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Rhinitis medicamentosa: Electron microscopic study

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Introduction

NASAL obstruction is a common symptom in ear, nose and throat practice. For treatment, decongestant nasal drops are almost always prescribed by doctors. The misuse or overuse of these local medications has injurious effects on the nasal mucosa. These changes have been termed 'rhinitis' medicamentosa'. The effects of prolonged use of various decongestant drops on the nasal mucosa have been studied by Fox (1931) and by Hunnicutt (1941). They found that amphetamine solution used three times daily for ten days produced mild inflammation and moderate purulent exudation in mice. Butler and Ivy (1944) studied the effect of prolonged medication with vasoconstrictor amines on normal adult rabbits' nasal mucosa. They found metaplasia and denudation of the epithelium with dilatation and engorgement of the subepithelial blood vessels.

The present work aims at studying the ultramicroscopic changes in the respiratory mucous membrane of the rabbit's nose following prolonged administration of decongestant nasal drops.

Material and Methods

Ten adult rabbits were used for this study; eight were the subjects of the experiment and two animals acted as the controls. One per cent ephedrine in normal saline was prepared, and by using a special fine dropper, two drops of the solution were instilled into the nasal cavities of the animals three times daily. Four of the animals were killed after two weeks and another four were killed three weeks after the beginning of the experiment. The mucous membrane over the nasal septum and turbinates was immediately dissected out under the operating microscope. The tissues were fixed in 4 per cent glutaraldehyde solution followed by 1 per cent osmium tetroxide solution buffered at pH 7·4 with phosphate buffer. The tissue blocks were embedded in araldite mixture (Luft, 1961), and cut with the automated ultramicrotome 111 type 8801 A (LKB). The sections were stained with 5 per cent uranyl acetate in 1 per cent acetic acid followed by 0·04 per cent lead citrate. Electron micrographs were prepared on a Siemens Elmiskope I.

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Results

Control animals: The mucous membrane of the septum and turbinates of the animals not subjected to instillation of the vasoconstrictor drops showed the expected normal pseudostratified ciliated columnar epithelium with a mixture of goblet and ciliated cells. The surface was lined with microvilli and normal motile cilia with the characteristic 9+2 pattern of microtubules. A rare finding was the presence of homogeneous cilia. No virus-like particles were seen. The tunical blood vessels were lined by a thin, smooth, almost continuous endothelial layer, with a few micropinocytotic vesicles and a few endothelial hairy cytoplasmic processes.

Experimental Animals: The specimens examined two weeks after daily instillation of the drops showed the appearance of abnormal cilia on the surface epithelium. They occurred in groups, each group formed of many cilia adherent to each other. These cilia were homogeneous, lacking the normal pattern of microtubules and of club-like shape (Fig. 1). The epithelium showed widening of the intercellular spaces and loosening of the epithelial cells. The cell membranes which were usually contiguous

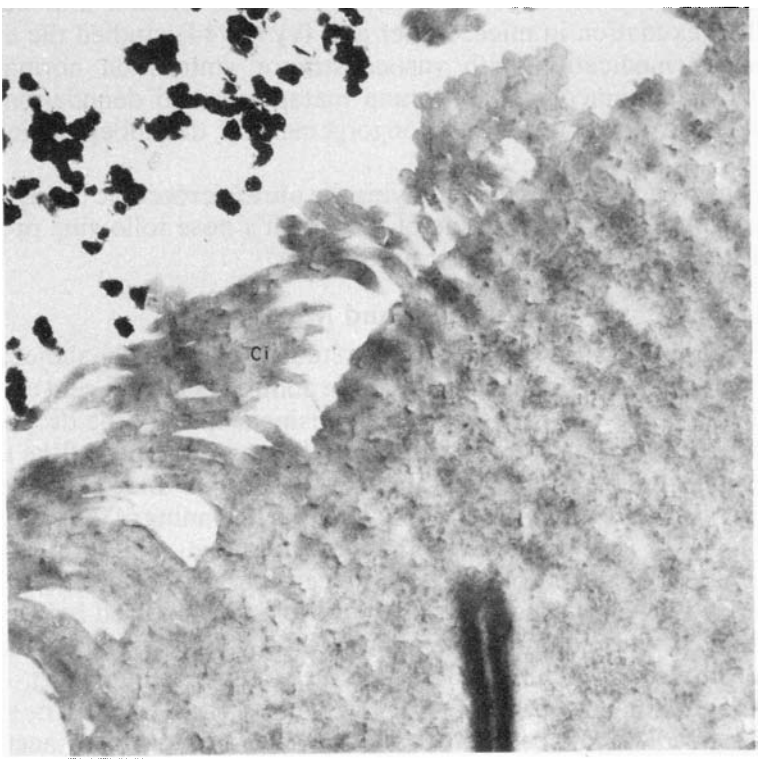


FIG. 1

Electron micrograph of the surface epithelium two weeks after daily instillation of vasoconstrictor drops, showing abnormal homogeneous cilia (Ci) lacking the normal microtubules and appearing in groups adherent to each other. ×25,000.

