# CORRELATION BETWEEN HISTAMINE LEVEL AND PHASES OF SEROUS INFLAMMATION IN CHRONIC RHINOSINUSITIS

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The tissue histamine was determined fluorimetrically and a parallel histological investigation made of the mucous membrane of the nose in the material obtained by operative removal of the nasal conchae and nasal polyps from patients with chronic rhinosinusitis. In serous inflammation the histamine level in the nasal mucosa varies with the phase of inflammation and is highest in the initial stage of the inflammatory reaction. A decrease in the histamine level is observed as the inflammatory reaction develops in the mucous membrane and the epithelial secretion increases. Correlation analysis of the results showed absence of correlation between the number of mast cells and the tissue histamine concentration, and also between the tissue eosinophilia and the histamine level. At the same time, correlation was found between the numbers of mast cells and of eosinophils.

Chronic rhinitis and rhinosinusitis in many cases recur as serous inflammation with marked edema of the tissue and hypersecretion of the glandular and respiratory epithelium. In patients with an allergic reaction the recurrences are particularly acute: the nose is suddenly obstructed, attacks of sneezing occur, and the secretion becomes profuse and rhinorrheic in character. Clinically this type of chronic nasal affection has been called allergic rhinosinusopathy [7].

The marked vasomotor phenomena, the rapidity of development of edema of the mucosa, and the suddenness and profuseness of the nasal secretion suggests the involvement of mechanisms locally and quickly changing the microcirculation in that region. Regulation of the microcirculation, on account of which the local capillary blood flow becomes adapted to the needs of the tissue at each given moment, is provided by humoral mechanisms of which the most important is the liberation of biogenic amines of the histamine, serotonin, and catecholamine type [17, 20, 22]. The role of histamine as a mediator of inflammation is well known [2, 8]. Liberation of histamine has also been shown in allergic conditions [1, 5, 6, 10].

The histamine level was studied in the nasal mucosa, in which inflammation is frequently superposed on an allergic basis.

## EXPERIMENTAL METHOD

To determine the histamine content in the nasal mucosa, nasal conchae and nasal polyps removed from 24 patients with chronic rhinosinusitis were investigated. In 10 patients the clinical course of the diseases corresponded to a picture of allergic rhinosinusopathy, and eight of them had recurrent nasal polyposis and polypous highmoritis. Allergic tests for diseases of the ear, nose, and throat [9] were positive in 10 patients; four patients had allergic diseases elsewhere.

Histamine was determined by Shore's fluorimetric method [19] in tissue homogenates of polyps and

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TABLE 1. Results of Cell Counts and Histamine Levels in Various Phases of Serous Inflammation

| Index | Phase of hyperemia and edema (patients without allergy) | Leukocytic phase | | Macrophagal phase (patients with allergy) | Remission (patients without allergy) |
|---|---|---|---|---|---|
| | | patients without allergy | patients with allergy | | |
| Number of observations | 4 | 4 | 8 | 6 | 2 |
| Histamine (in μg/kg tissue). | 10,18 ± 0,77 | 4,99 ± 1,01 | 7,30 ± 0,78 | 0,98 ± 0,23 | 1,2 и 0,12 |
| Eosinophilic leukocytes. . . | Single | 38,00 ± 11,50 | 300,60 ± 8,93 | 162,00 ± 15,00 | 10,0 и 12,0 |
| Mast cells . . . . . | 48,00 ± 3,24 | 40,00 ± 1,16 | 2,50 ± 0,83 | 22,50 ± 3,55 | 36,0 и 31,0 |
| Cells accumulating amines . . . . . | 0 | 0 | Single | 39,50 ± 7,65 | 27,0 и 69,0 |

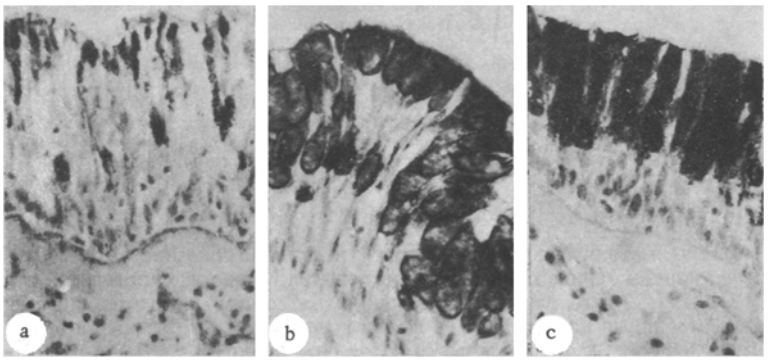


Fig. 1. Change in level of secretion of respiratory epithelium during development of serous inflammation of nasal mucosa: a) weak secretion of respiratory epithelium in phase of edema, histamine level in mucous membrane 12 μg/g; b) increase in number of goblet cells in leukocytic phase of inflammation, histamine level in mucous membrane 3.3 μg/g; c) hypersecretion of respiratory epithelium in macrophagal phase of inflammation, histamine level in mucous membrane 0.92 μg/g; PAS reaction, 200×.

nasal conchae. Excitation and fluorescence spectra of the material tested, at 365 and 450 nm, respectively, coincided with these spectra for a standard histamine solution treated with orthophthalic aldehyde.

