

Role of allergy in nasal polyposis: A review

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We propose a multivariate theory for the pathogenesis of nasal polyps. Turbulent flow of air in the lateral wall of the nose or viral-bacterial-host interactions produce an inflammatory change in the mucosa of the lateral wall of the nose. Ulceration and prolapse of the submucosa with reepithelialization and new gland formation may then follow. The structural cells of the nasal polyp, including epithelial cells and fibroblasts, have the ability to produce messenger RNA for granulocyte-monocyte colony-stimulating factor and other cytokines. Stimulation of such an effector capability by structural cell-derived cytokines would undoubtedly represent a major amplification pathway of the inflammatory response in nasal polyps. Allergy may be one mechanism for the development of this cascade of events. This microenvironmental structural inflammatory response in the nasal polyp, in turn, can affect the bioelectric integrity of the Na⁺ and Cl⁻ channels at the luminal surface of the respiratory epithelial cell. The change in the Na⁺ absorption, which has been demonstrated in our studies, may result in an increased movement of water into the cell and into the interstitial fluid. The resultant edema can lead to growth and enlargement of the nasal polyp. Finally, the rapid recurrence of nasal polyps despite adequate surgery may reflect some intrinsic phenotypic characteristic of nasal epithelial cells in the lateral wall of the nose, which is likely to be under genetic control. (OTOLARYNGOL HEAD NECK SURG 1995;113:724-32.)

In spite of recent advances in basic science, particularly immunology and molecular biology, the cause and pathogenesis of nasal and paranasal polyposis have still not been clarified. More specifically, the role of allergy, or IgE-mediated hypersensitivity, is still controversial. During the last decade, our laboratory has been addressing two aspects of this problem: (1) the distribution of antigen-presenting cells, immunocompetent cells in the nasal mucosa and nasal polyps, and both eosinophils and basophiloid cells in nasal polyps and have compared them to inferior turbinate mucosa from the same patients; and (2) the ion flux of sodium and chloride in these same tissues. The results of these studies and a review of the literature suggest that nasal polyps represent a *de novo* inflammatory growth arising from the lateral wall of the nose or the anterior ethmoidal air cells.

The purpose of this article is to summarize our work and review the concept of the microenvironmental differentiation hypothesis of nasal airway inflammation.¹ On the basis of this information, a theory for the development of nasal polyps will be considered.

DEFINITION

Nasal polyps represent, macroscopically, edematous tissue, yellowish to clear in appearance and soft in consistency in comparison with the middle turbinate. Histologically, the polyps are very clearly different than normal nasal mucosa, consisting of respiratory epithelium covering very edematous stroma infiltrated by a number of inflammatory cells with eosinophils predominating in most specimens. It is to be emphasized that one of the critical differences between normal nasal mucosa and the nasal polyp is the number and cytoarchitecture of the glands. The density of the glands in nasal polyps is significantly less than in the normal turbinate mucosa and demonstrates no evidence of true seromucinous gland development as in the inferior and middle turbinates. Finally, the density of eosinophilic and basophiloid cells is markedly greater in the nasal polyp than in the inferior turbinate.²

All of these findings together suggest that the nasal polyp is an inflammatory growth that is controlled by the local microenvironment. This concept

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Table 1. Epidemiology of nasal polyposis (the role of allergy)

Investigators	Year	No. of patients	Incidence of polyps
Caplin et al. ⁸	1971	3000	0.5%
Settipane and Chafee ⁹	1977	6000	Allergic asthma (5%) Nonallergic asthma (13%) Allergic rhinitis (1.5%) Nonallergic rhinitis (5%)
Drake-Lee and Pitcher-Wilmott ¹⁰	1984	200	No difference in histamine levels in polyps in patients with or without allergy
McMaster group ¹⁻⁷	1990s	50	Epithelial mast cells and eosinophils in polyps are no different in patients with and without allergy

has been championed by the McMaster group during the last decade.¹⁻⁷ These investigators in elegant molecular biologic studies have demonstrated consistently that various colony-stimulating factors and interleukins produced by constitutive cells such as epithelial cells and fibroblasts of the nasal polyp result in the up-regulation of inflammatory cells. These colony-stimulating factors and interleukins recruit, stimulate, and prolong the survival of various inflammatory cells such as eosinophils and mast cells. This vicious cycle of recruitment of inflammatory cells by interleukins and colony-stimulating factors and the secretion of interleukin-3 by eosinophils results in an autocrine up-regulation of inflammatory cells. There is some evidence that this microenvironmental hypothesis of airway inflammation is under some type of genetic control, either systemically or at the level of the nasal airway. With these concepts in mind, the role of allergy is of importance in that it is one of several possible immunologic mechanisms whereby mast cell mediators and eosinophils are recruited into the microenvironment of the nasal polyp.

