or are indicative of a more rapid distribution in the hypoxic group, is not clear from this study. The apparent myocardium/plasma partition coefficients for each chamber in each dog were calculated as follows:

$$P_{T/P}^{60\,min} = \frac{\text{myocardial concentration in nm/g (at 60 min)}}{\text{plasma concentration in nm/ml (at 60 min)}}$$

The values for $P_{T/P}^{60\,min}$ (right ventricle) were shown to be significantly larger ($p < 0.05$) in the hypoxic group (38.9 ± 13.3 ml/g) compared to the group respired with room air (4.0 ± 1.5 ml/g). Although the mean $P_{T/P}^{60\,min}$ values for the other chambers were 3–5 times greater in the hypoxic group, because of the large variance this difference was not statistically significant.

Comment. This investigation indicates that 1 h after the administration of digoxin i.v.; 1. there is an increase in myocardial digoxin levels in the hypoxic dogs together with a decrease in plasma levels and 2. accummulation of digoxin occurred in the right ventricle of hypoxic dogs. These results warrant further study on the effect of hypoxia on the distribution of digoxin at steady state to see if they explain in the clinical situation the increased risk of toxicity from digoxin in hypoxia[5,6].

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Dopaminergic mechanisms in thiophene-2-aldoxime tremor[1]

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Summary. Tremor induced by thiophene-2-aldoxime is enhanced or reduced in intensity and duration by agents which respectively interfere with or promote dopaminergic tone.

During an investigation of the pharmacology of certain oximes, thiophene-2-carboxaldehyde oxime (thiophene-2-aldoxime, THAO) was found to be a powerful, and chemically novel, centrally-acting tremorigen[2]. Tremor induced by THAO was accompanied by pronounced psychomotor depression and hypothermia, but lacked the rigidity and parasympathetic effects characteristic of tremorine-induced tremor[3]. Of the many classical tremor antagonists studied, d-amphetamine was shown to be the most effective agent in reducing the tremor and reversing the ataxic depression, whereas standard antitremor agents (e.g. atropine) were ineffective[2]. In view of the well-known association of amphetamine with central monoaminergic function[4], we assessed the ability of chemical agents which modify monoaminergic tone to influence the intensity and duration of THAO-induced tremor.

All experiments were performed on male naive albino mice, weighing 25–35 g, at ambient temperatures of

The effect of drug pretreatment on tremor induced by THAO (175 mg/kg)

Pretreatment	Dose (i.p.) mg/kg	Interval before THAO	Mice with tremor/total mice per group	Mean intensity	Duration of tremor (mean ± SE, min)
Saline controls	0.1 ml total	30 min	6/6	(2)	50 ± 5
p-Chlorophenylalanine	150 daily	3 days	6/6	(2)	53 ± 6
5-Hydroxytryptophan	100	60 min	6/6	(2)	56 ± 4
Cinanserin	10	30 min	6/6	(2)	54 ± 4
Reserpine	5	24 h	6/6	(3)	147 ± 7**
alpha-methyl-p-Tyrosine	50 daily	3 days	6/6	(3)	85 ± 2*
Chloropromazine	10	60 min	6/6	(3)	95 ± 1*
Haloperidol	2	45 min	6/6	(3)	110 ± 4**
Ephedrine sulfate	15	45 min	6/6	(2)	11 ± 1**
Chlorimipramine	100	3 h	6/6	(2)	23 ± 3*
Pargyline	50	3 h	6/6	(2)	16 ± 1*
Pargyline	100	4 h	6/6	(1)	15 ± 4*
L-Dopa	150	2 h	6/6	(2)	18 ± 1*
d-Amphetamine sulfate	5	45 min	5/6	(1)	8 ± 2**
d-Amphetamine sulfate	10	45 min	2/6	(1)	3 ± 1**
Clonidine	1	30 min	6/6	(2)	52 ± 9
Apomorphine	3	5 min	6/6	(1)	4 ± 1**

* $p < 0.01$; ** $p < 0.001$ (Student's t-test).

18-20 °C, since pronounced temperature variations were found to alter the duration of THAO tremor. Mice were housed in groups of 12 and randomly assigned to the treatment groups. 6 mice were used in each group. The presence of tremor was assessed by observation of the 4 limbs when the mice were lying on their side and when held up in the cupped hand. The degree of tremor for each animal was observed by a trained observer who was unaware of the pretreatment regimen and scored on a scale of 1-3, with 1 representing mild tremor and 3 the most severe tremor. The mice were also observed for loss of righting reflex, ptosis and other vital signs. The statistical significance of the differences in duration of tremor was assessed by the Student's nonpaired t-test. Thiophene-2-carboxaldehyde oxime was purchased from Aldrich Chemical Company, Inc. It was dissolved extemporaneously in dimethylsulfoxide to make a 10% solution and injected i.p. in volumes not exceeding 0.1 ml. Control animals given an equivalent volume of solvent showed no tremor. All other drugs were prepared as fresh solutions in saline and injected i.p., except haloperidol (Haldol), reserpine (Serpasil), Clonidine (Catapress) and chlorimipramine (Anafranil) where proprietary parenteral solutions were used.

