

EFFECTIVENESS OF INHALATION AS A METHOD
OF ADMINISTRATION OF ATOMIZED CARCINOGENS

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After inhaling benzidine for 13 months, 8 of 28 rats developed tumors: leukemia, fibroadenomas, carcinoma of the mammary gland, carcinoma of the male mammary gland, and hepatoma. In their localization and structure, these tumors were not significantly different from neoplasms arising in rats after intratracheal, subcutaneous, or oral administration of benzidine.

Many statistical analyses of clinical material [3, 4] have shown that workers coming into contact with benzidine develop tumors of the urinary bladder. Similar tumors have also been found in dogs after feeding with benzidine. In rats and mice, the animals most frequently used in experiments to study carcinogenic activity, no tumors of the urinary bladder have yet been obtained by feeding with or by subcutaneous injection of benzidine. However, in this case these methods of administration cannot be regarded as equivalent to industrial exposure.

The object of this investigation was to study the action of benzidine under conditions closely similar to those in the factory, i.e., when introduced into the lungs of experimental animals.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred albino rats of both sexes, bred at the Rappolovo nursery, and weighing 100-120 g. Benzidine base was used.

In the experiments whose results were published previously [1], benzidine was given to rats through an endotracheal tube in a dose of 10 mg 7 times at intervals of 1 month. In the present investigation 48 experimental rats received benzidine by inhalation while accommodated in four 100-liter dust inhalation chambers designed by the Institute of Work Hygiene and Occupational Diseases, Academy of Medical Sciences of the USSR (Fig. 1). A concentration of benzidine in the air of 10-20 mg/m³ was produced by means of Yu. G. Shirokov's electromagnetic doser. Pure air was provided in four chambers containing control rats. Inhalation was carried out for 4 h at a time, 5 times a week for 20 months.

Weak animals were sacrificed. Organs of dying and sacrificed rats were examined histologically.

EXPERIMENTAL RESULTS

In the early periods of the experiment foci of degeneration and necrosis of the parenchyma were observed in the liver of the experimental rats, followed by regeneration and hyperplasia of the reticulo-endothelial elements. After the experiment had been in progress for 11 months, proliferation of connective-tissue elements began.

The first tumor (myeloid leukemia) was noted in an experimental rat after 13 months of the experiment. Altogether 28 experimental and 21 control rats survived until this time. Tumors appeared in 8 experimental and 2 control rats.

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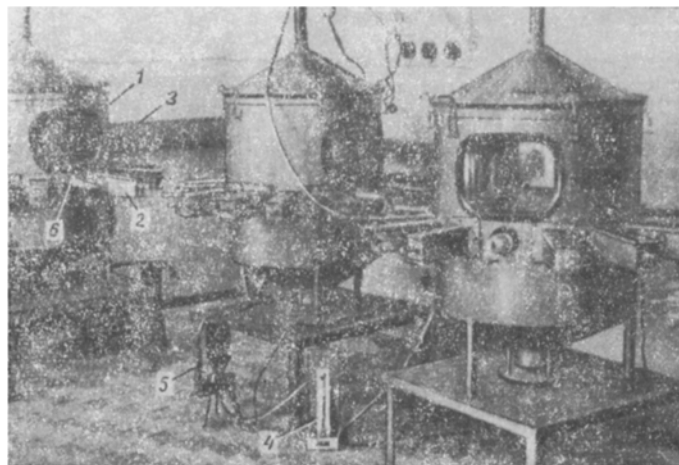


Fig. 1. General appearance of inhalation room. 1) Inhalation chamber; 2) container for rat; 3) air supply pipe; 4) rheometer; 5) doser; 6) socket for taking air samples from chamber.

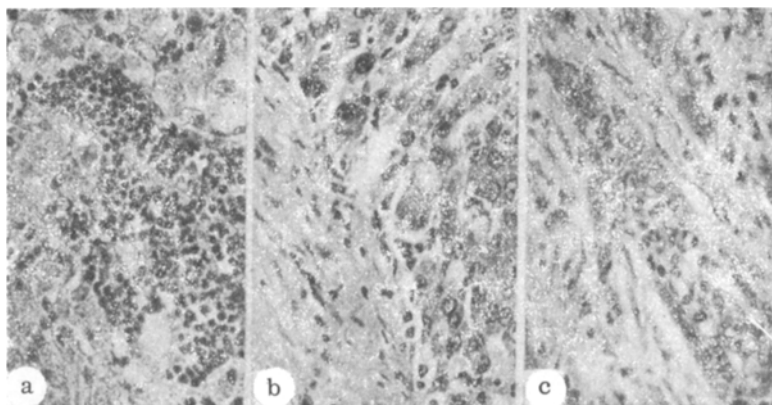


Fig. 2. Tumors in rats after inhalation of benzidine. a) Myeloid leukemia (foci of leukemic cells in adrenal); b) hepatoma; c) adenocarcinoma of the mammary gland. Hematoxylin-eosin, 400x.

The following tumors were found in the experimental animals: myeloid leukemia (Fig. 2a) in 5 rats (after 13, 22, 24, 25, and 28 months of the experiment), fibroadenoma of the mammary gland in 2 rats (15 and 16 months of the experiment), and one case each of squamous-cell keratinizing carcinoma of the male mammary gland (24 months), hepatoma (Fig. 2b, 28 months of the experiment), and adenocarcinoma of the mammary gland (Fig. 2c, 25 months). In two control rats adenomas of the mammary gland were observed (22 and 26 months of the experiment).

Inhalation of benzidine (total dose 27 mg) thus led to the development of leukemias, tumors of the liver, and carcinoma of the female and male mammary glands in 29% of (in 8 of 28) rats, and to the earlier appearance of benign tumors of the mammary glands than in the control. The writer showed previously [1] that after intratracheal administration of 70 mg benzidine, tumors appeared in 11 of 14 rats (79%) after 8 months of the experiment, made up of carcinoma of the male mammary gland in 6, carcinoma of the female mammary gland in 4, and cholangiocarcinoma of the liver in 1. Consequently, inhalation of a smaller total dose of benzidine led to a decrease in the incidence of tumors, an increase in the latent period, and also to the formation of leukemias, which were not observed in experiments with intratracheal injection.

According to published reports [2, 5, 6], rats fed or subcutaneously injected with benzidine also develop tumors of the male mammary gland and liver, and leukemia. It can thus be concluded that the

carcinogenic effect of benzidine, when introduced into the lungs of rats (intratracheally and by inhalation), does not differ significantly from the carcinogenic action of this substance when administered by another method.

The absence of tumors of the urinary bladder in rats receiving benzidine by inhalation or by intratracheal injection can be attributed to the special nature of the metabolism of aromatic amines in rats by comparison with other animals, for example dogs, and also with man. The results of the present experiments show that the character of action of aromatic amines is dependent mainly on the species of the experimental animal rather than on the mode of administration of the substance.

However, when tests of a compound are being undertaken to determine its carcinogenicity or otherwise, what is important is not the localization of the tumor, but simply its presence, and as these experiments have shown, tumors can be obtained by any method of administration of the carcinogenic aromatic amine to rats, including by the subcutaneous method which is usually employed. There is thus no need to resort to laborious experiments with inhalation or to prolonged experiments on dogs.

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