

On the aetiologic factors in nasal cancer

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SUMMARY

Exogenic factors seem to be of importance in the pathogenesis of nasal tumors. Experimentally these tumors have been produced by administration of various organic N-Nitrosocompounds. These experiments were repeated and expanded by the authors. Contrary to the findings of others no squamous cell carcinomas or adenocarcinomas could be produced in rats. Papillomas and esthesioneuroepitheliomas, however, were frequently found. A hypothesis on the mechanism of action of organic N-nitrosocompounds in the nose is put forward and discussed.

LITTLE is known on the aetiology of tumors in man. In the recent past it has become more and more clear that exogenic factors, chiefly chemical, play an important role. It has been suggested that the above statement is true in about 80% of cases (Haddow, 1970).

It is highly probable that in tumors of the nose and paranasal sinuses exogenous factors also play a significant role. The following examples point towards this view: Acheson, Hadfield and McBeth (1967) found a higher frequency of adenocarcinoma of the ethmoid in woodworkers in the furniture industry. Hadfield and McBeth (1971) have shown that those working with hard wood raw material are more endangered. Adenocarcinoma of the ethmoid was hardly ever found in men working in this industry but who were not exposed to wooddust. These observations were confirmed by Debois (1969) in Belgium and Gignoux and Bernard (1969) in France and the conclusion seems reasonable that the carcinogen is in the wood itself.

The leather industry showed very similar observations: squamous cell carcinoma and adenocarcinoma of the nose and paranasal sinuses are reported in higher frequency in people working with raw leather materials. (Acheson, Cowdell and Jolles, 1970).

The findings of Andrews and Michaels (1968) regarding nasopharyngeal tumors in bushpilots are also worth mentioning here: they found carcinoma of the nasopharynx in 3 bushpilots who flew through the thickly wooded distant parts of Canada. Two of the three tumors found, were of an anaplastic nature and one was a moderately differentiated squamous cell carcinoma. These men had been bushpilots for a period of 10 to 25 years. This is remarkable and significant finding as there are few such pilots.

Andrews and Michaels have suggested that fluctuations in pressure during take

off and landing play an aetiologic role. However prolonged flying over the woods could also play a role because of the presence of a carcinogen in the wood.

No suggestion of the exact nature of the possible carcinogen in wood and leather has been found in a survey of the most recent literature. Further studies on the causative factor should be carried out by experiments in animals in whom squamous cell carcinoma and adenocarcinoma of the nose and nasopharynx can possibly be experimentally induced.

In 1964 Herrold and Druckrey et al. independently produced these tumors in hamsters and rats respectively by the administration of certain organic N-nitrosocompounds. The carcinogenic effect of these compounds on other organs has been known since 1956. (Magee and Barnes).

According to Herrold and Druckrey et al. the nasal tumors are of various histologic types: papillomas, squamouscell carcinomas, adenocarcinomas and certain neuroepithelial tumors, and are indistinguishable from so-called spontaneous tumors arising in the nose and paranasal sinuses in man.

We decided to perform similar experiments with rats and the two main questions we had in mind were: is the rat a suitable experimental animal for reproducing adenocarcinomas and squamous cell carcinomas in the nose and paranasal sinuses, and if so, what is the explanation for the tumors arising especially in the nose when the toxic substances have been administered systemically e.g., subcutaneously? The experiment was initially carried out by a method similar to that of Herrold and Druckrey et al. i.e. known amounts of an organic N-nitrosocompound were administered to the experimental animals until death occurred. Diethyl-nitrosamine was chosen as the toxic agent and administered subcutaneously.

Many doses were experimented with and 7.5 mgm. per kgm. body weight twice weekly was decided upon. The mean survival period was 7 months. Extensive tumors were found and our initial impression was that these were inverted papillomas and poorly differentiated squamous cell carcinomas. The histologic picture was not clear due to the extensive spread of the tumor and hence it was decided upon to kill the animals at different stages and so at monthly intervals a few animals were studied.

