

## REGENERATION OF INJURY OF THE RABBITS' (*Oryctolagus cuniculus* var. *edulis*) TRACHEAL EPITHELIUM DUE TO THE INTRATRACHEAL ADMINISTRATION OF AN IODINATED CONTRAST AGENT

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### Abstract

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Ultrastructure of the rabbits' tracheal epithelium was studied 24 and 48 hours after intratracheal administration of 1 ml of iopamidol. Twenty four hours post exposure the ciliated cells revealed only mild signs of pathological alteration, the goblet cells were overstimulated.  $87 \pm 1\%$  of them were completely exhausted and degenerated. Layers of inspissated mucus embedding kinocilia presented signs of self-cleaning ability impairment. Highly condensed masses of iopamidol were encountered in the granulocytes and in a few phagocytic vacuoles in the ciliated cells' cytoplasm. Forty eight hours post exposure the differentiating secretory elements presented 60% of all secretory cells. The cells with isolated small electron-dense granules, typical serous-like cells and small mucous granule cells were observed. The contrast agent was completely removed from the epithelium. Only isolated small clusters of inspissated mucus were encountered in the area of the ciliary border. The damage to the airways' epithelium due to the iopamidol administration was not repaired completely in the course of 48 hours.

*Airways' epithelium, iopamidol, tracheobronchography, electron microscopy*

The important diagnostic method - tracheobronchography - is used both in human and in veterinary practice, but the effect of the intratracheal administration of contrast agents on the airway epithelium has not been studied. The authors dealt only with the mechanical damage produced in the mucous membrane by insertion of the catheter into the respiratory passages (Gordon and Lane 1976; Keenan et al. 1982, 1983; Lundgren et al. 1983; Nordin 1982). In our previous studies we therefore concentrated on the injury caused in the airway epithelium by the intratracheal administration of several new iodinated contrast agents (Konrádová et al. 1990, 1992, 1995). From the morphological point of view, the impairment due to the treatment with iopamidol could be classified as mild. This agent was less injurious to the mucosa compared with other studied agents (Konrádová et al. 1995). Therefore we decided to investigate also the process of regeneration of this epithelium 24 and 48 hours after iopamidol administration.

### Materials and Methods

In our experiments 6 healthy rabbits (body mass 1.500 - 2.000 g) were used. Using the same method described in our previous study (Konrádová et al. 1995), the rabbits were injected with 1 ml of iopamidol [N,N' - bis (2 - hydroxy - 1 - hydroxy - methyl - ethyl) - 2,4,6 - triiodo - 5 - lactamido - isophthalamide introduced by BRACCO, Industria Chimica di Milan, Italy, under the name IOPAMIRO] into their airways. The rabbits were divided into 2 groups. The material for the electron microscopical examination was collected from 3 animals 24 hours and 48

hours post exposure, respectively. For processing the material and for the quantitative evaluation of the ciliary border and of the functional state of the goblet cells the same methods as in our preceding study were used (Konrádová and Šrajer 1987, Konrádová et al. 1995). Twenty four and forty eight hours post exposure 600 and 576 goblet cells and 2,361.75  $\mu\text{m}^2$  and 2,063.75  $\mu\text{m}^2$  of the ciliary border with 12,101 and 8,813 cilia were evaluated, respectively.

## Results

### Ultrastructure of the tracheal epithelium 24 hours after intratracheal administration of iopamidol

Twenty four hours after intratracheal administration of iopamidol the rabbits' tracheae were lined with an altered pseudostratified columnar ciliated epithelium. The apical junctional complexes remained intact. At some places slightly dilated intercellular spaces were invaded by individual lymphocytes and rather numerous neutrophilic granulocytes. The granulocytes were rich in small granules filled with highly electron-dense material. In some degenerating ones voluminous clumps of this electron-dense substance were encountered in their markedly damaged cytoplasm (Plate I., Fig. 1).

