On the action of carbolic acid, atropia and convallaria on the heart : with some observations on the influence of oxygenated and non-oxygenated blood, and of blood in various degrees of dilution / by H.G. Beyer.

ON THE ACTION OF CARBOLIC ACID, ATROPIA AND CONVALLARIA ON THE HEART; WITH SOME OBSERVATIONS ON THE INFLUENCE OF OXYGENATED AND NON-OXYGENATED BLOOD, AND OF BLOOD IN VARIOUS DEGREES OF DILUTION.

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The experiments described in the following pages are for the most part rather of therapeutical than of purely physiological interest. They were, however, carried out in the physiological laboratory of the Johns Hopkins University, whose facilities for such work were placed at my disposal by Professor Martin. I have, accordingly, desired to publish them in this Journal.

The method of work employed has already been very well described by Howell and Warfield (*Studies from Biol. Lab.*, Johns Hopkins University, Vol. II, p. 329), and also by H. H. Donaldson and L. T. Stevens (*Journal of Physiology*, Vol. IV, p. 165). A full description of it can, therefore, be here omitted. There are, however, one or two minor points in the operation for isolating the heart of the terrapin, and preparing the same for as nearly as possible normal and uniform work, to which it is desirable to call attention.

When the plastron of a terrapin is removed, one can easily watch its heart beat through the transparent pericardium, filled with clear lymph. Careful observation shows that during systole the base of the ventricle broadens out and, with its attached auricles and blood-vessels, moves slowly but steadily in a direction towards the apex. The apex, on the contrary, is fixed in position by a narrow strip of fibrous tissue, which arises from a tough membrane stretching across anterior to the liver and is inserted into the apex of the ventricle. Out of nearly sixty terrapins which I had occasion to examine, this band was missing in only one. By fixing it with ligatures in, as nearly as possible, the place it had occupied before the operation of tying in cannulas, &c., the relation of the entire heart to the vessels springing from it, especially the aortæ, seemed much more secure, and no tilting up of the apex to interfere with the outflow could occur. Furthermore, as far as I know, only one venous or in-

flow cannula, and one arterial or outflow cannula have hitherto been used by experimenters; I have used for the purpose of feeding the heart, cannulas in two or more of the veins passing to the heart, and for the outflow have inserted cannulas in two or all three of the arterial stems arising from the ventricle. More natural conditions are thus afforded to the isolated heart.

The Influence of Mammalian Blood in different Degrees of Dilution upon the Work done by the Heart of the Slider Terrapin.

Rossbach (*Arb. aus d. physiol. Institut zu Leipzig*, 1874, Bd. ix, p. 90) found that the isolated frog's heart under the influence of defibrinated blood beat regularly, but that under serum its beats occurred in groups. Klug (*Arch. für Anat. u. Phys.* 1879, p. 435) was unable to confirm these results, but found that whether blood or serum were used, pulsations either in groups or at regular intervals might be obtained.

Since the heart of cold-blooded animals was first successfully isolated and kept alive for a number of hours outside the body while fed by some nutritive liquid, as serum, blood, &c., a variety of feeding fluids have been tested, with the object of ascertaining which would cause the heart to yield the maximum amount of work in a given time. Thus McGuire (*Arch. f. Anat. u. Physiol.* 1878) obtained the maximum amount of work by feeding the heart with a mixture composed of one part of mammalian blood and two parts of a 0.6 per cent. sodium chloride solution; and C. S. Roy (*Jour. of Phys.* 1883) mentions that his experiments led him to the same conclusion. Kronecker, in reporting on some investigations of Mr. May's (*Arch. f. Anat. u. Physiol.* 1883, p. 263) states that the maximum amount of work done, and the greatest number of pulsations, were obtained when the heart was fed with undiluted blood. H. H. Donaldson and L. T. Stevens (*Jour. of Phys.* Vol. IV, p. 165) in their experiments on the influence of digitaline on the heart of the frog and terrapin, made use of a mixture of equal parts of blood and 0.75 per cent. salt solution. The heart was kept under observation in some of their experiments for over ten hours, and had in the meantime been repeatedly drugged, and still was reported as doing well at the end of that time. After having made a rather large number of experiments on this point in my preliminary work on

the frog and slider terrapin, substituting the saline mixture proposed by Sydney Ringer * (*Journal of Physiology*, Vol. III, p. 39) for the 0.75 per cent. of normal salt solution as used in the experiments of Donaldson and Stevens, I feel very safe in saying that so far as defibrinated calf's blood is concerned, the maximum amount of work and the greatest number of pulsations can be obtained from the heart by feeding with a mixture of about equal parts of blood and Ringer's solution. Any greater dilution results sooner or later in undue dilatation, first of the sinus, then of the auricles, and at last of the ventricle. A mixture of one part of blood and two parts of the saline may give for the period of an hour as much, or even a slightly larger, amount of work, but it meanwhile injures the muscular substance of the heart, the results being undue relaxation and irregularity in its action; on the other hand undiluted defibrinated calf's blood, in my hands at least, has not given either the maximum amount of work or the greatest absolute number of pulsations. In experiment I, besides undiluted defibrinated calf's blood, six different dilutions were employed, their strength varying as stated in the last column of the table, p. 77.

The results show that the maximum amount of work is not done by the heart when supplied with simple defibrinated calf's blood, and that under almost any of these dilutions more work is done in a given time than with the undiluted blood. When the mixture 1 : 20 was turned on, the heart continued its regular beat for 10 minutes, and then suddenly became irregular in its action, and unable to overcome the hydraulic pressure opposed to its contraction; it partially recovered, however, under a mixture of three parts of blood to one of Ringer's solution.

In all the experiments described in this paper the "venous pressure" indicates the height above the heart of the bottom of the air tubes of the supplying Marriotte's flasks. For example, "venous pressure 7 cm." means that the liquid supplied to the heart entered the cannulas supplying that organ under the pressure exerted by a column of the nutrient liquid seven centi-

* The composition of this mixture is:

Normal salt solution (0.75 per cent.), . . .	100. cc.
Calcium chloride sol. (1.390), ...	5. cc.
Sod. bicarbonate sol. (0.50 per cent.), . . .	2.5 cc.
Sol. of potass. chloride (1.0 per cent.), . . .	0.75 cc.

metres in height, and so on. When different liquids were used they were contained in separate Marriotte's flasks, carefully adjusted so that the pressure under which liquid flowed out of them was the same for all. The supply tubes from these flasks had stop-cocks on them, and all met in a common tube from which in turn the heart was supplied. By closing and opening the proper stop-cocks, any one flask could at will be used to feed the heart. All the Marriotte's flasks stood on the same horizontal platform, and were raised or lowered equally by moving this platform, if it became desirable to change the venous pressure in the course of an experiment. The outflow cannulas coming from the aortæ, or, in some cases, also from the pulmonary artery, were all connected with a single tube, from the distal end of which the liquid pumped round by the ventricle flowed out, and was collected and measured. The height of the orifice of this tube above the heart is stated in each experiment as the "arterial pressure." Being kept constant throughout an experiment, any variation in the weight of blood pumped out in a unit of time was proportional to the variation in the work done: that is to say, the "lift" remaining the same, any change in the "work" was indicated by, and was directly proportional to, variations in the "load" lifted. As the specific gravity of the various liquids used in any one experiment differed very slightly, the "load" lifted was practically proportioned to the bulk of the liquid pumped out by the ventricle. Accordingly it is stated in the third column of each of the tables of experiments, in cubic centimetres. The temperature stated in the fourth column is that of the liquid supplied to the heart. It never differed more than 0.5° C. from the temperature of the box in which the terrapin was enclosed, and gives more accurately the actual temperature of the heart. A mercury manometer was connected with the outflow tube near the heart. Its pen wrote on the smoked paper of a revolving cylinder, on which also a chronograph recorded seconds.

