INDUCED ADENOMATOSIS OF THE LUNGS IN RABBITS *

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Spontaneous tumors of the lungs are extremely rare in rabbits [7, 13]. However, proliferative changes in the epithelium of the bronchi and alveoli of these animals, as a reaction of various factors injuring lung tissue, are frequently found [9, 11, 15, 17, 18].

The reactivity of the bronchial and alveolar epithelium, expressed as proliferation, is well known in the pathology of animals and man [5, 10, 14, 16]. The impression has been created that the epithelium of the small bronchi and bronchioles, and also the alveolar epithelium of rabbits, possess more marked proliferative properties than the analogous tissues of other laboratory animals. However, no information could be found in the literature concerning either spontaneous or induced adenomatosis of the lungs in rabbits, although it is considered that these processes are associated with proliferation of the bronchial or alveolar epithelium.

The object of the present investigation was to reproduce induced adenomatosis of the lungs in rabbits.

EXPERIMENTAL METHOD

Experiments were carried out on 25 adult rabbits.

In series I 15 animals (males and females) were used, and received intratracheal injections of 9,10-dimethyl-1,2-benzanthracene (DMBA) in a dose of 0.2 mg (4 rabbits), a condensate of cigarette smoke in a dose of 300-700 mg (3 rabbits), and radioactive isotopes in a dose of 1-3.3 μCi (8 rabbits), of which 5 received Ru^{103}, 1 rabbit received P^{32}, and 2 rabbits received Ru^{103} and P^{32}.

The substances for testing were injected by a syringe through a puncture wound of the tracheal wall in the region of the neck. The animals received the above doses once, twice, or three times at intervals of 1, 3, and 8 months.

In series II there were 10 rabbits (5 males and 5 females), which received intratracheal injections of a suspension of DMBA and dry ink in a protein blood substitute. Each animal received 15 mg of the carcinogen (3 injections, each of 5 mg, at intervals of 1 month).

The animals survived until natural death. The lungs, and in case of the discovery of pathological changes in them, the other organs also, of the dying rabbits were examined under the microscope.

EXPERIMENTAL RESULTS

Of the rabbits of series I, 5 died before one month, 2 died between 2 and 4 months, 2—between 5 and 8 months, 1—between 9 and 12 months, 2—between 13 and 24 months, and 3—between 25 and 32 months after the beginning of the experiment.

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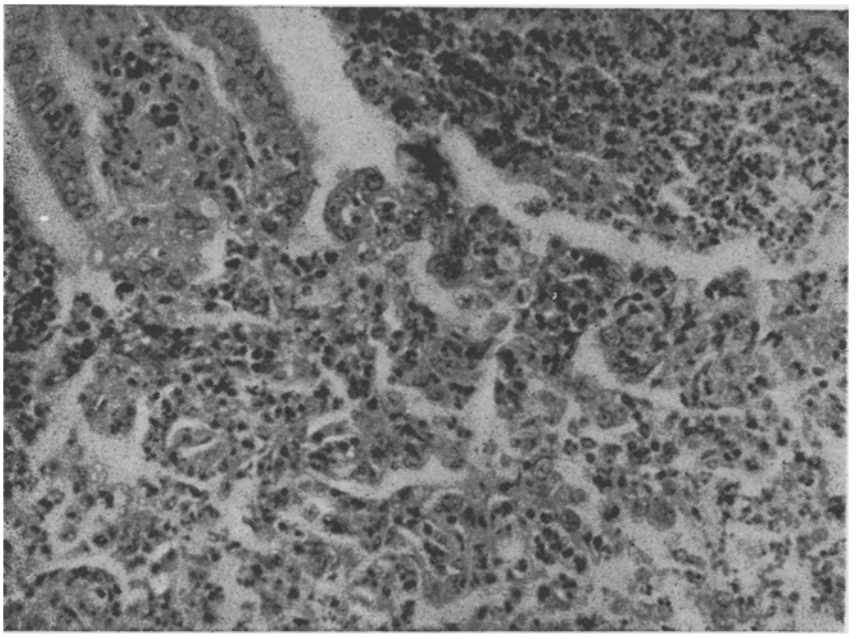

Fig. 1. Invasion of surrounding tissue by epithelium lining a small bronchus. Here and in Figs. 2 and 3, photomicrographs, magnification 240. Hematoxylin-eosin.

Characteristic changes in the lungs were observed in 3 animals.

