Chapter 7: Mechanisms and treatment of allergic rhinitis

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Definition and prevalence

Allergic rhinitis is an IgE-mediated hypersensitivity disease of the mucous membranes of the nasal airways characterized by sneezing, nasal blockage and discharge. Conjunctivitis and bronchial constriction often accompany these symptoms. Allergic rhinitis is mostly found in association with exposure to aeroallergens. A similar syndrome is occasionally observed in a minority of susceptible individuals following ingestion of certain foods, but an immunological basis for these reactions is as yet to be established. Allergic rhinitis is either seasonal (for example summer hayfever) or perennial. Perennial rhinitis with severe seasonal exacerbations is common.

The disease is extremely common and affects approximately 10-20% of North Americans and between 10 and 15% of north Europeans. Perennial rhinitis is probably more common in adults than children. There are several excellent reviews on the subject (for example Wassermann, 1982; Norman, 1985).

Immunopathology

Immunoglobulin E

Immunoglobulin E (IgE) (see Geha, 1984) has the unique property of binding reversibly to high affinity receptors on mast cells and basophils. The interaction of antigen with cell-bound IgE initiates the secretion of pharmacologically active substances that cause clinical manifestations of immediate hypersensitivity.

IgE is composed of two heavy chains (epsilon) and two light chains (kappa or lambda). The immunoglobulin classes are depicted diagrammatically. The intact molecule has a molecular weight of 188,000 with the heavy and light chains being of molecular weight 72,500 and 23,000, respectively. The sedimentation coefficient is 11S and the carbohydrate content of the molecule is 12%. IgE is heat labile. Heating for 2 hours at 56°C destroys its capacity to interact with Fc receptors but not its allergen-binding capacity.

IgE receptors with a high affinity have been identified on mast cells and basophils and tentatively termed 'Fc-epsilon1'. Low affinity receptors, apparently antigenically distinct, are present on subpopulations of T and B lymphocytes, monocytes and macrophages, eosinophils and platelets. The low affinity receptors have been tentatively termed 'Fc-epsilon2' (Capron and Capron, 1987).

Extensive work in rats has clearly shown that the development of an IgE response is dependent on T lymphocytes, cooperation between T and B lymphocytes, with regulation of IgE synthesis by a number of T-cell-derived soluble factors. It has been suggested that a defective suppressor T-cell function may underlie the atopic state in man, especially as a number of diseases with impaired thymus-dependent immunity have markedly elevated levels of IgE.
It has been shown in the rat that there are IgE potentiating and suppressing factors (Ishizaka, 1984). This isotype-specific regulation of IgE involves the conversion of virgin B cells bearing surface IgM to IgM-IgE double-bearing cells that are the precursors of IgE-forming cells. IgE-bearing memory B cells develop from these precursor cells after antigenic stimulation. These, in turn, form IgE-forming plasma cells. These various steps are regulated by T cells and their products. The scheme, worked out largely in mice and rats, has identified distinct IgE regulatory T cells which bear receptors for IgE. These receptors are shed and have the capacity to bind to IgE receptors on memory B cells. These Fc-epsilon associated binding factors are, if glycosylated, IgE potentiating factors but, if non-glycosylated, they are IgE suppressor factors. Glycosylation is dependent on the IgE regulating the T cell being influenced by either a glycosylation enhancing factor or glycosylation inhibitory factor. These in turn are derived from T-cell subsets with the production of glycosylation enhancing or inhibitory factors being determined largely by the nature of the adjuvant. For instance, aluminium hydroxide favours the secretion of glycosylated IgE helper factor, whereas complete Freund's adjuvant favours the secretion of non-glycosylated IgE suppressor factor.

Comparatively little is known about the regulation of IgE biosynthesis in man, although the data obtained so far are compatible with those from experimental animals. Normal peripheral blood lymphocytes do not synthesize IgE in vitro, whereas lymphocytes from atopic individuals spontaneously synthesize IgE with large amounts being observed during the season of grass or ragweed pollen. It has been shown that IgE-specific helper T cells reside within the CD4 subpopulation of T cells and secrete a glycoprotein which has an affinity for IgE and which enhances IgE synthesis by IgE-bearing cells. Conversely, there appears to be a suppressor T cell which predominantly resides within the CD8 subpopulation of cells which suppresses IgE synthesis. Serum from normal non-allergic individuals contains a low-molecular-weight factor (mol wt of 15,000) which specifically suppresses IgE synthesis. Thus an IgE suppressor factor has been isolated in normal serum and IgE helper factors have been identified in serum and supernatants from cell lines of individuals with high IgE. These observations have clear implications for therapy.

IgE-bearing B cells are usually detectable by the eleventh week of fetal life although IgE production in utero is negligible. At birth, the concentration of cord blood IgE is less than 1 international unit (1 IU = 2.4 nanograms). Over 50% of newborn infants have no detectable IgE. In adults the concentrations peak between 10 and 15 years and then tend to be stable from 15 to approximately 50 years, thereafter decreasing with age. Elevated serum levels are found in association with various metazoan parasitic infections, allergic asthma, hayfever and atopic eczema. IgE levels tend to correlate with the degree of antigen stimulation. For instance, IgE levels in hayfever sufferers rise significantly during the pollen season.

Although IgE is not essential for the maintenance of health, there is evidence to suspect that IgE may play a role in immunity to helminthic parasites. It may also serve in a more general role by facilitating increased permeability to allow the accumulation of IgE antibodies, complement and phagocytic cells to the site of invading foreign antigens.

The 'cross-linking' hypothesis is generally accepted as the means whereby mediator release is initiated (Ishizaka and Ishizaka, 1984). Antigen molecules are thought to interact with two adjacent cell-bound IgE antibody molecules so forming a bridge composed of IgE-antigen-IgE. Mediator release will only occur if the allergen is divalent or polyvalent, since
neither haptens nor Fab fragments of anti-IgE will give rise to histamine release. In addition, histamine release can be triggered by antibodies to the receptor molecule so indicating that IgE antibodies act only as a method of cross-linking the receptor molecules. It is likely that cross-linking the receptors allows the formation of a calcium channel and that calcium influx triggers the events that lead to histamine release. There are other mechanisms for triggering histamine release which bypass the requirement for receptor molecules and cross-linking. These non-IgE triggering release mechanisms include lectins, Compound 48/80, and anaphylatoxins (fragments cleaved from the third, fourth and fifth components of complement). A number of intravenous anaesthetic agents, radiocontrast media and plasma volume expanders are also associated with non-IgE release of mast cell mediators. Their effect is possibly through anaphylatoxin formation through activation of the alternative pathway of complement.

Mediators

Mediator release initiated by dimerization of cell membrane-bound IgE molecules by specific antigen with subsequent cross-linkage of cell membrane IgE (Fc) receptors is a secretory process that results in the elaboration of preformed mediators contained within lysosomal granules and membrane-derived lipid mediators. The initial signal is stimulated by phospholipid metabolism and adenylyl cyclase activity in the cell membrane so generating di- and monoacylglycerol and arachidonic acid and converts adenosine 5'-triphosphate (ATP) to adenosine cyclic 3':5'-monophosphate (cyclic AMP), respectively. A component of this altered phospholipid metabolism may include phospholipid methylation (Ishizaka and Ishizaka, 1984). However, it is now considered that stimulation of the phospholipid cycle with alterations in the biophysical properties of the cell membrane is the factor responsible for exposing channels allowing the influx of calcium ions and the progression of the secretory response to the cell cytosol. In both rat and human mast cells, cyclic AMP-dependent transport of ions and water across the perigranular membranes partially solubilize the packaged mediators prior to their extracellular discharge. Diacylglycerol, generated in the membrane, activates protein kinase C which has the capacity to phosphorylate the light chain of myosin with subsequent contraction of thin filaments. With utilization of energy, translocation of the granule to the cell surface occurs where fusion of the perigranular matrix and plasma membrane exposes the granular matrix to the extracellular environment. Mediators are released from the partially solubilized granular matrix at different rates of ion exchange.

In parallel with the events leading to granule secretion, stimulation of membrane phospholipases (C and A2) generates increased membrane levels of lysophospholipids, diacyl- and monoacylglycerol which are membrane fusagens and a substantial amount of polyunsaturated fatty acid, arachidonic acid. Subsequent metabolism of arachidonic acid by the cyclo-oxygenase pathway generates predominantly prostaglandin D2 (PGD2), while the lipo-oxygenase pathway generates leukotriene B4, a chemotactic factor, and leukotrienes C4 and D4 which constitute the biological activity previously recognized as the slow-reacting substance of anaphylaxis (SRS-A). Thus the non-cytotoxic secretory process of the mast cell is similar to that observed in exocrine and endocrine cells, but is unique in the specificity of the immunological stimulus which initiates coupled activation-secretion and in the spectrum of preformed and newly formed generated mediators which characterize the immediate hypersensitivity reaction.
Mast cells have been located interepithelially, although the largest numbers are observed in the submucosa. Basophils are often found in blown secretion from patients with rhinitis. Thus water-soluble allergens which are readily leached from air-borne particles would be free to interact with IgE-sensitized mast cells (and basophils) which, in turn, lead to the release of pharmacological mediators of hypersensitivity. These pharmacological agents include histamine, leukotrienes C₄, D₄, E₄ and B₄, kinin-like activity, prostaglandin E₂ and tosylarginine methyl ester esterase (TAME-esterase) activity (Naclerio et al, 1986). Rapid release of mediators from cells located in the epithelium or found free on the nasal mucosa would lead to increased permeability by the opening up of epithelial tight junctions so allowing allergen access to deeper mast cells. In fact symptoms, that is sneezing, occur within one minute when sensitive patients undergo nasal challenge. A number of mast cell or basophil-derived mediators have been detected in nasal secretions after challenge with appropriate allergen.