Experiment I.

March 6th, 1884. Terrapin, weighing 585 grms. Inflow cannulas in inferior vena cava and left superior vena cava; outflow cannulas in aorta and pulmonary artery. Nutrient liquid, calf's blood mixed with Ringer's saline in various proportions. Venous pressure, 7 cm. Arterial pressure, 25 cm.

Time. P. M.	Rate per min.	Work in C. C. per min.	Temp. Cent.	
3h. 00m.				Terrapin in box. Nutrient, undiluted defibrinated calf's blood.
30	31	31.5	21	
35	31	32		
40	31	32		Nutrient, blood and Ringer's solution (1 : 1).
43	32	45.5		
45	32	43.5		
46	32	44.5		Nutrient, blood 3, Ringer's solution 2, distilled water 1.
48	32	44.5		
51	32	44.2		Nutrient, undiluted blood.
56	31	31.5		
58	31	32		
4h. 00m.	31	31.5		
03	31	32		Nutrient, blood and Ringer's solution (1 : 1).
05	32	47.5		
07	32	45		
09	32	45.5		Nutrient, undiluted blood.
12	32	33		
16	32	33.5		
20	32	33.5		Nutrient, blood 3, Ringer's solution 2, distilled water 1.
23	33	47.5		
4h. 25m.	33	44	20.5	
27	34	42		Nutrient, blood and Ringer's solution (1 : 1).
30	34	42		
32	34	45		Nutrient, undiluted blood.
36	32.5	33.5		
39	33	34		
41	32.5	33.5		
43	33	34.5		Nutrient, blood and Ringer's solution (1 : 1).
46	34	47.5		
48	34	45		Nutrient, undiluted blood.
52	33	34		
55	33	34.5		
58	33	34		
5h. 00m.	33	34.5		Nutrient, blood 3, Ringer's solution 2, distilled water 1.
03	33	45.5		
05	35	42		Nutrient, undiluted blood.
09	33	33.5		
12	33	33		
14	33	33.5		
16	33	33.5	20.5	Nutrient, blood and Ringer's solution (1 : 1).
20	34	42.5		
21	35	43		Nutrient, undiluted blood.
25	32	34		
28	33	34		
31	33	34.5		Nutrient, blood 3, Ringer 2, distilled water 1.
33	34	47.5		
35	35	45.5		
37	35	44.5		Nutrient, undiluted blood.
40	33	34.5		
42	33	34.5		

Time. P. M.	Rate per min.	Work in C. C. per min.	Temp. Cent.	
5h. 44	33	35	20.5	
48	32	34		Nutrient, blood and Ringer's solution (1 : 1).
50	33	45		
53	34	44.5		Nutrient, undiluted blood.
57	33	34.5		
6h. 00m.	32	34		Nutrient, blood 3, Ringer 2; dist'd water 1.
02	33	45		
04	34	42.5		
06	34	43.5		Nutrient, undiluted blood.
09	32	34		Nutrient, blood and Ringer's solution (1 : 1).
14	34	45		Nutrient, undiluted blood.
19	32	34.5		
21	32	35		Nutrient, blood and Ringer's solution (1 : 1).
25	33	40.5		
27	34	40.5		
29	34	41		Nutrient, blood 3, Ringer 2, dist'd water 1.
33	34	45		Nutrient, blood and Ringer's solution (3 : 1).
36	34	42		
38	34	43		
41				Nutrient, blood and Ringer's solution (1 : 1).
44	33	42	20	
46	34	42		
49.30	34	42		Nutrient, blood and Ringer's solution (1 : 3).
52	35	49.5		
55	33	43		Nutrient, blood and Ringer's solution (3 : 1).
7h. 00m.	32	37		Nutrient, blood and Ringer's solution (1 : 3).
03	32	48		Nutrient, blood and Ringer's solution (3 : 1).
06	32	45	20	
07				Nutrient, blood and Ringer's solution (1 : 3).
23	32	50		
26	32	48		
29.30	31	46		
31	31	40		Nutrient, blood and Ringer's solution (3 : 1).
34	31	41		
38	32	48		
41	31	44		
46	31	45		Nutrient, blood and Ringer's solution (1 : 1).
50	31	39		
53	31	40		Nutrient, blood and Ringer's solution (1 : 7).
56	33	50		
8h. 00m.	32	45		
05	31	44		Nutrient, blood and Ringer's solution (1 : 20).
10	30	41		
12				Heart becoming distended and not contracting properly.
14	30	42		
18				Two ventricular to each auricular contraction.

An attempt was made to recover the heart by supplying it with a mixture of blood and Ringer's solution (3 : 1), but without success.

The preceding experiment seemed to show so clearly the su-

periority of defibrinated blood and Ringer's solution mixed in equal volumes, that I used this mixture in all subsequent experiments.

The Influence of Oxygenated and Non-oxygenated Blood upon the Work of the Heart.

One of the first to investigate the influence of different gaseous substances on the isolated heart of cold-blooded animals was Castell (*Arch. f. Anat. u. Physiol.* 1854, p. 226). According to this observer the heart of the frog, when cut out and placed under a bell glass, would on an average continue to beat for three hours, the ventricle ceasing its contractions long before the auricles. In rarefied air the heart beat only for thirty minutes. In an atmosphere of oxygen the heart was found to beat for twelve hours; surrounded by carbon dioxide gas, the contractions continued only six minutes; they were, however, resumed on the admission of air, and then continued for two hours. Cyon (*Comptes Rendus*, 1867), from some experiments made in the laboratory at Leipsic under Prof. Ludwig, came to the following conclusions: "Mes expériences ont demontré que l'oxygen excite surtout les ganglions moteurs du cœur tandisque l'acide carbonique agit de la même manière sur les ganglions regulateurs." McGuire (*Arch. f. Anat. und Phys.* 1878, p. 321), working under Kronecker's direction, arrived at the conclusion that oxygen exerted no perceptible influence on the heart's action, while carbon dioxide weakened it very much. A year later Klug (*Arch. f. Anat. u. Phys.* 1879, p. 435) published a number of experiments on the influence of oxygen and carbonic acid upon the frog's heart. The conclusions arrived at were, that oxygen very much increased both the intensity and the frequency of the heart's beat, while carbonic acid had the opposite effect. His experiments, therefore, were in perfect agreement with those of Castell made nearly twelve years previously. Some years later, Klug in connection with Desiter Velits undertook the same line of research on the mammalian heart. The gases were administered through the lungs, by means of an apparatus for artificial respiration which was in connection with gasometers containing oxygen and carbon dioxide gas respectively. It was found that in animals with divided spinal cord and vagi a 40 per cent. car-

