THE INFLUENCE OF TEMPERATURE AND OF ENDOCARDIAC PRESSURE ON THE HEART, AND PARTICULARLY ON THE ACTION OF THE VAGUS AND CARDIAC SYMPATHETIC NERVES.

By G. N. STEWART, M.A., D.Sc., M.D., *George Henry Lewes Student.*

(Plates III.—VI.)

(*From the Physiological Laboratory, Cambridge.*)

Section I. The influence of temperature on the activity of the cardiac nerves in the frog and toad.

Through the recent researches of a number of observers, and particularly of Gaskell[1], we have come to look upon the action of the cardiac nerves rather as a direct action upon muscular fibres than as a mediate action through nerve cells. The state of the heart itself, and particularly of the muscle of the heart, has come to be considered a great, and sometimes a decisive, factor in determining the effect of impulses reaching the heart along the cardiac nerves. The action of some of the chief cardiac poisons, notably muscarin, is, according to this view, essentially an alteration of the muscular fibres, an alteration which manifests itself in various ways, among others in the changed relations of the cardiac muscle to the cardiac nerves[2].

Now of all the physical conditions which affect physiological activity there is none which goes so deep as temperature. The action of heat, too, is a simpler action than that of poisons, or at least we seem to understand the first steps in it better. It imprints itself on the whole flow and movement of the vital processes in characters which are rarely quite illegible. The heart of a cold-blooded animal is normally subject to wide fluctuations of temperature, so that for a very great range the

[1] "On the Rhythm of the Heart of the Frog and the Action of the Vagus Nerve." *Phil. Trans.*, 1882, III. p. 993; This *Journal*, III. Nos. 5 and 6; *Brit. Med. Journ.*, 1882, p. 572; *Proc. Camb. Phil. Soc.*, Vol. IV. Pt. V; This *Journal*, IV. p. 43; &c.

[2] Gaskell, This *Journal*, IV. *loc. cit.*; VIII. p. 404.

conditions are still physiological. Further, by altering the temperature it is possible to alter the rate of physiological change in fairly strict gradation. And although it is not possible to confine the action to any particular constituent of the heart, yet for this very reason we are sure that the cardiac muscle is affected. And if, by inference or direct experiment, we can exclude the other elements, we may be able from the changes produced in the action of the cardiac nerves by change of temperature, to learn something of the process by which these nerves influence the heart, and to guess at the nature of the physiological linkage which binds the nerve fibre to the muscle. In the hope of being able to add a little to that common stock of knowledge in which the key to the solution of this great problem may some day be found, I thought it desirable for the above reasons, among others, to make a systematic series of observations on the influence of the vagus and sympathetic at temperatures ranging between the extreme limits compatible with the life of the tissues. So far as I am aware, no such observations have hitherto been made on the Batrachian sympathetic. The influence of temperature on the action of the frog's vagus has been studied to some extent by Luchsinger and J. M. Ludwig and others, but chiefly or solely by the method of simple inspection, which, of course, can give but imperfect information.

Section I. A. The influence of temperature on the action of the vagus.

Historical. The general question of the effect of heat on the heart is so mixed up with that of the effect of heat on the vagus function that it will be well not to separate the literature, although the influence of extreme temperatures on the heart itself will be afterwards discussed in a separate section. (See Section IV.)

Schelske[1] observed that when the frog's heart is heated to 28°—35° C. it beats more quickly, and then stands still; during this stimulation of the vagus by the interrupted current causes a tetanic condition, while single induction shocks are followed by single contractions.

Hoffmann[2] tried Schelske's vagus experiment on the carp, but failed to get his result. In the frog in one or two cases stimulation of

[1] *Ueber die Veränderungen der Erregbarkeit durch die Wärme*, Heidelberg, 1860.

[2] *Beiträge zur Anatomie u. Physiologie des N. vagus bei Fischen*, 1860; Diss. Giessen, 1860.

the vagus by induction shocks caused strong pulsations, first of the auricle then of the ventricle. The pulsations stopped when the current was shut off.

Cyon[1] stated that when the frog's heart was suddenly raised from the normal temperature by serum and air at 40° C. the beats, instead of becoming immediately more rapid and smaller, as happened in gradual warming, became larger and less frequent. The form of the curve registered by the manometer with which the heart was connected was quite like that given by stimulation of the vagus at the normal temperature. This continued 1 to 2 minutes. If the heart was kept longer at the high temperature, it ran through the same changes of rhythm as when gradually warmed. Cyon supposed that sudden raising of the temperature stimulated some inhibitory mechanism in the heart. But in gradual warming he concluded that the retarding factors failed before the motor factors.

Eckhard[2] repeated Schelske's experiment; but could never succeed in getting pulsation as a result of stimulation of the vagus, unless one of the electrodes was near enough to the heart to make escape of current probable. He found that when the heart, on cooling, began to beat again, stimulation of the vagus caused diastolic standstill.

A. B. Meyer[3], who gives a good resumé of previous work, failed to find any effect of stimulation of the vagus on the heat standstill of the frog's heart, except under conditions which favoured escape of the stimulating current or unipolar stimulation. After the heart began to beat again, it could not always be brought to a standstill by the vagus.

Aristow[4] investigated, under Dogiel's guidance, the effect of sudden alterations of temperature on the frog's heart. He stated that the heart which by warm water or ice is brought to standstill but can again beat if the temperature is altered is in diastole. When the heart is brought to standstill but has lost the power of beating under other conditions, it is in systole (tetanus). By standstill in systole he evidently means heat rigor. He argues that the true diastolic heat standstill is not caused by increased activity of the inhibitory apparatus in the heart, as Cyon had suggested, because electrical stimulation of the heart in this condition causes tetanus. Without having made any

[1] *Sächsische Berichte*, 1866, pp. 302, 303; *Ludwig's Arbeiten*, 1867, p. 118.

[2] *Experimental Physiologie d. Nervensystems*, 1865, p. 200; *Beiträge z. Anat. u. Physiol.* VII. 1873, pp. 3—6.

[3] *Das Hemmungsnervensystem d. Herzens*, Berlin, 1869.

[4] *Archiv f. (Anat. u.) Physiol.* 1879, p. 198.

experiments on the cardiac nerves, he concludes from his general results that the inhibitory apparatus is attacked, as the temperature rises, sooner than the motor centres. Aristow's chief result is that the cause of the heat standstill is paralysis of the ganglia, and not inability of the muscle to contract. According to him the intracardiac inhibitory apparatus also suffers paresis when the temperature is low. The beats are then quickened by electrical stimulation of the sinus.

Cyon had previously stated that stimulation of the sinus in the cooled frog's heart does not cause standstill, but at most lengthening of the pause.

Luchsinger and J. M. Ludwig[1] repeated the older experiments on the effect of temperature on the vagus. They found that in the frog cooling abolishes the action of the vagus even for the strongest stimulation. They seem to think that this is due merely to the diminished conductivity of the nerve fibres. In the warmed heart they not only found the vagus effective at the highest temperatures which could at all be borne, but its effectiveness even seemed to be increased. They explain this as due to a relatively greater increase of excitability of the inhibitory than of the motor apparatus of the heart with rise of temperature.

This is all the material I have been able to find in the literature of the subject, so far as the Batrachian heart is concerned, except an incidental statement by Heidenhain[2] that he was never able to demonstrate any action of the vagus on the heated heart, and particularly on the heart in the heat standstill, other than the ordinary inhibitory action; and an experiment of Petri's[3] in which he shewed that the muscarin standstill was removed by heating the heart to 42° C., but returned again at 17° C.

The still scantier results for the vagus in warm-blooded animals and in the tortoise will be referred to later on. The most important work on the subject in the case of mammals is that of Baxt[4] on the dog. His result for the vagus was negative. He could find no influence of temperature on its activity. But his sole test for that activity was a change in the rate of the heart.

The only criticism I have to make on the work of previous observers

[1] *Pflüger's Archiv*, Bd. xxv. p. 211, 1881.

[2] *Pflüger's Archiv*, Bd. xxvii. p. 383.

[3] *Beitrag zur Lehre von den Hemmungsapparaten des Herzens*, Bern, 1880.

[4] "Ueber die Stellung des Nervus vagus zum Nervus accelerans cordis." *Ludwig's Arbeiten*, 1875.

on the Batrachian heart, and particularly upon the excellent work of Luchsinger and Ludwig, is one which can almost always be cheaply made, in a rapidly advancing science, by anybody who happens to write ten years later than the author who is criticised. As I have said, Luchsinger and Ludwig took no graphic record of the contractions, but simply observed whether the heart was slowed or standstill produced by stimulation of the nerve.

Since Gaskell's work on the hearts of the frog and tortoise it is no longer possible to be content with an examination so limited. We now know that the inhibitory action of the vagus manifests itself in several ways, of which complete standstill is one only, and not the most certain. The analysis of Gaskell[1] has shewn us that the diminution in the force of the individual beats, with or without an alteration of rate, is, in the frog at least, the most constant and characteristic inhibitory effect of vagus stimulation.

Coats[2] and Nüel[3] before Gaskell, and Heidenhain[4] almost simultaneously with him, pointed out this effect.

Further, the different parts of the heart are not necessarily influenced in the same way, or to the same extent by the action of the vagus; and there are important effects on the normal sequence of the contractions. It is, therefore, impossible to make a satisfactory study of the vagus action, unless we can analyse the total effect.

In my experiments this was done by a modification of Gaskell's method which made it possible to immerse the heart in a dilute saline solution, the temperature of which could be raised or lowered at pleasure.

Method. On the same stand Pl. III. Fig. 1 were arranged two writing levers supported by elastic bands in the ordinary way, a holder carrying a bent glass rod with a small pulley at its end, and a holder supporting a glass vessel consisting of a bottle with its bottom removed and its neck closed below by an india-rubber cork, in which were fastened an outflow and an overflow tube, the former opening at the level of the upper surface of the cork, the latter at the level up to which it was intended to immerse the heart. The vagus was dissected out on one or both sides nearly up to the ganglion, ligatured and cut. The heart was then prepared in Gaskell's fashion, a silk ligature being attached to the

[1] *Phil. Trans.* 1882, *loc. cit.*

[2] *Sächsische Berichte*, 12th Dec. 1869.

[3] *Pflüger's Archiv*, Bd. IX. p. 183.

[4] *Pflüger's Archiv*, Bd. XXVII. p. 383, 1882.

very apex of the ventricle, the fraenum divided, the aortae cut across close to the bulbus and a tiny portion of the auricle pinched up and ligatured. The intestines, liver, lungs, etc. were now removed, care being taken in cutting away the liver not to injure the sinus. Then the lower jaw was carefully removed, and the whole of the body cut away, except the head, part of the œsophagus and the tissues connecting it with the heart. The head was fixed in a clamp sliding on an ordinary stand. The heart was held at the auriculo-ventricular junction in a modified Gaskell's clamp, supported on a separate stand. The handle of this clamp had an almost rectangular elbow, so that the jaws of the clamp could dip inside the glass vessel. The pulley was also brought inside the vessel and below the clamp. The thread from the ventricle passed round the pulley, and was attached to the lower lever, that from the auricle being attached to the upper. The pulley was kept well oiled with fresh olive oil, and there was not much friction. The salt solution (·6 %) was supplied to the vessel containing the heart from a reservoir at a higher level; and the temperature desired could be reached either gradually or suddenly according to the object of the experiment. Generally the successive temperatures marked on the tracings were obtained at once by putting in the solution already at the temperature required. A thermometer was suspended over the glass vessel so that its bulb was just immersed when the solution covered the heart. Two pairs of fine electrodes, carefully insulated by paraffin wax except at the very point, where a small portion of the upper surface of the wires was exposed, were arranged on stands, one at each side of the preparation, and connected by a Pohl's commutator without cross wires to a du Bois key, the connection of which with the secondary coil of the induction machine was broken by a Morse key in circuit with the electro-magnetic marker which recorded the beginning and end of stimulation. One or both vagi, one or both sympathetics (for precisely the same arrangement was used for the sympathetic), or the vagus on one side and the sympathetic on the other were put on the electrodes, through either pair of which shocks could be sent. There was, besides, the usual time-marker, marking two-second intervals in nearly the whole of the tracings, but seconds in a few.

Instead of using the pulley, I worked in a few experiments with a lower lever of such a form that the point of attachment of the ventricular thread to it was near the bottom of the glass vessel, so that complete immersion of the heart could still be secured. For this purpose it was necessary to immerse the axis of rotation of the

lever, and not merely to make a rectangular bend in its length; and it was further necessary in order to get a satisfactory tracing, that the writing point should be in the same straight line with the horizontal part of the lever inside the glass vessel, Pl. III. Fig. 2. The bent portion was of aluminium wire. The weight of the lever was counterpoised. This arrangement avoids the friction of the pulley; but I did not find it quite so convenient at first as the other method, to which I had become accustomed. Accordingly I did not think it worth while to change; and most of the tracings have been got with the pulley.

One other point must be mentioned. In a good many of the tracings the drum, the clockwork of which was in bad order, stopped altogether, or did not move at the same speed throughout the whole tracing. There is on this account sometimes an artificial appearance of acceleration, or the reverse, in the beat of the heart. The time trace will, however, prevent error. In the last half of the work there was no trouble from this cause, as I was able to obtain a good drum.

A special series of experiments was made, as a control, with the heart in situ and intact circulation. Here it was not possible to use the clamp; and the heating and cooling were done by passing water through a small glass worm in which the heart worked, a thread connecting the apex of the ventricle to a writing lever. The friction of the heart on the worm was reduced by oiling the latter. A worm was also generally used when it was desired to heat or cool only a part of the heart.

It was necessary to avoid complicating the results by any effects which alteration of the temperature of the nerve trunk itself might have. For, corresponding to the three parts of the physiological series, central organ, connecting nerve-fibre, and peripheral organ, the complete problem of the influence of temperature on the action of the cardiac nerves is a triple one. When the temperature of all three, or even that of the nerve trunk and the heart, is altered at once, as has commonly happened, especially in experiments on warm-blooded animals, the problem is made unnecessarily complex. We know that the excitability of a nerve trunk is, within certain limits, at least for stimuli of short duration like induction shocks, increased by heat and diminished by cold.

Accordingly, when the heart and the vagus trunk are both heated or both cooled, it is not allowable, without parley, to attribute any change in the effect of stimulation of the nerve to the change of temperature of the heart. The sole object of my experiments being to

learn how the state of the heart itself affects the action of its nerves, it was necessary to shew as a preliminary that the effect of temperature on the excitability of the nerve trunk was negligible; or to determine its amount and sense if it was not negligible; or to make sure that the temperature of the nerve should not be altered at the point of stimulation. The last course, as at once the simplest and the least liable to error if it could be followed, was the one which I determined to try first. The nerves being of fair length, it was possible to place the electrodes well above the solution. A small diaphragm was placed between this and the electrodes so as to eliminate any effect of radiation and convection. To avoid conduction along the nerve, the latter passed over a small leaden tube on its way to the electrodes. Water at the temperature of the room was kept circulating through the tube, and therefore the part of the nerve in contact with it was always approximately at the room temperature. The portion of the nerve on the electrodes, accordingly, could neither be cooled nor heated by conduction from the heart; and the diaphragm protected it from change of temperature in other ways.

Now I tested whether there was any noticeable difference in the effect of vagus stimulation, with constant strength of stimulus when observations were made successively on the same preparation, immersed in solution above or below the temperature of the room, first with the above arrangements for preventing change of temperature of the stimulated part of the nerve, and then without them, the nerve being still kept well above the solution and the electrodes as far away from it as possible. I found no difference which could in any way be connected with the temperature of the nerve. After this, the electrodes were simply kept well away from the solution; and no further trouble was taken on this score.

Changes of conductivity in the nerves in the neighbourhood of the heart, and *a fortiori* in the nerves of the auricular septum, are, of course, impossible to prevent when the whole heart is heated or cooled. The nearest approach to a condition in which the temperature of the cardiac muscle is altered, while that of the intracardiac nerves remains unchanged, is where the ventricle alone is heated or cooled. We shall have to describe such experiments later on. But, interesting as they are in other relations, they do not enable us directly to make the distinction in question. For it is impossible to release the ventricle from the bondage of the auricular lead, and this dependence of ventricular upon auricular rhythm complicates the mere effect of temperature.

The results of experiments on the vagus fall naturally into two divisions:

1. *The effect of temperature on the inhibitory action.*
2. *The effect of temperature on the augmentor action.*

Long ago Schiff[1], Ludwig and Hoffa[2], and others noticed that stimulation of the vagus in the frog might under certain conditions cause an increase in the rate or strength of the heart's contractions. It was afterwards observed by Schiff[3], Rutherford[4], Schmiedeberg, and others that this was a constant effect in animals poisoned by atropia.

From such circumstances it has long been suspected, and is now definitely known, especially through the researches of Heidenhain[5], and Gaskell[6], that there are two sets of fibres in the vagus of the frog which produce opposite effects upon the heart, the true vagus fibres and the sympathetic fibres. When the word "vagus" is used without qualification in this paper, it signifies the mixed vago-sympathetic nerve.

It may here be asked why, instead of using the mixed nerve, I have not begun by examining the effect of temperature separately on the action of the two groups of fibres. To this I have to answer that electrical stimulation of the intracranial vagus needs specially large frogs, and even with these is by no means easy where the experiments are complicated, and where it is not simply a question of adjusting the short and fragile vagus roots on well insulated electrodes, but of adjusting these and the whole preparation to five or six other pieces of apparatus. From the nature of the experiments a great many preparations are necessary; and it seemed better to *begin* by working under conditions which, if not theoretically the best, were yet, although sufficiently complicated, so much under control as to allow of comfortable and fairly rapid work.

We know besides from the experiments of Bowditch[7], and especially of Baxt[8] on the mammal, that the effect of simultaneous stimulation

[1] *Archiv f. physiol. Heilkunde*, VIII. p. 183, 1849.

[2] *Zeitschrift f. rat. Med.* Bd. IX. p. 107, 1850.

[3] *Moleschott's Unters.* 1865, p. 58; 1873, p. 189.

[4] *Journal of Anatomy and Physiology*, III. p. 408, 1869.

[5] *Pflüger's Archiv*, Bd. XXVII. *loc. cit.*

[6] This *Journal*, v. p. 46, 1884; *Proc. Physiol. Soc.* June 7, 1884; This *Journal*, v. p. xiii.

[7] *Sächs. Berichte*, 1873, pp. 158—179. [8] *loc. cit.*

of the inhibitory and augmentor nerves is not really a mixed effect, in the sense that the total effect is at any given moment the algebraic sum of two components, but is shewn by a curve in which the vagus effect comes first, that of the accelerans being postponed but not permanently suppressed nor even altered. In the normal curve of vagus stimulation in the frog the two effects are similarly separated in time, so that it is not difficult to see how each factor of the curve has been influenced by change of temperature.

It seemed likely that any difficulty in the interpretation of the curve of mixed stimulation would be greatly lessened by comparison with curves got by stimulation of *one* of the isolated groups of fibres; and, since there is no special difficulty in working with the sympathetic, it was determined to make the sympathetic experiments the next step.

Finally, it was resolved that when all the information which the other methods were capable of yielding had been got, a set of experiments should be made on the intracranial vagus, in order to settle any questions which still remained unanswered and seemed likely to be answered in this way.

These experiments were to begin with *chemical* stimulation of the medulla oblongata and the vagus roots, and to end with *electrical* stimulation.

The whole of this programme has been carried out except the electrical stimulation of the intracranial vagus.

In the results now to be detailed the following terms will frequently occur; and it will save trouble to define here the sense in which they are used.

By "inhibition" is meant any state brought about by the action of the vagus or by direct stimulation of the heart in which the rate of transformation of energy by the heart in its contractions is diminished, whether the beat is simply lessened in amplitude or stopped or only slowed.

By "augmentation" is signified any state produced by stimulation of the sympathetic or the mixed vagus in which the rate of transformation of energy by the heart in its contractions is increased, by an increase in the rate or the force of the beats, or by an increase in both. This is practically the sense in which Gaskell uses the terms.

"Medium" or "starting temperature" means the temperature of the room, which varied between 11° and 16° C., on different days, but did not vary much in the course of an experiment.

1. *The effect of temperature on the inhibitory action of the vagus.* (Pl. IV. Figs. 1—17.)

(1) The action of the vagus is very much influenced by the temperature of the heart, but in general only quantitatively and not qualitatively. For example, if stimulation of the vagus at the medium temperature causes, as its primary effect, inhibition in the broad sense in which it has been defined above, then, whether the temperature be raised or lowered, the primary action of the nerve, when its action still persists at all, is inhibitory. If, on the other hand, as occasionally happens, the primary action of the fresh nerve is augmentor at the medium temperature, it is also augmentor at any other temperature at which there is any action at all.

We see here the limit set to the influence which the state of the heart itself, so far as it is affected by temperature, can exercise on the result of stimulation of its nerves. We shall see immediately that this influence is characteristic and profound, within the boundaries which are allotted to it. But a change of temperature which causes no *permanent* change in the relation of the heart to its nerves never causes a reversal of the primary action of these nerves. By "permanent change" is here meant a change outlasting the alteration of temperature which caused it, but not necessarily an irrevocable change. The reason for this qualification will be seen directly.

We might have supposed *a priori* that if the state of the muscular tissue of the heart is really a factor in determining whether stimulation of the vagus shall cause a primary inhibition or a primary augmentation, as Gaskell thought at a time when he did not admit the necessity of postulating two sets of fibres in the vagus[1], such a very great change in the molecular activity of the cardiac tissue as is implied in a change of temperature from, say, 35° C. to 4° C., might well be sufficient to cause such a reversal.

Remembering how many circumstances can cause the inhibitory action of the vagus to fail at the ordinary temperature and give place to a primary augmentor action, in spite of the existence of definite inhibitory fibres; and remembering also the statements which have been made with regard to the influence of temperature on the vasomotor effects caused by stimulation of the peripheral end of a nerve like the sciatic containing both constrictor and dilator fibres—that stimulation causes vascular contraction if the limb has been warmed,

[1] This *Journal*, IV. *loc. cit.*

and dilatation if it has been cooled[1]—I thought it not impossible that by raising or lowering the temperature of the heart, either the augmentor or the inhibitory action of the mixed nerve might become the primary effect.

