NASAL ALLERGY

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The incidence of nasal allergy has been reported by several workers. Hansel[1] found that of 1,000 patients seen in routine office practice, there were 324 with all types of nasal complaints, and among these, 142 had nasal manifestations of allergy. In other words, about one-third of the patients had primary nasal complaints and 44 per cent of these had nasal allergy. The incidence of allergy among all patients was 14.2 per cent. Baum[2], according to a recent report, found that among 2,000 similar patients, 700 or about one-third had primary nasal complaints, 191 of which were found to be due to nasal allergy. Baum found, therefore, that 27.3 per cent of the patients with nasal complaints had allergy, and that the incidence of allergy in an otolaryngologic practice is about 10 per cent.

In a review of the cases of 514 patients seen in the Department of Allergy at the Cleveland Clinic during a six months' period in 1933, 326 or 63 per cent had, as major complaints, pollinosis, bronchial asthma, allergic bronchitis, perennial nasal allergy, and nasal allergy and sinusitis. In a review of cases of allergy seen in 215 children in 1934 and 1935, upper respiratory and respiratory allergy were noted in 166 or 77 per cent. An analysis of 1,174 consecutive new patients in the Department of Allergy during 1935 was made in an effort to classify the presenting major problems. Of these patients, 640 or 55.4 per cent had major problems of respiratory allergy, which included seasonal and perennial nasal allergy, nasal allergy and sinusitis, bronchial allergy, both asthma and bronchitis, and 534 or 44.6 per cent had symptoms of cutaneous, ocular, cerebral or gastro-intestinal allergy. This large incidence of respiratory allergy is due to several factors, chief of which is the interest that has been created in the study of respiratory allergy in otolaryngology, and secondly to the climatic conditions prevailing in the region of the Great Lakes.

NORMAL HISTOLOGY OF THE MUCOUS MEMBRANE OF THE NOSE AND PARANASAL SINUSES

The mucous membrane of the nose and paranasal sinuses is divided into parts controlling the respiratory and olfactory functions. Only a small portion of each nasal fossa is concerned with the functions of the olfactory sense.

The part controlling respiratory functions consists of normal epithelium of the stratified, ciliated, columnar type which is comprised of tall surface cells bearing cilia and irregular supporting columnar cells. The surface of the epithelium is interrupted by outlets of the glands. Varying numbers of goblet cells appear between the ciliated cells. The

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epithelium undergoes changes according to the presence of infections, irritants, etc., and then cuboidal, stratified cuboidal, squamous or transitional types are found.

Beneath the normal epithelium is the basement membrane, which is thin and collagenous in character and probably originates from connective tissue. These cells stain poorly. This layer is perforated with fine openings to permit the passage of leukocytes and tissue fluids.

The tunica propria, or stroma, extends from the basement membrane to the bone. This is a network of blood vessels, lymphatics, nerves, glands, and certain cellular elements. It is divided into three parts: (1) the subepithelial, which consists of a fine capillary network, and lies between the basement membrane and the area of the glands; (2) the area of the glands; (3) the portion from the area of the glands to the periosteum and vascular zone which contains large blood vessels and cavernous sinuses. The vascular supply is deep, periosteal, glandular, and subepithelial capillary. Innervation of this blood vessel system is derived from two sources—the vasoconstrictors which are derived chiefly from the cervical sympathetic system, and the vasodilator fibers which come mostly from the vidian nerve.

Three types of glands are present—the mucous, serous, and mixed. These are lined with mucous and serous secreting cells, and by means of small ducts they open upon the free surface of the epithelium.

The cavernous spaces represent the venous plexus and assume the character of erectile tissue. They are especially well developed along the dependent border of the inferior turbinate and posterior extremity of the middle turbinate and along the adjacent portions of the nasal septum. Circular and midlongitudinal bundles of smooth muscle are embedded in the walls of the venous channels and are enmeshed in connective tissue stroma. These are controlled by nerve reflexes which influence the filling and emptying of these spaces.

The paranasal sinuses, which are lined with mucous membrane, are continuous with the nasal fossa and are characterized by thin membrane, few glands, and no characteristics of erectile tissue.

Histopathology of Allergy

The changes which characterize the histopathology of allergy are well exemplified in the specific changes caused by allergy in the nasal mucous membrane and paranasal sinuses. Therefore, a brief review of these changes will illustrate the characteristic histopathologic findings of nasal allergy. Kline and Young[3] of Cleveland have considered the changes in allergic tissues as reversible or irreversible. In the reversible type there is resorption of edema which leaves no permanent change in the tissues. In the irreversible type, chronic edema and

certain other changes in the tissues become permanent in nature. However, for practical purposes, further study must be made of allergic disease of the nasal passages, a review from the standpoint of allergy alone not being sufficient. This is necessitated because secondary or superimposed infections and other irritating factors as well as allergy influence the permanent changes.

The work of several investigators has shown that the reactions due to allergy are dependent upon the degree of sensitivity of the tissues and the shocking dose of the offending allergen. The tissue changes may, therefore, vary from simple edema with eosinophilic infiltration, which has a tendency to resorb, to permanent changes with chronic edema and eosinophilic infiltration plus inflammatory changes which are the result of degeneration and necrosis, as noted in the Arthus' phenomenon. It must be noted that certain inherent tendencies appear to be present in the tissues of individual patients as far as the degree of edema or capillary permeability is concerned. The degree of sensitivity of the tissues rather than the nature of the offending allergen must play the most important part in this process. Kline and Young[3] have emphasized that this inherent and individual sensitivity of tissues must also be a factor in the determination of the nature of the secondary changes which occur in the blood vessels and other structures of the mucous membrane. This explains in part the tendency for sudden and extreme reactions of edema to develop quickly in the tissues of certain individuals whereas, in other persons, prolonged exposure to the same allergens does not produce such marked changes.