It has been shown that basophils are often present in blown secretions from allergic subjects, and mast cells have been observed from scrapings from the same patients. It was concluded that, during the pollen season, basophils migrate through the surface epithelium to the airway lumen whereas mast cells migrate only into the epithelium. The increase in epithelium mediator cells after allergen provocation and during the pollen season was associated with successful immunotherapy and corticosteroid treatment.

Before the importance or otherwise of a biochemical or pharmacological mediator can be established in the pathogenesis of disease, it must be able to evoke the symptoms, be detected in pathological fluids, and specific antagonists should ameliorate or modify the symptoms of the disease.

**Histamine**

Instillation of histamine into the nose produces immediate itching followed by sneezing, nasal discharge and blocking (Mygind, 1982). Thus the symptoms are very similar to those produced by allergens in the sensitized subject. It should be noted that allergen provocation, unlike histamine provocation, results in infiltration of inflammatory cells, particularly eosinophils, and heightened nasal reactivity. Small amounts of histamine can be identified in nasal washings after allergen challenge. Selective H₁ antagonists such as astemizole (Hismanal) inhibit sneezing and watery discharge but not nasal blockage.

Unilateral histamine provocation of the human nose causes a marked homolateral blockage, but only a short-lasting and insignificant challenge of contralateral nasal patency indicating that a direct histamine effect on blood vessels, and not reflex activity, may be important for any persistent nasal blockage in allergic rhinitis. Histamine affects the vascular tube by both H₁ and H₂ receptors resulting in dilatation of some, and constriction of other blood vessels and oedema formation. Histamine has a fairly weak H₂ mediator effect on mucous glands and appears to increase mucous glycoproteins without significantly affecting the total volume of nasal discharge. Thus the inability of ordinary histamines and the new selective H₁ antagonists to deal with nasal blockage in allergic rhinitis could be due to the presence of H₂ receptors in nasal vasculature. Combined use of H₁ and H₂ antagonists in the nose only partially prevents histamine-provoked vascular changes. Thus the effects of histamine are complex. Although there is slight bilateral blockage, there is considerable
bilateral hypersecretion after histamine instillation which is stimulated through H₂ receptors. Thus sneezing and a large part of mucus secretion appears to be reflex mediated.

Reports on the instillation of leukotrienes into the nose have been fragmentary although leukotrienes C₄, D₄, E₄ and LTB₄ have been identified in nasal washings after allergen but not methacholine challenge. The sulphidopeptide leukotrienes cause hypersecretion of mucus as well as constricting smooth muscle. They also dilate the vasculature, but it is unknown which part of the nasal vasculature is affected by these lipid mediators. LTB₄ is a powerful chemoattractant for neutrophils and, to a lesser extent, eosinophils. Studies on the effects of selective leukotriene antagonists in rhinitis have not yet been forthcoming. PGD₂ was observed during the early, but not late, phase reactions suggesting that basophils may be involved in the late phase reactions since PGD₂ is not derived from this cell type (see below). However, aspirin, a cyclo-oxygenase inhibitor which would prevent PGD₂ formation, is of no proven value in the treatment of allergic rhinitis and in an appreciable portion of individuals actually causes rhinitis symptoms. Thus the role of PGD₂ must remain unclear.

High-molecular-weight neutrophil chemotactic activity has also been identified in nasal washings from grass-pollen-sensitive patients challenged with aqueous extracts of pollen antigen. Kinin-like activity has been observed in nasal secretions but the significance of this observation is unclear. An enzyme which hydrolyses TAME-esterase has also been observed.

Late-phase reactions have been most extensively studied in the lower airways, but have also been reported in the nose and skin (Kay et al, 1984). Following the immediate reaction, a proportion of individuals will have a late-phase reaction developing 3-11 hours after the immediate response. The late-phase reaction is generally considered to be the result of infiltrating inflammatory cells since local accumulation of neutrophils, eosinophils and basophils is well documented.

Other immunoglobulins

Allergic rhinitis is associated, not only with allergen-specific IgE, but also with the presence of IgG and IgA antibodies in serum from untreated patients (Platts-Mills, 1982). IgE antibodies to a single allergen represent as much as 50% of the total IgE. The majority of sera from patients with hayfever contain less than 0.1 microg of IgE antibody to pollen allergens per mL. Using antigen-binding techniques, it has been possible to show that all sera contain detectable IgE antibody and detectable IgG antibody against the same allergen. The quantity of IgG antibody is on an average only three or four times greater than the IgE antibody. In sera from untreated patients, there is a good correlation between the IgG and IgE antibody responses. Most non-allergic individuals have no detectable IgG or IgE antibody. Generally speaking, none of the non-allergenic proteins in complex mixtures such as house dust induce IgG antibody responses in man. Thus, there is little doubt that, when antibody responses to inhalant allergens occur as a result of an actual exposure, the IgE and IgG antibody responses occur in parallel. It was further shown that IgG and IgA antibodies (in addition to IgE) are produced locally in pollen hayfever. It was suggested that the local response to pollen antigens in which the secreted antibody was produced was from mucosal plasma cells while the IgG and IgE antibodies in serum would derive from local lymph nodes (Platts-Mills, 1982). A possible model of the local immune response to pollen allergens was proposed in
which antibodies produced by plasma cells in the mucosa are predominantly secreted, whereas
the local lymph nodes are the main site of production of serum IgG and IgE antibodies to
pollen allergens.

Relationship of immunoglobulin concentrations to symptoms

Most non-allergic persons have negative skin tests and lack both IgG and IgE
antibodies to inhalant allergens (Platts-Mills, 1982). A proportion of people, however, are
unaware of any nasal symptoms but have positive skin tests. These asymptomatic people can
be divided into three groups:

(1) negative skin tests and negative serum antibodies
(2) negative skin tests and positive serum IgG antibodies
(3) positive skin tests and serum IgG and IgE antibodies.

A proportion of the skin test positive patients will develop symptoms in subsequent
years. Some patients spontaneously recover from hayfever. This has been estimated at a cure
rate of 8% in 3 years for hayfever. Some patients who have recovered from grass pollen
hayfever still have positive skin tests and detectable IgE antibodies. Although the evidence
is still incomplete, it appears that spontaneous cure of human allergic diseases is usually
allergen specific and involves a gradual reduction in the concentrations of IgG and IgE
antibodies. In general, it is thought that patients do not develop and IgE response for a second
time. This observation is not well documented and certainly there are no data available on the
mechanism by which 'relapse' is prevented. Similarly, there are very few data available on the
conditions for natural induction of IgE responses in man. While it is clear that symptoms of
hayfever may not develop until the age of 20 or later, it is not clear at what stage these
patients develop IgE antibodies. Immigrants to England from Hong Kong who never have
symptoms in their first summer often develop hayfever within 3 or 4 years. Sensitization to
laboratory animals can be particularly rapid. Persons who 'change' animals often become
allergic to a new species within a few months. In addition, several workers who had never
worked with a laboratory animal before became sensitized to rat urine proteins within 3
months. The development of IgE antibodies and the onset of symptoms in infants suggests
that the onset of sensitization was related to viral infections. Possibly inflammation of the
nasal mucosa allows more allergen entry or acts as an adjuvant and allows the allergic
response to one allergen to potentiate an antibody response to other allergens. The role of
short-term sensitizing IgG antibody and subclasses of IgG in the pathogenesis of hayfever and
related atopic disease remains unclear. At present there remains considerable doubt as to
whether short-term sensitizing IgG antibodies are responsible for immediate hypersensitivity
in any human condition. There is also no convincing evidence that IgG4 (or IgA) antibodies
play a direct role in mediating the symptoms of hayfever, perennial rhinitis or asthma.

The role of T cells in inhalant allergy is unclear, although T cells from allergic rhinitis
patients will respond in vitro to specific antigen and anti-IgE (Platts-Mills, 1982). It is
possible that sensitized T cells play a role in recruiting basophils to the nose. Experiments in
guinea-pigs suggest that basophil accumulation in the skin is, in fact, a form of delayed
hypersensitivity and can be mediated by the same T cells that mediate delayed
hypersensitivity. Although several groups have succeeded in measuring IgE produced by
human lymphocytes in vitro it is doubtful whether an in vitro suppressor phenomenon or T-
cell abnormalities and atopic diseases can be related to the aetiology of the disease or the mechanism of desensitization. In general, T cells from non-allergic individuals do not respond to allergens in vitro.

In hayfever there is a strong correlation between the sensitivity of mediator cells, that is peripheral blood basophils, and the severity of disease during natural pollen exposure. The amount of antigen required to release 50% of histamine from peripheral blood basophils remains fairly constant from season to season in most treated adults. This index of cell sensitivity varies considerably from patient to patient, although the severity of a patient's allergic symptoms during the ragweed season is directly related to the sensitivity of cells to ragweed antigen E. Serum levels of specific IgE antibodies also correlate with the severity of symptoms in untreated ragweed-sensitive patients. Similarly, leucocyte histamine release and serum levels of IgE antibodies also have a close correlation.

