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The management of hay fever in general practice

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MOST laymen feel they understand what hay fever is, just as they know what is meant by being 'run down'. The sound track of a recent medical film[1] starts with a prolonged sneeze and then opens with: "Hay fever—even those of us lucky enough not to suffer from it know the symptoms well enough—the incongruity of an apparent cold on a hot summer's day—the sneezing, the running nose, the red watery eyes. To sufferers it can be more than just a social embarrassment—a spoiler of holidays, a business nuisance. It can interfere very seriously with work in the examination hall or on the road. At its worst it may degenerate into full-blown pollen asthma, which may be lethal".

At first glance it seems as if it should be a simple problem to manage, but analysis soon shows otherwise. The very term 'hay fever' is clearly a misnomer for the disease has little to do with hay and nothing to do with fever. The term 'pollenosis' has been suggested but the syndrome may be produced by many other foreign proteins besides pollens. 'Seasonal rhinitis' is another label but this is no better because the inflammation, although certainly seasonal, is just as likely to involve the mucosa of the eyes and lower respiratory tract as of the nose. Even the word 'allergy' is open to different interpretations.

Allergy means 'altered in reaction' from the Greek 'allos' (altered) and 'ergon' (reaction). It was first used by Pirquet[2] in 1906. He included what we will come to see as all the immune states in his description of which the anaphylactic hypersensitivity reaction is only one type. He wrote: "The vaccinated person behaves in a different manner from him who has not previously been in contact with such an agent, yet he is not insensitive to it. So we can only say of him that his power to react has undergone a change. For this general concept of change I propose the term 'allergy'." So we must dig deeper.

Immune response

The first step in the general practitioner's management of hay fever is to learn more of the immune response. The term 'immunity' is derived from the Latin word 'immunus' (exempt). It was used to describe people who were exempt from military service and in that sense were protected from harm. As applied to man, immunity describes the factors which protect the body against invasion by foreign material, including micro-organisms and other poisons. The front-line defences of the body against such invaders are obviously the skin and mucous membranes. But once the attackers penetrate that defence line, much more specialized defence mechanisms are required.

The circulating phagocytes, most particularly the polymorphs, will attack and 'eat up' the invaders non-specifically, but there is a much more complex and specialized defence system than these neutrophils. Certain lymphocytes develop 'memory' of previous invaders and on a second or subsequent attack these memory cells can organize the release of specific chemical defenders. These are the antibodies.

Immunoglobulins

Antibodies are complex protein molecules produced in a vast, highly mobile cellular system; they have the power to recognize and attack invaders. They are transported in the globulin fraction of the plasma and are therefore known as 'immunoglobulins' (Ig). They may be classified most conveniently by their chemical composition. The more important immunoglobulins include those labelled IgG, IgM, and IgA. These three antibodies circulate freely in the body, ready to defend on the first sign of trouble. The invaders are known as 'antigens' or synonymously as 'allergens'. IgG is responsible for the acquired immunity following bacterial or viral invasion. The naturally occurring antibodies of the ABO blood groups system are of the

IgM type, while the IgA antibodies are thought to be concerned in the protection of the mucosae of the upper respiratory tract and gut from infection.

A fourth immunoglobulin, IgE, is the one most involved in the body defence mechanisms in hay fever. The particular characteristic distinguishing IgE from the other immunoglobulins is its propensity to bind firmly to mast cells and basophils. This explains why the protection afforded by immunoglobulins like IgE is sometimes called 'cell mediated immunity'. This is in contrast to 'humoral immunity', offered by the freely circulating Ig.

Recent studies in parasitic disease of the human bowel, especially in the tropics, have shown vigorous IgE response. The most likely explanation of this seems to be that this particular immunoglobulin is working as a defence mechanism against the invasion of parasites. Because most of the IgE is bound to the mast cells in the mucosa and to the basophils, it is not surprising to find that it is present in much smaller quantities in the plasma than the Ig which mediate humoral immunities. IgE makes up as little as 0·0014 per cent of all circulating Ig. A corollary is that it is found in relatively much larger quantities in the mucosa of the respiratory tract and gut. Understanding of these processes is based on the pioneering work of Ishizaka and colleagues in 1966.[3]

Still further elucidation is required about the immune response at the basic cellular level—and first about the lymphocytes.

The stem cells in the bone marrow are the precursors of the lymphocytes. Some of the products of these cells migrate to the thymus gland and mature into lymphocytes there.[4] They are consequently labelled 'T-lymphocytes'. Other lymphocytes mature in other parts of the lymphatic system and are called 'B-lymphocytes'. The 'B' does not come from bone marrow, but from the 'Bursa of Fabricius', a lymphoid appendage of the lower bowel in chickens. The removal of this appendage from chickens effectively prevents the production of circulating Ig in such birds.

When antigens meet the skin or mucosal barriers the local lymphocytes are immediately stimulated to multiply and divide. The T-lymphocytes produce effector T-cells and memory T-cells. It is these cells which are responsible for the production of IgE immunity. The B-lymphocytes are also activated to produce plasma cells. These B-cells, with their high surface concentration of immunoglobulins are responsible for humoral immunity. The role of the eosinophil, which was first discovered by Ehrlich over 80 years ago, is a mysterious protagonist in immunology and will be discussed later.

Just as thyroid tissue when in balance keeps the body euthyroid, or becomes diseased to produce hyperthyroidism or hypothyroidism, so it is with the lymphoid tissue of the immune system. We can then expect an abnormal immune response. Underproduction of Ig presents clinically as a group of rare diseases of deficient immunity, which may be classified as congenital or acquired. The child who has no built-in resistance to infection and requires complete isolation in some form of mobile polythene spaceman suit if he is to survive is well known to the press but is seen only rarely by the general practitioner. An example of acquired deficient immunity is to be found in the patient who has been accidentally exposed to high doses of ionizing irradiation. Cytotoxic drugs currently in vogue for the treatment of malignant conditions like Hodgkin's disease may produce similar effects.

Overaction of the immune system can be likened to the over-activity of the thyroid gland when it causes hyperthyroidism. This type of immune disease, when a patient becomes unusually sensitive to an antigen or similar invading chemical, is known as 'hypersensitivity'. In some susceptible people, then, there is an overaction which disturbs normal tissue or body function.

Gell and Coombs[5] in 1968 classified hypersensitivity into four types. Another two types have subsequently been added but only Type 1 concerns us here.

Type 1 hypersensitivity—the anaphylactic reaction

As early as 1923 Coca and Cooke[6] pointed out that there was a well recognized group of patients who developed 'abnormal hypersensitiveness'. This condition was called 'atopy', meaning 'out of place'. Although the original concept has been altered slightly over the subsequent 55 years by increased scientific knowledge, the hereditary tendency of this group of atopic disorders is still universally accepted. Hay fever, asthma, and constitutional eczema are a triad of diseases to be found in about 10 per cent of our families. Vernal kerato-conjunctivitis and gastro-intestinal milk allergy in infants are rarer examples of the same group of disorders.

It follows that the identification of atopic patients must be one of the corner stones of any plan in the management of hay fever in general practice. It can now be stated with certainty that one abnormality of an atopic patient is the tendency to over-produce IgE. Gleich[7] has claimed that specific IgE to pollens of grasses accounts for 30 to 50 per cent of the total IgE protein measured. It is of considerable significance that asthma and other atopic diseases are much less common in rural areas in the tropics where infestation with parasites is common, and it has been claimed that Type 1 hypersensitivity has increased as the parasitic infestations have decreased. A high incidence of allergy is seen in most severe cases of cystic fibrosis.[8] It seems that the abnormal mucosal permeability here allows for the freer invasion of antigens.

Over-production of IgE is not the sole abnormality in atopy, however. There is growing evidence that there is

also a diminished ability to mount a secretory IgA response. There is some evidence, too, that there is also an under-production of complement-fixing IgG.[9]

It is highly unlikely that all these different reactions, although hereditary, are the expression of a single gene. These different weaknesses may well be inherited individually. If so, it could well account for the great variety of presentations in atopic disorders, as well as the huge variations in the natural history of a disease like hay fever.

How does this apply to hay fever? In any atopic, particularly sensitive individual, an allergen or antigen such as grass pollen may invade the tissue of the upper respiratory tract. As already mentioned this will stimulate the T-lymphocytes. On the next or subsequent invasion the T-lymphocytes will then be stimulated to produce even more antibody. When the antibody and antigen meet they form a chemical bond on the mast cell wall. This product will almost immediately cause the release of mast cell granules, which in turn initiate a complicated series of events in which a number of vasoactive agents provoke the capillary and smooth muscle changes which give the clinical picture. The best known of these agents is histamine which is thought to cause increased capillary permeability, vasodilation, contraction of smooth muscle, and an accumulation of eosinophils. Two other lesser known agents are serotonin which causes capillary permeability and vasoconstriction, and 'slow releasing substance of anaphylaxis' (SRS-A), which causes smooth muscle contraction. There is a further group of agents which react with enzymes and circulate in the plasma globulin. These are the 'kinins', bradykinin and kalidin, which affect capillary permeability. Finally, there are also the prostaglandins of the 'E' and 'F' series.[8]

The eosinophil is also involved or closely linked with the activity of these various vasoactive agents.[10] After arriving at a site of immediate hypersensitivity reaction the eosinophil probably performs regulatory functions that could limit or even eventually terminate the allergic reaction. Eosinophil granules contain an enzyme capable of attacking histamine.[11] They also harbour arylsulfatase B which can degrade SRS-A.[12] All this work on the eosinophil in hypersensitivity is summarized by Goetzl.[13]

Peripheral blood eosinophilia is, of course, to be found in many parasitic infections like schistosomiasis, malaria, and tapeworm and roundworm infestation, but it is also found in malignant conditions like lymphosarcoma and multiple myeloma and it is common in patients with multiple hypersensitivities and other immune diseases like farmer's lung. It is almost invariable in asthma.[14] The appearance of the eosinophil in so many different roles makes the clinical interpretation of a rise in the eosinophil count both difficult and puzzling.

In any atopic individual there is a chemically dependent imbalance between the beta adrenergic and the cholinergic activity. In asthmatics, for example, response to adrenaline, which depends upon beta receptor stimulation, is less than normal. Similar responses are also found in the nasal mucosa.[15] In addition to all this, the nasal mucosa, particularly over the turbinates, behaves as an erectile tissue. Mucosal thickness is largely dependent on the amount of blood contained in the venous sinuses. If there is local inflammation, either from an invasion of micro-organisms, or of allergens, mucosal thickness will also be influenced by the amount of exudation from the capillaries into the interstitial tissues. Because the atopic patient's nerve response is affected by this process, the physician must be particularly aware that the nasal mucosa in this patient may respond more violently to changes in temperature and humidity, and other nonspecific irritants, as well as those which produce a histamine response. It may well be this degree of nervous sensitivity which makes an atopic patient sneeze so violently in a sunny room even on a winter's day.

Antigens in hay fever

The aeroallergens are the antigens which cause Type 1 hypersensitivity of the respiratory tract. If such an allergen is clinically important it must be buoyant, allergenic, and present in adequate quantities. The best known of the aeroallergens in this country are those pollens produced by the grasses which make our land so green. Other countries have their own special allergens. Grass pollens have grains of about 20 to 25 microns in size, and particle size is important because the ciliated epithelium of the upper respiratory tract will filter out most of the particles over five microns in size. The mucous blanket on the nasal mucosa adsorbs these larger particles, and most of them are moved backwards into the nasopharynx, and then swallowed harmlessly.

