THE PHARMACOLOGICAL ACTION OF ATROPINE

ON

CARDIAC MUSCLE

by

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REVIEW OF THE LITERATURE.

There has been a great deal of experimental work done on the heart with reference to the action of atropine, but little investigation of the problem with especial reference to the action on cardiac muscle.

Ringer (1879) found that atropia greatly slows and weakens the heart and often after some hours arrests it. It is probable that the slowing and weakening of the heart is due, he says, to the action of atropia on the excito-motary apparatus, or on the cardiac muscle or both. He exposed the heart of a brainless frog and then partially opened the pericardium and filled the pericardial sac with a 2 per cent solution of atropia. His results were as follows:- The hearts contractions were greatly slowed, became weak, and often wholly failed to recover, even after many hours.

The reason for this observed slowing of the heart was doubtless due to the great concentration of the drug used. Smaller concentrations of the drug must be used to obtain the non-toxic action of atropine. Also the way the drug was administered may have had something to do with the slowing.

Ringer (1882) has proven that atropine affects the heart in winter in a way very similar to that of cold. They both diminishing the number of beats, prolonging and strengthening the systole, prolonging diastole and increasing the diastolic dilation of the ventricle. The diastole is prolonged much more than the systole. In summer atropine lessens the amount of blood going to the ventricle during diastole, for during the auricular contractions, the ventricle still remains only partially filled and the ventricular contraction is weakened.

Gaskell (1882) says that the action of atropine on the heart is to bring about a certain maximum of rythmical power and a contraction force of such stable character that this maximum is with the greatest difficulty displaced in either one direction or the other. In the unfed heart outside of the body, its beneficial effects are followed, with a rapidity varying according to the extent of the dose, by a marked depressing action; the force of the contractions steadily diminish, the rythm becomes slower and slower. In the frog heart when removed from the body, this depressing effect on the rythmical power is manifested very early, so that, the rythm may be markedly slowed at the same time that the force of the contractions is as strong or even stronger than before. No doubt these depressing after effects are due mainly if not entirely to an overdose of the drug, combined with the absence of nutrient material.

Atropine produces the effects by directly modifying the various functions of the cardiac muscle, and in proportion to the stability of the effect so produced is the possibility of a modification of that effect by the direct stimulation of the muscle or by the action of the cardiac nerves. It is partially because the atropine acts in such a way on the muscular tissues as to keep the various muscular powers fixed in a relatively high state of activity, that the cardiac nerves are unable any longer to depress those powers. He further concludes that it is because atropine is able to restore the rythmical power of the muscle, that stimulation of the muscle and sinus is no longer able to produce inhibition; it is because the atropinized muscle contracts with the very first stimulus at its full strength, that neither the cardiac nerves nor the interrupted current is any longer able to diminish those contractions; it is because atropine repairs conduction, that stimulation of the vagus is no longer able to prevent the contraction wave passing from the sinus into the auricle. This view was later replaced by the work of Langley and Dickinson and that of Harnack and Hafeman.

He states that it not only prevents the action of the vagus nerves by its direct influence on the cardiac muscle, but also on the intra-cardiac nerves themselves, and especially perhaps on their ganglionic nerve cells. In the case of the frog, atropine applied to the sinus and auricle alone, prevented the whole action of the vagus,

not only on those parts of the heart, but on the ventricle as well. Atropine not only influences the muscular tissue but also the nervous structures of the heart in such a way that neither the direct action of the interrupted current nor stimulation of the vagus nerves are any longer able to produce their usual effects upon the various functions of the cardiac muscle.

According to Harnack and Hafeman (1883), we possess in atropine a completely reliable drug for determining the cause in any diastolic pause; also for excluding the inhibitory nerves on the heart without injuring the heart itself. Also, after large doses the heart is paralyzed, but before there is a paralysis, there is a slight stimulating action which is very weak and only lasts for a short time.

Langley and Dickinson (1890) were the first to demonstrate that atropine exerts its effect on the heart, so far as the effect is nervous, by the toxic action on the nerve endings in the muscle.

Krehl and Romberg (1892) are of the opinion that the point of action of atropine is not upon the heart ganglia. See table from their work on page 5.

TABLE FROM KREHL AND ROMBERGS WORK.

Time	Rate per min. Ventricle	auricle	Ligated auricles in auriculo-ventricular furrow. Ligatured arteries. Right vagus affects auricle, not ventricle.
3 hr. 40 m.	72	174	Resp. 40.
3 hr. 41 m.	—	—	0.001 muscarin (Bohm) injected into Jugular vein. Diastolic pause of ventricle.
After 10 sec.	—	—	Strong contractions of auricle. 0.0004 atropine sulphate in Jugular vein. Ventricle beat again.
3 hr. 43 min.	120	140	
3 hr. 45 m.	80	140	Resp. 40.
3 hr. 49 m.	—	—	Right vagus ineffective on ventricle and auricle.
3 hr. 50 m.	80	148	

According to Gaskell, Bowditch states that "atropine brings the contraction power of the muscle to a maximum straightway, so that the beneficial effects of successive stimuli disappear. We should expect to find that atropine improves the rythmical power and the conduction power in the same way as the contraction force, such an improvement being of a fixed and stable character, though not necessarily lasting."

"Sokoloff has shown that the application of atropine to the heart restores the rythmical power, when it has been depressed by the action of a variety of different drugs."

Cushny (1906) summarizes the present views as follows:- "Atropine paralyzes the inhibitory terminations of the vagus in the heart, and stimulation of this nerve therefore causes no changes in the pulse after administration. Small quantities of atropine have no further action on the heart than the paralysis of the inhibitory ends. The terminations of the accelerator nerve are unaffected and the heart muscle is neither stimulated nor depressed. In man following a theraputic dose and in the lower mammals in the blood pressure experiments, there is a marked quickening of the heart after atropine. But since, normally, impulses are constantly transmitted from the inhibitory center in the medulla to the heart, these prevent the heart from beating as rapidly as it would if freed from the nervous control. Stimulation of the vagus causes no retardation of the pulse after atropine."

"Large quantities of atropine, besides paralyzing the vagus, weaken and depress the heart muscle and the contractions consequently become slower and weaker and the output of the heart is less than normal. Hedborn states that large quantities accelerate the coronary circulation in mammals and increase the amplitude of the contractions. He is inclined to believe the latter alteration as due in part to the dilation of the coronary vessels, in part to a direct action on the heart muscle."

"It is not seldom stated that atropine, in addition to paralyzing the vagus ends, stimulates the heart muscle and thereby quickens the rythm. This assertion is somewhat difficult to disprove, but none of the alleged facts brought forward to support it have stood closer investigation. The error generally arose from the belief that atropine acted on the ganglia and not on the nerve ends or from the use of impure and irritant preparations and all of the phenomena on which it was based may be explained by the more modern theory, that the ganglia on the course of the inhibitory nerve fibers are left intact by atropine, while the terminations of the nerve are paralyzed."

Sollmann (1901) says "in animals in which the vagus is normally active (dog and man), its paralysis causes a greatly quickened heart rate. Atropine has in addition a direct action upon the heart muscle. It is

stimulated by small doses (an exhausted apex preparation will beat again.)"

Cushny (1910) states that the heart is sometimes slowed and weakened at first, owing to the stimulation of the inhibitory center in the medulla probably, but is later generally quickened from the paralysis of the inhibitory fibers in the heart, and after very large doses is weakened by the direct action on the muscle fiber.

However at the present time the view is still current that atropine is toxic to cardiac vagus endings and has a direct action on cardiac muscle.

In view of the discussion in the literature as to the extent to which atropine acts on the nervous system of the heart, a review of the present knowledge of the cardiac innervation is presented at this point. This review is particularly directed to the literature of the innervation of the terrapin, the animal used in this investigation.

According to Dogiel (1897), ganglion cells are found regularly in the hearts of the frog, turtle, fish, birds and mammals. In the hearts of these animals, the ganglion cells lie at the junction of the large veins in the heart and at the boundary between the auricle and ventricle. Delicate interlacing nerves run from the ganglionic rings later described by Gaskell, to the musculature of the auricle and to the ventricle of both sides. These nerves contain small ganglia and single

ganglionic cells.

Mills (1884) in his observations on the vagus and accelerators of the heart of the turtle, found that when either vagus is irritated, it has power to stop the heart action. When the ventricle of the heart is exhausted by stagnating blood, and the auricles are beating normally, stimulation of the vagus causes an inhibition of the auricles, but has no influence on the peristaltic movements of the ventricle. After kneading the ventricle and after the coordinated beat has returned, then the vagus influenced it as usual. In sea turtles there are accelerator nerves, their course being similar to that in mammalia and in Crocodyles. "In the latter the accelerator fibers leave the sympathetic chain at a large ganglion, corresponding to the ganglion stellatum of warm blooded animals, accompany the vertebral artery up to the superior vena cava, where they leave the artery and passing along the vein, anastomoses with branches of the vagus in the neighborhood of the heart."

Gaskell (1881-1884) has done good detailed work on the nerves of the heart of the turtle (Testudo Graeca), and I shall give quite a large amount of his work here.

He found that the left and right vagi nerves pass into a large accumulation of ganglion cells in the sinus, and thence along the auricular basal wall to the auriculo-ventricular groove. After they leave the ganglion groups in the sinus, a branch is given off from

the right nerve to accompany the large coronary nerve. At each extremity it is in connection with groups of ganglion cells, the sinus group on the one hand and with the ventricular groove on the other. During its free course it contains very few if any ganglion cells and just before entering the auriculo-ventricular groove, ganglia again become abundant. The largest accumulation of ganglia he found to be in the bifurcation of the large nerve trunks in the sinus, in the junction wall between the two auricles and in the termination of this wall in the auriculo-ventricular ring. In all of these places the ganglion cells are also found on the smaller branches of the nerves which ramify over the sinus and form a rich plexus in the junction wall between the two auricles and ventricles. The nerves with their accompanying ganglia are distributed around the whole junction of the sinus and auricles. From this ring as well as laterally from both sides of the junction wall between the two auricles, nerve fibers with ganglia are plainly seen passing into the auricular tissue. As the nerves pass further into the tissue, the ganglia become more and more scarce and soon disappear. At the junction of the auricles and ventricles, the nerve trunks passing from the junction wall of the two auricles anastomose and form a rich plexus containing large groups of ganglion cells along the line where the junction wall passes into the auriculo-ventricular ring. From this group of ganglion cells, a plexus of nerve fibers, also containing ganglia, though much more sparingly than the basal portion, passes

around the auriculo-ventricular ring. From this ganglionic nervous ring, fibers ramify over both the ventricle and auricles, in each case accompanied by ganglionic cells for a short distance. Similarly, the junction between the sinus and the auricles contains a ganglionic nerve plexus ring. Over the whole surface of the sinus, nerve fibers anastomose and carry ganglion cells with them.

STATEMENT OF PROBLEM.

The review of the literature shows that atropine poisons the nerve endings in the heart, but whether the muscle is stimulated or depressed is still an open question.

Gaskell's classic demonstration of the rythmic power of the muscle of the apex of the turtles' heart, together with his demonstration that this preparation is free from nerve cells which could regulate or control that rythmic power, gives a method not yet tried for the crucial testing of the question:-

Does Atropine influence the Cardiac Rythm and the Power of the Hearts Contractions by Direct Action on its Muscular Tissue, and if so, to what Extent and under what Conditions?

It is my purpose therefore in this work to determine the pharmacological action of atropine on cardiac muscle, using the heart strip in place of the whole heart, where one would obtain both the nervous and muscular effects.

MATERIAL AND METHODS.

Turtles were used as the source of materials for the work of this paper. The species used were Chysemys Emys, Emys Blandingii and Emys Rugosa. Strips of the muscle were cut from the apex of the ventricle by the method practised in the Physiological Laboratory of the University of Missouri as described below. These strips contain nerve endings it is true, but they have not been shown to contain any nerve cellular mechanism, hence the contractions developed in the muscle are to be ascribed to the inherent property of the cardiac muscle and to that alone. Strips of the sinus were used because they contain nerve ganglia. A comparison of the reactions of these two preparations, one with nerve ganglia and one free from nerve ganglia, may be expected to yield results from which one may conclusively determine whether the effect is upon the heart muscle or whether it is nervous. From these conclusions, the action of atropine on the whole heart can be more fully explained.

In making a preparation, the brain of the animal is crushed, and the heart exposed. The heart is then seized with forceps near the apex and a strip cut with scissors, beginning at the outer margin of the apex and cutting from right to left, as indicated in the figure below:

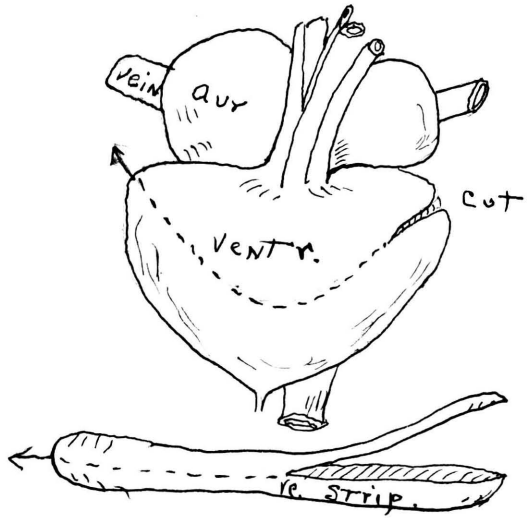

Figure I. Showing method of cutting heart strips.

