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THE DIRECT ACTION OF NICOTIN UPON THE MAMMALIAN HEART

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THE DIRECT ACTION OF NICOTIN UPON THE MAMMALIAN HEART.

By HENRY G. BEYER.

Although nicotin, the active principle of tobacco, is rarely, if ever, used by physicians on account of any therapeutic properties which it may possess, it must, nevertheless, be admitted that its influence on human life is second only to that of coffee, tea and the alcoholic stimulant.

While the effects of tobacco on the human organism have long since interested the physician and the pathologist, no very satisfactory attempt has yet been made to study its acute effect upon the mammalian heart, according to the latest and most approved methods, although that organ seems to be more particularly concerned, whenever the effects of tobacco are spoken of as being dangerous to the human body.

Hedbom[3] who, quite recently, has published some very interesting and painstaking experiments of his studies of the action of a number of drugs upon the isolated mammalian heart, has not included nicotin in his observations.

Since Vas[11] has shown that the poisonous effects that are usually attributed to the use of tobacco, are due to the nicotin found in tobacco-smoke and to no other alkaloid contained in the same, the results obtained in this research may have a practical bearing upon the subject.

The method employed in the following investigations being but a modification of the one originally devised by Martin and Applegarth, and, having been recently described in detail in connection with researches published by Porter,[4] Hyde[5] and especially, Magrath and Kennedy,[6] it would seem unnecessary to repeat an account of it in this connection. In nearly every case, undiluted, defibrinated dog's blood was used, freshly obtained from the animal. Dilution was only resorted to whenever the quantity obtained at the time seemed too small for an experiment.

In all the experiments on the isolated mammalian heart, made

according to the method referred to above, the life of the heart must, necessarily, be limited to a few hours only; its performance very gradually but surely and constantly declines from the moment of its first recovery from the operation to the time it stops beating. This fact should always be borne in mind whenever the records from such experiments are examined critically.

JULY 10, 1899. CAT'S HEART. UNDILUTED DEFIBRINATED DOG'S BLOOD. NICOTINIZED BLOOD 1 : 25,000. TEMPERATURE 36° C.

Time P. M.	No. of Drops.	No. of Pulsations.	Amplitude in mm.	Remarks.
2h. 30–31	68	140	8–10	On poisoned blood.
31–82	62	140	8–10	
32–33	62	140	6–10	On poisoned blood.
34–35	42	155	10–20	
35–36	29	135	2–3	On normal blood.
37–38	21	127	2–5	
38–39	24	126	5–12	
41–42	26	130	5–10	
42–43	19	82	3–8	On poisoned blood.
43–44	19	118	12	On normal blood.
44–45	18	121	4–8	
44–47	20	118	5–15	
48–49	15	62	6–10	On poisoned blood.
49–50	11	60	5	
51–52	12	58	2–4	
53–54	12	46	2	On normal blood.
3h. 2–3	52	136	14	
3–4	53	132	10	
4–5	52	130	10	Experiment ended.

In every one of the experiments recorded in this paper, the time was marked by a chronometer in seconds. The column marked "No. of Drops" represents the volume of the coronary circulation for a given time. The blood dropped from the end of a tube in the pulmonary artery on a triangular piece of aluminum which was so bent that the blood could not collect upon it but ran into a porcelain dish beneath and was fastened to the lever of an ordinary Marcy tambour. From this ran a rubber tube into a small and very sensitive recording tambour carrying a very light straw-lever which made a sufficiently large excursion for each drop that fell on the aluminum plate. The "number of pulsations" and the "amplitude" of the excursions which were recorded on the

revolving drum were, of course, counted and measured from one and the same record. This record was made by means of a Hürthle membrane-manometer connected with a rectangular glass tube, one end of which had been introduced into the left ventricle, through the left auricular appendix and mitral valves. The record, moreover, made by this piece of apparatus, while, of course, merely recording the number of ventricular contractions and the intraventricular pressure, would also furnish an indication of the relative amount of work done by the left ventricle. The pressure, under which the blood was forced into the coronary arteries, was uniformly fixed at 95 mm. of mercury, except during the period of recovery of the heart from the operation, when it was slightly lower.

JULY 13, 1899. CAT'S HEART. UNDILUTED DEFIBRINATED DOG'S BLOOD. NICOTINIZED BLOOD 1 : 10,000. TEMPERATURE OF BLOOD 39° IN THE BEGINNING, 34° C. AT END OF EXPERIMENT.

Time. P. M.	No. of Drops.	No. of Pulsations.	Amplitude in mm.	Remarks.
2h. 5–6	36	208	10–12	
6–7	40	206	10–12	On poisoned blood.
7–8	64	140	25–35	
8–9*	65	210	25–40	On normal blood for five minutes.
14–15	36	88	18	Auricles beat twice to ventr. once.
15–16	41	80	18	On poisoned blood.
16–17	42	82	18–30	
18–19	47	118	38	On normal blood.
19–20	27	110	18	
22–23	24	70	10–12	Auricles twice to ventricles once.
24–25	20	54	12	Accident to blood supplying app ended up.

Nicotin (Mercks') when used in the proportion of one to twenty-five thousand, as shown in this experiment, diminishes the volume of the coronary circulation, an effect which even a prolonged flow of normal blood through the heart does not seem able to overcome entirely. The number of beats in a given time seems at first very slightly increased, but quickly returns to the normal or falls even below that. As the heart's action grows more feeble under the prolonged influence of nicotinized blood, the auricles beat more frequently than the ventricles, a condition, however, which is changed by the readmission of nicot. blood, but returns on normal blood being turned on again. The amplitudes of the intraven-

tricular pressure-tracings are invariably, and very largely, increased under the influence of nicot. blood; the drug, furthermore, exerts a regulating influence on these tracings and, consequently, on the heart's action itself. Toward the end of the experiment, the heart-beats grew irregular and feeble; normal and well-oxygenated blood being run through for eight consecutive minutes, the heart had almost completely recovered its original vigor.

The blood in this experiment had, unobservedly, reached a temperature 39° C. and, perfusion being in progress before this somewhat elevated temperature was discovered, the heart was working at a rather rapid rate in the beginning. On turning on the nicot. blood of the strength 1 : 10,000, we noticed, in the first place, an increased coronary outflow; then a considerable decrease in the number of pulsations and, lastly, a very remarkable increase in the amplitude of the pressure-tracings. During the last ten seconds of the period marked with an asterisk in experiment, the heart beat at the rate of 312 times per minute. These results occur so uniformly with nicotin, used in certain definite proportions, that they must be looked upon as typical. Almost at the precise moment nicotin. blood reaches the heart, the slowing in the rate commences at once; the slowing gradually gives way to an acceleration and is accompanied by a steady and continued rise in the amplitude of the pressure-tracings, until both acceleration and amplitude have reached a certain maximum which, in every case, is determined by and proportional to the dose of the poison which acted on the heart at the time. The following Fig. 1 illustrates this.

The results also seem to harmonize with those obtained by Traube[12] on curarized, but otherwise intact, animals. Traube found that nicotin caused the pulse and arterial pressure to sink at once to half of what they were in the normal animal, when nicotin was injected, but in about 20 seconds the arterial pressure commenced to rise again, attaining a maximum of about two and a half times its normal amount, the pulse-rate also exceeding its original rapidity.

