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TOPICAL CORTICOSTEROID THERAPY

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Chairmen: Prof. D. Passali, Rome (Italy)
Dr. S.R. Durham, London (United Kingdom)

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Preface

The following papers represent the proceedings of a symposium entitled "Topical Corticosteroid Therapy" which was held at the joint meeting of the European Rhinologic Society and the British Society for Allergy and Clinical Immunology in London on June 27th, 1990. Contributions from the U.K., Europe and U.S.A. provide an overview of current practice in the diagnosis and management of rhinitis and nasal polyps. The meeting was well-attended by physicians and surgeons which provided a lively debate.

The inflammatory nature of allergic rhinitis was emphasized by several speakers. The use of topical nasal corticosteroid sprays has proved effective and safe in adults. However, we should not ignore the possibility of systemic side effects following local absorption. This is particularly relevant in the treatment of children and in adult patients when nasal corticosteroids are used long term and in addition to inhaled corticosteroid therapy for asthma. For these reasons the introduction of newer corticosteroids with high topical potency and a low potential for systemic effects is to be welcomed.

Members were saddened to hear of the death of Dr. Ulf Pipkorn shortly before the meeting. Dr. Pipkorn's manuscript was submitted in advance of the meeting and is published here along with the presented papers at a symposium which is dedicated to his memory.

London, June 1991

S.R. Durham,
Guest-Editor

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The inflammatory basis of rhinitis

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INFLAMMATION

In the medical dictionary the term inflammation is defined as "A protective tissue response to injury or destruction, which serves to destroy, dilute, or wall off both the injurious agent and the injurious tissues" (Dorland's Medical Dictionary 24th ed). The cardinal signs of inflammation, rubor, calor, tumor and dolor, were already known in ancient Greek and Roman times. They have been attributed to the Roman encyclopedist Celsus (30 BC-38 AD). Later functio laesa was added as a fifth sign of inflammation. Today, we regard cellular emigration and infiltration as another characteristic of the inflammatory reaction. The major signs of inflammation are largely the result of vascular reactions. Rubor and calor are the effects of vasodilatation and increased blood flow, while tumor is the effect of increased vascular permeability, blood pooling and other tumour-fascient changes. It is interesting to note that all these features can be studied with relatative ease in the upper airways.

BENEFICIAL EFFECTS OF ANTI-INFLAMMATORY DRUGS – A REASON TO CALL A DISEASE "INFLAMMATORY"

An alternative way of designating a disease as inflammatory, specifically in terms of airway disease, has been to use this term when "anti-inflammatory" drugs, such as glucocorticoids, have a clinically beneficial effect. This alternative use of the term inflammatory has been most obvious in the field of allergic airway disease where the trend in recent years has been to designate asthma, for example, as an inflammatory disease. This use of inflammatory disease on the basis of "beneficial effect of glucocorticoids" appears to contrast somewhat to the inflammatory infectious airway diseases in which the use of glucocorticoids so far has been contra-indicated. It is interesting to note that inflammation in this view is given a dual undertone in terms of being beneficial (infection) as well as pathogenic (asthma).

INFLAMMATORY REACTIONS IN THE UPPER AIRWAYS

The features of inflammation in the upper airways are similar to those in other locations. Thus, a local vasodilatation results in nasal stuffiness as well as an

increase in mucosal temperature. Changes in nasal patency (nasal stuffiness) can be measured indirectly using rhinomanometry (Pipkorn, 1988) and now directly using acoustic rhinometry (Hilberg et al., 1989). An increase in local nasal mucosal temperature has thus been described as a result of virus infections and of local challenges with allergens (Åkerlund and Bende, 1989; Seppey et al., 1989). The increase in local temperature has been determined directly using thermistors (Åkerlund and Bende, 1989) and indirectly using external thermography (Seppey et al., 1989). Using this approach an increase in local temperature of the magnitude of 1–3 degrees Centigrade has been shown.

The other vascular feature which is associated with inflammation is an increase in local vascular permeability (Svensson, 1990). The extravasation of plasma proteins induced during the inflammatory process may also contribute to the decrease in nasal patency. This process will also lead and contribute to the increase in nasal surface liquids which is often associated with nasal disease.

The generally accepted sign of inflammation is the infiltration of local tissue by inflammatory cells. This characteristic is also a partly vascular phenomenon and the extravascular appearance of the inflammatory cells such as granulocytes has been taken to be a morphological sign of inflammation. Whether the extravasated cells are activated or not has not been directly linked to the microscopic inflammation.

ALLERGIC RHINITIS AS AN INFLAMMATORY DISEASE

Is there a basis for calling allergic rhinitis an allergic airway disease? When the second type of definition is used, namely "beneficial effect of anti-inflammatory glucocorticoids", there is clearly a basis for using such a term. The inflammatory term could also be applied, however, if the first type of definition is used. All the vascular features described above are present: both the influx of inflammatory cells and the increase in vascular permeability. The specific trait of the allergic inflammation is the prominent presence of eosinophils. The vascular and cellular characteristics as well as the glucocorticoid effects have been described in the challenge setting as well as during natural allergen exposure.

EARLY INFLAMMATORY SIGNS IN THE CHALLENGE SITUATION

When the appropriately sensitized nasal mucosa is exposed to the relevant allergen in the challenge situation, a series of events with characteristic timing is initiated. After a few minutes the itching sensation is followed by the sneezing, both of which are mainly reflex-induced symptoms via "irritant receptors" in the nasal mucosa (Mygind, 1979). This is then followed by an increase in nasal surface liquid which is a mixed result of glandular activity and plasma leakage but is also influenced by other sources. The decrease in nasal patency which is also the result of vascular leakage and of a prominent decrease in the tone of the capacitance vessels then follows. These features have been termed the immediate phase of the allergic response and are reflex-mediated as well as being vascular phenomena.

LATE INFLAMMATORY SIGNS IN THE CHALLENGE SITUATION

The response to the allergen does not stop at this point, however. When the lower airways are studied for a prolonged period after laboratory exposure to allergen and using a physiological parameter for airway obstruction as the main study parameter, there is sometimes a second prolonged airway obstruction (Pepys and Hutchcroft, 1975). This appears to develop 2–4 hours after the initiating allergenic stimulus, reaches a maximum after 6–8 hours and then gradually fades. This second decrease in FEV in the dual response pattern has been given the name the "late phase response". The same term has been directly applied to the upper airways and is sometimes used indiscriminately for events occurring after the first hours. Since the term "late phase response" is so strongly associated with the determination of a single physiological parameter in the lower airways, one should perhaps avoid using this specific term for upper airway phenomena, especially since there is no generally accepted definition of this term in the upper airways. There appears to be a varied individual response pattern in terms of the different nasal symptoms such as sneezes, increase in nasal surface liquid, and nasal blockage (Naclerio et al., 1985). Other important features which are part of the late inflammatory events in the upper airways are the influx and subsequent activation of inflammatory cells (Bascom et al., 1988a; 1988b). The eosinophil is therefore a specific hallmark of allergic inflammation. Changes in local specific and non-specific reactivity and continuous vascular changes are also strongly associated with the later inflammatory events. The various features of the later inflammatory reaction occur simultaneously to a large extent. Although there have been speculations about pathogenic links between these various parts, such as between symptoms and basophil influx and activation and between the change in local reactivity and eosinophil influx and activation, the human in vivo data to support these speculations is generally lacking. In fact, a series of studies of putative links between eosinophil influx and the change in reactivity have failed to demonstrate a direct relationship in terms of the timing and strength of the reactions (Andersson et al., 1987; Bascom et al., 1989; Klementsson et al., 1990a). Furthermore, it has also been shown that it is possible to inhibit the local change in non-specific reactivity using antihistamines without any inhibition of the local eosinophil influx (Klementsson et al., 1990b). Similar effects were noted for a NSAID drug (Klementsson et al., 1990c).

When it comes to the alternative definition of inflammatory disease, namely susceptibility to anti-inflammatory glucocorticoids, this is clearly relevant for these later inflammatory signs after allergen challenge. Both oral and topical

glucocorticoids have been shown to inhibit late occurring symptoms, the influx of inflammatory cells and the induced change in specific and non-specific reactivity (Pipkorn et al., 1987a; 1987b). This even appears to be true for very short bursts of treatment with glucocorticoids, even if these are given after the initiating allergen challenge (Andersson et al., 1988).

