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[FROM THE PHYSIOLOGICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY.]

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INTRODUCTION.

IN a recently published article on nerve union, Langley and Anderson [1] have formulated the law that "the central end of any *efferent somatic* [2] fibre can make functional union with the peripheral end of any *preganglionic* fibre. . . ." But according to their review of the literature, it would appear that no conclusive evidence has as yet been obtained that motor fibres will make functional connection with the preganglionic fibres in the vagus nerve. Indeed, as late as 1900, Langley [3] stated that "a recovery of function, after section of the vagus nerve, has not been observed so far as regards its autonomic fibres. . . ."

But few attempts have been made to obtain union of efferent somatic fibres with the preganglionic fibres of the vagus nerve. Flourens [4] seems to have been the first investigator to have undertaken it. In 1828 he reported some experiments in which the fifth cervical nerve was sewn to the peripheral end of the vagus. He obtained no signs of functional union. In 1885 Rawa [5] sutured the hypoglossal to the vagus nerve in several species of animals. The physiological tests for regeneration were made from eighteen to twenty months after the operation and some days after cutting the vagus and hypoglossal nerves of the opposite side. He found that the sutured nerve behaved, so far as concerned its action on the heart, in every respect like a normal vagus nerve. Through it both direct and

[1] LANGLEY and ANDERSON: Journal of physiology, 1904, xxxi, p. 365.
[2] Italicized words have been substituted for letters in the original.
[3] LANGLEY: Schäfer's Text-book of physiology, London, 1900, ii, p. 665.
[4] FLOURENS: Ref., LANGLEY and ANDERSON, *Loc. cit.*
[5] RAWA: Archiv für Physiologie, 1885, p. 296.

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reflex inhibition of the heart were obtained, and through it the central nervous system exercised a tonic inhibitory control over the heart. But Langley and Anderson raise the valid objection to the work of Rawa that, in his final tests, cognizance had not been taken of the possibility of a downgrowth of fibres from the central stump of the divided vagus nerve. But although these experiments do not demonstrate conclusively that fibres of the hypoglossal nerve may usurp the functions of vagus fibres, still they prove that functional regeneration of the visceral fibres of the vagus nerve does occur.

The experiments of Henri and Calugareanu,[1] who cross-sutured the hypoglossal and vagus nerves, are open to the same objection, and their results have the same significance as Rawa's.

It was, therefore, to be expected that the negative results, reported by Langley and others, of experiments testing the power of the vagus to regenerate itself, would be accounted for by the brevity of the time allowed for regeneration. This was actually demonstrated in Langley's laboratory by Tuckett,[2] who found, in the rabbit, that three years after operation sutured vagi respond to stimulation almost normally.

While reviewing the literature on the subject of regeneration of the vagus nerve, we were impressed by the comparative sluggishness in the return of function after unions with it, a sluggishness which seems to be out of all proportion to the length of the nerve. At this time two possible explanations suggested themselves: (a) The small medullated fibres which occur in the vagus nerve, and which are probably its preganglionic fibres, may not grow as rapidly as large medullated fibres. (b) In the process of regeneration, fibres which are normally short may not extend beyond their normal length as rapidly as fibres whose normal length more nearly approximates that required of them in the regeneration.

We have no experimental evidence in support of the first possibility. Indeed Langley and Anderson[3] state, we think, however, without sufficient justification, " that small nerve fibres can much more readily unite with large ones than large ones with small."

With regard to the second possibility, if there is any truth in the

[1] HENRI and CALUGAREANU: Comptes rendus de la société de biologie, 1900, lii, p. 503; Journal de la physiologie et de la pathologie générale, 1900, ii, p. 709.

[2] TUCKETT: Journal of physiology, 1896, xix, p. 297. In this article negative results are reported. The completed work is reported in Journal of physiology, 1900, xxv, p. 303.

[3] LANGLEY and ANDERSON: *Loc. cit.*, p. 379.

statement made by Langley[1] that "the axon process of each cell wherever it is cut will, in favorable conditions, grow to its own length, neither more nor less," it is hardly to be expected that the short fibres of the hypoglossal could grow down to the heart. And the hypoglossal is the only nerve that has been used for this purpose in recent years. Although the latest work of Langley and Anderson[2] does not bear out tacitly the above-stated dictum, nevertheless we might be justified in expecting that the union of efferent spinal fibres with the vagus nerve would offer better chances of functional regeneration than the union of hypoglossal with vagus.

Furthermore we hoped that should signs of functional regeneration be obtained after the union of a spinal nerve with the vagus nerve, the interpretation of the results would not offer so many difficulties as in the case of union of one cranial nerve with another.

For these reasons it was decided to try, in the dog, the effect of uniting one of the branches of the cervical plexus with the peripheral end of the vagus nerve.

Methods.

With this object in view six dogs were prepared. In all excepting one the vagus nerve was cut at a point about 2 cm. above the inferior cervical ganglion, and the peripheral stump was sutured to the central stump of the most accessible branch of the brachial plexus. In most instances this was probably the trunk formed by the union of twigs from the fifth and sixth cervical nerves. In the case of the first dog operated upon, the central end of the hypoglossal nerve was united with the peripheral end of the vagus nerve. The cut surfaces of the nerves were secured to one another by two fine silk sutures passed on opposite sides of the nerve. No attempt was made to keep the sutures within the limits of the sheath of the nerves. In each instance, excepting the case of union of hypoglossus with vagus, a piece 4 to 5 cm. long was excised from the central stump of the vagus. The operations were performed aseptically, and none of the wounds became infected. Morphine and ether were used as anæsthetics. At the preliminary operations, the ether was administered through a cone; at the final operations, it was administered through a tracheal cannula.

[1] Langley: Journal of physiology, 1900, xxv, p. 417.
[2] Langley and Anderson: *Loc. cit.*

In order to test whether or not regeneration had occurred, a second and sometimes a third operation was performed, at which the sutured nerve was exposed and stimulated. The effect of this upon the pulse-rate was determined graphically with the aid of the sphygmomanometer devised by the author.[1]

In each experiment the nerves were examined histologically. As a rule cross-sections of the nerves were stained by the methods of van Giesen and of Weigert.