The pathology of allergic rhinitis will vary with the length of exposure and accompanying complications. In uncomplicated seasonal hayfever, submucosal oedema and infiltration with eosinophils and, to a lesser extent, neutrophils are the prominent findings. In long-standing perennial rhinitis, epithelial cell damage and thickening of the basement membrane may be observed.

**Allergens**

The term 'allergen' was originally used to describe any substance which could give rise to an altered reaction, that is either an immune or hypersensitivity response. It is now used in a limited fashion and describes only those substances which elicit an allergic response manifest by a hypersensitivity reaction. An 'atopic allergen' is one which gives rise to a type I immediate hypersensitivity reaction mediated by specific IgE antibody.

Extracts of allergen have been used since the early part of the century when Noon (1911) first undertook 'desensitization' using extracts of grass pollen. One of the major problems which has beset allergists ever since this form of treatment was introduced is the problem of clearly defining and standardizing extracts used for diagnosis (that is skin prick tests or the radioallergosorbent test - RAST) and immunotherapy. Even today the situation remains unsatisfactory, but there is considerable development in the field of allergen purification. Furthermore, there has been a rapid increase in the knowledge of the chemistry of allergens due to the development of several biochemical and biological techniques in vitro. Thus, it is now possible in many instances to purify, characterize and standardize allergen extracts fairly precisely.

Naturally occurring allergens have been shown to be proteins or glycoproteins, which are freely soluble and so easily absorbed through mucous membranes and usually have a molecular weight in the range of 10,000-40,000. Contrary to earlier belief, there do not seem to be any particular physicochemical features or characteristics for allergens. Thus neither the molecular size, hydrophobicity nor primary amino acid structure determines whether or not proteins will act as allergens.

The allergen proteins most frequently encountered in organic material and located normally in the human environment are derived from a number of source materials. The ones
most relevant to allergic rhinitis are the aeroallergens, such as pollens from wind-pollinated grasses, trees and weeds; mould spores and mycelia; mite proteins and proteins originating from animal dander, urine, saliva etc. Ingestants such as milk, soy, fish and cereals, eggs and nuts, also serve as source material for food allergens (which are probably of little importance in rhinitis).

Some of the proteins in source materials induce allergy in humans that are of higher frequency than others. These substances are termed *major* allergens. For instance, it was shown by skin prick testing that ragweed antigen E (RAE) was the major allergen from ragweed in contrast to the minor allergens RA3, RA4 and RA5. Major allergens have been defined as 'allergens that show specific IgE binding in more than 50% of the population allergic to that particular allergen and when they show strong IgE binding in at least 25%'. Minor allergens are those which give rise to IgE binding in less than 10% of patients. Allergens in between these extremes are defined as intermediate allergens. 'Binding' is a relative term, which is used in techniques such as crossed radioimmunoelctrophoresis, and refers to the association between allergen and specific IgE antibody.

Major allergens are very readily extracted from source material and are often the most abundant proteins in an extract, although they may only be a small percentage of the dry weight of an allergenic particle. For example, antigen P₁ from the faeces of the house dust mite and the major allergens of birch and rye grass pollens are released very rapidly. A notable exception is antigen E of ragweed. Allergens, in general, are remarkably stable to enzymatic biodegradation and chemical denaturation, possibly since they are already subjected naturally to a number of biodegradation processes, both from their own proteolytic enzyme system (for example pollens and fungi), as well as resisting various host defence mechanisms.

A further general characteristic of allergens is their ability to exist in multiple molecular forms which differ only slightly in their $pI$ values, but which carry the same allergenic determinants for combination with corresponding IgE antibodies (iso-allergens). These slight differences in the net charges of polypeptides are dependent, not only on differences in the ratio of acidic to basic amino acid residues, but also on minor structural differences which are, in turn, dependent on the nature of their carbohydrate moieties or, for example, differing degrees of amidation.

**Plant allergens**

**Grasses** (see Hubbard, 1984)

Allergy to grass pollen allergens is by far the most common cause of hayfever in the UK, especially as the climate is most favourable for the production of luscious green growth during a large part of the year (Hubbard, 1984). This abundance of grasses is almost entirely artificial in origin and due to the continual labours of many generations of our ancestors, together with the cumulative action of the grazing and treading of their domestic animals. Under the climatic conditions and on most soils, these artificial grasslands, when removed from the control of man and beast and left to the effects of competition and natural selection, gradually revert to scrub, and in most cases from scrub to forest.
Permanent grassland contains many species of grass. These include perennial rye-grass (Lolium perenne), large leaved Timothy-grass (Phleum pratense), cocksfoot (Dactylis glomerata), meadow fescue (Festuca pratensis), tall fescue (Festuca arundinacea), common bent (Agrostis tenuis), creeping bent (Agrostis stolonifera), Yorkshire fog (Holcus lanatus), red fescue (Festuca rubra), rough meadow-grass (Poa trivialis), and meadow fox-tail (Alopecurus pratensis). Amenity grassland covers about 850,000 hectares in the UK, or nearly 4% of the land surface.

The turf grasses include velvet bent (Agrostis canina subsp. canina), brown top (Agrostis tenuis) and Highland bent (Agrostis stolonifera), fine-leaved sheep's fescue (Festuca tenuifolia), hard fescue (Festuca longifolia), subspecies of red fescue (Festuca rubra), chewings fescue (subsp commutata), slender creeping red fescue (subsp litoralis), strong creeping red fescue (subsp rubra), crested dog's tail (Poa trivialis), smooth meadow-grass (Poa pratensis), small-leaved Timothy grass (Phleum bertolonii), large-leaved Timothy-grass (Phleum pratense), and perennial rye-grass (Lolium perenne).

Grasses are flowering plants (spermatophyta) whose pollens are dispersed by the wind (anemophilous). The flowers are usually perfect, that is they contain both pistils and stamens (Solomon, 1984). The grasses are all angiosperms and monocotyledons. Most of the grasses in the UK flower during May, June and July, the greatest number being in bloom towards the end of June and early in July. Woodland and mountainside species generally flower later than species of the same genera from open situations in the lowlands or from the south. Individual grasses have fairly regular daily flowering periods, although this is affected by the weather as the florets remain closed on dull or wet days. In the majority, flowering takes place in the early morning (mainly 04:00-09:00), in a few about midday, and in others during the afternoon and evening (15:00-19:00). Most species flower only once a day and this lasts for about 4-12 days (usually 7-8 days), depending on the type and size of flower heads. The majority of UK grasses are chasmogamous, their florets opening for the exertion of the anthers and stigma. Obviously only the wind-pollinated, rather than the self-pollinated, grasses are important in allergy.

Pollen grains become air-borne when they fall into an airstream or are scoured by turbulent eddies (Solomon, 1984). Pollens are projected through a relatively thin lamina boundary layer of still air into the constantly moving lower atmosphere. There are many factors which determine dispersal. These include the strength and proximity of upwind sources, diluting vertical and horizontal crosswinds, prevailing winds, local surface effects, that is vegetation screens, cul-de-sacs; on a warm day pollen-loaded air is higher, thermal inversions are thought to exist and rising air will not ascend further. The effect of thermal inversions is to cause second nightly peaks when the atmosphere cools and the pollen grains subside to the surface. Overall, levels of air-borne pollen are increased by warm, dry, clear conditions and fall during unreasonable cold or wet periods. Pollen grains can travel long distances and have been recovered in trans-Atlantic flights at an altitude of 3000 metres in summertime. However, most wind-borne pollens are lost within a few hundred metres of their source.

It has been found that the development of high concentrations of grass pollen in the air over London, as compared with Liverpool and Glasgow, respectively, is associated with
more rapidly rising values of accumulated temperature. In a study contrasting grass pollen and fungal spores in London and Davos, it was found that an earlier rise and sustained higher values of accumulated temperature were associated with higher counts. Prolonged rain washes the air free of particulate matter and very heavy rain washes pollens, and even the anthers which bear them, to the ground.

It appears that the pollen clouds flowing over British cities are mainly of an exogenous origin from such sources as crops, pastures and woodlands outside (Davies, 1969). The 5 km² of grassland in parks of central London are probably not a significant source of grass pollens. Buildings and open spaces and cities affect the deposition of grass pollens. Winds are deflected over the rooftops and large particles, that is pollen grains, pass into the relatively still air between the buildings and tend to settle quickly to the ground. On hot, sunny days street level temperatures one degree higher than those in the airstreams above the 25 metre high rooftops have been observed, and convection and turbulence will tend to inhibit the settlement of small spores, that is fungi (into the city).

Although no detailed survey has been undertaken into the prevalence of atopic disease in various regions of the UK, hayfever is probably less frequently diagnosed in the north-west and Wales than it is in the east and south-east England. Wales and the northern, north-western and east and west Ridings regions of England are ecologically similar and characterized by mountainous and upland areas with grass, heath and moorland type of vegetation. By contrast, in the other regions of England and Wales there is very little mountain and moorland, and the land is mainly devoted to arable farming or mixed crops with some stock raising. As a consequence, these areas are a greater source of seasonal allergens, particularly grass pollens. Also, because of the west and south-west prevailing winds, spore and pollen clouds over east and south-east regions of England will tend to be denser because of wind collections from the more westerly areas.

Pollen counts of 50 grains/mm³ or more seem to be associated with clinical symptoms in susceptible individuals. However, very sensitive individuals will experience symptoms from concentrations as low as one grain/mm³.

