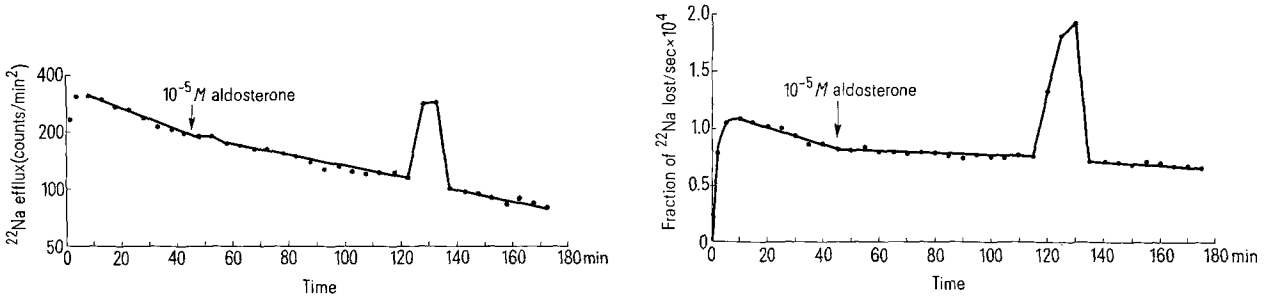

Fig. 2. Effect of external application of $10^{-5}M$ aldosterone. a) Efflux plot. b) Rate coefficient plot.

that aldosterone increased the size of the internally sequestered fraction of Na or increased the Na influx. Whatever one may think of these contradictory observations, it looks very much as if we now have the best of reasons for intensifying our work with aldosterone[10].

[10] Acknowledgment. This work was supported by a grant from the National Science Foundation.

Zusammenfassung. Es wurde gezeigt, dass die Natrium-Ausscheidung in der Muskelfaser von Entenmuskeln auf Aldosteron reagiert.

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Neurotoxic Effect of Leptophos

While organophosphorus insecticides may produce acute poisoning, with temporary muscle weakness from its cholinergic activity, only a few of these compounds produce delayed locomotor ataxia, which first develops 7 days or more after the administration of the compound, as described by Smith and Elvove[1], Smith and Lillie[2] and Johnson[3]. This effect has been demonstrated in 12 species including rodents, mammals and birds by Aldridge et al.[4]. In the original reports, the clinical condition in hens was very similar to that in man (Cavanagh[5]).

In the present study, 3 insecticides used currently in Egypt were tested for any delayed meurotoxicity in chickens. 2 of these compounds, leptophos (Phosvel) and cyolane were accused of poisoning and killing about 1,300 water buffaloes in the Nile delta in Summer, 1971 (Near East News Roundup)[6].

Materials and methods. Male chickens of local breed (Alexandrian) each weighing approximately 2 kg, and 5 months old, were placed in open pens. Each bird received a single dose of the insecticide in a gelatin capsule in the case of cyolane (2-(diethoxyphosphenyl)-1, 3-dithiolane) (97%) and cytrolane (2-(diethoxyphosphenyl)-4-methyl-1, 3-dithiolane) (98%, both obtained from American Cyanamide Co., Princeton, N.J. USA). However, with leptophos (*O*-(4-bromo-2, 5-dichlorophenyl) *O*-methyl phenylphosphonothioate) it was necessary to dissolve it in corn oil and administer it with oral intubation, since large doses were required to reach the toxic level. The birds were given free access to food and water. For each dose at least 5 birds (5–9 birds) were used. The dose killing 50% of the birds within 24 h is reported as LD_{50}. The surviving birds were observed every 2 days for 60 days or until they died. An adequate untreated group of chickens was included in every test.

Results and discussion. The present data demonstrate that cyolane and cytrolane have very high acute toxicity to male chickens. The LD_{50} for a single oral dose is 5.2 and 2.8 mg/kg for cyolane and cytrolane. The 2 values were used to determine the delayed neurotoxic effect for these 2 compounds. A single dose of 5.2 and 2.8 mg/kg of cyolane and cytrolane, respectively, were administered to 10 birds for each compound, and the surviving birds were observed for 2 months. No delayed neurotoxic symptons were detected in any of the surviving birds.