EPIDEMIOLOGY

Several studies incorporating analysis of a large number of patients with nasal polyposis have been published and are summarized in Table 1. Twenty years ago, Caplin et al.⁸ evaluated 3000 atopic patients and found that only 0.5% had nasal polyps. Settipane and Chafee⁹ analyzed more than 6000 patients with asthma or allergic rhinitis and found nasal polyps were most common in nonallergic patients with asthma older than 40 years. In the adult asthmatic group, nasal polyps were present in 13% of intrinsic nonallergic patients and in only 5% of allergic patients with asthma. The same tendency was seen in chronic rhinitis patients, with nasal polyps present in 5% of nonallergic subjects and in only 1.5% of subjects with allergic rhinitis.

Using careful history and skin and radioallergosorbent testing, Drake-Lee and Pitcher-Wilmott¹⁰ found no evidence of increased incidence of allergic disorders in 200 consecutive patients admitted for polypectomy. Furthermore, they found no difference in polyp histamine levels in patients with and without allergic rhinitis. Ruhno et al.¹¹ noted that the increased number of epithelial mast cells in nasal polyps and adjacent turbinates was not IgE dependent. This is also true for eosinophils in that the number of eosinophils is independent of the allergic status of the patient. Taken together, these studies would not support allergy as a common cause of nasal polyposis. Slavin,¹² in reviewing the relationship between allergy and nasal polyposis, quite bluntly stated that allergy is not a significant cause of nasal polyps and believed that an allergy workup is extremely cost-effective in instances such as allergic rhinitis, bronchial asthma, and anaphylaxis but that the routine allergic evaluation of patients with nasal polyps should be discouraged in the name of health care cost containment.

HISTOLOGY AND IMMUNOHISTOLOGY OF NASAL POLYPS

The conventional histology of the inferior and middle turbinates is well known. The inferior turbinates contain stratified squamous epithelium or pseudostratified columnar ciliated epithelium, under which a thickened basement membrane is noted in 70% of the samples that we have observed (Figs. 1 and 2). Multiple seromucinous glands are present in both superficial and deep layers and are separated by large venous sinusoids. The histology of the middle turbinates is very similar to that of the inferior turbinates, but with slightly more inflammatory cells. In contrast of this, the histologic appearance of nasal polyps varies from extremely edematous tissue with very few glands to tissue that has scattered glands. The unique features of nasal pol-

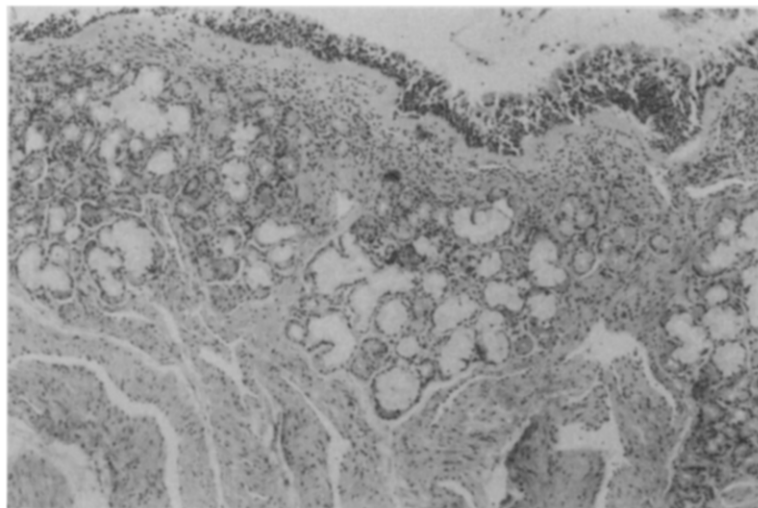


Fig. 1. Section of inferior turbinate. Typical morphology of inferior turbinate is shown with pseudostratified squamous epithelium and typical seromucinous glands. Note large arterioles at the bottom of figure. (Hematoxylin and eosin stain; original magnification $\times 100$.)

