The direct action of atropine, homatropine, hyoscine, hyoscyamine, and daturine on the heart of the dog, terrapin, and frog / by H.G. Beyer.

poses is possible, and for this reason no further examination of this point has been made in this paper.

Perhaps the peculiarly wide interest attaching to the subject itself will be considered an adequate cloak for the bareness with which the said facts have been presented.

3.

THE DIRECT ACTION OF ATROPINE, HOMATROPINE, HYOSCINE, HYOSCYAMINE, AND DATURINE ON THE HEART OF THE DOG, TERRAPIN, AND FROG.

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The alkaloid "atropia" was discovered about fifty years ago by Mein, Hesse, and Geiger. Since that time a host of experimenters have been engaged in the investigation of the action of this drug.

So difficult and perplexing, however, has been the study of its physiological properties, that more than half a century has elapsed without bringing the question to a final or generally satisfactory issue, notwithstanding the fact that many of the most prominent physiologists of the present day have been more or less engaged in grappling with the problem.

A perusal of the unusually rich literature of the subject, with its numerous controversies, bears, indeed, ample testimony of the great difficulty which the interpretation of even the most simple physiological phenomena may, at times, present, and points out the many dangers of forming erroneous conclusions from apparently the most precise and accurately performed operations. So far as the action of atropia on the heart is concerned, the best authorities still differ in about the following points: (1) That its action may be fully explained by assuming that a paralyzing influence is exerted on the terminal filaments of the pneumogastrics; (2) that atropia at first stimulates and then paralyzes these filaments; and (3) that it not only paralyzes the terminal filaments of the pneumogastrics, but also stimulates the vasomotor apparatus of the heart.

From some of my former experiments with atropia on the heart and bloodvessels of cold-blooded animals, I was led to conclusions which differ materially from those which are generally accepted by the majority of authors.

The results thus obtained seemed to point clearly to the fact that both the inhibitory and vasomotor apparatus of the heart became excited under the influence of atropia. The reduced ventricular rate fol-

lowing the increased rate was thought to be the result not only of the beginning of exhaustion of the musculo-motor apparatus from over-stimulation, but also of a still existing excitation of the inhibitory apparatus of the heart. This stage of atropine poisoning, however, is shortly followed by diastolic arrest, especially in warm-blooded animals, and to suppose that the inhibitory nerve-apparatus of the heart is still in a state of excitation immediately before diastolic arrest is produced as a consequence of musculo-motor exhaustion due to previous over-stimulation by atropia, would be equal to assuming that the inhibitory nerve-apparatus had never been paralyzed at any time before the death of the whole heart, but, on the contrary, continued in an excited state until the last; in other words, the normal influence of the inhibitory nerve-apparatus over the heart's action is merely inhibited by the over-excited condition of the musculo-motor apparatus and continues inhibited until the latter shows signs of exhaustion.

This view of the subject being clearly opposed to most of the at present received opinions, and the best authorities still differing greatly among themselves, it was our purpose to extend and enlarge the then limited material from which these conclusions had been drawn, and investigate the action of the entire atropine group on the heart of both cold- and warm-blooded animals. It is hoped that the results of these investigations may prove to be a useful addition to our knowledge of the physiological properties of atropine and its allies, not only on the heart but also with regard to its general action.

The method which was employed in experimenting on the frog and terrapin having already been given in detail in some of the previous papers published in this journal, I need here only mention the various steps for the successful isolation of the mammalian heart according to Martin's method, at the same time referring those more especially interested to the more detailed account published by Prof. Martin himself in the *Transactions of the Royal Society*, Part ii., 1883.

Isolation of the Heart of the Dog.—The animal having been placed under the influence of morphia, is fastened to a dog-holder, tracheotomy is performed and a canula introduced into the trachea. The external jugular vein is then dissected out and a canula filled with normal salt solution introduced with its open end pointing toward the heart. Through the latter canula about half a drachm of a one per cent. solution of curare is injected, after which injection artificial respiration is commenced. The vagi are now found and carefully divided. Canulas are introduced into the cardiac end of both common carotids, the arteries being clamped on the cardiac sides of the canulæ. The first two pairs of costal cartilages are now cut away together with the small piece of sternum which they embrace. Then the two internal mammary arteries are ligated just as they pass forward from the subclavians toward the breast-bone. The whole front and sides of the thorax are now cut

away and the right subclavian artery dissected out and tied just above the point where it separated from the common carotid. The superior vena cava is next prepared and a ligature placed loosely around the vessel for subsequently occluding it and tying a canula into its cardiac end.

Proceeding now to the left side of the chest, the subclavian artery of that side is ligated, and, the left lung being gently held aside, the arch of the aorta is isolated and cleared just beyond the origin of the left subclavian; a strong ligature is placed loosely around the vessel ready to be tightened. The azygos vein is next tied, and a ligature placed loosely around the inferior vena cava just as it appears above the diaphragm. Finally, a canula, previously filled with warm blood, is tied into the cardiac end of the superior vena cava, and the animal is prepared to be transferred into the warm, moist chamber in which it is to remain during the experiment.

The canula in the superior vena cava is at once connected with the common outflow-tube of several Mariotte's flasks, which contain the blood of proper temperature intended to feed the heart. The clamps are removed from the carotids, their canulas connected with the outflow-tube, which communicates with a mercury manometer writing on a continuous paper roll. The ligatures, which were but loosely placed around the aorta and inferior vena cava, are now tightened; the heart is washed out for a few moments with the blood from the Mariotte's flask until it is free from clots, and at last the outflow-tube is adjusted so as to secure the proper pressure for the normal working of the organ. The temperature of the circulating fluid may be read off at any time from the thermometer placed into the common outflow-tube.

The remainder of the apparatus consists in a warm, moist chamber, which must be large enough to accommodate the animal on the holder as well as the feeding flasks. The supplying flasks stand on a platform which can be raised or lowered according to the requirements of the particular case. The height of the bottom of the outflow-tube above the heart of the animal is referred to in the experiments as the venous pressure. This pressure, after once being adjusted, generally remains uniform throughout an experiment, and is the same for all the flasks. The outflow-tube, which is connected with the two common carotids, and from the end of which the blood pumped around flows out, and may be measured at stated intervals, is raised to a height which is deemed sufficient to maintain a normal pressure in the coronary arteries. Everything being in readiness, observations are begun a few minutes after the heart has performed normal work.

The drugs which were employed in these investigations came from the firm of Parke, Davis & Co., of Detroit, Mich. Hyoscyamine, hyoscine hydrobromate, and daturine were manufactured by the firm; the sul-

phate of atropine and homatropine hydrobromate had been obtained from Merck's establishment.

ATROPINE GROUP.—Chemically speaking, the remedies belonging to the atropine group, so-called, as atropine, daturine, hyoscyamine, and hyoscine, are probably all identical. Of late their chemical composition has been investigated more especially by Ladenburg, whose researches, however, according to Harnack,[1] have not as yet led to entirely satisfactory results. They all possess the common formula, $C_{17}H_{25}NO_3$, and have been found to consist of a basic tropine or pseudo-tropine, $C_8H_{15}NO$, and tropic acid, $C_9H_{10}O_3$, which has been artificially produced by Ladenburg and Rugheimer.

By boiling these alkaloids with acids or alkalies, they are decomposed into tropine and tropic acid. By the substitution of tropic with other acids, Ladenburg has succeeded in producing certain semi-artificial substances, which he has termed "tropëines."

Atropine is found in atropa belladonna, datura stramonium, hyoscyamus niger, and duboisia myoporoides. Daturine is mentioned as being a mixture of atropine and hyoscyamine. Hyoscyamine is derived from the same plants as atropine, and, like it, may be split up into tropine and tropic acid, but these products were formerly known as hyoscine and hyoscinic acid. Hyoscine is obtained from hyoscyamus niger, but may also be derived from hyoscyamine; it is much more difficult of crystallization, is isomeric with hyoscyamine, and decomposable into pseudotropine and tropic acid.

For hyoscine, Harnack has proposed the name of "Sikeranine," on account of the term hyoscine having formerly been applied to one of the products of decomposition of hyoscyamine. Homatropine is one of the semi-artificial tropëins obtained by the action of amygdalic acid on tropeïne, thus producing *oxytoluglytropeïn*.