Our results show that the acute toxicity in male chickens to leptophos is very low. The LD_{50} for a single oral dose is 4,700 mg/kg. The Table shows that the lowest dose tested, i.e., 140 and 160 mg/kg, caused no neurotoxicity. However, higher doses (180–3,000 mg/kg) caused delayed neurotoxic effect in some cases. This condition was characterized by ataxia developing 8 to 13 days after the beginning of the experiment. Early signs were less activity, loss of appetite, loss of feathers, lowering of hindquarters and reluctance to stand. As time passed, the signs progressed as incoordination of the leg movement, legs sprawling out in front, inability to stretch the legs, tendency to lay down on the side and paralysis of the wings. Once weakness and ataxia had appeared in the birds, decline was rapid, paralysis occurred and bird might collapse and die with respiratory failure. Recovery was never observed in any bird having developed ataxia. The severity of the neurotoxic signs and the number of birds that developed the condition were dose-dependent; but not matter how great the dose, the latent period before a neurotoxic appeared was never less than 8 days.

In conclusion, the present results clearly demonstrate that leptophos causes delayed neurotoxic effects when administered orally to male chickens. Since it is assumed

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Degree of delayed neurotoxic signs in male chickens given a single dose of leptophos

Dose (mg/kg)	No. of chickens	Ataxia		Death		Mortality after 60 days (%)
		No. of chickens	Days after dosing	No. of chickens	Days after dosing	
140	9			1	1	11
160	9			1	1	11
180	9			1	1	33
		1	9	1	15	
		1	13	1	23	
500	5	2	8	1	16	80
				1	20	
		2	10	2	22	
1000	5	5	8	1	16	100
				3	20	
				1	22	
1500	5	5	8	1	10	100
				1	14	
				1	16	
				2	20	
2000	5			1	1	100
		4	8	2	16	
				2	18	
2500	5	4	8	1	1	100
				3	16	
				1	18	
3000	5	5	8	1	15	100
				4	18	

that a compound showing such activity might produce the same effect in man, leptophos requires careful consideration before it is allowed to be freely used.

Zusammenfassung. Nachweis, dass Leptophos eine sehr niedrige akute Toxizität für männliche Hühnchen hat und einen neurotoxischen Effekt bei Dosen von 180–300 mg/kg verursacht. Dagegen haben Cyolane und Cytrolane eine hochakute Toxizität und verursachen nach oraler Verabreichung keine Neurotoxizität.

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On the Specificity of Dopamine Release by Amantadine

Amantadine causes its beneficial effects in Parkinsonian patients through an unknown mechanism, although it has been suggested that it acts through release of dopamine[1]. Amantadine has been reported[2] to increase both the synthesis and release of dopamine in the rat striatum in vitro and to increase the efflux of dopamine from brain structures in cats, most likely the caudate nucleus[3]. Comparable effects, as in the case of dopamine, have been reported for norepinephrine, both in vitro and in vivo[4]; however, relatively high doses of amantadine were necessary to show these effects in vivo. Lower doses of amantadine have been reported to cause release of dopamine in dopamine-loaded dogs[1], and it seemed of interest to determine whether amantadine could also be shown to release norepinephrine under these in vivo conditions. Evidence is presented that doses of amantadine that release dopamine do not release norepinephrine.

Methods. Mongrel dogs (6–11 kg) of either sex were anesthetized with Na pentobarbital (35 mg/kg i.v.) and bilaterally vagotomized. Blood pressure was recorded with a Statham P23Db pressure transducer and cannula inserted into the femoral artery. Additions of compounds were made via the contralateral femoral vein. Rabbits (2.1–4.0 kg) were anesthetized with urethane (1.25 g/kg i.p.) and prepared in the same manner as dogs, except that some experiments were performed in non-vagotomized animals.

Drugs used in these experiments were amantadine-HCl (Philips-Duphar), dopamine-HCl, morphine-H_2SO_4, norepinephrine bitartrate and phenoxybenzamine-HCl (S K and F). Solutions of all compounds were freshly

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