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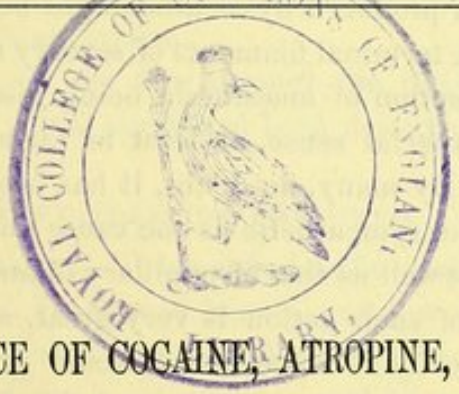

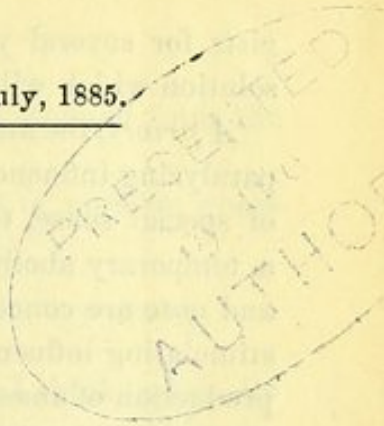

THE INFLUENCE OF COCAINE, ATROPINE, AND CAFFEINE ON THE HEART AND BLOODVESSELS.

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There are few known drugs that have, within such a short space of time, risen from comparative obscurity to such practical as well as theoretical importance as cocaine. Its great value as a local anæsthetic, and its wide application in all the branches of medicine and surgery, together with our comparative ignorance in regard to many points of its action on the animal organism, is perhaps quite sufficient argument in favor of any attempt calculated to throw more light on the subject.

The fact that cocaine, applied to mucous surfaces, will produce temporary localized anæsthesia being now firmly established and generally accepted, and, it being furthermore well recognized that it also produces dilatation of the pupil, the important question now arises how all this is done, and what is the mechanism of the production of these two conditions. This is a problem which is as yet far from being solved.

When we reflect that the experimental evidence, which so far has been adduced in explanation of the phenomenon of pupillary dilatation produced by atropine and that of pupillary contraction by opium, two such long and well-known drugs, is as yet far from being considered as generally satisfactory, we may perhaps be much better able to realize also the difficulty which must necessarily be in the way of solving a similar problem with regard to cocaine. It may require the work of many intelligent physiolo-

gists for several years to come in order to bring the problem to a final solution which will prove satisfactory to all.

A priori, the anæsthesia produced by cocaine might be due to its directly paralyzing influence on the terminal filaments of sensory nerves and nerves of special sense, the production of anæsthesia being also accompanied by a temporary abolition of special sense, at least as far as the mouth, ear, and nose are concerned. By many, no doubt, it has been supposed that a stimulating influence on the sympathetic is the cause underlying both the production of anæsthesia as well as that of pupillary dilatation, and, indeed, the probability in favor of such action is very great, and would explain everything very satisfactorily if experiment would prove it. By still others, the anæsthesia has been thought to be probably due to a temporary contraction of the capillaries, in consequence of which the tissues are, for the time being, deprived of their normal blood supply and thus rendered insensible to external impressions. The latter view has been advanced by Dr. Edward R. Squibb, in his *Ephemeris*, January and March, 1885, and has a great deal in its favor. A certain amount of blanching of those mucous surfaces to which cocaine has been applied is almost invariably present by the time anæsthesia has become established. A slight amount of capillary contraction may also be seen by any one in the expanded frog's web after the direct application or hypodermic injection of cocaine, more marked when the capillaries had previously been irritated and an artificial dilatation thus been produced.

It was with a view of throwing, if possible, some additional light on the influence of cocaine on the circulatory apparatus that the following observations were undertaken. Soon after beginning my experiments with cocaine on the heart of the terrapin I was very much impressed with the great similarity of the effect produced by cocaine and atropine. The action of the latter drug had formed the subject of some of my previous experiments, but, on account of the supposed peculiarity of some of them, they were not all published at the time.

This striking similarity made me subject atropine to renewed and more extended investigation with results to be referred to hereafter more in detail.

Caffeine was also afterwards taken up in addition to these because of the supposed similar action.

All the experiments here described were made in the laboratory of the Museum of Hygiene under the auspices of the Bureau of Medicine and Surgery, Navy Department, Washington, D. C. My thanks are, therefore, due to the chief of that bureau, Surgeon-General Francis M. Gunnell, and also to Medical Director John M. Browne and Surgeon C. H. White, for much kindness in facilitating my work.

The experiments fall into two groups—

I. Experiments on the work done by the heart when isolated from the central nervous system.

II. Experiments on the flow through the bloodvessels of animals whose brains and spinal cords had been destroyed.

METHODS OF INVESTIGATION EMPLOYED.

I. ON THE HEART.—This method as here used, was, I think, originally suggested by Prof. H. Newell Martin, and has since been employed in the laboratory of the Johns Hopkins University at Baltimore, by several of the advanced students in physiology, and become variously modified and perfected until now it forms one of the best and readiest means for studying the action of drugs on the heart of cold-blooded animals. The operation is nearly the same for both frogs and terrapins. If a terrapin is used it is weighed, its head cut off, and the spinal cord destroyed; the plastron is then removed, the pericardium opened, and canulas introduced into two or three of the great venous trunks leading to the sinus, designated as "inflow canulas," and usually two canulas into the arterial stems leading from the ventricle, designated as "outflow canulas," the remainder of the vessels directly connected with the heart are ligatured and the entire organ thus prepared is left *in situ*. I should like, here, to put stress on the necessity of placing at least two inflow as well as two outflow canulas into the afferent and efferent vessels of the heart respectively, for, unless this precaution is taken, the condition of the heart cannot be called entirely normal, as will be readily seen from a glance at the anatomy of that organ in the terrapin; only a portion of the heart would really be kept in circulation with only one arterial and one venous canula. The operation being finished, the animal is placed in a box especially made for the purpose. The box is of wood, with a suitable support inside of it, against which the back of the terrapin can rest securely, and is covered with a glass cover, which can be removed. The creature is thus protected from any injurious outside influences, such as draughts, etc.

The nutrient fluids are supplied to the heart from a system of Mariotte's flasks, each holding about 1000 c.c., and by means of rubber tubes and Y-shaped glass tubes, so connected that the flow from each passes through a common outlet. This outlet tube is in the same way connected with the two or three inflow or venous canulas leading into the sinus.[1] When different liquids are used, they were contained in separate Mariotte's flasks, carefully adjusted, so that the pressure under which the liquid flowed out

[1] In all the experiments on the heart described in this paper the venous pressure indicates the height above the heart of the bottom of the air-tube of the supplying Mariotte's flasks. For example, "venous pressure 4 cm." indicates that the liquid supplied to the heart enters the canulas supplying that organ under a pressure exerted by a column of the nutrient liquid four centimetres in height, and so on.

of them was the same for all. The supply tubes of these flasks had stop-cocks on them, by the closing and opening of which any one flask could at will be used to feed the heart. All the Mariotte's flasks stood on the same horizontal platform, and were raised and lowered equally by moving this support, if it became desirable to change the venous pressure in the course of an experiment.

The outflow canulas 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 liquid, pumped around by the ventricle, flowed out and was collected and measured at certain intervals. The height of the orifice of this tube above the heart is referred to 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 directly proportional to variation in the "load" lifted.

As the specific gravity of the various liquids used in any one experiment differed but slightly, the load lifted was practically proportional 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 inclosed, and gives more accurately the temperature of the heart. A mercury manometer was connected with the outflow-tube near the heart, its pen writing on the smoked paper of a revolving drum, on which also a chronograph recorded seconds.

Most of the experiments were made during the months of March, April, and May, a few also during the winter. From the experience gained by experimenting on animals of variable and usually low temperatures, I have learned that the season of the year exercises a much greater influence on the results attained than is generally believed to be the case. For instance, the inherent resistance of a terrapin's heart to the influence of drugs increases in direct proportion to the advancing season from winter to spring. It was found that the same dose which produced diastolic cardiac arrest in a terrapin's heart during the winter was only just sufficient to produce the characteristic stimulatory effect during the spring. This diminished resistance to the influence of drugs seems to be moreover independent of the temperature of the nutrient blood mixture used at the time, and also to a certain extent of the size and weight of the animal itself.

The same may be said as being true also of the amount of work done, which is much greater during the spring and summer months than it is during the winter, independent of the fact that the rate be made the same

in both seasons. The rate of beat of the heart, on the contrary, is directly dependent on the temperature of the circulating fluid, and may, in a terrapin's heart, even during the winter months, according to the temperature of the circulating fluid, be increased from 5 or 6 to 40 or 50 beats a minute as quickly as the supplying flasks can be made to feed the heart with the different nutrient fluids.

II. On the Flow through the Bloodvessels.—The method employed in the second group of these experiments was devised in the Biological Laboratory of the Johns Hopkins University about three years ago by Donaldson and Stevens (*Journal of Phys.*, vol. iv. p. 165), and is well adapted for determining the action of substances upon the bloodvessels of cold blooded animals as is shown in their study of digitaline. This method, at that time, consisted in cutting out the heart and inserting canulas into the aortic trunks and the venæ cavæ. The aortic canulas were connected with the Mariotte's flasks, placed at a certain height above the body of the animal from which flasks liquid was made to flow into the arteries. This liquid, after circulating through the capillaries and veins, was drained off from the venæ cavæ and measured at definite intervals. After this venous outflow had become constant, circulating fluid mixed with the drug was substituted for normal circulating fluid and the action of the drug on the bloodvessels determined from the change which took place in the amount of the outflow in a unit of time. A decreased outflow indicating increased resistance to the flow of the fluid through the vessels, in other words, a constriction of them, and an increased outflow a dilatation of them.

