HUNT (R.)

EXPERIMENTS ON THE RELATION OF THE INHIBITORY TO THE ACCELERATOR NERVES OF THE HEART

Presented

BY

REID HUNT, PH. D., M. D.

(FROM THE PHYSIOLOGICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY)

LIBRARY
SURGEON GENERAL'S OFFICE
OCT. 20 1899
654

FROM
THE JOURNAL OF EXPERIMENTAL MEDICINE
VOL. II, NO. 2, 1897

EXPERIMENTS ON THE RELATION OF THE INHIBITORY TO THE ACCELERATOR NERVES OF THE HEART.

By REID HUNT, Ph. D., M. D.
(From the Physiological Laboratory of the Johns Hopkins University.)

Part I.

INTRODUCTION.

The conclusions reached by Baxt* from his experiments upon the relation of the vagus to the accelerator nerves of the heart, published about twenty years ago, seem to have been very generally accepted. He states in this work that when the two nerves are stimulated simultaneously, the result during the stimulation is the same as when the vagus alone is stimulated, and that this is true even when the vagus is stimulated with a minimal and the accelerators with a maximal stimulus.

A few experiments have been published which indicate that this view of Baxt is not tenable. Thus Bowditch,† whose work preceded and suggested that of Baxt, stated that in his experiments in which the two nerves were stimulated simultaneously the accelerator overcame the inhibitory nerves as frequently as the latter did the former, and very similar results had been obtained by Schmiedeberg‡ still earlier; Bayliss and Starling§ showed that when the auricles had been slowed or brought to a standstill by stimulation of the vagus, the ventricles could be made to beat more rapidly by stimulating the accelerators; and Meltzer,‖ after a careful examination of Baxt's tables, expresses the opinion that the conclusion just the opposite to that reached by Baxt is to be drawn from them, viz., that when the

* Baxt, *Arbeiten aus der physiolog. Anstalt zu Leipzig*, 1875, p. 179.
† Bowditch, *Arbeiten aus der physiolog. Anstalt zu Leipzig*, 1873, p. 259.
‡ Schmiedeberg, ibid., 1871, p. 34.
§ Bayliss and Starling, *Journal of Physiology*, xiii, p. 414, 1892.
‖ Meltzer, *Arch. f. Anat. u. Physiol.*, physiol. Abth., 1892, p. 376.

LIBRARY
SURGEON GENERAL'S OFFICE
APR. 30 1900
654

nerves are stimulated simultaneously the effect of the accelerators is seen during as well as after the stimulation. Meltzer also calls attention to the fact that a stimulation of the vagus arising in the centre in the medulla can be overcome by the accelerators, since stimulation of these causes an acceleration when the vagi are intact and in tonic activity.*

An examination of Baxt's tables, moreover, shows that in many cases at least the stimuli which he employed for the two nerves were not at all comparable with each other as regards their strength, if we take their effect upon the heart as the measure, which is evidently the only practicable method. Thus his first table shows that the stimulus applied to the vagus, instead of being a minimal one, was sufficiently strong to cause a slowing of the heart of from forty-four to ninety-one per cent; in most cases the figures were nearer the latter than the former number. On the other hand, the stimulus applied to the accelerators in this series caused in one case an acceleration of thirty-nine per cent; as a rule the acceleration was much less. When the stimuli used for the two nerves differed so widely in their relative strengths we should naturally expect the inhibitory effect to predominate, and the results certainly cannot be regarded as showing that a "minimal stimulation of the vagus can overcome a maximal stimulation of the accelerators."

Still the conception of Baxt that these nerves are not real antagonists, but that a stimulation of the vagus, whatever its strength, will overcome the accelerators even when these are stimulated to a maximum, seems to be the prevailing one,† and has served as the basis for speculations as to the manner in which these nerves affect the heart.‡

* Since the completion of this paper Dr. Hough has told me of some experiments bearing upon this subject which he performed some time ago, but the results of which he has not published; he produced standstill of the heart by stimulating the vagus, and during the "escape" of the heart from this standstill (the stimulation of the vagus being continued) the accelerators were stimulated and a marked acceleration resulted.

† See, for example, Stewart, *Journal of Physiology*, xiii, p. 114, 1892, and Engelmann, *Pflüger's Archiv*, lxv, p. 163, 1896.

‡ Tigerstedt, Lehrbuch der Physiologie des Kreislaufes, p. 271. Leipzig, 1893.

I am convinced from the experiments described in this paper that such a view is not tenable; that as far as the ventricle is concerned (and this was the only part of the heart investigated in these, as was also the case in Baxt's experiments) these nerves do act as pure antagonists to all stimuli which can be fairly compared with each other as regards their strength, and the reason that their true relation is often concealed is readily accounted for by supposing the inhibitory apparatus to be more irritable than the accelerator, just as Rutherford showed that the laryngeal muscles respond to a weaker stimulus of the vagus than does the heart.

Before describing the experiments it may be added, in order that the problem under discussion may be kept clearly in view, that they relate almost exclusively to the effects of stimulating the nerves for short periods of time only, *i. e.*, for periods too short for the results to be complicated by the fatigue of the accelerator mechanism. This was the case in Baxt's experiments also; but in these the duration of the stimulation was often so brief that, as Meltzer points out, we cannot be sure that sufficient time was allowed for the full development of the effect of the accelerators, which are known to have a very variable and often quite long latent period. The effect of stimulating the two nerves together for a very long period is, to a large extent, a different problem from that discussed in this paper; a few experiments bearing upon it, however, will be described in the latter part.

The results of the experiments will be described under three heads: (1) the effect of stimulating the vagus alone, (2) the effect of stimulating the accelerators alone, and (3) the effect of stimulating the two nerves simultaneously. Under the first two heads some points relating to the physiology of these nerves which have been observed incidentally will be described.

The general method of experimenting was the same in all cases. The animals employed were dogs, cat and rabbits, which were always thoroughly anæsthetized in some manner. The heart rate and blood pressure were recorded by a mercury manometer in the usual manner. The currents to the induction coils used for stimulating the nerves were supplied by large storage cells, so that there was little danger of

the current becoming perceptibly weaker during the course of an experiment. Other details as to the technique will be given in the proper place.

Part II.

Stimulation of the Vagus.

