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Allergy Symposium

PRESENT CONCEPTS IN INTERNAL MEDICINE

COL Joseph L. McGerity, MC and Lottie B. Applewhite, M.S.

Letterman Army Medical Center
Presidio of San Francisco, California 94129

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Allergy Symposium

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) The ten-article symposium is devoted entirely to HAYFEVER. The immunologic mechanism of hayfever, allergic reactions of the conjunctiva, diagnostic tests, hyposensitization, are discussed. The natural history untreated hayfever is presented before four articles on the treatment of hayfever by drugs (over-the-counter antihistamines, noncatechol sympathomimetic drugs, corticosteroids, disodium cromoglycate.) A 9 page article on diagnosis and treatment of cerebrospinal fluid rhinorrhea is also included.		

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IN INTERNAL MEDICINE

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Volume VI, Number 5, September-October 1973

PRESENT CONCEPTS IN INTERNAL MEDICINE

VOLUME VI *September-October 1973* Number 5

ALLERGY SYMPOSIUM

CONTENTS

FORTHCOMING SYMPOSIA

NEUROLOGY

PULMONARY

FOREWORD

A revolution simmers within the medical profession. The educational values of three-quarters of a century are called into question. This or that disease problem demands our major attention. Various segments of the population cry for their "fair share" of available resources. Our legislators propose new social schemes, and our own leaders institute organizational reorganization. As individuals we can participate to a limited degree in decision making that will attempt to answer these problems of our time. The more immediate and perhaps more lastingly important effect of this ferment will be our reassessment of our personal relationships with the individual patient.

With increasing maturity our population has come to recognize that mere quantity does not answer the desires of their material or social-spiritual life. Mere possession, once attained, is not satisfying. Fitness of form and function in the relationship of life is beginning to be preceived as an ideal. Man seeks a role in the decisions of political or social life that will determine his destiny as a race and as an individual.

The proposal that the patient should share the power to decide the form of medical care for himself or his group is anathema to many physicians. These doctors assume a father role and regard their patients as children who must be spoon-fed their medical program. The use of such an authoritarian approach is rejected by today's youth and this failure of doctor-patient relationship will lead to further estrangement.

A reconciliation may be effected if we will return to our original role as doctors, i.e. to resume our position as teachers of proper ways to prevent disease and preserve health. Once again we must put our emphasis on the patient-environmental relationship and not only on the disease that disrupts this harmony. In the milieu of the modern teaching hospital the young physician is, and should be, concerned with the major task of diagnosing and curing or ameliorating life-threatening illness. However, with few exceptions (who develop policy for the majority of the profession), the remainder of the physician's career will be mostly spent dealing with developmental, infections, or chronic illness in an outpatient setting – a

stage for which he was not educated and upon which he is often uncomfortable, so much so that he often finds it easier to deal with the patient in the authoritative atmosphere of the hospital. One might speculate about the number of hospital admissions for "work up" that are induced by the physician's need to retain his psychological advantage.

Hayfever is an example of a chronic or recurrent, non-life-threatening disorder which offers an opportunity for the practitioner to exercise his ability as a teacher and to participate in a rewarding relationship of dependency and trust with his patient. Allergy history taking should serve as a diagnostic, educational, and therapeutic experience. To fulfil these expectations sufficient time must be allotted and an atmosphere of comfortable trust and understanding established. All too often the hayfever victim is treated by his physician as a passive recipient of skin tests, injections of allergy extracts, and a wide variety of pills and potions.

Ask any allergist "What is the primary principle of allergic therapy?" and, almost reflexly, he will answer that it is elimination or avoidance of the allergen. All too frequently this is merely lip-service to an ideal. How infrequently positive steps are taken to implement this goal. The patient is the one best situated to observe those factors in the environment that adversely affect him. He must be taught enough about allergens and the natural course of his disease to recognize the significance of what he observes. This education takes time of both the doctor and the sufferer. The physician must have patience with his patient who is unaware of the role that habits, diet, environment and emotion play in his disease. The patient must not expect an easy solution to all the allergic problems and must accept that advice is as an important part of treatment as the prescription given for immediate (but perhaps only temporary) relief. Both parties to the contract for care must participate.

> Instruction of this kind is not dramatic... No wide publicity will result, and great reputations are unlikely, but the practice of medicine is by definition a service profession, and unless services to patients in need, including education in proper health practices are given, the doctor is neglecting his major function, and that is all too frequently true.*

COL JOSEPH L. McGERITY, M.C.
Guest Editor

*Hundley JTT. Editorial. *Va Med Mon* 100:617, 1973

IMMUNOLOGICAL MECHANISMS IN HAYFEVER

LTC Richard Evans, MC, USA*

We are indebted to von Pirquet in 1906 for recognizing the common denominator between immunity and hypersensitivity and for introducing the term *allergy*. Hypersensitivity and immunity then are descriptive terms which are not mutually exclusive and which identify a clinical state of allergy.

The animal host is capable of mounting hypersensitivity responses which can be manifest immediately (within minutes), later (within hours), or delayed (within two to three days). In addition, the plasmoconstituents and cellular responses involved in these different manifestations of hypersensitivity are peculiar to the type of response.

It is the purpose of this review to discuss our current knowledge and understanding of the immediate (reaginic) hypersensitivity reaction. These reactions are characterized by a rapid release of short lived pharmacologically active agents. These agents are released by tissue cells after a reaction between the antigen (foreign substance) and the antibody (immunoglobulin) which is attracted to the cell surface. Anaphylaxis is an immediate hypersensitivity reaction. Allergic rhinitis and allergic asthma are other examples of immediate hypersensitivity reactions seen in man.

The complete mechanism of immediate hypersensitivity reactions is visualized as a series of reactions. These include (1) fixation of an antibody to the cell surface, (2) binding of antigen to this antibody with resultant conformational changes in the antibody, (3) activation of an energy requiring enzyme system and (4) a secretory response of mediator release.

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Immunoglobulin E and Reaginic Antibody

The antibody in immediate hypersensitivity reactions is reaginic antibody. It is found in the serum of allergic patients and is characterized by the ability to sensitize human skin. This was first demonstrated in the experiments of Prausnitz and Kustner /2/ in 1921. The serum of fish sensitive Kustner was injected intradermally into the skin of Dr. Prausnitz. The testing site was challenged twenty-four hours later with an extract of fish and the response was an immediate wheal and flare reaction. This sensitizing activity by passive transfer of human reaginic antibody is generally limited to the tissues of man, ape and monkey. In addition to skin, passive sensitization with human reaginic serum of human leukocytes and human and monkey lung fragments has been achieved.

The presence of immunoglobulin E (IgE) in human serum was first demonstrated in 1966 by the Doctors Ishizaka. /5/ This was done in the laboratories of the Children's Asthma Research Institute and Hospital, Denver, Colorado. Working with the serum of allergic patients, these physicians were also able to identify IgE as the carrier of reaginic antibody activity. /5/

Soon after the detection of IgE in human serum an IgE myeloma protein was discovered. /6/ The availability of this protein in high concentrations enabled physio chemical analysis. IgE is a glycoprotein with an electrophoretic mobility of gamma-1 globulins. It has a sedimentation coefficient in the ultracentrifuge of 8.0 and a molecular weight of approximately 200,000. As is found in most immunoglobulins, the IgE molecule is composed of two light chains of amino acids, and two heavy chains. The antigenic determinants specific to the IgE class of immunoglobulins are found in the F(c) portion of the molecule and the antibody combining sites are in the F(ab) portion. The immunoglobulin binds to the cell surface by the F(c) portion. /7,8/

IgE forming plasma cells are found in the respiratory and gastrointestinal mucosa, in tonsils and adenoids, and in bronchial and peritoneal lymph nodes. /9/ Small quantities of IgE have been found in nasal secretions of allergic patients. /10/

The most important immunochemical property of IgE is the ability to fix to target cells of immediate hypersensitivity. These target cells are the basophil in peripheral blood and the mast cell in tissue. When a monkey is given an intravenous injection of radiolabeled IgE myeloma protein (^{125}I-IgE) the label can subsequently be demonstrated attached to mast cells in the cementum, and in the lamina propria of the small intestine and bronchi. /11/ When human peripheral leukogytes are incubated with ^{125}I-IgE the label is found attached to the basophils. If these basophil fixed antibodies are challenged with antigen the basophil loses metachromatic granules and histamine is released. /12/ Ishizaka et al /13/ reported that the number of IgE molecules bound to basophil in allergy patients is between 10,000 and 40,000 IgE molecules per basophil.

Immunoglobulin E is present in very small amounts in normal human serum. The level slowly rises from a few nanograms per milliliter in adults. /17/ Patients with allergic rhinitis, extrinsic (allergic) asthma and atopic eczema have significantly raised levels of serum IgE. The IgE level is also increased by allergen stimulation. During a pollen season increase of IgE is found in patients with asthma and hay fever. There is no definite correlation between IgE level and severity of allergic state, however. High levels of IgE (micrograms per milliliter) have been found in parasitic infestations including Ascaris, Toxocara, hook worm and Echinococcus. /15/ Some human serum samples contain little or no measurable IgE. The significance of this is unknown.

Release of Chemical Mediators

Peripheral leukocytes of allergic individuals will release histamine on exposure to specific antigen. /16/ When the white cells are isolated and exposed in vitro to varying concentrations of antigen, histamine is released in proportion to the amount of antigen used and the sensitivity of the patient. The antigen requirement for induction of leukocyte histamine release in vitro is quite small and in the range of 0.1 to 0.00001 micrograms of antigen protein per milliliter. This phenomenon of antigen induced leukocyte histamine release provides an in vitro model of the

allergic reaction steps. Furthermore, when a symptom index score of the clinical severity of allergic sensitivity of the patient to a given allergen is compiled, this symptom index parallels the in vitro sensitivity of the patient's leukocytes for histamine release. /17/ The more severely affected patients require much less antigen in vitro to include leukocyte histamine release.

Sada et al /18/ have demonstrated that immunotherapy with allergen extract results in a diminution of sensitivity of the leukocytes to the antigen as manifest by in vitro histamine release. These patients also have an improvement in the symptom index score. /19/

Histamine is found in largest quantities in circulating basophils and tissue mast cells. When sensitized monkey or human lung fragments are challenged in vitro with specific antigen histamine is released. /20/ The sensitized lung fragments are obtained by using lung tissue of an allergic patient, /21/ by incubation of normal lung fragments in reaginic antibody containing serum /22/ or by incubation of the fragments in E myeloma serum. The antigen is one to which the patient is sensitive. An antiserum prepared against IgE can also be used. /23/

In addition to histamine, sensitized monkey and human lung fragments release slow reacting substance of anaphylaxis (SRS-A), /21,24/ and a factor chemotactic for eosinophils (ECF-A). /25/ SRS-A is an acidic lipid with a molecular weight of 900-1250. It is identified by its ability to cause a slow, prolonged contraction of guinea pig ileum in a Schultz-Dale preparation. SRS-A is released from the lungs of asthmatics on challenge by specific pollen allergen and it is a potent stimulator of human bronchial smooth muscle contractions.

ECF-A was first described in 1971./25/ This substance has a molecular weight between 500 and 1000 and is also released from the lungs of asthmatic patients when challenged by antigen. ECF-A is specific for the attraction of eosinophils.

Kaliner et al /27/ have more recently demonstrated the in vitro release of histamine, ECF-A, and a small amount of SRS-A from human nasal polyps with appropriate antigen stimulation.

Pharmacologic Control Mechanism

The immunologic release of the foremost chemical mediators from target cells is an energy dependent process, most probably enzyme mediated./28/ Thirty-six years ago, Schild /29/ observed that epirephrine inhibited the immunologic release of histamine from guineapig lung. This effect of catecholamines is now known to be by activation of an enzyme, adenyl cyclase, on the surface of the cell. This in turn increases the cellular content of cyclic adenosine 3' -5' monophosphate (CAMP). /30/ This system of CAMP is a cellular secretory system and was first described by Sutherland in 1958. /31/ Drugs capable of increasing cellular levels of CAMP (isoproterenol, epinephrine, methyxanthines and corticosteroids) will inhibit the release of histamine and SRS-A. /32,33/ These drugs are therefore capable of directly modulating the IgE mediated immediate hypersensitivity response.

COMMENTS

Immediate hypersensitivity reactions are characterized by a rapid release of short lived pharmacologically active agents. This phenomenon is mediated by reaginic antibodies of the immunoglobulin E class of immunoglobulins. The agents released include histamine from peripheral basophils and histamine and slow reacting substance of anaphylaxis from tissue mast cells. A new mediator, eosinophil chemotactic factor, released by sensitized lung tissue is also described. The release of these mediators is dependent upon cell fixation of the antibody, binding of antigen by the antibody, and activation of cellular enzyme and cellular secretory mechanisms subsequent to the binding of antigen. Pharmacologic inhibition of this reaction sequence is described.

Our understanding of immediate hypersensitivity reactions has been enhanced tremendously in recent years. The knowledge gained and concepts developing offer new directions in our goal of relieving patients suffering from allergic disorders.

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UNTREATED HAYFEVER
Natural History

MAJ Edward Spitz, MC

The natural history of untreated hayfever is not well studied. /1-4/ The studies that have been reported hint at answers to the following: (1) Does hayfever disappear if untreated? (2) What is the relationship between sinusitis, nasal polyps, and hayfever? (3) What is the incidence of asthma in hayfever?

Does hayfever disappear if untreated?

Most authors of allergy texts /1-4/ agree that a small population of hayfever patients become asymptomatic spontaneously without recurrence. Fontana /4p101/ states that this phenomenon is age dependent. If hayfever starts in childhood, 20 percent of patients will not be bothered after age 25. However, if it begins after age 25, most patients continue to be symptomatic even after age 50. The Baltimore group /1/ has studied a small number of patients with spontaneous remissions and noted that skin tests became negative and histamine releasing activity of leukocytes disappeared despite repeated seasonal allergen exposure and treatment with antihistamines alone.

Rackemann and Lamsa /5/ studied 120 patients with ragweed allergic rhinitis over a 20-year period most of whom were treated preseasonally. Thirty-eight of these 120 patients who were not treated with hyposensitization for at least three years before final followup had clearance of symptoms. Fourteen of these 38 were skin-tested on follow-up and seven had negative skin tests.

Smith /6/ in a 15-25 year retrospective interview study of 245 Iowa University allergy clinic alumni found that 75 percent of patients with well-documented hayfever and asthma who moved out West (where environmental

allergens presumably changed) improved considerably within the first year of moving and maintained this improvement. (Table 1). Ten percent became worse or stayed the same. Only 7 percent possibly developed new allergies. Forty percent of the whole group had hayfever alone. The number treated with hyposensitization is not stated. Of those that remained in the midwest, none improved within the first year, 62 percent gradually improved and 36 percent were the same or worse. Only 2 percent developed new allergies and 43 percent of this group had hayfever alone. About 60 percent were treated with hyposensitization from one to more than five years.

TABLE 1

RESULTS OF MOVING AWAY FROM IOWA IN PATIENTS WITH ASTHMA AND HAY FEVER*

CONDITION	EAST *Percent*	MIDWEST *Percent*	WEST *Percent*
Promptly all better	2	0	47
Promptly much better	27	0	28
Gradually all better	4	10	0
Gradually much better	37	52	8
Same	14	20	4
Worse	12	16	6
New allergy	4?	2?	7?

*From Smith /6/

Smith /6/ concluded that if, after a change in environment symptoms improve, this improvement is maintained. About as many patients not treated as treated (with hyposensitization) improved. However, comparison between these groups was not valid because the treated group was self-selected and probably had more severe and persistent difficulty.

Some patients become less symptomatic as they grow older /1,3,5/ although severe hayfever can occur at any age /2,5/ and symptoms can recur after a symptom free interval /3/ of 2 to 4 years (9 out of 122 patients) /5/. When patients were graphed according to age of onset and age at final followup, there was a tendency for symptoms to clear within 15 years of onset, or to clear with increasing

age. /5/ The ratio of cleared cases/decade to total cases/decade approached one as age increased. There is no clear explanation for this phenomenon. Decreased exposure to allergens with change in life style, change in organ threshold, lack of priming effect might all explain a decrease in symptoms with increasing age of the patient. Thus, a few patients with seasonal allergic rhinitis are cured spontaneously at an early age; others have fewer symptoms and may also clear completely as they grow older with or without hyposensitization therapy.