Such well-characterized tracings as are represented in Fig. 1 are, however, obtained only when nicot. blood flows through the heart for the first time during one experiment. The heart but slowly recovers its original state after the first strong dose of nicotin has been administered and, furthermore, seems to acquire an immunity or tolerance for the poison, shown by a diminished reaction on all

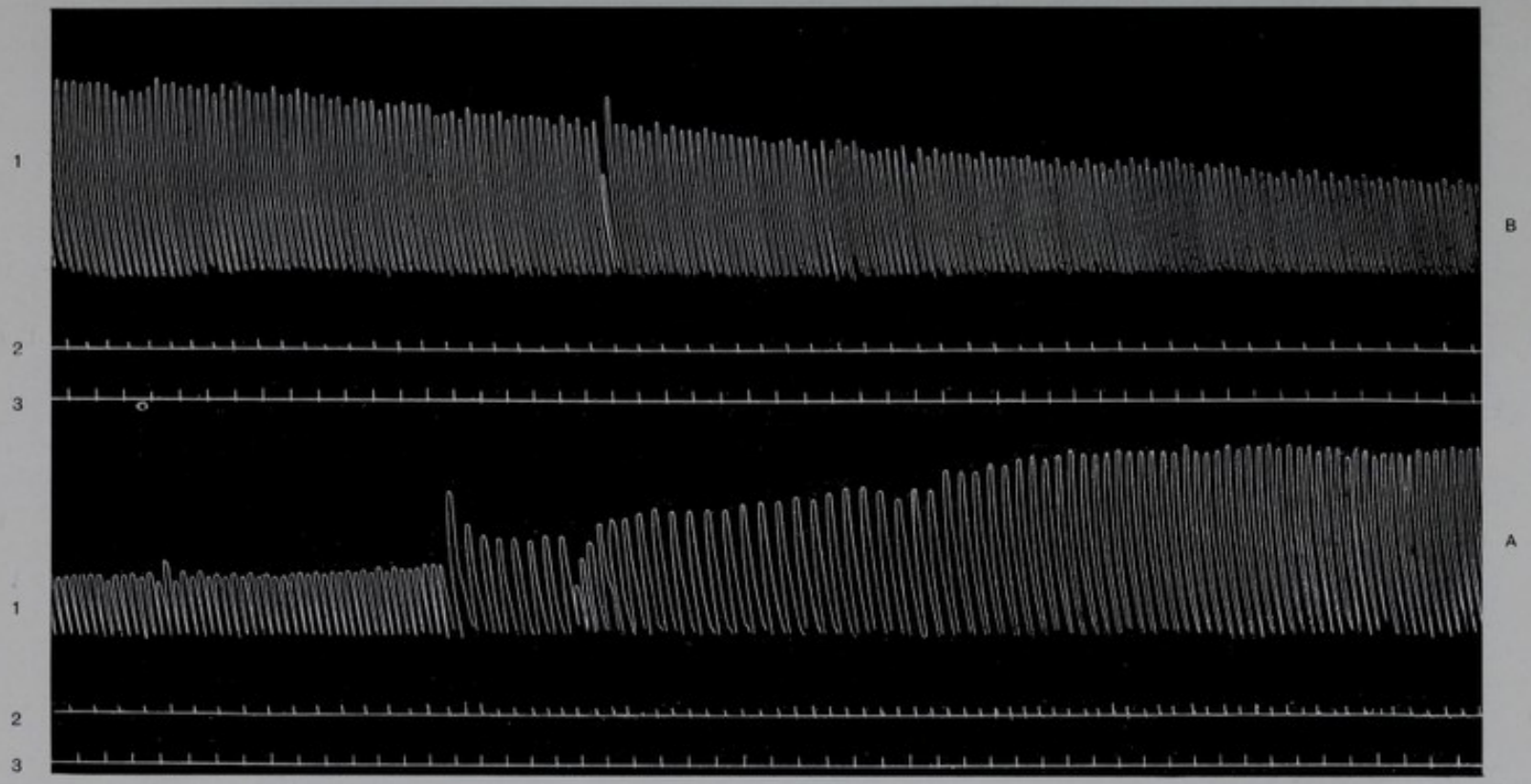


Fig. 1.—From a cat's heart under nicot. blood, 1:7500. Kept on for one minute. Curve 1 in both a and b (which are merely parts of the same tracing and continuous) is the intraventricular pressure-curve, drawn by a Hürthle membrane-manometer, connected with the left ventricle through the auricular appendix and mitral valves. Curve 2 is the quantity of blood passing through the coronary vessels into the right side of the heart and thence out through a tube, placed in the pulmonary artery. Curve 3 is time in seconds. Nicot. blood reached the heart at the mark. Read from left to right and from below upwards.

subsequent administrations of it. Thus, in this experiment, after allowing normal blood to run through the heart for five minutes, poisoned blood does not act as promptly as it did in the beginning nor quantitatively as decidedly, although quite in the same sense, as at first. The experiment also shows the power of nicotin to restore the regular rhythmical succession of beat between auricles and ventricles after this had been broken.

An accident to the blood-supplying apparatus unfortunately put an end to the experiment.

JULY 14, 1899. CAT'S HEART. UNDILUTED DEFIBRINATED DOG'S BLOOD. NICOTINIZED BLOOD 1 : 3000. TEMPERATURE 36° C.

Time. P. M.	No. of Drops.	No. of Pulsations.	Amplitude in mm.	Remarks.
1h. 45–46	74	150	12–15	
46–47	76	145	12–15	
47–48	76	145	12–15	
48–49	84	144	12–15	
49–50	78	140	18	
51–52	80	144	18	On poisoned blood.
[1]52–53	88	122	56	
53–54	68	184	56–15	
54–55	20	168	20–7	
55–56	5	104	4	Heart stopped.

The dose of nicotin used in this experiment being still larger than the one employed in the preceding, we shall notice that the primary showing in the rate is rather more marked, accompanied by a correspondingly large increase in the pressure-tracings and followed almost immediately by a great increase in the rate. Owing to the extraordinary strength of the nicotinized blood, the heart's action went down quickly after having produced its characteristic effect, stopped after a few minutes altogether, and was found to be beyond recovery. Figure 2 represents a part of the record obtained from this experiment, and shows for the first time that the tonus of the heart, under the conditions of the experiment, is at first lowered and then increased.

[1] The slowing in the rate occurred for the most part during the first twenty seconds of this period of observation, and acceleration had begun before the end of this minute. The rate during the first ten seconds was 15, during the last ten seconds of the minute it was 36.

As regards the influence of nicotin upon the volume of the coronary circulation, the records and tracings show that this is at first