It must also be borne in mind that the histologic nature of the paranasal sinuses is of such character as to influence the development of extensive edema and formation of polyps. The entire thickness of the mucous membrane may become involved in the edematous process so that the whole sinus cavity is occluded. This is particularly true of the anterior cells of the ethmoids and the tissues of the antrum. The tendency for edema to form near the ostia is noted and this is due to the looseness of the mucous membrane at this location.

Eosinophilic infiltration is the second characteristic reaction of tissues in the presence of allergy. Although considerable difference of opinion is expressed as to the formation of eosinophils, it is generally conceded that they form in the bone marrow and that blood eosinophilia is only an index of the number of cells in transit from the bone marrow to the tissues suffering from allergic shock. There is no constant relationship between the degree of blood eosinophilia and the symptoms of the patient. This can be said in part of tissue eosinophilia, there being no absolute index after the allergic reaction is firmly established.

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It is to be noted that the cellular changes of a secondary character, such as the presence of lymphocytes, plasma cells, and monocytes, are likewise noted in small amounts in the tissue reactions in allergy. There is a noticeable absence of the fibrous connective tissue proliferation that is so frequently seen in infections. In the acute cases, resorption of the edema takes place with a return to normal cytology, while in the chronic recurring forms, the edematous processes tend to become permanent because of injury to the blood and lymphatic systems. Likewise, superimposed acute and chronic infection promotes infiltration with inflammatory changes and eventual fibrosis of blood vessels and supporting tissues with predisposition to permanent changes.

Chronic edema and fibrosis produce closure of the ducts of the glands with resultant cystic formations.

Hansel[1] showed in the following table (Table 1) the changes in different tissues due to allergy, infection, and allergy and infection.

CYTOLOGY OF NASAL AND PARANASAL SINUSES IN ALLERGY

The shock tissues or tissues of reaction in allergy are characterized by edema and eosinophilic infiltration. The demonstration of eosinophils in secretion is utilized as a means of corroborating the diagnosis of nasal allergy. The investigation of many workers on the importance of determining the number of eosinophils in secretions from the nasal and paranasal sinuses has emphasized the value of a study of the cytology of these secretions as an aid in the diagnosis of allergy. The recognition of allergy as a factor in diseases of the nasal passages and sinuses has necessitated a reclassification of conditions which were once considered to be inflammatory, particularly the non-suppurative and polypoid forms of disease. These may be classed pathologically in the following manner:

1. Of infectious or suppurative origin
2. Of allergic origin
3. Of allergic origin with superimposed infection.

With a very careful history and clinical examination, a diagnosis can be made in a large percentage of patients. Often, it is not feasible or possible to take a biopsy of tissues, but the cytology of the secretions may be considered as an accurate index of the pathology occurring in the tissues. The physician should be capable of determining the presence or absence of allergic manifestations, and whether infection complicates the allergic state through the clinical history, the state of the nasal tissues upon examination, the roentgen examination of the sinuses, the bacteriology, the cytology of secretions, and the histopathology of nasal and paranasal sinus tissues.

In considering the cytology of the nasal secretions, it is often necessary to make repeated examinations, particularly if the clinical history

TABLE 1

	Allergy	Infection	Allergy and Infection
	GROSS CHANGES	GROSS CHANGES	
	Mucous membranes—pale, sometimes normal or red. Edematous thickening. Polyps. Tissue, soft. Secretion, watery or mucoid.	Mucous membranes—red. Firm, thick, swelling Polyps, rare. Tissues, firm, fibrous, granular. Secretion, purulent.	Mucous membranes—pale or pale red. Edematous thickening Polyps. Tissues more fibrous and firm. Secretions, clear and purulent.
Epithelium	MICROSCOPIC CHANGES Varying types. Normal to marked hyperplasia. Edema. Swelling.	MICROSCOPIC CHANGES Varying types of hyperplasia, often marked thickening assuming s q u a m o u s characteristics. Surface irregular and granular.	From simple swelling or thickening to marked squamous proliferation. May be granular in areas.
Basement Mucous Membrane	May be absent. Slightly thickened. Markedly thickened. (Asthma)	May be markedly thickened to wide layer. Increased fibrosis. Hyaline appearance.	Usually thickened in various degrees.
Subepithelial Layer Fibrous tissue	Edema. Mesothelial cysts.	Compact. Very fibrous.	Edema and fibrosis in varying degrees. Mesothelial cysts.
Glands	Dilated. Cystic.	Compressed. Atrophic. Fibrosed.	Dilated and cystic, or atrophic. Compressed and fibrotic.
Blood vessels	Dilated. Some thickening in areas. No definite increase.	Vessels thickened. Increased in number. May have thrombosis of arteries, veins, and lymphatics.	Thickening of blood vessels. Considerably increased in number. May have thrombosis.
Cellular infiltration	Eosinophilic infiltration, marked. Few lymphocytes and plasma cells.	Marked infiltration. Lymphocytes, plasma cells, monocytes, histiocytes, fibroblasts, occasional eosinophils.	Considerable number of eosinophils. Moderate or marked infiltration with lymphocytes, monocytes, histiocytes, fibroblasts.
Bone and Periosteum	No change except r a r e f a c t i o n of ethmoid.	Periosteum thickened. Sclerosis of bone. Osteomyelitis.	Thickened periosteum. Some bone sclerosis. Osteomyelitis with severe infection.

suggests that acute or chronic infection has been superimposed upon an allergic state, or in instances where meager secretions are present.

The technic of obtaining and preparing secretions for cytologic examination can be summarized as follows: Specimens should be taken from both nasal passages. These may be obtained by blowing

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the nose on waxed paper or into a glass receptacle or on a glass slide. If no secretion can be obtained by blowing, then secretions may be obtained with an applicator or stimulated by inserting a saline tampon into the nasal passages. Secretions from the sinuses may be obtained by puncture or washing. A thin serous discharge will show a sufficient number of eosinophils for identification, and a mucoid discharge usually reveals large quantities of eosinophils. Secretions are more likely to show many eosinophils immediately after an acute exacerbation of symptoms, due to migration of eosinophils through the epithelial layers.