There are thousands of different grasses throughout the world, but it is now clear that only those grasses which grow profusely in any area should be regarded as important. The research workers at Bencard Laboratories regard 12 grasses in this category in Great Britain, while their counterpart in Dome Laboratories have decided that seven are particularly important.[16] It is helpful to know that many grass pollens have cross-allergenicity; that is the specific IgE appears to be able to identify them as similar, and so react to them.

From my own practice, I was able to ascertain the most important grasses in this allergenic sense by checking the sensitivity of 31 patients to 12 common grasses. Six of these plants proved to be much more common as allergenic agents than the others, producing reactions in over 75 per cent of the group. The grasses in this important group were rye, meadow, fescue, cocksfoot, Timothy, and Yorkshire fog (Figure 1). The other six—dog tail, false oat, vermal, bent, brome, and foxtail—were less than half as potent as allergens. The first important group includes the most common

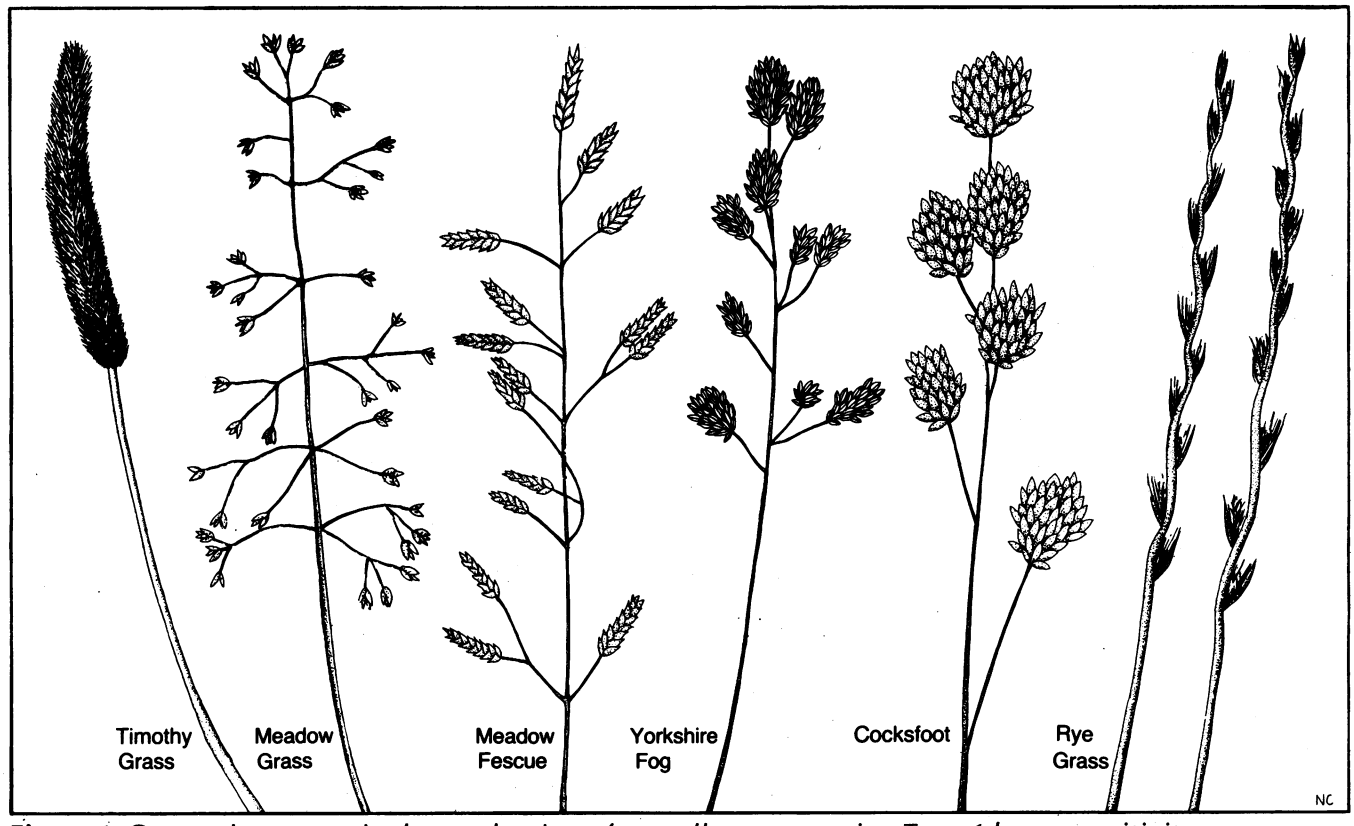

Figure 1. *Grasses important in the production of aeroallergens causing Type 1 hypersensitivity.*

cultivated and wild grasses in my area and equates well with those described by Brown.[16] It is still important to realize that some grasses are more allergenic than others. Timothy is said to be the most allergenic, but rye grass makes up to 95 per cent of all cultivated grass in the farmers' fields, so its sheer profusion makes it important.

Grass pollen is by no means the only allergen in seasonal Type 1 hypersensitivity. In my own series I have found that about half of my hay fever patients were allergic to grass pollen alone, but the other 50 per cent showed that they were also sensitive to other allergens; trees, shrubs, flowers, and such weeds as wormwood, goosefoot, and plantain have all been implicated.[17] This finding is particularly important when it comes to choosing the best treatment. Tree pollens vary in size from 20 to 60 microns, and are therefore considerably heavier than grass and weed pollen. It is probably for this reason that they do not reach so many patients, for they are certainly produced in very large numbers. Sometimes they can be seen as a cloud hanging over a tree during its pollenation season, and the pollen grains may be picked up by the handful, or even shovelful after they have settled to the ground. This is particularly true of the conifers, and Hesselman reported in 1919[18] that "spruce forests in Southern and Middle Sweden produce 75,000 tons of pollen annually"! This was matched by Koski more recently when he stated that Finnish forests produce between 10 and 80 kilograms of pollen per hectare per year (nine and 70 lbs per acre).[18] Although the conifers are prolific producers of pollen, other trees are also active, and poplar, elm, birch,[19] beech, oak, and ash are all known to release wind-borne pollen. Any of these may be responsible for causing hay fever and are much more likely to do so than the trees which are insect pollenated like the willow. The sycamore family of trees is highly allergenic and is therefore of particular interest in some areas;[20] for instance, the plane trees of the London parks are a cause of real concern to some residents there. More exotic species are also implicated in allergies with such trees as mountain cedar,[21] the cedar of Lebanon,[22] date palm,[23] Japanese cedar,[24] southern wax myrtle,[25] and mesquite.[26]

Some weeds are also highly allergenic, none more so than the American ragweed, of the tribe Ambrosia, not to be confused with the much more innocent ragwort *(Senecio jacobaea)* of these lands. Sadly, Ambrosia is starting to establish itself in Southern England. With its four main types and copious pollenation it will be a really unwelcome immigrant to these shores. Ragweed pollen is from 16 to 25 microns in size, and it causes a great deal of misery in the late summer in America and Canada. The hemp plant cannabis is also highly allergenic. It is said that one cannabis plant may produce 500 million pollen grains.[27]

Weed pollen like grass pollen is so light that it can be carried long distances in the wind. Ragweed pollen has been picked up in samples 400 miles out to sea from the Atlantic coast of America! It follows that patients living in built-up urban areas cannot expect to avoid these pollens, even though they are far removed from their

production lines in the country. Contrary-wise, brightly coloured flowering plants are of little importance in allergy. These plants are normally fertilized by insects, and their pollen grains are designed accordingly with large mass and sticky surface.

There is another important group of aeroallergens in hay fever, the moulds. These have been identified as allergens for at least 50 years, but their clinical importance is difficult to assess because they tend to be present throughout the year. Some of the 'field moulds' that grow on plant life may have an episodic life style, and are credited with being responsible for hay fever symptoms in the early spring and late autumn.[28] The 'storage fungi' like *Aspergillus* and *Penicillium* are common causes of rot in stored fruit and vegetables, and these two are thought to be among the most important of the mould antigens. The yeasts are another group which may well cause symptoms, but they require further study. It is always worth bearing in mind the yeasts when investigating a patient who gives a history of wine or beer allergy.

Assessing the problem

To summarize: in preparing his plan of action, the general practitioner will have to be able to identify his hay fever patient as one who is suffering from an hereditary disease, probably carried by more than one gene. This condition occurs in an abnormally sensitive individual or atopic patient, who over-produces IgE, and under-produces IgA and IgG. If this patient is once sufficiently stimulated by a specific allergen or allergens he will continue to overact on each subsequent invasion, perhaps for years to come. This over-reaction will in all probability include an imbalance between the sympathetic and parasympathetic autonomic nerve supplies to his respiratory tract. It follows that there will be wide differences in the clinical picture, both as it presents in different patients, and even at different times in one patient's life.

Prevalence

There is little doubt that atopy is one of the more common of the world's syndromes, with, as already stated, about 10 per cent of the human race being subject to asthma, eczema, perennial rhinitis, or hay fever. Figures vary enormously from country to country and area to area. Seriously affected families might migrate from a particular area in an attempt to escape a specific allergen. In this way a doctor in a seaside practice may find he has many more sensitive patients than he might deduce from his knowledge that pollen counts are much lower along coastal belts. Equally, doctors in high-risk inland areas might detect relatively smaller numbers. A national survey in the USA in 1963 estimated that there were 12·5 million sufferers with allergic rhinitis or asthma, or both;[29] that is, eight per cent of the whole population. Other authors, mostly working on smaller local samples, also found high figures. One survey of American college students[30] in 1969 found a rate of 20 per cent. A similar survey of 1,251 first-year students at Queen's University, Belfast, which I conducted in 1973, reported a prevalence of 9·6 per cent.[31] A larger series of 3,833 secondary school children in Hampshire revealed the prevalence of 4·1 per cent.[32] In his early paper Fry[33] recorded a prevalence of 2·8 per cent in his population, while smaller studies in Yorkshire and North London[34, 35, 36] showed prevalences of 4·2 per cent, and 1·2 per cent respectively.

Clinical features of hay fever

Nasal irritation with sneezing, and a similar equally uncomfortable sensation in the eyes labelled as blepharo-conjunctivitis, are the main presenting symptoms. The conjunctivitis is usually mild, consisting of redness, irritation, and watering of the eyes. Sometimes there is conjunctival oedema with milky opacities. The association between hay fever and constitutional eczema, asthma, and perennial rhinitis does not require any more emphasis, but if hay fever starts in childhood, it is more likely than not to be accompanied by eczema.

Mouth breathing in childhood, a common symptom or sign to the general practitioner, should be regarded as possibly having been caused by allergy, for over-activity of the lymphoid tissue in tonsils and adenoids may well have a basis in this immune disease, rather than in infection. Indeed, some cases of allergic rhinitis have presented only after tonsillectomy. Some patients, in addition to the above symptoms, complain of itching in the mouth, throat, or ears. A smaller number present with a loss of sense of smell or taste. Some observers report mood changes in hay fever sufferers, so that they may become more irritable and restless. Dunham[37] made attempts to measure objectively changes in children's performance during the pollen season. When they had hay fever there were significant increases in the number of errors made in speed and accuracy tasks, while there was no change in the speed of performing; that is, they worked as quickly but less efficiently. Sleep can also be disturbed.

