On the Effects of Afferent Stimulation of the Vagus upon Some Vegetative Organs.

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My recent observation¹⁾ has put forward the evidence that in rabbits the blood urea-nitrogen concentration, which increases when the peripheral end of the severed vagus is stimulated, is on the contrary decreased when its central stump is stimulated. This decrease is remarkably inhibited when the animal is deeply anaesthetized, sometimes even turning to an increase. Similar paradoxical phenomena are sometimes observed on the blood sugar, glycosuria, adrenaline secretion, blood pressure, heart beat, gastric movement etc. and have been brought about not only with regard to the vagus but also to the sensory nerves.

Bernard,²⁾ Starkenstein³⁾ and others have demonstrated glycosuria by the stimulation of the central stump of the vagus. This phenomenon is also manifested in an animal with its adrenal bodies extirpated. It has already been pointed out by Külz⁴⁾ and Griffith⁵⁾ that glycosuria and hyperglycaemia are brought about when the central stump of the vagus or the sensory nerves are stimulated.

According to Kodama⁶⁾ and Houssay and Molinelli⁷⁾ the same manipulation gives rise to an augmented adrenaline secretion.

1) Tashiro, Tohoku Journ. Exp. Med., 1926, 7, 221.

2) Bernard, Leçons sur la physiologie et la pathologie du system nerveux II, Paris 1858, 435.

3) Starkenstein, Zeitschr. f. exp. Pathol. und Therap., 1912, 10, 78.

4) Külz, cited by Greving in Müller's "Die Lebensnerven," Berlin 1924, 280.

5) Griffith, Americ. Journ. Physiol., 1923, 66, 18.

6) Kodama, Tohoku Journ. Exp. Med., 1923-24, 4, 166 & 465; Sugawara etc., Ibid., 1926, 7, 1.

7) Houssay and Molinelli, Cpt. rend. Soc. d. Biol., 1924, 91, 1056.

There are many experiments already made public, investigating the change brought upon the organs of the circulatory system by the centripetal stimulation of the vagus and the sensory nerves. Bayliss,⁸⁾ Martin and Mendenhall⁹⁾ saw the fall of the blood pressure when the central ending of the vagus was stimulated, while Sollmann and Pilcher¹⁰⁾ maintained that the stimulation of the central stump of the vagus or the sciatic nerve leads to a rise of blood pressure accompanied by a constriction of the peripheral vessels (reduced volume of limb). But the blood pressure appears to rise, as a rule, when the central endings of the vagus or the sensory nerves are stimulated. Its fall, if it occurs, depends on various conditions as mentioned below: deep anaesthesia or prolonged operation (Sollmann and Pilcher),¹⁰⁾ brain anaemia due to a large haemorrhage (Porter and Marks),¹¹⁾ stimulation with a weak electric current or diminished conductivity of the nerve stem caused by cold (Hunt),¹²⁾ severing of the splanchnics (Stewart),¹³⁾ etc.

In spinal animals, Mellé and Shipley¹⁴⁾ observed a rise of the pressure by stimulating the central endings of the splanchnics and Sherrington¹⁵⁾ demonstrated the same result also by a stimulation of the digital nerve.

With regard to the heart, Hooeker¹⁶⁾ observed in stimulating the central ending of the vagus and the sensory nerves of vagotomized dogs or rabbits that the rate of the heart beat increases, while Bainbridge¹⁷⁾ noticed that when the central ending of the vagus is stimulated, the heart beat shows a retardation, which fails to occur when the vagus of the other side is severed. According to H. E. Hering's¹⁸⁾ experiment, if the unsevered cervical vagus is tetanized with a comparatively weak current, the heart beat increases, while it decreases with a strong current.

As to the breathing, Rosenthal,¹⁹⁾ Meltzer²⁰⁾ and Hering¹⁸⁾ demonstrated a standstill of the respiration by stimulation of the central

8) Bayliss, *Journ. Physiol.*, 1908, **37**, 264.

