612.178.1

FURTHER EXPERIMENTS ON VAGAL INHIBITION OF THE HEART BEAT[1].

By G. L. BROWN and J. C. ECCLES.

(*From the Physiological Laboratory, Oxford.*)

(*Received June* 22, 1934.)

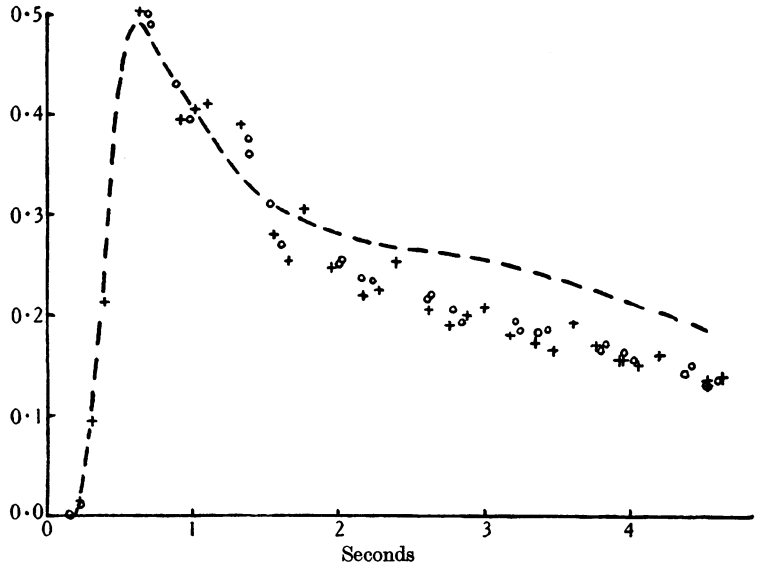
The inhibitory effect of two vagal volleys.

One volley down each vagus.

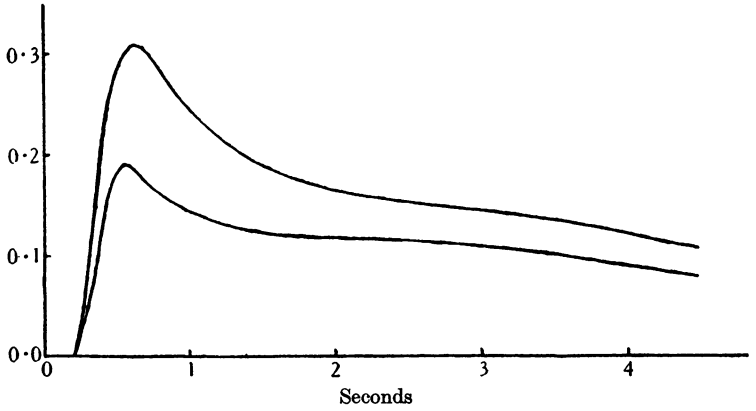
In the preceding paper it has been shown that a single volley in either vagus produces an inhibition of the rhythm of the pacemaker of the heart. If one vagus nerve is stimulated simultaneously with or at any time after the stimulation of the other vagus nerve, an additional inhibition is produced. A series of observations is shown in Pl. I, fig. 1, and in Text-fig. 1 the course of this combined inhibitory effect is represented by the method of plotting used with the single vagal inhibitions, the interval between the vagal stimuli being 90σ for the points represented by crosses and 16σ for the circles. Both series of points are seen to lie on the same curve, and in experiments in which the stimuli were applied simultaneously to the right and left vagi the curves so obtained have also been identical with those obtained with short intervals between the stimuli. This absence of any refractory period effect indicates that the right and left vagi are distributed independently to the pacemaker, *i.e.* there is no appreciable convergence of their pathways in the ganglia or elsewhere.

In Text-fig. 2 are shown the inhibitory curves for each vagus alone, and the broken line in Text-fig. 1 shows the curve derived by addition of the two curves of Text-fig. 2. In its earliest part this derived curve is in good agreement with the points actually obtained for the inhibitory lengthenings, but after several cycles the derived curve is definitely higher. Thus during the first few cycles after the double vagal stimuli

[1] For the introduction and the method of experiment the previous paper may be consulted.



Text-fig. 1. Points of an inhibitory curve plotted as in the previous paper, but obtained with two stimuli, one to the left vagus being followed at either 16σ (circles) or 90σ (crosses) by one to the right vagus. The broken line shows approximately the curve derived by summing the inhibitory curves obtained independently for the right and left vagi in Text-fig. 2. Normal cycle $=430\sigma$.



Text-fig. 2. Inhibitory curves of right and left vagi, the right vagal curve being the higher of the two.