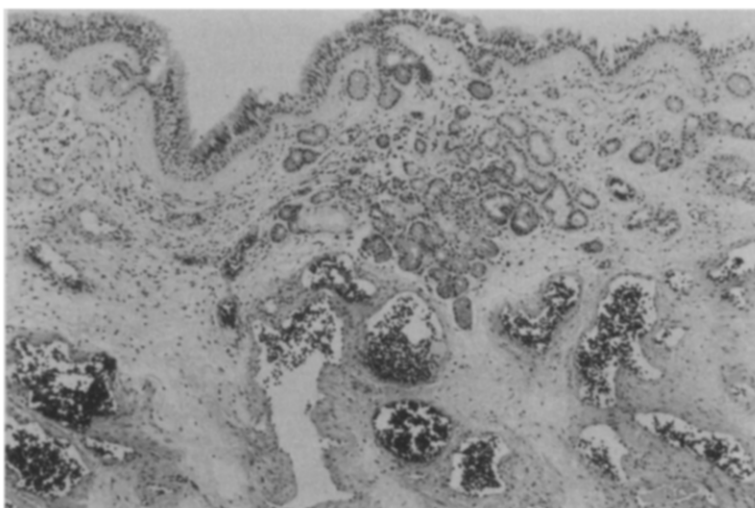


Fig. 2. Section of middle turbinate showing respiratory epithelium covering seromucinous glands and dilated sinusoids. (Hematoxylin and eosin stain; original magnification $\times 100$.)

yps are (1) an irregularity of the morphology of the cystically dilated glands, (2) a virtual absence of true seromucinous glands as found in the inferior and middle turbinates, and most importantly, (3) a large accumulation of inflammatory cells, particularly eosinophils (Fig. 3). The distribution of IgG subclasses in the nasal polyps is summarized in Fig. 4. In general, IgG₁, IgG₂, and IgG₃ can be found in the periglandular areas of the inferior and middle turbinates. The average number of cells is usually 1 to 10 immunocytes per high-power field. In general, there are more immunocytes synthesizing IgG in the

nasal polyps than in the inferior or middle turbinates.

IgA represents the most common immunoglobulin synthesized locally in the nasal mucosa (Fig. 5). This is true for all areas of the nasal mucosa and nasal polyps. In general, there are more IgA₁-producing cells than IgA₂-producing cells; however, they appear to have different distributions. For example, there are more IgA₁ plasma cells that are seen; however, IgA₂ appears to be present in the apices of the acinar and epithelial cells in contrast to IgA₁. However, IgA-producing plasma cells far out-

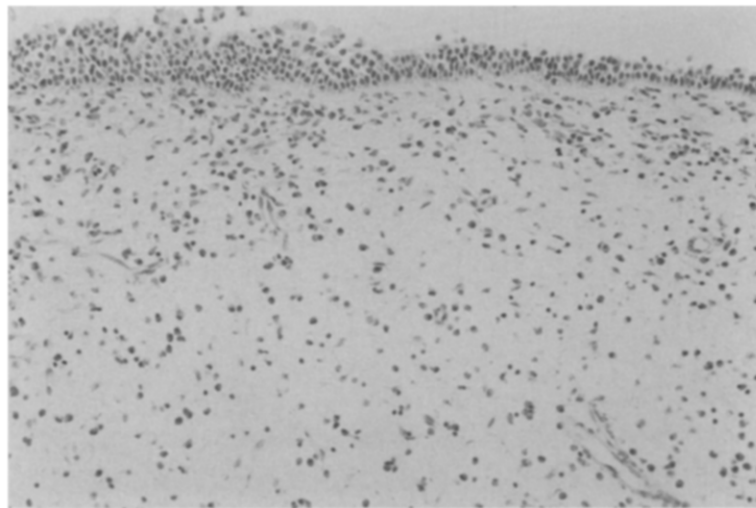


Fig. 3. Typical morphology of a nasal polyp with respiratory epithelium covering a very edematous stroma with multiple inflammatory cells that are mainly eosinophils. (Hematoxylin and eosin stain; original magnification $\times 200$.)