This is not the case. The effects of stimulation of the cardiac nerves do in a manner, as we shall see, keep pace with the varying state of the cardiac muscle as manifested in the beat of the heart. So that when the muscle is most facile in its movements, quick in contracting, prompt in relaxing, it is also most ready to obey the direction of its nerves. But this obedience is always true to the fundamental type of primary inhibition or primary augmentation, although it always clothes itself in a form which expresses the temporary state of the tissue. In other words, the fundamental type of the action is not determined by the state of the muscle. The "general idea," so to speak, is settled for the muscle by its permanent relations to the cardiac nerves, but it is the state of the muscle at any given time which determines how the "idea" is to be carried out.

The influence of temperature, which can affect the beat of the heart more than atropia, cannot, like atropia, affect the fundamental type of action of the vagus nerve. The strong slow beat of the cooled heart has a certain resemblance to the beat of an atropinised heart at the ordinary temperature, except that the rate is perhaps slower. But in the cooled heart, as will be seen, it is the inhibitory action rather than the augmentor which persists.

A primary inhibitory action of the vagus is occasionally replaced in the course of an experiment, during which the heart has been cooled or heated, by a primary augmentor action.

This is a very common occurrence in hot weather, far more common in my experience than in winter. It is worth noting that when the primary inhibitory action of the vagus is lost in this way, owing to the artificial and unphysiological surroundings, the change is by no means irrevocable. In some cases it seems to be due to the drying of the nerve, which may then recover its original action when it is moistened, or to permanent injury to the nerve at the point of stimulation, which is obviated by taking a fresh piece of nerve lower down. In other cases it is apparently due to changes in the heart itself, for no manipulation of the nerve can restore the action, although immersion of the

[1] Lépine, *Mémoires de Société de Biologie*, Mar. 4, 1876; Bernstein, *Pflüger's Archiv*, Bd. xv. p. 575.

heart in salt solution, at the temperature of the air, may do so. In still other cases neither moistening of the nerve nor of the heart suffices, and then, after immersion of the heart in salt solution at the ordinary temperature has failed, immersion in warm solution may cause the nerve to recover its original inhibitory power, and this when the greatest care has been taken to prevent the solution from reaching the nerve trunk. Heating of the heart without any previous moistening of the nerve also sometimes succeeds. And this is why we hedged about the definition of the phrase "permanent change" on p. 69. The inhibitory power thus regained does not at once disappear when the conditions are again altered, and may or may not ultimately disappear in the further course of the experiment. When it does disappear it may often be again restored by similar treatment. In some cases, curiously enough the lost inhibitory power returns, not while the heart is actually in the warm solution but after the solution has been removed; and this is not due to a temporary depression of the function of the nerve by the high temperature for re-immersion in the warm solution may leave the inhibitory power unaltered or may actually increase it. Possibly the coincidence of the return of inhibitory power with the removal of the warm solution was only accidental in the cases where it was observed; and this power might have been restored all the same had the solution been allowed to act a little longer.

The experiment from which Figs. 63 and 64 are taken is an instance in which the primary action of the vagus was at first inhibitory, then became augmentor, and was again made inhibitory. Only the last two stages are figured, viz. Fig. 64 (augmentor), and Fig. 63 (inhibitory).

The record of another experiment runs thus: Toad. Right vagus and left sympathetic prepared. Vagus causes inhibition before heart put on clamp. But afterwards only primary augmentation (acceleration and increase of force) can be got. Moistened nerve and immersed heart in salt solution at temperature of room. Still always get primary augmentation with every strength of stimulus. Tried rearranging nerve, but no inhibition can be got.

Now, without shifting anything, run off solution and put in solution at 35° C. Stimulate vagus now and get distinct standstill, which lasts for 11 seconds and is followed by secondary augmentation.

The restoration of inhibitory action cannot be due to accidental stimulation of the sinus when escape of current is made easier by the immersion of the heart, since it outlasts the immersion. It must be

due to a physiological change in the heart. The generally greater efficacy of a warm solution may be due to the greater facility with which interchange takes place between the heart and the solution, or, as seems likely, the physiological effect of the high temperature on the muscular tissue of the heart or on some weak link in the nervous chain within the heart may be the chief factor.

(2) *The effect of lowering the temperature of the heart on the inhibitory action of the vagus.*

As the temperature of the heart is lowered from the medium temperature, the inhibitory activity of the vagus is diminished, by whatever criterion that activity is estimated[1].

(*a*) If a strength of stimulus be chosen which is just sufficient at the medium temperature to bring out an inhibitory effect of any kind, say complete standstill, then when the temperature is lowered this effect will no longer be got unless the stimulus is strengthened. If we fix our attention on the chosen effect, we may accordingly say that the activity of the vagus is diminished as the heart is cooled.

(*b*) If at the medium temperature stimulation of the vagus

[1] How are we to compare the *amount* of the inhibitory action of the vagus when the heart is at different temperatures and, therefore, beating at different rates? This is a question which it is not easy to answer offhand even when the form which the inhibitory action takes at the temperatures compared is the same. If it is complete standstill, for example, we have still to enquire whether the absolute length of the standstill or its length in relation to the previous rate and force of the beat is the true criterion. Suppose that at 5° C. and at 20° C. the heart is beating at the rate respectively of 12 and 36 beats per minute and that the force of each beat is the same at both temperatures. Suppose further that stimulation of the vagus, with a given strength of stimulus, causes standstill for 20 seconds in each case. Are we to say that the inhibitory action is equal in amount at the two temperatures? Or must we consider what amount of work the heart would have done in the 20 seconds had the vagus not been stimulated? At 5°, 4 beats were prevented from taking place; at 20°, 12 beats. Three times as much work was prevented at 20° as at 5°. In one sense, then, the activity of the nerve was three times as great at the higher temperature as at the lower. But it is obvious that if the inhibitory action of the vagus is not a holding down of the activity of the heart but a diversion of it into a new channel, as there are good reasons for believing, we cannot apply this test unless we know that the heart, in proportion to the rate at which it was working before the inhibition, strives to terminate the standstill. So that it is necessary to take into account the circumstances of each particular case in trying to make quantitative comparisons. More than one test must be used where that is possible, and yet it must be seen that when comparisons are made between the results of different tests the quantities compared are really commensurable.

I have endeavoured in the following pages to state always the precise nature of the comparison where quantitative results are given, although it has seldom been possible or profitable to apply numerical measures.

causes complete quiescence of the whole heart, then as the temperature is diminished, it is possible to obtain with the same strength of stimulus only a diminution in the force of the auricular beats, accompanied at first perhaps with a diminution in the force of the ventricular beats. As the temperature is lowered still further, the effect upon the force of the ventricular beats first disappears, and then the effect upon the auricle. Ultimately, at a very low temperature (0°—2° C.), no effect whatever may be caused by the strongest stimulation of the vagus, although direct stimulation of the sinus or of the auricles may still be followed by distinct inhibitory effects, and especially by diminution in the amplitude of the auricular contractions.

By lowering the temperature it may often be shewn that the standstill caused at the ordinary temperature by stimulation of the vagus is really "quiescence" in Gaskell's sense, i.e., is due to diminution in the force of the auricular beats down to invisibility.

On the other hand, it will be seen directly that it is possible by raising the temperature from the medium to change a case of merely diminished contraction force into complete standstill, and so to graduate the process that the one can be seen growing out of the other. In this way I have often seen a striking verification of Gaskell's statement that the most common kind of complete standstill at the ordinary temperature in the frog's heart is that in which the auricular beats become invisible without any indication, before or after the standstill, of a marked change of rate.

Since in the cold the power of the vagus to cause complete standstill disappears far more readily than its power to lessen the force of the contractions, it requires a lower temperature than has hitherto been supposed necessary to abolish the inhibitory action altogether. In fact I have sometimes found it impossible at any temperature above 0° C. to abolish the action; and even with the heart surrounded by ice distinct traces of it have not infrequently been seen.

(*c*) If the primary effect of vagus stimulation at the starting temperature, be diminution in the force of the auricular beats not amounting to complete quiescence, accompanied with diminution or cessation of the ventricular beat, then as the temperature is lowered the diminution will become less marked, first in the ventricle, then in the auricle; and ultimately no effect will be caused on either.

(*d*) If the primary effect of vagus stimulation at the starting temperature be slowing of the beat without diminution in the amplitude, as is occasionally seen, this is also the effect at

lower temperatures. So far as I have had the opportunity to observe, this type of inhibitory action is not changed into any other type however much the temperature may be lowered; but, when the temperature reaches a certain limit, all effect of vagus stimulation simply disappears. It would be rash to conclude, from the comparatively few instances which have come under my notice, that this is always true. Occasionally I have noticed that at the ordinary temperature the vagus may diminish the force of the beat without marked alteration of rhythm, while at a very low temperature the only effect may be a fairly marked slowing without any diminution of the force. This change comes about gradually as the temperature is lowered, the effect on the size of the beats progressively diminishing, as it always does, while in these occasional cases the slowing rather increases.

(*e*) If the ventricle alone is cooled, complete quiescence of the heart may be obtained by stimulation of the vagus at a very low temperature, when it is obtained at the starting temperature; and cooling of the ventricle may in this case not appear to have affected the action of the vagus on it, for the ventricle will of course stop when the auricle stops. But if the vagus effect at the medium temperature is only to diminish the amplitude of the auricular beats, while causing a corresponding diminution or complete cessation of the ventricular beats, then when the ventricle alone is cooled, it is seen that the vagus action on it is affected; for the diminution of the ventricular beat is now less with the lower temperature; and ultimately the ventricle may not be at all directly affected by vagus stimulation, while the auricular beats are diminished as much as at first. An indirect effect on the ventricle is, however, often seen.

Gaskell has shewn that when the auricle is heated, the ventricle being at the ordinary temperature, the latter ceases to beat in sequence with the former, and responds only to every second or third auricular contraction. Stimulation of the vagus causes a partial or complete restoration for a time of the normal sequence. This occurs during the period of secondary augmentation, and is explained by Gaskell as due to an improvement in the conducting power of the muscular tissue of the auriculo-ventricular junction[1].

When the ventricle alone is cooled, the same change in the sequence occurs. So far as this goes, it is practically Gaskell's experiment, except that his "ordinary" temperature becomes here very low. But what I wish to point out is that even when the ventricle is at a low

[1] *Phil. Trans.* 1882, *loc. cit.*

temperature, stimulation of the vagus may be able to restore the normal sequence of ventricular and auricular beat. This may happen when the temperature is too low to allow of any primary diminution of the size of the ventricular beat; and it occurs after the diminished auricular beats have again begun to increase, and therefore properly belongs to the stage of secondary augmentation. Now, as we shall see, the sympathetic augmentor effects generally fail before the inhibitory effects of vagus stimulation, when the whole heart is cooled. The action which causes restoration of the sequence when the ventricle alone is cooled, though manifesting itself during the period of secondary augmentation of the auricular beat, must, if it is an action on the cooled ventricular tissue, take place at a lower temperature than the action of the sympathetic or vagus on the force of the ventricular contractions. If we suppose that it is only the conductivity of the auriculo-ventricular junction which is affected, and not the excitability of the ventricle, by the action of the vagus on a heart in which the ventricle alone is at a very low temperature, we do not require to make this assumption.

The ventricle, we must suppose on this view, is able, though cooled, to beat regularly with the auricle, if only every auricular contraction is able to spread beyond the junction. In other words, although the temperature of the auriculo-ventricular junction (the ventricle being not entirely immersed in the cold solution) may be presumably higher than that of the chief part of the ventricle, the conductivity at the junction may be more depressed by cold than the excitability of the ventricle. But when the temperature is low, the power of contraction of the ventricle is not affected by the action of the cardiac nerves. So that when it is brought to follow for a time the auricular lead, its beats are markedly smaller than before, to make up for the increased rate. This is an instructive contrast to the simultaneous increase of frequency and contraction force which is so common a form of augmentation at higher temperatures.

Exactly the opposite effect may be produced on the sequence of the beat by stimulation of the vagus when the ventricle, although cooled, is still beating with every beat of the auricle. When the temperature of the air is not very high and the auricle remains at that temperature, the ventricle may be very considerably cooled without ceasing to beat regularly with the auricle. In this condition stimulation of the vagus (or sympathetic) may cause the ventricle to respond for a time only to every second beat of the auricle; and the alteration begins during the augmentation of the auricular beat. This would be explained on

Gaskell's view by the failure of impulses, following each other too rapidly, to affect the ventricle. The ventricular beats during this stage are greatly increased in force. Occasionally, instead of missing every second beat of the auricle, the ventricle stops beating altogether after stimulation of the nerves, just as Gaskell observed it to do sometimes when the auricle alone was heated.

(*f*) Stimulation of the sinus (Figs. 22—24, and Fig. 25) is generally effective in causing inhibition at a lower temperature than stimulation of the vagus trunk. There have been well-marked inhibitory effects at the lowest temperatures I have tried. At a temperature very little above 0° C., I have seen distinct diminution of the amplitude of the beats, but not complete standstill at such a low temperature in the clamped heart; and generally diminution only of the auricular beats.

Stimulation of the auricle (Figs. 19—21) caused similar effects, although less marked for the same strength of stimulus, and more strictly confined to the auricular curve.

When in stimulation of the sinus the stimulus was made just strong enough to give an appreciable effect at the lowest temperature, this effect consisted in slowing of the rate for a beat or two without any diminution in amplitude. This slowing was preceded by a premature beat due to direct stimulation of the muscle. At temperatures a little higher, the same stimulus caused diminution of the force of the auricular beats.

I have sometimes seen long continued standstill of the heart in situ caused by stimulation of the sinus when the heart was surrounded by ice.

These results will be more fully discussed later on. The only point which it is necessary to notice here is Luchsinger's suggestion that at low temperatures the action of the vagus fails because the conductivity of the nerve-fibres is depressed by the cold. Now, I think it is perfectly evident that if the nerve trunk is cooled to 0° C. or below it, between the point of stimulation and the heart, all effect of stimulating the vagus must necessarily disappear, whatever temperature the heart may be at. To make sure, however, of the precise effect I made a few experiments in which a small portion of the nerve between the heart and the electrodes was cooled. At a very low temperature, as might be expected, it was of no moment whether the heart and the nerve were both cooled, or whether the heart alone, or the nerve alone was cooled; the vagus action was equally abolished. But above this point it is

cooling of the heart which is important; just as it is evidently the heating of the heart, and not of the nerve-fibres between the point of stimulation and the heart, which affects the action of the vagus at higher temperatures. Further, the fact to be mentioned later on, that the action of the sympathetic generally fails at a higher temperature than that of the vagus as the temperature of the heart is reduced, makes for the view that it is the state of the essential tissue of the heart, and not that of the nerve-fibres inside or outside of it, which affects the action of the nerves. Moreover, the inhibition or augmentation at different temperatures has peculiarities which cannot be explained merely on the hypothesis that a weaker or stronger excitation reaches the heart along its nerves according as the temperature is lower or higher, and which cannot be produced by varying the strength of the stimulus while the temperature is kept constant, but which are obviously related to the state of the muscular tissue. The fact that inhibitory effects are caused by stimulation of the sinus at a lower temperature than by stimulation of the vagus nerve may mean that the vagus fibres are paralysed by the cold higher up, or may simply mean that stimulation of the sinus is, as at ordinary temperatures, more effective as regards inhibition than stimulation of the nerve trunk. But if stimulation of the sinus acts through the nerve-fibres, these cannot be paralysed at a temperature at which stimulation of the vagus trunk has ceased to have any effect. It may be that the nerve-cells which Langley supposes to be on the course of the inhibitory fibres of the vagus in the heart[1] are paralysed by cold sooner than the nerve-fibres. Stimulation of the fibres above the cells (stimulation of vagus outside the heart) might therefore be without effect, while stimulation below the cells (direct stimulation of the heart) might still cause inhibition.

(3) *The effect of increase of the temperature of the heart on the inhibitory action of the vagus.*

As the temperature is increased from the medium temperature the inhibitory action of the vagus is increased, whatever effect be taken as the test of its activity.

(*a*) If a strength of stimulus be chosen which is just less than that needed to cause any of the inhibitory effects of stimulation of the vagus at the medium temperature, these effects will be caused by it when the temperature is raised.

[1] Langley and Dickinson. This *Journal*, XI. p. 277.

Suppose, for example, that at the ordinary temperature complete standstill of the heart can be got by stimulating the vagus. Let the stimulus be now gradually reduced in strength until complete standstill of the whole heart no longer occurs. If the temperature is now raised, complete standstill may be obtained with this strength of stimulus.

Or, if the strength of stimulus which is just sufficient to cause standstill be fixed for different temperatures of the heart, it will be found that this strength diminishes as the temperature rises above, and increases as the temperature falls below the medium temperature. For example, in one experiment the mimimum stimulus, fixed in this way, corresponded at 21° C. to a distance between the primary and secondary coils of 170 mm.; at 31° C., 176 mm.; at 35° C., 188 mm. In another experiment, at 31° C., 149 mm.; at 39° C., 160 mm.

(*b*) If the primary effect at the medium temperature be diminution in the amplitude of the auricular beats without complete quiescence, or only with quiescence of the ventricle, then at a higher temperature complete quiescence of the whole heart may be obtained. At the higher temperatures, in fact, complete standstill is generally got when the vagus has any inhibitory effect at all at the medium temperature; and sometimes when there is no inhibitory effect at the ordinary temperature, such an effect appears at higher temperatures. This is a rare occurrence. It has been seen, as already mentioned, in more or less exhausted preparations, in which primary augmentation at the ordinary temperature has given place to primary inhibition at higher temperatures. No instance has been noticed in which a primary augmentor action of a fresh vagus has been changed into an inhibitory action by alteration of the temperature of the heart. But in two or three cases a vagus without action of any kind at the ordinary temperature came to have a certain amount of inhibitory action when the temperature was raised.

Gaskell never found the vagus in the frog without action of some kind[1]. This, of course, refers to the ordinary temperature. I have not been so uniformly successful in avoiding preparations in which the vagus was totally inactive. Such preparations were not common, and no doubt some of them were due to faulty manipulation; but the two or three cases mentioned, although undoubtedly a very slender support for any dogmatic statement, would seem to shew that this was not always the cause.

(*c*) At very high temperatures (35° C. and upwards) the vagus is

[1] *Phil. Trans.* 1882, *loc. cit.*

still active; and while the heart is beating, however feebly, it can cause standstill. Here the beats are so small that a slight diminution in their size causes the lever to trace a straight line.

(*d*) Direct stimulation of the sinus, as has been pointed out by several observers, causes in the overheated heart not standstill but quickening of the beat, or even a more or less complete tetanus.

Aristow[1] is, however, certainly not justified in concluding from this that the inhibitory apparatus is attacked sooner, as the temperature is raised, than the motor factors. In stimulation of the sinus at least two elements are concerned, the direct stimulation of the muscular tissue, and the stimulation of the nerve-fibres. As to the nerve-fibres we have just seen that their inhibitory power is increased with rise of temperature when the stimulated part of the nerve is at the ordinary temperature. As the temperature rises up to a pretty high limit, the excitability of the nerve-fibres will be increased for stimuli of the kind employed; and this should all the more favour the inhibitory action of the fibres stimulated in the sinus. So that if we could stimulate these in the sinus without affecting directly its muscular tissue, we ought to obtain even deeper inhibition at the high temperature than at the low. But the motor excitability is also increased; and the tendency to inhibition may be overborne by the motor activity of the directly excited muscle. The relative excitability of the two factors is not the same at all temperatures; and it is possible by direct stimulation of the sinus, without changing the strength of the stimulus, to range from inhibition to augmentation merely by raising the temperature. So that here the change of temperature causes a change analogous to that caused by atropia, as regards direct stimulation of the sinus. It is not, however, an invariable rule that at high temperatures stimulation of the sinus no longer causes inhibition. Inhibition may sometimes be got just before the heart goes into heat standstill. On the other hand a tetaniform contraction, and not simply a quickening of the beat, may sometimes be caused.

Summary. So far we have considered the influence of temperature on the primary inhibitory effects of stimulation of the vagus. We have found that in whatever way this action is expressed at the medium temperature, whether in complete quiescence of the whole heart; or of the ventricle alone with diminished amplitude of the auricular beat; or in diminution of the force of the beats of both auricle and ventricle, or

[1] *loc. cit.*

only of the auricle; or in slowing of the rhythm with or without alteration in the force of the beats, the activity of the nerve is in all cases reduced as the temperature is lowered, and increased as the temperature rises. We have seen, further, that there is a lower limit of temperature below which no stimulation of the nerve, however strong, has any effect on the beat of the heart, but that this limit lies considerably below the temperature at which it becomes impossible to obtain standstill, and may sometimes be little, if at all, above 0° C.; that the paralysis of the inhibitory function of the vagus is not due to injury, but passes away when the temperature is again raised; and that even when stimulation of the nerve has failed to affect the cooled heart, direct stimulation of the sinus can still cause distinct inhibitory effects. We have seen that the power of the vagus over the ventricle fails first; and when this stage is reached the frog's heart is like the heart of the tortoise at the ordinary temperature in this respect, as well as in the inconspicuous secondary augmentation following stimulation of the vagus, which will be referred to directly.

On the other hand we have found no higher limit of temperature, while the heart continues to beat at all. On the very verge of the heat standstill we have seen the vagus active, as well as when the standstill is passing away. In a later section we shall try to follow it into the standstill itself.

2. *The influence of the temperature of the heart on the secondary augmentation caused by stimulation of the vagus.* (Fig. 18.)

Since the secondary augmentor action of the vagus in the frog is due largely at all events to the sympathetic fibres, this section might more logically be placed along with the experiments on the sympathetic. It is taken here in order to keep the experiments on the vagus all together.

Anticipating a little the results of the work on the sympathetic, we may say that in general the secondary augmentation following stimulation of the vagus is affected by temperature in the same way as the primary augmentation following stimulation of the sympathetic, which is an illustration in the frog of what has been found in the mammal, that the augmentor effect at all temperatures follows its own law independently of the simultaneous stimulation of inhibitory fibres, although not till the inhibitory action has completed its curve. The secondary augmentation is greater at the higher than at the lower temperatures especially with respect to

the increase in the force of the beat. At low temperatures the augmentation much more readily takes the form of increase of frequency without change of force.