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near the surface began to separate between the adjacent maculae adherentes. As the cells increased in depth, the intercellular spaces widened as the cell membranes diverged even at the desmosomal contact points. The number of desmosomes connecting the cells was reduced. They were on the whole restricted to the basal cell layer near the basal lamina, while the finger-like cytoplasmic processes were increased in number and length, and a large number of them were seen lying free in the distended intercellular spaces (Fig. 2). The cell contour was deformed. The epithelium was separated from the underlying connective tissue by an intact regular basal lamina. The subepithelial cell-free zone was oedematous, and contained fine irregularly arranged collagen fibrils (Fig. 2).

The specimens examined three weeks after daily instillation of the decongestant nasal drops showed marked reduction of the cilia, with only microvilli and a few scanty abnormal homogeneous cilia scattered on the surface epithelium. Virus-like particles were observed on the surface epithelium in most of the sections examined. They appeared in the form of

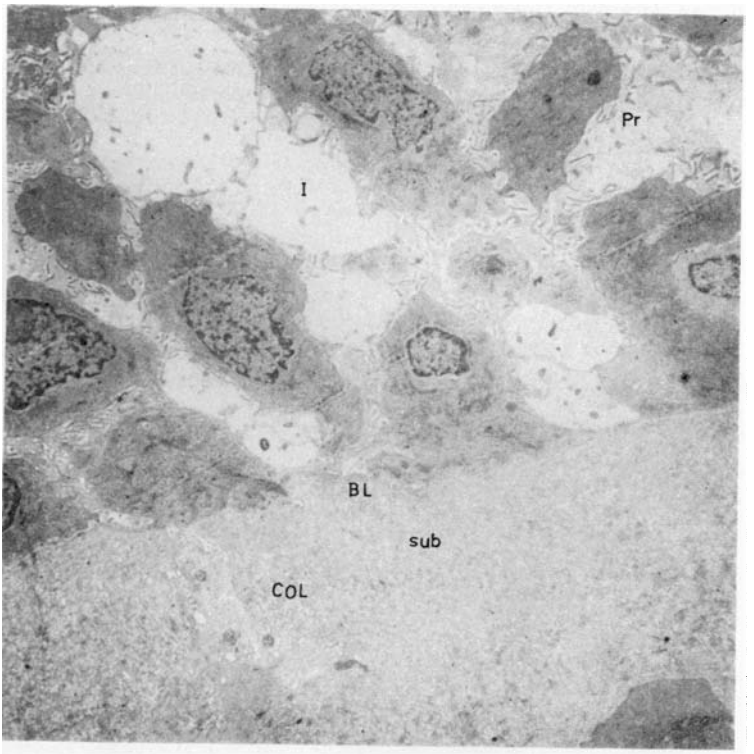


FIG. 2

Electron micrograph of the epithelium and subepithelial region two weeks from the beginning of the experiment, showing hugely distended intercellular spaces (I) with a large number of cytoplasmic processes (Pr). The subepithelial zone (sub) is oedematous, with fine irregularly arranged collagen fibrils (COL), and separated from the epithelium by a thin intact basal lamina (BL). ×7,500.

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spherical structures with an irregular core (Fig. 3). In some specimens there was evidence of destructive alteration of the epithelial cells. Oedematous infiltration of the epithelium was marked, with widening of the intercellular spaces even near the surface, and sometimes with the formation of cyst-like spaces between the epithelial cells (Fig. 4).

The tunica propria showed marked cyst-like oedematous changes (Fig. 5). By the third week, most of the venules in the tunica appeared congested and dilated. The endothelial cell junctions were often incompletely sealed and the endothelial basement membrane was thickened and consisted of several incomplete layers (Fig. 6). The capillaries were congested and there was an increase in number of the endothelial fine hairy cytoplasmic processes or pseudopodia extending into the capillary lumen. The number of micropinocytotic vesicles was increased (Fig. 7).