So far as their action is concerned, that of atropine and hyoscyamine is supposed to be identical, the two drugs differing only in their effects upon the central nervous system. Hyoscine is said to act, in some respects, stronger, and homatropine, in all respects, weaker than atropine. Tropine is said to have no effect on the pupil, and in the experiments made with some of the semi-artificial atropines (tropëines), where tropic acid has been replaced by other acids, the effect upon the pupil was found to be either wholly negative or very much modified. These observations are of considerable importance, for if, as Gaskell maintains, the dilatation of the pupil is an active phenomenon, due to stimulation of inhibitory nerve-structures, a close connection between the action of the tropic acid molecule contained in atropine and stimulation of inhibitory nerve-structures, seems thereby clearly pointed out. The undoubted double action of atropine stimulating, as we believe, both

[1] Lehrbuch, T. Arzneimittellehre, etc.

inhibitory as well as vasomotor nerve-elements, may yet find a satisfactory explanation through a careful study of the relation existing between its chemical constitution and its physiological action.

Literature of the Physiological Action of Atropia on the Heart.—According to Dr. Lauder Brunton, atropia paralyzes the inhibitory nerve-ganglia. On page 48 of his work on *Pharmacology*, he states that both atropia and curare completely paralyze the motor or efferent nerves; but, while a very large dose of curare is required to paralyze the cardiac and vascular nerves, a very small dose suffices to paralyze those going to the muscles. On the other hand, an enormous dose of atropia is required to paralyze the nerves going to the muscles; while very small doses are sufficient to affect the nerves of the heart and of other involuntary muscles; so that we get rapid circulation, dilatation of the pupil, and restless delirium. On page 53 of the same work, we find it mentioned that atropia, in very minute doses, renders the pulse slow; that larger doses make it exceedingly rapid; and still larger doses render it slow again. The accelerator ganglia are said to remain uninfluenced by the drug. In the opinion of H. C. Wood and others, the latter ganglia are decidedly stimulated by atropia; and Dr. Roberts Bartholow, in the fifth edition of his treatise on *Materia Medica and Therapeutics*, page 435, states "that in some subjects a decided slowing of the heart takes place immediately after the administration of a considerable dose of it (hypodermatically), and in all, most probably, an instantaneous retardation of the pulse-rate; but a very decided rise in the number of pulsations quickly follows." Bartholow, like Wood, believes that atropia not only paralyzes the filaments of the vagus, but also stimulates the cardiac accelerator nerves.

The question naturally arises, How are we to account for this primary slowing of the heart's action which follows the administration of certain doses of atropia? Is it produced by the stimulating influence which the drug exerts upon the vagus-centre, or upon the peripheral filaments, or both? In the work of Dr. Lauder Brunton, already referred to, we find atropia, hyoscyamine, and daturine enumerated among those substances which are capable of stimulating the vagus-centre in the brain, but which paralyze the inhibitory ganglia within the heart.

The peculiar action of atropia might, therefore, be easily explained by its power of stimulating the vagus-centre. It has been experimentally proven by injecting atropine into the carotids, in which case it reaches the brain before it does the heart, and an invariable slowing has been found to take place when the drug is thus administered. But when atropia is administered hypodermatically, as it was in Bartholow's cases, it would naturally reach the heart before it would the brain, and should, accordingly, paralyze the terminal filaments of the vagi in the heart before it could stimulate their centres in the brain. In this manner, however, no slowing of the heart's action could take place, for after the

terminal filaments of the vagus are once paralyzed, no amount of stimulation of its centres in the brain would produce the slightest effect. The view, therefore, which attributes to atropia a like action would seem clearly insufficient to account for all the phenomena observed.

Nothnagel and Rossbach[1] explain the phenomena as being due, not only to an excitation by atropine of the vagus-centres in the brain, but also to a similar influence on its terminations in the heart. According to these authors, the administration of large doses of atropine in man, the rabbit, and the frog, is always followed by a transient slowing of the pulse-rate, which is usually short in man, but which may at once culminate in diastolic arrest in other animals. These same authors further state it, as the result of numerous experiments, that the initial retardation is quickly followed by an acceleration of the pulse-rate, which may become from twice to three times that of the normal; they believe that finally we have paralysis of the inhibitory portion of the vagus nerves, so that their stimulation produces acceleration, rather than slowing.

This explanation by Nothnagel and Rossbach met with great opposition on the part of Harnack, according to whom the smallest doses of atropine produce paralysis of the inhibitory ganglia of the heart in warm-and cold-blooded animals alike; large doses, he said, paralyze the heart itself, but have a slightly irritating influence on it before paralysis occurs. The slowing of the heart's action is explained by Harnack as due to the paralyzing influence of atropia on the heart itself. Harnack is very decidedly against the view which admits that atropia stimulates the vagus in the heart; he even denies the correctness of the explanation given by Gnauck for the primary slowing in the heart's action produced by hyoscine as being due to a direct stimulation of the inhibitory ganglia by this drug.

The controversy seems not yet closed on this all-important point, although the majority of physiologists in Germany incline toward the explanation of the primary slowing given by Nothnagel and Rossbach, while American and English as well as French writers appear as yet slow in accepting it.

According to our conception of this question, there is no point in the whole history of the physiological action of atropia, the decision of which is of greater importance. Unless we know whether atropia paralyzes or stimulates the terminal filaments of the vagus, and under what conditions it exerts its influence, the administration of the drug cannot be said to rest on anything like a scientific basis. In reviewing the literature of the subject, we find the best authorities almost equally divided. The difficulty, therefore, of the correct solution of the question seems fully equal to its importance. No matter which of the two opposing views we may hold, we find ourselves supported by experimental evidence

[1] Lehrbuch J. Arzneimittellehre, etc.

of the first quality, and neither is easily set aside. Thus the well-known experiments of Schmiedeberg and Koppe on the antagonism of atropine and muscarine, and those of Fraser on the antagonism between atropine and physostigmine, which latter were repeated and confirmed by Lauder Brunton, are, to all appearances, so strikingly exact as to bear almost incontrovertible testimony of the fact that atropine paralyzes, and at no time stimulates, the terminal filaments of the vagus. Still it must also be admitted that the fact that atropine antagonizes muscarine-standstill need not necessarily imply that atropine paralyzes and muscarine stimulates the inhibitory ganglia, and that all the phenomena observed depend absolutely on such action. Again, the fact that physostigmine restores the normal function of the vagus over the heart after the latter had been atropized, and artificial stimuli could not be conveyed to it through its fibres, does not necessarily imply that atropia had paralyzed and physostigmine restored the normal function of the inhibitory ganglia of the heart, and our experiments will show that even without physostigmine the function of the terminal filaments and ganglia of the vagus may be fully restored after atropization. No matter what the explanation may be, we may divide the action of atropia on the heart into three distinct stages, namely: (1) The primary slowing, followed (2) by an acceleration, which again is succeeded by (3) a second slowing, which may be either followed by a return to the normal, or terminate in diastolic arrest. These three well-marked stages have been observed by all those who have subjected the drug to careful experimentation. The slowing following the stage of acceleration has been commonly observed in all animals, since von Bezold and Blœbaum first called attention to it; and Mitchell, Keen and Morehouse, and other clinical observers have noticed its occurrence in man, in whom, as a rule, it returned to the normal. This stage, therefore, must be explained, as well as the first two stages, and exhaustion alone will not sufficiently account for it. In presenting the experiments, only those will be given which are typical.

Exp. XXVI.—May 19, 1886. Small adult dog. Heart isolated at 3.20 P. M. under morphine and curare. Venous pressure 22 c. m. Arterial pressure equal to 140 m.m. mercury. Normal nutrient: defibrinated calf's blood. Atropine sulphate used in the proportion of 1 grm. dissolved in 4000 of calf's blood.

Time P. M.	No. of beats in 30 sec.	Work in c.c. per 30 sec.	Temp. of blood in Cent.	The circulating fluids were supplied to the heart at the time mentioned on the same line in the first column.
3.22	80	100	35°	Under normal blood.
23	80	100		
24	80	100		
25	81	102		
26	81	105	35	On atropized blood.
27	81	100		
28	66	85	...	On normal blood.
29	60 : 30	40	...	Auricles contracting twice, ventricles once.
30	60 : 30	0	...	Heart's action very irregular, pressure going down rapidly. Arrested in diastole; slight kneading still followed by solitary contractions.
31	...	0	35	

Exp. XXVII.—May 19, 1886. Small adult dog. Under morphia and curare. Heart isolated at 4.16 P. M. Venous pressure 22 c. m. Arterial pressure equal to 140 m.m. mercury. Normal nutrient: defibrinated calf's blood.