There is considerable variation in the course of the disease. The age of onset varies from extremes of a few months of age to over 60 years, although the latter is very uncommon. Many patients begin to have symptoms before puberty, but there is an equally large group who start their symptoms in the late adolescent era. Spontaneous 'cures' are relatively common, and a history of previous allergic rhinitis will often be elicited in a patient with late-onset asthma, although one may have to go back 20 or 30 years to find it. Remissions of allergic rhinitis in the 20s age group can be followed by a recurrence in later life. Some patients have attacks of hay fever over many years, with very little change in their severity.

One of the most difficult problems in assessing treatment is the fact that sensitivities vary from day to day and from season to season. One allergen may wax in its antigenicity while others may wane. As well as varying from year to year, hay fever symptoms may come and go in any one season. Many patients tend to exhibit more intense symptoms in the morning hours because aeroallergens are released in their greatest numbers from sunrise to 9.00 hours. While it is raining symptoms should diminish as the pollens are dampened down, and conversely, windy days may well aggravate the condition. Visits to the countryside, or work in the harvest field, or a picnic in the park, or a spell on the cricket pitch, would be expected to cause an exacerbation. Sensitivity to multiple allergens, coupled with a strong family history of allergenic disease, tends to be associated with a more chronic condition.

Diagnosis depends more than anything on the history. For this reason it is wise to follow a guide or chart, so that nothing will be missed. These charts are available in the UK from either of the two ethical companies who specialize in allergies, Dome Laboratories and Bencard Ltd. The physician must search for a family history, find out the main symptoms, year of onset, and then assess the severity of the condition. It is most important to find out what makes the symptoms vary: for example, going out of doors or the time of day. Some patients report nocturnal disturbance, while others may be worse on wakening. The seasonal nature of the illness must be noted with special reference as to when the symptoms start and finish and the time when they are at their height. With the possibility of perennial rhinitis being superimposed on, or simply mimicking hay fever, environmental factors have to be checked with great care. Enquiries have to include information on the age and style of the house in which the patient lives: whether there is any possibility of dry rot or dampness; individual details such as the age and type of filling in the pillows and mattress; and the type of bedding, floor covering, and curtaining in the bedroom. Moulds, house dust mite, and house dust are all major allergens. Animal contact with dog, cat, horse, rabbit, sheep, or cow, or their by-products, should be recorded with the possibility of one or more of these types of foreign protein being a major antigen. If a patient avoids eating certain foods, his dislike may be more than a food fad and could be a sign of allergy. Finally, the history should include a check on the past and present medication with an assessment of its efficacy. This information must include self-medication, with an enquiry about aspirin in all its forms, and the wide variety of nasal sprays and inhalants which can be bought over the counter without prescription, for these drugs may well be a cause of symptoms as well as a source of relief.

The signs of allergic nasal disease are variable and difficult to interpret, but nevertheless anterior rhinoscopy is a simple procedure which takes only a few seconds to complete. Traditionally, one should use a nasal speculum with a good light source and possibly a head mirror, but I find the ordinary auroscope satisfactory, although with some designs the patient's breathing may rapidly steam up the magnifying lens. This can easily be removed if it proves to be a problem. The typical allergic reaction is pallor and slight oedema, so that inside the nose is paler than the lips, with perhaps a slight bluish tinge. Any secretion should be watery. As the oedema increases frank polypi develop, and the nose becomes obstructed, perhaps completely. In the worst cases the polypi may appear at the external nares. But many of these changes are non-specific, and in any case super-imposed infection is extremely common. As with any inflammatory reaction there would be hyperaemia; crusting occurs, and the discharge may be purulent. In many cases diagnosis cannot be made with certainty, despite the strong history, and then it is necessary to undertake investigations for confirmation. The general practitioner in planning his management has to decide just how far he can go before handing over to the specialist, but he will certainly want to exclude foreign bodies lodged in the nose in children, before seeking this advice; and he will probably consider some of the following investigations.

Investigations

Examination of the nasal secretions for the presence of eosinophils is claimed by some[38, 39] to be a valuable and simply performed test. Their presence is said to be confirmatory of a diagnosis of allergic rhinitis, although their absence does not exclude it. Manners[40] points out that considerable practice is needed before this technique can be relied upon, but he found a high correlation (92 per cent) between nasal mucus eosinophilia and active hay fever, and therefore felt it was both cheap and simple and well worth carrying out to confirm the allergic component in rhinitis.

A full blood count with differential white cell count might be carried out, but as has already been pointed out, the presence of eosinophilia is not really helpful in diagnosis, although it seems that if there is a persistent rise of 20 per cent or more, then a full investigation might be rewarding.[41, 42] Such a study would include an examination of the stool for cysts and ova. A simple study of the lymphocytes with the present state of our knowledge is also quite valueless, although one might have to change this view in the future.[43, 44]

Investigation of the serum for IgE could prove helpful, but the very low levels cannot be detected by the standard precipitation tests used for the measurement of the other Ig. Single radial immunodiffusion can only measure down to one to 10 micrograms per millilitre although the process has now been modified to allow assessment of figures as low as 200 to 300 ng/ml.[45] The radio-immunosorbent test (RIST) makes use of in-

soluble 'Sephadex' particles coated with anti-IgE. IgE can be measured by an inhibition technique, or directly with the use of radio-labelled anti-IgE to estimate the amount of IgE bound to the insoluble matrix.

Total circulating IgE gives no indication of a patient's sensitization with an associated specific IgE. If this particular protein should require estimation another similar test to RIST has been developed. RAST or 'radio-allergo-sorbent-test' uses radio-labelled specific anti-IgE. The amount of radioactivity on the washed particles correlates with the level of that specific IgE antibody in the serum.

These two radioactive methods appear to be the best ways of studying IgE. The Widal reaction, the complement fixation tests, and the agglutination tests like Paul Bunnell and Rose Waaler, which are so well known to the practising physician, and which are also based on other immunological principles, are unfortunately not applicable to the study of Type I hypersensitivity.

Skin tests

Skin testing is the traditional *in vivo* test for Type 1 hypersensitivity. [46, 47, 48, 49, 50, 51] It depends on the release of histamine following stimulation of the skin of the forearm or back by the appropriate antigen. The classical 'triple response' occurs. First, there is an immediate erythema at the entry site. Secondly, oedema is produced locally, causing a raised pale wheal. Thirdly, the erythema extends beyond the wheal. The technique depends on a specially prepared drop of allergen being placed on the skin and then the skin is pricked through the solution introducing a minute quantity to the underlying tissue. If there is sufficient circulating specific IgE, and of course this is not always the case, then a histamine reaction will occur. Several different allergens can be tested during one examination. Each drop of special solution has to be spaced out at between four and five cms (1·5 to 2 ins) apart and they are usually set out in rows and identified with a skin pencil. The top test should be a control of an innocuous glycerine-saline solution which would be expected to produce no response. Some workers also use a histamine injection as a positive control. A few patients have dermatographism of varying degrees and the interpretation of wheals in these cases is extremely difficult. If the wheal is significantly larger than the control then it may well imply a positive result, but this cannot always be so, and so some alternative method of testing may be necessary.

Gaillard and colleagues[52] and Frankland[48] point out that the degree of severity of symptoms is not necessarily related to the degree of skin sensitivity. Dosage schemes for treatment should not necessarily be based on the evidence of one's eyes, but it is difficult to ignore the large angry irregular wheal produced by one allergen compared with the innocent prick mark of the control. Nevertheless, Freed[53] insists that positive skin tests prove nothing and negative skin tests disprove nothing, while Brown[54] also warns against the dangers of wrong interpretations and criticizes those who delegate skin testing "to a junior, or even a nurse".

The selection of the allergens to use in any patient depends on the judgement of the tester and is based more than anything else on the history. Seasonal rhinitis probably demands tests for grasses, trees, flowers, and moulds. In addition, it is usually necessary to test for such antigens as house dust and house dust mite. It may sometimes be advantageous to test for other household allergens such as feathers, sheep wool, cat, and dog.

Nasal provocation tests depend upon the same basic principle as skin testing.[55, 56] In this case, however, the allergen is introduced as a powder or solution directly to the patient's nasal mucosa. For one worker at least these tests are regarded as much more reliable than skin testing, and one can see why this should be so. Brown[54] states that the introduction in 1961 to his clinic in Derby of nasal provocation tests was the greatest step forward ever made. Nasal challenge much more faithfully reflects the pathological process in hay fever, and if there is specific IgE present in the mast cells then it should certainly respond to the stimulus. Freed[53] warns that nasal provocation tests are potentially dangerous and may precipitate anaphylaxis or asthma, overbreathing leading to tetany, or vasovagal attacks. Methods which attempt to show an increase in resistance to air flow, and thus provide an objective way of measuring the changes in nasal challenge, are still fairly primitive.[57] Bronchial challenge is both difficult and dangerous and outside the scope of the general practitioner.[58]

An understanding of all these new methods of investigating hay fever still requires considerable time and study. Fortunately with the degree of research now in progress [59, 60, 46, 61, 47, 36, 62, 63, 64, 65, 50, 66] there is considerable hope for advance in the near future.

The industrial planner in completing his work will want to make sure that he has checked all the variables, and so it is with the physician. In particular he will look at the differential diagnoses. There are only a few conditions which simulate hay fever. They include perennial rhinitis, due to a number of inhaled aeroallergens or aspirin sensitivity, other ingested allergens including many common foods and some food-colouring agents; and infective conditions from recurring coryza to sinusitis, acute or chronic. The other well known, if problematic entity, is vasomotor rhinitis. In addition, any or all of these conditions may be found in a patient who also suffers from hay fever.

The diagnosis of most of these conditions depends on the same principles as outlined above, most particularly the history and the investigations. If the allergens can be identified, treatment may well be modified. By far the most ubiquitous antigen discovered by Voorhorst *et al.*[67] in 1964 is the house dust mite. *Dermatophagoides pteronyssinus* is a foraging acarus which is present in countless millions throughout the world. It lives on

human skin scales and from the Midlands of England[68] to Tristan de Cunha[69]; and from Italy[70] to the Highlands of New Guinea[71] or Northern Zambia[72] it has been recognized as an important cause of allergenic disease.

Although house dust mite is the most important, there are many other allergens which should be considered. Animal danders give great trouble and any general practitioner may have a dog or cat lover who suffers terribly for his predilection. All these allergens can be identified separately and may act on the patient alone or in concert. In addition, food and drug allergies also cause rhinitis, with nasal obstruction or discharge. Aspirin is now widely recognized as a cause of nasal polypi and of asthma,[60, 73] so the physician must be aware of the dangers of missing self-medication with one of the many preparations containing this drug. Some workers have suggested that pregnancy or menstruation are causes of recurring rhinitis, while Maw[74] reports that sexual activity or sexual frustration may lead to nasal congestion. It is therefore not surprising to learn that the contraceptive Pill has also been implicated. The most recent paper on this subject fails to confirm this connection.[75] Chilla and Haubrich[75] showed that although 32·7 per cent of 205 women taking the Pill were thought to have rhinitis, so were 30·2 per cent of a slightly larger control group of 255 women. They also studied the different compositions of the Pills used, and verified that this did not affect the results in any way.