The experiments will be presented in the order in which the final tests for regeneration were made.

Experiments.

Dog No. 2. *Union of the peripheral end of the right vagus nerve with a branch of the right cervical plexus.* — Operation Feb. 26, 1904. At the second operation, performed 80 days later (May 16), it was found that the two nerves had united beautifully. The central end of the vagus terminated in a bulbous enlargement. Stimulation of the sutured vagus nerve distal to the point of union had no influence upon the heart-rate. We were about to close the wound when the animal died as the result of careless anæsthetization.

Histological examination. — The vagus nerve just below the point of union is a solid mass of large medullated nerve fibres. The recurrent laryngeal nerve near its point of origin from the vagus consists of medullated fibres which appear to be somewhat smaller than those seen in the vagus. The fifth cervical nerve just central of the suture appears to be normal.

Dog No. 3. *Union of the peripheral end of the right vagus nerve with a branch of the right cervical plexus.* — Operation March 1, 1904. The second operation was performed 109 days after the nerves had been united (on June 17, 1904). The result of stimulation of the sutured nerve was totally negative so far as the rate of the heart-beat was concerned. But while the dog was lightly anæsthetized, sensory effects, such as hurried respirations and whining, were observed. Stimulation of the opposite vagus with the secondary coil at 14.5 gave complete cardiac inhibition.

During the course of this operation it occurred to us that the existence of the normal connection of the heart with the central nervous system through the intact vagus nerve of the opposite side might

[1] Erlanger: Johns Hopkins hospital reports, 1904, xii, p. 53.

exert some deleterious influence upon the establishment of new peripheral connections. Therefore a piece of the left vagus nerve 4 cm. long was excised. This was associated with the usual effects of section of both vagi, — namely, a marked increase in the heart-rate and a marked slowing of the respirations. The wound was then closed. After recovery from the anæsthetic, and until the animal's death five days later, the respirations remained slow and labored, and apparently none of the food ingested was retained.

At autopsy it was found that the sutured nerves had united nicely. The central stump of the vagus terminated in a bulbous enlargement.

Histological examination. — The vagus nerve some distance from the point of suture and the recurrent laryngeal nerve near its origin from the vagus contain medium sized medullated nerve fibres and very many nuclei.

Dog No. 6. *Union of the peripheral end of the right vagus nerve with a branch of the right cervical plexus.* — Operation March 4, 1904. The dog was found dead on October 14, 1904, *i. e.*, 224 days after the first operation. At autopsy it was found that the sutured nerves had united nicely. The central stump of the cut vagus nerve ended in a bulbous enlargement.

Histological examination. — The fifth cervical nerve, the vagus nerve distal to the point of union, and the recurrent laryngeal nerve contain large medullated fibres.

Dog No. 5. *Union of the peripheral end of the right vagus nerve with a branch of the right cervical plexus.* — This dog was a fully grown, active fox terrier. At the first operation, which was performed on March 3, 1904, the peripheral end of the right vagus nerve was united with what appeared to be the uppermost trunk of the right cervical plexus. The second operation was performed on December 31, 1904, 303 days after the first operation. At this time it was found that apparently good union had occurred between the sutured nerves. The central stump of the right vagus nerve had not grown down along the carotid artery. Stimulation of the right vagus nerve distal to the point of union with the cervical nerve resulted in partial inhibition of the heart with the secondary coil at 10. With the secondary coil at 6, complete inhibition was obtained, which, however, did not last longer than the time occupied by two heartbeats. The effect of stronger stimulation was not tested. Stimulation of the left vagus nerve with the coil at 12 gave complete inhibition, from which the heart soon escaped. Upon cutting the left vagus nerve, the respirations at once became slow. The heart-rate was not materially affected. Thus before section of the left vagus nerve 54 pulsations were inscribed upon a given space of record; 55 pulsations were inscribed in the same space after section of the nerve. It was doubtful if reflex inhibition now occurred upon stimulation of the central end of the left vagus nerve. After excising a piece of the left vagus nerve the wound was closed.

Immediately after the operation the dog did well. The respirations were slow, but the animal seemed to be perfectly comfortable. Food was taken with apparent relish, and on the first day, at least, it was retained when given in small quantities. But, on the second day after the operation, retching and vomiting began and gradually increased in intensity. The weight of the animal increased for eleven days and then began to fall off. On January 20, twenty-one days after section of the left vagus nerve, and 324 days after the first operation, it was decided to make the final test, because it was thought the animal's appearance did not warrant further delay.

The animal was anæsthetized in the usual way, and the pressure in the femoral artery and the respirations were recorded. The sutured vagus nerve, including the neuroma at the point of union, was dissected free from the surrounding tissue and placed on shielded electrodes.

The results which follow demonstrate that, so far as its action on the heart is concerned, the sutured vagus nerve behaved in every respect like a normal vagus nerve.

In the first place it should be stated that stimulation of the central stump of the right vagus nerve did not slow the heart-rate.

By direct stimulation of the sutured vagus nerve any degree of inhibition could be obtained. In one trial the heart was held in complete inhibition for seventeen and three-fourths seconds before it escaped, and for more than a minute thereafter the heart-rate remained slow. The fall of blood-pressure that often follows the recovery from inhibition occurred regularly. Thus in one instance (Fig. 1) the mean blood-pressure before stimulation was 106.5 mm. Hg. Immediately after the heart had recovered from inhibition, the blood-pressure rose to 107, but fell secondarily to 75.

Weak stimulation of the central end of the left (unsutured) vagus nerve gave no perceptible changes in the heart-rate or blood-pressure. But strong stimulation of this nerve gave reflex slowing of the heart.