Time P. M.	No. of beats in 30 sec.	Work in c.c. per 30 sec.	Temp. of blood in Cent.	The circulating fluids were supplied to the heart at the time mentioned on the same line on the first column.
4.20	74	110	36°	Under normal blood.
21	74	112		
22	73	108		
23	73	108		
24	73	106	36	On atropized blood, 1 : 8000.
25	70	120		
26	67	126		
27	71	128	...	On normal blood.
28	70	136		
29	70	124	36	On atropized blood, 1 : 8000.
30	70	128		
31	65	138		
32	66	144		
33	67	136		
34	68	130	36.5	
35	68	126	...	On normal blood.
36	70	116		
37	72	102		
38	74	102	36.5	
39	72	102	...	On atropized blood, 1 : 8000.
40	72	130		
41	72	128		
42	71	130		
43	73	130		
44	73	90		
45	70 : 35	54	...	Auricle contracting twice, ventricle once.
46	62 : 28	20	...	Heart action irregular; distended.
47	...	0	37	Stopped pumping wound: pressure sinks; arrest quickly takes place; cutting away pericardium negative; slight kneading still followed by solitary contractions.

Exp. XXX.—Terrapin, 1605 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 c. m. Arterial pressure 30 c. m.

Time P. M.	Rate per min.	Work in c.c. per min.	Temp. Cent.	
2.24	30	55	20°	
27	31	55		
32	31	56		
35	31	56	...	On atropized blood, 0.04 : 100 c. c.
36	31	52		
37	31	53		
38	30 : 15	56	...	Auricles contract twice to ventricles once.
39	30 : 15	55		
40	30 : 15	52		
41	30 : 15	52	20	On normal nutrient.
43	30 : 15	56		
44	30	57		
50	30	53		
57	32	52	...	On atropized blood, 0.03 : 100 c. c.
58	32	50		
59	31	49		
3.00	31	49		
03	30 : 15	?	...	Auricles contract twice, ventricle once.
05	30 : 15	53		
10	30 : 15	52		
15	31	53	20	
20	31	55		
25	31	54		
30	31	...	...	On atropized blood, 0.08 : 100 c. c.
35	31			
36	30 : 15	...	...	On normal blood mixture.
37	30 : 15			
38	30 : 15			
39	30 : 15			
40	30 : 15	20	...	Heart still in good condition. Experiment discontinued.

Exp. XXI.—May 12, 1886. Small adult dog. Under morphine and curare. Heart isolated at 2.38 P. M. Venous pressure 26 c. m. Arterial pressure 144

m. m. mercury. Calf's blood the normal nutrient. Homatropized blood used in different degrees of strength.

Time P. M.	No. of beats in 30 sec.	Work in c.c. per 30 sec.	Temp. of blood in Cent.	The circulating fluids were supplied to the heart at the time mentioned on same line in the first column.
2.49	81	146	35°	Under normal blood.
50	81	146		
51	81	142		
52	82	146		
53	82	148	35	On homatropized blood, 1 : 6000.
54	89	152		
55	86			
56	86	156	...	On normal blood.
58	82	150		
59	84	148		
3.00	86	144	36	
01	88	140	...	On homatropized blood, 1 : 6000.
03	88	164		
04	90	162		
06	89	173	...	On pure blood.
07	89	173	37	
08	90	175	...	On homatropized blood, 1 : 6000.
09	91	180		
10	90	178		
11	88	174		
12	90	.....	...	On normal blood.
13	90	.....	37	
14	90	144		
16	90	136		
17	88	130		
18	89			
19	88	128	...	On homatropized blood, 1 : 2000.
20	86	86	37.5	
21	84	74	...	On normal blood.
22	84	106		
23	84	114		
24	84	128	37.5	
25	84	140		
26	83	140		
27	85	140		
28	85	139	...	On homatropized blood, 1 : 4000.
29	85	120	38	
30	84			
31	84	120		
32	82	120		
33	83	120		
34	84	122	38	
35	84	124		
36	83	112		
37	82	106		
38	82	98	38	
39	82	96		
40	82			
41	81	94		
42	80	82	38	
43	80	82	...	On normal blood.
46	82	78		
48	82	77		
50	81	74		
51	81			
52	82	96	...	On homatropized blood, 1 : 4000.
53	84	80	38	
54	84	76		
55	83	70		
56	84	66		
57	85	56		
58	86	54		
59	87			
4.00	84	40		
01	84	32		
03	82	24	...	Beginning irregular heart's action.
05	76	10	...	Great distention, followed by arrest. Slight kneading followed by single, though ineffectual contractions.

In Experiment XXVI. very strongly atropized blood was used, and the effect produced by it was, accordingly, very marked. During the first five minutes of observation, while the heart was working under normal calf's blood of the temperature of 35° Cent., the rate kept at 80

to 81 beats per thirty seconds, and the amount of blood pumped round in half a minute varied from 100 to 105 c. c. From 3 h. 26 m. to 3 h. 28 m., judging from the quantity of blood which ran through the heart during these two minutes, the latter had been exposed to the influence of about 0.05 grm. of the sulphate of atropia. The rate was quickly reduced from 81 to 66 beats in thirty seconds, the work done from 105 c c. to 40 c. c. for the same period of time; then the heart's action became irregular, the auricles beating at the rate of 60 times to the ventricle 30 times, the work being *nil;* at last the action of the heart became still more irregular, the pressure suddenly went down, and diastolic arrest ensued, mechanical stimulation, however, still being followed by single, and not very powerful contractions. This is the typical result which follows the admission of strongly atropized blood into the mammalian heart.

In Experiment XXVII. atropized blood of only half the strength of that used in the preceding experiment was employed, and the result, as may be seen, is quite different. An increase, instead of a decrease, in the amount of work done may be noticed, accompanied by a slight decrease in the rate, followed by an attempt on the part of the latter to return to the normal. All this occurs while atropized blood is still circulating through the heart, but becomes much more apparent after this is withdrawn, and normal blood is again allowed to flow through. Finally, after repeated atropization, we obtain the effect of large doses of atropine on the heart, namely, rapid reduction of rate and work, irregularity in its action, and arrest in diastole.

In these, as well as in other similar experiments, after diastolic arrest was apparently complete, gentle kneading of the ventricle was still followed by contractions, showing that the muscular substance of the heart was still in possession of a certain amount of irritability.

In all the experiments made with homatropine on the mammalian heart, its effects were found to be identical with those of atropine used in very small doses. Its influence upon the inhibitory nerve-apparatus of the heart is decidedly less powerful than that of atropine, which is in apparent accordance with its effect upon the pupil, which is but transient when compared with that of atropine. Experiment XXI. has been selected to represent the typical action of homatropine on the mammalian heart, as well as that of very small doses of atropine. An examination of this experiment shows that during the first three observations which were made with homatropized blood, the rate is slightly increased, and the work done very considerably augmented. Homatropized blood of the strength of 1 : 2000, however, invariably reduces both rate and the work done, while when it is used in the proportion of 1 : 4000, or even less strong, it produces the opposite effect. Blood of this strength was kept circulating through the heart for 15 minutes, and, while no

increase in the rate or the work done was noticed, both were only very slowly and gradually reduced, the former from 85 to 80, the latter from 140 to 82 c. c. per 30 seconds. Atropized blood of the same strength in all the experiments made with it on the mammalian heart, never failed to produce diastolic arrest within three to four minutes. The most marked feature, however, in the effect produced by very small doses of atropine or medium doses of homatropine, is an acceleration in the heart's action, followed by a slowing, instead of, as is the case with the medium doses of atropine, at first a slowing, followed by an increase in the rate. This apparently contradictory result will be explained satisfactorily later on.

Experiment XXX. on the heart of the terrapin, represents but a portion of an experiment published elsewhere, but which, nevertheless, may with propriety be reproduced here, for the reason that it represents in a typical manner the effect produced by large drops of atropine on the heart of cold-blooded animals. The point which it is desirable to emphasize, is the reduction, by certain definite doses of atropine, of the rate of the ventricle, that of the auricles, though much weakened, remaining numerically unchanged. It happens, after atropized blood of about the strength of that used in this experiment has circulated through the heart a certain length of time, that there follows a period during which the rate of the ventricle becomes just half that of the auricles. This change in the ventricular rate comes on suddenly as a rule. After awhile, however, atropized blood being kept on, the ventricular rate is still further reduced, and, finally, diastolic arrest of the entire heart ensues. During this stage of atropization, the ventricle is from twice to three times its normal size, but the work done, in spite of the reduced rate of contraction, is generally increased. In some of my former experiments with regard to this point, published in the *Proceedings of the U. S. National Museum for* 1855, the work done by the heart during this stage is increased 100 per cent. Atropized blood being withdrawn and normal blood readmitted, the ventricle, after a short time, will be found to resume its normal number of contractions in as prompt a manner as it passed from the normal to the reduced rate. This singular phenomenon may be reproduced many times during the course of a single experiment, and the dose of atropine producing it, so graduated as to keep it up any desired length of time.