**Structural features in the identification of pollens**

Most pollens are between 12 and 17 microm in diameter and are usually spheres or sphere-like particles (Solomon, 1984). The distinctive surface features depend on the intactness or otherwise of the tectum and other exterior features. Grains can be smooth (psilate) or roughened (scabrate or verrucate). Sometimes they have club-shaped projections (clavate). Apertures in the exine are referred to as pores or furrows if they are elongated. Grain regions are termed 'polar' or 'equatorial'. Anemophilous grains may have one or more pores alone (porate), furrows alone (colpate) or furrows with central pores (colporate).

Determination of pollen output by anemophilous species is not well understood, but appears to include temperature, humidity, rainfall and life intensity. Davies and Smith (1973) were able to estimate the annual start and eventual intensity of grass pollen exposure from measurements of accumulated spring temperatures.
Thus pollen is either distributed by insects or by the wind. Pollens which are insect-borne are derived from plants with flowers which have colour and a scent to attract the insect, and the grains themselves are sticky and adhere to the insect. Wind-borne pollens are lightweight, can be carried long distances, and must be profuse in quantity. Since there is no need to attract insects, an attractive flower is unnecessary.

Allergy to flower pollens probably does not exist and it is dubious as to whether extracts of flower pollen should appear in skin test kits.

In the UK, the pollen seasons of importance to the allergist are: tree pollen allergy in the spring, grass pollens in the summer, and weed pollen allergy in the latter part of the summer and early autumn. In the USA there are also roughly three pollen seasons of importance to the hayfever/asthma sufferer. These are trees, grasses and weeds, with pollination appearing locally at about the same time. The 'pollen season' extends over a much broader period, although this will of course vary from place to place.

**Fungi**

Fungi are a unique group of organisms and classified as a separate kingdom from plants and animals on the basis of their ability to absorb nutrients and their multinucleate character (Austwick, 1981). Fungi may be unicellular (yeast-like), filamentous (mould-like), or both (dimorphic). Fungi may form reproductive propagules through an asexual production by mitotic nuclear division (for example buds, sporangiospores or conidia) and/or through a sexual process of meiotic division (for example zygospores, ascospores or basidiospores). It is the conidia of several common fungi which are of importance in IgE-mediated allergy. A number of fungi are also associated with extrinsic allergic alveolitis.

All fungi possess a true nucleus (eukaryotic), are incapable of forming all of their nutritional requirements (heterotrophic), and lack chlorophyll (achlorophyllous). It is a fourth feature - the ability to release extracellular enzymes which break down nutrient stores and to absorb the nutrients - which distinguishes fungi from most other living organisms. Thus, animals ingest nutrients, plants synthesize nutrients, and fungi absorb nutrients. A further important characteristic of fungi is their multinucleate structure. In other words, the entire developing body of the organism lacks complete cross-walls (septa). Some have incomplete septa, but in all fungi there is direct communication throughout the whole of the organism.

Most species grow optimally at slightly acid pH and at room temperature (20-25°C), although there are notable exceptions to these rules. Most fungi are strict aerobes, although many yeasts are facultative anaerobes. Most fungi grow at relatively high humidity, although the wall surrounding asexual and sexual propagules inhibits desiccation and permits fungi to survive extreme or prolonged droughts. Conidia become air borne as a result of various changes in the environment. These include wind, rain, light and changes in relative humidity. In an outdoor environment there are two daily peaks of conidial discharge at 03:00-06:00 when the relative humidity is highest, and 15:00-18:00 - the driest, windiest part of the day. There are, of course, seasonal variations.

The number of outdoor air spores may vary from between 200 and 2,000,000 per mm² of air, averaging on a daily basis 10,000-20,000 per mm² with peak concentrations rarely
exceeding 200,000 per mm² for short periods only. Such peaks usually correspond with conditions favouring the formation and liberation of numerous ascospores or basidiospores and seldom occur with conidial fungi. *Cladosporium* sp usually produces the most numerous spore type in the air during daytime but at night it is replaced by spores of *Ascomycetes*, *Basidiomycetes* and *Sporobolomyces* spp. Concentrations in England vary between 3200 and 6500 spores per mm² with peaks up to 240,000 per mm² for short periods. Spores of *Alternaria* sp are the next most abundant by day, but mean daily concentrations may be only 50-150 spores per mm².

The abundance of the night-time air spores has only been appreciated with the use of continuously operating spore traps. These have shown that balistospores of *Sporobolomyces* and ascospores of *Didymella exitialis* may often be abundant, exceeding 200,000 spores per mm² under suitable conditions close to their source.

Rain may cause an initial increase in spore numbers, due to the tap and puff effect but, if prolonged, it washes all spores out of the air. However, it may subsequently stimulate ascospore release. Indoors, the composition of the air spore is greatly influenced by local sources. In the absence of a source, the type of spores present in the air may be similar to outdoors but with smaller numbers. However, in the presence of a dry rot fruitification, up to 360,000 spores per mm² of air have been found and, when mouldy fodders are disturbed, up to $10^{10}$ spores per mm².

The spore types associated with fodders and other stored products depend on the way in which they have been stored, their water content and degree of spontaneous heating. *Actinomyces* sp associated with farmer’s lung, for instance, occurs in hay stored wetter than 35% water content which heats to 50-70°C. The *Aspergillus* species - *A. glaucus*, *A. versicolor*, *A. nidulans* and *A. fumigatus* - predominate in hay stored at 25%, 29%, 31% and 40% water content, respectively.

*Common allergenic fungi* (Salkin and Haines, 1984)

**Alternaria**

These are the most common air-borne fungal propagules. They are characterized by septation in two planes, a narrow projection from one end, and dark pigmentation. However, their morphology is quite variable in respect of size, shape, and number of septa. These asexual structures are usually encountered outdoors from July to September in the late afternoon. Spores of *Alternaria* are found when the atmosphere is warm and dry, have their origins on the surface of vegetation and are especially abundant when cereals are harvested. In the air over London alternaria spore concentrations reach 100 per mm² (or, rarely, 1000).

**Cladosporium**

The kinetia of this fungus are the most common air-borne fungal propagules found outdoors. They are characterized by dark pigmentation, the presence of one or several septa, and linkage in short, branch chains. Spores of *Cladosporium* occur in the atmosphere when the air is warm and dry and, as for *Alternaria*, their origins are on the surface of vegetation.
and when cereals are harvested. Indoors, spores of *Cladosporium* will colonize wallpaper and even painted surfaces. Outdoors the concentrations of spores of *Cladosporium* (and *Alternaria*) rise to a peak in the late summer and early autumn. In the air of London, spore concentrations of *Cladosporium* reach 10,000 per mm$^3$.

**Aspergillus**

The kinetia of this mould are among the most common indoors and can be identified by their relatively small size (frequently less than 4 microm), their uniform round shape and their formation in chains on specialized physicular heads. The morphology of the kinetia developing on specialized types is used to identify the species.

The spores of *Aspergillus* are phialospores, that is they develop from the tip of short, modified hyphacallsterigma (or phylophor), several hundred of which are arranged over the surface of a claviscolen end of an erect hypha (condiophore 4). This is the typical structure of the sporing head of *Aspergillus*. As each sterigma tip expands, so a cross-wall develops below and cuts off the spore. The process is then repeated so that each sterigma bears a single line of spores; on each head is a column of many thousands of spores.

*Aspergillus* sp like *Penicillium* is sometimes called a storage fungus, since both are common causes of rot in stored grains, fruits and vegetables. *Aspergillus*, in particular, will thrive on substances with a low moisture content (12-16%). They are the two moulds most commonly cultured from houses especially basements and dark areas.

**Penicillium**

The kinetia of this mould are also very common indoors. They are characterized by their almost round shape and formation in chains on broom-shaped kinetial heads. They can be isolated all the year round. (Many spores such as those of *Aspergillus* and *Penicillium* cannot be morphologically without colony characteristics.)

Other possible allergens to be considered in IgE-mediated hypersensitivity include *Fusarium* and *Aureobasidium (Pullularia)* spp.

**House dust mite**

House dust mite contains many different agents which may be allergenic in man, each of which may be an important allergen in any particular household (Mosbech, 1985). Apart from the house dust mite, which will be considered in some detail, material derived from domestic animals such as cat saliva are important sources of house dust allergen, as are fungal spores, tree grass and weed pollens, insects (particularly in the USA where cockroach allergy is common), textile fibres, human dander and other agents. It was appreciated in the 1920s that an extract of house dust obtained from vacuum cleaners and certain types of pillows and mattresses gave positive skin prick tests in atopic individuals. It was not until 1964 that clear evidence was presented that pyroglyphid mites (*Dermatophagoides* sp) were a major source of the skin test reactivity in house dust. Voorhorst, Spieksma-Boezeman and Spieksma (1964) demonstrated that allergen accumulated progressively in mite cultures and that allergen
activity of house dust from different parts of the world correlated well with the number of mites.

Mites are more closely related to spiders and scorpions than to insects. They have eight legs in the adult stage and body segmentation is lacking. The primary house dust mites are *D. pteronyssinus* (Dp), *D. farinae* (Df) and *Euroglyphys maynei* (Ep), all belonging to the Pyroglyphidae family. Early mite cultures were grown on human skin scales, horse dander, fishmeal and/or wheatmeal. However, they are not grown on various types of non-allergenic media and skin responses to mite extracts are highly specific. It is now clear that mites are present in many parts of the world and dust mites are regarded as an allergen of major importance in Australia, Japan, Hong Kong, the West Indies, South Africa, the continent of Europe and the USA. In general, it is in the areas with the highest relative humidity that mites thrive; in contrast, areas with long periods of dry weather have poor mite growth. Thus the prevalence of the different mites is related to climate rather than to geographical conditions. In general Dp is found predominately in northern Europe, New Zealand and Australia whereas Df is found largely in North America and central Europe. Ep appears to be more prevalent at higher altitudes.