The circulating fluid used was a 75 per cent. salt solution, because it was found that defibrinated blood, which first suggested itself, appeared to clog the capillaries.

Last year Mr. Stevens, in conjunction with Mr. Lee, considerably improved the method by replacing the heart of the animal by an instrument which, like the heart, forced intermittingly into the arteries, at a constant and uniform rate, equal amounts of the circulating fluid. A full description of this instrument will be found in *Studies from the Biological Laboratory of the Johns Hopkins University*, vol. iii. No. 2, page 101. For the sake of comparison, both constant and interrupted pressures were used in my experiments, and the results proved in the main identical. Regarding the operation on the animal, since it was desirable for my purposes to exclude the central nervous system and to determine the direct action of the various drugs on the bloodvessels themselves, the brain and spinal cord were destroyed and the abdominal viscera and hind-legs alone kept in circulation.

The authors of the method, in the course of their investigation, have, I think, sufficiently proven that the circulation with salt solution can be kept up for at least two hours without producing any very great changes

in the pressure or in the elasticity of the bloodvessels, and also without seriously affecting their contractility. As circulating fluid I have given the preference to Ringer's Saline, the composition of which is as follows :—

Normal salt solution (0.75 per cent.)	100	c.c.
Calcium chloride sol. (1 : 390)	5	c.c.
Sod. bicarbonate sol. (0.50 per cent.)	2.5	c.c.
Pot. chloride sol. (1.0 per cent.)	0.75	c.c.—Mix.

This mixture was first proposed by Sydney Ringer (*Journal of Physiology*, vol. iii. p. 39), as a substitute for the normal salt solution, and answers excellently well.

Cocaine, Atropine, and Caffeine.

I. Experiments on the heart.

II. Experiments on the bloodvessels.

A. Cocaine.

In reviewing the literature, only so much of it will here be considered as has a direct bearing on the subject in question. A few points in connection with the history and evolution of *erythroxylon coca*, Lam., and its alkaloid *cocaine*, may, perhaps, prove of some interest.

In 1565, Nicolas Monardes published at Seville a History of Medicinal Plants brought from the New World, in which, among others, he gave a description of coca leaves, their mode of collection and drying, stating that they formed the most important article of commerce, being used for barter or exchange of money among the South American Indians. The use which the latter are said to have made of it was manifold. First, they chewed the leaves mixed with powdered calcined oyster shells, the paste, after being allowed to ferment, was made into boluses or troches and dried; during long journeys these boluses were sucked, and under their influence hunger and thirst were alleviated and bodily strength sustained. Second, when eaten for the purpose of producing pleasure and intoxication, the coca was chewed by itself. Third, it was mixed with tobacco and smoked.

Coca being also used by the Incas in their religious rites, where it was treated with great reverence, a council of bishops, that met in 1659, condemned its use, stating, that the belief entertained by the Indians that the habit of chewing coca gave them strength was an illusion of the devil. Dr. Weddell (*Journal of Pharmacy*, 1854), a traveller noticed that it did sometimes produce evil consequences, and that, in some instances, a peculiar aberration of mind occurred, indicated by hallucinations. In the year 1750, Joseph de Jussieu sent the first botanical specimen to his brother Antoine Laurent de Jussieu, who referred it to the genus *Erythroxylon*, and subsequently Lamarck designated it as *Erythroxylon coca*. The alkaloid was first produced by Garnecke in 1855,

and by him called *Erythroxyline.* Two years later, S. R. Percy presented to the Academy of Medicine of New York a small quantity of the alkaloid, and at the same time called attention to the fact that it possessed the property of paralyzing, temporarily at least, the sensibility of the tongue. An account of this may be found in the *Proceedings of the Academy of Med. of New York*, November 4th, and December 2d, 1857 In 1859 Niemann produced and called the alkaloid *cocaine*, and Lossen extracted another principle from it which he called *hygrine.* This author states that cocaine augments arterial pressure when used in small doses, but that when used in larger doses it paralyzes the sensory nerves and the posterior columns of the cord. In 1860 Dr. Mantegazza, of Milan, then a practising physician in South America, wrote on the dietetic and medicinal properties of *Erythroxylon coca* (*Journal of Pharmacy*, I. i. 1860, pp. 606, 618), in which article he gave a detailed account of its marvellous properties. In experimenting with it on himself, he found that coca increased the heart's action. In 1862 Schroff (*Zeitschrift f. Wiener Aerzte*, Nos. 30–34), first experimented with it on man, and found that in large doses it caused vertigo, slight deafness with disturbances of memory and coördination of thought. A year later, Fronmüller (*Prager Vierteljahrschrift*, 1863) reported fourteen cases in which sleep had been produced by the administration of about five grains of cocaine, and Ploss, during the same year, reported that after taking about 20 grains of cocaine, he fell into a tranquil sleep, and upon awaking, experienced pain in the abdomen with dryness of the mouth, vomiting, vertigo, and anuria, lasting for twenty-four hours; intelligence remained normal. Moreno (Recherches sur l'Erythroxylon Coca, *Thèse de Paris*, 1870), then proved by experiment, that local injections of cocaine abolished reflex movements. Alexander Bennett (*British Med. Journal*, April 18, 1874), after experimenting on over one hundred animals, concluded as follows: (1) In small doses cocaine causes cerebral excitement and partial paralysis of sensibility. (2) In somewhat larger doses, cerebral excitement, complete paralysis of sensibility, tetanic spasms and death. (3) Paralysis of the entire posterior columns of the cord, and also of the entire system of the peripheral sensory nerves, but the anterior columns of the cord and the peripheral motor nerves were not paralyzed. Sir Robert Christison, experimenting upon himself, mainly confirmed the results attained by others in regard to the strength sustaining properties of coca. Dr. Isaac Ott (*Med. Record*, 1876), after chewing 60 grammes of the leaves during nine hours, discovered dilatation of the pupil, frontal headache, drowsiness, increase in the pulse and temperature, and a decrease in the amount of chloride of sodium excreted by the kidneys. From experiments on lower animals, he found among others, that it did not possess the property of paralyzing the pneumogastrics. In 1880, Von Aurep (*Pflueger's Archiv*, Bd. 21) found that sensibility of the skin was abolished by hypodermic

injections of cocaine, and that the tongue became numb when touched with strong solutions, and he also noticed that the pupils became dilated when the solution was applied to the conjunctiva. Tauvel (*L'Union Médicale*, 1877) also was one of the first who used cocaine for its beneficial effects on the larynx and pharynx, and Aschenbrandt must (*Deutsche Med. Wochenshrift*, 1883, No. 50) be mentioned as regarding cocaine as a stimulant and a retarder of destructive tissue metamorphosis. Rossbach (*Handbuch d. Arzneimittellehre*, by Nothnagel and Rossbach, p. 625, 4th edition, 1880) makes the prophetic remark, that cocaine producing localized anæsthesia further researches on the subject might prove of advantage. Yelinek (*Wiener Med. Wochenshrift*, 1884, Nos. 45 and 46), was one of the first to direct attention to the anæsthetic effect produced by cocaine on the larynx and pharynx and to make practical use of this discovery.

But the priority in this new era in the literature of cocaine, from a careful review of all passed and present writings on the subject, belongs undoubtedly to young Dr. Koller.

Since the reading of Dr. Koller's paper before the last ophthalmological congress at Heidelberg, a large number of experiments have been made with cocaine mainly with regard to the anæsthetic effects which it produces on most any mucous surface with which it may be brought in contact. The literature is of rather recent date, and no doubt still fresh in the minds of many, so that most of it may here be omitted. There are, however, a few facts which, on account of their having a practical bearing on the subject here treated of, I must cite. Thus, Paul Bert, in a communication to the Biological Society of Paris, on the 17th of January, 1885, made the following observation: He injected into a blister, produced by a Spanish fly-plaster, a small quantity of the alkaloid cocaine and thus attained loss of sensibility of the denuded surface. He then covered the denuded surface of another similarly produced blister with perforated lint soaked in a solution of cocaine, and found after a while that those points of the denuded surface which had remained uncovered by the lint retained their normal sensibility, while the covered portions had lost it, evidently a proof of the fact that its action is a mere local one. On the other hand, we have the statement of Dr. Brown-Séquard (*Société de Biol.*, March 14, 1885) that, on the contrary, cocaine does not act merely locally in producing anæsthesia, but that it also produces inhibition at a distance. This view of Brown-Séquard, it would seem, receives also a certain amount of support from the experiments made by Drs. Hall and Halsted. One of these gentlemen gave Mr. Locke, a medical student, an injection of 9 minims of a 4 per cent. solution of cocaine into the substance of the inferior dental nerve at the point where it enters the inferior dental canal. The result was, that in from four to six minutes there was complete anæsthesia of the tongue on the side where the injection was made, extending to the median line and backward to the base as

far as could be reached with a pointed instrument. There was complete anæsthesia of the gums anteriorly and posteriorly, and all the teeth on that side were insensible to blows. The soft palate and uvula of the same side were *anæmic* and insensible. Although it might perhaps be possible to produce loss of sensibility by the merely local action of cocaine on a large nerve-trunk all over the area of distribution of its fibres, the anæmia of the palate and tonsil could scarcely be explained in this way, as produced by Drs. Hall and Halsted. Therefore, it is not unlikely but rather probable, as will also be seen from these experiments later on, that cocaine inhibits at a distance.