The interpretation of the cytology of the secretions rests with the individual worker. The nature and character of the clinical history, the nasal changes, the presence or absence of infection, and the amount of secretion must be taken into consideration. There is no minimum diagnostic percentage of eosinophils. The interpretation must be made after careful consideration of other pertinent clinical findings. Repeated smears are essential.

A predominance of eosinophils on more than one occasion is highly suggestive of the presence of allergy. Repeated smears in which there is a predominance of neutrophils indicate an acute or chronic infection. In patients with nasal polyps, the greatest degree of stagnation with secondary infection occurs, and necessarily there is some increase in the number of neutrophils. However, in most instances of nasal polyps, the predominant cell will be the eosinophil. A study of the cytology of the nasal secretions is particularly helpful in patients being treated because, in these instances, the nature of acute exacerbations will determine the immediate future treatment.

CLASSIFICATION OF NASAL ALLERGY

Hansel[1] has suggested that nasal allergy may be classified as follows: Nasal allergy is classified according to *seasonal occurrence:*

1. Seasonal allergic rhinitis
    A. Hay fever or pollinosis
        (1) Tree
        (2) Grass
        (3) Weed
    B. Mold allergy
2. Perennial allergic rhinitis
3. Seasonal and perennial allergic rhinitis.

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Nasal allergy is classified according to *etiology:*
1. Pollen
2. Mold
3. Epidermal, as animal dander, feathers
4. Miscellaneous inhalants, as orris root, house dust, emanations of insects
5. Food
6. Bacteria
7. Combined types

Nasal allergy is classified according to *pathologic changes:*
1. Gross nasal changes—permanent, transitory, residual
    a. Red type
    b. Pale or simple edema (acute or chronic)
    c. Chronic edematous thickening
    d. Polyposis (acute or chronic)
2. Gross paranasal sinus changes—permanent, transitory, residual
    a. Simple edema (acute or chronic)
    b. Chronic edematous thickening
    c. Polyposis (acute or chronic)

Nasal allergy is classified according to *associated allergic clinical states:*
1. Respiratory allergy, as bronchial asthma and bronchitis
2. Gastro-intestinal allergy
3. Cerebral allergy, as allergic headache
4. Cutaneous allergy
    Eczema, urticaria, angioneurotic edema
5. Drug allergy
6. Contact dermatitis
    Local or systemic

Nasal allergy is classified according to complications of *acute and chronic infection and nonspecific and associated nonallergic states.*

THE CLINICAL COURSE AND SYMPTOMATOLOGY

The onset of nasal and paranasal allergy may be gradual or sudden, depending upon the nature of the etiologic factors and the intrinsic and extrinsic factors. The onset may be influenced by acute and chronic infections, acute infectious diseases of childhood such as measles, scarlet fever, or whooping cough, operations upon the ear, nose and throat, major operative measures, anesthesia, injections of therapeutic sera, occupational and environmental contacts such as undue exposure to allergens and certain general conditions as puberty, menses, pregnancy, menopause, or physical or psychic shock.

The clinical course of the symptoms is influenced by acute and chronic infections and the amount of discomfort is influenced by the

anatomic or pathologic anatomic conditions of the nasal passages and paranasal sinuses such as deflected septa, narrow, small nasal passages, adenoid tissue, chronic edematous mucous membranes, polyps which produce obstruction, stagnation, and infection superimposed on the allergic state.

The clinical course may be prolonged or brief, the allergy may disappear following therapy, or more rarely it may clear up spontaneously. On the other hand, it may disappear, only to be exhibited as another clinical manifestation of allergy. When acute or chronic infection is superimposed, the clinical course may become much more severe, and therapy may be a very difficult problem.

The nasal symptoms of allergy are:

Sneezing
Itching
Nasal obstruction (stuffiness, sense of fullness, and congestion)
Nasal discharge
Loss of sense of smell
Headache

Other symptoms of allied allergic manifestations may be present.

GROSS PATHOLOGIC CHANGES

The gross pathologic changes in the nasal passages which are observed upon examination are dependent primarily upon the extent, amount, and duration of edema. The edema is seldom uniform throughout the nose except in acute exacerbations of symptoms. It is more marked along the lower edge of the middle turbinate, in the middle meatus, sometimes on the anterior end of the inferior turbinate, and over the tubercle of the septum. In patients with continuous allergic reactions, the changes are more likely to be widely and fairly uniformly distributed, and the tissues appear to be boggy and covered with serous nasal discharge. During periods of quiescence, the edema tends to resorb. Pathologic changes may be transitory, permanent, or residual.

Chronic symptoms result, in most instances, in thickening of the tissues due to edema and the occurrence of polyps. Marked pathologic changes of a permanent nature are usually bilateral and are confined to certain regions of the nose. This is dependent upon two factors: First, predisposition of the nasal mucous membrane to edema is largely controlled by its histologic structure and, in this respect, the mucous membrane covering the structures in the middle and superior meatus has a more delicate supporting stroma than is found in other tissues of the nose. Secondly, the inspiratory zone determines the location of the most marked changes. The middle meatus is, therefore, subject to the greatest degree of irritation, both from specific allergens and from nonspecific agents. The areas for most marked pathologic

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changes are (1) on the edges of the meatus semilunares, (2) in the infundibulum, (3) at the ethmoid ostia, (4) at the ostium frontale, (5) at the ostium maxillare, (6) on the edge of the middle turbinate, (7) on the edges of the accessory furrows of the middle turbinate, (8) on the ethmoid bulla, and (9) in the ethmoid cells. The degree of edema and pathologic change is dependent upon the severity of active symptoms, the stagnation of secretions present, particularly purulent secretion, and the presence of superimposed infections. During periods of quiescence, either spontaneous or under therapy, small or medium sized polyps may disappear. On the contrary, during acute infections, inflammatory edema is superimposed and swelling is greater.