A thread is then tied at each end of the strip while still moist in serum. A sinus strip includes about 15 mm. of the left vena cava. These strips are prepared as follows:- A ligature is first placed around the left cava, then passed beneath the posterior vena cava and tied. The strip is then removed from the attached auricles and veins and is mounted in the same way as the ventricular strip. Because of its delicacy, the sinus strip was made to contract against a tension of only a part of the weight of the lever.

A glass rod is bent at right angles, and is clamped on to a stand so that it is vertical. The lower end of the rod is so bent that one end of the strip can be attached to it, while the other end can be attached to the muscle lever which is clamped on to the stand above the rod. The muscle lever consists of a straw, on one of which is a narrow writing point of paper. To the other end of the straw is attached the upper end of the cardiac strip. A few centimeters from this end there is a needle acting as a fulcrum. A one gram weight is so

placed on the long arm of the lever, that there will be one gram tension on the muscle. As soon as possible the strip is put into a bath of physiological saline solution, which was shaken up in air to get as much oxygen as possible into solution before using. The bath of the saline solution was used until the strip began contracting rythmically, after which, Weaker Ringer's solution, composed of .7 per cent Sodium Chloride, .015 per cent Potassium Chloride and .013 per cent Calcium Chloride, was then substituted. A time marker to record seconds and the muscle lever were then adjusted so that they would write on a smoked paper kymograph, which revolved slowly. The exact time when the drug is put on and when taken off, is marked very carefully. After the administration of the drug, the strips were washed with Ringer's solution to remove the excess of drug before permanent immersion in the normal solution.

TABLE I. Showing the effect of ~~.005~~ 1/ per cent Atropine on Strips of Cardiac Muscle taken from the Apex of the Ventricle. Weaker Ringer's solution is used as the Normal and the Atropine is dissolved in this Solution. The Rate and Amplitude are taken Before the Bath of the Drug and During and after the the Bath. The Rate represents the Number of Contractions of the Heart Strip per minute. The per cent of the Normal is calculated for both the Rate and Amplitude During and After the Bath of Atropine.

Turtle No.	Strip No.	Experiment No.	Temp. Cent.	Strength of Solution	Time on	Rate per minute Before	Rate per minute During	Rate per minute After	Per cent of normal During	Per cent of normal After	Amplitude of cont. Before	Amplitude of cont. During	Amplitude of cont. After	Per cent of normal During	Per cent of normal After	Remarks
19	a	1	21	0.1	2	16	16	16	100	100	5.9	6.1	5.7	103	97	
19	a	2	21	0.1	3.5	10	14	8	140	80	5.6	5.4	4.5	97	881	
19	b	2	21	0.1	3.5	16	14.4	12.4	90	78	2.7	2.5	2.8	93	103	
19	a	3	21	0.1	3	98	90	82	92	84	2.8	2.7	2.8	97	100	
19	b	3	21	0.1	3	12	11.0	98	92	82	5.1	5.0	5.1	99	100	
19	a	4	21	0.1	4	84	10.4	82	123	98	2.8	2.6	2.8	93	100	
19	b	4	21	0.1	4	90	9.8	÷ 90	108	100	5.1	4.9	4.9	97	97	
19	b	11	21	0.1	2	82	64	8	79	98	4.1	4.1	3.7	100	91	
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TABLE 2. Showing the effect of 0.02 per cent Atropine on Strips of Cardiac Muscle taken from the Apex of the Ventricle. Weaker Ringer's Solution is used as the Normal and the Atropine is dissolved in this Solution. The Rate and Amplitude are taken Before the Bath of the Drug and During and After the Bath. The Rate represents the Number of Contractions of the Heart Strips per minute. The per cent of the Normal is calculated for both the Rate and Amplitude During and After the Bath of Atropine.

Turtle No.	Strip No.	Experiment No.	Temp. Cent.	Strength of Solution	Time on	Rate per minute			Per cent of normal		Amplitude of cont.			Per cent of normal		Remarks
						Before	during	After	During	After	Before	During	After	During	After	
19	a	7	20	.02	2	8	10	9	125	112	2.0	2.2	2.2	110	110	
19	b	7	20	.02	2	8.2	10	8.4	121	102	5.1	4.9	5.0	97	99	
19	b	9	20	.02	1	8.4	8.7	5.0	103	60	4.6	4.6	4.6	100	100	
19	b	10	20	.02	2	5.8	6	5.8	103	100	4.0	4.5	4.3	107	102	

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Tables

TABLE 3.

Showing the effect of 0.01 per cent Atropine on strips of Cardiac Muscle taken from the Apex of the Ventricle. Weaker Ringer's Solution is used as the Normal and the Atrópine is dissolved in this Solution. The Rate and Amplitude are taken before the Bath of the Drug and During and After the Bath. The Rate represents the Number of Contractions of the Heart Strips per minute. The per cent of the normal is calculated for both the Rate and Amplitude During and After the Bath of Atropine.

Turtle No.	Strip No.	Experiment No.	Temp. Cent.	Strength of Solution	Time on	Rate per minute			Per cent of normal		Amplitude of cont.			Per cent of normal		Remarks
						before	during	after	during	after	before	during	after	during	after	
15	a	1	18.0	.01	14	18	15	stop	84	0	24	26	0	108	100	
15	b	1	18	.01	14	15	10	"	67	0	18	19	19	105	105	
18	a	1	22	.01	2	17.3	18	17.9	128	97	12	13	14	108	106	
18	b	1	22	.01	2	18.2	18.8	18	132	99	23	25	26	108	113	
18	a	2	22	.01	2	16.8	16.2	14.4	97	86	10	11	12	110	120	
18	b	2	22	.01	2	20.7	18	15	91	73	25	27	28	108	112	
18	a	3	22	.01	4	22.8	20.4	18	90	79	9	10	11	111	122	
18	b	3	22	.01	4	21.9	21.9	19.2	100	88	30	30	30	100	100	
18	a	4	22	.01	2	17.8	18	19.8	101	111	12	12	12	100	100	
18	b	4	22	.01	2	18.4	18	17	98	93	26	26	27	100	103	
18	a	5	22	.01	2.4	12.8	14	13.8	108	108	9	9	9	100	100	
18	b	5	22	.01	2.4	14.4	15.8	15.6	109	108	27	27	28	100	103	
18	a	6	22	.01	2.5	12.6	12	11.6	96	92	8	9	9.5	112	118	
18	b	6	22	.01	2.5	14	14.4	14.8	102	105	26	27	25	103	97	
18	a	7	22	.01	4	12	11.6	11.8	67	84	8	8	8	100	100	
18	b	7	22	.01	4	15.8	15.6	15.8	99	100	22	22	22	100	100	
19	a	6	20	.01	4	9	9	9	100	100	19	22	21	115	110	
19	b	6	20	.01	4	8	9	9	112	112	49	50	50	120	120	

TABLE IV

Showing the effect of 0.001 per cent Atropine on strips of Cardiac Muscle taken from the Apex of the Ventricle. Weaker Ringer's Solution is used as the Normal and the Atropine is dissolved in this Solution. The Rate and Amplitude are taken before the Bath of the Drug and During and After the Bath. The Rate represents the Number of Contractions of the Heart Strips per minute. The per cent of the normal is calculated for both the Rate and Amplitude During and After the Bath of Atropine.

Turtle No.	Strip No.	Experiment No.	Temp. Cent.	Strength of Solution	Time on	Rate per minute			Per cent of normal		Amplitude of cont.			Per cent of normal		Remarks
						before	during	after	during	after	before	during	after	during	after	
21	a	1	22	.001	4	17	31	17	182	100	29	26	29	89	100	great increasing rate.
21	b	1	22	.001	4	15	17	14.9	113	99.9	19	22	24	126	126	
21	a	2	22	.001	1	15	19	15	130	99.9	24	20	22	84	92	
21	b	2	22	.001	1	14	15	15	100	107	21	21	21	100	100	
21	a	3	22	.001	2	13	16	13	123	128	23	20	23	87	100	
21	b	3	22	.001	2	14.4	20	18.4	138	128	17	16	17	95	100	
22	a	1	20	.001	2	11.6	10.8	10.8	99.4	94	43	41	40	96	94	
22	b	1	20	.001	2	12	11.8	12.4	99.9	133	21	20	21	96	100	
22	a	2	21	.001	3	10	10	10.5	100	105	16	15	16	94	100	
22	b	2	21	.001	3	13	13.9	12.5	99.9	97	18	19	18	105	100	
22	a	3	21	.001	10	10.5	12.6	12.5	120	119	16	15	9	57	60	
22	b	3	21	.001	10	12.5	13	12	100	96	18	18	18	100	100	
22	a	4	20	.001	3	9.2	10.4	11	113	119	14	14	14	100	100	
22	b	4	21	.001	3	13.3	14.8	14	111	105	17	18	18	105	105	

TABLE V

Same description as TABLE IV except that 0.005 per cent Atropine was used on Cardiac Strips.

Turtle No.	Strip No.	Experiment No.	Temp. Cent.	Strength of Solution	Time on	Rate per minute before	during	after	Per cent of normal during	Per cent of normal after	Amplitude of cont. before	during	after	Per cent of normal during	Per cent of normal after	Remarks
15	a	2	22	.005	5	16	11	9	75	57	39	38	36	98	93	
15	b	2	22	.005	5	11	8	7	73	64	16	16	16	100	100	
15	a	3	22	.005	22	8	8	11	100	137	33	34	29	103	88	
15	b	3	22	.005	22	7	8	10	116	142	15	15	14	100	94	
15	a	4	22	.005	6	8.5	8.5	7	100	82	28	26	26	93	93	
15	a	4	22	.005	6	7	7.5	7	102	98	9	9	9	100	100	

TABLE VI

Same description as TABLE IV except that 0.002 per cent Atropine was used on Cardiac Strips.

Turtle No.	Strip No.	Experiment No.	Temp. Cent.	Strength of Solution	Time on	Rate per minute before	during	after	Per cent of normal during	Per cent of normal after	Amplitude of cont. before	during	after	Percent of normal during	Percent of normal after	Remarks.
14	a	2	23	.002	14	9	10	9	111	100	16	15	11	94	69	
14	b	2	23	.002	14	11	11	10	100	91	14	14	14	100	100	
14	a	3	23	.002	5	9	10	11	111	122	11	8	5	73	46	
14	b	3	23	.002	5	10	9	14	90	140	1	irreg.	5	100	50	
16	a	1	23	.002	5	11	5	13	100	108	30	29	26	97	87	
17	a	1	24	.002	5	16	15.9	17	97	107	33	37	107	112	82	
17	b	1	24	.002	5	14.9	14.4	16	84	92	14	16	14	114	100	
17	a	2	24	.002	3	18	15	16	94	94	25	26	25	104	100	
17	b	2	24	.002	3	15	14	14	99	93	7	7	8	100	114	
24	a	2	23	.002	3	15.2	15	14	119	91	9	8	9	99	100	
24	b	2	23	.002	3	13	15.5	13	100	104	8	8	8	100	100	
24	a	3	23	.002	2	14	14.1	14	100	108	9	9	9	100	100	
24	b	3	23	.002	2	12	12	13	109	108	8	8	9	100	112	
24	a	4	23	.002	3	11.9	13	12	115	115	8	8	7	100	75	

TABLE VI --concluded.

Turtle No.	Strip No.	Experiment No.	Temp. Cent.	Strength of Solution	Time on	Rate per minute before	Rate per minute during	Rate per minute after	Per cent of normal during	Per cent of normal after	Amplitude of cont. before	Amplitude of cont. during	Amplitude of cont. after	Per cent of normal during	Per cent of normal after	Remarks.
24	b	4	23	.002	3	13	15	15	115	115	8	8	7.8	100	75	
24	a	5	23	.002	3	12.9	13.3	13	103	100	9	8	8	89	89	
24	b	5	23	.002	3	15	15	16	100	106	78	7	6	99	77	
24	a	6	23	.002	5	15	15	12	101	79	11	11	11	100	100	
24	b	6	23	.002	5	14.8	15	14.3	101	96	7	7	7	100	100	
24	a	7	23	.002	7	12.2	12.2	12.3	100	100	11	11	10	100	91	
24	b	7	23	.002	7	14.2	13	12	92	85	7	7	7	100	100	
25	a	1	20	.002	5	10	10	10.5	105	100	1	1	1.5	100	150	
25	b	1	20	.002	5	9	8.5	9	94	105	16	18	17	112	106	
25	a	2	20	.002	3	9	8.5	9	95	100	3	2	4	67	133	
25	b	2	20	.002	5	7.5	7.8	7.6	104	101	18	18	16	100	89	

TABLE VII

Same description as TABLE IV except 0.0001 per cent Atropin was used on Heart Strips.