So far as the influence of cocaine on the circulation is concerned, we have the further statement of Dr. Wm. Oliver Moore that it increases the frequency of the pulse (*N. Y. Med. Journal*, Jan. 3, 1885), and of Dr. Hermann Biggs (*Journ. Am. Med. Assoc.*, Jan. 17, 1885) that it has a depressant action on the heart, reducing the force and frequency of its pulsation and finally paralyzing it (both auricles and ventricles) in diastole. Biggs furthermore concludes from his experiments on the frog that cocaine kills by paralysis of respiration, and that it also paralyzes the pneumogastrics, which are said by Ott not to be paralyzed by cocaine.

Dujardin Beaumetz has made the observation that in several cases in which cocaine was used hypodermically, syncope of brief duration ensued. He attributes the occurrence to cerebral anæmia, and states that it never occurred while the patient was kept in the prone position, and this is another instance against the view of cocaine acting merely locally.

Finally another series of interesting experiments which requires some notice in this connection are those made by Dr. Erroyd, who, after hypodermic injections of cocaine found that the pulse may become either accelerated or slowed, but always becomes stronger and fuller than normal.

Much valuable information may be found in Squibb's *Ephemeris* for 1885, and also in the compilation of the literature on cocaine made and published by Parke, Davis & Co., of Detroit and New York, 1885.

1. *Influence of Cocaine on the Heart.*

Experiment XXIV. has been selected from a large number as a typical one illustrating at a glance: First the initial stimulating or exciting influence of cocaine on the heart's action by slightly increasing its normal rhythm and the work done per minute. In the second place, it shows the peculiar but typical inhibitory influence which it exercises over the ventricular rhythm while that of the auricles continues unchanged. That this reduced ventricular rhythm is not a state of paralysis but merely one of inhibition may well be inferred from the amount of work the ventricle is still performing, being in some instances much greater even than under normal conditions. This point is still better seen when (at 4.55 P. M.) the venous pressure was raised to 14 cm., the ventricle

still beating at the rate of 13 per minute, the auricles at 26, with the result of increasing both its rate as well as the work done, just what takes place under normal conditions when the venous pressure is raised and the heart happens to be powerful enough to propel the extra amount of blood thus forced into it. I see, therefore, nothing in the way so far of interpreting these phenomena, as due to the stimulating influence of cocaine on the heart's action. Larger doses of cocaine, however, than were used in this experiment or cocainized blood of the same strength as used here, longer continued will finally produce standstill in diastole of both auricles and ventricle. But even after this diastolic arrest is complete, and both auricles and ventricle over-distended with blood which they are unable to propel, it is in most cases possible to cause the heart to recover perfectly in a comparative short space of time, as many of my experiments show and make it continue to beat as often and do as much work as before. During the winter months, however, this stimulatory effect is less pronounced, and therefore much easier overlooked.

From these experiments it is concluded: (1) That cocaine is exceedingly prompt and uniform in its effects upon the heart. (2) In small doses it is a powerful stimulant to the heart's action. (3) In medium doses it has an inhibitory influence over the ventricular contractions, and (4) in large doses it produces diastolic arrest from which, however, the heart may be recovered under suitable condition.

Experiment XXIV.—April 18, 1885. Terrapin 1350 grms. Calf's blood and Ringer's saline (1 : 1½). Inflow canulas in inferior and left superior venæ cavæ. Outflow canulas in pulmonary artery and right aorta. Venous pressure 4 cm. Arterial pressure 25 cm. Cocoainized blood contained 0.004 grm. of the bromide of cocaine: 100 c.c. of the normal nutrient blood mixture.

Time. P.M.	Rate p. min. Aur.	Ventr.	Work in c. c. p. min.	Temp. Cent.	The circulating fluids were supplied to the heart at the time mentioned on the same line in first column.
3.20	22	22	38	24°	
40	22	22	38		
45	22	22	39		
50	22	22	38		
55	22	22	39	...	On cocainized blood for ½ minute.
4.00	22	22	38		
05	22	22	42	24	
11	23	23	54	...	On cocainized blood for one minute.
14	23	23	48		
17	23	23	49	...	On cocainized blood for one minute.
20	24	12	43	...	Ventricular rhythm became reduced to one-half normal 2 minutes after cocainized blood had been turned on the last time.
24	24	12	44		
27	24	12	42	23.5	
30	26	26	55		
33	26	26	55	...	On cocainized blood for 1½ minute.
35	26	26	48	...	Ventricular rhythm was reduced at 4.36.
38	24	12	55		
41	24	12	56		
43	26	26	47	23.5	At beginning of this obs. normal rhythm returned.
45	26	26	47	...	On cocainized blood for two minutes.
47	...	...	...	...	Two auricular to 1 ventricular contraction.
51	26	13	48		

Time. P.M.	Rate p. min. Aur.	Ventr.	Work in c. c. p. min.	Temp. Cent.	The circulating fluids were supplied to the heart at the time mentioned on the same line in first column.
55	26	13	46	...	Venous pressure raised to fourteen cm.
58	26	26	74		
5.00	28	28	84	23.5°	Venous pressure lowered to four cm.
06	26	26	60		
13	26	26	55	...	On cocainized blood for three minutes.
19	26	13	50	...	Ventricular rhythm became reduced before cocainized blood was withdrawn.
22	26	13	47		
29	26	13	45		
32	26	13	55	23	
35	26	13	58		
39	26	13	60		
45	26	13	59		
50	26	13	59		
55	26	13	58		
6.00	26	26	60	23	Experiment discontinued.

2. *Influence of Cocaine on the Bloodvessels.*

Experiment XIV.—April 7, 1885. Terrapin 1470 grms. Ringer's saline. Venous pressure 0. Arterial pressure 23 cm. Inflow canulas placed into the two aortic trunks. The other arteries are tied. Outflow canula in sinus. Brain and cord destroyed. Constant pressure.

Time P. M. From	to	Temp. Cent.	Total outflaw.	Outflow p. min.	The circulating fluids were supplied to the vessels at the time mentioned on the same line in second column.
3.30	...	...	...	...	Terrapin in box.
41	3.43	18°	90	45	
43	45	...	94	47	
45	47	...	96	48	On cocainized saline containing 0.002 : 100 c.c. 1 minute.
47	49	...	85	42.5	
49	51	...	68	34	
51	53	...	70	35	
53	55	...	74	37	
55	57	18	93	46.5	
57	59	...	92	46	On cocainized saline, as before, one minute.
59	4.01	...	88	44	
4.01	03	...	88	44	
03	05	...	102	51	On cocainized saline one minute.
05	07	...	95	47.5	
07	09	...	80	40	
09	11	18	104	52	
11	13	...	100	50	On cocainized saline two minutes.
13	15	...	90	45	
15	17	...	70	35	
17	19	...	90	45	
19	21	...	92	46	
21	23	...	92	46	On cocainized saline four minutes.
23	25	18	85	42.5	
25	27	...	64	32	
27	29	...	80	40	
29	31	...	82	41	
31	33	...	80	40	On cocainized saline containing 0.004 : 100 c.c. four minutes.
33	35	...	72	36	
35	37	...	45	22.5	
37	39	18	57	28.5	
39	41	...	60	30	
41	44	...	76	25.3	
44	47	...	90	30	
47	50	...	80	26.6	
50	52	...	52	26	
52	54	...	50	25	On cocainized saline, as above, six minutes.
54	56	18	40	20	

Time P. M. From.	to.	Temp. Cent.	Total outflow	Outflow p. min.	The circulating fluids were supplied to the vessels at the time mentioned on the same line in second column.
56	58	...	40	20	
58	5.00	...	40	20	
5.00	02	...	35	17.5	
02	04	...	34	17	
04	06	...	32	16	
06	09	...	30	10	
09	12	18°	30	10	
12	15	...	25	8.3	
15	20	...	44	8.8	
20	25	...	41	8.1	
25	30	...	38	7.6	
30	35	...	40	8	
35	40	18	40	8	Raised arterial pressure to thirty cm.
30	45	...	73	14	
45	50	...	85	17	
50	55	...	90	18	
55	6.00	...	90	18	Experiment ended.

Experiment XXIII.—April 17, 1885. Terrapin 2350 grms. Ringer's saline. Venous pressure 3 cm. Arterial pressure 20 cm. Inflow canulas in right and left aortic trunks. Outflow canula in sinus; rest of vessels tied except right subclavian, which is reserved for a pressure canula to be connected with mercury manometer. Brain and cord destroyed. Interrupted pressure. Cocainized saline contains 0.1 : 50 c.c.