The female Ep produces 20-40 eggs once or twice during life. They are hatched after 6 days and the total immature life lasts about 25 days. The mature adult lives for about 2 to 3.5 months, in houses, the bedroom is the preferential breeding ground, particularly the bed itself. Here, sufficient food is supplied in the form of human scales and the temperature is optimal. The mattress is the most important habitat from which bed clothes are repopulated after laundry. Dusts from overstuffed furniture, carpes and unlaunched clothing can contain high numbers of house dust mites.

The optimal temperature for growth of Dp is 25°C with a relative humidity of 70-80%. (For Df, a temperature of 25-30°C with a 50-60% relative humidity is ideal.) Thus mites are more abundant in humid homes and, in temperate climates, the number of house dust mites increases during the humid summer months, whereas during the heating season when the indoor relative humidity is low, mite numbers decline. The low humidity during the winter seems to be an important factor in the survival of the mite population. Similarly, the lower numbers of mites at high altitudes might be related to a low indoor relative humidity in the regions investigated.

### Allergen purification

The development of techniques for growing mites on non-ectodermal heat-denatured mammalian material greatly facilitated the purification of mite allergens. It was shown by Chapman and Platts-Mills (1980) that the major allergen from Dp is a glycoprotein with an apparent molecular weight of 24,000 which is freely soluble in aqueous solution. This was designated Dp, antigen P₁. By means of crossed radioimmunoelctrophoresis, 29 different components derived from Dp have been identified; 44-72% of the IgE against Dp was directed against antigen P₁ (which is identical to the antigens termed Dp 42 and Dpt 12).

The major allergen P₁ appears to represent as much as 20% of the protein in aqueous extracts of the cultures. Although P₁ is present as multiple iso-allergens with a very wide
range of PI values, it migrates as a discrete band on polyacrylamide-gel electrophoresis (PAGE) and this band is coincident with the heaviest protein band seen in the crude extract. Most of the allergen in cultures appears to be associated with mite faeces while mite cuticle and eggs contain negligible quantities. Antigen PI elutes very rapidly from dust, from mite cultures and from mite faeces (greater than 90%) in 2 min) while elution from live mites is very slow. Thus the major allergen present in mite cultures is associated with a particle of similar size to pollen grains, elutes very rapidly, has a molecular weight of 24,000 and is abundant 'in aqueous extracts'. These properties are similar to those of other inhalant allergens. By contrast, the mite allergen does not appear to have any chemical properties in common with pollen allergens. (Faeces 10-40 microm in diameter contain 0.1 nanog antigen PI per particle, equivalent to 10 mg per emulsed elution.)

Environmental exposure to antigen PI has been assessed by measuring the antigen PI content of dust extracts and by comparing the distribution of antigen PI in air-borne particles. Dust samples from houses in the Harrow area of London contained 100-100,000 nanog antigen PI per g of dust. In contrast, the dust samples from schools or hospital wards contained very little allergen (less than 10 nanog). In a particle sizing experiment, using a cascade impactor, it was not possible to detect air-borne allergens in undisturbed rooms. However, when the dust in a room was disturbed, for example by vacuum cleaning, most of the allergen was associated with particles of greater than 10 microm in diameter. Some of these particles were identified as mite faeces by immunodiffusion and electron microscopy. As pointed out by Tovey et al (1979) natural exposure to dust mite allergens is quite different to formal bronchial or nasal provocation testing in that the rate of decomposition, although continuous, is very slow. Thus natural exposure to dust mite allergen would be in the form of a few faecal particles, perhaps 100 per hour, although only 10% of these would be expected to enter the airway.

Clinical features

The symptoms of allergic rhinitis vary from minor trivial inconvenience to profuse symptomatology to a point where symptoms adversely affect the quality and enjoyment of life (Wassermann, 1982). Certain individuals, when untreated, are incapacitated for several days.

Seasonal rhinitis

(1) The first symptom of the hayfever season is usually sneezing. In severe cases paroxysms of sneezing occur at frequent intervals throughout the day. Sneezing is probably largely due to histamine release acting through reflexes.

(2) Excessive fluid and mucus secretion (rhinorrhea) is believed to be the response of serous and seromucous glands to mast cells/basophil-derived mediators.

(3) Nasal obstruction or blockage is the result of vascular engorgement, that is vasodilatation and oedema.

(4) Itchiness of the nose, eyes, palate are common features.
(5) Tearing, itching and redness of the eyes together with some degree of periorbital oedema is usual in hayfever. Other symptoms include tightness of the chest (sometimes with wheezing) and a burning or raw sensation in the throat.

**Perennial rhinitis**

The symptoms of perennial rhinitis differ slightly from seasonal rhinitis largely as a result of long-standing nasal mucosal inflammation in the untreated situation. Sneezing, itchiness and nasal discharge are prominent, but the rhinorrhea may be more viscous or purulent depending on the degree of cellular recruitment. Conjunctivitis is far less frequent in perennial rhinitis than in allergic rhinitis. Perennial rhinitis is also accompanied by varying degrees of loss of smell (anosmia), loss of taste (ageusia) and symptoms associated with the eustachian tube (hearing defects and ear pain).

On examination, patients with perennial rhinitis or hayfever (during the pollen season) have pale, boggy nasal mucosa covered with thin mucus or mucopurulent secretions. Hyperaemic conjunctiva is noted in hayfever. Examination of the nose is best accomplished with the use of a nasal speculum. The colour of the membrane, the degree of oedema, the presence and types of secretions and tumours or mucosal ulcerations or the presence of polyps should be assessed.

**Laboratory investigations**

Confirmation or otherwise of a diagnosis of allergic rhinitis can be achieved by skin testing or, when appropriate, by the radioallergosorbent test. Skin testing is inexpensive, accurate, rapid and can be undertaken with a wide variety of antigens at a single skin testing session. Skin prick tests are preferred to scratch or intradermal tests because of their reproducibility, low instance of false positive reactions, less risk of systemic anaphylactic reactions, better accuracy (especially with food antigens) and patient preference. It should be remembered that a **positive histamine control** and a **negative diluent control** must always be used. A number of agents interfere with the immediate skin prick test. These include antihistamines and oral sympathomimetic agents. It should be remembered that astemizole (Hismanal), being a recently introduced selective H1 antagonist, has a long half-life and skin testing should be performed at least 28 days after stopping this preparation.

A radioallergosorbent test is indicated under several circumstances. These include the presence of dermatographism or extensive skin disease where skin prick testing is impractical and where, as stated above, the patient has been taking medication that interferes with the interpretation of the skin prick test. The radioallergosorbent test is less sensitive than the skin test and is relatively expensive taking several days to perform and is limited by the fact that in most routine laboratories only a limited number of antigen assays are available. The radioallergosorbent test is more quantitative than skin tests and this may be desirable when patients are being monitored for immunotherapy.

Nasal cytology is sometimes helpful in the differential diagnosis of nasal complaints. Samples may be obtained either by blown secretions or by gentle scrapings of the lateral nasal wall. The material is smeared on to a glass slide, fixed in ethanol and stained with May
Grunwald/Giemsa. The presence of eosinophils, neutrophils, basophils, mast cells, epithelial cells and bacteria should be recorded.

**Diagnosis**

The diagnosis of seasonal hayfever in the UK is usually straightforward and based on a seasonal history of symptoms together with a positive skin prick test to grass and/or tree and weed pollens. Occasionally, patients' symptoms are confined to the tree pollen season and this is confirmed with the appropriate skin tests. Seasonal hayfever in association with weeds or fungal antigens in the absence of pollen hypersensitivity is rare. On the other hand, many highly atopic individuals will have positive skin tests to grass, tree and weed pollens as well as fungal spores and their symptoms will extend sometimes from early April to the end of August.

The diagnosis of perennial rhinitis is sometimes more difficult, although a history of sneezing and rhinorrhoea all the year round together with positive skin prick tests to the house dust mite and/or animal danders is usually sufficient to make the diagnosis. It is important to recognize, however, that several forms of rhinitis may coexist.

In patients whose main symptom is obstruction of the nasal passages and where sneezing and rhinorrhoea are either minimal or absent, a diagnosis of a deviated septum, non-specific hypertrophy of the inferior turbinates, nasal polyps, rhinitis medicamentosa, atrophic rhinitis, or blockage with tumour or foreign body should be excluded. In patients whose primary symptom is posterior rhinorrhoea with sneezing and nasal obstructing being minimal or absent, acute or chronic rhinosinusitis, acute or chronic nasopharyngitis, or neoplasia may be responsible. Patients with sneezing with little obstruction or rhinorrhoea, but with negative skin tests or skin test which do not correlate with a clinical history, may have eosinophilic non-allergic rhinitis or primary nasal mastocytosis.

**Differential diagnosis**

It is important to recognize that several forms of rhinitis may coexist. Other causes of rhinitis apart from allergy include mechanical obstruction, hyper-reactivity to a wide range of non-specific irritants (dust, fumes, odours, strong light, cold air), immune deficiency (causing infection), mucous abnormalities, ciliary dyskinesia (primary or secondary), granuloma, malignancy, hormonal (menstrual, pregnancy), drugs (rhinitis medicamentosa) and emotional factors.