Method. — When the effect of stimulating the vagus alone is to be compared with that produced when the accelerators are stimulated at the same time, it is obviously necessary to use some form of stimulation which will give uniform and constant results. This requirement is difficult to meet in the case of the vagus, especially as we must often deal with minimal or almost minimal stimuli. Both Bowditch and Baxt call attention to the inconstancy of the results obtained by stimulating the vagus with the ordinary induced current. It seemed probable that a current the efficiency of which could be governed by the number of interruptions of the primary circuit as well as by the position of the secondary coil, could be made to give more constant results and at the same time admit of finer gradations. To obtain such a current the primary circuit of an ordinary Du Bois-Reymond induction coil was interrupted by an "oscillating rod" kept in vibration by an electro-magnet, the number of interruptions per second being determined by the length of the rod set into vibration. The vibrations were recorded upon a drum kymograph by means of a Desprez signal; a pen marking seconds wrote directly beneath this, so that the rate of vibration could be read off at any time. Three to nine double vibrations per second were found sufficient as a rule. By altering the number of interruptions of the primary circuit and changing the position of the secondary coil, the desired effect upon the heart could be produced when the vagus was stimulated; and it was found that this effect remained very constant during a number of succeeding stimulations as well as during a long-continued stimulation of the vagus. Numerous examples of the effect of stimulating the vagus in this manner for short periods (ten to fifteen seconds) will be given later; here the results of a stimulation continuing for some time will be described.

Effect upon the heart of a long-continued stimulation of the vagus with the slowly interrupted current.—During the course of a more or

less prolonged stimulation of the vagus in this manner slight changes in the rate of the heart occurred; the most common of these was a slight escape soon after the beginning of the stimulation. Hough* has recently described such an escape when the heart was slowed slightly by stimulating the vagus with the ordinary rapidly interrupted current. Judging from Hough's account, I think the escape occurs less frequently and is less complete when the slowly interrupted current is used; indeed, in some cases no escape whatever occurred, and in others, sometimes with, sometimes without a slight escape at the beginning, the rate of the heart decreased slightly but regularly as the stimulation continued. The following experiments will illustrate these points.

1. Cat. Ether anæsthesia. Vagi and accelerators cut. Peripheral end of l. vagus stimulated by current interrupted nearly 4 times per second; secondary coil 12 cm.

Time.			Heart-beats in 10 seconds.	Blood-pressure.	
hr.	min.	sec.			
3	53	50	40	107 mm.	
	54		30½	90+	Stimulus on vagus.
		10	28+	83+	
		20	28+	77	
		30	28½+	74	
		40	29−	71+	
		50	29	68	
	55		30½	64+	
	56		32½	65+	
	57		32	65	
	58		32	64	
4	1				Stimulus off vagus.
4	1	10	40½	99	

2. Cat. Ether. Vagi and accelerators cut. L. vagus; 4 interruptions per second; secondary coil 9 cm.

hr.	min.	sec.	Heart-beats in 10 seconds.	
3	30	30	19½	
		40	17	Stimulus on vagus.
		50	14+	
	31		15−	
		10	15	
		20	15+	
	32		15+	
	33		15½−	

* Hough, *Journal of Physiology*, xviii, p. 161, 1895.

The above experiments have been selected especially to illustrate the fact that the heart escapes from weak stimulation of the vagus after section of the accelerators.

3. Bitch. Morphine and ether, curare. Vagi cut; accelerators intact. R. vagus; $5\frac{2}{3}$ interruptions of primary circuit per second; secondary coil 0 cm.

hr.	min.	sec.	Heart-beats in 10 seconds.	Blood-pressure.	
2	24	40	50	70 mm.	
		50	33+	67	Stimulus on vagus.
	25		32+	63+	
		10	33+	63+	
		20	35½	63	
	26		35½	60	
		30	35½	59+	
		40	45½	67	Stimulus off vagus.
	27		49½	69	

The accelerators were now cut and the vagus again stimulated with the same strength of current.

hr.	min.	sec.	Heart-beats in 10 seconds.	Blood-pressure.	
2	46	10	32½	56 mm.	
		20	22	44	Stimulus on vagus.
		30	20½+	41	
		40	20½−	38	
		50	20½−	37	
	47		20½−	37	
	48		20½−	39	
	49		20−	41	
	50		19½−	42	
	51		18+	43	
	52		18−	43	
	56	10	35+		Stimulus off vagus.

The second of the foregoing tables illustrates the gradual slowing of the heart which sometimes occurs during the course of a prolonged stimulation of the vagus; such results, as well as the entire absence of escape, have been observed most frequently after section of the accelerator nerves, but not exclusively then, as the following shows.

4. Rabbit. Morphine and chloral. Vagi cut. Accelerators intact. L. vagus stimulated; secondary coil at 20 cm.; about 4½ interruptions of the primary circuit per second.

hr.	min.	sec.	Heart-beats in 10 seconds.	Blood-pressure.	
4	2	30	28½−	51 mm.	
		40	26+	48	Stimulus on vagus.
		50	25+	48	
	3		25+	48	
		30	25+	48	
	4		25	48	
	5		25−	48	
	6		24+	48	
	7		23½	48	
	8		23	48	
	10		23	48	
	12		23	48	
	14		23	48	
	16		22½	48	
	17		21½	47	
	18	10	24+	48	Stimulus off vagus.
	19		26−	50	

Another point of interest in this connection is the fact that when the vagus is stimulated in the course of a prolonged stimulation of the accelerators, the heart escapes just as when the vagus is stimulated alone; an experiment illustrating this will be described in the latter part of this paper.

Effect of section of the accelerators upon the result of stimulating the vagus.—My experiments have not been sufficiently numerous or the results sufficiently constant to admit of very positive statements upon this point. In addition to the fact noted above that in general the escape of the heart from slowing produced by stimulation of the vagus seems to be less complete after section of the accelerators, the effect of the stimulation seems to be greater, as described long ago by Sustschinsky.* Thus in the above-quoted experiment upon the dog the maximum slowing before section of the accelerators was 36 per cent; after their section it was 50.7 per cent, when the same strength of current was used. No special attention, however, has been given to this point. Reflex stimulation of the vagus is much more effective after section of the accelerators; this point, however, will be discussed in a later paper.

* Sustschinsky, *Unters. aus dem physiol. Laborat. in Würzburg*, iii, p. 164, 1868.

PART III.

STIMULATION OF THE ACCELERATOR NERVES.

Effect upon the heart rate of cutting the accelerators.—In most of my experiments all the nerves going to the stellate ganglia, except the ventral limb of the annulus of Vieussens, were cut; this gave an opportunity of making observations upon the question of the tonic activity of the accelerator nerves, the evidence for which seems to be accumulating.* The ganglia were thoroughly exposed by opening the thorax and resecting the first ribs some time before the nerves were cut. With the ganglia thus exposed, it was very easy to cut all their connections without doing any injury to surrounding parts, so that the possibility of causing a reflex slowing of the heart through the vagi, in case these were not cut, was much diminished. In almost every case removal of the stellate ganglia caused a considerable decrease in the heart rate whether the vagi were cut or were intact. This is well shown in the experiment upon the dog already quoted (p. 156).

hr.	min.	Heart-beats in 10 seconds.	Blood-pressure.
2	28	49	71 mm.
	29	R. stellate ganglion cut out.	
	30	41+	66
	40	L. stellate ganglion cut out.	
	43	33	52

A point of interest not well shown in the above experiment is the difference almost always observed in the result of removing the right and left ganglia. In almost every experiment removal of the right ganglion caused a considerable slowing of the heart with little effect upon the blood pressure, while removal of the left had less effect upon the heart rate and more effect upon the blood pressure. This occurred whichever ganglion was removed first, and whether the vagi were cut or intact. A rather extreme case is the following:

* Timofeew, *Centralblatt f. Physiologie*, 1889, p. 235. Stricker and Wagner, *Wien. medizinische Jahrbücher*, 1878, p. 370.

