powerful effect in attracting leukocytes and in causing inflammatory reactions. Kinins are generated outside the cell and, apart from their further vasodilator effect, contribute to oedema and stimulate nerves [14].

The leukotrienes and the prostaglandins, other than D2, are produced by a variety of other cells, and this is also true for platelet activating factor (PAF or PAF-acether). PAF is formed not only by mast cells, but also by neutrophils, monocytes and platelets. Its effect is to aggregate platelets which may also release histamine, and it attracts and activates eosinophils. While antigen-induced bronchoconstriction is probably caused largely by other mediators, PAF has the important additional effect of enhancing non-specific airway reactivity [15].

There may be an increased ability to produce inflammatory mediators in atopic subjects. Atopic white cells have been shown to have abnormal concentrations of fatty acids. Polymorphs and monocytes have increased levels of the main essential fatty acid, linoleic acid, and reduced concentrations of its metabolite arachidonic acid [16]. Since this is the precursor of both prostaglandins and leukotrienes, factors which affect arachidonic acid metabolism could be important. Dietary supplementation with unsaturated fatty acids such as eicosapentaenoic acid (EPA) in fish oil leads to their incorporation into membrane phospholipids in place of arachidonic acid and to the generation of mediators less potent than those derived from arachidonic acid itself, e.g., leukotriene B1 instead of B4 [17,18]. This may point to new therapeutic approaches.

Because of the complex interactions of mediators and chemicals, they do not only potentiate one another but, through the recruitment of other cells, lead to a considerable amplification of the overall response. The result is to produce oedema and congestion of the nasal mucosa, with mucus secretion and rhinorrhoea. There also appears to be a role for lymphocytes in allergic rhinitis. It is known that histamine cannot induce suppressor T cell function normally in allergic subjects [19,20], and this appears to be due to impaired production of histamine-induced suppressor factor by atopic lymphocytes. In allergic rhinitis, lymphocytes show an increased proliferative response to allergen, and this falls towards normal after hyposensitisation therapy (personal observation).

In addition to the immediate reaction which occurs within minutes and is short-lived, a late reaction occurs in up to 50% of patients [21] whose symptoms recur 2 to 11 hours after allergen challenge without re-exposure to allergen. Similar late reactions can be demonstrated in the skin after intradermal tests or in the lung after bronchial challenge. It has been suggested from studies on the skin that with a large enough dose of allergen all patients would develop a late reaction [22]. Indeed, the cumulative effect of natural exposure and late reactions to allergen throughout the pollen season may be important.
in the pathogenesis of hay fever. Whereas the immediate reaction is characterised by sneezing, rhinorrhea and nasal congestion, the dominant symptom in the late reaction is nasal congestion, suggesting that different mechanisms may be involved. Since the late reaction does not involve the release of prostaglandin D2 [23], it is possible that mast cells are not involved at this stage but that basophils may be responsible for the histamine released in the late reaction.

It is tempting to look for comparison between the late response in the nose and the late response following bronchial allergen challenge in asthmatics. There is insufficient evidence of the influx of neutrophils and eosinophils, or the other features of inflammation, which have become a recognised part of the late asthmatic response [24,25] but remain to be studied in hay fever. However, patients with allergic rhinitis do show evidence of activated eosinophils as has been demonstrated by chemiluminescence [26].

Migration of basophils and mast cells

It seems likely that in man, as in the rat, there are at least two distinct mast cell phenotypes [27] but clearly there are species differences. Distinction of mast cell subsets in man, and their distinction from circulating basophils, is likely to be important in the understanding of allergic disorders. A role for basophils in allergic rhinitis has been strongly suggested, but is still unclear, largely because of the difficulty in distinguishing cell types by staining techniques alone. Degranulation of basophil-like cells has been demonstrated in the nasal mucosa, and this fits with the pattern of mediator release into nasal secretions after antigen challenge. The basophil is the major metachromatic cell in nasal secretions and this cell is formalin-sensitive, in this respect resembling the rat mucosal mast cell. In nasal biopsies or scrapings, formalin-sensitive cells predominated [28,29].