Recurring viral or bacterial infections of the upper respiratory tract, with or without an association of sinusitis, are the next group to be differentiated, and as with the other causes they may occur on their own or be superimposed on a true allergic picture. Infective processes with the standard reactions of heat, pain, redness, and swelling of any inflammatory process, and the associated purulent discharge or post-nasal drip, are usually regarded as simple to diagnose, but it is always worth bearing in mind an underlying atopic condition as an associated cause of the symptoms. Certainly if one traces the past history of a hay fever sufferer, it is common to find a story of severe recurring 'colds' in childhood.

If we exclude all these conditions there is still a further group of patients with chronic rhinitis who have neither an infection nor an immunological disturbance. The first of these usually, though not invariably, follows trauma and is caused by a deviated nasal septum. This is simple to spot with anterior rhinoscopy and usually requires surgery for its cure. The second group is known as 'vasomotor rhinitis'. It is so called because many non-specific stimulants act upon the autonomic nerve supply of the erectile tissue of the nose, and especially in the area of the turbinates. As a result, changes in body or air temperature, or of the level of humidity in the atmosphere may rapidly induce rhinorrhoea. Horner's syndrome, fortunately rarely seen nowadays, is associated with unilateral nasal obstruction from an overactive mucosa on that side, caused by damage to the sympathetic nerve supply. The clinical features of vasomotor rhinitis are similar to hay fever, but the seasonal variation is absent, and the nasal discharge is likely to be more mucoid and to contain fewer eosinophils. Skin tests rarely correlate with the history, nor do other provocation tests.

Climatic differences

Obviously variations in climate profoundly affect the production of pollen. Bagni and colleagues[76] have carried out an interesting comparison of pollen counts in cities in Western Europe. They show that the hay fever season starts in Italy as early as 1 April, while London's hay fever season does not start until 10 weeks later. In all the areas studied there were two peaks of pollen production: in Italy the peaks were in April and May, while further north they were in mid-June and early July.

Davies and Smith[77] developed a method of estimating the date of onset of any hay fever season by studying the mean air temperatures for the months of April and May in London. In America, where the weather is dependent on quite different factors such as the enormous land mass, other correlations have been found. There, it has been claimed, the onset of the pollen season is dependent on the amount of light the plants receive. Thus, the further north one travels, with the longer summer days, the earlier the pollenation. The predictable date for the onset of ragweed pollenosis in the northern states is 15 August, paradoxically perhaps, for the Canadian border is just about the same degree of latitude as Paris, France.

It is quite clear that any individual practitioner must therefore adjust his plan to take account of local conditions, and he can find world-wide information in recent articles spreading round the five continents.[78, 79, 76, 80, 81, 18, 82, 83, 84, 85, 86, 87] Wherever he is, the physician will have to depend on the analysis of pollen carried out in his own area, according to the techniques available there.[88] Results from the Air Ministry roof in London are valueless in Cardiff, Edinburgh, or Belfast.

The final set of variables to be considered is the cost in time, money, and equipment. In drawing my original plan I was fortunate in being able to have my nursing sister trained in skin testing techniques by Bencard Ltd at their clinic in Brentford, Middlesex. At that time the company were able to offer a week's residential course completely free. They still offer the same free training but they cannot now offer free accommodation. Following such training it is necessary to invest in the testing solutions, storage cabinet, and needles, in addition to the usual skin cleansing solutions, cotton wool, adhesive tape, and so on. At today's prices one would have to be prepared to spend between £15 and £40 of practice funds.

One trained nurse in our four-doctor group practice is able to carry the workload in allergy skin testing alongside her ordinary nursing duties. Continuity is invaluable because interpretation of results often depends on experience; again, in my practice I have been lucky to have the help of the same trained nurse, who has carried out history taking and skin testing for the past six years on 492 different patients—an average of 82 per year. If this specially trained nurse were not available to my practice I should have to rely on referral to the local allergy clinic, which now has a two-year waiting list, or on the intermittent visits of the local territory manager of Dome Laboratories. This skilled worker offers an excellent service to any general practitioner in our area. With an average of two or three patients presenting every week during the winter and spring, it clearly would not be possible to investigate immediately, or even adequately, using these alternatives. The common practice of guessing the allergens from the history alone is only to be deprecated, but in my experience the general practitioner's often heard cry of "I cannot find the time" usually takes precedence over the allocation of the hour per patient required.

Treatment

Unlike some of the allergens of perennial rhinitis, it is extremely difficult for the hay fever sufferer to avoid contact with the airborne pollens and moulds, so any attempt to exclude patient contact is not likely to meet with much success. Keeping the house windows tightly closed is an obvious first step, not always welcomed by other residents on hot summer days or nights, while moving home to a seaside domicile is an even more drastic step which will certainly be considered by the severely affected patient. Physicians at University College Hospital, London,[89] feel it is worthwhile issuing a set of instructions to patients (Table 1).

Table 1. Pollen precautions.

1. *Never* walk through long grass—even after you have had benefit from treatment.
2. During June and July sleep with bedroom windows closed.
3. During June and July do not go for country holidays or outings and do not go camping.
4. During June and July, if you have to travel by train, keep the windows closed.
5. You can only do yourself harm by neglecting these principles.
6. If you have injection treatment for pollen allergy, it is usually necessary for it to be continued for at least three years.

Antihistamines

If one rules out avoidance, then the first line of treatment is the use of the group of drugs known as antihistamines. These drugs have been available for about 30 years[90, 91] and their benefits and drawbacks are so well known as to require little amplification. There are three different subgroups, depending on whether a nitrogen, oxygen, or carbon atom is joined to the basic molecule. Ethylamines (oxygen linkage) are potent effective histamine antagonists at the H_1 receptors. They have a marked tendency to cause sedation and atropine-like side-effects. One of the earliest to be marketed was diphenhydramine ('Benadryl'), while 'Histryl' and 'Lergoban'[92, 93] are two others in this group, which despite their different presentations and bases contain the same drug, diphenylpyraline. Ethylenediamines (nitrogen linkage) are also highly effective at the H_1 receptors, but they too can cause drowsiness and also are credited with gastrointestinal side-effects. 'Phenergan' and 'Vallergan' are commonly used drugs in this group. Alkylamines (carbon linkage) also work well in fairly low dosage. They are thought to have fewer side-effects, but drowsiness may still be a serious problem. 'Dimotane', 'Daneral SA', and 'Piriton' are well known preparations in this category.

Relatively few papers have been published in recent years [90, 92, 93, 94, 95] and only one new antihistamine, working at the H_1 receptors, has been marketed.[96] This drug, azatadine ('Optimine') is a nitrogen analogue, and is claimed to have potent antihistamine, anticholinergic, antiserotonic, and anti-anaphylactic properties. It is stated that it took four times the recommended dose of 'Optimine'[97] to affect performance in driving tests. 'Polaramine' caused much more serious side-effects in 4 mg doses. Research workers appear to have diverted their attention to a different aspect of histamine activity. Histamine, after all, is widely distributed throughout the body and it reacts with another separate group of nerve endings, the H_2 receptors. All this research effort has been rewarded by the marketing of a new 'wonder drug' for the treatment of peptic ulceration. This is the widely prescribed drug cimetidine ('Tagamet').[98] McGuinness[92] states that the symptomatology of all responses in the nose to physical or chemical irritants, including infections, may be referred to as being due to histamine release. Others would surely disagree with this opinion, but whether it is true or not it is quite clear that general practitioners prescribe this group of drugs widely, either separately or in combination. Thirty-six of the 76 preparations listed in the *Monthly Index of Medical Specialities (MIMS)* under the heading 9C for "Expectorants, cough suppressants, mucolytics, and decongestants" contain antihistamines. These are in addition to the 20 or so drugs listed in section 12A as "Anti-allergic drugs". It seems more than likely that those in 9C are as effective for their sedative and atropine-like properties as for any direct effect as histamine antagonists! While oral antihistamines will be the first line of treatment for mild hay fever, one must never forget that occasionally a patient will be found who has the most profound side-effects. Unconsciousness for 24 hours from one tablet[99]

or death[100] have been reported. For over 30 years antihistamines have been available for local application. The one most widely used in Britain was 'Antistin-Privine' made by Ciba. At a later date this was superseded by 'Otrivine Antistin'. Pelikan and De Vries[101] in 1974 carried out an important and interesting study on drugs "which can theoretically influence either the antigen-antibody reaction (antihistaminics, antiserotonics, corticosteroids) or the changes of the nasal mucosa due to this reaction (alpha-sympathomimetics)". After applying the appropriate drugs to the nasal mucosa the patient was subjected to a nasal provocation test, using a measured dose of histamine or house dust. The antihistamine they used was pyranisamine hydrochloride. They used a topical application and compared the results with an intramuscular injection. When histamine was used as the agent in the provocation test the results appeared excellent with either route. More importantly, there was no protective effect to be gained by either route when the challenge came from house dust rather than from histamine. They deduced that it was "unlikely that the route of administration of these drugs can influence significantly their effect upon the nasal mucosa". Dolowitz[102] suggested that histamine challenge tests offered different histopathology to clinical allergic rhinitis. He also felt that antihistamines applied intranasally had better effect on a histamine challenge test than in a true histamine release following an antigen-antibody response. Drury[103] and Blair[104] say that antihistamine drops are good for the unpleasant eye symptoms of hay fever, but Frankland[99] points out that they are not really to be recommended because they have an anaesthetic effect which makes corneal damage a real possibility.

Vasoconstriction

More popular is the application of vasoconstrictors. Self-medication of 'over the counter' therapies will certainly be found in this category. 'Otrivine' [103, 105, 106, 107, 109, 110] certainly works in this way, purely by easing the symptoms of nasal blockage and rhinorrhoea. Similar benefits are also found from several other vasoconstrictors, the most recent of which to be marketed is 'Iliadin'. The danger of these products lies in their undoubted ability to cause 'rebound' symptoms, so that before long they are causing rather than curing persisting symptoms.

Disodium cromoglycate

The antihistamines and vasoconstrictors have their drawbacks. The general practitioner will search for other pathways in the hope of blocking the antigen-antibody reaction in hay fever. The next line of treatment will be the local application of disodium cromoglycate (DSCG). This product has now been widely accepted as a valuable preventive measure in the treatment of asthma. Regular six-hourly inhalations of 'Intal'

powder have been reported as highly effective.[111, 112] It was therefore a natural development for Fison to develop a powder for application to the nose. Their product, 'Rynacrom', is now used extensively. It comes as a capsule applied with an insufflator. Subsequently, the same manufacturers offered a liquid by nebulizer which can be sprayed on to the nasal mucosa.[113, 114, 115, 116, 117, 118, 119, 120, 121] Pelikan and colleagues[122] studied its effects, using nasal provocation tests and confirmed that it gave definite protection for over two hours. They state: "This compound has in pharmacological studies neither an antihistamine, antichoinergenic, antiserotonic, antibradykininic, or anti-SRS-A activity, nor a bronchodilating activity". It has been suggested that DSCG inhibits the release of the mediators from mast cell (Type 1) or possibly other cells (Type 3). Doubts have recently been cast about the efficacy of DSCG in hay fever. Greenbaum[123] reports poor results against ragweed pollenosis, and it is clear from several studies that this drug must be used very frequently, and be applied evenly to the sensitized mucosa. The former problem meets with patient resistance and the latter is certainly in question when the insufflator and powder are used; it would be reasonable to expect better results from the nebulizer.