INFLAMMATORY SIGNS DURING NATURAL ALLERGEN EXPOSURE

In recent years it has been possible to validate the various challenge findings during natural allergen exposure as well. It has thus been demonstrated that allergen exposure is associated with some of the signs which appear soon after the allergen exposure in the challenge setting, such as vascular leakage (Andersson et al., 1989), but also signs characteristic of the later inflammatory events in the challenge setting, such as the change in reactivity and eosinophil influx (Pipkorn et al., 1988). It was thus found that the eosinophil influx was an early sign following natural allergen exposure and that the number of eosinophils on the surface reflected the degree of pollen exposure as well as the symptoms the patients experienced to some degree. Using the lavage approach during natural allergen exposure it was also possible to demonstrate that there was increased levels of plasma-derived proteins on the mucosal surface during natural allergen exposure (Andersson et al., 1989; Svensson et al., 1990) and that there was a correlation between this phenomenon and the symptoms the patients experienced. In the same study it was also possible to demonstrate local signs of eosinophil activation during the active disease (Figure 1).

Used topically for hay fever treatment glucocorticoids are one of the most effective treatment alternatives and nasal symptoms are relieved to a great extent. In a recent study it was also possible to demonstrate that topical glucocorticoids also inhibited the various signs of inflammation such as plasma leakage, cellular influx and change in non-specific reactivity during natural allergen exposure (Klementsson et al., 1990d).

NON-ALLERGIC NON-INFECTIOUS INFLAMMATION

In recent years we have considerably extended our knowledge of the pathophysiology of allergen induced inflammation. The challenge in the years to come will be to extend our knowledge of the pathogenesis of the perennial non-allergic rhinitis moiety. It has been shown that some patients appear to share common pathways in the pathogenesis such as mediator release and the presence of late occurring events (Togias et al., 1985; 1989). Whether these are common phenomena and whether the glucocorticoid effects are similar in these diseases remains to be investigated.

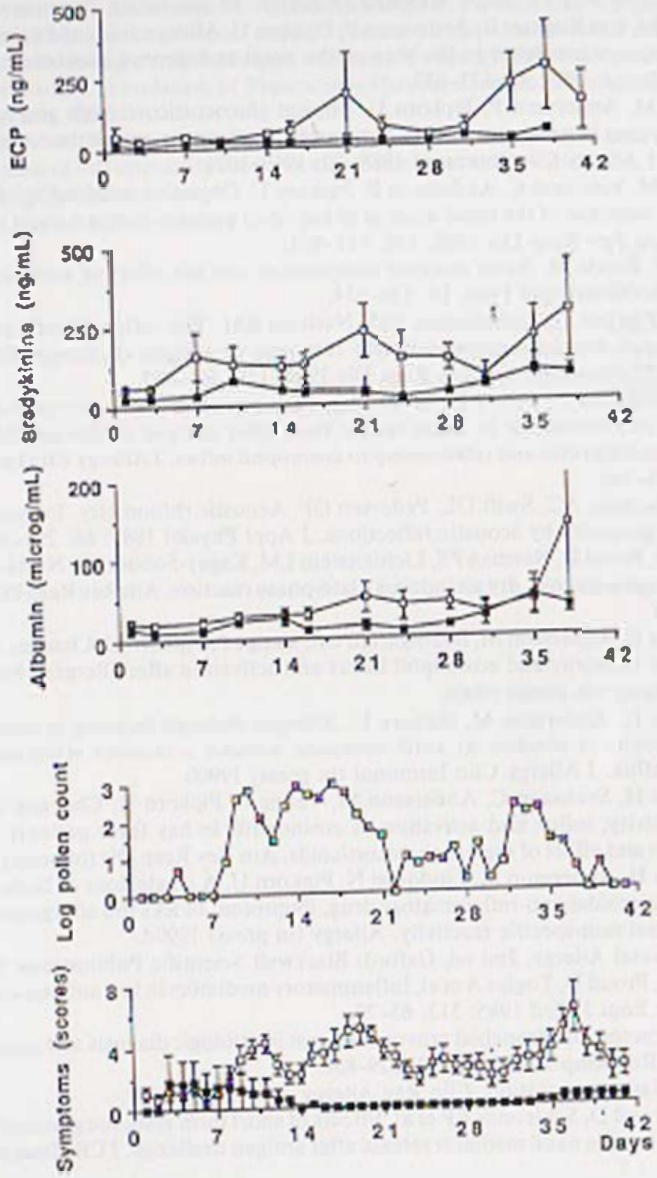

Figure 1. Combined figure showing the concentrations of ECP, bradykinins and albumin in nasal lavages performed during the birch pollen season in 9 pollen allergic subjects and 5 normal controls. The lowest panels show the pollen count of birch pollen for the study area and the mean total symptoms experienced by the pollen allergic subjects.
From Svensson et al. 1990, reprinted with permission from J Allergy Clin Immunol 1990; 85, 386–389.
□ allergic patients, ■ normal controls.

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Differential diagnosis of perennial rhinitis

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Perennial rhinitis can be defined as a non-seasonal complex of nasal symptoms in which obstruction and discharge predominate. It is thought that up to six million people per year in the United Kingdom lose time off work with chronic sinusitis and, therefore, at least three times that number will suffer the predisposing symptom complex of rhinitis. Most are managed successfully with topical nasal medication but three groups are considered for surgery:

1. Those with a predisposing structural cause such as a deviated nasal septum or enlarged turbinates that do not vasoconstrict.
2. Those who develop recurrent sinusitis as a result of rhinitis.
3. Those in whom the symptoms of obstruction and discharge are refractory to medical treatment.

The author measures this with a visual analogue scale. The patients indicate on 2 x 100 mm scales the severity of their symptoms (obstruction, discharge). Those with a score of over 120 are considered for surgery.

This paper, however, will only deal with the differential diagnosis and possible precipitating causes of perennial rhinitis.

HISTORY

1. *Age*

In children with perennial rhinitis, several factors must be considered as primary causes. The commonest will be nasal obstruction secondary to adenoid enlargement. This is often accompanied by enlarged, engorged turbinates which settle when the adenoids are removed.

Atopy from inhalant allergens does not usually develop till later childhood but, in very young children, nasal symptoms can occur as a result of hypersensitivity to foods such as milk and wheat (Mygind and Weeke, 1986). Both of these allergic reactions can occur primarily but may also be a presenting feature of coeliac disease which may be present without the classical florid manifestations.

Ciliary dyskinesia can be congenital or acquired (Afzelius, 1976; Greenstone et al., 1985). The commonest congenital condition is Kartagener's syndrome, characterised by bronchiectasis, sinusitis and situs inversus. Electron microscopic examination of the cilia reveals disorganized microtubules and the absence of dyncin arms.

A number of other congenital conditions have ciliary abnormalities, including Polynesian bronchiectasis, Usher's syndrome, Laurence-Moon-Biedl syndrome and Cockayne's syndrome. In both cystic fibrosis and Young's syndrome, the abnormality is in the mucous rather than the cilia.

Acquired ciliary dysfunction can come from environmental factors such as air conditioning and central heating, specific toxins such as nitrogen dioxide, sulphur dioxide, nicotine and local anaesthetic agents such as cocaine and adrenalin. A variety of viruses have been implicated in ciliary damage, including influenza A and B, adenovirus, parainfluenza, respiratory syncytial virus and herpes simplex. Bacteria such as mycoplasma pneumonia, bordetella pertussis, pseudomonas aeruginosa, Haemophilus influenzae and Streptococcus pneumonia can also inhibit ciliary beating.

In all age groups, trauma to the septum causing deviation and altered airflow or more rarely to the lateral nasal wall can result in chronic rhinitis.

In the geriatric population, rhinitis can develop for two main reasons. Firstly, with cartilaginous laxity developing, the nasal valve can collapse causing a long-standing deviated nasal septum to be noticed for the first time. Secondly, autonomic dysfunction can cause profuse watery nasal discharge which is well recognized in the elderly and often precipitated by changes in temperature and humidity.