On the apical portion of the ciliated cells, isolated small cytoplasmic protrusions were observed. Inside these blebs individual axonemes of kinocilia were exceptionally revealed (Fig. 2). In the ciliated cells cytoplasm, slightly dilated cisternae of the granular endoplasmic reticulum and of the Golgi complex, and a mild increase in the number of tiny vacuoles and lysosomes were encountered. In some cells also larger vacuoles entirely filled with homogenous, highly electron-dense substance were observed. Together with the other partly

Table 1  
Quantitative evaluation of the functional state of goblet cells (GC) in the tracheal epithelium of rabbits after intratracheal administration of iopamidol (relative values)

	controls	iopamidol 5 min	iopamidol 24 hours	iopamidol 48 hours
non-stimulated GC	97 ± 1%	57 ± 6%	3 ± 2%	80 ± 4%
mucus-discharging GC	3 ± 1%	27 ± 7%	10 ± 3%	6 ± 2%
degenerated GC	0	16 ± 4%	87 ± 1%	14 ± 4%
stimulated GC (mucus-discharging + degenerated)	3 ± 1%	43 ± 6%	97 ± 2%	20 ± 4%
GC arranged in groups	6 ± 3%	9 ± 2%	8 ± 2%	7 ± 2%

n = 3, mean ± SD, \* — \* values differ significantly (p = 0.0003) from each other

Table 2  
Quantitative evaluation of the ciliary border of the tracheal epithelium of rabbits after intratracheal administration of iopamidol (relative values)

	controls	iopamidol 5 min	iopamidol 24 hours	iopamidol 48 hours
intact kinocilia	98.8±0.1%	88.3±2.4%	96.8±1.6%	98.2±0.4%
pathological cilia	0.5±0.2%	1.2±0.2%	0.9±0.5%	1.0±0.3%
degenerating cilia	0.3±0.1%	8.3±4.1%	1.8±1.1%	0.1±0.1%
malformed kinocilia	0.4±0.2%	2.2±3.6%	0.5±0.3%	0.7±0.2%
altered kinocilia (pathological + degenerated + malformed)	1.2±0.1%	11.7±2.4%	3.2±1.6%	1.8±0.2%

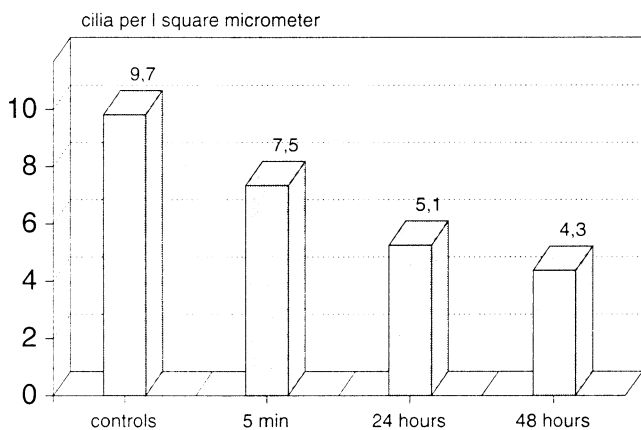
n = 3, mean ± SD, \* - \* - values differ significantly (p = 0.00025) from each other

degraded cytoplasmic material, an electron-dense substance was also encountered in more voluminous vacuoles (Fig. 3). Rather numerous voluminous ciliated vacuoles were also noticed in the ciliated cells' cytoplasm. The differentiating ciliated cells containing clusters of basal bodies in different stages of development in their cytoplasm rich in ribosomes were observed only exceptionally.

The secretory cells were scattered among the ciliated ones. Only  $8 \pm 2\%$  of them were arranged in tiny groups (Tab. 1);  $3 \pm 2\%$  of the goblet cells did not reveal signs of secretion. Only about half of them were packed with large, light mucous granules. The others contained developed granular endoplasmic reticulum, voluminous Golgi complex, not very numerous, rather small mitochondria and isolated moderately large highly electron-dense granules in their cytoplasm.