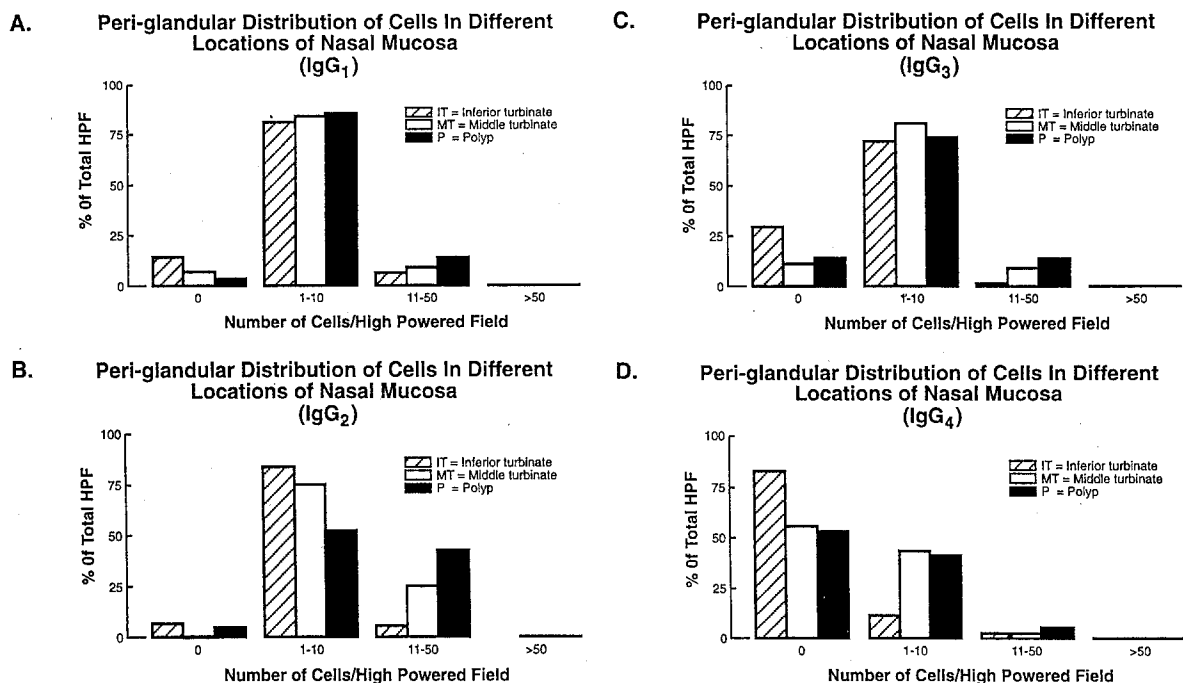
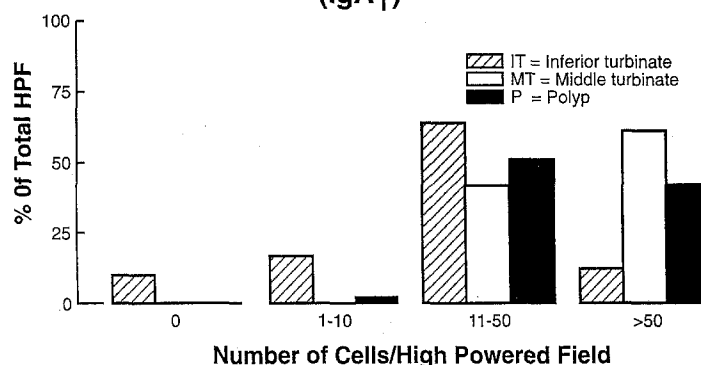


Fig. 4. Periglandular distribution of cells in different locations of nasal mucosa: **A**, IgG₁; **B**, IgG₂; **C**, IgG₃; **D**, IgG₄. HPF, High-power field.

number IgG-producing plasma cells in the nasal mucosa and the nasal polyps, and as such, the nasal mucosa and the nasal polyps represent part of the local secretory immune system. Other immunoglobulins such as IgM and IgD are also found.

