PATHOPHYSIOLOGY OF THE CILIARY EPITHELIUM *
(a review of the present knowledge)

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Historical data

It has generally been assumed in the literature that in 1684 the Dutchman Anton de Heide from Middelburg was the first to discover ciliary movement in the mussel. Some years before, however, Antoni van Leeuwenhoek of Delft had already reported in one of his letters (October 9th, 1676) to the Royal Society on the presence of cilia in protozoa. Another of his letters (april 5th, 1680) contains a description of cilia and ciliary movement in the mussel, whose "gills were densely occupied by thin hairs with which the mussel made large movements". In 1682 he described similar observations in the oister. Therefore, there is no doubt that on several occasions van Leeuwenhoek, preceded de Heide in describing cilia and ciliary movement (A. Schierbeek).

Anatomical data

1. The internal nose and the sinuses are lined by a columnar or cylindrical epithelium, with mucus producing goblett cells in between. In the posterior two-thirds of the nose (the olfactory region excluded) and in the sinuses this epithelium is a ciliary epithelium. In the anterior-superior part of the internal nose the mucosa is mostly non-ciliated (Hilding, Dixon et al. '49). This is also the case at the anterior ends of the turbinates. These places are the first to come into contact with the unconditioned inspired air. Consequently non-ciliated epithelium may also be expected at other places in the nose when the normal nasal anatomy is disturbed and the air takes an abnormal route through the nose on inspiration.

2. Each ciliary cell has about 250-300 cilia on its surface and each cilium is about 8 microns long and 0,3 microns in diameter (Rhodin 1959, Spoendlin 1959) From the various electronmicroscope studies it has been concluded that the structure of the ciliated cells in man is approximately identical to that in animals and some plants. This conclusion is an important one in view of the possible techniques of investigation of the ciliary functions.

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3. The normal nasal epithelium is covered by a layer of mucus. This layer consists of two sheets (Lucas and Douglas, 1934):
a. an outer layer with a higher viscosity on the tips of the cilia, in which larger particles are caught and transferred and
b. an inner layer of lower viscosity suitable for the movement of the cilia. An explanation of these two layers of mucus has recently been given by Breuninger (1964). Breuninger found that nasal mucus can be changed from a gel into a sol and back, by changing the PH. With a low PH the mucus is a gel, with a high PH it is a sol. Breuninger now assumed that the carbon dioxyde of the air changes the PH of the upper mucus layer to the acid side, thereby bringing the mucus from the sol in the gel state and liberating a considerable amount of water at the same time. In this way the double layer of the mucus would be explained. This hypothesis also offers interesting aspects concerning the process of humidification of the air by the nose.

Physiological data

Our present knowledge of the physiology of the ciliary epithelium is mainly derived from two types of studies: a. ciliary beat studies and b. mucus flow studies.
Ciliary beat can be studied both in vitro as well as in vivo on excised pieces of mucosa. Mucus flow, on the contrary, should be investigated in vivo, as a normal transport requires an intact blood and nerve supply of the mucosa.
Ciliary beat studies have been carried out in animals as well as in man. The more modern recording techniques with the high speed motion camera and the stroboscope, however, have mainly been used in animals. With these methods beat rates of 600-1500/min. have been measured in various animals (Dalhamn c.s. '56, '59, '60, Krueger '57, '58, '59, Toremalm '61). As no great difference between the ciliary cells in animals and man has been noticed a ciliary beat frequency of ca 1000/min. is therefore assumed in the human (Ewert '65).
Mucus flow studies have been done both in animals and man. In vivo measurements in man were made by Frenckner ('39), Tremble ('48), van Ree and van Dishoeck ('62) and Ewert ('65). Their results are remarkably equal. In all investigations a speed of the mucus flow of about 5 mm/min. was found in normal persons.
Several factors influence the ciliary function as measured either by means of the beat frequency or by means of the mucus flow speed.
a. **relative humidity** of the air is the most important factor influencing ciliary function. Drying of the mucosa causes irreversible damage to the cilia in a short period of time. At first the viscosity of the mucus increases, the ciliary movement then slows down and ultimately stops. Dalhamn ('56) found that in vitro a relative humidity of 70% is required to maintain ciliary movement. At a relative humidity of 50% the cilia stop beating in 8-10 min., at 30% their activity ends in 3-5 min. Similar data were obtained by Ewert ('65), when he measured the effect of the relative humidity of the inspired air on the speed of the mucus flow in the human nose. He found a positive correlation between relative humidity and flow rate. Above 70% relative humidity a mucus flow was present in all test persons, whereas at progressive lower levels cessation of

the flow was observed in an increasing number of cases. Between 40% and 70% relative humidity the drying effect of the air is still partly compensated by the secretion of mucus. Below 40% however this is not the case and the ciliary movement stops.

b. temperature. Proetz (1934) was the first to observe that heating of the mucosa increases the ciliary beat frequency up to a certain level. According to the more recent studies 40° C is about the optimum temperature. With a cooling of the tissues the cilia work slower although the temperature should be under 10° C before the ciliary beat activity stops completely.

c. PH. A third factor influencing ciliary function is the PH. Values under 6 and more than 9 diminish ciliary activity.

d. certain **ions** are considered necessary for normal ciliary function. Ciliary movement continues in vitro for a much longer time, when the piece of mucosa is laid in Ringer or Tyrode solution than when it is placed in physiological saline solution.

e. autonomic nervous system. Whether or not the autonomic nervous system influences ciliary function is a matter of dispute. Several authors observed no effect from section of autonomic nerves or from the administration of drugs like adrenaline, atropine, acetylcholine etc. Others on the contrary claim effects in different ways. However, as remarked by Melon (1964) in his monograph other processes such as the amount of mucus production, and the composition of the mucus are also influenced in these experiments.

