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Pathogenesis of nasal polyps

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SUMMARY

On the basis of studies on the glands of the nasal mucosa and polyps as well as the structure of the latter, some previous pathogenetic theories are analysed. The authors advance their own theory of polyp formation: Infiltration and oedema in the nasal mucosa result in rupture of the epithelium and formation of granulations which gradually become lined with pseudostratified columnar epithelium. During growth of the polyp there occurs formation of mucous glands which owing to growth of the polyps become long and stretched.

IN our previous studies using the whole-mount method we have described the distribution and density of the mucous glands in the nasal mucosa of foetuses (Tos and Mogensen, 1976 a), neonates (Mogensen and Tos, 1976), and adults (Tos and Mogensen, 1976, b and c). The density increases evenly from the 15th foetal week until birth at which it is 34 glands/mm^2. At that time physiological new-formation has been completed. Through childhood there is a gradual fall of density; in adults it is 7-8 glands/mm^2 in the lateral wall and 8-9 glands/mm^2 on the septum. The glands are tubulo-alveolar, seromucous, and in most areas distributed in two layers: A deeper layer in which the gland mass is situated most profoundly in the lamina propria and a fairly long duct coursing vertically to the surface, and the superficial layer having somewhat smaller glands with short ducts of a subepithelial situation.

By the same methods we have studied 102 nasal polyps (Tos and Mogensen, 1976 d). All polyps held glands, but many of them only a few. In the majority the density was less than 0.5 gland/mm^2. These glands were tubular, simple or branched, very different from those in the nasal mucosa, forming from the surface epithelium of the polyp after the latter had attained a certain size. None of the glands in the polyps were derived from the original nasal mucosa, and they did not grow from the nasal mucosa into the polyp. Owing to stasis of mucous flow, the majority of glands gradually degenerated, dilated, and the secretory epithelium became inactive, leading to cysts in the polyps. Particular interesest attaches to 1-8 mm long tubular glands whose orifice was often situated in the distal half of the polyps and the tubule running parallel with the long axis of the polyp and towards its stalk (Figure 1). These glands have been passively stretched during growth of the polyp.

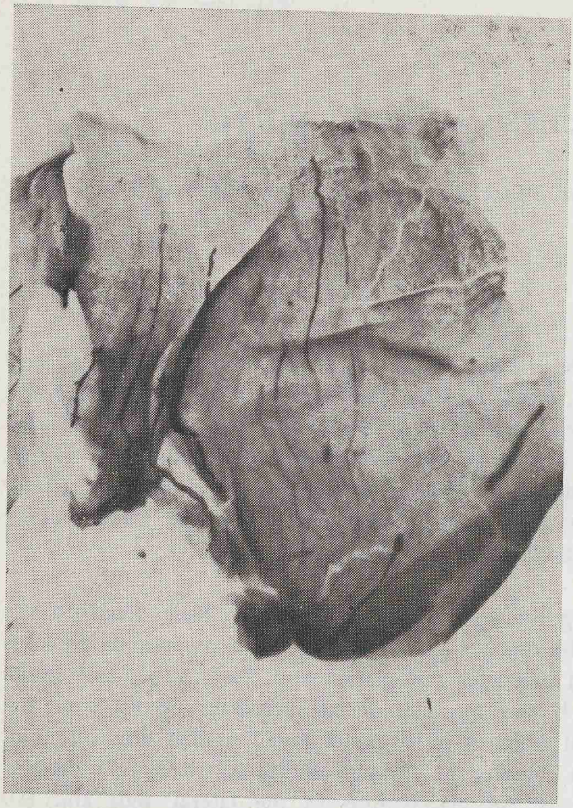


Figure 1. Several long, tubular glands whose orifices are caudally in the polyp and whose tubules course parallel with the long axis of the polyp up towards its stalk.
PAS-alcian blue-stained whole mount x 10.