Antigen-presenting cells such as macrophages are found in highest quantities in the nasal polyps in comparison with both the middle turbinates and inferior turbinates (Fig. 6). Furthermore, there are more B cells found in the nasal polyps than in the

**Peri-glandular Distribution of Cells In Different
Locations of Nasal Mucosa
(IgA₁)**



**Peri-glandular Distribution of Cells In Different
Locations of Nasal Mucosa
(IgA₂)**

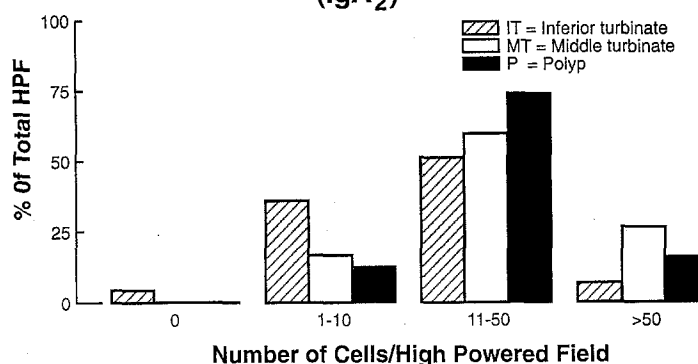


Fig. 5. Periglandular distribution of cells in different locations of nasal mucosa: IgA₁ (top) and IgA₂ bottom. HPF, High-power field.

Table 2. Maximal bioelectric properties of cultured human nasal polyp and turbinate epithelial cells

Tissue	n	V _i (mV)*	R _i (Ω · cm ²)*	I _{sc} (μA/cm ²)*
Polyp (12 patients)	37	-11.2 ± 1.5	243 ± 15	43.6 ± 4.2
Turbinate (7 patients)	9	-5.3 ± 1.4	187 ± 24	28.5 ± 5.7

*Expressed as mean ± SE.

inferior turbinate. Finally, it is interesting to note that secretory component, which is the receptor for the J chain, stains very heavily in the middle and inferior turbinate mucosa, but its synthesis in the surface epithelium and glands is markedly reduced in the nasal polyps. Taken together, the nasal polyps appear to be tissue in which there is an up-regulation of antigen-presenting cells and immunocompetent cells such as B cells and immunocytes, and, most

importantly, there is a significant increase in the number of eosinophils and mucosal and connective tissue mast cells in nasal polyps compared with the inferior turbinates. Furthermore, the presence of eosinophils and mast cells does not appear to be related to the presence or absence of allergy in the patients. This work from our laboratory confirms the work from the McMaster group, which also emphasizes the lack of relationship between IgE-mediated

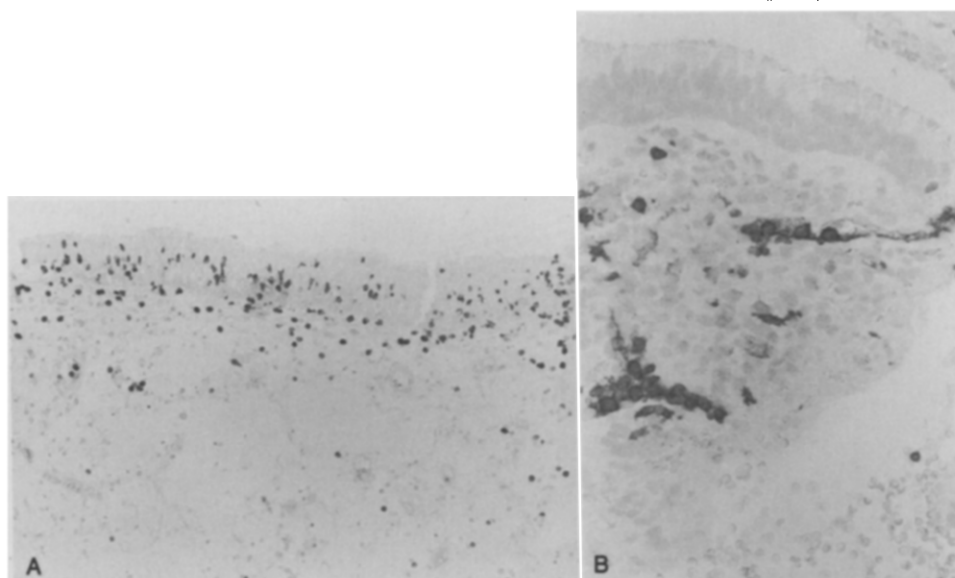


Fig. 6. **A**, MAC 387 staining for macrophage in the nasal polyp showing significant staining of interepithelial cells as well as in the lamina propria. (Immunoperoxidase stain; $\times 200$.) **B**, MAC 387 staining in nasal polyp showing significant margination of monocytes in blood vessels of the nasal polyp. (Immunoperoxidase stain; original magnification $\times 400$.)