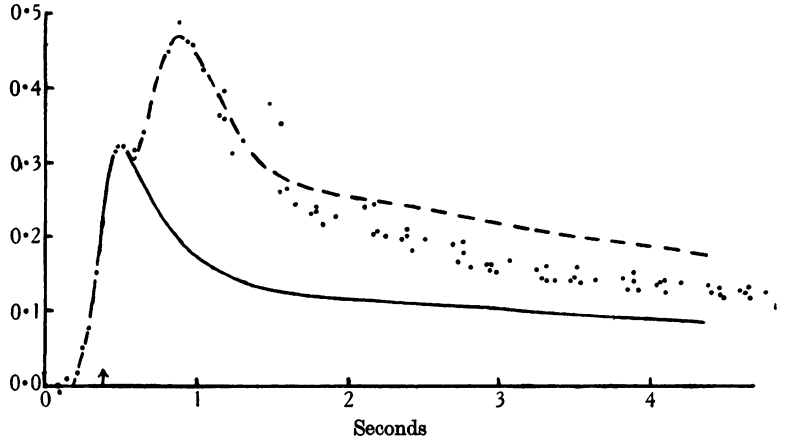
there is a summation of inhibitory lengthenings; for later cycles, however, the double vagal stimuli are less effective than would be expected from direct summation. This deficiency of the double inhibitory effect begins at the same time as a submerged secondary inhibitory wave appears in the single inhibitory curves, so the "occlusion" of the inhibitory effect seems to be due to "occlusion" of this secondary wave. In six other experiments of this type similar results were obtained in four, *i.e.* there was summation of the inhibitory lengthenings for a few cycles after the vagal stimuli and, with the appearance of the secondary inhibitory wave, "occlusion" developed.

The remaining two experiments were irregular, double vagal stimuli producing sometimes a lengthening in excess of the summed effect of the single vagal curves, but more frequently a deficient lengthening. However, in these experiments the secondary inhibitory wave was also associated with "occlusion." Displacement of the pacemaker may explain the deficient lengthening observed in these two abnormal experiments, but the action potentials of the beats also indicated that displacement of the pacemaker probably occurred in some of the experiments where summation of the inhibitory curves was observed. Further experiments are therefore needed before these anomalous results can be explained.

Since, as was seen above, the right and left vagi are distributed independently to the pacemaker, a volley down each would produce a concentration of A.C. substance equal to the sum of the concentrations produced by either volley alone. The observed summation of the inhibitory lengthenings during the primary inhibitory wave is therefore in agreement with observations in the previous paper which indicated that within limits the lengthening of the cycle produced by A.C. substance was directly proportional to its concentration. The "occlusion" of the secondary wave is in agreement with the conclusions derived from comparisons of maximal and submaximal inhibitory curves, and from the effects of eserine and atropine [Brown and Eccles, 1934]. "Occlusion" is always a characteristic feature of the secondary wave, and it should eventually be of importance in indicating the way in which that wave is produced. The "occlusion" of the secondary wave has made it impossible to determine the effect of summation on the descending part of the primary wave. Hence it has not been possible to obtain any evidence bearing on the complications considered in the previous paper, namely, the relatively slower rate of the enzymatic destruction with large concentrations of A.C. substance, and the "adaptation" of the rhythmic mechanism to the inhibitory effect of A.C. substance.

Both volleys down the same vagus.

More extensive series of observations have been made of the effect produced by applying both stimuli to the same vagus nerve. When the second stimulus follows at a long interval, the double vagal curve for the first few cycles may correspond with a direct summation of two single vagal curves, *e.g.* in Text-fig. 3 with an interval of 390σ the broken line represents the summed curve and the points the actual experimental observations. Such observations are similar to those usually obtained when one volley was fired down each vagus, so it may be concluded



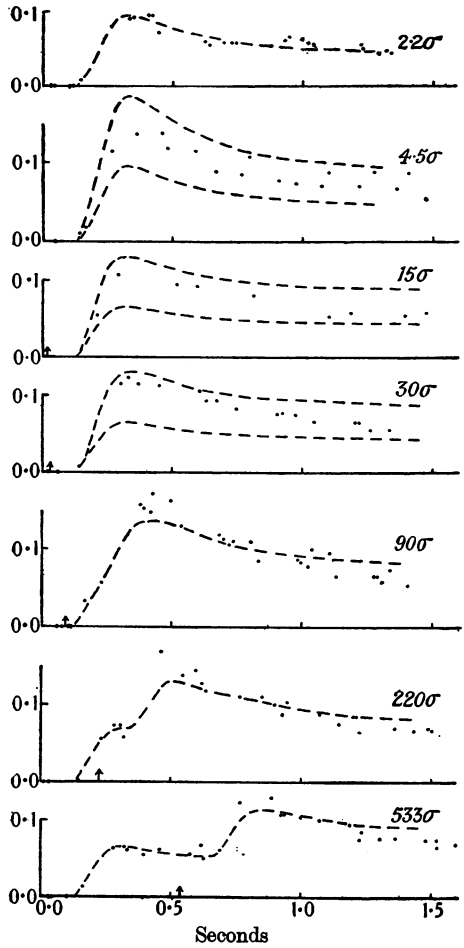
Text-fig. 3. Points of an inhibitory curve obtained with two stimuli to the right vagus at an interval of 390σ. The second stimulus is shown by the arrow. The curve derived by summing the two single inhibitory curves at that interval is shown by the broken line, the single inhibitory curve by the continuous line.

that the second volley has liberated the same amount of A.C. substance as the first volley, *i.e.* that there has been a complete recovery in the "secretory" mechanism.