What is the relationship between sinusitis, nasal polyps, and hayfever?

This question has two parts: (a) as hayfever continues, do polyps, and sinusitis become more common, and (b) if sinusitis and polyps are present, how do they affect prognosis?

Criep /7/ attempted to answer this in a study of 972 consecutive, unselected allergy patients who had what he considered adequate therapy with avoidance, hyposensitization, and medication for at least one year. In a group of 247 patients with perennial allergic rhinitis, the older patients and those with untreated rhinitis for many years had a high incidence of sinusitis (type undefined). The incidence was 10 percent if rhinitis was present less than five years and 80 percent if present more than 16 years. Nasal polyps were present in 9 percent and 75 percent respectively. These patients had marked improvement to the therapy in only 35 percent of the cases whereas another group without sinusitis and polyps (probably not matched for age) followed for 1 to 15 years showed marked improvement in symptoms in over 80 percent of the cases after similar therapy.

Criep /7/ also studied 182 patients with seasonal hayfever and found again that as the duration of hayfever increased, sinusitis, and polyps became more frequent although not as frequent as seen in perennial rhinitis. Again, if these complications were present, response to therapy was not as good as if they were not present.

Smith /6/ found that 14 of 29 patients who had not done well 15 to 25 years after diagnosis of hayfever and asthma had nasal polyps. These 14 patients, however, were only 5 percent of the total group of patients. These patients were not specifically analyzed concerning treatment and diagnosis.

Other authors /2,4p137/ state that untreated hayfever can lead to sinus infection. Secondary infection in seasonal rhinitis can lead to perennial symptoms and, especially with "lingering infection", can lead to nasal polyps. /8 / If these complications occur, the patient becomes more difficult to treat. /4p137/

What is the incidence of asthma in hayfever?

Two recent epidemiologic studies "do not support the time-worn adage that a child whose allergic rhinitis is left untreated will develop asthma with a high degree of probability ." /9/

The epidemiologic studies in Tecumseh, Michigan /10,11/ relied on questionnaires administered in the home pertaining to all household members over eight years, some between six and eight, and none less than six years. Each person was then examined by a physician in the clinic and laboratory tests were done. Diagnoses were entertained at this time and reviewed at a later date by another group of physicians. Neither asthma nor hayfever were rigidly defined. Asthma included any and all manifestations occurring alone or with infection; hayfever included any upper respiratory symptoms believed to be allergic and seasonal. Eighty-eight percent of the population known by census was interviewed and examined. The cumulative prevalence rate of asthma and hayfever was 4 percent and 6 percent respectively.

The relationship between hayfever and asthma was examined in a number of ways and in each case asthma did not commonly follow hayfever.

- In persons with hayfever at risk to develop asthma (asthma not present before or concurrently with hayfever), asthma developed in only 7 percent.

- In persons with both asthma and hayfever in whom retrospectively the sequence of development was known (87 of 128 patients), 23 percent had hayfever first, 26 percent had asthma first and 51 percent had onset of both within the same year.

- The age of onset of hayfever and asthma was compared. It was found that asthma most commonly began before age five (31 percent)while hayfever began most commonly after age five (5 to 9: 16 percent; 10 to 14: 18 percent; 15-19: 17 percent). Furthermore, there was no corresponding rise in the rate of asthma in hayfever patients from ages 15 to 24 (Table 2).

- To support the contention that allergists are exposed to a selected population of hayfever patients where the prevalence of asthma would be high, the following was observed: 62 percent of hayfever patients who had injection therapy and skin tests had a history of asthma while only 23 percent of hayfever patients who had never received injections nor skin tests had a history of asthma. The assumption is made that an allergist did not see patients who were never skin tested.

TABLE 2

DISTRIBUTION OF AGE OF ONSET*

AGE OF ONSET	ASTHMA		HAYFEVER	
	Number	*Percent*	*Number*	*Percent*
0 - 4	69	31	33	10
5 - 9	37	17	55	16
10 - 14	22	10	61	18
15 - 19	24	11	57	17
20 - 24	13	6	37	11
25 - 29	14	6	30	9
30 and over	43	19	73	19

* From Broder et al /10/

Smith /12/ interviewed 166 rural Iowan children five years after an initial interview determined that 199 children under the age of 20 were "allergic" (not defined) in a total population of 1760 families. Initially, 66 children reported moderate to severe seasonal allergic rhinitis without asthma; only two developed asthma within the five years followup. Initially, 46 children had moderate to severe rhinitis with asthma. Twenty-six of these reported less or no asthma on followup while retaining rhinitis. Neither group of children received hyposensitization. Smith /12/ concluded that "the transition from asthma to hayfever was much more frequent, than the transition from hayfever to asthma."

In contradistinction to these epidemiological studies many allergists /2,4/ including the Michigan group /8/ state that severe hayfever can lead to asthma. All agree that hyposensitization in hayfever does not increase the incidence of asthma. Johnstone /13/ and others /2,4/ suggest that hyposensitization protects the child with hayfever from developing asthma. He studied 175 children referred because of allergic asthma or rhinitis. After two years of therapy with different doses of ragweed extract or placebo, valid followup was available in 112 children. Of the 12 patients with hayfever alone treated with placebo, five developed asthma while 0 of 7 treated with the highest tolerated dose of ragweed (1:200-1:500 dilution) and 0 of 11 treated with a high dose (1:5000) developed asthma. These differences are significant.

The apparent contradiction in these studies could be explained if indeed more severe hayfever predisposed to asthma and if indeed allergists see a skewed population of patients with more severe hayfever.

CONCLUSIONS

- Hayfever can disappear spontaneously although it probably persists in most cases. In some cases

symptoms can lessen with age.

- Sinusitis and polyps can occur in hayfever, especially if the hayfever is severe and untreated. When theydo occur, symptoms remain severe and difficult to control.

- In the general population, the presence of hayfever does not predispose one to develop asthma, although the more severely affected patients, usually seen by the allergist, probably is more likely to develop asthma.

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DIAGNOSIS AND TREATMENT OF CEREBROSPINAL FLUID RHINORRHEA

Ronald Brisman, M.D.*

History

The history of cerebrospinal fluid (CSF) rhinorrhea can be traced back to the ancient societies. Galen /1/ spoke of an excremental liquid which was expressed from several parts of the brain into the ventricles and excreted as mucus, under physiological conditions, into the nose through the ethmoid bones and hypophysis. Willis /2/ (1664) later emphasized that the passage of CSF from the intracranial space into the nose "via nervous processes and their membranes" occurred either through the cribriform plate or the sphenoid bone and sinus. He had a more modern concept of the circulation of the CSF than Galen and regarded the nasal passage for CSF as an accessory outflow mechanism /3/, which is important under pathological conditions when there is a superabundance of intracranial CSF. Thomas /4/ (1899) compiled 21 cases of spontaneous rhinorrhea in the absence of known trauma or tumor and established this as a well-defined clinical entity. He had no treatment to suggest.

Classification

Much of the CSF rhinorrhea literature is concerned with classification, often focused on the concept of "spontaneous rhinorrhea". This usually refers to non-traumatic rhinorrhea. Cairns /5/ (1937) regarded most cases of "spontaneous rhinorrhea" as secondary either to hydrocephalus, frontal and ethmoid osteomas, or pituitary tumors. According to Coleman and Troland /6/ (1947), primary or spontaneous rhinorrhea occurs in the absence of any definite demonstrable cause. They treated three cases successfully by operating intracranially and sealing the area of the cribriform plate with muscle, although no pathological condition was found at surgery. A more recent classification of CSF rhinorrhea

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is provided by Ommaya et al /7/ (1968). They avoid the category of "spontaneous" and divide all cases by etiology into either traumatic or non-traumatic origin. The latter group is subdivided into high pressure leaks (tumors. hydrocephalus) and low pressure leaks (congenital anomalies, osteomyelitis erosion, "focal" atrophy - olfactory or intrasellar).

A complete classification of CSF rhinorrhea must include not only the factors of trauma and intracranial pressure, but also the anatomical location of the dural defect. A defect in the anterior fossa, which is most frequently present, may cause a CSF leak through the frontal or ethmoid sinuses. A middle fossa abnormality may result in CSF passing through the sphenoid sinus. A rare form of rhinorrhea results from a middle or posterior fossa lesion, which allows CSF to enter the middle ear and exit "paradoxically" through the eustachian tube.

TRAUMATIC RHINORRHEA

Trauma (accidental or homicidal) is the most common cause of CSF rhinorrhea and occurs in approximately two percent of unselected head injuries. /8/ The rhinorrhea usually begins within 48 hours of injury; and in 95 percent of cases, it begins within three months. A longer delay in onset of rhinorrhea is rare but has been reported to occur fifteen years after injury. /9/ Traumatic rhinorrhea ceases within a week in 50 percent of the cases but may continue for longer than one month in 10 percent. /8/ Anosmia is present in 75 percent of the cases and aerocele in 20 percent. Headache is uncommon. Men are affected as often as women. The amount of leakage is usually small unless a fracture occurs in the middle fossa and enters the chiasmatic cistern. The dural defect and fracture are usually in the anterior fossa, though middle or posterior fossa injuries ("paradoxical rhinorrhea") may be responsible.

Postoperative (iatrogenic traumatic) rhinorrhea occurs occasionally after transphenoidal hypophysectomy. It was noted in six of Bateman's /10/ first 50 cases, but only once in his next 100 cases. Transphenoidal pituitary surgery should not be done if preoperative pneumoencephalography demonstrates intrasellar CSF. Transnasal approaches to

intracranial lesions, especially the "nasal encephalocele" may result in CSF rhinorrhea. A bony defect in the floor of the anterior fossa may be found on skull polytomography and will facilitate the preoperative diagnosis. An intracranial approach is indicated.

Postoperative CSF rhinorrhea is an infrequent complication of intracranial procedures. Only 11 cases were noted in a series of 16,000 craniotomies. /9/ The incidence of postcraniotomy rhinorrhea can be decreased if appropriate precautions are taken. When tumors involving the cribriform plate are removed, especially meningiomas, postoperative rhinorrhea may be prevented by covering the cribriform plate with a pericranial graft, during the primary operation. Openings made into the frontal sinus should also be covered with pericranium.

NONTRAUMATIC RHINORRHEA

Nontraumatic rhinorrhea is rare; fewer than 150 cases have been reported. Flow is insidious, intermittent, and often profuse. Spontaneous arrest occurs in about one-third of the cases. Aerocele is unusual and the sense of smell is usually preserved. Coleman and Troland /6/ thought that "spontaneous rhinorrhea", in the absence of trauma, tumor, or apparent preoperative etiology, was caused by a defect in the cribriform plate in the anterior fossa. Only recently has the importance of the middle fossa in such cases been recognized. /7,9/ In a series of nine patients with "spontaneous rhinorrhea", six had primary defects in the middle fossa and sphenoid sinus. /9/ Four of these had CSF ("empty") sellas.

The primary subarachnoid CSF ("empty") sella is a frequent cause of nontraumatic rhinorrhea. /11/ These patients have an incompetent diaphragma sellae which permits the intrasellar extension of the CSF within the subarachnoid space. The pulsatile pressure of the CSF may cause enlargement of the sella with thinning and penetration of its floor, and leakage of intrasellar CSF into the sphenoid sinus, then out the nose. Obese middle-aged females are usually affected. They often have headache. Neurologic examination, visual fields, and acuity are normal. Most have subclinical laboratory evidence of mild hypopituitarism.

INTRACRANIAL PRESSURE

CSF rhinorrhea may occasionally serve as a spontaneous decompression for elevated intracranial pressure. This is seen more often in cases of nontraumatic rhinorrhea. The increase in intracranial pressure is usually caused by an obstruction to the normal CSF circulation, with resultant hydrocephalus or pseudotumor. Repeated episodes of meningitis, which can be caused by rhinorrhea, may also result in basilar arachnoidal adhesions and subsequent hydrocephalus; thus the rhinorrhea is potentiated.

Rhinorrhea associated with intracranial tumor (especially pituitary adenoma) often results from raised intracranial pressure (secondary to obstructive hydrocephalus). Erosion of bone and dura may occur in the area of the cribriform plate or sella turcica, usually from increased intracranial pressure, and less often from direct tumor invasion. Rhinorrhea, in association with an intracranial tumor, is usually a late manifestation. It is highly unlikely for rhinorrhea to be the initial presentation of a tumor without other abnormal neurological findings or changes in the plain skull roentgenogram. /9/

DIAGNOSIS

The first problem is ascertaining if a CSF fistula is present. This is usually established by noting the high sugar, low protein, and low specific gravity in the nasal fluid. In the normal fasting patient (without meningitis), CSF sugar will be at least two-thirds of blood sugar. Quantitative glucose determinations should be done because the glucose-oxidase test papers often give positive results on normal nasal secretions. /12/ This may be caused by the small amount of sugar present in lacrimal fluid. When the nature of the leaking fluid is still in doubt, iodinated ^{131}I human serum albumin may be given intrathecally, and cotton pledgets in the nose may be counted for radioactivity.

The patient's "history of present illness" may reveal recurrent bouts of meningitis, sometimes as the presenting complaint. The leaking CSF may have been only a small quantity and forgotten, or it was swallowed while the patient was supine. Positional change in quantity of rhinorrhea is often seen; increased nasal flow may occur when the head is flexed and bent forward. Unilaterality of nasal discharge is frequent and often corresponds with the side of dural defect. Headache, which is relieved by the onset of flow, is characteristic of nontraumatic rhinorrhea associated with elevated intracranial pressure. Previous cranial trauma, either accidental or surgical, should be noted. Symptoms of intracranial neoplasm, especially pituitary adenoma (visual impairment or hypopituitarism) should be elicited.

When physical examination is performed, the physician should note the presence or absence of anosmia, since this may give a clue to a possible abnormality near the cribriform plate. Visual fields and acuity should be determined because of the frequent association of pituitary tumors with nontraumatic rhinorrhea. Visual fields are normal with primary subarachnoid CSF ("empty") sellas, but are frequently abnormal when pituitary tumors or cysts are responsible for the rhinorrhea. The tympanic membrane should be examined for a possible fluid level, which may be seen with "paradoxical" rhinorrhea. Evidence of meningeal irritation should also be sought.

Plain skull roentgenograms are helpful in locating a fracture, aerocele opacified sinus, enlarged sella, or fluid level in the sphenoid sinus. Air-fluid levels may be detected more easily if the patient is kept supine for at least 30 minutes before roentgenograms are taken. Polytomograms (2 mm cuts) may reveal bony defects or a pathological sinus condition. Many iophendylate (Pantopaque®) injection techniques have been described /13/, but they are not without morbidity /14/. Iodinated ^{131}I serum albumin scanning has been helpful in demonstrating the site of the fistula. /15,16/ Pneumoencephalography can help diagnose a CSF sella, pituitary tumor, or hydrocephalus.

Endocrine function tests will reveal hypopituitarism, usually advanced, in patients with pituitary adenoma and CSF rhinorrhea. More than half of those with primary

subarachnoid CSF sellas have mild hypopituitarism, as evidence by a decreased response of plasma growth hormone to insulin induced hypoglycemia. / 17/

TREATMENT

Initially, the patient should be placed in a semi-Fowler's position (head elevated) and nasal treatments avoided. Some advocate frequent lumbar punctures to help diminish intracranial CSF, but the efficacy is not established.

There is a high (25 to 59 percent) risk of meningitis (usually pneumococcal or streptococcal) in patients with persistent CSF rhinorrhea. Surgical repair is therefore recommended. Immediate surgery is not usually indicated in cases of closed head traumatic rhinorrhea, but it may be necessary to prevent infection if the wound is open, the brain is herniated into a sinus, or the rhinorrhea is profuse. In the absence of these, plans for surgical repair of the rhinorrhea is delayed for two weeks. This allows for stabilization of the patient, resolution of the edema, treatment of associated facial fractures. /9/ In most cases, there is also spontaneous cessation of rhinorrhea. /9/

A different approach was advocated by Lewin. /8/ He suggested that traumatic rhinorrhea or aerocele indicated a significant dural tear which would rarely heal, even if the rhinorrhea stopped spontaneously. He advocated surgical repair for all such cases.