Material for histological examination was fixed in 10% buffered formaldehyde solution and embedded in paraffin wax; sections 7 μ in thickness were stained with azure–eosin and the PAS reaction was carried out to study the epithelial secretion. The objects of the histological investigation were to assess the inflammation and determine the extent of the secretion and behavior of the cells relative to biogenic amines. For this purpose the number of mast cells, eosinophilic leukocytes, and cells accumulating amines [3] were counted (among 1000 cells from the focus of inflammation).

## EXPERIMENTAL RESULTS

Fluorimetric investigation of histamine showed that its level in tissue samples varies within wide limits (from 0.12 to 12 μg/g). Histological study of the material showed that individual cases could be grouped together by phases of the inflammatory process (Table 1). A high histamine content was found in the initial phase of inflammation when severe congestion and marked tissue edema were present (Table 1). Migration of leukocytes had not yet begun – they were merely arranged at the periphery of the vessels. A feature of this phase is that with a high histamine level the mast cells remained intact and were numerous, except that in the subepithelial zone of the mucous membrane there were a few mast cells with signs of degranulation; a few eosinophilic leukocytes could be seen.

The mean values of the histamine concentration agreed with those obtained in the leukocytic phase of inflammation, but clear differences were found in the differential cell counts in patients with allergy or with normal reactivity. In the former the inflamed area was infiltrated with large numbers of eosinophils and degranulation of the mast cells was observed, so that their number was sharply reduced. The picture of degranulation of the mast cells was expressed as a gradual decrease in size of the granules and in the intensity of their metachromatic staining [4, 14]. In patients with normal reactivity the tissues contained far fewer eosinophils but the number of mast cells remained high, although the proportion of them with

evidence of degranulation was increased. The histamine level in the patients with allergy was significantly higher in this phase than in the nonallergic patients.

In the leukocytic phase of inflammation cells resembling small lymphocytes migrated from the blood vessels, together with the eosinophils, into the tissue; there they underwent certain changes: the nucleus became larger and less dense; a notch appeared making the nucleus bean-shaped; finally, the cells acquired the morphological features of macrophages. Fragments of the degenerating eosinophils began to undergo phagocytosis by some of these macrophages. Initially eosinophilia could be seen in their cytoplasm, but this was followed by azurophilic granulation with the appearance of which the cytochemical reaction for monoamines became positive. The appearance of macrophages of this type was observed at the end of the leukocytic phase, while in the macrophagal (proliferative) phase of inflammation their number increased sharply. The proliferative phase of inflammation, like the period of remission (two cases), was characterized by a low histamine level.

Changes in the level of secretion of the respiratory epithelium also were studied. In the first phase of inflammation, when the histamine level was high and edema well marked, the secretion could be assessed as weak (Fig. 1a). This was reflected clinically as swelling of the mucous membrane and obstruction of the nose, so that nose breathing was impossible, but no secretion was yet being discharged from the nose. The leukocytic phase of inflammation was characterized by increased secretion, reflecting in particular an increase in the number of goblet cells (Fig. 1b), and the level of secretion increased while the histamine level fell. Clinically this period corresponded to the appearance of a discharge from the nose. In the macrophagal phase, if desquamation of the epithelium had not begun, the secretion reached its maximal intensity, and the cylindrical cells were almost entirely converted into goblet cells (Fig. 1c).

The tissue histamine level in the nasal mucosa thus varies with the phase of inflammation: it is highest in the early stages of serous inflammation and falls as the inflammatory reaction develops. According to the literature [16], the initial phase of inflammation is determined by the histamine of the mast cells, which is set free during their degranulation. The results of the present investigation do not confirm this view, for a high histamine concentration was observed in the phase of edema when the mast cells were intact, and in the leukocytic phase in patients with allergy associated with degranulation of the mast cells, and a low histamine level was found in the proliferative phase, again in the presence of mast cells. The tissue histamine evidently has other sources, and the role of the mast cells as the dominant factor in this process is somewhat exaggerated. Investigations [15, 21] have shown that the histamine content and histidine decarboxylase activity are unrelated to the number of mast cells. Meanwhile, nearly all tissues possess histidine decarboxylase activity, by which histidine is converted into histamine. It is also known [13] that histamine unconnected with mast cells participates in the general physiological reactions of the body.

This comparison of the histamine content with the eosinophil count in the various stages of inflammation is not in harmony with data on the chemotaxic affinity of the eosinophils for histamine [12, 18]. The correlation coefficient was calculated between the histamine level and the number of mast cells and eosinophilic leukocytes both for the series of observations as a whole and for their subdivision into phases. To assess the degree of significance of the correlation coefficients for the samples, Fisher's Z-transformation was used [11]. Because of the very small number of observations in some groups it was necessary to be content with a 5% level of significance. In all the groups examined the coefficient of correlation between the histamine concentration and the number of mast cells and also between the histamine concentration and the number of eosinophils was not significant; it was significant between the number of mast cells and the number of eosinophils (excluding the macrophagal phase) and its values were as follows: for the whole series (22 observations) $r = -0.88$, for the phase of edema (four observations) $r = 0.9$, for the leukocytic phase (12 observations) $r = -0.9$.

It can be concluded from the results of correlation analysis of the data that there is no connection between the number of mast cells and the tissue histamine concentration or between the tissue eosinophilia and the histamine level. It can be postulated that the factor attracting the eosinophils is somehow connected with degranulation of the mast cells.

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