In the paranasal sinuses, gross pathologic changes, except for those in the ethmoid area, must be determined by means other than rhinologic examination. It is well to bear in mind that in allergic states of the nasal passages, corresponding changes of similar degree appear in the paranasal sinuses. In the majority of instances, roentgen examination with or without lipiodol will determine the extent of involvement.

Mucous polyps are considered by many workers to be primarily influenced by the allergic condition of the nose and paranasal sinuses. Kern and Schenck[4] have found the clinical incidence of mucous polyps in allergic conditions to be 26.5 per cent as shown in the following table:

TABLE 2

CLINICAL INCIDENCE OF MUCOUS POLYPS IN ALLERGIC CASES
(Kern and Schenck)

	Total Cases	No. with polyps	Per cent
Bronchial asthma	600	183	30.5
Vasomotor rhinitis	104	15	14.4
Hay fever (seasonal)	118	16	13.5
Hay fever and perennial asthma	52	18	34.6
	874	232	Av. 23.2

The incidence of mucous polyps in routine examination of patients with nonallergic disease as a major complaint is shown in Table 3.

TABLE 3

INCIDENCE OF MUCOUS POLYPS IN ROUTINE EXAMINATION OF PATIENTS
WITH NONALLERGIC DISEASE AS MAJOR COMPLAINT

Presenting disease	Total Cases	No. with nasal polyps
Bronchiectasis	73	1
Lung abscess	17	0
Pulmonary tuberculosis	82	6
Arthritis	200	7

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In patients who complained chiefly of nasal polyps, the incidence of allergy is shown in Table 4.

TABLE 4

Total number of cases	25	
Personal allergy discovered in	22	
Familial allergy found in	20	
Positive skin tests found in	17	(2 negative; 6 not tested)
Entirely negative for allergy	1	(on section found to be papillary hypertrophy, not mucous polyp)

Kern and Schenck reached the following conclusions regarding the relationship between allergy and nasal polyps.

I. Mucous polyps are extremely common in allergic conditions of the respiratory tract.

II. In patients with presenting symptoms of nonallergic diseases of the respiratory tract, mucous polyps are comparatively rare, even in the presence of extensive and chronic sinus infection.

III. All patients with mucous polyps have been found to have a personal history of allergy.

IV. Mucous polyps occur particularly in those types of respiratory allergy that are protracted and perennial, suggested that a bacterial factor is present.

V. The rôle of bacteria in the production of polyps is uncertain; it is suggested that true hypersensitiveness to bacteria is the usual mechanism.

VI. The treatment of patients with mucous polyps must include attention to the allergic factor; the failure to reckon with this factor is the prime cause for the postoperative recurrence of the condition.

DIAGNOSIS

As a rule, a definite diagnosis of nasal allergy can be made on the basis of symptomatology and careful intranasal examination. However, instances occur in which neither a careful evaluation of the symptomatology nor the gross pathologic changes are sufficiently characteristic to definitely establish a diagnosis. Therefore, certain clinical and laboratory data are necessary in order to prove or rule out the presence of allergy, and also to determine other factors which may influence the onset and the clinical course of the disease. We suggest that the following characteristics of allergy be considered in the routine diagnosis and investigation of all patients with nasal allergy.

1. A positive family history of allergy. This has been found in from 60 to 70 per cent of the cases.

2. Past and present history of other manifestations of allergy.

3. The nose and paranasal sinuses.
   a. Nasal symptoms, sneezing, itching, serous or mucoid discharge, obstruction.
   b. Changes in mucosa, pallor, edema, polyps.
   c. Secretions—eosinophilia.
   d. Roentgen examination positive—edema, polyps, retained secretion.
   e. Histopathology—edema, eosinophilic infiltration.
4. Skin reactions—positive in 80 per cent of cases.
5. Blood eosinophilia.
6. Complications.
   a. Acute and chronic infections
   b. Non-specific factors.

The cardinal characteristic findings of nasal allergy cannot be demonstrated in every instance but in only a few cases will the investigator fail to find the characteristics listed under headings 3, 4, and 5. In a definite percentage of cases, a history of family and personal manifestations of allergy will not be elicited. This, however, does not preclude the possibility of allergy. The symptomatology and the characteristic clinical and laboratory findings are of greater importance than the history in the doubtful cases. It is obvious that complete studies are necessary.

INVESTIGATION OF THE PATIENT WITH ALLERGY

The following table summarizes the investigations in making a diagnosis of allergy:

TABLE 5
INVESTIGATION OF THE ALLERGIC PATIENT

History—personal, family, allied conditions
Physical examination—special examinations as indicated by history and physical examination
Laboratory studies
  Cytology of secretion
  Biopsy of tissues, histopathologic picture
  Blood studies—digestive leukocyte response,
    blood eosinophilia, red blood cell sedimentation rate,
    blood chemistry
  Bacteriologic studies—secretions, sputum, stool
  Roentgen studies—sinuses, chest, gastro-intestinal tract, kidneys, ureters,
    bladder, skull
  General studies—gastric analysis, basal metabolism, hormone assays
Protein tests
  Scratch, intracutaneous, passive transfer, intra-ocular, intranasal, patch
Diets, elimination; food diary
Avoidance of common inhalants

Confusing ideas concerning investigation of the patient with allergy occasionally occur. Often some skin tests are substituted for a complete and thorough study. In no way does this imply that allergy

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is correctly investigated. When the investigator completes his study, he should be able to answer all the criteria established by Hansel under the classification of nasal allergy, namely, the seasonal occurrence of symptoms, the etiology, whether due to pollens, molds, epidermals, miscellaneous inhalants, foods, bacteria or a combination of these, the gross nasal and paranasal changes, the associated manifestations of allergy, the complications, whether by acute or chronic infection, and any associated nonallergic states.