This produced a completely different picture of these tumors. The anterior part of the nose (respiratory region) showed inverted papillomas arising next to metaplastic squamous epithelium. The posterior part of the nose (olfactory region) showed proliferation of the basal cells with transition to metaplastic squamous epithelium. Neuroepithelial tumors indistinguishable from esthesioneuroepitheliomas in man were found, and these also arose in the basal cell layer of the olfactory epithelium. Papillary adenomas were found in the olfactory region in a few animals. Squamouscellcarcinomas and adenocarcinomas as described by Herrold and Druckrey were not found. These investigators were most probably misled by the extensive growth and the mixed histologic pattern. In our own experiments we sometimes found a mixture of extensive proliferation of the basalcell layer of the olfactory region and undifferentiated esthesioneuroepithelioma and this looked like squamouscellcarcinoma (Figure 1). Certain areas in the esthesioneuroepithelio-

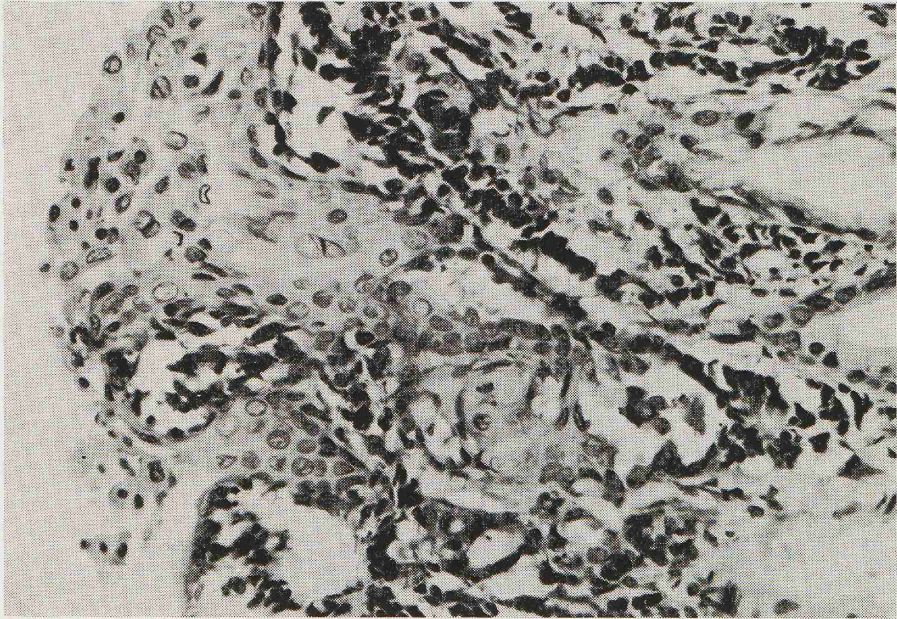


Figure 1. Mixture of extensive proliferation of the basal cell layer of the olfactory region and undifferentiated esthesioneuroepithelioma, suggestive of squamous cell carcinoma. H.E. x 330.

ma showed duct-like structures resembling adenocarcinoma. P.A.S. positive material was never found and an adenocarcinoma is unlikely.

The answer to the first question is that squamous cell carcinoma and adenocarcinoma can not be reproduced in the nose of rats at least not by administering diaethylnitrosamine. It is possible however to produce other types of tumors, (Ewing's papillomas, esthesioneuroepitheliomas) which are also found in man. The part played by N-nitrosocompounds in the aetiology of these tumors in man is not known. The presence of small amounts of N-nitrosocompounds in cigarette smoke has been demonstrated (Neurath et al., 1964), while in human gastric juice organic N-nitrosocompounds could be possibly formed by secondary amines and nitrites, both occasionally found in food (Sander, 1967). The second question put forward at the start of the experiments was the mechanism of action of organic N-nitrosocompounds on the nasal mucosa. In the experiments diaethylnitrosamine was injected subcutaneously and no changes ever occurred at the site of injection.

The initial changes in the nose (loss of polarity) occurred in the superficial layer of the epithelium. The impression gained from this was that the mode of action is from the outside i.e.: the lumen. Loss of polarity was first found in the olfactory region. The glands of Bowman showed abnormalities in the early stages (ectasy of glands, atrophy of the acinous epithelium). On the basis of these findings the following hypothesis regarding the mechanism of action of diaethyl-