Quantitative studies of glands in the nose and other parts of the respiratory tract have shown that the glands do indeed degenerate and become inactive, but they do not disappear. Therefore, analysis of the distribution, situation, shape, and architecture of glands in the polyps and in the nasal mucosa may form the basis of studies on the genesis of the polyp as well as of a critical analysis of previous pathogenetic theories. Some of these theories are based upon the glands and cysts of the polyp and upon the glands of the nasal mucosa.

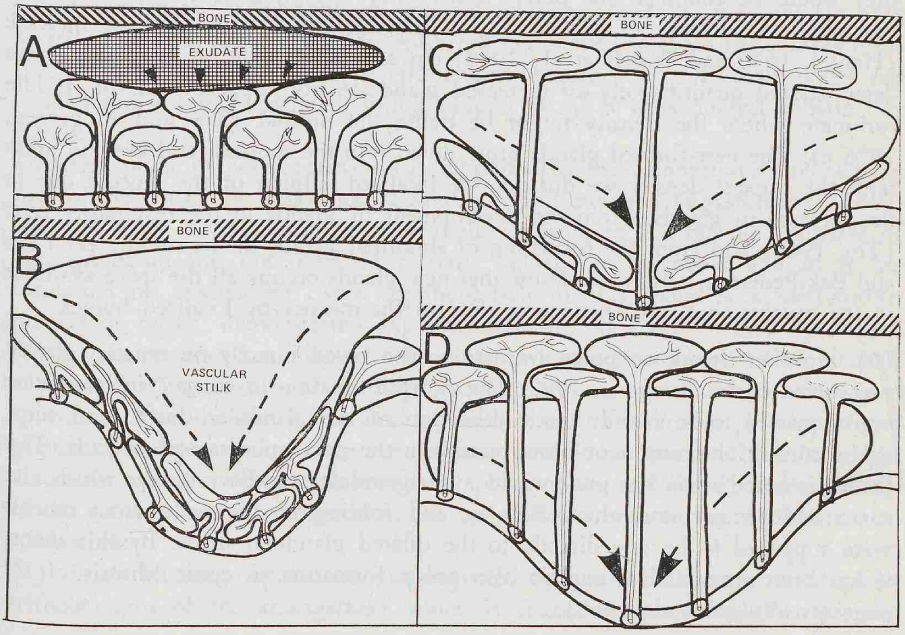
PATHOGENETIC THEORIES

(1) Older theories that owing to a content of many glands the polyp is an adenoma (Billroth, 1855), owing to lack of glands a soft fibroma (Hopmann, 1885), or myxomatous degeneration of the mucosa (Mackenzie, 1884) were refuted already in the past century, int. al. by Zuckerkandl (1892) who regarded polyps as inflammatory hyperplasia of the nasal mucosa. So was Woakes' (1885) theory that necrotising ethmoiditis leads to necrosis of bony septa and to a myxomatous focus projecting from the ethmoid into the nose in the form of a polyp (Zuckerkandl, 1892 and Hajek, 1896).

(2) Unlike Woakes (1885), Hajek (1896) believed that the formation of a polyp started in the nasal mucosa by an accumulation of effusion (Figure 2 a) which was pressed caudally. A vascular stalk would form, and vascular congestion would increase the volume of the polyp. Hajek's pathogenesis still has many adherents. On the basis of gland findings, we shall try to comment on it: According to this theory, the distal part of the polyp is supposed to contain seromucous nasal glands. We found none. Furthermore, these glands are supposed to be of a special situation and shape, compressed subepithelially in the polyp (Figure 2 b). This was also not found in whole mounts or in sections. On the other hand, we demonstrated that all glands of the polyp form after the polyp has attained a certain size and that none of the glands were derived from the nasal mucosa.