In the investigation of the patient with nasal allergy, we have established the following phases of study:

Personal history, family history, allied conditions: One learns that a careful clinical history is the most important procedure in the diagnostic survey. Through this, one may first ascertain whether or not the patient is an allergic individual. Such information is strengthened by finding a strong family history of allergy. In a consecutive series of 166 cases of nasal allergy, we were able to elicit a family history in 120 cases or 72 per cent. A history of associated manifestations of allergy is important. In this same series of 166 patients with nasal allergy, we obtained a history of other allergic phenomenon of clinical importance in 84 or 50.6 per cent. The history must be very complete, not only in regard to the suspected allergic state but to any condition that may alter the patient's health from normal. Failure to evaluate the importance of associated disorders results in poor relief of symptoms; this is particularly true in the presence of metabolic disorders, glandular dysfunction, focal and systemic infections.

Physical Examination: In our cases, a physical examination is made routinely. This consumes a brief period of time and occasionally some further clue is noted as to the true nature of the problem. More than this, the investigator is assured of the absence of organic disturbances in most instances and, where questionable, further special investigation will prove or disprove the presence of organic pathology. The necessity for special examinations will be indicated by a careful physical examination.

Laboratory Tests: Routinely in our work at the Clinic, complete blood counts, estimation of the blood sugar, the Wassermann reaction, and urinalysis are carried out. In addition to these tests, blood eosinophilia, cytology studies of the secretions of the nose and sinuses, and the sedimentation rate of the erythrocytes are of greatest value. In the 166 cases cited, blood eosinophilia of greater than 3 per cent was found in 62 per cent of the patients. The average eosinophil count was 6 per cent. This observation was based, as a rule, upon one determination for eosinophils. Previously, the importance of careful

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examination of nasal secretions was discussed. This is one of the most valuable of laboratory procedures. In many instances, where it is difficult to determine the influence of allergy and infection in the production of nasal symptoms, this single laboratory procedure will prove of value in definitely establishing the factor of allergy or infection or a combination of the two. The entire procedure is simple and if the results secured by study of the nasal smears are interpreted in the light of careful history, thorough clinical examination, and other laboratory findings, very few errors will be made in diagnosis.

The third laboratory procedure of value in determining the factors of infection and allergy in nasal and paranasal sinus problems is the sedimentation rate of the erythrocytes. We have used the method of Rourke and Ernstene which we believe is the most accurate. In pure uncomplicated allergy, there is no increase in the sedimentation rate of the erythrocytes as shown by determinations we have made in more than 1,000 patients with allergy of the upper respiratory tract. Where acute or chronic infection complicates the picture, there is definite increase of the sedimentation rate, which is proportionate to the acuteness and severity of the infection. This is greatly increased if purulent material is retained in a sinus cavity and drainage is not established. We believe this laboratory test is of as great significance as the cytology studies of nasal secretions in establishing definitely the presence or absence of infection in nasal problems, and if present, the severity and extent of infection.

Roentgen Studies: Very comprehensive studies have been made by a number of observers in the comparison of transillumination and roentgen examination of the sinuses in allergy of the nose and paranasal sinuses. The general consensus of opinion has been that the roentgen examination gives better results. It is generally agreed that transillumination is usually ineffective in showing the presence of edematous mucous membranes and polyps in the antra because of the tendency of these tissues to transmit light. In our experience, this has been borne out in several instances, although in the majority of cases, findings by transillumination and roentgen examination have agreed.

Kern and Schenck[5], Kern and Donnally[6], Baum[2] and Hansel[1] found upon reviewing large series of cases which totaled more than 1,000 that positive roentgen evidence was secured in 90 per cent of the patients with active symptoms of respiratory allergy. Hansel made roentgen examinations of 56 children with active symptoms of allergy and found the sinuses to be clear in only three. The cloudiness was confined chiefly to the antrum and the ethmoids. In 13 selected cases of this group, the antra were punctured and washed. The washings were clear in five; they contained mucus in three and purulent material in five.

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Our experience with roentgen examination of patients who have respiratory allergy with active symptoms differs from that of Hansel and other workers in the percentage of positive findings. We recognize that clouding of the sinuses, particularly of the antra and the ethmoids, occurs in severe allergic reactions of the upper respiratory tract. In a series of more than 300 cases, we were able to obtain positive findings in about one-third of the cases. In the group demonstrating positive roentgen findings, a small percentage of the patients were found to have some active infection, although a primary allergic reaction existed.

The limitations of the roentgen examination as a single factor in making a diagnosis should be realized and a diagnosis should never be made from the roentgen evidence alone. When roentgen findings are carefully correlated with the clinical history and other laboratory data, especially those concerning the cytologic and bacteriologic analyses of the secretions from the nose and paranasal sinuses, they may be evaluated more accurately. The transitory nature of the edema which occurs in the mucosa of the paranasal sinuses in allergy adds to the unreliability of the roentgen examination in establishing a diagnosis. Marked changes, as indicated by roentgen studies at one time, may be absent at a repeated examination when the active symptoms of allergy subside. Repeated examination with and without lipiodol are often necessary to determine the extent of chronic or permanent changes in paranasal sinuses.

Studies of the *bacteriology* of the secretions of the nose and paranasal sinuses have been confined largely to the identification of the organisms and the preparation of autogenous antigens to be used as therapeutic aids. Where definite infection exists or where some of the symptoms appear to be due to bacterial allergy, autogenous vaccines are made and tested intracutaneously. Oftentimes, antigens made from secretions fail to cause any striking skin reactions. These are discarded and fresh specimens are obtained for further preparation and this procedure is continued until antigens are secured which give both excellent skin reaction and some focal reaction. The interpretation of the skin test with the bacterial antigens depends not so much on the immediate urticarial wheal type of skin response as noted in true atopic reactions, but in the erythematous, inflammatory type of reaction, as noted in the tuberculin reactions. These reactions are noted in 12, 18, 24, and 48 hours after the time of injection of the antigen.