bon dioxide mixture blown into the lungs produced no perceptible change for forty seconds. During the last third of the first minute and during the second minute the number of beats decreased, arterial pressure went down, and continued to fall until death ensued at the end of five or six minutes. In animals treated with oxygen, the pulse rate was considerably increased and arterial pressure raised. Klug and Velits concluded that oxygen exerted a stimulating influence upon the intracardiac nerve-centres, while carbon dioxide paralyzed them. Relative to the influence of carbon dioxide upon the intracardiac nervous apparatus, I find the following statement in an article by Dastre and Morat, who exposed the heart to asphyxiated blood: "Il est possible d'admettre au moins dans certain cas une excitation direct des centres nerveux intracardiacques, mais cette effet est extrêmement tardif, souvent obscur, et il n'intervient en definitive que par une faible part dans le processus asphyxique du cœur." According to Dastre and Morat asphyxiated blood has a stimulant action upon all the tissues (*Archive de Phys. norm. et path.* 3m. ser., tome 3, 1884). Granting that there exists a certain amount of evidence in favor of each of the opinions quoted in this short review of the literature of this important subject, it is nevertheless certain that oxygen cannot stimulate and be indifferent to, or carbonic acid stimulate and paralyze the same tissues at the same time and under the same circumstances. When in addition Paul Bert states that oxygen under several atmospheres of pressure exerts a poisonous action on living tissues, the strong and just criticism his assertions met with from Cyon (*Arch. f. Anat. et Phys. Supp. Bd.* 1883), and from Lehmann (*Pflüg. Arch.*, Vol. XXXIII, p. 173, 1884), might have been foreseen. Cyon and Lehmann have definitely established the fact that oxygen, even under very high pressure, does not destroy the vitality of a tissue, but may render its manifestation latent. Lehmann after exposing hearts at a somewhat low temperature to a pressure of thirteen atmospheres of oxygen, still obtained a reappearance of regular pulsations after the lapse of twelve hours, and lasting for days.

The experiments which I am about to describe show the very decided influence which is exerted on the heart's action by even very small doses of oxygen and carbonic acid respectively. The

way in which asphyxiated and oxygenated blood were prepared is as follows: a quantity of defibrinated calf's blood previously mixed with an equal volume of Ringer's saline was divided into two portions, and each portion put into a bottle; one was allowed to stand quiet while the other was shaken up for a few seconds every now and then, until a perceptible difference in color was noticed; this was brought about in from five to fifteen minutes. Then the two bottles were turned into Marriotte's flasks by inserting the proper stoppers and tubes, and when the time came for an observation, the blood was allowed to run through the heart and its effect noted. From Experiment II it will be seen at a glance that the rate and the amount of work are always increased on supplying the heart with oxygenated blood. The rate, at first, very little, later on a difference of five beats per minute exists. The work done increases from 30 to 175 per cent. per minute. A very slight agitation of the blood before returning it into the flask will increase the work done by the heart, even when the difference in color is not perceptible to the eye. The importance of this point will be readily seen by those who have worked on the action of drugs on the heart. The plan of getting the drug into the blood followed out in all the experiments described later in this paper, was to dissolve it in Ringer's saline first, and then mixing it with defibrinated blood, required no more shaking than preparation of the control mixture of equal parts of blood and Ringer's solution; thus uniformity was reached in this respect. If the drug be directly added to the blood mixture and well shaken up with it, effects really due to better oxygenated blood may be ascribed to the drug under examination.

The following table gives the data of one experiment; several others were made which agree with it in all essential points.

Experiment II.

January 4th, 1884. Terrapin, weight 1100 grms. Calf's blood and Ringer's saline 1:1. Inflow cannulas in inferior vena cava and hepatic vein; outflow cannulas in left aorta and pulmonary artery. Venous pressure at start, 5 cm. Arterial pressure, 18.5 cm.

Time. P. M.	Rate per min.	Work in C. C. per min.	Temp. Cent.	The phrases "On CO_2 blood" and "On O-blood" in this column indicate that non-aërated and aërated blood respectively were supplied to the heart immediately after the time stated on the same line in column one.
2h. 20m.				Terrapin in box.
3h. 20m.	22	49	20.5	
25	21	49		
30	21	49		On O-blood.
35	21	51		
40	21	53		Venous pressure lowered 1.5 cm.
45	21	49		
50	20	48		
55	21	48		On CO_2 blood.
4h. 00m.	21	38		
05	21	36		
10	21	37		Off CO_2 blood; on O-blood.
15	21	46		
20	21	48		
25	21	48		
30	21	47		
40	21	40		On CO_2 blood.
45	21	26		
50	21	28		
55	21	24		
5h. 00m.	21	26		On O-blood.
05	22	44		
10	23	45		
15	24	47		On CO_2 blood.
20	22	15		
25	22	16		On O-blood.
30	25	45		
35	26	47	21	
40	27	48		On CO_2 blood.
45	23	17		
50	22	14		On O-blood.
55	29	46		
6h. 00m.	29	45		On CO_2 blood.
05	25	20	21	
10	25	23		On O-blood.
15	29	47		
20	29	45		On CO_2 blood.
25	26	19		
30	25	19		On O-Blood.
35	29	45		

The experiment was continued until 8.30 P. M. with like results.

The Influence of Carbolic Acid upon the Heart of the Terrapin.