Table 3. Bioelectric properties of cultured human nasal polyp and turbinate epithelial cells

Condition	Polyps ($n = 21$)			Turbinates ($n = 3$)		
	V_t (mV)	R_t ($\Omega \cdot \text{cm}^2$)	I_{eq} ($\mu\text{A}/\text{cm}^2$)	V_t (mV)	R_t ($\Omega \cdot \text{cm}^2$)	I_{eq} ($\mu\text{A}/\text{cm}^2$)
Basal	-7.8 ± 1.2	173 ± 16	44.1 ± 6.2	-2.4 ± 1.0	103 ± 17	20.8 ± 6.6
Amiloride (10^{-4} mol/L)	$-4.0^* \pm 0.5$	$208^* \pm 20$	$20.6^* \pm 2.0$	-1.1 ± 0.3	104 ± 15	10.4 ± 1.5
Isoproterenol (10^{-5} mol/L)	$-4.3^* \pm 0.5$	194 ± 15	$22.8^* \pm 2.2$	-1.3 ± 0.4	100 ± 16	12.7 ± 2.9
ATP (10^{-4} mol/L)	$-6.7^* \pm 1.1$	$142^* \pm 13$	$64.0^* \pm 11.4$	-1.7 ± 1.8	77 ± 15	30.6 ± 11.1

All data expressed as mean $\pm$ SE.

*Significant change from preceding value, $p < 0.01$, with paired t test.

hypersensitivity and the presence of metachromatic cells and/or eosinophils in the nasal polyps.

BIOELECTRIC PROPERTIES OF CULTURED POLYP AND TURBINATE EPITHELIAL CELLS

In collaboration with Dr. James Yankaskas, our laboratory has studied the voltage (V_t), resistance (R_t), and short circuit current (I_{eq}) of cultured polyp and turbinate epithelial cells.¹³ Most polyp specimens cultured in collagen matrix support dishes produce measurable and significant bioelectric properties. The maximal voltage, resistance, and short circuit currents of these cultures are summarized in Table 2. The most striking observation is the increased voltage and short circuit currents in polyp

cells compared with that in turbinate cells. We have found this to be the case both in polyps from patients with cystic fibrosis (CF) and in non-CF polyps. To evaluate the regulatory pathways of ion transport, specimens have been evaluated in Ussing chambers under basal conditions and during exposure to selected chemicals such as amiloride, isoproterenol, and adenosine triphosphate (ATP). The overall results are summarized in Table 3. The basal current was significantly decreased by amiloride and was increased by both isoproterenol and ATP. Turbinate cultures had similar, but smaller, responses. Similar studies in CF cultures (data not shown) demonstrated the ion transport regulatory properties that characterize CF. In particular, amiloride caused a

dramatic decrease in I_{eq} , and there was no response to isoproterenol, but the ATP response was retained.

DISCUSSION

Numerous hypotheses have been formulated to explain the cause of nasal polyps. Although theories involving dysfunction of the autonomic nervous system of the nose¹⁴ and abnormalities of carbohydrate metabolism¹⁵ and vasomotor imbalance¹⁵ have been suggested, the two most plausible, widely discussed theories involve allergy¹⁶ and inflammation.¹⁷

Mechanisms other than allergy, however, appear to be involved in the accumulation of inflammatory cells in nasal polyps because of the observed increase in the number of mucosal mast cells in the nasal turbinate epithelium of patients with polyps who do not have IgE-mediated hypersensitivity¹¹ and the epidemiologic data strongly suggesting that nasal polyposis occurs more commonly in nonatopic patients than atopic patients.⁹ This study confirms and extends the observations of Tos et al.,¹⁸ who argue that nasal polyps cannot represent edema of the nasal mucosa. Polyps are very different histologically from normal mucosa because there are no seromucinous glands in nasal polyps and the prominent cell in the nasal polyp is the eosinophil.

