lesions; at the same time it produces pronounced fluid-accumulations in the peritoneum, pleura and subcutaneous tissues, with multiple hemorrhages, nervous disturbances and a high mortality. The syndrome is regarded as essentially similar to that previously produced by other investigators through combined treatment with DOCA and renin. The ability of thyroxin to produce cardiac and renal damage under these conditions—unlike the comparable effects of STH—is not prevented by adrenalectomy.

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Influence of 9-Alpha Fluorohydrocortisone on Contractility and Na Content of Isolated Cat Papillary Muscle.* (22419)

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The effect of steroids upon tissues other than the components of the pituitary-adrenal and renal axis has been studied by many workers, including Ingle, Szego and Eisenberger(1-3). Previous studies(4,5) have shown that under certain conditions progesterone and cortisone exert a negative inotropic action (*i.e.* contractility) on the heart. With a simple electronic system perfected in this laboratory, we have measured a previously unreported inotropic effect of 9-alpha fluorohydrocortisone‡ (9-a FF) on isolated cat papillary muscle. This synthetic hormone was chosen for this study because of its marked mineralocorticosteroid and glucocorticosteroid activity(6).

Methods. The cat papillary muscle preparation employed was that first described by Cattell and Gold(7). Cats anesthetized with ether were killed by cardiectomy. At least 2 and sometimes 3 papillary muscles, varying from 2-15 mg in weight, were removed from the right ventricle. These muscles were individually dissected, leaving the chorda tendinae and some valvular tissue attached to one end, and a tab of myocardium to the other. The papillary muscle was thus isolated without causing tissue injury. A hook, which also served as one electrode on a muscle holder, was placed through the chorda tendinae. From the other end of the muscle a suture attached to the papillary:myocardial juncture was tied to an extension on the pin of an electronic transducer tube (RCA 5734). The transducer tube transformed slight mechanical displacements into electrical potentials which were in turn picked up by a direct-writing Sanborn EKG instrument. A control and a treated muscle were stimulated in two identical chambers which were attached to the electronic system in such a manner that both control and experimental observations could be recorded simultaneously.

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TABLE I. Results Obtained with 9-alpha fluorohydrocortisone.

Exp.	Drug conc. (μg/ml)	Counts/sec. /ml buffer	Counts/sec. /G.	Ratio:* Exp./Cont.	△ inotropic action (%)†
	Control	1000	246		
1	.625	"	440	1.8	+ 83.7
2	.625	"	480	2.0	+ 56.2
	Control	"	256		
3	.625	"	2955‡	11.0	+ 36.8
4	.50	"			+102.2
	Control	2000	916		
5	.50	"	1172	1.3	+154.5
	Control	"	685		
6	.50	"	1276	1.9	+117.6
	Control	"	705		
7	1.00	"	708	1.0	+ 12.5
	Control	"	236		
8	.625	"	620	2.6	+136.0
9	.625	"	360	1.5	+168.5
	Control	"	356		
10	.625	"	1040	2.9	+ 46.5
	Control	3000	695		
11	.50	"	2753	3.9	+ 76.0

* In counts/sec./G.

† Measured from just prior to the administration of drug to the highest point reached after administration.

‡ Probable experimental error.

Krebs-Ringer bicarbonate solution enriched with dextrose was used as the perfusing medium. The perfusing solution in which both the control and experimental muscles contracted contained 0.1 ml/liter of carrier-free Na^{22} (half-life 2.6 years).§ A mixture of 95% O_2 and 5% CO_2 was bubbled through the buffer by means of a sintered glass filter fixed to the base of the muscle chambers. The muscles were stimulated throughout the experiment at 60 times per minute and maintained at a constant temperature of 38°C and recordings taken at intervals. 9-a FF in small amounts (0.5-1.0 μg ml as indicated in Table I), was added to the buffer bathing one of the muscles. At the conclusion of an experiment, the muscles were carefully dissected from the chorda tendinae and myocardial tab, washed and weighed rapidly then digested in H_2SO_4 and the total radioactivity determined in a well counter. The uptake of isotopic Na was expressed in counts sec./G. and then in terms of the ratio of radioactivity of the samples treated with 9-a FF to that of the control samples.