Discussion and Conclusion

Within the first two weeks following daily instillation of the vasoconstrictor drops in the rabbit's nasal cavities, the cilia started to lose

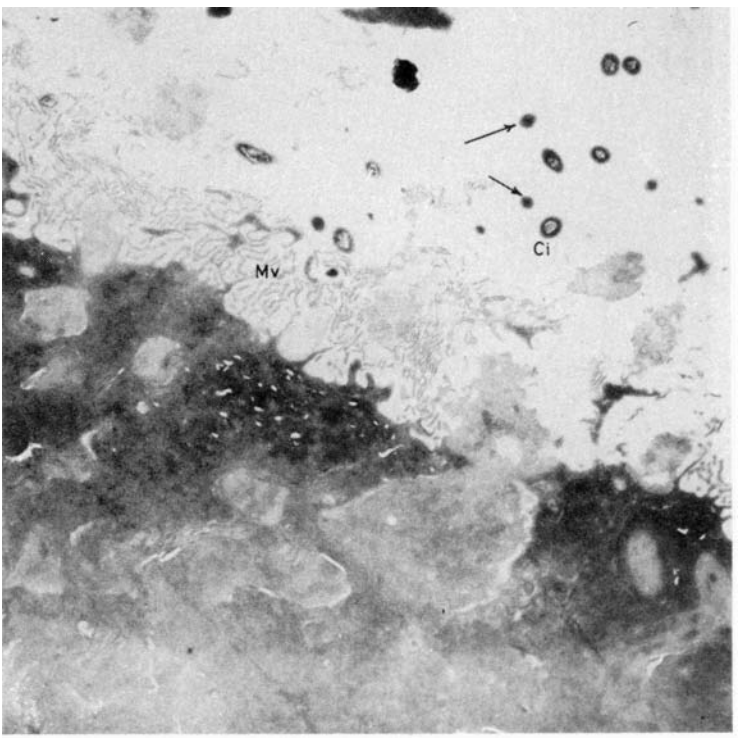


FIG. 3

Electron micrograph of the surface epithelium three weeks after continuous use of the drops, showing microvilli (Mv) and few scattered abnormal cilia (Ci) with virus-like spherical particles (arrows). ×12,500.

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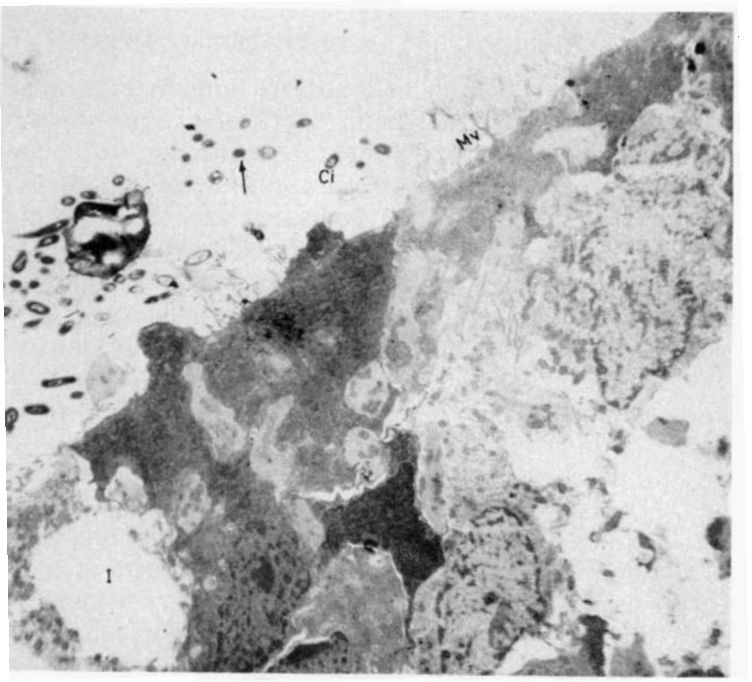


FIG. 4

Electron micrograph of the epithelium three weeks after daily use of the decongestant drops, showing a few cilia (Ci) with virus-like particles (arrows) and a few scattered microvilli (Mv). The intercellular spaces are distended (I) with distortion of the cells. ×7,500.