As is illustrated in Fig. 2, after a latent period of about two heart-beats, the heart-rate was distinctly slowed. Thus, before stimulation,

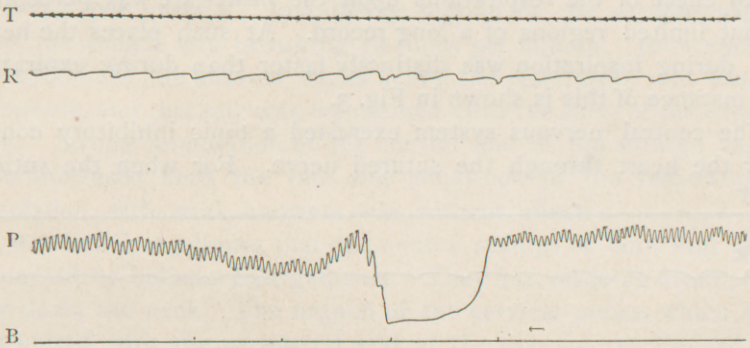

FIGURE 1. — One-fourth the original size. Showing the effect on the heart-rate, blood pressure, and respiratory rate of stimulating the sutured vagus nerve. Dog No. 5. T = Time in seconds; R = Respiration; P = Pressure in femoral artery; B = Base-line and signal.

23.5 pulse-waves were recorded in ten seconds (141 per minute). During the first 8.75 seconds of stimulation, 13 waves were recorded (89 per minute), but the rate gradually increased so that during the last five seconds of stimulation 11.5 beats were recorded (138 per minute).

The blood-pressure before stimulation was 87.5 mm. Hg. While the nerve was being stimulated, it rose to 122.5 mm. Hg; twenty

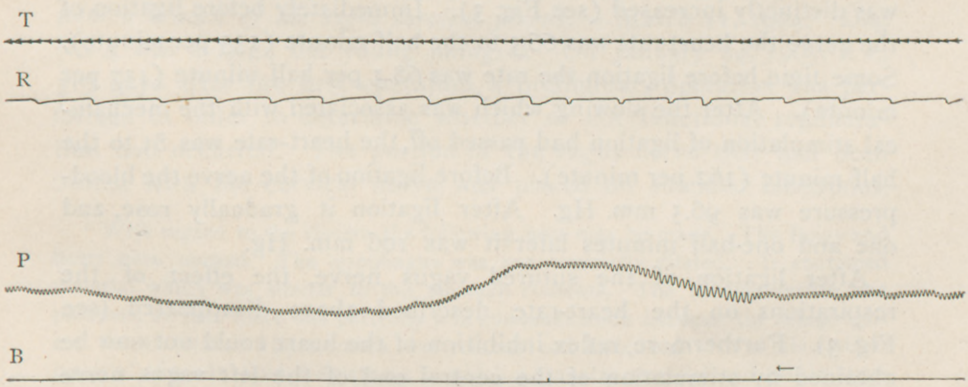

FIGURE 2. — One-third the original size. Showing the effect on the heart-rate, blood-pressure, and respiratory rate of stimulating the central end of the left vagus nerve. Dog No. 5. T = Time in seconds; R = Respiration; P = Pressure in femoral artery; B = Base-line and signal.

seconds after stimulation it was 71 mm. Hg; and it then gradually rose to the level it had had previous to stimulation of the nerve.

An effect of the respirations upon the heart-rate was perceptible in but limited regions of a long record. At such places the heart-rate during inspiration was distinctly faster than during expiration. An instance of this is shown in Fig. 3.

The central nervous system exercised a tonic inhibitory control over the heart through the sutured nerve. For when the sutured

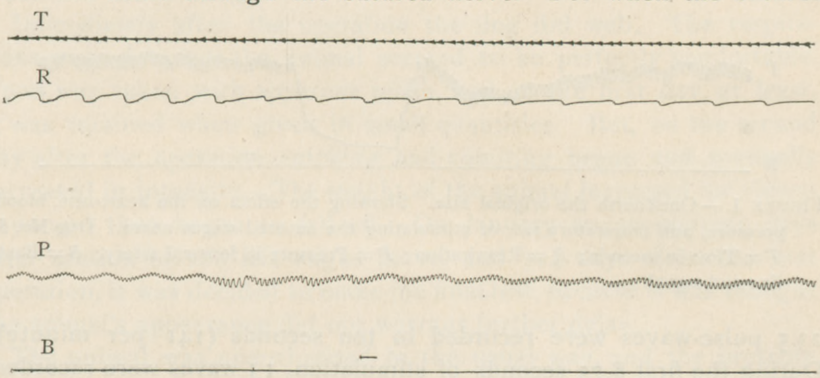

FIGURE 3. — One-fourth the original size. Showing the effect of the respiration on the heart-rate before and after ligation of the sutured nerve, and the effect of the ligation on the heart-rate. Dog No. 5. T = Time in seconds; R = Respiration; P = Pressure in femoral artery; B = Base-line and signal.

nerve was ligated (cut) the heart-rate, after a preliminary slowing, was distinctly increased (see Fig. 3). Immediately before ligation of the nerve the heart-rate was 66.5 to the half minute (133 per minute). Some time before ligation the rate was 68.5 per half minute (137 per minute). After the slowing which was associated with the mechanical stimulation of ligation had passed off, the heart-rate was 81 to the half minute (162 per minute). Before ligation of the nerve the blood-pressure was 96.5 mm. Hg. After ligation it gradually rose, and one and one-half minutes later it was 106 mm. Hg.

After ligation of the sutured vagus nerve, the effect of the respirations on the heart-rate described above disappeared (see Fig. 3). Furthermore, reflex inhibition of the heart could not now be obtained by stimulation of the central end of the left vagus nerve although thereby the blood-pressure was increased. Stimulation of the peripheral end of the sutured vagus still gave the usual cardiac inhibition. Stimulation of the central stump had no effect on the heart-rate, but it increased the blood-pressure.

The results obtained with regard to the relation of the sutured vagus nerve to the respiratory system were not definite. At the beginning of the experiment the respiratory rate was remarkably slow, 13.5 per minute. Just before section of the sutured vagus nerve, the animal was breathing 12 times per minute. Immediately after section of the sutured vagus nerve, the respiratory rate was 14 per minute, and this rate was maintained until the close of the experiment. Strong stimulation of the central end of the sutured vagus nerve increased both the rate and amplitude of the respirations. Stimulation with weak currents was without effect.