During the ragweed pollen season, in ragweed allergic subjects, the peripheral blood basophil count rises, the number of circulating metachromatic cell-precursors falls and the number of formalin-sensitive nasal mast cells rises [30]. This suggests that mast-cell and/or basophil precursors traffic from the blood to the nasal mucosa. This has been confirmed in several studies, despite the use of varying criteria for identifying different cell types.

A rise in the numbers of mast cells in the nasal mucosa has been reported during the grass pollen season [31]. Other studies suggest there is little change in the total number of nasal mast cells, but mast cells seem to migrate during the pollen season from the connective tissue to the more superficial layers of the nasal mucosa, from which they can be recovered by surface ‘imprints’, [32] and where they are likely to have better contact with the allergen.

Nasal anatomy and physiology

One of the functions of the nose is to heat and humidify inspired air. There is a high mucosal blood flow which is under neurological control but which can also change quickly in response to humoral factors. Large amounts of blood can be shunted through the arteriovenous anastomoses of the turbinates, by-passing the capillary bed, so that the degree to which air is warmed or cooled can be rapidly adjusted. Breathing tends to occur more through one nostril and then the other, and there are cyclical changes in airways resistance between the two nostrils, controlled by a varying degree of engorgement of the cavernous sinusoids in the turbinates. Enlargement of these vessels probably also contributes to the nasal congestion in allergy, which, contrary to common belief, has nothing to do with muscle spasm. (In contrast to the bronchi, there is no smooth muscle in the nose.)

The nose filters large volumes of air each day, and most of the large particles (>10 µm) are impacted and do not pass through. These particles include pollen grains 15–30 µm in diameter, which also impact on the conjunctiva. When nasal obstruction develops, this filtering effect is lost and there is a switch to mouth breathing which may be harmful not only because more particles reach the lungs but also because bronchial heat loss may occur. Inhaled particles trapped in the nasal mucosa are cleared quickly by muko-ciliary transport which takes them backwards towards the pharynx where they are swallowed. Soluble protein is, however, eluted from some particles (e.g. pollen grains) sufficiently quickly to pass through the basement membrane and be presented to lymphocytes.

Bronchial reactivity in allergic rhinitis

Most patients with seasonal allergic rhinitis do not have clinical asthma but have an increased bronchial reactivity during the pollen season as shown by an increased bronchoconstrictor response to a challenge with methacholine or carbachol [33,34]. Furthermore, patients with pollen rhinitis who also have an associated asthma tend to develop asthmatic symptoms later in the season than their rhinitis, suggesting that they may be responding to repeated exposure to allergen. The implication of these findings is not clear, but it is known that patients with allergic asthma who are challenged with antigen develop not only bronchoconstriction but also a non-specific increase in bronchial reactivity which may last for several days. The repeated generation of increased non-specific bronchial reactivity could thus be important in this process. In addition to the observed increase in non-specific sensitivity in the lung, it is possible that there may be similar changes in non-specific reactivity in the nose. In keeping with this, many patients with allergic rhinitis have an increased susceptibility to irritants such as smoke or dusty atmospheres.

Clinical features

The diagnosis of hay fever can nearly always be made on the history alone, aided by a knowledge of the season for different allergens. Skin prick tests or laboratory tests for specific IgE antibodies can be used to confirm the clinical diagnosis but are often not essential. While the most usual complaints are sneezing, watery rhinorrhea and nasal obstruction, some patients with
hay fever also have conjunctivitis and a few have conjunctivitis alone. Nasal congestion can range in severity from mild nasal stuffiness to complete nasal obstruction, with mouth breathing. Those who have eye problems complain of itching, redness, grittiness or watering of the eye and in more severe cases can develop conjunctival oedema with blistering or even keratitis, ulcerative blepharitis, and inflammatory changes in the tarsal plate (vernal catarrh) [35]. Patients may also complain of itching of the palate, pharynx or external auditory meatus. Asthma can occur and is often undiagnosed. This may be because the symptoms are mild, but patients often do not volunteer symptoms such as cough or exercise-induced wheeze if it occurs only in the pollen season. Highly sensitive individuals may develop urticaria on contact with the allergen, eg around the ankles after walking through grass.