Steroids

The other well established group of drugs in allergy therapy are the steroids.[124] Brostoff[125] writes: "All corticosteroids are beneficial in hay fever, though why is not known. Steroids have little or no influence on IgE levels, do not block allergen-IgE bindings, and do not inhibit histamine release from mast cells. They do, however, reduce tissue reactivity and capillary permeability and also diminish tissue histamine production, but these effects are insufficient to explain their total effectiveness. Immediate Type 1 skin or provocation tests are not blocked by steroids whereas immune complex Type 3 reactions are readily inhibited." Slott[126] confirms that skin tests are unaffected by a one-week course of steroids or antihistamine, although there was an eosinopenia following the use of the corticosteroids. One way of using steroids is to spray them locally on to the nasal mucosa.[127, 128, 129, 130, 131] If the mucosa is already too oedematous then the steroid may not help, but usually it works well. Mygind's[132] 1973 double-blind cross-cover trial confirmed that intranasal beclomethasone dipropionate aerosol was effective for the nasal symptoms and eliminated the need for other treatments. Brostoff and Czarny[133] showed in another double-blind cross-over trial that their patients preferred the steroid nebulizer to 'Otrivine'. They confirmed that fewer antihistamines were required and that there was no adrenal suppression. Pelikan and De Vries[101] do cast some doubt on its value. Some worry about local application of steroids still remains. Skin atrophy is well known to occur with prolonged use there, and the physician must be aware that similar changes might develop in the nose. Anyone who has seen a patient with chronic atrophic rhinitis with the appalling sickly sweet smell (ozaenia) and the gross crusting, would not be willing to run the risk of producing it iatrogenically; yet the habit of freely issuing repeat prescriptions without accurate record will inevitably produce this result sooner or later. The dictum "If a thing works, go on using it" requires qualification in these circumstances. As far as the hay fever sufferer is concerned, steroid sprayed intranasally at four to six hourly intervals can be expected to help, if symptoms are troublesome.

Oral steroid is equally or more effective than that locally applied, but nevertheless it is rarely prescribed for hay fever, for the fear of cortisone dependence is now deeply ingrained. But many general practitioners find the injection of depot steroid quite acceptable. The young student who is totally incapacitated during the examination season can be virtually guaranteed a cure within 12 hours of receiving an injection, deep intramuscularly. Triamcinolone acetate ('Kenalog') 80 mg in 2 ml or methylprednisolone acetate ('Depo-Medrone' 80 mg) are suitable for the adult. Lower doses than this are likely to be ineffective and the drug should never be used in children. Because it is so effective one must be even more alert to the dangers of such a potent medicament. Local fat atrophy at the site of the injection is serious enough, and such disfigurement must be avoided by choosing the gluteal site rather than the deltoid, but suppression of pituitary function is inevitable initially and may last for weeks or months.[134, 135] The *Lancet*[136] was happy to accept the use of depot-steroids and stated that this drug could be "repeated once or twice during the season". McMillin[134] and Brostoff[137] as well as Ganderton and James[135] in careful studies do not agree. The patient who suffers from perennial rhinitis rather than seasonal rhinitis may well return with a request for further injections, and a casual doctor might well give in to such pressure. Last year I attended such a patient who had received five injections of 'Kenalog' in the previous 12 months, fortunately without serious pituitary suppression.

To avoid these hazards, several authors[138, 139, 140, 141] have suggested the use of ACTH instead of corticosteroid. This can be administered intranasally[138] or by injection[141] and one can choose the natural product in a gel[141] or a synthetic product.[140] Dosage of 80 units weekly or twice weekly is required while doses of up to 200 units have been used.[139] Glick points out in his paper[139] that the therapeutic effect of corticotrophins often persists many hours after the plasma levels of cortisol have returned to their base value. The exact site of action is therefore not yet fully understood. The discomfort of repeated injections with the reappearance of symptoms as the effect wears off, or the pollen count rises,[142] is clearly a drawback to this line of treatment. Much more serious, however, is the report of two deaths[143] and several serious anaphylactic reactions

after the injection of the synthetic ACTH tetracosactrin ('Synacthen', 'Synacthen Depot', or 'Cortrosyn Depot'). These serious adverse effects have occurred in some patients after repeated, apparently safe, use. Therefore, all patients receiving synthetic ACTH must be kept for an hour on the surgery premises and appropriate treatment for anaphylaxis must be available.

All the treatments mentioned so far—vasoconstrictors, antihistamines, DSCG, and the various forms of steroid—are attempts to treat the disease at, or just before, the point of histamine release. But prevention is always regarded as better than cure, and so the physician who is concerned about this common, though self-limiting problem, will look hard at the possibility of prophylaxis.[144, 16, 145, 146, 142, 52, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159] Most of these authors confirm that the results are very good, even back to the early experiments of Noon and Freeman[160] with watery extracts of grass pollen in 1911. Although the results are good with some reservations, for example with the SDV vaccines of Bencard Ltd, there is the need to give between 20 and 40 injections per patient, and this is definitely counterproductive. In recent years, several attempts have been made to slow down the absorption of the antigen from the injection site. The principle is that graduated stimulation of the patient's immune system will create a state of hyposensitization. This state may have to be sustained by maintenance doses of the vaccine, or by repeated courses in subsequent years. There are now two main slow absorption vaccines available. In 1959, Fuchs and Strauss[161] described a method of extracting ragweed pollen by means of pyridine and then precipitating the extract with aluminium hydroxide. This was subsequently marketed in this country by Dome Laboratories in their 'Allpyral' range and by Bencard in their 'Alavac' range with very good clinical results.[144, 16, 146, 142, 52, 149, 152, 153, 158] The second type of vaccine is also offered by Bencard Laboratories. This is another complex molecule, using a glutaraldehyde-pollen-tyrosine adsorbate. It requires fewer injections, three instead of eight or nine, than its counterpart, and is marketed for hay fever with the trade name of 'Pollinex'. Results here seem to be equally good.[148, 150, 151, 154, 155, 156, 157, 159]

In addition to the specific vaccines against grass pollen, the manufacturers produce individual vaccines for patients, mainly prescribed on the results of skin tests. In my own original plan I tended to give grass pollen vaccine to every hay fever sufferer, but I had to review this following poor results in some patients. It soon became clear that the latter group were allergic to trees and/or flowers as well as to grass. More meticulous skin testing and prescribing corrected this anomaly with vastly improved results. Symington[157] found a similar effect when birch pollenosis was a significant factor. In my series just about half of the hay fever sufferers are allergic to grass pollens alone, while the others show multiple sensitivities which also require desensitization.

It follows that in undertaking a desensitization programme the patient has to be prepared to accept skin testing, followed by a series of injections each spring varying from three to nine in number. He or she must remain in the surgery for 20 minutes after the injection because of the potential danger of anaphylaxis. The cost to the NHS drug bill is about £18 per course, so this is a highly expensive exercise in both time and money. Each patient requires encouragement and careful management by the doctor and the practice nurse if the course is to be completed.

With the modern vaccines just described the untoward anaphylactic reactions of former years are now extremely rare. A few patients do complain of unpleasant side-effects, especially pain and redness at the injection site, a feeling of drowsiness, or very occasionally frank hay fever or asthma. It is paradoxical that those who do suffer such reactions may well be in the greatest need of the course of desensitization. The benefits of these injections appear to be dose related. Comparisons of dosage between Dome products and Bencard's are sometimes obscure because Dome use protein nitrogen units (p.n.u.) while their rivals, Bencard, use Noon units. It is helpful to know that one p.n.u. = two Noon units. There has been some evidence recently that a fourth injection with a larger dose may prove to be necessary to provide full protection with the course of 'Pollinex', but up until now this has not been marketed.

Control

After surveying these alternative treatments and seeing the fairly obvious and also the more sinister side-effects from them, one might well be driven towards a philosophy of nihilism. I am reminded of what Sir William Osler, the doyen of British physicians, said about coryza. "The only way to treat a common cold is with contempt." Could it be that hay fever is in this category too?

Antihistamines are still the most popular first line of treatment and will be used for all minor cases. A single dose of a long-acting product used nocturnally will reduce the very real danger of the most serious side-effect—drowsiness. McGuinness[92] has pointed out that antihistamines are used "not only for the truly allergic upper respiratory tract response but also for the common cold or coryza". He goes on to say: "It is to be admitted that neither of these disorders is anything but self-limiting; neither threatens life, and neither is likely to provide research material for a Nobel prize winner". West[95] remains dubious about the antihistamines. "Nearly all reported trials fail to meet the necessary modern standards of well controlled, randomized, double-blind nature. The best two fail to show any benefit for antihistamines in coryza. Indeed the atropine-like side-effects may insipissate sputum and

therefore slow recovery." Serious synergic effects may follow if antihistamines are combined with any of the central nervous system depressants, especially tranquillizers, sedatives, and alcohol. Many are aware of the dangers of a drug like 'Mandrax', but should be equally alert to drug interactions like that with the mono-amine-oxidase inhibitors.

A single dose of depot steroid is the next most popular line of treatment. It is extremely effective, yet it carries a risk. One has no way of identifying the patient who is going to suffer a prolonged and potentially serious suppression of his cortisol levels. The patient, if he suffered from perennial rhinitis, may plead for second and third doses without being aware of the risk that such a régime would create. ACTH—the natural extract but not the dangerous synthetic product[143]—is probably safer than steroid but its effect is much shorter lived, and the patient does not enjoy having to return every five to seven days for further uncomfortable injections. There is nuisance value too if the symptoms recur in the interval, so that they may wax and wane in a highly unsatisfactory way. It is clear that further research is needed on this aspect.

DSCG and local steroid both work, but demand regular use, perhaps as often as every two or three hours. This dosage schedule is complicated by the fact that these treatments are preventive rather than curative. It is probably for this reason that they are prescribed less frequently.

As I continue to research the literature I find that a multitude of other approaches have been made. Surgery demanding antral lavage, submucosal diathermy to the inferior turbinates[162] and even submucous resection of the septum have all been considered. A more recent approach has been with the local application of cold instead of intense heat. This is called cryosurgery[163, 164] and it does not require local or general anaesthetic. Puhakka[164] reports results as high as 80 per cent cures with this method. Two other variations of the same theme are with the use of long wave ultraviolet radiation[165] and "Endo-nasal Ar ± laser beam guide system".[166] Acupuncture combined with measurement of IgE levels (something old and something new) also produced fairly good results[167] while elimination diets[168] and "the effect of immune milk"[169] have also been reported. Neither are the mental factors ignored. Johnstone[170] discusses the possible risks of going into hospital, surgery, and anaesthesia on the development of asthma and hay fever in children, while from Poland Czubalski[171, 172] and colleagues stressed the role of the psychic or mental factors. So, in this modern age of Jumbo jets we appear to have a veritable Gadarene horde of possible solutions (presumably more elusive than elephantine, more poristic than porcine). But each one of the herd is naturally able to demonstrate its own self-destructive potential!