It was found at autopsy that the central stumps of both vagi were terminated by bulbous enlargements. They had made no attempt to grow down the neck. The branch of the cervical plexus which had been united with the peripheral end of the vagus nerve derived its fibres from the fifth and sixth cervical nerves, each of which sent a twig into it. The point of union of the sutured nerves was marked by a small fusiform swelling.[1]

Histological examination. — The following were removed for histological examination: A piece of the sutured vagus nerve about 1 cm. above the inferior cervical ganglion, a piece of the recurrent laryngeal nerve, and a piece of the fifth cervical nerve. The vagus and recurrent laryngeal nerves were found to consist of solid masses of uniformly large medullated fibres. The fifth cervical nerve appeared to be perfectly normal.

Dog. No 4. *Union of the peripheral end of the right vagus nerve with a branch of the right cervical plexus.* — March 11, 1904. Dog No. 4 was a large but young mongrel. On January 24, 1905, *i. e.*, 319 days after the first operation, a preliminary operation was performed in order to determine whether or not functional regeneration had occurred. The portion of the vagus nerve that had been united with the cervical nerve was placed on shielded electrodes.

[1] With regard to the viscera the following note may be made. The lungs and heart were normal. The œsophagus was not especially dilated. It contained material which was similar to the stomach contents. The cardiac orifice was patulous, so that there was perfectly free communication between the œsophagus and the stomach. The stomach was relaxed and distended with a bile-stained material of a semi-fluid consistency in which a granular material and rather large pieces of bone were suspended. The pylorus was so tightly contracted that considerable pressure was required to express the gastric contents into the duodenum. The small intestines were relaxed and almost empty. All but the uppermost 3 cm. of the large intestines were filled with a hard scybalous mass.

As indicated by the sphygmomanometer attached to the animal's leg, partial inhibition of the heart was obtained when the nerve was stimulated with the secondary coil at 8 and at 6. A piece of the left vagus nerve 3 cm. long was then removed. Now stimulation of the sutured nerve gave but very slight inhibition. The results obtained at this preliminary test were not so decided as were those obtained at the similar test made on Dog No. 5.

The wound healed quickly, and the sutures were removed on the seventh day. But the animal did not do well. Food given by mouth was retained but a very few moments. Retching and vomiting were almost incessant. When neither food nor drink was given, the dog vomited a stiff, frothy material which probably consisted of swallowed saliva.[1]

In nine days following the operation the animal lost over 3 kgm. in weight. At this time his condition appeared to be so serious that it was decided to make the final test for regeneration, although it was surmised that a sufficient interval of time had not elapsed since the section of the left vagus nerve to permit of a readjustment to the new conditions.

The methods used in the final tests follow. A continuous record was made of the pressure in the femoral artery, of the respirations and of the time in two second intervals. The positions of the stimulations were indicated with a stimulating marking pen, which was also used to inscribe the base-line. After obtaining a normal record, the effect was tested of stimulating with the induced current the sutured (right) vagus nerve distal of the point of union, the central stump of the left vagus nerve, and the sixth cervical nerve of the left side. The central stump of the cervical nerve that had been united with the vagus was too short to be dissected out and stimulated. Then an attempt was made to establish a block to the passage of impulses through the sutured nerve by freezing it. For this purpose the following simple device was used. A piece of glass tubing of 5 mm. bore was bent sharply on itself until the two arms were parallel to one another and

[1] An attempt to feed the animal through a stomach tube resulted in failure. Apparently the tube passed into the stomach without meeting with any obstruction, but the material injected was immediately regurgitated. Then rectal feeding was begun, but although the enemata were well retained, the animal continued to lose in weight. As the vomitus was always of an alkaline reaction, it was thought that the addition of an acid to the food given by mouth might help to empty the stomach through the pylorus. But this likewise was of no avail.

TABLE OF RESULTS. — Dog No. 4.

Remarks.	Procedure.	Pulse-rate per min.	Blood-pressure. Max.	Blood-pressure. Min.	Respirations per min.
Normal at beginning of exp.		147.6	123	94	11.5
(Period of stim. too brief for estimation of resp. rate)	Before	133.7	117	89	
	Stim. sutured vagus : coil at 11				
	During	115.8	116	82	Rate incr. slightly.
	Before	143.6	128	97	
	Same : coil at 9				
	During	117.4	100	80	
	Before	150.0	124	96	
	Same : coil at 8				
	During	112.9	113	80	Rate incr. markedly.
	Before	143.2	126	98	
	Same : coil at 6				
	During	126.8	106	83	Same.
					10.5
	Before	129.7	121		
	Stim. central end left vagus : coil at 10				
	During	126.0	169		Exp. tetanus.
	Before	140.5	148		
	Same : coil at 8				
(Period of slowest pulse-rate)	During	127.6	211		Exp. tetanus then incr. rate.
	Before	128.6	152	138	
	Stim. left 6th cerv. coil at 12				
	During	108.9	136	118	Rate incr. slightly.
	Before	121.6	134	117	
	Same : coil at 10				
	During	109.6	126	103	Same.
	Before	124.9	127	106	
	Same : coil at 8				
	During	112.9	118	96	Same.
					6.5
Test before cooling sutured nerve	Before	141.6	108	91	
	Stim. sutured vagus : coil at 7				
	During	120.0	98	80	Rate incr. markedly.

TABLE OF RESULTS. — Dog No. 4 (*Continued*).

Remarks.	Procedure.	Pulse-rate per min.	Blood-pressure.		Respirations per min.
			Max.	Min.	
Normal just before cooling		126.4	114	92	7
Nerve cooled to 1° C.		134.0	121	103	10
Nerve cooled	Stim. sutured vagus: coil at 7 — Before	134.2	121	103	
	During	130.3	101	86	No change.
Nerve cooled	Stim. left vagus: coil at 7 — Before	129.2	127		
	During	133.3	196		Exp. tetanus then rate incr.
Nerve cooled	Stim. left 6th cerv.: coil at 7 — Before	129.3	132	117	
	During	126.6	114	100	Rate incr. slightly.
Nerve warmed: normal		124.0	116	100	7.5
Nerve warmed	Stim. sutured vagus: coil at 7	104.4	85	73	Exp. tetanus.
Some bleeding: resp. stopped: art. resp. during rest of exp.					
Before cutting cord	Stim. sutured vagus: coil at 7 — Before	109.5	106	90	
	During	101.7	86	72	
	Same: coil at 7 — Before	116.2	112	102	
	During	103.6	95	82	
				Mean	
Cord cut in upper cervical region	Same: coil at 7 — Before	104.5		42	
	During	80.0		44	
	Same: coil at 7 — Before	97.9		40	
	During	88.2		42	
	Stim. left 6th cerv.: coil at 7 — Before	94.4		Not appreciably changed.	
	During	93.2			
	Same: coil at 5 — Before	90.0			
	During	94.0	Same.		