At moderately high temperatures increase of both force and frequency is marked. At still higher temperatures, with a rapidly beating heart, the augmentation is prone to shew itself by increase in the force of the contraction without any change or with only a slight change in the rate.

There is one interesting point which must be noted. It very seldom happens even at the lowest temperatures that a secondary augmentation, (naturally under the conditions taking the form of a secondary acceleration) cannot be seen, if it has been got at the ordinary temperature, so long as a distinct primary inhibitory effect is seen at the low temperature. A secondary acceleration can apparently be got after stimulation of the vagus with a moderately strong stimulus at very low temperatures with greater readiness than a primary acceleration after stimulation of the sympathetic with a very strong stimulus. In other words, a very low temperature, which as we shall see as a rule abolishes the action of the sympathetic more readily than the inhibitory action of the vagus, also abolishes the primary augmentation caused by stimulation of the sympathetic more readily than the secondary augmentation caused by stimulation of the mixed vagus. The meaning of this is, I suppose, that the true vagus fibres themselves cause a certain amount of secondary augmentation as a consequence of the inhibition, and that this part of the total augmentation persists under conditions of temperature which permit the primary inhibitory action to manifest itself, but paralyse the augmentor function of the sympathetic.

Heidenhain, indeed[1], generally got only inhibitory effects by chemical stimulation of the medulla; and the beats did not usually regain their original strength. But Baxt, in the dog, found a certain amount of acceleration following the inhibitory effects of stimulation of the vagus, which he could not satisfactorily account for as being due to separate accelerating fibres.

Gaskell, too, found secondary augmentation following stimulation of the intra-cranial vagus in the frog, the ultimate effect of such stimulation being to strengthen the heart.

In this connection it is of interest that the secondary acceleration

[1] *Pflüger's Archiv*, Bd. XXVII., *loc. cit.*

following stimulation of the mixed vagus in the frog should apparently persist at lower temperatures than the acceleration caused by the sympathetic. For it tends to shew a near and complementary relation between the true secondary augmentation and the preceding inhibition. But experiments more specially directed to this point than any of mine have hitherto been, and, above all, experiments on the effect of temperature on the action of the intra-cranial vagus with electrical stimulation would be needed, before one could make a definite statement either as to the constancy or the cause of this result.

The effect of stimulation of the vagus during the heat standstill of the heart. (Figs. 26 and 27.)

When the heart has entered into heat standstill stimulation of the vagus can in some cases (particularly where the standstill has been obtained at a comparatively low temperature, or has lasted only a short time) cause a series of beats. This confirms a statement made by Schelske[1] long ago, but which has been contradicted by many observers[2], and explained as due to direct stimulation of the heart by escape of current.

Schelske's result can no doubt be obtained with great readiness by providing for such an escape; and I am quite inclined to agree with what has been pointed out by more than one of his critics, that his description shews that in many of his experiments there was such an escape of current. He found that a tetanic condition or a peristaltic contraction, a "Wogen oder Wühlen," was caused by stimulation of the nerve, and stopped when the current was shut off, while single shocks caused single contractions. This is precisely what generally happens when the heart is directly stimulated in heat standstill, and what never happens when the heart is roused from the standstill by genuine stimulation of the vagus or sympathetic. In the latter case a tetanus or a state of peristaltic contraction is not caused, but a series of regular, rapid, and sometimes strong beats, which do not stop as soon as the current is shut off, and may not even begin, if the stimulation is short, till after the shutting off of the current. Further, single induction shocks applied to the vagus or sympathetic have not the slightest effect on the heart in heat standstill when the electrodes are properly insulated, while single induction shocks applied directly to the over-

[1] *Op. cit.*

[2] Eckhard, Meyer, Luchsinger and Ludwig, Heidenhain.

heated heart are very apt to be answered by single contractions. It is quite possible that Schelske never saw the heart roused from standstill by genuine stimulation of the vagus, and that it is not quite correct to say that my experiments confirm Schelske's result. It is of no consequence whose result it is. The point is that careful stimulation of the vagus, or, as we shall see, of the sympathetic, may cause the heart which has stopped beating in heat standstill to resume its contractions for a time. So far as my experience goes, this does not happen in more than a small proportion of experiments. But as I have usually noticed the phenomenon casually in the course of observations made for other purposes, and have only made a small number of special experiments, the proportion of cases in which a positive result can be obtained may be larger than I suppose[1]. One condition which undoubtedly favours a positive result is that the heat standstill should be caused at as low a temperature as possible; and we shall see in Section IV. that it is possible by the mode of heating and in other ways to lower the temperature of heat standstill. Then again, if only part of the heart, e.g. the ventricle alone, is in heat-standstill, the conditions are very favourable for its being caused to beat again by stimulation of the cardiac nerves. That the resumption of beating is not an accidental revival of the activity of the heart, unconnected with the action of the nerves, is very easily shewn. The temperature of the heart at which standstill takes place must, of course, be maintained during the experiment. When this is done, it is the rarest thing in the world for the heart to begin beating of itself; and, if it does, it only gives one or two beats. When it is roused to activity by the stimulation of its nerves, there is a longer or shorter group of beats,

[1] This is the case as I have found by special experiments since the above was written. It is by no means difficult to obtain the phenomena in a very large proportion of cases, at least in summer weather. I do not wish to imply that it is not equally easy in winter, but only that I do not know whether it is as easy.

The best indication of success seems to be a tendency to marked secondary augmentation as a result of stimulation of the vagus or even primary augmentation coming on in the course of an experiment. The vigour with which the heart beats after being roused from the standstill varies immensely in different cases; and as would be expected, is generally less in a second or third observation than in a first. Sometimes, although the heart cannot be made to resume beating while it is still immersed in the warm solution, stimulation of the vagus causes it to do so after the removal of the solution and while it is cooling. Of course it is necessary to distinguish in this case an action due to spontaneous recovery of the heart from that due to stimulation of the vagus, the test being that the former action goes on indefinitely while the latter gives way again to standstill which is finally broken by spontaneous beats.

after which the heart relapses into standstill, from which it may be again roused by a second stimulation of the nerves, or even by a third or a fourth. Ultimately, however, the temperature at which standstill was originally caused being of course maintained, stimulation of the nerves ceases to have any effect, although direct stimulation of the heart still causes it to beat, and although it is capable of beating spontaneously when the temperature is reduced.

The explanation of the effect I take to be as follows. We know that the inhibitory fibres of the vagus are active immediately before the heart goes into heat standstill, and as soon as the heart begins to beat again the vagus can stop it. This visible sign of the activity of the nerve cannot of course be seen during the heat standstill. The diminution of tone which is so general an accompaniment of vagus standstill can hardly be expected in a heart already quiescent, for, sometimes at least, in the heat standstill such a diminution can be seen to have already taken place. The secondary augmentor effects of vagus stimulation are therefore the only mechanical expression of the activity of the nerve which we can expect; and these effects are often marked at high temperatures just before and just after heat standstill. If, then, the augmentor function of the vagus, or of the sympathetic fibres in it, is not paralysed at the very moment when the heart stops, we ought to be able to rescue the heart from the standstill by stimulating the nerve.

Now, what are the probabilities? There is nothing in the mere fact of standstill which would lead us to expect sudden and complete paralysis of the augmentor function. The heart which has been brought to standstill by the application of muscarin to the sinus can at first be caused to beat again by stimulation of the vagus (Löwit[1]). Gaskell[2] has shewn that stimulation of the sympathetic has the same effect on the toad's heart. If the dose is increased, this effect is no longer got. When the ventricle of the frog or toad is reduced to standstill by tightening the clamp in the auriculo-ventricular groove, stimulation of the vagus, or of the sympathetic alone, can cause it to recommence beating. If the clamp is made tighter, this action will disappear. In other forms of partial or complete standstill of the heart, one of which will be described in Section V, the cardiac nerves have a similar effect. So that the mere fact that the heart is in standstill does not make it impossible nor even improbable that its nerves may be still active.

[1] *Pflüger's Archiv*, Bd. xxvii. p. 333.

[2] This *Journal*, viii. 1881, p. 404.

We have, therefore, to consider in the next place whether there is any peculiarity in the heat standstill which makes it impossible that the activity of the cardiac nerves should remain.

A very high temperature, of course, can not only temporarily but permanently paralyse both the heart and its nerves. With such a temperature we have nothing to do. The heat standstill, in its only legitimate sense, is a temporary condition of the heart, which has ceased to beat, but is perfectly able to beat again under changed conditions. The necessary change in the conditions may be brought about in several ways. Lowering of the temperature is one of them. If the temperature is lowered, the heart will begin beating of itself. But it is not necessary that the temperature should be lowered. Direct stimulation of the heart, the temperature remaining unchanged, will cause it to beat for a time, just as direct stimulation can generally cause one or more beats in other forms of standstill. Whenever the properties of the cardiac tissue on which the rhythmical beat depends are sufficiently restored, the heart will beat. But these properties are exalted in a great variety of circumstances by stimulation of the mixed vagus trunk or of the sympathetic. In the midst of conditions which previously hindered the heart or a part of it from beating, the cardiac nerves, by producing internal changes in the cardiac tissue, can cause the heart to beat. It is very probable that the vagus fibres in the heart can be temporarily paralysed by heat; but there is no known reason why the temperature at which this may happen should be precisely the same as that which suffices to paralyse the rhythmical power of the heart. And other conditions which temporarily abolish the rhythmical contractions do not at the same moment paralyse the cardiac nerves. It is true a continuance or a strengthening of the action which has brought about the cessation of rhythm will ultimately make it impossible for the nerves to affect the heart. An increase in the dose of muscarin or in the pressure of the clamp in Gaskell's experiments will abolish the action of the nerves. And so we must expect will the continuance or increase of a high temperature. And, indeed, since the latter undoubtedly causes a severe strain upon the vitality of the heart, it is to be expected that the injurious limit will be very readily overstepped, and that, in a number of hearts heated at random up to standstill without any particular care to use the very lowest temperature for the very shortest time which will suffice, only a small proportion should be able still to respond to stimulation of the cardiac nerves.

When the heart is roused from the standstill by the vagus or sympathetic the beats are sometimes of great size and rapidity. About the greatest rate I have ever seen in the frog's heart has been in some of these cases. Thus in one experiment the maximum rate was 2·33 beats per second and these beats were of considerable force. Sometimes the beats are feeble though quick.

It is pretty often seen that when the ventricle alone is in heat standstill while the auricles continue beating, stimulation of the vagus, which produces its ordinary effects on the auricle, may cause the ventricle to resume beating for a time, the contractions beginning when the auricular beats are augmented. In Gaskell's phraseology the excitability of the ventricle, or the conductivity of the tissue at the auriculo-ventricular junction, which has been reduced by the high temperature, is restored by the action of the nerve, notwithstanding the continuance of that temperature.

SECTION I. B. THE INFLUENCE OF THE TEMPERATURE OF THE HEART ON THE ACTIVITY OF THE CARDIAC SYMPATHETIC NERVE. (Figs. 28—41.)

The sympathetic was prepared in the usual way by isolating it, ligaturing it below the second ganglion and dividing it below the ligature. Generally stronger stimulation was used than for the vagus. In the vagus experiments it was chiefly the inhibitory action which was to be studied, and such strong stimulation was not necessary. In some experiments the vagus on one side, generally the right, and the sympathetic on the other were prepared and placed on the electrodes. The effect of temperature on the action of the two nerves was compared by stimulating each nerve successively at each temperature. In other experiments the same strength of stimulus was used for each nerve so as to compare the effect of temperature on the secondary augmentation of the vagus and the primary augmentation of the sympathetic. Some of the results of these comparative experiments have necessarily been touched upon in the description of the work on the vagus.

We may say that in general the effect of temperature on the action of the sympathetic is even more marked than on the inhibitory action of the vagus. The question as to the proper quantitative tests for the activity of the cardiac nerves, which we have discussed already in the case of the vagus, seems more easily answered for the sympathetic. A true measure of its activity certainly seems to

be the increase caused in the transformation of energy per unit of time by the heart, or, what is all we can at present practically observe in the frog's heart, the increase in the part of the transformed energy which is converted into mechanical work. But this comparison will only give good results when the heart before and after stimulation of the augmentor fibres is still working at a rate considerably below its possible maximum.

(1) *The effect of lowering the temperature on the action of the sympathetic.*

When the temperature of the heart is diminished below the medium temperature, we may say in a general way that the activity of the sympathetic is lessened as regards the alteration both in the rate and in the amplitude of the beat. This statement must, however, be interpreted and qualified by what follows.

(*a*) If a strength of stimulus be chosen which is just sufficient to cause an effect of either kind at the medium temperature, this will be inefficient when the temperature is lowered. At very low temperatures, the activity of the sympathetic is abolished even for strong stimuli; and this generally happens at a higher temperature for the ventricle than for the auricle.

(*b*) Of the two alterations which stimulation of the sympathetic may cause in the beat, increase of rate and increase of amplitude, the former is that which is relatively most prominent at low temperatures. It very seldom happens that an augmentor effect which at the ordinary temperature manifests itself as a change of rate without any increase in the size of the beat or with the slight decrease in size generally associated in this case with the quicker beat, becomes at lower temperatures a change of strength; while the opposite is often seen, that is to say, an augmentor effect changing in type from a curve in which increase in the size of the beats is the most prominent feature to one in which increase in the frequency is alone present.

Occasionally at the lower temperature the increase in the amplitude of the beat is relatively greater than at the medium temperature. But it is instructive to note that precisely in these cases the force of the beats before stimulation, is smaller at the lower than at the medium temperature instead of being as large or larger, as is normally the case. This happens when the heart is plainly becoming exhausted;

and the sympathetic action suits itself to the state of the heart, causing chiefly an increase in the amplitude of the beats, when these are small as in the heart at very high temperatures, and chiefly an increase in the rate when the beats are large, as in the cooled heart they normally are.

(*c*) When the activity of the sympathetic is estimated by the alteration which stimulation of it produces in the frequency of the beat—say by the ratio of the frequency before, to the maximum frequency after stimulation—and a curve is drawn of which the ordinates are proportional to this ratio and the abscissae to the temperature, this curve in general sinks towards the abscissa axis, as the temperature is diminished below the ordinary temperature, till it reaches a minimum, at which it may remain when the temperature is still further diminished, or it may even begin to rise again. (Pl. III. Fig. 3, Curve *C*.) Ultimately, with still falling temperature, the curve again bends towards the abscissa axis, until it cuts it at the temperature at which the stimulation of the sympathetic ceases to produce an alteration in the rate.

When the activity of the sympathetic is estimated by the increase in the amplitude of the beats, its curve is much flatter at temperatures below the medium than the one described; and generally cuts the abscissa axis at a much higher temperature.

(*d*) When the vagus on one side and the sympathetic on the other are stimulated alternately as the heart is progressively cooled, the sympathetic generally becomes ineffective at a temperature for which the vagus is still active. (Figs. 42—45.)

It is astonishing, however, at what low temperatures the sympathetic can still shew a distinct influence. Baxt[1] found that the power of the accelerans in the dog to quicken the beat of the heart was greatly lessened even at 27°—30° C., suggesting that a further reduction of temperature would have abolished it altogether. Baxt did not reach this limit in any of his experiments; nor do the curves which he gives make it likely, so far as I can see, that his lowest temperature was near it. The curve by which he shews the ratio of the excess of the accelerated beats to the number of normal beats in a given time rises in one case up to 39°—40° C.; then falls during the cooling; then gradually rises as the cooling goes on; and ultimately becomes nearly horizontal at 27°—28° C. at as high a level as the first maximum.

[1] *Op. cit.*

In the frog I have sometimes found considerable acceleration caused by the sympathetic at 4° C., and a distinct effect at 3° C. and even at 1·5° C. Of course there is a great difference in the hearts of different frogs. Naturally we cannot expect anything of this sort in the warm-blooded heart. It is precisely in points which involve the temperature factor that the warm- and cold-blooded hearts may be expected to differ most. At 39°—40° C. the dog's heart is beating normally. At this temperature the frog's heart is going into heat standstill. At 15°—20° C. the frog's heart is at its best; the dog's heart is probably dead or near death. The cold-blooded heart can bear without injury a rise or fall of 20° C. Its nerves will retain their activity within a range of nearly 40° C. There cannot be a strict comparison between the two. Still we may say that in both the general result of diminution of temperature is to diminish the activity of the augmentor nerves. But while Baxt found that the inhibitory power of the vagus was not affected by temperature within his limits, I find that in the frog, within my limits, the vagus is affected by cooling in the same sense as the sympathetic, but not in general to the same extent.

But it has sometimes not been possible to say that the sympathetic in the frog failed before the vagus. Since, however, the vagus has not been found to fail before the sympathetic, unless where the activity of the former had been permanently weakened or destroyed; and as, moreover, the quantitative results of vagus stimulation at low temperatures, so far as it is possible to speak of a quantitative comparison of inhibitory and augmentor effects, are generally more striking than those of stimulation of the sympathetic, I think the general statement made above on the differential action of lowered temperature on the two nerves is justified. If nerve cells on the course of the inhibitory fibres in the heart are really a weak link in the chain, one might at first thought expect the vagus action to fail in the cooled heart before the sympathetic action. But the whole course of my experiments has shewn that the state of the heart itself is probably the most important factor. On this view primary augmentation fails before inhibition because it is less easy for the cooled heart to pass into the state of primary augmentation than to pass into the inhibited state.

I was hopeful at first that the difference might have been great enough to allow of the elimination of the sympathetic factor from the result of stimulation of the vagus trunk, and that by cooling the heart to a moderate extent it might be possible to use the mixed nerve instead of the intra-cranial vagus for work on the pure inhibitory fibres. This

would have been a considerable advantage; but unfortunately the difference is too small.

We do not know how alteration of the temperature of the nerve trunk itself affects the relative excitability and conductivity of the two sets of fibres. At the ordinary temperature the inhibitory effects of stimulation of the vagus are got with weaker stimuli than are necessary to cause marked augmentor effects; and this is sometimes expressed by saying that the sympathetic fibres are less excitable than the true vagus fibres. We do not know, however, whether there is a difference of excitability in the strict sense of the word, or whether the difference is in the power of the heart to respond. It is just possible that by heating or cooling the nerve alone the activity of the sympathetic fibres might be altered relatively to that of the true vagus fibres. Baxt took no account of any possible effect of temperature on the accelerans and vagus fibres themselves. They were necessarily, with his arrangement, cooled and heated along with the heart and the whole animal.

(2) *The effect of increasing the temperature of the heart on the activity of the sympathetic.*

(*a*) A stimulus which is just too weak to cause any effect at the medium temperature may cause an effect at a higher temperature.

(*b*) As the temperature is increased from the medium temperature, the activity of the sympathetic, for a given strength of stimulus sufficient to cause augmentor effects at the ordinary temperature, increases remarkably; and while this is true, up to a certain limit, both of the increase in the rate and of the increase in the amplitude of the beats, the latter becomes relatively more marked the higher the temperature. This is true even where at the medium temperature the chief or sole effect is increase of the rate. The limit of temperature up to which the increased activity of the sympathetic is shewn in both ways fluctuates greatly, not only in different hearts but in the same heart at different stages of an experiment. In general, from the medium temperature up to, say, 18°—25° C. the rate is more increased by stimulation of the nerve than at the medium temperature itself, notwithstanding that the heart before stimulation is beating faster. Above 18°—25° C., and even up to the temperature of standstill, the sympathetic is still able to quicken the beat; but the ratio of the frequency after, to that before stimulation is seldom more, and generally less than at the medium temperature.

It is of course evident that if the frequency of the beat continually increases with rise of temperature, which up to a temperature a little below that of heat standstill is generally the case, there must be a limit to the accelerating power of the sympathetic. In the dog, Baxt's curves shew such a limit for the accelerans, although his highest temperatures were only 2 or 3 degrees above the normal, and although we should, perhaps, expect the warm-blooded heart to be more elastic in this respect than that of the frog. For example in one experiment the rate was 80 beats per minute, after stimulation of the sympathetic with the heart at a temperature of 30° C. Before stimulation the rate was 58 per minute. Now, if a rate of 80 beats per minute was really the highest effort which that particular heart was capable of, it is plain that if we started from a rate of, say, 70 per minute and caused this to increase to the limit of 80 per minute by stimulation of the sympathetic, the relative acceleration would be much less in the second than in the first experiment; but the activity of the sympathetic could not in any true sense be said to be less. It is only when the accelerated rate is still far from the possible rate that this part of the action of the sympathetic can be quantitatively estimated from the ratio of the frequency after, to that before stimulation.

As regards the increase in the force of the beats, it is easy to see that with increasing temperature this becomes more and more the characteristic expression of the action of the nerve. This is particularly true of the auricle, which yields much less readily than the ventricle at high temperatures to a depression which is not affected by the sympathetic.

(*c*) The curve of activity of the sympathetic when the activity is estimated only from the maximum acceleration, generally rises at first as the temperature is increased from the medium temperature; reaches a maximum; and may decline with further increase of temperature.

When the activity is estimated from the ratio of the maximum amplitude of the auricular beat after stimulation to the average amplitude before stimulation, the curve rises at first slowly, then more rapidly; and it is doubtful whether it reaches a maximum.

In both cases the rousing of the heart from heat standstill is excluded. Here we might say that the ordinate suddenly becomes infinite.

(*d*) It has already been incidentally mentioned in describing the

occasional effect of stimulation of the vagus in rousing the heart from the heat standstill that the sympathetic could do the same. Indeed there is no doubt that it is to the sympathetic fibres in the vagus that the action is to be chiefly, if not altogether, attributed. As I have already discussed the subject pretty fully, it is only necessary here to refer to one or two points which belong more particularly to the phenomenon when it is seen as the result of stimulation of the sympathetic.