2. *Race*

While this article is written from a Northern European department of rhinology, cognizance must be taken of the many nasal diseases that are endemic in other parts of the world and which may be seen in Europe in the immigrant population (Wilson and Montgomery, 1980; Maran and Lund, 1990).

a. Rhinoscleroma – This is caused by the Klebsiella rhinoscleromatis and it occurs frequently in Central and South America, Africa, the Middle East and India where it is associated with a poor standard of health and living conditions. The disease goes through three phases: rhinolitic, infiltrative and nodular, finally resulting in adhesions, stenosis and atresia. The large red tumour-like masses of the nodular phase are characterized histologically by the presence of Mikulicz cells and by Russel bodies which are plasma cells with eosinophilic staining cytoplasm and prominent nuclei. The coarsening of the external nose has been called a tapir nose.

b. Leprosy – It is estimated that 12 to 15 million people are still affected by this disease worldwide. It is caused by mycobacterium leprae. Two forms are recognized, tuberculoid and lepromatous, though some patients fall into a borderline group between the two. There is a diffuse infiltration of the skin, mucous membranes and nerves and a nodular thickening of the mucous membrane, especially at the anterior end of the inferior turbinate. The septum is progressively involved with perforation of the cartilage, collapse and stenosis (Barton, 1985).

c. Glanders – This infection caused by the pseudomonas mallei is parasitic in horses and donkeys and can occur in people working with these animals. An initial pyrexia and rash is followed by the appearance of small subcutaneous and intramuscular nodules which ulcerate and heal. These cause a generalized rhinitis with crusting.

d. Tuberculosis – Apart from lubus vulgaris, the nasal cavity is rarely affected by tuberculosis and is almost always secondary to pulmonary involvement. The lesions can be nodular or ulcerative and are found on the anterior cartilaginous septum, inferior turbinate and in the choanal region.

e. Syphilis – Infection with treponema pallidum can occur at any age but is becoming rarer. In acquired syphilis a primary cancer can occur around the vestibule three to four weeks after contact, secondary syphilis which may present as a simple catarrhal rhinitis occurs at six to ten weeks and a gumma which invades mucous membrane, the nasal septum and the bridge of the nose, occurs very much later. Congenital syphilis may show the lesions of either secondary or tertiary syphilis.

f. Leishmaniasis – This protozoal infection is transmitted by insects such as sandflies and occurs in Central and South America. It causes destruction of the nasal septum and is diagnozed histologically.

g. Myiasis – This is a condition occurring in India between September and November and is produced by the chrysomyia fly which lays its eggs in mucous membrane already damaged by chronic infection.

h. Fungal infection – The commonest fungus to affect the nose is the Aspergillus and it is most often seen in the Sudan. It causes a granulomatous lesion of the nasal septum and polyps and spreads into the sinus and subcutaneous tissues. Rhinosporidiosis is a granular condition of the nose seen in India, Sri Lanka and Africa and is contracted from horses or cattle dung (Waxman et al., 1987).

3. *Sex*

It is still debatable whether or not there are oestrogen receptors in the nose. Certainly they are present in some people and certainly more females than males are affected by rhinitis (Wilson et al., 1966).

The effect of hormones on the nasal lining is well known (Watson-Williams, 1952). All world record sneezing bouts have occurred in pubertal girls, the epistaxis of vicarious menstruation has been known for centuries, and the effects of sexual excitement or honeymoon rhinitis are well established. In pregnancy many women either develop rhinitis or have an exacerbation of existing symptoms which is thought to reflect the increasing oestrogen levels.

Many patients with HIV infection may also present with a watery rhinorrhoea (Berlinger, 1985).

4. *Environment*

The carcinogenic effect of many inhalants in the nose is well established. The risk of a hard woodworker developing adenocarcinoma of the ethmoids is similar to the risk of a cigarette smoker developing lung cancer. The carcinogenic risk of exposure to nickel and chrome is not as high. People working in dusty atmospheres such as brickworkers, miners and bakery workers may suffer rhinitis.

Patients with atopy to animals will obviously have difficulty working with them on farms or in animal labs; nearly everyone with a rhinitis will find that it is made worse, even though they are not atopic, by exposure to strong odours such as perfume, petrol and paint. The new prolific crop of oil seed rape may also cause rhinitis in those living near it or in the direction of the prevailing wind.

Rhinitis may be precipitated by formaldehyde which may be in the atmosphere in some laboratories but which can be released from glues integrated into some newer wood materials used in kitchen construction. Thus, people moving into new buildings may suffer nasal symptoms when these woods are heated.

Finally swimmers may get a nasal hypersensitivity due to chlorite or chlorine used to disinfect pools. This is obviously worse in public pools where the chlorite becomes more toxic when mixed with urea.

5. *Past medical history*

While it is unlikely that a dental infection will cause a primary rhinitis, it could be related to a sinusitis caused by an apical abscess penetrating the maxillary sinus (Killey and Kay, 1975).

It is important always to enquire about previous surgery. Patients, however, are usually very vague about what was done to their nose and the majority of nasal procedures are also multiple. Obtaining the operative details from previous hospital records is often not illuminating – what was the extent of the septal surgery, what was the extent of the ethmoidectomy, etc. It is, thus, imperative to perform a CT scan on any patient with a history of previous nasal surgery. The alteration of nasal tissue and the nasal anatomy also often precludes the successful use of medical therapy.

Many of the other related medical events of importance in a case of rhinitis such as immunodeficiency, bronchiectasis, endocrinopathy, allergy, asthma and trauma have been previously mentioned.

6. *Drug history*

The most notable drug induced rhinitis is rhinitis medicamentosa which is produced by prolonged exposure to alpha-adrenergic agonists (Rijntjes, 1982). The rebound congestion results in a secondary hyperemia encouraging the further use of medication. It is thought that mucosal vessels are eventually desensitized with loss of alpha-adrenergic tone and this persists as long as the medication is used (Hall and Jackson, 1968). The nasal cycle is suppressed for up to six months after cessation of treatment. Some agents are more potent than others. Naphazoline was one of the worst offenders but even dilute solutions of oxymetazoline should be used with caution and not for longer than two weeks.

Aspirin intolerance can also produce rhinitis by inhibiting the cyclo-oxygenase pathway which leads to preferential lipo-oxygenase metabolism and an increase in leukotriene production and slow reacting substance S (Chafee and Settipane, 1974; Sczaklik et al., 1975). Symptoms may be confined to a watery rhinorrhoea but a group of patients may also suffer from asthma and polyps as a result of aspirin intolerance.

Many antihypertensive drugs such as guanethidine can cause nasal symptoms and it is thought the more commonly used beta blockers can affect the nasal mucosa. This is very often seen in the elderly who are using drugs such as Timoptal® for glaucoma which can pass down the nasolacrimal duct bathing the mucosa of the nose and causing nocturnal nasal obstruction (Malm, 1974).

A few patients presenting with rhinitis with no obvious case may, among other things, be suspected of abuse of cocaine or marihuana.

SYMPTOMS

The main chance of diagnosing a cause for perennial rhinitis comes from the history and nasal examination. Some assessment of the symptoms, however, must also be made.

1. *Blockage*

The patient must be asked about the length of the history and at that point the examiner should seek to correlate any history of trauma, medical conditions, drug therapy or environmental change. The laterality of this symptom is important because unilateral symptoms are likely to be related to a deviated nasal

septum, an organic nasal disease or a dentally related pathology. It is important to know if the symptom is constant or intermittent and what factors alter the constancy. One of them might be the use of local nasal medications and so drug efficacy can be assessed.

2. *Discharge*

The character of the discharge is obviously important. Any pus suggests secondary infection and probably sinusitis. Usually, however, the discharge is mucoid or watery. Most sinus related discharges go posteriorly. Anterior watery discharges are usually due to vasomotor rhinitis which this author considers to be one of the autonomic dysfunction conditions. Again the effect of drugs on the symptom is important to establish, especially cromoglycate, ipratropium and steroids.

3. *Secondary symptoms*

Most cases of perennial rhinitis will have co-existing secondary sinusitis, reduced olfaction or facial discomfort.