TABLE OF RESULTS. — DOG NO. 4 (*Continued*).

Remarks.	Procedure.	Pulse-rate per min.	Blood-pressure. Max.	Blood-pressure. Mean.	Respirations per min.
	Before	104.3		32	
	Stim. central end left vagus : coil at 5				
	During	105.4		34	
	Before	97.8		30	
	Stim. left 7th cerv. : coil at 5				
	During	97.0		32	
Before cooling sutured nerve		96.0		30	
After cooling		73.0		26	
Nerve cooled	During stim. sutured vagus : coil at 7	66.3		30	
	Before	71.2		26	
Nerve cooled	Stim. sutured vagus : coil at 7				
	During	67.5		30	
After warming		79.2		24	
	Stim. sutured vag.	62.1		28	
	Before	80.3		24	
	Same : coil at 7				
	During	63.6		27	
Nerve cooled		66.4		24	
Nerve cooled	Same : during stim.	64.6		26	
	Before	66.5		22	
	Same : coil at 7				
	During	66.0		26	
After warming		77.4		25	
	Same : during stim.	59.3		27	
	Before	78.5		25	
	Stim. left 7th cerv. : coil at 7				
	During	79.3		27	

separated by an interval of 2 mm. One arm of this U tube was then cut off within 6 mm. of the concavity of the bend. After the nerve had been slipped into the concavity of the bend, the inflow tube was fastened into the short arm of the U tube. The temperature of the circulating medium was determined as it issued from the cooling tube.

This cooling apparatus was placed on the sutured nerve just distal of the shielded electrodes with which the nerve was stimulated. After having cooled the nerve to 1°–0.5° C., the order of stimulation that had been employed before cooling was repeated. The results obtained are given on pages 382 to 384 in tabular form.

Upon inspection of this Table, it may be seen that undoubted partial inhibition of the heart was obtained both by direct stimulation of the

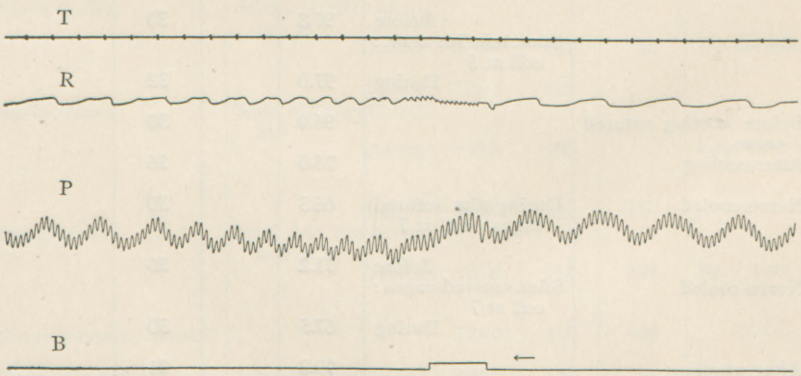

FIGURE 4. — One-third the original size. Showing the effect on the heart-rate, blood-pressure, and respiratory rate of stimulating the sutured vagus nerve. Dog No. 4. T= Time in 2 seconds; otherwise legend same as in preceding figures.

vagus nerve that had been sutured to the cervical nerve (Fig. 4) and reflexly, through this nerve, upon stimulation of the central stump of the opposite vagus nerve (Fig. 5), and of the cervical nerve opposite to the one that had been sutured to the vagus nerve.

It was not possible to obtain complete inhibition of the heart by stimulating the sutured nerve, but thereby the heart-rate was materially reduced. Special attention should be called to the fact that before section of the cord stimulation of the sixth left cervical nerve gave reflex inhibition which was fully as marked as, if not more marked than, the reflex inhibition that resulted from stimulation of the central stump of the left vagus nerve. Thus with the secondary coil at 12 (not included in the Table) and at 10, stimulation of the central stump of the left vagus nerve produced practically no inhibition of the heart. The maximum effect, which was obtained with the coil at 8, was a reduction of the heart-rate from 140.5 to 127.6 beats per minute. Stimulation of the sixth left cervical nerve with the coil at 12 reduced the heart-rate from 128.6 to 108.9 beats per minute. When the strength of the stimulus was increased, the inhibitory effect diminished, but it still remained as marked as that obtained by stimulation of the central end of the vagus. Thus, with the coil at 10, the rate was reduced from 121.6 to 109.6, and with the coil at 8 it was reduced from 124.9 to 112.9 beats per minute.

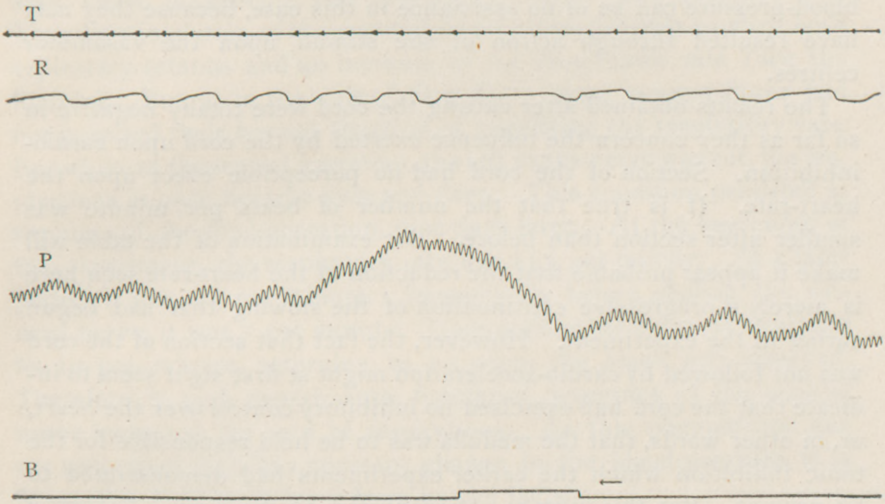

FIGURE 5. — One-fourth the original size. Showing the effect on the heart-rate, blood-pressure, and respiratory rate of stimulating the central end of the left vagus nerve Dog No. 4. Legend same as in Fig. 4.