1. Rabbit No. 8 (8 months from beginning of experiment). This animal received 2.3 μCi of P^{32} and 1 μCi of Ru^{103}. Macroscopically, foci resembling pneumonia were seen in the upper lobes of the lungs. Microscopic examination of the preparations showed well marked proliferation of the epithelium of the large and small bronchi. In some places foci of epithelium of bronchial type apparently lining communicating cavities of different shapes and sizes could be seen. The cell polymorphism was slight. The epithelium lining the alveoli in the circumscribed foci likewise showed proliferation, forming papillae projecting into the cavity. The name given to this process is adenomatosis.

2. Rabbit No. 12 (9 months after first injection of tobacco smoke condensate. Altogether about 700 mg of the substance administered [1]. At necropsy, an abundance of white, mucoid masses resembling sputum was found in the lumen of the trachea and the large bronchi. In all the lobes of the lungs, whitish dense foci were scattered. Microscopic examination revealed marked proliferation of the bronchial epithelium. In some places lightly stained cells lining the middle-sized and small bronchi invaded the surrounding tissues (Figs. 1 and 2). Cuffs of gland-like tissue, composed of light oval and fairly monomorphic cells were situated around the large bronchi. The same type of tissue could be seen in the peribronchial lymphatics, but was not seen in the peritracheal lymphatics. Diagnosis: malignant adenomatosis.

3. Rabbit No. 11 (17 months after the first injection of DMBA. Altogether 4.2 mg of this substance given.) At necropsy a colorless fluid was secreted from the nostrils. In the lower lobes of both lungs, nearer to the hilum, whitish soft nodules were present. Under the microscope changes were seen analogous to those in the lungs of rabbit No. 12. The cells contained mucus. The inflammatory infiltration around the neoplastic tissue was more marked. These changes were defined as malignant adenomatosis.

Of the 10 rabbits of series II, two died before one month, 3—between 1 and 4 months, 3—between 5 and 8 months, and 2—between 9 and 10 months after the end of the experiment.

In 6 rabbits changes resembling those in the lungs of the rabbits in series I were found.

1. Rabbit No. 9 (2 months after first injection of DMBA). Macroscopically, at the apices of both lungs and in the upper lobe of the right lung, multiple foci were observed, yellow in color and in some places confluent. Microscopically, adenomatous foci were found in the lungs just as in the rabbit No. 8 (series I). Diagnosis: adenomatosis without signs of malignancy.

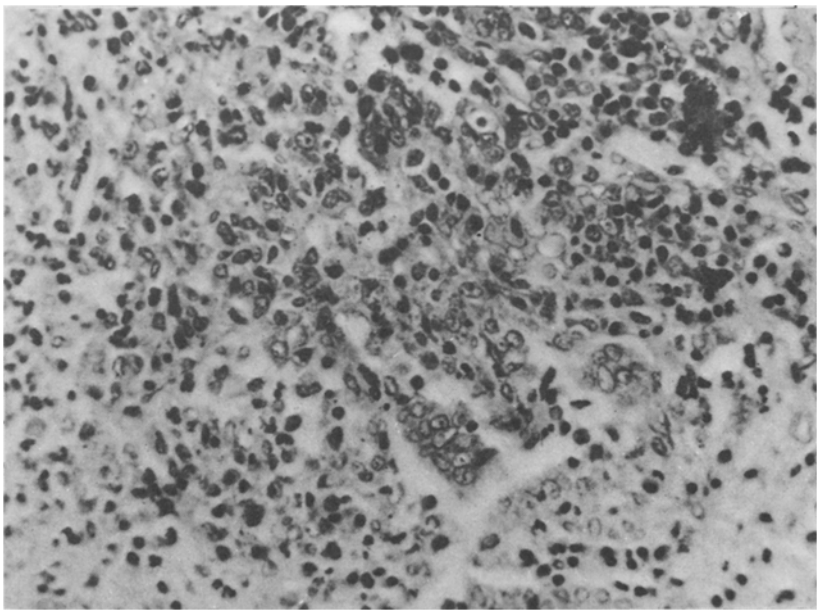

Fig. 2. Small groups of atypical cells infiltrating the inflamed lung tissue.