Time P. M. From	to	Temp. Cent.	Total outflow.	Outflow p. min.	The circulating fluids were supplied to the vessels at the time mentioned on the same line in second column.
4.00	...	...	...	...	Terrapin in box.
10	4.12	15.5°	46	23	
12	14	...	50	25	
14	16	...	50	25	
16	18	...	53	26.5	
18	20	...	53	26.5	
20	22	...	52	26	
22	25	...	75	25	Injected twenty minims of solution of coc.
25	27	15.5	40	20	
27	29	...	50	25	
29	31	...	54	27	Injected twenty minims of coc. saline.
31	33	...	44	22	
33	35	...	48	24	
35	37	...	52	26	Injected twenty minims of coc. saline.
37	39	15.5	50	25	
39	41	...	44	22	
41	43	...	42	21	
43	45	...	36	18	
45	47	...	35	17.5	
47	49	...	32.5	17.5	
49	51	...	40	20	
51	54	16	51	17	
54	57	...	64	21.3	
57	59	...	43	21.5	
59	5.01	...	48	24	
5.01	03	...	54	27	Injected twenty minims of coc. saline.
03	05	...	37	18.5	
05	07	...	32	16	
07	09	16	26	13	
09	11	...	30	15	
11	14	...	51	17	
14	16	...	51	25.5	Injected twenty minims of coc. saline.
16	18	...	44	22	
18	20	...	40	20	
20	22	...	48	24	Injected forty minims of coc. saline.
22	24	...	30	15	
24	26	...	25	12.5	
26	28	...	22	11	

This experiment was continued one hour and thirty minutes longer, with the same results.

The preceding two experiments with cocaine on the bloodvessels of the slider-terrapin show a decrease in the amount of outflow due to the action of this drug. A constriction of the vessels must be assumed to be the cause of this decreased outflow, for the following reasons: 1. In Experiment XIV., in which constant pressure was used, the outflow invariably decreased in amount on the admission into the bloodvessels of cocainized saline, but increased again in the proportion that cocaine was washed out by the normal saline until it reached its normal standard. The pressure remaining at the same level throughout the experiment, the calibre of the bloodvessels formed the only variable factor, and, therefore, the conclusion that cocaine produces a constriction of the bloodvessels is obvious. 2. In Experiment XXIII., in which interrupted pressure was used, not only the pressure, but also the amount of fluid forced into the arteries by the "artificial heart" in a unit of time remained constant, and here again, the calibre of the vessels being the only variable factor, any decrease in the outflow must necessarily be due to a diminution of the lumen of the bloodvessels. Cocaine, therefore, in small or large doses produces contraction of the bloodvessels, independent of the central nervous system.

These experiments, together with those on the heart, admit of the further conclusion, namely: A rise in the blood-pressure, consequent upon the administration of cocaine is due to a direct action of the drug on the heart and bloodvessels, stimulating the former and constricting the latter; a fall in blood-pressure coming on after the rise must be accounted for by the action of cocaine on the heart alone, since its constricting influence on the bloodvessels outlasts the stimulating influence it exerts over the ventricle of the heart.

B. Atropine.

The literature of the action of atropine on the circulation having already been considered in a recent paper (see *Studies from Biol. Lab. Johns Hopkins Univ.*, vol. iii. No. 2, Dec. 1884, p. 85), reference need now only be made here to a few treatises of more especial interest in connection with the present one. Von Bezold and Bloebaum (*Unters a. d. Phys. Lab. zu Wurzburg*, Heft i.) found, as the result of the smallest doses of atropine, in rabbits as well as in dogs, an increase in the frequency of the pulse-rate and a rise in the arterial pressure. In somewhat larger doses they observed 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 of the pulse-rate, which decrease, after some minutes, was followed by an acceleration and a fall in arterial pressure; the latter, however, rose again but finally remained lower than normal. A dose of 0.1 grm. injected at

once into the heart of the rabbit paralyzed it almost immediately. They agree with Rossbach and Fröhlich in believing that atropine paralyzes the terminal filaments of the vagus within the heart.

Quite recently, Mr. W. B. Ransom published some exceedingly interesting observations on the heart of the octopus. Ransom says that the predominant effect which prevailed throughout all the experiments made with atropine on the octopus's heart was an excitation of the muscular fibre. Whether by increased rhythm or increased contraction, the ventricle invariably manifested the action of a stimulant, which much exceeded in importance the similar influence of the drug in vertebrates. But what was even more remarkable, he continues, the action of the poison on the nerves deviated still more from the ordinary paralyzing influence which it exercises on the vagus endings of the frog. If the nerves were injured at all, *they were the last to be affected*, while all through the observations the atropine seemed to pick out the muscle for its field of action. If the heart was beating, he remarks, there followed almost immediately an arrest in systole on the addition of a small quantity of the sulphate of atropine to the salt water in the canula of the ventricle, the curves far out-topping the preceding ones, and closely resembling the ideo-muscular contractions obtained by applying digitaline to the frog's heart, and which Luciani (Ransom) has described as also produced by atropine.

Von Bezold and Bloebaum, from their observations on the effect of atropine on the mammalian heart in different doses, have proved conclusively that the contractions of the ventricle may, according to the dose of atropine used, be either increased or retarded, or they may be even entirely arrested, and the heart stop beating in diastole. Ransom's observations on the molluscan heart, although perhaps differing slightly from those of the two preceding observers on the mammalian heart, in a few unessential details, are, to all appearances, practically identical in their results. For Ransom has observed that this phase of standstill in systole, which is produced by atropine (called by him "cardio-tonus"), gradually passes away, and is succeeded by a phase of standstill in diastole, or by one in which beats are resumed with less vigor (and frequency?) than before. In all cases, he adds, the heart shows a marked exhaustion produced by the long-continued contraction; and if the dose given be large, the irritability may become reduced almost to zero, so that stimulation of the quiescent heart with even the strongest interrupted currents produces no beats but only a slight contraction.

The rather large number of observations made on the terrapin's heart during the past two winters have enabled me to confirm the results of previous writers with regard to the initial exciting and final exhausting actions of atropine on the heart. I have seen the ventricle of the terrapin's heart shrink to almost one-third its normal size on the first admis-

sion into it of a certain dose of the poison, and continue in almost constant systolic contraction, the auricles at the same time being largely dilated and over-distended with blood, which they were unable to propel or force into the contracted ventricle. On the other hand, the heart of the terrapin may be almost at once made to stop beating in diastole by large doses of atropine. So far, then, as the actually observed phenomena are concerned, they may be considered identical for both vertebrates and invertebrates. All the more surprising is it, therefore, to find so wide a difference to exist in the action of atropine on the nerves of these different animals. Ransom, with regard to the viscerals in octopus finds that they are least and last affected, and all the other writers agree that the first and most marked action of atropine on the frog and turtle is to entirely cut off the influence of the nervous inhibitory mechanism.

In the succeeding experiment the stimulating influence of atropine on the heart is well demonstrated. A decided increase in the rate and in the work done can be plainly noticed as being due to the direct influence of the drug. But, besides this, it shows furthermore that atropine, like cocaine, exercises an inhibitory influence over the ventricular contractions, while the rate of the contractions of the auricles remains unaltered. This peculiar synchronism in the auricular and ventricular contractions may be kept up for many minutes at a time, and be reproduced at will many times during the course of one single experiment, after the strength of the dose of the drug required to call it forth has once been ascertained. In some instances the doses varied considerably, so far as atropine is concerned, which fact may, perhaps, be due to the quality of the drug as oftentimes as to the resistance offered by the heart; with cocaine, however, the dose, once ascertained, may always be relied upon as producing a certain effect.

How this inhibitory influence is brought about must, for the time being, remain unexplained. The present general belief is that atropine paralyzes the vagus endings contained within the vertebrate heart, and, therefore, it would seem irrational to assume, even to possibility, of such a thing as atropine having a stimulating influence on the intracardiac inhibitory ganglia coming on at a late stage of the poisoning, as was apparently the case in the heart of the octopus. Upon this assumption, however, the action of both cocaine and atropine might, nevertheless, readily be explained. The effect of these two drugs of increasing the pulse-rate, and also the amount of work done by the heart, would, then, have to be attributed in part to their stimulating influence on the muscular fibres (which is especially true for atropine, less so for cocaine), and in part also to the same influence on the accelerator or augmentor fibres of sympathetic origin; in other words, their stimulating influence on the muscular fibres and the sympathetic becomes manifest long before that on the terminal filaments of the pneumogastric.

The time when the ventricular contractions become reduced would have to be looked upon as marking the beginning of muscular exhaustion, as well as the beginning of stimulation of the filaments of the pneumogastric; the increased work which is done during the first stages of reduced ventricular rhythm would have to be considered as due to the simultaneous excitation of the augmentor fibres (Gaskell), counteracted, as far as rate is concerned, by the equally excited inhibitory ganglia of the pneumogastric. The final stage of exhaustion is the natural result consequent upon over-stimulation of both nervous and muscular structures composing the heart.

The following instance of "Dissociation of the Auricular and Ventricular Movements of the Heart," reported by Professor A. Chauveau, in the *Revue de Médecine*, may be of some interest in this connection. It was the case of a man, a patient in the service of Professor Boudet, who had a radial pulse of only twenty-one to twenty-four per minute, the auricles pulsating sixty-six times per minute. These auricular pulsations were tolerably regular, but perfectly independent of the ventricular rhythm, being sometimes presystolic, sometimes post-systolic.