(3) Eggston and Wolff's theory (1947), which also has many adherents, is based upon the demonstration of chronic vascular changes in the nasal mucosa. Recurrent infections lead to periphlebitis and perilymphangitis, which again leads to blocking of intercellular fluid transport in the mucosa and oedema of the lamina propria. If the oedema involves major areas, the result is prolapse of the mucosa and the formation of polyps.
This theory also does not fit into our findings of the distribution of glands in the nasal mucosa and in polyps: If the oedema forms predominantly deep in the lamina propria, beneath the deepest glandular layer, this would lead to the situation already discussed under Hajek's theory (Figures 2 a and b). If the

Figure 2. Schematic presentation of Hajek's (a and b) and Eggston and Wolff's (c and d) theories on polyp formation and distribution of glands (cf. text).



oedema arises predominantly between the deeper and the superficial layers of glands (Figure 2 c), the superficial layer will be pressed into the polyps and would be found there — but we did not. The ducts from the deeper layer of glands would be stretched and gradually fairly long, coursing through the stalk of the polyp, while the gland mass would be pressed up towards the bone. Such glands were not found by us in the stalk. If the oedema is localised predominantly subepithelially, i.e. between the epithelium and the superficial layer of glands, the epithelium would bulge out in the form of a polyp and pull along the ducts of the nasal glands (Figure 2 d). In that case, the stalk would be supposed to contain many long ducts of a caudal direction, which we did not find, as stated already. That the gland ducts may be stretched and shaped according to the space available was demonstrated during the development of the glands in the lower respiratory tract (Tos, 1966) and in the nose (Tos and Mogensen, 1976 a). A particularly convincing example of gland stretching may be observed during the development of adenoid vegetations at the top of the rhinopharynx (Tos, 1976): The glands form and develop in the middle of the lamina propria. Thereafter, the development of lymphoid tissue starts between the gland layer and the epithelium. As the lymphoid tissue thickens, the glandular ducts are not torn, but enormously elongated, while the gland mass is pressed into the basal direction.

(4) Krajina (1963) believes that in the course of chronic infectious or allergic actions there will occur localised infiltrates in the nasal mucosa and localised increase of nasal glands which will cause bulging of the mucosa. If the glands of the nasal mucosa were to cause mucosal bulging and polyp formation directly, they would be found in the polyp, which they were not. Several authors have described an increase of glands in allergy, but not a circumscribed increase (Hansel, 1930 and Puskás et al., 1969). In an autopic case of nasal allergy we demonstrated quantitatively an increased gland density, especially in the middle turbinate where the density might be treble the normal (Tos and Mogensen, 1976 e). The new-formed glands grow down into the mucosa, and even in areas with the highest density we did not see localised bulging of the mucosa due to the increase in glands. From the development of glands in the respiratory tract (Tos, 1966) and from the formation of abnormal glands in the middle ear (Tos and Bak-Pedersen, 1972), we know that new glands occupy all the space available in the mucosa, but that they never deform the mucosa by localised bulges.

(5) Another theory on polyp formation, also based directly on mucous glands, was advanced by Yonge in 1907. The polyp formation in chronic inflammation was supposed to be mainly cystic dilatation of the glandular ducts and acini, again causing obstruction of blood vessels in the nasal mucosa and oedema. This theory is based upon the presence of a periglandular capillary plexus which also surrounds the excretory duct. Bulging and folding of the oedematous mucosa were supposed to be due directly to the dilated glandular ducts. By this theory it has been attempted to explain also polyp formation in cystic fibrosis of the pancreas (Rulon et al., 1963).

According to our investigations cystic dilatation occurs particularly among new-formed abnormal glands. Thus, in certain diseases of the middle ear up to 90% of the glands show cystic dilatation, without any prominences or bulging of the mucosa (Tos, 1974). In an allergic nose there is rarely dilatation of the glands, and we have never seen such a glandular dilatation that might result in bulging of the mucosa and polyp formation (Tos and Mogensen, 1976 e). A considerably more common finding is degeneration in atrophic rhinitis (Holopainen, 1967), in which the mucosa is thin without polyp formation.

The formation of cysts is due to stagnation of mucous flow in the gland (Tos and Bak-Pedersen, 1972), whose epithelium gets thin and loses its secretory activity. This per se will stop further growth of the cyst. Moreover, an increased pressure in the cyst will lead to rupture of its epithelium rather than the formation of mucosal bulges. Cysts, often found in the polyps, represent degenerated glands which have formed in the polyps and have no connection with the nasal mucosa.