Studies of the *blood chemistry* other than determinations of the blood sugar are rarely made unless they are indicated by the presence of clinical problems of a nonallergic nature. In a series of determinations for serum calcium and phosphorus, we have never encountered a single deviation from the normal that could be attributed to allergy.

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Special laboratory tests are carried out if indicated by the clinical history and examination. Determinations of the basal metabolic rate have been used most frequently and with more apparent value. In our experience, one-third of the patients exhibit either hypometabolism or true hypothyroidism. Hypometabolism, which is common in respiratory allergic states, responds well to thyroid medication and, as the hypometabolism approaches a normal state, lessening of the dosage can be effected and finally discontinued.

In several hundred patients, determinations of *gastric acidity* have been made, and there has been no more deviation from the normal than would be expected in an average group of patients with any type of problem.

Finally, it is to be remembered that the histopathology of allergy is a very definite picture. In problems where diagnosis cannot be established by other measures or where tissues for pathologic examination can be secured without difficulty, specimens should be taken. There can be no mistake in diagnosis when the histopathology of allergy is studied.

ALLERGY TESTS

From the foregoing discussion, it is obvious that we consider allergy tests as only a part of the investigation of the patient's problem. Each patient must be individualized and several methods of skin testing may necessarily be used in the same patient. In the majority of patients with respiratory allergy, the scratch method is employed first. This insures against the possibility of constitutional reactions which are discouraging both to the patient and the physician. In a small percentage of patients, allergic reactions will be of sufficient severity that this type of testing is satisfactory; however, in the majority of cases, further investigation is necessary and then the intracutaneous method is employed. This is particularly true if the patients do not have pollen allergy. We have found that at least three dilutions of each allergen are necessary in intracutaneous testing. For the chronic low grade allergy, and particularly where refractive types of skin are encountered, we have used the undiluted stock solutions, except in pollen allergy where tests are always by the scratch method. The majority of patients respond best to the 1:10 dilutions of the regular stock or undiluted antigens. For patients with a more acute and easily elicited response to allergens, complete series of antigens are used with 1:100 and 1:1000 dilutions. If the proper dilution is selected for each patient, skin reactions are easily elicited and interpretation of reactions is not difficult. Through this method of individualizing the tests for each patient, we have obtained much more satisfactory responses from the skin tests and have secured a higher percentage of excellent clinical relief.

The third method of testing for allergens is the passive transfer as elaborated by Prausnitz-Küstner. The indirect method of testing is necessary where the following conditions exist:

1. In children where physical and mental shock render direct methods of testing inadvisable.

2. In patients with severe cutaneous lesions where extensive involvement and lichenification of the skin renders sites for testing impossible.

3. In the group of patients who present a generalized hypersensitive, nonspecific response to any substance applied. This response probably is due to trauma and release of histamine-like bodies locally and is not infrequently seen in cases of eczema and urticaria.

4. In the acutely ill patient.

During the past four years we have used the passive transfer method for complete allergy tests in more than 300 patients and the clinical results have been comparable or superior to the direct method of testing. Briefly, the method is as follows: Under sterile precautions, 30 cc. of blood is withdrawn by venipuncture. The blood is centrifuged under sterile precautions and the serum drawn off. No filtering for sterilization is needed if sterile precautions are observed throughout the procedure. Using quantities of one-fourth to one-third cc. for each site, the undiluted serum is injected intracutaneously into a professional test person. By means of tests, history, and examination, this individual has previously been proved to be nonallergic. *A relative of a patient is never used.* These sites, which usually number from 32 to 48, are marked by making a linear skin incision with a sharp scalpel. At the end of 48 or 72 hours, the sites are used for testing by the intracutaneous method. If a sharp reaction occurs at a site, it is not used for further testing because the reagins present in this site will have been exhausted. By repeatedly going over the sites, after 48 hours have elapsed between tests in order that antigens may be absorbed, one is able to make from 80 to 100 tests which, if judiciously selected after careful history, will suffice in most instances for a complete allergy examination.

Ophthalmic and intranasal tests have their place in the allergic survey in the hands of most workers. These are performed by simply placing in the conjunctiva or blowing against the nasal mucosa small quantities of purified dried powder of the substance that is suspected. If hypersensitivity exists, an immediate reaction is noted, and the substance can readily be washed out with normal saline and weak solutions of adrenalin. Often a severe reaction occurs which may be discomforting to the patient for a few days. Because of this undesirable reaction and because testing by scratch, intracutaneous, and passive

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transfer methods are reliable in respiratory allergy, we have not employed ophthalmic and intranasal tests.

The fallibility of determining allergens by skin testing has received considerable criticism from time to time. In most instances, this has been stimulated by the failure to identify causative agents, and the number of false positive reactions that are encountered occasionally. Undoubtedly, skin tests are not accurate in 100 per cent of the cases, but it is true that skin testing, in the hands of an experienced worker who uses reliable and potent extracts, gives a working knowledge of the problem which cannot be paralleled by any known diagnostic procedure. In respiratory allergy, skin tests give the most accurate results, being reliably correct in 90 per cent of the patients.

Finally, one may use all three methods of testing for allergens in order to obtain sufficient information. Seldom does this combination of methods result in failure, but if such an instance occurs where food allergy is suspected, further investigation through food diary, elimination diets of individual or stock type, and the use of the digestive leukocyte response, as recommended by Vaughn[7], gives information which is of undeniable value.

ALLERGENS

Any protein substance may be allergenic. In Table 6 a summary is given of allergens known to produce at least 95 per cent of allergic reactions. Pollens of trees, grasses, and weeds rank as the largest factors in the production of respiratory allergy.

