IV. THE EFFECT OF VAGAL STIMULATION AND OF COOLING ON THE LOCATION OF THE PACEMAKER WITHIN THE SINO-AURICULAR NODE.¹

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In a recent paper² we have shown by using the method of initial electric negativity to locate the origin of the heart beat, that stimulation of the vagus nerve might remove the seat of impulse formation from one part of the mammalian heart to another. So far as could be determined by means of initial negativity the pacemaking function always remained in some portion of the specialized tissue. Not only might the pacemaker migrate from the sinus region to the auriculo-ventricular node, but as first demonstrated by Zahn³ it might be restricted in its location to certain parts of the latter. This we confirmed, and in one case we were able to convert a coronary sinus rhythm into an auriculo-ventricular one by vagal stimulation.

The discovery that the auriculo-ventricular node need not function as a whole but that a part may act as the seat of impulse formation suggested at once that the sino-auricular node be investigated along similar lines. Such an investigation, however, was brought to mind not only by this previous work on auriculo-ventricular rhythm but also by certain curves we had obtained on comparing various parts of the sulcus terminalis with each other.

¹ The preceding papers of this series have appeared in Heart, 1914, v, Nos. 2 and 3.
² MEEK and EYSTER: Heart, 1914, v, No. 3.
³ ZAHN: Archiv für die gesammte Physiologie, 1913, cl, p. 247.
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Usually an electrode could be placed on a point which histological examinations had taught us was near the head of the node with assurance that this point would precede all others along the sulcus terminalis in negativity. At times, however, the area of initial negativity was lower than expected. A possible explanation was that the node was not functioning as a whole but that in these cases the lower part was acting as pacemaker. Experiments testing this idea seemed of value not only of themselves but for the light they might throw on the mechanism of vagus action and on the gradual shortening of the As-Vs interval which is often observed during the appearance and disappearance of auriculo-ventricular rhythm.

There is no experimental evidence which shows how small an amount of automatic tissue may function as pacemaker. The sinus node is, however, of considerable size and a division into functional parts seems quite possible. According to careful measurements by Lewis, Oppenheimer and Oppenheimer the sinus node in 7 dogs averaged 13.7 mm. in length and 2 mm. in width. Koch found the node 7 mm. long in a rabbit's heart. In 4 dogs' hearts examined histologically by ourselves the nodes averaged a trifle over 15 mm. in length. The sinus node is then of sufficient size to allow an analysis into parts by the electrical method of initial negativity.

Experimental Methods

In our first series of experiments the upper, middle and lower parts of the sinus node were compared with each other by means of the string galvanometer before, during and after periods of vagal stimulation. Non-polarizable electrodes were used which were attached to the heart with pieces of woollen yarn, the latter being stitched to the epicardium by a fine thread. This means of attachment insured a constant contact during all parts of the cardiac cycle. With suitable keys any of the points to be studied could be connected through the galvanometer and a photographic record of the movement of the string made on bromide paper with a long roll photographing apparatus. Precedence in activity

1 Lewis, Oppenheimer and Oppenheimer: Heart, 1910-11, ii, p. 147.
was then determined by the direction of the auricular wave. To identify this wave the mechanical contraction of the auricle was also recorded by air transmission to a Marcy tambour.

Although these experiments were positive, showing that during vagal stimulation the lower part of the sinus node might precede the upper in activity, it was felt that the results were not conclusive evidence of the shift of the pacemaker within the sinus node itself, since the beats at this time might have been arising in the auriculo-ventricular node, a condition which might show the lower part of the sinus node negative before the upper. To meet this objection it seemed necessary to compare the upper part of the sinus node with the lower, and the sinus node with the auriculo-ventricular node simultaneously. With the aid of two galvanometers this has now been done and it is these experiments that we wish to report at this time.