Professor Chauveau adds the results of his investigations as to the pathogeny of this condition. By cutting one of the pneumogastrics in a horse, he obtained some dissociation in auricular and ventricular movements. But, by slightly stimulating with a galvanic current the left vagus, he obtained a sphygmographic tracing of dissociated rhythm which almost completely resembled that obtained from his patient. The inference was that a slight irritation of the vagus was the cause of the dissociated rhythm (*Med. Record*, April 4, 1885).

In the case of the terrapin's heart, I was able to produce dissociation in the auricular and ventricular movements by directly stimulating the auricles. During the first few seconds of stimulation, each auricular contraction was followed by a ventricular contraction. Both were much increased in frequency. Soon, however, the auricular contractions become perfectly independent of the ventricular ones, the auricles contracting as many as five times for the ventricle once. No such result was found to follow direct stimulation of the ventricle.

1. *Influence of Atropine on the Heart.*

Experiment XXV.—April 20, 1885. Terrapin 1645 grms. Calf's blood and Ringer's saline (1 : 1½). Inflow canulas in left superior vena cava and inferior vena cava. Outflow canulas in right aorta and pulmonary artery. Venous pressure 4 cm. at start. Arterial pressure 30 cm. Atropized blood of different strength, as indicated in each case.

Time. P.M.	Rate p. min. Aur.	Ventr.	Work in c.c. p. min.	Temp. Cent.	The circulating fluids were supplied to the heart at the time mentioned on the same line in first column.
1.00	...	...	...	...	Terrapin in box.
40	27	27	36.5	20°	
45	27	27	38	...	Raised venous pressure to 5 cm.
50	27	27	50		
55	28	28	52		
2.00	28	28	52.5		
05	28	28	53		
10	28	28	54		
15	28	28	53	20	On atrop. blood (0.004 : 100 c.c.) ½ min.
16	30	30	70		
17	30	30	59		
20	30	30	55		
24	30	30	55	...	On atrop. blood (0.008 : 100 c.c.) 2 min.
27	31	31	55		
32	31	31	56		
35	31	31	56	20	On atrop. blood (0.04 : 100 c.c.).
36	31	31	52		
37	31	31	53		
38	30	15	56		
39	30	15	55		
40	30	15	52		
41	30	15	52	...	On normal nutrient blood.
43	30	15	56	20	
44	30	30	56		
50	30	30	57		
57	32	32	53	...	On atrop. blood (0.03 : 100 c.c.).
58	32	32	52		
59	31	31	50		
3.00	31	31	49		
03	30	15	?	20	Off atrop. blood; on normal blood.
05	30	15	53		
10	30	15	52		
15	31	31	53		
20	31	31	55		
25	31	31	54		
30	31	31	62	...	On atrop. blood (0.08 : 100 c.c.).
35	31	31	52	20	
36	30	15	58	...	Off atrop. blood; on normal blood.
37	30	15	60		
38	30	15	58		
39	30	15	59		
40	30	15	57	20	Discontinued experiment.

The preceding experiment includes five observations on the action of atropized blood on the heart from which it is concluded (1) that atropine in certain doses increases the rate of beat of the heart and also the amount of work done; (2) that it exercises an inhibitory influence over the contractions of the ventricle.

2. *Influence of Atropine on the Bloodvessels.*

Experiment XXII.—April 14, 1885. Terrapin 2356 grms. Ringer's saline. Inflow canulas placed in right and left aortic trunks. Outflow canula in sinus. Venous pressure 0. Arterial pressure 20 cm. Brain and cord destroyed. Constant pressure used. Atropinized saline contains 0.004 grm. of sulphate of atropia in every 100 c.c. of saline. Cocainized saline contains 0.1 of Parke, Davis & Co.'s bromide of cocaine in 50 c.c. of the saline.

Time P. M. From	to	Temp. Cent.	Total outflow.	Outflow p. min.	The circulating fluids were supplied to the vessels at the time mentioned on the same line in second column.
3.30	3.54				Terrapin in box.
54	56	23°	50	25	
56	58	...	52	26	
58	4.00	...	52	26	
4.00	02	...	52	26	
02	04	...	52	26	
04	06	...	52	26	
06	08	...	51	25.5	
08	10	23	48	24	
10	12	...	48	24	
12	14	...	46	23	
14	16	...	46	23	On atropized saline one minute.
16	18	...	30	15	
18	20	...	43	21.5	
20	22	...	48	24	
22	24	23.5	55	27.5	
24	26	...	52	26	On atropized saline one minute.
26	28	...	39	19.5	
28	30	...	38	19	
30	32	...	40	20	On atropized saline two minutes.
32	34	...	41	20.5	
34	35	...	...	21.5	
35	36	23.5	...	22	
36	38	...	48	24	
38	40	...	44	22	
40	42	...	44	22	
42	44	...	40	20	On atropized saline two minutes.
44	46	...	48	24	
46	48	...	52	26	
48	50	23.5	42	21	
50	52	...	39	19.5	On atropized saline four minutes.
52	54	...	50	25	
54	56	...	54	27	
56	58	...	60	30	Injected 20 minims of coc. saline.
58	5.00	...	45	22.5	
5.00	02	...	35	17.5	
02	04	23.5	41	20.5	
04	06	...	40	20	On atropized saline two minutes.
06	08	...	46	23	
08	10	...	71	35.5	Injected twenty minims of coc. saline.
10	12	...	50	25	
12	14	...	28.5	14.2	
14	16	...	33	16.5	
16	18	24	25	12.5	
18	20	...	23	11.5	
20	24	...	26	13	
24	26	...	25	12.5	On atropized saline six minutes.
26	28	...	36	18	
28	30	...	54	27	
30	32	...	70	35	
32	34	24	52	26	
34	36	...	40	20	
36	38	...	40	20	Injected twenty minims of coc. saline.
38	40	...	28	14	
40	43	...	25	8.3	
43	45	...	37	18.5	
45	49	...	71	17.7	
49	54	24	38	7.6	
54	59	...	65	13	
59	6.02	...	40	13.3	
6.02	04	...	38	19	
04	06	...	22	11	
06	08	...	16	8	
08	10	...	24	12	
10	12	24	35	17.5	Experiment discontinued.

Three experiments were made with atropine on the bloodvessels; from these Experiment XXII. was selected because it not only illustrates what was found in all of them, the typical action of atropine on the vessels, but it also shows, at the same time, the influence of cocaine on the vessels after atropization. From this and other experiments it may be concluded (1) that atropine first causes a contraction and afterwards a dilatation of the bloodvessels; (2) that cocaine acts on atropized vessels in the same way that it does on normal ones, *e. g.*, it causes their contraction.

Experiment XV. is intended to illustrate in a still more striking manner than the two previous ones the similarity in the action of the two drugs, cocaine and atropine, on the heart. The solution of the sulphate of atropine was injected into one of the inflow tubes leading directly into the sinus, while normal saline was running through it. After the heart had been slightly cocainized for the first time a slight increase in the rate with a diminution in the work done may be noticed; this occurs also when atropine is used in merely stimulating doses. This diminution in the work done is due to the fact that the ventricle becomes reduced in size, its systole longer, and its diastole shorter, owing to the stimulus to contraction which the heart has received from the drug. When, at 2.25 P.M., cocainized blood was turned on, and immediately afterwards fifteen minims of the solution of atropine was injected, so as to bring the heart at once under the influence of both these drugs, we find as the result that the characteristic and typical cardiac synchronism produced is much more profound than when either of the drugs was used alone. (See Figs. "*c*" and "*d*," Plate II.) In addition to the reduced ventricular rate of contraction the tracings show a very marked diastolic descent which is not seen in the tracings from those experiments in which either cocaine or atropine was used alone. The reduced rate in this instance continued for over one hour, namely, from 2.30 P. M. to 3.34 P. M., thus showing conclusively the similarly directed influence of the two drugs on the heart.

Further on in the experiment, when atropine and cocaine were used alternately, it will be seen that the effect produced is identical although not as long continued as under the influence of the combined drugs.

But while, as thus far shown, the action of the two drugs on the heart is almost identical there is also a difference to be noted. In some cases the dose of atropine which is required to call forth this characteristic inhibitory action on the rate of the ventricle must be ten times larger than a dose of cocaine producing a similar result.

The initial stage of stimulation by cocaine is much shorter, and may likewise be produced by doses considerably smaller than is the case with atropine, and in this lies the main, if not the only, difference between cocaine and atropine in their action on the heart. The only explanation for this difference which I have to offer is that atropine is one of the most

powerful muscular stimulants, while the same cannot be said to apply with equal force to cocaine, which latter, probably, exerts a good share of its stimulating influence on the heart through its action on augmentor (Gaskell) or trophic (Ransom) nerve-fibres contained within its substance.

The combined Influence of Cocaine and Atropine on the Heart.

Experiment XV.—April 8, 1885. Terrapin 1505 grms. Lamb's blood and Ringer's saline (1 : 1). Canulas in left superior vena cava and inferior vena cava; in right aorta and pulmonary artery. Venous pressure 5 cm. Arterial pressure 27 cm. Cocainized blood contains 0.002 grm. of muriate of cocaine to 100 c.c. of blood mixture. The solution of atropia used for injection contained 0.1 grm. of the alkaloid to 50 c.c. of Ringer's saline.