It is a remarkable fact, that very small doses of the drug never produce this effect. Atropized blood, mixed in the proportion of 1 : 10,000, may be allowed to circulate through the heart for several hours in succession, and no such result will follow, even if the heart, during that time, has been exposed to the influence of a much larger total amount of atropia than would suffice to produce it when used in a more concentrated form. Under these circumstances the rate is increased from three to five beats per minute, the size of the entire heart undergoes great

reduction, its systole is lengthened, its diastole correspondingly shortened, the work done greatly reduced in amount. This condition may go on until it almost resembles one of systolic arrest, the diastole becomes completely abolished, and no blood whatever is being pumped around. Small doses of atropine, therefore, produce an apparently opposite result from that which is produced by large doses, and this is a point upon which it is desired to lay particular stress in this connection.

Thus Bowditch and Luciani found the contractions both of the frog's heart containing the ganglia and of the apex alone, were rendered more powerful by atropine, while Gnauck, on the contrary, found that the contractions of the ventricle were diminished both by atropine and hyoscyamine. Kronecker and Schapiro believed that they had found that both these apparently contradictory results were correct, but at different temperatures. They state that when the temperature is low (70–80° C.) the ventricular contractions are enlarged by atropine, but diminished by it when the temperature rises above 15° C. We believe that this explanation is insufficient, if not entirely wrong. The phenomena observed by Kronecker and Schapiro depend entirely on the temperature of the heart, or the circulating medium, and have little or nothing to do with the action of atropine on that organ.[1] From the experiments which are here published, as well as elsewhere, it is, I think, clear that the difference in the character of the contractions observed by Bowditch and Luciani on the one hand, and Gnauck on the other, as to the effect of atropine on the heart, is a matter of *dose of the drug* rather than of temperature. In experimenting on the heart with circulating media of different degrees of temperature, it will be found that those of low temperature will cause a reduction in the rate as well as an increase in the size of the contractions, and *vice versa*. The heart, therefore, in this respect, and under the influence of blood of different degrees of temperature, behaves somewhat similar to what it does when under the influence of different doses of atropine, larger doses of atropine corresponding in their effect to circulating media of low temperatures, the smaller ones to circulating media of higher temperatures, and this, perhaps, explains the errors made by Kronecker and Schapiro.

EXP. XII.—April 29, 1886. Dog, 5400 grms. Under morphine and curare. Heart isolated at 4.35 P. M. Calf's blood. Venous pressure 16 c. m. Arterial pressure 138 m. m. mercury at start. Hyoscinized blood, 1 : 4000

Time P. M.	No. of beats per 30 sec.	Work in c.c. per 30 sec.	Temp. of blood in Cent.	
4.39	85	75	40°	Under normal blood.
40	85	75		
41	85	75		
42	84	76		
43	85	78	40	On hyoscinized blood.
44	80	50		
45	78	34		
46	74	26	...	On normal blood.

[1] See the author's explanation of the influence of blood in different degrees of temperature on the heart of the terrapin.—Proc. U. S. Nat. Mus., 1885. Washington, D. C.

Time P. M.	No. of beats per 30 sec.	Work in c.c. per 30 sec.	Temp. of blood in Cent.	
4.47	80	40	40°	
48	78	44		
49	78	64	...	On hyoscinized blood.
50	70	33	...	On normal blood.
51	74	30		
52	75	30	40	
53	75	30		
54	74	28		
55	73	26		
56	73	28	...	Arterial pressure fixed at 124 m. m.
57	73	30		
58	73	30	40	On hyoscinized blood.
5.00	67	...		
01	66	13	...	On normal blood.
03	65	24		
04	63	20		
05	63	...		
06	62	24		
08	60	28	40	On hyoscinized blood.
10	58	16		
12	58	8	...	On normal blood.
13	57	0		
14	56	0	...	Arterial pressure fixed at 100 m. m.
16	59	6		
17	64	4		
19	62	0	...	Stopped pumping wound; pressure sinking grad-
20	60	0		[ually.
21	55	0		
22	53	0		
23	51	0	...	Heart greatly distended. Final arrest in diastole.

EXP. XI.—April 29, 1886. Dog, 4970 grms. Under morphine and curare. Heart isolated at 3.10 P. M. Venous pressure 18 c. m. Arterial pressure 150 m. m. mercury. Calf's blood. Hyoscinized blood, 1 : 6000.

Time P. M.	No. of beats per 30 sec.	Work in c.c. per 30 sec.	Temp. of blood in Cent.	
3.16	95	86	38.5°	Under normal blood.
18	94	85		
20	95	85	39	On hyoscinized blood.
21	90	76		
22	86	62		
23	84	60	...	On normal blood.
24	90	56		
26	95	80	39.5	
28	96	76		
29	95	72		
31	94	71		
33	94	71		
34	94	68	40	On hyoscinized blood.
35	89	60		
36	88	50		
37	88	32	...	On normal blood.
39	86	...	40	
40	86	10	...	Pressure begins to go down.
41	85	0	...	Stopped pumping wound.
42	80	0	40	Heart in diastolic distention; arrest.

EXP. XXXI.—May 25, 1886. Small adult dog. Under morphine and curare. Heart isolated at 2.22 P. M. Calf's blood. Venous pressure 18 c. m. Arterial pressure 136 m. m. mercury. Hyoscinized blood contained 1 grm. of the drug in 800 c. c. of calf's blood.

Time P. M.	No of beats per 30 sec.	Work in c.c. per 30 sec.	Temp. of blood in Cent.	
2.31	86	60	35°	Under normal blood.
32	86	58		
33	88	60		
34	88	62		
35	88	65	35.5	On hyoscinized blood.
36	93	50		
37	92	53	...	On normal blood.
38	90	55		
39	94	70		
40	95	70	35.5	
42	97	68	...	On hyoscinized blood.
43	97	60		
44	99	24	...	On normal blood.
45	103	0	...	Stopped pumping wound.
47	0	0	36	Pressure rapidly sinking; arrest in diastole.

Exp. XXVII.—March 4, 1886. Terrapin, 890 grms. Beef's blood and Ringer's saline (1 : 1). Canulas as usual. Venous pressure 6 c. m. Arterial pressure 16 c. m. Hyoscinized blood (*a*) 0.03 : 100 c. c.; (*b*) 0.25 : 100 c. c.; (*c*) 0.5 : 100 of normal blood mixture.

Time P. M.	Rate per min.	Work in c.c. per min.	Temp. Cent.	
3.20	32	14	18°	Under normal blood mixture.
25	32	14		
30	32	14		
35	32	15		
40	32	15	18	On hyoscinized blood (*a*).
41	35	16		
42	33	16		
43	31	13		
44	31	12		
45	30	12		
46	30	12	...	On normal blood mixture.
55	32	20	19	
4.00	32	15		
03	33	17		
06	33	16	...	On hyoscinized blood (*b*).
07	32	15		
08	32	14		
09	31	11		
10	30	11		
11	28	10		
12	28	11		
13	26	11	20	
14	25	11		
15	25	10.5		
16	25	12		
17	25	13		
18	25	12.5	20	
19	25	12.5	...	On normal blood mixture.
20	25	12.5		
21	25	12		
22	25	13		
24	28	13		
28	29	15		
32	31	13		
36	32	14	...	On hyoscinized blood (*c*).
37	31	13		
38	30	11		
39	28	10		
40	26	10		
41	25	7		
42	24	7		
43	24	6		
44	24	5		
45	24	4		
46	23	3.5	...	Auricles largely distended; contractions barely [perceptible.
47	23	3		
49	22	3	...	Heart's action getting to be irregular. Obser-
55	20	1	21	[vations discontinued.

In Experiment XII. on the heart of the dog, hyoscine was used in the proportion of 1 grm. of the drug dissolved in 4000 c. c. of defibrinated calf's blood. The first observation with blood of this strength shows a decrease in the rate of 9 beats in 30 seconds, or 18 beats per minute, and a total decrease in the work done of 52 c. c. per 30 seconds, or 104 c. c. per minute. The maximum reduction of both rate and work was reached after hyoscinized blood had run through the heart three minutes. Upon the readmission of pure blood, the rate went up to 80 per 30 seconds, or 6 beats, but finally remained at 78; the amount of work done was increased from 26 to 64 c. c. Hyoscinized blood being again turned on, for only one minute, the rate went down suddenly from 78 to 70 and the work done from 64 to 30 c. c. in 30 seconds. Pure blood now readmitted, though slightly increasing the rate, did not give rise to a corresponding increase in the work. During the entire experiment with hyoscine the

rate of the heart was reduced from 85 beats to 51 beats per 30 seconds, the temperature of the circulating blood varying 1° C., being 40° at the beginning and 39° at the end. The heart was finally arrested in diastole, the muscular walls still responding to mechanical stimulation.