When the sutured nerve was cooled to 1° C., there was good reason for believing that functional connection of the heart with the central nervous system through this nerve was practically severed. For now stimulation of the sutured nerve reduced the heart-rate less than 4 beats per minute, whereas, before cooling, stimulation had regularly reduced the heart-rate more than 20 beats per minute. The effect of such functional section of the sutured vagus was to increase the heart-rate from 126.4 beats per minute to 134. Subsequently, upon warming the nerve, the rate became 124. It would, therefore appear, although the result is by no means striking, that the central nervous system had assumed tonic inhibitory control over the heart through the sutured nerve.

The effect upon the blood-pressure of cooling the sutured vagus nerve may perhaps be taken as additional evidence of the existence of such tonic activity. For before cooling and after warming the nerve the pressures were 114–92 and 116–100, respectively, and while the nerve was cooled, it was 121–103 mm. Hg.

Cooling the sutured nerve practically stopped all reflex cardio-inhibition which before cooling had been obtained upon stimulation of the central stump of the left vagus nerve and of the sixth left cervical nerve. The slight effects upon the heart-rate here seen probably fall within the error of the methods employed. The effects upon the blood-pressure can be of no assistance in this case, because they may have resulted through action of the stimuli upon the vasomotor centres.

The results obtained after cutting the cord were totally negative in so far as they concern the influence exerted by the cord upon cardio-inhibition. Section of the cord had no perceptible effect upon the heart-rate. It is true that the number of beats per minute was smaller after section than before. But examination of the table will make it appear probable that the reduction of the heart-rate seen here is merely a progressive continuation of the slowing that had begun earlier in the experiment. However, the fact that section of the cord was not followed by cardio-acceleration might at first sight seem to indicate that the cord had exercised no inhibitory control over the heart, or, in other words, that the medulla was to be held responsible for the tonic inhibition which the earlier experiments had demonstrated to be present. But this view is not supported by the facts. For after section of the cord, functional section of the sutured vagus nerve by cooling did not increase the heart-rate; indeed, it had just the opposite effect. Thus, upon alternate warming and cooling of the sutured nerve, the following heart-rates were recorded: 96, 73, 79.2, 66.4, and 77.4. This result is sharp and incontestable. However, we have not the data upon which a satisfactory explanation might be based. That the slowing of the heart-rate was the result of the slight rise of blood-pressure which was always associated with the stimulations, seems improbable.

It is also worthy of remark that, after section of the cord, stimulation of the sutured nerve, whether cooled or not, causes a slight but constant rise of the blood-pressure, this rise being approximately the same, irrespective of the effect upon the heart-rate.

After the cord had been cut, it was still possible to obtain well-marked cardio-inhibition by direct stimulation of the sutured vagus nerve. But now stimulation of the left sixth and seventh cervical nerves and of the central stump of the left vagus, gave no reflex slowing of the heart.

It is interesting to note that in this experiment, as well as in the other successful experiment of this investigation, the normal influence of the respiration on the heart-rate is occasionally seen. Thus at one place, in equal intervals of time, 8.5 heart-beats were regularly recorded during expiration to 9 beats during inspiration.

Likewise, in this animal, the presence in the sutured nerve of sensory fibres influencing the respiratory centre was demonstrated. Thus by stimulation of the sutured nerve it was possible to elicit both expiratory tetanus and an increase in the respiratory rate (see the figures). But, as in the case of Dog No. 5, these sensory fibres had not acquired their normal function of regulating the respiratory rate. For when, at the second operation, the left vagus nerve was cut, the respirations at once became slow and deep. This condition persisted at the time of the final operation, nine days later. At the beginning of the experiment, the respiratory rate was 11.5 per minute. At a later period, it was 6.5 per minute. Immediately before cooling the sutured nerve, it was 7 per minute. Upon cooling the nerve, it increased to 10 per minute, returning to 7.5 when the block was removed. Therefore, in both experiments, functional severance of the sutured nerve increased the rate of respirations. As this phenomenon was not associated with any constant change in the blood-pressure, it is impossible to account for it from known facts.

In the case of neither animal was there any obvious evidence of a restoration of the normal innervation of other organs in which the vagus nerve is distributed. The bark of all the animals remained hoarse, and in those in which the left vagus nerve was severed persistent retching and vomiting indicated either that the regenerating fibres had not yet reached the organs of the gastro-intestinal canal, or that, if they had grown into them, they had not assumed the normal functions of vagus fibres. It is also interesting to note that although, after section of the second vagus nerve, the appetite remained unimpaired, the vomitus which, from the evidence we have obtained, apparently came from the stomach, always had an alkaline reaction.

At autopsy it was found that the nerve that had been sutured to the peripheral end of the vagus was one of the two trunks of the sixth cervical nerve. The point of union was marked by a spindleformed swelling. This was considerably larger than the one found in the case of Dog No. 5, indicating that the suture had not been as neatly made. It is possible that this may have accounted for the greater intensity, in Dog No. 4, of the symptoms which followed section of the left vagus, and for the impossibility of obtaining complete cardio-inhibition by stimulation of the sutured nerve.

A neuroma about the size of a pea had developed on the central stump of the right vagus nerve at the place of section. From the distal end of this neuroma a tapering projection, about 3 cm. long, extended peripherally along the course of the carotid artery. The base of the projection was about 1 mm. in diameter, and had the appearance of a nerve trunk. Peripherally it seemed to fork, although at this point it became so frail that it was difficult to distinguish it from the surrounding connective tissue. One branch appeared to follow the carotid artery for a short distance, but every trace of it had disappeared while still at a distance of about 4 cm. from the neuroma on the sutured nerve. The other branch seemed to pass into the sterno-mastoid muscle. Two pieces of this outgrowth, one just distal of the neuroma, the other 1 cm. further from it, together with a piece of the sutured nerve near the inferior cervical ganglion, were removed for histological examination.[1]

Histological examination. — The piece of the sutured vagus nerve taken from a point near the inferior cervical ganglion was made up largely of connective tissue through which there was scattered a considerable number of large medullated nerve fibres. The proximal piece of the outgrowth from the central stump of the right vagus nerve was composed of medullated fibres which were somewhat smaller than those seen in the sutured nerve. The tissue taken from the more distal position contained no nerve fibres.