Time. P.M.	Rate p. min. Aur.	Rate p. min. Ventr.	Work in c.c. p. min.	Temp. Cent.	The circulating fluids were supplied to the heart at the time mentioned on the same line in first column.
12.30	...	...	...	...	Terrapin in box.
1.25	27	27	52	18°	
30	27	27	50		
35	27	27	50		
40	27	27	52		
45	27	27	52	...	On cocainized blood for one minute.
46	28	28	60		
47	28	28	43		
48	28	28	42.5	18	
52	28	28	47		
55	28	28	48	...	On cocainized blood for two minutes.
56	28	28	40		
57	28	28	35	...	Immediately after this observation two auricular to one ventric. beat occurred.
2.00	30	15	50		
03	30	15	52		
05	30	30	48	18	Injected five minims of solution of atropine into one of the inflow canulas.
10	30	30	47		
13	31	31	46		
20	31	31	50.5		
22	31	31	52		
25	31	31	45	...	On cocainized blood for two minutes, and fifteen minims of solution of atropine injected into one of the inflow canulas.
30	32	16	47		
32	32	16	53	18.5	
35	32	16	52.5		
38	32	16	50		
41	32	16	53		
50	32	16	49		
55	33	16.5	52		
3.00	33	16.5	53		
05	32	16	52	18.5	
10	32	16	52		
15	32	16	52		
20	32	16	51		
25	32	16	50		
30	32	16	51		
34	...	...	...	...	Normal sequence returned.
35	32	32	20	19	Ventricle small, and in almost constant systolic contraction.
39	32	32	24	...	Auricles somewhat dilated; injected ten minims of atropia.
39.30	...	...	...	...	Cardiac synchronism commenced.
40.30	32	16	45		
42	32	16	47		
50	32	16	55		
55	32	16	55		

Time. P.M.	Rate p. min. Aur.	Ventr.	Work in c.c. p. min.	Temp. Cent.	The circulating fluids were supplied to the heart at the time mentioned on the same line in first column.
56.30	...	...	...	19°	Normal rhythm returned; auricles slightly distended; ventricle small and constantly in a state of contraction.
59	32	32	25		
4.02	32	32	20.5	...	On cocainized blood two minutes; immediately after two auricular to one ventricular contraction occurred.
04	32	32	20		
07	30	15	42		
09	30	15	41		
11	32	32	16	...	Normal sequence returned at beginning of this observation.
15	32	32	18	19	Injected ten minims of solution of atropia.
16	32	16	41		
20	32	16	48		
22	32	32	20	...	Normal sequence returned at beginning of this observation.
28	32	32	15		
30.30	...	...	...	...	Injected solution of cocaine, same strength as that of atropia, ten minims.
31.30	30	15	47		
35	32	16	42	19	
37	32	16	45	...	Normal sequence returned immediately after the last observation was taken; experiment discontinued.

The Influence of Morphine and Cocaine on the Heart.

Atropine has always been considered one of the physiological antidotes of opium, and cases of opium poisoning are on record where atropine undoubtedly has done good service.

In the year 1874 Dr. W. H. Bentley (*Therapeutic Gazette*, 1880, p. 253) employed coca as a means of curing the opium habit apparently with excellent results; and in 1880 Prof. E. R. Palmer, of the University of Louisville, Ky., reported some very striking examples in testimony of coca as a means of counteracting the habit of opium eating. The similarity in the action of cocaine and atropine on the heart having so far been sustained, and also for reasons above given, it occurred to me to try and ascertain by experiment, in how far the antagonistic properties of cocaine to morphine applied to the heart. Several experiments were, consequently, made with regard to this point, and the following is intended to show the extent of this antagonism existing between cocaine and morphine as far as the heart of the terrapin is concerned.

Experiment VII.—March 14, 1885. Terrapin 625 grms. Beef's blood and Ringer's saline (1 : 1). Inflow canulas in inferior and left superior venæ cavæ. Outflow canulas in pulmonary artery and right aorta. Venous pressure 5 cm. Arterial pressure 20 cm. Cocainized blood contains 0.001 grm. for every 100 c.c. of normal nutrient blood mixture. Morphinized blood the same.

Time. P.M.	Rate p. min. Aur.	Ventr.	Work in c.c. p. min.	Temp. Cent.	The circulating fluids were supplied to the heart at the time mentioned on the same line in first column.
2.30	...	...	...	...	Terrapin in box.
3.15	24	24	18	17°	
20	24	24	18		
23	24	24	18	...	On morphinized blood one minute.
25	25	25	16		
28	25	25	16.5		On morphinized blood two minutes.
30	26	26	16.5		
33	26	26	15.5		
35	26	26	15.5	17	
40	24	24	17		
43	24	24	19.5		
45	24	24	19	...	On morphinized blood fifteen minutes.
47	25	25	21		
49	26	26	21		
51	27	27	18		
4.00	27	27	16	17	On cocainized blood four minutes.
02	25	25	16.5		
04	24	24	14	...	On morphinized blood three minutes.
07	24	24	14	...	Heart smaller than before morphinization.
10	25	25	14	...	Ventricular systole abnormally prolonged.
15	24	24	13.5		
17	24	24	14	...	On cocainized blood three minutes.
21	24	12	19	17	
24	24	12	18		
29	24	24	12	...	On cocainized blood three minutes, immediately after morphinized blood instead of the normal nutrient.
32	24	24	10		
55	24	24	8		
40	24	22	12	...	Ventricle missed two normal contractions.
43	24	24	16	...	On cocainized blood.
46	24	24	15	17	On morphinized blood.
49	24	18	15	...	Left auricle more energetic than right.
51	24	22	14		
54	24	22	13		
58	24	24	12	...	On cocainized blood three minutes.
5.00	24	24	14		
03	24	12	20		
05	24	12	20		
08	24	12	19	...	Heart passed from under influence of cocaine immediately after 5.08 P. M.
15	24	24	14	...	Experiment discontinued.

From this experiment it is concluded that morphine antagonizes the action of cocaine on the heart within certain limits; comparatively large doses of morphine are required to produce this effect.

Influence of Cocaine on the Muscarinized Heart.

Experiment XXVIII.—April 28, 1885. Terrapin 1920 grms., vigorous animal. Calf's blood and Ringer's saline (1 : 1). Inflow canulas in left superior vena cava and inferior vena cava. Outflow canulas in pulmonary artery and right aorta. Venous pressure 6 cm. Arterial pressure 30 cm. Cocainized blood contains 0.004 grm. of Parke, Davis & Co.'s bromide of cocaine in every 100 c.c. of blood mixture. Muscarinized blood contains 0.1 grm. of muscarine (Merk) for 100 c.c. of blood mixture. The solution used in first part contains 0.1 : 50 c.c. of saline.

Time. P.M.	Rate p. min. Aur.	Rate p. min. Ventr.	Work in c.c. p. min.	Temp. Cent.	The circulating fluids were supplied to the heart at the time mentioned on the same line in first column.
1.00	...	...	...	...	Terrapin in box.
30	38	38	49	23.5°	
35	38	38	48		
40	38	38	47	...	Injected ten minims of sol. of muscarine into inferior vena cava.
43	38	38	44		
48	39	39	44	...	Injected twenty minims more.
51	39	39	44		
56	40	40	42	...	On musc. blood for two minutes.
58	30	30	65	23.5	Between this and next observation heart was paralyzed for 25 seconds, but quickly recovered.
2.01	21	21	69		
04	38	38	55		
08	38	38	54	...	On cocainized blood for 1½ minutes.
09	...	...	...	...	Two aur. to one ventric. beat commenced.
11	34	17	25		
12	...	...	...	...	No blood being pumped over; contractions of heart ineffectual.
...	...	...	...	23°	
15	...	...	...	...	Blood beginning to come again.
17	36	18	30		
20	38	19	45		
25	38	19	50		
30	38	19	54	...	On muscarinized blood for two minutes; thirty seconds after normal sequence returned but rate is lowered.
32	30	30	50	23	
33	17	17	54		
38	38	38	58	...	On cocainized blood for 1½ minutes.
40	38	19	50		
43	38	19	50	...	On musc. blood for 1½ minutes.
46	33	33	50	...	Twenty seconds after musc. blood was turned on normal sequence returned, rate was lowered.
48	38	38	57	23	
51	38	38	57		
57	38	38	56.5		
3.02	39	39	55		
07	39	39	54	23	Experiment discontinued.

This and the following experiments were made with a view of further testing the action of cocaine on the heart in its relation to muscarine and curari. A careful perusal of Experiment XXVIII. will, I think, show, first, that muscarine in very small doses will slightly increase the rate of beat of the heart, and decrease the work done, apparently manifesting the action of a moderate stimulant; second, that large doses quickly reduce its rate, and finally produce standstill in diastole, from which, however, the heart may recover; third, that cocaine does not prevent the occurrence of muscarine standstill as atropine has been found to do; fourth, that muscarine will quickly restore the characteristic irregular sequence in the contractions between auricles and ventricles set up by cocaine to the normal sequence, at the same time lower the rate of contractions of both.

Influence of Cocaine on the Curarized Heart.

Experiment XXVI.—April 26, 1885. Terrapin 2520 grms., vigorous animal. Calf's blood and Ringer's saline (1 : 1). Inflow canulas in left superior and inferior venæ cavæ. Outflow canulas in pulmonary artery and right aorta.

Venous pressure 6 cm. Arterial pressure 30 cm. Cocainized blood contains 0.004 grm. of Parke, Davis & Co.'s bromide of cocaine to 100 c.c. of normal blood mixture. Curarized blood contains 10 c.c. of 3 per cent. solution to 100 c.c.