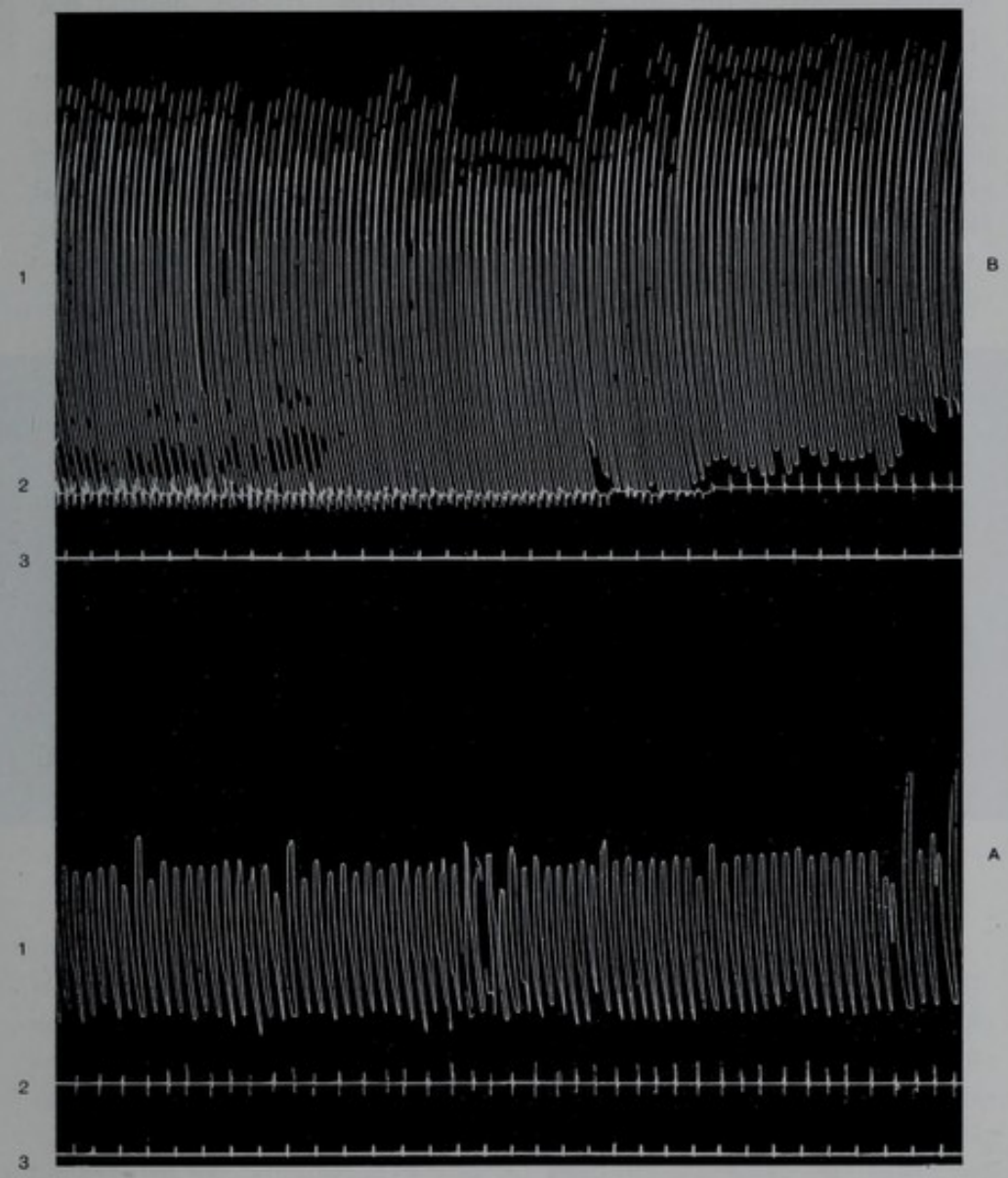


FIG. 2.—From cat's heart of July 14, 1899. Nicot. blood 1:3000. a, heart under normal blood; b, under poisoned blood; shows increased amplitude of pressure-tracings as well as acceleration in rate due to nicotin; primary loss in the tonus of the heart from which it recovers later on; numbers same as in Fig. 1.

increased. This increase, however, is of short duration, beginning to change into a positive decrease even before the typical primary

effect of the poison upon the heart has begun to disappear. It has been repeatedly shown in many published accounts of experiments made on the isolated heart, according to the method employed in this research, that the volume of the coronary circulation, under normal conditions, is entirely proportional to the number and the amplitude of the intraventricular pressure-tracings. Their increase runs, in other words, a parallel course with the quantity of blood circulating in the coronary vessels. This proportion is not manifest during the action of nicotin upon the heart. On the contrary, the amplitude and pressure-curve increase, while the coronary circulation is diminished.

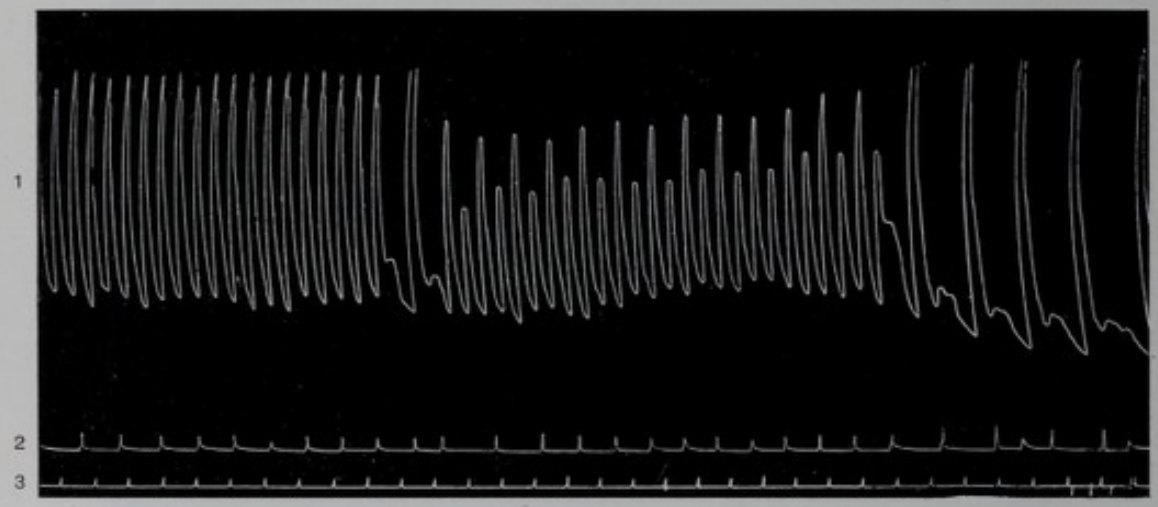


FIG. 3.—From cat's heart, July 12, 1899. Nicot. blood, 1:10,000; numbers as in preceding figures.

The accompanying Fig. 3 is intended to show the effect of the prolonged influence of nicotin upon the heart's action; this is almost as typical as its primary effect upon it. The ventricle drops one regular beat, its contractions not following those of the auricles in regular succession and, finally, the heart either passes into fibrillary contractions or stops beating altogether.

From the evidence afforded by our experiments, we are led to believe, with many others, that the slowing of the heart-rate, noticed to occur under nicotin, is due to a stimulating influence exerted by this substance upon the inhibitory nerve-endings in the heart.

As regards the acceleration which follows the slowing in the

rate so promptly and invariably, our evidence cannot be considered so conclusive. Whether, moveover, the increase in the amplitude of the pressure-curves may be attributed to a similar stimulating influence of nicotin upon augmentor-nerves or not, we are equally left uncertain about.

JUNE 23, 1899. CAT'S HEART. UNDILUTED DEFIBRINATED DOG'S BLOOD. RIGHT VAGUS PREPARED FOR STIMULATION. TEMPERATURE OF BLOOD 36° C. NICOTINIZED BLOOD 1 : 10,000. FIRST COLUMN OF NUMBERS STANDS FOR SUCCESSIVE OBSERVATIONS OF TEN-SECOND-PERIODS EACH, MADE AT INTERVALS IN THE CASE OF THE ELECTRICAL STIMULATIONS, BUT BEING CONTINUOUS WHEN HEART IS ACTING UNDER NICOTIN.

	HEART-RATE.			
Obs.	Before.	During.	After.	Stimulation of Right Vagus.
1	26	26	26	Stimulations were made at intervals varying
2	28	28	28	from one to three minutes, ten seconds
3	28	28	28	at a time.
4	28	28	28	
	Nicotinized.			
1		13		Vagus excited for 9½ seconds.
2		15		
3		24		
4		27		
5		30		
6		34		On normal blood.
				Right vagus stimulated three minutes later,
				ten seconds at a time, at varying intervals.
1	24	12	18	
2	24	16	22	
3	30	20	30	
4	32	22	30	
				An interval of five minutes; stim. resumed.
1	28	28	28	
2	28	28	23	Experiment ended.