**Irritants**

Many individuals, particularly young women, experience obstruction and rhinorrhoea which is aggravated by a variety of minor environmental stimuli, such as exposure to dusts, fumes, odours, strong light, cold air, spicy foods, changes in humidity. In these patients, sexual arousal or defaecation may be associated with similar symptoms. This condition is a form of nasal hyper-reactivity but is sometimes termed 'vasomotor instability' or 'vasomotor rhinitis'. In any event it is a diagnosis by exclusion. It should be noted that many of the stimuli may affect patients suffering from other forms of rhinitis, but by definition patients with vasomotor instability have no other primary cause for their reactivity. In some cases
systemically administered drugs caused obstruction and rhinorrhoea. These are usually agents affecting adrenergic regulation and include hypertensive agents (that is alpha-methyldopa) and beta-adrenergic agents and agonists. Hormonal medications and agents such as the contraceptive pill may be causative. Rhinitis of pregnancy is an important example of this problem as are drugs used in the treatment of hypo- and hyper-thyroidism. Obstruction and rhinorrhoea secondary to systemic medications are usually differentiated from rhinitis caused by the topical use of alpha-adrenergic medications capable of irritating the nose. Rhinitis secondary or sprays used for the treatment of other causes of rhinitis is secondary by nature and termed 'rhinitis medicamentosa'.

**Eosinophilic non-allergic rhinitis**

Some patients with perennial nasal symptoms of paroxysms of sneezing, profuse watery rhinorrhoea and pruritus of the nasopharyngeal and conjunctival mucosa have negative prick or intradermal immediate skin tests, negative serum radioallergosorbent tests to common inhalant allergen, and negative methacholine provocation challenges. These patients characteristically have eosinophilia in nasal biopsies with inactivated cilia, damaged nasal epithelium, thickened basement membrane and an oedematous submucosa infiltrated with plasma cells, lymphocytes, eosinophils and neutrophils, and the occasional mast cell. This form of inflammatory rhinitis seems to be responsible for about 15% of non-infectious non-structural chronic rhinitis in adults in certain parts of the USA. In one-third of the patients, there is associated nasal polyposis and sinusitis. Symptoms are aggravated by a variety of non-specific inciting agents such as odours, weather changes and irritants. In general, nasal obstruction and discharge and anosmia are more marked than the episodes of sneezing and conjunctivitic characteristic of allergic rhinitis. Some patients, particularly those with polyps, have exacerbation of symptoms after the ingestion of non-steroidal or anti-inflammatory drugs. The nasal mucosa appears pale and oedematous and is associated with thick yellow mucus. The underlying pathological mechanism is unknown. It is not thought to involve specific IgE although the activation of mast cells by non-immunological mechanisms has been suggested. The condition does not respond to disodium chromoglycate.

**Other conditions**

An uncommon form of chronic rhinitis is nasal mastocytosis in which mast cell are prominent in nasal scrapings. This disorder is most commonly seen in adults and is characterized by nasal obstruction and watery rhinorrhoea.

Atrophic rhinitis is observed particularly in patients who have undergone extensive nasal surgery although the condition was once common in the elderly. The nasal passages feel obstructed and irritated and dry. Infection and bleeding are frequent complications. The turbinates are small, the mucosa thin and there are diminished numbers of mucous glands and goblet cells, and scanty cellular infiltrate except in the presence of secondary infection where neutrophils are abundant.

**Allergy and sinusitis**

The association between allergy and sinusitis is essentially two-fold. First, allergic mechanisms may contribute to obstruction of the sinus ostia and, in that sense, represent a
predisposing factor. Secondly, perennial allergic rhinitis has some of the features of chronic sinusitis, particularly nasal discharge and obstruction.

In sinusitis, obstruction of the sinus ostium produces hypoxia leading to vasodilatation, ciliary dysfunction and mucous gland dysfunction. These cause transudation of fluid, stagnation and the production of viscid fluid, respectively, which in turn all lead to the production of retained thick secretions. If bacteria are carried into the sinuses, ideal situations exist for bacterial multiplication.

**Complications**

Seasonal rhinitis is sometimes associated with mild bronchial asthma and about 50% of patients with rhinitis have increased non-specific bronchial hyper-reactivity. It has been suggested that patients with rhinitis without symptoms, but who show non-specific bronchial hyper-reactivity in the range of asthmatic subjects, will be those who proceed to develop symptomatic asthma with time. However, the course of seasonal rhinitis is very variable. Some patients will spontaneously remit even after many years of symptoms and hayfever is common in the elderly. In children, rhinitis may predispose to an increased incidence of otitis media, serous otitis and chronic sinusitis. Otitis media and middle ear infections occur more frequently in allergic children. The pathophysiological changes in allergic rhinitis may lead to obstruction of the eustachian tube with dysfunction and middle ear effusion. Serous otitis is not an allergic disease but a frequent complication of nasal allergy particularly in children.

**Treatment**

The management of hayfever and perennial allergic rhinitis can be considered in terms of allergen avoidance, anti-allergic drugs and hyposensitization. The drugs can be subdivided into those for prevention and those for relief.

**Allergen avoidance**

Although the concept of allergen avoidance is simple, straightforward and obvious, in practice it is often very difficult to undertake. Generally speaking, it is virtually impossible to avoid exposure to pollens and spores during the appropriate seasons, unless the patient is prepared to travel to areas of the country where air-borne levels are insufficient to cause symptoms. On the other hand, inhaled air can usually be efficiently cleansed of allergens, although maximal efficiency often requires extensive and elaborate devices. Mechanical filters can remove particles of greater than 1-5 microm from the air but must have the capacity to recirculate frequently since multiple passages are required for effective cleaning. Devices such as electrostatic precipitators and high efficiency particulate air filters are particularly efficient. They can clean the air of 99% or more of particles. Individual hayfever helmets can be purchased (the Hincherton hayfever helmet). The device consists of a plastic globe (spaceman's helmet) connected to a small battery-driven air filter. Apart from being somewhat unsightly the helmet heats up in direct sunlight (the greenhouse effect). Hayfever sufferers should obviously avoid prolonged exposure to the countryside and should drive with their car windows closed. Generally speaking, air filtering systems in cars do not filter out pollens. Wearing glasses may prevent pollen settling in the eyes and thus prevent discomfort.
Exposure to mould spores can sometimes be reduced. For instance, patients should avoid barns and mowing grass or raking leaves since high concentrations of mould spores may be found in these situations. Garden sheds and cabins which have been closed for several months may have a high mould spore concentration as will the basement of houses and certain foods and beverages. As with pollens, air conditioning and air filtration systems are the only way of reducing exposure on a 24-hour basis. In theory, avoidance of domestic animals such as cats and dogs is readily manageable, although sensitive patients are often unwilling to accept such obvious advice. It should be remembered that animal danders, particularly cat, dog, guinea-pig, mouse, rabbit etc (allergens derived from) may take 6 weeks or more of repeated cleaning to remove from a house. Most allergists do not allow asthmatic children to continue to live with a domestic animal to which they are sensitive. Similarly, patients with symptoms in association with laboratory animals should continue to avoid working with them unless there are extremely efficient filtering devices to avoid exposure.

The role of allergen avoidance in association with house dust mite remains controversial. One of the problems is that it is still unclear whether the recommendations usually given to patients or parents for cleaning the house, particularly the bedroom are effective at reducing the allergen content of the dust. It has been assumed that the bedroom is the single most important source of allergen exposure, but there is no reason for believing this and, in centrally heated houses, high levels of dust mite allergen are often found in living room floors or furniture. In order to reduce allergen exposure successfully, it may be necessary even to change flooring, furniture and cleaning practices in the whole house. With the development of better assays for the allergen content of dust samples or room air it should be possible to give better advice on methods for cleaning houses. Killing of mites in dwellings by temperature alone is seldom feasible, at least in temperate climates. In colder regions, it is possible to expose mattresses, blankets, pillows and eiderdowns to the necessary -18°C for two days. The same effect could be accomplished by heating to more than 45°C for 2 hours. Humidifiers should be avoided in homes of house dust mite allergic patients. Materials which conceal mites and prevent cleaning are obviously more heavy infected, that is carpets compared to plain floors and mattresses with inner springs or kapok compared with foam mattresses. Unfortunately repeated vacuuming does not remove mites completely from carpeting and vigorous vacuuming of bedding is also relative ineffective at getting rid of mites. Mites are highly resistant to germicides. Gamma-benzene hexachloride (Lindane) kills mature Dermatophagoides pteronyssinus, but at unacceptably high concentrations. Natamycin, a fungicide with less toxicity, appears to have some effect on symptoms in an uncontrolled clinical trial. It acts on fungi which are important for the growth of Dermatophagoides sp.