About 1 sec. after the second vagal stimulus the points definitely lie below the summed curve, showing that an "occlusion" has developed in the combined inhibitory effect. As previously observed this "occlusion" runs parallel with the secondary inhibitory wave, which in Text-fig. 3 is recognizable only as a hump on the descent of the primary wave. The well-developed secondary wave in Text-fig. 5 is more markedly occluded.

Text-fig. 4 shows a series of curves obtained with different intervals between the two vagal stimuli. At long intervals the maximum double

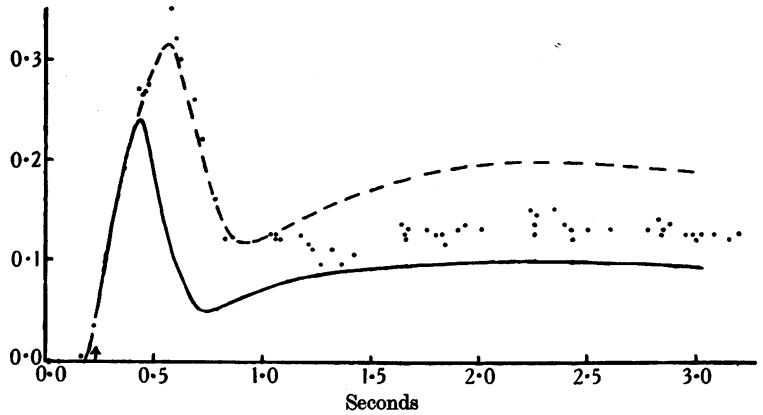
vagal effect is somewhat greater than additive, but at an interval of 30σ the double vagal effect is definitely less than additive. At an interval



Text-fig. 4. Points of a series of inhibitory curves obtained by applying two stimuli to the right vagus at the intervals stated for each figure. Normal cycle $=275\sigma$. The second stimulus is shown by the arrow in the last five figures. In the first four the curve for the single stimulus is shown by a broken line, and in all but the first a broken line shows the curve derived by combining two such single inhibitory curves at the stimulus interval obtaining for each figure.

as short as $4{\cdot}5\sigma$ the double vagal effect has decreased but little further, while at $2{\cdot}2\sigma$ the second vagal stimulus is without any effect. This of course is due to the absolutely refractory period of the nerve fibres, a

value of 2·2–4·5σ being given for the B_2 group [cf. Brown and Eccles, 1934] by Bishop and Heinbecker [1930]. The deficiency at 30σ could not be due to a relatively refractory period of the nerve fibres, though the existence of a synaptic relay in the ganglion must not be forgotten; however, in the superior cervical ganglion the action potential indicates that the relatively refractory period of the synaptic transmission is not longer than 10σ for the fast B_2 fibres [Eccles, 1934*a*], and Brown [1934] finds a relatively refractory period of not more than 15σ for conduction through the superior cervical ganglion. Moreover, at an interval of 30σ the double vagal stimulus produced little further inhibition than at 4·5σ,



Text-fig. 5. Points of a double inhibitory curve obtained concurrently with the single inhibitory curve of Text-fig. 8 [Brown and Eccles, 1934], the time of the second stimulus being shown by the arrow. The broken line shows the curve derived by summation of two single inhibitory curves at the stimulus interval, and the continuous line shows the single inhibitory curve.

so it appears that two factors are involved in producing the deficiency of summation. The one at short intervals is presumably due to the refractory state of the nerve fibres, and the other is only recovered from after a relatively long interval. The latter effect might be due to the vagal volley producing a partial exhaustion of the "secretory" mechanism of postganglionic fibres, so that there would be a diminished liberation of A.C. substance by the second volley reaching those fibres. In the experiments of Text-fig. 4 recovery from this exhaustion appeared to be complete in 90σ. A possible alternative explanation would be that some fibres in the vagus trunk exerted an inhibitory effect on the postganglionic cells, *i.e.* a second volley finds some of those cells inhibited and so sets up a smaller postganglionic volley. An inhibitory effect of

this type actually occurs in the superior cervical ganglion [Eccles, 1934*b*].

In some experiments the recovery was not nearly complete in 0·5 sec., while in other experiments a second vagal volley even as short as 12σ after the first produced its full effect. In such cases it was not possible to distinguish a deficiency effect apart from the relatively refractory period. It may be that the inhibitory terminals were provided with a store of A.C. substance sufficient to enable the second vagal volley to liberate the full amount in spite of the closely preceding volley.

Witanowski [1925], Plattner [1926], Engelhart [1930] and Chang and Gaddum [1933] have found that alcoholic extracts of the heart contain considerable quantities of A.C. substance, which in mammals is chiefly confined to the auricles. The first three observers found that this A.C. substance was considerably increased by prolonged tetanic stimulation of the vagus, and so it has been assumed [cf. Feldberg and Krayer, 1933] that the vagus acts primarily by forming A.C. substance, and not by liberating it from a preformed store. Chang and Gaddum have criticized this view on the grounds that even in the absence of nerve stimulation large quantities of A.C. substance may be extracted from tissues. In addition they found that nerve stimulation for even half an hour or longer failed to increase the A.C. equivalent of the submaxillary gland.