9) Martin and Mendenhall, *Americ. Journ. Physiol.*, 1915, **38**, 98.

10) Sollmann and Pilcher, *Americ. Journ. Physiol.*, 1912, **29**, 303.

11) Porter and Marks, *Americ. Journ. Physiol.*, 1908, **21**, 460.

12) Hunt, *Journ. Physiol.*, 1895, **18**, 381.

13) Stewart, cited in his "Manual of Physiology," London 1918, 188.

14) Mellé and Shipley, cited in Bayliss' "Vasomotor System," London 1923, 57.

15) Sherrington, *Ibid.*, 58.

16) Hooeker, *Americ. Journ. Physiol.*, 1907, **19**, 417.

17) Bainbridge, *Journ. Physiol.*, 1914, **48**, 332.

18) Hering, *Pflüger's Arch.*, 1924, **203**, 100.

19) Rosenthal, *Arch. f. Anat. und Physiol.*, 1881, **48**, 39.

20) Meltzer, *Arch. f. Anat. und Physiol.*, 1892, **59**, 341.

ending of the vagus, which, according to Rosenthal and Hering, is an inspiratory standstill, while Meltzer thinks it an expiratory one. Gruber²¹⁾ infers that the stimulation of various sensory nerves leads sometimes to the inspiratory standstill, sometimes to the expiratory one. Waller²²⁾ observed that when the vagus in the neck are severed on both sides and the central stump on one side is stimulated, the count of breathing is quickened.

Mangold²³⁾ has observed in the muscle-stomach of the fowl that when the unimpaired vagus is stimulated, its movement is inhibited and its tonicity relaxes, and that, if the nerves are severed and its central ending stimulated, the result will also be the same. Kato²⁴⁾ demonstrated also a slight inhibition of the intragastric pressure of hens' muscle-stomachs by the stimulation of the peripheral stump of the vagus. Iwai and Takeda²⁵⁾ found in dogs and rabbits that when the central stump of the vagus was stimulated, the tonicity of the stomach was relaxed while it was augmented by the stimulation of its peripheral stump. No such result was evident by the sensory nerve stimulation.

Thus we see that when the central stump of the vagus is stimulated an opposite effect is sometimes brought upon the blood sugar, adrenaline secretion, blood pressure, respiration, movement of the stomach, etc. from that of the peripheral stimulation of the nerve. Such effects often resemble those which are experienced during the sensory stimulation, but sometimes not, thus leading to a divergence of opinions among the investigators. I therefore attempted by routine experiments to examine, what effect is brought upon the blood pressure, heart beat, breathing and movement of the stomach and intestines when the central stump of the vagus is stimulated, and by comparing the results with those of the sensory stimulation, to ascertain the nature of those paradoxical phenomena.

METHOD OF EXPERIMENT.

In all experiments rabbits were chiefly used. They were bound in a holder equipped with an electric warmer. The vagus in the neck was

21) Gruber, *Americ. Journ. Physiol.*, 1917, **42**, 450.

22) Waller, cited in Flack and Hill's "Textbook of Physiology," London 1919, 266.

23) Mangold, *Pflüger's Arch.*, 1906, **III**, 163.

24) Kato (T.), *Pflüger's Arch.*, 1914, **159**, 6.

25) Iwai and Takeda, *Chosen-Igakkwai-Zasshi*, 1923, **45**, 338 (Jap.).

severed and a sling was fastened to its central stump. Of the sensory nerves the crural or sciatic nerve was used. The exposed part of the nerve was covered with cotton saturated with body-warm Ringer's solution. The blood pressure was registered from the carotid and the count of heart beats was conducted partly by auscultating through the stethoscope and partly by counting them on the kymograph. The breathing was registered on the kymograph by inserting a glass tube closely into the nostril and connecting it with a tambour.