According to Pawlow,[7] there exists no constant relation between the slowing of the heart-rate and the blood-pressure consequent upon vagus-stimulation. The exhaustion of the inhibitory action of the vagus, which follows a stimulation of two minutes' duration, manifests itself in three different forms: The most common form is a general increase in the pulse-rate, notwithstanding the stimulation being continued; sometimes the slowing becomes periodical; then again, the rhythm changes suddenly from a slow to a rapid one. Looking over the tracings before us, it is, indeed, easy to find repre-

sentatives of all three forms above-mentioned. If, therefore, stimulation of the inhibition fibres alone fails to account for all the phenomena observed during electrical stimulation of the vagus-nerve, it likewise fails to do so for all the phenomena observed in a heart acting under the influence of nicotin.

There are indeed some very excellent reasons for the assumption that the accelerator nerve-endings in the heart are stimulated by nicotin. In the two preceding experiments, as well as several others not recorded here, during the last ten seconds of the first observations with nicotin, the heart-rate in all is increased over sixty

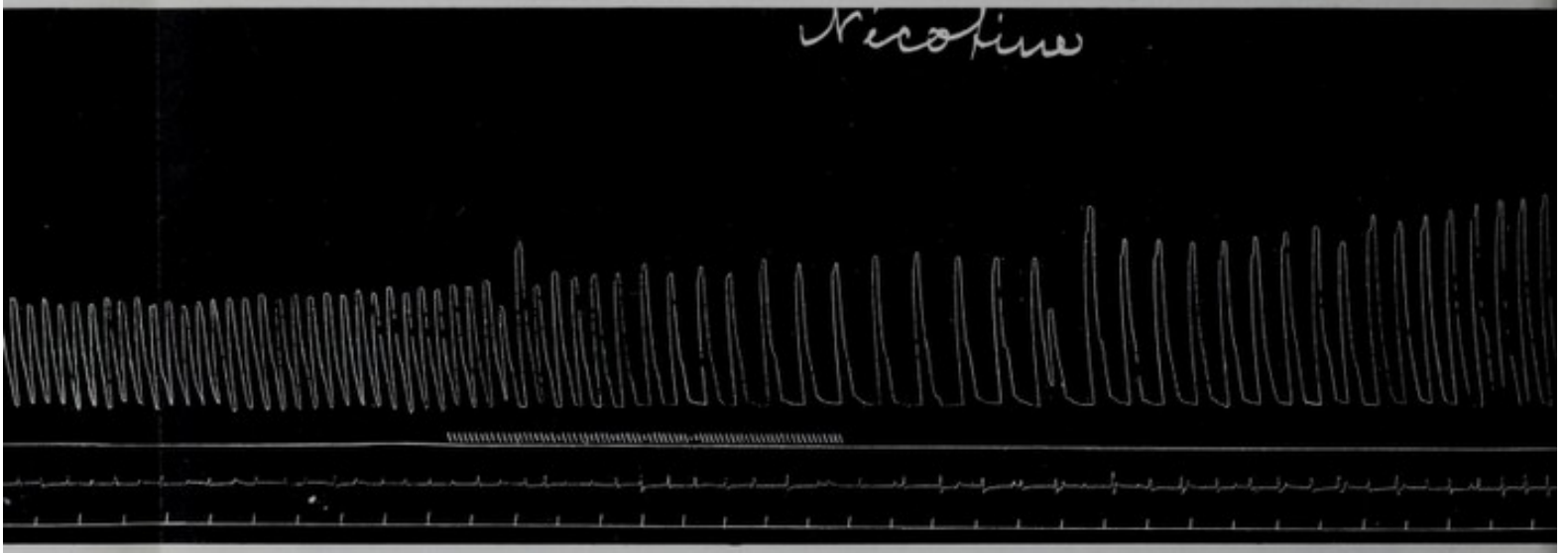


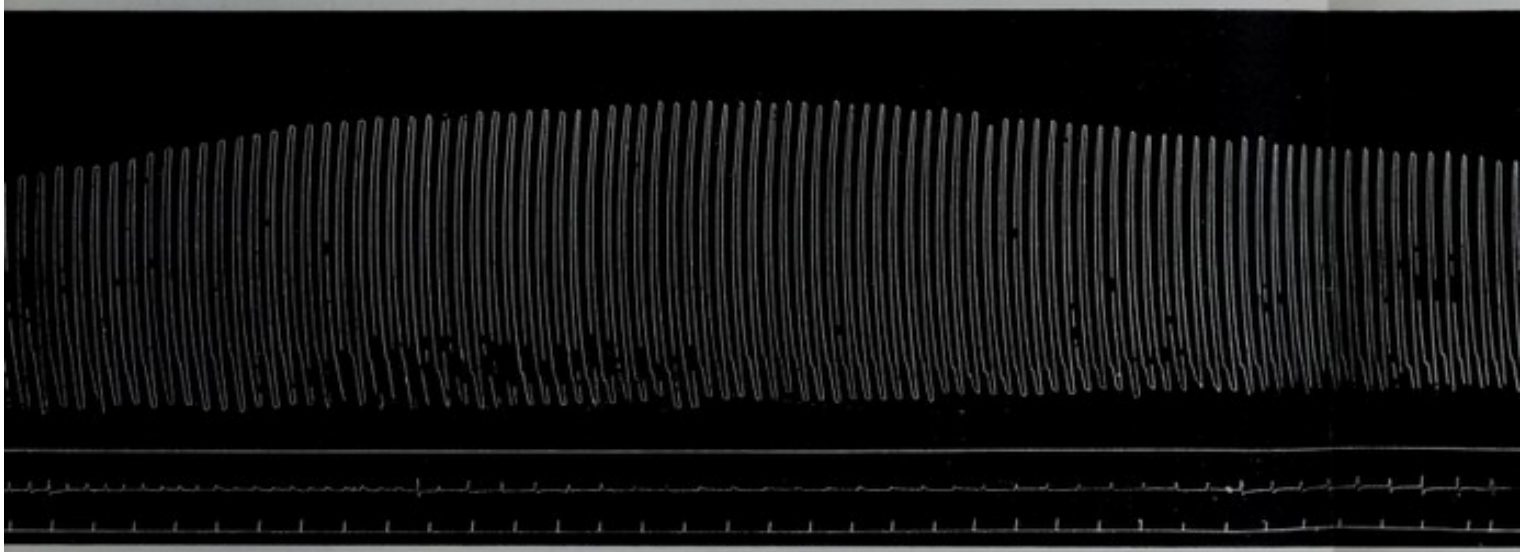
FIG. 4.—From experiment of June 23, 1899 (Porter and Beyer). Cat's heart, fed with dog's blood; vagus-nerve embedded in electrode the line below this was drawn by the writing-point of an electro-magnet, showing the time and the number of interruptions of the

per cent above the previous normal average. Some, of course, would say that this is due to a paralysis of the inhibitory nerves of the vagus through nicotin. We may, however, be permitted to doubt that so large an increase in the rate can be accounted for by the mere exhaustion or paralysis of the inhibitory portion of the vagus-endings alone, even if such a paralyzing effect of nicotin upon these endings was a fact established beyond the possibility of a doubt, which it is not, and which the following experiment is calculated to show.

