A MODEL OF EXPERIMENTAL LUNG CANCER CAUSED BY INTRATRACHEAL INTRODUCTION OF RADIOACTIVE CERIUM

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The overwhelming majority of observations on the cancerogenic action of ionizing radiation have been related to tumors of the skeleton, skin, gastrointestinal tract, liver, kidneys, endocrine glands, mammary glands, etc., arising in animals after external irradiation or the introduction of radioactive materials into the organism. As far as lung tumors are concerned, induced by radioactive substances inhaled into the organism, the literature contains only a small amount of data pertaining to the frequency with which these tumors develop, and the dependence of their development on the amount of energy absorbed, the physicochemical properties, character of distribution, and excretion of the radioactive materials from the lungs, and the species of the animals [1,2,4,6-15]. In this case, the morphological investigations are limited to the diagnostics of the tumors.

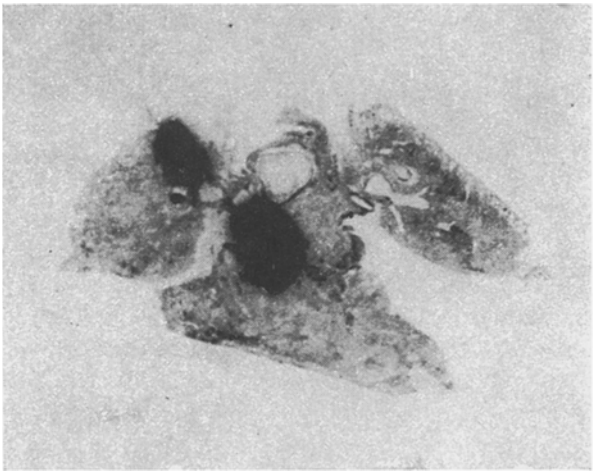

Fig. 1. Autograph of a histotopographic section of the lung. Exposure of 10 days. Blackening of the photoemulsion at the site of cerium-144 accumulation around a major bronchus, out of which there developed a tumor, and in the region of the right lung root.

One of the most frequent routes for access of radioactive substances into the organism is via the organs of respiration. Thus, experimental study of the histogenesis and pathogenesis of lung cancer is of important theoretical and practical interest, this lesion being one of the most possible, primary localizations of malignant tumors in individuals that come into contact with radioactive substances in the course of their work.

The reproduction of lung tumors is associated with great difficulties [3]. The observations noted above, relative to the cancerogenic action of ionizing radiation, were performed mainly on small laboratory animals. However, for complex, multifaceted investigation of the same material, it is more expeditious to develop models of malignant tumors in larger animals.

We set up experiments for the reproduction of lung cancer in rabbits, using a radioactive material.

EXPERIMENTAL METHOD

The basis of the experiments are the data of Cember [9], who produced lung cancer in white rats of the Sprague Dowley line, after intratracheal introduction of a colloidal solution of cerium-144 fluoride. The experiments were performed on 20 rabbits of the chinchilla family, weighing from 2.5 to 3 kg, and 220 white rats, weighing 180 ± 20 g. The colloidal solution of cerium-144 fluoride ($Ce^{144}F_3$) was prepared from cerium-144 chloride.* The dimensions

*Cerium-144 is always found in equilibrium with praseodymium-144. Cerium-144 is a β-γ-radiator, with an energy of its β-particles of 3.1 MeV, and its γ-quanta, 1.25 MeV. The half-life of cerium-144 is 275 days, and of praseodymium-144, $17\frac{1}{2}$ min. The period of half-excretion of cerium-144 chloride from the lungs, with introduction of inhalation, is 24 h [5], and cerium-144 fluoride, 8 days (our data).

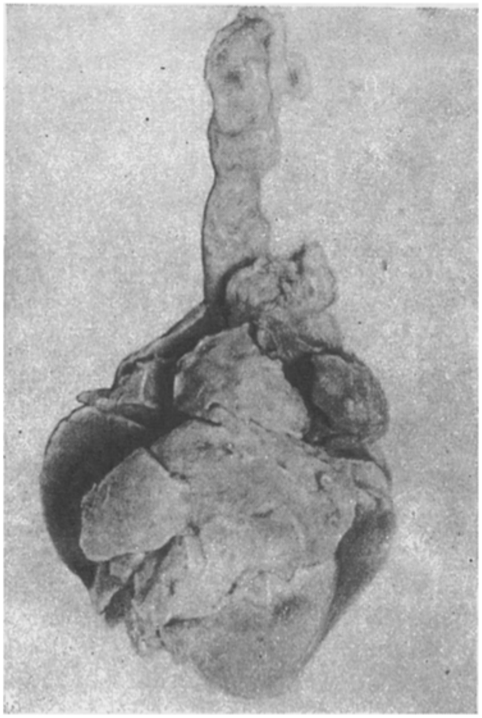

Fig. 2. Malignant tumor of the right lung, with penetration into the mediastinum, 327 days after introduction of the cerium-144.