Ninety seven  $\pm 2\%$  of the goblet cells had been stimulated to discharge their mucus. Twenty four hours post exposure only  $10 \pm 3\%$  of them still discharged their secretion (Tab. 1). These cells widely communicated with the airways' lumen and mucus was evacuated simultaneously from several apical granules. Exceptionally also the detachment of whole packets of granules was observed.

Eighty seven  $\pm 1\%$  of goblet cells were exhausted (Tab. 1). Only remnants of their condensed highly electron-dense cytoplasm were observed in the apical portion of the



Graph. 1 Mean number of cilia per 1 square micrometer of the ciliary border in the trachea of rabbits after intratracheal administration of iopamidol

cilia disturbing their regular arrangement. On average  $5.1 \pm 0.2$  cilia per  $1 \mu\text{m}^2$  were counted (Graph 1).

In the ciliary border mostly intact cilia with the  $9+2$  inner pattern were noticed (Tab. 2). The altered ones amounted only to  $3.2 \pm 1.6\%$ . The slightly damaged pathological cilia containing tiny vacuoles in their shafts, or revealing local swellings of their limiting membrane formed  $0.9 \pm 0.5\%$  of all kinocilia. The degenerated ones, represented mostly by axonemes incorporated into apical cytoplasmic blebs, amounted to  $1.8 \pm 1.1\%$ . The malformed cilia with axonemes that differ in number or arrangement of microtubules from the typical  $9 + 2$  ones reached only  $0.5 \pm 0.3\%$ . In some places voluminous layers of condensed mucus embedded the kinocilia (Fig. 5).

#### Ultrastructure of the tracheal epithelium in rabbits 48 hours after intratracheal administration of iopamidol

Forty eight hours post exposure an altered columnar pseudostratified ciliated epithelium was found in the rabbits' tracheae. The apical junctional complexes were intact and the intercellular spaces were slightly dilated only just above the basal lamina.

A few tiny cytoplasmic blebs with a small number of the axonemes of the degenerating kinocilia were revealed on the apical portions of the ciliated cells. In their cytoplasm a slight increase in small secondary lysosomes and voluminous intracytoplasmic ciliated vacuoles were sometimes observed. Only exceptionally the differentiating ciliated cells appeared in the epithelium.

The secretory cells were mostly observed singly in the epithelium, only  $7 \pm 2\%$  of them forming tiny groups (Tab. 1).  $80 \pm 4\%$  of the goblet cells were not stimulated, but only a quarter of them were completely filled with large, light mucous granules. In the epithelium also cells with the cytoplasm rich in ribosomes containing tiny mitochondria with rather electron-dense inner matrix and a few small granules with highly condensed content were revealed (Plate II., Fig. 6). These cells communicated widely with the lumen of the respiratory passages and their apical portions often bulged among the free kinocilia (Fig. 7). At some places isolated portions of their cytoplasm were encountered lying freely in the area of the ciliary border. Isolated cells with developed cisternae of the granular endoplasmic reticulum, voluminous Golgi complex and several larger highly electron-dense secretory

epithelium. They often bulged above the level of the surrounding cells and after sloughing off they lay free above the epithelium (Fig. 4).

A slightly impaired ciliary border was revealed above the epithelium. Remnants of degenerated cytoplasm of the sloughed exhausted goblet cells, isolated cytoplasmic blebs of the apical portions of altered ciliated cells and remnants of membranes were situated among the

granules were also found in the epithelium (Fig. 8). They usually did not form apical cytoplasmic protrusions. Some non-stimulated secretory cells were packed with rather small, but mostly electron-lucent secretory granules separated by wide cytoplasmic septa (Fig. 9). The process of blebbing was again recorded at their apical portions.