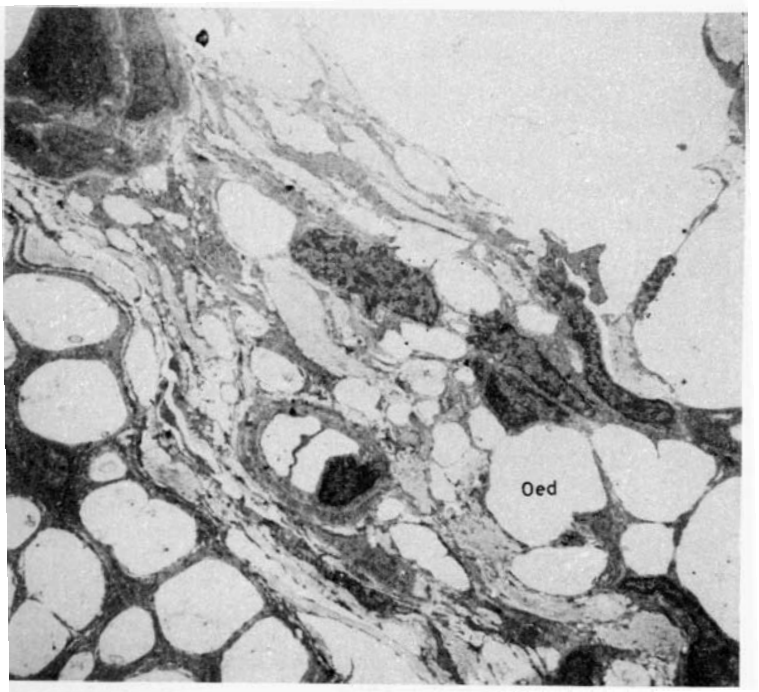


FIG. 5

Electron micrograph of the tunica propria three weeks after instillation of the drops, showing cyst-like oedematous degeneration of the stroma (Oed). ×7,500.

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FIG. 6

Electron micrograph of a venule showing the lumen (L) containing red blood corpuscles (RBC), gaping of inter-endothelial junction (J) and thickened endothelial basal lamina (Ebm). ×7,500.

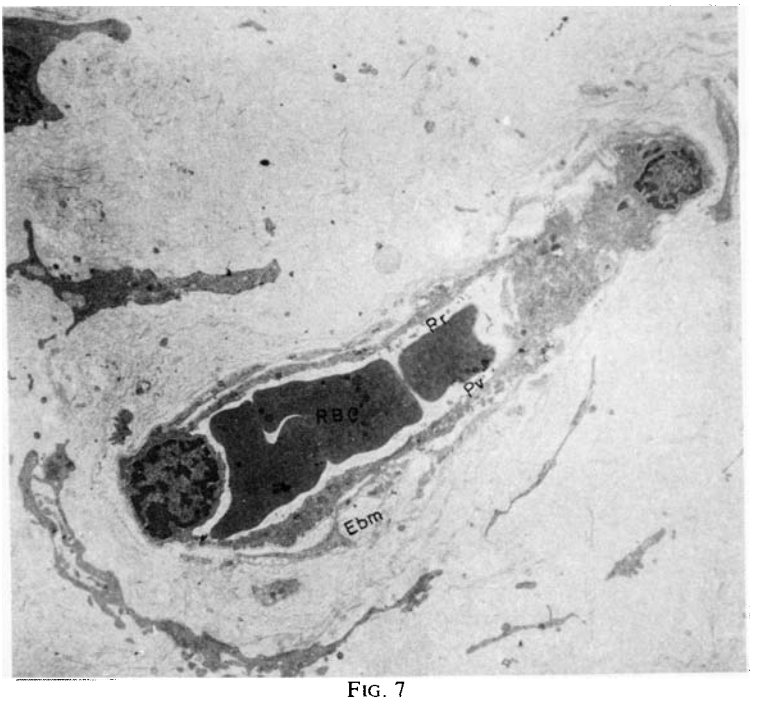


FIG. 7

Electron micrograph of a capillary showing the lumen filled with erythrocytes (RBC), numerous cytoplasmic processes (Pr) and micropinocytotic vesicles (Pv); note the multilayered endothelial basal lamina (Ebm). ×7,500.

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their normal ultrastructure lacking their normal 9+2 pattern of microtubules and appeared in deformed, homogeneous groups. One week later, most of the cilia were destroyed. Some abnormal homogeneous cilia with virus-like particles were seen dispersed over the mucosal surface. A similar observation was described by Hilding and Hilding (1970) following the experimental alteration of the airflow. A latent virus infection of the respiratory epithelium may exist in rabbits and it may be activated by mechanical or chemical injury or by alteration of the airflow.

The increase of intercellular fluid in the epithelial layer was due to enhanced transudation from the dilated and congested tunical blood vessels. This resulted in huge distension of the intercellular spaces with deformity of the cell contour and loosening of the epithelial cells.

The tunical blood vessels showed some evidence of increased permeability in the form of widened inter-endothelial gaping and fenestration, and the increased number of endothelial hairy cytoplasmic processes and micropinocytotic vesicles. The endothelial basement membrane reacted by duplication, lamination and increased thickening as a natural protective attempt to act as a barrier against this abnormal state.

To our knowledge this is the first study of its kind that uses the electron microscope in studying such a vital problem. Vasoconstrictor drops should not be prescribed haphazardly by doctors, neither should they be misused by patients.

Summary

The deleterious effect of decongestant drops on the rabbit respiratory nasal mucosa was studied with the aid of the electron microscope. The cilia were severely damaged, with the appearance of virus-like particles. The epithelium showed characteristic morphological details suggestive of oedematous infiltration. The tunical blood vessels revealed ultrastructural changes of their endothelial lining and basal lamina indicative of increased permeability.

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