Results. Fig. 1 shows the effect of adding 9-a FF to the perfusing fluid of 7 muscles, (see Table I, expt. 1-7). The average values of these 7 experiments are plotted in terms of % height of the initial contraction and were measured at intervals throughout the experiments. The broken line represents data from the treated samples and indicates a marked positive inotropic effect on comparison with mean control values represented by the solid line.

Results from individual experiments are tabulated in Table I. The positive inotropic effect is demonstrated in each experiment upon the addition of 9-a FF. Furthermore, the Na^{22} content of each treated muscle was increased on comparison with its control from the other chamber.

Discussion. These data are presented as evidence that marked positive inotropic activity is exhibited by a steroid substance, other than the glycosides or aglycones. In addition, it has been shown that under the influence of 9-a FF, measurable changes in isotopic sodium content take place in the contracting muscle. The possibility that the in-

§ Specific activity = 496 mc/G., (<0.02 μg/ml); contaminating Na = 0.52γ/liter; (a negligible quantity in a buffer containing 140 mEq/L. of sodium).

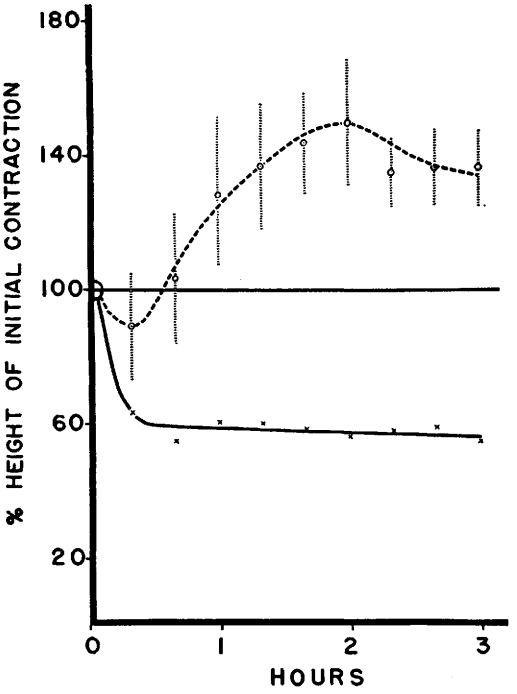

FIG. 1. Upper curve shows positive inotropic action when 9-a FF is added. Vertical lines represent calculated stand. error. Lower curve shows the mean of 11 control experiments.

crease in counting rate of muscles treated with 9-a FF might represent an exchange was considered. However, it does not seem likely that the concentration of intracellular sodium in heart muscle, which has been reported to be from 13.7 to 22.9 mM/K (rat)(8), could show an apparent rise to values which in some cases are over ½ that of the buffer (140 mEq./L.), by a process of exchange alone. Unfortunately, we were unable to obtain direct chemical measurements on the sodium uptake because of the minute size of the muscles studied. It is possible that part, or all of this increase in the treated muscles is a reflection of a marked rise in the intramuscular extracellular fluid. The high sodium content of the controls is in agreement with the observation by Reiter(8) that exercise increases the sodium content of heart muscle. In addition, Flückiger and Verzár(9) have presented evidence that steroid effects on glucose metabolism may be associated with the regulation of muscle electrolyte content. Present work in this laboratory is aimed at establishing the microanatomic site of this change in electrolyte distribution and to decide whether this change represents the cause or the effect of the reported positive inotropic action.

Summary. (1) A new method is described for quantitating inotropic effects in the cat papillary muscle preparation. (2) When 9-alpha fluorohydrocortisone (9-a FF) is added to the perfusate in a concentration of 0.5 to 1.0 μg/ml there is observed a direct effect on the muscle as manifested by a marked positive inotropic action and an increased uptake of radioactive Na.

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