TABLE 6

ALLERGENS

Inhalants
    Pollens _____Tree, grass, weed—occasionally flowering plants.
    Molds _____Chiefly families of alternaria, aspergillus, cephalo-thecium, hormodendrum, monilia, penicillium.
    Epidermals _____Feathers, animal dander
    Miscellaneous _____Flaxseed, glue, orris, pyrethrum, silk, kapok seed, cottonseed, tobacco, emanations of insects, Indian gum, house dust.
Ingestants _____Food, bacteria, drugs, molds
Cutaneous _____Animal or plant protein drugs
Parenteral _____Sera, toxins, viruses, drugs
Intrinsic _____Infections
Ill-defined _____Smoke, odors, vapors

Second to the pollens, epidermal substances are considered by many workers to be the largest factor. However, since the advent of mold allergy, many patients with both seasonal and perennial nasal symptoms

have been found to be sensitive to mold and with the large factor that house dust plays, this group of etiologic factors threatens the place of the epidermal substance as the second most common cause of respiratory allergy. All workers in allergy recognize the importance of house dust allergy in patients who suffer with a distinct seasonal respiratory allergy or an intensification of a perennial respiratory allergy in the winter season. This is particularly true where contact with house dust is imminent as in those domestically employed.

Occasionally, patients with allergy have intense reactions to one of the miscellaneous substances other than house dust; this is particularly true of animal epidermals, silk, kapok seed, cottonseed, and orris root. In these instances, such a single intense reaction may well be the major factor in the production of symptoms, and immunization therapy usually gives excellent results.

Bacterial allergy is a prominent factor where allergy and infection have existed in the nasal passages and paranasal sinuses. We have used stock bacterial vaccines in skin testing in these cases, but our findings show that autogenous antigens are by far superior to the stock vaccines. In every patient where infection is superimposed upon allergy, secretions, either nasal, sinus, or bronchial, are secured for preparation of autogenous vaccines. Although seldom the major factor in the production of allergic reactions, therapy with bacterial vaccine in carefully chosen cases has been of distinct value.

Food allergy is a distinct factor in the production of respiratory allergy. Although many of our patients have definite allergy to inhalants and bacteria, the majority have sufficient food allergy to require strict dietary management. Grains, particularly wheat, and milk and eggs, in the order given, are most important. The investigator should never overlook this important phase of food sensitiveness in the study of any patient with respiratory allergy despite the fact that severe reactions are obtained to the inhalants.

DIFFERENTIAL DIAGNOSIS

Common conditions of the nose that must be differentiated from allergy are frequent colds, acute rhinitis and sinusitis, hypertrophic rhinitis, chronic sinusitis, chronic sinusitis in sinus chest diseases, chronic nasal discharge and headaches, lues, headache with nasal obstruction, and pallor of the mucous membrane due to poisoning from coal tar products.

Other conditions such as severe secondary anemia, hypothyroidism, states of malnutrition and deficiency disease may result in vascular disturbances with changes in color of the nasal mucous membrane, suggesting primarily an allergic state.

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It is well known that deflected septa produce chronic nasal obstruction and increased nasal secretion. Physical agents, such as gas, smoke, fumes, mechanical and chemical irritants, atmospheric conditions with extremes and sudden changes of temperature, winter weather with enforced residence in buildings where breathing of dry, unhumidified air and contact with coal smoke and coal dust is unavoidable for prolonged periods of time without proper ventilation and air conditioning, produce exacerbation of nasal symptoms which may simulate allergy. Nasal allergy is often a basis or an aggravating factor in manifesting or prolonging these conditions, but careful history and examination will prove the presence or absence of allergy.

In patients who complain of chronic nasal obstruction and discharge and in whom chronic thickening of the nasal mucous membranes and polyposis with suppurative processes are noted, the possibility of a primary allergic condition must be considered. Hyperplastic ethmoiditis, chronic edema, and polyposis of the sinuses must be looked upon as allergic in origin until proved otherwise. Repeated clinical examinations of nasal secretions and detailed survey of the history should be made before the presence of allergy is excluded. It should be kept in mind that cerebrospinal rhinorrhea may rarely be encountered in patients with profuse watery discharge from the nose, and differentiations can be made by a chemical examination of the nasal secretion.

Mulberry hypertrophy of the posterior tips of the inferior turbinates can be distinguished from nasal polyps by their location, which is usually in the middle meatus.

The possibility of malignant tumors of the carcinoma type should be kept in mind when the process is unilateral and pain and bleeding are present.

TREATMENT

Correct diagnosis is imperative in order to institute proper therapeutic measures. It is discouraging to treat a patient for nasal allergy if he is actually suffering with an acute or chronic infectious involvement of the nose and paranasal sinuses.

With the diagnosis correctly made, the next survey includes knowledge as to the adequacy of clinical investigation. No short cut to diagnosis is possible in any patient and each problem deserves the thorough investigation that has been reviewed in the preceding pages. Careful study will accord patients with respiratory allergy such excellent clinical relief as to insure the permanency of allergy in the field of therapeutic medicine.

In our experience, one of the greatest causes for failure to obtain reasonable clinical success in patients who are definitely allergic is not

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due entirely to inadequate investigation, but to the failure of the physician to convey to the patient the understanding of allergic reactions, of allergenic substances, and what is to be done about them. This phase of the program demands time and detail on the part of both the patient and the physician. We give not only complete verbal instructions, but also carefully written instructions in an attempt to educate the patient in regard to the meaning of allergy and the necessary care and consideration that is a feature in the proper therapy of every problem. A satisfactory allergy regimen and control cannot be accomplished unless this policy is strictly adhered to.

Allergens which can be avoided or eliminated: As a rule the common inhalants, with the exception of pollens and molds, can be avoided unless the patient is extremely sensitive. When inhalation allergy is proved to be of distant clinical importance and elimination is not possible, immunization therapy is necessary.