Mild or moderate nontraumatic rhinorrhea which persists for two to four weeks should be treated with craniotomy and intradural exploration. Profuse rhinorrhea should be repaired sooner. If preoperative studies are negative, the anterior fossa should be explored first, then the middle fossa. The dura is repaired with temporal fascia or pericranium, and the bony defect is packed with muscle, absorbable gelatin sponge, bone wax, bone chips, or synthetic plastics. There should be no operative mortality and minimal morbidity. /8,9/

The prophylactic use of antibiotics in the treatment of rhinorrhea is highly controversial. /18/ Although Anderson et al /19/ suggest their effectiveness in treating nontraumatic rhinorrhea, the prolonged course of this disease increases the opportunity for resistant organisms to develop. In traumatic situations the course of the disease is much shorter and the use of prophylactic antibiotics may be more effective, but the data are uncontrolled and inconclusive. Ampicillin or penicillin, either alone or in combination with chloramphenicol, have been used most often.

CONCLUSION

The management of CSF rhinorrhea can be highly successful when accurate localization of the dural defect is combined, in selected cases, with proper surgical therapy.

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ALLERGIC REACTIONS OF THE CONJUNCTIVA

MAJ Robert B. Calson, MC*

The frequency of exposure of the conjunctiva to a variety of airborne allergens, contactants, drugs, and bacteria makes it an important and common site of allergic reactions. Just as the mucous membranes of the respiratory tract may react following contact with allergens, so too, the conjunctiva may be directly sensitized and may later react to systemic or local exposure to the offending agent. This reaction has long been utilized in clinical allergy in the form of conjunctival testing. In addition, the conjunctiva may act as the site of antigen entry into the body, resulting in systemic reactions. Weinberg and Julien /1/ in 1913, reported fatal anaphylactic reactions in horses following instillation of Ascaris toxin into the conjunctival sac. Chait /2/, in 1950, reported a positive Prausnitz-Küstner (P-K reaction to peanut extract in the skin of a recipient with complete dacryostenosis when the antigen was applied to the conjuctiva. Despite its importance and frequency as a clinical entity, the diagnosis of allergic conjunctivitis is often difficult because of its similarity to forms of infectious or irritant conjunctivitis. Differentiation can usually be made, however, on the basis of history, physical examination, laboratory evaluation, and response to therapy. Theodore /3,4/ has classified these allergic reactions (Table 1) and also has listed the causes of eosinophilia in conjunctival scrapings (Table 2).

TABLE i

CLASSIFICATION OF ALLERGIC REACTIONS OF THE CONJUNCTIVA*

Atopic conjunctivitis	Allergic dermatoconjunctivitis
Microbiallergic conjunctivitis	Vernal conjunctivitis
Other forms of conjunctivitis	

*Modified from Theodore /3/

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TABLE 2

CAUSES OF EOSINOPHILIA IN CONJUNCTIVAL SCRAPINGS*

Vernal conjunctivits
Atopic conjunctivitis
Allergic dermatoconjunctivitis
Chemical irritants (lye, lime, ipecac, turpentine)
Conjunctival parasites, myiasis, insects, hymenopthra strings, sporotrichosis, and trypanosomiasis
Ocular phemphigus (later stages)

* From Theodore /4/

Atopic conjunctivitis is a manifestation of a Type I or immediate hypersensitivity reaction occurring usually in a person with other manifestations of allergic disease such as hayfever or asthma. There is frequently a family history of allergy. Allergens include pollens, animal dander, fungi, mites, dust, and foods.

The acute form of atopic conjunctivitis is marked by immediate hyperemia, edema, intense itching, burning, photophobia and tearing. Intense chemosis may be present and the reaction is usually bilateral. /3-6/ The discharge is initially watery, but may become mucopurulent. Large numbers of eosinophils may be present in conjunctival scrapings. Early epidemic keratoconjunctivitis may present the same picture, but is almost always accompanied by obvious pre-auricular lymphadenopathy.

Chronic atopic conjunctivitis frequently exhibits little objective evidence to explain the complaints of itching, burning, photophobia, and dryness. The conjunctiva may be pale with mild edema, or, if the reaction is subacute, injection and chemosis may be present. Eosinophilia is present in the conjunctival scrapings. /4/ The diagnosis is complicated by the similarity to irritant reactions to substances such as lime, lye, and smog. Irritant reactions are generally more localized but may be accompanied by marked eosinophilia. Topical

vasoconstrictors and systemic antihistamines produce symptomatic relief in chronic atopic conjunctivitis but are ineffective in irritant conjunctivitis.

The most common allergens associated with atopic conjunctivitis are the airborne pollens. In the United States, the most important pollens are the weed pollens, especially ragweed. Grass pollens predominate in importance in the rest of the world. Atopic conjunctivitis due to pollinosis is usually associated with allergic rhinitis and may be the major presenting complaint in early hay fever. Conjunctival symptoms may diminish over the years as nasal symptoms increase. Reactions to pollen generally begin with itching in the inner canthus which spreads rapidly to involve the entire conjunctiva. Examination reveals papillary hyperplasia and chemosis. Symptoms are seasonal and patients exhibit immediate skin reactions to the offending pollen. Conjunctival testing may be dangerous and severe reactions and occasionally permanent damage may result. /4/

Acute or chronic atopic conjunctivitis may be caused by a variety of other plant antigens including cottonseed, kapok, orris root, pyrethrum and jute. Other important allergens include house dust, mites, animal epidermals, fungi, and foods, the latter after direct contact or as part of a more generalized reaction following ingestion. Except for reactions to fungi which seem to be greater during the summer and occasionally in the winter /4/, reactions to these antigens have no seasonal variation. All result in the same clinical picture, either acute or chronic, and all respond to avoidance of the allergen, topical vasoconstrictors, systemic antihistamines, and topical steroids.

MICROBIALLERGIC CONJUNCTIVITIS

Little has been written on microbiallergic conjunctivitis in the past 15 years. Microbiallergic conjunctivitis results from the development of delayed hypersensitivity to bacteria, fungi, and occasionally to intestinal parasites. The most important and frequent form is due to the Staphylococcus. Factors important in the pathogenesis of this conjunctivitis are chronic and repeated infections and the

formation of an antigenic exotoxin by the Staphylococcus with subsequent development of delayed hypersensitivity by the host. Patients usually have no history of allergic disease. Clinically, the reaction is characterized by dryness, absence of purulent discharge, marginal blepharitis and slight secondary corneal changes. Staphylococci may or may not be cultured. There is no eosinophilia in the conjunctival scrapings. An identical clinical picture may be produced by pure infection, or by instillation of staphylococcal toxin into the conjunctival sac. Patients with the allergic form are reportedly recognized on the basis of an extremely high degree of cutaneous sensitivity to staphylococcal toxin; reportedly they develop large delayed hypersensitivity reactions (greater than 3 x 3 cm to 1:100 dilution) to intracutaneous injections of minute amounts of toxin. /4/ The most effective form of treatment for this conjunctivitis is reported to be hyposensitization with staphylococcal toxoid or toxin /7/, although there are no good studies confirming this.

Microbiallergic conjunctivitis due to fungi results from a delayed hypersensitivity reaction to a primary focus of infection, usually with Trichophyton or Candida. The eyelids are the most frequent site of involvement, but occasionally the conjunctiva may be involved in an "id" reaction. Treatment is directed at the primary infection.

Microbiallergic conjunctivitis has also been reported in association with intestinal infestations with Oxyuris, in finger-to-eye contact in laboratory workers due to Ascaris, and occasionally in malaria. /4/

ALLERGIC DERMATOCONJUNCTIVITIS

Allergic dermatoconjunctivitis is a form of contact hypersensitivity generally due to drugs, cosmetics, clothing, jewelry, animal or vegetable products, and plastics. Reactions are caused by ophthalmic drugs, and may also result from systemic use. The most important sensitizers include the antibiotics (penicillin, streptomycin, neomycin, sulfonamides); local anesthetics (especially pontocaine, butacaine and larocaine), mercurial antiseptics, antihistamines, and the preservatives in ophthalmic

solutions. Ointments are more likely to sensitize than are solutions. Reactions occur 24-48 hours after exposure in patients who may have no history of allergic disease and the reactions may take days or weeks to subside. Clinically, they are characterized by itching, papillary conjunctivitis, eczema of the eyelids, and mucopurulent discharge. Eosinophils are present on conjunctival scrapings, especially if the reaction has been present for several weeks. /4/ Dermatoconjunctivitis resulting from use of ophthalmic drugs usually develops first along the path of tears. Reactions to ointments develop first along lid margins and those to cosmetics appear first on the skin of the upper lid.

Diagnosis is based on the history, appearance, presence of eosinophils, and confirmatory patch test. Treatment consists of avoidance of the allergen and topical steroids. It is interesting to note that even topical steroids have been implicated in the development of allergic dermatoconjunctivitis, probably because of sensitivity to preservatives in the solutions.

VERNAL CONJUNCTIVITIS

Vernal conjunctivitis is a bilateral conjunctival disease occurring predominantly in prepubertal males (sex ratio of 3:1). About 80 percent of the patients are 15 years or less when the condition begins. Family history of allergy is frequently present and 28 percent of the patients give a family history of vernal conjunctivitis. Only 11 percent give personal history of other allergies. Symptoms are worse in the spring and summer in 55-90 percent of the patients. Thirty-four percent have mild symptoms in the winter and 10 percent have no seasonal variation in symptoms. Symptoms consist of itching and photophobia. Giant fibrotic papillae are present, especially in the upper palpebral conjunctiva presenting the characteristic "cobblestone" appearance. Limbal vernal conjunctivitis is characterized by papillary hypertrophy of the corneoscleral junction. A stringy exudate composed of mucopolysaccharide and containing many eosinophils is present. It is important that this condition be differentiated from trachoma. The cause of vernal conjunctivitis is unknown. Several features suggest an allergic etiology, including

eosinophils in conjunctival scrapings, prepubertal age incidence, family history of allergy, and recurrence of attacks in spring. Allansmith /8/ in a study of 35 patients with vernal conjunctivitis found that 66 percent gave a family history of allergy. Twenty-five (71 percent) had positive immediate skin tests to grass and of these, 40 percent had serum capable of producing positive P-K tests. Sixty-nine percent had hemagglutinating antibodies to grass. Serum protein electrophoresis was normal. /9/

Vernal conjunctivitis responds best to topical or systemic steroids. The condition persists for an average of 5-7 years, but may persist as long as 28 years.

OTHER FORMS OF CONJUNCTIVITIS

Phlyctenular keratoconjunctivitis /4,6,10/ is characterized by extreme photophobia, an inflammatory nodule near the limbus and an adjacent corneal ulcer. This reaction apparently arises due to hypersensitivity to tuberculoprotein and patients frequently manifest a site of active tuberculosis. Treatment is topical steroids.

Allergic granulomatosis is a systemic disease consisting of asthma, fever, eosinophilia and vascular embarrassment of multiple organs. The vascular lesions are similar to those of polyarteritis nodosa, however, there are widespread granulomas in vessel walls and connective tissue. In the conjunctiva these consist of a central eosinophil core with fibrinoid changes in collagen, surrounded by macrophages and giant cells. Treatment is directed at the systemic disease.

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... we shall add some remarks on catarrh which derives from their serous elements, and show as concisely and precisely as possible:

1. of what it consists
2. what its commonest causes are
3. along with passages and routes it is secreted
4. finally by what curative methods it may be stopped

From: Richard Lower
DE CATARRHIS, 1672

DIAGNOSTIC TESTS IN HAYFEVER

COL Joseph L. McGerity, MC

Hay fever (*i.e.* hayfever) was recognized as seasonal and named by the English public before the first medical description was written by John Bostock /1a/ (1773-1846) of Liverpool and London. Despite the 153 years since publication, the good doctor's description of his own affliction each June and July retains its imagery of acute discomfort. The inflamed pruritic conjunctivae were his earliest warning of the nasal congestion, rhinorrhea, and sneezing, associated with dyspnea which were to develop later. Often poorly appreciated today, but well-recognized by Bostock, were the associated generalized fatigue and poor disposition. In his case, the paroxysmal pattern of eye symptoms and sneezing was marked.

The dejected, red eyed, mouth breathing, sniffling patient, box of tissues in hand, is found in almost any physician's office here in California in May and June at the peak of the grass pollen season. In the eastern United States, States, his counterpart appears in August and September during ragweed pollination. The patient greets one with an upward sweep of the palm across the tip of the nose in allergic salute as he attempts to open the congested nasal passages and to handle the stream of watery mucoid nasal discharge. His sometimes-reddened and often-creased nose is interposed between the edematous eyelids and the periorbital shadows of the "allergic shiner". Altogether he or she presents an unhappy picture of the effects of "flower power".

The public of the early 19th century and their descendants today call the affliction "hayfever" even though it is uncommonly associated with new hay and is not usually associated with fever. Bostock /1b/ called his disorder "Catarrhus Aestivus" or "Summer Catarrh". More modern terminology would suggest "seasonal allergic rhinitis" but the *Index Medicus* goes with the people's preference and uses

HAY FEVER for its listing.

Hurwitz /2/ relates that Elliotson, in 1831, first suggested that pollen was the probable cause of these seasonal symptoms. It remained, however, for the Massachusetts Yankee, Morrill Wyman /1c/, to publish the first studies which clearly identified pollen as the causative agent of the hayfever which plagued him and his son each September during the pollination of Roman wormwood (a member of the mugwort or sage family). He confirmed the relationship of the symptoms to the pollen by having his patients inhale pollen and thus provoking attacks of rhinitis, conjunctivitis, or asthma corresponding to their usual symptoms.

Wyman /1c/ was also the first investigator to publish recognition of a family predisposition to rhinitis and asthma of varying etiological background. He attributed this predisposition to a peculiar sensitivity of the respiratory nervous system. His description indicates that the familial abnormality he is describing is an end-organ ("or shock organ") sensitivity distinct from an immunological disturbance. This was not well-recognized in the allergy literature until the past decade. This nervous system abnormality is currently under extensive investigation by Andor Szentivanyi, J. A. Nadel, and others who are attempting to clearly define the role of the nervous system in allergic disorders. The major portion of their efforts is directed towards various reactions occurring in the lung. There is reason, however, to believe that such studies of autonomic nervous system function or dysfunction will have pertinent application to the neurovascular component of the nasal mucosal tissue and hence to hayfever.

The atopic diseases (strange disease), as presented by Coca, were considered to be primarily an immunological hypersensitivity. In hayfever, as in asthma, it is probable that there is an underlying neurological abnormality of the tissue and that the reagin-related immunological injury associated with the pollen exposure of hayfever is only one of several possible initiators of a common reaction to injury. Minden and Farr /3/ have stressed that the recognition of both components of the allergic disorder is

important in the management of the patient and has diagnostic therapeutic and prognostic implications in the care of the individual patient.

The lack of recognition for many decades of Wyman's observation of nervous system (or "shock organ") abnormality can be attributed in part to the influence of a classic paper on hayfever by Charles Harrison Blackley. Blackley was a homoeopathic general practitioner in Manchester, England, who suffered from Summertime hayfever. His extensive studies of hayfever, with himself as subject, were performed for many years before the first publication of his results in 1873. /1d/ In 1859, he made the chance observation that his sneezing developed immediately after he had produced a small hanging cloud of pollen while examing a vase containing grass which had been placed by his children as a decorative edition to one of the bedrooms of the home. /1e/ While Blackley himself was attracted to the idea of inhalation challenges as a method of diagnosis and study of the disorder of hayfever, his attention and that of the medical profession was perhaps distracted from this area by his studies during the summer of 1865 on the effect of pollen placed on the abraded skin. The diagnostic and immunological implications of such reagin mediated immediate skin reactions occupied the attention of allergists and immunologists for most of the next century. Only recently has the usefulness of the provocative test been once again assayed.

SKIN TEST

Blackley's description of the pruritus and local swelling of his skin when pollen was applied to an abraded area is somewhat atypical of that seen in the usual immediately positive skin test of an atopic individual. His was not a diagnostic but rather a physiologic study. The American, Oscar Menderson Schloss, proposed the use of the scratch test as a diagnostic procedure in 1912 and R.A. Cooke of New York developed the intracutaneous test in 1915. As early as 1918 Rackemann /4/ in reporting on use of skin tests in patients with bronchial asthma proposed the following dictums:

> Skin tests are great assistance in confirming the diagnosis.
>
> Skin tests alone are of no value unless reasonably compatible with the patient's history or experience.
>
> A positive skin test is a necessary preliminary to successful specific treatment.