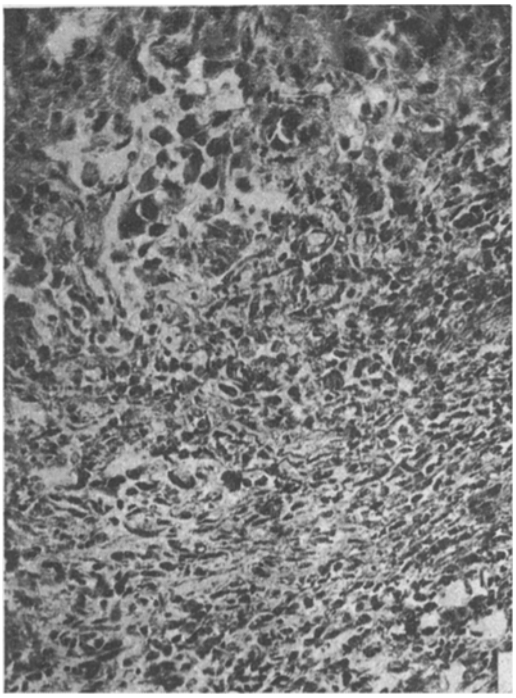

Fig. 3. Bronchogenic carcinoma of the lung, 238 days after introduction of cerium-144. Stained with hematoxylin-eosin. Objective 10 ×, ocular 5 ×.

of the particles of this material were equal to 25 millimicra, and the charge (Z-potential) to $2.4 \cdot 10^{-2}$ microvolts. Intratracheal introduction of the material into the rabbits was carried out with a syringe, by piercing the anterior wall of the trachea without incision of the skin or the use of anaesthesia; in the case of the rats, the animals were narcotized and a skin incision first made. In the first case, each animal was given 0.5 ml of the solution, and, in the second, 0.1 ml. In both cases the activity of the material within the indicated volumes was equal to 25 microcuries. The rabbits were observed up to the time of their natural deaths, in order to ascertain the possibility and frequency of arisal of the tumors. The rats were sacrificed at various intervals after introduction of the material for dosimetric and autographic investigations.

EXPERIMENTAL RESULTS

In the first few days, the cerium-144 fluoride was more or less equally distributed in one or both lungs; then, it was very rapidly concentrated (4th-6th day) in the root zone of the lungs and in the lymph nodes of the mediastinum, remaining there in large amounts for a long period of time (Fig. 1). Thus, for example, after 128 days, approximately 20% of the material introduced was observed in the lungs. The period required for excreting half the material from the lungs was 8 days. Thus, prolonged ionization of the pulmonary tissue took place, especially in the region around the lung roots.

Microscopic investigation of the lungs from the dead animals showed that, beginning with the first days after introduction of the cerium-144 fluoride, an acute bronchopneumonia could develop, with transition into the chronic form. In this case, we traced all the stages in the development of pneumosclerosis, beginning with the development of granulation tissue and up to the formation of coarse-fibered connective tissue with associated massive bronciectasis. As a rule, these changes were observed in the lung root zone, and in the interstitial tissue of the mediastinum, corresponding to the localization of the radioactive material. Sometimes the bronchiectases attained huge proportions, forming large abscesses more than 2 cm in diameter. These abscesses, as well as the fine bronchectactic cavities, always contained purulent exudate. After longer periods of time (100 days or more), it was possible to observe the signs of proliferation and atypical growth of the altered cells in the bronchial epithelium, in addition to metaplasia and proliferation of the alveolar epithelium with formation of the glandular-like structures characteristic for pneumosclerosis of any etiology. At later intervals, these formations took on a highly branching structure. Half the animals died from the lung changes described above in the period from 60 to 238 days after introduction of the material. One rabbit died on the third day, from acute suppurative bronchopneumonia.

The first tumor was observed in a rabbit that died on the 238th day. Subsequently we observed the development of malignant tumors in an additional 5 animals. Thus, out of 20 rabbits used in the experiment, tumors arose in 6 (30%); in 5, bronchogenic and alveolar lung cancer; in one, noncornifying, squamous cell carcinoma of the esophagus. These were solitary formations, sometimes attaining very large dimensions (Fig. 2). We did not observe metastases from the tumors to other organs and tissues. Massive growth of the malignant tumor was observed only in one case, originating from a large bronchus, with penetration into the interstitial tissue of the mediastinum and the cupola of the diaphragm. Microscopically, these tumors did not differ in their structure from the so-called spontaneous tumors (Fig. 3).

The minimum amount of energy absorbed by the lung tissue at the time the first tumor was observed (238th day) was equal to 51.4 krad, and the maximum (327th day), 68.9 krad, which correspond to the existing concepts of the optimal amount of absorbed energy necessary for the production of tumors.

Thus, the data we obtained testifies to the possibility of producing lung cancer in rabbits with the use of colloidal radioactive cerium-144. In this case, it is necessary to maintain the conditions which if fulfilled, to a large degree guarantee the arisal of malignant tumors in any localization. In the first order, this means correct selection of a radioactive material, whose physicochemical properties make it capable of remaining in one or another tissue or organ for a sufficient length of time. This guarantees that the tissue will absorb the optimal amount of energy, necessary for the development of a malignant tumor. In addition, the radioactive material must be used in amounts that do not cause severe general illness, leading to early death of the animals. As shown by in vivo observations, the rabbits in our experiments did not suffer from radiation sickness in its typical form.

The frequency with which lung cancer arose in the rabbits of these experiments corresponds to the limited amount of data obtained in experiments on small laboratory animals (20-30%). However, the markedly large dimensions of the organ and, correspondingly, the tumors themselves, permits the simultaneous use of a large number of the usual histological and histochemical investigative methods, differing from one another in the method of fixation of the tissue, and preparation of the microscopic sections.

The model described can be used successfully for studying chronologically remote sequellae of radioactive materials entering the lungs. This model makes it possible to localize the tumor inducing agent precisely, to control its dosage, and to trace tissue changes in detail, starting from the moment the radioactive material enters the lungs, and up to the obvious development of a tumor; all these features make this ideal for resolving theoretical questions in cancerogenesis and, in particular, the histogenesis of lung cancer.

SUMMARY

The authors developed a model of experimental cancer of the lungs in rabbits, induced with intratracheal administration of colloidal solution of cerium-144 fluoride in a dose of 25 μC. Tumors of the lungs were revealed in 30% of the animals between the 238th and 327th day after administration of the radiosubstance. Authographic and dosimetric determination of radiosubstance was done; the rate of its elimination from the lungs was also studied.

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