Dog No. 1. *Union of the central end of the right hypoglossal nerve with the peripheral end of the right vagus nerve.* — At the first operation, which was performed on February 24, 1904, the hypoglossal and vagus nerves were sewn together, and a piece of the central stump of the vagus about 1.5 cm. long was excised. After the operation the dog developed a severe keratitis, but otherwise his recovery was uneventful.

[1] *Post-mortem* examination of the rest of the organs was negative. The œsophagus was somewhat dilated. The fundic portion of the stomach was contracted and contained a small amount of a bile-stained fluid of an alkaline reaction. The cavity of the stomach was in free communication with the lumen of the œsophagus which was filled with the same material seen in the stomach. The pylorus was so tightly contracted that the gastric contents could be expressed into the duodenum only with the greatest of difficulty. The gall-bladder was distended with bile. The intestines presented nothing remarkable. The lungs and heart were apparently normal.

On May 14, 1904, eighty days after the first operation, the sutured nerve was exposed below the point of union, and stimulated. The result was totally negative. On February 9, 1905, 351 days after the first operation, the physiological test for regeneration was repeated, but the results were again negative. No slowing of the heart-rate was obtained with the secondary coil at 0. And with the secondary coil at 5 the rate of the respirations was not affected. Stimulation of the left (unsutured) nerve with the secondary coil at 15 gave complete inhibition of the heart.

A third test was made on March 15, 1905, 385 days after the nerves had been united, and again the results were totally negative. At this operation a piece was excised from the vagus nerve of the opposite side. Section of this nerve was associated with a slowing of the respirations and an increase of the heart-rate. After this operation the dog did quite well; indeed, very much better than any of the other dogs in which both vagi had been cut. Although this dog had more or less constant vomiting, the vomitus was always reingested, and finally it was retained. In twenty-one days the animal lost but 0.8 kgm. in weight. At this time the respiratory rate was 10 per minute.

On May 5, 1905, 406 days after the first operation, stimulation of the sutured nerve again gave totally negative results. The dog died on the table after all of the tests had been made.

At autopsy it was found that the central stump of the vagus nerve had made no visible attempt to grow down the neck. The usual neuromata were found, one at the place of union of the sutured nerves, the other on the central stump of the vagus nerve. These were separated by a distance of about 1.5 cm., and were connected by some dense tissue. This tissue, together with two pieces of the sutured nerve, one taken from a place near the point of union, the other from a place near the inferior cervical ganglion, were removed for histological examination.[1]

Histological examination. — The tissue obtained from this dog was fixed in osmic acid and teased on the slide. In the tissue that united the two neuromata was found a bundle of medullated fibres. The size of the fibres was very variable; roughly, the frequency of

[1] The œsophagus was somewhat dilated, but the cardiac orifice of the stomach, as well as the pylorus, were closed. The stomach was distended with large pieces of undigested meat. In the left ventricle was found a comparatively fresh, large, white thrombus.

large and small fibres was approximately equal. As the bundle was torn in teasing, no estimate could be made of its size, but it undoubtedly contained a considerable number of fibres.

The hypoglossal vagus nerve near the point of union contained medullated fibres, most of which were of the large variety. Likewise, medullated fibres were found in it near the inferior cervical ganglion, but here most of the fibres were of the small variety.

Although the results of this experiment are negative, in so far as they concern functional regeneration, still they are of interest in at least two particulars. In the first place, they serve to indicate that, in experiments on cross-suturing of nerves, resection of a piece of a central stump which is left free in the wound may not suffice to prevent a re-establishment of normal innervation.

In the second place, it is interesting to note that, although vagus fibres had undoubtedly united with the sutured nerve, they had not yet assumed control of vagus functions. This apparent sluggishness might be accounted for in one of three ways: (a) It is of course possible that the connection of vagus with vagus had not been established long enough to allow of functional regeneration. (b) Vagus fibres might not regenerate as rapidly as other fibres. (c) The presence in the regenerating nerve of fibres derived from two sources might in some way have interfered with the process of regeneration. The data of this experiment do not suffice for a discussion of the relative importance of these possibilities.

Summary and Discussion.

The results of the experiments herein described demonstrate that when the central end of a spinal nerve is sewn to the peripheral end of the vagus nerve the fibres of the former may make functional connection with the vagus end-apparatus in the heart, if sufficient time be allowed for regeneration. Complete inhibition of the heart may be obtained by direct stimulation of such regenerated fibres. Such fibres may serve as the efferent path of cardiac reflexes which are associated with the act of respiration, and of reflexes started by electrical stimulation of afferent nerves. And finally through these fibres the central nervous system may exercise a tonic inhibitory control over the heart.

In one of the instances of successful union, an attempt was made to locate the inhibitory centre, that is, to determine whether the reflex centre still maintained its normal position in the medulla, or whether it had moved to the cells of origin of the spinal nerve which was performing the functions of the vagus. It will be recalled that, after cutting the cord in the upper cervical region, stimulation of the central end of the unsutured vagus nerve or of the sixth cervical nerve, no longer caused reflex cardiac inhibition. But this does not prove that the reflex centre had not moved into the cord. Nor is the situation of the centre in the medulla proved by the fact that after transsection of the cord in the upper cervical region no acceleration of the heart-rate followed functional section of the sutured nerve. For it is possible that transsection of the cord may have produced spinal shock, a condition in which, according to Sherrington,[1] the portion of the cord aboral of the mechanical injury suffers a more or less complete suppression of nervous function.