In Experiment XI. hyoscine was used in the proportion of 1 grm. to 6000 c. c. of calf's blood. The effect which is produced on the rate is quite as decided as in the preceding experiment, while the work done does not experience the same amount of reduction.

In Experiment XXXI., in which hyoscine was used in the proportion of 1 : 8000, the result, as may be seen, is quite different. An increase instead of a decrease in the rate follows the admission of hyoscinized blood into the heart; the work, however, is slightly decreased. This is the usual result obtained with hyoscine used in this proportion. Out of three experiments including eleven observations, an initial increase in the work done was noticed only once.

In Experiment XXVII. on the terrapin we have an illustration of the effects of both large and small doses combined; the latter causing an increase in the rate and the amount of work done in a given time, the former giving rise to a decided decrease in both.

Comparing the effect of hyoscine with that of atropine on the heart, the great similarity with which both influence that organ must be apparent. The only difference which is noticed is a quantitative not a qualitative one. Both, no doubt, stimulate the vasomotor as well as the inhibitory ganglia and their nerve filaments. Atropine, however, seems to have a somewhat more powerful influence on the vasomotor portion of the nerve apparatus than hyoscine has; besides, hyoscine does not seem to stimulate the muscular substance to the same extent as is done by atropia. Both resemble each other in that larger doses are required to produce inhibitory excitation, and smaller ones only suffice to stimulate the vasomotor ganglia. As in the case of atropine, diastolic arrest is brought about by stimulation of the inhibitory nerve apparatus and the accompanying musculo-motor exhaustion.

Exp. VII.—April 27, 1886. Dog, 5445 grms. Under morphine and curare. Heart isolated at 3 P. M. Calf's blood. Venous pressure 15 c. m. Arterial pressure 134 m. m. mercury. Hyoscyamized blood, 1 : 4000.

Time P M.	No. of beats per 30 sec.	Work in c.c. per 30 sec.	Temp. of blood in Cent.	
3.08	60	80	34°	Under normal blood.
09	60	80		
10	63	75		
11	65	70		
13	70	65	35.5	
15	70	65		
16	70	60		
17	69	65	...	On hyoscyamized blood.
18	61	49	36	
20	60	35		
22	60	30	...	On normal blood.
23	70	22		
25	71	46		

Time P. M.	No. of beats per 30 sec.	Work in c c. per 30 sec.	Temp. of blood in Cent.	
3 27	72	44		
29	71	42	...	On hyoscyamized blood.
31	62	25		
33	57	15		
35	51	0	...	Stopped pumping wound; pressure going down quickly; great distention. Final arrest in diastole. Gentle kneading still followed by contraction.
38	48	0		

Exp. XXXII.—May 25, 1886. Small dog. Under morphia and curare. Heart isolated 3.40 P. M. Venous pressure 22 c. m. Arterial pressure 136 m. m. mercury. Calf's blood. Hyoscyamized blood 1 : 8000.

Time P. M.	No. of beats per 30 sec.	Work in c.c. per 30 sec.	Temp. of blood in Cent.	
3.47	100	110	37.5°	Under normal blood.
48	100	108		
49	100	110		
50	100	112		
51	100	112	37.5	On hyoscyamized blood.
52	94	162		
53	92	158	...	On normal blood.
54	91	98		
55	91	100		
56	91	100	38	
57	91	100	...	On hyoscyamized blood.
58	91	110		
59	92	114		
4.00	92	118	39	On normal blood.
01	92	112		
02	92	102		
03	93	106	...	On hyoscyamized blood.
04	92	80	39	
05	92	68		
06	92	14	...	On normal blood.
07	100	0	...	Stopped pumping wound; pressure rapidly sinking. Diastolic arrest quickly followed.
08	102	0	39	

Exp. XL.—June 2, 1886. Small adult dog. Under morphine and curare. Heart isolated at 3.40 P. M. Venous pressure 22 c. m. Arterial pressure 150 m. m. mercury. Calf's blood. Hyoscyamized blood, 1 : 8000.

Time P. M.	No. of beats per 30 sec.	Work in c.c. per 30 sec.	Temp. of blood in Cent.	
3.44	92	140	40°	Under normal blood.
45	92	140		
46	93	140		
47	94	142	...	On hyoscyamized blood.
48	93	152	40	
49	93	148		
50	88	140		
51	88	138		
52	88	138	40.5	On normal blood.
53	88	132		
54	89	138		
55	90	146		
56	90	143	...	On hyoscyamized blood.
57	86	156		
58	91	148	41	
59	91	138	...	On normal blood.
4.00	92	140		
01	92	140		
02	93	142		
03	93	150	41	
04	93	156	...	On hyoscyamized blood.
05	90	164		
06	91	136	...	On normal blood.
07	92	100	...	Beginning irregularity in the rhythm.
08	92	0	41	Stopped pumping wound; arrest.

Exp. VI.—January 23, 1886. Frog, 110 grms. Beef's blood and Ringer's saline (1 : 1). Inflow canula in inferior vena cava. Outflow canulas in two aortic trunks. Venous pressure 4 c. m. Arterial pressure 12 c. m. Hyoscyamized blood, (*a*) 1 : 10,000, (*b*) 1 : 5000.

Time P. M.	Rate per min.	Work in c.c. per min.	Temp. Cent.	
4.00	35	9	18°	Under normal blood mixture.
05	35	9		
10	35	9		
15	35	9	...	On hyoscyamized blood (*a*).
17	40	9	18	
19	40	9.5		
21	38	11		
23	35	10		
25	35	10	18	
30	35	10		
35	33	10		
40	33	10	18	
44	30	9	...	On normal blood mixture.
46	34	9		
50	34	9		
55	36	8.5		
59	36	8.5	18.5	On hyoscyamized blood (*b*).
5.01	44	10		
03	41	9.5		
07	38	9		
11	35	8.5		
15	35	8	18.5	
20	35	8		
25	34	7 5		
30	34	7	...	On normal blood mixture.
35	31	7		
40	31	7		
45	35	8		
50	35	8.5		
55	35	9	19	Observations discontinued.

In Experiment VII. hyoscyamine was used in the proportion of 1 : 4000. During the first observation with hyoscyamized blood, the rate was reduced 9 beats per 30 seconds, and the work done was decreased from 60 c. c. to 30 c. c. for the same interval. Pure blood being now turned on, the rate promptly returned to the normal, the work, though increasing somewhat, did not again reach the normal amount. The result of the second observation with hyoscyamized blood was a reduction in the rate from 69 to 48 beats per 30 seconds and the work became nil. The heart, especially the ventricle, was largely distended, stopped pumping around, the pressure quickly went down and diastolic arrest followed.

In Experiment XXXII. hyoscyamine was used in the proportion of 1 : 8000. We notice here also a reduction of 4 beats in the rate during the first minute and of 3 additional beats per 30 seconds, during the following two minutes. The reduction in the rate takes place much more gradually in this experiment than in the preceding one, due to the diminished strength of hyoscyamized blood. The later observations show an increase in the rate. The work is increased in the beginning and decreased toward the end of the experiment when the heart is arrested in diastole.

In Experiment XL. we again find at first a decrease and then an increase in the rate due to hyoscyamized blood. This observation is of great importance, and throws considerable light on the character of the action of hyoscyamine on the heart. Hyoscyamine, like atropine, excites both inhibitory and accelerator nerves, the latter being influenced by comparatively small doses which, however, are themselves insufficient to affect the inhibitory apparatus. On the other hand, when the dose of

the drug, applied to the heart, happens to be sufficiently large to stimulate both these nervous structures alike, inhibitory stimulation becomes manifest before that of the accelerator nerves in the same manner as this occurs when electrical stimulation is applied. Hence the primary decrease, as due to the action of hyoscyamine, being followed by a subsequent rise in the rate of the heart.

