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NASAL ALLERGY WITH SPECIAL REFERENCE TO EOSINOPHILIA AND HISTOPATHOLOGY

By

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According to the opinion generally accepted at present, allergic illness requires six preparatory steps: exposure to an allergen, formation of antibodies, fixation of antibodies in tissues, re-exposure to the same antigen, release of histamine as a result of antigen-antibody union, and the effect of histamine on smooth muscles, mucous glands, and capillaries.

The underlying basis of allergy is the increased permeability of the blood vessels and cells and a corresponding disturbance in the tissue fluid balance. This results in a localized oedema. Oedema and eosinophilia are patho-anatomical changes characteristic of the allergic reaction and they are found on the nasal mucosa of persons with nasal allergy. In these patients eosinophilia occurs also in the blood and in the nasal secretions. The exact role of the eosinophil in allergy is unknown, but it has been suggested that it is concerned with the disposition or elimination of foreign or broken-down protein in the blood and tissue. Code has shown that the eosinophil is a carrier of histamine, but it is not known whether it carries this substance to the tissues or away from them.

The present article is a report of studies on 30 persons with allergic rhinopathy. Twenty of them had polyps in the nose; the remaining 10 were typical cases of allergic rhinitis without polyps. In each case the blood picture and the eosino-

phils in the nasal secretion were determined and biopsy specimens removed for histological study from the medial surface of the inferior turbinate and the anterior border of the middle turbinate. In 14 cases eosinophil determinations were also made from maxillary sinus secretions. In a considerable proportion of the cases biopsy specimens were taken also from polyps (20 cases) and from the mucous membrane of the ethmoid cells and maxillary sinus (12 cases). Besides oedema and eosinophil cells, attention was paid in the histologic examination of other pathological changes.

Samples of nasal secretion were taken from the nasal passages by means of a cotton applicator. The applicator was immediately rubbed off on a slide, and after drying, the smear was stained as follows (Hansel's eosin-methylene blue staining) :

1. Staining for 1 min. with eosin (eosin 0.5 + methyl alcohol 100.0).
2. Washing for 1 min. with distilled water.
3. Rinsing in 96 per cent alcohol.
4. Staining for 10 sec. with methylene blue solution (methylene coeruleum 0.5 + methyl alcohol 100.0).
5. Washing for 30 sec. with distilled water.
6. Rinsing in 96 per cent alcohol.
7. Drying in air or carefully with blotting paper.

In some cases the smears were also stained by the May-Grünwald technique.

In samples of nasal secretion these two methods generally revealed detached epithelial cells and varying amounts of neutrophilic leukocytes, lymphocytes and eosinophils.

The histological sections were stained by the Weigert-eosin technique. With this stain the eosinophil cells stand out clearly when examined with an oil immersion lens. In most cases the Weigert-van Gieson stain was used in addition.

All 30 patients were adults. With the exception of 5 cases, they were all under treatment at hospital. Seven patients also

had asthma and a few had had eczema. The number of surgically treated patients (25) is very high in this series.

A *blood eosinophilia* of 4 per cent, or more, was considered pathological. Such an eosinophilia was found in 14 patients of 30. In a previous study (1949) based on 110 cases, eosinophilia was present in 75 cases; or 68 per cent, thus considerably more often. In the present series eosinophilia occurred equally often in patients with polyps (10:20) as in those having no polyps (4:10). The highest degree of eosinophilia was 17.4 per cent (leucocytes 4300, sedimentation rate 17).

As is known, a decrease in the number of eosinophils—eosinopenia—occurs at the early stage of various infections. Eosinophilia, on the other hand, is common at the recovery stage of acute infections. Operation, though associated with penicillin treatment, also seems to cause a fall in the eosinophil count. In two cases in which the Caldwell Luc operation and resection of the ethmoid cells were performed, the results of blood studies before operation and one week after it were as follows:

	Before operation	After operation
Leucocytes	4200 6000	4600 6000
Eosinophils	6.0 % 7.6 %	0.4 % 4.9 %
Sedimentation rate	6 9	31 24

Nasal smear eosinophilia was diagnosed in about 50 per cent of the cases (16:30). The diagnosis of pathological eosinophilia is to some extent difficult and there exists a diversity of opinion on this question. A differential count is time-consuming and also misleading, as the eosinophils are never distributed evenly among the other cells but are usually seen in small heaps. Andersen diagnosed an eosinophilia of the secretion on the presence of eosinophils amounting to 1/10 of the total white blood cells or on the presence of eosinophils

in clusters. In this study I have used the same criterion. Thus the presence of a few isolated cells has been interpreted as a negative result.