In order to observe the movements of the stomach, the abdominal wall was cut open and a small rubber water-bag, with a glass tube attached to its one end, was inserted from the duodenum into the stomach through the pyloric portion, while the other end of the glass tube was connected by a rubber tube to the piston-recorder, thus making it to register on the kymograph. The intestinal movements were observed by ligating both ends of an intestinal loop of 5-8 cms. length, taking care not to disturb its blood supply and inserting the wider end of a funnel-shaped glass tube into an opening scissored in the wall near the anal end of the loop. The funnel tube was tied up tightly round the intestinal wall and filled, together with the intestinal canal, with luke-warm Ringer's solution and a piston-recorder connected with it enabled it to register the change of the intestinal pressure on the kymograph.

In experiments not specially mentioned no anaesthetics were used. The stimulation was made with an induction coil connected with a 2-volts accumulator, using platinum electrode.

THE EFFECT ON THE BLOOD PRESSURE.

Stimulation of the central vagus stump with a strong tetanizing current by means of a du Bois Reymond's induction coil at the coil distance of 30-0 cms. gives rise in non-anaesthetized animals to convulsion-like movements and agitation in the majority of cases accompanied by a rise of the blood pressure. There are various ways of showing the rise, the most common manner being that it falls temporarily soon after the stimulation and then shows a sudden rise, recovering the height previous to the stimulation, in a gradual way. Sometimes it rises suddenly without any preliminary fall; sometimes it falls for a time after the stimulation is interrupted, but is raised gradually again, and remains elevated for some time. Occasionally it is observed that a slight fall is kept up during the stimulation, but it turns suddenly to a marked rise when the stimulation

is stopped. Even under such strong stimulations, the blood pressure is sometimes reduced, but in such cases it usually rises if the coil distance is shortened.

If the coil distance is extended to 50–100 cms. the blood pressure falls slightly or remains unchanged. Even when the central stump of the vagus is stimulated by a weak current, a fall is observed, as was noted by Hunt¹²⁾ in the stimulation of the sensory nerves.

The rise of the blood pressure, due to the centripetal stimulation of the vagus is by no means affected by atropine administration, after which the stimulation of the peripheral vagus stump is non-effective. In an animal anaesthetized by an A.C.E. mixture or by paraldehyde, if the anaesthesia is relatively weak, the blood pressure makes a fall on being stimulated strong enough to cause its rise before the anaesthesia. In such cases, if the stimulation is strengthened, the blood pressure sometimes rises. If the anaesthesia is deepened, as the corneal reflex disappears or nearly so, the effect is, as a rule, a marked fall even with such a strong stimulation as the coil distance is nearly naught. The blood pressure curve under these conditions very much resembles the depressor fall (Fig. 1. A). This has been observed by Bayliss,⁸⁾ Sollmann and Pilcher¹⁰⁾ and others, and Bayliss⁸⁾ called it "depressor reflex."

A similar phenomenon was observed by Hunt¹²⁾ during the stimulation of the sensory nerve. I obtained the same result in an animal with its vagus together with the sensory, especially the crural nerve, stimulated. In an animal anaesthetized with A.C.E. mixture or paraldehyde, if the anaesthetic effect is not sufficient, the stimulation of the crural nerve with a coil distance of 30–10 cms. brings about a marked rise of the blood pressure, but with the advance of the anaesthesia, the blood pressure is lowered, showing a curve resembling the depressor curve.

Depression of the blood pressure in a deeply anaesthetic condition due to the stimulation of the central vagus stump or of the sensory nerve was clearly demonstrated even after the severing of the cervical vagi on both sides (Fig. 1. B).

The rise of the blood pressure by the sensory and afferent vagus stimulations is believed due to the contraction of the peripheral vessel (Sollmann and Pilcher)¹⁰⁾ or vessels in the splanchnic region (Stewart).¹³⁾ I have observed, upon the stimulation of the central vagus stump of a rabbit with both its splanchnics severed, a marked fall of the blood pressure. The same result was also obtained in an animal with all its abdominal viscera, save the stomach, liver, adrenals, kidneys and urinary

Fig. 1.

Upper tracing, carotid pressure under deep anaesthesia (corneal reflex being abolished); upper line, zero-line and stimulus indicator; lower line, time in 6 seconds.

