PULMONARY CARCINOGENESIS FROM PLUTONIUM-CONTAINING PARTICLES

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The potential pulmonary effects of inhaled plutonium have been summarized in recent years (1,2) and the need for further animal research has been emphasized. The results presented here are the outgrowth of an effort to assess the tumorigenesis of focal plutonium sources in the Syrian hamster respiratory tract (3,4). Because localized radiation (hot spots) in bone was known to be more tumorigenic than diffuse radiation, it was thought that this same phenomenon may prevail in the lung tissue. Based primarily upon studies with beta irradiation of the skin (5) models were developed as guidelines for our "hot particle" research.

MATERIALS AND METHODS

To create well-controlled plutonium sources localized in specific numbers in the Syrian hamster lung it was decided to use the intravenous (IV) route of administration. Ceramic spherical particles of zirconium dioxide were manufactured such that fixed small amounts of plutonium could be homogeneously incorporated in them, to control the strength of each particle's radiation field (6). The particles were uniformly 10 μm in diameter (6) and were injected into the jugular vein (7), after which they lodge in the lung capillary bed. A ^{57}Co tag was also added so that retention characteristics could be determined through periodic whole-body counting.

The aerosol particles for inhalation (INH) studies were of two different chemistries. In the earlier work it was decided to nebulize a mixture of the ZrO_2 sol used in the hot particle microsphere manufacture; into the sol was incorporated the desired amounts of ^{238}Pu or ^{239}Pu and ^{57}Co. The sol was nebulized (8) and the droplets passed through a heating column at $\sim 900^{o}C$. The animals were exposed in a nose-only setup (9). The resulting aerosol was polydispersed with a aerodynamic mass median diameter of $\sim$ 1.8 μm and a geometric standard deviation of $\sim$ 1.8. The second type of aerosol was from plutonium dioxide generated in a similar fashion, but the starting material was a suspension of $^{239}PuO_2$ in distilled water. The aerosol samples for analysis were collected with cascade impactors (10) or electrostatic precipitators (11).

The Syrian hamsters were allowed to live out their lifespan and were sacrificed only when moribund. They were necropsied as soon as feasible, and routine gross and microscopic pathological examinations were performed (12, 13).

RESULTS

Data on the tumor incidences in all three (IV and INH) studies are presented in Tables 1-3. The histology slides for the PuO_2 studies have not been completely read so the available results only are presented in Table 3. The types of tumors are indicated in Tables 2 and 3, primarily to show the ratios of adenomas to adenocarcinomas.

TABLE 1. Pulmonary neoplasm incidence following intravenous injection of microspheres in Syrian hamsters

No. of Spheres Per Hamster	Lung Burden (nCi)	No. of Hamsters	Fraction of Lung Irradiated (%)	No. of Tumors	Lung Tumor Incidence (%)
CONTROL	0	521	0	3	0.6
2360	140	68	1	0	0
10 900	97	17	5	0	0
58 800	120	160	28	19	12
312 000	130	25	80	2	8

TABLE 2. Pulmonary neoplasm incidence following inhalation of Pu-ZrO_2 aerosol particles by Syrian hamsters

Initial Lung Burden (nCi)	No. Of Hamsters	Tumor Incidence (%)	Adenoma	Adeno-Carcinoma	Squamous Cell Carcinoma
0	144	0.7	1	0	0
6	40	5	2	0	0
8	43	12	5	0	0
76	50	28	11	6	0
87	50	40	12	8	0
101	44	50	10	9	3

DISCUSSION

It is obvious that plutonium alpha irradiation distributed focally is not tumorigenic (Table 1). When less than 5% of the pulmonary tissue receives the radiation dose, there are no observed

tumors at death. More diffuse irradiation does lead to the formation of tumors.

TABLE 3. Pulmonary neoplasm incidence following inhalation of PuO_2 aerosol particles by Syrian hamsters

Initial Lung Burden (nCi)	No. of Hamsters	Tumor Incidence (%)	Fraction Slides Read*		
			Adenoma	Adeno-Carcinoma	Undifferentiated Tumors**
0	50	0	0	0	0
40	63	4	1/23	0	0
96	66	13	6/54	0	1/54
110	60	7	1/46	1/46	1/46
144	65	16	7/49	1/49	0

* All animals in this study have not been processed; hence, the incidences are based upon fewer than the total exposed in each group.

** Carcinomas and Sarcomas

Inhalation studies are much more productive in the induction of lung tumors, as shown in Table 2. A trend of increased tumor incidence with increasing initial lung burden is obvious. There is also an apparent trend from adenoma induction to more invasive types of tumor, with increasing initial lung burden. The same dosage-incidence trend may be forthcoming in the PuO_2 studies (Table 3), but more data await analysis. A currently unexplained effect is the apparently greater tumor yield produced by Pu-ZrO_2 compared to PuO_2. Averaging the last 3 dose groups of the latter gives 12 ± 3% tumors from a mean lung burden of 117 nCi while averaging the last 2 dose groups of the Pu-ZrO_2 aerosol gives 45 ± 6% from 94 nCi. Particle size and residence time do not account for any difference.

SUMMARY

Plutonium administered as an alpha radiation source to the respiratory tracts of Syrian hamsters has resulted in various incidences of neoplasia. Adenomas are the primary lung tumor observed, but adenocarcinomas are also prevalent.

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