Thus, the dust avoidance measures can be summarized as follows: smooth, uncluttered easily cleaned surfaces are recommended and bare floors and walls are suggested. Small objects such as toys, books and records should be placed in drawers or closed cabinets. If carpeting is unavoidable low pile types are preferred. Pillows and mattresses should be enclosed in air-tight plastic or fabric encasing. Feather and down pillows should be avoided and synthetic pillows should be replaced every 2-3 years. A dust mask should be worn when cleaning the room.
Anti-allergic drugs

The most effective drugs for the relief of symptoms are antihistamine preparations, whereas local corticosteroids and disodium cromoglycate are effective for prevention. Systemic medication with histamine H\textsubscript{1} antagonists lessen itching, sneezing and eye symptoms, but have relatively little effect on nasal blockage. The classic antihistamines cause sedation which many patients find unacceptable. This problem has been largely overcome by the introduction of the selective H\textsubscript{1} antagonist terfenadine (Triludan) and astemizole (Hismanal). These compounds are largely free from the anticholinergic sedative effects of the classical antihistamines. They rarely cause sedation or psychomotor impairment and do not potentiate the effects of alcohol or benzodiazepines. Astemizole has the advantage of a once daily dosage but it takes several days to achieve its full effect. The drug is given as a single daily dose of 10 mg, but a loading dose of 7 days of 20-40 mg is sometimes recommended. Astemizole can cause weight gain. The very long half-life of astemizole (21 days) has caused concern. The recommended dose of terfenadine is 60 mg twice daily. The drug acts fairly rapidly, but there is some evidence that suggests that tachyphylaxis can occur with prolonged usage (that is several days). Neither astemizole nor terfenadine are recommended in pregnancy.

Many patients with relatively mild hayfever find that the older antihistamines, such as chlorpheniramine (Piriton) and azatadine (Optimine), are quite satisfactory, especially when taken at night. There is in fact a bewildering array of classic antihistamines on the market, some of which are combined with decongestants (that is Actifed (triprilodine and pseudoephedrine), Dimotapp (brompheniramine and phenylephrine)). Oral sympathomimetics alone or in combination with an antihistamine are contraindicated since they are less efficient than topical treatment and may cause serious systemic adverse effects. Drugs for relief include corticosteroids and disodium cromoglycate. At the present time four different corticosteroid sprays are available for the treatment of allergic rhinitis. These are beclomethasone (Beconase - as a freon propelled pressurized aerosol, or as an aqueous spray), budesonide (Rhinocort - freon delivery only) and flunisolide (Syntaris - aqueous spray only). These preparations successfully control nasal symptoms and the four preparations available seem to have similar efficacy and are equally acceptable to patients. Twice daily dosage is now advised and, once patients are stabilized, they may be able to reduce the dose to once daily. With the recommended dose local corticosteroid side-effects are minor and systemic effects are not a problem. Effects related to the delivery system have to be considered since freon delivered aerosols may cause drying and crusting of the nasal mucosa and, occasionally, slight bleeding.

Disodium cromoglycate is available for nasal application as an insufflation, a spray or as drops (Rynacrom). The eye drops have the trade name Opticrom. Disodium cromoglycate is only effective if used prophylactically and has to be applied at least four times a day. In seasonal rhinitis it is probably as effective as corticosteroids as a prophylactic agent.

Oral corticosteroids or ACTH are sometimes indicated although symptoms are rarely severe enough to warrant shirking their untoward effects. Short courses of oral prednisolone are effective and can be titrated to individual requirements, whereas injectable depot preparations are expensive and their dosage inflexible.
Ketotifen (Zaditen) causes sedation and weight gain and has no particular advantages. The manufacturer's recommended dose is one tablet twice daily.

**Hyposensitization (immunotherapy)**

This should be considered only in patients who fail to respond adequately to anti-allergic medication. It should be remembered that the adverse effects can be life-threatening and doctors have to be prepared to deal with general anaphylaxis. Patients should be observed for up to one hour after each injection. (Recently a controversial recommendation stated that observation should be continued for 2 hours.) Benefit appears to be dose dependent and maintenance therapy over 3 years of treatment is usually advised. The subject of hyposensitization has been admirably reviewed by Norman (1980) and Adkinson (1982).

Serial injections of pollen extracts were first used by Noon, and Freeman, in 1911, with the aim of eliminating 'the toxic effect' of pollens. Despite its extraordinary popularity, it is a sad fact that 75 years later there is still a considerable area of ignorance regarding this form of treatment. Views range from great enthusiasm to considerable scepticism. The treatment of patients with IgE-dependent allergic disorders by serial injections of allergic extracts is an attempt to provide some protection from natural exposure to the antigens which induce the untoward symptoms. For this reason the term 'immunotherapy' is preferred to desensitization and hyposensitization. (In fact there is little evidence that target cell reactivity is diminished and, therefore, the terms 'desensitization' and 'hyposensitization' are probably inappropriate.) Desensitization is more appropriately applied to situations in which adverse reactions to agents, such as insulin or penicillin, are treated by rapid administration of the agent over a period of hours in order to administer therapeutic amounts of the material in question. In 1954, Frankland and Augustin carried out the first placebo-controlled trial of desensitization employing both crude and partially purified grass pollen extracts in patients with hayfever and seasonal asthma. The active preparation was significantly better than placebo in relieving symptoms of rhinitis and asthma, although it was confirmed that a large proportion of patients (30-40%) had a potent placebo response. Lowell and Franklin (1965) were the first to provide evidence that immunotherapy was specific for the allergen used. Similar evidence in ragweed versus grass pollen sensitivity was provided in the 1970s. Generally speaking there is good evidence that immunotherapy is effective in seasonal rhinitis due to grass pollens, ragweed pollens and mountain cedar pollens and probably also to the house dust mite, although results from house dust mite studies vary considerably. There is reasonable evidence of benefit for allergic asthma, especially in children, but many remain sceptical. The one single absolute indication for immunotherapy is in those at risk from local or general anaphylactic reactions to venoms of Hymenoptera (insect sting allergy).

**Clinical indications**

Specific immunotherapy has no place outside of allergic rhinitis, allergic asthma and sensitivity to Hymenoptera. There is evidence that oral hyposensitization is ineffective and there is no evidence for the use of bacterial vaccine in asthma. There are a limited number of controlled trials of immunotherapy with moulds and animal allergens, but there has been insufficient work in this area to recommend this form of treatment for these conditions.
Selection of patients for immunotherapy

For reasons of time and expense, the decision to embark on a course of immunotherapy needs to be weighed carefully. Patients must have a convincing history that natural exposure to the aero-allergen induces clinically significant allergic symptoms. In certain instances provocational evidence is also required. Detection of IgE antibody specific for the relevant environmental allergen is also essential. Allergic rhinitis (or asthma) in which the symptoms correlate with skin tests or the radioallergosorbent test results and the condition is severe and non-responsive to other treatment, is usually an indication for specific immunotherapy. The requirement for positive skin tests to the relevant allergen is absolute because there is no evidence that desensitization works in patients who do not have positive skin tests.

Finally adequate avoidance measures and/or well-tolerated symptomatic medications should also be established. In general, immunotherapy is restricted to patients with moderate to severe IgE-mediated symptoms attributed to aero-allergens which are unavoidable for more than two months of the year. Immunotherapy may be justified in less sensitive patients with limited sensitivities if drug regimens are either ineffective or poorly tolerated or where for reasons of job or profession (acting, broadcasting etc) total release from symptoms is essential.

What immunotherapy involves

Immunotherapy involves serial subcutaneous injections of immunogenic extracts of relevant allergens administered in progressively increasing doses until a potent immunogenic dose or maximal tolerated dose is achieved. Usually a potent immunogenic dose is one which is significantly greater than that required for a specific IgG response. For most allergenic extracts the immunogenic dose is poorly defined but is probably not reached until the concentrations of 1 to 100 w/v or stronger are employed. Thus sufficient allergen must be administered to induce the immunological changes necessary for successful therapy. Putting it another way, once the decision has been made to use this form of treatment, sufficient quantities have to be administered. Relief of symptoms is related to higher doses and/or prolonged treatment and, therefore, the achievement of a maximum tolerated dose is a therapeutic goal once the commitment to undertake immunotherapy has been made. The maximum tolerated dose is the highest dose which can be administered without producing unacceptable side-effects. Some degree of local discomfort and swelling around the injection site normally accompanies immunogenic doses in highly sensitive patients and, therefore, must often be endured if therapeutic success is to be achieved.

Theories regarding the mode of action of immunotherapy

The way in which immunotherapy prevents allergic symptoms is still incompletely understood. Symptomatic relief can be achieved after 6-20 weeks of intensive treatment provided that sufficient quantities of allergen are administered. During the first year of immunotherapy, skin test reactivity to the allergen in question changes little, if any, and antigen-induced leucocyte histamine release is likewise unaffected. These observations suggest that the cellular reactivity of IgE-laden skin mast cells and circulating basophils have not been
appreciably altered. Thus, immunotherapy does not appear to desensitize the effector cells of the allergic response.

The concentration of circulating IgE antibody, assessed by radioallergosorbent assays or similar techniques, usually increases during the early part of immunotherapy. Thereafter, the levels gradually decline and it may take several years before the serum IgE antibody levels return to pretreatment levels. Thus neutralization or depletion of circulating IgE by injected allergen is also an unlikely explanation of the effects of immunotherapy. Likewise, the induction of immunological tolerance is an unlikely explanation since immunotherapy is associated with large amounts of serum-blocking antibody predominantly IgG. This IgG antibody competitively competes for antigen with cell-bound IgE on basophils and mast cells and may thereby induce a significant shift of the dose responsive to relevant environmental allergens. Although a protective effect of passively effused IgG antibody has been demonstrated in insect allergy, there is as yet no direct evidence which indicates that IgG 'blocking antibody' is principally responsible for symptom amelioration observed in inhalant allergy immunotherapy. Quantitatively blocking antibodies do not correlate very well with the response to treatment and, in some instances, patients who have responded well clinically produce very little IgG antibody. Blocking antibodies also increased in nasal secretions but the rise is far less than in the serum. Calculations of the concentration of allergen and quantities of blocking antibody suggest that binding of allergen by IgG antibody might not be rapid enough to prevent induration with mast cells. The association between IgG antibody levels and symptom amelioration is weak and subject to numerous exceptions indicating that there is not a simple quantitative relationship between IgG antibody and protection from allergic exposure.