A half century later the validity of these statements remains unchanged. Skin tests may remain positive after clinical sensitivity is no longer evident because of changes in the environment of the patient, change in end-organ reactivity, or immunological blockade (either spontaneous or induced by hyposensitization). A positive skin test also may foretell future clinical symptoms under certain conditions of exposure to the antigen, but have no relationship to the current problem of the patient. A man raised on a ranch in the Sacramento Valley of California may lose all clinical symptoms of grass hayfever by moving into the city of San Francisco and remaining there for college and his early working career. With increasing family needs and financial resources, in later years he may move to the semirural suburban environs of Marin with consequent return of the almost-forgotten childhood rhinitis. His skin test response to grass pollen could well remain positive throughout this entire period.

The incidence of positive skin tests of the immediate type will depend on the number and the specific antigens selected for testing. Also important will be the concentration of the antigens used for testing and the presence or lack of either a family or personal history of allergic disease. Individuals will react only to those pollen antigens to which they have been previously exposed and sensitized. However, we are still learning of common antigenic relationships within the group of tree, grass, and weed antigens. For example, recent work in our laboratories would indicate a strong common antigen shared by the Mountain cedar of Texas or the Rocky Mountain states and the winter pollinating junipers so commonly used as a foundation plantings in Northern California. Japanese investigators have reported a cross antigenicity between the most common

airborne pollen of Japan, Japanese Cedar (Sugi) and Mountain Cedar of the United States. /5/

In a group of medical students, Whitcomb /6/ found positive skin tests in 10 percent of those with a negative personal or family history of atopic diathesis. Negative skin tests reaction to the nine inhalant and eight food antigens tested were present in 10 percent of those with a positive family or personal history of atopy. /6/ He felt the high incidence of atopy found in these medical students possibly indicated that those with health problems were attracted to medical practice. There are no good recent studies of the incidence of "false" positive immediate type skin reaction in a population normally distributed by age, sex, vocational interest, or educational attainment. We cannot at this time state the incidence of "false" positive skin reaction occurring in asymptomatic individuals with a negative personal history or family history in the military population that we serve.

The significance of a positive skin reaction in an asymptomatic individual of college age is estimated by a recent study at Brown University. /7/ The frequency of new hayfever that developed among 614 senior students who had no clinical manifestations of allergy as freshman was ten times higher in students with an initially positive pollen scratch tests as a freshman (18.2 percent) than in students with a negative pollen scratch test (1.7 percent).

Many allergists would not agree with Swineford's /8/ use of patient relief with appropriate hyposensitization as a criterion for the significance of a particular positive skin test reaction. However, the majority of allergists feel as he does that a positive skin test to a particular allergen is clinically significant if relief can be repeatedly obtained by avoiding completely that antigen or symptoms can be provoked at will by either eating or inhaling the specific allergen. /8/

PROVOCATIVE TESTING

Both Wyman /1c/ and Blackley /1d,e/ recognized the

value of provocative testing in confirmation of a clinical history suggestive of inhalation allergy. If a pollen administered under controlled condition can be shown to provoke the symptoms characteristic of the clinical attack when the same pollen is naturally in the air in large amounts it is usually thought that a diagnosis of specific pollen sensitivity has been confirmed. Blackley described his attempts to measure quantitatively the degree of allergic sensitivity by observing the subject's breathing in a test room in which the pollen concentration was known. Only recently, however, has appropriate equipment been devised by Connell /9/ that can deliver quantitative amounts of pollen to the nasal membranes. In the same period, methods for accurate measurements of the effect of pollen on nasal patency have become available. /10/ With these instruments it is apparent that a certain number of individuals with positive skin tests will not respond to provocative testing. What is less sure is the number of patients with negative skin tests who will respond to provocative testing. The number of these patients who have a strong clinical history of seasonal rhinitis with negative skin test is somewhat limited. In a series of patients with *perennial* rhinitis and asthma studied by Hosen /11/, scratch testing and intradermal testing (with a 1:1,000 dilution) was performed. In 46 of 46 cases in which the scratch and intracutaneous tests to ragweed antigen were both negative, the nasal provocative test was also negative. Ninety-six patients with skin tests negative to tree allergens were all negative to provocative testing with the same antigen. However, of 97 cases with negative skin test to grass antigens five cases were positive to provocative testing and 92 cases were negative. Thus a rare but perplexing problem exists when a patient's symptoms and environmental exposure history indicate strong sensitivity to a specific allergen but the skin test is negative even when skin sensitivity (as measured by histamine reactivity and mass cell release of histamine with intradermal morphine) appears normal. It is this patient which would appear to benefit most by provocative testing with the suspected allergen. To date, however, there are no adequate series of such patients with seasonal nasal allergy subjected to such challenge study.

In some areas of Europe where provocative testing of

asthmatic patients has had wide popularity over the past decade, a positive provocative test is often required before initiation of specific hyposensitization. There are several objections to the requirement for provocative testing before clinical diagnosis of allergic disease. The procedures are cumbersome, expensive for the patients, and demanding of the physician's time. They are not without some risk in producing severe allergic symptoms, and the possibility of inducing sensitivity exists. /12/

The recent data by Connell /13/ concerning the "priming" affect on the nasal mucosa of repeated provocative challenges suggest that both false negative and false positive provocative tests as compared to the patient's usual response to environmental exposure may occur. The total antigenic load of the environment is difficult to estimate and to match in the laboratory. Also it would be difficult to match in the laboratory the normally existing cyclic and emotional variations of autonomic vasomotor control of the nasal mucosa. However, in the European literature the results of provocative testing still appear to be standard to which the validity of skin test results or clinical history is compared.

RADIOALLERGOSORBENT TEST (RAST)

Taylor and Shivalkar /14/ found no positive quantitative correlation between nasal sensitivity and skin sensitivity. They suggest that the local production of IgE in the area of the nasal mucosa was critical to the production of clinical nasal sensitivity. They imply that the specific reagin sensitizing the skin is an "overspill" from the local nasal production. If this is true, then there would be little rationale in using as a diagnostic procedure the provocation of systemic symptoms by intradermal or subcutaneous injections of allergens. Indeed, Hosen /15/ who has been the major apologist for such provocative skin tests no longer uses them for diagnosis.

If the circulating IgE is merely an "overspill" from production of IgE in the local tissue that occurs when all binding sites for IgE in the area are occupied, it might be

expected that that there would be little relationship between the amount of circulating specific IgE as measured by Prausnitz-Küstner (P-K) testing or *in vitro* methods. Such, however, is not the case -- the higher the P-K titer, the worse season the patient experiences. /16/

The recognized inaccuracy of patient history, the lack of specificity of skin testing, and the difficulties associated with provocative testing have spurred the search for an *in vitro* laboratory test that would either eliminate or supplement the aforementioned procedures. While some reliable and interesting techniques such as monkey ileum contraction, leukocyte release of histamine, release of histamine and SRS-A from primate lung, and the red-cell-linked antigen-antiglobulin reaction have been developed over the past decade for the detection of circulating reagin to specific allergens, their use has been limited to the research setting because of various inherent problems. Recently, a new *in vitro* technique was developed in Scandinavia which indicates with a high degree of accuracy and sensitivity the presence of circulating reaginic (IgE) antibody to specific allergen. /17/ Known as the "RAST" test (radio-allergo-sorbent-test) the principle of the test is schematically illustrated in Figure 1. It is an antiglobulin test based on the detection of allergen antibodies

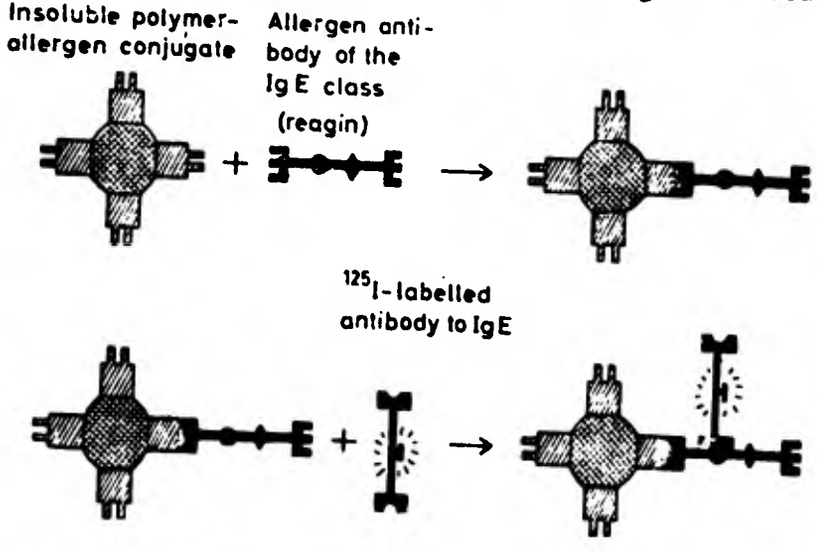

Figure 1. The principle of the radioallergosorbent test (RAST)

of the IgE type, by ^{125}I-labelled anti-IgE, on particles to which allergens have been coupled (allergen particle complexes, APC). The results of Aas and Johansson /17/ suggest that if the result of a provocative test with specific pollen is considered 100 percent accurate for diagnosis, then the result of skin test (1/10,000 weight/volume) and case history will agree in 80 percent of instances of timothy pollen induced allergy. This is an excellent correlation. On the other hand the RAST test to timothy pollen correlates with provocative testing in only 66 percent of cases with approximately equal number of false negative and false positive reactions. The accuracy of the RAST test as compared with provocative testing to housedust however, is greater (59 percent) as compared with the correlation of history and skin testing to provocative testing (34 percent). In five different antigens studied by Aas and Johansson /17/ the diagnostic accuracy was 82 percent by history plus skin testing as compared with 73 percent by the RAST test. By itself the RAST test will appear inferior to the history and skin test as a diagnostic modality even though it rates high in convenience for the patient and the physician. However, Aas and Johansson /17/ interpret their results to suggest that the RAST test with proper interpretation may supplement the case history and skin test (1/10,000 W/V intradermally for pollens) such that in a high proportion (82 percent) of the overall case material provocation testing by inhalation would not be necessary. Because of the saving in time, staff, and equipment that this could entail if provocative testing were the accepted mode for diagnosis in an area the RAST test would appear quite valuable. If provocative testing is not accepted as a usual diagnostic tool -- as it is not in most areas of the United States -- it would appear that the RAST would still be a somewhat useful although an expensive adjunct to the diagnostic armamentarium. /18/ This would be especially true in the investigation of perennial allergens such as housedust.

COMMENT

It would appear at this time that we are not much farther along in the diagnosis of hayfever than was Blackley /1d/ in 1873 when he wrote the following...

> [There are] certain conditions which are required in the case of any agent which is to be accepted as the exciting cause of hay fever. In the first place, it should be shown that this agent, whatever it may be, will, when brought into contact with the respiratory mucous membrane, produces the symptoms of the disease to which it is supposed to give rise. In the second place, it should be shown that the disorder manifests itself whenever this agent begins to be produced in large quantity. In the third place, the attacks of the disease should be entirely absent during those parts of the year in which the latter is not generated.

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USE OF OVER-THE-COUNTER ANTIHISTAMINES IN HAYFEVER

COL Joseph L. McGerity, MC

Histamine, when synthesized in 1907, was a chemical curiosity with no known natural occurrence or function. Over the next three years, however, Sir Henry Dale in England found it to be a contaminant of ergot preparations (resulting from the bacterial decarboxylation of histidine). He also discovered that it stimulated a number of smooth muscles, and it had an intense depressor action. Displaying intuitive brilliance he drew attention to the fact that in the experimental animal an injection of histamine could mimic the effect of an antigen-antibody produced anaphylactic reaction. It was not until 1927 that Dale and his coworkers definitely showed that histamine was a natural constituent of the body, and not until the 1930s was it demonstrated that histamine was released in the experimental anaphylaxis of animals. Work at the University of California Medical School in San Francisco suggested the presence of material with histamine-like activity in the nasal secretions of patients with common colds and with allergic rhinitis./1/ More recent work by Dolovich /2/ has proven the presence of histamine and bradykinin-like activity in nasal secretions obtained from allergic subjects immediately following antigenic challenge. Kaliner et al/3/ have just reported *in vitro* studies wherein histamine and slow reacting substance of anaphylaxis (SRSA) were released from nasal polyps upon challenge with appropriate antigen. In addition, his studies show the release of an eosinophilic chemotatic factor under the same conditions. It, therefore, appears that histamine is only one of a number of mediators released from antibody (IgE) sensitized nasal mucosa upon challenge with appropriate antigen.

Histamine is 4-(2-amino-4)-imidazole. It is formed by decarboxylation of the amino acid histadine. There are at least two different types of mammalian histadine decarboxylating enzymes. One is specific for histadine and is found

in mast cells and other tissues and is not inhibited by alpha-methyl-dopa. The non-specific enzyme is extremely sensitive to alpha-methyl-dopa, and in addition to histadine this material decarboxylates other aromaticamines. Histamine release appears to occur in two stages under the stimulus of the antigenic challenge of sensitized tissue. The first is immediate release of histamine from pre-formed stores in the mast cell of the tissue or the basophil of the blood. It would also appear that, at least in the guinea pig and the rat, the rate of histamine formation is accelerated following an anaphylactic reaction. This accelerated formation may persist for some 48 hours. The newly formed histamine is believed to be largely of non-mast cell origin, and there is some question as to the ability of the usual antihistamine to block its action. /4/

As indicated so far in this discussion it should be possible in allergic rhinitis to block the release of histamine and its end effect by blocking the antigen antibody reaction. This is what has been attempted through the use of specific hyposensitization.

Inhibition of histidine decarboxylase and the formation of new histamine has been possible in part by the use of pyridoxine deficient diets, semicarbazide, corticosteroids, hydroxyzine compounds, alpha-methyl-dopa, and alpha-methyl histidines, but these compounds have found no practical application in the care of the human patient at reasonable dosage levels for control by this mechanism.

Since the release of histamine appears to be an energy dependent reaction, a variety of materials have been found that will block the metabolic process but these materials are not suitable for human use for the most part. Disodium cromoglycate is one agent which appears to block the metabolic release of histamine without toxic side-effects.*

The most probable role of histamine in the production of the symptoms of hayfever is its dilating effect on the arterioles and venules of the nasal mucosa and the

conjunctivae. This mucosal flush is reflected in the acute inflamed appearance of the mucosa seen in the early stages of acute rhinitis. Only later when the nasal dilation has led to increased venule permeability and tissue edema is there the so-called characteristic pale blue boggy appearance of the allergic nasal tissue. This vasodilation is only partially prevented by pre-medication with antihistamines and is not at all significantly reduced by anticholinergics. It is not reversed by either drug. It is important to emphasize that antihistamines give the best results in the treatment of hayfever when used before the antigen exposure. The vasodilation can be prevented or reversed by the appropriate use of oral, parenteral, or local application of sympathomimetics. Thus the combination of antihistamines and sympathomimetics in many preparations would appear to be a logical development.

The characteristic profuse, clear watery nasal discharge of acute hayfever probably arises in part from the tissue edema, plus, perhaps the loss of the mucosal basement membrane described by Connell. /5/ It may also result from direct action on glandular structures such as the lacrimal glands. While antihistamines do not suppress the direct action of histamines on gastric secretion, they do appear to suppress salivary gland secretion in response to histamine. One probable mechanism in the suppression of secretions by antihistamines is an anticholinergic side-effect of most of the drugs. Frequently the patient states that the nasal congestion persists despite relief of rhinorrhea.

The eye irritation and itching of hayfever often appears to be secondary to the frictional irritation of the engorged arterioles of the conjunctivae. Nasal itching is often the prematory sign of an acute attack of hayfever and can occur before there is objective evidence of mucosal inflammation. Histamine has the capability of stimulating the cutaneous nerve endings in the skin and it is assumed that the same phenomenon is occurring in the nasal mucosa when the antigen-IgE-mast cell release of histamines occurs. This hypothesis is suggested by the clinical effectiveness of the antihistamines' preventing the nasal itch and the sneeze of hayfever.