Examination reveals nasal mucosal hypertrophy with watery nasal secretions, and there may be signs of conjunctivitis or of more severe eye problems.

Patients with an isolated pollen allergy lose their symptoms when the pollen season ends, but multiple allergies are common and not infrequently patients with a perennial rhinitis (eg due to allergy to house dust mite or cats) also have a seasonal exacerbation due to pollen allergy. In the United Kingdom, tree pollens occur in the spring (with a peak in March and April, although some occur in early May). The grass pollen season extends from about mid-June (or earlier in the south) to late July, but it varies with the location and climate. Flower and shrub pollens appear later in the summer, usually after the grass pollen season. Thus, a patient with grass pollen allergy, the most common type of hay fever, has symptoms in June and July, tree pollen allergy occurs in March to April, and a patient sensitive to tree, grass, weed and flower pollens could have symptoms from March to September.

There is a broad correlation between hay fever symptoms and pollen counts, but symptoms do not usually begin until the pollen count rises above the initial, very low level. Even in the most sensitive patients symptoms due to grass pollen allergy (as opposed to pollen counts) rarely begin before the end of the first week of June and patients with less severe forms of hay fever may only have symptoms for 2-4 weeks of a 6-week pollen season. Studies from St Mary’s Hospital in central London show that by the time the grass pollen count reaches 50 grains per cubic metre, all those who are going to develop symptoms will have done so (Dr R. R. Davies, personal communication). However, asthma symptoms tend to appear late in the season.

Although the symptoms of hay fever are often trivial, they can be distressing and interfere with concentration or efficiency at work or at school. Diagnosis and effective treatment is therefore important.

**Confirmatory tests**

Specific IgE antibodies to pollen can be detected either by skin prick tests or by radioallergosorbent test (RAST). Skin prick tests are simple, cheap, quick, and can be carried out with very little initial training. An aqueous solution of allergen extract is pricked into the skin with a stylet, and the appearance of a wheal and flare within 10-15 minutes indicates that allergen has bound to the relevant IgE antibody on the surface of cutaneous mast cells and so triggered histamine release. A number of allergens can be tested simultaneously and the test provides an answer while the patient is still in the clinic. A new dry skin prick testing system is available, using lancets with tips coated with allergen, which may be more convenient for doctors who normally test only a small number of patients. The RAST measures specific IgE in the serum and its results correlate well with the results of skin tests. It is expensive, time consuming, and requires good laboratory facilities but can be helpful if skin tests are not available or require corroboration. They are also useful in patients who have extensive skin disease or who are taking drugs which might impair the skin response.

These tests indicate atopy, and only a proportion of atopic subjects develop clinical allergy. The tests should therefore be interpreted only in conjunction with the history and are never, by themselves, an indication for treatment. Contrary to popular belief, the severity of symptoms in allergic rhinitis does not relate to the titre of specific IgE [36]. Since specific IgE levels can be raised without a rise in the total IgE level, measurement of the total IgE level is of no value in excluding allergic rhinitis.

Skin tests or RASTs are not essential to the diagnosis of hay fever except in the rare case in which hyposensitising injections are contemplated. They are much more helpful in patients with perennial rhinitis, where on the history it can be difficult to distinguish allergic from non-allergic causes or to be sure if there is a seasonal exacerbation. They are also helpful in patients who are uncertain about the timing of their symptoms or the circumstances in which exacerbations occur. The value of precise identification of the allergen(s) is two-fold. The introduction of topical preparations or antihistamines is most effective at the onset of symptoms, and if the allergens are identified the patient can be warned when to expect symptoms to begin. Secondly, it is possible to reduce the exposure to some allergens, particular flowers or trees, once the allergens are known. Even in the case of grass pollen, sensible measures can result in some reduction in exposure.