INVESTIGATIONS

Rhinoscopy should in 1990 always be done endoscopically using first the 0° endoscope and then the 30° endoscope. It should be done before and after decongestion and it is inappropriate in an article like this to list the abnormalities that can possibly be seen (Draf, 1983; Howard and Lund, 1986). At this point the examiner is likely to have diagnosed the cause of the rhinitis in 90% of cases. Every patient should have sinus imaging, either by coronal polytomography or preferably by CT scan with correct window settings depending on availability. This will probably not help in the diagnosis of the primary cause but it will help in the evaluation of the problem and the creation of a treatment plan.

Those suspected of an allergic diathesis should be obvious from the history. We do not consider that skin test findings and RAST results should form the basis for a diagnosis if they do not tie in with the history.

Ciliary dyskinesia can be assessed grossly by one of the mucociliary clearance tests and more exactly by measuring ciliary beat frequency (Stanley et al., 1984; Wilson et al., 1986).

Finally it is unlikely that studies of nasal airflow will help the diagnosis and biopsy may be of use if a specific mucosal abnormality is suspected.

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Pharmacological management of perennial rhinitis

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CASE HISTORY AND EXAMINATIONS

As we all occasionally have nasal symptoms, it is difficult to make a distinction between normal and abnormal. When a person visits his doctor due to sneezing, rhinorrhoea and nasal blockage, and they last for at least one hour on most days, he suffers – per definitionem – from perennial rhinitis, although signs can be absent and all tests negative.

The situation is even more difficult in children who often get accustomed to nasal symptoms. They consider it to be "normal" and will often not complain. In many cases, they are referred by parents and school teachers, who find the signs of the disease annoying and unacceptable.

As symptoms range from the negligeable to the disabling, it is important to get information about the severity of the disease (hours per day with symptoms, approximate number of sneezes and nose blowings per day). It is also relevant to know what is the dominant symptom. Some patients, 'sneezers', sneeze and have associated rhinorrhoea and blockage. Other patients, 'blockers', have nasal blockage as the main symptom. 'Nose blowers' predominantly suffer from watery rhinorrhoea without sneezing.

Rhinoscopy, as part of an ENT examination, is always indicated in perennial rhinitis. The nasal mucusa will often present pale-bluish and wet and the inferior turbinates markedly swollen and hyperplastic, but rhinoscopy can be completely normal.

Examination of repeated nasal smears for eosinophils can be helpful for making a distinction between eosinophilic (allergic and non-allergic) and non-eosinophilic rhinitis. The eosinophilic subgroup responds better to antihistamines and steroids than the non-eosinophilic subgroup.

Inquiry about NSAID-provoked eye itching, nasal symptoms, asthma and urticaria is of relevance, especially in patients with nasal polyps and hyperplastic sinusitis.

Allergy testing is a matter of course in all patients with perennial rhinitis. For inhalant allergy, all diagnostic tests show, in principle, the same. Skin prick testing is cheaper than RAST and less laborious than eye and nasal allergen provocation. The major difference between skin testing, RAST and allergen provocation testing concerns diagnostic sensitivity and specificity. A localized allergy, which only can be demonstrated in the diseased organ, does – in my opinion – not exist.

PHARMACOTHERAPY

Therapy for perennial rhinitis consists of allergen avoidance, pharmacotherapy, immunotherapy, surgery, or a combination. This paper will only deal with pharmacotherapy.

Cromoglycate

Cromoglycate has been used for more than 20 years. It is a mast cell stabilizing agent in animal experiments and in in vitro models. However, there is no hard data to support that this is the only mode of action in man. A large number of molecules with similar effect in experimental studies have failed in the therapy of allergic rhinitis. In addition, an efficient mast cell stabilizing agent could be expected to have a marked effect in allergic rhinitis. Although cromoglycate is significantly better than placebo, it is less effective than antihistamines and topical steroids. Application 4–6 times a day gives a 30% symptom reduction, so the cost-effectiveness is low. In children, it is a valid argument that cromoglycate is almost without any side effects. It can also be used as eye drops, but it is less effective than modern antihistamines.

Vasoconstrictors

Many in vitro studies of animal and human tissue have shown that alpha-adrenoceptor agonists stimulate secretion from serous glandular cells. However, in vivo studies in man have shown that this type of drugs only have a clinical effect on nasal blockage.

Oral medication has a moderate effect on nasal patency and it is an advantage that the entire nasal lining as well as the paranasal sinuses are treated. However, it is, in principle, inexpedient to constrict the vasculature of the entire body in order to open up a blocked nose. Ordinary doses of pseudoephedrine and phenylpropanolamine (50 mg three times a day) is just at the border of what causes systemic side effects. Intranasal medication is very efficacious, or in fact too efficacious, as it gives an unphysiologically patent nasal airway. Long-term therapy carries a risk of rhinitis medicamentosa, which does not occur with oral medication. Possibly, the risk relates to the extremely high concentration of alpha adrenoceptor agonist at the receptor level.

It seems likely that most systemic side effects as well as rhinitis medicamentosa can be avoided if alpha adrenoceptor agonists are given topically in a low concentration. The theoretical advantage of alpha$_1$ agonists (constriction of capacitance vessels) over alpha$_2$ agonists (constriction of capacitance and resistance vessels) remains to be documented in in vivo studies.

Antihistamines

Many patients have suffered from the sedative side effects of the classical H_1 antihistamines. The introduction of a new generation of non-sedating or marginally sedating antihistamines has been the most important progress in rhinitis therapy in the last 10 years, and perennial rhinitis can now be treated with considerably less adverse reactions.

H_1 antihistamines block nervous and vascular H_1 receptors. They have a marked clinical effect on sneezing and rhinorrhoea, but not on blockage. This can be explained by the importance of other biochemical mediators for nasal blockage and by the existence of vascular H_2 histamine receptors. However, combined use of H_1 and H_2 antihistamines cannot inhibit histamine-induced nasal blockage completely, and the existence of another histamine receptor on nasal vasculature is a possibility.

Interestingly, H_1 antihistamines are effective not only in allergic rhinitis, but also in a proportion of non-allergic rhinitis, suggesting that mast cells and histamine also play a role in this condition. Added efficacy from an antihistamine and a steroid spray has been demonstrated and patients with severe perennial rhinitis will benefit from combined therapy.

Terfenadine is the most widely used new H_1 antihistamine. It does not cause any sedation, even when it is given together with alcohol.

Astemizole is more effective, but weight gain can be a problem. This drug has special kinetics with an almost indefinite binding to histamine receptors. Thus, allergy skin testing cannot be relayed upon for up to six weeks after cessation of astemizole treatment.

Certirizine causes an impressive reduction of histamine- and of allergen-induced skin reactions. In addition, experimental evidence suggest that this compound inhibits eosinophil influx. Whether this provides any added benefit in the treatment of rhinitis patients remains to be established.

Loratadine has, like terfenadine, an impressive safety margin with regard to sedative side effects.

Acrivastine, in contrast to the above mentioned drugs, is short-acting, and medication 2–3 times daily is necessary. An advantage is that it can be used by patients with occasional symptoms according to circumstances.

Cholinoceptor antagonists

Some patients, who predominantly suffer from watery rhinorrhoea will not respond to antihistamines or to steroids. As most watery rhinorrhoea is caused by stimulation of glandular cholinoceptors, these patients can be helped by the topically active cholinoceptor antagonist or anti-cholinergic drug, ipratropium. This nasal spray is effective within minutes, and the effect lasts for more than eight hours. The spray can be used on a regular basis in perennial rhinitis, as well as before provoking factors, such as cold air and spicy food. Controlled trials have shown that the overall reduction of nose blowings is about 30%. When a high dose is given in a normal nose, an unpleasant feeling of 'dryness' will follow. Therefore, the dosage must be matched to the severity of symptoms in the single patient. When patients have daily symptoms, a high dosage (2-6 puffs of 20 µg into each nostril) can be given in the morning, when rhinorrhoea is usually worst, and the spray can then be used as required during the rest of the day. Patients with occasional symptoms can exclusively use the spray according to circumstances. It must be emphasized that ipratropium is not a new wonder drug, suitable for all types of perennial rhinitis. It has a monosymptomatic effect, and it can be used when other treatments have failed. Two groups will benefit: the few rhinitic patients with severe daily watery rhinorrhoea, and the many 'normal' person, who now and then have rhinorrhoea, during a common cold or following known provoking factors.