This experiment was made by Dr. W. T. Porter and myself. The heart was isolated as usual; the left vagus-nerve was exposed, embedded in a Ludwig's hard-rubber electrode and, after every-

thing was made ready for recording the observations, the nerve was stimulated by means of an induced current, interrupted at the rate of seventy times in ten seconds and at stated intervals. Stimulation of the left vagus proving ineffectual, neither altering the rate of the heart nor producing any change in the pressure-tracings after repeated trials, the right vagus was prepared and electrodes attached.

The records of the observations show plainly that stimulation of this nerve also failed to influence the heart-rate in any way. The heart was now put under the influence of nicotinized blood



cted with an inductorium and an interruptor. Nicot. blood 1 : 10,000. The uppermost tracing is the intraventricular pressure-curve; ting current when in operation. The third curve shows the volume of the coronary circulation; the fourth gives the time in seconds.

and the typical nicotin effect became apparent the moment this blood reached the heart. The primary slowing in the rate, due to nicotin, was accentuated by the stimulation of the vagus, electrically, for a period of $9\frac{1}{2}+$ seconds.

Nicotinized blood was turned off and normal blood allowed to run through the heart for three minutes, after which period stimulation of the right vagus was resumed, and the records will show that stimulation this time was effectual, lowering, as it did, the rate regularly and promptly, though less and less greatly, as the heart recovered from the effects of nicotin, until, finally and again, stimulation left the rate, as in the beginning of the experiment and before nicotin had acted on the heart, entirely unchanged.

In view of the results of such experiments as the preceding, it seems difficult to believe that nicotin paralyzes the vagus in any part of its course. And, instead of blocking the way for stimuli passing down the vagus-nerve to the heart, it would seem, on the contrary, that it was aiding in removing such an obstacle.

Nicotin undoubtedly stimulates the inhibitory portion of the vagus-endings in the heart. While it is perfectly conceivable that such stimulation may be carried beyond the point of fatigue, as may that of any other nerve, we are scarcely warranted in calling nicotin a paralyzer for the vagus-endings.

The large increase in the heart-rate noticed by Pawlow (loc. cit.) was most probably due to the stimulation of accelerator fibres running in the vagus, which fibres simply survived the functional activity and endurance of the inhibitory fibres; thus they operated after the inhibitory fibres were already exhausted. The case of nicotin seems to offer an example liable to a similar interpretation. Moreover, Reid Hunt[19] has made the interesting observation that section of the accelerators in the neck, vagi cut, in the otherwise intact animal, causes an impairment in the conductivity of impulses traveling from the auricles to the ventricles (which impaired function is restored on stimulation of their peripheral ends?). This condition, under which the auricles beat more frequently than the ventricles, occurs so frequently during experiments on the isolated hearts of both cold-blooded and warm-blooded animals with drugs, that even a probable explanation to account for this singular and interesting phenomenon would be most welcome.

In the course of our experiments with nicotin, it has been a matter of frequent observation that this drug promptly restores the broken conductivity between auricles and ventricles to the normal. Reasoning from analogy, as we must, the question we would ask is: may this effect of nicotin not be accounted for by assuming that it has a stimulating effect upon the accelerator nerve-endings in the heart? There is the further probability that the phenomenon is a direct result of a temporary fatigue of the accelerator nerve-endings induced by the prolonged chemical stimulation of these endings by nicotin, since it has been shown to be an after-effect, occurring, as it does, after nicotin has acted repeatedly upon the heart and can be removed by renewed stimulation through nicotin. blood.

It has already been mentioned elsewhere in this paper that the second, as well as all subsequent administrations of nicotin fail to produce the same strong and decided reactions on the part of the heart that are produced by it whenever nicotin is admitted to the heart for the first time in one experiment. Since Hunt[13] has shown that a general lowering of the degree of irritability is one of the results of prolonged accelerator stimulation, and which may even produce death in the animal, we are tempted to explain the rapidly acquired " tolerance " for nicotin on the part of the heart on similar grounds. We are led to this conclusion partly also from the fact that the heart-muscle, when removed from under the influence of the nervous regulating mechanism, shows much greater endurance and bears a much larger dose and a much more prolonged influence of the poison, in experiments on the apex, for example, than it does when the entire heart is placed under its influence.

JULY 20, 1899. CAT'S HEART. DOG'S BLOOD $\frac{1}{5}$ DILUTED WITH 0.8 PER CENT. NORMAL SALINE. NICOTINIZED BLOOD 1 : 10,000 CONVALLAMARIN SOLUTION IN NORMAL SALINE 1 : 1000.

Time. P. M.	No. of Drops.	No. of Pulsations.	Amplitude in mm.	Remarks.
3h. 05–6	130	128	12–15	
6–7	130	140	12–15	
9–10	124	140	10–18	Injected 1 cc. convall. sol. then nicot. blood was turned on immediately.
10–11	82	164	18	
11–12	46	176	18	
12–13	24	168	10–15	On normal blood.
14–15	18	162	6–8	
15–16	22	150	4–5	
16–17	26	152	6–8	
19–20	40	148	4–6	
20–21	60	142	3–5	Experiment ended.

Dr. Bogojavlensky, quoted by Pawlow, made the interesting observation that convallaria majalis poisoning caused stimulation of the vagus in the neck to give rise to a sinking and a flattening of the pulse-curve without producing any change in the rhythm, and P., therefore, infers that this drug might, perhaps, serve the purpose of separating the slowing fibres from other fibres that are supposed to run in the vagus, and the following two experiments were undertaken with the view of testing this peculiar action of convallaria in its relation to that of nicotin upon the heart.

This experiment shows that nicotinized blood in the prop. of 1:10,000 turned on immediately after the injection of 1 cc. of convallamarin solution into the arterial cannula causes a rapid diminution in the coronary outflow; an increase—not preceded by a slowing (!)—in the heart-rate and no increase in the amplitude of the pressure-tracings, but rather a decrease which, however, comes on gradually.

This heart did not recover from under the influence of the combined poisons. The coronary circulation, though increasing slightly in volume under normal blood, did not attain anything like its original volume. The pressure-tracings gradually decreased in amplitude, the rate went down slowly, and the heart stopped in systole, showing, apparently, the preponderating influence of convallamarin.[10]

JULY 21, 1899. CAT'S HEART. UNDILUTED DEFIBRINATED DOG'S BLOOD. NICOTINIZED BLOOD 1 : 5000. CONVALLAMARIN SOLUTION 1 : 1000. TEMPERATURE 38° C.

Time. P. M.	No. of Drops.	No. of Pulsations.	Amplitude in mm.	Remarks.
2h. 20–21	136	206	8	
21–22	140	214	8	
22–23	142	214	6	
25–26	102	200	5	
27–28	78	196	5	
28–29	72	200	5	On nicot. blood.
29–30	106	104	5–25	On normal blood.
30–31	74	206	25–10	
31–32	66	214	8–10	
32–33	56	206	6	
33–34	42	202	4	
34–35	64	194	6	Injected 1 cc. conv. sol., then on nicot. blood.
35–36	82	208	6–12	
36–37	30	186	10	
37–38	18	144	6	
38–39	16	140	2	Heart stopped in systole.

Convallamarin, therefore, may be said to prevent the primary slowing of the heart-rate as well as the increase in the amplitudes of the pressure-tracings, both of which are so characteristic of the action of nicotin upon the heart; it also causes a diminished coronary circulation. The drug seems to paralyze the inhibitory vagus-endings as well as the endings of the augmentor-nerves supposed to run in the vagus to the heart.