- A. Effect of stimulation of central vagus stump.
- B. Effect of the same after division of both vagi.

change in the stimulation effect of the central vagus stump, there being always a rise of the blood pressure. In such cases also the stimulation of the crural nerve raised the blood pressure. Thus, when the central end of the vagus is stimulated, though the large brain is removed, the blood pressure may be raised as long as the medulla oblongata remains intact.

THE EFFECT ON THE HEART BEAT.

On stimulating the central vagus stump the rate of the heart beat is, in most cases, reduced, although sometimes an increase is noticed. Either increase or decrease seems to be dependent upon the strength of the stimulation. And whether it is stimulated in the neck or in the abdo-

organs, removed. In such cases the manner in which the blood pressure falls resembles the depressor fall. All these suggest that, in this rise of blood pressure, the excitement of the splanchnics may play an important rôle.

Next I examined the effect of the stimulation of the central vagus stump in an animal whose central nervous system had been cut at various sections, after it had been ascertained that the rise of the blood pressure, due to the stimulation of the central vagus stump, was not affected by opening its cranial cavity.

After setting a transversal section in the brain through the optic chisams, the afferent stimulation of the vagus is still followed by a marked rise of blood pressure. Lower sections, through the pituitary body, the pons Varolii or the proximal margin of the bulb, after which the corneal reflex disappeared and the breathing stopped, so that it required artificial respiration, showed no

Table I.

Pulse rate (in 6 seconds)	Blood pressure (mm Hg)	
30	116	Stimulation of central vagus stump, coil distance 40 cms.
25	134	
25	134	
24	136	
27	116	
28	116	
28	118	Stimulation of central vagus stump, coil distance 20 cms.
28	118	
27	120	
23	130	
23	136	
25	132	
25	134	Stimulation of crural nerve, coil distance 40 cms.
31	130	
28	—	
28	118	
29	108	
28	—	
29	—	Stimulation of crural nerve, coil distance 20 cms.
27	106	
29	106	
28	—	
28	116	
27	—	
32	114	Stimulation of crural nerve, coil distance 20 cms.
28	—	
28	110	
—	146	
—	124	
—	150	
26	126	
29	115	
28	—	

men, no special difference in the effect on the heart beat is noticeable (Table I).

Again, when the sensory nerve is stimulated, the rate of the heart beat shows a general tendency to decrease, showing sometimes, however, an increase.

Bainbridge's¹⁷⁾ announcement that when the central stump of the vagus is stimulated the rate of the heart beat is retarded, while on the sensory stimulation it is accelerated, is not in accordance with the result of the majority of my experiments, in which the sensory stimulation has shown a tendency to decrease as

in the case of the vagus stimulation.

The change in the heart beat does not necessarily go hand in hand with that in the blood pressure (Table I).

The fact that the rate of the heart beat decreases in most cases on the afferent stimulation of the vagus is probably due to the same kind of process as the reduction or the standstill of the heart beat in psychic emotion (Wagner)²⁶⁾ or at Goltz's abdominal-tap test.

26) Wagner, cited in Zuntz und Loewy's "Lehrbuch der Physiologie des Menschen," Leipzig 1920, 145.

THE EFFECT ON THE BREATHING.

The most frequent change affected, when the central end of the vagus is stimulated at 50-10 cms. of coil distance, is that the breathing comes to a standstill either at the expiratory or inspiratory period, but that it is only of short duration, followed soon after by a shallow, frequent breathing, and then by a deep, frequent breathing. The deep and quick breathing sometimes occurs during the stimulation, but more often after the stimulation is suspended. It seldom happens that deep, full and slow breathing is observed during the stimulation, but this gradually changes either into quick, deep breathing or is only reduced in depth.

The sensory stimulation gives rise often to deep and quick breathing, which is sometimes preceded, especially when the stimulation is strong, for a while by apnoea. Or it often happens that slow, deep breathing continues during the stimulation, afterwards being markedly accelerated. At a weak stimulation in many cases it only increases its frequency to a slight extent.