In the first place it would seem, although I desire to speak guardedly here, that stimulation of the sympathetic is more frequently followed by this effect than stimulation of the vagus. If this is the case, it may mean that even during the standstill the vagus can cause a sort of latent inhibition, which lasts long enough to allow the depressing effect of the high temperature to overcome the stimulating action of the sympathetic.

When the heart has almost but not quite stopped beating, as in Fig. 26 stimulation of the vagus may be followed by beats which burst out with immense suddenness after the preliminary standstill. While the general similarity of the groups of beats following stimulation of the vagus and sympathetic in that tracing is evident, they differ in the abruptness with which the maximum is reached. After stimulation of the sympathetic the increase both in auricle and ventricle, although not slow, is not so sudden as in the vagus group. It is difficult to avoid connecting the abrupt outbreak of contraction with the previous inhibition.

Near the beginning of the tracing from which Fig. 26 is taken, it was seen that the heart had stopped beating at the ordinary temperature (15° C.), and that stimulation of the sympathetic (with the coils at a distance of 30 mm.) roused it to action again. The marked difference in size and frequency of the beats at this temperature and in the outburst at 28·5° C. is worth noting. It may also be remarked that at 15° C. the first beat took place 5″ after the beginning of stimulation, while at 28·5° C. it did not appear till 6·5″, although, as will be stated directly, the latent period of the sympathetic is notably shortened, in the case of the beating heart, by increase of temperature. The comparatively long latent period perhaps points to the necessity for a greater amount of preliminary change than is required when the sympathetic augments the action of the already beating heart, or even when it stirs up a heart flagging from exhaustion at the ordinary temperature. This agrees with what we have said, that being brought to heat standstill is a severe strain upon the heart.

It must not be supposed, from this example, that it is only exhausted hearts which can be roused from the heat standstill by the sympathetic. It is certainly true that any condition which favours the production of heat standstill at a comparatively low temperature is favourable to this action of the nerve. But I have seen it in fresh and vigorous hearts, in which standstill did not take place till 36° or even 40° C. had been reached. It may be asked whether it is legitimate to call the standstill which is produced at 28° C. or 25° C. in previously cooled or exhausted hearts a heat standstill. I can only reply that the temperature of the heat standstill is always dependent on the state of the heart; that it is not constant for the same heart, but can be obtained at a lower temperature the second time than the first, and can be obtained at a much lower temperature if the heating is gradual and long continued than when it is sudden and transient. All I have to say is that when the rhythmical beat of the heart has been temporarily stopped by a temperature considerably above the ordinary temperature, it can sometimes be restored by stimulation of the vagus or sympathetic; and that the lower the temperature is at which standstill has taken place, the greater is the probability that stimulation of the nerves will have this effect.

(*e*) Sometimes when the heart is at a high temperature and the ventricle is beating feebly, stimulation of the sympathetic, while greatly increasing the amplitude and to some extent the rate of the auricular beats, may cause at the same time diminution in the size of the ventricular beats.

I suppose this is not due to a negative or depressing action of the sympathetic on the ventricle, but simply to the ventricle having got into a state in which stimulation of the nerve does not affect it at all. When the call for quicker beats arises, the ventricle follows the auricular lead; but, being in a feeble state, it cannot increase the frequency and maintain the force of its contractions at the same time, just as the normal heart generally beats less strongly when rise of temperature compels it to beat more quickly.

(*f*) The latent period of the sympathetic is diminished as the temperature is raised, and increased as the temperature is lowered. This agrees with Baxt's observations on the accelerans in the dog within a smaller range of temperature; and is, of course, what would be expected. I should like to point out, however, that while the absolute length of the latent period varies in this way, there may be quite as many unaltered beats, after stimulation has begun, at

a high temperature as at a low; in other words, what we may call the functional latent period may not be markedly altered.

It is not possible to estimate the latent period exactly. It is a function of other variables besides temperature. In Table II., which only covers a small portion of my tracings, I have measured the interval from the beginning of stimulation to the beginning of the first systole of the auricle which is separated from its predecessor by a shorter pause than the normal interval before stimulation, or is stronger than the preceding contractions. It is impossible to say whether the first altered systole is the first mechanical change; or rather we know that the time of the first mechanical change must be put somewhere between the end of the last unaltered beat and the beginning of the first altered beat. When there is no alteration in the rate before the first altered systole, i.e. where the first change is an increase in the force of the beat, we may take the beginning of this contraction as the first alteration. But when the first alteration is a diminution in the pause, with or without a change in the size of the succeeding beat, all that we can say is that the time of the first mechanical alteration is somewhere in that pause. But as we do not know at what time the length of the pause is determined, and may just as well say that the length of the pause which follows a beat is determined by the condition of the heart immediately after that beat as that it is determined by some change preceding the appearance of the next beat, I do not see how it is possible to decide whether the beginning of the shortened pause, or the beginning of the contraction which follows it is the first mechanical change. It is of little importance whether the beginning, or the maximum, or the end of the auricular systole which is fixed on as the point of first change is taken. I have taken the beginning, but have only measured the tracings roughly. They were taken for quite other objects than the determination of the latent period, with a slowly moving drum, and are therefore unsuited for the measurement of fine differences. But such differences are of little consequence on account of the larger error due to the impossibility of fixing the precise point at which the change begins, not to mention the influence which the particular phase of the heart's contraction at the moment of stimulation may have. The effect of temperature on the latent period is, however, too marked to be overlaid even by errors of such possible magnitude.

Discussion of the results of the experiments on the sympathetic.

A moderate amount of depression of any function of the cardiac muscle which the action of the sympathetic can influence is, at the ordinary temperature, rather favourable than otherwise to the production of a striking effect, because the greater the depression the more room is there for restoration. So in the heated heart the small quick beat may undergo a great relative increase without overtopping or even equalling the size of the normal beat at the ordinary temperature. And frequently the augmentation does not go beyond this. That is to say, the effect of stimulation of the sympathetic is sometimes to make the heart beat with what we may call the normal strength, the strength with which it beats at the ordinary temperature, under abnormal conditions. When the sympathetic is not stimulated, the state of the heart determines the nature of its action for any given temperature. Some hearts will beat both strongly and rapidly at 25° C. Others will beat feebly and rapidly. The high temperature making a rapid beat necessary, the strength of the beat will depend on the rapidity with which energy is transformed in the cardiac tissue. When there is a sufficiently rapid transformation, the increased rapidity of beating can be maintained without diminution in the force. Where the increase in the rapidity of transformation, with rising temperature, outstrips the increased demand upon the heart caused by the growing frequency of its beat, there may be an increase in the force of the contractions as the temperature is raised. And if the rapidity of transformation of energy in the heart is increased at any given temperature by the action of the sympathetic, the heart in its changed state will still find itself conditioned by the temperature; it will comport itself differently according to the temperature. Probably we are not to look upon the sympathetic action as something which directly controls the nature of the heart's activity, as if it determined directly whether the beat should be increased in force, or in rate, or in both. It is the heart itself, conditioned by its internal state at the time, however that state may have been produced, conditioned by its external circumstances, by temperature above all, which determines how it shall beat. A heart in which the metabolic processes have been quickened by the action of the sympathetic will at one time quicken its beat, the amplitude being perhaps slightly diminished, just as a heart in which the metabolism has been increased by a moderate rise of temperature will do. And this is most likely to happen when the heart, before stimulation of the

nerve, is beating slowly and strongly at a not very high temperature. Since there are limits beyond which the heart cannot drive the rate or the force of its beats, it gets rid of its surplus energy, so to speak, in the easiest and most natural way. When the beats are slow and strong, as in the cooled heart, it is comparatively easy to quicken the rate, but less easy to force up the strength towards the limit. When the rate is very quick and the beat weak, as in the heated heart, it is easier for the sympathetic, when it raises the heart for a time to a higher metabolic plane, to increase the strength than to drive up the rate.

Baxt[1] has pointed out the analogy between the effect of temperature alone and the effect of stimulation of the accelerans on the rate of the heart in the dog; but the accelerans can always increase the rate beyond what is due to the temperature itself. In the frog this does not always happen after stimulation of the sympathetic at high temperatures. As I have said, increase in the size of the beat rather than increase of the rate is here the characteristic effect; and sometimes the rate may not be increased at all.

As to the analogy with the effect of temperature, there is, of course, in the heart whose activity has been increased by the sympathetic, no parallel to the increased irregular vibration of the molecules in the heated heart. If there was, the heart would become hot on stimulation of the sympathetic. But the definite processes connected with contraction, the molecular rearrangement, which this increased vibration favours in the moderately heated heart, are undoubtedly favoured, though necessarily in some other way, by the action of the sympathetic. The power of the heart to transform energy is increased both by heat and by the action of the nerve. The earlier stages in the process by which this change is brought about must be utterly different in the two cases, but the result in both is to make the chemical and physical changes connected with the contraction easier and more rapid. There are, however, very distinct differences. For example, it is only for a small range that elevation of temperature increases the amplitude of the beats, while stimulation of the sympathetic may do so for a great range. Above 20—25° C., rise of temperature diminishes the force of the beat while quickening the rate; stimulation of the sympathetic generally increases the force to a marked extent. That is really all we can at present say about the matter. But when once the sympathetic has caused its action on the internal processes of the cardiac tissue, the heart, so to speak, takes the reins in its own hands, and beats according

[1] *Loc. cit.*

to its internal state and the external conditions under which it finds itself.

So that, as has been already hinted, the phases, "activity of the sympathetic," "activity of the vagus," should probably be amplified so as to express more directly the fact that it is the activity of the *heart*, after stimulation of the sympathetic or vagus, which we observe. When we say that, as the temperature rises, the "activity of the sympathetic is increased," what we mean is that the heart at the higher temperature passes more readily into the state of increased activity associated with stimulation of the nerve, and shews that activity in a higher phase than at a lower temperature.

Is the effect of temperature on the initiation and the continuance of the action of the cardiac nerves the same?

The question naturally arises here, how far the power of the sympathetic (and the discussion will apply also to the vagus) to cause those preliminary changes which, so far as the effect of temperature on the augmentor function enables us to judge, are probably alone to be called its "action" depends on the temperature. When I use the word "preliminary," I do not at all mean to imply that the whole action of the nerve on the tissue of the heart is hurried through during stimulation or soon after it, and that henceforth there is necessarily nothing of the nature of regulation, or even of periodic regulation, of the cardiac beat. But there must, I suppose, come a time after stimulation of the nerve is over, when the sum total, the stock, so to speak, of what it is going to effect in the heart is potentially *fixed*, so that if the heart be now put under new conditions of temperature, it will still carry with it this augmentor tendency or bias or capability, and beat out the remainder of the effect under the new conditions in a manner determined now by them and by its own state.

It is conceivable that a temperature which is most suitable for the starting of inhibition or augmentation by the vagus or the sympathetic might not be suitable for the full development and persistence of these effects. It is conceivable that at a high temperature it should be more easy for the vagus to produce an effect, complete standstill say, than at a low temperature, and yet that the effect, once produced should be more permanent at the low temperature than at the high, so that stimulation of the vagus with the heart at a comparatively high temperature, followed by rapid cooling, might be the ideal method

of obtaining a prolonged inhibition. These are possibilities which, so far as I know, have not been tested by experiment, and which are perhaps difficult to test in a satisfactory manner on account of the difficulty of altering the temperature of the heart with sufficient promptitude and without causing excitation. I have made the attempt, however, and have so far succeeded, that I think it is worth while to give some account of the work in this place.

I had noticed occasionally that if the vagus when stimulated at the ordinary temperature causes standstill, the standstill is lengthened when, just at the moment of stimulation or a little after stimulation has begun, saline solution at a very low temperature is brought in contact with the heart, although, after the heart has begun to beat again in the cold solution, complete standstill may no longer be obtained, nor perhaps any effect except a slight diminution in the size of the beats. This seemed to shew that although the initiation of the inhibitory action of the vagus is more difficult at a low temperature, it lasts longer, when once induced. The long continued standstill which I sometimes obtained by direct stimulation of the sinus in the greatly cooled heart, and especially in the heart in which only the ventricle was directly cooled, seemed capable of being explained in the same way. When the ventricle was cooled by ice or cold solution, the cooling would after a little time extend to the auricles and sinus. If, then, the sinus was stimulated before it was sufficiently cold to make the initiation of the inhibitory process difficult; and if the cooling was going on so rapidly, that during the standstill the motor excitability was further considerably diminished, the ideal conditions for long standstill would probably be present.

In a few experiments which I made with chemical stimulation of the medulla oblongata, it was found that the exceedingly long continued standstill could not be abolished by cooling the heart, although, as we have seen, the action of the vagus can be greatly weakened or entirely abolished by cooling. On the contrary, when, as the result of chemical stimulation of the medulla, the heart has not gone into complete standstill, but has had its action greatly diminished so that it just continues to beat and no more, cooling may cause complete standstill. And that this standstill is not due to the cooling alone can be shewn by dividing the vagi, so as to allow the heart to resume beating, and then cooling to the same temperature as before, when standstill will no longer be obtained. If the heart is cooled before the strong salt solution is applied to the medulla, it is apparently less easy for

standstill to be produced than if the heart is at the ordinary temperature.

All this seemed to shew that there are initiatory processes caused in the heart by the vagus which are prevented or imperfectly performed when the temperature is low; but that once these are over, the low temperature is not in itself inimical, but, on the contrary, favourable to the continuance of the inhibitory action.

On the other hand, although a high temperature is favourable to the initiation of inhibition, it is not necessarily favourable to its continuance. So far is this from being the case, that the standstill obtained by chemical stimulation of the medulla oblongata at the ordinary temperature can be removed by gradually raising the temperature of the heart. And with electrical stimulation of the mixed vagus nerve the standstill, which is more easily obtained at a high temperature than at a low, often passes off sooner. I find it stated by Luchsinger and Ludwig[1] that they sometimes obtained very long-continued standstill in the over-heated heart. It seems very easy by the method of simple inspection to confound a heat standstill coming on after vagus stimulation with a lasting inhibition. I can only say that I have never seen an instance of it.

Starting from these hints, gleaned from the previous part of this work, I came next to try some more direct experiments.

THE INFLUENCE OF TEMPERATURE ON THE ACTIVITY OF THE CARDIAC NERVES WHEN THE TEMPERATURE IS RAISED OR LOWERED AFTER THE INHIBITORY OR AUGMENTOR ACTION HAS ALREADY BEGUN.

I. The influence of secondary[2] alteration of the temperature of the heart on the activity of the vagus.

A. *On the Inhibitory Action.*

The vagus was stimulated with the heart at a given temperature, and immediately afterwards the temperature was raised or lowered. This was managed by first immersing the heart in salt solution at the temperature at which stimulation was to be made, then rapidly removing this solution, and, quickly filling the vessel with solution at the other temperature nearly to the level of the apex of the ventricle but not

[1] *Op. cit.*

[2] "Secondary alteration of temperature" means any alteration which takes place after stimulation of the nerve has begun.

quite touching it. Stimulation was then made, and on the heels of this the vessel was filled up, so that the heart was very quickly subjected to the new temperature. Of course as small a vessel as possible was used, so as to reduce the time of filling and emptying to a minimum. Evidently this is a very crude method of producing rapid changes of temperature in the tissue of the heart. But the temperature of an object like the heart of a frog, with a sensible heat capacity, must in any case take an appreciable time to change by 10° C. And although I have tried other methods, I have not been able to make any real improvement.

Of course there is some risk of "stimulation" by the sudden change of temperature itself; and I think that such stimulation of the heart was distinctly seen in all my experiments when the heart was suddenly cooled during the inhibitory standstill, although no such immediate effect was apparent after sudden heating.

The general procedure was as follows. The vagus was first stimulated in the ordinary way at the temperature which, in the next observation, was to continue only during the time of stimulation. This was generally the temperature of the air. After a sufficient interval of rest the nerve was again stimulated at this temperature with the same strength of stimulus and for the same time, but immediately after stimulation was over the temperature was raised or lowered and the curve now completed at this new temperature. Then, after an interval of rest, while the new temperature was still maintained throughout, the vagus was again stimulated and a third curve obtained. The first and third curves served for comparison with the second.

By varying the initial and the secondary temperatures a great variety of experiments could be made. Practically I have used only three temperatures, low, medium (that of the air) and high; and generally the combination has been low, high; high, low; medium, high; or medium, low.

In Figs. 46—48 it will be seen that when the temperature was suddenly lowered from 19·7° to 4° during standstill caused by $rV90$, 3 or 4 beats followed at once, breaking through the standstill, and, as it seemed for the moment, cutting it short. But note the marked inhibitory effects which follow those beats of excitation, an inhibition more marked than that at the ordinary temperature. In fact the inhibitory effect although broken through for the time by these accidental beats has not been abolished but postponed; and in the cold it is now able to maintain itself for a much longer time

than it did when the temperature of stimulation was maintained throughout.

It might be said that if the sudden lowering of the temperature is able to call forth cardiac beats it is also able to stimulate the intra-cardiac inhibitory nerves, and, therefore, that the inhibition following the beats is not the postponed residue of the former effect but a new inhibition following a fresh stimulation. But there is no evidence of any such inhibition when the normally beating heart is suddenly cooled to the same extent.

It may be noted that the tone is greatly increased during the beats of excitation, as happens always when the normally beating heart is cooled.

The effect of cold in maintaining inhibitory action seems to be most marked when the time of stimulation is short. Since in my experiments the temperature was not altered till the stimulation was over, this probably only means that the sooner after the initiation of the inhibitory effect the temperature is lowered, the better. We must expect this to be so if a low temperature tends to husband and a high temperature to exhaust the inhibitory action, for the greater will be the unexpended portion of that action when the low temperature begins to take effect.

Further, since a low temperature tends to diminish the call upon the heart for contraction, the tendency to break through the inhibition will be lessened. At first sight it almost seems as if the statement that inhibition is prolonged because the inhibitory action is spun out and made to last longer in the cold, is only a paraphrase of the statement that the anti-inhibitory action is diminished in the cold. And in truth they cannot be entirely separated except in idea. But according as we consider the inhibitory action as a grip which gradually relaxes of itself or is burst open by the gathering motor force of the heart it will be found necessary to emphasise the one factor or the other.

In any case we must suppose that at the higher temperature the molecules, moving more freely, are more easily guided into the new distribution which corresponds to the inhibitory standstill, but for the same reason it is more difficult for any distribution to be long preserved.

At a low temperature, when all the molecular motions are slower and everything is more firmly locked in the particular distribution of any given moment, it is more difficult to bring about the new distribution corresponding to the inhibitory standstill, but once it has been brought about, it is proportionally more stable.

The assumption here is that there is a tendency to recovery from the inhibitory state, that is, that the inhibitory distribution is not a state of stable equilibrium. This is, of course, perfectly true, but is only another way of saying that inhibition occurs in a living tissue. Why is it not a state of stable equilibrium? Because the force which produces inhibition soon ceases to act, the inhibitory mechanism being, as we say in metaphorical language, exhausted, and the molecules, abandoned to the next impulse of cardiac rhythm, fall at once into the systolic distribution? Or, because, in spite of the inhibitory force, the stress of the contractile "effort" becomes strong enough to force the molecules from their diastolic moorings.

B. *On the Secondary Augmentor Action.* (Figs. 49—51.)

It is easier to investigate the effect of a secondary change of temperature on this than on the inhibitory action of the vagus or on primary augmentation. For the latent period in both the latter cases is too short to allow the change of temperature to coincide with the beginning of inhibition or augmentation. In the case of secondary augmentation on the other hand the temperature can be changed long before the period at which the beating would naturally be resumed. And experiments in which, after the stimulation of the vagus, the temperature of the heart was altered at different intervals from the beginning of the standstill seemed likely to throw some light on the question how the sympathetic action is represented in the heart during the simultaneous stimulation of the inhibitory and augmentor fibres. At the end of the period of stimulation the augmentor action must be represented in some latent form; must have brought about some change in the heart, so that in one way or another the augmentor effect is already during the inhibitory standstill potentially present. We know nothing of the steps by which this potentiality becomes translated into actual augmentation.

We cannot put our finger on a point in the inhibitory standstill or in the latent period which precedes it, and say, Here now it is inevitable that augmentation should occur. Nor can we say whether a modification of the external circumstances of the heart, a change of temperature for example, would produce the same effect on the latent augmentation at different points of the inhibitory standstill as would be produced when the shadowy forerunner of the augmentor effect had developed into actual beats. We know that when stimulation of the

vagus standstill, under ordinary temperature conditions, is followed by well-marked secondary augmentation, the heart is being prepared during the standstill to execute a very definite curve, just as when the temperature is raised during the standstill an invisible preparation makes it ready to take up at once the rhythm corresponding to the higher temperature.

As regards the influence of temperature the secondary augmentation may be affected: (1) By the temperature of the heart during the time of stimulation or during part of that time.

(2) By the temperature of the heart during the period of inhibition or part of that period.

(3) By the temperature of the heart at the end of the period of inhibition, during the actual augmentation.

Now let it be supposed possible to vary any of these three temperatures in either sense, and it will be seen that we have a considerable number of cases to investigate even if we use only two standard temperatures, a high and a low. There are then the following eight possible cases:

No.	Temperature		
	During stimulation.	During inhibition.	After inhibition.
1	high	low	high
2	low	low	low
3	high	low	low
4	high	low	high
5	high	high	low
6	low	high	high
7	low	low	high
8	low	high	low

The first two cases, where the temperature is the same throughout, have been considered in former portions of this paper. In practice I have not found it possible to alter the temperature more than once in the course of an observation; so that of the remaining six cases only, Nos. 3, 5, 6 and 7 were available.

In an example of case 6 there was considerable secondary augmentation, as much for the time, although not so lasting, as in case 1 with the high temperature all through. Here, however, the "low" temperature was only the air temperature, at which the preliminary augmentor

changes undoubtedly go on well. The effect here of raising the temperature after stimulation would seem to be to convert what would otherwise be a low temperature augmentation (that is, an augmentation shewn chiefly as acceleration and spread over a longer time) into a typical high temperature augmentation occupying a shorter time. The effect of the rise of temperature at this stage is not necessarily to increase the total augmentation, as apparently is the case when the temperature is high throughout, but only to alter its type.