Nasal polyps appear to arise either from the lateral wall of the nose or from the anterior ethmoid sinus mucosa. Although nasal polyps may also arise from the maxillary sinus and sphenoid sinus, by far the most common areas are the lateral wall of the nose and the anterior ethmoidal sinus mucosa. Nasal polyps therefore arise in areas in which the aerodynamics are different from those in the lower third of the nose.¹⁹ In the lateral wall of the nose there is an increased turbulence of air molecules and therefore a greater chance for irritative factors to deposit in this area and trigger inflammation. The data from our laboratory demonstrate a significantly greater number of immunocompetent cells in the middle turbinate and polyps than in the inferior turbinate mucosa. Furthermore, there are many more inflammatory cells, particularly eosinophils, in the lateral wall of the nose than in the inferior turbinate. There appears to be a progressive increase in the number of antigen-presenting cells and plasma cells synthesizing immunoglobulins as one ascends in the nose from the inferior turbinate to the middle turbinate. Thus the immunologic response and the host response are greater in the areas in which nasal polyposis occurs.

Our findings agree with the studies of Brandtzaeg.^{20,21} We observed a slightly higher frequency of

IgA₂-positive immunocytes in our patients than has been described by Brandtzaeg, although IgA₁-positive cells were by far more common, as has been shown. Intracellular IgA₂ may have been especially well preserved in the plasma cell cytoplasm of the formalin-fixed tissues that were used for our studies. In the tonsil tissue that served as control, the distribution and frequency of IgA₁- and IgA₂-positive cells were identical to those of previous reports,²² confirming the validity of reagents and tissue-processing protocols used in the study.

Secretory component is not observed exactly in the same intracellular distribution as IgA₂. Whereas IgA₂ appears to be limited to a site around the nucleus in the respiratory epithelial cells, antibodies to secretory component stain the entire cytoplasm of the respiratory epithelial cells. In the serous glands, IgA₂ is most frequently located in the apical portion of the epithelial cells, whereas antibody to secretory component stains the entire cytoplasm of serous gland epithelial cells.

Our observations are similar to those of Stoop et al.,^{23,24} who also demonstrated that local immunologic and inflammatory processes play a prominent role in the development of nasal polyps. In their studies eosinophil infiltration was a striking feature in many nasal polyps; eosinophils were significantly increased in nasal polyps compared with the mucosa of the middle and inferior turbinates. Stoop et al.^{23,24} have also identified an abundance of HLA-DR-positive cells in the stroma and epithelial regions of nasal polyps and middle turbinates compared with inferior turbinates. Our observations agree that HLA-DR cells are more prominent in the lamina propria of nasal polyps than in the inferior turbinate mucosa, although we could not corroborate the presence of HLA-DR-positive cells in the epithelia of either the middle turbinates or nasal polyps.

Structural cells such as epithelial cells and fibroblasts, as well as vascular endothelial cells of nasal polyps from both atopic and nonatopic patients, can secrete cytokines and growth factors.³⁻⁷ Those mediators are capable of stimulating cell differentiation and modulating function of blood-borne, bone marrow-derived cells. The studies at McMaster University emphasize the importance of microenvironmental influences on allergic and non-allergic airway inflammation and point out potentially new approaches to the diagnosis and therapy of nasal polyposis, allergic rhinitis, and asthma. Our study and the above-mentioned investigations support the idea that inflammation is the predominant mechanism involved in the development of nasal polyposis. The precise order and sequence of interactions

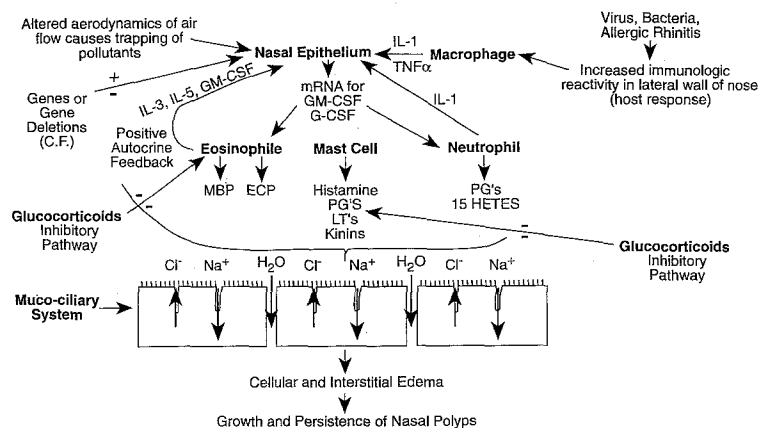


Fig. 7. Multivariate hypothesis for pathogenesis of nasal polyposis. *IL*, Interleukin; *TNF α* , tumor necrosis factor- α ; *GM-CSF*, granulocyte-monocyte colony-stimulating factor; *G-CSF*, granulocyte colony-stimulating factor; *MBP*, major basic protein; *ECP*, eosinophilic cationic protein; *PG's*, prostaglandins; *LT's*, leukotrienes; *HETES*, hydroxyeicosatetraenoic acids.