The incidence of eosinophilia was much the same in cases of polyp (11:20) as in the other patients (5:10). In two cases eosinophils were present in extremely great numbers and epithelial cells only were found in addition. Those patients (2 cases) whose blood showed leucocytosis of high degree (over 10,000), had neither eosinophilia in the blood nor in the nasal secretion. The incidence of eosinophilia in blood or nasal secretion, or in both blood and nasal secretion, was 73 per cent (22:30). In Andersen's series, consisting of 57 cases of clinical allergy, the corresponding incidence figure was 80 per cent (45:57).

The maxillary sinus secretion was examined for eosinophilia in 14 cases, 8 of which yielded a positive result. In 3 of these latter a biopsy specimen taken from the nasal passage was negative for eosinophilia.

As pathological *tissue eosinophilia* was regarded the approximative occurrence of more than 10 per cent of all the wandering cells, *i.e.* leucocytes, lymphocytes, and plasma cells (Andersen). The sections prepared from the biopsy specimens were carefully examined with both high-power and oil immersion lenses. Eosinophils were present chiefly in the subepithelial layers and in the area of oedema, but to a less extent around the blood vessels and glands. In a few cases the eosinophils could be seen traversing through the epithelium into the nasal secretion. In some patients there were eosinophil cells in the turbinates and polyps also in the subepithelial tissue in areas of squamous metaplasia. Biopsy material was removed in a few cases also from the mucosa of the upper lip in connection with the Caldwell Luc operation: eosinophils were not found in these specimens.

Eosinophilia was noted in the inferior turbinate in nearly half the cases (13:30), in the middle turbinate considerably more often (23:30), and in very nearly each case of polyp (18:20). Only in the operatively treated cases was mucous

membrane from the ethmoid cells and the maxillary sinus removed for examination. Eosinophilia was also diagnosed in most cases in the ethmoidal region (20:23) and in the maxillary sinus mucosa (10:12). These observations show that eosinophilia is an almost regular phenomenon in nasal polyps and in the mucosa of the ethmoid cells and the maxillary sinus. Commonly it was also observed in the middle turbinate, but in only half the cases in the lower turbinate. Eosinophilia in the locations stated was equally frequent in patients with polyps as in others with allergic rhinopathy. Biopsy specimens from the polyps, the ethmoidal region and from the middle turbinate showed dense eosinophilic cell infiltration more often than those from the maxillary sinus and the inferior turbinate.

Tissue eosinophilia was noted in some area in all the patients of this series, except one. This patient, however, showed high-degree eosinophilia in the nasal secretion.

The *epithelium* in the biopsy specimens was generally of the ciliated respiratory type. In a few cases there was in addition squamous epithelium in a small area in the inferior turbinate (8:30), the middle turbinate (2:30), and polyps (3:20). In none of the cases was cornification observed. Saxén found islands of metaplasia especially in the distal part of polyps and in the mucous membrane of the maxillary sinus. Such islands may occur also in other parts of the nasal cavity if they are exposed to direct air currents and to drying.

The respiratory epithelium had undergone pathological changes in most cases. The cilia were desquamated in places. The epithelium was often hyperplastic, the cells were enlarged and arranged in several layers. Often the cells were distended with large mucus globules. Goblet cells occurred in most cases in the turbinates, polyps, ethmoid cells, and maxillary sinus. The superficial layers of the epithelium were sometimes desquamated in the inferior and middle turbinates.

The great increases of mucus content of the epithelium in these cases is evidently due chiefly to the allergic state. It should be noted, however, that this is common also in various

kinds of rhinitis and sinusitis. The animal experiments carried out by Hilding have shown that occlusion of the nose causes similar changes: the cilia disappear, the cells become distended with mucus globules and this may involve the glands which undergo cystic dilatation.

The histological structure of the *stroma* depended greatly on the amount of the oedema fluid. Connective tissue fibrils and cells appeared in varying amounts. In the polyps they were rather scanty. Increase in the number of fibres occurred in some cases, but intense fibrosis was noted in the lower turbinate in only two cases and in the mucosa of the ethmoid cells and the maxillary sinus in one case. The fibrosis in these patients was probably due to chronic infection.

Glands were present in most of the specimens removed from the lower turbinate (28:30) and from the middle turbinate (25:30). They were more rare in the ethmoid cells (10:23), maxillary sinus (4:12), and polyps (4:20). The glands were usually smaller in these sites than in the turbinates.

In two cases retention cysts of varying size were observed in the area of the stroma in both the polyps and the maxillary sinus mucosa. Here and there the cilia had disappeared from the cyst walls and there were mucus globules in the epithelium. In one of these cases there was well marked eosinophilia in the cyst mucus of the maxillary sinus mucosa, and isolated eosinophils were seen in the cyst epithelium.

