QUANTITATIVE STUDY OF PULMONARY LESIONS AND EPITHELIAL PROLIFERATION FOLLOWING INHALATION OF $^{239}PuO_2$ IN RATS

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Morphometric analyses of lung parenchyma exposed to $^{239}PuO_2$ indicated a volumetric increase in pulmonary fibrosis, epithelial metaplasia, and neoplasia with increasing time after exposure. Metaplastic and neoplastic lesions usually occupied less than 1% of the total lung volume.

Inhaled $^{239}PuO_2$ induces pathological sequelae characterized by radiation pneumonitis, fibrosis and epithelial metaplasia leading to neoplasia. This study attempted to quantitatively measure the development of these pulmonary lesions. In addition, cell turnover of normal and abnormal pulmonary epithelium was investigated, using ^{3}H-thymidine and autoradiography.

Thirty-two rats were given a single exposure to $^{239}PuO_2$ aerosol and killed at 250-530 days after exposure; each rat was also given an intraperitoneal injection of 1.5 nCi ^{3}H-thymidine about 2 hr prior to necropsy. Lungs fixed with glutaraldehyde-formaldehyde at 20 cm H_2O were embedded in methacrylate, and 0.5- to 1.0-mm-thick sections were cut for morphometric analysis and autoradiography using Ilford K-5 emulsion. The terminal lung burden in all groups averaged 1.5-41 nCi. Lung sections were analyzed by point-counting morphometric methods for relative volume of normal tissue, pneumonitis with or without fibrosis, epithelial metaplasia, and lung tumors.

The volume of normal lung tissue decreased from 100% for controls to about 85% for $^{239}PuO_2$-exposed rats at 530 days after exposure (Table 14). Nearly all abnormal lung tissue was characterized as fibrotic, due to radiation damage from ^{239}Pu. Epithelial metaplasia ranged from 0.026% at 257 days to 0.42% at 530 days; metaplasia was not found in control lungs. Epithelial tumors (adenocarcinoma and squamous-cell carcinoma) also increased in volume with increasing time after exposure, up to an average of 1.35% at 530 days. Linear regression analyses indicated a statistically significant decrease in normal lung tissue, and a significant increase in pulmonary fibrosis, epithelial metaplasia, and epithelial tumor volume.

Visual inspection of autoradiograms indicates a much higher labeling of metaplastic and neoplastic cell nuclei with ^{3}H-thymidine than for normal lung epithelial cells, indicating an increased cell turnover rate for epithelial lesions (Figure 16). Labeling index studies are continuing.

TABLE 14. Relative Volumes of Normal and Pathologic Tissue in Rat Lung Following Inhalation of $^{239}PuO_2$

Days After Exposure to $^{239}PuO_2$	Number of Rats	Amount of ^{239}Pu in Lung at Death	% of Lung Volume[a]			
			Normal	Fibrosis	Epithelial Metaplasia	Epithelial Tumor
Unexposed Control						
468	2	0	100	0	0	0
530	2	0	100	0	0	0
Exposed						
257	8	32 ± 14	98 ± 1.0	1.8 ± 1.1	0.026 ± 0.010	0
319	8	31 ± 10	97 ± 1.6	2.9 ± 1.6	0.15 ± 0.056	0.069 ± 0.069
375	5	11 ± 2.6	94 ± 2.4	3.3 ± 1.5	0.19 ± 0.094	0.18 ± 0.18
412	5	18 ± 5.6	92 ± 3.7	7.8 ± 3.7	0.094 ± 0.038	0
468	3	41 ± 8.6	96 ± 1.4	3.1 ± 1.2	0.25 ± 0.16	0.36 ± 0.36
530	3	1.5 ± 0.64	84 ± 3.3	12 ± 3.4	0.42 ± 0.24	1.35 ± 1.20