Time. P.M.	Rate p. min. Aur.	Rate p. min. Ventr.	Work in c.c. p. min.	Temp. Cent.	The circulating fluids were supplied to the heart at the time mentioned on the same line in first column.
2.00	...	...	...	...	Terrapin in box.
3.00	35	35	64	24°	
05	35	35	63		
10	35	35	62		
16	35	35	62		
20	35	35	61	...	On curarized blood twelve minutes.
22	38	38	73	24	
26	40	40	70		
32	40	40	72	...	On cocainized blood for two minutes.
34	40	20	45		
37	40	20	40		
40	40	20	52	24	
45	38	19	60	...	On curarized blood fifteen minutes.
49	38	19	69		
55	38	38	60		
4.00	40	40	68	...	On cocainized blood five minutes.
02	40	20	72	24	
03	40	20	69		
06	40	30	58		
08	38	38	63	...	Experiment discontinued.

In connection with Experiment XXVI. it is certainly interesting to note the effect of curare on the rate of beat of the heart as well as that on the work done; the former was promptly increased from 35 to 40 per minute, and the latter from 61 to 72 c.c. per minute. Cocainized blood being turned on after curarized blood had run through the heart for the period of twelve minutes the characteristic effect of cocaine on the heart was produced two minutes from that time. The same thing was repeated, and, after fifteen minutes' curarization, cocaine still produced its usual effect; hence, it is concluded, 1, that cocaine acts on a curarized heart as it does on a normal one; 2, curare acts as a stimulant on the isolated heart; 3, if curare paralyzes the vagus endings in the heart, the characteristic action of cocaine on the heart cannot be explained by its possessing a possible stimulating influence on the vagus endings.

C. Caffeine.

Dr. R. Amory (*Boston Med. and Surgical Journal*, 1868), in some of his experiments on the physiological action of caffeine, found that the number of the pulsations of the heart was increased; that there was some congestion of the brain and cerebellum after the death of the animal, and that the heart continued to pulsate several minutes after death. He concluded that the drug poisons by exhausting the muscular contractility throughout the body, affecting last of all the muscles of the heart. Voit (*Unters. über d. Einfluss des Kaffee's, etc., auf die Muskelbewegungen*, München, 1868), noticing the peculiar swelling of the muscles which accompanies tetanus produced by caffeine, attributes it not to changes in the muscular substance itself, but to a dilatation of the bloodvessels and consequent exu-

dation of liquor sanguinis. Bennet (*Edinburgh Medical Journal*, 1873), almost invariably found immediately after death from theine (which he used as identical with caffeine) the heart still beating, the bloodvessels engorged with blood, the integument, the thoracic and abdominal viscera deeply congested.

Leblond (*Etude Phys. et Thérap. de la Caféine*, Paris, 1883), one of the latest investigators of the normal action of caffeine, observed as a *constant phenomenon* a diminution in the frequency of the pulsations of the heart; under physiological doses he obtained a rise in arterial pressure and an increase in the height of the pulse-curves. The rise in blood-pressure he attributes in part to a constriction of the bloodvessels.

Riegel (*Berliner Med. Wochenschr.*, xxi. 19, 1884), upon the recommendation of Huchard (*L'Union Médicale*, Sept. 1882), and Lépine (*Soc. des Sciences Méd. de Lyon*, 1882), experimented with caffeine during a whole year, and from the experience gained he finally concluded that caffeine is equal to digitaline, and even surpasses it in those cases where digitaline is indicated.

C. Becher (*Wiener Med. Bl.*, vii. 21, 1884), experimenting with caffeine almost at the same time as Riegel, and in the same general direction, has also come to the same conclusions.

Both from the renewed therapeutical interest which caffeine has received through the researches of Riegel and Becher, as well as from the supposed similarity of its action to that of cocaine, and also in order to clear up a few of the contradictory results hitherto recorded, with regard to its effects on the pulse-rate and the bloodvessels, it seemed to me desirable to include caffeine in this series of observations.

The following experiments will show that the conclusions of Leblond will have to suffer considerable modification, both as regards the constant slowing effect of caffeine on the pulse-rate, as well as in view of the part played by the bloodvessels in the rise of arterial pressure due to caffeine.

1. *The Influence of Caffein on the Heart.*

Experiment X.—April 1, 1885. Terrapin 610 grms. Beef's blood and Ringer's saline (1 : 1). Inflow canulas in left superior vena cava and inferior vena cava. Outflow canulas in right aorta and pulmonary artery. Venous pressure 5 cm. Arterial pressure 20.5 cm. Caffeinized blood contains 0.2 grms. of bromide of caffeine in every 300 c.c. of blood mixture.

Time. P.M.	Rate p. min.	Work in c.c. p. min.	Temp. Cent.	The circulating fluids were supplied to the heart at the time mentioned on the same line in first column.
12.00	...	...	...	Terrapin in box.
35	34	34.5	21°	
45	34	35		
1.00	34	35		
10	34	35		
15	34	35		
20	34	35	...	On caffeinized blood one minute.
22	36	37		
24	36	36		
26	36	43		
34	37	43		

Time. P.M.	Rate p. min.	Work in c.c. p. min.	Temp. Cent.	The circulating fluids were supplied to the heart at the time mentioned on the same line in first column.
38	38	44		
48	38	45	...	On caffeinized blood one minute.
50	38	47		
55	40	47		
2.02	40	47		
07	40	47		
12	40	48	...	On caffeinized blood two minutes.
14	40	50		
17	40	47		
21	40	47.5		
30	40	49		
35	40	47	...	On caffeinized blood (0.4 : 300 c.c.) 1 min.
37	41	51		
41	41	46		
45	42	49		
50	41	46		
55	41	48	...	On caffeinized blood (0.4 : 300 c.c.) 1 min.
57	43	49		
3.02	43	49		
10	43	48		
15	45	45		
20	44	45	...	On caffeinized blood, as above, 2 minutes.
25	42	46		
30	42	46		
32	40	49		
34	42	46		
36	42	46		
41	43	50		
45	42	47		
50	41	47.5	...	On caffeinized blood, as above, 3 minutes.
51	42	46		
55	42	46		
4.00	42	46		
06	40	42		
08	41	42	...	On caffeinized blood (0.6 : 300 c.c.) 3 min.
13	41	44		
18	40	43		
22	41	43		
28	40	40		
32	40	42		
50	40	42		
5.00	40	41	...	On caffeinized blood (0.6 : 300 c.c.) 5 min.
02	37	35		
05	22	26		
09	37	40		
13	40	42		
17	42	43	...	Experiment discontinued.

During the whole length of the preceding experiment the regular rhythmical sequence in the contractions of the heart never varied from its normal standard; it was perfect and vigorous. The influence of caffeine in relatively small doses upon the rate, is, I think, well shown. It decidedly increases the rate of beat at the same time that it renders the contractions stronger and increases the work done, and it was only when very strongly caffeinized blood was used for a longer space of time than in the previous observations that the rate and work went down. During this time the heart's action became somewhat sluggish, the auricles were larger than normal, contracting imperfectly, the ventricle contracted peristaltically and incompletely. The entire heart, however, quickly recovered under normal blood. From this experiment it is further concluded that caffeine possesses a slight cumulative action.

2. *Influence of Caffeine on the Bloodvessels.*

Experiment XVIII.—April 11, 1885. Terrapin 1340 grms. Ringer's saline. Inflow canulas placed in the right and left aortic trunks. Outflow canula in sinus. Brain and cord destroyed. Caffeinized saline contains 0.08 grm. of bromide of caffeine (Mercks) in every 100 c.c. of saline. Venous pressure 0. Arterial pressure 16 c.m.

Time P. M. From	to	Temp. Cent.	Total outflow.	Outflow p. min.	The circulating fluids were supplied to the vessels at the time mentioned on the same line in second column.
3.00	3.25	...	...	...	Terrapin in box.
35	37	17°	28.5	14.2	
37	39	...	27.5	13.7	
39	41	...	26	13	
41	43	...	25	12.5	
43	45	...	25	12.5	
45	47	...	26	13	
47	49	...	27	13.7	
49	51	17	30	15	
51	53	...	29	14.5	
53	55	...	31.5	15.7	
55	57	...	30	15	
57	59	...	30	15	
59	4.01	...	30	15	
4.01	03	...	32	16	On caffeinized saline two minutes.
03	07	17.5	10.6	26.5	
07	09	...	56	28	
09	11	...	26	14.5	
11	13	...	16	8	
13	15	...	15.5	7.7	
15	17	...	19	9.5	
19	19	...	15	7.5	
19	21	17.5	18	9	On caffeinized saline one minute.
21	23	...	20	10	
23	25	...	54	27	
25	27	...	29	14.5	
27	29	...	15	7.5	On caffeinized saline one minute.
29	31	...	22	11	
31	33	...	55	27.5	
33	35	17.5	31.5	15.7	
35	37	...	21	10.5	On caffeinized saline one minute.
37	39	...	23.5	11.7	
39	41	...	52	26	
41	43	...	34.5	17.2	
43	45	...	23	11.5	
45	4.47	...	21	10.5	On caffeinized saline one minute.
47	49	18	29	14.5	
49	51	...	46.5	23.2	
51	53	...	41.5	20.7	
53	55	...	18.5	9.7	
55	57	...	27	13.5	
57	59	...	28	14	
59	5.01	...	24	12	
5.01	03	18	35	17	
03	05	...	28	14	
05	07	...	20	10	On caffeinized saline two minutes.
07	09	...	41	20.5	
09	11	...	51	25.5	
11	13	...	41.5	20.7	
13	15	18	41.5	20.7	
15	17	...	41.5	20.7	
17	19	...	42	21	On caffeinized saline four minutes.
19	21	...	21	10.5	
21	23	...	45	22.5	
23	25	...	82.5	41.2	
25	27	...	78	38	
27	29	...	56	28	
29	31	18.5	45	22.5	
31	33	...	35	17.5	On caffeinized saline six minutes.
33	35	...	36	18	