The original descriptions of hayfever often included a

history of associated bronchospasm. /6/ When it was found that many asthmatics developed bronchospasm upon the inhalation of histamine solutions, it was hoped that antihistamines by their blockade of histamine's effect on tracheal smooth muscles (as had been demonstrated in some animals) would make these agents a useful mode of therapy for asthma in man. It was a disappointment when the response was poor in most cases. Because of the anticholinergic-like drying effect of the antihistamines on respiratory mucosa, the use in asthma was proscribed by most authorities because these drugs might contribute to the accumulation of mucoid bronchial plugs in the asthmatic patient. The Drug Committee of the American College of Allergists conducted a study in which 33 patients from age 12 to 40 with perennial rhinits and asthma were treated on alternate weeks with chlortrimeton 12 mg twice daily or placebo. No adverse effect of the antihistamine on the severity of asthma, as determined by symptom and medication scores, was evident./7/

Karlin /8/ has recently reviewed the use of antihistamines in asthmatic patients and reported a study of 25 pediatric in patients at the National Jewish Hospital who had perennial asthma. Nineteen had significant positive skin tests and 13 had concomitant allergic rhinitis. The conclusion was that diphenhydramine, tripelennamine, and chlorpheniramine in usual doses had no significant influence on asthma. Some suggestion that promethazine in usual dose might be harmful was present. The presence or absence of hayfever or positive immediate skin test did not influence response.

During World War II Halpern /9/ first demonstrated in clinical trials in humans the usefulness of the specific synthetic chemical antagonists of histamine which had been recently developed by his fellow Frenchmen, Bovet and Staub. The widespread, successful, therapeutic use of a variety of antihistaminic drugs in hayfever for the past three decades supports the concept that histamine is a strong, if not the strongest, mediator of the allergic nasal reaction. The fact that the antihistamines are not successful in preventing all cases of hayfever suggests that other biogenic amines with histamine-like activity are important in some individuals or that endogenous histamine formation and release may be occurring in such close proximity of the postulated

receptors that the antihistamine drugs are not able to antagonize fully the agonist by competitive inhibition.

For those of us who have relatively recently become responsible for the care of the hayfever patient, it is difficult to recognize with what enthusiasm the development of the antihistamines was received. In retrospect, at that time there was no treatment for the patient with hayfever except for avoidance (which usually meant seasonal breaks in usual life patterns), hyposensitization which even then was viewed with some distaste by many practitioners, or the use of sympathomimetics with attendant side-effects. Because of some uncomfortable effects of the first antihistamines, attempts were made to develop related chemical agents with less side-effect. A wide variety of compounds appeared of which about fifty are still in clinical use. It appears that all of these compounds contain at least one nitrogen atom. Each either has an aliphatic amino side chain (ethyl-, or propyl-amine) resembling somewhat the side chain of histamine, and/or a cyclic or heterocyclic ring (pyridine, piperidine, pyrrolidine, piperazine, or phenothiazine or imidazole, as in histamine itself). It is not clear that there is any basic chemical configuration essential for antihistamine activity; nor is it clear exactly what role their effect on cell wall or other membrane activity, histamine release from mast cells, or endogenous formation or destruction of histamine plays in their characteristic action.

Based on **structural** relationships, the antihistamines can be arbitrarily classified several ways. Table 1 is based on the classification of Melville. /10/ The wide variety of available antihistamines indicates that none of the individual agents can be considered the drug of choice for therapeutic antagonism of the allergic reaction of the hayfever victim. All have potentiality to prevent the increased capillary permeability (obstruction), itching (sneezing), and glandular secretion (rhinorrhea) resulting from mediator release in the allergic reaction.

Antihistamines were released for over-the-counter (o-t-c) sale at midcentury and recently the retail cost of drugs via this source was estimated at 300 million dollars which is equivalent to the trade in the same drugs generated by

TABLE 1

CHEMICAL PROTOTYPES OF ANTIHISTAMINES

Ethylenediamine
Derivative of basic structure >N-C-C-N<

Methapyriline
Thonzylamine
Tripelennamine

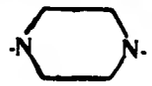
Aminoethyl Eithers (Ethanolamine)
Derivative of basic structure -O-C-C-N<

Phenyltoloxamine
Doxylamine
Diphenhydramine

Propylamines (Alkylamines)
Derivatives of basic structure -C-C-C-N<

Chlorpheniramine

Piperazine
Compound containing piperazine nucleus

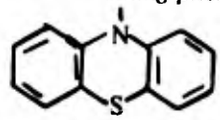


Meclozine

Piperidine
Compounds containing piperiding nucleus

Cyproheptadine
Phenindamine

Phenothiazine
Compounds containing phenothiazine nucleus



Promethazine
Alimemazine

the doctors' prescriptions. Recent Federal Drug Administration policy changes are forcing a hard look at the various combinations in which these drugs are employed and at the formerly extravagant claims with which they were promoted. Most allergists, I think, would agree that they serve a useful function in the treatment of hayfever sufferers. Many of the estimated 10-20 million Americans with seasonal or household environmental allergic rhinitis are adequately controlled with reasonable doses of the o-t-c preparations and have thus avoided becoming a burden to an overcrowded medical care system.

Most antihistamines sold over-the-counter for hayfever are also combined with a sympathomimetic. In addition, an analgesic or antipyretic is often enclosed. Table 2 outlines the contents of some of those over-the-counter products handled through the local Post Exchange. Information

TABLE 2
COMPOUNDS WITH ANTIHISTAMINES

PRODUCT	SYMPATHOMINETICS	ANTIHISTAMINE	OTHER INGREDIENTS	AVERAGE DAILY COST/TAB	DOSE	COST/DAY
Allerest ® tablet	Phenylpropanolamine HCL 25 mg	Chlorpheniramine maleute 1 mg Methapyrilene fumarate 5 mg		0.04	1-2 tab q 4 hr	0.24
Anahist ®	P-Propadrine HCL 12.5 mg	Thonzylamine HCL 62.5 mg Phenyltoloxamine citrate 6.25 mg	ASA Phenacetin Caffeine	0.03	2 tab q 4 hr	0.24
Alkaseltzer ® Plus cold tablets	Phenylephrine	Chlorpheniramine	ASA Ascorbic acid	0.035	2 tab q 4 hr	0.28
C-3 capsule	Propanolamine 50 mg	Chlorpheniramine 4 mg	Dextromethorphan HCL		1 q 12 hr	
Contact ® capsule	Phenylpropanolamine 1 + cl. 50 mg	Chlorpheniramine 4 mg	Belladonna alkaloid 0.2 mg	0.075	1 bid	0.15
Coricidin "D" ® tablets	Phenylephrine 10 mg	Chlorpheniramine 2 mg	Aspirin 0.39 gm Caffeine 0.03 gm	0.03	2 stat then 1 q 4 hr	0.15
Dristan tablets	Phenylephrine 5 mg	Phenindamine tartrate 10 mg	Aspirin Caffeine Aluminum hydroxide Magnesium carbonate	0.022	2 tab q 4 hr	0.18
Ny Quil ®	Ephedrine sulfate	Doxylamine succinate	Dextromethorphan alcohol 25%	0.16/oz	1 oz qid	0.64
Sine-off ®	P-Propadrine 12.5 mg	Chlorpheniramine 1.0 mg	ASA 325 mg		2 q 4 hr	
Sominex ®		Methapyrilene HCL 25 mg/tab	Scopolamine Aminoxide HBr 0.5 mg Salicylamide 200 mg	0.04	2 tab h.s.	0.08
Cope ®		Methapyrilene fumarate 15 mg	Aspirin 421.2 mg Caffeine 32 mg Alum Hydroxide 25 mg Mg hydroxide 50 mg			

on other proprietary compounds which patients may be using is available from the *Handbook of Non-Prescription Drugs* published by the American Pharmaceutical Association, 2215 Constitution Avenue, N.W., Washington, DC 20037. It is the unusual patient who presents with hayfever who has not tried an o-t-c remedy. Many have obtained some success with these drugs and it may be useful to match their current remedy with a similiar combination from the hospital pharmacy. It may well be that the patient not eligible for government care can obtain satisfactory relief with an o-t-c preparation properly administered at far less cost than he would with a similiar prescription item. Patients will tend to treat their conditions with means that are available readily, convenient to their home, and generally inexpensive. These o-t-c medications available at their nearest drug store, supermarket, or Post Exchange meet these criteria. If we recognize that our patients are going to engage in self-medication then we should give them advice which will best enable them to benefit from such therapy. This of course implies that we have the knowledge and skill in the use of antihistamines necessary to teach others.

It will be necessary to recognize that the patients are taking antihistamines before finalizing our evaluation of their history and skin tests. The patient who has been taking Sominex® each night may not recognizie that it contains a significant amount of the potent antihistamine methapyriline. It is the sedative side-effect of this ethanolamine type antihistamine which is being utilized for its sudorific effect. The patient and her doctor may not recognize that perhaps her relative freedom from nasal symptoms during the night is from the antihistamine combined with the drying effect of the continued scopolamine rather than avoidance of allergens during the night hours. Many of us have failed to utilize the significant sudorific effect of the ethanolamine group of antihistamines for treatment of patients with a variety of disorders. /11/ It is easy to forget that the patient who complains of irritability and fatigue (because he has had several nights of restless sleep) and who can not tolerate an ethanolamine antihistamine during the day might well benefit by benadryl or other antihistamines of the same class at bedtime.

The ubiquitous and unrecognized presence of antihistamines in many compounds can lead to other misinterpretations of the allergic history. For example, we might attribute improvement of allergic symptoms during menses or the premenses period to hormonal changes when in reality it was simply due to the use of Cope® during that period. Such a reaction might also well be unrecognized during skin testing. Skin tests might be falsely reported as negative./12/ The antihistamines will have no effect on nasal secretion eosinophilia. It is important to recognize the use of antihistamine in patients on a program of hyposensitization. In a patient on program of increasing dosage of extract, the local reaction to injection (which may be a harbinger of systemic reactions in the future) may be masked. The antihistamine may mask the early warning symptoms of an anaphylactic reaction. They do not appear to prevent in humans the development of either shock or bronchospasm associated with an anaphylactic reaction. /10/

A perusal of the manufacturer's recommended dosage scales for the o-t-c antihistamines shows that, while there is wide variance, most tend to be in the minimal dosage range as compared with what we would order with an equivalent drug in a prescription. Chlorpheniramine, an alkylamine, is used by most manufacturers probably because, while moderately potent, it has only moderate side-effects. The dosage of 8 mg per day is half that of the usual prescription; 2 mg q.i.d. is a usual dose for a six year old. As Rapp /13/ has indicated, the dosage of *most* antihistamines can be safely increased if it does not cause sedation or undesirable side-effects. Often children can tolerate higher doses than adults. My own philosphy is is that no antihistamine should be discarded as ineffective in a particular patient unless it has been tried in the highest tolerated dose in that patient. I believe that underdosage is the most common cuase of so-called antihistamine resistance. Also, since the antihistamines are merely symptomatic therapy and not curative, I believe they should be used in that dosage that makes the patient comfortable without significant side-effect. The patient is the best judge of effective relief and not some arbitrary objective standard set by the physician.

A patient may find after he has been on continuous

daily doses of antihistamine for a period of several weeks (the most effective way to use in prolonged allergy seasons) that the same amount is no longer effective. He can then attempt an increase or switch to another type of preparation. In o-t-c preparations he might switch from one containing the alkylamine chlorpheniramine to one such as Anahist® containing ethanolamines, Allerest® containing an ethylenediamine, or Dristan® containing a piperidine (phenindamine tartrate). The tolerance seen frequently to develop may in part be associated with increased synthesis of liver microsomal hydroxylating enzymes (enzyme induction) concerned with the metabolism of these agents. The antihistamines are mainly metabolized and inactivated in the liver. It can be postulated that because of enzyme induction the metabolism of steroids is also increased. The possibility that therefore allergic patients on antihistamines might be more resistant to the action of corticosteroids under clinical conditions has not been adequately investigated. /10/ It may also be that a patient on barbiturates may be resistant to action of antihistamines through the same mechanism. /14/

The same enzyme induction can shorten the duration of action of diphenylhydantoin. This might be of some concern in epileptics on Dilantin®. This is of special concern in children in whom central nervous system (CNS) stimulation can be associated with the use of antihistamines. Phenindamine, the antihistamine in Dristan® tablets is reported to be especially prone to produce stimulation in children./14/ The English literature contains frequent references to the eliptogenic potential of the antihistamines, but this adverse effect is questioned in reports from American sources. /15/ At the same time the depression of the CNS by alcohol and tranquilizers is potentiated by antihistamines.

The sedative effect and adverse effect of the antihistamines on coordination and visual accommodation has been recognized as a contraindication to their use in pilots. /16/ The presence of these drugs in many o-t-c products should be stressed to flying personnel and others engaged in occupations demanding alertness. The literature suggests that of the o-t-c antihistamines Dristan®, containing phenindamine, would be appropriate combination to try in those

non-flying personnel to whom mental alertness is critical./17/

The antihistamines have a wide margin of safety which makes their use in o-t-c preparations reasonable. Acute poisoning in the adult man is rare. Wyngaarden and Seevers /18/ reported survival in an adult who ingested 2 gm of diphenhydramine over a 48-hour period. He presented with marked disorientation and lethargy. I have seen a 17-year-old girl present with a grand mal seizure several hours after ingestion of large number of diphenhydramine capsules. Oral antihistamines act in 15-20 minutes and the peak blood concentration occurs in about one hour. Children are more prone to symptoms of CNS stimulation with toxic doses, while adults more frequently present with signs of depression. Some of the symptoms in children are suggestive of atropine poisoning. /19/

COMMENT

While histamine is not the sole mediator of allergic reactions in the nasal mucosa, antihistamines acting as antagonist of the histamine (while often having other pharmacologic actions) afford significant relief to many hayfever sufferers and with minimal side-effects in the majority of the users. The wide margin of safety possessed by these drugs permits their over-the-counter distribution for self-medication. Antihistamines with different chemical structures which are easily available permit adjustment of type and dosage to each patient. This is helpful and expeditious since the antihistamines produce differences in responsiveness (regarding therapeutic effectiveness, development of tolerance, and adverse side-effects) in individuals and within an individual at different times. The patient's previous response to specific o-t-c antihistamines can be a useful guide to the physician in the future management of the problem.

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'Call your Catarrh a Rheum, whene'er it flows
Towards the chest; if to the throat it goes,
A Cough; and a Coryza, if to th' nose.'

From the school at Salerno as quoted by:
Richard Lower
DE CATARRHIS, 1672

NONCATECHOL SYMPATHOMIMETIC DRUGS IN HAYFEVER

MAJ Edward Spitz, MC

Sudafed®, a brand of pseudoephedrine hydrochloride, is a naturally occurring dextrostereoisomer of ephedrine and is classified as a sympathomimetic amine. In addition to the usual effect exerted by sympathomimetic amines through action on sympathetic nerves and ganglia, it acts directly on smooth muscle even in small doses.

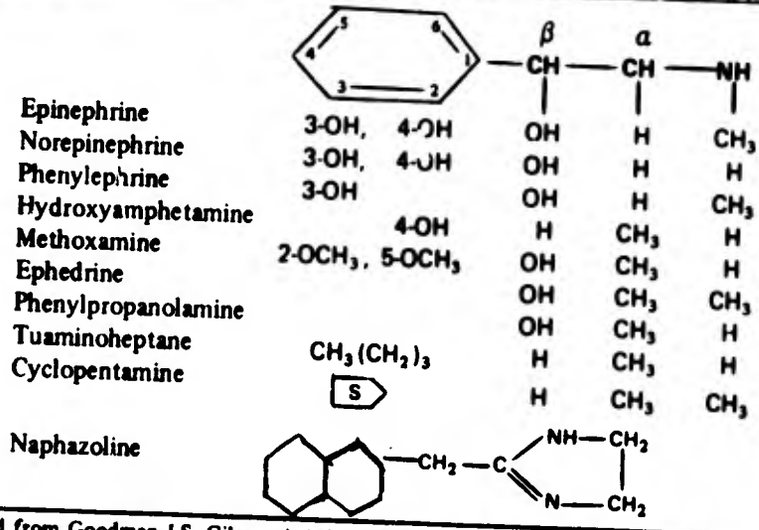
> The action of pseudoephedrine hydrochloride is apparently somewhat more specific on the blood vessels of the nasal and respiratory tract mucous membrane and less specific for the blood vessels of the systemic circulation. It is an excellent decongestant absorbed rapidly and efficiently when administered by mouth, and shrinks swollen mucous membrane lining the nasopharynx, sinuses, eustachian tube and lower respiratory tract.
>
> —*Drug insert for Actified®* Burroughs Wellcome and Co.*

The sympathomimetic amines used clinically for the treatment of hay fever are the noncatechol amines (Table 1) and, therefore, they lack the hydroxyl groups substituted in the 3 and 4 position of the benzene ring (the catechol amines, epinephrine and norepinephrine, have both these hydroxyl groups). They act by releasing epinephrine from nerve and ganglion storage areas as well as by direct muscle relaxant effects. Their onset of action is slower but more sustained than the catechol amines. They are effective orally as well as topically. Ephedrine was probably the first noncatechol amine to be used for nasal congestion. It is found naturally in many plants and was used in China for over 5000 years before being introduced into Western medicine in 1924 /1/, and being prepared synthetically since 1927. /2/

*How well these claims (which appear in the drug insert for Actifed®) are substantiated is not well proven.