Dog. Morphine and ether. Vagi intact.

hr.	min.	sec.	Heart-rate in 10 seconds.	Blood-pressure.
1	20		32½	108 mm.
	25		R. stellate ganglion cut out.	
	25	10	31	
		20	30+	
		30	30−	
		40	29	
		50	28−	
	26		26+	
		10	24+	
		20	24−	
		30	23½	
		40	23	
		50	22½	
	28		22	103
2	4		18	103
	6		L. stellate ganglion cut out.	
	8		18−	60

It will be shown in the next section that stimulation of the right annulus of Vieussens in these cases had a much more marked effect in accelerating the heart than did that of the left; this fact taken with the above seems to indicate that more accelerator fibres pass from the right stellate ganglion than from the left.

Similar results were obtained with cats, as is shown in the following:

Cat. Ether. R. vagus cut.

hr.	min.	Heart-beats in 10 seconds.	Blood-pressure.
11	51	37	106 mm.
	53	L. stellate ganglion extirpated	
	55	36	98
12	24	35	114
	26	R. stellate ganglion extirpated.	
	29	28+	109

Such experiments would seem to indicate that the accelerator centre is in tonic activity, but the possibility that the centre had been stimulated in some manner, as, *e. g.*, by the anæsthetics used—morphine and ether in the case of the dog, ether in the case of the cat—(just as morphine is known to stimulate the cardio-inhibitory centre*) must be remembered. In fact the excessively rapid heart often observed

* Gscheidlen, *Unters. aus dem physiol. Laborat. in Würzburg*, iii, p. 15. 1868.

after section of the vagi in dogs under the influence of morphine is very suggestive of such an action on the part of this drug, but I know of no experiments bearing upon this point. On the other hand this result, viz., slowing of the heart after section of the accelerators, has been observed under such various conditions and when no drug had been used (*e. g.*, when anæsthesia was produced by section of the crura cerebri) that I am inclined to accept the view that the accelerator centre is usually in tonic activity. In a few experiments it was impossible to cause, by stimulation of the accelerators, a greater frequency of the heart beat than existed before section of these nerves; apparently in such cases the accelerators had been in a state of maximal activity when they were cut.

One thing is certain, the slowing of the heart following section of the accelerators in these experiments cannot be referred to a reflex action through the vagus, for it occurred as often in animals in which the vagi had been cut or had been paralyzed by atropine as in those in which the vagi were intact; indeed it occurred more frequently in those in which the vagi were cut, a fact which I think can be explained by the following observation: All my experiments go to show that in properly anæsthetized animals, operative procedures tend to cause a diminution of the tonic activity of the cardio-inhibitory centre rather than to increase it. This is especially marked in dogs under the influence of morphine, upon which so many of my experiments were performed; in such animals I have repeatedly observed an increase of the heart rate, continuing often for several minutes, to follow such an operation as cutting the sciatic nerve, and as this has occurred in animals in which the stellate ganglia were completely removed, it can be explained only by supposing the tonic activity of the vagus centre to have been diminished. What appears to be a similar thing occurred in a few of my experiments upon the accelerators; thus in one the vagi were intact and the heart was beating at the rate of 43 beats in 15 seconds; the extirpation of the stellate ganglia caused an increase in the heart rate of 9 beats in 15 seconds, and this rate was but slightly increased by the subsequent division of the vagi.

The manner in which the slowing following section of the accelera-

tors occurred is interesting; it did not occur immediately upon section of the nerves, but developed gradually in the course of a period varying from one to several minutes. In other words the slowing of the heart from section of the accelerators is strikingly like the return of the heart rate to the normal after stimulation of these nerves. The second of the experiments described above illustrates this point very well.

Stimulation of the accelerators.—The accelerator nerves were stimulated in various parts of their course. In the dog those fibres running in the ventral limb of the annulus of Vieussens were usually stimulated; at times, however, the stimulus was applied to the rami communicantes passing to the stellate ganglion or to the small nerves given off from the annulus or the inferior cervical ganglion. In the cat the "nervus accelerans," as described by Boehm,* was stimulated.

There was seldom any difficulty in obtaining a marked acceleration of the heart when any of the above nerves was stimulated on the right side. The percentage of acceleration varied greatly in different experiments; the maximum effect I observed was an increase from 16 to 32 beats in 10 seconds, or an acceleration of 100 per cent.

Stimulation of these nerves on the left side in both dogs and cats has almost always in my experiments been much less effective than that of the nerves on the right side. Thus in the experiment recorded on page 159, stimulation of the right annulus caused an increase in the heart rate from 19 to 30 beats in 10 seconds, or an acceleration of nearly 58 per cent, while stimulation of the left annulus and of the rami communicantes passing to the left stellate ganglion caused a slight rise of blood pressure, but no change in the heart rate.

Occasionally a slowing of the heart, sometimes with, sometimes without a succeeding acceleration, resulted from the stimulation of the annulus; this occurred especially frequently when the left annulus was the one stimulated. Roy and Adami† describe results similar to these and suggest that they may be due to the stimulation of vasoconstrictor nerves of the coronary vessels. In some of my experi-

* Boehm, *Arch. f. exp. Pathol. u. Pharmakol.*, iv, p. 256, 1875.

† Roy and Adami, *Phil. Trans.*, clxxxiii B, p. 294, 1892.

ments this slowing was evidently a reflex effect through the vagi, for it could no longer be obtained when the vagi were cut. That afferent nerves may pass through the ventral branch of the annulus (especially on the left side) is shown by the fact that when this is stimulated, reflex movements of the legs and of the respiratory muscles sometimes occur; section of the vagi prevents the recurrence of these reflexes.

Stimulation of the accelerators after section of the vagi.—Since the vagi are usually in tonic activity, especially in dogs, we should expect to find the maximum to which the heart can be accelerated by weak stimulation of the accelerators to be greater after section of the vagi than before, that is if we assume that the two nerves are antagonistic. A few of my experiments indicate that this is the case, and I think it not improbable that the reason the others do not is due to the fact that the stimulus used was sufficiently strong to overcome completely the action of the vagi, and consequently the maximum rate was the same before as after section of the vagi. The "after-effect" of the stimulation of the accelerators, however, is markedly prolonged by the section of the vagi.