PRESENT PATHOGENETIC THEORY

It was attempted to clarify that the polyp formation does not include a prolapse or bulging, of the epithelium alone, of the epithelium and part of the lamina propria, or of the entire mucosa. Moreover, it was demonstrated that the glands of the nasal mucosa are not involved in the formation of polyps, either in their active or in their degenerated, cystic form.

As the polyp arises from the nasal mucosa, there remained only one possibility, viz. *rupture of the epithelium* as a result of tissure pressure from an oedematous and infiltrated nasal mucosa (Figure 3 a). The infiltrated and oedematous lamina propria prolapses, in the form of granulation tissue, caudally, the vascular stalk is established, and at the same time epithelisation of the prolapsed tissue takes place from the edges of the ruptured epithelium (Figure 3 b). A small polyp has formed and acquired epithelial lining (Figure 3 c). It does not yet contain any glands.

This first phase of polyp formation is supported by the demonstration of oedema and infiltration of the nasal mucosa in allergy and infection (Eggston and Wolff, 1947; Krajina, 1963) which increase tissue pressure in the mucosa. Rupture of the epithelium was not observed directly, but is very probable, and so is the formation of granulation tissue. Epithelisation of this tissue is a well-known process of repair, demonstrated experimentally in the nasal mucosa by Burian (1960). In studies of middle-ear polyps we have seen granulation tissue, situated in a marginal perforation of the drum, acquire on one side stratified, keratinised epithelium from the skin of the auditory meatus, on the other side pseudostratified ciliated epithelium arising from a metaplastic middle-ear mucosa. New-formation of glands was also demonstrated in aural polyps (Tos and Bak-Pedersen, 1974). In the nasal polyps investigated by us we observed several forms of stratified epithelium:

(1) Fairly immature epithelium predominated by basal cells having round nuclei without signs of the arrangement which is characteristic of columnar pseudo-

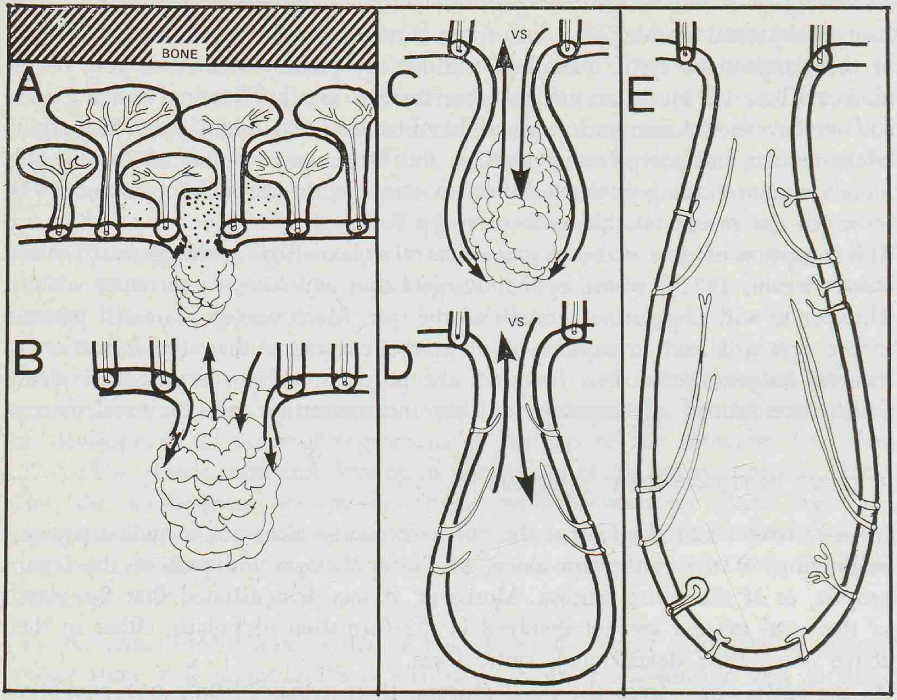


Figure 3. Schematic presentation of authors' theory on polyp formation.
(a) Infiltrate and oedema of the nasal mucosa with two layers of glands, rupture of the epithelium, and formation of granulation tissue.
(b and c) Epithelisation of the granulation tissue and formation of the vascular stalk (VS).
(d) Formation of glands.
(e) Passive elongation of the long tubular glands.

stratified epithelium. In whole mounts there were large areas without goblet cells. Such epithelium was found especially in polyps having a very loose stroma, scattered eosinophilia, and round-cell infiltration. As a rule there were only a few, young glands.