**Treatment**

**Allergic rhinitis**

The established treatments for hay fever—oral antihistamines and topical corticosteroids or sodium cromoglycate—have all been compared extensively with placebo and shown to be effective.

**Steroids.** Steroids inhibit mediator release by interfering with the conversion of phospholipids to arachidonic acid and PAF. They have potent anti-inflammatory effects and cause vasoconstriction and reduced permeability of mucosal capillaries. Although they have traditionally
been shown to block only the late phase reaction on allergen challenge, more recent work shows that following several weeks of treatment the immediate reaction can also be blocked. This may be due to effects on mast cell recruitment and differentiation.

Topical steroids are highly effective in the treatment of allergic rhinitis. In normal dosage systemic absorption is extremely small and of no clinical importance. A variety of nasal sprays are available: beclomethasone dipropionate (Beconase), flunisolide (Syrantis) and budesonide (Rhinocort). Beclomethasone is the most widely studied, and there seems little to choose between beclomethasone and flunisolide; both have been found to have comparable effects in a number of clinical trials [37]. The propellant in aerosols occasionally causes sneezing, but this can be overcome by the use of aqueous preparations.

Systemic steroids should be avoided, but very disabling symptoms occasionally justify their use for short periods, for example in students taking important examinations.

**Sodium cromoglycate.** Although sodium cromoglycate is said to be a mast cell stabiliser, the mechanism of action of this drug in immediate hypersensitivity reactions remains unclear. It is a weak mast cell stabiliser in vitro and drugs which are more potent in this respect have been found to have negligible therapeutic efficacy. It has been suggested that it may work by inhibiting the activation of inflammatory cells such as eosinophils or by neural effects. Topical sodium cromoglycate is available in a variety of formulations for the nose (Rynacrom), and aqueous preparations cause less irritation than the powder. In studies comparing nasal steroids and cromoglycate, steroids are generally found to be superior [38,39] although some show equal efficacy. A recent study showed beclomethasone aqueous suspension and flunisolide to be more effective than cromoglycate in the treatment of ragweed rhinitis. It also demonstrated that all these nasal treatments considerably reduced the symptoms of seasonal asthma [40].

**Antihistamines.** Antihistamines act as H1 receptor antagonists and influence only the histamine mediated component of the type I reaction. This however is important in seasonal rhinitis. The usefulness of these drugs has been increased by the introduction of two non-sedative antihistamines, terfenadine (Triludan) and astemizole (Hismanal) which cross the blood-brain barrier to only a minimal extent. Other non-sedative antihistamines are being developed and acrivastine (Semprex) and cetirizine (Zirtek) have recently been marketed. It should be remembered, however, that the older antihistamines such as chlorpheniramine maleate (Piriton) cause sedation in only a proportion of patients, are more effective in some, and are much cheaper.

Astemizole has a slow onset of action over about seven days and, because of its long half-life, its effects may persist for up to four weeks after withdrawal of the drug. The effects of terfenadine are of rapid onset and shorter duration than astemizole, and this is more appropriate to the intermittent or short-term use which is often required in the management of seasonal rhinitis. Both are equally efficient, although a recent study suggested astemizole gave better control of hay fever symptoms [41]. In a comparative study of astemizole tablets and beclomethasone nasal spray, both treatments were equally effective in the treatment of the rhinitis but astemizole was superior in the control of eye symptoms [42]. However, intranasal steroids are often effective in relieving mild allergic conjunctivitis and this has been confirmed in a formal study [40].

