VAGAL STIMULATION BEFORE THE WEBERS

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I. Introduction

THE classical note by Eduard Weber and his brother Ernst Heinrich Weber[1] reporting "Experiments proving that the vagus nerves, stimulated by a galvano-magnetic apparatus, can slow and even arrest the movements of the heart" provided the first indisputable evidence for the suppression or inhibition of the activity of an organ by stimulation of an appropriate nerve. The enormous impetus to physiological thinking given by these observations is recognized even today in the widespread application of the concept of inhibition to the central nervous system and other physiological processes, and in the recent demonstration by Loewi, Cannon and others of the humoral factor in the activity of the autonomic nervous system.

While to the Webers is rightly due the credit for making the essential observations of the effects of vagal stimulation and for recognizing their real implications, a survey of earlier physiological literature reveals that cardiac inhibition by vagal stimulation had, in fact, been observed in animal experiments, and reports of these experiments published as early as two centuries before the brothers Weber. Their failure to be fully appreciated can be ascribed neither to the obscurity of their authors nor to the meager circulation of the journals in which they were reported, for both Boyle and Lower were involved, and Haller, as well as Senac, discussed them in the most eagerly read physiological publications of the time. Their neglect must be attributed rather to the circumstances in which they were carried out, and to the particular orientation to them of the physiological thinking of those days. Only when seen in their proper setting as part of a general investigation of the nature and cause of the heart beat is it possible to understand why experiments which demonstrated clearly the influence on the heart of stimulation of the vagus nerves were performed, and why also their significance should have escaped recognition.

II. The Cause of the Heart Beat

A. *The "subtle flame" of Hippocrates.* The problem of the cause of the heart beat has always been a subject of great interest among physiologists. The controversies which raged until recently between protagonists of the so-called "neurogenic" and "myogenic" theories were but the continuation of a discussion that has been carried on since antiquity. Hippocrates[2] was the earliest of those who have left their theories of the causation of the heart beat.

Within the heart, wrote Hippocrates, there burned a sort of vestal fire, so subtle that it escaped immediately through any incision made to reveal it. Air coming into the heart from the trachea and lungs fell upon the flame and was set into a violent effervescence which drove it out through the openings of the great arteries, and at the same time caused the swelling of the heart known as a diastole. In a similar

fashion a candle placed in a room without air currents will cause the air to move, now more, now less, just as the heart, containing more air than any part of the body, attracts and causes to move throughout the body the vital spirits. It is interesting to note that this idea of a vital flame in the heart, probably already very old at the time of Hippocrates, persisted to the time of Descartes[3] who wrote in his "Treatise on Man":

For this blood thus contained in the veins has no exit by which it can leave save that which leads it into the right chamber of the heart. And in the heart there is one of these flames without light, of which I have spoken, which renders it so hot and ardent that as fast as the blood enters into one of the two chambers, it swells promptly, and dilates, just as you can see for yourself to happen when you let blood or milk fall drop by drop into a hot flask. The fire which is in the heart has no other function than to dilate, heat and rarify the blood, which falls continually, drop by drop, by a passage from the vena cava into the right side of the heart, from where it exhales into the lungs, and from the pulmonary veins into the other ventricle from where it is distributed throughout the entire body.

This theory was modified to conform with the alchemical views of the early sixteenth century by Sylvius. The alkaline venous blood, meeting the acid chyle and also the acid bile, became effervescent and caused diastole. To this theory the learned Boerhaave objected that the blood was not alkaline, nor the chyle or gall acid, and even if they were mixed together no effervescence would take place, and further they never did come together in the heart.*

Richard Lower† was the first to put these theories to direct experimental test in the earliest recorded attempt to perfuse a living animal with a fluid other than blood:

But to decide experimentally whether or not any ebullition of blood helped the blood's movement at all, it occurred to me to see if the Heart would continue its movement undiminished, after I had drawn off the blood, and had replaced it intravenously by an equal quantity of other fluids, less likely to become lighter or to froth up. With this object in mind I drew off through the jugular vein of a Dog almost half of its total blood volume, injecting instead through the crural vein an equal amount of beer mixed with a little wine. This procedure I repeated several times in succession until, instead of blood, the fluid coming from the vein was merely a solution with less colour than the washings of meat, or than claret several times diluted. The Heartbeat, meanwhile, became only slowly more feeble, so that practically the whole of the blood was replaced by beer before life was replaced by death.