Can we hope for some solutions from biochemistry?[173] Not according to May![174] He states

that hyposensitization has been carried out since 1911 but only now is a critical evaluation possible. He writes: "I was unable to find an immunochemical response to injection of allergen extracts into sensitive persons which would provide either a rationale for treatment or a basis for a promising dosage régime worthy of a clinical trial". Others have not been so totally disheartening. Halpern[175] claims that by measuring total IgE it is possible to select the correct dose of allergen with which to start immunization treatment. Anfosso[59] showed that IgE rises rapidly during the pollen season to a post-seasonal peak. "Immunotherapy causes even higher rises in the first few months of treatment. Afterwards serum levels decreased progressively and after two years were below initial readings. At the same time, specific IgG are formed and these are involved in the clinical improvement." Herein I am sure we must seek our salvation.

That great English clergyman, wit, and essayist, the Reverend Sydney Smith (1771-1845) once wrote: "If consumption is too powerful for physicians, at least they should not suffer themselves to be outwitted by such little upstart disorders as hay fever". As we physicians carry on with this search, I hope that we will not be like another of whom the same essayist wrote, "He has spent all his life in letting down buckets into empty wells; and he is frittering away his age trying to draw them up again". Personally, I am going to continue to seek for the best answer, although the old adage is almost too appropriate.

Acum in meta faena quaerere

References

1. Bencard Ltd (1975). 'Pollinex' (film).
2. Pirquet, von C. (1906). Allergie. *Munchener Medizinische Wochenschrift,* **53,** 1457.
3. Ishizaka, K., Ishizaka, T. & Hornbrook, M. M. (1966). Physicochemical properties of reaginic antibodies. *Journal of Immunology,* **97,** 840-853.
4. Leuchao, E. *et al.* (1973). Studies on T-cell precursors. *International Archives of Allergy,* **45,** 237.
5. Gell, P. G. H. & Coombs, R. R. D. (eds) (1968). *Clinical Aspects of Immunology,* 2nd edition. Oxford: Blackwell.
6. Coca, A. F. & Cooke, R. A. (1923). On the classification of the phenomenon of hypersensitiveness. *Journal of Immunology,* **8,** 163.
7. Gleich, G. J. (1975). Immunoglobulin E antibodies to pollen allergens account for high percentages of total immunoglobulins E protein. *Science,* **190,** 1106-1108.
8. Holbrow, J. & Lessof, M. (1978). Immunological mechanism in health and disease. *Medicine,* **1,** part 1, 3rd series, 37-46.
9. Taylor, G. (ed)(1975). *Immunology in Medical Practice,* p. 280. London: Saunders.
10. *Lancet* (1977). What eosinophils do. Editorial, **2,** 388-389.
11. Zeiger, R. S., Yurdin, D. L. & Colten, H. R. (1976). Histamine metabolism. *Journal of Allergy and Clinical Immunology,* **58,** 1(2), 172-179.
12. Wasserman, S. I., Goetzl, E. J. & Austen, K. R. (1975). Inactivation of slow reacting substance of anaphylaxis by human eosinophil arylsulfatase. *Journal of Immunology,* **114,** (2 Part 1), 645-649.
13. Goetzl, E. J. (1976). Modulate of human eosinophil polymorphonuclear leukocyte migration and function. *American Journal of Pathology,* **85,** 419-435.
14. Lowell, F. C. (1967). Clinical aspects of eosinophilia in atopic disease. *Journal of the American Medical Association,* **202,** 875-878.
15. Reed, C. E. (1974). Abnormal autonomic mechanisms in asthma. *Journal of Allergy and Clinical Immunology,* **53,** 34-41.
16. Brown, H. M. & McIntyre, D. (1977). Immunotherapy for grass pollenosis with allpyral allergen extracts. *Acta Allergologica,* **32,** 321-332.
17. Wüthrich, B., Much, T. & Kopper, E. (1977). The importance of plantain, artemesia, and chenopodium pollen for the specific diagnosis of pollenosis (a comparison between RAST and in vivo tests). *Zeitschrift fur Hautkrankheiten,* **52,** 87-94.
18. Faegri, K. & Iversen, J. (eds) (1975). *Textbook of Pollen Analysis,* 3rd edition. Oxford: Blackwell Scientific.
19. Sandler, B. B. (1977). Birch pollen in Kuztnetsk. *Sovetskaia Meditsina,* **7,** 145-147.
20. Anfosso, F., Soler, M. & Mallea, M. (1977). Isolation and characterization *in vitro* of an allergen from planetree *(Platanus acerifolia)* pollen. *International Archives of Allergy and Applied Immunology,* **54,** 481-486.
21. Pence, H. L., Mitchell, D. Q., Greely, R. L. *et al.* (1976). Immunotherapy for mountain cedar pollinosis. A double-blind controlled study. *Journal of Allergy and Clinical Immunology,* **58,** (1 Part 1), 39-50.
22. Nikiforov, lul., Ruguzov, I. A. & Kuznetsov, S. I. (1975). An analysis of cedar of Lebanon (*Cedrus libani* A. Rich) pollen grain development. *Ontogenez,* **6,** 277-283.
23. Mahran, G. H., Abdel-Wahab, S. M. & Attia, A. M. (1976). A phytochemical study of date palm pollen. *Planta Medica,* **29,** 171-175.
24. Takayama, S., Saito, Y., Hasegawa, M. *et al.* (1976). The examinations of Japanese cedar pollinosis by radioallergosorbent test. *Journal of Otolaryngology of Japan,* **79,** 133-141.
25. Prince, H. E. & Meyer, G. H. (1977). Hay fever from Southern Wax-Myrtle *(Myrica cerifera)*—a case report. *Annals of Allergy,* **38,** 252-254.
26. Novey, H. S., Roth, M. & Wells, I. D. (1977). Mesquite pollen—an aero allergen in asthma and allergic rhinitis. *Journal of Allergy and Clinical Immunology,* **59,** 359-363.
27. Floreaag, E. (1977). Rhino-conjunctival Hashish allergy. *Tidsskrift for den Norske Laegeforening,* **97,** 563-564.
28. Agarwal, M. K., Singh, K. & Shivpuri, D. N. (1974). Strides on the atmospheric fungal spores and pollen grains: their role in the etiology of respiratory allergy. *Indian Journal of Chest Diseases,* **16,** Suppl. 26, 268-285.
29. US National Center for Health Statistics (1963). Chronic conditions & activity limitations, *Public Health Service Publications* No. 1000, Series 10.
30. Hagy, G. W. & Settipane, G. A. (1969). Bronchial asthma, allergic rhinitis and allergy skin tests among college students. *Journal of Allergy,* **44,** 323-332.
31. Harland, R. W. & McBride, N. A. (1974). Allergic respiratory syndrome in general practice. *Proceedings of the British Student Health Association,* 18-23.
32. Roberts, T. E. (1967). Hay fever in adolescents. *The Medical Officer,* 3098, **CXVIII,** No. 23, 290-294.
33. Fry, J. (1963). The natural history of hay fever. *Journal of the College of General Practitioners,* **6,** 260-264.
34. Perkin, J. M. (1972). Allergy in general practice. *Practitioner,* **208,** 776-783.
35. Coffman, D. A. & Chalmers, C. P. (1974). Incidence of hay fever in a North London practice. *Journal of the Royal College of General Practitioners,* **24,** 170-184.
36. Fairsheter, R. D., Chiu, J. T. & Wilson, A. F. (1977). Large airway obstruction in allergic rhinitis. *Journal of Allergy and Clinical Immunology,* **59,** 243-246.
37. Dunham, M. (1976). Thesis for diploma in clinical psychology. University of Manchester.
38. Bickmore, J. T. & Marshall, M. L. (1976). Cytology of nasal secretion: further diagnostic help. *Laryngoscope,* **86,** 516-523.
39. Viner, A. S. & Jackman, N. (1976). Retrospective study of 1,271 patients diagnosed as perennial rhinitis. *Clinical Allergy,* **6,** 251-259.
40. Manners, B. T. (1974). The diagnostic value of detecting