Since section of the vagi causes an increase in the heart rate, the percentage of acceleration from stimulating the accelerators is less after than before the vagi are cut. Still in such cases I have found no difficulty in obtaining an acceleration varying from 10 to 63 per cent. An acceleration has also been obtained after the administration of atropine till stimulation of the peripheral end of the vagus no longer caused a slowing of the heart.

Such experiments as the above corroborate the results of others, and show how incorrect is the statement, recently made,* that after section of the vagi or the administration of atropine no increase in the heart rate can be caused by stimulation of the accelerators.

* Roy and Adami, *op. cit.*, pp. 267 and 296. These authors describe, nevertheless (p. 246), an experiment in which stimulation of the left annulus caused an increase in the heart rate from 17 to 24½ beats in 10 seconds, after the vagus had been completely paralyzed by atropine.

PART IV.

SIMULTANEOUS STIMULATION OF THE VAGUS AND THE ACCELERATORS.

The results of these experiments will be described under three heads: (1) stimulation of the accelerators during a prolonged stimulation of the vagus, (2) stimulation of the vagus during a prolonged stimulation of the accelerators, and (3) stimulation of the two nerves begun at the same time.

1.

Stimulation of the Accelerators during a Prolonged Stimulation of the Vagus.

This phase of the subject does not seem to have been considered by Baxt. Bearing in mind, however, the great uniformity of the results obtained in a long-continued stimulation of the vagus, this method seems especially adapted to the solution of the problem of the relation of the two nerves.

The following experiment is a good illustration of what has invariably occurred:

Dog. Morphine and ether; curare. Vagi and accelerators cut. R. vagus stimulated; secondary coil at 0 cm.; primary circuit interrupted 5¾ times per second. R. annulus stimulated; secondary coil 10 cm.

hr.	min.	sec.	Heart-beats in 15 seconds.	Remarks.
2	46		49½	
		15		Stimulation of vagus begun.
	47		31½−	
	51		27+	Maximal slowing 43.2%.
	52		28	
		15	58	R. annulus stimulated for 15 seconds.
		30	58½	Acceleration of 108.9%, or 18.1% above the normal rate.
		45	44½	
	53		40½	
	56		39−	Stimulus off vagus.
		30	54½	

The stimulus was taken off the vagus while the after-effect of the stimulation of the accelerators was still evident.

The accelerators were now stimulated alone with the same strength of current as was used in the above. The results were as follows:

hr.	min.	sec.	Heart-beats in 15 seconds.	Remarks.
2	58	30	53+	
		45	75½	R. annulus stimulated for 15 seconds.
	59		77	Acceleration of 45.3%.
3			63	
	2		60	

These results are shown in the plotted curves in Fig. 1.

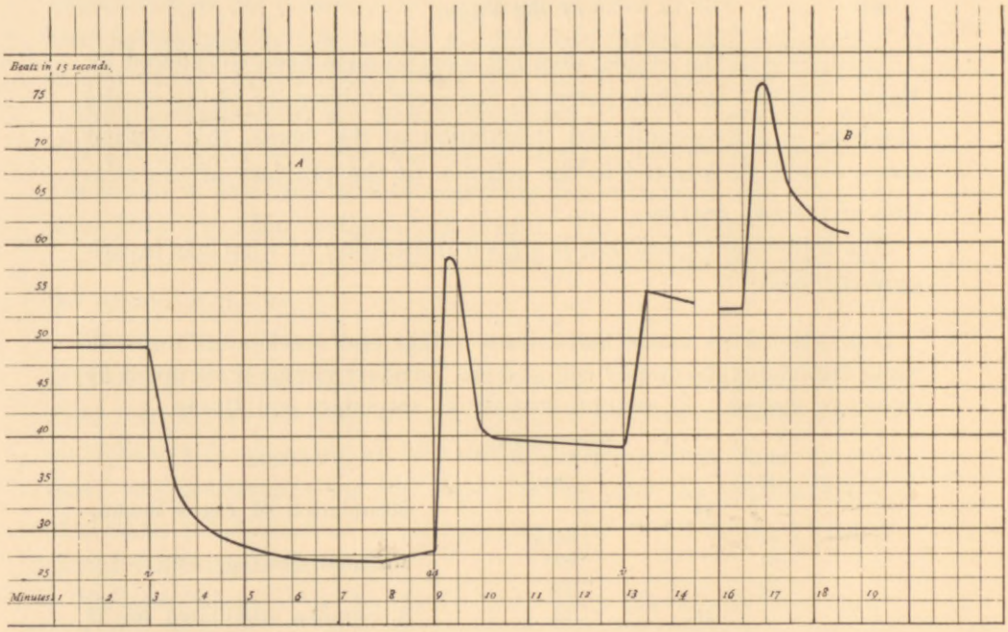


Fig. 1.—Stimulation of the accelerators during a prolonged stimulation of the vagus. The ordinates represent the heart rate in 15 seconds; the abscissæ the time in minutes.

A. The vagus was stimulated from *v* to *v* (10 minutes); the accelerators from *a* to *a* (15 seconds).

B. Stimulation of the accelerators alone (15 seconds).

Comment on these figures is scarcely necessary. They show that a stimulation of the vagus of sufficient strength to cause a decrease of the heart rate of 43.2 per cent is not only completely overcome by a stimulation of the accelerators, but that the latter causes an acceleration of 18.1 per cent above the rate at which the heart was beating

before the vagi were stimulated and an actual acceleration of 108.9 per cent. That the effect of the vagus on the other hand was not lost is shown by the fact that the maximum rate reached while both nerves were stimulated was but 58½ beats in 15 seconds as compared with 77 when the accelerators alone were stimulated; or while the acceleration above the normal rate was but 18.1 per cent in the former case, it was 45.3 per cent in the latter.

It might be thought that if the vagus and accelerators are purely antagonistic, a stimulation of the accelerators of sufficient strength to cause an acceleration of 45 per cent would just neutralize the effect of the vagus or cause but a very slight acceleration above the normal when the vagus was being stimulated with a current of sufficient strength to cause a slowing of 43 per cent, while in this experiment there was an acceleration of 18 per cent. However, it must be remembered that in general a slowly beating heart is more powerfully influenced by a stimulation of the accelerators than is one beating more rapidly; moreover, there are so many other factors entering into the problem that we could scarcely expect the result to be the exact algebraic sum of the results of the separate stimulations.

Results similar to the above have been obtained in experiments upon cats,* as the following table will show.