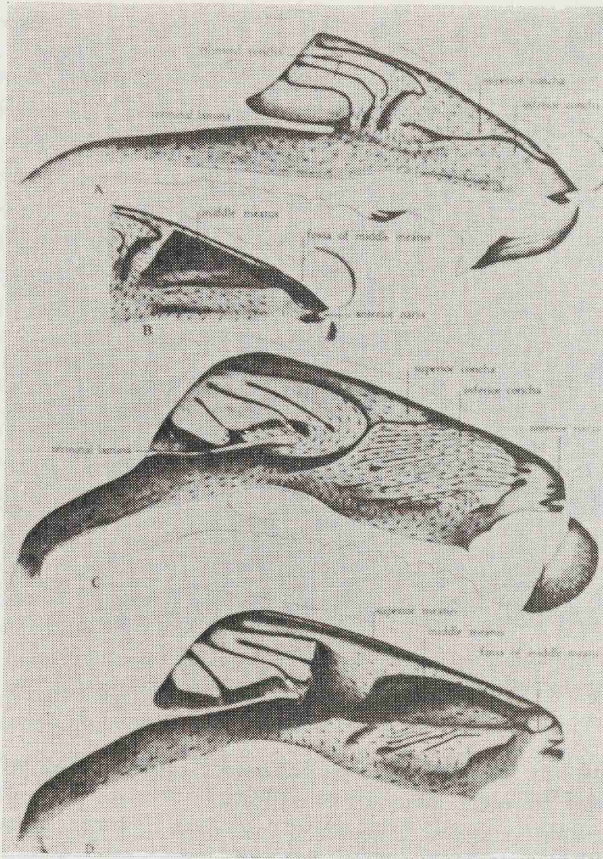
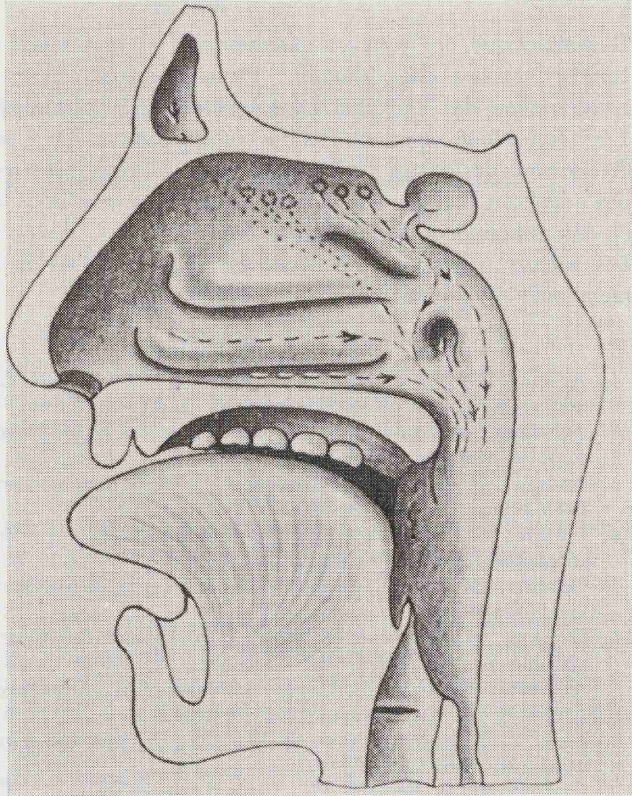


Figure 2. Direction of ciliary streams in mammals. (from Lucas cited by Negus).

nitrosamine on nasal mucosa appears tenable. Diaethylnitrosamine or a catabolite is excreted by the glands of Bowman in the nasal mucus and exercises its influence on the outer surface. In addition the following observations also support this hypothesis.

1. The abnormalities in the respiratory region as in the olfactory region were most pronounced in the posterior areas. It is known that stagnation of nasal mucus easily occurs in the posterior parts of the olfactory region so that an oncogenic material in the nasal mucus can exercise its influence for a longer period. The flow of nasal mucus from the olfactory region to the pharyngeal duct follows the posterior part of the respiratory region. An oncogenic substance in the nasal mucus can exercise its effect on the posterior part of the respiratory region in this way.
2. The vestibulum nasi where nasal mucus is scarce never showed abnormalities.
3. The organ of Jacobson, the maxillary sinus and the various groups of glands (except for the glands of Bowman) showed no abnormalities. These structures are protected from the action of substances in the nasal mucus by their anatomically secluded positions.

Figure 3. Direction of ciliary streams in men. (after Negus).



The development of adenocarcinoma especially in the ethmoid region in woodworkers can be better understood on the basis of this hypothesis, the carcinogens after absorption by the nasal mucosa and perhaps also the buccal mucosa and the lower respiratory tract being excreted in the nasal mucus possibly in altered form by Bowman's glands. In this way the prolonged and concentrated action on the ethmoid region is understandable.

This hypothesis could also account for the epipharynxcarcinoma which is frequently found in Southern China and the aetiology of which is much speculated on.