**Nasal decongestants.** Nasal obstruction is the most difficult symptom to treat and, if marked, interferes with the efficacy of topical steroids, since they can only be delivered to a reduced area of mucosa. In such patients, it can help to prescribe a nasal decongestant (phenylephrine or oxymetazoline) in addition to a topical nasal steroid for the first four days. Prolonged use of decongestants should be avoided because such use can lead to rebound congestion.

**Allergic conjunctivitis.**

If treatment is required for allergic conjunctivitis, sodium cromoglycate eye drops or oral antihistamines should be used. The cromoglycate eye drops can cause initial stinging, and better results are obtained when they are introduced early, before the eyes become very inflamed. Severe problems may require steroid eye drops which should be given for as short a period as possible. Once severe conjunctivitis has been controlled, it is preferable to use cromoglycate eye drops for maintenance therapy. Patients who have more complex eye problems, or who need to use steroid eye drops for more than three months, must be reviewed by an ophthalmologist. The long-term use of steroid eye drops carries an increased risk of glaucoma and patients should have their intraocular pressure measured if they are receiving this treatment.

**Approach to drug selection**

Many patients will have tried antihistamines, some of which can be bought without prescription. A reasonable approach may therefore be to start with a nasal steroid preparation, since this works in the majority of patients (Fig. 1). This also has the advantage of being preventative and of blocking the late reaction. The technique for their proper use and the need for regular (prophylactic) therapy must be explained to the patient. Alternatively, cromoglycate may be more useful in a minority of patients, especially those who complain of nasal soreness or of nosebleeds while using steroids.

Antihistamines are often more helpful than nasal sprays in patients with troublesome symptoms at multiple sites, for example itching of the palate, pharynx or ears or conjunctivitis, and may be preferred to cromoglycate in those for whom the use of steroids is limited by side effects.

**Reducing exposure to allergen**

Clearly, it is not possible to avoid exposure to airborne allergens, such as pollens, but some knowledge of the
Figure 1. Plan for drug treatment of hay fever.

- Rhinitis ± mild conjunctivitis
  - Rhinitis + troublesome conjunctivitis
    - Nasal corticosteroid + SCG eyedrops
    - Antihistamine
  - Severe conjunctivitis
    - Corticosteroid eyedrops (short course)
    - SCG eyedrops and/or antihistamines
      - if ulcerative changes or keratitis
      - Ophthalmologist
  - Itching pharynx or ears
  - Asthma
    - Inhaled selective β2 agonist
      - if regular use

- Nasal corticosteroids or Antihistamines* or Nasal SCG
  - control severe failure due to excess secretions aerosol causes sneezing
    - Combination therapy Powdered SCG Aqueous corticosteroid

* = non-sedative, if necessary
SCG = sodium cromoglycate
factors determining pollen counts can lead to ways of reducing allergen exposure. Large cities, such as London, can be viewed as concrete islands in a sea of grass. The irregular buildings cause turbulence and the wind usually blows pollen over the tops of buildings. Within a city, pollen counts are highest in parks and open spaces and much lower in built-up areas, but the counts at the top of a building (eg 25 m above street level) are much higher than those at street level. A patient at an open window at the top of a tower block is therefore exposed to more pollen than at street level. Patients with hay fever should avoid parks, and close car windows when driving through the countryside.

The pollen count also varies with the time of day, and the mean daily counts mask peaks and troughs which occur during the day. Windows should be opened in the early morning when there is little pollen, and shut by midday as the concentration of grass pollen rises in the afternoon and evening; by midnight there is little pollen left in the air.

The June peak pollen counts fell between 1961 and 1980 in the UK, suggesting there is now less pollen in the air. This probably reflects changes in agricultural practice. Different species of grass produce different amounts of pollen, the most prolific pollen producer being cocksfoot (Dactylis glomerata). Cocksfoot has now disappeared from the grass seed mixture planted by farmers and has been replaced mainly by rye grass, a lower pollen producer. Many farmers also cut some of their grass early, in May, before flowering occurs, to make grass silage, thus further reducing the pollen production. However, these changes in peak pollen counts would only modify symptoms for short periods during the pollen season.