Turtle No.	Strip No.	Experiment No.	Temp. Cent.	Strength of Solution	Time on	Rate per minute before	Rate per minute during	Rate per minute after	Per cent of normal during	Per cent of normal after	Amplitude of cont. before	Amplitude of cont. during	Amplitude of cont. after	Percent of normal during	Percent of normal after	Remarks.
8	a	1	21	.0001	35	9	3	3	33	31	33	34	35	109	113	
8	b	1	21	.0001	35	9	6	6	67	67	14	11	11	79	79	
9	a	1	22	.0001	30	16	10	11	63	72	9	65	6	73	67	
9	b	1	22	.0001	30	9	11	9	133	100	5	4	3	80	60	
11	a	1	19.4	.0001	10	8	13	11	162	137	29	29	28	100	97	
11	b	1	19.4	.0001	10	8	12	13	150	162	38	35	33	93	87	
11	a	2	20	.0001	20	12	11	11	92	92	25	26	29	104	111	
11	b	2	20	.0001	20	9	9	10	100	111	31	23	25	103	81	
11	a	3	20	.0001	20	7	7	8	100	114	25	28	25	112	100	
11	b	3	20	.0001	20	9	8	8	89	111	35	35	33	100	92	

TABLE VII --continued.

Turtle No.	Strip No.	Experiment No.	Temp. Cent.	Strength of Solution	Time on	Rate per minute: before	during	after	Per cent of normal: during	after	Amplitude of cont.: before	during	after	Per cent of normal: during	after	Remarks
11	a	4	20	.0001	25	5	5	6	100	120	23	22	23	96	100	
11	b	4	20	.0001	25	9	5	5	56	56	22	20	20	91	91	
12	a	1	21	.0001	15	15	14	14	94	94	21	22	21	109	100	
12	b	1	21	.0001	17	15	14	13	94	89	20	21	20	104	100	
12	a	2	23	.0001	5	15	16	16	106	106	19	16	17	85	90	
12	b	2	23	.0001	5	14	15	15	107	107	19	18	18	95	95	
12	a	3	23	.0001	12	14	15	13	107	93	16	15	14	94	88	
12	b	3	23	.0001	12	13	16	15	123	115	11	11	11	100	100	
13	a	1	21	.0001	10	18	17	17	95	95	22	18	11	82	50	
13	b	1	21	.0001	10	18	16	16	89	89	23	21	19	96	83	
26	a	2	23	.0001	24	9.2	10	10	108	108	42	39	40	93	96	
26	b	2	23	.0001	24	11.8	12	10	101	85	26	26	25	100	97	
26	a	3	24	.0001	7	11	11.2	11	101	100	37	35	35	95	95	
26	b	3	24	.0001	7	10.5	11.9	11.8	112	112	27	24	25	89	93	
26	a	4	24	.0001	2	11.6	11.8	11	101	95	34	36	33	105	98	
26	b	4	24	.0001	2	11.1	10	10	91	91	28	26	26	93	93	
26	a	3	33.5	.0001	4	12	12	11	100	92	37	36	35	98	95	
26	b	5	33.5	.0001	4	10.9	11.3	11	102	100.9	27	25	28	93	103	
26	a	6	33.5	.0001	4	11	10	11	91	100	32	30	33	96	103	
26	b	6	33.5	.0001	4	10.5	11	11	104	104	24	23.5	22	96	92	
26	a	7	24	.0001	3	11	12.2	11.2	110	101	30	29.4	31	98	103	
26	b	7	24	.0001	3	10	10.6	9	106	90	25	24	24	96	96	
26	a	8	24	.0001	2	10.9	11.2	10.3	102	95	32	32	31	100	97	
26	b	8	24	.0001	2	10.1	10.3	10	101	99.9	24	23.5	24	98	100	
26	a	9	24	.0001	3	12	12.2	11.5	101	96	28	27.2	27	98	97	
26	b	9	24	.0001	3	9	9.9	8.7	109	67	24	23	23.5	96	98	

TABLE VIII

Showing the effect of 0.00006 per cent Atropine on Strips of Cardiac Muscle taken from the Apex of the Ventricle. Weaker Ringer's Solution is used as the Normal and the Atropine is dissolved in this Solution. The Rate and Amplitude are taken Before the Bath of the Drug and During and After the Bath. The Rate represents the Number of Contractions of the Heart Strips per minute. The per cent of the Normal is calculated for both the Rate and Amplitude During and After the Bath of Atropine.

Turtle No.	Strip No.	Experiment No.	Temp. Cent.	Strength of Solution	Time on	Rate per minute			Per cent of normal		Amplitude of cont.			Per cent of normal		Remarks
						before	during	after	during	after	before	during	after	during	after	
28	a	2	24	.00006	3	14	17.5	15	121	107	29	28	27	97	94	
28	b	2	24	.00006	3	13	15	12.5	115	97	17	17	19	100	111	
28	a	3	24	.00006	2	15	17.5	14.5	116	97	27	25	25.5	93	95	
28	b	3	24	.00006	2	12.5	14.5	12	116	96	19	19	19	100	100	
28	a	4	24	.00006	2	12.5	13	13.5	104	108	28	26	27	93	97	
28	b	4	24	.00006	2	13	8.5	9.5	70	77	25	28	37	112	108	
28	a	5	24	.00006	10	13.5	3.9	3.0	140	148	27	7	3	26	8	
28	b	5	24	.00006	10	9.5	17	16.5	179	174	27	24	31	89	78	

TABLE IX

Same description as TABLE VIII except that 0.00004 per cent Atropine was used.

Turtle No.	Strip No.	Experiment No.	Temp. Cent.	Strength of Solution	Time on	Rate per minute			Per cent of normal		Amplitude of cont.			Per cent of normal		Remarks
						before	during	after	during	after	before	during	after	during	after	
27	a	1	25	.00004	2	12	12	10.5	100	88	31	31	31	100	100	
27	b	1	25	.00004	2	6.9	9	13	130	188	34	33	37	98	108	
27	a	2	25	.00004	3	6.9	9	13	130	110	28	20	27	72		
27	b	2	25	.00004	3	9.5	9	8	95	85	37	36	36	98	98	
27	a	3	25	.00004	4	12.5	13	11	104	88	19	16	19	85	100	
27	b	3	25	.00004	4	10	9.5	8.5	95	85	34	34	34	100	100	

TABLE X

Same description as TABLE VIII except that .00002 per cent Atropine was used.

Turtle No.	Strip No.	Experiment No.	Temp Cent	Strength of Solution	Time on	Rate per minute			Per cent of normal		Amplitude of cont.			Per cent of normal		Remarks
						before	during	after	during	after	before	during	after	during	after	
26	a	10	24	.00002	4	11.3	12	11	106	98	29	30	30	103	103	
26	b	10	24	.00002	4	9.5	9.8	9.3	103	98	24	24	24	100	100	
26	a	11	24	.00002	5	11	10.4	10	95	91	30	30	29	100	97	
26	b	11	24	.00002	5	9.8	9.2	8.8	94	90	25	24	24	96	96	

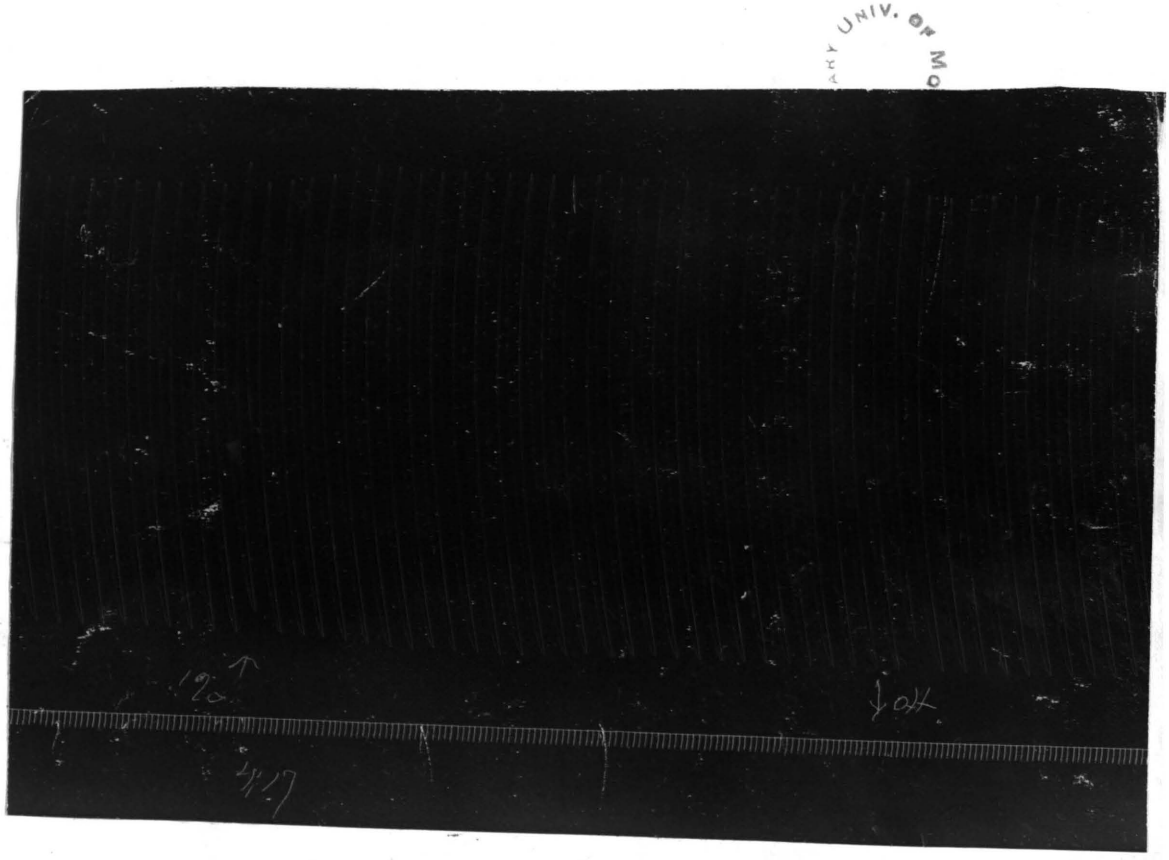
TABLE XI

Showing the effects of Atropine when applied to same Strip consecutively. Weaker Ringer's Solution is used as the Normal and the Atropine is dissolved in this Solution. The Rate and Amplitude are taken Before the Bath of the Drug and During and After the Bath. The Rate represents the Number of Contractions of the Heart Strips per minute. The per cent of the Normal is calculated for both the Rate and amplitude During and After the Bath of Atropine.

