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Studies of the Action of Calcium on the Vertebrate Heart.

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These studies are based upon a series of experiments upon the hearts of 52 animals perfused with oxygenated Locke's solution by a modified Langendorff technique. The essential features in the modification of this method were: (1) Complete water bath circulation about the perfusion fluid, maintained at a constant rate of flow by means of a pump and regulated at a constant temperature by means of a thermostat. (2) Control of the pressure head of the perfusing fluid by graduation of the pressure of flow against a mercury manometer. (3) Introduction of a warm air chamber about the beating heart. (4) The recording simultaneously of auricular and ventricular contractions by means of pins, attached through the auricles and ventricular apices. The series of animals was composed of one turtle, 2 cats, 3 dogs and 46 rabbits. Calcium was introduced into the perfusing fluid, in varying quantities of a 0.25% solution of the chloride. Observations upon the beating heart were made by direct inspection and notation at the time of experiment and by

TABLE I.

Effect.	Turtle		Cat		Dog		Rabbit	
	No. of admin.*	% occur.†	No. of admin.	% occur.	No. of admin.	% occur.	No. of admin.	% occur.
Increased strength of systole	23	73.9	27	96.3	15	86.6	453	93.7
Increased myocardial tonus	23	65.2			15	6.6	453	13.2
Bradycardia	23	13.0	27	37.0	15	33.3	453	24.7
Tachycardia	23	17.4	27	3.7	15	6.6	453	2.9
Alternating effects of Bradycardia and tachycardia	23	4.3					453	7.3
Auricular-ventricular dissociation					15	6.6	453	1.9
Fibrillation					15	13.3	453	1.3
Flutter							453	0.6
Alternation of the beat	23	4.3						
Systolic death							‡hearts 36	91.7
Diastolic death							hearts 36	8.3

* Numbers of administrations of calcium chloride.
† Percentage occurrence of effect.
‡ Number of hearts.

means of kymographic tracings. The commonest effects of the pharmacological administration of calcium upon the perfused heart are noted in the accompanying table.

As a normal amount of calcium ions is necessary for the ordinary strength of the heart's contraction so the addition of more calcium results in a greater force of both auricular and ventricular systole, often but not invariably associated with an increase of myocardial tonus. Just as Brull[1] found in the perfused hearts of dogs and rabbits, and as Bowler and Walters[2] learned by electrocardiogram studies in dogs injected intravenously with calcium chloride, large doses resulted in the production of varying types of cardiac arhthymias. Anatomically, the site of the different actions of varying amounts of calcium on the vertebrate heart has not been certain. In the excised heart it cannot be responsible to changes centrally effected in the vagus and sympathetic innervation. That these effects are probably not upon the intrinsic conducting system of the heart has been demonstrated in these experiments by section of the auriculo-ventricular bundle in the beating heart. During the course of resulting complete auricular-ventricular dissociation, the addition of calcium to the perfusing fluid has resulted, as in the intact heart, in the recorded effects of increased strength of systole, bradycardia, and with smaller amounts tachycardia in the ventricular muscle. The B.P. tincture of digitalis, diluted 1-100 with Locke's solution and mixed with the perfusing fluid in a like manner, has produced neither increased strength of systole nor bradycardia. Consequently we believe the site of action of the calcium ion to be directly upon the myocardial cell, probably upon the colloidal system of the cell membrane.

Functionally, it is manifest that all the properties of heart muscle tonicity, contractility, rhythmicity, irritability and conductivity may be effected by calcium. Of changes in rate, bradycardia has been found much the more frequent, occurring equally in both auricle and ventricle in the rabbits' heart, where the bradycardia due to a partial heart block has been a relatively infrequent occurrence. Hence we are unable to support Brull's conception in the rabbit at least, that the bradycardia following calcium administration is in most instances due to partial auricular-ventricular dissociation. We regard it rather as a myocardial effect. Andrus and Drury[3] have shown that a pH lower than normal, pH 7.0 caused the excitatory process

[1] Brull, *Arch. internat. de méd. expér.*, 1925, 1, 613.

[2] Bowler and Walters, *J. Am. Med. Assn.*, 1924, lxxx, 111, 1232.

[3] Andrus and Drury, PROC. SOC. EXP. BIOL. AND MED., 1925, xxii, 21.

to be propagated more slowly in the mammalian auricle. The hydrogen ion concentrations of our solutions unfortunately were not determined. Tachycardia has been observed much less often, although it has been noted on 19 occasions in the hearts of the turtle, rabbit, cat and dog. Brull regarded bradycardia as always the change in rate produced by calcium administration. The systolic death noted in the frog's heart was absent in a series of 42 experiments upon rabbits and dogs, according to the latter author's results. The state of ventricular arrest in our perfusion experiments was possible of recording upon the kymographic tracing, where the increasing tension of a rising ventricular tonus produced at the end of the experiment a vertical upstroke upon the smoked paper. This observation was verified in each instance by palpation of the ventricle and by actual measurement of its diastolic and systolic diameters with calipers. In 33 rabbits' hearts examined in this manner, the characteristic and practically constant effect has been a cessation of the heart's action in systole with a well marked calcium rigor. The failure of this effect in the perfused heart of the rabbit following treatment with calcium we believe to indicate the absence of the opportunity for the complete calcium action to have exerted itself upon the ventricular muscle.

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Anticomplementary Action of Purified Heparin.

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The writers, in a previous paper,[1] reported on the anticomplementary action of heparin. It was found that the antihemolytic effect is not due to an action upon the erythrocytes. Although an ancillary action upon amboceptor could not be excluded, the action was found to be upon the complement. Further investigation demonstrated that the anticomplementary effect of heparin is due to its interference with the heat-stable factor or the so-called third component of complement. Complement inactivated by heat and by NH_3, containing in both instances the third component, reactivates heparin-inactivated complement. Previous admixture of a small

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[1] Ecker, E. E., and Gross, Paul, *J. Infect. Dis.*, (in press).