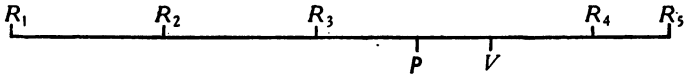
In the above experiments it has been seen that a second stimulus only 12σ after the first produced its full inhibitory effect, *i.e.* an impulse passing along a postganglionic fibre only 12σ after a previous impulse liberated a full amount of A.C. substance. This quick recovery of activity is evidence supporting the view that the A.C. substance is liberated from a preformed store. However, an amount of A.C. substance can be extracted from the mammalian auricle (vagus not stimulated), which is vastly in excess of that liberated by two vagal volleys, so it is surprising that in some experiments a second vagal volley liberates a deficient quantity of A.C. substance even at an interval as long as 0·5 sec. after a previous volley. In such cases the preformed store of A.C. substance which is indicated by the extraction experiments must require some time for its mobilization.

THE ACTION OF A SINGLE VAGAL VOLLEY SET UP DURING THE CYCLE SUBSEQUENT TO A PREMATURE BEAT.

In a previous paper [Eccles and Hoff, 1934*a*] the cycle following a single premature beat has been studied by observing the effect of a second premature beat set up at varying phases of this premature beat cycle.

In the present paper the premature beat cycle is subjected to further investigation by setting up single vagal volleys at varying times throughout its course.

Pl. I, fig. 2, shows a series of observations from one of the eight experiments in which this investigation has been carried out. In observations 1, 3, 7, 9 and 11 a premature beat was set up by a stimulus applied to the pacemaker and 160σ later an induction shock was applied to the vagus nerve. In observations 3, 9 and 11 the vagal volley obviously produces a great lengthening of the premature beat cycle, while in observations 1 and 7 the vagal volley is much less effective. The other observations are controls, 5 and 13 showing the effect of a premature beat alone, and 2, 4, 6, 8, 10, 12 and 14 showing the action of a vagal volley when it was not preceded by a premature beat. On account of their longer curtailed cycles and consequent shorter premature beat cycles observations 1 and 7 may be distinguished from observations 3, 9



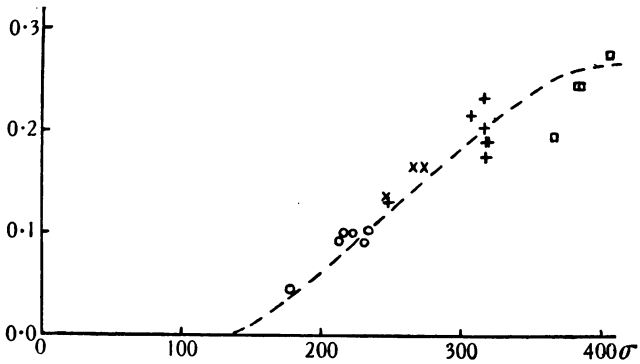
Text-fig. 6. Diagram showing action of a single vagal volley set up during a premature beat cycle. Full description in text.

and 11. The vagal volley would be set up nearer to the end of such short premature beat cycles and this would provide a simple explanation of its much smaller inhibitory effect in observations 1 and 7. Observations 12 and 14 show that a similar small shift of the vagal stimulus relative to a normal cycle is also accompanied by a very great increase in the inhibitory lengthening of that cycle.

A closer investigation of the effect of single vagal volleys on premature beat cycles is facilitated by the method of plotting illustrated by Text-fig. 6. R_1, R_2 and R_3 are the consecutive normal beats of the pacemaker, and P is a premature beat which would be followed by the premature beat cycle PR_4, if the inhibition produced by a vagal volley set up at V had not lengthened the cycle to R_5. For any duration of the curtailed cycle R_3P, the duration of the premature beat cycle PR_4 may be determined from the control observations with single premature beats alone. R_4R_5 is the inhibitory lengthening of the premature beat cycle and it may be expressed as a fraction of the normal cycle R_2R_3 in order to make the curve comparable with the normal inhibitory curve. This step is justified by previous work [Eccles and Hoff, 1934*a*] which showed that the building up of excitement is the same during the latter parts

of premature beat cycles and of normal cycles. The inhibitory curve is constructed by plotting for each observation the quotient R_4R_5/R_2R_3 as ordinate against VR_5 as abscissa.

The points of Text-fig. 7 have been calculated in the above way and are seen to be in fairly good agreement with the normal inhibitory curve, shown by the broken line. A series of observations taken with any one interval between the stimulus to the pacemaker and that to the vagus does not give a sufficient range of the inhibitory curve. Several series of observations therefore have to be taken with different intervals, *e.g.* the observations of Text-fig. 7 are made up of four series with intervals ranging from 0·285 to 0·575 of a cycle.



Text-fig. 7. Points of an inhibitory curve for a single vagal volley derived from the inhibition of premature beat cycles by the calculation described in the text. Normal cycle = 360 σ. The broken line shows the inhibitory curve obtained with normal cycles. The points show four series of observations with different intervals between the stimulus setting up the premature beat and the vagal stimulus, the intervals, measured as fractions of a normal cycle, being as follows: circles, 0·575; oblique crosses, 0·50; upright crosses, 0·435; squares, 0·285.