Turtle No.	Strip No.	Experiment No.	Temp. Cent.	Strength of Solution	Time on	Rate per minute			Per cent of normal		Amplitude of cont.			Per cent of normal		Remarks
						before	during	after	during	after	before	during	after	during	after	
26	a	2	23	.0001	27	92	10	10	108	108	42	39	40	93	96	
26	a	3	24	.0001	7	11	11.2	11	101	100	37	35	35	95	95	
26	a	4	24	.0001	2	11.6	11.8	11	101	95	34	36	33	105	98	
26	a	5	23.5	.0001	4	12	12	11	100	92	37	36	35	98	95	
26	a	6	23.5	.0001	4	11	10	11	91	100	32	30	33	96	103	
26	a	7	24	.0001	3	11	12.2	11.2	110	101	30	294	31	98	103	
26	a	8	24	.0001	2	109	112	103	102	95	33	32	31	100	97	
26	a	9	24	.0001	3	12	12.2	11.5	101	96	28	27.2	27	98	97	

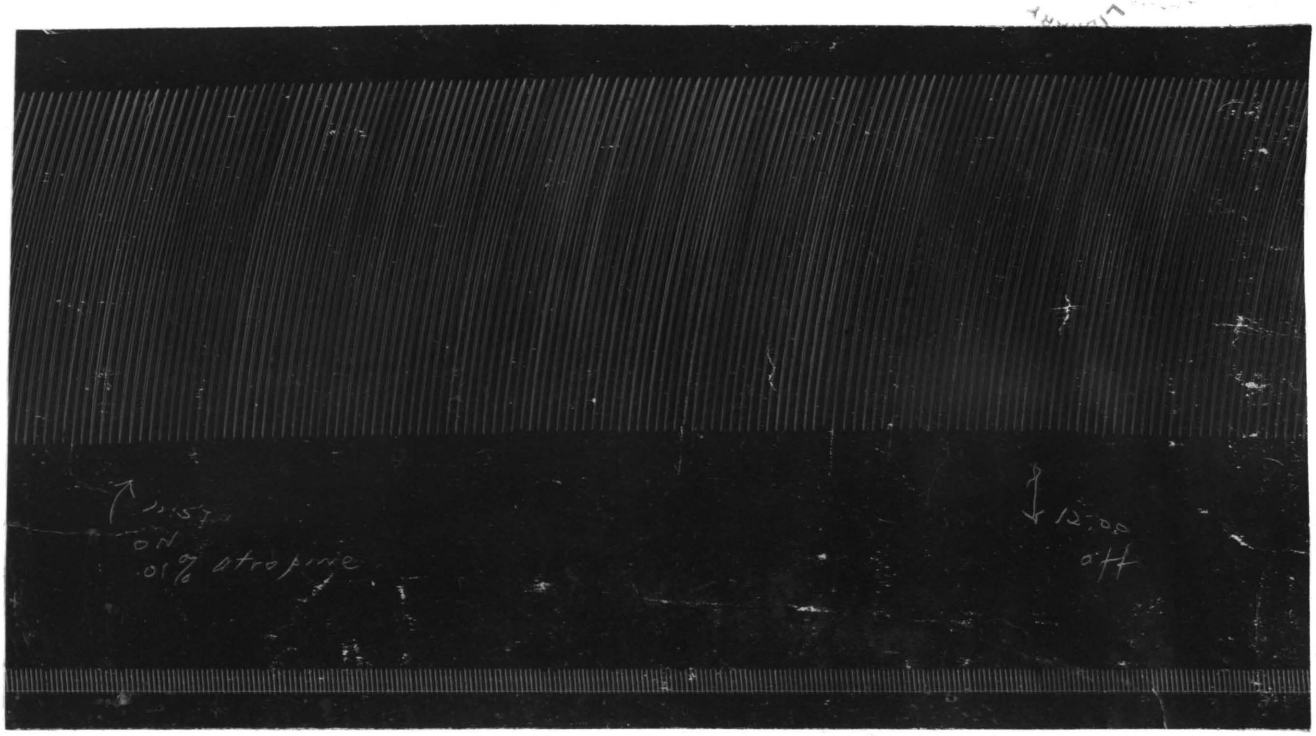
Tracing taken from TABLE 1.

19,2, a.



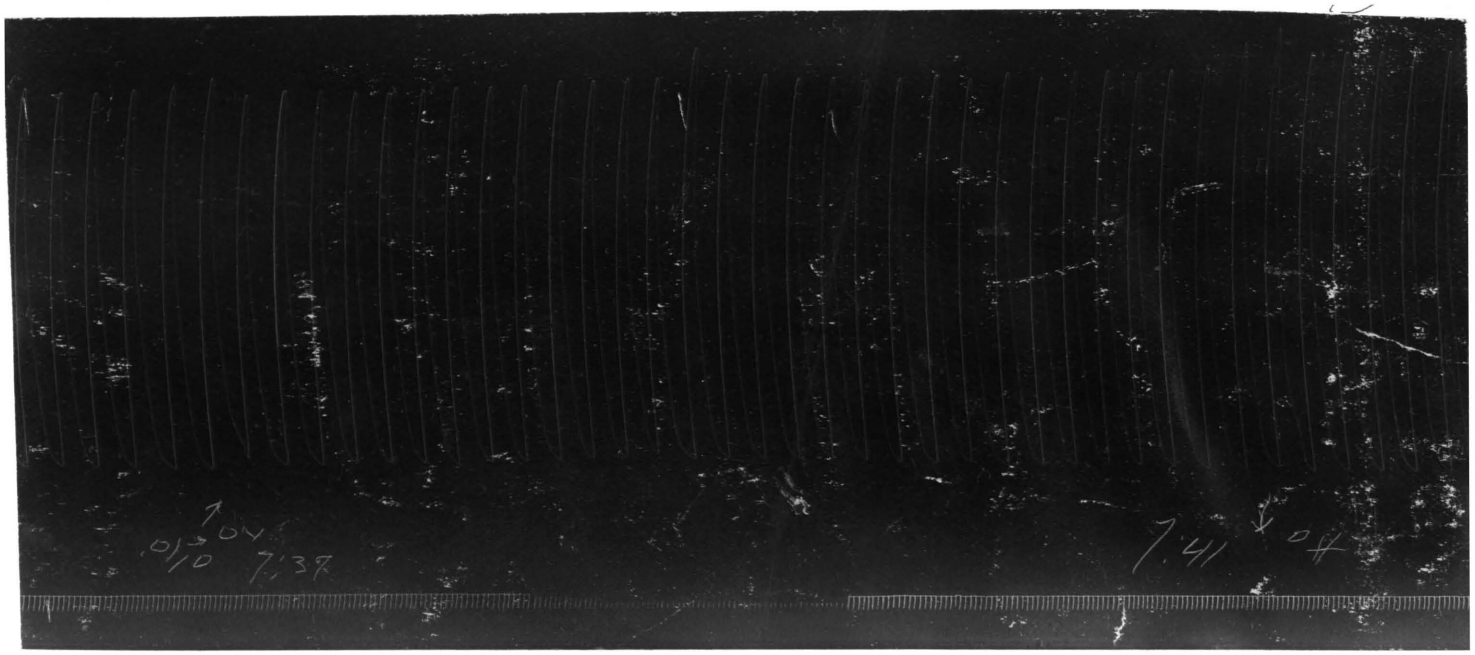
Tracing taken from TABLE 3.

Turtle #1, Experiment #5.



Tracing from TABLE 3.

Turtle # 19,

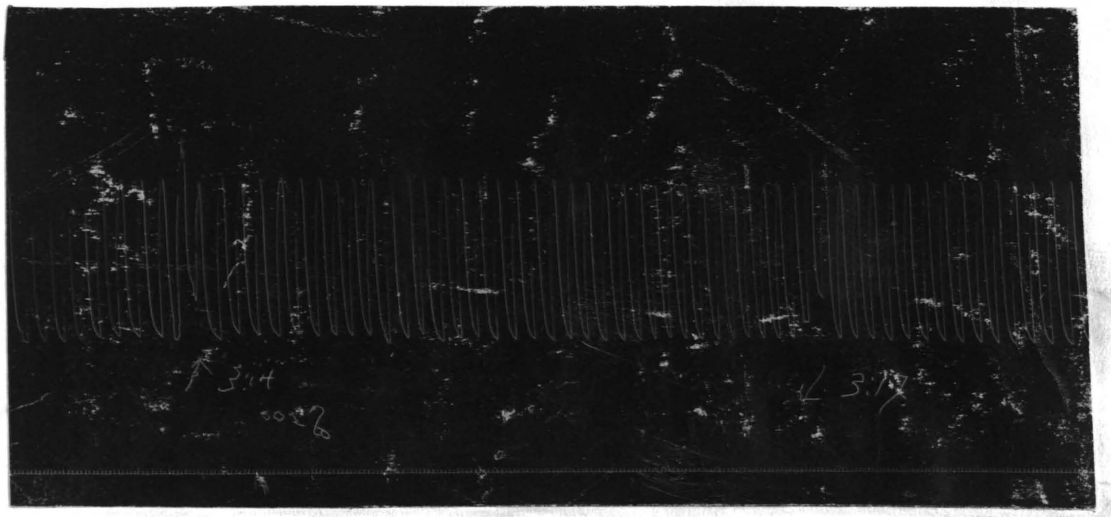


Tracing from TABLE 14.

Turtle # 1, Exp. 2.

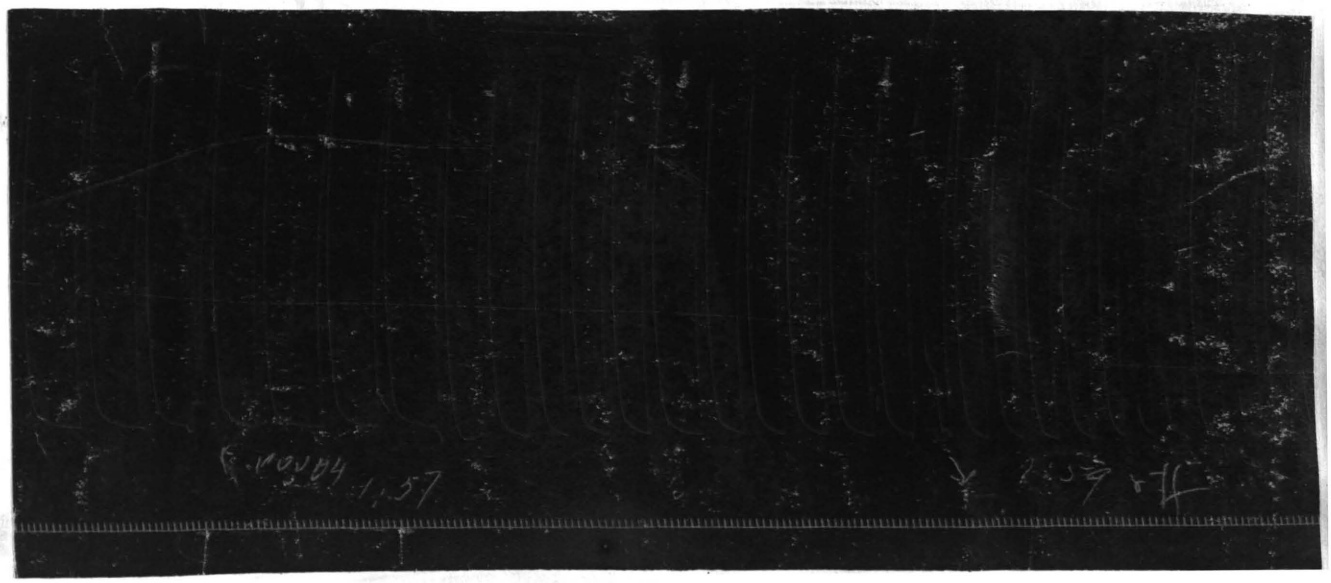
Tracing taken from TABLE 6

Turtle # 24, Experiment # 2.



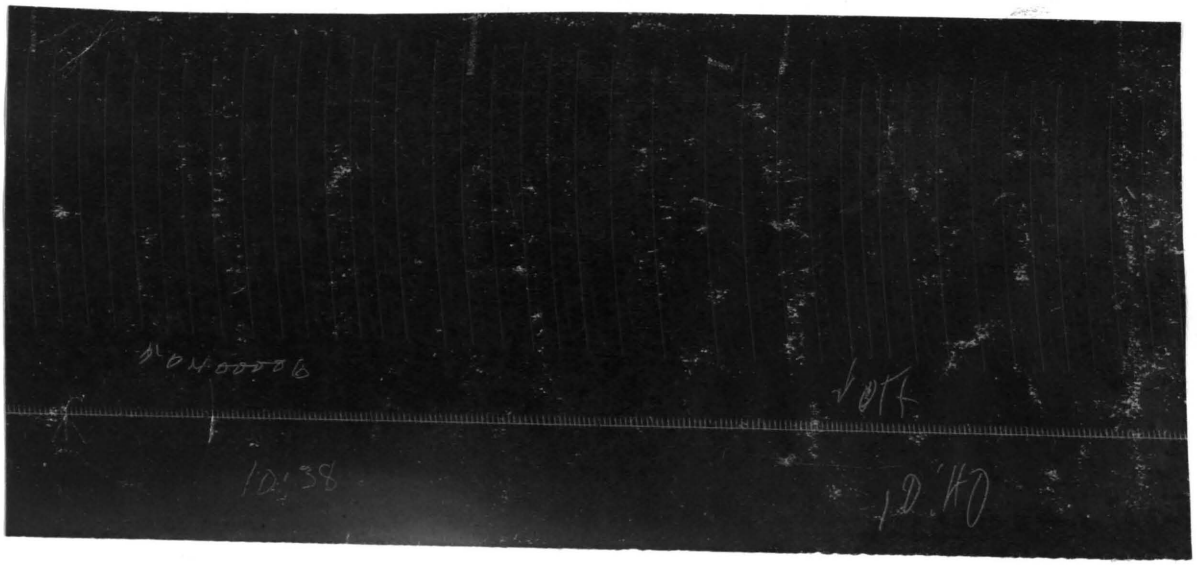
Tracing taken from TABLE 9.

Experiment 1, Turtle 27.



Tracing taken from TABLE 8.

Turtle # 28, Experiment # 3.



Tracing taken from TABLE 8

Turtle # 28, Experiment # 2.

OBSERVATIONS ON THE EFFECT OF ATROPINE ON CARDIAC MUSCLE.

The following discussion is based on the tables of experimental results. The tables are presented in the order of the concentration of the drug used, and not in the order in which the experiments were performed. The experiments with the stronger solutions are presented first, and those with the weaker solutions follow in order. The heading of each table gives a full description of the experiments presented in it.

