Daily Administration of Massive Oral Doses of Thonzylamine Hydrochloride. (17850)

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Now that certain of the newer antihistamine drugs are being sold directly to the public, the question has been raised in some circles whether they are safe for mass consumption. In order to supply additional information regarding the safety of these drugs, we report in the following paragraphs on the daily administration of massive oral doses of one of the antihistamine drugs, Thonzylamine hydrochloride.†

Experimental and results. Six young male dogs, inoculated against distemper and maintained on a stock diet, were observed for one month and then placed on test. Two dogs were maintained as untreated controls; 2 were given 20 mg and 2 were given 40 mg of Thonzylamine Hydrochloride per kg, orally each day. The animals were kept on test over a period of 26 to 52 weeks. Complete blood counts and urinalyses for reducing substances and albumin were performed monthly while weights were recorded weekly. During the test period all animals were in apparent good health and displayed none of the signs of spasticity or CNS excitation observed with other antihistamines at equal or lower dose levels(1,2). The findings (Table I) disclose no significant difference (Analysis of Variance and "t" test) between treated and control animals. Growth rates were not suppressed. The hematologic findings remained within the normal range specified by Downey (3) and urinalyses were consistently negative in all animals. At the conclusion of the study gross and microscopic examination of tissues disclosed no organ pathology.‡

Discussion. It has been reported that doses as high as 200 mg/kg of Thonzylamine

TABLE I.
Findings in Dogs Fed Massive Doses of Thonzylamine Hydrochloride.

	Untreated		Fed Thonzylamine				Normal data (Downey) Means (Limits)
			20 mg/kg		40 mg/kg		
	Control No. 1	Control No. 2	No. 1	No. 2	No. 1	No. 2	
Erythrocytes ($\times 10^6$)*	7.37	6.99	6.63	7.40	6.94	7.22	6.0 (5.6-7.6)
Leukocytes ($\times 10^3$)	8.36	10.51	9.42	7.78	9.57	9.33	11.17 (5.65-19.2)
Lymphocytes (%)	38	37	36	37	38	36	20 (9.34)
Large mononuclear cells (%)	1	2	1	2	2	2	4 (1-10)
Polymorphonuclear cells (%)	58	59	60	61	57	60	74 (56-87)
Eosinophiles (%)	2	2	2	2	3	2	2 (0-7)
Basophiles (%)	0	0	0	0	0	0	0 (Rare)
Initial wt, kg	12.4	15.2	15.2	12.7	6.4	7.3	
Final wt, kg	16.7	21.7	21.7	19.9	10.0	10.9	
Gain in wt, %	34.7	42.8	42.8	56.7	56.3	49.3	

* Mean values given for hematological data.

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† Originally reported under the name Neohetramine and currently sold also under the trade name "Anahist", Thonzylamine is 2-(N-dimethylaminoethyl-N-p-methoxybenzyl)-aminopyrimidine monohydrochloride.

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‡ We are indebted to Dr. William Antopol of the New York Beth Israel Hospital for the preparation and examination of tissue sections employed in this study.

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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