The stimulated goblet cells amounted to  $20 \pm 4\%$  (Tab. 1). Only  $6 \pm 2\%$  of them were discharging their secretion. Mucus was mostly evacuated from apical mucous granules, and  $14 \pm 4\%$  of goblet cells were exhausted, degenerated. The remnants of their sloughed off degenerated cytoplasm were found in the area of the ciliary border only exceptionally.

The ciliary border with  $4.3 \pm 0.2$  cilia/ $\mu\text{m}^2$  (Graph 1) showed signs of impairment. Portions of the apical cytoplasmic protrusions of the secretory and ciliated cells and remnants of membranes together with clumps of condensed secretion were situated among the kinocilia (Fig. 10). The intact cilia amounted to  $98.2 \pm 0.4\%$  and the pathological, degenerating and malformed ones represented  $1.0 \pm 0.3\%$ ,  $0.1 \pm 0.1\%$  and  $0.7 \pm 0.2\%$ , respectively (Tab. 2).

### Discussion

In the course of the whole experiment the rabbits' tracheae were lined with an altered pseudostratified ciliated epithelium. The junctional complexes were intact and the slight dilatation of the intercellular spaces was recorded only 24 hours post exposure. In this period the vacuoles of the granulocytes invading these spaces contained highly electron-dense material representing the administered contrast agent. These cells played apparently a role in the removal of iopamidol from the airways. Forty eight hours post exposure the intercellular spaces were narrow again and the leukocytes completely disappeared.

The injury due to the ciliated cells by the administration of the contrast agent was only mild. In the course of 48 hours the process of apical blebbing gradually disappeared. Twenty four hours post exposure the presence of the contrast agent was recorded in some ciliated cells. Iopamidol was apparently injurious for their cytoplasm. The electron-dense substance was contained in phagocytic vacuoles, often it was revealed in voluminous autophagosomes, in the most damaged cells the contrast agent was observed intermingled with the remnants of the degenerated cytoplasm. The cells containing iopamidol were removed from the epithelium in the course of the next 24 hours. The ciliated cells, that did not take part in the contrast agent removal, revealed no sign of pathological alteration 48 hours after iopamidol administration. Compared with controls the amount of the differentiating ciliated cells did not rise in the course of the whole experiment.

The peak of the goblet cells' reaction due to the contrast agent administration was encountered 24 hours post exposure. At this phase the injury to the goblet cells was classified as severe. After rapid mucus evacuation they did not take part in further secretory cycles but they mostly degenerated and were gradually expelled from the epithelium. In the course of the whole experiment mucus was evacuated from apical mucous granules and exceptionally the detachment of whole packets of granules was also noticed. The most rapid mechanism of secretion when tandem fusion and fission of the neighbouring mucous granules membranes was followed by the chain exocytosis of the whole mucus load from the cell (Specian and Neutra 1980; Roumagnac and Laboissee 1987), was never recorded.

Although individual differentiating goblet cells were already found 24 hours after iopamidol administration, an excessive differentiation of new goblet cells was observed 48 hours post exposure, when differentiating secretory elements in various stages of their development represented as much as 60% of all goblet cells in the epithelium.

Cells containing only a few small highly electron-dense granules in their undifferentiated cytoplasm represented the first stages of the secretory elements' development. Typical serous cells were also found in the epithelium. These cells were already described in the tracheae of some animals (Ramphal et al. 1979; Pack et al. 1981; Spicer et al. 1990) including rabbits (Plopper 1983; Plopper et al. 1983a,b, 1984) born and bred in sterile conditions. In 1983 Reid with her fellow-workers proved that these cells were able to transform quickly into the typical goblet cells after exposure to different noxious agents (Reid et al. 1983; Rogers et al. 1993). The next developmental stage of the secretory elements could be the cells containing numerous small secretory granules with the typical mucous appearance. These cells had a character of „small mucous granule cells“ described by McDowell and her co-workers (1983, 1987) as differentiating secretory elements in the trachea of the guinea-pigs.