When immunotherapy is continued for 3 or more years, additional immunological changes are observed in many patients. Serum IgE antibody begins to decline slowly suggesting possible suppression of IgE antibody resynthesis. However, the evidence that alterations to suppressor cells which control IgE production play a role in human desensitization is very poor. There are no studies that show that a 3-month course of injections lead to significant reduction in serum IgE antibody or in skin tests of sensitivity. In most studies, after 3-6 months of treatment serum IgE antibody has risen slightly. On the other hand there is evidence that long-term immunotherapy is associated with reductions in IgE antibody, reduction in seasonal boost of IgE antibody and, possibly, a long-term decrease in skin sensitivity. Most studies have been too short to fully document these effects. There are a number of T-cell-related effects and many studies have established that the response in vitro of T cells to allergen is changed after desensitization. These changes have been documented in a variety of ways; they include an increased production of macrophage inhibiting factor (MIF), reduced lymphocyte proliferation, increased suppressor cell effects in vitro and changes in the number of suppressor T cells. The interpretation of these findings in vitro is presently unclear and is unlikely to be related to suppression in vivo of IgE since most of the T-cell effects were observed at a time when IgE antibody concentrations were not altered. There are other ways in which T-cell changes might be relevant to the success of immunotherapy. Thus T cells might directly contribute to chronic symptoms, produce agents which affect mediator release and may be involved in basophil chemotaxis.

It was seen nevertheless that complete suppression of IgE antibody would presumably lead to a 'cure' of the disease. For this reason there have been many efforts to accelerate the
decline of IgE antibody by manipulating the immune system with a variety of modified allergens.

**Allergen extracts used in specific immunotherapy**

In general, grass weed and tree pollen extracts are the most reliable and well-standardized extracts for immunotherapy with inhalant allergens (Dreborg, Einarsson and Longbottom, 1986). Mould spore extracts have considerable variability in the quality and standardization of fungal extracts which limits their usage. Similar problems are true for animal epidermal (dander) extracts. In general, animal dander allergy is readily managed by avoidance so that immunotherapy is only rarely indicated, for example in occupational exposures. House dust 'extracts' are highly variable in composition. House dust mite extracts have been used successfully in certain instances. The other pollen subjected to controlled study is mountain cedar (because of standardization problems the optimum dose is still difficult to describe but a dose of crude, unaltered extract adequate to ensure symptomatic relief will often be accompanied by a considerable risk of a large local or systemic allergic reactions).

Most studies of house dust sensitivity gave mixed results. The bacterial vaccines have consistently failed to be efficacious in a number of controlled studies of the treatment of asthma related to respiratory infections, a recent study showing occasional bronchial reactivity by immunization with cat dander on very few subjects. Although there have been a large number of placebo controlled, and mostly blind, studies on the effect of injection immunotherapy on house dust mite or house dust allergy, the results have been variable. Two showed no effect at all, the rest showed varying effects ranging from clinical improvement without immunological changes to effects on both immunological variables and symptoms, including bronchial hyper-reactivity. The general unimpressive lack of effect might have been due to the selection of patients, the allergen doses administered, the duration of treatment and the reliability of objectivity of the parameters for assessment.

In the USA, the high prevalence of positive skin tests to a cockroach allergen have been demonstrated in indigenous asthmatic populations. The use of cockroach allergen for immunotherapy is still under evaluation. Substances not recommended for specific immunotherapy include foods, whole body extracts of stinging insects, feathers, synthetic material (for example kapok), bacterial extracts, gums and glues, enzymes (for example subtilis) and occupational allergens.

Aqueous allergen extracts are still the most commonly employed materials for immunotherapy. They are the most economical form of therapy and less likely than precipitated and/or pyridine extract materials to contain allergens that are denatured or lost by processing. Aqueous extracts may be purchased commercially in buffer saline in lyophilized form or 50% glycerin. Potency is usually expressed on a weight per volume basis or in protein nitrogen units (PNU) or in biological units. For many pollen allergens 1 mL of a 1:20 allergen extract is approximately equivalent to 25,000 PNU. A predictable relationship between PNU and weight per volume ceases to exist for non-pollen allergens, especially for foods and fungal extracts where the protein extracted from the given weight of material is highly variable.
Applications of immunotherapy

There is no evidence that mixtures of several allergens are efficacious, although within the 'family' of allergens there is considerable if not complete cross-reactivity. For instance, an extract of Timothy grass is probably as effective as a mixture of several grass pollens but combining, say, Timothy with house dust mite or even Timothy with tree and weed pollens is to be discouraged. In any event, any allergen to which the patient is extremely sensitive should be given separately so as not to eliminate the amount of other allergens given due to recurrent large, local or systemic reactions. Allergens are given subcutaneously once or twice weekly until the maintenance dose has been achieved or the maximal tolerated dose is achieved. The interval between injections is then increased to 2 weeks, and, if clinical improvement continues, the intervals may be 3 or 4 weeks. A suitable extraction concentration for initiation of therapy varies from 1:10,000 (w/v) to 1:25,000 (w/v) depending on the sensitivity of the patient. This is one-tenth or one-hundredth of a biological unit. Twenty to 35 injections are usually required to reach a satisfactory maintenance level of 0.2-0.5 mL of 1:100 (w/v) or 1 mL of 100,000 biological units per mL. In sensitive patients, the dosage schedule may require individual modification because of local or systemic reactions. Once maintenance dose is achieved it is usually continued perennially; however, for pollens it is the practice in the UK to recommend that allergen therapy is discontinued during the pollen season and recommenced the following winter. There appears to be no rationale in this point of view and co-seasonal maintenance injections are given by some practitioners. Sometimes it is necessary to reduce doses temporarily during the major allergen season if reactions to immunotherapy appear to occur more frequently. Some adverse reactions are to be expected in the course of immunotherapy in a highly sensitive patient, but are not predictable by any known immunological or clinical tests. Some practitioners prefer a cluster regimen to minimize the number of attendances at the clinic. Using this regimen maintenance levels could be achieved by week 5. There is some debate as to whether conventional or semi-rush regimens are associated with more or less side-effects. Sometimes a rush regimen is used in which maintenance dose is achieved over a 24-hour period. This is always undertaken under strict supervision on an in-patient basis.

Successful immunotherapy is usually apparent within 6 months after achieving a maintenance level dose. Many patients continue to improve during the second and third year of treatment and, therefore, 3 years' treatment is usually advised for all forms of immunotherapy. Very sensitive patients may respond immunologically and clinically even though the maximum tolerated doses are substantially less than the usual maintenance levels. When immunotherapy is discontinued, symptoms usually return over a period of several years although some patients remain symptom free. Unfortunately, there is no way to predict in advance which patients will benefit most from immunotherapy, although most patients who receive adequate doses can expect to experience fewer symptoms and require less anti-allergic medication. Environmental control should still be instituted. There is no practical way of monitoring immunological variables in patients undergoing immunotherapy for aeroallergens. Allergen sensitivity by skin tests is unlikely to change within the first years of treatment even in the face of a good clinical response. Serum IgE antibody levels determined by radioallergosorbent test and measurements of serum IgG antibodies may be useful in venom immunotherapy. Conjunctival reactivity is sometimes recommended as a useful monitor for efficacy.
Immunotherapy should be discontinued if the patient cannot be advanced to a satisfactory dose level because of persistent adverse reactions or if the patient is poorly compliant and fails to receive injections regularly. If no clinical improvement is observed after 3 years of maintenance, or if the patient is essentially symptom free after two consecutive years, or the patient has been on immunotherapy continuously for 6 or more years, then these are all indications for stopping treatment.

There are many reasons for treatment failure. These include inadequate environmental control and avoidance of allergens particularly in the home, and the development of new sensitivity since the initiation of treatment. The allergen may be administered in insufficient doses or potency of the treatment materials may decline. An incorrect initial diagnosis should also be considered. An inadequate trial period is a possibility as is the masking of partial benefit due to progression of the underlying disease.

**Allergen immunotherapy with modified allergens**

Immunotherapy results in the reduction of symptoms but does not eliminate them, and patient must not have false expectations. During recent years there have been a number of attempts to improve immunotherapy with the use of modified allergens, with the hope of decreasing allergenicity in the side-effects but maintaining immunogeneity.

Some examples of major directions and attempts to improve allergen immunotherapy include water-in-oil emulsion (to reduce rate of allergen absorption), purification of antigens, alteration of antigen to reduce allergenicity but retain immunogenicity (allergoids), preparation of agents that selectively suppress IgE antibody production (antigen:polyethylene glycol). Water-in-oil emulsions were abandoned because of the production of sterile abscesses and the danger of myeloma. Purified antigens are expensive and do not reduce the risk of anaphylactic-type reactions. In Europe, pyridine-extracted aluminium hydroxide-absorbed extracts have largely replaced aqueous extracts during the last decade.

Too little is known about dose regimens and the maximum doses with conventional aqueous, depot and modified extracts. Modified allergens, showing less allergenicity, with retained immunogenicity have less side-effects. There is no evidence that any of these components have a suppressive effect on the ongoing IgE response. Local immunotherapy, that is local nasal and oral administration, has not proved to be effective. Induction of anti-idiotypic antibodies may be a possibility in the future.