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Effect of Myocardial Destructive Agents on Creatine Content of the Rabbit's Heart.

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For a further experimental study of the creatine changes in damaged heart muscle we have employed the method of Fleischer and Loeb¹ for the production of myocarditis. This involves the intravenous administration of caffeine or sparteine, followed in a few minutes by adrenalin intravenously.

Caffeine-sodio-benzoate (25 mg./kilo) was injected intravenously in the marginal ear vein of rabbits; after a wait of 3 minutes this was followed by the adrenalin (0.1 mg./kilo), given very slowly, taking 3 or 4 minutes for the injection. Some of the animals died within a few minutes. Of those that survived, 15-20% were found dead the following morning, with fluid in their pleural and pericardial cavities. A few more succumbed in the following days, but most of those alive 24 hours after the injection survived until sacrificed.

In a series of 69 rabbits the chemical changes have been followed at time intervals up to 31 days. The creatine content of the heart was determined by Myer's modification² of the method of Rose, Helmer and Chanutin; these values were reduced to terms of dried weight by drying one sample to a constant weight at 105°C. and calculating the percentage of solids.

Normal Values. The total creatine value for the normal rabbit determined on 25 comparable hearts, *i. e.*, from animals 1200-1500 gm., was found to be 165 mg. % with a standard deviation of 14.7. The dried weight averaged 21.7% of the moist weight.

Spontaneous Deaths. In the 6 animals that died immediately after injection, the creatine values averaged 169 mg. %. Eleven rabbits died spontaneously in the 18-24 hour interval. The creatine content ranged from 68 to 91 mg. %, averaging 83 mg. %. The edema present was shown in the lowered total solids, which averaged 18.55%, with limits of 17.62% to 20.20%.

Later spontaneous deaths were, one at 4 days: creatine 55 mg.%, solids 15.88%; one at 13 days: creatine 125 mg. %, solids 20.28%; and one at 20 days: creatine 110 mg. %, solids 20.14%.

¹ Fleischer, M. S., and Loeb, L., *Arch. Int. Med.*, 1909, **3**, 78.

² Seecof, D. P., Linegar, C. R., and Myers, V. C., *Arch. Int. Med.*, 1934, **53**, 574.

Preagonal Sacrifice. In these animals, with death seeming imminent at periods from 1 to 9 hours, the creatine values were normal or slightly low, but all were definitely lower than corresponding animals sacrificed while showing no abnormal signs, as described in the next paragraph.

Sacrificed Animals. The myocardial creatine content (Table I) was elevated to an average of 193 mg. % in the period from 1 to 12 hours after injection. In these, the solids which averaged 22.4% were uniformly higher than the normal. The values found in the animals sacrificed after longer periods of 1 to 31 days averaged 132 mg. % (20.5% solids) with a definite tendency toward more normal values as time went on.

TABLE I.
Creatine Changes in Experimental Myocarditis.

No. Animals	Exp. Condition	Time	Death	Fresh Muscle Creatine mg. % Wet Weight Aver.	Solids %
25	Controls	Instant	Sacrificed	165 mg. % ± 14.7 S.D.	21.6
11	Caffeine + Adrenalin	18-24 hr.	Spontaneous	83	18.6
3	" "	4-20 days	Spontaneous, occurring later	89	18.8
14	" "	1-31 "	Sacrificed	132	20.5
8	" "	1-9 hr.	" (preag.)	159	22.7
13	" "	1-12 "	"	193	22.4
2	Adrenalin only	12 "	"	223	23.2
3	" "	24 "	"	136	20.7
2	" "	48 "	"	126	20.0

Adrenalin alone, so far as studied up to 48 hours, seemed to produce a cycle of myocardial creatine changes which paralleled the course of chemical events produced by the combination of caffeine and adrenalin.

This method of producing myocardial damage seems to have a consistent influence on the myocardial creatine. In the first 12 hours the creatine is increased approximately 20-25% above normal. After that time the values begin to drop. It is suggested that the drop is related to the amount of myocardial damage. Although the critical point is not sharp, when the values drop to about 2/3 of normal, the animal dies. In other hearts the drop is not so low, and as reparative processes ensue, the creatine content gradually rises toward normal.