In the course of the whole experiment a slightly altered ciliary border was observed above the epithelium. The most serious injury to the ciliary border was ascertained 5 min post exposure. Nevertheless, even in this early phase, the amount of pathological and degenerating cilia did not reach the 10% level. In the next phases the number of pathological and degenerating cilia gradually decreased to the values that did not differ significantly from controls, reflecting thus the decreasing rate of apical blebbing on the ciliated cells. The low

Table 3  
Evaluation of the degree of injury to the tracheal epithelium after intratracheal administration of iopamidol

	Injury to the epithelium		
	mild I	moderate II	severe III
stimulated GC	< 50%	50-90%	> 90%
ratio $\frac{\text{discharging GC}}{\text{degenerated GC}}$	> 1	0.1-1	< 0.1
mean number of cilia/ $\mu\text{m}^2$	> 7	3-7	< 3
altered cilia	< 2%	2-10%	> 10%
signs of impairment of self-cleaning ability	0	+	++

	iopamidol 5 min	iopamidol 24 hours	iopamidol 48 hours
stimulated GC	43% I	97% III	20% I
ratio $\frac{\text{discharging GC}}{\text{degenerated GC}}$	$\frac{27\%}{16\%} = 1.7$ I	$\frac{10\%}{87\%} = 0.1$ II--III	$\frac{6\%}{14\%} = 0.4$ II
mean number of cilia per $1 \mu\text{m}^2$	7.5 I	5.1 II	4.3 II
altered cilia	11.7% III	3.2% II	1.8% I
signs of impairment of self-cleaning ability	+ II	++ III	± I-II

GC = goblet cells

proportion of malformed cilia showed that by means of intratracheal administration of the contrast agent the ciliogenesis was not significantly impaired. The only sign of some alteration of kinocilia formation was a slight increase in the number of the voluminous intracytoplasmic ciliated vacuoles.

In the course of the experiment a continuous decrease of the average number of cilia per  $1 \mu\text{m}^2$  was recorded. We suppose that this process was due to the high degree of goblet cells' stimulation and differentiation. The stimulated goblet cells widely communicated with the lumen of the airways, thus affecting the regular arrangement of cilia. Later the extensive differentiation of new goblet cells caused the relative decrease in the number of ciliated cells in the epithelium.

Immediately after administration of iopamidol, the contrast agent appeared as tiny needle-shaped highly electron-dense particles in the lumen of the airways (KONRÁDOVÁ et al. 1995). In the next phases we did not find any particles of iopamidol in the area of the ciliary border.

During the whole experiment, signs of the impairment of the self-cleaning ability of the airways' epithelium were found. They were the most severe 24 hours after iopamidol administration. Forty eight hours post exposure small clusters of condensed mucus observed in the area of the ciliary border demonstrated a gradual improvement of the mucus flow in the airways.

Five minutes after iopamidol administration the degree of damage to the tracheal epithelium was classified as mild, but the increase in number of altered cilia caused the impairment of the self-cleaning ability of the epithelium (KONRÁDOVÁ et al. 1995). Twenty four hours post exposure the injury to the epithelium was moderate to severe (KONRÁDOVÁ 1991). The high degree of goblet cells' stimulation was reflected in severe disturbances of the mucus-flow in the airways. Forty eight hours after iopamidol administration the injury was again classified as mild to moderate (Tab. 3). We arrived at the conclusion that the damage to the airways' epithelium due to the intratracheal administration of the iopamidol was not completely repaired in the course of 48 hours post exposure.

