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Influence of Site of Subcutaneous Injection upon Toxicity Figures.

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Cupreine (M.W. 310) and quinine, its methyl ether[1] (M.W. 324), were injected subcutaneously in the flank in guinea pigs, chiefly males, in M/4 solutions in HCl to form very nearly the dihydrochlorides. Table I, Series 1, shows the results, deaths with-

TABLE I.
Influence of Site of Subcutaneous Injection upon Toxicity Figures of Cupreine and Quinine.

	Date	Series 1. Flank Injections. Doses in mg.-mol. per kg. 0.4		0.6		0.8	
Quinine	Feb. 22	1/10	(1/10)	5/10	(7/10)	7/10	(8/10)
	Mar. 8	0/10	(1/10)	1/10	(2/10)	7/10	(8/10)
	Mar. 16	0/10	(0/10)	—	—	—	—
	Totals	1/30	(2/30)	6/20	(9/20)	14/20	(16/20)
Cupreine	Feb. 22	2/10	(4/10)	6/10	(8/10)	4/10	(10/10)
	Mar. 8	0/10	(3/10)	0/10	(1/10)	3/10	(7/10)
	Mar. 16	2/10	(3/10)	—	—	—	—
	Totals	4/30	(10/30)	6/20	(9/20)	7/20	(17/20)
		Series 2. Dorsal Injections.					
Quinine	Mar. 16	—	—	—	—	9/10	(9/10)
Cupreine	Mar. 16	—	—	—	—	0/10	(0/10)
		0.5	0.75	1.00	1.25	1.50	1.75	2.00
Quinine	Various	5/56	19/36	50/57 16/19†	—	—	—	—
Cupreine	Various	—	—	—	0/5 (0/5)	0/5 (0/5)	1/5 (1/5)	2/11 7/19†

† Animals previously injected with cinchona bases and recovered.

in 48 hours first, those within 7 days next and in brackets. The 48-hour toxicity curves intersect, although an earlier report[1] assigned to cupreine a toxicity to the guinea pig half that of quinine. With cupreine great irregularity is here seen and late deaths are frequent. Necropsies showed evidence of passage of both bases from the flank site toward or into the abdominal cavity, internal hemorrhage, mesenteric vascular engorgement, intestinal adhesions and necrosis all

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[1] Grimaux, E., Laborde and Bourru, *Compt. rend. acad. des sciences*, 1894, **118**, 1303. Von Oettingen, W. F., Therapeutic Agents of the Quinoline Group, Chemical Catalog Co., 1933.

being noted. It was thought that cupreine might penetrate tissue and reach the peritoneal cavity more readily than quinine, and undergo in this experiment more frequently an accelerated absorption. Later therefore (Series 1 and 2) the site of injection was shifted for half the animals to the dorsum so as to hinder penetration into the abdominal cavity. The toxicity of the cupreine plainly fell (March 16), that of quinine remained of the same order as before. Late deaths became negligible. Further observations (Series 2) indicate that this shift of injection site makes little difference in the 50% lethal dose of quinine but probably doubles that of cupreine. It is clear that in comparative toxicity determinations the use of relatively large numbers of animals on each dose may by itself be inadequate to give reliable results; the method must be given close scrutiny.

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Creatine Content of Heart in Experimental Cardiac Hypertrophy Due to Hyperthyroidism.

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Cowan[1] has recently reported that the administration of thyroxin to rats, while producing an increase in ventricular muscle mass, resulted in a loss of creatine. Before the publication of Cowan's data, we had independently observed the same phenomenon in rats receiving desiccated thyroid. Indeed, the creatine values were depressed to much lower levels in our experiments than in those of Cowan. While it is to be recognized that the response to thyroid varies somewhat in different individuals, and depends upon a variety of factors to be described later, our results have been averaged as outlined in Table I for the purpose of comparison with Cowan's data. The usual daily dose of the powdered thyroid was 200 to 250 mg. per 100 gm. of body weight.

That the increased size of the heart represents a true hypertrophy is indicated by the fact that the water content of the hyperthyroid ventricles was practically the same as that of the normal ventricles (average of 76.48% for 11 hyperthyroid hearts and 76.21% for 6 normal hearts). On histological examination the hearts of the

[1] Cowan, D. W., *Am. J. Physiol.*, 1934, **109**, 312.