The only evidence which favors the location of the reflex centre in the cord consists in the observation that reflex inhibition of the heart was more easily obtained by stimulation of a cervical nerve than by stimulation of the central end of the vagus nerve. However, this evidence can be considered suggestive only, for under normal circumstances reflex inhibition of the heart may be obtained by stimulation of any afferent nerve in the body.

As these experiments have failed to locate positively the so-called cardio-inhibitory centre, a discussion of the way in which the central nervous system has adapted itself to the changed conditions resulting from union of a spinal nerve with the vagus nerve could not be expected to lead to a positive conclusion. Nevertheless a discussion of the possibilities might not be out of place.

From what is known of regenerative processes within the central nervous system, it is highly improbable that axons of the cells of the vagus centre could grow through the cord and cervical nerve and so reach the heart. And there is no evidence, even if we admit Bethe's hypothesis,[2] that a growth of fibres could occur along the same course in the reverse direction.

But it is possible that the resistance to the passage of impulses along descending fibres, which probably connect the vagus centre with spinal nuclei, might have been diminished as a result of their unwonted activity. In this way they might have become the natural path of discharge of the normal cardio-inhibitory centre.

[1] SHERRINGTON: Schäfer's Text-book of physiology, London, 1900, ii, p. 846.

[2] BETHE: Allgemeine Anatomie und Physiologie des Nervensystems, Leipzig, 1903, p. 182.

Finally it might be assumed, and it will be remembered that we have obtained some evidence in favor of this view, that the inhibitory centre has actually taken its abode in the nucleus of origin of the cervical nerve. In this connection attention should be called to the opinion first expressed by Bernstein [1] that the tone of the inhibitory centre is probably not the result of automatic activity of the centre, but rather the result of the continual arrival in it of afferent impulses. Whether or not the cardio-inhibitory centre selects and adapts afferent impulses so as to make them subserve the best interests of the organism, it is impossible to state. The great differences in the response of the inhibitory centre to stimulation of various afferent nerves might, perhaps, be taken as evidence of such a selective action. But here it is again possible that, through inheritance or exercise, certain tracts have become the paths of least resistance. It is, therefore, not necessary to assume that the cardio-inhibitory centre possesses automaticity. The facts do not debar the view that the continual variations in the tone of the cardio-inhibitory centre are the result merely of the arrival and spread of impulses of all kinds in the central nervous system. And it might, in addition, be admitted that when the vagus nerve connects the heart with the central nervous system, this spread of impulses, modified to some extent by the resistance offered to their passage along the various paths, affects the heart through the cells of origin of the vagus fibres. But should the axis cylinders of any other group of cells in the central nervous system make connection with the inhibitory mechanism in the heart, then the spread of impulses might affect the heart in the same way and with an intensity which might vary with the efficiency of the impulses acting upon the cells of origin of the nerve fibres. In other words, such a group of cells might become the reflex centre for cardio-inhibition. Therefore, in the case of the cardio-inhibitory centre it would not be necessary to conclude with Rawa [2] that "the nerve centres will perform just those functions which are demanded of them by the peripheral organs with which they are connected."

Our observation that the transmission of reflexes to peripheral organs along fibres which do not normally make connection with such organs is not unique. As has been stated, Rawa's instances are not perfectly clear. It is possible that in his experiments vagus

[1] BERNSTEIN: Archiv für Anatomie und Physiologie, 1864, p. 633.

[2] RAWA: *Loc. cit.*

fibres may have resumed their normal connections. But Mislavsky [1] has undoubtedly obtained reflex contraction of the laryngeal muscles after union of the thoracic end of the cervical sympathetic with the recurrent laryngeal nerve. Perhaps the most striking instance of this kind is seen in the case reported by Cushing,[2] in which, after union of the central end of the spinal accessory nerve with the peripheral end of the facial nerve in man, the subject gradually regained voluntary control of individual facial muscles. It should be stated here that Cunningham [3] maintains that in the dog normal control is never regained over abnormally innervated voluntary muscles. Furthermore, the recovery of voluntary control in such a case might not be comparable to the recovery of a reflex control. In the former case the recovery of function might be facilitated by training; in the latter case training could not play a part.

Our experiments do not permit of the formulation of a positive conclusion with regard to the rate of regeneration of fibres of different origin when united with the vagus nerve. Nevertheless, when viewed in conjunction with the experiments of others, they do indicate that spinal fibres make functional connection more rapidly than fibres of the hypoglossal and vagus nerves. In our most successful case, complete inhibition of the heart was obtained 303 days after the cervical and vagus nerves had been sutured. In one instance of union of the hypoglossal (and vagus ?) with the vagus nerve, no signs of functional regeneration were obtained 406 days after sewing the nerves together. However, Henri and Calugareanu [4] describe one instance in which complete inhibition of the heart was obtained 170 days after the same operation. Many investigators have tested the power of the vagus to regenerate itself. All final tests made within a year of the operation have yielded negative results.[5]

Neither has conclusive evidence been obtained with regard to the influence which an intact vagus nerve exerts upon the rate with which a regenerating vagus nerve will make functional connection with the end apparatus in the heart. However, one fact seems to indicate that it has a retarding influence. At the last preliminary operation

[1] MISLAVSKY: Comptes rendus de la société de biologie, 1902, liv, p. 841.

[2] CUSHING: Journal of nervous and mental diseases, 1903, xxx, p. 367.

[3] CUNNINGHAM: This journal, 1898, i, p. 239.

[4] HENRI and CALUGAREANU: *Loc. cit.* These authors do not give the results of *post-mortem* examinations.

[5] TUCKETT: *Loc. cit.*

in Experiment 5, it was found that strong stimulation of the sutured nerve had but a slight effect upon the heart-rate. The inhibition that resulted did not last longer than the time occupied by two heart-beats. Only twenty-one days later strong stimulation of the sutured nerve held the heart in complete inhibition for seventeen and seven-tenths seconds. It is rather improbable that this sudden change in the response of the heart to vagus stimulation would have occurred in the course of an uninfluenced regeneration.

Finally, it might not be superfluous to state that the fact that impulses carried to the heart through spinal fibres may bring the heart to rest, favors the view that cardiac inhibition results from the action of ordinary nerve impulses upon a peculiar end-apparatus.