This experiment shows, first, the typical action of nicotin on the heart's action and, second, that convallamarin prevents the initial slowing of the heart-rate as well as the rise in the amplitude of the pressure-curve. The coronary circulation seems to diminish much more rapidly under the influence of the combined poisons than under nicotin alone.

Thus, both experiments with convallamarin seem to point with a certain directness to the fact that this drug, when injected into the circulation immediately before nicotin reaches the heart, does indeed influence, perhaps paralyze, those nervous structures within the heart, the stimulation of which causes a slowing in the rhythm and an augmentation of the pressure-curve.

The next experiment will show how atropinization will affect the action of nicotin on the heart.

JULY 31, 1899. CAT'S HEART. DOG'S BLOOD ¼ DILUTED WITH 0.8 PER CENT. NORMAL SALINE. TEMPERATURE 37° C. NICOTINIZED BLOOD 1 : 7500. SOLUTION OF ATROPIN IN NORMAL SALINE 1 : 1000.

Time P. M.	No. of Drops.	No. of Pulsations.	Amplitude in mm.	Remarks.
1h. 45–46	120	244	14–24	
46–47	120	240	14–24	
48–49	94	222	24–30	
50–51	86	180	24–30	
51–52	81	156	14–24	Injected 1 cc. atrop. sol. into arterial cannula.
52–53	130	160	22–34	
53–54	98	160	24–32	
54–55	90	160	24–32	
54–55	90	160	22–32	On nicotin. blood.
55–56	48	144	8–10	
57–58	38	114	4–10	On normal blood.
58–59	44	130	8–12	
2h. 1–2	36	124	8–12	
2–3	32	122	8–12	On nicot. blood.
3–4	30	122	8–10	
4–5	22	120	6–8	On normal blood.
5–6	26	122	6–8	
8–9	16	102	6–8	
9–10	12	92	4–6	Experiment ended.

This experiment shows that atropin causes a dilatation of the coronary vessels and, consequently, an increased coronary outflow. The rate is not changed, but the amplitudes are largely increased.

Nicotinized blood now being turned on, the absence of the typical nicotin-effect may be noted. The slowing is gradual and uniformly distributed over the entire period of observation; is, in fact, what follows when the action of large doses of the poison is allowed to continue after the first typical effect of it has passed away. The

FIG. 6.

FIGS. 5-8.—In all the figures, the uppermost curve was drawn by the lever connected with the apex of the heart by a small hook; the lower curve represents time in second-intervals. Fig. 5 shows the heart under normal blood; Fig. 6 gives the change taking place under nicot. blood; Fig. 7 shows the heart's apex still beating under poisoned blood, but taken five minutes later than the preceding; and Fig. 8 shows the resulting decline in amplitude, shortly after which the apex stopped beating altogether.

usual rise in the amplitudes is absent and in its place we find a decline. The coronary outflow, after atropinization of the heart, shows a steady decrease under nicotin.

Nicotin on the Dog's Apex.

Wood says "the action of the drug (nicotin) upon the heart is very complicated and has not yet been well determined." "Upon the cardiac muscle itself, the poison appears to have but very little influence."

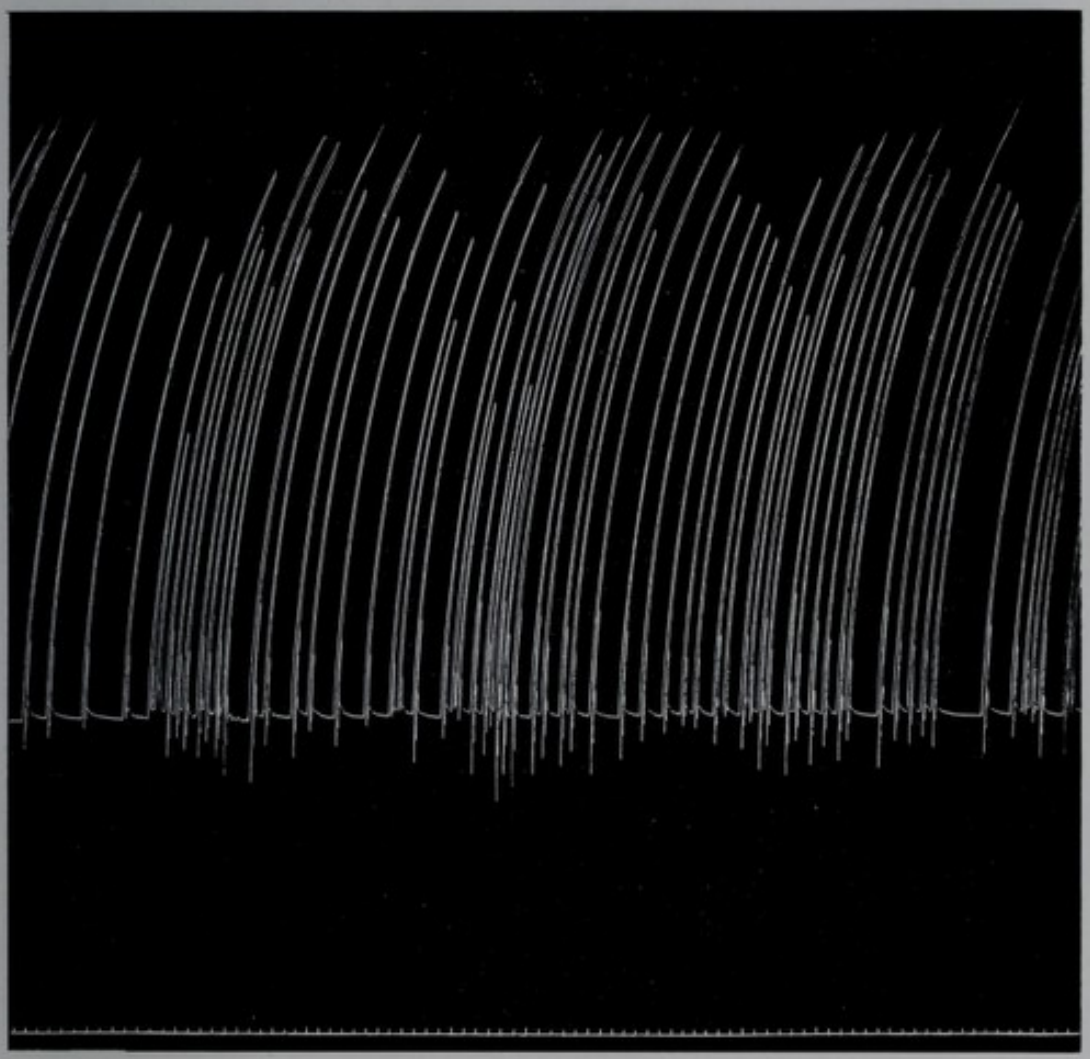


Fig. 6.

In order, therefore, to determine this influence with more exactness, two experiments on the dog's apex were made. The technique of the method, employed in this instance, has been described in sufficient detail by Porter[14] and Cleghorn[15] and need not, therefore, be described again here.