As mentioned before, three non-polarizable electrodes were placed as well as could be judged on the upper, middle and lower parts of the sinus node. To reach the auriculo-ventricular node a long curved glass electrode was passed down the external jugular vein and its end adjusted against the auricular septum just above the middle tricuspid valve. The middle sinus and auriculo-ventricular electrodes were now connected through the first galvanometer and the upper and lower sinus electrodes through the second. The electrodes were so connected that upstroke on the photographic curve in each case represented primary activity of the first member of the couple compared. In order to identify positively the auricular wave the mechanical contraction of the right auricle was recorded by means of air transmission. A signal to show the beginning and end of procedures and time in one-fifth seconds were also registered on the records. All the above were recorded on a single record, bromide paper of 12 cm. width being employed for this purpose.

Dogs were used in all experiments. The animals were morphinized, the chest opened and the heart exposed under ether anesthesia. The excellent artificial respiration apparatus recently described by Gesell and Erlanger was used. To this was added an electric heating coil which was thrown into circuit by a thermo-
regulator and relay. In this way the air delivered from the tank was maintained at 55° C. and the mixture leaving the ether bottle was kept at approximately 37° C. With this slight modification of the Gesell-Erlanger apparatus the difficulties and inconveniences of artificial respiration seem almost entirely overcome.

The hearts were removed after the experiment and preserved in formalin. The position of the auriculo-ventricular electrode was carefully noted and in the first experiments histological examinations of the sinus region were made. In all hearts examined the position of the electrodes was either on or near enough the part desired to justify our conclusions. In the latter experiments the hearts have not been studied histologically but the electrodes were placed with extreme care and judging from the fairly constant position of the sinus node we feel certain they were either on or near the ends of the sinus node.

The vagi were stimulated with tetanizing currents from a Harvard induction coil. The most desirable strength of stimulus was found to be one that only slightly showed the heart. Pencils of ice and ethyl chloride sprays were used to cool the sinus node.

**Experimental Results**

1. *Vagal Stimulations.*—Three experiments were carried out in which comparisons of the upper sinus region with the lower, and of the sinus node with the auriculo-ventricular node, were made simultaneously during vagal stimulation. Thirty records were taken in 19 of which the right vagus was stimulated and in 11 the left. The following are the most important results obtained by a study of these records.

In 10 of the 30 records instances were found either of single beats or series of beats in which the upper curve comparing sinus and auriculo-ventricular node remained unaltered in direction, while the lower curve comparing the upper and lower parts of the sinus node had reversed. Fig. 1 illustrates a case of this kind. In the first two cycles of this record the auricular wave of each curve begins with an upstroke, indicating that the sinus node preceded the auriculo-ventricular node (upper curve) and that the upper part of the sinus node was active before the lower
(lower curve). In the third cycle at the end of a two-second period of left vagal stimulation the upper curve remains the same in direction, but the auricular wave of the lower curve has reversed. This indicates that while primary activity was still in the sinus region as shown by the upper curve, the point of initial activity, as shown by the reversal in the lower curve, had shifted from the upper to the lower part of the sinus node. In this case the condition did not persist, for the fourth cycle shows a return of the curves to their original forms.

In Fig. 2 is reproduced a portion of a record showing the

![Image](http://ajplegacy.physiology.org/DownloadedFrom/10.220.33.3)
return to normal after a left vagal stimulation which had lasted three seconds. A reversal of the lower curves was produced which consisted of 14 beats and outlasted the stimulation two and one half seconds. The last two cycles of this series are the first two showing in the figure. The return of the pacemaker to the upper part of the sinus node is made evident by the third and fourth cycles of the lower curve beginning with an upstroke. It is such examples as these which have led us to conclude that vagal stimulation may depress only a part of the sinus node, allowing another part to take up the pacemaking function.