Topical steroids

The introduction, in 1974, of beclomethasone dipropionate has been the most important progress in rhinitis treatment since the development of the first antihistamines in the 1940s. It is proven that a modern steroid spray exerts its anti-rhinitis activity by a local mode of action. This is due to a high local concentration of a potent steroid molecule. It is absorbed from the airway mucosa, but it is rapidly metabolized in the liver and has a short plasma half-life.

With regard to efficacy and risk of side effects there does not seem to be much difference between the commercially available steroid molecules (beclomethasone dipropionate, flunisolide, budesonide). The steroid can be given from a pressurized canister, as a solution or a suspension from a pump spray, or as a powder. The efficacy of these administration forms does not seem to differ significantly.

A steroid spray is the most effective basic therapy (with the exception of oral steroids) for allergic and for most cases of non-allergic rhinitis. In contrast to antihistamines, there is a good effect on nasal blockage. There is some effect on the impaired sense of smell in perennial rhinitis, but unfortunately not in patients with nasal polyposis.

Concomitant use of eye drops (not steroids) can be necessary, and proper patient instruction in use of the nasal spray is important. Side effects are confined to

slight immediate irritation, mainly during the first days of the therapy, and occasional nose bleeding. Very rare cases of septal perforation have been described. While a steroid spray can be used freely in adults, most pediatricians agree that this should not be a first choice therapy for perennial rhinitis in children. When severe perennial rhinitis in a child cannot be controlled by other means, it seems justified to add a steroid spray, used once daily in the morning in the lowest dose, which can control the symptoms.

Systemic steroids

Systemic steroids are effective on all nasal symptoms, especially blockage. In contrast to a steroid spray, systemic steroids will reach all parts of the nasal and paranasal cavities. Apparently, a short-term therapy (two weeks) can have a long-lasting effect, indicating that some vicious circles are broken. Systemic steroids can be a valuable additive to topical steroids in adults with severe perennial rhinitis, especially in order to open-up a blocked nose, so the spray can be adequately distributed. In rhinitis patients with nasal polyps it can be used for 'medical polypectomy'. The risk of side effects is very low when short-term systemic steroids are not used more frequently than every third month. In the rare case, a patient with severe polyposis is prepared to run the risk of taking a small daily dose of prednisolone in order to maintain the sense of smell.

Combined therapy

The best management of perennial rhinitis consists of combined therapy. In perennial allergic rhinitis, allergen avoidance is first considered, but most patients will need drug therapy; immunotherapy can be added in selected cases. In perennial non-allergic rhinitis, minor surgery can assist pharmacotherapy, which is not always as effective as in allergic rhinitis.

With regard to pharmacotherapy, one should not look upon the different types of drugs as competitors. The patient will often benefit from combined drug treatment, and from matching the drug profile to his specific symptoms (Table 1).

Table 1. Therapeutic drug profile.

	sneezing	discharge	blockage	anosmia
cromoglycate	++	+	+	-
vasoconstrictor	-	-	+++	-
antihistamine	+++	++	+	-
ipratropium	-	++	-	-
topical steroids	+++	++	++	+
systemic steroids	++	++	+++	++

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Immunology and treatment of seasonal rhinitis

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INTRODUCTION

Although frequently trivialized seasonal allergic rhinitis represents a major cause of morbidity in the United Kingdom and elsewhere. Over the last 30 years there has been an approximate four-fold increase in the prevalence of hay fever and currently there are over one million G.P. consultations per year with 10–15% of the population being affected (Fleming and Cromby, 1987). The major cause of seasonal rhinitis in the United Kingdom in June and July is grass pollen whereas tree pollen predominates in March through May and allergy to weeds and fungal spores occurs in August through October. It is of interest that although the prevalence of hay fever has increased in the United Kingdom over the past 30 years, pollen counts have, at least in London and the South East, fallen over this period, largely due to changes in agricultural practice. A possible reason for this paradoxical increase in hay fever in the face of falling pollen counts may be environmental pollution. For example in Japan the emergence of allergy to Japanese cedar pollen over the past 25 years has accompanied a dramatic increase in pollution due to automobile fumes (Muranuka, 1986). This increase in sensitization was confined to urban rather than unpolluted rural areas. Japanese workers have shown in animal models that particles in diesel exhaust fumes have an adjuvant effect on antibody production against cedar pollen (Muranaka, 1986). Clearly similar studies are required to investigate the influence of environmental pollution on pollen allergy in Europe.

DIAGNOSIS

The diagnosis of hay fever is made on the basis of a history of seasonal symptoms in which watery nasal discharge and blockage are frequently accompanied by itching, sneezing and eye symptoms with or without chest symptoms. Skin prick testing, although not essential, provides helpful supportive evidence and may serve to reassure both the patient and the physician. Measurement of blood con-

centrations of allergen-specific IgE (by RAST or ELISA etc.) is only rarely indicated, for example in the presence of skin disease (which may confound interpretation of skin prick tests) or during concurrent treatment with antihistamines.

IMMUNOLOGY

Improvements in the treatment of allergic rhinitis must depend upon a greater understanding of the basic mechanism involved. There is increasing evidence that seasonal allergic rhinitis like bronchial asthma, may be considered an "inflammatory" disease. Thus allergic rhinitis is accompanied by an intense cellular infiltration of the nasal airways, release of pharmacological mediators and a good therapeutic response to corticosteroids, features in keeping with an inflammatory disorder. Immediate nasal symptoms of itch, rhinorrhoea and sneezing may result from neural reflexes and/or the interaction of allergen with IgE on the surface of mast cells or basophils, the classic cells involved in immediate-type reactions. However, IgE has been identified on the surface of other cell-types including platelets, eosinophils and macrophages. These alternative cells may be activated directly by antigen without the requirement for preactivation of mast cells (Durham, 1989). Late allergic responses and chronic ongoing allergic symptoms in the nose and at other tissue sites are characterized by tissue eosinophilia. Traditionally, the recruitment of eosinophils has been thought to occur as a consequence of the release of chemotactic factors following mast cell degranulation. However, recent evidence supports a pro-inflammatory role for T lymphocytes during late responses both in terms of the local induction of IgE and the recruitment, maturation and persistence of eosinophils at allergic tissue sites. For example allergen-induced late cutaneous responses demonstrated an increase in CD4+(helper) T cells and "activated" eosinophils as indicated by staining with the monoclonal antibody EG2 (an antibody which recognizes only the secreted form of eosinophil cationic protein (ECP) which is released from activated cells) (Frew and Kay, 1988). There was a significant relationship between numbers of CD4+ and EG2+ cells during late responses. The number of eosinophils correlated with the size of the late cutaneous response. Thus eosinophil and T cell infiltration may be important in cutaneous late responses.

The pathology of seasonal rhinitis has been investigated in terms of local allergen provocation to the nose and during natural seasonal exposure to pollens. During immediate allergen-induced rhinitis mediators such as histamine, prostaglandin D2, TAME-esterase, leukotriene C4 and mast cell tryptase have been detected in nasal lavage fluid (Shaw et al., 1985; Castells and Schwartz, 1988). Mediators have also been detected during late nasal responses (Naclerio et al., 1985) where their release is inhibited by previous treatment with corticosteroids (Pipkorn et al., 1987). Eosinophils are prominent in nasal washings during late responses and prednisolone therapy inhibits both the inflammatory cell influx as well as late

clinical symptoms following allergen provocation (Bascom et al., 1988). The dynamics of the cellular response during natural allergen exposure has been investigated in patients with isolated birch pollen allergy before and during seasonal exposure (Pipkorn et al., 1988). Measurements in nasal lavage fluid demonstrated increases in eosinophils, whereas studies of cellular imprints on plastic strips applied to the nasal mucosa demonstrated an increase in nasal mucosal mast cells. There are relatively few studies of the histology of the nasal mucosa during seasonal rhinitis. A careful light and electron microscopic study demonstrated an increase in mediator cells during the pollen season (Kawabori et al., 1981). Recent studies of nasal biopsies fixed in Carnoy's solution identify an increase in mast cells during seasonal exposure (Viegas et al., 1987) and a reduction in mast cells after treatment with corticosteroids (Pipkorn and Enerbäck, 1987). The only reported immunohistological study identified an increase in dendritic (CD1+) cells within the nasal epithelium during the pollen season (Fokkens et al., 1989). Thus seasonal pollen-induced symptoms are accompanied by a specialized cellular infiltrate within the nasal mucosa. The precise contribution of these varying cell types to the development of late responses and ongoing symptoms has yet to be determined.