In the first experiment, made on August 1, 1899, nicotin was used in the proportion of 1 : 7500 of undiluted dog's blood. The apex began to beat shortly after the blood-supply was turned on and perfusion had begun under a pressure of 95 mm. of mercury. At first the rhythm was somewhat irregular, but after a few minutes

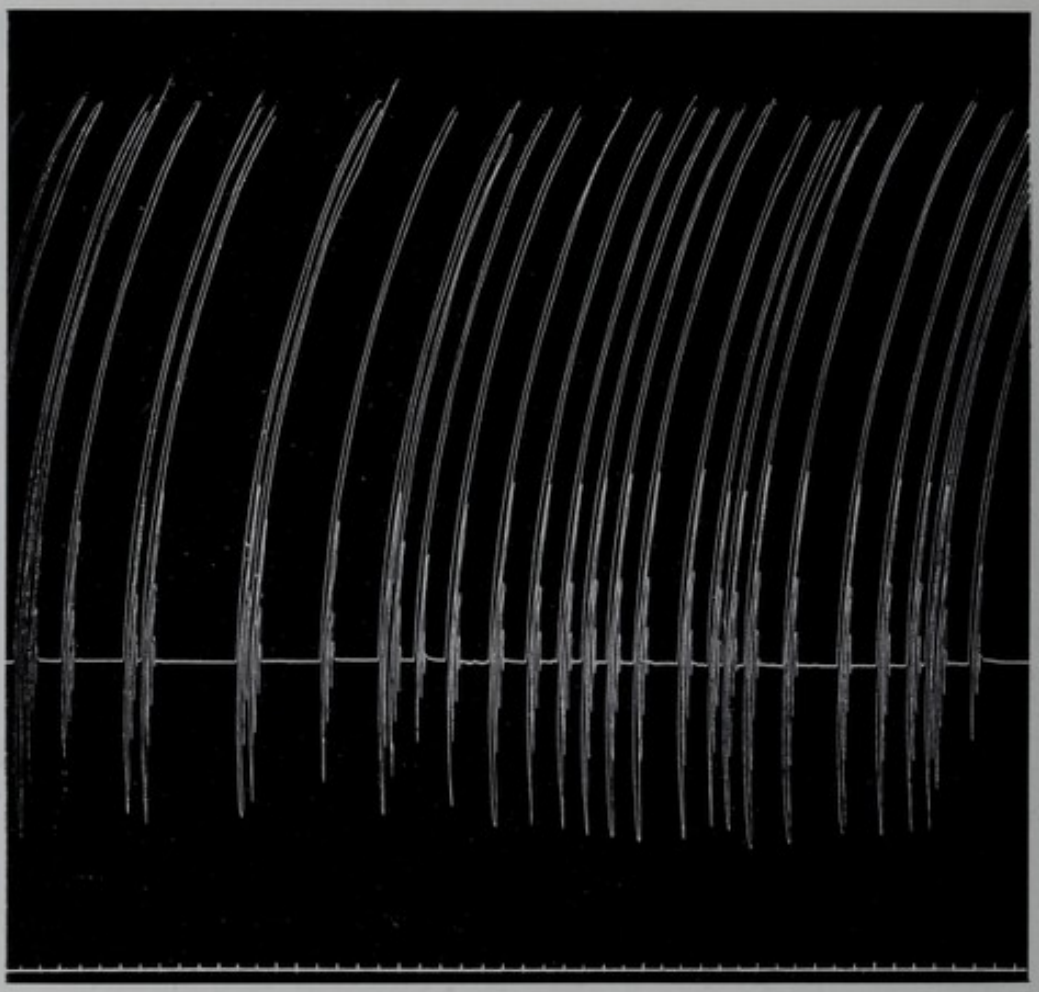


FIG. 5.

contractions appeared in rhythmical groups and at the rate of about fifteen in thirty seconds. Nicotinized blood now being supplied, the apex at once commenced to beat with great force and regularity and at the rate of sixty times in thirty seconds, the amplitude increasing markedly at the same time. There was no preliminary slowing, but the moment nicotin reached the heart or the muscle,

the altered rhythm commenced at once and continued for a few seconds after nicot. blood had been changed for normal blood. Indeed, although the rate went down under normal blood, the amplitude of the tracings continued for many minutes at the same height. Nicotinized blood being turned on for half a minute at

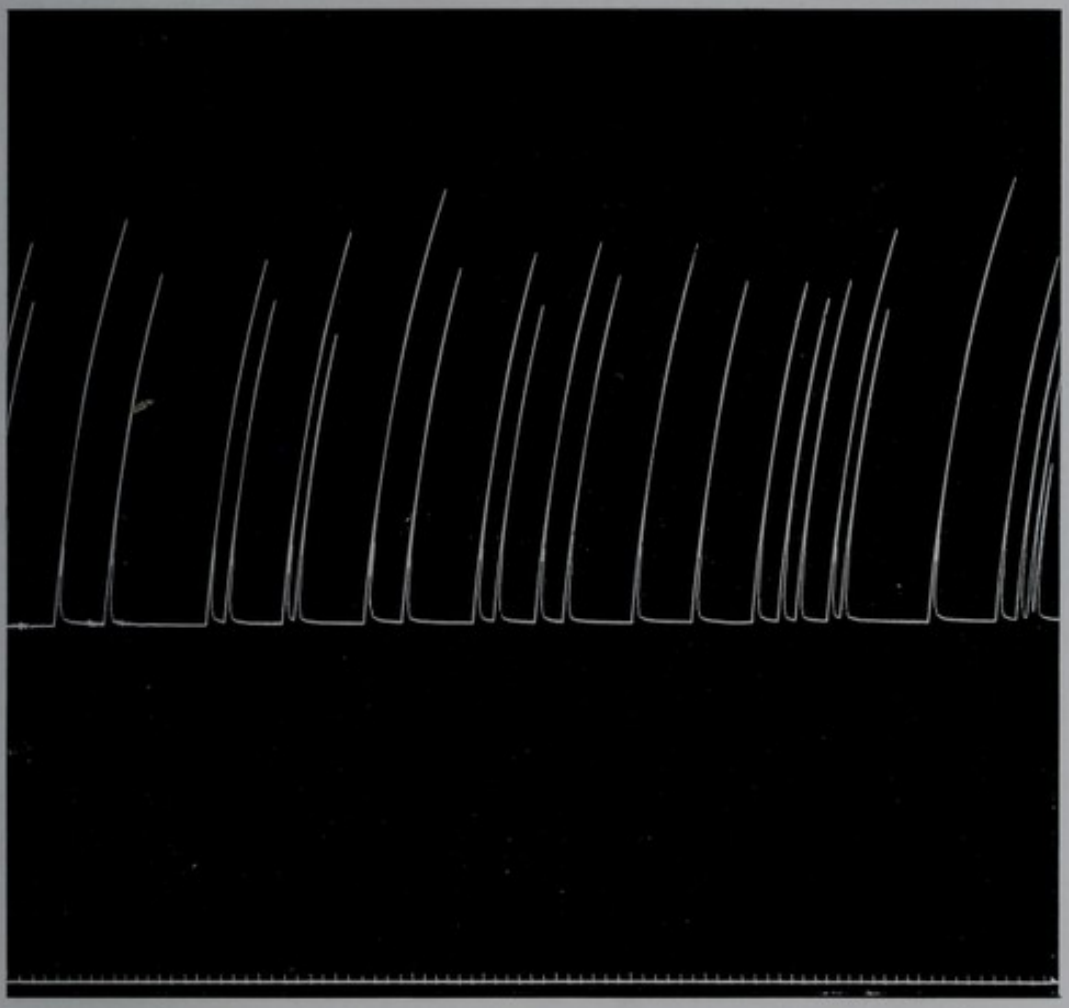


FIG. 8.

a time repeatedly during this experiment invariably increased the rate without further increasing the amplitude. At last, nicotin. blood being kept on to the end, both rate and amplitude went down only very gradually until the heart stopped. Instead of a decrease in the tonus of the muscle occurring under nicotin, as had

been expected, we were able to note a positive increase in it from the beginning to the end of the experiment; see Figs. 5 to 8.

