

Comparison of Efficiency-Increasing and Toxic Effects of Theophyllinated Scillaridin* on Isolated Cat Heart.†

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Recently a new material prepared by replacing the sugar moiety in squills glycoside with 2 molecules of theophylline per molecule of genin has been made available for study.

Two reports^{1, 2} dealing with its toxicity indicate that the material is appreciably less toxic than either the genin alone, or the glycoside, though the toxic effects, qualitatively, are essentially similar.

The general plan and logic of the experimental procedure has already been discussed.³ Although the investigation cannot be considered complete, it is deemed worthwhile to make the present data available now because the new drug compares so favorably with the accepted cardiotonics, as judged by similar criteria, and because further studies on this problem have been indefinitely postponed.

Twenty-one experiments were done with the completely isolated cat heart, according to a method previously described.⁴ Diastolic volume was recorded continuously in all experiments, and coronary flow in 5. The drug was administered dissolved in water, 1 mg per cc.

A dose causing a decrease in diastolic volume was accepted as exerting an efficiency effect. The onset of persistent irregularities within 4 hours of the time of administration of the drug constituted the criterion for toxicity. Experiments in which cardiac failure before the 4-hour period placed the interpretation in doubt were discarded.

The results are presented in Table I. In experiment 29, a dose of 1.5 mg/100 g produced a prolonged efficiency effect, irregularities appearing just at the close of the 4-hour period. In experiment 18 the same dose produced a marked efficiency effect uncomplicated by

* Furnished by Parker Dorn, Inc., Worcester, Mass.

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¹ Riseman, J. E., and London, S. B., *Science*, 1940, **92**, 384.

² DeGraff, A. C., and Lehman, R. A., *PROC. SOC. EXP. BIOL. AND MED.*, 1941, **46**, 36.

³ Moe, G. K., and Visscher, M. B., *J. Pharm. and Exp. Therap.*, 1938, **64**, 65.

⁴ Lorber, V., *Am. Heart J.*, in press.

TABLE I.

Exp. No.	Dose in mg/100 g of ventricle	*Duration of vol. effect, min.	Onset of irregularities, min.	Remarks
5	36.0	30	20	Efficiency effect with toxic manifestations
10	12.4	127	127	"
11	5.2	128	217	"
29	1.5	225	239	Minimum irregularity dose (C.I.D.)
18	1.5	240	Regular rhythm at 4 hours	Efficiency effect without toxic manifestations
20	0.96	240	"	"
26	0.65	210	"	"
13	0.41	180	Failed before 4 hours	Minimum efficiency dose (C.E.D.)
17	0.38	Questionable vol. effect	Regular rhythm at 4 hrs	Probably no effect
14	0.1	None	Discontinued at 3½ hrs. Regular rhythm	No effect

*Measured to the point of least diastolic volume.

toxic manifestations. Accordingly this dose is taken as approximating the minimum cardiac irregularity dose (C.I.D.) or least dose that will produce toxic irregularities within 4 hours.

Below this level the efficiency effect was the only one noted. The minimum cardiac efficiency dose (C.E.D.), or least dose producing an efficiency effect was found to be 0.41 mg/100 g. Though failure occurred before 4 hours in this experiment, it could be accepted since the dose was considerably smaller than the C.I.D. It should be stated that in the experiments discarded because of early failure, the relationship between dose and efficiency effect was not as regular as noted in the other experiments, some relatively large doses causing trivial volume changes. This can probably be ascribed to the poor condition of the heart in these experiments. In the main, however, the deleted experiments support the tabulated results.

The relationship of the efficiency-increasing and toxic effects of the drug on the isolated heart can be expressed in the ratio C.I.D./C.E.D., a measure of the margin of safety of the drug. The numerical value of the ratio in these experiments is 3.65, compared with values of 2.46, 1.04, and 2.00, for ouabain, K strophanthosid, and lanatosid C, respectively, determined on the isolated cat heart in similar experiments.⁵ This suggests a wider margin of safety for the theophyllinated scillaridin, as judged by these criteria.

The expectation that inclusion of the theophylline molecule in the new preparation might lead to enhanced coronary flow has not been

⁵ Moe, G. K., unpublished data.

fulfilled under the conditions of this study. In the 5 experiments in which coronary flow was measured, there was no effect in 3 cases, a slight decrease in flow in one, and a slight increase in one. The dose in the last case was below the C.E.D.

Summary. A new cardiac drug, a dimethylxanthine genate, has been studied in the completely isolated cat heart. It has been found to exhibit marked cardiotonic properties, and low toxicity. It exerts no appreciable coronary dilator effect on the completely isolated heart.

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Antibody Response of Persons with Pellagra, Beriberi and Riboflavin Deficiency.*

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During the past two decades, extensive animal experimentation has shown that in certain instances a direct relationship exists between the severity of an induced infection and the nutritional state of the animal. In a large group of persons with naturally occurring pellagra, beriberi, and riboflavin deficiency, Riddle, Spies and Hudson¹ found a depression of the blood's bactericidal power for streptococci and staphylococci, and demonstrated a characteristic flora of hemolytic strains of these organisms from oral and ocular lesions in riboflavin deficiency. The present report is concerned with observations on the relationship between these deficiency states in human beings and the response of their immune systems to antigenic stimulation.

Materials and Methods. Fifty patients were selected from the Nutrition Clinic of the Hillman Hospital, Birmingham, Alabama, using the following criteria:

1. A history indicating that their economic status and food-habits made it unlikely that they would or could change their diet significantly during the 5-month period of observation from May to Sep-

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¹ Riddle, Jackson W., Spies, Tom D., and Hudson, N. Paul, *Proc. Soc. Exp. Biol. and Med.*, 1940, **45**, 361.