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Electron microscopy in rhinology

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SUMMARY

In rhinology, electron microscopy has been a useful research tool for the past 15 years, but provided only a few direct clinical applications. In this review, the author's work on the human nasal mucosa and the studies of other investigators are discussed, with the emphasis on allergic reactions and disturbances of the autonomous nervous system as well as the immotile cilia syndrome.

Transmission electron microscopy has been used in otologic research for 30 years, however in rhinology only for the past 15 years. The purpose of this paper is to review both the results of our own work on the human nasal mucosa since 1969 as well as to discuss the studies of other authors (Table 1). These fundamental morphologic aspects of nasal diseases may interest the clinician as much as the researcher.

Table 1. Electron microscopy of human nasal mucosa.

1. normal	7. parasymph. denerv.
2. S/P laryngectomy	8. mucoviscidosis
3. acute allergy	9. hered. telangiectasia
4. chronic allergy	10. immotile cilia
5. polyps	11. papilloma
6. sympath. denerv.	12. esthesioneuroma

What are the indications for electron microscopy in rhinology? First of all, to demonstrate details not possible with light microscopy or scanning electron microscopy and to correlate, as much as possible, the fine structure with clinical and functional findings. Pathologic mechanisms may be demonstrated at the cellular level, e.g. in allergy. Causal factors of certain diseases may be searched for, e.g. in polyps, mucoviscidosis or papillomas. Electron microscopy as a diagnostic aid in rhinology, e.g. in the immotile cilia syndrome or in the differential diagnosis of malignant tumours, may be important under certain circumstances. Though the human nasal mucosa is easily accessible to obtain fresh material for

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electron microscopy, there are limitations of this expensive and time consuming technique. The number of patients studied and the amount of tissue from a circumscribed area are relatively small. Moreover, there are normally epithelial lesions by various exogenous factors such as chronic infection, use of nose drops and – in general – the "hostile environment".

Knowledge of the normal fine structure of the human nasal mucosa is the basis for the interpretation of pathologic changes (Jahnke, 1972). The physiologic changes in the anterior part of the inferior turbinate which occur under the influence of air currents differ clearly from the electron microscopic picture of respiratory mucosa with typical ciliated epithelium. Electron microscopically, this functional alteration is characterized particularly by a loss of cilia without evidence of ciliary regeneration. On the other hand, following the elimination of nasal breathing subsequent to laryngectomy, numerous mature cilia appear in this anterior part of the inferior turbinate (Jahnke, 1972).

The fine structure of the allergic human nasal mucosa is of special interest in rhinology and has recently been reviewed (Jahnke and Theopold, 1983). The morphologic changes differ according to the stage of the allergic reaction. In the acute stage immediately after allergen challenge, massive transudation occurs from the subepithelial vessels into the dilated intercellular spaces. Favoured by increasing permeability of the zonulae occludentes, the fluid quickly reaches the surface as excessive nasal secretion. There are morphologic signs of the disturbed microcirculation, with increased permeability of the dilated capillaries and venules, with evidence of congestion and "sludging" of the red blood cells as well as endothelial gaps (Figure 1).
In chronic allergy, i.e. in patients with perennial allergic rhinitis when seen during an acute exacerbation, the epithelial layer is considerably more damaged, with loosening of the cells and transudation in the greatly dilated intercellular spaces as well as eosinophilic infiltration. Endothelial lesions are regularly observed. Our allergy findings have been confirmed by other authors.
Endonasal polyps from patients with allergic rhinitis show a very pronounced intra- and extracellular edema, ciliated cells are frequently present; characteristic is the absence of nerves.
Of interest are also disturbances of the autonomic nervous system (Jahnke and Theopold, 1983) which is so important for the sensitivity of the nasal mucosa towards endogenous and exogenous stimuli. Following sympathetic denervation after unilateral stellate ganglion blockage the clinical and electron microscopic picture correspond to nonspecific nasal hyperreactivity or vasomotor rhinitis, with excessive transudation as well as stimulation of the goblet cells and nasal glands with large secretory vacuoles. Such changes are influenced by parasympa-