Notwithstanding the great medical and surgical importance to which carbolic acid has risen within the last two decades, and in spite of the deaths caused by it, which from time to time have been recorded, its physiological effects upon the circulatory

apparatus, more especially on the heart itself, seem as yet not very satisfactorily determined. Opinions are still at variance as to whether carbolic acid introduced into the animal organism may or may not be at first a stimulant to the heart and blood-vessels, thus increasing the blood pressure; or whether its depressing and poisonous effects are exhibited at once. Hoppe-Seyler (*Pflüger's Archiv*, v. 1872) obtained a rise in arterial and venous pressure just before convulsions came on; Salkowsky (*Pflüger's Archiv*, v. 1872, p. 344) noticed an increase in the rapidity of the blood-flow in the capillaries of the frog's web, followed by a slowing of the flow. Labbée (*Archives générales*, 6^{m} ser., tome 18, p. 451, 1871) also noticed an increase in the strength of the systoles in the early stages of the poisoning and a contraction of the vessels. On the other hand, Rudinger (*Einige Beiträge zur Lehre d. Wirkung d. Carbolsäure*, Greifswald, 1874) noticed a slowing in the circulation in the web of frogs under the influence of carbolic acid, and Gies (*Zur Kenntniss d. Wirkung d. Carbolsäure, auf d. Thier Organismus, Archiv. f. exp. Path. u. Therapie*, xii, S. 401) found that lowering of the blood pressure and the decrease in the pulse rate took place almost simultaneously with the introduction of carbolic acid into the circulation, and that after a time the normal pressure and pulse-rate returned. If we add to this the observations of Salkowsky, Labbée, and a few others, that circulation survives respiration in carbolic acid poisoning, we have in few words about all that is known about the effects of carbolic acid on the circulatory apparatus. So far as the heart itself is concerned the subjoined experiments III and IV (which are selected from a considerable number, all concordant) show, first, that carbolic acid in the smallest, as well as in the largest doses, acts as a depressant from first to last, reducing its rate of beat and its work. Second, that the heart as long as it is supplied with well oxygenated blood, will, up to a certain degree, show what almost amounts to an immunity from the poisonous effect of the drug.

Experiment III.

January 18th, 1884. Terrapin, weight 935 grms. Calf's blood and Ringer's saline 1 : 1. Inflow cannulas in inferior vena cava, left superior vena cava, and hepatic vein; outflow cannulas

in right and left aortæ and pulmonary artery. Venous pressure, 4 cm. Arterial pressure, 24 cm. Carbolized blood contained 0.1 per cent. of carbolic acid in the first part of the experiment, and 0.2 per cent. in the second.

Time. P. M.	Rate per min.	Work in C. C. per min.	Temp. Cent.	
3h. 00m.				Terrapin in box.
45	16	34.5	20.5	Oxygenated blood mixture turned on.
4h. 00m.	18	54.5		Same blood returned without shaking.
15	17	45.5		
20	16	41.5		
22				On oxyg. blood mixture.
25	19	49.5		
30	18	50.2		On non-oxyg. blood.
35	18	44.5		On oxyg. blood.
40	19	52.5		On non-oxyg. blood.
45	18	46.5		On oxyg. blood.
50	20	54.5		
55	20	56.8		On non-oxyg. blood.
5h. 00m.	20	50		On carbolized oxyg. blood (0.1 : 100 cc.)
05	20	37.5		On oxygenated blood.
10	19	52.5		On carbolized non-oxyg. blood.
15	18	39.5		On oxygenated blood.
20	19	52.5		
25	20	55.5		
30	21	58.5	21	On carbol. non-oxyg. blood (0.2 : 100 cc.)
35	10	15.5		On oxygenated blood.
40	18	54.5		
45	20	57.5		
50	21	57.5		
55	21	57.		On carbol. blood (0.2 : 100 cc.) oxyg.
6h. 00m.	15	25.5		
02	15	23.		On oxyg. blood.
06	19	58.5		
10	21	60.		On carb. oxyg. blood (0.2 : 100 cc.)
15	18	30.5		
16.30				On oxyg. blood.
20	20	57.8		
25	21	59.2		Ended experiment.

Experiment IV.

January 16th, 1884. Terrapin, 1235 grms. Calf's blood and Ringer's saline. Cannulas in left superior vena cava, hepatic vein, inferior vena cava, right and left aortæ and pulmonary artery. Carbolized blood used in different strengths. Venous pressure, 6.5 cm. Arterial pressure, 22 cm.

Time. P. M.	Rate per min.	Work in C. C. per min.	Temp. Cent.	
4h. 20m.	16	32.5		Terrapin in box at 2h. 15m. Heart fed with oxygenated non-carbolized blood until 5h. 00m.
25	16	34		
35	16	34.5		
45	16	34	19.5	
50	16	33.5		
5h. 00m.	16	32.5		On carb. blood containing 0.1 : 500 cc.
05	16	18.5		On oxyg. blood.
10	16	32.5		
15	17	36		On carb. blood well oxyg. containing 0.2 : 500 cc.
20	19	45		On oxyg. blood.
25	18	38		On carb. blood, same as at 5h. 15m.
30	20	44.5		
35	20	46.1		On oxyg. blood.
40	21	38		
45	21	38		On carb. blood well oxyg., contain'g 0.4 : 500 cc.
50	21	43		
55	22	45		
6h. 00m.	22	48		
05	21	50		On oxyg. blood.
10	20	40		On carb. blood well. oxyg., contain'g 0.6 : 500 cc.
15	21	53		Heart slightly disturbed.
20	22	45		
25	21	43		
30	21	45	19.5	On blood well oxyg.
35	19	45		Heart contracting more perfectly.
40	20	42		
45	20	42		On carb. blood well oxyg., contain'g 0.8 : 500 cc.
50	12	23		On oxyg. blood.
55	13	23.5		Heart somewhat distended and contracting imperfectly ; on well oxyg. blood.
7h. 00m.	19	49.5		
05	19	48		On carb. blood same as at 6h. 45m.
10	10	22.5		
15	10	23		On well oxyg. blood.
20	18	46.5		
25	19	49		On carb. well oxyg. blood, contain'g 1.0 : 500 cc.
30	9	18.5		
35	11	21.5		
40	9	18.5		On well oxyg. blood.
45	17	45.5		Heart working very well.
50	17	45	20	On carb. blood same as at 7h. 25m.
55	9	19.5		On oxyg. blood.
8h. 00m.	15	42		
05	18	45.5		On carb. blood well oxyg., contain'g 1.2 : 500 cc.
10	7	18.5		Heart distended ; two faint auricular beats to one ventricular.
15	8	16.2		
20	5	10.5		On well oxygenated blood ; heart very much distended ; auricles at a stand-still ; ventricle beats once in two minutes. No blood pumped up to outflow orifice.
35	15	47	20	Heart has completely recovered.
40	16	45		
54	17	45		Experiment ended.

The two preceding experiments (and others which quite accord with them) seem conclusive that the depressant and paralyzing action of carbolic acid upon the heart can be considerably diminished, or be held at bay entirely, by a good supply of well-oxygenated blood; thus showing the great importance of the respiratory activity in cases of carbolic acid poisoning where there is danger from failure of the circulation and heart's action.

On the Action of Atropia on the Isolated Heart of the Terrapin and the Antagonism existing between it and Carbolic Acid.