TABLE I

CHEMICAL STRUCTURES OF IMPORTANT SYMPATHOMIMETIC DRUGS



*Adapted from Goodman LS, Gilman A (eds): *The Pharmacological Basis of Therapeutics*, fourth edition, 1970, p 485, p 512

EXPERIMENTAL DATA

Experimental evidence indicates that sympathomimetic drugs produce intranasal decongestion and carotid artery vasoconstriction. Using anesthetized dogs, Aviado et al /3/ measured both responses to intravenously or intraarterially administered drugs (Table 2). One group of drugs caused carotid vasoconstriction as intense as the epinephrine did but a lesser degree of nasal decongestion. /3,4/ Another group caused relatively more nasal decongestion as compared to carotid vasoconstriction. Pseudoephedrine (Sudafed) activity overlapped both groups. Drugs in the latter two groups cause more nasal decongestion than expected on the basis of carotid vasoconstriction and presumably have direct effects on nasal mucosa or local nasal arterioles. In more recent experiments /4/ pseudoephedrine given intraarterially decreased perfusion pressure of eustachian tubes of anesthetized dogs. Topical application was more effective in lesser doses and with much less tachyphylaxis. Intravenous administration did not produce any significant changes

TABLE 2

EFFECTS OF CAROTID VASOCONSTRICTION AND NASAL DECONGESTION OF DRUGS WHEN COMPARED TO EPINEPHRINE

DRUGS	CAROTID VASOCONSTRICTION			NASAL DECONGESTION	
	more	less	overlap	more	less
Epinine® (3,4-dihydroxyphenylethylemthylamine)	X				X
Synephrine® (hydroxyphenylmethylaminoethanol)	X				X
Vasoxyl® (methoxamine)	X				X
Propradrine® (phenylpropanolamine)	X				X
Ephedrine	X				X
Sudafed® (pseudoephedrine)			X		
Neo-Synephrine® (phenylephrine)		X		X	
Privine® (naphazoline)		X		X	
Clopane® (cyclopentamine)		X		X	
Paredrine® (hydroxyamphetamine)		X		X	
Tuamine® (tuaminoheptane)		X		X	

presumably because of increase in systemic blood pressure. The decreased perfusion pressure presumably reflects increased potency of the eustachian tubes produced by pseudoephedrine.

CLINICAL DATA

Topical Drugs

Clinically, use of decongestants can be studied in local or systemic preparations. Local application of drops or sprays in the nose is recommended for acute decongestion with the warning that "after congestion" or "rebound phenomena" may occur or that long-term use may lead to chemical rhinitis (rhinitis medicamentosum). /2,5-8/ Only one double-blind study evaluating the effectiveness of nose

drops could be found in the literature. This study by Connell /9/ who studied 15 patients (ranging from 14 to 49 years of age), eight with allergic rhinitis, six with acute coryza, and one with idiopathic nasal congestion. Studies were repeated in five patients, so that 20 studies were performed. No medication was allowed 12 hours before testing. An unknown solution was sprayed in the smaller nostril and the area of the nasal airway was measured hourly for the next five hours. On the following two mornings, the other unknowns were sprayed in the smaller nostril.

The results showed that within the first hour oxymetazoline (AFRIN 0.5%) and phenylephrine (Neo-Synephrine 0.5%) were significantly superior to saline. Oxymetazoline remained significantly superior to saline for the next five hours while phenylephrine did not. /9/

In 14 of 20 studies, responses were observed to oxymetazoline, in 12 of 20 phenylephrine, while in only four of 20 were responses noted to saline within the first hour. Rebound phenomena were not found in any of 16 cases who responded to oxymetazoline but was seen in three of 12 cases who responded to phenylephrine. Some patients who were not aware of severe nasal congestion before treatment made inaccurate subjective evaluations of the result of treatment which suggests that objective measurements would offer a more reliable test of drug efficacy.

In an uncontrolled study of oxymetazoline 0.025 percent (AFRIN), three drops in each nostril every eight hours in 30 ambulatory children from 4 to 10 years of age with "persistent or relatively fixed allergic rhinitis," Cohen and Duffy /10/ found that nasal resistance decreased after three days of treatment from control values, significantly decreased after seven days of treatment, 14 days of treatment, and remained significantly decreased seven days and 14 days after treatment was discontinued. However, for these last two values, he had only half to one-third of his original sample. When he compared subjective response to nasal resistance measurements, a low order of correlation was found ($p>0.10$).

Finally, Seebohm and Hamilton /11/ described a method for measuring nasal resistance and showed one case where one

percent ephedrine applied topically to a congested nostril reduced the pressure to the same level as the uncongested nostril within five minutes.

Oral Drugs

Oral sympathomimetic drugs are recommended for nasal decongestion of allergic rhinitis /2,6,8,12/ provided side effects are not intolerable. These include increased blood pressure, increased heart rate, excitement, and nervousness. There is no evidence that oral sympathomimetics relieve nasal decongestion in colds, in contradistinction to topical drugs.

A double-blind study tested the effect of ephedrine 25 mg, pseudoephedrine (Sudafed®) 60 mg, phenylephrine(Neo-Synephrine®) 10 mg, phenylpropanolamine (Propadrine) 25 mg, and placebo on blood pressure and heart rate, subjective response to therapy and rhinometric objective response. /13/ Eighty-eight patients had a chief complaint of nasal obstruction, with signs of nasal congestion and diagnoses of "acute coryza, acute and chronic sinusitis, allergic or vasomotor rhinitis, and hypothyroidism." Medication was given the morning of testing and that night in random fashion from Monday through Friday. Results showed no significant effect on heart rate or blood pressure. Subjective improvement in symptoms was noted in all drugs and placebo in about 60 percent of the cases except for phenylephrine where less than half improved. Rhinometric evaluation after complicated mathematics showed that ephedrine was better than the other three drugs and placebo at 5 percent level; however, the other three drugs and placebo all reduced nasal resistance, especially if control values were high. The scatter of pressures was too great for easy statistical analysis. There was no statistical correlation between objective and subjective findings.

In another double-blind study, measuring only subjective responses, Lipschultz /14/ found that pseudoephedrine (Sudafed®) relieved nasal congestion significantly better than did placebo in allergic rhinitis. However, in non-allergic rhinitis, both pseudoephedrine and placebo worked well. These results might explain the effectiveness

of placebo in the previous study. If patients with acute coryza had been separated from those with allergic rhinitis more valid results may have been available. Of course, Lipschultz /14/ did not measure changes in an objective way and, although double-blind, it is subject to the errors of subjective studies.

Finally, Gaarde and Maytum /15/ in 1927 is an uncontrolled clinical trial with 36 patients showed that both oral and topical ephedrine relieved subjective nasal obstruction, but was accompanied by side-effects in almost every case.

COMMENTS

In summary, objective double-blind studies have not yet been done to prove that oral sympathomimetics relieve nasal congestion of allergic rhinitis. A double-blind subjective study has shown pseudoephedrine (Sudafed) to be effective. A good objective double-blind study has shown that oxymetazoline (AFRIN) works longer than phenylephrine (Neo-Synephrine) when applied topically. Both are superior to saline. In an uncontrolled study oxymetazoline provided objective nasal decongestion over a 14-day period of treatment. Most physicians describe favorable clinical impressions for both topical and oral sympathomimetic drugs in relieving nasal congestion of allergic rhinitis.

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Almost everyone is agreed, then, that the substance of catarrh consists of the serum of the blood, and that it originates and is caused generally by blocked perspiration through the pores of the body. There is no need to set this out any further.

From: **Richard Lower**
DE CATARRHIS, 1672

USE OF CORTICOSTEROIDS IN HAYFEVER

COL Joseph L. Mc Gerity, MC

In 1949, within a year of the first clinical use of adrenocorticotropic hormone, Bordley et al /1/ of The Johns Hopkins Hospital reported its beneficial effect in asthma. Their evaluation included detailed examination of the upper respiratory tract. Three of the patients had findings consistent with vasomotor rhinitis -- "a pale edematous polypoid nasal mucosa which was bathed with a thick mucopurulent discharge. During therapy the membrane bacame bluish pink in color, was covered with clear mucus, and edematous, polypoid appearance was no longer present." In the early spring of 1950 workers from the Mayo Clinic /2/ reported the beneficial effect of parenteral cortisone in ragweed asthma and hayfever.

The original enthusiasm for steroid therapy in allergic conditions waned when it became obvious that their use frequently resulted in serious adverse side effects. A major fear is suppression of the normal stress response of the hypothalamic-pituitary-axis. The less frequent complications of moon-facies, weight gain, striae, osteoporosis, and growth retardation in children are difficult to justify when occurring as a result of therapy for a non-fatal and relatively non-disabling condition such as hayfever.

Among various approaches to steroid therapy used to overcome the drug's propensity to induce iatrogenic disease were attempts to maximize the steroid concentration at the site of inflammation while minimizing systemic absorption of significant amounts. It was hoped that when applied directly to the inflamed mucosa the amount of drug required would be markedly less than the dose required by ingestion or parenteral injection to produce an equivalent local tissue concentration. A number of steroid analogues were directly applied to the nasal membranes by fluid nebulization, sprays, drops /3/ "snuff" (hydrocortisone dust) inhalation, and aerosol delivery. The reports were reviewed by Aaron and Muttitt /4/

in 1964 and found to be favorable in most cases with improvement evident both in seasonal and perennial allergic rhinitis.

At the present time Decadron® turbinaire (dexamethasone sodium phosphate) is the only commercially available steroid preparation in the United States designed for patient use in the local application of corticosteroid to the nasal mucosa. This aerosol delivers 170 sprays containing approximately 0.084 mg of dexamethasone per spray. The maximum dose for an adult indicated in the package insert is 12 sprays per day. Theoretically this would deliver a maximum dose of 1.0 mg dexamethasone per day or an amount approximately equivalent in anti-inflammatory potency to 6-7 mg of prednisone per day. It is recognized that a small but undetermined part of the dose is retained in the plastic adapter and not delivered to the mucosa.

The clinical efficacy of this mode of therapy reported by Aaron and Muttitt /4/ was confirmed by Norman and Winkenwerder /5/ in a double-blind study using two inhalations in each nostril three times per day over a two-week period during ragweed season. Their final evaluation indicated that approximately three out of four patients benefited from the aerosol therapy.

Before the introduction of aerosolized dexamethasone for nasal use (Decadron® turbinaire) the same preparation had been used for control of asthma (Decadron® respihaler). Small but significant absorption of the dexamethasone with the use of the respihaler had been reported. In a study by Arbesman et al /6/ the incidence of clinical side-effects using a maintenance dose of 0.64 mg of sprayed dexamethasone per day in divided doses was low. In 123 patients only three had marked weight gain, two children developed "moon facies", and one developed minor hirsutism. /6/ However, Liddle /7/ had demonstrated incomplete suppression of adrenal function, as measured by 17-hydroxycorticosteroid excretion and employing an ACTH suppression test, with as little as six inhalations per day. Forsham /8/ indicated that 12 inhalations per day in normal subjects produce an average reduction of 50 percent in the urinary 17-hydroxycorticosteroid excretion. With 12 inhalations per day, he calculated that one-third of the delivered dose or approximately 0.4 mg of dexamethasone was absorbed systemically. /8/ The propensity

of dexamethasone administered by any route to produce adrenal suppression has been recognized.

Similiarly, observation by Liddle /9/ suggested that 1.0 mg of dexamethasone administered by nasal aerosol (12 sprays) is equivalent in metabolic effect to 0.3 to 0.5 mg administered orally. Norman et al /9/ demonstrated that a programed 4 sprays of nasal dexamethasone t.i.d. was effective in treating hayfever symptoms while oral dexamethasone in dose of 0.1 mg t.i.d. was no more effective than placebo in reduction of symptoms of recurring hayfever.

The possibility that therapeutic doses of intranasal dexamethasone might produce adrenal suppression was recognized early by Aaron and Muttitt /4/ and confirmed by them the following year /11/ and by Norman et al in 1967./10/ Using a two week program with four sprays of dexamethasone four times per day the first week and two sprays two times per day the second week, Michels et al /12/ showed mild to marked adrenal suppression in 11 of 17 patients.

In an effort to minimize the side-effects while retaining the therapeutic usefulness of the dexamethasone aerosol over a longer period than the usual two week study McDonald and I /13/ modified the protocol for administration. Our patients were instructed to use the turbinaire to give two sprays in each nostril four times per day for five days. Then the turbinaire was to be used to give two sprays each notstril once daily only between 0600 and 0800 for the next twenty-three days. Twenty patients initially entered the study during the spring grass pollen season of 1970. Four failed to return for 0800 plasma cortisol on the twenty-eighth day and in three patients use of estrogens made plasma cortisol values invalid. In the 13 remaining patients individual 0800 plasma cortisol levels were normal before (average 15.5 μg percent) and at the end (average 16.4 μg percent) of the therapeutic period. Thus, there was no gross suppression of adrenal function although as has been clearly demonstrated a normal AM plasma cortisol does not indicate that response to ordinary stress of life or clinically induced stress tests will be normal. /14/

Total eosinophil counts were performed pretherapy in all patients with average of 336/mm^3. The eosinophil count was

measured in 19 patients on the morning of the sixth day (before that morning's therapy). In only three was the level higher than before therapy. The average on the sixth day was 254/mm^3. Thirteen counts were done on morning of 22nd day of study and five individuals had counts higher than initial and the average count of all 13 was 276/mm^3. No correlation between symptoms and total eosinophil count at any stage was evident.

The percent of eosinophils reported in differential count of white blood cells (WBC) was found to compare roughly with total eosinophil count but wide variance was present in several individual cases. No correlation of eosinophilia measured as percent of total WBC with symptomatic response was evident. The total eosinophil count calculated from percent of eosinophils times total WBC also showed poor correlation with clinical symptomatic response.

The percent of eosinophils in the pretherapy nasal smear showed marked variation from 0 to 90 percent. The average value of the group was 22 percent. After five days of turbinaire therapy the average was four percent with only one subject with over five percent eosinophilia. At 28 days this decrease was still evident with an average of 4.5 percent includes one subject with 40 percent eosinophilia who had not used the turbinaire for four days before the nasal smear.

Of the 18 subjects five percent reported none or only fair response, seven (40 percent) good or moderate response and six percent marked or excellent response, as measured by the subjective impression of symptom-severity.

Our study showed that approximately 75 percent of patients obtained significant relief with the Decadron turbinaire. There was no gross deterioration in adrenal function as measured by an 0800 plasma cortisol level after one month of therapy. The decrease in nasal eosinophilia when initially present was much more dramatic than the minor decrease noted in the systemic eosinophilia. It was our impression that the nasal problem was brought under control during the first three to four days of high dose therapy in most of those who improved, and that this was maintained by the prolonged low dose therapy.

It did not appear that either gross appearance of the nasal mucosa or initial nasal smear eosinophilia was a reliable guide to the response to be expected with Decadron turbinaire. We feel that intranasal dexamethasone is a most useful addition to the therapeutic aramentaria to be used when avoidance, oral antihistamines, nasal decongestants, and hyposensitization fail to give adequate relief of allergic nasal congestion. However, further evaluation of its effect on adrenal function when administered over the long periods of antigen exposure, such as the pollen seasons present in California, is indicated.

The utilization of only morning doses of the nasal dexamethasone spray is an attempt to take advantage of the diurnal variation in pituitary stimulation of the adrenal. This supposes that low plasma glucocorticoid levels shortly after midnight allow pituitary stimulants of the adrenal to proceed. A short-acting steroid such as prednisone would appear to be more ideal than dexamethasone for such a program but this compound is not commercially available in a nasal spray.