Cat. Ether. Vagi and accelerators cut. L. vagus stimulated; 4 interruptions per second of primary circuit; secondary coil 10 cm. R. annulus stimulated; secondary coil 11 cm.

hr.	min.	sec.	Heart-beats in 20 seconds.	Remarks.
2	53	20	42	
		40	23	Stimulation of vagus begun.
	54		20½	
	55		29	
	56		30	Heart slowed 28.5%.
		20	45½	Accelerators stimulated for 20 seconds.
		40	38	Acceleration of 51.6%
	57		34	
	58		30½	
4	2		30	
	23		30	Stimulus off vagus.
		20	38	

* Dr. D. W. Harrington and I have since obtained similar results in an experiment upon an opossum.

2.

Stimulation of the Vagus during a Prolonged Stimulation of the Accelerators.

The following experiments will serve to illustrate this side of the subject; a somewhat similar experiment will be described in the next section of this paper.

Young dog. Morphine and ether; curare. Vagi and accelerators cut. R. vagus stimulated; primary circuit interrupted $3\frac{5}{6}$ times per second; secondary coil at 4, later at 5 cm. L. annulus stimulated with ordinary induced current; secondary coil 15 cm. The vagus was first stimulated alone twice for the purpose of comparison.

hr.	min.	sec.	Heart-beats in 15 seconds.	Remarks.
12	35		48−	
			41½	Vagus stimulated 15 seconds; coil 5 cm.
	37		47	
			40−	Vagus stimulated 15 seconds; coil 4 cm.
	41		46	
		15	57	Stimulation of accelerators begun.
		30	56	
		45	55+	
	42		46−	Vagus stimulated 15 seconds; coil 4 cm.
		15	54+	
	43		54	
		15	48	Vagus stimulated 15 seconds; coil 5 cm.
		30	52½+	
	46		53½	
		15	46	Vagus stimulated 15 seconds; coil 4 cm.
		30	52+	
	47		53	
		15	47	Vagus stimulated 15 seconds; coil 5 cm.
	48		53+	

Some of these results are shown in Fig. 2.

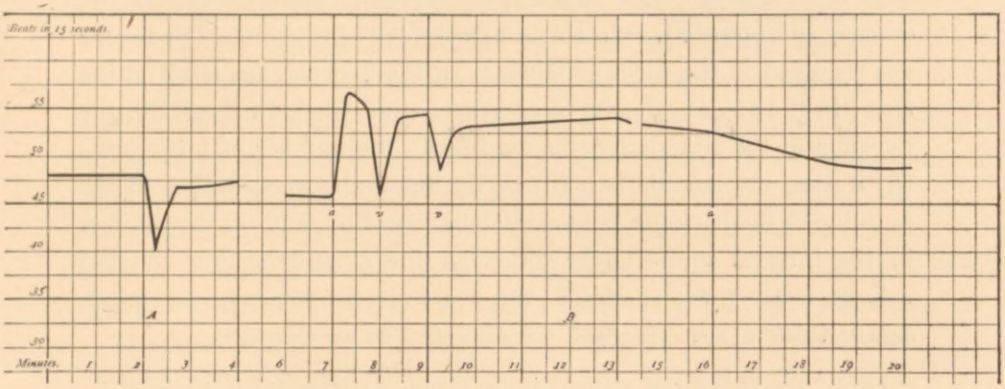


Fig. 2.—Stimulation of the vagus during a prolonged stimulation of the accelerators.

A. Stimulation of the vagus alone (15 seconds).

B. The accelerators were stimulated from *a* to *a* (9 minutes); the vagus was stimulated twice (at *v* and *v'*) for 15 seconds.

The first stimulation of the vagus in this experiment just overcame the effect of the stimulation of the accelerators and the heart was brought back to its normal rate; that the accelerator effect was not lost, however, is shown by comparing the rate of the heart when the vagus alone was stimulated (not quite 40 beats in 15 seconds) with that when both nerves were being stimulated (46 beats in 15 seconds). Stimulation of the vagus a second time, with a weaker current, caused a diminution of the accelerator effect, but the heart was not brought back to its normal rate. The two subsequent stimulations of the vagus show how constant were these results.

3.

Stimulation of the Vagus and Accelerators begun simultaneously.

The results of stimulating the two nerves simultaneously (a) for short periods (ten to fifteen seconds) and (b) for longer periods (several minutes) will be described in this section.

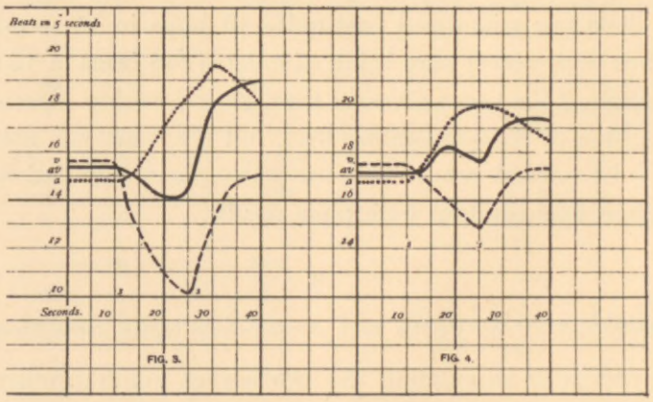
a. *Simultaneous stimulation of the vagus and accelerators for short periods.*—Experiments will be described first in which the vagus was

stimulated with the slowly interrupted current, and the accelerators with the ordinary rapidly interrupted current. Each nerve was frequently stimulated alone to obtain figures for comparison. The results are arranged in the form of tables. In the first column is given the time; in the second, the nerve or nerves stimulated; in the third, the duration of the stimulation; in the fourth, the number of heart beats (d) during the stimulation, (b) in the interval corresponding to the duration of the stimulation immediately preceding, and (a) the number in the interval immediately following the stimulation; in the last column is given the change in the heart rate in per cent, the minus sign indicating a slowing and the plus sign an acceleration.

Dog. Morphine and ether; curare. Vagi and accelerators cut.

hr.	min.	sec.		seconds.	b.	d.	a.	
5	2	40	R. vagus; coil 0 cm.; 4⅜ interruptions per second.	15	47½	35	45	−26.4%
	5	30	R. annulus; coil 12 cm.	15	45−	51½	56½	+21.1%
	8	10	Both nerves; coils, etc., as above.	15	47	44	55	−6.3%

These results are shown more satisfactorily in Fig. 3, in which the heart beats are given in periods of 5 seconds.



Figs. 3 and 4.—Stimulation of the vagus and accelerators begun simultaneously. The ordinates represent the heart rate in 5 seconds; the abscissæ the time in intervals of 10 seconds; "*a*" stimulation of the accelerators alone; "*v*" stimulation of the vagus alone; "*a v*" stimulation of the two nerves simultaneously. The stimulations continued in each case for 15 seconds (from *s* to *s*) and followed each other at short intervals. The strength of the current was different in the two cases.