The ultimate automaticity of a part is determined by its rate of discharge. If according to the hypothesis of vagal action which will be presented later in this paper, a region of high automaticity, the upper part of the sinus node, has been depressed by vagal stimulation, and a region of less automaticity, the lower part of the

Figure 2. Comparisons the same as in Fig. 1. Impulse formation was shifted to the lower part of the sinus by vagal stimulation. The reversal of the auricular wave in the third cycle of the lower galvanometer shows the return to normal.
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sinus node, has taken on the pacemaking function, then the heart rate should be slower. This idea is amply borne out by our records. The second cycle in Fig. 1 is about .08 sec. longer than the average. In Fig. 2 the cycles showing reversal of the lower curve are .03 sec. longer than the normal.

Although most of the cycles occurring with the pacemaker in the lower part of the sinus node have shown shortened As-Vs intervals as may be seen in the third cycle of Fig. 1, we have not felt like drawing conclusions from such results since the As-Vs interval may be greatly modified by the dromotropic influence of the vagus. Such data we believe will be much more valuable from experiments in which the sinus node is depressed in some way, as by localized cooling, which would not produce a widespread influence on conduction.

In several records we have observed during vagal stimulation a splitting of the auricular wave in the sinus node - auriculo-ventricular node lead. Examples of this may be seen in Figs. 1 and 2, the condition disappearing in the latter record as vagal influence ceased and the pacemaker returned to the upper part of the sinus node. We have previously shown 1 that a sino-auricular interval exists amounting to about .025 sec. In these curves it seems that the sino-auricular conduction was so depressed by vagal action that the contraction of sinus as well as auricle produced its effect on the galvanometer. This occurrence we have noted in previous experiments and have discussed its possible significance in a former paper. 1 The lower record does not show the two waves since here the two electrodes were each on sinus tissue and the contraction of the auricle produced little or no effect.

In our experiments the left vagus was much more effective in shifting the pacemaker to the lower part of the sinus node than the right. In only two cases did we secure results from the right vagus. This at first seems somewhat contradictory to the recent work which is in favor of a relative homo-lateral distribution of the vagi, but on closer analysis our results rather support such conclusions. Removal of the pacemaker from one part of the sinus node to another can only be brought about by weak vagal stimulation. This is evident from the absence of extra systoles,

1 Eyster and Meek: Archives of internal medicine, 1913, xi, p. 204.
reversed cycles and block in all our successful records. This proper
degree of stimulation may have been easiest obtained with the
left vagus for the very reason that it sends fewer fibers to the
sinus node. Our stimulations of the right vagus were usually
strong enough to produce extra systoles and other irregularities
and consequently fewer cycles with the pacemaker removed
merely to the lower part of the sinus node.

2. Cooling the Upper Part of the Sinus Node with Ice and
Ethyl Chloride. — It seemed to us that if it was the depressant
action of the vagus on the upper part of the sinus node which
allowed the lower part of the node to express its automaticity by
assuming the pacemaking function, then any procedure which would
depress the upper part of the node ought to give similar results.
Experiments were therefore planned in which the upper part of
the sulcus terminalis was cooled with ice or ethyl chloride sprays.
Seven such experiments were carried out in each of which long
series of reversals were obtained indicating that the pacemaker
had shifted to a lower part of the sinus node.

In Figs. 3 and 4 may be seen the removal of the pacemaker to
the lower part of the sinus node and its return as portrayed by
the electrical curves. A pencil of ice was applied to the upper
part of the sulcus terminalis two seconds before the beginning of
Fig. 3. The sixth cycle of the figure shows a reversal of the
auricular wave in the lower curve. Between Fig. 3 and Fig. 4
a space amounting to four and one half seconds of the record and
including 10 cycles with reversed auricular waves has been omitted.
In the fourth cycle of Fig. 4 the auricular wave of the lower curve
begins with an upward stroke, showing the return of initial activity
to the upper part of the sinus node.