In four other experiments there has also been good agreement between the inhibitory curve derived from premature beat cycles and the normal inhibitory curve, and in one of these experiments there was good agreement when the rhythm was slowed by tetanic stimulation of the other vagus. The three experiments in which agreement was not present will be considered later.

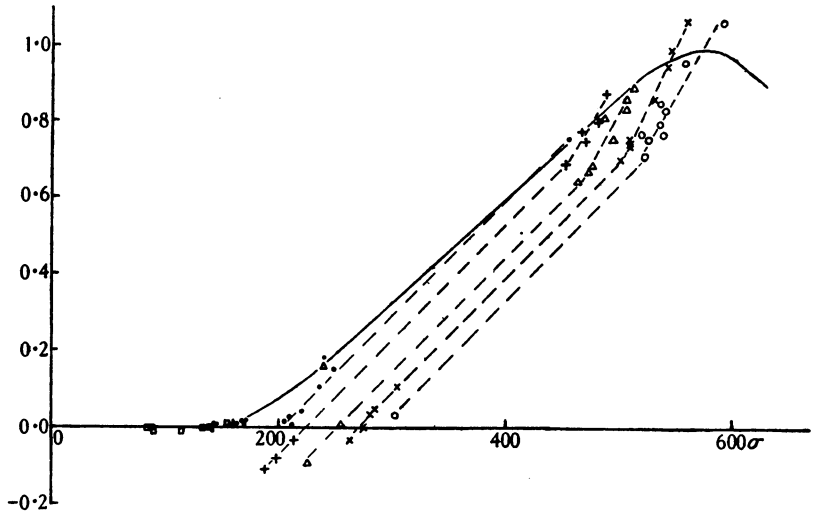
In discussing the action of a single vagal volley the conclusion was reached that the lengthening of a cycle was related to the concentration of the A.C. substance at the end of that cycle, the next beat being delayed until the increase of excitement above threshold quantitatively just antagonized the inhibitory effect of the A.C. substance. The similarity

between normal inhibitory curves and those derived from premature beat cycles indicates that, when the end of a premature beat cycle is delayed by inhibition, the building up of excitement continues in exactly the same way as it would do with a normal cycle. Moreover, this building up of excitement beyond the normal end of a premature beat cycle follows the same course no matter what the length of the preceding curtailed cycle, for in a series of observations, *e.g.* Text-fig. 7, the premature beats were set up at all possible phases of a normal cycle. Therefore not only is the building up of excitement during the latter part of a premature beat cycle similar to the rise of excitement in the normal cycle [Eccles and Hoff, 1934*a*], but, when the termination of a premature beat cycle is delayed by a vagal volley, the building up of excitement continues to follow a course which is similar to that occurring with a normal cycle similarly lengthened. The inhibitory lengthening of the cycles following a premature beat cycle is also normal in amount, being unaffected by the preceding premature beat. This finding is in agreement with the previous conclusion that the setting up of a beat has no influence on the inhibitory effect of the A.C. substance.

Aberrant inhibitory curves calculated from subsequent cycles.

In three experiments the inhibitory curve calculated from premature beat cycles has shown a systematic deviation from the normal inhibitory curve. This deviation has been particularly obvious in the experiment illustrated by Pl. I, fig. 3. The first six observations of this figure are arranged from above downwards in order of diminishing duration of curtailed cycles, the next two observations are controls of the premature beats alone, and the last three are controls of the vagal volley alone. Observations 1–4 seem fairly normal, being comparable with the observations of Pl. I, fig. 2. Thus on account of the long curtailed cycle the premature beat cycle is almost unaffected by the vagus in observation 1 (cf. observations 1 and 7, Pl. I, fig. 2), but in observations 2, 3 and 4 it suffers a considerable inhibitory lengthening (cf. observations 9, 10 and 11, Pl. I, fig. 2); however, in these three observations the inhibitory lengthening diminishes as the curtailed cycle shortens. The further shortening of the curtailed cycles seen in observations 5 and 6 has been accompanied by a sudden accentuation of this diminution of inhibitory lengthening. In fact a comparison with the control observation 8 shows that the vagal volley has actually shortened the premature beat cycle.

In this experiment five other series of observations were taken with different intervals between the stimuli setting up the premature beat and the vagal volley, and, as the curtailed cycle was shortened, a similar sharp transition occurred in all except the series with the longest interval,