Betamethasone-17-valerate (Fig 1) is a glucocorticoid with great vasoconstrictor ability (supposedly an index of anti-inflammatory effect) which is equivalent in terms of topical potency to dexamethasone. It has been reported to have comparatively low tendency to produce adrenal suppression either topically or when taken orally. When used as a nasal spray in a study in England /14/ at a dose of 0.2 mg two times per day over seven days, it was found effective in reducing nasal symptoms, but in one of 12 patients adrenal suppression occurred as measured by a short corticotrophin test. In a further test /15/ treating an unstated number of patients with allergic rhinitis with 0.14 mg two times per day satisfactory clinical results were obtained during a seven-day trial with no adrenal suppression evidenced by short-term synactin testing.

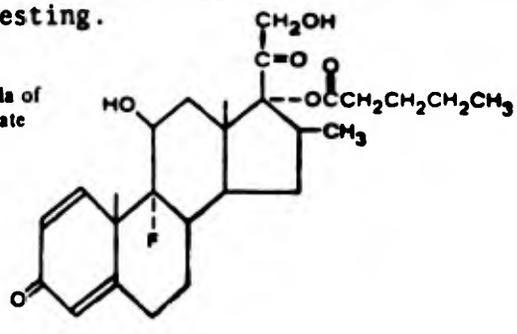

Fig 1. Structural formula of Beclomethasone-17-valerate

The recent introduction of a new corticosteroid, beclomethosone (Fig 2), gives new hope for a drug with potent local effect without adverse side effects. This new steroid appears to have excellent topical activity. In the therapy of asthma the aerosolized form of beclomethosone dipropionate has produced excellent response without any depression of plasma cortisol levels at the recommended dose. Several reports from England where it was developed have been enthusiastic about its use in asthma /17/ and I expect we will soon be receiving reports of its use in allergic rhinitis.

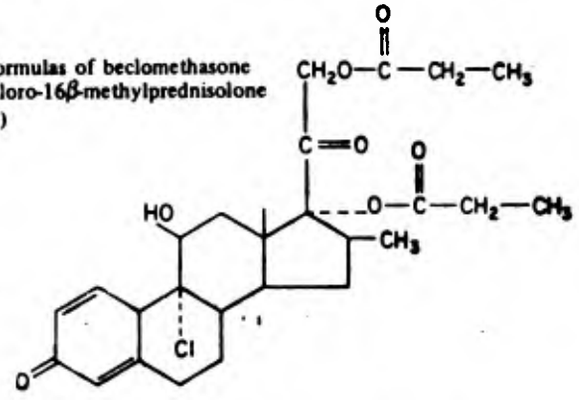

Fig 2. Structural formulas of beclomethasone dipropionate (9α-chloro-16β-methylprednisolone 17, 21-dipropionate)

Oral steroids were found to be effective for control of allergic rhinitis some 20 years ago. The propensity for the development of iatrogenic Cushing's disease and adrenal suppression leads to their avoidance by most allergists as the symtpoms of hayfever were not felt sufficiently severe in the majority of patients to warrant the use of such dangerous agents. With the recent recognition of the clinical advantages of alternate morning administration of steroids it would appear warranted to test such a program in seasonal allergic rhinitis.

With the self-administration of nasal sprays or oral forms of corticosteroid, the danger of patient abuse is recognized. For this reason some physicians prefer the injection of depot corticosteroids. With these injections there is continuous 24-hour release of steroids over several weeks and a great chance of inducing rather prolonged adrenal suppression. /18/ The local injection of steroids into nasal submucosa has enjoyed some limited favor in hands of otolaryngologists in recent years. /19/

COMMENT

The development of effective locally active steroids with minimal systemic absorption and thus minimal attendant production of pituitary-adrenal suppression and cushinoid side-effects suggests that further evaluation of these agents in hayfever is indicated. Increasing skill in the administration of these agents to permit advantageous use of normal diurnal variations in hypothalamic-pituitary stimulation of the adrenal will minimize adverse effects and make reasonable their application to what is usually a symptomatic but minimally disabling and non-fatal disorder.

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DISODIUM CROMOGLYCATE (DSC)
Therapy for Hayfever

COL Joseph McGerity, MC

In 1947, the successful use of khellin, an extract of the seeds of the plant Khella (Ammi visnaga), in the treatment of asthma, was reported from Cairo. /1/ The active principle was di-methoyx-methyl-furano-chrome. Its beneficial action was attributed to the relaxation of bronchial muscles. Khellin had been used in the Near East for centuries as an anti-spasmodic in renal colic.

In the mid-sixties Altounyan /2/ attempted to further develop this substance and similar derivatives with less objectionable side-effects. Using himself as a subject, he found that the inhalation of one of these derivatives, disodium cromoglycate (DSC), 1,3 - bis (2 carboxy-chromotn-5-yloxy) -2-hydroxypropane (Fig 1), preceding the inhalation of antigen would prevent the development of asthma. This occurred even though it did not have the expected muscle relaxant action. /3/

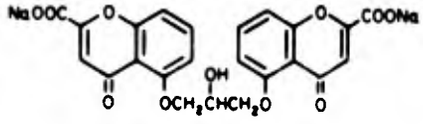

Fig. 1. Structural formula of disodium cromoglycate

The commercial name Intal (Fisons, Ltd), a drug prepared in England for use in asthma, was derived from the fact that it interfered with the allergic reaction. /4/ It does not prevent antigen-antibody combination. It is not an antihistaminic nor does it interfere with activity of the known mediators of inflammation or muscle contraction. It has no muscle relaxant effect. It has no steroid activity in animal studies. /5/ It does appear to limit mast cell disruption. /6/

It appears to inhibit those enzymes responsible for

mast cell wall permeability to certain chemical mediators released from mast cell granules as a result of the type I (IgE) allergic reactions. The mechanism of this inhibition is unknown, but a clue may be that it also prevents exercise induced bronchospasm in some asthmatics. In one study /7/ of asthmatics the inhalation of DSC before exercise was associated with a drop in plasma 17-hydroxycorticoids during exercise. One of the postulated causes of such a drop was a greater tissue uptake of the steroid under the conditions of DSC inhalation plus exercise. The mode of action of DSC might thus be theorized as membrane stabilization through steroid-binding during the early phase of mediator release.

DSC prevents the in vitro release of slow reacting substance of anaphylaxis from sensitized human lung by appr
yet unexplained reasons DSC i
vivo local anaphylaxis where t
Data concerning the effect of
lease of histamine from human
/8,10/ There is some evidence f
the release of the mediator kno
tatic factor of anaphylaxis (EC
The mechanism of action of DSC i
type III pulmonary hyposensitivit
A recent study /13/ suggests that
some factor capable of inhibiting the
from the mast cell.

.1/
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DSC is poorly absorbed from the gastrointestinal tract but is rapidly absorbed across the mucous membrane of the lower respiratory tract. It is administered therapeutically to asthmatics by inhalation through the mouth. By this route 96 percent of the inhaled dose is swallowed and 4 percent is absorbed through the lung. Maximum plasma concentrations were obtained within 15 minutes and the average plasma half life was 81 minutes. Most of the absorbed dose is rapidly excreted unchanged in urine or bile and no metabolites of DSC in man have been detected. /14/ Absorption efficiency through the nasal mucosa membrane has not been determined.

The success of DSC in inhibiting asthma due to inhaled antigens suggested study of its effect in hayfever. DSC as a white hydrated crystalline powder for nasal insufflation is prepared in capsules of 10 mg mixed with lactose as a dispersant and marketed by Fisons, Ltd., as Rynacrom. By means of a special spin-type insufflator the powder is introduced into the nose four times a day. With improvement the frequency of insufflation is decreased.

The initial studies involved controlled challenge of the sensitized nasal mucosa of the allergic subject with appropriate antigen with and without prior application of DSC powder or lactose powder (placebo). /15-17/ The results indicated that DSC increased the tolerance to antigen challenge although there was a wide variance in individual response. These favorable reports encouraged clinical trials in many lands and from Finland, /18/ England /19-21/, Sweden /22/, Australia /23/, Netherlands /24/, and Switzerland /25/, have come documentation of the effectiveness of the drug in allergic rhinitis without significant side effects.

The safety of the drug has been amply demonstrated in over three years of chronic use in childhood asthma. /26/ It does not appear to have any sedative or autonomic effect at clinical dosage levels and would appear possibly as a useful drug in flying personnel.

In Coffman's study /21/of its use in allergic rhinitis, it was noted that those patients with sneezing and rhinorrhea obtained better results than those whose primary complaint was nasal obstruction. This suggested that some clinical failures of the drug might be due to its inability to reach posterior and superior portions of the nares. My similar experience using the Decadron® phosphate Turbinaire® suggests the usefulness of the application of local nasal decongestants 10 to 15 minutes before insufflation of powder for at least the first several days of therapy. Hopper's study /27/ of the results of DSC in perennial rhinitis also suggested the usefulness of prior treatment with nasal decongestants. Table 1.

TABLE I

SEASONAL ALLERGIC RHINITIS

Effectiveness of Disodium Chromoglycate (DSC)

	COFFMAN /21/		ENGSTROM et al /22/		CAPAL & McKELVIN /19/	
	Success	Failure	Success	Failure	Success	Failure
DSC	9	7	14	6	9	13
Placebo	5	11	5	13	1	18

The study by Engstrom , et al /22/ from Sweden differs from Coffman's report /21/ in that the patient's treatment with DSC or the placebo was begun well before the onset of the pollen season. Thus, she was theoretically preventing a priming effect on the nasal mucosa. The study additionally recorded eye symptoms and in this case no difference between DSC and the placebo group as regards eye irritation was found.

A more recent study of the effect of the direct application of DSC to the eye suggests its usefulness in seasonal allergic conjunctivitis. Its usefulness in vernal conjunctivitis had been previously demonstrated./28/ Engstrom and coworkers' experience /22/ confirmed the failure of inhaled DSC used for the treatment of seasonal asthma to control the eye and nasal symptoms as reported previously by Morrison-Smith and Mills. /29/ These studies indicate that the amount absorbed across the respiratory mucosal area is not sufficient to protect a distal tissue such as the conjunctivae.

The results of Capal and McKelvie /19/ are not as encouraging as either Engstrom et al /22/ or Coffman /21/, but they do seem to indicate that there is a selected group of seasonal hayfever patients who will benefit from DSC therapy. Since the drug is somewhat expensive and cumbersome to use, we must attempt to select from the rhinitis population those who will clinically benefit from the drug. The effect of the drug on antigen challenge is compared to

its clinical effect over a pollen season has not yet been reported. We have no other indicators that will predicate clinical response in the group of patients with seasonal hayfever.

Hetherington /23/ reported a good to fair response overall in all 19 of his patients on the drug. However, when specific symptoms were evaluated the results were more conservative. Table 2.

It is noted, in his cases, the complaint of nasal blockage responded slightly better than that of rhinorrhea to DSC in contrast to the impression given by Engstrom's group. /23/

TABLE 2

SYMPTOM RESPONSE OF SEASONAL HAYFEVER /23/

SYMPTOM	DSC		PLACEBO	
	Good/Fair	Poor	Good/Fair	Poor
Rhinorrhea	14	5	8	8
Blocking	15	4	11	5
Severity	19	0	10	6

Since perennial rhinitis is less often clearly identifiable as atopic in origin the usefulness of DSC had to be separately investigated in that condition. In at least three studies /27,30,31/ involving patients who suffered from perennial rhinitis, DSC produced objective or symptomatic improvement in a significant number. There was no clear relationship between the skin test results and the clinical response evident to Silver. /30/However, as indicated in Table 3, there was a slight tendency for better results in the group with positive skin tests. That this might be true is suggested by a previous study with DSC suppression of exercise induced asthma, wherein, there was much better results in those asthmatics who had positive skin tests. /32/

TABLE 3

RESPONSE TO DSC IN PERENNIAL RHINITIS /30/

	SKIN TEST RESULTS (NO. OF CASES) Negative	Positive
Marked improvement	8	14
Slight improvement	1	11
No improvement	9	7

Nasal polyps are frequently an accompaniment of allergic rhinitis but may also occur without an associated atopic disorder. Donovan and Kapadia /33/ studied the effect of one month of twice daily DSC therapy on a group of patients with nasal polyps. No change in the appearance of the polyps resulted from the therapy. The patients were later classified as atopic by positive skin tests, or as non-atopic on the basis of negative skin tests and negative personal and family history of atopy. Sneezing and rhinorrhea were more improved in the atopic group. Nasal obstruction improved in about half of each group. IgE levels in these patients did not appear related to the clinical assessment of atopy nor did they change with DSC therapy. /33/

COMMENT

This review of the literature would indicate that disodium cromlglycate has found acceptance in many areas of the world as a significant aid in the prophylaxis of both seasonal and perennial rhinitis. It has no significant side-effects and is therefore an acceptable mode of therapy in military situations where alertness and visual acuity are required. It has not been approved for

therapeutic use in hayfever in the U.S.A. by the Federal Drug Administration. Clinical trials of DSC in rhinitis are scheduled to begin in this country this year.

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HYPOSENSITIZATION

COL Harold S. Nelson, MC*

Allergy injection therapy was introduced in its modern form as a treatment for grass pollen hayfever by Noon /1/ and Freeman /2/ in 1911. This method of treatment became widely used for the treatment not only of seasonal allergic rhinitis but also of perennial allergic rhinitis and allergic bronchial asthma. Other pollen extracts came to be employed in this treatment. House dust was discovered to contain an antigenic substance to which many allergic persons reacted, and later allergy to a variety of seasonal and indoor molds was described. Finally, the use of a mixed bacterial vaccine was introduced based on a theory that allergy to respiratory bacteria explained the observed exacerbations of asthma which regularly accompanied respiratory infections in many patients. Tree, grass, and weed pollens, molds, house dust, and bacterial vaccine with the occasional addition of animal dander became the common antigens used in allergy treatment.

Although the use of hyposensitization gained widespread acceptance among allergists and their patients, there was honest doubt about its effectiveness on the part of some physicians. There was no lack of testimonial reports of the efficacy of hyposensitization, but for many reasons these uncontrolled observations could not be accepted as proof that the treatment was effective. The long duration of the treatment permitted variations in the degree of exposure and the natural severity of the disease; injection therapy was usually only one aspect of the treatment program; in the absence of objective criteria, judgment of effectiveness could only be based on the patient's symptoms as compared to his memory of preceding years; and finally, there is an undeniable placebo effect of long-term injection therapy in some individuals.

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Only carefully controlled double-blind studies could establish the effectiveness of hyposensitization. Despite the difficulties involved in conducting a long-term controlled study, a number of these were reported: Frankland and Augustin /3/, Johnstone /4/, and Lowell and Franklin /5,6/. These studies /3-6/ established the effectiveness of hyposensitization in pollen hayfever, but left unresolved the use of this treatment in perennial rhinitis and allergic asthma, and did not address the question of the mechanism by which the improvement was produced. More recent reports /8/ have confirmed the effectiveness of hyposensitization in seasonal allergic rhinitis. Investigators /7, 9-15/ have described many immunologic changes which accompany this symptomatic improvement; others /16-20/ have reported hyposensitization with other antigens and have evaluated the response of bronchial asthma to injection therapy /16,17,19, 20/.

MECHANISM OF ACTION OF HYPOSENSITIZATION

There are three immunologic effects which have been observed following hyposensitization, particularly with a potent antigen such as ragweed extract: induction of blocking antibody, decline in specific skin sensitizing antibody (SSA) and alterations in the sensitivity and reactivity of sensitized leukocytes exposed to antigen.