(2) Pseudostratified epithelium showing signs of cellular differentiation into ciliated cells and goblet cells. The density of goblet cells in the whole mount was still low.

(3) Typically arranged, completely mature columnar pseudo-stratified epithelium with ciliated cells and goblet cells, in places of very high density.

(4) Transitional epithelium and stratified squamous epithelium of different thickness seen on the largest polyps having a firm stroma in which most glands were old and degenerated. These types were observed in sites facing the nasal cavity, viz. on the most anterior polyp and on the caudal ends of the anterior polyps which are exposed to air. Here, metaplasia of pseudostratified columnar into stratified epithelium has occurred, presumably due to the action of the respiratory air.

The next phase of polyp formation is the development of mucous glands growing from the epithelium into the depth (Figure 3 a). From embryological studies we know that gland formation in the respiratory tract is one link in the differentiation of embryonic epithelium into pseudostratified ciliated epithelium, which takes place in the sequence: First the ciliated cells differentiate, thereafter the glands form, and finally the goblet cells differentiate (Tos, 1966; Tos and Poulsen, 1976). A similar sequence may be traced during the formation of polyps. At the same time, the volume of the polyp increases, according to most authors due to gravity and the haemodynamic conditions with congestion of the venous discharge through the thin stalk (Figures 3 d and e). Through passive growth of the polyp the characteristic, very long, tubular ducts arise (Figures 1 and 3 e), and this explains the much lower density of glands than observed in the nose. With increasing age of the polyp, fibrosing and round-cell infiltration of the stroma increase, the glands degenerate and become cystic.

As already described by Zuckerkandl (1882), polyp formation occurs in certain sites from the middle meatus and the roof of the nose — never from the caudal part of the nasal mucosa which is also infiltrated and oedematous in allergy and infection. Neither do they arise from the mucosa of the lower respiratory tract. In our opinion, the explanation can only be the chronically reduced current of air through the upper part of an allergic and chronically infected nose. This is indeed the corner stone of our pathogenetic theory. In areas with a satisfactory current of air granulations will rapidly be smoothed out and the epithelial rupture will close: The best proof is closure of a tracheostomy. The granulation tissue forming in the stoma, which at first appears as a prominence in the lumen, will quite soon be smoothed out and undergo epithelisation.

Repeated recurrences of polyps are also comprehensible, as the current of air at their site of origin has hardly been essentially improved after polypectomy. New polyps may grow from the stalks of previous ones. Only a radical removal including ethmoidectomy can improve the current of air so as to avoid recurrences. The favourable effect upon polyps of beclomethasone dipropionate (Becotide) (Mygind et al., 1975) is presumably attributable to reduction of the oedema and a better current of air.

RÉSUMÉ

Sur la base d'études portant sur les glandes de la muqueuse nasale, sur les polypes et leur structure, les auteurs analysent les diverses théories pathogèniques. Ils présentent leur propre théorie de la formation des polypes; une infiltration et un oedème de la muqueuse nasale entrainent la rupture de l'épithélium et la formation de granulations qui progressivement sont bordées par un épithélium cylindrique pseudostratifié. Pendant la croissance des polypes, apparaissent des glandes muqueuses, qui en raison de l'augmentation de volume des polypes, deviennent longues et étirées.

REFERENCES

1. Billroth, T., 1855: Über den Bau der Schleimpolypen. Georg Reimer, Berlin.
2. Burian, K., 1960: Über die Restitutionsfähigkeit des Flimmerepithels der Nase nach totaler Zerstörung des Epithels. Z. Laryng. Rhinol. Otol., 39, 387.