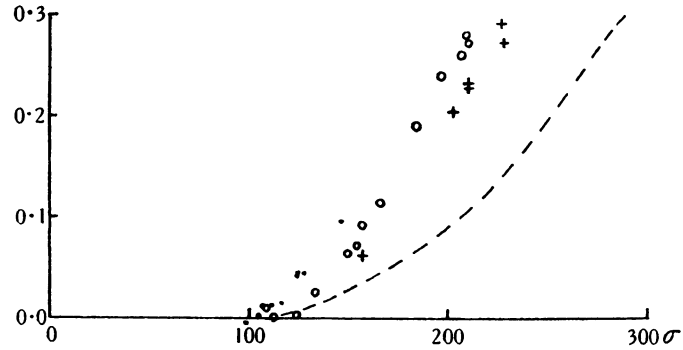


Text-fig. 8. Points of aberrant inhibitory curves for premature beat cycles derived as in Text-fig. 7. Normal cycle=335σ. The continuous line shows the normal inhibitory curve [see Fig. 19, Brown and Eccles, 1934]. There are six series of observations with different intervals between the premature beats and the vagal stimuli as follows: squares, 0·74; dots, 0·595; upright crosses, 0·53; triangles, 0·45; oblique crosses, 0·385; circles, 0·335. On the lower part of the normal curve lie all observations of the first series, and those observations of the series shown by dots (8), upright crosses (1) and triangles (1) which have long curtailed cycles. With the shorter curtailed cycles of these three latter series and even with long curtailed cycles of the series shown by oblique crosses and circles the points lie on the oblique broken lines beginning usually slightly above the normal inhibitory curve near its summit and descending downwards and to the left as the curtailed cycle shortens. Finally, as the curtailed cycle shortens to less than 0·61 there is a sudden transition (indicated by the oblique broken lines) to those groups of points lying slightly above or below the base line.

the critical length of the curtailed cycle being always about 0·61 of a normal cycle. In Text-fig. 8 all the observations with the inhibited premature beat cycles of this experiment are plotted after calculation in the above way, and the normal inhibitory curve for a single vagal volley is also drawn. When the curtailed cycle is almost 1·0 in duration, there is in all series fairly good agreement with the normal inhibitory curve. A progressive deviation occurs as the curtailed cycle shortens

to 0·61, at which point there is an abrupt transition in all series except that with an interval of 0·74 of a cycle between the two stimuli. In all observations of Text-fig. 8 except two in the series with an interval of 0·385, the cycle next following the premature beat cycle suffered a normal inhibitory lengthening. In these two exceptional cases the lengthening of that cycle was also much less than normal.

Thus in this experiment the inhibitory effect of a vagal volley distinguishes sharply between normal cycles and premature beat cycles following short curtailed cycles. No such



Text-fig. 9. Another aberrant series of inhibitory curves derived from premature beat cycles. Background tetanic stimulation of right nervi accelerantes (cycle=260σ). The broken line shows the normal inhibitory curve. There are three series of observations with different intervals as follows: dots, 0·66; circles, 0·59; crosses, 0·50. The points of each series lie on a different curve. The temporal order of the observations (middle series first) showed that this was not due to a gradual change in the preparation.

difference of behaviour has been detected by setting up a second premature beat during a premature beat cycle [Eccles and Hoff, 1934*a*], but this effect of two premature beats has not been investigated in any of these three aberrant experiments. However, in the above experiment the control observations with single premature beats alone showed no change corresponding to the sudden transition in the vagal effect as the curtailed cycle is shortened to less than 0·61 of a normal cycle. In the only control observation (Pl. I, fig. 3) of a single premature beat with a curtailed cycle shorter than 0·61 (observation 8), the premature beat cycle is seen to be terminated by a beat having an abnormal action potential. But in other control observations of this experiment a normal beat has terminated the premature beat cycle, even when the curtailed

cycle was shorter than the critical duration, and the cycle next following the premature beat cycle has been normal in duration.

Inhibitory curves derived as above from premature beat cycles have been very similar to Text-fig. 8 in one of the other two experiments giving aberrant curves, but there was in this experiment no sharp transition, even though the curve similarly fell below the base line (0·0) with short curtailed cycles. In the remaining experiment the inhibitory curve derived from premature beat cycles has shown the reverse deviation from the normal inhibitory curve. Text-fig. 9 shows the points calculated as above from observations obtained with three different intervals between the stimuli setting up the premature beat and the vagal volley. The normal inhibitory curve is also drawn. With long curtailed cycles the calculated points lie close to the normal inhibitory curve, but, as the curtailed cycle shortens, the inhibitory lengthening of the premature beat cycle increases much more rapidly than is the case in the normal type of experiment, *i.e.* the premature beat cycle becomes much more susceptible to inhibitory lengthening than is a normal cycle. The observations of Text-fig. 9 were taken during tetanic stimulation of the right nervi accelerantes. With normal rhythm the inhibitory curves calculated from premature beat cycles deviated in the same direction from the normal inhibitory curves, but to a much less extent.

The aberrant inhibitory effects on premature beat cycles are similar in many respects to the early and late subsequent beats which may follow two premature beats set up at a short interval apart, and both phenomena are almost entirely restricted to those experiments in which there was a relatively great lengthening of single premature beat cycles [Eccles and Hoff, 1934*b*]. It therefore seems probable that there is a common explanation for these two types of behaviour. In the previous paper it was shown that the production of early subsequent beats could be satisfactorily explained on the basis of fractionation of a rhythmic centre composed partly of exciting and partly of inhibiting components. This hypothesis has already been suggested as a possible explanation of the double-wave type of inhibitory curve [Brown and Eccles, 1934], and it might well be extended to cover the aberrant effects of vagal volleys on premature beat cycles.