In table 1, showing the effect of 0.1 per cent atropine, there is shown a slight increase in the rate of the contractions. This amounts to a 3 per cent increase when the average of the eight trials is taken. There is however a decrease in the rate in four instances and in four an increase. When the atropine is applied to the same strip successive times, there is at one time an increase and at another a decrease. In one, the depression amounted to 92 per cent of the normal rate while the increase was as much as 113 per cent. Following the removal of the drug, there was always a great decrease in the rate, except when the drug was applied for the first time, this time the rate remained the same. The amplitude with the 0.1 per cent was decreased in every experiment except the first, in which there was a slight increase in the amplitude of the contractions. After atropine of different strengths had been applied to the same strip ten times, then when

in the eleventh time 0.1 per cent is used, there was a marked decrease in rate and amplitude. This tends to show that such strong strengths of atropine depress the muscle.

Table 2 gives the action of 0.02 per cent atropine. This strength of solution is not as injurious to the muscle as the 0.1 per cent. With this concentration I got an increase averaging 13 per cent in rate. There was also an increase in amplitude of 3 per cent while the drug was on, and 2 per cent increase after the removal of the drug. This concentration of atropine was also tried after several different strengths had been used. When the rate fell to 60 per cent of the normal in the table, the strip was becoming very irregular, the amplitude of the contractions remaining the same. It later returned to normal.

Table 3 shows the observations with the 0.01 per cent concentration. In eight instances, I got a decrease in rate averaging 14 per cent, but in nine instances there was an increase in rate averaging 10 per cent. Averaging all of the trials, there was a decrease in rate of 2 per cent and in two instances there was a fall in rate of 33 per cent. After the drug was removed, there was an after decrease in rate in eleven trials and an increase in seven. In the first experiment with 0.01 per cent while the atropine was on, the heart ceased, but soon returned to normal again when the Weaker Ringer's solution was applied. In another instance in the same experiment, the heart strip ceased beating after the drug had been removed. The amplitude of

the contractions under the influence of 0.01 per cent atropine increased in every instance, the average being 16 per cent increase. However after the drug was removed, there was an increase of 7 per cent, there being just one instance of a decrease in the eighteen trials.

In Table 4 is shown the effect of 0.001 per cent concentration of atropine. As a whole this strength of atropine stimulated the heart muscle, for in sixteen trials, there was an increase of 15 per cent in rate. In two experiments the rate remained practically normal. In one case the rate almost doubled, this being the largest increase in rate that was obtained in all of my experiments. After the drug was removed, there was still an after increase of 5 per cent. When there was a decrease in rate, it was very small, and there were no instances of an increase rate of more than 20 per cent. With this increase in rate of 15 per cent with the 0.001 per cent concentration, there was a decrease in the amplitude of 13 per cent. In the instance where the rate almost doubled, there was only a decrease in amplitude of 11 per cent. The amplitude fell in one experiment 43 per cent, when there was an increase in rate of only 19 per cent. The amplitude and rate later returned to normal. The amplitude after the drug was removed, showed still a decrease of 9 per cent. But this would not be so large were it not for the large decrease mentioned above.

With the 0.005 per cent strength of the drug, as is shown in table 5, there is a average decrease in rate of 6 per cent. After the rate decreased the first time 27 per cent, the

second time the drug was applied, it increased to 16 per cent and the third time to 2 per cent. With this average decrease in rate, there whould be expected an increase in the amplitude, but there is a very slight decrease of 1 per cent. After the drug is removed, the rate is till 4 percent below normal, while the amplitude is decreased 6 per cent.

In table 6, there are shown the results with the 0.002 per cent strength. There is an average increase of 1 per cent in rate in the 25 trials with this concentration. The highest increase with his strength was 19 per cent and the lowest 16 per cent. Most of the experiments show very little increase or decrease, but remain very near normal. The amplitude going with this heart rate shows a decrease of 2 per cent. Looking through the experiments with 0.002 per cent from the standpoint of applying atropine successively to the strips, there seems to be a slight stimulation followed by depression. After the drug is removed, there still remained an increase in rate of 1 per cent, but a decrease of 4 per cent in amplitude over the normal. In one case there was a decrease of 54 per cent, going with an increase in rate of 22 per cent.

Table 7 shows the effect of 0.0001 per cent atropine. There is an average decrease of .9 per cent in rate in 36 experiments. In one trial the rate fell 77 per cent, but there was an increase of 9 per cent in amplitude going with it. The highest increase in rate was 23 per cent, the amplitude remaining normal during this increase. The amplitude during the whole series of experiments averages .6 per cent decrease. After the drug was removed, there was

a decrease in rate of 10 per cent, together with a decrease in amplitude of 5 per cent.

In table 8, the experiments with 0.00006 per cent concentration are given. With this strength of atropine the average percentage increase in rate in eight experiments was 20 per cent. There was an accompanying decrease in amplitude of 11 per cent, which can not be considered as compensatory. The rate in the last experiment of this series almost doubled, the percentage increase being 79 and the decrease in amplitude only 11 per cent. Again in another experiment, there was a decrease in amplitude of only 4 per cent with an increase in rate of 40 per cent. After the drug was removed, the rate fell back to an increase of 9 per cent, while the amplitude fell to 14 per cent. In the case where the amplitude fell to 74 per cent, it later fell to 6 per cent.

In table 9 is shown the effects of 0.00004 per cent atropine. There is an average increase in rate of 7 per cent, while the amplitude is decreased 8 per cent. After the drug is removed, there is an average increase in rate of 6 per cent. In one experiment, the percentage increase in rate was 88 per cent, and at the same time there was an increase in amplitude of 8 per cent.

Table 10 shows the effect of 0.00002 per cent atropine on cardiac muscle. The results were only obtained on one turtle. In averaging four experiments with this concentration of the drug, there was no change in rate and amplitude. The greatest increase in rate in any experiment

with this drug was only 6 per cent. There was an increase in the amplitude accompaning this increase in rate of 3 per cent. The greatest change in the amplitude was a decrease of 4 per cent. After the removal of the drug the average rate of the four experiments fell 6 per cent below normal and the amplitude fell 1 per cent.

The influence of 0.00002 per cent atropine on the rythm and the amplitude of the ventricle muscle was very slight in this series. It was therefore taken as the minimal strength of atropine that influences the reactions of ventricular muscle.

Strips of the sinus muscle were experimented upon in the same way as with the muscle of the apex of the ventricle. With two exceptions, the rythmic contractions, when demonstrated, were unchanged. The percentage change in either case was not over 8 per cent, this large increase occuring after the removal of the drug.

Turtle No.	Experiment No.	Strength of Solution	Time on	Temp. Cent.	Rate per minute before	during	after	Percent of normal during	aft
3	1	.002	4	21	40	41	41	102	102
4	2	.0001	3	21	12	12.5	13	104	108
6	1	.001	5	20	22	22	23	100	104

The greatest increase in rate was obtained with 0.0001 per cent atropine. The other strength of the drugs did not produce a very great effect. Averaging the experiments, there is an increase in rate of 3 per cent while the drug is on and 7 per cent after the removal of the drug. Along with the slight increase, there was noticed a very slight decrease in tone. The length of the tone waves remained almost constant, there being very little difference in the waves while the atropine is on and when it is off the muscle.

DISCUSSION OF THE EXPERIMENTS ON THE PHARMACOLOGICAL ACTION OF ATROPINE ON HEART MUSCLE.

There seems to be very little difference in the strength of the atropine used, because the weaker solutions have an average effect upon the cardiac muscle not strikingly different from that of the stronger solutions. In the 0.1 per cent, there was an average increase in rate of 3 per cent, while with the 0.002 per cent there was an increase in rate of 13 per cent. With the 0.01 per cent there was an average decrease in rate of 2 per cent, and in two cases with this concentration of the drug, the percentage change in normal was 33 per cent. There seemed to be almost paralysis in one experiment with the 0.01 per cent, but finally the heart strip regained its normal rythm. With the 0.001 per cent, there was an average increase in rate of 15 per cent and a decrease in amplitude of 13 per cent. The rate almost doubled in one experiment, while there was a decrease in amplitude of only 11 per cent. With the 0.005 per cent there is an average decrease in rate of 6 per cent, accompanied by a decrease in amplitude of 1 per cent. The 0.002 per cent does not seem to have very much effect upon the cardiac muscle, there being an average increase of only 1 per cent in 25 experiments. Looking through the experiments with 0.002 per cent from the standpoint of applying atropine successively to the strips, there seems to be a slight

increase in amplitude and rate followed by a decrease in rate and amplitude. This fact seems to be true throughout the experiments with from .0001 to 005 per cent concentration, that the activity of the muscle is first increased above that of the normal, and then to depress the muscle in successive experiments below normal. This is shown in table 1. But averaging all of the experiments where atropine is applied the first time to the strip, there is shown an increase of only 2 per cent in rate. When the weaker solutions have been applied to the strip a number of times, the stronger solutions seem to be more active and cause a marked depression of the rate and amplitude, of the cardiac strip. The .0001 per cent atropine does not have very effect upon the muscle. The rate remaining the same, but there was an increase of amplitude of 9 per cent. There was never a great increase in rate in any of the experiments with this concentration, the greatest being 23 per cent. The largest average increase in all of my experiments with the different concentrations of atropine, was obtained with the 0.00006 per cent atropine. The increase being n this case 20 per cent. There was an accompanying decrease in amplitude of 11 per cent, but this cannot be considered as compensatory. With the 0.00004 per cent and 0.00002 per cent, there is very little effect. With the former however, there is an average increase in rate of 7 per cent, and also there was obtained an increase in rate of 88 per cent accompanied by an increase in amplitude of 8 per cent, in one experiment with this concentration.

Two curves are plotted in attempt to represent

TABLE XII

Showing the effect of Atropine on Heart Strips when applied the first time on each Strip. Weaker Ringer's Solution is used as the Normal and the Atropine is dissolved in this Solution. The Rate and Amplitude are taken Before the Bath of the Drug and During and After the Bath. The Rate represents the Number of Contractions of the Heart Strips per minute. The per cent of the Normal is calculated for both the Rate and the Amplitude During and After the Bath of Atropine.

Turtle No.	Strip No.	Experiment No.	Temp Cent	Strength of Solution	Time on	Rate Per minute			Per cent of normal		Amplitude of cont.			Per cent of normal		Remarks
						before	during	after	during	after	before	during	after	during	after	
8	a		21	.0001	35	9	2	3	23	34	52	24	25	109	113	
8	b		21	.0001	35	9	6	6	67	67	14	11	11	79	79	
9	a		22	.0001	30	16	10	11	63	25	9	65	6	73	67	
9	b		22	.0001	30	9	11	9	122	100	5	4	3	80	60	
11	a		19.4	.0001	10	8	13	11	162	37	29	29	28	100	97	
11	b		19.4	.0001	10	8	12	13	150	62	38	35	33	93	87	
12	a		31	.0001	17	15	14	14	94	94	21	22	21	109	100	
12	b		21	.0001	17	15	14	13	94	87	20	21	20	104	100	
13	a		10	.0001	10	18	17	17	95	95	22	18	11	82	50	
13	b		10	.0001	10	10	16	16	89	89	23	21	19	96	83	
17	a		24	.002	5	16	15.9	17.4	99	108	30	29	26	97	87	
17	b		24	.002	5	14.9	14.4	16	97	107	33	37	37	112	82	
25	a		20	.002	5	10	10	10.5	100	105	1	1	15	100	150	
25	b		20	.002	5	9.5	8.9	10	94	105	16	18	17	112	106	
15	a		18	.01	14	18	15	stop	84	0	24	26	100	108	100	
15	b		18	.01	14	15	10	later	67	0	18	19	19	105	105	
18	a		22	.01	2	17.3	18	17.9	128	97	12	13	14	108	116	
18	b		22	.01	2	18.2	18.8	18	132	99	23	25	26	108	113	