Experiment VI. on the heart of the frog, shows an initial increase in rate followed by a decrease below the normal. Small doses invariably give rise to an increase in the rate, but if hyoscyamized blood is allowed to run through the heart for a longer time than is sufficient to produce the maximum increase, the rate begins to fall as under larger doses, so that, in this experiment, we have the effects of small as well as large doses. As a rule, the mammalian heart reacts much more promptly than does that of cold-blooded animals.

Exp. XIX.—May 11, 1886. Dog, 9750 grms. Under morphia and curare. Heart isolated 2.38 P.M. Venous pressure 16 c.m. Arterial pressure equal to 146 m.m. mercury. Calf's blood the normal nutriment. Daturine used in the proportion of 1 : 8000.

Time P. M.	No. of beats in 30 sec.	Work in c.c. per 30 sec.	Temp. of blood in Cent.	The circulating fluids were supplied to the heart at the time mentioned on the same line in the first column.
2.41	83	116	36°	Under normal blood.
43	83	115		
44	82			
45	82	115		
46	82	115	36	On daturine blood.
47	85	100		
48	86	100		
49	82	100	...	On normal blood.
50	85	100	36	
51	85	102		
52	89	104		
53	90	102		
54	92	102		
55	96	104		
57	96	110	...	On daturine blood.
58	97	94	37	
59	96	70	...	On normal blood.
3.00	94	70		
01	95	70		
02	96	90		
03	95	109		
04	96	109		
05	97	110	38	On daturine blood.
06	95	90		
07	95	75		
08	93	65	38	On normal blood.
09	93			
10	93	68		
11	93	70		
12	92	80		
13	91	...	38	
14	91	85		
15	91	90		
16	92	...	...	On daturine blood.
17	89	55	38	
18	88	50		
19	86	45		
20	84	20		
21	84	0	38	Heart's action becoming irregular; stopped pumping wound; great dilatation, followed by sudden arrest in diastole.

Exp. XXIII.—February 24, 1886. Terrapin, 960 grms. Beef's blood and Ringer's (1 : 1). Canulas as usual. Venous pressure 7 c.m. Arterial

pressure 18 c. m. Daturine blood, (*a*) 0.01 : 100 c. c., (*b*) 0.02 : 100 c. c., (*c*) 0.04 : 100 c. c.

Time P. M.	Rate. per min.	Work in c.c. per min.	Temp. Cent.	
3.00	35	25.5	...	Under normal blood-mixture.
05	35	26		
15	35	26		
20	36	25		
25	36	25		
30	36	24		
36	36	24	...	On daturine blood (*a*).
37	38	40		
38	36	47		
39	35	40		
40	35	32	...	On normal blood-mixture.
42	36	38		
50	36	38		
55	36	38		
4.00	36	37		
05	37	39		
10	37	40		
15	36	41		
18	36	40	...	On daturine blood (*b*).
19	38	45		
20	36	35		
21	36	35		
22	34	26		
23	33	25		
24	31	28	...	On normal blood-mixture.
25	31	37		
26	30	43	22.5°	
27	31	41		
29	29	45		
35	32	50		
40	33	40		
45	35	41		
50	36	40		
55	36	39	...	On daturine blood (*c*).
56	38	42		
57	34	37		
58	32	30		
59	30	27		
5.00	29	24		
03	24	20		
05	26	18		
07	26	18	...	On normal blood-mixture.
09	26	15	...	Auricles greatly distended; barely perceptible contractions.
15	27	22		
20	28	27		
25	29	28		
30	30	30	...	Auricles almost recovered.
35	32	33	...	Observations discontinued.

Three experiments were made with daturine on the dog's heart, from which No. XIX is selected as representing what occurred in all. Small doses cause a slight increase, large ones a decrease in the rate. Out of the ten observations with daturine, divided between three experiments, a slight increase in the work occurred but once on small doses, which, although giving rise to an increase in rate, as a rule, decrease the amount of work done.

As shown in Experiment XXIII. on the terrapin, a slight initial increase in the rate occurs every time daturine blood is admitted into the heart. The increase in the work amounts at times to 100 per cent., the decrease coming on only after daturine blood has been kept circulating through the heart for a long time, this being equal to the effects of large doses, which latter, when applied to the heart at once, always reduce the rate very considerably. In the terrapin the auricles seem to become paralyzed long before the ventricle does when weak blood has

been flowing through the heart for a long time. Strong daturine blood produces diastolic arrest of auricles and ventricle simultaneously.

Before discussing the phenomena as observed in the foregoing experiments, it will be necessary to review briefly some of the important fundamental points in relation to the innervation of the heart, more especially in the light of the more recent researches on the sympathetic nervous system by W. H. Gaskell.[1]

According to the views most generally received, the heart of both cold- and warm-blooded animals contains three kinds of nervous ganglia, endowed with different functions, namely: motor ganglia, accelerator ganglia, and inhibitory ganglia. The motor ganglia are supposed to be connected by an intermediate apparatus with the inhibitory ganglia on the one hand, and by a similar apparatus with the accelerator ganglia on the other; the former retarding or stopping, the latter accelerating or augmenting the muscular contractions presided over by the motor ganglia.

The researches of Gaskell appear to have placed the existence of at least two such ganglionic masses within the heart, beyond any possible doubt, and these are the inhibitory and accelerator or augmentor ganglia. Gaskell has shown conclusively that both accelerator and inhibitory nerve-fibres go to the heart in cold-blooded animals, as well as in mammals. "The vasomotor (accelerator or augmentor) nerves of the heart," according to Gaskell, "originate in the spinal cord, passing from it in the rami viscerales of the second and third and lower thoracic nerves, as fine medullated nerve-fibres, upward into the ganglion stellatum. From the ganglion stellatum, they either pass directly to the heart or else reach that organ from the annulus of Vieussens and the inferior cervical ganglion."

"When examined in their passage from these ganglia, they are found to be, without exception, non-medullated. These cardiac fibres, then, pass into the ganglion stellatum (ganglion cardiacum basale of Gaskell and Gadow) as fine medullated nerve-fibres, and pass out of it as non-medullated fibres. Their stimulation produces acceleration and augmentation in the heart's action."

"The cardio-inhibitory nerves," according to the same author, "leave the central nervous system in the rami viscerales of the vagus and accessory nerves, retaining the same fine medullated nerve-structure until they reach the heart, where they enter into connection with the ventriculo-auricular ganglia or Bidder's ganglia, and cannot be traced further, the nerves proceeding from these ganglia being almost entirely composed of non-medullated fibres; their stimulation either retards or altogether stops the heart's action."

We have, therefore, not only physiological proof of the existence of

[1] Journal of Physiology, vol. vii., No. 1.

these two kinds of nervous structures, but Gaskell has also added histological proof, which never before had been made out so clearly as was done by him.

Both inhibitory and accelerator nerves being efferent nerves, it now remains for us to pass briefly in review what is known with regard to the afferent nerves of the heart.

The well-known depressor nerve of Ludwig and Thiry carries stimuli from the heart to the brain, and stimulation of its central end produces all the phenomena which ordinarily follow stimulation of inhibitory nerves; its connection with the vaso-inhibitory centre in the brain is, therefore, rendered more than probable. Fibres are also supposed to run within the vagus which cause reflex contraction of the vessels and rise of blood-pressure; these are called the "pressor fibres." According to Lauder Brunton, the depressor fibres of the vagus seem to act on the vasomotor system through the medulla itself, while the "pressor fibres" affect it through a centre in the brain, so that, when the brain is perfect, irritation of the central end of the vagus causes increased contraction of the vessels and increased blood-pressure; but, when the brain is removed, or its function abolished by opium, it causes dilatation of the vessels, and a decrease in the blood-pressure. Most all the sensory nerves of the body may, however, affect the heart reflexly.

Drugs or other stimuli, accordingly, may affect the heart's action in either one or all of the following ways, viz.: (1) *Reflexly*, or through irritation of some sensory nerve; (2) *indirectly*, or through irritation of certain centres in the brain; and (3) *directly* through their influence on the heart and its contained ganglia.

In experimenting with drugs on the isolated heart, we can, of course, only speak of their direct action on that organ, and to this our further discussion on the subject will be confined.

In studying the foregoing experiments, we find, in the first instance, that the enormous acceleration which follows the administration of certain doses of atropine, and which forms so conspicuous a symptom in the second stage of atropine poisoning, is absent. If, however, as Harnack believes, the very smallest doses of atropine are sufficient to paralyze the terminal filaments of the vagus, and that their paralysis is the cause of the great increase in the number of pulsations, then, it would seem that there is no reason why this occurrence should not take place in the isolated heart as well as in that of the intact animal. We find, on the contrary, that the smallest doses of atropine, in the mammalian heart, increase the number of contractions only from four to twenty beats per minute, and in that of cold-blooded animals about five beats.