**Hyposensitisation or allergen immunotherapy**

Hyposensitisation or allergen immunotherapy consists of a series of injections of allergen extract(s) given over months or years, with the aim of reducing the patient’s sensitivity to that allergen. This type of treatment has been widely used since it was first initiated by Noon in 1911, but although there is good evidence that it can be effective [43,44] there is still controversy over the circumstances which favour effective immunotherapy without the risk of anaphylaxis. Practice varies considerably in different countries, and the role of immunotherapy has been reviewed by the European Academy of Allergology and Clinical Immunology [43]. The mechanism by which hyposensitisation achieves its effect is not clear. The production of IgG (so-called ‘blocking’) antibody may prevent the allergen binding to IgE on mast cells. This seems to be a factor in bee venom immunotherapy, in which hyperimmune serum given together with allergen can inhibit the development of adverse reactions during immunotherapy [45,46]. However, the titre of IgG antibody induced by immunotherapy does not always correlate well with clinical improvement. Other effects may therefore be important. IgE antibody levels often fall late in treatment and this may reflect the induction of antigen-specific suppressor T cells [47]. There is, in addition, a reduced lymphocyte proliferative response to allergen (personal observation). Immunotherapy has also been shown to reduce the late asthmatic reaction [48,49] and abolish the generation of eosinophil and neutrophil chemotactic activity [50,51], effects compatible with blocking of mast cell activation, or possibly with alteration of T cell responsiveness.

The best results of hyposensitisation are seen in the treatment of bee sting allergy [52], and there is some evidence of efficacy in grass, ragweed and birch pollen allergies [43,53,54]. There are however problems with many of the investigations carried out: the allergen extracts used have often been crude and unstandardised, patients vary in their sensitivity, and most studies are fairly short term. Furthermore, fatalities, although rare, have occurred, mostly when treatment has been inappropriately given by relatively inexperienced staff. This has prompted the Committee for Safety in Medicines to issue guidelines on hyposensitisation which effectively preclude its use in general practice and, by recommending a two-hour observation period after each injection, make it difficult to carry out even in hospital [55].

Despite these problems, it is clear that this form of treatment can be effective. The availability of safe and effective drug treatments, such as topical corticosteroids, however, makes them the preferred first-line therapy. While hyposensitisation should not often be considered, it may be indicated in a small number of carefully selected patients. In deciding whether to use hyposensitisation, one must balance the variable degree of efficacy against the risk of allergic reactions, which can range from local swellings to generalised reactions including angioedema, laryngeal oedema, asthma or anaphylaxis. There is a greater risk of serious reactions in patients with a history of asthma. Hyposensitisation should therefore only be carried out by doctors experienced in its use or by trained staff who are directly supervised by a doctor. Further doses should be delayed or reduced after an intercurrent infection, a recent exacerbation of asthma or rhinitis, or an adverse reaction to a previous injection.

There is evidence to suggest that efficacy, but also risks, increase if larger doses of allergen are given [56,57]. The choice of extract may therefore be important and, in very sensitive subjects, starting doses should be low. Pre-seasonal hyposensitisation has traditionally been given for pollen allergy, often for three consecutive seasons, although this is based on anecdote, and treatment for at least three to five consecutive seasons is recommended by the WHO/IUIS Committee. Perennial hyposensitisation for a seasonal allergy is likely to be more effective.

There are not many studies comparing hyposensitisation with drug therapy, but a recent study found an alum adsorbed grass pollen preparation (of only moderate potency) to have the same effect as topical sodium cromoglycate [58]. It is of interest, although not of statistical significance, that the only patients to become symptom-free were in the hyposensitisation groups.

The future of this method of treatment remains uncertain, but with the identification of some of the major allergens a number of new preparations for hyposensitisation are being developed. It is likely that improved preparations, which are both safe and effective, will
become available and that this therapy will remain an option for those with severe symptoms who do not respond to drug therapy.

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