Pharmacological data

Several pharmaca which are used for local application in the nose influence ciliary movement to some degree.
Although the number of investigations in this field is rather limited some results are worth mentioning in this review.

a. Vasoconstrictors

Proetz (1933) and Hutcheon and Cullen (1955) studied the effect of various vasoconstrictors.

	Ciliary activ. 50% inhibited	Conc. in use	Index
Tetrahydrozoline (Tyzine)	1,2 %	0,1 %	12
Phenylephrine	4,2 %	0,5 %	8,4
Naphazoline (Privine)	0,4 %	0,1 %	4
Ephedrine	2,5 %	1 %	2,5
Adrenaline	ca 0,02%	0,1 %	0,2

Table 1. Effect of vasoconstrictors on ciliary activity (after data of Hutcheon and Cullen, 1955 and Proetz, 1933)

The results are given in table 1. Of the drugs investigated adrenaline appears to be the drug with the worst ratio and tyzine as the drug with the most favourable ratio between inhibiting concentration and concentration in use.

b. Anesthetics

According to Kimura ('50) procaine and cocaine are the most harmless. The concentrations necessary to abolish ciliary movement were found to be much greater than those in general use.
For lidocaine and tetracaine the situation appeared to be less favourable: the concentrations at which ciliary activity decreases and stops are about the same as the concentration commonly used (table 2).

	Ciliary activity decreased	Ciliary activity stopped	Concentr. in use
Procaine HCl	1,5 %	> 50 %	1 - 2 %
Cocaine HCl	1,5 %	> 20 %	1 -10 %
Buthethamine HCl (Monocaine)	2 %	> 3 %	1 - 2 %
Lidocaine HCl (Astrocaine, Xylocaine)	2 %	7,8 %	2 - 4 %
Tetracaine HCl (Pantocaine)	0,25%	0,82%	0,5- 2 %

Table 2. Effect of anesthetics on ciliary activity (after data of Kimura, 1959)

c. Antibiotics

Antibiotics also inhibit the cilia to a different extent. Neomycine, streptomycine and kanamycine already diminish ciliary movement in concentrations of more than 0.0001%. Chloramphenicol and bacitracine on the other hand have no effect except in concentrations of 10% and 1-10% respectively (table 3).

	Ciliary activity inhibited
Chloramphenicol (S)	10%
Bacitracine (P)	1-10%
Thyrothricine (S)	5%
Gramicidine (S)	0.5%
Tetracycline (S)	0.1%
Kanamycine (P)	0.0001-0.1%
Streptomycine (P)	0.0001%
Neomycine (P)	0.0001%

Table 3. Effect of antibiotics on ciliary activity (after data of Salerno (1955) and Pacilio (1961))

d. Cigarette smoke

Cigarette smoke has a very strong ciliostatic effect. This has been studied extensively by Dalhamn and coworkers (1965). From their experiments it can be concluded that the smoke of 3 cigarettes (smoked without interruption) completely stops the ciliary activity of the tracheal mucosa in the rat; 5 cigarettes smoked with intervals of 5 minutes have the same result.
This strong ciliostatic effect of cigarette smoke was confirmed by Ewert ('65), when he found that the mucus flow speed in the nose in smokers is considerably smaller than in non-smokers.

Pathological conditions

Our knowledge concerning the ciliary activity in pathological conditions is limited. Only a few studies in this field are available.
a. Infection. In infection ciliary activity is not distorted unless the epithelium becomes destroyed, as is often the case in the first days of an acute rhinitis, However, regeneration with restoration of normal function is very rapid.
In acute and in chronic sinusitis ciliary activity is unaffected. The mucus flow speed seems to be influenced only when the secretions have a high viscosity.

b. Allergy. With regard to allergic conditions opinions differ. In cases of chronic nasal allergy no evident ciliary disturbance has been noted, although further study seems necessary.
In acute allergy Chevance (1957) and Matsumota (1958) observed a ciliostasis in the immediate region where a pollen allergen is brought into contact with the mucosa. This effect accounts for the rapid penetration of allergens into the mucosa and the immediate appearance of the allergic symptoms after the inhalation of the allergen.

c. Pathological nasal anatomy. The nasal epithelium is or becomes non-ciliated at places where unconditioned air hits the mucosa. Normally this is the case at the anterior end of the turbinates. It is also found at the anterior ends of septal deviations and spurs. Consequently it may also be expected in other instances of abnormal nasal anatomy such as after conchotomy and after endonasal ethmoidectomy. In these cases other regions with non-ciliated epithelium will appear. These regions are functionally silent, secretions will accumulate so that crusts are formed.
The same process takes place when the production of mucus is insufficient to counteract the drying effect of the inspired air. This is the case in atrophic rhinitis and ozena where atrophy, insufficient mucus production and abnormal airway result in a disappearance of almost all cilia.
Therapy in these diseases should basically be directed against both these factors.
On the other hand when performing a surgical intervention in the nose we should try to imagine what may be its consequence on the ciliary function either directly or due to the many influencing factors discussed above.

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