B. *Willis and the neurogenic theory.* "The System of Willis," says Haller,* "was much more subtly constructed and therefore received a much greater and more lasting support." Willis[6] realized, as had indeed many before him, that the heart was a muscle, and from the analogy with the other muscles of the body concluded that the heart, like them, depended upon the activity of the nerves supplying it for its rhythmic contraction. He recognized that the heart was different from skeletal muscles in that it was not under the control of the mind, and explained this difference by the mistaken anatomical finding that the nerves to the heart arise or are controlled from the cerebellum, while the voluntary nerves originate from the cerebrum. The more primitive structure of the cerebellum, its ab-

* Haller,[4] vol. 1, p. 905.

† Ref. 5, p. 66.

* Ref. 4, vol. 1, p. 905.

sence of convolutions, its smaller size, were all evidences that it played a more humble part and served the involuntary functions, while the more complex cerebrum carried out the more important duties. Thus it was that injuries to the cerebellum were so very dangerous, and led invariably to death, while injuries to other parts of the brain were less often fatal.

Willis was supported by a large number of experimenters who damaged the cerebellum, or removed it entirely, and observed the sudden death of the animal. Among the most ardent supporters of this doctrine was Mayow,[7] who attributed to the dura mater a contractile force, which in the cerebellum was the cause of the heart beat:

> Wherefore I consider it likely that the thicker meninges which surrounds the brain undergoes a sort of pulsation, and that by its contraction the blood driven to the brain is compressed; and that thus the nitro-aerial particles are pressed out of the mass of the blood, and driven into the brain in a way not very unlike that in which the other motive particles are forced into the motor parts by the constriction of the muscles. Such a pulse of the dura mater is confirmed by autopsy itself; for, in the fracture of the skull, part of the brain comes into view, it is seen to rise in a tumor, and immediately in turn to subside, which seems to be a motion of the brain after the manner of the heart's pulsation. For indeed, when I consider the thickness, the strength, and the nervous fibres of the dura mater, I can imagine nothing else but that that membrane like all others, is intended for the production of motion. . . .
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> Further I am not sure whether the pulsation of the heart or even the respiration, both of which are periodic, do not depend on the pulsation of the harder meninges surrounding the cerebellum.

But Vieussens, although his experiments seemed to corroborate Willis' theory, had remarked that the nerves of the heart did not in reality arise from the cerebellum, but from the brain-stem itself.* It soon also became apparent that injuries to the cerebellum were not invariably fatal as Haller† showed in the dog and cat:

> Exp. 152.—on a dog; from the notes of Mr. Zinn. The cerebellum having been pierced in the centre, all parts of the animal were agitated by convulsions. Nevertheless it did not die, even when the cerebellum was destroyed by turning the tourniquet around: for the heart continued to beat after this cruel operation.
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> Exp. 154.—on a cat. 28 Nov. 1750. I destroyed the brain and cerebellum of the animal, it lived after this enormous wound, and its thorax being opened I saw there the movement of the heart, and of the lung of the other side. Ferocious by nature, the animal still wanted to bite. The peristaltic movements and those of the heart continued for some time.

C. *Stimulation of the vagus.* But the argument remained that since the heart was a muscle it ought to receive its stimulus to contract from its nerves. Haller summarizes the question in a most lucid paragraph:‡

> Since the heart is in fact a muscle it would seem that it should have some characteristics in common with other muscles, therefore it should possess an intrinsic contractile force, and also another which comes from the nerves. Experiments with all muscles have shown that when the nerve to a muscle is stimulated that muscle rapidly and forcefully contracts which is called a twitch: but if the nerve be ligated all the force is lost with which the limb was previously moved. But the zealous dissectors were not satisfied with a bare analogy, and attempted to demon-

* Ref. 4, vol. 1, p. 908.
† Ref. 8, vol. 1, p. 208.
‡ Ref. 4, vol. 1, p. 882.

strate by experiments on the heart itself that this most important of all muscles depends for its contraction on the nerves. The majority chose for their experiments the eighth (vagus) nerves, without doubt because not only do the nerves of the human heart spring from them, but also the branches originating in the great sympathetic trunk follow along with the vagus nerves, according to the ancient dissectors, especially Fallopius. They therefore ligated and cut these nerves in living animals, and expected to see as a result the cessation of the heart beat, or the death of the animal.