3. Eggston, A. A. and Wolff, D., 1947: Histopathology of the Ear, Nose and Throat. Williams and Wilkens, Baltimore.

4. Hajek, M., 1896: Über die pathologischen Veränderungen der Siebbein-Knochen im Gefolge der entzündlichen Schleimhauthypertrophie und der Nasenpolypen. Arch. Laryng. Rhinol., 4, 277.

5. Hansel, F. K., 1930: Clinical and histopathologic studies of the nose and sinuses in allergy. J. Allergy Clin. Immunol, 1, 43.

6. Holopainen, E., 1967: Nasal mucous membrane in atrophic rhinitis with reference to symptomfree nasal mucosa. Acta oto-laryng. (Stockh.) Supp. 227, 1.

7. Hopmann, A., 1885: Über Nasenpolypen. Mschr. Ohrenheilk., 19, 161.

8. Krajina, Z., 1963: A contribution to the aethiopathogenesis of the nasal polyps. Pract. oto-rhino-laryng., 25, 241.

9. Mackenzie, M., 1884: Die Krankheiten des Halses und der Nase. A. Hirschwald. Berlin.

10. Mogensen, Chr. and Tos, M., 1976: Nasal glands in newborn infants. Rhinology. 15, 39, 1977.

11. Mygind, N., Brahe Pedersen, C., Prytz, S. and Sørensen, H., 1975: Treatment of nasal polyps with intranasal beclomethasone diproprionate aerosol. Clin. Allergy, 5, 159.

12. Puskás, F., Módis, L., Jakabfi, I. and Kósa, D., 1969: Histologische und histochemische Untersuchungen bei allergischen Rhinitis. Z. Laryng. Rhinol. Otol., 48, 188.

13. Rulon, J. T., Brown, H. A. and Logan, G. B., 1963: Nasal polyps and cystic fibrosis of the pancreas. Arch. Otolaryng., 78, 192.

14. Tos, M., 1966: Development of the tracheal glands in man. Acta path. microbiol. scan. Suppl. 185, 1.

15. Tos, M., 1974: Production of mucus in the middle ear and Eustachian tube. Ann. Oto-Laryng., 83, 44.

16. Tos, M., 1976: Mucous glands in the developing human rhinopharynx. Laryngoscope. In press.

17. Tos, M. and Bak-Pedersen, K., 1972: The pathogenesis of chronic secretory otitis media. Arch. Otolaryng., 95, 511.

18. Tos, M. and Bak-Pedersen, K., 1974: Density of mucous glands in chronic otitis media. Arch. Otolaryng., 99, 180.

19. Tos, M. and Mogensen, Chr., 1976 a. Dichte der Mukösen Drüsen der foetalen Nase. Z. Laryng. Rhinol. Otol., 55, 21.

20. Tos, M. and Mogensen, Chr., 1976 b. Density of mucous glands in normal adult nasal septum. Arch. Ohr.-Nas.-Kehlkheilk. 214, 125, 1976.

21. Tos, M. and Mogensen,, Chr. 1976 c. Density of mucous glands in normal adult nasal turbinates. Arch. Ohr.-Nas.-Kehlkheilk. In press.

22. Tos, M. and Mogensen, Chr., 1976 d: Mucous glands in nasal polyps. Arch. Otolaryng. In press.

23. Tos, M. and Mogensen, Chr., 1976 e: Nasal glands in nasal allergy. Acta Oto-laryng., Stockh. In press.

24. Tos, M. and Poulsen, J., 1975: Mucous glands in the developing human nose. Arch. Otolaryng., 101, 367.

25. Woakes, E., 1885: Über nekrotisierende Ethmoiditis und ihre Beziehung zur Entwichlung von Nasenpolyppen. Brit. Med. Journ., 4, 701.

26. Yonge, E. S., 1907: Observations on the determining cause of the formation of nasal polypi. Brit. Med. Journ., 12, 964.

27. Zuckerkandl, E., 1882: Normale und pathologische Anatomie der Nasenhöhle und ihrer pneumatischen Anhänge. Vol. II. W. Braumüller, Wien.

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