eosinophilia of nasal secretions in allergic rhinitis. *Journal of the Royal College of General Practitioners,* **24,** 397-399.
41. Hubscher, T. (1975). Role of the eosinophil in allergic rhinitis. 1.ED1—an eosinophil-derived inhibitor of histamine release. *Journal of Immunology,* **114,** 1379-1388.
42. Venge, P., Dahl, R., Zetterstrom, O., Roxin, L-E. & Olsson, I. (1977). Low levels of eosinophil cationic proteins in patients with asthma. *Lancet,* **2,** 373-375.
43. Hirsch, S. R. & Kalbfleisch, J. H. (1976). Circulatory basophils in normal subjects and in subjects with hay fever. *Journal of Allergy and Clinical Immunology,* **58,** 676-682.
44. Saraclar, Y. *et al.* (1977). Lymphocyte sub-populations of atopic children and the effects of therapy upon them. *Journal of Allergy and Clinical Immunology,* **60,** 301-305.
45. Rowe, D. S. (1969). Radioactive single radial diffusion: a method for increasing the sensitivity of immunochemical quantification of proteins in agar gel. *Bulletin of the World Health Organization,* **40,** 613-616.
46. Ebner, H. & Kraft, D. (1975). A comparative study of the value of skin tests and RAST in inhalation allergies. *Wiener Klinische Wochenschrift,* **87,** 627-631.
47. Eriksson, N. E. (1977). Diagnosis of reaginic allergy with house dust, animal dander, and pollen allergies in adult patients. II. A comparison between skin tests and provocation tests. *International Archives of Allergy and Applied Immunology,* **53,** 341-348.
48. Frankland, A. W. (1963). In *Clinical Aspects of Immunology* (Ed. Gell, P. G. H. & Coombs, R. R. A.). p.320. Oxford.
49. Godfrey, R. C. & Griffiths, M. (1976). The prevalence of immediate positive skin tests to *Dermatophagoides pteronyssinus* and grass pollen in school children. *Clinical Allergy,* **6,** 79-82.
50. Rheim M. *et al.* (19). Value of clinical history skin testing and nasal allergen challenge in diagnosis of perennial rhinopathy. *Laryngologie, Otologie* (Stuttgart).
51. McNicol, K. N. & Williams, H. B. (1973). Spectrum of asthma in children. *British Medical Journal,* **4,** 7-20.
52. Gaillard, G. E., Schellin, R. & Mayers, R. A. (1962). Observations on alum-precipitated pyridine pollen extract. *Annals of Allergy,* **20,** 81-89.
53. Freed, D. L. J. (1976). The management of allergic rhinitis in general practice. *Practitioner,* **216,** 330-335.
54. Brown, H. M. (1970). Some aspects of clinical allergy. *British Journal of Clinical Practice,* **24,** 513-522.
55. Munzell, M. (1975). The diagnostic value of intranasal tests in allergic rhinopathy. *Rhinology,* **13,** 135-139.
56. Mygind, N., Johnsen, N. J. & Thomsen, J. (1977). Intranasal allergen challenge during corticosteroid treatment. *Clinical Allergy,* **7,** 69-74.
57. Enzmann, H. (1974). The perennial rhinitis and the diagnostic possibilities of rhinomamometry. *Laryngologie, Rhinologie, Otologie und Ihre Grenzgebiete,* **53,** 723-730.
58. Rosenthal, R. R., Norman, P. S. & Summer, W. R. (1975). Bronchoprovocation. *Journal of Allergy and Clinical Immunology,* **56,** 338-346.
59. Anfosso-Capra, F., Autran, P. & Charpin, J. (1975). Blocking antibody and reagin changes during specific desensitization to pollen. *Nouvelle Press Medicale,* **4,** 791-794.
60. Dahl, R., Rosenhall, L. & Zetterstrom, O. (1976). Aspirin disease, bronchial asthma, and rhinitis caused by analgesics, food colouring agents, and food preservatives. *Ugeskrift for Laeger,* **138,** 2721-2723.
61. Eriksson, N. E., Ahlstedt, S. & Belin, L. (1976). Diagnosis of reaginic allergy with house dust, animal dander, and pollen allergens in adult patients. I. A comparison between radioallergosorbent tests, skin tests, and provocation tests. *International Archives of Allergy and Applied Immunology,* **52,** 335-346.
62. Gnazdowski, R. (1976). Values of diagnostic tests in detection of sensitization to grass pollens in allerogological practice. *Otolaryngologia Polska (Warszawa),* **30,** 489-494.
63. Holopainen, E., Turkiainen, E. & Malmberg, H. (1976). Nasal challenge. *Rhinology,* **14,** 181-188.
64. Nagaya, H., Lee, S. K., Reddy, P. M., Pascual, H., Jerome, D., Sadai, J., Gupta, S. & Lauridsen, J. (1977). Lymphocyte response to pollen; a correlation with radioallergosorbent test and effect of immunotherapy. *Annals of Allergy,* **39,** 246-252.
65. Okuda, M. (1977). Basic study of nasal provocation test first report: site of the nose, size and site and allergen amount. *Archives of Otolaryngology (New York),* **214,** 241-246.
66. Subira, M. L. & Oehling, A. (1975). Diagnostic value of total IgE and antigen specific IgE using radioallergosorbent test in pollenosis. *Allergologia et Immupalhologia (Madrid),* **3,** 9-16.
67. Voorhorst, R., Spieksma-Boezeman, M. I. & Spieksma, F. T. (1964). Is a mite *Dermatophagoides pteronyssinus* the producer of the house dust allergen? *Allergie and Asthma (Leipzig),* **10,** 329.
68. Smith, J. M., Disney, M. E., Williams, J. D. *et al.* (1969). Clinical significance of skin reactions to mite extracts in children with asthma. *British Medical Journal,* **1,** 723-726.
69. Mantle, J. & Pepys, J. (1974). Asthma among Tristan da Cunha islanders. *Clinical Allergy,* **4,** 161-170.
70. Crifo, S. & Filiacci, F. (1964). House dust mite allergy in Italy. *Rhinology,* **12,** 79-84.
71. Anderson, H. R. (1974). The epidemological and allergic features of asthma in the New Guinea Highlands. *Clinical Allergy,* **4,** 171-183.
72. Buchanan, D. J. & Jones, I. G. (1974). Mites and house dust mite allergy in bronchial asthma in Northern Zambia. *Postgraduate Medical Journal,* **50,** 680-682.
73. Settipane, G. A. & Chafee, F. H. Nasal polyps in asthma and rhinitis: review of 6,037 patients. *Journal of Allergy and Clinical Immunology,* **59,** 17-21.
74. Maw, A. R. (1976). The stuffy nose. *Practitioner,* **217,** 893-897.
75. Chilla, R. & Haubrich, J. (1975). Vasomotoriache rhinitis. Eine nebenwirkung hormonaler kontrazeption, University HNO Klin. Gottingen, **23,** 202-205.
76. Bagni, N., Charpin, H. & Davies, R. R. (1976). City spore concentrations in the European Economic Community (EEC). 1. Grass pollen, 1973. *Clinical Allergy,* **6,** 61-68.
77. Davies, R. R. & Smith, L. P. (1973). Forecasting the start and severity of the hay fever season. *Clinical Allergy,* **3,** 263-267.
78. Amin, R. & Bokhari, M. H. (1977). Survey of atmospheric pollens in Shiraz, Iran. *Annals of Allergy,* **39,** 192-195.
79. Apostolou, E. K. & Yannitsaros, A. G. (1977). Atmospheric pollen in the area of Athens. *Acta Allergologica,* **32,** 109-117.
80. Cardoso, R. R., Camoes, S. C. & Mendonca, I. F. (1975). Atmospheric pollen counts in Brasilia, Brazil. *Revista Brasileira de Pesquis Medicas e Biologicas,* **8,** 397-399.
81. Daz, Carrasco, E. (1977). Period of pollenization of allergic species in urban areas of Santiago. *Revista Medica de Chile,* **105/6,** 415.
82. Khakberdyev, M. M. & David'ian, A. A. (1975). Specific diagnosis and therapy in pollenosis. *Sovetskaia Meditsina,* **(1),** 42-45.
83. Mullins, J., Warnock, D. W., Powell, J., Jones, I. & Harvey, R. (1977). Grass pollen content of the air in the Bristol Channel region in 1976. *Clinical Allergy,* **7,** 393-395.
84. Orren, A. & Dowdle, E. B. (1977). Studies on Bermuda grass pollen allergens. *South African Medical Journal,* **51,** 586-591.
85. Reiss, N. M. & Kostic, S. R. (1976). Pollen season severity and meteorologic parameters in central New Jersey. *Journal of Allergy and Clinical Immunology,* **57,** 609-614.
86. Shafiee, A. (1976). Studies of atmospheric pollen in Tehran, Iran, 1974-75. *Annals of Allergy,* **37,** 132-137.
87. Soloman, W. R. (1975). A volumetric assessment of pollen levels in the air of Ann Arbor, Michigan. *Michigan Medicine,* **74,** 699-702.
88. Batchelder, G. L. (1977). Sampling characteristics of the Rotorod, Rotoslide, and Andersen Machines for atmospheric pollen and spores. *Annals of Allergy,* **39,** 18-27.
89. McAllen, M. (1972). The prevention and treatment of hay fever. *Practitioner,* **208,** 757-766.
90. Edwards, N., Elcock, H. W. & Ryke, R. (1973). An antihistamine-sympathomimetic amine combination in vasomotor rhinitis. *Practitioner,* **211,** 220-223.
91. McGovern, J. P., McElhenney, T. R., Hall, T. R. & Burdon, K. B. (1959). Evaluation of effectiveness, dosage, and toxicity of "Para-bromdylamine maleate" in allergic rhinitis of infants and children. *Annals of Allergy,* **17,** 915-922.
92. McGuinness, B. W. (1976). Trial of a long-acting antihistamine in the treatment of coryza. *British Journal of Clinical Practice,* **30,** 15-16.

93. Puhakka, H., Rantanen, T. & Virolainen, E. (1977). Diphenyl pyraline ('Lergobine') in the treatment of patients suffering from allergic and vasomotor rhinitis. *Journal of International Medical Research,* **5,** 37-41.
94. Sheriff, J. M. & Wallace, M. G. (1976). A comparative study of clemastine ('Tavegil') and chlorpheniramine maleate in the treatment of hay fever. *Current Medical Research and Opinion,* **4,** 245-249.
95. West, S., Brandon, B., Stolley, P. *et al.* (1975). A review of antihistamines and the common cold. *Paediatrics,* **56,** 100-107.
96. Tozzi, S., Roth, F. E. & Tabachnick, I. I. (1974). The pharmacology of Azatadine, a potential anti-allergy drug. *Agents and Actions,* **4,** 264-270.
97. Schering Corporation, USA Medical Research Files (1976). The effects of azatadine maleate and polaramine on performance in driving ability test. Personal communication.
98. Forrest, J. A. (1976). New histamine antagonists. *Scottish Medical Journal,* **21,** 2-3.
99. Frankland, A. W. (1970). Treatment of summer hay fever. *Update,* **2,** 155-156.
100. Schulz, E. (1977). Fatal triaminic poisoning in an infant. *Anaesthesiologische und Intensivmedirinsche Praxis München,* **13,** 93-95.
101. Pelikan, Z. & De Vries, K. (1974). Effects on some drugs applied topically to the nasal mucosa before nasal provocation tests with allergen. *Acta Allergologica,* **29,** 337-353.
102. Dolowitz, D. A. (1971). Drug treatment in allergic disorders. *Otolaryngologic Clinics of North America,* **4,** 591-598.
103. Drury, V. W. M. (1977). Hay fever in general practice. *Prescribers Journal,* **17,** 40-45.
104. Blair, H. (1977). The management of hay fever. *Update,* **14,** 1137-1144.
105. Bumbalo, T. S. (1960). Xylometrazoline HCL: a new nasal medication for paediatric use (an evaluation). *Western Medicine,* 9-11.
106. Chatterjee, S. & Hatua, N. R. (1960). Clinical evaluation of a new imidazoline vasoconstrictor. *Journal of the Indian Medical Association,* **35,** 397-399.
107. Deblasio, S. (1961). Analysis of a new decongestant in office rhinology. *Clinical Medicine,* **8,** 1958-1960.
108. De Sa, J. V. (1960). Clinical evaluation of a new topical vasoconstrictor in rhinology. *The Indian Practitioner,* **12,** 723-728.
109. Jacques, A. A. (1960). A new topical nasal decongestant for infectious and non-infectious disorders. *International Record of Medicine,* **173,** 683-685.
110. Pelz, H. (1973). On treatment with nose drops. *Medizinische Welt,* **32,** 1603-1605.
111. Cox, J. S. (1967). Disodium cromoglycate (FPL, 670, Intal)—a specific inhibitor of reaginic antibody—antigen mechanisms. *Nature,* **216,** 1328-1329.
112. Howell, J. B. L. (1968). Disodium cromoglycate in asthma and other allergic disorders of the airways. *Update,* **1,** 205-207.
113. Blair, H. & Viner, A. S. (1975). A double blind trial of a two per cent solution of sodium cromoglycate in perennial rhinitis. *Clinical Allergy,* **5,** 139-143.
114. Braydoy, B., Gronas, H. E. & Torjussen, W. (1975). Sodium cromoglycate (Lomudal nasal) in allergic rhinitis. *Tidsskrift for den Norske Laegeforening,* **95,** 1732-1733.
115. Cohan, R. H., Bloom, F. L. & Rhoades, R. B. (1976). Treatment of perennial allergic rhinitis with cromolyn sodium. Double blind study on 34 adult patients. *Journal of Allergy & Clinical Immunology,* **58,** 121-128.
116. Glazer, I. & Leventon, G. (1975). Topical treatment of hay fever with disodium cromoglycate (DSCG) solution. *International Archives of Allergy and Applied Immunology,* **49,** 125-128.
117. Knight, A., Underdown, B. J. & Demanuele, F. (1976). Disodium cromoglycate in ragweed-allergic rhinitis. *Journal of Allergy and Clinical Immunology,* **58,** 278-283.
118. Lofkvist, T. & Svensson, G. (1975). An open assessment of lomudal (disodium cromoglycate) (two per cent) nasal spray in seasonal allergic rhinitis. *Acta Allergologica,* **30,** 89-95.
119. Manners, B. T. B. (1975). A comparison of sodium cromoglycate nasal solution and powder in hay fever. *British Journal of Clinical Practice,* **29,** 153-154.
120. Nizami, R. M. & Baboo, M. T. (1977). Efficacy double blind, crossover study of sodium cromoglycate in patients with seasonal allergic rhinitis. *Annals of Allergy,* **38,** 42-45.
121. Topilsky, M., Grief, J., Kuri'at, D. *et al.* (1976). Disodium cromoglycate in the treatment of seasonal and perennial rhinitis. *Annals of Allergy,* **36,** 246-248.
122. Pekikan, Z., Snoek, W. J., Booij-Noord, H. *et al.* (1970). Protective effect of disodium cromoglycate on the allergen provocation of the nasal muscosa. *Annals of Allergy,* **28,** 548-553.
123. Greenbaum, J., Gockcraft, D. & Hargreave, F. E. (1977). Sodium cromoglycate in ragweed allergic conjunctivitis. *Journal of Allergy and Clinical Immunology,* **59,** 437-439.
124. Brenn, H. (1977). The treatment of hay fever with depot corticosteroid. *Praxis,* **66,** 82-85.
125. Brostoff, J. (1972-74). Immediate hypersensitivity and allergy. *Medicine,* **29,** 1714-1723.
126. Slott, R. I. & Zweiman, B. (1974). A controlled study of the effect of corticosteroids on immediate skin test reactivity. *Journal of Allergy and Clinical Immunology,* **54,** 229-234.
127. Brown, H. M. & Storey, G. (1973). Beclomethasone dipropionate steroid aerosol in treatment of perennial allergic asthma in children. *British Medical Journal,* **3,** 161-164.
128. *British Medical Journal* (1976). Intranasal beclomethasone: wonder drug or hazard? Editorial, **2,** 1522-1523.
129. Halpern, G. M. (1977). Use of intranasal beclomethasone dipropronate for allergic rhinitis. *Nouvelle Press Medicale,* **6,** 1324-1325.
130. Malm, L. & Wih, J. A. (1976). Intranasal beclomethasone dipropionate in vasomotor rhinitis. *Acta Allergologica,* **31,** 245-253.
131. Marland, J. & Tabart, J. (1977). Results obtained with beclomethasone dipropionate treatment in allergic rhinitis. *Nouvelle Press Medicale,* **6,** 1307-1308.
132. Mygind, N. (1973). Local effect of intranasal beclomethasone dipropionate aerosol in hay fever. *British Medical Journal,* **4,** 464-466.
133. Brostoff, J. & Czarny, D. (1969). Effect of intranasal betamethasone 17-valerate on allergic rhinitis and adrenal function. *Journal of Allergy,* **44,** 77-81.
134. McMillin, W. P. (1971). Triamcinolone acetonide ('Kenalog') in treatment of cases of hay fever and its effect on pituitary-adrenal axis. *Ulster Medical Journal,* **40,** 176-179.
135. Ganderton, M. A. & James, V. H. (1970). Clinical and endocrine side effects of methylprednisolone acetate as used in hay fever. *British Medical Journal,* **1,** 267-269.
136. *Lancet* (1975). Hay fever. Editorial, **1,** 786-787.
137. Brostoff, J. (1975). Hay fever and corticosteroids. *Lancet,* **1,** 1424.
138. Felber, J. P., Aubert, M. L. & Deguillaume, R. (1969). Administration by nasal spray of an 18 amino acid synthetic polypeptide with corticotropic action. *Experimentia,* 25/11.
139. Glick, I. W. & Friedman, M. (1969). High dosage short-term corticotrophin therapy in acute asthma. *Thorax,* **24,** 415-420.
140. Keenan, J., Thompson, J. B., Chamberlain, M. A. & Besser, G. M. (1971). Prolonged corticotrophic action of a synthetic substituted 1-18 ACTH. *British Medical Journal,* **3,** 742-743.
141. Parr, E. J. (1976). Hay fever treated with ACTH gel. *Clinical Allergy,* **6,** 479-486.
142. Frankland, A. W. & Noelpp, B. (1966). Summer hay fever treated with aqueous and alum-precipitated pyridine extracts. *Practitioner,* **196,** 766.
143. Committee on Safety of Medicines (1975). Reactions to tetracosactrin (Synacthen Depot-Cortrosyn Depot) *Current Problems No. 1.*
144. Brown, H. M. & Thantry, N. (1976). Rapid extraction of grass pollen allergens and separation of their active fractions. *Acta Allergologica,* **31,** 22-24.
145. Evans, R. G. (1968). Treatment of seasonal respiratory allergy with alum-precipitated pyridine extract incorporating pollen and spores. *Acta Allergologica,* **23,** 240-251.
146. Fagerberg, E., Nilzen, A. & Wiholm, S. (1972). Studies in hyposensitization with Allpyral: objective evaluation of the results. *Acta Allergologica,* **27,** 1-14.
147. Girard, J. P. & Huguenin-Dunmittan, S. (1964). Traitement de la rhinite saisoniere au moyen de complexes pollen-L tyrosine. *Schweiz Rundschan Med. (PRAXIS),* **63,** 1554-1556.
148. Johansson, S. G., Miller, A. C. & Mullan, N. (1974).