Bartholow, in the fifth edition of his *Mat. Med. and Therapeutics*, makes the following statement: "I am indebted to Dr. A. C. Post, of New York, in a verbal communication, for the important fact that atropine is a physiological antagonist to the systemic symptoms induced by carbolic acid. He was induced to administer atropine in a case of poisoning by carbolic acid on observing the minutely contracted pupil and the failing circulation. The result was successful. Similar success has attended the same practice in other cases. Experiments on animals have also demonstrated the existence of this antagonism, which may now be regarded as an established fact." This statement, coming from and being endorsed by good authority, I determined to endeavor to find out in how far it might be true of the isolated heart. As far as experiments on animals are concerned, I am unable to find any published cases. In going over the literature on the physiological effects of atropia, I wish here, as elsewhere, to confine myself to that part of it which has reference to the circulatory apparatus. H. C. Wood (*Am. Jour. of Med. Sciences*, April, 1873), in four experiments on dogs whose pneumogastrics had been cut, obtained in one a slight rise, in the rest a more decided rise in arterial pressure and an increase in the frequency of the pulse rate; he believes that the enormous increase in the number of heart beats per minute seen in atropia poisoning is not entirely due, as has been believed, to paralysis of the vagi, but also to a direct stimulant action upon the antagonists of the latter. Von Bezold and Blœbaum (*Ueber die Wirkung d. Schwefel. Atropins, Unters. aus d. Phys. Lab. zu Würzburg, Heft* I), states that after section of the vagi and spinal cord, artificial respiration being maintained, atropia fails to increase arte-

rial pressure. Lemaitre (*Archives générales*, Aug. 1865, p. 49) claims to have shown that, notwithstanding division of the vagi, the action of the heart is still increased under atropia. Dr. John Harley, after experimenting on man, horse and dog, comes to the conclusion that atropia exerts a powerfully stimulating action on the heart (*Med. Times and Gazette*, March, 1868). Bartholow (Prize Essay, *Proceedings of the Am. Med. Association*, 1869) noticed an increased flow through the blood-vessels in frogs, with a slight contraction of the calibre of the vessels, which contraction was followed by an evident relaxation after some hours. In this Lemaitre, Minnot and Bartholow agree. In one of his experiments on frogs, Bartholow noticed, after the injection of ¼ grain of atropia sulphate, an increase in the pulse rate of from 40 to 52 per minute, also an increase in the contracting power of the heart. Schiff (*La Nazione*, 1872, No. 235) made the remarkable observation that a quantity of atropia slightly larger than that which is sufficient to dilate the pupil, lessens the sensibility of the heart to such an extent that the arterial pressure may be at first increased to three times its normal extent and then diminished to one-half or even one-third of that amount, without any change in the pulse rate being produced. If we assume that atropia paralyzes the extrinsic cardiac nerves, this is in accord with the experiments of H. Newell Martin on the isolated heart of the dog. Martin has shown (*Stud. Biol. Lab., Johns Hopkins University*, Vol. II, p. 213) that a heart set free from extrinsic nervous control is not affected as regards its pulse rate by variations in arterial pressure. Wood, as stated by Dr. Lauder Brunton (*London Med. Record*, 1873), found that in a certain class of frogs small doses (0.0001–0.001 gram) caused slowness of pulsation and sometimes complete stoppage in diastole, even after division of the vagi. After a shorter or longer stage the pulsations could be arrested by very weak interrupted currents applied to the venous sinus, but later, when the pulsations began to become quicker, stronger irritation was necessary to produce this effect. At the same time that the atropia produces slowness of the heart's beats and longer diastole, it makes the systoles stronger and longer. The phenomena have been interpreted as showing that atropia strongly stimulates the inhibitory and musculo-motor nerve tissues in the heart, the former predominating

over the latter. In another set of frogs, atropia seemed to paralyze these nervous tissues without previously stimulating them. In a third class the inhibitory centres were rapidly paralyzed while the musculo-motor ones were only slightly or not at all affected. In this class the end of the vagus in or near the heart seemed paralyzed before the inhibitory centre, so that, shortly after the administration of the poison, irritation of the nerve may have no effect, while the beat can still be arrested by irritation of the venous sinus. Von Bezold and Blœbaum found as the result of the smallest doses of atropia, in rabbits as well as in dogs, an increase in the frequency of the pulse rate and in the arterial pressure. In somewhat larger doses, an increase in the frequency of the pulse rate, but a fall instead of a rise in arterial pressure; still larger doses produced a decrease in the pulse rate, which, after some minutes, was followed by an acceleration and a fall in the pressure; the latter, however, rose again, but finally remained lower than normal. Finally, a dose of 0.1 gram, brought at once into the heart of the rabbit, paralyzed it immediately. They agree with Rossbach and Fröhlich in believing that atropia paralyzes the terminal filaments of the vagus within the heart. Meuriot, *De la methode phys. en Therapeutique et de ses applications à l'etude de la Belladonne*, Paris, 1868), formulates his conclusions as follows: small doses of atropia accelerate the heart and augment arterial pressure; the former is brought about by a paralysis of the terminal fibres of the pneumogastrics, the latter is due to increased muscular tonicity in the blood-vessels. In large doses, the muscular tonicity is impaired, and arterial pressure falls; the pulse rate, also, is diminished in frequency.

Experiment V.

March 4th, 1884. Terrapin; 845 grms. Calf's blood and Ringer's saline in equal parts. Inflow cannulas in left superior vena cava and inferior vena cava; outflow cannulas in left aorta and pulmonary artery. Venous pressure at first, 3.5 cm. Arterial pressure, 24.5 cm. The atropinized blood contained 0.002 grm. of atropia sulph. to 100 cc. of the blood mixture.

Time. P. M.	Rate per min.	Work in C. C. per min.	Temp. Cent.	The liquid stated in this column was supplied to the heart in each case immediately after the time stated on the same line in column one.
2h. 40m.				Terrapin in box, and heart fed with non-poisoned blood.
4h. 00m.	27	29	18.5	
05	27	29		
10	27	29.5		
15	27	30		
20	27	30		
25	27	31		Atrop. blood turned on.
28	27	31.5		On unpoisoned blood.
31	27	30		
34				On atrop. blood.
37	27	30		On unpoisoned blood.
42	27	31		
45	29	29.5		On atrop. blood.
50	27	31.5		On unpoisoned blood.
56	27	27.5		
5h. 00m.	27	27.5		On atrop. blood containing 0.004 : 100 cc. of blood.
02				On unpoisoned blood.
04	27	54		Ventricle somewhat distended.
08	27	38		
10	28	31	18	
20	28	25.5		On atrop. blood.
23				On unpoisoned blood.
28	28	28.5		
30				Raised venous pressure to 6 cm.
33	28	45		
38	28	44		
46				On atrop. blood.
48				On unpoisoned blood.
52	27	43	17.5	On atrop. blood.
54				On unpoisoned blood.
55				Pressure vacillating between 22 and 25 mm. Hg.
6h. 00m.	29	29		
02	28	22.5		
04				On atrop. blood.
06	28	44		
08				On unpoisoned blood.
15	28	38		
18	28	40		
23	27	35		
23.30				On atrop. blood.
25	28	40	17.5	
27.30				On unpoisoned blood.
36	27	43		On atrop. blood.
39	27	35		
41	27	40	17	On unpoisoned blood.
44	27	62.5		
52	27	42		
7h. 04m.	27	40		On atrop. blood.
06	27	41		
09				On normal blood.
23	26	35.5	16.5	
24				On atrop. blood.
28	26	40		
31	26	40		
32				On unpoisoned blood.
35	25	35		
44	26	31	16.5	Heart still working tolerably well. Ended experiment.