In case 3, (High, low, low) the augmentation is perhaps altogether as great as it would be in case 1, although it is altogether different in type; so that here we may suppose that the essential part of the process is finished at the high temperature, that is just before the end of the stimulation, and that the low temperature cannot now prevent the augmentation as it could to a great extent have done had it been present from the beginning, but can only alter its type.

In case 6, with fairly low initial temperature (about 10° C.), the secondary augmentation seems not to take place or to take place only to a small extent. We may suppose that the essential preliminary changes have not occurred at the low temperature. All that the high temperature can then do is to make the heart beat as it would a normal heart. In other words, it is the first stage, the stage of stimulation and the time immediately following it, which settles whether there is to be augmentation or not. Not only so, but, as will be seen in Fig. 50, where the augmentor nerve was alone stimulated, the action has so much stability near the beginning of stimulation that it can go on for a little time at the new temperature with the type of the initial temperature.

II. The influence of secondary alteration of the temperature of the heart on the activity of the sympathetic.

In this series of experiments the sympathetic was stimulated with the heart at a given temperature, high, low or medium, and just as the stimulation was stopped the temperature was suddenly altered. The curve so obtained was compared with curves taken before and after from the same preparation when the first and second temperatures were maintained respectively throughout.

The conditions here are much the same as in the case of secondary augmentation, except that the preliminary period is not lengthened by an intervening inhibition. In practice, therefore, one is never able to

anticipate the coming augmentation by a change of temperature; and we cannot act upon the preliminary stages of the augmentor effect.

The possibilities here are: (1) That the whole course of the augmentation, as to amount and type, is determined during the preliminary period, so that at a new temperature the heart would still work off the augmentation in just the same way as if the original temperature had been maintained. If this were the case, we should probably be entitled to conclude that the action of the sympathetic is strictly directive, and not merely a diffuse and general action.

(2) That while the amount of the augmentation is determined during the preliminary period and is related to the temperature during that period, the precise manner in which the augmentation shall shew itself depends on the temperature at which the heart works at the end of this period.

(3) That the action of the nerve consists not only in causing general changes, but to a certain extent in directing the manner in which these changes shall be manifested. For instance, it is conceivable that the manner of the heart's action is absolutely fixed for a certain time after the preliminary period, but that later on it yields more and more to its external conditions, and works out the residue of the augmentation more and more in accordance with these.

(4) That the original type of the augmentor action is stable against slight changes in the external conditions, but has to yield to great changes. This is a particular case of (1).

So far as my experiments go, the first possibility, as was to be expected, is never fully realised. The change of temperature always carries with it sooner or later, and before the augmentation has spent itself, a change in the type of the augmentor effect. For example, it frequently happened that when the sympathetic was stimulated there was considerable increase both in the frequency and the force of the beat. When the temperature was now suddenly raised, say about the time when the maximum augmentation had been reached, the tone of the heart would suddenly give way, the line of relaxation would rise, the rapidity of beating would increase, but there would be no series of strong rapid beats to represent the balance of the augmentation. This balance, however, would be represented by an excess of frequency over that of the unaugmented heart at the same temperature. This excess would gradually disappear.

To a certain extent, however, the form of the augmentation, as well as the amount, seems to be determined during the earlier portion of the

period of stimulation in accordance with the then state of the heart as regards temperature (rate of beating). For when the temperature is suddenly raised as soon as possible after the end of the latent period, the typical form seems to persist for some time after the alteration of temperature, this stage being followed by one in which the unexhausted remainder of the augmentor effect has adapted itself, so to speak, to the new conditions, and is henceforth manifested merely as an increase on the new lines in the general working power of the heart.

In accordance with this the typical effect disappears at once when the temperature is altered at a later period of the augmentation, and is not replaced by an augmentation such as would be produced by stimulation of the nerve at the given temperature, but merely by an increase in the normal action of the heart at that temperature.

If the temperature could be altered very early, say just before the end of the latent period, it is perhaps possible, although, I fear, the point is not capable of experimental proof, that the augmentation might from the beginning take on the type peculiar to the new temperature when stimulation is made in the ordinary way at that temperature.

And this would be some indication that during the latent period the changes are of a general kind, the special bias not being received till the heart, overcharged with energy, as it were, but still free to work off this overplus according to the external conditions in which it may find itself at the end of the latent period, bursts into a series of rapid and strong beats if the temperature be high, or passes into the typical low temperature augmentation.

Summary and comparison of the influence of the temperature of the heart on the action of the vagus and sympathetic.

In recalling the chief points which have been made out in this investigation, one cannot fail to be struck with the fact that in general the influence of temperature on both nerves is in the same direction. We have seen that as the temperature is lowered, the inhibitory action of the vagus becomes less complete and less easily produced; the augmentation caused by the sympathetic, whether its fibres are stimulated by themselves or in the mixed vagus trunk, becomes less and less marked, more and more difficult to be obtained at all. As the temperature is raised beyond the ordinary temperature, we have seen the inhibitory action of the vagus becoming more complete and more easily obtained, and the augmentor effects of stimulation of the sympathetic

increasing enormously. We have seen the vagus stop the heart on the very border of the heat standstill, and the sympathetic, or the sympathetic fibres in the vagus, cause it to beat again when it had passed into the standstill.

In a general fashion it may be said that a temperature which is unfavourable to the action of one of the nerves is unfavourable to the action of the other. When the normal changes in the heart are rendered sluggish by cold, it is not only less easy to quicken its beat, but it is less easy to stop it. When these changes are quickened, when the molecular mobility of the heart is increased by heat, it is easy for it to slide either into inhibition or into augmentation.

It is true the resemblance is not complete when the quantitative changes are taken into account. In general the function of the sympathetic is more depressed by cold and far more exalted by heat than the inhibitory function of the vagus. But after every allowance has been made for differences of this sort, the general agreement is sufficiently striking; and emphasises from a new point of view the remark of Baxt that the accelerator and inhibitory nerves cannot be considered antagonistic.

The old simile of the vagus reining in the heart, as a horse is reined in by its rider, is poetical but misleading. If it were true, the more vigorous the heart is, the more rapid its metabolism is, the more difficult should it be for the vagus to pull it up. The reverse of this is the case. If similes were of any use in physiology, the stopping of the "way" of a vessel in stays would give a better idea of what seems to happen when the heart is stopped or slowed by the action of the vagus. The more way the vessel has, the easier is it for the steersman to put her up in the wind. The vessel is not stopped or slowed by the steersman nor by the rudder, but only put on such a course that the constantly acting resistance, the friction of the water, which formerly was overcome by the force of the wind, now acts unopposed or rather reinforced by the changed relations of direction of wind and course of vessel. The heart is not "reined in" suddenly by the vagus, any more than the ship is checked at full speed by a sudden strain upon an invisible hawser. The vagus acts the part of steersman, or at most of steersman and steering gear together. It may be that the heart contains within its own contractile tissue the steering mechanism which it is the function of the vagus merely to set in motion. Or it may be that this mechanism belongs rather to the nerve than to the muscle.

In either case constantly acting "resistances," or forces which in the normally beating heart make for rhythmical contraction, but which in the heart under the influence of the vagus may be placed in a different relation to the motor activity, may bring about the actual inhibition.

To take another analogy, the vagus action seems rather a shunting of the activity of the heart into a new path than the stopping of it dead. The vagus adjusts the points, but does not apply the brake; or if it does so, the pressure is only regulated by the vagus mechanism; the power is not supplied by it. The speculation of Pflüger[1], that the action of the inhibitory nerves may consist in so changing the path of the oxygen atoms that they do not come within the sphere of activity of the carbon atoms, is very suggestive. This would amount to a sort of negative "assimilation" in Hering's sense, or a negative "anabolism" in Gaskell's, a prevention of the normal destructive change being in a manner equivalent to an active building up, on the principle of "magnum vectigal est parsimonia."

Comparison of the results of Section I. with the literature of the subject in other animals than the frog and toad.

What degree of generality the above results may have it is impossible to say. As regards the augmentor nerves we have already discussed the experiments of Baxt on the dog, so far as a comparison could be made. He recorded merely the blood pressure curve, and, therefore, took account only of the rate of the heart as a whole. My tracings shew that in the frog the changes in the size of the beats, and the relation of these changes to temperature are at least as important as the changes in the rate. Then again, the simultaneous record of auricular and ventricular contractions has brought out various interesting relations; and we have no data for comparing these with corresponding phenomena in the mammalian heart.

As regards the vagus, we have already mentioned that Baxt, using minimal stimuli, and taking the maximum slowing as the test of the activity of the nerve, found no effect of temperature on it. Considering how important a part the diminution in the force of the contractions is in the total action of the vagus, it is perhaps doubtful whether Baxt's result has settled the question even for the dog, and for his range of temperature.

[1] *Pflüger's Archiv*, Bd. XVIII. p. 247, 1878.

Horvath[1] found the vagus action abolished in greatly cooled rabbits.

Schiff[2] stated that in the rabbit the vagus loses its action when the animal is heated, and regains it on cooling; while Lauder Brunton[3] found the vagus action still present in this animal at a temperature just sufficient to cause death. This quite agrees with what happens in the frog. But Brunton's rabbits were deeply chloralised; and Langendorff[4] and Vulpian[5] found that chloral strengthened the vagus action and made it more lasting; and, therefore, it is not certain that Brunton's result was not due to the chloral. In etherised rabbits and cats, on the other hand, Gianuzzi[6] found that when the pulsations had become weak and slow, stimulation of the vagus strengthened and quickened them.

In hibernating animals Valentin found in the marmot[7] that in deep winter sleep stimulation of the vagus had no effect on the frequency of the pulse; with sleep less deep it caused quickening; when the sleep was still less deep, the usual slowing. I have not been able to see Valentin's original paper, and do not know whether the temperature at which the different experiments took place was recorded. It seems possible that the want of vagus action in deep winter sleep, if it really was altogether absent, was due to the low temperature associated with that condition. In any case the slow metabolism of the heart in the hibernating animal might be expected to be unfavourable to the action of the cardiac nerves. But it is difficult to explain the acceleration in the intermediate stage of sleep.

Lépine and Tridon[8] have stated that in the tortoise the action of the vagus persists when the heart is cooled; but is abolished when it is heated, returning again on cooling; while Luchsinger and Ludwig[9] state that it is abolished by cooling.

It is evident, I think, that there is no complete agreement as to the action of temperature on the vagus. This seems due partly to the

[1] *Wiener med. Wochenschrift*, 1870.

[2] *Arch. d. scienc. phys. et natur.* LXIII. Genève, 1878.

[3] *St Bartholomew's Hosp. Reports*, 1871, p. 216. *Text-book of Pharmacology*, 1885, p. 35.

[4] *Mittheil. d. Königsberger physiol. Lab.* 1873.

[5] *Compt. Rend.* LXXXVI. p. 1303.

[6] *Rivista scientif. d. Accad. de Fisiocratici*, p. 46, Siena, 1872; quoted by Auber; in *Hermann's Handbuch.*

[7] *Moleschott's Unters.* XI. 4.

[8] *Mémoires de Société de Biologie*, 1876, Mars.

[9] *Loc. cit.*

experimental difficulties in the case of warm-blooded animals. In the tortoise, however, there are no special difficulties. Accordingly, I have made a few experiments to try to settle the question of the influence of temperature on the action of the vagus in that animal.

Section II. The influence of temperature on the heart of the tortoise, and especially on the activity of the vagus.

The method of experiment was the same as that used in Section I. The heart was prepared according to Gaskell's method, the aorta being divided and the cardiac end of it held in a pair of bull-dog forceps.

In general I find that the inhibitory action of the right vagus is affected by temperature in the same sense as that of the vagus in the frog; although the effect seems to be less marked than in the frog, and a much greater change of temperature is necessary to cause a sensible alteration in the inhibitory activity of the nerve. At very low temperatures it is unquestionably more difficult to obtain complete standstill of the heart than at the ordinary or at a higher temperature. But for a considerable range above and below the ordinary temperature it may be difficult to demonstrate any marked difference. It is by no means easy to shew in the tortoise, what is seen in the frog, that the minimum strength of stimulus, needed to produce a given inhibitory effect, increases as the temperature falls and decreases as the temperature rises. It needs a considerable fall of temperature to appreciably increase the minimum stimulus.

I have found complete standstill caused by the left vagus in the proportion of about one third of the tortoises I have used. I formed the impression that, in a case where standstill was not caused by stimulation of the left vagus at the ordinary temperature, it could be caused when the heart was heated to a higher temperature, just as in the frog a vagus, which at the ordinary temperature only causes diminution of the force of the beat, may cause complete quiescence at a higher temperature. It would be interesting if it should turn out that the incomplete inhibitory action of the left vagus in the tortoise could be rendered more complete by altering the temperature of the heart. I cannot, however, positively assert that this does ever happen, as the material at my disposal for the few experiments I made was far too scanty to enable an answer to be given to all the questions which arose; and I was obliged to confine myself to the one originally proposed.

As to the effect of temperature on the secondary augmentation there is nothing in the tortoise comparable to what is seen in the frog. Since the secondary augmentation in the tortoise at the ordinary temperature is very slight or absent, we could not expect change of temperature to have much influence on it. So far as I have seen, it is as likely to occur at a low temperature as at a high temperature, provided that a well-marked inhibitory effect occurs at the low temperature. This bears out the view taken of the slight secondary augmentation seen in the frog's heart at a temperature low enough to abolish the action of the sympathetic, that it is essentially due to the inhibition and not to the action of augmentor fibres. The want of any distinct favouring action of a high temperature on secondary augmentation in the tortoise is quite in accordance with the idea that by far the greater part of the secondary augmentation at the ordinary and at higher temperatures in the frog's heart is due to the sympathetic fibres.

Heat standstill of the tortoise's heart.

This does not seem to differ materially from that of the frog's heart. A higher temperature seems generally to be required. For example, in one experiment the heart was exposed to a temperature of 49° C. for a sufficiently long time to allow the whole of the tissue to take on approximately that temperature, as shewn by a thermometer in the ventricle. The ventricle, when the heart was taken out of the solution, was apparently in heat rigor and hard, but the auricles continued to beat well. On squeezing the ventricle between the fingers, a curious phenomenon was seen. A single slow and apparently very shallow contraction passed over its surface. The contraction was localised and only spread over the part subjected to pressure. One is reminded of the statement of Kussmaul[1] that skeletal muscle which has passed into heat rigor may be again made capable of contraction by stretching and kneading, perhaps because some of the fibres are not really in rigor but mechanically hindered from contracting by those which are. It may be that the mode of treatment (pressure, stretching) temporarily increases the excitability of muscular fibres which are bordering on, but not yet in, the state of permanent rigor. But Heubel[2] has shewn that various forms of rigor in the frog's heart, including heat rigor, can at first be removed by the action of frog's or rabbit's blood. There can, therefore,

[1] *Arch. f. pathol. Anat. u. Physiol.* XIII. p. 289.
[2] *Pflüger's Archiv*, Bd. XLV. p. 461, 1889.

apparently be a real physiological recovery of fibres in which the rigor has not gone too far, although the fibres, if left to themselves, do not recover. When the heart, in this experiment, was further heated to 55° C. the auricles also were found in rigor. The ventricle did not now shew any trace of contraction on being squeezed.

Heat standstill can be obtained at a much lower temperature when the heating is gradual and long-continued, just as in the frog's heart. But stimulation of the vagus was never seen to cause rousing of the heart from the heat standstill, as it does in the frog, a fresh proof, I think, that the chief part, at least, of that effect is due to the sympathetic fibres.

The effect of heat and cold on the rate of the heart of the tortoise.

The only point worth noting is that the maximum rate is reached at a higher temperature than is usually the case in the frog. The slower rate at the ordinary temperature leaves more room than in the frog's heart for progressive increase with rising temperature, e.g. in one experiment the rates were

Temperature.	Beats per 100″
6·4°	6·4
18·5°	26
28·9°	62
37·2°	105
40·2°	97

In the greatly cooled heart (4°—6° C.) one peculiarity was the irregularity of the rhythm. The amplitude and rate in some cases varied from beat to beat, in marked contrast to the strong regular beat of the cooled frog's heart.

The question now arises, whether the apparent influence of temperature on the action of the cardiac nerves is really connected with the temperature directly or is not rather due to the alteration of the rhythmical activity of the heart which change of temperature produces. In other words, is it because the heart is at a high temperature, or because it is beating quickly, that the action of the nerves is increased with increase of temperature? Take, for example, the diminution of the latent period. Is this due to the preliminary changes being got over more quickly in the heated tissue independently of the other fact

that the changes connected with the normal beat also take place more quickly, or does it simply mean that the "inertia" of the heart always carries it on through a certain fairly constant number of contractions before it yields to the guiding influence of its nerves? In the latter case the latent period would, of course, vary inversely as the frequency of the beat, and, therefore, inversely as some function of the temperature.

Now I think there is no doubt that many of my tracings shew a remarkable constancy, for the same heart at different temperatures and for the same stimulus, in the number of beats in the latent period of the vagus; and the same is true of the sympathetic, when stimulation is begun at the same phase of the contraction. At extreme temperatures this constancy is not so marked.

There must evidently be a very close relation between the processes concerned in the production of the normal beat and those concerned in inhibition or augmentation, for the pace of the former cannot be altered without a corresponding alteration in the pace of the latter. This again shews that the vagus or the sympathetic does not strike in like a *deus ex machina* athwart the normal action of the heart. The sympathetic, unlike the motor nerve of a skeletal muscle, does not directly incite to contraction; it has to begin its work far back on the chemical and physical sequence of which contraction is the final term. And this must be the reason why the length of the latent period is related to the rate of the unaugmented heart.

We should, therefore, expect that an alteration in the rate of the heart caused in other ways than by change of temperature should equally affect the length of the latent period. When the vagus causes standstill in a heart already accelerated by stimulation of the sympathetic we should suppose that the latent period would be shortened. And as a matter of fact this is the case. This brings us to the question of the possible antagonism of inhibitory and augmentor nerves; and since this question has not hitherto been studied in the frog, as Baxt and others have studied it in warm-blooded animals, and since further it is intimately connected with the general subject of this paper, I have made a series of experiments on the point. Although these experiments are not so numerous as I could have wished, only about forty hearts having been used, they have still, I think, yielded enough information to enable us to compare in outline the process in the frog with the more detailed results in warm-blooded animals.

Section III. Some relations of augmentor to inhibitory action in the frog and toad.

We know that in the dog minimal stimulation of the vagus is sufficient to suspend the activity of the accelerator fibres for the time. But this is not because the vagus struggles with the accelerans and overcomes it. There is no struggle, because there is apparently no resistance. The vagus shunts the activity of the accelerated heart into its new path at least as easily as it does the activity of the normally beating heart. Let us see whether it is so in the frog.

It is already evident that when the inhibitory and augmentor fibres are stimulated simultaneously with the same strength of stimulus the inhibitory effect, when there is any, sets aside the augmentor effect for the time and precedes it. For this is what happens when the mixed vagus trunk is stimulated. It is another question when there is minimal stimulation of the inhibitory fibres alone or, what seems to be much the same in this case, of the mixed vagus, along with simultaneous maximal stimulation of the augmentor fibres, and still another question when minimal stimulation of the inhibitory fibres takes place with the heart already under the influence of maximal stimulation of the augmentor nerve.

The latter case is the one which has most interest in connection with the work of Section I., and all my experiments relate to it.

The heart was always at the air temperature. The sympathetic was stimulated generally with a fairly strong or maximal stimulus. Immediately afterwards, and while the heart was still augmented, the vagus was stimulated, generally with minimal shocks. The interval between the end of the sympathetic stimulation and the beginning of the vagus stimulation was varied in different observations. Of course the observations could be indefinitely multiplied by varying the temperature also, and this would not be without interest.

One objection to my results may possibly be that the mixed vagus trunk was used as the opponent of the sympathetic. And although minimal stimuli as a rule cause little or no action of the sympathetic fibres in the vagus, or at any rate little or no action which is shewn as secondary augmentation, and, although with even strong simultaneous stimulation of the inhibitory and augmentor fibres under normal conditions, the augmentation is postponed to the inhibitory action, it is possible that even minimal excitation of the sympathetic fibres, falling into a heart already augmented, might tend, in the manner of a relay,

to support the rhythm of the heart against the inhibitory onslaught. But since, as will be seen, the augmented heart yields as readily, or almost as readily, to the inhibitory influence as the normally beating heart, except with stimuli of the bare minimal strength, and may, in certain circumstances, yield to it more readily, any possible effect of this kind may be discounted. For the circumstances in which the inhibitory power seems diminished (minimal stimulation of the vagus after maximal stimulation of the sympathetic) are also the circumstances in which "relay" excitation of the sympathetic fibres in the vagus would be least likely. And the conditions under which the inhibitory power seems undiminished or increased are also those under which the "relay" excitation would be most likely to take place.

The results of this section may be summed up as follows, what has been already said as to the quantitative comparison of the activity of the cardiac nerves being borne in mind:

(1) If we take the measure of that activity as the total quantity of mechanical action which in a given time has been produced or prevented compared with what would, in the absence of excitation of the nerves, have been produced, it can be said that the inhibitory activity of the vagus is in general greater when the heart is under the influence of a previous stimulation of the sympathetic than when it is beating normally at the same temperature.

(2) If we take the absolute minimum of mechanical action during a given portion or the whole of the inhibitory period as inversely proportional to the activity of the inhibitory fibres, then in general the activity of inhibition is as great when the heart is under the influence of a previously produced augmentation as in the normally beating heart at the same temperature. But with minimal stimulation of the vagus the inhibitory action is sometimes less, and occasionally very much less, in the augmented than in the normally beating heart. Where, however, the heart, before stimulation of the sympathetic, is in bad condition and beating feebly, not only the relative but also the absolute amount of inhibitory action as measured, say, by the length of the standstill, or the diminution of force, or the slowing, may be greater for a given strength of stimulus in the augmented than in the normally beating heart.

(3) If we take the minimum strength of stimulus which will produce an inhibitory effect, say, complete standstill, as the criterion of inhibitory activity, no increase of activity can in general be made out in the augmented heart. On the contrary the minimal stimulus, as

has been indicated in (2), may sometimes be higher for the augmented than for the normal heart. In this respect the heart which is beating rapidly on account of a previous stimulation of the augmentor fibres differs from the heart which is beating rapidly at a high temperature.