These changes in respiration seem to agree with those observed by Rosenthal,¹⁹⁾ Meltzer,²⁰⁾ Hering¹⁸⁾ and Gruber,²¹⁾ the stimulation of the central stump of the vagus bringing about effect similar to those of the sensory stimulation.

THE EFFECT ON THE MOVEMENT OF THE STOMACH
AND OF THE INTESTINES.

According to Auer's²⁷⁾ experiment the movement of the stomach of a rabbit is temporarily depressed when the animal is fastened, commences to inhale ether and the abdominal wall is incised. It also seems slower at the time of hunger than when it is well-fed. I tried also to perform an experiment on a hungry rabbit and found the movement of the stomach so slow and weak that I could not carry out my project. With the stomach full the movement commenced a short time after a rubber ball was inserted into it. So before the experiments I fed all the animals to their hearts' content.

If one side of the cervical vagus is cut and its central end is stimulated at a coil distance of 100-50 cms., the movement of the stomach is quickened and increases in amplitude, sometimes also in tonicities (Fig. 2. A).

27) Auer, *Americ. Journ. Physiol.*, 1907, 18, 347.

It is sometimes observed that the tonicity is augmented without increasing the amplitude. The acceleration of the movement used to discontinue so soon as the stimulation is interrupted, but in some cases lasts on for some time after the stimulation. Occasionally it comes forward after a while elapses after the commencement of the stimulation.

Fig. 2.

Upper tracing, stomach pressure (piston-recorder); upper line, time in 6 seconds; lower line, stimulus signal.

- A. Stimulation of central vagus stump, coil distance 10 cms.
- B. The same, coil distance 50 cms.

Under a strong stimulation at the coil distance of 30–0 cms., wild movements of the lever are sometimes brought about at the first stage of the stimulation, owing to the animal's convulsion; but after a short while the movement of the stomach is inhibited, the amplitude being abated and the tonicity relaxed, or is completely stopped (Fig. 2. B). The movement is often noticeably accelerated after the stoppage of the stimulation, or continues for a time in a depressed condition, finally being restored to its former state.

The same result was obtained by a similar experiment in which the other side of the vagus had been severed. Mangold²³⁾ has asserted that the inhibition of the move-

ment observed in a fowl's stomach, when the central end of the vagus was stimulated, failed to occur when the other side of the vagus was severed. But in my experiments on the rabbit, the movement was brought to a depression by strong stimulation, whether the other side of the vagus was cut or not.

In regard to the effect of the sensory stimulation upon the movement of the stomach, when the central stump of the crural nerve is stimulated at various coil distances, the automatic movement is quickened (Fig. 3. B). Under such a stimulation the stomach, atmost inactive before the stimulation, sometimes repeats several contractions during the process, or the

movement is accelerated, its amplitude and tonicity increasing. But if the stimulation is very strong, the result is, on the contrary, inhibition, the automatic motion is stopped and the tonicity retarded (Fig. 3. A). This behaviour remains the same if the vagus in the neck is cut on one or both sides, the movement being accelerated by a weak stimulation and depressed by a strong one.

Similar evidence is also ascertained in the automatic movement of the intestine. Thus the latter is accelerated on a weak stimulation applied to

the central end of the vagus or the sensory nerve, sometimes accompanied by augmented tonicity. On the contrary, it is arrested and the tonicity slackened when the stimulation is strong (Figs. 4 & 5).

GENERAL CONSIDERATIONS.

As above stated, when the central stump of the vagus is stimulated the effect on the blood pressure, rate of heart beat, respiration and movement of the stomach and intestine, seem to be similar to that of the stimulation of the sensory nerve. From this fact, it is believed proper to consider the effect brought about by the vagus stimulation as a sort of reflex phenomenon. This assumption is also supported by the evidence that the rise of blood pressure caused by the afferent stimulation of the vagus, like that

Fig. 3.

Upper tracing, stomach pressure (piston-recorder); upper line, time in 6 seconds; lower line, stimulus indicator; mark x, convulsion of animal.