### **Regenerace poškození tracheálního epitelu králíků (*Oryctolagus cuniculus* var. *edulis*) po intratracheální aplikaci jódované kontrastní látky**

Ultrastruktura tracheálního epitelu králíků byla studována 24 a 48 hodin po intratracheální aplikaci 1 ml iopamidolu. 24 hodin po aplikaci jevíly řasinkové buňky jen mírné známky patologické alternace pohárkové buňky byly však výrazně stimulovány,  $87 \pm 1 \%$  z nich bylo úplně vyprázdněných a degenerovaných. Jako známky narušení samočistící schopnosti epitelu byly nalezeny vrstvy zahuštěného hlenu vyplňující prostory mezi řasami. Vysoce kondenzované masy iopamidolu se nacházely v granulocytech a v několika fagocytárních vakuolách v cytoplazmě řasinkových buněk. 48 hodin po aplikaci představovaly diferencující se sekreční elementy 60 % všech sekrečních buněk. V epitelu se vyskytly buňky s izolovanými, malými, elektronově denzními granuly, buňky podobné typickým serózním buňkám a buňky s malými hlenovými granuly. Kontrastní látka byla již kompletně odstraněna z epitelu. V oblasti řasinkového lemu byly nalezeny jen izolované malé shluky zhuštěného hlenu. Poškození epitelu dýchacích cest způsobené aplikací iopamidolu nebylo během 48 hodin zcela reparováno.

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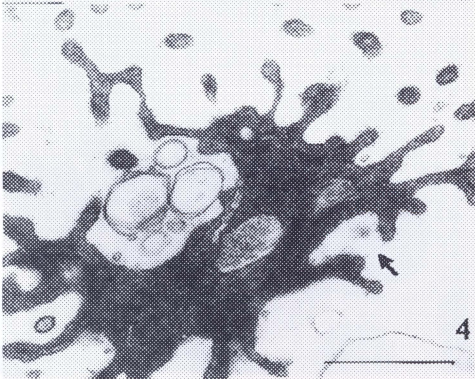
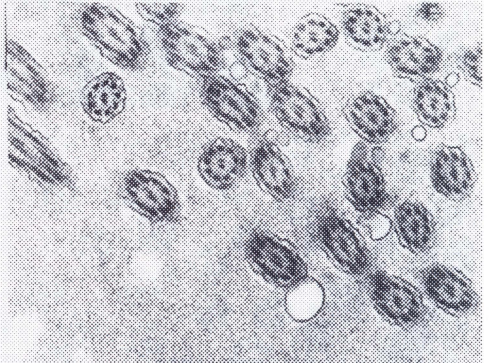
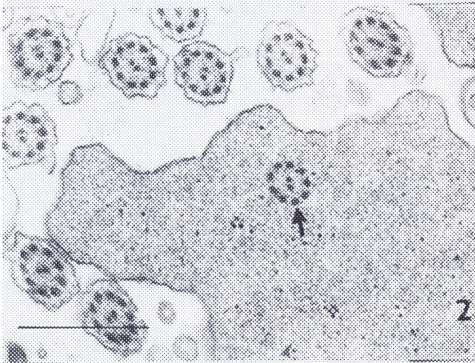
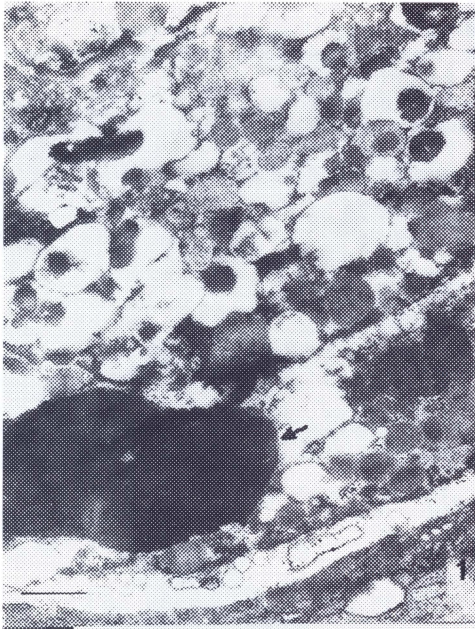
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### Description of figures

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Plate I.