In a few cases so-called "mesothelial cysts" or "pseudo-cysts" occurred both in the polyps and in the mucous membrane of the maxillary sinus. These formations are actually enormous tissue spaces filled with tissue fluid.

Besides the eosinophils, *cell infiltration* was a constant feature in all cases. Lymphocytes were present in each specimen, most often subepithelially. In the polyps they were usually rather scanty. In one case a fully developed lymphoid follicle was seen in the submucosa of an ethmoid cell. There were no eosinophils in the area of this follicle, but around it they were numerous. Such aberrant scattered lymphoid fol-

lices in different stages of development are more commonly met with in material from cases of non-suppurative sinusitis than any other condition, but they also occur in chronic infective sinusitis (Lucas).

Neutrophilic polymorphonuclear granulocytes were present in only part of the cases in small numbers in the subepithelial layers.

Plasma cells were observed very often in small numbers in the inferior and middle turbinate, in the ethmoidal region, and in the maxillary sinus. In polyps they were scanty in most cases. In a very old case of allergy, in which polyps had been removed repeatedly, these cells were numerous, and there was intense and widespread plasma and eosinophilic cell infiltration.

Andersen and Lucas have found that plasma cells are always present in allergic polyps in variable numbers. Lucas has shown that they are produced locally and arise from the cells of the reticuloendothelial system. Lymphocytes and plasma cells, which are the ones most commonly met with in all cases of sinusitis, are both derived from the reticuloendothelial system and their function is to render innocuous the foreign substances and bacteria which gain entrance to the tissues. They fulfil this function by the formation of antibody globulin. It has been demonstrated that nasal polyps rich in plasma cells contain more globulin than the patient's serum.

Oedema occurred about equally often as eosinophilia in the specimens removed from the various sites. Thus oedema was found in the inferior turbinate in nearly half the cases (12:30); in the middle turbinate it was considerably more frequent (25:30), and in the polyps, ethmoidal cells and maxillary sinus mucosa it was invariably present (20:20, 23:23, and 12:12 respectively). Demonstration of oedema fluid in the histological specimen is not usually difficult, unless the oedema is of very slight amount. At the clinical examination, allergic oedema often appears in the mucosa as pallor.

The fact that oedema and eosinophilia generally occurred in the same specimens is in favour of the view that, in these cases, oedema was chiefly due to allergy. Secondary infection played a less important part in its formation. On the other hand it is well known that acute infections in nasal allergy may produce an inflammatory oedema or even acute polyposis, which disappear when the acute infection subsides.

Berdal has investigated the antibody content of fluid taken from polyps of patients sensitive to different allergens. He demonstrated that the polyp fluid contained specific antibodies to substances to which the patient was sensitive, in a concentration far higher than the blood serum. This shows that oedema is due to an active process, allergy, and not to passive congestion.

Oedema is due to increased capillary permeability and when this reaches an excessive degree in a localized area, polyps result. In nasal allergy oedema is present in greater degree and more frequently in the upper part of the nasal cavity—at the site of polyps—than in the inferior turbinate. Thus it is obvious that a nasal polyp is initially an oedematous fold of the mucous membrane, which, being in a narrow and rigid-walled cavity, can only expand in one direction and so becomes polypoid. In the maxillary sinus, oedema is also common, but as there is more room polyps are infrequent in this location.

SUMMARY

Eosinophils were determined from the blood and nasal secretion in 30 cases of nasal allergy and in another 14 cases from the maxillary sinus secretion. Eosinophilia occurred equally often in the cases with polyps as in other patients. The incidence of eosinophilia in blood or nasal secretion or in both was 73 per cent (22:30).

Pathological tissue eosinophilia was found in almost every polyp (18:20) and in almost every biopsy specimen from the mucosa of the ethmoid cells (20:23) and of the maxillary sinus (10:12), very frequently in the middle turbinate

(23:30), but considerably more rarely in the inferior turbinate (13:30).

Oedema and eosinophilia were about equally frequent in the various sites studied. It is evident that the polyp is initially an oedematous fold of the mucous membrane; in a narrow and rigid-walled cavity this fold can only expand in one direction and so becomes polypoid.

There are quite often pathological changes in the respiratory epithelium, e.g. epithelial hyperplasia, desquamation of the cilia, mucus globules, and islands of squamous epithelium.

In the stroma, cell infiltration was present in each specimen; the infiltration was mainly lymphocytic; in one case there was a lymphoid follicle in the submucosa of an ethmoid cell; plasma cells were frequently seen in small numbers, and occasionally a few neutrophilic granulocytes. Definite increase of connective tissue was observed in some cases. Two patients showed retention cysts in a polyp and in the submucosa of the maxillary sinus.

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