Glutaraldehyde-pollen-tyrosine: clinical and immunological studies. *Clinical Allergy,* **4,** 255-263.
149. Liebeskind, A. (1968). Treatment with 'Allpyral' pollen extracts in highly sensitive hay fever patients. *Acta Allergologica,* **23,** 39-45.
150. Miller, A. C. (1976). A comparative trial of hyposensitization in 1973 in the treatment of hay fever using Pollinex and Alavac P. *Clinical Allergy,* **6,** 551-556.
151. Miller, A. C. (1976). A trial of hyposensitization in 1974/5 in the treatment of hay fever using glutaraldehyde-pollen-tyrosine adsorbate. *Clinical Allergy,* **6,** 557-561.
152. Munro-Ashman, D. (1966). An alum-precipitated pyridine extract in the treatment of hay fever. *Practitioner,* **196,** 771-774.
153. Norman, P. S. Winkenwerder, W. L. & Lichtenstein, L. M. (1972). Trials of alum-precipitated pollen extracts in treatment of hay fever. *Journal of Allergy and Clinical Immunology,* **50,** 31-44.
154. Palmer, W. R. & Balacescu, A. (1977). A multicentre trial of pollen-tyrosine adsorbate. *Acta Allergologica,* **32,** 44-57.
155. Purser, J. R. (1976). Treatment of hay fever in general practice by hyposensitization using 'Pollinex'. *Current Medical Research and Opinion,* **4,** 124-127.
156. Sychlowy, A. (1977). Use of a grass pollen vaccine adsorbed onto tyrosine ('Pollinex') in the treatment of pollenosis. *Pharmatherapeutica,* **1,** 378-380.
157. Symington, I. S., O'Neill, D. & Kerr, J. W. (1977). Comparison of a glutaraldehyde-modified pollen-tyrosine adsorbate with an alum-precipitated pollen vaccine in the treatment of hay fever. *Clinical Allergy,* **7,** 189-194.
158. Tuft, L. (1966). Treatment of allergic conditions with alum-precipitated ('Allpyral') extracts of allergens other than ragweed. *Acta Allergologica,* **21,** 414-429.
159. Verstraeten, J. M. *et al.* (1975). Experience clinique en Belgique pendant la saison pollinque 1973 avec un extract de pollen adsorbe sur tyrosine. *Revue Francais d'Allergolie et d'Immunologie Clinique,* **15,** 173-174.
160. Noon, L. (1911). Prophylactic inoculation against hay fever. *Lancet,* **1,** 1572-1573.
161. Fuchs, A. M. & Strauss, M. B. (1959). Clinical evaluation and the preparation and standardization of suspensions of a new water-insoluble whole ragweed pollen complex. *Journal of Allergy,* **30,** 66-82.
162. Devgan, B. K. & Leach, W. (1976). Submucosal diathermy of inferior turbinates. *Eye Ear Nose Throat Monthly,* **55,** 156-158.
163. Ozenberger, J. M. *et al.* (1974). Cryosurgery in allergic rhinitis. *Minerva Medica,* (Torina), **65,** 3714-3715.
164. Puhakka, H. & Rantanen, T. (1977). Cryotherapy as a method of treatment in allergic and vasomotor rhinitis. *Journal of Laryngology and Otology,* **91,** 535-539.
165. Svetleishii, A. M. (1977). Use of long wave UV radiation in the treatment of vasomotor rhinitis. *Zhurnal Ushnykh, Nosovykh: Gorlovykh Boleznei,* **3,** 64-69.
166. Lenz, H., Eichler, J., Knof, J., Salk, J. & Schafer, G. (1977). Endonasal Ar ± laser beam guide system and first clinical application in vasomotor rhinitis. *Laryngologie, Rhinologie, Otologie, vereingt mit Monattsschrift fur Ohrenheilkunde,* **56,** 749-755.
167. Lau, B. H., Wong, D. S. & Slater, J. M. (1975). Effect of acupuncture on allergic rhinitis: clinical and laboratory evaluations. *American Journal of Chinese Medicine,* **3,** 263-270.
168. Ogle, K. A. & Bullock, J. D. (1977). Children with allergic rhinitis and/or bronchial asthma treated with elimination diet. *Annals of Allergy,* **39,** 8-11.
169. Le Ferman, K. M. *et al.* (1975). The effect of immune milk as a treatment for ragweed pollenosis. *Annals of Allergy,* **35,** 367-371.
170. Johnstone, D. E. *et al.* (1975). Factors associated with development of respiratory allergies: roles of hospitalization, surgery, and anaesthetics. *Revue Francais d'Allergologie et d'Immunologie Clinique,* **15,** 127-131.
171. Czubalski, K. & Zawisza, E. (1975). Importance of the mental factor in hay fever and non-seasonal allergic rhinitis in the light of psychosomatic studies. *Polski Tygodnik Lekarski,* **30,** 809-812.
172. Czubalski, K. & Zawisza, E. (1976). The role of psychic factors in patients with allergic rhinitis. *Acta Oto-Laryngologica,* **81,** 484-488.
173. Osterhage, F., Wippler, M., Kalden, J. R. & Deicher, H. (1977). Determination of specific IgE and IgG serum antibodies during immunotherapy in hay fever patients by RAST. *Zeirschrift fuer Immunitaetsforschung,* **153,** 189-203.
174. May, C. D. (1975). Treatment of allergic disorders with injections of allergen extracts. *Pediatric Clinics of North America,* **22,** 221-225.
175. Halpern, G. M. (1974). Clinical significance of serum IgE determination. *Annals of Allergy,* **33,** 67-71.

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Nonspecific vaginitis

To assess the cause of nonspecific vaginitis, we performed a prospective case control study of vaginal flora and a randomized unblinded trial of different therapies. *Haemophilus vaginalis* was isolated from 17 of 18 women with signs of vaginitis but only one of 18 normal matched controls ($p<0\cdot002$). The concentration of anaerobic bacteria in vaginal washings also was increased in patients. Clinical improvement and eradication of *H. vaginalis* occurred in one of seven patients given sulphonamide vaginal cream, two of 15 given oral doxycycline, nine of 27 given oral ampicillin, and 80 of 81 given oral metronidazole. On the seventh day of therapy signs of nonspecific vaginitis persisted in 31 of 31 with, and in two of 92 without, persistent *H. vaginalis* infection ($p<0\cdot001$). These data suggest the causal role of *H. vaginalis* in nonspecific vaginitis, possibly in concert with vaginal anaerobes. The widespread use of sulphonamide creams is inappropriate. Metronidazole is effective, but its efficacy must be weighed against its possible toxicity.

Reference

Pheifer, T. A., Forsyth, P. S. *et al.* (1978). *New England Journal of Medicine,* **298,** 1429-1434.