In this case the figures representing the result of stimulating the two nerves simultaneously are not far from being the algebraic sum of the figures obtained when the two were stimulated separately. These figures show conclusively that neither nerve has overcome the effect produced by the other; both have made their influence felt and to almost equal degrees, the inhibitory effect slightly predominating. After the stimulation the accelerator effect appeared to almost the same extent as when this nerve was stimulated alone, as was described by Baxt. This latter fact is readily understood when we remember that the accelerators have a long after-effect, while the vagus has not.

The results of a few subsequent stimulations made in the same experiment will be given to illustrate the effect of altering the strength of the stimuli. In the first table it will be observed that the number of vibrations per second of the oscillating rod was increased.

hr.	min.	sec.		seconds.	b.	d.	a.	
5	50		R. vagus; coil 0 cm.; $5\frac{5}{8}$ vibrations per second.	15	49½	33½		−32.3%
	51		Vagus; coil, etc., as above. R. annulus; coil 12 cm.	15	49½	37	56	−25.2%

The current by which the annulus was stimulated was now strengthened by moving the secondary coil up to 10 and then to 8 cm.

hr.	min.	sec.		seconds.	b.	d.	a.	
5	52	30	Vagus (as before). R. annulus; coil 10 cm.	15	49	44½	56	−9.1%
	54	30	Vagus (as before). R. annulus; coil 8 cm.	15	51	44	56	−13.7%

The vagus effect still predominated, though to a less degree. It will be observed that the second increase of strength in the stimulus applied to the accelerators did not cause a corresponding increase in the effect upon the heart; such irregularities frequently occurred, but still the effect of the stimulation of the accelerators is plainly seen if the rate of the heart during the stimulation of the vagus alone ($33\frac{1}{2}$ beats in 15 seconds) is compared with that during the stimulation of the two nerves (44 in 15 seconds).

The current by which the vagus was stimulated was weakened by

diminishing the rate of the oscillating rod, and now the accelerators slightly predominated, as is shown in the following:

hr.	min.	sec.		seconds.	b.	d.	a.	
5	57		R. annulus; coil 8 cm. R. vagus; coil 0 cm.; 3½ interruptions.	15	52	54	57½	+3.8%
	59		R. vagus (as above).	15	52	47	48½	−10.0%
6	5		R. annulus; coil 8 cm.	15	51½	57	58	+10.6%

These results are shown in Fig. 4 (p. 168).

In the foregoing experiment there was a tendency for the inhibitory effect to predominate; in the following the tendency was rather for the accelerator effect to be more marked.

Small bitch. Morphine and ether; curare. Vagi and accelerators cut.

hr.	min.	sec.		seconds.	b.	d.	a.	
3	49		R. annulus; coil 14 cm.	15	34½	44	47	+27.5%
	52		L. vagus; coil 5 cm.; 3¾ interruptions per second.	15	33½	25		−25.3%
	59		Both nerves; coils, etc., as above.	15	32½	35½		+9.2%

The stimulus for the vagus was now made stronger and the nerves again stimulated.

hr.	min.	sec.		seconds.	b.	d.	a.	
4		3	R. annulus; coil 14 cm. L. vagus; coil 4 cm.; 3¾ interruptions per second.	15	34−	34½	46	+4.4%

The current by which the accelerators were stimulated was now weakened, but one of the above-mentioned irregularities occurred.

hr.	min.	sec.		seconds.	b.	d.	a.	
4	7		L. vagus; coil, etc., as above. R. annulus; coil 16 cm.	15	32½	37½	45½	+15.4%
4	10		Vagus (as above).	15	33−	25+		−24.2%
4	15		Vagus (as above). R. annulus; coil 17 cm.	15	31	30½+	43½+	−1.0%

These tables show that when the stimuli applied to the two nerves are properly selected, the effect of one nerve can be made exactly to

counterbalance that of the other. Similar figures could be given from many other experiments. Irregularities, such as were pointed out above, frequently occurred when the results of the use of stimuli of different strengths were compared with each other; but all the experiments, without a single exception, lead to the same conclusion, viz., that when the two nerves are stimulated simultaneously with stimuli at all comparable in strength (as judged by their separate effects upon the heart), the effect of each is plainly visible during the stimulation; the stimulation of one has never caused the complete obliteration of the effect of stimulating the other. If, however, the stimulation of one nerve is very strong in comparison with that of the other, then its effect alone may appear. This is sufficiently well known when the vagus is stimulated with a strong current; the following experiment shows that the reverse may occur, namely, the accelerator effect alone appear.

Dog. Morphine and ether. Accelerators cut. R. vagus intact. Central end of l. vagus stimulated with the ordinary induced current, and the heart thus slowed reflexly. The accelerators were stimulated with the slowly interrupted current.

hr.	min.	sec.		Duration of stimulation.	Heart-beats. b.	Heart-beats. d.	Change of heart rate in %.
3	44		Vagus; coil 10 cm.	20 sec.	52	47½	−8.6%
	47		R. annulus; coil 5 cm.; 3⅜ interruptions per second.	20	54	67½	+25.0%
	50		Both nerves; coils, etc., as above.	20	55	69½	+26.4%
	52	30	Vagus; coil 10 cm.	20	57	48½	−14.9%

Later in this experiment the peripheral end of the vagus was stimulated with the ordinary rapidly interrupted current and the accelerators with the slowly interrupted current; as the following figures show, the results are the same as when the methods of stimulation were reversed, as was the case in the experiments previously quoted. The slowly interrupted current was usually used to stimulate the vagus only because it seemed to give, as a rule, more constant results.

hr.	min.	sec.		Duration of stimulation.	Heart-beats. b.	d.	a.	Change of heart rate in %.
4	10		L. vagus; coil 21 cm.	15 sec.	39	34½	37½	−11.5%
	11	30	L. vagus; coil 21 cm. R. annulus; coil 5 cm.; 3⅔ interruptions per second.	15	38	41+	48	+7.9%
	13		L. vagus; coil 21 cm.	15	37	33	37	−10.8%
	15		Both nerves; coils, etc., as above.	15	36½	42	46½	+15.3%
	17		L. vagus; coil 21 cm.	15	37½	34+	37	−9.3%
	19		Annulus (as above).	15	36½	46½	49	+27.4%
	21		Both nerves; coils, etc., as above.	15	37−	44+	46½	+18.9%
	23		Vagus; coil 21 cm.	15	36	34½	35½	−6.9%

During these stimulations the irritability of the inhibitory nerves seemed to decrease, that of the accelerators to increase.

(b). *Simultaneous stimulation of the vagus and accelerators continuing for some time.*—Having found that when the two nerves are stimulated together for short periods, the effect of either can be neutralized by that of the other, so that the rate of the heart is scarcely affected, the effect of stimulating both for a longer period was tried.

