EFFECT OF DUST OF RARE EARTH METALS CONTAINING A RADIOACTIVE COMPONENT ON INCIDENCE OF RETICULOSARCOMA OF THE LUNG

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Data on the incidence of reticular tumors of the lungs in rats following intratracheal administration of dust and concentrates with different levels of specific radioactivity are given. By the 15th-21st month after administration of the dust the incidence of tumors of the lung was eight to ten times higher than in the control at the corresponding time of observation. It is considered that the dust and radioactive factors, especially the latter, play a role in the pathogenesis of the tumors, for the higher the level of radioactivity, the higher the incidence of tumors. Reticulosarcomas were distinctly more frequent than epithelial tumors.

The presence of the long-life radioactive elements uranium and thorium in mineral dust, occurring as isomorphic inclusions in the crystal lattice of natural minerals, may promote the onset of carcinogenesis in the lungs, for which the minimal carcinogenic dose is close to 1000 rad [1, 2, 14, 13, 7, 18, 10]. Spontaneous lung tumors are rare in albino rats [3, 9], and the term "lymphoma" of the rodent lung which appears in the literature [4] is simply the result of the absence of precise criteria of tumor growth in the peribronchial lymphoid tissue [11]. This may account for the fairly higher percentage (6-7) of spontaneous reticuloblastomas of the lungs reported by a number of workers [16, 17].

The effect of radioactive dusts on the incidence of reticulosarcoma of the lungs in rats was studied.

TABLE 1. Incidence of Tumors of the Lungs in Rats Depending on Specific Activity of Dust Injected

Group	Characteristics of dust tested		Activity administered (μCi/kg body weight	Time from beginning of poisoning to observed effect (months)[1]			Total No. of tumors
	thorium content (%)	specific radioactivity (Ci/g)		15	18	21	
1	0,01	1×10^{-10}	1×10^{-5}	0/7	0/12	0,6	0/25
2	0,1	1×10^{-9}	1×10^{-4}	0/9	0/10	0/6	0/25
3	1,0	1×10^{-8}	1×10^{-3}	2/8	1/13	0/3	3/24
4	10,0	1×10^{-7}	1×10^{-2}	3/12	5/14	2/8	10/34

[1]The other times, when no tumors were found to have developed, are not included in the table.

Note: Denominator gives number of animals investigated histologically; numerator gives number of tumors in lungs.

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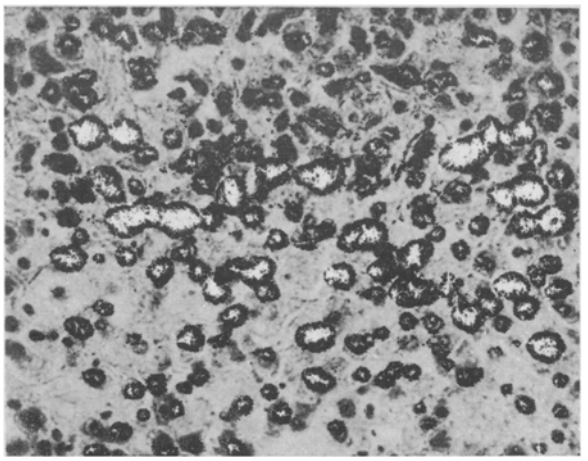

Fig. 1

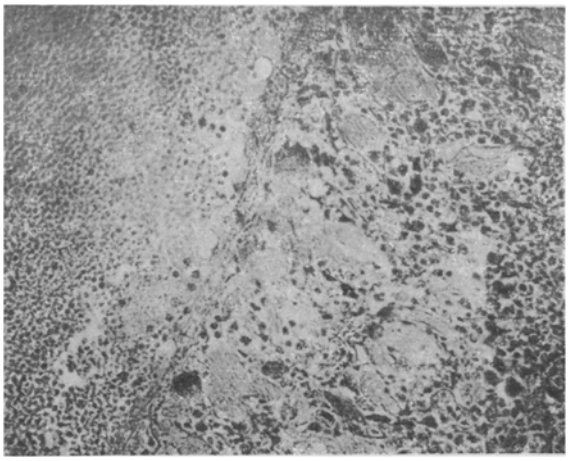

Fig. 2

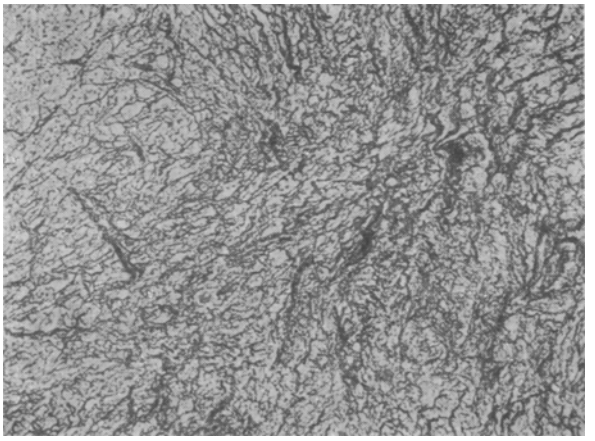

Fig. 3

Fig. 1. Reticulosarcoma of the lungs of a rat developing after administration of loparite mineral dust containing thorium dioxide. Hematoxylin-eosin, 450 ×.