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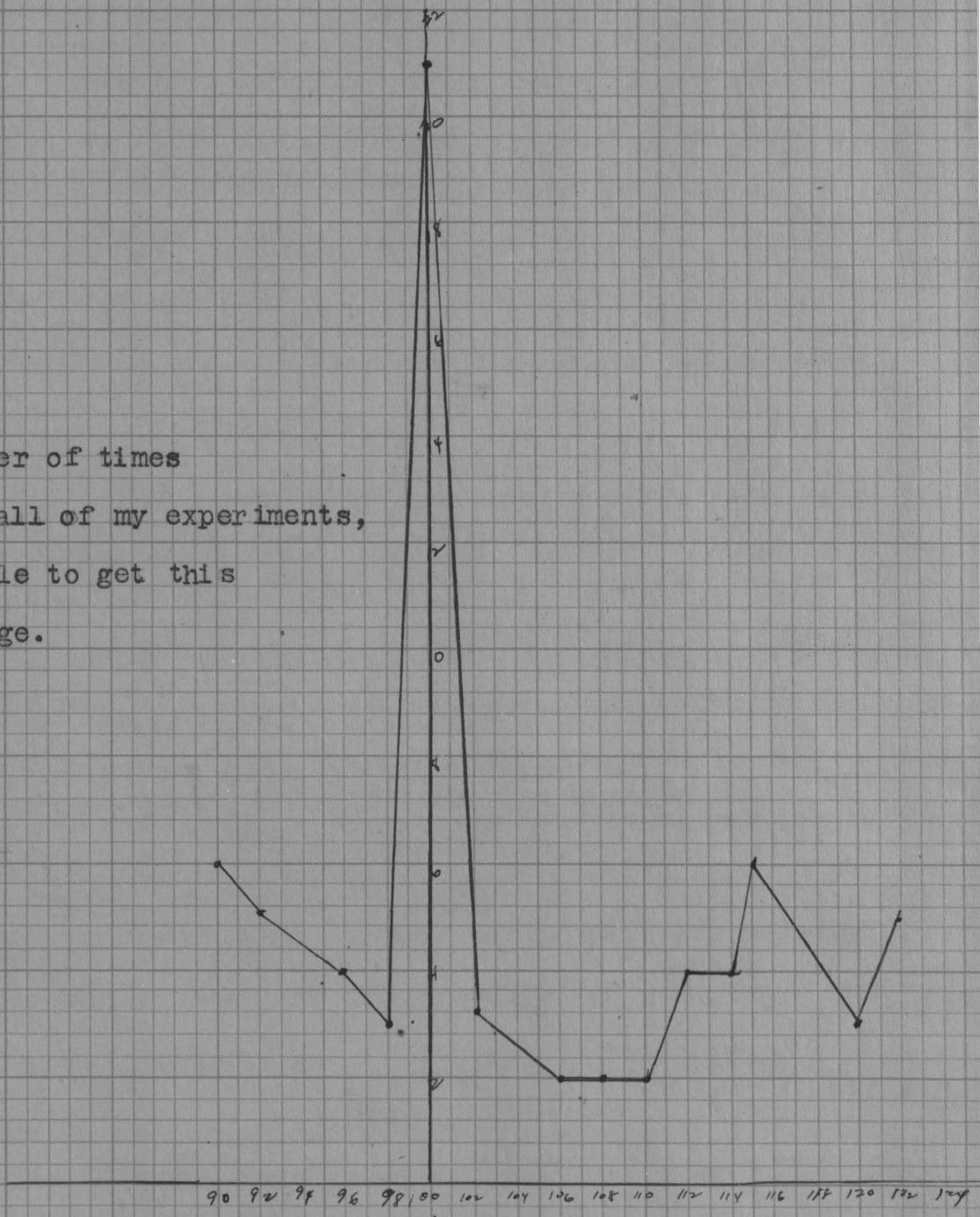
graphically, the variations in the effect of atropine on the heart muscle of the turtle. One of these curves represents the effect on the rate of contraction and the other represents the effect on the amplitude of contraction. The figures represent the change while the drug is on the strip. The horizontal in each case represents the percentage change in normal while the bath is on the strip, while the vertical represents the number of times that in all of my experiments I was able to get that particular change in amplitude or in rate. It is very plainly seen that the curve rapidly falls on each side of the normal to very near the base line, then becomes very irregular. This is true for both curves.

The work on the sinus muscle shows that there is only a very slight increase in rate, the maximum being 8 per cent after the removal of the drug. Along with this there was a slight decrease in tone. With stronger solutions there is noticed a marked depression both in rate and amplitude. Since there is very little difference in the results with the ventricular strips and the sinus strips, so far as the rate and amplitude are concerned, shows evidently that the presence of nerve cells in the sinus strip exert no appreciable influence on the response of this tissue to atropine.

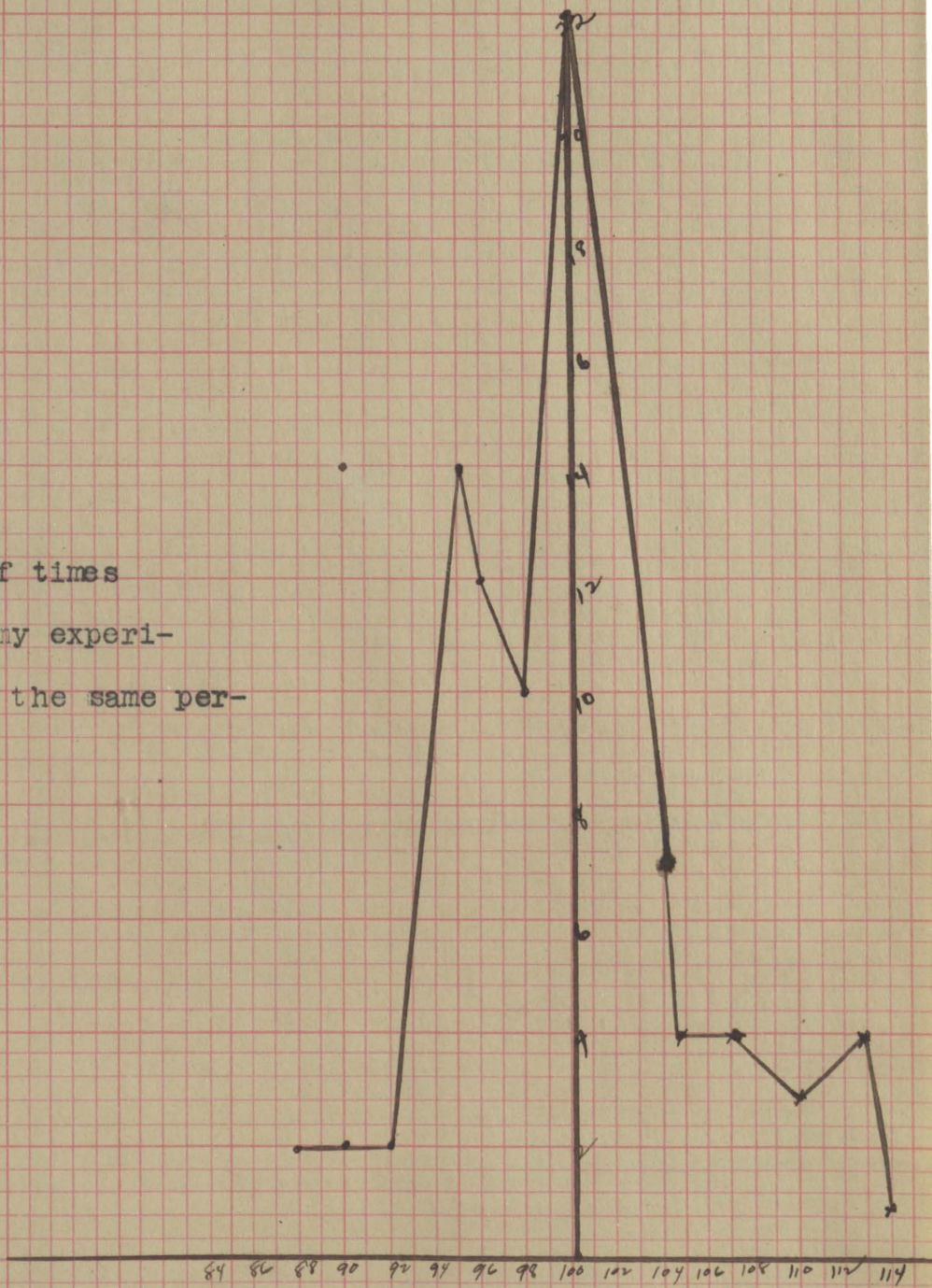
TABLE SHOWING THE EFFECT OF ATROPINE ON THE RATE OF THE HEART MUSCLE CONTRACTIONS.



The number of times that in all of my experiments, I was able to get this percentage.

The percentage change in RATE of the contractions, while the drug is on.

TABLE SHOWING THE EFFECT OF ATROPINE ON THE AMPLITUDE OF THE CONTRACTIONS OF HEART MUSCLE.



The number of times that in all my experiments, I got the same percentage.

The percentage change in amplitude, while the drug is on.

SUMMARY OF THE WORK ON THE ACTION OF ATROPINE ON HEART MUSCLE.

1. Atropine is a stimulant to cardiac muscle, when weaker solutions are used. 0.00006 per cent atropine produces the greatest stimulation.

2. Atropine of from the 0.0001 per cent to the 0.005 per cent concentration produce very wide variations. Such variations as occur seem partly to be stimulated above the normal and others are depressed below the normal.

3. Stronger solutions of atropine, 0.1 and 0.01 per cent cause a depression of the rythmicity and the amplitude of the heart muscle. This is especially true after the muscle has been experimented upon with weaker solutions before the bath of the stronger solutions.

4. When atropine is applied to the same strip successively in concentrations which produce very little change in the heart muscle, 0.0001 to 0.005 per cent, such variations as occur, seem at first to increase the activity above that of the normal muscle, and then in successive applications to depress the normal.

5. In most of the experiments where there is an increase in rate, there is usually a decrease in amplitude and vica versa, but this cannot be considered as compensatory.

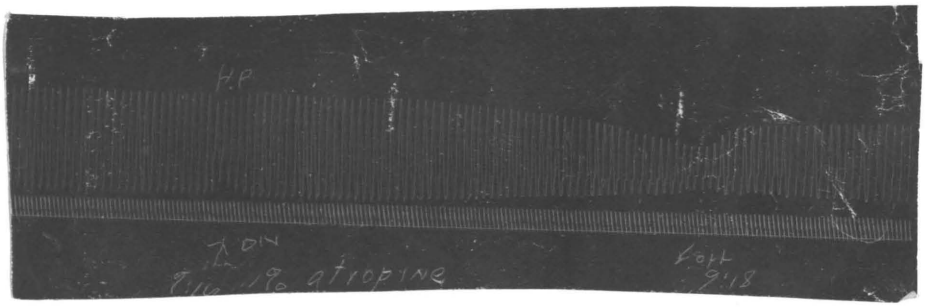
6. The effect of atropine on the sinus strip is almost negative. There is however a very slight depression of rythmicity and amplitude with very strong solutions, and with the weaker solutions as is the case with the ventricular strips, there is produced a slight stimulation of the rate. Accompanying this there is a slight decrease in tone.

TABLE XIII

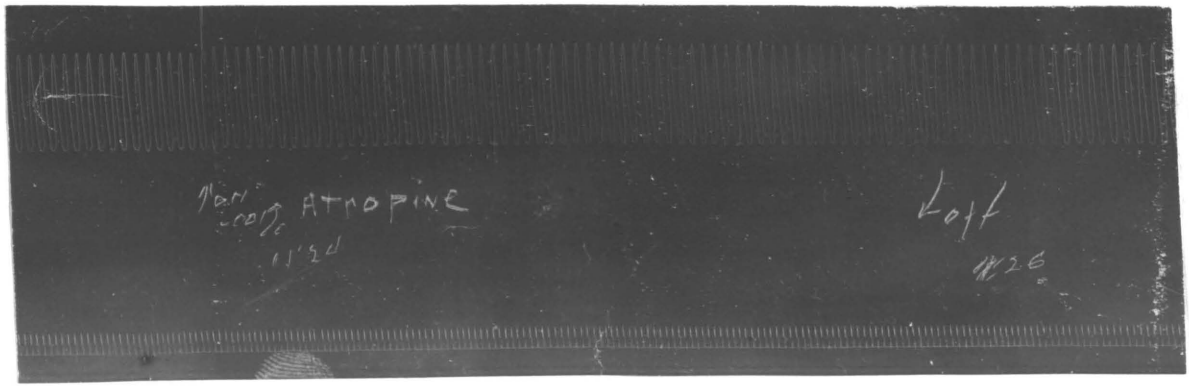
Showing the effect of the perfusion of different strengths of Atropin through the Frogs' Heart. Weaker Ringer's Solution is used as the Normal and the Atropine is dissolved in this Solution. The Rate and Amplitude are taken Before the Bath of the Drug and During and After the Bath. The Rate represents the Number of Contractions of the Heart Strips per minute. The per cent of the Normal is calculated for both the Rate and Amplitude During and After the Bath of Atropine.

Frog No.	Strip No.	Experiment No.	Temp. Cent.	Strength of Solution	Time on	Rate per minute			Per cent of normal		Amplitude of cont.			Per cent of normal		Remarks
						before	during	after	during	after	before	during	after	during	after	
3	2			.001	4	32	32	32	100	100	10	.8	10	50	100	great decrease in amplitude
3	2			.001	2	30.5	30.5	31	100	101	1.1	9	.9	82	82	
3	3			.001	2	31	31.	34	100	109	9	9	.9	100	100	
4	1			.01	4	100	15	16	100	100	10	1 3	1 5	130	150	caused heart to beat after sodium and R. refused.
4	1			.01	2	36	36.3	36.	100.8	100.5	15	14	13	94	87	
4	1			.1	1	36	36.	35	100	98	1 3	7	1 15	54	89	
4	1			.1	2	38	35	34	102	100	11	8	11	73	100	
4	4			.1	2	36	38	38	102	102	11	5	8	46	73	heart did not contract normally again.
5	1			.001	1	33	34	35	103	106	11	10	10	100	100	
5	1			.001	4	39	40	36	100	93	10.5	10.5	11	100	104	
5	1			.001	3	39	39	37	100	95	11.5	10	12	67	40	
5	1			.001	5	38	39	39	102	102	10	9	11	90	100	
5	3			.001	2	30	30.8	30	103	100	128	128	128	100	100	
5	3			.01	2	30	30.1	32	100.3	106	128	128	128	100	100	
5	3			.01	1	32	32	32	100	100	128	128	128	100	100	

Tracing taken from TABLE 13.
Frog # 4, Experiment # 1.