From a careful examination of the results of our experiments in regard to this point, we have come to the conclusion that the smallest doses of atropine which in the intact animal give rise to a great increase in the

number of pulse-beats, do not only not paralyze the filaments of the vagus, but also are quite insufficient to stimulate them—in other words, leave these structures quite intact. By small doses of atropine the vasomotor apparatus alone is stimulated, and the vagus, though also capable of excitation in much less time even than the vasomotor nerves, requires a much stronger stimulus to excite it. It is well known that, when a stimulus is applied to both these nerve-structures which is sufficiently strong to excite them, the vagus nerves would be the first to respond, and the vasomotors last. This is exactly what takes place when atropized blood is allowed to circulate through the heart of sufficient strength to excite them both. Under these conditions we obtain, first, a decrease in the frequency of pulsations, and afterward the latter will approach the normal once more, or may even exceed that number. This is shown in almost every experiment which we have made. While, however, it takes a stronger stimulus to excite the vagus, the vasomotors, though slower in responding, are aroused by much weaker stimuli, and, therefore, capable of much greater excitation than the vagus by the same stimuli, and hence the probability is very strong in favor of the latter being inhibited to the extent that the vasomotors are over-stimulated.

So far, we have found no evidence in favor of the paralyzing action of atropine on the terminal filaments of the vagus, but, on the contrary, have every reason to believe that these structures are excited by this drug, and Rossbach and Fröhlich are, in our opinion, perfectly correct in believing that the primary slowing in the heart's action due to atropine is caused, in part, by the stimulating influence which the latter exerts on the terminal filaments of the vagus within the heart. This stage does not become apparent on small doses being used, and, for this reason, it may have been overlooked by some.

The second stage, or that stage in which there is more or less acceleration in the heart's action, is, therefore, due to vasomotor stimulation only; this will be the greater, the smaller the dose of atropine used. With doses even slightly larger than are sufficient to excite the vagus simultaneously with the vasomotors, there will be either no acceleration at all or the number of beats above the normal will be very small. This is well shown in those experiments in which extremely small doses of atropine were used, but in which their influence was extended over a long period and the effect of larger doses was, finally, attained. Here we invariably noticed an acceleration followed by a slowing in the pulse-rate. Therefore, according to our interpretation, even during the stage of acceleration the vagus filaments are not paralyzed, but, if at all affected, they must be excited, the stimulation of the vasomotor apparatus being capable of much more intense stimulation than the inhibitory, simply gains the mastery, though for a short period only. In the experiments which were made on cold-blooded animals with very small doses,

a condition of the heart was reached after a certain time which was almost identical with systolic arrest. The ventricle gradually became one-third its normal size, and the auricles diminished in about the same proportion, so that no blood entered the heart and none was consequently pumped around. This would be exactly what we should expect to find, if the stimulation of the vasomotor apparatus of the heart was unantagonized by inhibitory stimulation, and this condition may obtain in the case of atropine being used in very small doses, or when very weak atropized blood flows through the heart a certain length of time, which is insufficient to excite simultaneously the inhibitory apparatus. A further proof of the fact that atropine does not paralyze the vagus filaments, is found in those experiments in which very small doses of the drug having repeatedly produced an acceleration in the pulse-rate, large doses still produced the slowing which is characteristic of them. If the ganglia and filaments of the vagus had been paralyzed by small doses of atropine, it would not have been possible to excite them afterward with slightly larger doses. According to the strength of atropized blood which is allowed to flow through the heart, we may produce either acceleration or slowing; the former is invariably brought about by small doses, the latter by larger doses of the drug. The fact that either may be produced alternately several times during one experiment and on one animal, seems strong proof in favor of small doses of atropine not paralyzing the inhibitory nerves, and of larger doses stimulating instead of paralyzing the structures. The increase in the amount of work done during a certain stage of atropine-poisoning seems to be another proof in favor of this view of the subject. Vasomotor stimulation, pure and simple, causes the heart to beat more frequently, at the same time shortens the diastole and diminishes the carrying capacity of the ventricle, so that a decreased amount of work would be what we should expect to find under these conditions. We find, however, that the amount of work is increased during a certain stage of atropization; this stage is of short duration in the mammalian heart, but lasts much longer in the heart of cold-blooded animals. The immense amount of work which is done during this stage is due to the presence of inhibitory as well as vasomotor excitation, the former favoring the relaxation of the ventricle, hence increasing its capacity; the latter giving rise to increased frequency in the contractions; or in case the latter are decreased in number, as is the case when the inhibitory stimulation is about to gain the mastery, simply adds the extra amount of force required to pump around the abnormally large amount of blood, without increasing the number of the contractions. As soon, however, as the increased number of cardiac contractions gives way to a decrease, we also know that inhibitory excitation is beginning to gain the upper hand, and, unless the heart is quickly withdrawn from under the influence of atropine, diastolic arrest is certain to follow in a

short time. This is the condition which prevails during the so-called third stage of atropine poisoning. Our experiments show that the heart may recover perfectly from this condition, when atropized blood is withdrawn and pure blood is admitted, in time to prevent complete vasomotor exhaustion. The action of atropine being kept up, the heart is finally arrested in diastole as a consequence of vasomotor exhaustion from overstimulation and of inhibitory excitation. The muscular substance of the heart still responding to mechanical irritation even after diastolic arrest is complete, the order in which the different structures composing the heart are paralyzed is probably as follows: First, the vasomotor ganglia and their filaments. Second, the inhibitory ganglia and their filaments. Third, the muscular substance. Thus far, then, all the phenomena observed on the heart under the influence of atropia have been explained by the stimulating influence of the latter on the inhibitory and vasomotor nerve apparatus alone, and without the assumption of the inhibitory nerve apparatus being paralyzed at any time before diastolic arrest is produced. If, however, atropine stimulates the inhibitory nerve structures of the heart, it would seem that it ought also to stimulate these structures in organs other than the heart. The question now arises, What evidence have we of the stimulating influence of atropine on the inhibitory nerve elements supplying organs other than the heart?

When we take into consideration the large amount of work which the heart has to perform, and the powerful contractions which it has to execute constantly, it must become apparent, even without any other evidence to favor the view, that the vasomotor nerve-supply of this particular organ must be enormous when compared to that of other organs. This fact, therefore, must be kept in mind when we attempt to compare the effect of atropine on other similarly innervated organs to that which this drug exerts upon the heart. The pupil and the small intestine are examples of organs which are capable of contraction and relaxation. These organs, like the heart, are supplied with both motor and inhibitory nerve ganglia, but it is not at all likely that, quantitatively, their motor nerve supply is in any degree as great as that of the heart, and therefore the influence of atropine on the nervous structures of these organs cannot form so prominent a feature as it does in the case of the heart. This, of course, must also be true to a certain extent, at least, of the inhibitory nerves going to these organs. Smaller doses of atropine must, therefore, suffice to produce the characteristic effects of the drug than are required in the case of the heart. Nevertheless, in every other respect and if the interpretation of the nature of the action of atropia upon the automatic nerve ganglia of the heart, which is here given, be correct, and it is further to be presumed that the same stimuli must naturally affect allied organs, the histological structure and physiological function of which is similar, alike, or nearly so, then the evidence

ought not to be wanting which favors the similarity or identity of the action of atropine on these organs with that which the latter drug has upon the heart.

With regard to the pupil, Gaskell says:

"It is a striking and highly suggestive fact that the anatomical course and the histological characters of the nerves which dilate the pupil, are precisely similar to the inhibitory nerves of the circular muscles of the intestines, etc., which run in the abdominal splanchnics. In both cases they leave the central nervous system in the thoracic outflow of visceral nerves, the one passing out in those upper rami viscerales directed upward to form the cervical splanchnics; the other in those lower rami viscerales which pass downward to form the abdominal splanchnics. In both cases they leave the central nervous system among the fine medullated fibres of the anterior roots, the special anterior roots which contain the dilator fibres of the pupil being, according to Budge, the second, third, and fourth thoracic—according to my own observations in the dog, more especially the second thoracic; in the frog they pass out in the anterior root of the fourth nerve.

"In both cases they pass over the lateral ganglion (main sympathetic chain) along the corresponding splanchnic nerves to the distal ganglia before they alter their histological characters; the one passing directly to the superior cervical ganglion in the bundle of fine medullated fibres which can be dissected out of the conjoint vago-sympathetic in the neck, the other in the bundle of similar fibres which passes along the abdominal splanchnics into the semilunar ganglia. In both cases, they cannot be traced further as medullated fibres. In the one case they, in all probability, lose their medulla in the distal semilunar ganglion; in the other, with equal probability, in the distal superior cervical ganglion.