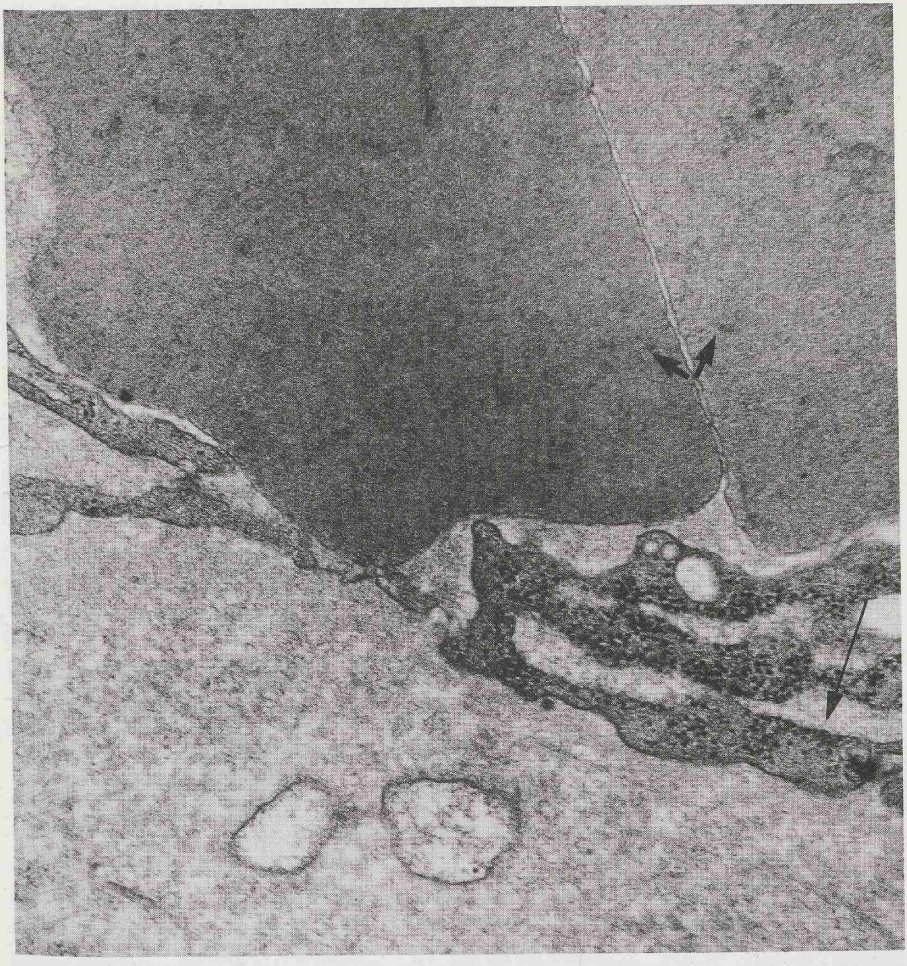

Figure 1. Acute allergic reaction: Pronounced interstitial oedema (arrow) in a dilated capillary with evidence of "sludging" of the red blood cells (2 arrows).

thetic denervation following Vidian nerve transsection: The nasal glands shrink with signs of decreased activity, there is also periglandular fibrosis with frequently large amounts of collagen.

A congenital metabolic disease which is of interest for the rhinologist is mucoviscidosis. In this disorder of the exocrine glands even the clinically and histologically normal appearing nasal mucosa exhibits characteristic changes with intra- and extracellular edema and an increased number and activity of the goblet cells (Jahnke and Theopold, 1983). The cilia show membrane damage and are bent by the abnormal viscosity of the nasal secretions. The endonasal polyps in mucoviscidosis differ from allergic polyps by the absence of eosinophilic infiltration.

Of interest for the rhinologist is also the fine structure of hereditary telangiectasia (Rendu-Osler-Weber's disease). The large vascular channels are lined with a single layer of endothelial cells on a continuous basement membrane. Smooth muscle cells in the walls of the vessels are not continuous and apparently not adequate as a contractile element; there is evidence that the altered vessels are primarily weak rather than thinned out due to dilatation (Jahnke, 1970).

In 1976 Afzelius as well as Peddersen and Mygind used electron microscopy to demonstrate specific cilia abnormalities as cause of the mucociliary dysfunction in Kartagener's syndrome (situs inversus, bronchiectasis, chronic sinusitis), and the term immotile cilia syndrome or ciliary dyskinesis is now generally preferred; about half the cases of immotile cilia syndrome have situs inversus. We described the fine structure of cilia in several cases of Kartagener's syndrome (Theopold and Jahnke, 1979) and observed the specific abnormalities in the nose, sinuses, trachea, bronchi and middle ear in patients with complete situs inversus even when symptoms and signs of sinus or bronchial disease were absent.