Induction of Blocking Antibody

Historically, the first immunologic result of allergy injection therapy to be demonstrated was the production of blocking antibody /21/, so named because it interfered with the reaction between antigen and skin sensitizing antibody or reagin. Although the induction of blocking antibody could be regularly demonstrated, most workers have found no correlation within the treated population between blocking antibody titers and symptomatic improvement. /7,9,10,15,22, 23/ There were two exceptions, however. Loveless/24/ followed a group of patients during several years of treatment and showed a parallelism in most patients between blocking antibody titers and symptoms. Melam et al /13/ found that

there was an increase in serum antigen binding (blocking ab) which preceded the improvement in symptoms experienced during the patients' first ragweed season after treatment started. At that time blocking antibody was the only detectable immunologic response. /13/

Decline in Skin Sensitizing or Reaginic Antibody Titer

Sprecace et al /25/ reviewed the effect of long-term hyposensitization on the level of SSA as measured by direct skin testing. They found that skin test reactions to antigens included in the treatment changed significantly in the great majority of patients, while the reactions to antigens with which the patient was not treated showed no significant change. Treatment with doses which consistently induced local reactions was much more often associated with significant decrease in skin reactivity. /25/ Connell and Sherman /11/ confirmed this progressive decline in titer of SSA by passive transfer studies and in a small number of patients showed that improvement in symptoms coincided with fall in the SSA titers. In an earlier study, the same authors /9/ found that symptoms during the ragweed season correlated well with the titer of SSA determined before the onset of the season without regard to which (if any) hyposensitization regimen the patient was receiving. They concluded that allergy injection therapy continued perennially over a number of years may well prevent symptoms mainly through decrease of sensitization evidenced by reduced SSA titer. The mechanism of this fall in SSA titer was demonstrated, in the case of ragweed, by Levy et al. /15/ They found that normally there is a booster effect during the ragweed pollen season followed by a gradual decline in titer until the next pollen season. In patients given hyposensitization this seasonal booster effect did not occur; the result of this was a progressive decline in titer of SSA over the three years they followed their patients. Melam et al /14/ also noted that decline in ragweed specific reagin levels correlated well with clinical improvement.

Alteration in the Sensitivity and Reactivity of Sensitized Leukocytes Exposed to Antigen

In 1941, Katz and Cohen /26/ demonstrated that the addition of allergens to the blood of a patient clinically sensitive to those allergens resulted in release of histamine by the blood cells. As the test is presently performed, washed leukocytes are used. Probably most of the histamine is released by the basophils, but there is strong evidence that histamine is also released by other cells, perhaps eosinophils, through an IgE-mediated mechanism. /27,28/

Leukocyte histamine release has gained popularity as a research tool in atopic diseases for several reasons: (a) it is possible to demonstrate SSA by passively sensitizing the leukocytes of a nonallergic donor; (b) it is possible to demonstrate blocking antibody by incubating the antigen with serum from a donor who has received hyposensitization; and, most significantly, (c) in untreated patients the degree of sensitivity of the leukocytes (defined as the amount of antigen required to release 50 percent of the histamine in the leukocytes) correlates well with the symptoms experienced on subsequent exposure during the pollen season. /29/

The changes induced by hyposensitization in the ability of patients' leukocytes to release histamine on exposure to antigen have proved to be complex. Cell sensitivity may be defined as the amount of antigen required to induce release of 50 percent of the leukocyte histamine. /10/ Sensitivity has been found to correlate well with serum levels of specific IgE. /15/ Cell reactivity is the total amount of the histamine in the leukocytes which can be released using optimal amounts of antigen. /10/ Cell reactivity does not correlate with specific IgE levels. /15/

Many workers have now confirmed that when patients are treated with relatively large doses of antigen the sensitivity of their leukocytes is often decreased, so that more antigen is required to release 50 percent of the contained histamine. With increasing frequency, as larger doses of antigen are used, the cell reactivity is also reduced, so that the cells will no longer release 50 percent of their

histamine, and, in some cases, will release none at all. /7,10,12,13,15,29/ The mechanism of loss of cell reactivity is unclear. It occurs despite continuing high levels of specific reaginic antibody in the patient's serum. There are at present conflicting reports /7,10,15,29-31/ whether or not the decreased reactivity is immunologically specific for the antigen used for treatment. Decreased cell reactivity may well prove to be a heterogeneous response, specific under some conditions and non-specific under others.

Although patients may experience good clinical relief with hyposensitization in the absence of any change in leukocyte response to antigen /10,12,14,15,29/, those who do develop decreased leukocyte reactivity as a result of treatment (and the small number of allergic individuals who have relatively nonreactive leukocytes before treatment), in general, experience fewer symptoms on antigen exposure /7, 10,13,15,29,31/ and in some cases none /7,12/.

Evidence of Effectiveness of Hyposensitization with Non-Pollen Antigens

Since its discovery by Cooke, house dust antigen has been considered the principal perennial allergen, although, in some people, foods, animal danders, or molds may be more important. The nature of the house dust antigen or antigens was for years a subject of speculation. Recent work by a number of Dutch workers /32/ confirmed by workers in England /33/, Japan /34/, and the United States /35/ has established that the principal antigen of house dust, for most patients, is produced by the body parts and feces of small mites which dwell particularly in mattresses and other moist, warm, human dander-rich environments.

One of the first controlled studies of hyposensitization employed house dust antigen. In 1949, Bruun /36/ found that 78 percent of asthmatic patients receiving house dust were improved as opposed to 34 percent of patients receiving the placebo. Nevertheless, commercially available house dust extracts do not have the potency of pollen extracts. Strong skin reactions are much less common and weak reactions on skin testing are often thought to be due to irritating substances in the extract rather than on an

immunologic basis. Using the leukocyte histamine release, May et al /17/ however, studied house dust extracts. He found that a positive skin test to house dust was invariably accompanied by release of histamine from the subject's leukocytes exposed to the extract in vitro, while absence of skin test reaction was accompanied by a negative test. House dust thus appeared to be associated with typical IgE-mediated allergy. Despite these findings, injection therapy with these same commercial extracts rarely produced the degree of blocking antibody, or alteration in leukocyte histamine release, demonstrated regularly with ragweed antigen. /17/

The recognized deficiencies of commercial house dust antigen, presumably due to the small amount of mite antigen in ordinary household dust /33/, have led to two studies /18,19/ of hyposensitization with extracts prepared from mites. Maunsell et al /18/ treated two groups of adult asthmatics, one with mite extract and one with commercial house dust. They found that 78 percent showed definite improvement with the mite extract as opposed to only 38 percent who improved on house dust. Furthermore, most of those improving while on house dust gave a history of a major environmental change which reduced dust exposure, whereas improvement with the mite extract was equally common in the group who did not move during the course of therapy.

In a double-blind study, Smith /19/ treated two small groups of adult asthmatics with either mite extract or human dander extract as a placebo. Those receiving mite extract did significantly better in overall assessment, and specifically in the amount of daytime breathlessness, nighttime asthma, and nighttime use of an inhaler. Those patients receiving the mite extract who were on corticosteroids were able to discontinue the use of these agents, while none of those receiving the placebo could.

Aas /20/ used commercial dust extracts in a double-blind study in children of long-term, relatively high-dose hyposensitization. The principal means of assessing response to treatment was by documenting the change in response to bronchial challenge following the course of therapy. Complete bronchial tolerance to house dust

developed in 67 percent of the treated children, as opposed to 25 percent of placebo-treated; and 87 percent of the dust-treated had at least a 75 percent increase in threshold, as opposed to only 32 percent of placebo-treated controls. In addition, symptoms were recorded during the period of October to March, when house dust represents the principal antigen in Norway. In general, the improvement in symptoms correlated with bronchial threshold changes, but there were some notable discrepancies.

No double-blind studies have been reported with a number of other antigens. An uncontrolled study of the effectiveness of hyposensitization with animal dander suggested that it is relatively ineffective, especially if the pet continues to reside in the home. /37/

While no controlled study has been performed, data collected by the Insect Allergy Committee of the American Academy of Allergy strongly supports the effectiveness of hyposensitization with hymenoptera antigen. The committee gathered reports from a large number of hymenoptera-sensitive patients who had been restung. Of 647 restung while receiving hyposensitization, 90 percent had a less severe reaction and in only four percent was it worse than following their previous sting. In 763 not receiving hyposensitization, the reaction was less severe than following their previous sting in only nine percent and more severe in 65 percent. Prior history in the group on hyposensitization indicated their experience with repeated stings had been similar to the untreated group until they began hyposensitization. /38/

Pollens, mold spores /31/, house dust, and animal dander all are inhaled; all caused symptoms shortly after exposure in sensitive patients; and when added to peripheral leukocyte preparations of sensitive persons all will cause release of histamine. The other commonly used extract, bacterial vaccine, is different. There is no convincing evidence that a reagin-mediated mechanism exists by which bacteria can cause allergic respiratory disease. A number of double-blind studies have been performed to evaluate bacterial vaccine. With one exception /39/, these have failed to demonstrate any evidence that bacterial vaccine influences the course of bronchial asthma,

even in patients in whom infections appear to be an important precipitating cause of attacks /40/.

HYPOSENSITIZATION IN THE TREATMENT OF BRONCHIAL ASTHMA

Although allergic asthma, like allergic rhinitis, is mediated by reaginic antibodies, lack of knowledge of the mediators involved in the two conditions and the possible presence of an underlying autonomic defect in bronchial asthma /41/ make it hazardous to use the results of hyposensitization in allergic rhinitis as proof that it is effective in asthma. Several controlled studies /19,20,36/ have been conducted to evaluate hyposensitization in the treatment of bronchial asthma. As mentioned earlier Bruun, /36/ Smith, /19/ and Aas /20/ all conducted double-blind studies employing either house dust or house dust mite extracts, and in each study, the cases demonstrated significant improvement in the group treated with the specific extract.

Johnstone and Dutton /16/ treated 130 children with allergic asthma caused by a number of allergens. They treated the patients perennially with all the antigens which seemed clinically important until the child reached age 16. At that time 22 percent of those who had received placebo injections were free of asthma, as opposed to 72 percent of those who had received the specific allergy treatment.

HYPOSENSITIZATION TECHNIQUES

Preseasonal versus Perennial Therapy

When allergy injection therapy was originally introduced for the treatment of seasonal hayfever it was administered each year for a few months preceding the particular pollen season, a schedule referred to as preseasonal. Although this method is still used and has certain advantages in clinical research, it is now much more common to administer hyposensitization on a perennial basis. Although unquestionable studies demonstrating that perennial therapy

is more effective are lacking, it is the obvious therapy for patients allergic to a number of allergens which occur through all or a large portion of the year. Furthermore, once a maintenance level has been reached, the total number of injections per year is often less with perennial than with preseasonal treatment (maintenance injections can generally be administered at monthly intervals). Recently, Norman et al /8/ demonstrated that the immunologic response and symptomatic improvement obtained with a course of preseasonal ragweed therapy could be maintained during the subsequent year by administration of only eight injections at six-week intervals.

Dosage

It has become apparent with controlled studies that the response to hyposensitization is dose related. Johnstone and Dutton /16/ found that very dilute extracts (1:10 million), as had been recommended by some allergists in the past, were no more effective than the placebo.

Franklin and Lowell /6/ demonstrated that a reduction to 5 percent of the maintenance level three months before the season caused significantly poorer results. Norman /29/ found no significant effect in the treatment of ragweed pollinosis with total preseasonal doses of less than 2500 PNU.

Furthermore, it has been found that the degree of clinical improvement and the magnitude of immunologic changes in the blocking antibody, leukocyte histamine release and serum SSA titers are all greater and more consistently produced if the dose of extract is close to tolerance. /13,15,17, 25/ The doses required far exceed those administered in many allergy clinics.

Modified Antigens

The aqueous extracts which have been used since the introduction of hyposensitization are crude. Attempts have been made to improve them by isolating the significant allergens or by incorporating adjuvants. The latter would enhance the immunologic response and, by slowing absorption, decrease the incidence of local and systemic reactions which often limit the amount of antigen which can be administered.

As noted before, there is evidence suggesting that house dust mite extract /18,19/, when it becomes commercially available, may offer an improvement over the presently available weakly antigenic house dust extract. Other attempts to develop purified antigens have not met with as great success. Antigen E contains much of the clinically significant antigenic material of ragweed, but it appears to lack antigens which are significant sensitizers in some patients, and clinical effectiveness of treatment with antigen E is probably less than with crude ragweed extract. /42,43/

A widely used alternative to aqueous extract is pyradine extracted, alum precipitated extract marketed as Allpyral. Again, in comparative studies with aqueous extract, Allpyral has been found inferior in inducing immunologic responses and producing clinical improvement. /44,45/

Thus at present it would appear best to continue to use aqueous extracts. Even with aqueous extracts quality varies greatly. Baer et al /46/ compared six commercial ragweed extracts. The labeled PNU content was as much as five times the actual PNU count. Furthermore, for any given actual PNU strength the antigen E content varied over twentyfold among the six extracts. Similar results were reported from Sweden using the radioimmunosorbent assay to compare potency of extracts. /47/ They found the biologic potency varied by factors of several hundred for different commercial extracts of the same stated strength.

The best safeguard against these variations is to purchase from a large, established manufacturer. Even then, if there is doubt as to the potency of an extract, skin tests on persons of known sensitivity would provide a rough but valid index of extract potency. It is to be hoped that in the near future some better means of assessing the strength of commercial extracts than the present weight by volume or PNU assay will become available.

CONCLUSIONS

•Controlled studies have demonstrated that seasonal allergic rhinitis caused by pollen can in many cases be benefited by injection of allergy extracts provided the following stipulations are met: (a) the diagnosis of respiratory allergy and identification of the responsible allergen is correct; (b) an extract is used which contains adequate quantities of the significant allergens; and (c) the extract is administered in adequate amounts for a sufficient period of time.

•The degree of improvement for most patients is only partial.

•Although controlled studies are not yet available, perennial rhinitis is associated with the same evidence of a reagin-mediated reaction: immediate occurrence of symptoms upon exposure, positive immediate skin tests, and release of histamine from blood leukocytes upon addition of the antigen. Furthermore, injection of the antigens which are normally responsible - molds, house dust, and animal dander - induces the same type of immunologic responses as do pollen extracts. It is not unreasonable to believe that hyposensitization is effective in perennial allergic rhinitis provided the stipulations are met. The adequacy of mold extracts has not been examined. House dust is a weak extract, probably because it contains only small amounts of mite antigen, while animal dander is a potent antigen, often causing systemic reactions. For these reasons decreased environmental exposure is stressed in the treatment of these perennial allergies, and in the case of animal dander hyposensitization is not ordinarily employed.

•Bronchial asthma may be triggered by different mediators than rhinitis and may in addition be associated with an underlying autonomic defect; but when there is an allergic component to the asthma, it again shares with hayfever the immediate occurrence of symptoms following exposure, the immediate wheal and flare skin test, and evidence on leukocyte testing of IgE-mediated histamine release.

Treatment by hyposensitization has been employed in four controlled studies /16,18-20/ of bronchial asthma, two in

children and two in adults. In each case the response to specific treatment has been significantly better than to the placebo injections. It is hoped that more controlled studies of the use of hyposensitization in bronchial asthma will be forthcoming. Until further data are available, the clinical impression of many allergists over many decades, supported by these four controlled studies, would appear to provide ample basis for the continued use of hyposensitization in bronchial asthma.

•Not all patients with reagin-mediated respiratory allergy require hyposensitization. The most effective form of treatment of allergic disease is avoidance. This may significantly ameliorate allergic symptoms resulting from house dust and is usually the principal approach to the treatment of allergy to animal dander.

Symptomatic treatment should be given a thorough trial. For patients with mild symptoms, or only brief seasonal allergic rhinitis, symptomatic treatment may be all that is required.

When avoidance is not possible, and symptomatic treatment gives inadequate relief or causes distressing side-effects, hyposensitization should be considered. It is particularly appropriate when the patient has significant allergic symptoms which extend throughout a major portion of the year. We would be more prone to employ hyposensitization if the patient had asthma as well as rhinitis.

•Although no controlled studies are available, the mass of statistical data indicating protection for hymenoptera-sensitive persons by hyposensitization is impressive. It is recommended that all persons having systemic reactions to hymenoptera stings be placed on therapy, and that this be continued once maintenance is reached at four to six-week intervals for an indefinite period of time. /38/

•There does not appear to be evidence for a reagin-mediated mechanism by which bacteria induce or aggravate asthma. Furthermore, nearly all controlled studies have failed to demonstrate improvement in patients with asthma treated with bacterial vaccine. Therefore, the use of bacterial vaccine in the treatment of bronchial asthma is on an entirely empirical basis.

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If catarrh is developing nothing is more appropriate for its suppression (provided always that there is no fever) than thrist endured for a considerable period. I have known many people entirely freed from catarrh by abstaining from drink for a period of three or four days.

. . . . . .

But if there is any suspicion of fever as indicated by the pulse, urine, or restlessness and heat of the body, let the body first be evacuated and then after a little time blood should be drawn...

. . . . . .

Finally if one wishes to prevent this evil altogether nothing is more useful as a precaution than to be well protected against external cold and make sure of proper perspiration, even (should the situation demand it) by moving to a hot and dry climate.

From: **Richard Lower**
DE CATARRHIS, 1672

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