Riolan, according to Haller,* was the first to try this experiment, ligating the vagus nerve in the neck of a living animal, with such meager results that the animal was not for a moment hindered in running about. One Propiscus Fortunatus Plempius concurred in this opinion. Nevertheless, Richard Lower† repeated the experiment, and found immediate change in the heart beat:

> The heart is, functionally, extremely important and necessary, and nature therefore exerts such care and solicitude in the execution of its movements, that, in addition to the important nerve-branches distributed thickly all over it, she has also prepared the cerebellum as a storeroom of animal spirits, so that there may be a continuous inflow of them into the heart. This organ is so dependent on their liberal and continuous inflow that, if this is cut off for even the smallest period of time, the heart's movement ceases there and then. If the nerves of the eighth pair are tightly ligatured in the neck, or are divided (which is much the same thing as far as the animal is concerned) it is remarkable how great a change suddenly occurs! The heart, which before beat quickly and regularly, begins to palpitate and quiver as soon as the ligature is applied; the wretched animal prolongs a weary life for a day or two to the accompaniment of heart tremor and excessive dyspnoea, and finally dies without warning.
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> The reason it does not die immediately after this ligature, is that besides the assistance which is brought to it by the recurrent nerve, there are beneath the ligature several small nerve branches from the intercostal spaces which are inserted into the eighth pair at the entry to the chest, before they send their little branches to the heart, and these branches furnish enough spirits to maintain a feeble movement. . . .

A dog on which Willis* performed the same experiment showed somewhat similar results, but Robert Boyle was able to obtain a clear cessation of heart beat for a time as the following report from the minutes of the Royal Society for 1664 indicates†: "There was also read an extract of Mr. Boyle's letter to the secretary, containing experiments of cutting in dogs the sixth pair of nerves, called par vagum; whereupon the pulse was quite altered and intermitted, and the dogs continued near four days alive; though under great discomposure."

By far the most complete report of the effects of vagal stimulation due to ligation is given by Ens, in his thesis for the Doctorate at the University of Utrecht in 1745.[10] The thesis as a whole is reprinted in Haller's "Disputationes Anatomicarum" and an abstract in French appears in the second volume of Senac's classical "Traité de la structure du coeur."‡ Immediately after ligation of both vagi in a dog, he reported, the respiration stopped, the voice disappeared, the arteries collapsed while the veins became engorged, the bladder discharged, and movements ceased. A few

* Ref. 4, vol. 1, p. 883.
† Ref. 5, p. 86.
* Ref. 4, vol. 1, p. 883.
† Ref. 9, vol. 1, p. 504.
‡ Ref. 12, vol. 2, p. 596.

feeble beats of the heart were noticed before death occurred.

If on the other hand, the ligatures were removed before death took place, the animal recovered rapidly. The heart beats, which were slow and weak, became stronger and gradually increased in rate. At first the ventricle beat but once to every six auricular contractions, but soon beat once to every five, then to every two, and finally the normal ratio was reestablished.

Sudden death following vagal ligature was also reported by Bohn, Berger, and Varignon* and by Haller himself who describes it in his "Mémoires sur les parties irritables et sensibles,"† the 181st experiment: "I ligated a nerve of the eighth pair, an experiment not too easily performed. The animal did not seem to feel this loss. I ligated the same nerve of the other side, and while I was tying the knot, the animal expired in a convulsion." He attributes this and other similar occurrences to an "unfortunate accident."

In the experiments we have recounted we find the complete picture of the effects of vagal stimulation, in all these cases by the tying of a ligature or by cutting: slowing and even complete cardiac arrest, profound A-V block returning to normal through states of diminishing block, and in the "trembling and palpitation" of the heart in Lower's experiments is to be recognized the irregular beat of ventricular "escape" from vagal influence.

In no instance, however, did the author realize that what he had in reality done was stimulate the vagus by the mechanical effect of tying the ligature; on the contrary he hoped by means of the ligature to suppress the supposed normal motor impulses to the heart.

* Quoted by Haller,[4] vol. 1, p. 885.
† Ref. 8, vol. 1, p. 224.

Whytt* does speak of attempting to stimulate the vagus mechanically, but the animals used were those in which the heart had already stopped, and where it was thought that by stimulation the heart could again be made to contract. Senac† credits the anatomist Petit with pinching the vagus nerves of a living animal without having noticed an increase in movement, while he himself stimulated the vagi in a dead animal without starting the heart to beat again. Fontana‡ stimulated the vagus of a living animal with electric shocks, without effect.

D. *The intrinsic nature of the heart beat.* These experiments were rapidly discredited by the steadily accumulating evidence that the heart could contract in the entire absence of any nervous system. Boyle[13] was able to keep a chick alive for two hours after its head had been cut off, and Redi§ removed the entire brain of a tortoise in November and it lived until the following May. Hooke** reported to the Royal Society in 1667 "that he had taken a whelp out of the uterus, and dissected it in the evening, and the heart beat the next morning when he came to look at it again."