The preceding experiment includes twelve observations on the action of atropized blood on the heart. A small increase in the work done by the heart, due to the action of atropia, can, I think, be plainly noticed, more strongly marked with the stronger dose of the drug. Twice, however, a marked increase in the diastolic expansion of the ventricle occurred after turning on normal blood, and a consequent increase in the work done. This is, I think, to be explained in this way: atropia, being a stimulant to the heart muscle, causes the ventricle to work within certain limits of dilatation only; it checks the full diastole. The drug being suddenly withdrawn, the ventricle relaxes and receives more blood, without, however, being rendered unable to pump it out in its systole. At 5h. 04m., two minutes after normal blood was turned on, 54 cc. were thrown over in a minute, this quantity goes down steadily until at 5h. 20m. it has decreased to 25.5 cc. which was less than had been done at any previous time in the course of the experiment. At 5h. 30m. the venous pressure was raised, and consequently the quantity of blood received and pumped out by the heart increased. The heart then was atropinized without any marked increase in its work being observable. Unpoisoned blood mixture was then turned on, and this was followed by a considerable decrease in the work done until, at 6h. 02m., only half the original quantity of blood was pumped over in each minute. Atropinized blood being again turned on, the heart's work was brought up promptly to its former standard. This experiment shows well the stimulant action of atropia on the heart. When the heart is doing its normal work only a slight increase is observed under atropia. When, however, the muscular tone of the heart is lowered, then atropia exerts a powerful stimulating influence on the heart's action. The decrease in work, noted twice during the experiment after atropia was withdrawn, is probably due to the reaction which is apt to follow every stimulatory action on the tissues.

Experiment VI.

March 28, 1884. Terrapin, weight 1160 grms. Calf's blood and Ringer's saline (1 : 1). Inflow cannulas in hepatic vein, and inferior vena cava; outflow cannulas in left aorta and pul-

monary artery. Venous pressure, 7 cm. Arterial pressure, 30 cm. Carbolized blood contained 0.6 per cent. of carbolic acid. Atropized blood contained 0.02 grm. of atropia sulphate in 300 cc. of the blood mixture.

Time. P. M.	Rate per min.	Work in C. C. per min.	Temp. Cent.	The circulating liquids mentioned in this column were supplied to the heart immediately after the time stated on the same line in the first column.
4h. 00m.				Terrapin in box. Heart supplied with the normal blood mixture.
5h. 00m.	29	30	21	
10	29	31		
15	28	31.5		
25	29	31		
35	29	31		
45	28	31.5		
50	28	29.5		
57	28	30		On carb. blood.
				Carb. blood turned off at 5h. 57′30″; on good blood.
58				Heart cavities over-distended and almost motionless.
6h. 00m.				Blood ceased to come over through outflow tube.
16				Blood begins to come, drop by drop.
20	30	35		
25	30	35		On atropized blood.
27	34	35		
29	34	36		
31				On normal blood mixture.
35	32	32.5	21	
39	32	37		On atropized blood.
42	33	37.5		
44	33	38		On normal blood mixture.
49	35	39		On atropized blood.
54	32	37.5		On normal blood mixture.
7h. 02m.	32	40		
06	33	40		On atropized blood.
10	34	37		
12	32	33		Heart smaller than before; contracting more vigorously.
15	32	33		On carb. blood.
15½				Carbol. blood off and atropized blood turned on.
16				No blood pumped out of outflow tube. Heart enormously distended, contractions of auricles scarcely perceptible, ventricular contraction peristaltic.
25				No blood coming over yet.
29				Blood begins to drop over.
36	28	25		Auricles still abnormally distended, but growing smaller after each contraction.
40	33	30		
43	34	29		On normal blood mixture.
47	34	17	20	Auricles twice as large as under atropia, ventricles smaller.
50	33	15		Auricles almost motionless.
51				On atropized blood.

EXPERIMENT VI.—Continued.

Time. P. M.	Rate per min.	Work in C. C. per min.	Temp. Cent.	The circulating liquids mentioned in this column were supplied to the heart immediately after the time stated on the same line in the first column.
				Auricles contract vigorously and completely at 7h. 52′ 30″.
7h. 55m.	34	31		On normal blood.
8h. 10	33	34.5		On atropized blood.
17	34	30		On normal blood mixture.
19				Auricles again abnormally distended.
21	34	30		Auricles still very large.
24	34	31		On atropized blood.
30	34	26		Auricles smaller on normal blood mixture.
34				Irregular ventricular contractions.
43	22	19		Auricles again enormously distended, irregular action of the heart, peristaltic waves passing in different directions.
9h. 06m.				Condition same. Experiment ended.

The preceding experiment shows, first, that after the heart has been carbolized, atropia increases its rate and also its work; second, that a more rapid recovery takes place after carbolization when blood containing atropia sulphate is supplied than under normal blood mixture. The experiment is one of several which illustrate the same facts.

Convallaria Majalis.

In 1858 two alkaloids were found in this plant, and their discovery was announced by Walz (*Deutsche Naturforsch. Versamml. Berichte*, 34, pp. 175–9). One was called convallarin, the other convallamarin. The former was said to act as a purgative, the latter to possess very decided action on the heart. The literature on the physiological effects of convallaria, as well as that of clinical observations, is of more recent date. The drug has been tested especially in Russia, whence it travelled westward. The principal Russian experimenters in this line are Troitsky Bogoiarlensky, Ysaieff, and Kalmykoff. Their results are mostly published in Russian, but from an extract in the *Revue des Sciences med. en France et a l'Étranger*, I find that a number of experiments on dogs and birds, as well as clinical observations on man, give the following results: Convallaria does not excite the cardiac ends of the vagus nerve, nor the cardiac accelerator nerves; it stimulates the central inhibitory

apparatus and paralyzes the intra-cardiac nerve-centres. The results obtained in Russia all agree in this respect. As regards arterial pressure, it rises in the beginning and falls later on; if the dose has been large the fall occurs at once.