One approach to treatment of seasonal hay fever involves allergen injection immunotherapy. In a recent study, successful immunotherapy for hay fever was accompanied by inhibition of grass pollen induced late cutaneous responses (Durham et al., 1991). Immunohistology of these late cutaneous biopsies demonstrated a marked inhibition of the usual T cell and eosinophil infiltrate. A surprising finding in these biopsies was an increase in the number of cells expressing the CD25 marker (interleukin 2 receptor) which is expressed on the surface of "activated" T lymphocytes and, to a lesser extent on tissue macrophages, and an increase in class 2 molecule expression (HLA-DR). The significance of these findings is unclear. However, they suggest that specific immunotherapy may modify the allergen-induced late T cell infiltrate, possibly with inhibition or modification of the profile of inflammatory cytokines thereby released.

Local corticosteroid therapy is highly effective in seasonal allergic rhinitis and other allergic inflammatory disorders. It is of interest that corticosteroids, which have little direct effects on eosinophil or mast cell activation or degranulation in vitro, have profound effects on T cell proliferation and cytokine release (Schleimer, 1990). It is possible that steroid suppression of late responses and the accompanying eosinophilic infiltrate may result from an indirect effect on T cells. If confirmed, this would suggest that T cell systems should be used as models in vitro for the evaluation of new potential therapeutic agents with similar efficacy compared with corticosteroids and hopefully fewer side effects.

TREATMENT

The first principle of treatmem of allergic disease is allergen avoidance. This is particularly relevamt for the control of chronic symptoms associated with perennial allergy to house dust mite, animal danders and certain occupational sensitizers. House dust mite avoidance measures have proven efficacy in both children (Murray and Ferguson, 1983) and adults (Dorward et al., 1988). The recent demonstration that the level of mite exposure at age 1 is an important determinant of childhood asthma focuses on the need for the further development of effective environmental comrol measures (Sporik et al., 1990). In relation to seasonal hay fever, it is not possible to avoid pollen completely. However, simple precautions may help. For example patiems should be advised to wear sunglasses, close car windows and avoid barks and open spaces, since these measures will help to reduce exposure. Similarly, evening country walks should be avoided and windows closed from late afternoon onwards, the time when pollen counts are rising. Grass cutting should be avoided and if possible the patient with severe symptoms may be advised to take a holiday by the sea or abroad at the time of peak seasonal exposure!

Most patients will require medical treatment. The major therapeutic advances in recent years include the availability of H_1 selective histamine receptor antagonists and intranasal corticosteroid preparations for regular prophylactic use. Topical sodium cromoglycate should be regarded as first choice in children and is effective as topical eye drops in adults. The commonest cause of failure of this form of therapy is that patients often do not appreciate the need for regular prophylactic treatment. This may be due to inadequate explanation on behalf of the doctor or poor patient compliance.

Despite these measures, there remains an occasional patient who has persistem troublesome seasonal symptoms. Whereas regular use of topical corticosteroids with or without antihistamines will control symptoms in over 90% of hay fever sufferers, there remains the occasional patient who fails to respond to these measures. Alternatives include use of short courses of oral corticosteroid, for example prednisolone 20 mg for 5–10 days or for chronic persistent symptoms, the use of allergen injection immunotherapy. This form of therapy is widely used in the U.S.A. and Europe whereas in the United Kingdom, its use has declined following the publication of a report by the Committee of Safety of Medicines in 1986 (CSM Update, 1986). In general this report was welcomed in that it emphasized the importance of performing immunotherapy in specialist centres, which, in view of the possibility of untoward inumediate reactions including anaphylaxis, could provide specialist expertise and resuscitative facilities. The report also emphasized the dangers of immunotherapy in patients with asthma. However, the recommendation that patients should be under supervision for at least two hours following injections has made this form of treatment impracticable for both patients and doctors. The report also questions the efficacy of this form of treatment for hay fever. In view of the recent availability of partially purified and biologically standardized allergen extracts we performed a double-blind placebo controlled trial of immunotherapy (using Timothy grass pollen, Alutard SQ, ALK Ltd., Denmark) in 40 adult patients with severe hay fever unresponsive to conventional medical treatment (Varney et al., 1991). The results indicated an approximate 60% reduction in symptoms and 80% reduction in rescue medication requirements within the actively treated group compared with the placebo group. Local reactions at the injection site were minor and required no treatment. There were two episodes of systemic reactions, one involving chest tightness and flushing (anaphylaxis) which came on within five minutes and responded promptly to treatment with adrenaline; there was one episode of delayed urticaria occurring at 2½ hours. This form of treatment was highly effective. However, we would emphasize that immediate reactions may occur which highlights the need for careful patient selection and performance of this form of treatmem in specialist centres.

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Nasal polyps. State of the art

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In the 1990's, nasal polyps still remain an enigma with the pathogenesis and high recurrence rate remaining major problems. In some situations, nasal polyps are really the tip of the iceberg since they may be associated with severe diseases such as non-allergic asthma, cystic fibrosis, Young's syndrome, Kartagener's syndrome, Churg-Strauss syndrome and aspirin intolerance (triad of nasal polyps, asthma, and aspirin intolerance). The pathogenesis remains unknown. Various theories have been postulated with the latest, being Bernstein et al. (1990). They state that a greater rate of transepithelial ion transport is the primary lesion in nasal polyps and this causes movement of water into interstitial tissue resulting in edema and polyp formation. What is known, though, is that the frequency of nasal polyps increases with age (Settipane and Chafee, 1977). The frequency of nasal polyps in those patients 40 years or older is 12.4% while the frequency in patients between 20 and 39 years of age is 3.8%. It is of interest that polyps are frequently associated with aspirin intolerance (acute bronchospasm within one and one-half hours of ingestion), and this latter condition also increases with age. However, a common pathogenic mechanism between nasal polyps and aspirin intolerance has not been established.

The main thrust of our recent research centres on the recurrence rate of nasal polyps with various types of treatment. In our past studies done on 167 patients with verified nasal polyps, 57 (40%) required a second polypectomy for recurrence (Settipane, 1987). Some patients required six or more polypectomies. When we compared the number of positive allergy skin tests to pollens, danders, or molds, it became apparent that those patients with positive skin tests had a higher rate of recurrence and subsequently a greater number of polypectomies (Settipane, 1987) (Table 1). In our present investigation, we correlated the month of polypectomy with the season associated with the positive pollen skin test and found that 89% of those patients had polyp recurrence during that season. We also noted that 28% of patients had a recurrence of nasal polyps following upper respiratory infections. This exacerbation of nasal polyps during the pollen season

Table 1. Frequency of polypectomies in patients with positive allergy skin tests (Settipane and Chafee, 1977; Settipane, 1984).

no. of polypectomies	total patients*	no. with positive allergy skin tests	%
none	24	12	50
one or more	143*	81	57
two or more	57	33	58
three or more	34	20	59
four or more	22	15	68
five or more	17	12	71
six or more	11	8	73

* total patients = 167
one patient did not have a skin test (81/142 = 57%)

in sensitive patients is reinforced by data from Berdal (1952) and Chandra and Abrol (1974), who reported that concentrations of IgE (and also IgA) were markedly higher in polyp fluid than in corresponding serum. This increased concentration of IgE may produce in atopic patients an exaggerated allergic reaction with an extravasation of fluid and increased polyp formation. From this data on allergy and nasal polyps, it appears that allergy and upper respiratory infections are important causes of recurrence of nasal polyps.