Aberrant inhibitory effects on premature beat cycles are interesting because they agree with the effects of early premature beats in showing that the functioning of a rhythmic centre is not susceptible of a simple explanation. For example, after a premature beat the rhythmic centre

may appear to be behaving perfectly normally and yet its response to a single vagal volley may be as extraordinary as those shown in Pl. I, fig. 3, and Text-figs. 8 and 9. It has been shown that the responses to early premature beats are not explicable simply by assuming a temporary displacement of the pacemaking function to some other rhythmic centre in the sino-auricular node or elsewhere [Eccles and Hoff, 1934*b*], and a similar conclusion also holds for aberrant effects of vagal volleys on premature beat cycles.

Conclusions.

The conclusions drawn in this and the previous paper may be arranged under five headings.

(1) *The negative chronotropic fibres of the vagus.* The right and left vagi are distributed independently to the pacemaker, there being no demonstrable common pathways in the ganglia or elsewhere. Impulses are conducted in the preganglionic fibres at about 30 metres a second, and the absolutely refractory period is less than $4{\cdot}5\sigma$.

(2) *The liberation of* A.C. *substance from the postganglionic fibres of the vagus.* In some experiments a second volley has liberated the same amount of A.C. substance as the first, even when it follows at an interval as short as 12σ. This supports the view that the A.C. substance is liberated from a preformed store. However, in other experiments a second volley produces a smaller amount of A.C. substance even when it is at a much longer interval after the first volley. This may be due to a delay in the mobilization of the preformed A.C. substance.

(3) *The time course of the concentration of the* A.C. *substance acting on the pacemaker.* There is a latent period of rather more than 100σ before a volley in the postganglionic fibres produces an inhibitory effect on the pacemaker. It is probable that most of this time is occupied in diffusion of A.C. substance from the point of its liberation to the site of its action on the rhythmic mechanism of the pacemaker, but a part of the delay may occur in the rhythmic mechanism of the pacemaker. The concentration of A.C. substance acting on the pacemaker continues to increase for about 0·3 sec., but even during this period it is being rapidly destroyed by the specific esterase present in the tissues, and after the maximum is attained this rapid enzymatic destruction continues, the concentration of A.C. substance being halved in every 0·4–0·8 sec.

(4) *The action of* A.C. *substance on the rhythmic mechanism of the pacemaker.* The following provisional hypothesis has been put forward.

The rhythmic mechanism of the pacemaker sets up a beat when its excitement reaches a certain threshold intensity. A.C. substance inhibits by acting as a quantitative antagonist to this excitement, the setting up of a beat being delayed until the excitement is built up to such an intensity that the uninhibited excitement attains a threshold value. For about 0·3 of a cycle after the normal time of a beat the excitement increases linearly, and so the concentration of the A.C. substance is proportional to the lengthening of the cycle, but thereafter the excitement increases at a progressively slower rate.

(5) *The action of the rhythmic mechanism of the pacemaker.* The above increase of excitement usually follows a similar time course with premature beat cycles, but in some experiments the aberrant inhibitory curves which have been obtained with premature beat cycles seem to indicate that there has been a fractionation of the rhythmic centre. A similar explanation has also been suggested for the common double-wave type of inhibitory curve, for no simple explanation has proved satisfactory.

SUMMARY.

The inhibitory curve for two vagal volleys, one being in each vagus, usually is identical with the sum of the primary waves of the two single inhibitory curves. There is always occlusion of the secondary inhibitory waves. When both volleys are in the same nerve and at a sufficiently long interval, the primary wave of the double inhibitory curve is also usually identical with the summed curve. Two factors seem responsible for the deficiency obtaining with short stimulus intervals. The relatively and absolutely refractory states following the first volley will diminish the effect of a second stimulus applied at intervals less than about 12σ after the first. But in many experiments the first volley has a diminished effect at much longer intervals—even at 0·5 sec. This may be due to a partial exhaustion of the mobilized A.C. substance in the postganglionic fibres.

Single vagal volleys have been set up at varying times during premature beat cycles. Inhibitory curves have been constructed from such inhibited premature beat cycles, and, as would be expected, they usually appear to be identical with the inhibitory curves obtained from normal cycles. But in two experiments the inhibition of the premature beat cycles was much less than that of normal cycles, and in one experiment the inhibition was much greater than normal, the deviation from normal increasing in all cases as the curtailed cycle was shortened. In some

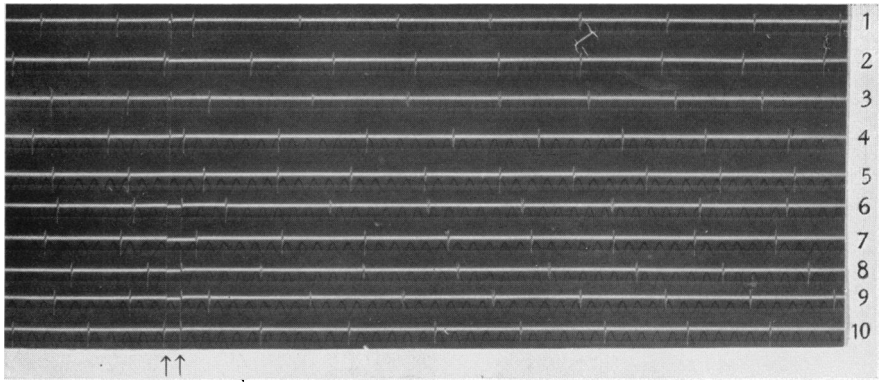


Fig. 1.

