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What is This?
Dose-Response of Submandibular Glands to Carcinogen Pellets in Rats and Hamsters

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SYNOPSIS IN INTERLINGUA

Le Relation inter Dose de Granos de Carcinogenos e le Responsa del Glandulas Submandibular in Rattos e Hamsters.—Pro studiar le effecto carcinogenic de 5, 10, e 20 pro cento 7:12-dimethylbenz-γ-anthraceno mixte con glycerol polyethyleneic, granos continente le mixtura experimental esseva implantate in le glandulas submandibular de rattos e hamsters durante un periodo de 24 septimanas. Un augmento in le dose del carcinogeno resultava in un augmento correspondentemente in le induce tumeurs maligne in ambe species. Tamen, plus carcinomas de cellulas squamose eseva notate in le rattos e plus sarcomas in le hamsters. Iste statisticamente significative differentia in le typo de tumor inducees es attribuite a specificitate de tissu o de specie.

It has been found1 that when 0.05 cc. of 0.5 per cent 7:12 dimethylbenz(a)anthracene in liquid petrolatum was injected into the submandibular gland of 3-month-old hamsters, fibrosarcomas were produced. It was postulated that the carcinogen, when administered by injection, destroyed the ducts and the acini of the glands, replacing them with scar tissue which, by further exposure to the carcinogen, had resulted in fibrosarcomas. It was also speculated that if the carcinogen were administered in the form of pellets, the resulting gradual absorption would act on the glandular components and produce squamous cell carcinomas as demonstrated earlier2-4 in guinea pigs, mice, and rats, but not in hamsters. Pellets containing 0.8 mg. of the carcinogen and 0.32 mg. polyethylene glycerol† were implanted in surgically exposed submandibular glands of hamsters. Surprisingly, the overwhelming response still consisted of fibrosarcomas. Of the 11 animals that survived the 24-week period, 7 developed sarcomas, while none showed squamous cell carcinoma. Since this was contrary to the findings in other species, the present investigation was undertaken to determine if this difference is a function of the dosage levels of the carcinogen and its mode of administration or of the species or tissue specificity.

Materials and Methods

Fifty male albino rats and fifty male Golden Syrian hamsters were used in this investigation. Within each species the animals were matched on the basis of weights and then randomly assigned to the various treatment groups. They were singly caged and maintained on a standard laboratory diet‡ and water ad libitum.

After pentobarbital sodium was given intraperitoneally, a vertical incision was made in the midline of the ventral surface of the neck. By means of blunt dissection, the right and left submandibular glands were exposed and separated from each other. A small cut was made with a scissor in the gland substance, nearly halfway through its thickness, near the lower pole. A pellet, approximately 1 mm.3, containing varying concentrations of the carcinogen, was inserted through the incision into the gland and covered by it. A similar procedure was used to insert the polyethylene pellets, without carcinogen, into the left gland to serve as control. The neck wound was closed in layers with silk sutures. The procedure was the same for both the rats and the hamsters.

The rats were divided into three groups, and different concentrations of the carcinogen were used in each of the groups. The

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1 Purina Lab Chow,Ralston Purina Co., St. Louis, Mo.
three concentrations were 0.2, 0.4, and 0.8 mg. of 7:12 dimethyl(a)anthracene mixed with 0.32 mg. of polyethylene glycol in pellet form; thus, the pellets contained 5, 10, and 20 per cent carcinogen, respectively. The hamsters were given only 5 and 10 per cent dosages in the present investigation, with a 20 per cent group being provided from a preceding investigation carried out at our laboratory.

All animals were sacrificed at the end of 24 weeks, at which time the tumors were excised and fixed in 10 per cent formalin for routine histologic sections. Only tumor-bearing animals were subjected to necropsy for gross or microscopic evidence of metastases.

**Results**

Table 1 presents the incidence of sarcomas and carcinomas in the rats at various dosage levels of the carcinogen. Twelve of the forty-four surviving animals (27 per cent) developed malignant tumors. Four were sarcomas and eight were squamous cell carcinomas. Furthermore, it was also evident that an increase in the concentration of the carcinogen resulted in corresponding increase in the tumor yield.

Table 2 shows the incidence of malignant tumors in the hamsters. Fourteen of the fifty-four animals (25.5 per cent) developed malignant lesions, which were all sarcomas. The difference in relative frequency of the type of tumors induced in the two species was statistically significant at less than 0.01 level as determined by chi-square test. Furthermore, an increase in the carcinogen concentration was associated with a corresponding increase in the incidence of sarcomas. This increase was significant at less than .001 level of confidence (chi-square test).

Only one hamster developed pulmonary metastases from fibrosarcoma resulting from the implantation of a 10 per cent carcinogen pellet. No adenocarcinomas, collision tumors, or so-called mixed tumors of the salivary glands were noted.

**Discussion**

There are few well-planned studies concerning experimental carcinogenesis in the submandibular glands of animals. The most commonly employed laboratory animals have been rats and hamsters; the most commonly used carcinogens, the hydrocarbons—chiefly dimethylbenz(a)anthracene (DMBA), methylcholanthrene (MCA), and benzpyrene (BP). The mode of administration has been either by injection or implantation of pellets.

In spite of enormous complexities in the problem of carcinogenesis in general, and that of the submandibular glands in particular, agreement still emerges on some
aspects of the problem. For example, it is the consensus of various investigators\textsuperscript{5, 4-6} that DMBA, when administered to rats intraglandularly in the form of pellets, produces mostly squamous cell carcinomas with few sarcomas. This is well substantiated in the present investigation in which the ratio of epidermoid carcinomas to fibrosarcomas in rats was found to be 2.5 to 1. The sequence of events that led to the formation of epithelial malignant tumors consisted of metaplasia of ductal epithelium, ductal proliferation, epidermoid cysts, dyskeratosis, carcinoma in situ, and, finally, frank squamous cell carcinoma. Cataldo and his coworkers\textsuperscript{6} feel that changes both in the acini and the ductal epithelium contribute to the development of carcinomas. This view is not shared by others.\textsuperscript{4, 5}

Recently Cataldo and Shklar\textsuperscript{7} have demonstrated that when 5 mg. DMBA pellets are implanted in the submandibular glands of hamsters, fibrosarcomas are produced with an occasional epidermoid carcinoma. This finding is also confirmed by the present investigation. It further demonstrates that the difference in the type of tumor induced in the two species is significant irrespective of the dose of DMBA when administered in the pellet form. This indicates that the difference may be due to the tissue or species specificity rather than the dose or the mode of administration of the carcinogen. However, further experimentation is needed. It will be interesting, for example, to find out the incidence and type of tumors induced in the two species when different concentrations of the carcinogen are administered by direct injection into the submandibular gland. No such study is available in the literature.

Summary

An increase in the concentration of DMBA resulted in a corresponding increase in the incidence of malignant tumors of the submandibular glands in both hamsters and rats. Implantation of 0.2, 0.4, and 0.8 mg. carcinogen pellets in the submandibular glands of rats and hamsters resulted in different types of tumors in the two species. More squamous cell carcinomas were produced in the rats, while more sarcomas were produced in the hamsters. This statistically significant difference may be a result of tissue or species specificity. This hypothesis needs further investigation due to the complex nature of carcinogenesis.

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