The effects on other organs and systems do not immediately concern us in this connection. Stiller (*Versuche ueber Conv. maj. bei Herzkrankheiten*, *Wiener med. Wochenschrift*, No. 44, 1882) publishes the results of twenty-one observations, which are in direct contradiction with the clinical results obtained in Russia. Stiller says: In 17 cases the effect produced was absolutely nil, there was neither modification in the rhythm of the heart, nor a diminution in the number of pulsations, nor an increase in their strength. In 9 out of these 17 cases digitalis was afterwards used with marked success. Twice convallaria produced diuresis without any other effect. In France one of the principal advocates of convallaria is Prof. Sée. His experiments with it have been both physiological and clinical. He states that in the dog, it first slows the action of the heart and increases the blood pressure, respiration at the same time becoming slower and fuller. Toxic doses cause rapid and irregular pulsations, blood pressure still remaining above normal; finally arterial pressure falls, the pulsations grow feeble, and death takes place through syncope; the ventricle is arrested in systole, the auricles in diastole; the heart of the tortoise was found to possess more resistance to its action than that of other cold-blooded animals. He recommends convallaria, as indicated in all cases of cardiac disease and as counter-indicated in none. He also states that convallaria does not possess a cumulative action, but is very promptly eliminated from the system. Fillond Lavergne (*Étude sur le conval. maj.*, etc. Paris, 1883, *Thesis*) from some experiments and clinical results comes essentially to the same conclusions as Sée. Noguès (*Essai sur le convall. majalis*, Paris, 1883) arrives at the conclusions that the good effects of convallaria on patients affected with heart disease are inconstant, and may be depended upon only in some lesions very far advanced. Durieux disfavors convallaria (*Étude comp. du muguet et de la digitale*, *These de Bordeaux*, 1882), concluding from some physiological and clinical studies that under its influence an irregular and intermittent heart rarely recovers its normal

rhythm; pulse and temperature are not modified; the diuretic effect is inconstant. In every case of dropsy and œdema due to cardiac disease he states that the results have been unsatisfactory. This author very much prefers digitalis to convallaria. Desplats (*Journal des Sciences Med.*, Lille, 1882, *Action du muguet sur le cœur et sur les reins*), on the contrary, has found that convallaria has a decided effect upon the heart and kidneys, and he obtained in cases of cardiac disease in which it was administered, a slowing in the pulse rate, an increase in the energy and regularity of the heart, and an abundant diuresis. He adds, that if its use is continued more than eight or ten days without suspension, it produces a diminution in the force and energy of the heart. Marmé (*Schmidt's Jahrbücher*, Bd. CXXXIV. p. 166) found that convallaria kills by direct action upon the heart, and in moderate doses first slows and then quickens the pulse; previous division of the vagi does not interfere with these phenomena. In America, convallaria has likewise met with varying success, its virtues having been expounded by Taylor of New York, and questioned by Robinson of Philadelphia. With regard to its physiological properties, I. Ott (*Archives of Med.*, February, 1883) concludes that it increases arterial tension greatly at that stage of its action in which the heart begins to beat more frequently; that the subsequent decrease in cardiac frequency is not due to cardio-inhibitory excitation, but to an action on the heart itself, probably its muscular structure; that the rise in arterial tension is mainly due to stimulation of other vaso-motor apparatus than the main vaso-motor centre in the medulla oblongata.

Experiment VI.

February 15, 1884. Terrapin, weight 715 grms. Calf's blood and Ringer's saline in equal proportions. Inflow cannulas in inferior vena cava and left superior vena cava. Outflow cannulas in right aorta and pulmonary artery. Venous pressure, 4 cm. of the circulating liquid. Arterial pressure, 27 cm. Conv. blood contains 0.002 of convallamarin to 100 cc. of blood.

Time. P. M.	Rate per min.	Work in C. C. per min.	Temp. Cent.	
2h. 30m.				Terrapin in box. Heart supplied with normal blood mixture.
3h. 30m.	25	25	19.5	
35	25	24		
40	24.5	23.5		
45	24.5	23.5		
50	24	23.5		
55	24	23		
4h. 00m.	24	22.5		On conv. blood.
03	26	26		On normal blood mixture.
06	26	25.5		
08	26	26		
10	26	25.5		
12	25	25.5		
14	25	25.5		
16	25	25		
18	25	25.5	20	
20	25	25.5		
25	25	25.5		
26				On conv. blood, and kept on for 3 minutes; then substituted by normal blood mixture.
30	25	23.5		
35	26	23	20	
40	26	25		
45	26	25.5		
50	26	26		
55	26	27		
5h. 00m.	26	27.5		On conv. blood; kept on 6 minutes; then normal blood mixture turned on instead.
09	27	22.5		
10	27	24.5		
14	27	26.5		
20	27	28.5	20	
25	27	28		
28	28	27.5		
29	29			On conv. blood.
35	27	21		Auricles very small and contracting sluggishly.
39	28	19		Left aur. pale; right still contracting pretty well.
41	29	18		Ventricle $\frac{1}{3}$ its normal size, never fully expanding, but actively contracting.
43	29	18		
44				On normal blood mixture.
50	31	17		
53	34	18.5		
55	34	18		
58	34	18.5		
6h. 00m.	33.5	19		
03	34	20	20	
09	33	21.5	20	
13	33	22.5		Left auricle begins to expand and look normal.
19	33	25.5		
23	33	25.5		
28	33	27		Heart working with great vigor.
33	33	26.5		

EXPERIMENT VI.—Continued.

Time. P. M.	Rate per min.	Work in C. C. per min.	Temp. Cent.	
6h. 35m.	32.5	26.5		
40	32.5	26	20	
45	33	26		
46				On conv. blood.
50	33	21.5		
52	33	18.5		
55	35	16.5		On normal blood mixture. Entire heart much smaller than usual; very pale and bloodless; peculiar peristaltic but ineffectual contractions; both auricles shrunken.
57	36.5	0	20	
7h. 02m.	38	1.5		
05				Heart ceases to pump blood up to the outflow orifice; it contains some blood which it cannot propel; movements peristaltic.
12				No blood comes over yet. Raised venous pressure 2.5 cm.
14				Auricles slightly larger, but not working; ventricle again actively contracting.
17	33	2		Lowered venous pressure 2.5 cm.
20	33	2		Ventricle making 7 to 8 contr. to one auricular.
30	25	7.5		Left auricle and left side of ventricle bright red; rest dark red and apparently shrunken and not working.
45	33	9		
53	35	7		Left auricle and left side of ventricle working; right auricle and right portion of ventricle inactive and apparently beyond recovery.
8h. 00m.	34	6		
05	36	7		
10	38	7.5		Ended experiment.

All the rest of the experiments made with convallamarin, seven in number, show when small doses are used, a primary slight increase in the pulse rate and a slight increase in the work done; and a final arrest of both auricles and the ventricle in systole. Medium doses, or small doses often repeated, at first increase the rate, but diminish the work, and then arrest the ventricle in systole; the auricles, although much shrunken, being not so contracted as under a small dose. Large doses paralyze the heart in a short time, and arrest the heart at any point between systole and diastole.