Fong and Walsh (1971) suggested that organic N-nitrosocompounds play a role. They found in dried fish, which is an important component of the daily food in this region, 0.6-9 ppm. dimethylnitrosamine and 1.2-21 ppm. diaethylnitrosamine. If one accepts that these substances or their catabolites, excreted by the glands of Bowman in the nasal mucus exert an aetiologic role, then the maximal effect will be found in the epipharynx where mucus from both nasal cavities accumulates. According to Negus (1958) the cilia in rodents direct the mucus from the ethmoid to the lower part of the nasal cavity initially and then towards the epipharynx (see Figure 2), whereas in man the mucus is directed immediately towards the epipharynx (see Figure 3).

RÉSUMÉ

Il semble que des facteurs externes sont d'importance dans la pathogénie des tumeurs du nez chez l'homme. Plusieurs investigateurs ont causé des tumeurs nasales chez des animaux expérimentaux par administration des nitrosamines. Les auteurs ont répété et étendu ces expériences chez le rat.

À l'opposé des autres observateurs nous n'avons pas trouvé des épithéliomas et des adenocarcinomas dans le nez. Conforme à eux nous avons vu des papillomas et des esthésioneuroépithéliomas.

Les auteurs proposent une hypothèse regardant l'action des nitrosamines sur la membrane muqueuse du nez.

REFERENCES

1. Acheson, E. D., Hadfield, E. H. and MacBeth, R. G., 1967: Carcinoma of the nasal cavity and accessory sinuses in woodworkers. *Lancet* I, 311-312.
2. Acheson, E. D., Cowdell R. H. and Jolles, B., 1970: Nasal cancer in the Northamptonshire boot and shoe industry. *Brit. med. J.* I, 385-393.
3. Andrews, P. A. J. and Michaels, L., 1968: Nasopharyngeal carcinoma in Canadian Bush pilots. *Lancet* 2, 85-88.
4. Bottema, T., 1971: Experimentele gezwollen in het neusslijmvlies van de rat, Thesis, Amsterdam, V.U.
5. Debois, J. M., 1969: Tumors of the nasal cavity in woodcarvers. *Tijdschrift v. Geneeskunde*, 25, 92-93.
6. Druckrey, H., Ivankovic, S., Mennel, H. D. and Preussmann, R., 1964: Selektive Erzeugung von Carcinomen der Nasenhöhle bei Ratten durch N-N. Di-Nitrosopiperazin, Nitrosopiperidin, Nitrosomorpholin, Methyl-allyl-, Dimethyl- und Methyl-vinyl- nitrosamin. *Z. für Krebsforschung* 66, 138-150.
7. Fong, Y. Y. and Walsh, E. O. F., 1971: Carcinogenic nitrosamines in cantonese salt-dried fish. *Lancet* II, 1032.
8. Gignoux, M. et Bernard, Ph., 1969: Tumeurs malignes de l'etmoïde chez les travailleurs du bois. *J. de Méd. de Lyon* 50, 731-735.
9. Haddow, A., 1970: De huidige kennis betreffende de mogelijke oorzaken van kanker. *Abbotempo* 4, 8-11.
10. Hadfield, E. H. and MacBeth, R. G., 1971: Adenocarcinoma of ethmoids in furniture workers. *Ann. Oto-Rhino-Laryng.*, 80, 699-704.
11. Herrold, K. M., 1964: Epithelial papillomas of the nasal cavity. *Arch. Path.* 78, 189-195.
12. Herrold, K. M., 1964: Induction of olfactory neuroepithelial tumors in syrian hamsters by diethylnitrosamine. *Cancer* 17, 114-121.
13. Magee, P. N. and Barnes, J. M., 1956: The production of malignant primary hepatic tumours in the rat by feeding dimethylnitrosamine. *Brit. J. Cancer* 10, 114-120.
14. Negus, V., 1958: Comparative anatomy and physiology of the nose and paranasal sinuses, Livingstone, Edinburgh.
15. Neurath, G., Pirmann, B. und Wichern, H., 1964: Zur Frage der N-Nitrosoverbindungen im Tabakrauch. *Beiträge zur Tabakforschung*, Band 2/7, 311-319.
16. Sander, J., 1967: Kann Nitrit in der menschlichen Nahrung Ursache einer Krebsentstehung durch Nitrosaminbildung sein? *Archiv für Hygiene und Bakt.* 151, 22-28.

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