(4) For a strength of stimulus which produces standstill both in the accelerated and in the normally beating heart the latent period of inhibition is in general shorter in the former when the excitation is thrown in at the same phase of the cardiac cycle.

(5) It is not infrequently seen that in the augmented heart the inhibitory action affects the auricle far more than the ventricle, while in the normally beating heart both may have been affected greatly and approximately to the same extent. It seldom happens that there is not on the ventricular curve in the augmented heart some slight indication of the inhibitory action, but this is often quite disproportionate to the effect on the auricles and to the effect on both auricles and ventricle in the normally beating heart.

In fact the ventricle in the augmented heart of the frog at the ordinary temperature is sometimes nearly as refractory to direct inhibitory action as the ventricle of the normal tortoise's heart or of the frog's heart in the cold. Shall we say that the exaltation of conductivity at the auriculo-ventricular junction in the frog's heart during augmentation is not so easily nor so quickly removed by the inhibitory action as the force of the auricular contractions is depressed or their rhythm slowed? Or is it that the force of the ventricular beat is less under the control of the inhibitory fibres than is the case with the auricle, so that just as when the heart is cooled the ventricle escapes first from the inhibitory yoke, it is also less easily quelled when once its action has been augmented by the sympathetic?

In a tracing not reproduced here a stimulus which in the normally beating heart caused complete or almost complete quiescence of the auricle, with distinct but less marked inhibitory effects in the ventricle, caused in the augmented heart quiescence of the auricle as before, but had scarcely any effect on the ventricle, which went on beating under the influence of the previous augmentation. It should almost seem as if the ventricle might, in certain circumstances, go on to complete the curve of augmentation in the face of an inhibitory action which interrupts the auricular curve. But other tracings make it likely that this can only happen when the auricle still keeps the augmented rate, although the contractions are greatly reduced in force by the action of the vagus. It is curious that the vagus should thus be able to abolish

one part of the augmentor effect in the auricle, (increase in force) while the other part, (increase in rate) is scarcely, if at all affected, and in the ventricle neither part is touched.

(6) While a stimulus somewhat stronger than minimal is as effective in causing inhibition when it is thrown in during the height of the augmentation as at a later period, and as effective as in the normally beating heart, a truly minimal stimulus is often more effective when the augmentation, though still present, has begun to decline, than at an earlier period. This suggests that the stability of an already established augmentor effect in the presence of a succeeding inhibitory excitation of minimal strength is greater when the augmentation is still vigorous. In connection with this we may recall the fact mentioned in Section I. that the stability of type of the augmentor effect against a change of temperature seemed to be greater, the sooner after the end of the latent period the change of temperature was made.

Before completing this Section, I may mention here some miscellaneous observations I have made in the course of these experiments, and which I do not recollect to have seen described before, although very possibly this has been done.

When stimulation of the vagus causes in the normal heart a diminution in the force of the beat along with acceleration, it may sometimes be seen that in the heart already under the influence of previous excitation of the sympathetic no diminution of force is at first produced by stimulating the vagus with a stimulus of the same strength, but, as the acceleration diminishes, more and more diminution may be produced, the diminution being now associated with fresh acceleration. This suggests that in certain cases the diminution in force is bound up with the acceleration in such a way that the former cannot be produced unless the rate of the heart is sufficiently slow to allow acceleration to take place readily. This is not merely a case of the well-known fact that a beat of small amplitude is generally quicker than a stronger beat. For it may happen when the vagus undoubtedly still possesses inhibitory power.

I have also, however, (Fig. 64) seen an instance in which the diminution in force, with accompanying increase in rate, caused by stimulation of the vagus was clearly due to the action of the sympathetic fibres alone. The heart at the ordinary temperature, when forced to beat more quickly by the primary augmentor action of the vagus, began to beat at the same time with less force, giving the appearance of a slight inhibitory action. That this was really due to the augmentor fibres was shewn

when the sympathetic was now stimulated with the same strength of current. A precisely similar though somewhat greater acceleration, accompanied with some diminution in the force, was obtained.

Primary acceleration of the beat, along with diminution in the force too great apparently to be accounted for merely by the acceleration, is sometimes seen as a result of stimulation of the vagus. There may not be a trace of preliminary slowing; yet a stronger stimulus, and even at a later period in the experiment the same stimulus, may cause well marked inhibition; so that probably the primary acceleration and the accompanying diminution in force are the signs of co-existing inhibitory and augmentor action.

In some cases where this primary acceleration and inhibition exist together when the vagus is stimulated with the heart beating normally, there may be an equal diminution in the force when the vagus is stimulated after a previous stimulation of the sympathetic and while the heart is still markedly augmented, while there is no alteration in the rhythm, the beat remaining accelerated although diminished in force. Here there is apparently persistence of one part of the augmentation in the presence of the inhibitory action, which removes the other part.

When the vagus causes standstill in a heart already under the influence of the sympathetic, it is clearly seen that the curve of augmentation is only interrupted and completes itself after the inhibition has disappeared. This agrees with what happens in the mammalian heart. Generally the rate and force of the beat are about the same when the heart resumes beating as when it stopped, or they have only slightly diminished, so that the general type of the augmentation is preserved.

But sometimes, as in Fig. 63, there is a change of type after the inhibition, the beats being markedly slower after than before but reaching a new and much greater maximum of force.

When pronounced secondary augmentation follows stimulation of the vagus in the normally beating heart, this is naturally absent when the nerve is stimulated while the heart is still under the influence of a previous stimulation of the sympathetic, since the heart, before the inhibition, is already beating at or near its maximum.

SECTION IV. THE EFFECT OF EXTREME TEMPERATURES UPON THE ACTION OF THE HEART.

1. *The effect of high temperatures.*

In the résumé, given at the beginning of this paper, of the literature of the subjects already treated the effect of a high temperature upon the heart's action, apart from its effect on the activity of the cardiac nerves, has several times been mentioned. I only intend to consider here the extreme limit of the process, the heat standstill.

When the temperature of the heart is gradually raised the beats are, as has long been known, quickened. There may be at first in addition to the quickening an increase in the force of the beats; but this is not constant, and with a very moderate increase of temperature gives place to decided diminution. As the temperature is still raised the ventricular beats diminish in force more rapidly than the auricular, while the rate of contraction of the heart increases to a maximum, and then remains constant or diminishes somewhat. At this stage the ventricle may or may not be able to respond to every auricular beat. Finally, the heart goes into standstill, and this happens first for the ventricle. The more exhausted the heart is before the heating, the lower is the temperature needed to cause standstill of the whole heart, and the greater is the difference between the temperatures at which the ventricle and auricles respectively stop. When the heart has been long worked with, the ventricle may be brought to rest at a temperature at which the auricle is still beating vigorously. Indeed nothing is more conspicuous in these tracings than the way in which the excursion of the ventricular lever, generally very considerably greater than that of the auricular lever at the ordinary temperature, becomes first equal to, and then decidedly less than, the latter as the temperature is raised.

As has been already said, the longer the exposure, the lower is usually the temperature required to cause standstill. And this is true even when the shortest time of exposure is not too short to allow the heart to come approximately to the temperature of the solution in which it is immersed. The sinus goes into standstill at a still higher temperature than the auricle.

We may sum this up by saying that the temperature of heat standstill varies inversely with the rhythmical power of the muscle.

According to Engelmann's observations[1] the heat standstill of the bulbus aortae takes place at an enormously high temperature. It may beat up to 46·5° C.; and up to 48° C. pulsations may still reappear on cooling. These temperatures are higher than even the sinus can bear, so far as my reading and experience go, and much higher than the ventricle can bear. That the bulbus should continue to beat at a temperature above that which is sufficient to produce standstill of the ventricle, is quite in accordance with the superiority of rhythmical power in the bulbus and the peculiarities which led H. Munk[2] to assume the existence of ganglion cells in it. Although Engelmann[3] denies that Löwit's so-called bulbus ganglion[4] is of nervous nature, and although, indeed, the existence or non-existence of ganglion cells in any part of the heart, has come to be looked upon as a question of no great interest in this connection, the rhythmical peculiarities of the bulbus tissue remain. That the bulbus, however, should be able to stand a higher temperature than the sinus is certainly surprising. The considerable internal pressure (5—20 mm. of mercury) with which Engelmann worked may explain this, for the temperature at which standstill occurs in the heart as a whole, or in the apex preparation seems to be raised as the pressure is increased. Also a very short exposure even to a temperature of 65° C. does not kill the heart, as Aristow found. A normal fresh heart I have found to go into standstill at a temperature of 32°—40° C. according to the time of exposure, any exposure under 1 minute being omitted, and the "individuality" of the heart. My frogs were not particularly large specimens of Rana temporaria, in fair but not prime condition. In an exhausted heart the ventricle has often gone into standstill at a temperature of 20°—30° C. I have sometimes had the opportunity to observe that an unexhausted heart, previously cooled to 1°—8° C. and beating vigorously though slowly at that temperature, goes into heat standstill at a comparatively low temperature, the ventricle, as in all cases, succumbing first. This reminds one of the rapid rigor mortis which occurs in a frozen muscle when the temperature is allowed to rise, and lends a certain amount of support to the suggestion of Luchsinger[5] that the temporary heat paralysis of many tissues is connected with changes preliminary to heat rigor, but, unlike the actual rigor, reversible.

[1] Engelmann, Hartog, and Verhoeff, *Pflüger's Archiv*, Bd. xxix. pp. 425—468.
[2] *Arch. f.* (*Anat. u.*) *Physiol.*, 1878, p. 569.
[3] *Loc. cit.*
[4] *Pflüger's Archiv*, Bd. xxv. p. 399, 1881.
[5] *Pflüger's Archiv*, Bd. xviii. p. 478.

As to the nature of the heat standstill of the heart and even as to the phase of the cardiac cycle in which the standstill takes place, there has been some difference of opinion in the past; and, to judge from the description of the phenomenon in some recent English text-books, complete agreement has not yet been reached. One reason for this seems to be that the distinction between the condition in which the heart is still able to beat when the temperature is lowered, and which alone should be called the heat standstill, and the condition of true heat rigor has not always been observed.

Schelske thought the heart was contracted in the standstill.

Cyon[1] saw the frog's heart, when brought suddenly from a surrounding temperature of 0° C. into a temperature of 40° C., execute a series of beats, following each other so quickly that it ultimately fell into what he calls tetanus. This lasted at most 15—30 seconds, and the heart then relaxed. But he does not make it clear whether by this "tetanus" he means standstill of the heart in systole due to fusion of the contractions; and the possibility must not be lost sight of that in this sudden heating the sinus should get the start, so to speak, of the rest of the heart, and that the ventricle or both auricles and ventricle, not being able to follow the rapid lead of the sinus, should stand still altogether, as Gaskell observed the ventricle sometimes to do when the auricle alone was heated. There is another point to be remarked in this experiment of Cyon's. The heart was connected by cannulae in the inferior vena cava and aorta with a manometer and pressure apparatus. And we shall see directly that the heart under fairly high endocardiac pressure does not react to change of temperature in the same way as the empty heart or the heart *in situ*.

Aristow[2], working with the empty heart, found that the heat standstill was always diastolic.

Lauder Brunton[3] describes the heart as beating "quicker and quicker as the heat increases until at last it stands still in heat tetanus. On again cooling it by the ice its pulsations recommence...."

McKendrick[4] says, "As the temperature rises up to about 40° C. the heart beats become quicker and quicker, until the organ passes into a state of heat-rigor....As already mentioned the heat-rigor may be removed by cooling." I cannot quite understand the sense in which McKendrick here uses the term "heat-rigor." Heat rigor in its

[1] *Sächs. Berichte*, 1866, p. 256.
[2] *Loc. cit.*
[3] *Text-book of Pharmacology*, 1887, pp. 302, 303.
[4] *Text-book of Physiology*, 1889, Vol. II. p. 232.

ordinary sense scarcely applies to a condition which can be removed by lowering the temperature. I presume McKendrick means that the heart stops in a condition outwardly resembling heat rigor but removable by cooling, i.e. in systole.

I can fully confirm Aristow's result. The contractions get feebler and feebler, but always rise from the base line of the relaxed heart. This holds when the circulation is intact as well as for the excised empty heart; and it is well seen when the contractions of auricle and ventricle are separately recorded. But we have still to consider whether under special conditions "heat tetanus" of the heart can be obtained. And this is evidently a part of the more general question whether the cardiac muscle is capable of entering into true tetanus at all, that is, whether by any means the beats may be made to succeed each other so rapidly that they are fused into a continuous contraction.

E. Weber[1] saw a circumscribed contraction of the frog's heart around the electrodes when a strong interrupted current was passed through it.

Ludwig and Hoffa[2] confirmed Weber's observation, but could never find a true tetanus.

Heidenhain[3] describes the phenomenon as a "tumultuary tetanus," which seems almost a contradiction in terms.

Luciani's "tetanic paroxysm" (tetanischer Anfall)[4] has been shewn by Kronecker and Stirling[5] to be probably artificial, and need not therefore be considered as an example of tetanus.

Aubert[6], from whom, not being able to consult the original memoirs, I have borrowed several of the references in this paper, concludes that a tetanus of the cardiac muscle analogous to that of skeletal muscle has not been observed.

Kronecker[7] denies the existence of a true tetanus of the heart. He considers that all forms of so-called tetanus are really a tonically strengthened systole.

Löwit[8] agrees on the whole with Kronecker, although he found

[1] *Wagner's Handwörterbuch d. Physiol.* III. 2, p. 36, 1846.

[2] *Zeitschrift f. rat. Med.* IX. p. 107, 1850.

[3] *Arch. f. (Anat. u.) Physiol.* 1858, p. 479.

[4] *Sächs. Berichte*, 1873, p. 1.

[5] *Ludwig's Festgabe*, 1874, p. 173.

[6] *Hermann's Handbuch*, Bd. IV. 1.

[7] "Das charakteristische Merkmal der Herzmuskelbewegung," *Beiträge zur Anat. u. Physiol.*, Leipzig, 1874, p. 185.

[8] *Pflüger's Archiv*, Bd. XXV. p. 399, 1881.

that his ventricle preparation, under the influence of atropia or his alkaline fluid, went into a tetanus-like condition.

Gaskell[1] found that alkaline solutions caused a kind of systolic standstill, but this was not to be considered a tetanus, but rather a change corresponding to the "idiomuscular contraction."

Cyon[2] and Aristow[3] stated that stimulation of the heated heart by the interrupted current caused tetanus. From my experiments on stimulation of the auricle and sinus I think this statement must be qualified by a reference to the part of the heart which is stimulated and the strength of the stimulus. There is no doubt that by stimulating the heated ventricle with a strong interrupted current and in many cases by stimulating any part of the heated heart a tetaniform condition may be got, the separate contractions being completely or almost completely fused, or at least following each other so quickly that they have not time completely to relax, so that the curve shews a series of rapid small contractions rising from a base line corresponding not to complete diastole but to partial systole. As we know that heat reduces the refractory period enormously, there is really no *a priori* reason to doubt that a true fusion of the cardiac contractions may be in this way obtained. And this seems to be the only condition in which anything approaching a true tetanus can be got in the heart. But it is very different from a "heat-tetanus," that is a tetanus caused by an increase in the frequency of the rhythmical contractions by heat without external stimulation. A true heat tetanus in this sense does not exist, so far as my experiments go; and I have used at least 200 frogs, most of the experiments, indeed, not being specially directed to this point, but nearly all of them incidentally involving it.

When, however, the heart is acted on by the constant stimulus associated with a high endocardiac pressure, the conditions, when it is heated, are different from those in the empty heart and the heart *in situ*. I, therefore, made a few experiments on this point.

The effect of heat on the heart under a high endocardiac pressure.

A double cannula was tied into the inferior vena cava, and connected with a frog manometer and a pressure apparatus containing normal saline solution. The temperature of the solution could be varied at will. A vessel arranged to slide on a stand below the heart was filled with

[1] This *Journal*, III. p. 48.

[2] *Loc. cit.* [3] *Loc. cit.*

saline solution at the particular temperature to which it was desired to expose the heart. The vessel was then slid up the stand till the heart was immersed. The temperature of the solution in the vessel could also be gradually raised. In this way the heart could be subjected either to a gradual or a sudden increase of temperature. The arrangement was practically that of Cyon. But my experiments, exclusively on the effect of endocardiac pressure on the phenomena of heat standstill, regarded only the modifications caused by such pressure in the action of heat on the heart; his were directed to the effect of the change of temperature alone without special regard to the pressure, which was merely an incident of his method of recording.

Another set of experiments, not many, it must be said, but still agreeing sufficiently well, was made in the same way on the "apex" preparation.

The results may be stated as follows:

1. When the heart is distended with liquid at a high pressure (20—40 c.m. of normal saline), and is then heated, a stage of imperfect "tetanus," in which a series of rapid small contractions is superposed on a more lasting contraction, which one does not know whether to call tonic or tetanic, precedes the relaxation into diastolic standstill. When the temperature is lowered the heart again begins to beat, unless it has been heated more than is sufficient to produce this standstill.

2. When the apex has been brought to beat rhythmically by being distended with salt solution at a high pressure (20—30 c.m., or more, of salt solution), and is then heated, or when, although quiescent before the heating, it begins to beat when the temperature is raised, it behaves like the distended heart; but goes into standstill in the relaxed position at a lower temperature. The higher the pressure, the higher is, as a rule, the temperature at which the apex goes into heat standstill. The preparation generally begins to beat again when the temperature is reduced, without requiring any external stimulus; but such a stimulus may be needed.

The following two experiments on the apex preparation may be quoted as a specimen.

Experiment, Jan. 16, 1891.

Apex preparation on double cannula. Pressure raised at intervals from 6 c.m. to 19 c.m. in the course of an hour; but the preparation had not then

begun to pulsate, although it always contracted on stimulation with weak induction shocks.

Now immersed in saline at 32° C. It began to beat, and continued beating when it was allowed to cool to the temperature of the room (7° C.)[1]. The rate at this temperature was 5 beats per minute.

Now immersed in saline at 35° C. The beats increase in strength, but especially in rapidity. Soon complete relaxation does not take place, the beats being superposed on a lasting contraction. Then comes a short stage where no separate beats can be detected, the preparation being in a state of extreme contraction. Soon this contraction gives way, and the apex remains quiescent in the relaxed condition. The warm solution being now removed, the apex soon begins to beat again, pretty rapidly at first, then more slowly.

When the preparation, as it is beating at the temperature of the room, is immersed in solution at 40° C., the stage of increased rapidity of beat and tonic (tetanic?) contraction gives place more quickly than at 35° C. to standstill in relaxation. On removal of the saline it soon recommences to beat.

After a short immersion in solution at 44°—45° C. the preparation was still able to beat on removal of the solution, but not until it had been stimulated with weak induction shocks; and when contraction did begin, it was confined to the parts farthest from the very apex. The actual apex was dead; it did not beat any more even when directly stimulated. And the rest of the preparation never relaxed quite as much as before the last immersion, but was always crumpled, as if partial heat rigor had taken place.

Experiment, Jan. 19, 1891.

Apex. Pressure of solution 9 c.m. Begins to beat in 2 or 3 minutes after being put on cannula. Rate 8 per minute at temperature of room. Immersed in solution at 38° C., it immediately stops beating in diastole without any preliminary quickening.

Saline removed after 10″. Apex at once commences to beat fast—rate 16 per minute. After an interval of 1 minute it was immersed in solution at 34° C.; stopped in relaxed state after one or two beats.

Saline removed after 10″. Recommences beating at once. After an interval of 1 minute, immersed in solution at 32° C. Standstill in diastole after several beats. The solution is removed after 25″; but preparation does not begin beating till 30″ later. After an interval of 3 minutes it is beating very slowly with long pauses.

[1] This was not the room in which the experiments of Section I. and many of the other experiments were done. It is necessary to explain this, as the low temperature of the air does not correspond with the limits of room temperature given in Section I. The weather was very cold at this time.

Immersed in solution at 41° C. during a pause. No beat is given; and it remains relaxed for 15″ after removal of saline.

Pressure now increased to 20 c.m. The systole is much more prolonged than at former pressure. The contraction gives one the impression of a slow determined lift against the high pressure. It gives way gradually and as if with reluctance. (This is very characteristic of the beat under high pressure not only in the apex preparation but in the whole heart, where, however, the stress of the systole falls on the ventricle.)

Immersed in solution at 38° C. Commences to beat more quickly, then passes for a short time into a strong tonic (tetanic?) contraction, superposed on which rapid small beats may be seen. Then it relaxes completely but almost at once passes again into a similar contraction; then relaxes and stands still in diastole. All this takes place in 30″, at the end of which time the solution is removed. 20″ later the apex recommences to beat. It is decidedly more difficult to obtain heat standstill in diastole than at the lower pressure at the beginning of the experiment.

Pressure now made 22·5 c.m. The apex is in standstill in the relaxed state. Immersed in solution at 36° C. In about 5″ a strong contraction takes place, which lasts a little time and then relaxes. Then follows a contraction of the same kind, which relaxes; and the apex stands still in diastole. The contraction is peculiar. It begins very slowly and gradually; then jumps suddenly to its maximum. In 15″ after the removal of the solution the preparation again commences to beat.

Pressure reduced to 11 c.m. The apex beats slowly. Immersed in saline at 40° C. during diastole. For 10″ it remains in diastole. Then follows a strong contraction which maintains itself for some time, with quick small contractions superposed on it. This relaxes, and is followed by another contraction of the same kind, and then standstill in diastole.

Saline removed, and, in 20″ after, the preparation begins to beat well. Immersed in solution at 35° C. during diastole, it remains relaxed for a few seconds. Then comes a strong and long-continued contraction with small contractions superposed, followed by diastolic standstill. Recommences to beat after removal of solution.

Pressure now made 30 c.m. The preparation is already somewhat contracted and never relaxes as much as before. Immersed in saline at 39° C. The only effect of this is to increase the permanent contraction a little. The preparation is now nearly inexcitable.