As was pointed out at the beginning of this paper, however, this problem is somewhat different from the one we have been discussing, for now the possibility of the exhaustion of one or the other of the nerves must be considered. It is well known that the heart can be kept beating at a very slow rate for many hours by stimulating the vagus; I have been unable to find references to any experiments bearing upon the question of the fatigue of the accelerator nerves in mammals. Boehm,* it is true, says it is doubtful whether these nerves can be fatigued at all; but he does not seem to have stimulated them for periods longer than two minutes, and he is certainly not justified in drawing such a conclusion from stimulations of so short a duration.

I have performed a large number of experiments in order to determine how easily the accelerators are fatigued, or whether they are fatigued at all; the results of these experiments I hope soon to publish in full. Although these results are complicated and difficult to interpret, I think the following general conclusions may be drawn from them. When a moderately strong stimulus is applied to the accele-

* Boehm, *loc. cit.*

rators the rate of the heart rapidly rises to a maximum and remains at this level for a very variable period, occasionally for 8 or 10 minutes, but usually for a much briefer period. The rate then decreases, at first very rapidly and then very slowly; in many cases it reaches an almost constant level, which it may maintain as long as the stimulation continues. Frequently this constant level has almost coincided with the rate at which the heart was beating before section of the nerves, and this may be taken to represent the normal rate of the heart. The rate reached during a long-continued stimulation of the accelerators has seldom, if ever, in my experiments remained greater than the normal (using "normal" as above); usually it has been less, though still greater than that at which the heart was beating immediately before the stimulation began.

The fact that the heart can, by stimulating the accelerators, be maintained at its maximum rate for but a very short time might be attributed either to fatigue occurring in the cardiac muscle or in the endings of the nerves, or, as Professor Howell suggested, to a local effect upon the nerve at the point stimulated, that is, to what Professor Howell has called "stimulation fatigue."* In fact both of these factors seem to be involved; there is undoubtedly a local effect upon the nerve at the point stimulated which is the first cause of the decrease of the heart rate, but there also seems to be distinct evidence, which will be presented in a future paper, of fatigue occurring in the heart itself.

In any case the heart cannot be kept in a condition of maximum acceleration or beating at a rate much above what we may consider the normal rate for more than a very few minutes, offering in this respect a marked contrast to its conduct upon stimulation of the vagus.

What will be the final result of stimulating the two nerves together for a long period? Will the accelerators become completely exhausted and then the result be as if they were not being stimulated at all and the vagus exert its full influence? It is evident that the answers to these questions have interesting bearings upon the problem as to the manner in which the nerves affect the heart, and especially upon Gaskell's theory of the metabolic functions of these nerves. I hope

* Howell, Budgett and Leonard, *Journal of Physiology*, xvi, p. 311, 1894.

to investigate this question more fully in the near future, but will give here a few figures from experiments bearing upon it. In these experiments the local effect of the stimulus on the accelerators is disregarded, which I think may be done without affecting the general conclusions. In the first experiment recorded below the accelerators had been stimulated several times earlier in the experiment, so that they were probably more easily fatigued than they would otherwise have been.

Bitch. Morphine and ether; curare. Vagi and accelerators cut. R. vagus stimulated by slowly interrupted current; secondary coil 0 cm.; 7 interruptions per second of the primary circuit. R. annulus of Vieussens stimulated with the ordinary rapidly interrupted current; secondary coil at 15, then at 17 cm.

hr.	min.	sec.	Hearts-beats in 10 seconds.	Remarks.
3	19	30	46	
		40	37	Stimulation of vagus begun.
		50	34	
	20		33+	
	21		34½	
		40	34½	
		50		Stimulation of accelerators begun.
	22		51	
	23		49−	
	24		47+	
	26		45½−	
	28		45½−	
	30		45−	
	31		44+	
	33		43	
	34		42½	Stimulus off annulus.
	35		37½	
	36		36+	
	38		35−	
		10	43½	Stimulation of annulus begun; coil 17 cm
		20	47½	
		30	48	
	39		45	
	40		44	
	42		42½	
	43		41½	
		10		Stimulus off annulus.
		20	36½+	
	45		45+	

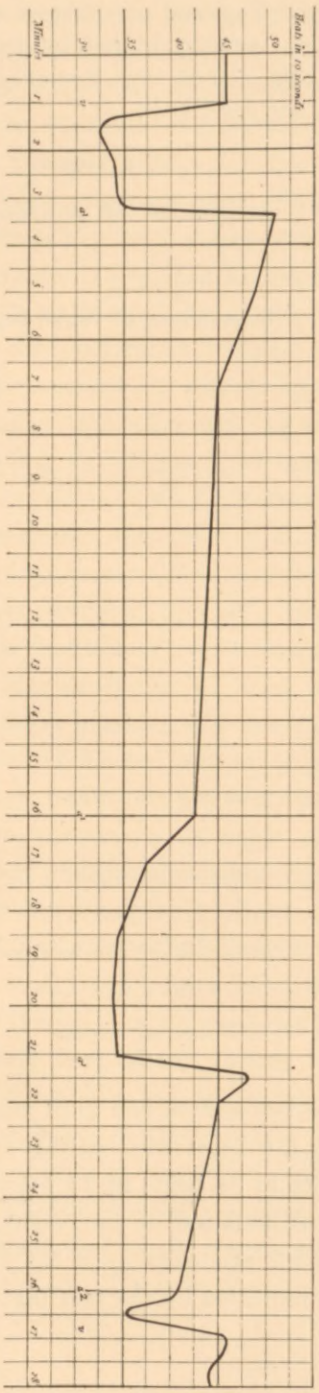


Fig. 5.—Long-continued stimulation of the vagus and accelerators. The ordinates represent the heart rate in 10 seconds; the abscissæ, the time in minutes. The vagus was stimulated from v to v (25 minutes); the accelerators were stimulated twice—from a^1 to a^1 (12½ minutes) and from a^2 to a^2 (9 minutes).

We see that in this experiment when the two nerves were stimulated together neither completely overcame the effect of the other in 12½ minutes, though the vagus gradually decreased the effect of the accelerators. That the effect of the stimulation of the accelerators was not completely overcome is shown by the fact that the heart rate is greater during the combined stimulation than during that of the vagus alone; also when the stimulation of the accelerators was discontinued, the heart rate quickly fell to what it had been under the influence of the vagus alone. It will be noticed that during the stimulation of the two nerves the heart rate fell below what it had been before the stimulation began; what the result would have been had the stimulation continued still longer it is impossible to say. (See Fig. 5.)

In the following experiment the nerves were stimulated together for more than half an hour. Changes in the condition of the animal almost necessarily occurred in such a long time; the depth of the anæsthesia and the temperature of the animal doubtless varied. The blood pressure fell and the heart was beating more slowly after than before the stimulation. The results, however, are interesting and very suggestive.