[a] Values are mean ± standard error of the mean

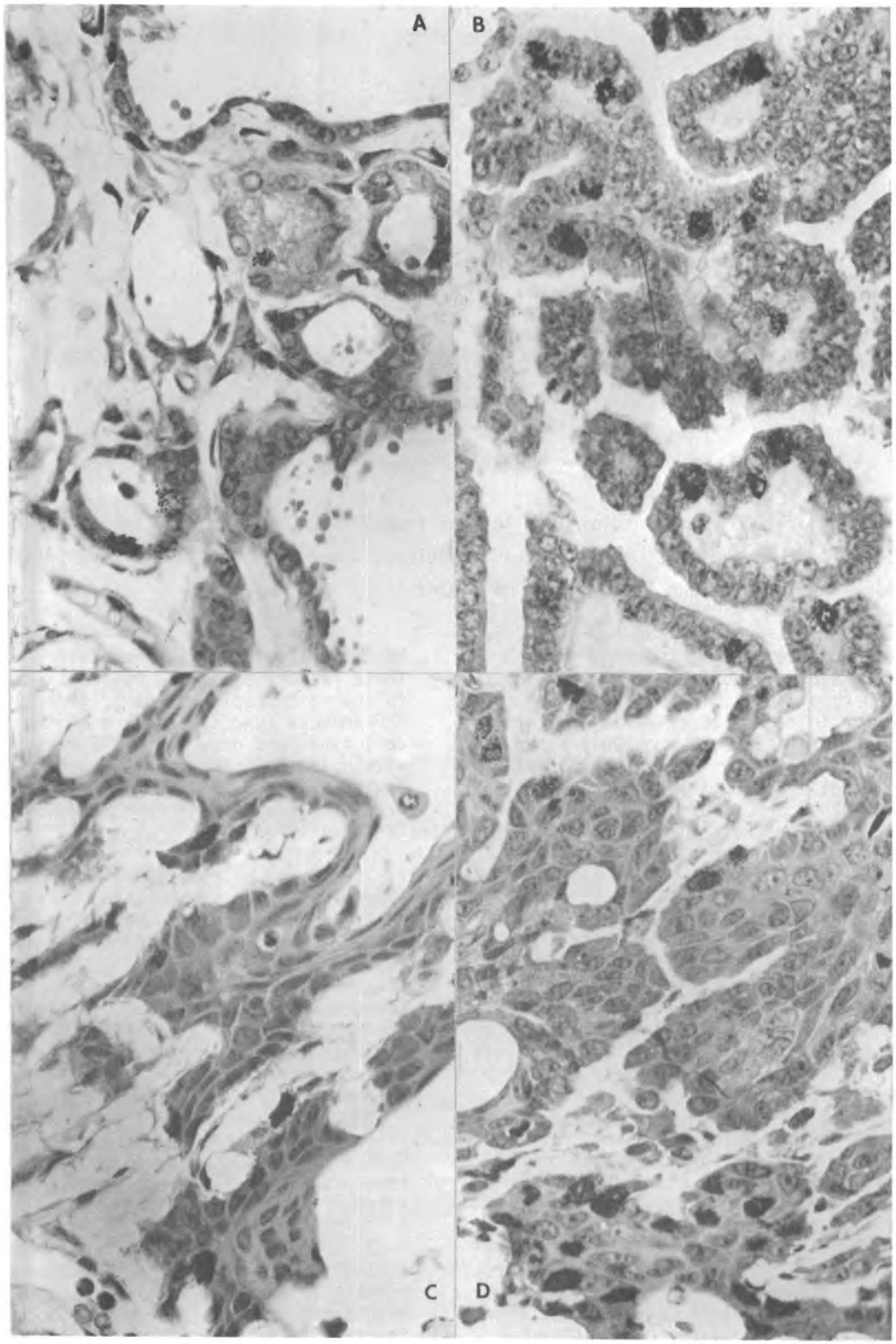

FIGURE 16. Autoradiographs of Epithelial Metaplasias and Neoplasias Following Exposure to a $^{239}PuO_2$ Aerosol. Rats were given 1.5 μCi ^{3}H-thymidine/g body weight 2 hr before autopsy. Exposure time of autoradiographs, 2 wk. Note location of $^{3}HTdR$-labeled cells. All at 220X magnification.

A. Adenomatosis, 375 days postexposure; terminal lung burden, 9.2 nCi ^{239}Pu.
B. Adenocarcinoma, 375 days postexposure; terminal lung burden, 12 nCi ^{239}Pu.
C. Squamous cell metaplasia; same lung as A.
D. Squamous cell carcinoma, 319 days postexposure; terminal lung burden 37 nCi ^{239}Pu.