The diagnosis of immotile cilia or ciliary dyskinesis is made by three fine structural defects (Parker et al., 1983): Transposition of microtubules; absence of dynein arms, an ATPase protein essential in the generation of ciliary motion; lack of radial spokes, essential for the coordination of ciliary motion (Figure 2). Other

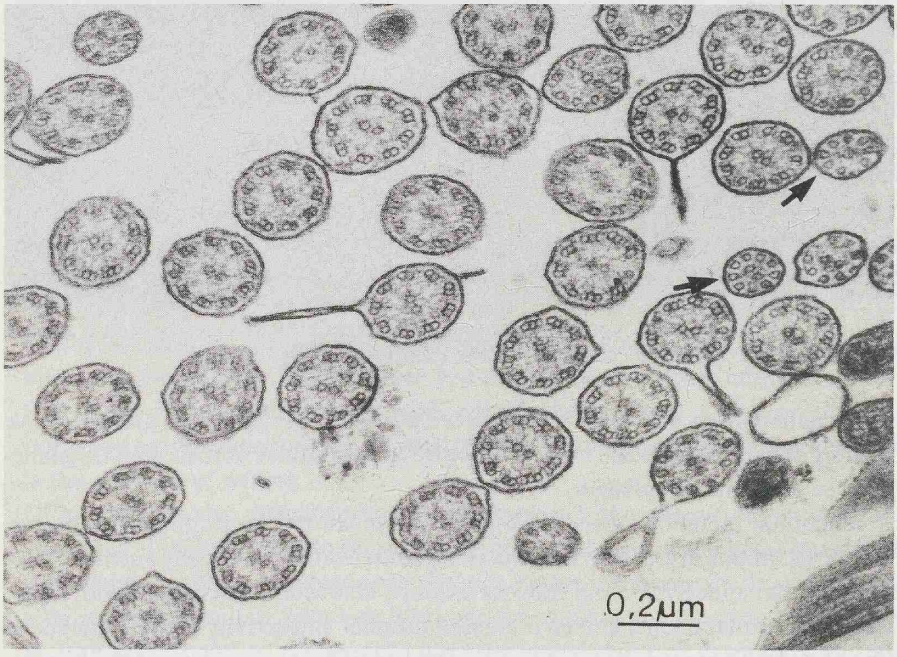

Figure 2. Cilia in Kartagener's syndrome: Next to normal axonemes with the 9 + 2 pattern incomplete configurations without doublet microtubules (arrows); dynein arms are missing.

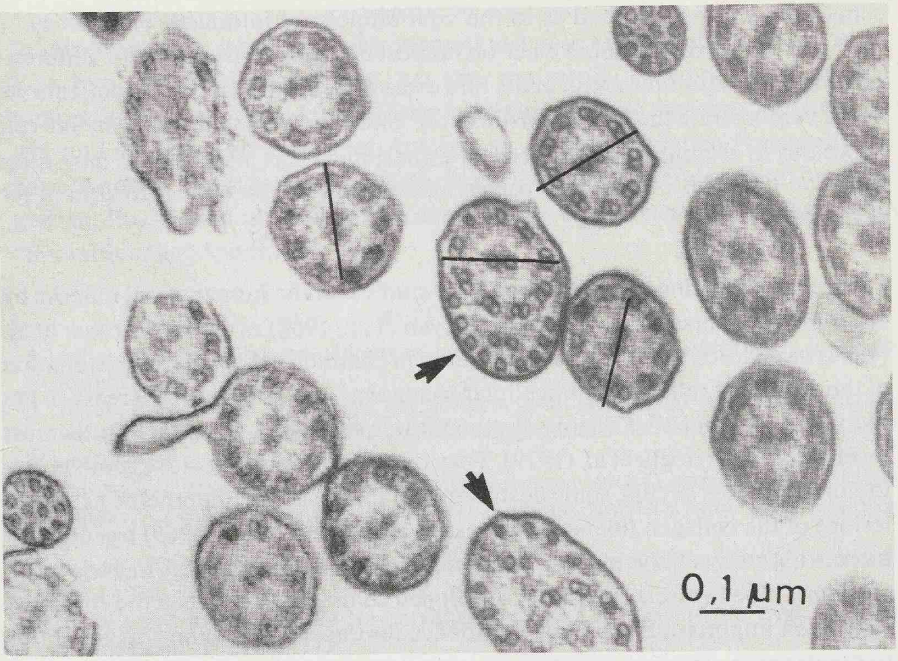

Figure 3. Cilia in Kartagener's syndrome: Compound cilia with irregular single microtubules (arrows) and disoriented axis through which the cilium moves (line through the 2 central microtubules).