Bitch. Morphine and ether; curare. Vagi and accelerators cut. R. vagus stimulated; secondary coil 2 cm.; primary circuit interrupted 4 times per second. R. annulus stimulated; coil 15 cm. Several stimulations of the annulus had preceded the one described here.

hr.	min.	sec.	Heart-beats in 15 seconds.	Remarks.
12	20	45	61	
	21		68	Stimulation of accelerators begun.
		15	70	
		45	67	
	22		56	Stimulation of vagus begun.
		15	52½	
		30	46	
		45	56	
	24		57½	
	26		57½	
	28		57	
	30		57	
	32		56½	
	36		56	
	38		55−	
	40		54½−	
	42		53½	
	44		54	
	46		53½	
	50		53½+	
	52		54	
	53		54+	
	55		53½	Stimulus off vagus.
		30	60½	
	56	45	59	
	57	15	49½	Stimulus on vagus.
	58		50+	
	59		52+	
1			52½	Stimulus off accelerators.
	1	15	48	
	3		47	
	5		45	Stimulus off vagus.
		30	52½	

These figures show that after the two nerves had been stimulated together for about twenty minutes, the heart was beating at a rate which remained nearly constant (53½ to 54 beats in 15 seconds) for the next 13 minutes, *i. e.*, till the stimulation of the vagus ceased. That this rate is a result of the effects produced upon the heart by the stimulation of the two nerves is indicated by the fact that as soon

as the stimulus was removed from the vagus the heart rate increased from 53½ to 60½ beats in 15 seconds. Of course it may be objected that this was merely the return of the heart to its normal rate, which had been 61 before the nerves were stimulated, and the conclusion drawn that the accelerators had become completely exhausted and were no longer exerting any effect upon the heart. But the rate after the stimulation was but 51 in 15 seconds, and it is very probable that this number, rather than 61, represents the normal rate at this period of the stimulation. All doubt, however, as to whether the stimulation of the accelerators was still producing an effect upon the heart is at once removed by examining the figures immediately following. These show that when the vagus was again stimulated and the heart was beating at the rate of 52 beats in 15 seconds, taking the stimulus off the annulus caused the heart rate to fall to 45 in 15 seconds, which was the slowest rate reached during the experiment.

This experiment shows that the heart can be kept beating for a considerable period of time at a rate not far from the normal, but one which is determined by the stimulation of the vagus and accelerators. This is the result which I think would be expected on the theory that the vagi are anabolic and the accelerators katabolic nerves, provided that the two nerves were stimulated to about equal degrees. What the result would be of stimulating the nerves for a long period with currents unequal in strength my experiments are not sufficiently numerous to decide, but they suggest the following: When the vagus effect is the stronger, the heart rate finally reached is one below the normal, but above that produced by stimulation of the vagus alone; on the other hand I have failed so far to see a case in which stimulation of the accelerators kept the heart beating above the normal rate for a very long period, though, as in the experiment quoted above, it might maintain the rate at the normal, notwithstanding a continuous stimulation of the vagus.

Such results as the above, which my experiments so far indicate, might, I think, be easily explained on Gaskell's theory, for we know that stimulation of the vagus will keep the heart slowed almost indefinitely, and if this be due to an anabolic action of this nerve, the

weak stimulation of nerves causing katabolism, *i. e.*, the accelerators, would be expected to destroy a part, but only a part, of the products of this anabolism, and the final effect would be that the heart rate would reach a level below the normal, but still above that caused by the stimulation of the vagus alone; and this seems to be what actually occurs. On the other hand it is difficult to see how katabolic nerves, however powerfully stimulated, could cause any prolonged increase of the heart rate above the normal, for the supply of the products of anabolism would soon be exhausted, even though the anabolic nerves were being stimulated at the same time; in other words, the katabolism cannot be greater than the anabolism for any great length of time. Hence the final result of a long-continued stimulation of the accelerators with a maximum stimulus combined with a weaker stimulation of the vagus would be the production of a heart rate about the normal, but which is still determined by the two stimulations. This is what seems to have actually occurred in the second experiment described above; that the stimulus applied to the accelerators was at least a maximal, and probably a super-maximal, stimulus is shown by the fact that a weaker current caused the same maximum acceleration.

I desire to add, however, that these views are put forward only tentatively; subsequent experiments may show them to be incorrect. The chief object in introducing these experiments here at all is to show for what long periods the two nerves may be stimulated together without either overcoming the effect produced by the other.

CONCLUSION.

The experiments described in Part IV of this paper show that in whatever manner the problem of the relation of the vagus to the accelerators is approached, whether the accelerators are stimulated during a stimulation of the vagus, or the vagus during a stimulation of the accelerators, or both are stimulated simultaneously, either for a short or for a longer period, the result is the same, viz., the effect upon the rate of the heart is determined entirely by the relative strength of the stimuli applied to the two nerves. If the stimuli are of approximately the same strength, as judged by the effect of stimulating the nerves separately, the rate of the heart is but slightly

affected; if the stimulus applied to the vagus is the stronger, the heart is slowed; if it is weaker, the heart is accelerated. In all cases the result of stimulating the two nerves simultaneously is approximately the algebraic sum of the results of stimulating them separately; sometimes the inhibitory effect slightly predominates, but not more frequently than does the accelerator effect. Moreover, the two nerves may be stimulated simultaneously for a considerable period of time without either completely overcoming the effect of the other.

Thus as far as their effect upon the rate of the ventricular beat is concerned, the vagus and accelerator nerves seem to be purely antagonistic; the statement that a minimal stimulation of the one can completely overcome a maximal stimulation of the other is undoubtedly incorrect, and the hypotheses as to the mode of action of these nerves upon the heart, based upon this statement, lose their chief support.

NOTE.

Results very similar to those described in the above paper were obtained by Mr. Conant and myself in an experiment upon a crab.* One of the accelerator nerves of this animal was stimulated a number of times during the standstill produced by a long-continued stimulation of one of the inhibitory nerves; in each case the heart began to beat and continued beating during the stimulation of the accelerator, stopping completely again as soon as this stimulation was discontinued. The accelerator alone was now stimulated and a marked acceleration obtained; while this stimulation continued the inhibitory nerve was stimulated, with the result that while the acceleration was diminished the heart rate was still about the normal. The stimulus was removed from the accelerator nerve, while that on the inhibitory remained; total inhibition resulted.

It is interesting to note that in the crab the irritability of the inhibitory and accelerator nerves seems to be much more nearly equal than is the case in the mammal; in the above experiment a stimulus of sufficient strength just to cause total inhibition was sufficient to cause an almost maximal acceleration.

* For a description of the cardiac nerves in the crab, see the article by Conant and Clark, *The Journal of Experimental Medicine*, i, p. 341, 1896.