Tracing taken from table 13.
Frog # 5, Experiment # 3.

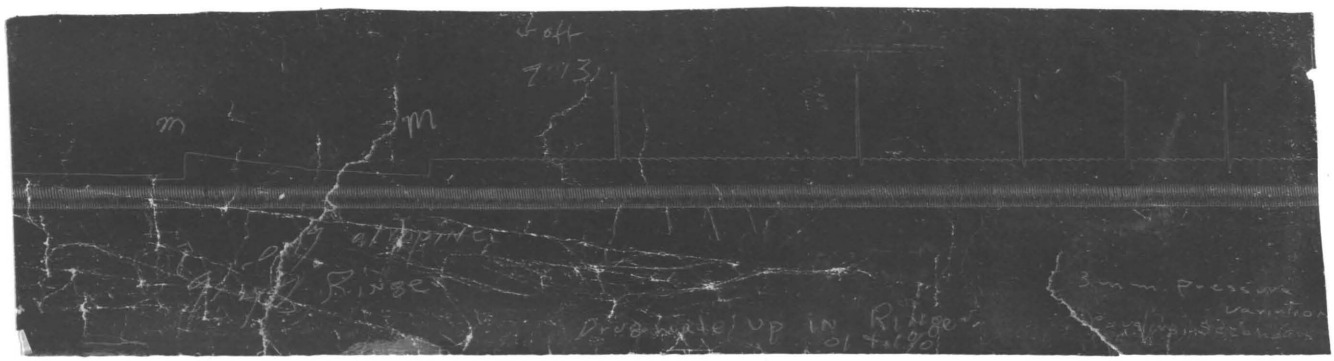


TRACING FROM TABLE 13.

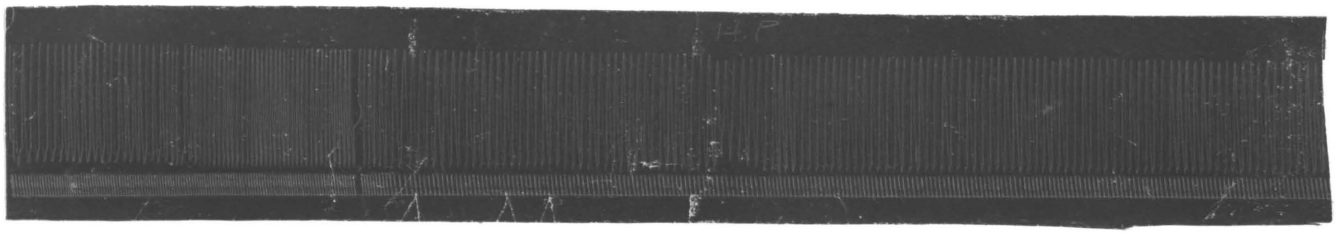
FROG # 4, EXP. #1.

Showing the atropine produce the normal rythm of the heart.

Heart beginning to contract.



Heart regained the normal rythm.



PERFUSION OF THE FROG'S HEART WITH ATROPINE.

Two aspirator pressure bottles, with tubulated foot for attaching rubber tubing, contained the solutions to be perfused. These were clamped to a stand. One of these bottles contained the physiological normal solution and the other contained the drug, dissolved in the same normal solution as used in the other bottle. Each bottle was provided with a rubber stopper and constant level tube, about 2 mm. in diameter, extending through it and down below the surface of the solutions. The two tubes were set at the same level. The rubber tubing from the aspirator bottles connected the two branches of a glass perfusion canula. The canula was so shaped that it could readily be inserted into the inferior vena cava. The special feature of this canula is that at the junction of the branches of the canula, there is a vertical open limb, about 4 centimeters in height, out of which the solution overflows when the pressure becomes too great for the heart perfused, this insuring a constant pressure on the heart itself. A pinch cock was placed on each length of the rubber tubing near the bottle, so that the solutions can be poured into both bottles and the air expelled from the apparatus each time before the canula is inserted. A recording lever was supported on a separate stand. This lever was like the one previously described as used for the heart strip, except that a vertical arm, 4 centimeters long, was sealed on to the fulcrum with wax. This permitted the heart of the frog to lie in a normal

position in the body. The frog's used for this perfusion were carefully pithed, the thorax opened and the pericardium removed. The apex of the heart was turned anteriorly, a ligature placed under the inferior vena cava, an incision made into this vein and the canula inserted and ligatured. One of the aortae was cut to allow the outflow of the perfused solution. A small "S" shaped wire hook, which is attached to a thread, is hooked into the apex of the ventricle. The other end of the thread is attached to the upright arm of the recording lever. The tension of the lever was regulated by a light movable weight placed on the long arm of the lever. The writing-point was then adjusted to the smoked kymograph and a time marker used to record seconds.

OBSERVATIONS ON THE PERFUSION OF ATROPINE THROUGH THE FROGS HEART.

In table 13 is seen the records of a series of experiments on the perfusion of atropine. The effect seems to be very slight on the frogs heart, there possibly being an increase in rate. However this increase was not very large, it being never over three percent. This could have been due to a change in pressure, although I was not able to detect it at the time. Accompanying this slight increase in rate, there was a decrease in amplitude. The average percentage change in amplitude was a decrease of 5 per cent, while after the drug was removed, there was a decrease of 3 per cent. The rate after the drug was removed increased .7 per cent, while there was an increase of .7 per cent while the drug was on. With the 0.1 per cent solution which was tried, the heart was paralyzed and would not contract normally again. The weaker solutions which were tried on the heart strips, such as the 0.00004 per cent and 0.00006 per cent, had no effect, the heart remaining normal. The best solution was found to be 0.001 per cent, for it could be tried any number of times and the heart would always return to normal, and would never show any after effects.

Another point which was brought out by the perfusion of the frogs heart was the fact that atropine increases the irritability of the heart. After 0.7 per cent saline and both the Ringer and the Weaker Ringer's Solutions had failed to start the heart to contracting, atropine when

perfused started the heart to contracting and soon had a normal rythm.

The well established fact that the vagus nerve of the frog when stimulated produces inhibition of the heart and after the perfusion of atropine, the effects of the nerve was removed was again established.

SUMMARY OF THE ACTION OF ATROPINE WHEN PERFUSED THROUGH THE FROGS HEART.

1. Atropine when perfused through the frogs heart causes an increase in rate accompanied by a decrease in amplitude.

2. After the heart has been at rest for some time, the application of atropine will produce the normal rythm.

3. 0.001 and 0.002 per cent atropine are the least injurious to the heart muscle.

4. Strong solutions (0.1 per cent) depress the rythmicity and amplitude and almost paralyzes the muscle.

5. Atropine destroyes the influence of the vagus over the heart.

TABLE XIV

Showing the effect of Perfusion of different strength of Atropine through Turtle's Heart. Weaker Ringer's Solution is used as the Normal and the Atropine is dissolved in this Solution. The Rate and Amplitude are taken Before the Bath of the Drug and During and After the Bath. The Rate represents the Number of contractions of the Heart Strips per minute. The per cent of the Normal is calculated for both the Rate and Amplitude During and After the Bath of Atropine.

Turtle No.	Strip No.	Experiment No.	Temp. Cent.	Strength of Solution	Time on	Rate per minute			Per cent of normal		Amplitude of cont.			Per cent of normal		Remarks
						before	during	after	during	after	before	during	after	during	after	
1	1			.001	4	29	29	29	100	100	28	29	31	103	110	
1	2			.001	5	30	30.1	30.1	100.1	100.1	36	36	36	100	100	
1	3			.001	2	301	30.1	301	100	100	36	35	35	98	98	
1	4			.001	2	31	30	30.5	97	99	43	47	47	109	109	
1	5			.001	12	30.5	32	31	104	101	471	471	471	100	100	
1	6			.01	2	32	32	32	100	100	471	46	46	98	98	
2	1			.01	3	30.8	32	31.2	103	101	47	456	470	98	100	
2	2			.01	2	31.2	31	31	99.4	99.4	475	471	471	99.2	99.2	
2	3			.01	3	32	32.5	32	101	100	46	451	46	99	100	
3	4			.01	3	31.5	31.5	32	100	101	46	45	46	99	100	
3	5			.01	12	30	28	28.5	94	95	39	29	39	98	100	
3	6			.01	5	30	27.8	27	93	90	40	27	37	68	93	
47	1			.1	15	30	24	8	80	30	39	44	39	112	100	

TABLE XV

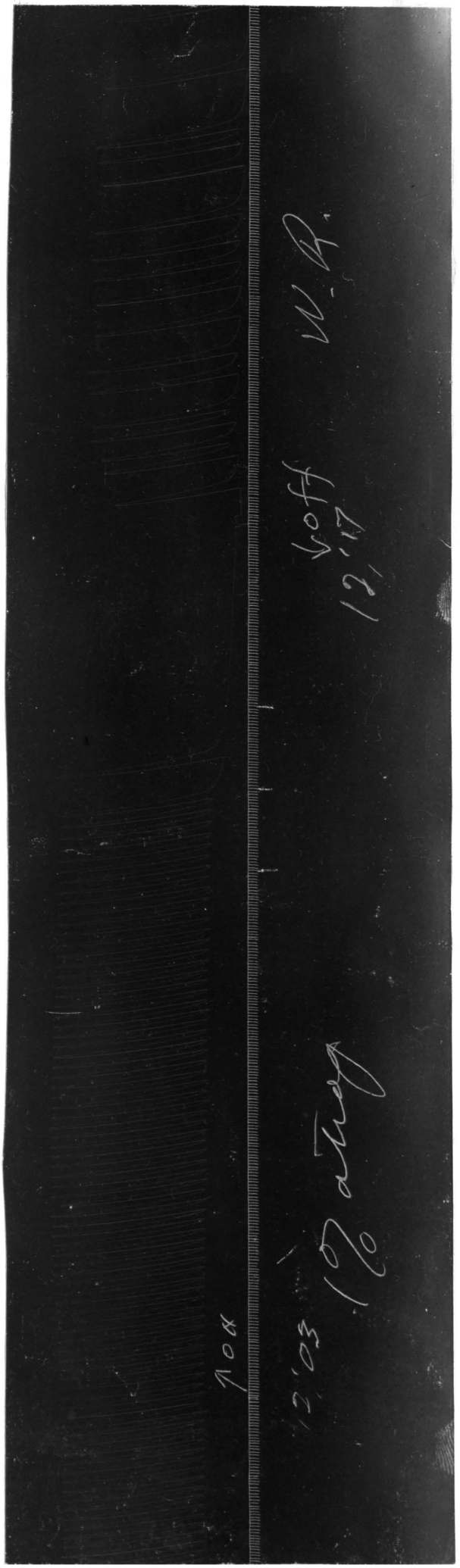
Effect of perfusion of .001 per cent Atropine through the Turtle's Heart. Normal blood diluted with Weaker Ringer's Solution is used as normal and the atropine is diluted with this Solution. The Rate and Amplitude are taken Before the Bath of the Drug and During and After the Bath. The Rate represents the Number of Contractions of the Heart Strips per minute. The per cent of the Normal is calculated for both the Rate and Amplitude During and After the Bath of Atropine.

Turtle No.	Strip No.	Experiment No.	Temp. Cent.	Strength of Solution	Time on	Rate per minute			Per cent of normal		Amplitude of cont.			Per cent of normal		Remarks
						before	during	after	during	after	before	during	after	during	after	
4	1			.001	7	32	32.5	32	105	100	10	10	10	100	100	
4	3			.001	3	32.8	34	33	105	102	11	90	90	82	82	
4	3			.001	5	30	31	30.5	103	101	15	14	13	94	87	
4	4			.001	2	30	30	30	100	100	13	12	12	93	93	
4	5			.001	4	29	30	30	103	103	11	80	11	73	100	
4	6			.001	10	30.5	31	30	101	99	9	9	9	100	100	
6	1			.001	3	30	30	30	100	100	31	29	28	94	90	
6	2			.001	3	30	30.4	30.3	101	101	36	35	35	98	98	
6	3			.001	9	30.2	31	30.5	102	101	30	28	29	94	97	
6	4			.001	12	30.4	30	30	99	99	32	30	30	94	94	

Tracing from

Turtle #15.