abnormalities like compound cilia or disorientation of the cilia (Figure 3) suggesting asynchronous beating are sometimes seen in chronic respiratory diseases and not specific for ciliary dyskinesis. The inherited lack of ATPase dynein which causes non-motility of cilia and the other ciliary abnormalities observed in the immotile cilia syndrome may be the cause of chronic diseases in the upper and lower respiratory tract of patients without situs inversus. It is of clinical importance that the early diagnosis can be made by electron microscopy of a nasal biopsy. Further quantitative studies are necessary because there is some variability of the normal ciliary structure, and it is not yet certain to which extent these abnormalities interfere with the normal ciliary motility.

Electron microscopy as a diagnostic aid has also been used for a possible evidence of a viral etiology in intranasal papillomas (Jahnke, 1971). The epithelial cells of inverted papillomas show characteristic extension of the cytoplasmic processes into the underlying connective tissue while the surrounding basement membrane is intact. This morphology may be correlated with the clinical behaviour of inverted papillomas as regards their tendency to recur after incomplete removal and their potential malignant change. Furthermore we observed intranuclear particles; their structure and size is suggestive of virus particles though a definite

conclusion was not reached as to the viral etiology of intranasal papillomas. Under certain circumstances electron microscopy may be useful in the differential diagnosis of tumours, e.g. in the rare esthesioneuroma. In several patients we could demonstrate the characteristic dense core vesicles and many axon like cell processes to establish the diagnosis of esthesioneuroma after various false diagnoses on the basis of light microscopy had prevented the correct treatment for many years.

Let me now mention some very valuable studies on the human nasal mucosa by other investigators. Catherine Smith (Bryan et al., 1968) as well as Winther et al. (1984) have described the nasal epithelium in common colds. There is exfoliation of the epithelial cells with intracellular changes as well as an early increase in the number of neutrophils. The nasal mucosa was studied in atrophic rhinitis most recently by Katircioglu et al. (1979). They described a metaplastic squamous epithelium with loss of cilia, some destruction of the basement membrane as well as lesions of the collagen fibers, blood vessels and glands. Ohki (1965) has done an interesting study on the mucosa of Kiesselbach's area; his findings include intraepitheliai blood vessels and poorly developed connections between the epithelial cells as an important morphologic evidence for the cause of hemorrhages at this particular area. The fine structure of scleroderma was described by Talaat et al. (1980) as severe fibrosis, loss of cilia and considerable damage of the small blood vessels and glands.
Finally it should be known to the rhinologist that the fine structure of the maxillary sinus mucosa is similar to the respiratory mucosa, but shows fewer cilia and a more delicate and looser epithelium than the nasal mucosa, a decreased activity of the glands and fewer vessels (Toppozada and Talaat, 1980). Albegger (1978) has demonstrated cilia abnormalities in chronic sinusitis which correspond to the dysfunction in sinusitis: cilia with a single axonema and excess cytoplasmic matrix; compound cilia and giant cilia with 2–4 and more complete or incomplete axonemata. Furthermore he observed the very rare occurence of secretory granules and normal cilia in one cell as possible evidence of enhanced regeneration.

In rhinology, electron microscopy has thus far provided only a few direct clinical applications. But as a research tool it has contributed to a better understanding of the physiologic, pathophysiologic and biochemical aspects of nasal diseases. There remains a broad area of opportunity for morphologic research, particularly by combining transmission electron microscopy with scanning electron microscopy and the freeze edging technique, or by using it in conjunction with enzyme- or immune histochemical and autoradiographic methods. Last not least, for aesthetic reasons alone, it is a real pleasure to do electron microscopy.

ZUSAMMENFASSUNG

In der Rhinologie wird die Elektronenmikroskopie seit 15 Jahren als wertvolle Forschungsmethode angewendet, hat aber nur wenig direkte klinische Bedeutung gefunden. In diesem Übersichtsreferat wird über die eigenen Untersuchungen und die Ergebnisse anderer Autoren an der menschlichen Nasenschleimhaut berichtet, unter besonderer Berücksichtigung der Veränderungen bei allergischen Reaktionen und Störungen des vegetativen Nervensystems sowie beim "immotile cilia"-Syndrom.

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