Despite this correlation between nasal polyp formation and atopy, a large portion of patients with nasal polyps are non-atopic and do not have positive skin or RAST tests (Settipane and Chafee, 1977). In our past studies comparing several hundred non-allergic asthmatic patients, and over 1000 allergic asthmatic patients, the frequency of nasal polyps was almost three times as great in non-allergic asthma than in allergic asthmatics (Settipane and Chaffee, 1977).
In addition, nasal polyps are closely associated with aspirin intolerance which is known to be due to a non-allergic etiology (Settipane et al., 1974). The probable mechanism of aspirin intolerance is thought to be mediated through the arachidonic acid metabolism with pathogenic inhibition of the cyclooxygenase system and an abnormal reaction to the ratio of leukotriene and PG(E). No similar mechanism has been found to exist in the production of nasal polyps. Therefore, it is safe to state that the etiology of nasal polyps is not associated with allergy; but when the two conditions co-exist in the same patient, allergies cause an exacerbation of nasal polyps. This co-existence is not unusual since allergies effect over 20% of the general population some of which include patients with nasal polyps.
Our recent investigation concentrates on the interval of polyp recurrence following surgical and medical treatment. Surgical procedures usually include

simple removal of polyps and occasionally a more extensive procedure was used. Medical treatment consisted of a burst of prednisone starting at 60 mg and reducing the dose by 5 mg daily until termination of the treatment in 12 days. Occasionally, a second burst of prednisone was used within one month because of treatment failures and these were not counted as recurrences.

In our surgical category, 29 patients underwent 49 surgical polypectomies for a recurrence rate of 1.7 and a mean interval between recurrence of 6.3 years. In our category of medical polypectomy (prednisone bursts) 10 patients underwent 34 polypectomies for a recurrence rate of 3.4 and an interval of 0.9 years (Table 2). Patients were given topical nasal steroids (flunisolide or beclomethasone) following either the surgical or medical procedure. It appears, therefore, that although medical polypectomy is less traumatic, the recurrence rate is higher and the mean interval between reoccurrence is shorter than in the corresponding surgical procedure.
We next examined the recurrence rate and mean interval between recurrences following surgical polypectomy in aspirin intolerance and aspirin tolerant patients (Table 3). Although the recurrence in both categories was similar, the mean interval between recurrence was shorter in aspirin intolerant patients than in aspirin tolerant patients (3.7 years, vs 11.6 years). Therefore, caution and patient education should take into consideration this data when dealing with aspirin intolerant patients.

Table 2. Occurrence after surgical and medical polypectomy.

type	total patients	polypectomies	mean interval (yrs)	range (yrs)
surgery	29	49	6.3	1–24
prednisone bursts	10	34	0.9	0.2–7

Table 3. Polyp recurrence in aspirin intolerance.

condition	total patients	total polypectomies (surgical)	mean interval (yrs)	range (yrs)
ASA intolerant	5	8	3.7	1–5
ASA tolerant	24	41	11.6	1–24
total	29	49	6.3	

An added benefit for those asthmatic patients undergoing surgical nasal polypectomy is that subsequently asthma tends to improve (Slavin et al., 1982; Settipane, 1987). Maintenance steroid requirement may be reduced. However, methacholine challenge does remain essentially the same before and after polypectomy (Downing et al., 1982; Miles-Lawrence et al., 1982). This improvement is probably mediated through the rhino-sino-bronchial reflex. The obstructive and inflammatory consequence of nasal polyps may be improved to the point of increasing sinus outflow causing less stimulation to the trigeminal, facial, and glossopharyngeal nerves. This in turn causes less stimulation of the vagal nucleus in the medulla and less vagal tone to the lungs (Settipane, 1984).

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Clinical and physiological effects of fluticasone propionate aqueous nasal spray in the treatment of perennial rhinitis

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INTRODUCTION

Corticosteroids have been used topically in the nose for over 16 years (Foulds et al., 1957; Godfrey et al., 1957). Initial trials with dexamethasone by Boxer (1962) showed the occurrence of both local and systemic effects; the development in the 1970s of a second generation of agents, such as beclomethasone dipropionate and budesonide, which were poorly absorbed and which underwent extensive first pass deactivation in the liver, removed the unwanted systemic effects (Mygind, 1973; Pipkorn, 1980). Such preparations have proved highly effective, especially against allergen-induced nasal obstruction, and safe. Common side effects are nasal dryness and minor epistaxis; alterations in circulating steroid levels have been noted only with betamethasone nasal drops when used in excess of the routine four twice daily dosage (Stevens, 1988).

Fluticasone propionate (FP) is a newly-developed topically active nasal steroid which has twice the potency of beclomethasone dipropionate as judged by skin vasoconstrictor tests, but which shows less absorption from the gastro-intestinal tract. There is extensive first pass metabolism of this drug in the liver (Harding et al., 1990). The results of toxicology studies indicate that the swallowed portion of an inhaled dose of FP would have no systemic effects at doses well above the suggested clinical range (Jackson et al., 1990). Thus FP should combine high topical potency with a low potential for systemic effects.

We undertook to test the safety and efficacy of FP in perennial rhinitis in an open year-long trial.

PATIENTS AND METHODS

Sixty patients (32 males, 28 females) with an age range of 18–74 years and a mean age of 37.3 ± 14 years were enrolled into the study. All had a history of perennial

rhinitis. Fifteen of them had proved resistant to therapy with existing nasal corticosteroid preparations. Pregnant or lactating females or those without adequate contraception, children under the age of 18 and individuals with serious chronic disease were excluded. Other exclusion criteria were nasal polyps or other serious structural abnormality, infection of respiratory tract or sinuses, serious or unstable concurrent disease, any contraindication to corticosteroids, recent nasal surgery (within six weeks), oral inhaled or intranasal corticosteroids in the previous month, sodium cromoglycate in the past month or astemizole in the past six weeks.

After an initial assessment as detailed below, patients were started on FP as an aqueous suspension administered by an atomizing spray pump, using two puffs each nostril twice daily, i.e. 400 mcg per day.

The patients were seen seven times over the following year and asked to give a subjective assessment of each of their nasal symptoms on a 0-3 basis, where 0 = none, 1 = mild, 2 = moderate and 3 = severe. Rhinoscopy was performed on each occasion. Blood was taken at visits 1, 3 and 6 (pre-treatment, and after 16 and 52 weeks treatment respectively) for measurement of haemoglobin, red cell indices, white cell count and differential, platelet count, urea and electrolytes and liver enzymes. These were repeated at visit 7 (the follow-up visit which took place two weeks after cessation of treatment) if abnormal at visit 6. Urine was tested for pH, protein and glucose at visits 1, 3 and 6.

The following tests were performed at visits 1 and 6 i.e. before, and after one year's treatment with fluticasone propionate aqueous nasal spray.

Nasal mucociliary clearance

A small fragment of saccharin was placed on the inferior turbinate 1cm from the anterior end. The time taken for the patient to perceive a sweet taste was noted (Andersen, 1974).

Olfaction

A shortened version of the University of Pennsylvania scratch and sniff smell test with three odours (smoke, chocolate and lilac) was used as an initial screen. Patients identifying less than two correctly were given the full 40 odour test (Doty, 1979).

Peak expiratory flow rate

The best of three values obtained with an oral Wright peak flow meter was used.

Forced expiratory volume in 1 second/forced vital capacity

After two practice attempts followed by a rest these values were recorded from a Medistar Pulmonary Function Analyser.

Nasal airways resistance

This was measured by active anterior rhinomanometry at 150 Pascals using a Mercury NR6 rhinomanometer, taking an average of five readings on each occasion.

RESULTS

Patient acceptance

35 of the 60 patients completed the trial. The numbers attending at each visit and the reasons for drop-out are shown in Figures 1a and 1b. The adverse events noted there were minor, being urticaria in two patients, asthma, pharyngitis, dyspepsia and a staphylococcus facial infection each occurring in one individual.

Efficacy (Table 1)

There was an improvement in overall symptom score at three months, which was maintained at one year in those individuals who continued on FP. The effect on individual nasal symptoms is shown in Figure 2.