Time P. M. From.	to.	Temp. Cent.	Total outflow.	Outflow p. min.	The circulating fluids were supplied to the heart at the time mentioned on the same line in first column.
35	37	...	63	31.5	
37	39	...	83	41.5	
39	41	...	77	38.5	
41	43	...	66	33	
43	45	18.5°	45	22.5	
45	47	...	38.5	19.2	
47	49	...	32	16	
49	51	...	27	13.5	
51	53	...	28.5	14.2	
53	55	...	26	13	
55	57	...	28.5	12.2	
57	59	18.5	24.5	12.2	
59	6.01	...	24	12	Experiment ended.

Experiment XXVII—April 22, 1885. Terrapin 2010. Ringer's saline. Caffeine solution which was injected was a saturated solution of caffeinum bromidum in Ringer's saline. Inflow canulas in right and left aorta. Arterial pressure 20 cm. Outflow canula in sinus. Venous pressure 0. Brain and spinal cord destroyed. Interrupted pressure used.

Time P. M. From	to	Temp. Cent.	Total outflow.	Outflow p. min.	The circulating fluids were supplied to the vessels at the time mentioned on the same line in second column.
3.15	...	...	...	...	Terrapin in box.
31	33	28°	25	12.5	
33	35	...	25	12.5	
35	37	...	25	12.5	
37	39	...	25	12.5	
39	41	...	22	11	
41	45	...	50	12.5	
45	47	...	23	11.5	
47	49	...	20	10	
49	52	...	31	10.3	
52	54	...	24	12	
54	56	...	28	14	On caffeinized saline.
56	58	...	20	10	
58	4.00	...	18	9	
4.00	02	...	16.5	8.25	
02	04	...	33	16.5	
04	06	...	34	17	On normal saline.
06	08	...	25	12.5	
08	10	...	25	12.5	
10	12	...	32	16	Injected 20 minims of caffeinized saline.
12	14	...	32	26	
14	16	...	52	26	
16	18	...	27	13.5	
18	20	...	15	7.5	Injected 20 minims of caffeinized saline.
20	22	...	25	12.5	
22	24	...	30	15	
24	26	...	25	12.5	Injected 20 minims of caffeinized saline.
26	28	...	25	12.5	
28	30	. .	30	15	
30	33	...	31	10.3	Injected 23 minims of caffeinized saline.
33	35	...	33	16.5	
35	37	...	25	12.5	
37	39	...	24	12	
39	42	...	35	11.6	
42	48	...	68	11.3	On caffeinized saline.
49	52	...	37	12.3	
52	54	...	70	35	
54	56	...	74	37	Experiment discontinued.

The first observation with caffeine in this experiment was evidently followed by diminished outflow, which might have been due to a contraction of the arterioles. Thinking that perhaps very small doses might

normally produce this effect from the start, instead of running caffeinized saline through the vessels, normal saline was turned on, and occasional injections of 20 mimims of the solution made directly into the circulation, and the result was invariably an increase in the outflow denoting a slight dilatation of the arterioles. When towards the end of the experiment again caffeinized saline was turned on for eight minutes, the outflow per minute became about three times that of the normal, showing that the effect is constant, and that the first decrease in the outflow must have been due to other causes.

The conclusion, therefore, is that caffeine in small as well as large doses produces dilatation of the bloodvessels in the terrapin; any rise in arterial pressure due to caffeine is, consequently, to be explained only by the stimulating effect caffeine exerts on the heart itself.

EXPLANATION OF PLATES.

All the tracings were taken by means of a mercury manometer connected with the cardiac end of the outflow tube, and to be read from left to right.

PLATE I.

From Experiment XXIV.—*a*, normal tracings; *b* and *c*, beginning to show the effect of cocaine, and finally passing into "*d*," the state in which two auricular to one ventricular contractions occur; of the two auricular contractions, one is pre-systolic, the other post-systolic. The tracings shown in "*b*" and "*c*" do not always occur, and more often, especially after the first observation has been made, the transition from the normal to the abnormal sequence is sudden.

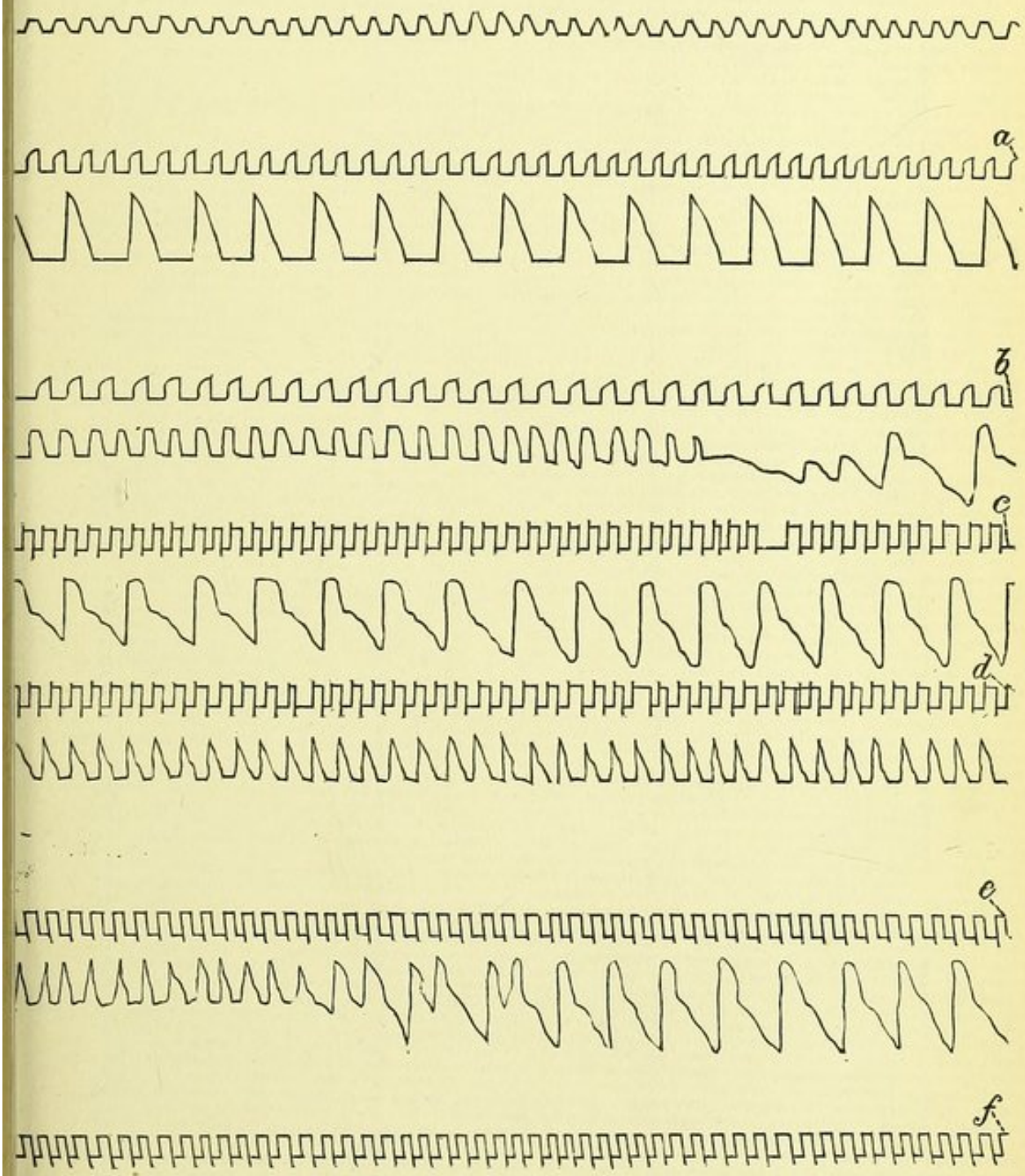
PLATE II

Tracings "*a*" and "*b*" are from Experiment XXV., with atropine.—"*a*" showing the primary effect of stimulation of the ventricle when it becomes reduced in size, but is still beating at an increased rate and following the auricular contractions regularly; "*b*" shows the condition in which two auricular and one ventricular beats occur.

Tracings "*c*" and "*d*" are from Experiment XV., showing the effect of cocaine and atropine combined on the heart. Note the diastolic descent in the curves, not seen when either of the drugs is used alone. The same will be noticed in "*e*" and "*f*," which are taken from Experiment XXVIII., with cocaine and muscarine combined, showing that either cocaine and atropine, or cocaine and muscarine, act on the heart in the same general direction.

PLATE I.

PLATE II.



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