within this inflammatory tissue and the development of nasal polyposis in general is not known. However, these inflammatory mediators may have an effect on the movement of electrolytes into the cell and out of the cell in such a way that water retention occurs within the cell and in the lamina propria, leading to edema, which is the fundamental pathologic finding in nasal polyps.

In CF there is an extraordinarily high incidence of granulomatoid polypoid disease in the sinuses and nasal cavity. However, in this disease there is a defect in the CF transmembrane regulator gene-dependent Cl^- channel as a result of a single codon deletion or other mutations in the CF transmembrane regulator gene on chromosome 7.²⁵ This defect leads to absence or dysfunction of the cyclic AMP-dependent Cl^- channel on the luminal surface of the respiratory epithelial cell to develop properly. As a result there is an inability for the respiratory cell in CF to secrete Cl^- , at least after cyclic AMP activation of protein kinase A.²⁵ The data from our study suggest that the nasal polyp epithelial cell in patients without CF has a normal luminal Cl^- channel. However, the other defect in CF is the significant increase in Na^+ absorption across the cell,²⁶ and indeed, in nasal polyps from both patients with and without CF, there is an abnormal Na^+ absorption. We have suggested that this increase Na^+ absorption may be related to the increased levels of inflammatory mediators in nasal polyps, which in turn could lead to water retention in the polyp epithelial cell and in the lamina propria of the nasal polyps.²⁷

Despite the fact that excellent and meticulous surgery can relieve the patient of nasal obstruction, there is unfortunately a very high recurrence rate of polypoid mucus membrane in some patients with nasal polyposis. This is particularly true in CF and in patients with aspirin intolerance.²⁸ In the latter disorder there is an extraordinarily high percentage of eosinophils in the nasal polyps and nasal mucosa. Although there is little information on the genetic control of the nasal mucus membrane, there is a suggestion that this tendency for polypoid recurrence may be under genetic control.²⁹

The success of glucocorticoids in the medical treatment of nasal polyps is probably related to a number of factors, which include the inhibition of synthesis of multiple cytokines derived from eosinophils and basophils in nasal polyps.³⁰

On the basis of the information presented in this article, we propose a multivariate theory for the pathogenesis of nasal polyps. An overview of this hypothesis is reviewed schematically in Fig. 7. Turbulent flow of air in the lateral wall of the nose or viral-bacterial-host interactions produce an inflammatory change in the mucosa of the lateral wall of the nose. According to the theory of Tos et al.,¹⁸ there may be ulceration and prolapse of the submucosa with reepithelialization and new gland formation. This may be the beginning of a nasal polyp. The structural cells of the nasal polyp, including the epithelial cells, vascular endothelial cells, and stroma, all have the ability to produce messenger RNA for granulocyte-monocyte colony stimulating factor. Stimulation of such an effector capability by

structural cell-derived cytokines would undoubtedly represent a major amplification pathway of the inflammatory response in nasal polyps. This microenvironmental structural inflammatory response in the nasal polyp, in turn, can affect the bioelectric integrity of the Na^+ and Cl^- channels at the luminal surface of the respiratory epithelial cell. The change in the Na^+ absorption that has been demonstrated in our studies may result in an increased movement of water into the cell and into the interstitial fluid. The resultant edema can lead to growth and enlargement of the nasal polyp. Finally, the rapid recurrence of nasal polyps despite adequate surgery may reflect some intrinsic phenotypic characteristics of nasal epithelial cells in the lateral wall of the nose, which is likely to be under genetic control. The complex interaction of cytokines and colony-stimulating factors derived from such nasal epithelial cells has an effect on Na^+ absorption and Cl^- permeability. These events may result in recurrent development of edematous mucosal disease of the lateral wall of the nose, namely, recurrent nasal polyposis.

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