If the patient is allergic to food, only simple elimination is necessary. Desensitization to foods, either oral or parenteral, is not practical or helpful. In making substitutions in the diet, special attention must be given to assure a diet that is adequate, nutritious, and palatable. We employ not only the physician's knowledge of this, but also the cooperation of our Dietetic Department. Where major foods are eliminated, it is desirable not only to rearrange the diet according to the permitted foods, but to give additional vitamins A, B, and D, and calcium. We feel that this insures against disturbances of nutrition and often is of value in maintaining the physical well being of the patient. The length of time that foods must be avoided is dependent upon the individual patient and his symptoms. It is reasonable that no food which has definitely been proved to be a specific factor should be returned to the diet in less than six months. The program to be followed in each particular case can be determined only by experience.

Allergens which cannot be avoided or eliminated: Sensitivity to pollens of trees, grasses, weeds, and occasionally to pollens of flowering plants necessitate hyposensitization. It is recognized and accepted that pollen allergy can be adequately treated by hyposensitization with satisfactory relief in 90 per cent of the cases. Of the three methods of therapy—coseasonal, preseasonal, and perennial—we feel that the perennial method is the most satisfactory and gives a high percentage of relief in the majority of patients.

Allergy to house dust and mold, particularly if there is a distinct variation during the winter season, demands immunization therapy if clinical symptoms are persistent and annoying. The necessity of immunization with house dust antigens can be determined by eliciting

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a careful history of symptoms on exposure to dust and by interpreting the degree of skin reaction to house dust antigens. Mold allergy is a distinct and large factor in perennial respiratory allergy. If its significance in the problem is firmly established, immunization therapy is necessary.

Occasionally, patients with respiratory allergy are extremely sensitive to one of the inhalant allergens other than dust, mold, or pollen. These are orris root, silk, epidermals, kapok seed, cottonseed, and emanations of insects. Immunization in this group practically always affords excellent relief.

Previously, a discussion of bacterial antigens and bacterial vaccine therapy was given. We have used only autogenous vaccines and found this phase of therapy to be a valuable adjunct if treatment is continued over an extended period of time.

In hyposensitization therapy it should be emphasized that doses of antigens should not be large enough to produce too great local reaction and never symptoms of a constitutional reaction. It is obvious that signs and symptoms of systemic reaction are evidence of shocking tissues and not stimulating immunity. This particular principle has a counterpart in that it renders any type of immunization treatment a long and tedious process. In immunization therapy, it is best to consider measures that may last several years.

General measures in treatment: The commonly associated nonallergic states are hypometabolism or true hypothyroidism and mild hypochromic anemia. Occasionally, a patient has a nutritional deficiency which is either due to enforced dietary restrictions or failure to assimilate ingested food substances due to the marked allergic state. This is not uncommon in patients with food allergy. The general measures most commonly employed with these patients are control of the hypometabolism or true hypothyroidism with small doses of thyroid and control of the secondary anemia.

We study all patients carefully from the viewpoint of any general disturbance and if such a disturbance is present, treatment is given as indicated by the problem involved.

Nonoperative treatment of the nasal passages: Definite allergy of the nasal passages often is complicated by pathologic conditions such as badly deflected septa, nasal spurs, nasal polypi, polypoid degeneration of the turbinates, or sinusitis. Conservative measures are indicated in these problems until the allergy is controlled. These membranes are hypersensitive and the use of drugs usually does not result in any relief but only adds to the irritation and congestion and the amount of edema. In the presence of such pathologic conditions, conservative treatment should be instituted in order to secure drainage of

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any purulent material in the sinus areas or the nasal passages. If treatment is required, only mild drugs should be used. We have found weak solutions of ephedrine, neosynephrin hydrochloride, and cocaine to be most satisfactory. However, it should be emphasized that unless it is absolutely necessary, local therapy to the nasal passages or the intranasal sinuses should be avoided. If the condition is primarily of allergic origin, proper investigation and therapy will result in satisfactory relief of the nasal problem.

Surgical indications: The surgical indications in diseases of the nasal sinuses and nasal passages in the presence of allergy were discussed by the late Dr. W. V. Mullin[8] in a study of 216 patients who were seen in the Department of Otolaryngology and the Department of Allergy at the Cleveland Clinic. His findings summarize our opinion concerning the diseases of the nasal passages and paranasal sinuses due to allergy. In his group of 216 patients, 52 had had previous operations upon the nasal sinuses but had secured no relief from symptoms. In these 52 patients, no study to determine the presence of allergy had been made. Dr. Mullin found it necessary to carry out surgical measures after the allergic condition was diagnosed and treated in only 16 of these 52 patients. He concluded that in this group of patients careful studies to determine the presence of allergy would have eliminated more than two-thirds of the nasal operations to which these patients had been subjected. In summarizing the 216 cases, Dr. Mullin felt that allergy was a definite factor in the production of nasal and paranasal symptoms in 35 per cent. The importance of primary allergic studies in these patients and the necessity for conservative surgical procedures were emphasized. Further studies in a larger group of patients have led us to believe that the importance of primary allergic investigation in diseases of the nasal passages should not be overlooked, and that a conservative surgical attitude should be continued.

In primary allergic states where pathologic conditions exist that demand surgical measures, the allergy should be completely investigated and a regimen established in which elimination and hyposensitization measures are carried out. This should be continued for a period of two to six weeks before any surgery is undertaken. By this, the edema that is characteristic of allergy will have essentially disappeared, permitting satisfactory surgical results. If surgical measures are undertaken before the allergy is controlled, it has been our experience that a stormy convalescence follows and this is due primarily to the intense edema that takes place after any operative procedure where an active and acute condition of allergy exists. In many problems, we find it necessary to make not only complete allergy investigation and prescribe the proper treatment, but also to institute conservative surgi-

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cal measures in order to give the patient complete and satisfactory relief of symptoms. The most sincere cooperation is necessary between the allergist and the otolaryngologist.

In order to insure the permanency of allergy in the field of therapeutic medicine, adequate and thorough investigation of the allergic problem and proper measures of therapy, with consideration of associated nonallergic factors, must be made in every instance.

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