The second experiment, made on August 2, 1897, nicot. blood 1 : 3000, gave results that are in the main identical with those of the first. In accordance with the increased strength of the blood that was used in this instance, the action on the apex muscle was much more decided and marked than it was in the preceding experiment. The rate at once became very rapid and the amplitude of the tracings exceeded by far that in the case of the first experiment (see Fig. 9). This action of nicotin on the apex of the adult dog's heart is in perfect agreement with what Pickering[2] found in the case of the embryonic heart. Pickering found that nicotin causes at first an acceleration, then a depression with a final arrest in diastole. The exception is that the tonus in the adult apex seems to be increased.

Nicotin on the Coronary Vessels.

July 6, 1899. Cat's Heart. Undiluted Defibrinated Dog's Blood. Nicotinized Blood 1 : 50,000. Temperature 38° C. Shortly after Operation and the admission of Blood, Heart went into Fibrillary contractions. The following are the Observations made on the Coronary Circulation during this condition.

Running Time.	No. of Drops.	
2h. 2 10″	44	
10′ 20″	50	
10′ 40″	50	
11′	46	
11′ 20″	44	
11′ 40″	46	
		On nicot. blood.
12′ 20″	24	
12′ 40″	22	
13′	20	
13′ 20″	20	
13′ 40″	19	

Normal blood, passed through the heart for ten minutes after these observations were taken, failed to bring the coronary circulation back to its former volume, and the experiment was ended; heart still in state of fibrillation.

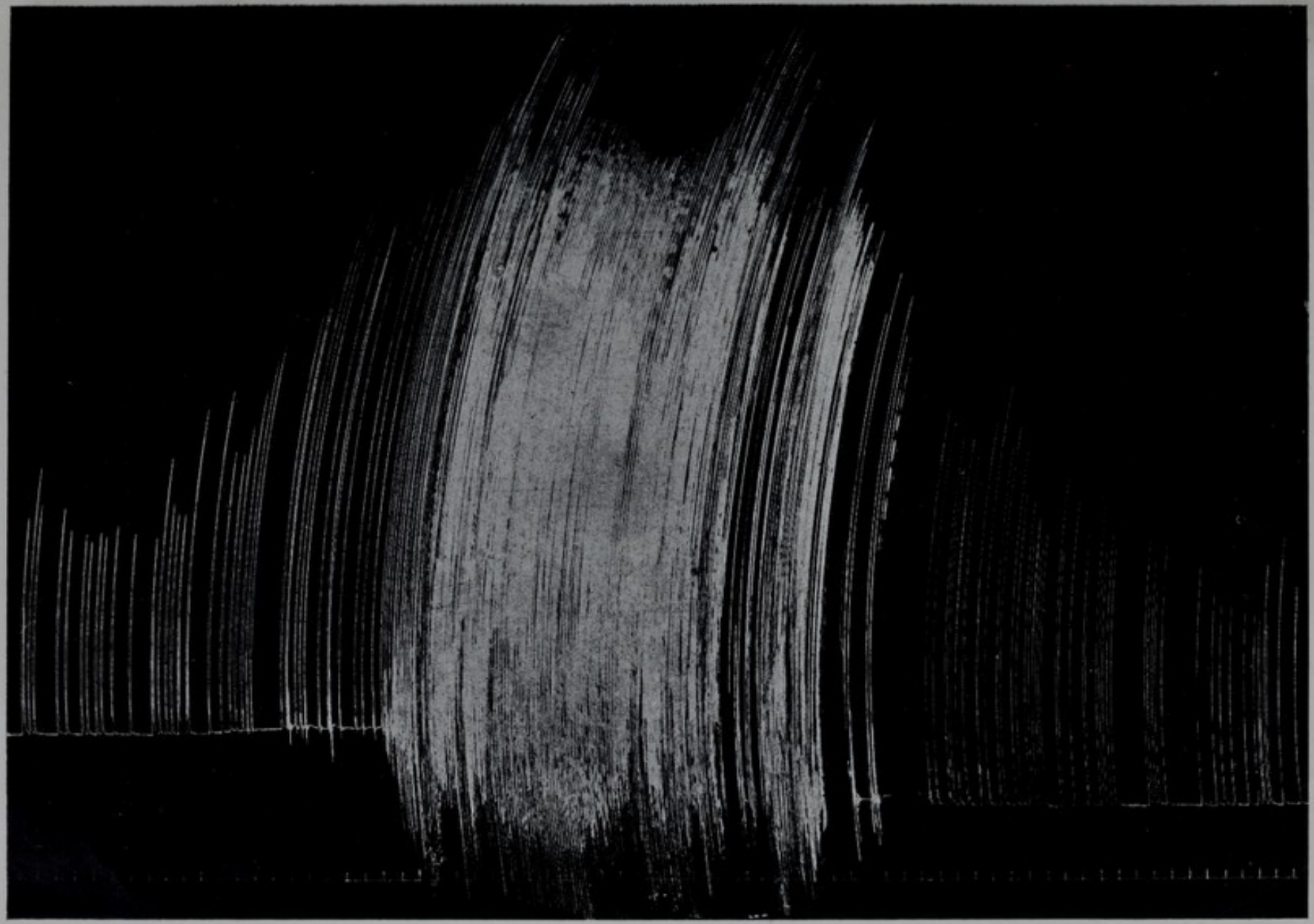


Fig. 9 shows effect of stronger dose of nicotin; time intervals in lower line mean five seconds.

JULY 11, 1899. CAT'S HEART. UNDILUTED DEFIBRINATED DOG'S BLOOD. HEART FIBRILLATING. NICOTINIZED BLOOD 1 : 25,000. TEMPERATURE 37° C.

Time. P. M.	No. of Drops.	Remarks.
2h. 30–31	62	
31–32	68	
32–33	62	
34–35	72	On poisoned blood.
35–36	60	On normal blood.
36–37	50	
39–40	38	
41–42	96	
42–43	100	On poisoned blood.
44–45	64	
45–46	58	On normal blood.
47–48	60	
48–49	62	
50–51	116	
53–54	132	On poisoned blood.
54–55	116	
55–56	104	
57–58	68	
58–59	52	
59–60	44	Experiment ended.

This experiment seems to prove conclusively that nicotin, in the fibrillating heart, when used in the proportion of 1 : 25,000, causes a decided reduction in the coronary outflow; it proves, also, what has been frequently noticed throughout, that nicotin is unable to restore a fibrillating heart to normal action.

In our experiments on the heart, we had occasion to note frequently that nicotin. blood caused at first an increased flow of coronary blood, which was followed by a diminished flow. This might possibly be due to a double action of the nicotin regarding different nerves and which action becomes noticeable at different time-intervals. Atropin, under the influence of which blood-vessels will sometimes dilate and sometimes contract, has this same double action, the nature of which has not yet been fully explained. When, however, the atropin-molecule is split up, it was found that sodium tropate always causes dilatation and tropin hydrochlorate contraction in the blood-vessels of the leg of the dog.*

The increased outflow of coronary blood that follows immediately upon the admission of nicot. blood to the heart, is most prob-

ably due to the increased activity of the heart itself and not so much to the direct action of nicotin on the coronary vessels themselves. Two apparently good reasons seem to argue in favor of this opinion, namely: (1) the increased outflow is of short duration, giving way to a decrease below the normal amount long before the increased activity of the heart, induced by nicotin, subsides; (2) in the fibrillating heart in which nicotin does not cause any very appreciable increased activity nor alters the heart's action in any way, nicot. blood gives rise to a decreased coronary outflow at once and without its being preceded by an increased outflow.[1]

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