In this experiment it will be seen that at first, with a comparatively low pressure (9 c.m.), the tetaniform condition was not obtained, that is to say the continually acting stimulus was too weak to resist the tendency of the apex to stop in diastole in the warm solution. When

the pressure was increased, the stimulus became so strong or the excitability of the distended preparation so great—for it does not matter in which way we express the effect of the pressure—that it became able to prevent immediate standstill, and, acting on the heated tissue, to cause strong and comparatively lasting contraction, sometimes even inducing a second spasm just after the first had for a moment relaxed.

It would also seem that in the course of the experiment the excitability became permanently increased, for after a time a pressure of 11 c.m. was enough to give the characteristic contraction, although at the beginning a not much lower pressure was insufficient.

As to the influence of the manner of heating, whether sudden or gradual, a word or two may be said.

Marchand[1] found that in the complete empty ventricle sudden is more certain than gradual heating to cause the appearance of pulsations if the ventricle is not previously beating, although, if contractions are already present, there is no difference. In the empty apex neither sudden nor gradual warming ever caused pulsations.

Cyon found that sudden heating is more favourable than gradual heating for the appearance of tetaniform contractions.

This is possibly true for the heart under a low pressure; but I do not find that the empty heart is affected much by the manner of heating; a tetaniform contraction is not caused in it by sudden any more than by gradual rise of temperature. Again, when the endocardiac pressure is high either sudden or gradual heating will cause such a contraction. But "gradual" does not here mean slow heating, but merely heating which is not abrupt and therefore not of itself likely to act as a stimulus. When the pressure is low, it would be expected that the stimulating action of a sudden rise of temperature might be able to determine the tetaniform contraction in a heart already disposed to it by moderate distension. When the internal pressure is high, however, it may override the influence of the manner of heating, because the distension is itself sufficient to determine the contraction, as soon as the favourable temperature is reached, apart from any extra stimulus. But since the tetaniform contraction is evidently exhausting and does not last more than a comparatively short time, and since a high temperature is also in the end harmful to the tissue, it is clear that when the heating is slow the energy of the heart may be frittered away, so to speak, in

[1] *Pflüger's Archiv*, Bd. XVIII. p. 511.

gradually quickened single beats instead of being concentrated in one or two dead-lift spasms, and the stage of "tetanus" may be slurred over.

To sum up the results of this section, it would seem that heat tetanus of the heart does not really exist. The intact heart, the empty excised heart, and the perfused heart beating under low endocardiac pressure go into heat standstill in diastole without a preliminary stage which can be called a tetanus. And although under a high endocardiac pressure a preliminary tetaniform condition can be obtained, this, even if the name of tetanus be granted to it, is not a heat tetanus any more than the tetaniform condition caused by direct electrical stimulation of the heated heart. For in both cases the condition depends upon extraneous or artificial stimuli, the action of which is favoured by heat. In any case the tetaniform condition in the distended heart is transient, and is succeeded by the true diastolic heat standstill.

So much having been said as to the phase of the cardiac cycle in which the standstill occurs, we have now to consider its real nature and cause. Various explanations of it have been given. Cyon[1] considered that in certain circumstances the diastolic heat standstill might be due to stimulation of an inhibitory mechanism by a sudden rise of temperature. Aristow[2] pointed out in opposition to this, that the standstill was obtained all the same in a heart poisoned by atropia; and he further objected that sudden cooling ought equally to act as a stimulus to the inhibitory mechanism, if Cyon's explanation were correct. He also supposed, as has been already said, that the inhibitory mechanism was weakened or paralysed at high temperatures. I have no doubt that Aristow is right in denying that heat standstill is due to stimulation of an inhibitory mechanism, but his second objection is inconclusive and his third is erroneous. The inhibitory power of the vagus is rather increased than lessened at the high temperatures; and it is quite possible that a sudden rise of temperature might cause inhibition by stimulating an inhibitory apparatus, and yet that a sudden reduction of temperature, although equally fitted, *qua* stimulus, to excite that apparatus, might fail to do so because there was sufficient time for the low temperature before inhibition could be produced to diminish the activity of the inhibitory mechanism. Nevertheless, Aristow is right when he says that Cyon's theory is wrong.

We come now to Aristow's own theory. He concluded that because the cardiac muscle was still excitable to direct stimulation in the stand-

[1] *Loc. cit.* [2] *Loc. cit.*

still, the cause of the standstill could not be the inability of the muscle to contract, and must therefore be due to paralysis of the motor ganglia. Luchsinger and Ludwig also favoured this view. We know that such a temporary paralysis and subsequent restoration of nerve cells in the central nervous system can be caused by raising and lowering the temperature[1]. And at a time when the ganglia were still looked upon as an essential factor in the maintenance of the rhythm of the heart, nothing was more natural than such an explanation. But the importance of the ganglia in this relation diminished when it was known that the ganglion-free apex of the frog's heart could pulsate rhythmically under certain conditions when isolated from the rest of the organ by section[2]; that the apex which was still anatomically connected with the heart but brought to rest by the crushing of an intermediate zone of tissue[3] could also be caused to beat again with a rhythm of its own, particularly by raising the pressure inside the heart; that the "heart" preparation of Luciani[4] and Rossbach[5], although it contains ganglia, remained in standstill for some time after isolation from the higher parts of the heart, and was affected by internal pressure and nutritive liquids of different kinds much in the same way as the ganglion-free apex; and that the isolated ventricle of a heart from which Bidder's ganglia had been removed could also be brought to rhythmical pulsation[6]. We know further that the bulbus aortae in the frog can, as already mentioned, be made to pulsate[7]; that strips of the ventricle of the tortoise[8], also free from ganglia, can be made to beat rhythmically; that the rhythmical contractions of the smooth muscle of the ureter of the rabbit and dog are affected by distension much as the cardiac muscle is[9]; and finally that even ordinary skeletal muscle can contract in a rhythmical manner under the stimulus of a certain tension and in certain saline solutions[10].

[1] Luchsinger, *Zur Physiol. d. irritabeln Substanzen*, Bonn, 1879.

[2] Bowditch, *Sächs. Berichte*, Dec. 1871; Kronecker, *Op. cit.*; Merunowicz, *Ludwig's Arbeiten*, 1875, p. 132; Stiénon, *Arch. f. (Anat. u.) Physiol.* 1878, p. 263; Gaule, *Arch. f. (Anat. u.) Physiol.* 1878, p. 291.

[3] Bernstein, *Centralblatt f. d. med. Wiss.*, 1876, p. 385; Bowditch, this *Journal*, I. p. 104; Aubert, *Pflüger's Archiv*, Bd. XXIV. p. 355.

[4] *Sächs. Berichte*, 1873.

[5] *Ludwig's Arbeiten*, 1874, p. 90.

[6] Löwit, *Pflüger's Archiv*, Bd. XXV. p. 399, 1881.

[7] Engelmann, *loc. cit.*

[8] Gaskell, this *Journal*, IV. *loc. cit.*

[9] Luchsinger and Sokoloff, *Pflüger's Archiv*, Bd. XXVI. p. 464.

[10] Biedermann, *Sitzungsber. d. Wien. Akad.* Bd. LXXXII., 1880.

To-day we place the cause of the normal rhythm of the heart in the cardiac muscle. To-day, therefore, we must translate the theory of Aristow into more modern language, and we must look for an explanation of the heat standstill, not in a temporary failure of automatic ganglia, but in a temporary failure of the rhythmical power of the muscle itself. In what this failure precisely consists we can only know when we know in what essentially the rhythmical power consists. Conversely, we may say that the cause of the rhythm of the heart lies hidden among the conditions the removal or alteration of which is followed by standstill. If we know why the heart stops, we may say that we know why it beats. All we can say at present is that it beats because the rhythmical power of its muscle is sufficiently great, and stops because that power has been diminished. The experiments on the heating of the "apex" preparation shew, as was to be expected, that the heat standstill of the ganglion-free cardiac muscle differs in no essential respect from that of the entire heart.

One thing is clear, it is not the power of the muscle to contract but its power to contract spontaneously which is lost. The starting point of the rhythmical contraction of the frog's heart is normally the sinus tissue. When the temperature is only sufficiently high to cause the ventricle to stop, it may be said that the reason of the standstill is, to use Gaskell's phraseology, the depression of conductivity at the auriculo-ventricular junction or the diminished excitability of the ventricle. The contraction power is not lost, for direct stimulation will cause the ventricle to beat. The sudden manner in which beating often begins when the heart in cooling comes spontaneously out of the standstill, large contractions occurring at once, would perhaps be in favour of the view that the contraction power was strong even during the standstill, but was hindered from manifesting itself by defect in other properties of the cardiac muscle. Again, when both auricle and ventricle have stopped and the sinus is alone beating, the same terms may be applied, not to explain, for that they cannot do, but to describe what has happened. Finally, when the sinus has stopped beating and the whole heart is at rest, it may be said that the rhythmical power is in abeyance. But there is not the least logical reason why the stoppage of the whole heart should be taken as the point at which the high temperature has first affected that property of the muscle on which the rhythmical power depends. The independent rhythm of the ventricle when it has been developed by distension with liquid or by tightening the clamp in the auriculo-ventricular groove, and the independent rhythm of the apex

are also paralysed by heat and restored by cooling, and so is the rhythmical power of the bulbus aortae. Not only so but the rhythmically contracting sartorius has its favourable limits of temperature, and may be said to have its heat standstill. So, doubtless, would it be with the rhythmically contracting ureter. The pulsations of the veins of the bat's wing cease at a high temperature in diastole[1]. Nor are there wanting analogous conditions far beyond the limits of rhythmically contracting organs and tissues. The amoeba has its heat standstill[2]. So have the Rhizopods investigated by Schultze[3] and Kühne[4]. And according to the same observers even the protoplasmic movements of plants shew a similar effect. The movements of the leaves of Hedysarum gyrans stop at a temperature of about 48°, and return on cooling[5]. Even glandular tissue is capable of being put into a state quite analogous to heat standstill. The sweat glands, for example, in man and the cat are temporarily paralysed at low and at high temperatures[6]. Kühne has, indeed, used the term "heat tetanus" to describe the phenomenon in these lowly organisms and particularly in the amoeba. This "heat tetanus" may be really "a contraction which causes a constant change of form lasting for a long time and shewing the same appearance as is brought about by tetanising with induction shocks"; or it may only be a preliminary and passing stage, which is soon replaced by heat paralysis. Kühne has given some reasons for regarding the drawing in of the pseudopodia and the assumption of the spherical form as the expression of a state of active contraction; but he has given no reasons which make it unlikely that heat paralysis, which everywhere else succeeds such a state of heightened activity, follows rapidly on the heels of this contraction. Such a paralysis would not be shewn by any change of shape in an amoeba already in the spherical form. For why should the amoeba in complete paralysis relax in one direction more than in another, if the amoeba in complete contraction does not contract in one direction more than in another?

All these phenomena are evidently connected. There is in all, with the possible exception, if it is an exception, of Kühne's "heat tetanus," a depression of functional activity connected with a high temperature stopping short of that sufficient to kill the tissue, just as there is a

[1] Luchsinger, *Pflüger's Archiv*, Bd. xxvi. p. 445, 1881.
[2] Kühne, *Untersuchungen über das Protoplasma*, 1864, p. 45.
[3] *Das Protoplasma*, 1863. [4] *Op. cit.*
[5] Mentioned by Luchsinger, *Pflüger's Archiv*, Bd. xviii. p. 478.
[6] Luchsinger, *Ibid.*

depression of functional activity by extreme cold. Is this due immediately to a chemical or to a physical cause? Is the diminished metabolism associated with the depression at low temperatures also associated with that at high temperatures?

We know especially from the researches of Pflüger and his pupils that for a long range the amount of metabolism of the tissues increases with the temperature. Is this increase checked or changed into a decrease as the temperature of heat standstill is approached, or is the physical condition of the heated tissue, in spite of an active metabolism unfavourable to rhythmical contraction?

Regnard found that in excised muscle the production of carbonic acid increased rapidly from 20° C. to about 40° C., and at higher temperatures declined. This and the fact that sometimes the heart can be roused from the standstill by stimulation of the sympathetic, which is supposed to render the destructive metabolism easier, perhaps rather support the first view, that the over-heated heart is no longer able to beat spontaneously because the metabolism of the muscle, or at least that portion of the total metabolism which is specially connected with the high effort of rhythmical contraction and is the preliminary to it, is no longer adequate. If it be objected that at low temperatures the total metabolism must be even less, and yet that the heart is able to beat and to beat well, though slowly, there is perhaps something to urge in reply. The portion of the metabolism which for a want of a better name, we may call the chemical "waste," the portion, that is, which does not contribute to the keeping up of the contractions but which goes on merely because the tissue is a living tissue, whether it is functionally active or not, and therefore is subject to constant dissociative processes dependent on the temperature as well as to the periodic decompositions which depend on the inner nature of the tissue in relation to the temperature and other external conditions,—this chemical "waste" must be exceedingly slight at very low temperatures, and must increase within certain limits as the temperature rises; so that at the low temperature, what metabolism there is is nearly all directed to the production of the beat, while at high temperatures it is nearly all "waste."

But it is also possible, and, so far as I know, there is no evidence which would enable us to decide the question, that the physical condition of the heart at the high temperature, the increased irregular vibration of the molecules, is unfavourable to that definite and ordered relative movement which we must suppose the individual molecules, or groups of them, to make when the muscle contracts, so that the contraction can no longer be performed without a special external stimulus.

After this was written, Engelmann's[1] statement that the position in which cilia come to rest in the temporary heat standstill is that of strongest forward flexure, was pointed out to me. This seemed to indicate a tetanic condition, and cilia appeared therefore to form an exception to the general rule that the heat standstill in contractile tissues is a state of paresis and not a state of excitation. On looking further into the matter, however, I found that Engelmann[2] took the view that the position of relaxation of cilia from the frog's mouth was the position of forward flexure.

On the other hand, Kühne[3] describes the cilia of the gills of Anodon as stopping in the straight position in an atmosphere of H, or in air containing much CO_2 or NH_3. And he considers that this proves that the standstill caused by NH_3 is not tetanic "as the analogy of the ammonia-tetanus of muscle might lead one to expect." So that for Kühne the position of forward flexure in heat standstill would indicate a tetanic condition.

Considering the rapidity of ciliary motion and how entirely inexhaustible the energy of the cilia or of the ciliated cells seems to be, it seemed not unlikely that with a favouring rise of temperature the rapidity should so increase that ultimately the separate contractions would be blended together and a condition of true heat tetanus result. There is, indeed, no contractile tissue in which the conditions would seem so favourable for the production of such a tetanus.

I have made some observations on the subject which may as well be described here, although it is rather a digression from the main purpose of the paper.

THE HEAT STANDSTILL OF CILIA.

After examining with some care the behaviour of the cilia of the gills of Anodon and of the buccal epithelium of the frog and toad on the hot stage, I cannot find any evidence of a lengthened period of removable heat standstill which can properly be called a heat tetanus. On the contrary, so far as I have seen, the temporary heat standstill, which undoubtedly can be obtained with great ease in the case of the frog's cilia and with less certainty in those of Anodon, corresponds to the diastolic standstill of the heart; it is a standstill of relaxation and not of contraction, or at least not of maximal contraction, although it

[1] *Hermann's Handbuch, Flimmerbewegung.*

[2] *Over de trilbeweging, Nederland. Arch.* III. 2, p. 304; *Henle's Bericht* 1867, p. 34.

[3] *Arch. f. mikroscop. Anat.* II. 1866, p. 372.

may be preceded by a condition of very rapid contraction and strong forward flexure approximating to the tetanic state.

When a scraping from the gills of Anodon, or a piece of a gill with the ciliated cells in situ, is heated gradually in normal saline or in the water from the mussel itself, the ciliary motion, of course, increases at first in rapidity, so that it is quite impossible to follow the individual cilia. But, as the temperature is still raised, it is seen that in some parts (heat standstill does not occur simultaneously in all the cells) the cilia slacken and then stop in a position not at right angles to the ciliated surface, but sloping somewhat in the direction of the stream, i.e. in the direction of forward flexure. If now the stage is cooled it will be seen that these cilia, or certain tracts of them, begin gradually to get into motion again. And while the motion is still slow, or at the very first lash, it may be seen that the cilium starts from its flexed position and lashes forward, flexing itself still more, and then returning to its former position. During the heating an immense number of the rounded ciliated cells get detached. This happens far more easily in Anodon than in the frog. These cells move with great rapidity, and spin round and round, seething about the ciliated border. The effect of temperature can be readily studied by following one of these isolated cells. In the heat standstill the sheaf of cilia attached to one end of the cell may in many of them be seen to be bent in two directions, rather strongly away from the direction in which they lash where they join on to the cell, and more slightly in the forward direction towards their free ends. When they recommence their motion they may be seen to lash in the direction of the smaller flexure. In some of the cells, after heating and again cooling, the cilia seemed to be permanently bent from all sides towards the body of the cell like the legs of a crab, and they lashed towards the body in the direction of flexure. Heat standstill in these was seen to take place in a position farther away from the cell body than the position of maximum forward flexure during the motion. In other cells the cilia stuck nearly straight out in heat standstill, with only a slight forward flexure, far less than the maximum flexure during motion.

In some cells, after heating, the bunch of cilia remained permanently curved like a hook, this curvature not being removed by cooling. On cooling, the cilia began to lash in towards the concavity of the hook, and on being again heated to the temperature of standstill, they were seen to relax just to the line of the permanent curvature.

In the cilia of the frog and toad it is certainly easier to obtain

removable heat standstill than in Anodon. For in the mussel, even with careful heating, the cilia of many cells do not recover their motion once it has been completely stopped, while in the frog's cilia standstill can be again and again induced and removed.

The cilia here are, as in Anodon, generally bent somewhat in the forward direction during the standstill, but are sometimes nearly straight. In one observation the cilia of a cluster of cells were moving rather slowly at the ordinary temperature and lashing downwards, coming into and going out of focus according to the phase of movement. On heating, the movement was, of course, quickened, but the coordination was impaired, the cilia did not move so well together as before, and a sort of boiling motion was caused. When heat standstill was brought on the cilia rose up like a bunch of tangles in a wave, so that it was now necessary to focus up in order to see them clearly. On cooling, they began to lash down again, and it was now necessary to focus down in order to follow them. This was repeated again and again.

When the edge of a group of cells is looked at, it is seen that in temporary heat standstill the cilia are always flexed to some extent, but the angle between the direction of the cilia and the tangent to the surface is larger than that between the direction of the cilia and the normal to the surface. During motion, in the position of maximum flexure the latter angle is greater than the former.

In one observation most of the cilia along the edge of a group of cells were at rest at the ordinary temperature before the preparation had been heated at all. Others were working. When the temperature was now raised it was noticed that the slope of the cilia originally at rest was neither more nor less than that at which the active cilia came to rest in heat standstill. It was impossible to tell by the amount of flexure which groups had been originally at rest and which had been originally active. There was no doubt that the flexure was less than the maximum flexure during motion.

Spermatozoa (guineapig). It is difficult to know what position the tail of a spermatozoon ought to take up in the tetanic state. In heat standstill the tail takes up various positions. In a single specimen some of the spermatozoa have the tail strongly flexed to one side and curved towards the head; others have it curved into a complete loop at the free end; in some it is slightly flexed to one side, and in others it is almost straight and in line with the long axis of the head. It seems more difficult to obtain temporary heat standstill than in the frog's cilia. At comparatively high temperatures the spermatozoa still move

with extreme rapidity and energy. It seemed as if those which came to rest with the tail in the position of simple lateral flexure were most likely to recover on cooling.

Spermatozoa paralysed at the ordinary temperature by the vapour of a mixture of chloroform, ether and alcohol in equal proportions have the tail generally slightly bent to one side, but in some the lateral flexure is very considerable, and in others the tail is straight in the long axis of the head.

On the whole, while admitting that cilia from their great power of prolonged activity would be expected, if any tissue would, to shew a true tetanic heat standstill, I find no reason to doubt that, as in other contractile tissues, the removable heat standstill is ultimately of the diastolic type, that is a paresis and not a tetanus.

If the temporary heat standstill is not in the position of maximum forward flexure, i.e. is not tetanic, the question arises whether the position of permanent heat standstill corresponds to the contracted position of a skeletal muscle or to the position of the heart in heat rigor. If so, when the temperature is raised sufficiently above that required to cause temporary standstill there ought to be a distinct increase in the amount of flexure. I have not, however, been able to observe any marked change in this respect. Further, when the frog's cilia are paralysed with chloroform, ether and alcohol vapour, they come to rest, as Kühne has said, in a more or less straight position, although on some cells they are in the position of forward flexure, generally not flexed so much as in temporary heat standstill, but sometimes as much. If the temperature is now raised to the height necessary to produce permanent heat standstill in a normal preparation, no increase in the flexure of the cilia can be seen. Apparently then maximal flexure is not necessarily the position of permanent heat rigor.

2. *The effect of a low temperature on the heart.*

Complete standstill of the heart at a low temperature has been described by several observers. In my experience it is very seldom obtained with the suspended heart even at 0° C.; so that I have nothing whatever to say about the cold standstill. But there are one or two points in the behaviour of the cooled heart, which are brought out by my tracings, to which it may be worth while to devote a few words.

(1) In the first place, at low temperatures the tone of the heart and particularly of the ventricle is decidedly increased. Although the contractions are so slow, the relaxation is less than at the ordinary or at higher temperatures.

(2) The beats at low temperatures are large and vigorous, although slow. It is often stated that a low temperature diminishes the size of the beat, and no doubt this is so for a temperature bordering on that at which the heart stops in cold standstill. But the contractions are often quite as large at a temperature a degree or two above zero as at the ordinary temperature.

(3) In most of the tracings (Fig. 20 e.g.), just after the point where a low temperature is marked, there is a descent in the ventricular curve broken by two, three, or more contractions much smaller than those which precede and follow them, and relaxing only imperfectly. The appearance suggests that the ventricular lever had in some way been accidentally disturbed; and the first time I noticed it, I thought that a piece of ice might have come in contact with the thread attaching the apex to the lever. But it was soon evident that there was nothing artificial in the curve. The explanation is, I suppose, as follows.