The results are summarized in the table. A dose of THAO (175 mg/kg) which was found in previous experiments[2] to be the threshold dose which produced tremor and loss of righting reflex in all mice (ED 100) was administered to saline-pretreated mice. These served as controls. Pretreatment of mice with agents which are known to alter the content of serotonin or its actions in the central nervous system (5-hydroxytryptophan, p-chlorophenylalanine, cinanserin) failed to affect the intensity and duration of tremor significantly.

A wide spectrum of substances which interact with brain catecholamines was tested. Agents which deplete catecholamines (alpha-methyl p-tyrosine, reserpine) or antagonize their central actions (haloperidol, chlorpromazine) significantly increased the intensity and duration of the tremor and the loss of righting reflex. Conversely, pretreatment with agents which enhance catecholaminergic tone (apomorphine, pargyline, d-amphetamine, chlorimipramine, ephedrine, L-dihydroxyphenylalanine, but not clonidine) reduced the duration and intensity of tremor. The most effective agent, aside from d-amphetamine, was apomorphine. In view of the evidence for dopamine receptor stimulation by apomorphine[5], its antagonism of THAO tremor implicates a dopaminergic mechanism. This is further supported by the enhancement of this tremor by haloperidol, an agent shown to possess marked dopamine receptor blocking action[6]. However, an adrenergic component may also be operative, since the monoamine oxidase inhibitor pargyline and the antidepressant chlorimipramine were moderately effective in reducing the tremor.

1 This project was supported by a grant from the Lebanese National Research Council. We thank the following companies for the indicated drugs: Abbott (pargyline), Specia (chlorpromazine), Squibb (cinanserin).
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Kinetics of transformation of aflatoxin B_1 into aflatoxin M_1 in lactating mouse: An ELISA analysis

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Summary. A new enzyme-linked immunosorbent assay (ELISA) was used to study the kinetics of transformation of aflatoxin B_1 into aflatoxin M_1 in lactating mice. Aflatoxin M_1 concentration in the milk samples reached a maximum 30 min after injection of aflatoxin B_1 and decreased thereafter. At the maximum time, the levels of aflatoxin M_1 in the samples were proportional to the dosages administered. Aflatoxin B_1 was also detected in the milk samples but at a lower concentration.

Aflatoxin M_1 (afla M_1) is one of the major aflatoxin B_1 (afla B_1) metabolites produced by a number of animal species and has been found in animal livers, urine, feces and milk[3-7]. Since afla M_1 was found to be toxic as well as carcinogenic to test animals[8-10], the presence of this toxin in cow's milk has been considered to be potentially hazardous to human health. A rigorous regulatory program for afla M_1 in foods has been established in the U.S. as well as in other countries. The extent of afla M_1 contamination in dairy products and the impact of afla M_1 on human and animal health have been recently reviewed[11].

Since the discovery of excretion of afla M_1 in the milk of cows consuming afla B_1 contamined feeds, considerable efforts have been made by various investigators to elucidate the mechanism and kinetics of transformation of afla M_1 in to afla B_1 in animals and its subsequent excretion into the milk[12,13]. Most excretion studies were done with large animals including cows, sheep and ewes[7,11-13]. Studies with small animals such as rats[14] and mice were hindered by the unavailability of a suitable analytical method to detect these metabolites in a small amount of milk. Recent developments on the immunochemical assay of aflatoxins in our laboratory and others[15-18] have led to a sensitive, simple and specific microplate enzyme-linked immunosorbent assay (ELISA) for afla M_1 in which as little as 0.25 ppb of afla M_1 in a 25 µl of milk sample can be readily detected[18]. With the availability of this method, we have selected mouse as the test animal to carry out the present study. The objectives of this study are 2-fold: a) to test the feasibility of using this new ELISA procedure for metabolic studies and b) to analyze the kinetics of transformation of afla B_1 into afla M_1 in the lactating mice.

A colony of lactating mice (strain-HA/ICR, Sprague Dawley, Madison, WI) with an average size of 50 g was divided into 2 groups (4-5 mice each). Mice in the 1st group were injected i.p. with 5 µg each of pure afla B_1 prepared according to the method of Chu[19] and mixed with a small amount of ^{3}H-afla B_1 (Moravek Biochemicals, City of Industries, CA) in 0.1 ml dimethylsulfoxide. The