This shifting in the point of negativity we have secured re-
peatedly in each of the seven experiments by cooling either with
ice or ethyl chloride. That the response was due to some specific
effect on the upper part of the node was proved in each experi-
ment by cooling the lower part of the sulcus terminalis. This
procedure was invariably ineffective. On freezing the entire sinus
node with ethyl chloride auriculo-ventricular rhythm appeared.

In these experiments as in the previous ones concerned with
vagal stimulation, the descent of the pacemaker to a lower part of
the sinus node was always marked by a lengthened cardiac cycle. This is best seen in Fig. 4 where the shortening of the cycles as the pacemaker returns is easily noted. The length of cycle during the time in which the auricular wave was reversed equalled .458 sec. This shortened down to .411 sec. as the pacemaker migrated upward.

Another point of great interest was the shortening of the As-Vs interval which occurred as the pacemaker moved downward. This may be most clearly seen in Fig. 3. The As-Vs interval of the first two cycles equals .102 sec. while in the last cycle of the figure the interval has become reduced to .091 sec. This reduction though slight has been constant. Its significance will be discussed in the next section.
3. Injection of KCl. — On the basis of Howell's theory that vagal inhibition is due to a liberation of K ions in the automatic tissues it seemed that a migration of the pacemaker from the upper part of the sinus node might be expected if an amount of KCl just sufficient to depress this part could be injected into the blood stream. This was accordingly tried in three experiments and in a fourth the sulcus terminalis was painted with 5 and 10 per cent KCl solution.

In two of the experiments following injections of KCl there was a reversal of the lower curve showing that the pacemaker had left the upper part of the sinus node. In the first of these cases the condition was brought on by an intravenous injection of 6 c.c.

1 Howell and Duke: This journal, 1928, xxi, p. 51.
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of a 5 per cent KCl solution in $1\frac{1}{2}$ minutes. This had, however, been preceded shortly before by an injection of 4 c.c. In this experiment the tracings did not return to normal and investigation showed that a coronary sinus rhythm had been produced. This might be readily explained on the basis that the dose of KCl was large enough to paralyze the entire sinus node. In another experiment following an injection of 10 c.c. of a 5 per cent KCl solution in $1\frac{1}{2}$ minutes there was a shifting of the pacemaker from the upper to the lower part of the sinus node as shown by reversal of the lower curve and the absence of any change in the upper. The curves later returned to normal.

Although these experiments are few in number they show that in KCl we have another means of depressing the upper part of the sinus node with the assumption of impulse formation in some lower part. This elective depressant action would seem to lend support to Howell's theory of vagus inhibition.

**DISCUSSION**

Most of the recent physiological work has emphasized the part played by the specialized tissue of the heart in the initiation and conduction of excitation. Our own work has shown that with the heart in situ beats arising outside of the specialized tissue are extremely infrequent, if they occur at all. By electrical methods we have found in agreement with Ganter and Zahn\(^1\) and Zahn\(^2\) that if the sinus node as a whole is destroyed, depressed or isolated some lower part of the specialized tissue at once takes on the pacemaking function. Strong vagal stimulation was found to be an effective means of depressing the entire sinus node and producing auriculo-ventricular beats. In the present paper we have shown that with weak vagal stimulation or other means of moderate depression such as local cold, the seat of impulse formation may migrate from the upper to the lower part of the sinus node.

Following the principle long ago laid down by Gaskell and Engelmann and so often insisted on by Hering, that the most

\(^1\) Ganter and Zahn: Archiv für die gesammte Physiologie, 1912, cxxv, p. 335.

\(^2\) Zahn: Archiv für die gesammte Physiologie, 1913, cli, p. 247.
automatic part of the heart is the pacemaker at that given mo-
moment, our experiments detailed above have led us to the following
conception of the action of the specialized tissue and the vagal
mechanism of the heart. The specialized tissue of the heart
exhibits from above downward progressively diminishing degrees
of automaticity. When the dominant rhythm of the heart arises
from the highest parts of this system the rate is maximal, other
conditions remaining constant, and when it arises from the lowest
parts the rate is minimal. Intermediate rates result from some
part between these assuming the role of pacemaker. Each part
of the specialized tissue has of course its own maximum and
minimum rate, the exact rate at which it functions at any time
depending on nervous influences, temperature and other factors
affecting it. It is this maximum which is highest for the upper
part of the specialized tissue, that is the sinus node, and which
decreases progressively downward.