Fig. 2. Invasion of wall of large blood vessel at the hilum of the lung by reticulosarcoma cells. Hematoxylin-eosin, 350 ×.

Fig. 3. Reticular fibers in stroma of reticulosarcoma of the rat lung are interwoven between all the tumor cells. Impregnation by Pap's method, 300 ×.

EXPERIMENTAL

Experiments were carried out on 700 noninbred albino rats divided into five groups with 140 rats in each group. The first group acted as the age control while the rats of the other four groups received a single intratracheal injection of dust samples from loparite and yttroparisite ores and concentrates and dust of oxides of the rare earths (50 mg per rat in each case as a suspension in 1 ml physiological saline). The animals were poisoned with dust containing 0.001-0.01% (group 1), 0.1% (group 2), 1% (group 3), and 10% (group 4) thorium. The specific radioactivity of the dust was thus between $1 \cdot 10^{-11}$ and $1 \cdot 10^{-7}$ Ci/g. The degree of dispersion of all the dusts was practically the same. Histological investigations were carried out on 300 animals, including 50 controls. The distribution of thorium particles in the lung tissue was studied by histoautoradiography, using type A-2 (Research Institute of Photographic Chemistry) emulsion.

EXPERIMENTAL RESULTS

Of 250 animals of the experimental groups examined histologically tumors of the lungs were found in 13 (5.2%). In every case the lung tumors did not appear until 15, 18, or 21 months after intratracheal injection of the dust. Of 250 animals of the experimental groups investigated, 83 were still alive at the age of 15 months, and if the incidence of tumors is calculated for this number of animals it rises to 19.6%. In nine cases various precancerous states of the lungs were observed (metaplasia of the bronchial epithelium and glands, proliferation of the bronchiolar epithelium, well-marked hyperplasia of the centers of the bronchial lymphoid follicles). In the control group there was only one case of anaplastic carcinoma of the lungs (Table 1).

The tumors found in the lungs consisted of the following histological forms: reticulosarcomas, 11; endothelioma (endothelial sarcoma), 1; anaplastic dedifferentiated carcinoma, 1. The absence of highly differentiated carcinomas (squamous-cell and adenocarcinomas) will be noted. All tumors from the lymphoid and reticular tissue of the rat lungs appeared in the region of the hilum as pale gray, friable nodules around the bronchi; sometimes the tumor nodules were distributed throughout the lobe of the right lung or the upper and middle portions of the left lung. Dense, whitish tissue grew along the course of the bronchi and blood vessels as far as the pleura. In three cases tumor masses invaded the mediastinum, and in two cases they invaded the pericardium, epicardium, and myocardium of the right ventricle. Only in one case were metastases found (autochthonous development?) in a lymph gland close to the bronchus of the right lung, but in no other cases were metastases present. On microscopic examination the lymphatic follicles around the bronchi were enlarged and the germinal centers showed marked hyperplasia and consisted of polymorphic cells of reticular type with numerous normal mitoses. However, around the germinal centers there was a barrier of mature small lymphocytes (the picture resembled changes of the type found in Brill–Simmers macrofollicular lymphoma). A difference between neoplastic growth and reactive hyperplasia of the lymphoid and reticular cells in the region of the tumor was disturbance of the structure of the lymphoid follicle (Fig. 1). Many mitoses, mostly abnormal, were observed, together with autophagia, erythrophagia, and, finally, infiltrative growth of the tumor cells into the muscular walls of the great vessels and into the epicardium and myocardium (Fig. 2).

The differential diagnosis between reticulosarcoma and small-cell lymphocyte-like carcinoma [the cells of the latter are smaller and less polymorphic and they do not form a dense network of reticular fibers in the zone of growth of reticulosarcomas (Fig. 3); the cell nuclei of the lymphocyte-like carcinoma have a narrow border of cytoplasm] indicates that these tumors belong to the reticuloblastomatosis group. The combined action of dust and radiation probably was responsible for the formation of the tumors under these experimental conditions, for the ionization effect was transmitted from a tissue with average radiosensitivity (the walls of the alveoli and bronchioles) to the highly radiosensitive lymphoid tissue [8, 12, 15].

Intratracheal administration of 50 mg dust of loparite and yttroparisite ores and concentrates, together with oxides of the rare earth, with a specific activity due to α rays from the thorium component was between $1 \cdot 10^{-8}$ and $1 \cdot 10^{-7}$ Ci/g, into albino rats thus led to the development of a tumor (reticulosarcoma) in 7-20% of cases. The process of reticulosarcoma development goes through a phase of precancerous hyperplasia of the lymphoid tissues. Tumors appeared 15-21 months after injection of the dust in the hilar zones of the lungs, close to (but not in the center of) the sites of concentration of the radioactive substances. The inflammatory component of the combined effect of dust and radiation probably plays an important cocarcinogenic role by stimulating proliferation of the immunocompetent cells of the lungs and thereby increasing their radiosensitivity.

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