It was also found that the heart was able to beat for longer or shorter periods after it was completely removed from the body of the animal, which Boyle[13] himself noticed in the viper and in other cold-blooded animals. Urbain Tosetti, in a letter published by Haller,¶ reports a similar observation in a dog:

> We repeated the experiments on the ir-

* Ref. 11, p. 355.
† Ref. 12, vol. 2, p. 319.
‡ Ref. 8, vol. 3, p. 230.
§ Ref. 11, p. 386.
** Ref. 9, vol. 2, p. 184.
¶ Ref. 8, vol. 2, p. 186.

ritability of the heart, the stomach, the intestines, the bladder, and the muscles of the thorax. We separated the heart from its vessels and placed it on the table. It continued its movements, which diminished progressively, for seven minutes and thirty-two seconds, when it stopped altogether.

Says Whytt*:

Even in man the heart retains a power of motion for some little time after its separation from the body; as appears particularly from the well known story of Lord Verulam concerning a malefactor, whose heart, having been out of his body, and thrown immediately into fire, leapt several times upward to a considerable height.

Harvey[14] was able to show that a heart of a cold-blooded animal might be cut up into small pieces, yet every individual piece would continue to beat. He likewise observed that the heart of the embryo chick is the first part to show movement. At about the same time Saviolus† also studied the chick embryo, and reported that:

. . . by the third day of incubation there is hardly a visible vestige of a brain in a chicken; nevertheless the movement of the heart is clearly noticed; it could hardly be attributed to the nerves.

That is not all: I tore away these obscure and unformed rudiments of the brain, but the movements of the heart were not in the least interrupted.

In the face of this steadily growing body of evidence for the intrinsic nature of the heart beat the few experiments which seemed to demonstrate a nervous action on the heart were discredited. Senac criticizes the experiments of Bohn in which ligature of both vagi caused cardiac standstill in the following words: "Such experiments attempted on old animals are always open to suspicion; the thorax is open, the lungs collapse, and blood stagnates there; thus the left auricle receives no more of this fluid and falls therefore into an inaction that can be attributed to the interruption of the circulation."*

But, he states:

It is difficult to prove that these nerves are entirely without action on the heart; the functions of nerves are not all the same, some are destined for voluntary movements, while others are the instruments or the organs of emotions: There are others that produce involuntary movements. We do not know what may be the function of the vagus nerves; we can however be certain that their action on the heart is not necessary for each movement of that organ; for its alternate dilatations and contractions persist for several days without the assistance of these nerves.†

It can be seen that the failure to recognize the true significance of the fairly numerous observations of vagal inhibition was largely due to the overwhelming interest in the cause of the heart beat itself. Secondarily, it resulted from the failure to recognize that a slowly tied ligature actually stimulated the nerve instead of suppressing its activity. With the conclusive summary of the evidence in favor of the intrinsic nature of the heart beat by Haller‡ and the fuller realization of the functions of the autonomic system resulting from the work of Bichat, the way became clear for an understanding of the regulatory function of the vagus nerve supply to the heart.

The only essential factor still missing was an adequate stimulating method and that too was soon to be provided. At almost the same time that Ens was

* Ref. 11, p. 356.
† Ref. 12, vol. 2, p. 597.
* Ref. 12, vol. 2, p. 597.
† Ref. 12, vol. 1, p. 425.
‡ Ref. 4, vol. 1, pp. 879-970.

writing his thesis at Utrecht, two zealous professors in Leyden were giving themselves and their wives electric shocks with what was the first Leyden jar. The story of how these experiments led through Galvani, Volta, and others to an appreciation of electro-physiology is told elsewhere, but it meant that the Webers had at their disposal an apparatus suitable for delivering tetanic stimuli. Vagal inhibition could now be produced consistently, and with the improved understanding of the heart and nervous system, its essential implications could be appreciated.

III. Summary

1. The effects on the heart of vagal stimulation were described nearly two centuries before the classical report by the brothers Weber. Slowing and even complete cardiac arrest, A-V block of varying degree, and vagal escape were observed following the stimulation by ligature or section of the vagus nerves.

2. Such experiments were offered as proof that the stimulus for cardiac contraction came from the central nervous system via the vagus nerves, since cutting or ligation of these nerves resulted in cardiac arrest. The overwhelming evidence that the heart beat does not depend on nervous factors led to the discrediting of these early studies.

3. Full appreciation of the results of vagal stimulation awaited the development of the proper stimulating devices, as well as a more complete understanding of the regulatory functions of the autonomic nervous system.

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