Those fibers of the vagus that influence the rate of the heart,
the chronotropic fibers, are distributed to the specialized tissue
comprising the sino-auricular and auriculo-ventricular nodes and
their branches. The specific function of the chronotropic fibers of
the vagus is to depress automaticity in the specialized tissue.
The mass of innervation, that is to say the number of fibers dis-
tributed to any region, is an important factor in determining the
amount of effect produced on this region when the vagus trunk is
stimulated. With weak stimulation of the vagus only those regions
would be affected which receive a proportionately large number of
fibers. With stronger stimulation the effect might spread to other
regions of specialized tissue receiving a less profuse chronotropic
innervation. The greater number of vagus chronotropic fibers are
distributed to the most automatic part of the sino-auricular node,
that part which normally acts as pacemaker for the whole heart.
Other parts of the sinus node, with a smaller degree of inherent
rhythmicity, receive relatively fewer chronotropic fibers. The
auriculo-ventricular node and its connections, representing that
part of the specialized system which has a relatively lower degree
of automaticity, receives a still smaller number of chronotropic
vagus fibers.

Light vagal stimulation, as in stimulation of the vagus trunk
with a weak electrical current, will affect to an appreciable degree only that part of the sino-auricular node which possesses the highest degree of automaticity. The automaticity of this part will be depressed until it is lower than that of some other portion of the node and the latter will at once assume the control of the heart rhythm, or in other words, become the pacemaker. The net result is a slowing of the whole heart.

To give a concrete example one may suppose that there are two points within the sino-auricular node, \(A\) and \(B\), which have different degrees of automaticity, such that \(A\) is able to excite excitations at the rate of say 100 to 70 beats per minute, while \(B\) can initiate impulses as a result of its inherent automaticity only at rates between say 80 and 50 per minute. Unless there is still a third region which has a higher rate of discharge, \(A\) will dominate all other regions and will act as pacemaker for the whole heart at a rate somewhere between 100 and 80. If now the vagus is stimulated, and if this nerve due to more profuse distribution of its fibers to \(A\) has a greater influence on this region than on \(B\), then the automaticity of \(A\) may be so reduced that its power to discharge impulses will fall below that of \(B\), say to 70 or 75 per minute, \(B\) not being markedly depressed since it has a less profuse vagal innervation, will now be the most automatic part of the heart and will at once assume the role of pacemaker for the whole heart. Change in rate is due first to depression of \(A\) and second to a change in the seat of impulse formation from a point of higher to lower automaticity.

Still stronger stimulation of the vagus may now depress the power of \(B\) and the pacemaking function will then be assumed by a third region of still lower automaticity. In this way it may be understood how a stronger and stronger stimulus may cause a progressive reduction in heart rate accompanied by a migration downwards of the pacemaker. If finally the stimulation of the vagus becomes sufficiently strong so that even the lower parts of the specialized tissue with their poor innervation are depressed, all impulse formation may cease and we have for a time a complete vagal inhibition of the heart.

We are aware that there have been intimations of some such conception of the automatic tissues of the heart and of vagal action
as that presented above, but we do not believe it has been previously presented in a complete form and certainly it has never been supported by the physiological evidence now at hand. This theory of the specialized tissues in the heart and of vagal action has support in and has been deduced from the following experimental facts.

1. As shown in the present paper slight degrees of vagal stimulation may cause the pacemaker to migrate from the upper to the lower part of the sinus node. This change is always accompanied by a slight slowing in rate.