Table 3, a, 1.



PERFUSION OF THE TURTLES HEART WITH ATROPINE.

The method of perfusing the turtles heart with atropine is precisely the same as that for perfusing the frogs heart. The heart is exposed and the canula inserted in the inferior vena cava. A heavier weight is required to equalize the tension than in the frog. To prevent the movements of the oesophagus and muscles in the region of the heart, a clamp was put on the aorta to hold it steadily and prevent getting an effect on the record except that of the heart beat.

In table 14 is shown the effects of the perfusion of different concentrations of atropine through the turtles heart. The rate in this table was decreased 2 per cent with a decrease in amplitude of 2 per cent. After the drug was removed there was a decreasein rate of 7 per cent. This large decrease was due to a great fall of 70 per cent with 0.1 per cent concentration. Otherwise it would only be a decrease of 2 per cent. The amplitude increased after the removal of the drug to .5 per cent. The amplitude remained normal during the large fall in rate with the 0.1 per cent concentration. The turtles heart seemed very much more resistant to atropine than the frogs heart. However the change in the rate and amplitude may be due to a change in pressure as I stated in the case of the frog, it being such a small per cent change. After very large concentrations, the heart never returns to normal. The weaker sol-

utions had very little effect upon the heart, but as in the case of the frog with the 0.001 per cent, the heart was always uninjured after the perfusion. Several times when the heart refused to contract with Ringer's solution and with physiological saline solution it began to contract after the perfusion of atropine.

The vagus nerve was procured and stimulated. There was slight inhibition produced, but not complete. After the perfusion of atropine, there was not the least trace of inhibition and the rate before stimulation was the same as it was after stimulation.

In table 15 there is shown the results when atropine diluted with the blood of the same animal, is perfused through the heart of the turtle. I obtained an increase in rate of 2 per cent with a decrease in amplitude of 10 per cent, when mainly the .001 per cent was used. After the drug was removed there was still an increase in rate of .8 per cent with a decrease in amplitude of 7 per cent. There were no marked changes either in amplitude or in rate.

SUMMARY OF THE ACTION OF ATROPINE ON THE TURTLES HEART.

1. The effect of atropine on the turtles heart is almost negative, the increase in rate never being over 2 per cent in averaging the tables and the largest decrease in amplitude being only 10 per cent.

2. In large doses the heart seems to be paralyzed.

3. When the heart has been still for some time, the atropine produces normal rythm.

4. The heart does not show inhibition after the perfusion of atropine, when the vagus is stimulated.

TABLE XVI

Effect of the perfusion of atropine through the isolated mammalian Heart. Normal blood diluted with Weaker Ringer Solution is used as normal and the Atropine is diluted with this Solution. The Rate and Amplitude are taken Before the Bath of the Drug and During and After the Bath. The rate represents the Number of Contractions of the Heart Strips per minute. The per cent of the Normal is calculated for both the Rate and the Amplitude During and After the Bath of Atropine.

Cat No.	Strip No.	Experiment No.	Temp. Cent.	Strength of Solution	Time on	Rate per minute			Per cent of normal		Amplitude of cont.			Per cent of Normal		Remarks
						before	during	after	during	after	before	during	after	during	after	
1	b	1	36	.001	30	93	108	99	116	106	42	44	32	104	77	
1	a	1	36	.001	65	96	91	114	95	118	33	33	30	100	91	
1	b	2	36	.001	15	117	132	144	112	123	135	185	16	137	11'	
1	a	2	36	.01	35	87	72	78	83	90	11	12	8	109	73	
1	b	3	36	.01	10	81	81	81	100	100	155	165	155	108	100	
1	b	4	36	.01	33	81	78	72	97	89	15	13	1	87	67	

TABLE XVII

Effect of the perfusion of Atropine through the isolated mammalian Heart. Normal blood diluted with Weaker Ringer's Solution is used as normal and the Atropine is diluted with this Solution. The Rate and Amplitude are taken Before the Bath of the Drug and During and After the Bath. The rate represents the Number of Contractions of the Heart Strips per minute. The per cent of the Normal is calculated for both the Rate and the Amplitude During and After the Bath of Atropine.

Cat No.	Strip No.	Experiment No.	Temp. Cent.	Strength of Solution	Time on	Rate per minute			Per cent of normal		Amplitude of cont.			Per cent of normal		Remarks
						before	during	after	during	after	before	during	after	during	after	
2	c	3	37.5	.001 atropine	23	89.4	102	174	114	194	9	7	1	88	111	
2	a	4	38	.001	14	69	78	132	113	191	8	6	8	75	100	
2	a	5	38	.001	11	66	87	138	131	209	6	3	1	50	166	
2	b	6	38	.001	12	78	90	132	115	169	6	3	7	50	116	
2	b	7	38	.001 nicotine	12	60.6	70.8	13.8	116	327	5	4	7	80	140	
2	b	8	40	.001	26	180	180	198	100	154	11	9	31	42	290	
2	a	9	40	.001	10	192	192	210	100	109	12	13	57	108	475	
2	a	10	36	.001	15	150	150	168	100	112	14	36	44	185	314	
2	a	11	36	.001	27	144	144	162	100	112	6	28	33	866	550	
2	a	12	55	.001	56	132	132	120	100	91	7	5	3	72	43	
2	a	13	35.5	.001	60	132	132	120	100	91	6	5	4	84	67	

TABLE XVIII

Effect of the perfusion of Atropine through the isolated mammalian Heart. Normal blood diluted with Weaker Ringer's Solution is used as normal and the Atropine is diluted with this Solution. The Rate and Amplitude are taken Before the Bath of the Drug and During and After the Bath. The rate represents the Number of Contractions of the Heart Strips per minute. The per cent of the Normal is calculated for both the Rate and the Amplitude During and After the Bath of Atropine.

Cat No.	Strip No.	Experiment No.	Temp Cent	Strength of Solution	Time on	Rate per minute			Per cent of normal		Amplitude of cont.			Per cent of normal		Remarks.
						before	during	after	during	after	before	during	after	during	after	
3	a	1	35	.001	35	96	102	114	106	118	108	14	1ᵇ	175	125	
3	a	2	35	.001	30	108	114	108	104	100	14	17	13	121	93	
3	b	3	35	.001	30	102	90	90	89	89	15	16	13	106	87	
3	c	4	35	.001	21	78	78	78	100	100	11	16	1ᵇ	145	91	
3	c	5	35	.001	39	78	78	72	100	93	1ᵇ	17	8	170	80	
3	a	6	35	.001	48	77.5	63	69	82	90	8	14	6	175	75	Paralysis of auricle noticed particularly with large increase of amplitude while drug is on.
3	a	7	35	.001	38	69	66	63	96	92	6	1	5	166	84	
3	b	8	35	.001	42	54	48	48	89	89	4	8	3	200	75	

ACTION OF ATROPINE ON THE ISOLATED MAMMALIAN HEART.

For the perfusion of the cats heart, the canula is made in one piece together with two spiral tubes. The latter are in an ordinary condenser one foot in length, and the canula projects from one end which is below and clamped in place for perfusion. A side branch from the canula, near the condenser, is supplied with a short rubber tube and a pinch cock. The condenser acts as a water jacket by means of which heated water can be kept by circulating around the spiral tubes which contain the perfusing fluid and atropine solution. The upper ends of the spiral tubes connect with the reservoirs containing the normal and the drug solutions. The perfusing fluids are forced into the aorta and coronaries by oxygen under pressure (110 cm. of water) which is run into the perfusion solutions. The solutions are thus well oxygenated before entering the heart. The metallic points of the Gutherie Cardiograph connect with the auriculo-ventricular ring on the one side and with the apex of the ventricle on the other. These are connected with a writing lever, which with a time marker beating seconds, record simultaneously on the smoked drum revolving at a uniform speed. There was no means of keeping the heart warm and occasionally it was necessary to warm some normal blood and put the heart in it for a few minutes.

The cat is prepared in the following way for the mammalian heart experiment: The cat is etherized and a canula, which has been previously washed in magnesium sulphate solution is inserted into the carotid artery of one side, and as much blood as possible is drawn. While this is being drawn, it is being defibrinated. This blood is then diluted with Weaker Ringer's solution. The thorax after bleeding the animal is opened and the heart excised with sufficient amount of the aorta to be ligated to the canula, and so that the valves of the aorta are not interfered with. The heart after excision is placed in warmed Ringer's solution (37°C.) and massaged to wash out the uncoagulated blood. The aorta is then tied on to the canula and the perfusion solutions, which have previously been run through the canula, started. The temperature was kept as near 37°C. as possible throughout the experiment. The normal and the drugged blood was caught in separate receptacles and used the second time.

The drug was atropine sulphate that was used through this experiment on the isolated heart. As a rule the 0.001 per cent atropine was used, it being apparently less injurious to the heart than the other concentrations.

The effect of atropine on the whole heart can probably be best studied by this method. However only rather large hearts can be used on account of the large size of the canula.

Tables 16. 17, 18, give the results of the perfusion of three isolated cat hearts. 16 and 17 agree in nearly every detail, showing that there is stimulation, but in 18 there is a decrease in rate of 5 per cent and an increase in amplitude of 57 per cent, while the drug is on and when removed, a decrease in rate of 4 per cent and a decrease in amplitude of 12 per cent. Averaging tables 16 and 17 there is an increase in rate of 51 per cent with an increase in amplitude of 2 per cent. The first and second times the drug was applied to the heart, there was an increase in rate of 5 per cent. The average of the first trials in 16 and 17 show that there was an increase in rate of 15 per cent. After about the second time that the drug was applied, there came depression of rythmicity and amplitude, the rate falling greatly below normal and the amplitude falling a very small amount. I was unable to get the heart back to normal after the perfusion with this concentration. In table 18, I noticed after the perfusion of 0.001 per cent atropine that the auricles, which nearly always beat twice to the ventricles once before the perfusion, became paralyzed after a while. After leaving the normal perfuse for a while the auricular rythm returned to normal. Through the heart of the second cat there was perfused a 0.001 per cent sol-

ution of Nicotine, which caused first stimulation and later depression. After this, 0.001 per cent atropine when perfused caused no change, because the heart was so nearly dead after the severe test with Nicotine.

SUMMARY OF THE ACTION OF ATROPINE ON THE ISOLATED MAMMALIAN HEART.

1. 0.001 per cent atropine causes first a stimulation and later depression of the heart in its rythmicity and amplitude.

2. The heart is paralyzed by great concentrations.

3. 0.00004 per cent atropine has very little effect upon the isolated mammalian heart.

4. With the 0.001 per cent concentrations of the drug, there is paralysis of the auricles, which soon recover after perfusing with the normal solution.

I wish to express my appreciation to Dr. C. W. Greene for kindly suggesting the line of investigation, and for guiding me through all of my experiments.

GENERAL CONCLUSIONS.

1. Atropine is a stimulant to cardiac muscle, when weaker solutions are used. 0.00006 pee cent atropine produces the greatest stimulation.

2. Atropine of from the 0.0001 per cent to the 0.005 per cent concentration produce very wide variations. Such variations as occur seem partly to be stimulated above the normal and others are depressed below the normal.

3. Stronger solutions of atropine, 0.1 and 0.01 per cent cause a depression of the rythmicity and the amplitude of the heart muscle. This is especially true after the muscle has been experimented upon with weaker solutions before the bath of the stronger solutions.

4. When atropine is applied successively to the same strip in concentrations which produce very little change in the heart muscle, 0.0001 to .005 per cent, such variations as occur, seem at first to increase the activity above that of the normal muscle, and then in successive applications to depress the norma/.

5. In most of the experiments where there is an increase in rate, there is usually a decrease in amplitude and vica versa, but this cannot be considered as compensatory.

6. The effect of atropine on the sinus strip is almost negative. There is however a very slight depression of rythmicity and amplitude with very strong solutions, and with the weaker solutions as is the case with the ventricular strips, there is produced a slight stimulation of the rate. Accompanying this there is a slight decrease in tone.

7. Atropine when perfused through the frogs heart, causes an increase in rate and a decrease in amplitude of the contractions, if weaker solutions be used.

8. Strong solutions depress the rythmicity and amplitude. At times almost paralyzing the heart.

9. Atropine destroyes the influence of the vagus over the frog's heart and the turtles heart.

10. If a frog's heart or a turtle's heart at rest is perfused with atropine for the first time, rythmic contractions will be produced.

11. The effect of atropine on the turtle's heart is practically negative, except in very large concentrations, when the heart is depressed if not paralyzed.

12. Weaker solutions of atropine (0.001 per cent) produce a stimulation and later depression of the isolated mammalian heart in its rythmicity and amplitude of contractions.

13. The isolated mammalian heart is paralyzed after the use of strong solutions of atropine.

14. With the 0.001 per cent of atropine there is produced a paralysis of the auricles, which soon recover after perfusing with the normal solution.

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