A. Stimulation of crural nerve, coil distance 5 cms.

B. The same, coil distance 4 cms.

Fig. 4.

Upper tracing, movement of intestine (piston-recorder); upper line, stimulus signal; lower line, time in 6 seconds.

- A. Stimulation of central vagus stump, coil distance 80 cms.
- B. The same, coil distance 7 cms.

Fig. 5.

Upper tracing, movement of intestine (piston-recorder); upper line, stimulus signal; lower line, time in 6 seconds; mark x, convulsion of animal.

- A. Stimulation of crural nerve, coil distance 80 cms.
- B. The same, coil distance 30 cms.

due to the sensory stimulation, is depressed by deep anaesthesia.

The effects of the stimulation of these two nerves on the blood pressure and the movements of the stomach and the intestines, except the rate of heart beat and respiration, agree with each other on the point that the stimulation yields opposite results according to whether it is strong or weak. Considered from the change in the automatic movement of the stomach and intestines, when the afferent stimulation is relatively weak, the effect is rather similar to that of parasympathetic excitement, while a relatively

strong stimulation, on the contrary, gives rise to symptoms corresponding to sympathetic irritation. In the effect on the blood pressure we can also ascertain similar mechanism. Thereby, it appears regardless as to whether the conduction of the centripetal stimulation is carried on through the vagus or the sensory nerve.

Similar facts are also observed in psychic affection as well as in other reflex phenomena. Under strong psychic emotion, the blood pressure rises, the gastro-intestinal movement is depressed, cold on the skin accelerates for a time the movement of the stomach; besides there is a stand-still or depression of the heart beat under a psychic emotion or by Göltz's abdomen-tap test, etc.; all these are presumably due to a nervous mechanism similar to that of afferent nervous stimulation.

When we consider the changes in the rate of heart beat and respiration from the stand point of view of the changes in blood pressure and the movements of the stomach and intestines caused by comparatively strong nervous stimulations, our conception of the functions of the vegetative nervous system in all the organs seemingly throws us into a contradiction. But these afferent nervous stimulations are diffusely distributed in the central nervous systems regardless as to whether the vagus or sensory nerve is stimulated or as to whether the stimulation is strong or weak. Now, the effects brought upon the peripheral organs are different according to their susceptibility or according to the excitability of the sympathetic, parasympathetic, vaso-constrictor or vaso-dilatator centres.

During deep anaesthesia the blood pressure does not rise, but falls by a strong afferent stimulation, this is because the vaso-motor and vegetative centres are paralyzed.

SUMMARY.

1. The centripetal stimulation of the vagus, if comparatively strong, brings pressor effect and if comparatively weak, depressor effect on the blood pressure.

But, in an animal, whose splanchnics are severed or whose abdominal viscera are removed, a strong afferent stimulation of the vagus gives rise rather to a lowering, not to a raising, of the blood pressure.

Also in an animal deeply anaesthetized, the blood pressure is markedly lessened by a strong afferent stimulation. In one with its vagi on both sides cut the result is the same.

Even when the large brain is removed, so far as the medulla ob-

longata is preserved, the afferent stimulation produces a pressor effect.

2. The afferent stimulation, regardless of its intensity, lessens the rate of heart beat. An increase is rarely observed.

3. Respiration is depressed by the stimulation of the central vagus stump.

4. The automatic movement of the stomach and intestines is more or less inhibited by a relatively strong stimulation of the central vagus stump and is accelerated by a relatively weak stimulation.

5. Changes in blood pressure, rate of heart beat, respiration and movement of the stomach and intestines due to afferent vagus stimulation are similar to those caused by sensory nerve stimulation, with regard to the fact that they show themselves in opposite ways according to whether the stimulation is strong or weak and to the evidences shown in the experiments of anaesthesia, decerebration, etc. It may, therefore, be presumed that the change brought about by the stimulation of the central vagus stump is a reflex phenomenon similar to that due to the sensory nerve stimulation.