hydrochloride could be fed to weanling rats over protracted periods of time with no evidence of toxicity(4,5). Our present findings extend the earlier work to include a larger animal species and are of special significance because of the large dose administered daily for a period as long as one year. In view of the lack of toxicity in experimental animals it is not surprising to find that the drug is well tolerated in man(6-10).

Summary. Thonzylamine hydrochloride was administered to dogs at doses of 20 and 40 mg/kg, p. o., daily for a period of 6 months to one year. The animals grew at a normal rate and showed no evidence of blood dyscrasia throughout the experimental period. At necropsy there was no sign of gross or microscopic organ pathology.

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Assay of Methylcholanthrene-Induced Mammary Tumors of Mice for the Mammary Tumor Milk Agent.* (17851)

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It has been demonstrated that carcinogenic hydrocarbons induce mammary tumors in certain inbred strains of mice(1-4). Not only were these cancers induced in stocks in which the incidence of spontaneous mammary tumors is high, but also in strains with a low incidence which do not possess the mammary tumor milk agent. While the development of spontaneous mammary cancer in mice is usually dependent upon the combined influence of the milk agent and hormonal factors in animals of appropriate genetic susceptibility(5), mammary tumors were induced by the action of chemical carcinogens in mice of susceptible strains from which the milk agent had been excluded by foster nursing(6). However, tumors have appeared earlier and in higher frequency in mice of identical genetic constitution when the milk agent was present(6) and breeding resulted in a more precocious development of induced tumors(7,3). Dmochowski and Orr (8) recently reported that the milk agent could not be demonstrated in extracts of

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TABLE I.
Results on the Assay of 4 Tumors, Induced in Mice Without the Milk Agent, for the Presence of the Agent in Tumor Extracts. The incidence in the control test animals was 1.4%.

Tumor tested, No.	Dose, g equiv.	No. injected	% Ca.	Avg age in days	
				Cancer	Non-ca.
176	2×10^{-2}	28	3.6	223	563
176	10^{-3}	35	0		493
185	10^{-2}	18	0		573
185	10^{-3}	25	0		391
174	10^{-2}	41	2.4	268	484
174	10^{-4}	26	3.8	528	510
161	10^{-2}	21	0		416
161	2×10^{-3}	40	0		490
161	10^{-3}	18	0		447
Total		252	1.2		

tumors induced with methylcholanthrene in females of the IF and C57 black strains, nor in extracts of tumors induced in males by the combined action of methylcholanthrene and estrone. Both strains are relatively non-susceptible to spontaneous mammary tumors and do not carry the milk agent. When mammary tumors were induced in males of the high mammary cancer C3H stock by the hydrocarbon and estrone, extracts of these tumors were found to contain the milk agent. The authors concluded that the carcinogen did not cause the agent to appear in mice which did not possess it before treatment.

For the present study mammary tumors were induced by methylcholanthrene in breeding females of subline 212 of the dilute brown stock which did not have the mammary tumor milk agent (line D_2b—agent excluded by foster nursing). Animals were skin painted 3 times a week for 6 weeks with a 0.25% solution of methylcholanthrene in benzene, as described previously(3). Mice of subline 212 are susceptible to the development of either spontaneous or induced mammary tumors(7,9), whereas mice of the fostered line (D_2b) have given a low spontaneous incidence (unpublished data).

Four induced mammary tumors were tested for the presence of the milk agent. The preparation of the extracts for injection was similar for each tumor. Tissue was ground with sand in a mortar and extracted with distilled water to give a 10% suspension. Extracts were centrifuged for 10 minutes at approximately 2500 r.p.m., following which supernatants were removed and used at the concentrations given in Table I. Fractions were injected intraperitoneally and doses are expressed as the amount derived from the original tissue on a weight basis. Thus, a dose of 10^{-2} g equivalents represents the amount from 10^{-2} g of wet tissue in one cc. This method of biological assay has proved very satisfactory for the detection of the milk agent when present in very low concentrations in extracts of tissues(10,9).

Test animals were ZBC females, 21-26 days of age at the time of injection, which lack the milk agent and usually develop mammary tumors only when it is administered. These mice are back-cross hybrids produced by reciprocal matings between animals of the fostered A and Z (C3H) stocks. The incidence of mammary tumors in breeding ZBC females and their mothers, numbering over 2,000, has been 1.4%.

Three mammary tumors (1.2%) developed in 252 mice which received extracts of the 4 induced tumors (Table I). Sixty-two other animals were injected but are not included in the tabulations since they failed to survive for 223 days, at which time the first tumor was noticed. Thus, the mammary tumor milk agent could not be demonstrated in the extracts of 4 carcinogen-induced mammary tumors from mice of the dilute brown stock

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from which the milk agent had been eliminated by foster-nursing.

Few mammary tumors develop in mice of strains susceptible to spontaneous tumors if they do not have the mammary tumor milk agent, and the incidence cannot be significantly increased by the injection of estrogenic hormones(11,12). As opposed to these findings, mice of strains both susceptible and relatively resistant to the development of spontaneous mammary cancer have developed tumors following treatment with methylcholanthrene. These observations indicate that there is no positive correlation between the inherited susceptibility to spontaneous and to carcinogen-induced tumors(3,4). In fact, mice of different sublines of the same inbred stock may not show the same response. Breeding females of one subline of the C57 black stock revealed no induced mammary tumors(3) although when animals of the same line obtained the milk agent by nursing the incidence of spontaneous mammary tumors was at least 40% (unpublished data). Mice of another subline of the same strain, with a lower incidence of spontaneous tumors when they possess the milk agent, developed a few carcinogen-induced mammary tumors when females without the agent were maintained as either virgins or breeders and tumors appeared in the males when they were treated with both estrone and methylcholanthrene(4).

In the present study the extracts of 4 mammary tumors induced in the absence of the milk agent in mice susceptible (demonstrable when the agent is present) to the development of spontaneous mammary tumors were found to be free of the agent. Thus, the action of the carcinogen was not dependent upon the presence of a milk agent nor did it induce the genesis of an agent. Squamous metaplasia is characteristic of carcinogen-induced mammary adenocarcinomas and the tumors tested in this study had areas of keratinized stratified squamous epithelium. Dmochowski and Orr(4,8) observed that the degree of squamous metaplasia was greater in induced tumors developing in the low susceptible C57 black stock than in males of the high cancer C3H strain. The microscopic structure of mammary tumors that developed in mice free of the milk agent was similar to that of the carcinogen-induced tumors(13).

Summary. The mammary tumor milk agent was not demonstrable in the aqueous extracts of 4 mammary carcinomata induced by methylcholanthrene in female mice which were susceptible to the development of spontaneous mammary carcinoma but did not possess the milk agent before treatment because of foster-nursing. The action of the carcinogen was thus not dependent upon the presence of a milk agent.

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Experimental Artificial Left Heart to Permit Surgical Exposure of Mitral Valve in Cats.* (17852)

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The most promising among the methods devised to make practicable intracardiac surgery appear to be those which artificially support the circulation and render the heart bloodless for finite periods of time(1-10). The difficulties encountered in these various

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