Figs 1 - 5 represent rabbit's tracheal epithelium 24 hours after intratracheal administration of iopamidol.

Fig. 1. Portion of the cytoplasm of degenerating granulocyte containing a voluminous clump of highly condensed contrast agent.

Fig. 2. Tiny apical cytoplasmic protrusion with an axoneme of degenerating cilium.

Fig. 3. Focal cytoplasmic degradation with a clump of highly condensed contrast agent in the ciliated cell cytoplasm.

Fig. 4. Portion of a sloughed off, degenerated goblet cell's cytoplasm in the area of the ciliary border.

Fig. 5. Layer of condensed mucus embedding free cilia.

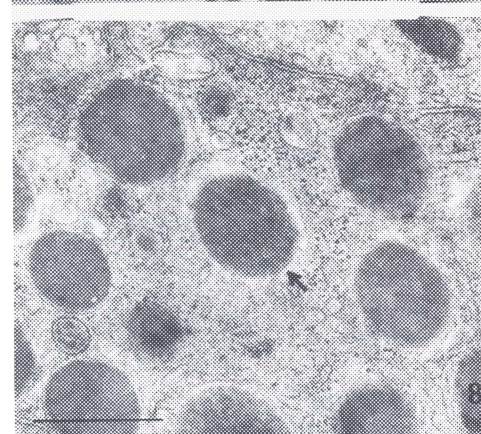
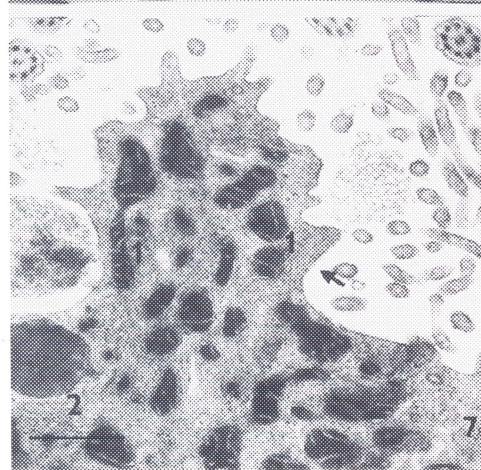
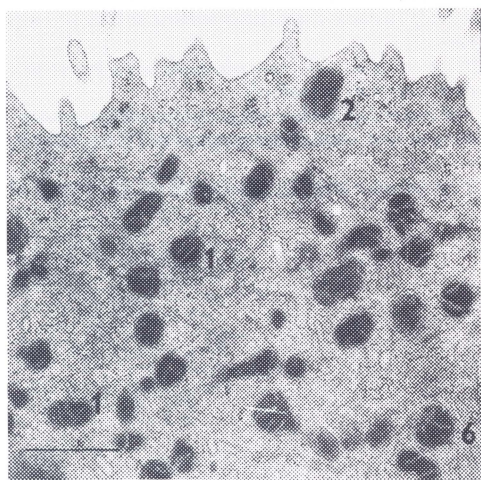


Plate II.

Figs 6 - 10 represent rabbit's tracheal epithelium 48 hours after intratracheal administration of iopamidol.

Fig. 6. Apical portion of a differentiating secretory cell containing numerous small mitochondria with dense inner matrix (1) and isolated small electron-dense secretory granules (2).

Fig. 7. Cytoplasmic protrusion on the apical portion of a differentiating secretory cell containing tiny mitochondria with dense inner matrix (1) and an isolated small electron-dense secretory granule (2).

Fig. 8. Portion of the cytoplasm of a serous-like secretory cell containing isolated larger electron-dense granules.

Fig. 9. Apical portion of a small mucous granule cell containing isolated smaller mucous granules (1) separated by wide cytoplasmic septa.

Fig. 10. Slightly altered ciliary border with remnants of a cytoplasmic bleb (1), membranes (2) and clumps of condensed secretion (3) among the kinocilia.