2. Other depressing agents such as ice and ethyl chloride when applied to the upper part of the node cause the seat of impulse formation to remove to lower parts of the node.

3. If the sinus node be subjected to extremes of vagal stimulation or cooling with ice and ethyl chloride, or if the node be injured, destroyed, or isolated by crushing, cutting or the application of drugs, the pacemaker of the heart migrates temporarily or permanently to lower parts of the specialized tissue, usually the auriculo-ventricular node.

4. Flack has shown that there is a profuse supply of chronotropic fibers to the sino-auricular node, greater than to other parts of the heart.

5. In auriculo-ventricular rhythm, in which the pacemaker resides in the auriculo-ventricular node, the chronotropic action of the vagus is very much reduced.

The shortening of the As-Vs interval observed in our experiments when the lower part of the sinus node became pacemaker seems to us of considerable interest. The gradual shortening of this interval, sometimes seen as auriculo-ventricular rhythm appears or disappears, has always been a difficult thing to understand. We have recently ventured to suggest that such variations of the As-Vs interval were in large measure associated with a shifting of the physical location of the pacemaker. The data now at hand seems to substantiate that view.

We have previously shown that conduction from the sinus

1 Flack: Journal of physiology, 1910-11, xli, p. 64.
2 Eyster and Meek: Heart, 1914, v, p. 119.
node to the auriculo-ventricular node cannot be by way of the auricle. The path to the auricle is probably a diffuse one directly across the sulcus terminalis while the path to the auriculo-ventricular node is a linear one, just how well circumscribed we are not able at present to say. As the seat of impulse formation passes downward the time of access to the ventricle shortens and that to the auricle remains the same or lengthens. Since it is now known that the lower part of the sinus node and the auricular portion of the auriculo-ventricular node may act as pacemaker, the gradual shortening of the As-Vs interval may well be explained in large part at least by the migration of the pacemaker through these regions.

On the hypothesis that the specialized tissue of the heart is the seat of all automatism and conduction, then any point to which the pacemaker is forced should lie in this system. The migration of the seat of impulse formation from the head of the sinus node first to a lower part of the node thus becomes very suggestive. If there is a definite path between the sinus node and the auriculo-ventricular node, then this new seat of impulse formation should be in it. If there is a special path from the higher auricular parts to the lower, it seems that it must pass through the lower part of the sulcus terminalis. If the connection between the sinus node and the auriculo-ventricular node is diffuse, then the migration of the pacemaker to the lower part of the sinus node has no interest so far as a circumscribed path of conduction is concerned.

**Summary**

With the aid of two string galvanometers, one comparing the upper with the lower part of the sinus node and the other comparing the sinus node with the auriculo-ventricular node, it has been shown that by means of vagal stimulation, cooling of the upper part of the sinus node or injection of potassium chloride, the point of initial negativity may be made to shift from the upper to the lower part of the sinus node. This has been interpreted as showing that during these procedures the pacemaker of the dog's heart may move from the upper to the lower part of the sinus node.
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During the time that the seat of impulse formation resides in a lower part of the sinus node there is a lengthening of the cardiac cycle and a shortening of the Ap-Vs interval.

On the basis of work presented in this paper and others of the series, a theory has been presented which correlates our experimental results on the automatic and vagal mechanisms of the vertebrate heart. It is believed that the specialized tissues of the heart exhibit from above downward progressively diminishing degrees of automaticity. Vagal chronotropic innervation of the specialized tissue also diminishes from above downwards. The most automatic portion of the specialized tissue acts as pacemaker for the heart. The function of the chronotropic fibers is to depress this automaticity. When the automaticity of the pacemaker is reduced below that of a lower part the latter assumes dominance and becomes pacemaker. In this way the vagus, if the stimuli are properly graded, may cause the pacemaker to descend from the upper part of the sinus node where it resides normally, to the lower part of the sinus node, and finally even to the auriculo-ventricular node.