In order to more accurately determine the influence of convallamarin on the contractions of the heart of the terrapin, the apparatus invented by Roy (*Journal of Physiology*, Vol. I, p. 452) was used in a somewhat modified way. The heart of the terrapin

being considerably larger than that of the frog, a wide-mouthed glass bottle was taken and its bottom cut off, a rubber cork was then tightly fitted in and perforated for the reception of two glass cannulas, one of which was introduced into the sinus, the other into one of the aortae; the heart was now filled with blood from a Mariotte's flask under a pressure of six cm. and immersed in the glass bottle which had previously been cemented on the brass stand and filled with blood; the base line was determined from the lowest extremity of the tracings on the drum, taken under an outflow pressure of about fifteen cm., which was afterwards lowered to ten cm. After having run through normal blood for fifteen to twenty minutes and finding no leak and no change in the tracings, convallamarin blood was substituted. Out of ten experiments made in this way three only were successful, on account of leakage. The tracings of one of the successful experiments hereto appended (Pl. VII, Fig. 3) show in a typical manner what occurred in all the three; namely, a gradual diminution of the volume of the heart and a steady decrease in the extent of its rhythmic variations in volume, until finally the entire heart, including sinus, auricles and ventricle, became very much shrunken and was arrested in systole. In one case one of the auricles was distended and showed no contraction; on further examination it was found filled with dark blood which could not escape on account of a slight twist which had occurred, preventing the free passage of blood from auricle to ventricle.

My experiments with convallamarin, so far as the isolated heart of the terrapin is concerned, seem to indicate that it increases the pulse rate, at least for a time, and slightly increases the work done; but that auricles and ventricle are arrested in systole when medium doses, or repeated small ones, are used. Large doses arrest the heart at once. The drug probably produces these results by a direct action on muscular substance of the heart. It has a decided cumulative action, acting more slowly than digitalis, and being much more persistent, after the heart is once under its influence.

So far as the results of these experiments allow me to form an opinion, convallamarin is a powerful and, under the proper circumstances, a very useful agent in the treatment of cardiac diseases, but it is certainly contra-indicated in advanced cases

in which the muscular structure of the heart has undergone degeneration and change. The varying results which clinical observations have given is to be accounted for by the fact that the peculiar morbid conditions under which convallaria is useful are not yet thoroughly understood. Not more than one or two full medicinal doses should be given daily on account of the cumulative action of the drug.

Before closing I desire to express my obligations to Prof. H. Newell Martin and Mr. H. H. Donaldson, to whose kindness and suggestions I am much indebted.

EXPLANATION OF PLATE VII.

All tracings to be read from left to right.

Fig. 1. Tracing taken by means of mercury manometer connected with the cardiac end of the outflow tube, in Experiment VI. The portion of the tracing reproduced in the figure commences before the heart had fully recovered under unpoisoned blood from the effects of a dose of carbolic acid, and continues until the normal beat is nearly regained.

Fig. 2. From the same experiment: shows recovery under atropinized blood from a dose of carbolic acid.

Fig. 3. Tracing taken with Roy's tonometer of the beat of the heart under a dose of convallamarin. To the left the tracing is normal; to the right the effect of the convallamarin in decreasing or almost abolishing the diastole of the heart is manifest.

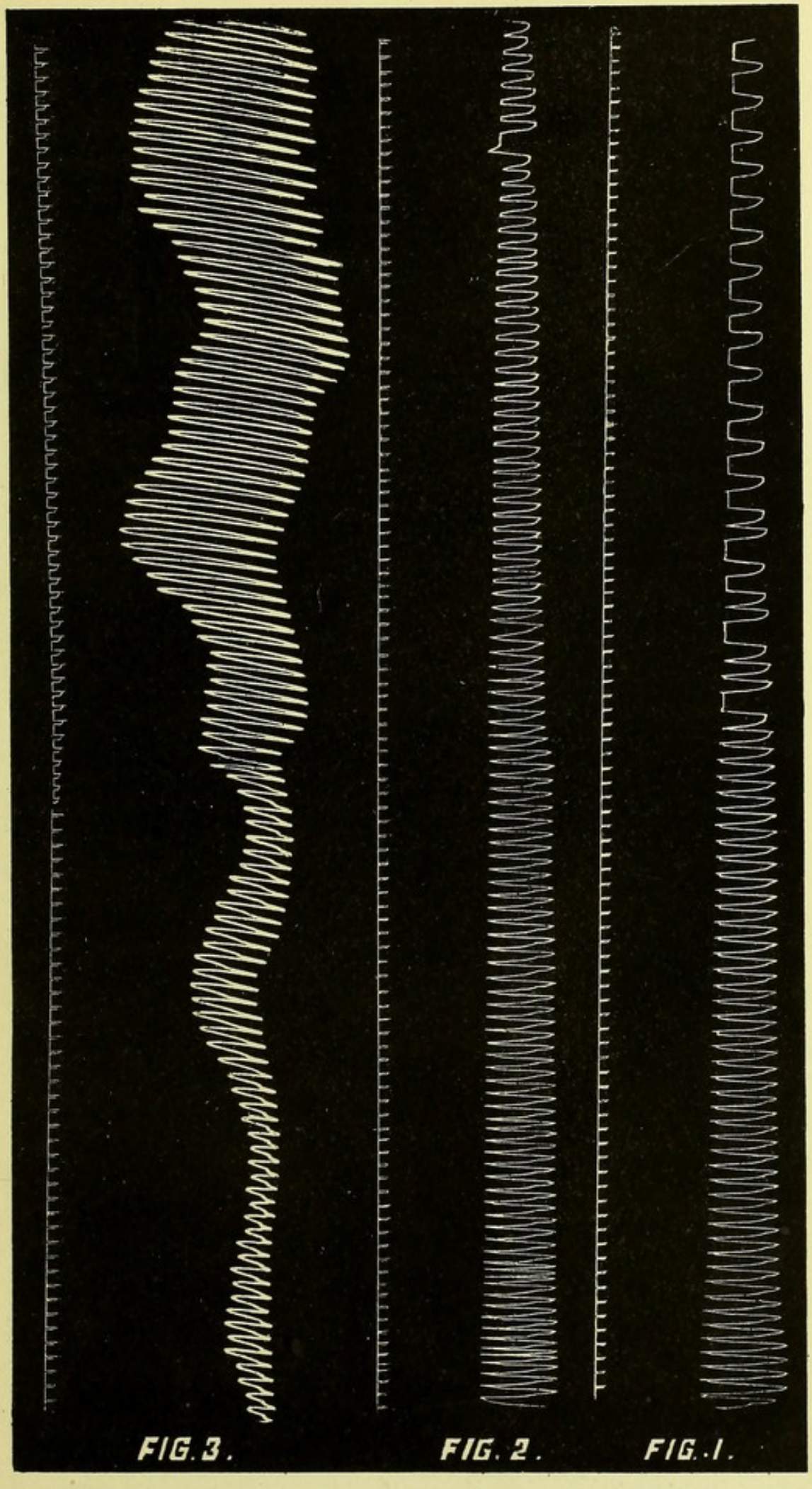
FIG. 3.
FIG. 2.
FIG. 1.