2. Rabbit No. 1 (3.5 months from the beginning of the experiment). The upper and middle lobes of the right lung and the upper lobe of the left were dark red in color and firm. In the liver, under the capsule, a firm white nodule measuring 0.3 · 0.5 cm was present, not well demarcated from the surrounding tissue. Microscopic examination showed proliferation of the bronchial epithelium. The interalveolar septa were thickened on account of proliferation of the light, slightly polymorphic cells with a vesicular nucleus, frequent mitoses, but no mucus (Fig. 3). In most of the lung the cells formed fairly compact masses, with a sparse collective-tissue stroma (but rich in blood vessels). Here and there the epithelial lining of the small bronchi was interrupted, and the epithelium merged with the surrounding neoplastic tissue. Microscopic examination of the nodule found in the liver showed a picture very similar to that of a metastasis. In this case malignant adenomatosis was present.

In the lungs of the remaining 4 rabbits, which died 5-10 months after the beginning of the experiment, the changes resembled the lesions in the preceding rabbits, but the inflammation was more marked. These changes were regarded as malignant adenomatosis.

Hence, as a result of the intratracheal injection of various carcinogenic agents into 25 rabbits, 9 of them developed a multifocal neoplastic process—adenomatosis of the lungs. In some animals the process appeared to be benign, and in others malignant. Undoubted metastasization into the submucosa of the trachea was observed in one case and in another a metastasis was found in the liver.

Sometimes the epithelium forming the adenomatous foci was similar to the epithelium of the adjacent bronchiole, and contained mucus. In some cases zones of transition from the epithelium lining the small bronchi and bronchioles to the surrounding neoplastic tissue could be seen. Evidently in this case the adenomatosis was bronchiolar in origin. In other cases, the predominant finding was a thickening of the interalveolar septa on account of the proliferation of the right polygonal epithelial cells forming papillae and masses of a solid structure. In these animals the process may be considered to be alveolar in origin.

Induced adenomatosis of the lungs in rabbits is interesting for three reasons. First, it may be either benign or malignant, like many other tumors. Evidently benign adenomatosis may become malignant. This confirms the view that neoplasms develop in stages, as observed during the study of several other induced tumors [4]. Second, adenomatosis of the lungs in experiments on rabbits arise after the injection of chemical and radioactive carcinogenic agents, whereas spontaneous adenomatosis of the lungs in certain animals and in man is regarded by many authors to be a disease of virus origin [6, 8]. The possibility of induction of identical processes by means of agents of different nature is evident that these processes have a multiple etiology. Third and last, during the study of experimental carcinogenesis in the lungs of different laboratory animals, the impression has been created that the reaction of the

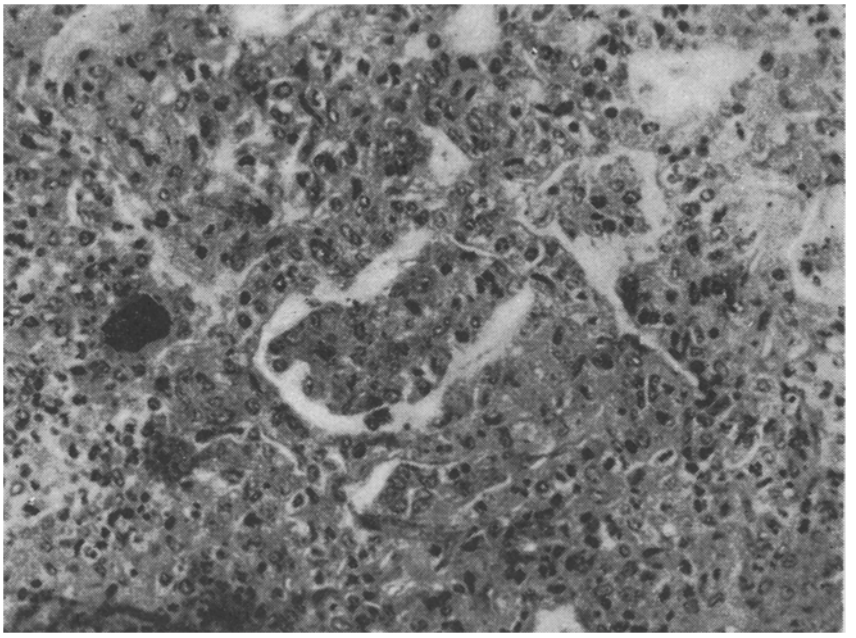

Fig. 3. Diffusely growing neoplastic tissue. Remains of the alveolar cavity in the form of a slit. A particle of ink can be seen.

tissues to carcinogenic agents exhibits species specificity, because the intratracheal injection of carcinogenic substances into rats and hamsters [2, 12] is followed by the appearance of solitary bronchogenic carcinomas, in mice – by adenomas [3], and in rabbits – by adenomatosis of the lungs.

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