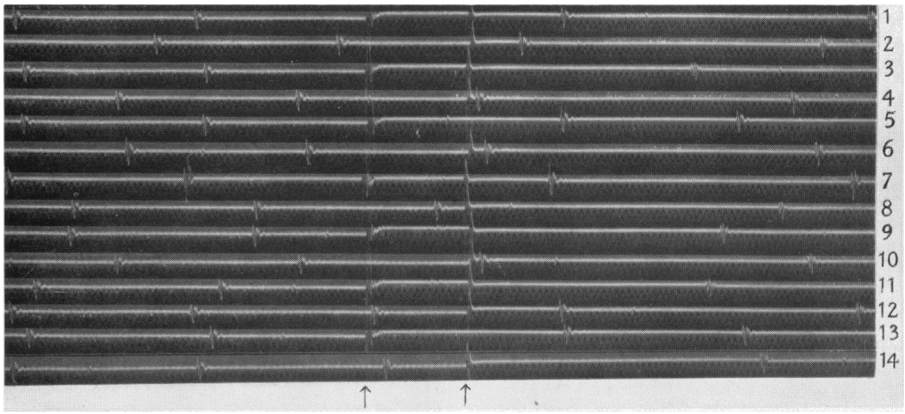


Fig. 2.

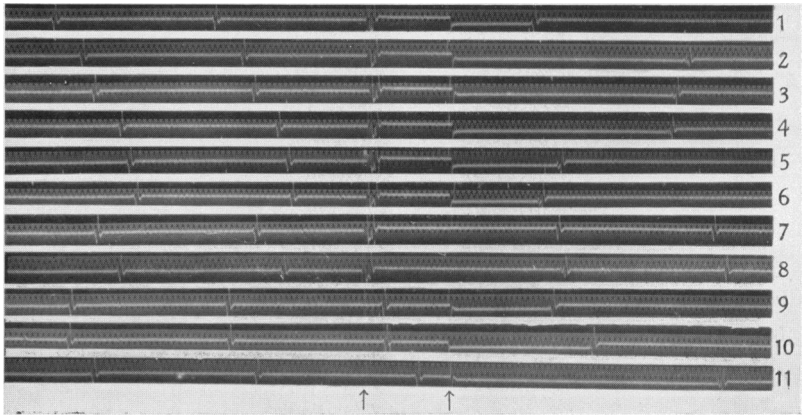


Fig. 3.

To face p. 257

respects these three experiments were similar to the experiments with early premature beats.

We have to thank the Christopher Welch Trustees for defraying the cost of the photographic materials, and one of us (J. C. E.) wishes to express his gratitude to the Medical Research Council for a personal grant.

REFERENCES.

Bishop, G. H. and Heinbecker, P. (1930). *Amer. J. Physiol.* **94**, 170.
Brown, G. L. (1934). *J. Physiol.* **81**, 228.
Brown, G. L. and Eccles, J. C. (1934). *Ibid.* **82**, 211.
Chang, H. C. and Gaddum, J. H. (1933). *Ibid.* **79**, 255.
Eccles, J. C. (1934 *a*). *Ibid.* **81**, 8 *P.*
Eccles, J. C. (1934 *b*). *Ibid.* **82**, 25 *P.*
Eccles, J. C. and Hoff, H. E. (1934 *a*). *Proc. Roy. Soc.* B, **115**, 327.
Eccles, J. C. and Hoff, H. E. (1934 *b*). *Ibid.* B, **115**, 352.
Engelhart, E. (1930). *Pflügers Arch.* **225**, 721.
Feldberg, W. and Krayer, O. (1933). *Arch. exp. Path. Pharmak.* **172**, 170.
Plattner, F. (1926). *Pflügers Arch.* **214**, 112.
Witanowski, W. R. (1925). *Ibid.* **208**, 694.

EXPLANATION OF PLATE I.

Fig. 1. A series of observations as in Pl. I, fig. 1 of previous paper, but in observations 1, 3, 6, 8 and 9 one stimulus was applied to the left vagus and one to the right, the interval being 16σ with the first two and 90σ with the remaining three observations (the times of the stimuli are indicated by the two arrows). In observations 2 and 7 one stimulus was applied to the left vagus only, and in observations 4 and 10 to the right vagus only. In observation 5 neither vagus was stimulated. Tuning fork, 1 d.v. $= 100\sigma$.

Fig. 2. A series of observations in which premature beats have been set up by single induction shocks applied to the pacemaker (shown by first stimulus artefact), a single stimulus (shown by second stimulus artefact) being applied to the right vagus during the cycle subsequent to the premature beats. The times of the two artefacts for all observations are indicated by the two arrows. Many observations are controls with either the premature beats or the vagal stimuli alone. Full description in text. Tuning fork, 1 d.v. $= 10\sigma$.

Fig. 3. A series of observations as in Fig. 2, but in another experiment. Full description in text.