"The histological, anatomical, and physiological evidence, all point to the conclusion that in the sphincter muscle of the iris we have yet another example of a muscular stucture supplied by two nerves of opposite character, the one motor, the other inhibitory."

In this manner Gaskell has furthermore shown that the muscular tissues of the visceral and vascular systems are supplied by two sets of nerves, of which the one sets these tissues in activity and causes their contraction; the other inhibits their contractions, and causes their relaxation. The accelerator nerves of the heart, according to Gaskell, belong structurally, as well as anatomically, to the group of vasomotor nerves, and the nerves which retard or stop the heart's action, to the class of inhibitory nerves.

The question, therefore, arises, What analogy do we find in the action of atropine and its congeners, on the heart, and that which these drugs have on other similarly innervated organs? Let us first examine their action on the pupil.

1. *The Pupil.* It is a well-known fact that all the members of the atropine group cause dilatation of the pupil. Dilatation of the pupil, however, according to the latest researches, is brought about by a stimulation of the inhibitory nerves supplying it, paralysis of these nerves being followed by contraction of the pupil. We have, therefore, here an example of atropine stimulating inhibitory nerve-structures as it does in the heart, the analogy appearing to be quite complete. Atropine, how-

ever, is also known to be a vasomotor stimulant when used in very small doses, and stimulation of the vasomotor nerves supplying the pupil would cause its contraction. It is well known that, under conditions hitherto not yet fully determined, atropine sometimes causes transient but slight contraction of the pupil before dilatation comes on. This would be due, according to our interpretation, to too small doses of atropine, and as soon as a sufficient amount of atropine is absorbed, dilatation must supervene; for the vasomotor nerve apparatus, though quickly and intensely stimulated, is rapidly exhausted by too large doses; the inhibitory nerve apparatus, on the other hand, requiring larger doses to set it into full activity. We have here, as in the case of the heart, simply to regulate the dose according to the effect we wish to produce. If the smaller doses of atropine were sufficient to paralyze the inhibitory nerve-apparatus, then contraction of the pupil would have to follow invariably, and the application of larger doses would not change anything in this result. The facts, however, are quite different, as is well known. In the pupil, therefore, we have a very perfect example illustrating the action of atropine on the two kinds of nerve-structures, exactly as this was made out in the case of the heart.

2. *The Intestine.* The best text-books state that atropine, in very small doses, increases the peristaltic movements of the intestine; moderate doses completely arrest these movements, but do not destroy the irritability of the muscular fibres; large doses stop the movements, and also paralyze the involuntary muscular fibres so that they contract either very feebly, or not at all, on direct irritation. In the case of the intestine, we have yet another example of small doses of atropine stimulating vasomotor nerves, and of larger doses stimulating inhibitory nerves.

3. *The Bloodvessels.* In experiments with atropine on the bloodvessels, published by me in this journal for July, 1885, it was clearly shown that atropine causes at first contraction, and then dilatation of these vessels. We have, therefore, here, as elsewhere, evidence of vasomotor stimulation preceding inhibitory stimulation when small doses are used. In the experiment referred to, it was, however, also shown that this initial contraction took place only during the first, and, at most, the second observations, but not the subsequent ones, apparently indicating that the vasomotor nerves lost their excitability long before the inhibitory nerves did.

The evidence in favor of the uniformity of the action of atropine on these different organs might be still further increased, but the examples cited above are deemed quite sufficient to prove our point. Atropine has long been a favorite remedy of clinicians in all painful spasms of involuntary muscles, such as lead colic, simple colic, asthma, the spasms set up by renal and biliary calculi, painful spasmodic contraction of the circular muscular fibres of the neck of the womb in parturition, etc. Clinical evidence, therefore, is not lacking in proof of the fact that atro-

pine and its allies cause the relaxation of involuntary muscular fibres, by their stimulating influence on inhibitory nerves and their ganglia.

From this brief consideration of the more prominent facts brought out by these experiments, the conclusions are as follows, viz.:

1. Atropine, homatropine, hyoscine, hyoscyamine, and daturine are stimulants of the sympathetic nerve apparatus of the heart.

2. The vasomotor portion of this nerve apparatus is affected by comparatively small doses of these drugs, giving rise to either acceleration or augmentation in the heart's action.

3. The inhibitory portion is excited by larger doses only, giving rise to slowing of the heart's action, and, finally, causing diastolic arrest.

4. The muscular substance of the heart is greatly excited by atropine, homatropine, and daturine, and only slightly so by hyoscine and hyoscyamine.

5. The vasomotor nerves and their ganglia are the first to become exhausted, the inhibitory nerves and their ganglia are the next, and the muscular substance is exhausted last of all.

6. The slowing of the heart's action which follows the administration of these drugs in the intact animal, may be sufficiently accounted for by their influence on the inhibitory nerves and ganglia of the heart itself.

7. The acceleration following the administration of certain doses of these drugs cannot be sufficiently accounted for by their action on the accelerator nerves and ganglia within the heart, but is principally due to causes resident outside this organ.

In conclusion, I have to acknowledge my indebtedness to Professor H. Newell Martin for kindly placing at my disposal the well-equipped laboratory under his charge at the Johns Hopkins University, Baltimore, where the experiments on the heart of the dog were made. I also take this opportunity to thank Dr. John C. Hemmeter for valuable assistance rendered me during some of the preliminary work on the dog's heart. The experiments on the heart of the frog and terrapin were performed at the laboratory of the Museum of Hygiene, under the auspices of the Bureau of Medicine and Surgery, Navy Department, Washington, D. C.

TYPHOMALARIAL FEVER.

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The early use of any new medical term is necessarily somewhat indefinite, especially when those responsible for the name have not at first clearly indicated the condition which it is intended to signify. In America the term typhomalarial fever is widely used, if we may judge

from the number of communications on the subject to the medical journals and societies in all parts of the United States and Canada. To the majority of English practitioners, whose experience has been limited to their own country, the name is unfamiliar, and to all it is wanting in accurate definition. Now that we have admitted the term into our nosology, under official sanction, it is well that we should endeavor clearly to understand to what class of cases it should apply. Although it has been used for a quarter of a century, the term typhomalarial fever is not yet so well defined as to bear a universal significance. The London College of Physicians, in its nomenclature of disease, defines it as a *combination of malarial and enteric fevers.*[1] The Section of Medicine at the International Medical Congress held in Philadelphia in 1876, expressed the opinion[2] that "typhomalarial fever is not a special or distinct type of disease, but the term may be conveniently applied to the compound forms of fever which result from the *combined influence of the causes of the malarial fevers and of typhoid fever.*"

A similar though somewhat different view is well stated by Dr. E. G. Russell in a paper on malarial fevers read before the Epidemiological Society of London in 1881.[3] He says:

"When a distinctly malarial complication accompanies and is bound up with true enteric fever, we have the disease that has been recognized, and described by numerous writers of divers periods and lands, as paludo-enteric or typhomalarial fever."

If any distinguishing term is required for such cases, which undoubtedly exist, I should prefer the term "malarial enteric fever" which I proposed in my paper on "Fever at Suakim."[4] The most correct description would be to put down both diseases, enteric fever and malaria, just as one would enter syphilis and scarlet fever if the two coexisted. But again, Dr. Russell says:

"Typhomalarial fever may be taken as affording an illustration of the parallelogram of forces; the malarial poison and the typhoid poison being the two forces acting on a point—the patient—and being represented in magnitude and direction by the two sides of the parallelogram, each produces its full effect in its own proper direction; the resultant being represented in magnitude and direction by the diagonal through this point—*i. e.*, by typhomalarial fever."[5]

Other observers consider typhomalaria to be, not the resultant between two causes, but describe it as enteric fever *modified* or even *induced*, by *malaria.* The chief exponents of this view are Sir Joseph Fayrer and M. Léon Colin. The former writes:

"I believe that in India enteric lesions are apt to come on in the course of miasmatic fever, and that in this condition they not only resemble but *become*

[1] The Nomenclature of Disease. Second edition. London, 1885.
[2] Transactions Int. Med. Congress, Philadelphia, 1876, p. xxxviii.
[3] Transactions Epidemiological Society, vol. iv., part iv., p. 559.
[4] Transactions Med.-Chir. Society, 1885–86, vol. lxix. p. 247.
[5] Transactions Epidemiological Society, vol. iv., part iv , p. 559.