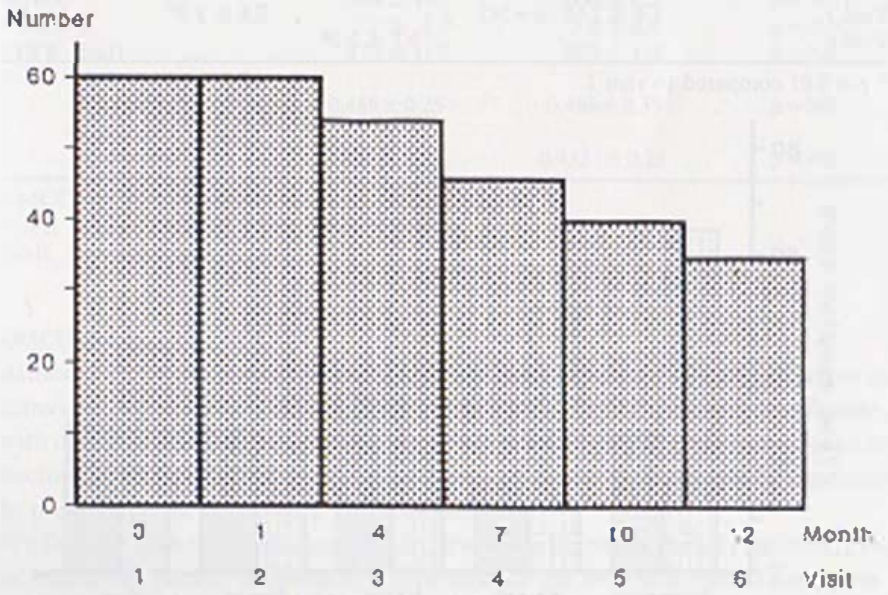

Figure 1a. Number of patients attending at each visit.

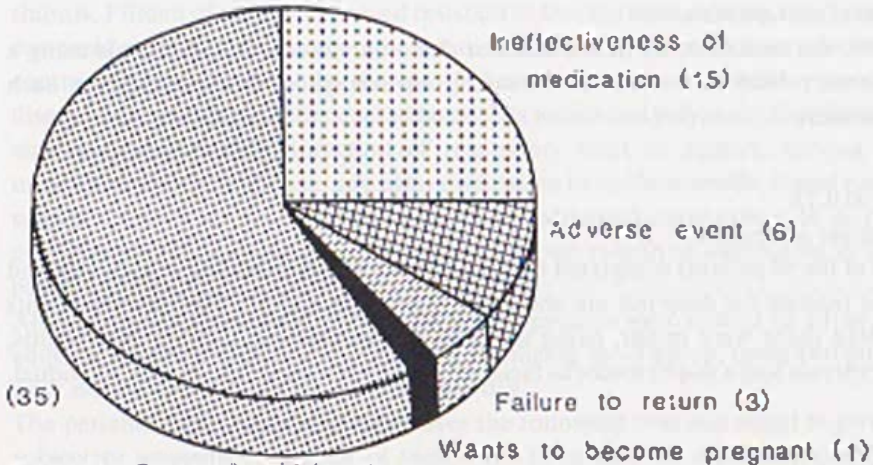

Figure 1b. Reasons for withdrawal.

Table 1. Mean scores at visits 1, 3 and 6.

	all patients attending	those who completed trial (n = 35)
Visit 1	7.6 ± 2.5 (n = 60)	8.1 ± 2.8
Visit 3	3.6 ± 2.6* (n = 54)	2.8 ± 2.0*
Visit 6	3.7 ± 3.2*	

* $p < 0.01$ compared to visit 1.

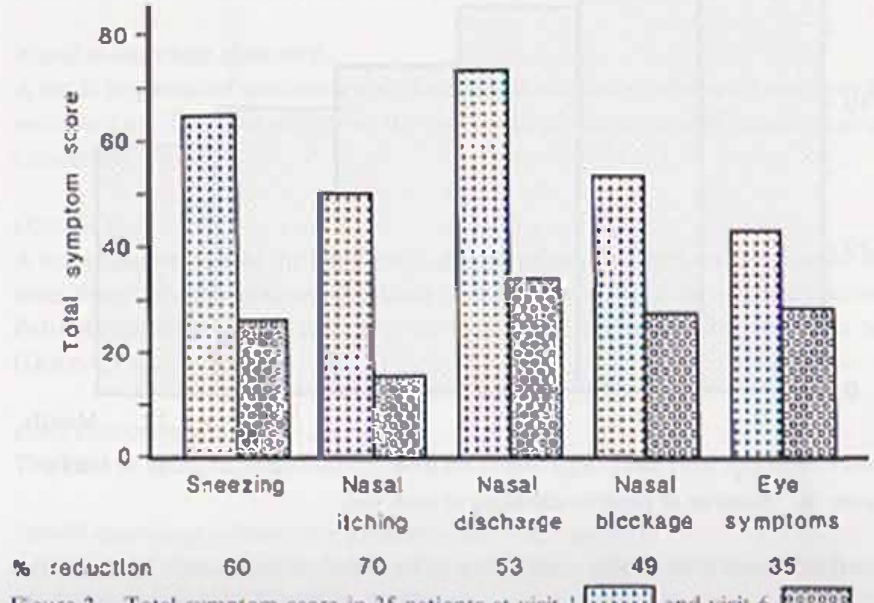

Figure 2. Total symptom score in 35 patients at visit 1 and visit 6.

Safety

No significant abnormalities were seen on blood or urine testing.

Physiological measurements (Table 2)

Nasal mucociliary clearance: The time taken to taste saccharin shortened following one year's treatment from 19.6 ± 10.2 to 14.6 ± 8.3 minutes, $p < 0.05$ (t-test).

Olfaction: The mean number of odours identified was significantly increased at visit 6 compared to visit 1, being 2.2 ± 1 initially and 2.9 ± 0.4, $p < 0.001$ (t-test).

Respiratory function: The mean peak flow showed no significant change at one year.

Rhinomanometry: There was no significant change in the mean airways resistance.

Post trial effects: After discontinuation of FP 28 patients became symptomatic within two weeks. Treatment with an already available corticosteroid proved helpful except in one individual.

Table 2. Physiological measurements.

	1st visit	6th visit	significance
NMCC	19.6 ± 10.2	14.6 ± 8.3	$p < 0.05$
Olfaction	2.2 ± 1.0	2.9 ± 0.4	$p < 0.001$
PEFR (oral)	473 ± 117	503 ± 118	p = NS
NAR - inspiratory total resistance	0.468 ± 0.25	0.486 ± 0.33	p = NS
- expiratory total resistance	0.450 ± 0.21	0.433 ± 0.25	p = NS

NMCC = nasal mucociliary clearance
PEFR = peak expiratory flow rate
NAR = nasal airway resistance

DISCUSSION

Although there are already topical corticosteroids which are safe and effective in intranasal use, the possibility for improvement exists and fluticasone propionate, with its low oral bioavailability and possible increased potency when compared to beclomethasone dipropionate in the skin vasoconstrictor test, might be expected to prove superior to existing preparations.

We found it effective and acceptable in 58% of our perennial rhinitis patients, 25% of whom had proved resistant to one or more of the available topical corticosteroids. Side effects were few and minor and there was no evidence of serious adverse effects on blood cells, renal or liver function or on glucose metabolism. Symptomatic improvement was roughly the same for all nasal symptoms, which was unexpected since usually topical corticosteroids are more effective against

nasal blockage than against sneezing and rhinorrhoea. Eye symptoms, as expected, showed the least improvement. Only dexamethasone, which is systemically active when used topically, has proved to have much action against conjunctival inflammation (Norman et al., 1965).

Active anterior rhinomanometry did not confirm the subjective decrease in nasal obstruction. This is in accordance with previous studies (Eccles, 1989) and with our own findings during nasal allergen challenge which have demonstrated the lack of correlation between symptoms and physiological measurements.

Nasal mucociliary clearance and olfaction both improved significantly from visit 1 to visit 6 in the 35 patients completing the study. This is unlikely to be a learning effect since on the first occasion the patients were not given any feedback about the correctness or otherwise of their observations.

Several of the patients in the later stages of the trial spontaneously dropped their daily dosage of FP to 200 mcg daily since this controlled their symptoms. Unfortunately few were able to continue for more than two weeks without treatment after the cessation of FP. However, 14 out of 15 FP treated patients subsequently responded to medication which had previously proved ineffective, possibly because regular use of FP had established control of their condition. Thus FP aqueous nasal spray proved both safe and effective over one year in perennial rhinitis.

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