

Electrocardiographic Changes Produced on the Syrian Hamster (*Cricetus auratus*) by Diphtherial Toxins. (17331)

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The golden hamster, *Cricetus auratus*, is sensitive to diphtherial toxin and exhibits neurotoxic symptoms when toxins exposed to alkaline reactions are administered, whereas toxins kept at slightly acid or neutral reactions do not exert apparent effects on its nervous system.^{1,2} Since the clinical syndrome of diphtheria is characterized by neurological disturbances as well as abnormalities in the cardiac function, it was decided to study the effect of diphtherial toxins on the heart of the golden hamster.

Methods. Toxin samples were prepared from filtrates of 8 day cultures of *Corynebacterium diphtheriae* (Park No. 8 strain). With the aid of highly diluted HCl or NaOH the toxins were brought to the proper pH level and kept at it for 8 days at 30°C as described elsewhere.^{1,2} Clinical and electrocardiographic examinations were made on a total of 24 hamsters; special attention was paid to the appearance of peripheral paralysis. Limb leads electrocardiograms were taken on a portable amplifier instrument. Small (0.5 : 1.2 cm) electrodes of German silver were applied after the skin had been rubbed with electrode jelly.

Results. In 5 apparently normal hamsters electrocardiograms were taken at 3 day intervals for one month. They showed within this period a constant pattern, the various deflections being similar to those of the human electrocardiogram. The P wave was indistinct owing to the rapid heart rate, 300-400 per minute, as shown in Fig. 1, left side.

Ten hamsters received minimal lethal doses of a toxin kept at pH 6.7; their average survival time was 8 days. No neurotoxic symp-

toms appeared; daily electrocardiograms did not reveal any disturbance of the heart function. In 4 animals we succeeded in obtaining electrocardiograms 4 hours before death; they were found to be normal. At gross pathological examination the classical signs of diphtherial intoxication were found: edema and necrosis at the site of injection and hemorrhages in the adrenal glands.

Another group of 11 hamsters received minimal lethal doses of a toxin exposed to pH 7.3. In 5 of them paresis appeared and their electrocardiograms showed marked abnormalities, summarized in the upper part of Table I. These changes preceded by some days the appearance of neurological abnormalities. In 6 other animals the electrocardiogram and the neurological functions remained normal.

A third group of 8 animals received minimal lethal doses of a toxin exposed to pH 8.5; their average survival time was 21 days. All of them showed paresis and marked electrocardiographic disturbances, summarized in the second part of Table I. (*cf.* Fig. 1, right).

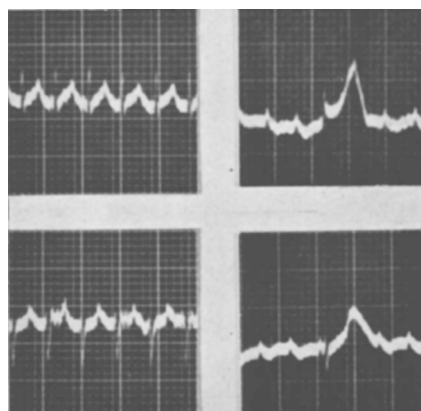


FIG. 1.

Left: Electrocardiogram (leads II and III) in a normal hamster.

Right: Auriculo-ventricular block after the injection of a diphtherial toxin kept at pH 8.5.

¹ Olitzki, L., Stuczynski, L. A., and Grossowicz, N., 4th Internat. Cong. f. Microbiol. Copenhagen, 1947; *Rep. Proc.*, 1949, p. 180.

² Olitzki, L., Stuczynski, L. A., and Grossowicz, N., *J. Immunol.*, 1948, **60**, 419.

TABLE I.
Paresis and Heart Disturbances Produced in Hamsters by Minimal Lethal Doses of Diphtherial Toxins Exposed to Alkaline Reactions.

No. hamster	Toxin kept at pH	First appearance (days) of disturbances of the		Survival, days	Functional abnormalities observed
		Nervous system	Heart function		
1	7.3	4	3	5	Ectopic beats
2	7.3	8	6	9	" "
3	7.3	10	7	25	" "
4	7.3	5	4	6	Partial auriculo-ventricular block
5	7.3	11	7	12	Ectopic beats
6	8.5	23	23	30	" " , later total auriculo-ventricular block
7	8.5	25	25	28	Like No. 6
8	8.5	7	7	9	total auriculo-ventricular block
9	8.5	7	7	12	Like No. 8
10	8.5	22	22	28	Like No. 8
11	8.5	22	22	30	Ectopic beats
12	8.5	8	8	18	Partial auriculo-ventricular block
13	8.5	8	8	14	Like No. 12

TABLE II.
Paresis and Heart Disturbances Produced in Hamsters by Sublethal Doses of Diphtherial Toxins Exposed to Alkaline Reactions.

No. hamster	Toxin kept at pH	Paresis, day of		Ectopic beats, day of	
		First appearance	Recovery	First appearance	Recovery
1	7.3	16	46	9	90
2	8.5	10	44	20	150
3	9.0	17	35	22	150
4	9.0	17	45	22	270

In a group of 4 hamsters the action of sublethal doses (0.2-0.5 MLD) of toxins was examined. In this group the neurotoxic symptoms were of a transient character and disappeared about 3 to 4 weeks after their first appearance. The electrocardiographic abnormalities, on the other hand, persisted much longer and in one hamster were apparent 9 months after the injection of the toxin. (Table II).

Summary and conclusions. Diphtherial toxins exposed to alkaline reactions produced in the golden hamster, in addition to neurotoxic symptoms, marked disturbances in the heart function as indicated by electrocardiographic

abnormalities. Acid-treated toxins on the other hand, did not cause any electrocardiographic changes. The first appearance of the electrocardiographic changes frequently preceded that of the paralytic symptoms, and when sublethal doses were administered, the electrocardiogram remained abnormal even after the neurological symptoms had disappeared. Electrocardiographic examination of the heart function seems, therefore, to be a more sensitive method of measuring the action of certain diphtherial toxins than the observation of the neurotoxic symptoms.

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