The ventricle being downwards in the suspended heart, the cold solution first came in contact with it, and the point at which the temperature is marked on the tracing indicates the time at which the solution had just reached the ventricle. It reached the auricle a little later, the interval depending on the rapidity with which the solution was being run in. Now it will be seen that in many cases these small ventricular beats have precisely the same frequency as the beats preceding them, and that they correspond to unaltered auricular contractions. The ventricle although cooled before the auricle continues to follow the auricular lead, and therefore beats at first at a rate more rapid than would naturally correspond with the low temperature if the whole heat was cooled at once, and the size of the beats diminishes to make up for the excessive rate. When the auricle and sinus are reached by the cold solution, the ventricle, having now to respond much less frequently, does so and with a much larger contraction.

Occasionally it is seen that just after the application of the cold solution both auricle and ventricle beat more frequently than at the preceding higher temperature. This appears to be the quickening described by Cyon and Aristow when the heart is very suddenly cooled; and is apparently due to some kind of stimulation caused by the sudden change of temperature.

Section V. The influence of endocardiac pressure on the action of the vagus and sympathetic.

Before the great influence which distension of the heart exerts on its action was known, various effects were attributed to the solutions used to "feed" the heart which are now known to be due wholly or in part to the mechanical stretching of the tissue.

Schiff[1] asserted that washing out the heart of the frog with normal saline solution made the vagus inactive, and also made stimulation of the sinus ineffective as regards inhibition.

Merunowicz[2] considered that even normal saline solution was not an indifferent liquid for the heart.

Löwit[3] stated that it was a property of many sodium salts in a certain concentration to abolish the inhibitory action of the vagus. This effect lasted a long time in the frog; but in warm-blooded animals passed quickly off.

Luchsinger and Ludwig[4] repeated Schiff's experiments, and came to the conclusion that his result was not due to the saline solution but to the pressure used in washing out the heart. They found that the higher the endocardiac pressure is, the more difficult is it to obtain standstill of the heart by stimulation of the vagus. And since they also found that the higher the pressure the more rapid and powerful is the heart-beat, they explained the failure of the vagus as due to an increase of excitability of the heart wall by the pressure. Stimulation of the vagus in the greatly distended heart sometimes caused marked quickening of the beat.

Sewall and Donaldson[5] found that in the frog and "slider" terrapin Luchsinger and Ludwig's chief result held true. The change in the vagus action comes on gradually. But they generally found no notable increase of the rate of the heart with increase of pressure, as the German observers had found. They concluded that "changes of intra-cardiac pressure, when experienced by the ventricle alone, are without effect on the cardio-inhibitory function of the vagus"; and that "the mechanism through which variation of pressure within

[1] *Arch. d. sciences phys. et natur.* LXIII. Genève, 1878; *Pflüger's Archiv*, Bd. XVIII. 1878, p. 202.

[2] *Ludwig's Arbeiten*, 1875, p. 148.

[3] *Pflüger's Archiv*, Bd. XXV. p. 482.

[4] *Pflüger's Archiv*, Bd. XXV. *loc. cit.*

[5] This *Journal*, III. p. 357.

the heart can affect the action of the vagus nerve lies largely, if not wholly, within the venous sinus."

In warm-blooded animals Lustchinsky[1] found that section of the spinal cord caused an increase in the activity of the vagus; and in the dog a rise of endocardiac pressure, caused by clamping the pulmonary artery or aorta, diminished the inhibitory action of the nerve.

Schiff[2] confirmed this.

My experiments on the subject in the frog and toad lay no claim to completeness; but, as they have brought out one or two new points, they may be worth recording here. They were made incidentally in the course of the work described in Section IV. on the heat standstill of the heart under pressure, and in that to be described in Section VI. on the electromotive effects of stimulation of the cardiac nerves during standstill. The arrangement was the same as that described in Section IV.; but all the experiments on the action of the cardiac nerves on the distended heart were made at the temperature of the air, which varied at this time from 7° to 10° C. If the work had been done independently, it would have been perhaps better to use Roy's tonometer or some modification of it such as Gaskell's; but it was necessary in the scheme of the experiments originally draughted that the heart should be freely accessible. I have not made any experiments in which the temperature and the endocardiac pressure were both altered at the same time, although in the light of the results of Section I., I now see how interesting such observations would be. One or two extracts from the record of the experiments may be given here.

Experiment I., *Jan.* 21, 1891.

Frog. Cannula in inferior cava connected with pressure apparatus. Both vagi prepared, and proved to be active.

Pressure 9 c.m. Auricle greatly distended, and stops beating. Ventricle beats rapidly.

Pressure increased to 20 c.m. Ventricle still goes on beating. Stimulation of vagus soon after this increase of pressure causes slowing, followed by increase in rate and strength. But after a short time stimulation of the vagus causes primary quickening of the beat.

A peculiar phenomenon was now seen. Regularly after stimulation of the vagus a stage appeared where the ventricle gave two contractions for each complete relaxation. Starting from relaxation there was first a strong contraction which lasted long and then gave way partially, the relaxation

[1] *Würzburger Physiol. Unters.* 2ter Th. 1869, p. 161.

[2] *Arch. d. sciences phys. et natur.* Genève 1878, p. 30.

being very incomplete and followed by a fresh contraction, which then gave place to complete relaxation. This would be repeated five or six times, and then the ventricle would go on again relaxing completely after every contraction. Occasionally there would be a long standstill in diastole.

Experiment II., *Jan.* 22, 1891.

Frog curarised. Cannula in inferior cava. Right sympathetic and left vagus prepared. With pressure null, stimulation of either nerve increases rate and strength of beats.

Pressure 7·5 c.m. Before stimulation rate is 12 per minute: after stimulation of sympathetic 16 per minute.

Pressure 39 c.m. Rate before stimulation of sympathetic 12 per minute; after stimulation 16 per minute.

Two points in this experiment may be noted. In the first place the rate at the very high pressure of 39 c.m. is the same as at 7·5 c.m., which supports Sewall and Donaldson's observation that the rate is not generally affected by the pressure, in opposition to Luchsinger and Ludwig. The other point is that the amount of acceleration produced by stimulation of the sympathetic is the same at the two pressures. It would be interesting to know whether the activity of the sympathetic is quantitatively affected by changes of pressure when the temperature is constant, or whether the influence of pressure extends only to the inhibitory action of the vagus. My observations are far too few and too casual to decide this point.

Experiment III., *Jan.* 22, 1891.

Frog. No curari. Cannula in inferior cava. Right sympathetic and left vagus prepared. Pressure null. Stimulation of vagus causes standstill; stimulation of sympathetic, acceleration and increase in force of beats.

Pressure 39 c.m. Auricle greatly distended, and ceases to beat. Ventricle beats with slow, stubborn contractions which relax at first reluctantly, and then suddenly give way. Stimulation of the vagus now causes quickening and strengthening of the beat of the ventricle, without any visible effect on the greatly distended auricle; and stimulation of the sympathetic does the same.

Pressure suddenly reduced to 6·5 c.m. A long-continued standstill of the heart in diastole follows. This standstill can at once be put an end to by stimulating the heart electrically or mechanically; and both auricles and ventricle then continue to beat. Standstill can be again obtained by again increasing the pressure and then suddenly lowering it. At the high pressure the first few beats after stimulation of the sympathetic had the peculiar

double character described in Experiment I., Jan. 21. But later on in the experiment the same phenomenon appeared to follow rapid increase of pressure after the heart had been beating for some time at a low pressure. The whole ventricle did not relax at the same time, and therefore it was puckered for a moment by what might be called "local systoles." Then its surface became smooth again in complete relaxation.

The diastolic standstill was now again brought on by suddenly lowering the pressure; and just after it began, the sympathetic was stimulated. After a well marked latent period, the heart began to beat; and the beating, once started, went on a long time, and was increased in rate and strength by further stimulation of the sympathetic. The systole was made by the action of the nerve far longer than before, but this was more than compensated by the shortening of the pause. Sometimes the systole became a sort of tonic contraction, occasionally giving way a little and then contracting again. This refers to the state of matters for some time after the stimulating current was shut off, and therefore the effect could not be due to escape of current.

By raising the pressure and suddenly lowering it again, standstill was once more obtained; and was again removed by stimulation of the sympathetic. Ultimately, after the heart had been several times exposed alternately to high and low pressure, the standstill caused by sudden diminution of pressure was no longer affected by stimulation of the sympathetic, although direct stimulation of the heart or increase of the pressure caused it to beat again. This is conclusive proof that the results formerly obtained by stimulation of the nerve were not due to bad insulation.

Direct stimulation of the heart under 37·5 c.m. pressure, when the auricle had stopped beating in excessive relaxation, did not cause an auricular beat, even when the auricle itself was stimulated, but the contractions of the still beating ventricle were quickened and its relaxation lessened. When the stimulation was very strong, the systole of the ventricle became almost continuous.

Summary of Section V. The points which I should like to emphasize here are the following.

(1) The activity of the sympathetic in the frog is not abolished nor apparently reduced, and is possibly even increased, though definite experiments on the last point are wanting, by an increase of endocardiac pressure far above that which suffices first to weaken and then to destroy the inhibitory action of the vagus.

We have seen that temperature influences the inhibitory action of the vagus and the augmentor action of the sympathetic in the same

general sense. Endocardiac pressure affects them in a different sense. If a rise of endocardiac pressure increases the excitability of the heart wall, this increase is bound up with a change of molecular mobility very different from that associated with the increased excitability of the heated heart. In the heated heart both inhibition and augmentation are easier; the stability of the normal action, so to speak, is lessened. In the heart under a high endocardiac pressure this stability is increased, but with a bias towards augmentation. Part of the explanation lies apparently in the continuous stimulation caused by the distension, which of course opposes inhibition but not augmentation.

Sewall and Donaldson's result that it is only by the pressure in the sinus that the vagus action is affected is what we should expect when the effect of the vagus on the rate is alone considered, for the sinus gives the time to the rest of the heart. It is probable, however, that increase of pressure in the ventricle alone in the frog would affect the power of the vagus to diminish the ventricular contractions. Unfortunately it is difficult satisfactorily to record the auricular and ventricular contractions of the frog's heart under pressure in a manner which admits of easy interpretation of the curve.

(2) The increase in rate and strength of the beat which was sometimes observed by Luchsinger and Ludwig, and Sewall and Donaldson as a result of stimulation of the mixed vagus trunk is due to the sympathetic fibres in it.

(3) Under certain conditions such as a moderately high endocardiac pressure, the systole may apparently be lengthened at the same time that the rate of the heart is accelerated by stimulation of the sympathetic.

This would be a rather curious point if the lengthening of the systole should prove to be constantly produced in the circumstances in which I have occasionally noticed it. Baxt[1] has shewn that by stimulation of the accelerans in the dog the systole is up to a certain limit shortened as well as the pause. Before this, the general view was that the acceleration only affected the length of the pause. A systole lengthened in acceleration seems a paradox. But we must consider that the effect of the pressure is of itself to cause a tendency to long continued tonic contraction of the heart muscle, which looks like a struggle to overcome the pressure. It is evident that the state of the muscle will affect its capacity for such contractions, just as the amount of the pressure, in a given condition of the cardiac muscle, will

[1] *Archiv f. (Anat. u.) Physiol.* 1878, p. 122.

determine the strength of the peculiar stimulus or incitement to such contraction to which the muscle is exposed. If, then, the sympathetic causes an increase in the capacity of the muscle to transform energy into work this transformation, to restate the view urged all along, will take place in a manner determined by the circumstances in which the heart finds itself. In the normal empty heart or in the heart under a low endocardiac pressure there is no tendency for the beats to take the form of tonic contractions; and therefore such a tendency is not caused by the action of the sympathetic. (The apparent increase of general tone very often seen during augmentation in the normal heart is quite another thing from the periodic tonic contractions of the heart under pressure). The transformation of energy is increased on the lines on which the heart is already beating. In the heart under a high pressure there is normally a tendency to strong tonic contraction, a tendency to struggle, as we have termed it, with the pressure. When the sympathetic has increased the capacity for work of the heart under pressure, it does not take up a new style of beating. It simply increases its rate of working in its own fashion. The systolic "struggle" may be prolonged because it is intensified, and at the same time the heart may be able to return to the struggle more quickly. In the undistended heart we have seen that increase of temperature alone has to a certain extent the same effect as stimulation of the sympathetic; the transformation of energy is increased, but the type of the beat is not changed. In the distended heart increase of pressure alone lengthens and strengthens the systole, just as stimulation of the sympathetic may do at a lower pressure, the "tonic" type being always maintained. And when a high temperature conspires with a high endocardiac pressure, the tonic systole lengthens itself out for a little into tetanus or tetaniform contraction.

(4) The standstill in diastole caused by sudden relief of pressure is a curious contrast or complement to the long-drawn contraction of the frog's ventricle which Goltz[1] obtained by sudden, strong filling of the heart with blood. In the one case the sudden withdrawal of the stimulating pressure seems to render the heart unable for a time to beat, although it can beat quite well at the lower pressure when once it starts. In the other case the sudden stimulus of distension seems to render the ventricle unable to relax for a time, although it is quite able to do so when it has once become accustomed, so to speak, to the new conditions.

[1] *Arch. f. pathol. Anat.* XXIII. p. 493, 1861.

Section VI. Some electromotive phenomena of the heated heart and the heart under pressure.

In 1854 Kölliker and Müller[1] observed the negative variation in the active heart of the frog.

Donders[2], Nüel[3], Engelmann[4] and Marchand[5] investigated the subject further, the work of Engelmann and Donders being specially important.

Burdon Sanderson and Page[6] found that heating of a limited portion of the surface of the "resting" heart by radiation from a platinum spiral caused the heated spot to become transiently positive towards a normal point. If the heating was carried farther, the positive phase was succeeded by a permanently negative condition of the heated part.

Since this observation of Sanderson and Page's is of interest in connection with the electrical behaviour of the heart, when it passes into heat standstill, it may be discussed briefly here. There are two well known facts which occur to one in connection with this positive variation.

(1) The fact discovered by Hermann[7] that warmer living skeletal muscle is positive to muscle less warm; and (2) the "local diastole" already mentioned in a former part of this paper.

(1) As to Hermann's observation, Worm Müller[8], indeed, denied that the observed electrical difference was due to anything more than a thermo-current caused by a change in the electromotive force at the surface of contact of the warmed muscle and the warmed sodium chloride solution of the electrodes.

Hermann, while admitting that a marked change of E.M.F. between the Zn and Zn SO_4, causing a current in the same direction as his effect, could be produced by unequal temperatures of the electrodes[9], maintained that there was really an electrical difference between warm

[1] *Verhandl. der Phys. Med. Gesellschaft in Würzburg*, VI. p. 529, 1855.
[2] *Onderzoek Physiol. Labor. Utrecht*, I. p. 246, 1872.
[3] *Bull. de l'Académie Royale de Belgique*, XXXVI. p. 335, 1873.
[4] *Pflüger's Archiv*, Bd. XV. p. 116, 1877; Bd. XVII. p. 68, 1878.
[5] *Pflüger's Archiv*, Bd. XV. p. 511; Bd. XVII. p. 137.
[6] *Proc. Roy. Soc.* 1878, p. 410; this *Journal*, II. p. 384.
[7] *Pflüger's Archiv*, Bd. IV. p. 163.
[8] *Untersuch. aus d. physiol. Labor. in Würzburg*, Heft IV. p. 183.
[9] *Pflüger's Archiv*, Bd. XIV. p. 485.

and cold living muscle like that between living and dead muscle. Grützner[1] confirmed Hermann's view.

Although Sanderson and Page do not, in any paper which I have had access to, state how they eliminated any possible electromotive effect of the heating of the electrode in contact with the warmed tissue, yet it is unlikely that their carefully localised heating would affect the temperature of the zinc sulphate or the zinc. We may suppose, therefore, that the effect was truly a physiological one. But in that case was it anything more than Hermann observed in skeletal muscle?

(2) The possible connection of the effect with the phenomenon of local diastole suggests itself here. This condition may be caused in many ways, one of which is local heating. When the heating is moderate, the condition is transient. With greater heating it becomes more permanent. Now this corresponds closely to Sanderson and Page's effect. Moderate heating of a spot on the surface of the resting heart causes it to become positive for a few seconds. Moderate heating of the beating heart causes a short local diastole which of course would be electrically indicated by a transient positive change not only with reference to a part in systole but, since the relaxation between two beats is normally less than in complete rest, with reference to a part in diastole. More severe heating of a limited area of the resting heart causes a permanent negative change, preceded it may be, by a momentary positive effect, just as in the beating heart greater heating causes a permanent change which prevents the affected area from conducting the contraction wave, i.e. causes permanent injury, which would be accompanied with a lasting negative change.

In the beating heart Sanderson and Page observed that moderate heating of the neighbourhood of the auriculo-ventricular groove intensified the second phase of the variation (apex negative to base) while heating of the apex obliterated or reversed this phase. This effect soon disappears. This is easily explained on the assumption that in both cases the spot warmed remains for some time in local diastole, which is precisely what it would do if heated in the way described. I am aware that Luchsinger[2] explains the local diastole as really a local condition of increased excitability of the muscle, so that the systole passes very rapidly over it leaving it again in diastole while the rest of the muscle is still in systole. But this would not alter the fact that during by far

[1] *Pflüger's Archiv*, Bd. xxv. p. 255, 1881.

[2] *Pflüger's Archiv*, Bd. xxviii. p. 556.

the greater part of the contraction of the rest of the muscle the heated spot would be in diastole, and the galvanometer indication would depend on the average state of the area. But how will this explanation apply to the resting heart? It will not apply unless it is possible that the heated portion of the heart can relax somewhat more than the rest. Now we know that when the beating heart is heated the relaxation between the beats may be increased, and when the heart goes into heat standstill the tone is apparently as much diminished as it is in vagus standstill at the ordinary temperature. But in vagus standstill the relaxation seems to be greater than in the resting non-inhibited heart. So that in the heat standstill the relaxation is probably greater than in Sanderson and Page's resting heart. Now although it may not be allowable to call the local diastole caused by heating a portion of the beating heart, a local heat standstill, the fact that in the resting heart these observers found that a longer exposure with the spiral at the same distance as sufficed with a short exposure to cause the positive effects brought on the permanent negative effect indicating permanent injury to the tissue, shews that there must have been, even with the shorter heating, a very considerable increase of the temperature, possibly enough to cause heat standstill if the whole contracting heart were exposed to it, but in any case sufficient to bring about a portion of the increased relaxation which the temperature of heat standstill would presumably cause. If this is the case, the heated spot in the resting heart would naturally tend to become positive towards an unaffected point. So that it is perhaps possible to explain Sanderson and Page's result in the resting heart without having recourse to Hermann's effect. Their results in the beating heart seem undoubtedly to be connected with the local diastole. But is there any chance that even in the locally heated skeletal muscle a condition analogous to that of local diastole, a relaxation or tendency to relaxation, may be connected with the electrical difference?

It is possible, of course, that in the local heating a remnant of excitation which does not shew itself in the diastole of the beating heart or in the resting heart by a removable "tone" may be got rid of.

I now come to my own electrical experiments. And I may say at the outset that as regards their main object, the tracing of the action of the cardiac nerves during standstill of the heart by means of electrical effects, the work has been fruitless. I have, therefore, nothing to offer but a few scraps and fragments, which perhaps are not worth recording, but which I am loath to throw away altogether.

The effect of a very high temperature on the electromotive properties of the heart.

Method. It was of course not permissible to heat the heart in saline solution for the electrical experiments. It was, therefore, while still in connection with the rest of the animal, drawn through a small glass worm by a thread attached to the apex of the ventricle. The thread was connected with a writing lever supported by an elastic band. Water of the required temperature was passed through the worm, but it was found that the temperature of the heart was always sensibly less than that of the water. A heat section was made on the apex of the ventricle; and one electrode, of course non-polarisable, was put in contact with this section, the other being pushed through an opening between two coils of the worm so as to touch the ventricle a little below the auriculo-ventricular groove. The electrodes would of course be heated along with the heart, but approximately to the same temperature; and besides they were of such a form that only the clay could be appreciably warmed. They were connected in the usual way to the galvanometer. At first it was attempted to compensate the demarcation current during the heat standstill, but this was given up when it was found that there was no constant measurable effect of stimulation of the nerves.

When the heart was heated the vibrations of the image at first increased in extent and rapidity; but soon, while still increasing in rapidity, diminished greatly in amplitude, the mean point of the swings gradually moving in the direction of the demarcation current, until ultimately, at a temperature still below that necessary to cause heat standstill, the excursions were very slight, the range being only about 5 divisions (the whole scale contained 500) on each side of the mean point. The appearance was just like that got with a differential rheotome when the speed is rather too small. Of course the vibrations were not at all a measure of the action current at different temperatures, because the galvanometer was far too slow to follow the quick changes. At the higher temperatures it really compounded the action currents and the demarcation current, and the mean point gave their algebraic sum. The deflections with the heart at the ordinary temperature were sometimes quite unmanageable; but at the higher temperatures it was perfectly easy to fix the mean point. If the temperature was now raised further, the vibrations ceased rather suddenly, and then there

was a marked swing in the direction of the demarcation current, and the spot came to rest. This corresponded in time with the heat standstill. If the vagus was stimulated before heat standstill had taken place, and stopped the heart, a precisely similar swing occurred, which settled down exactly at the same point as that caused by the heat standstill.

If while the heart remained in heat standstill, the temperature not being raised further, the vagus or the sympathetic was stimulated, or if, the heart having been brought to rest by the vagus at a temperature a little below that of heat standstill, stimulation of the nerve was continued after the heart had ceased beating, no further constant change was observed. Occasionally, however, stimulation of the sympathetic during the heat standstill was followed by a small movement in the direction of diminished difference of potential between the uninjured ventricular tissue and the injured apex; but when this happened it was succeeded by electrical changes associated with actual beats. And when the heart of itself broke again into contraction after the standstill there was often a similar prelude, not so far as I could see less marked than that caused by stimulation of the sympathetic.

I made experiments in this way on 14 frogs and toads; and if the number seems a small one, it is small because I got no constant positive results, and it seemed useless to continue the search further, at least under the conditions which I was able to produce.

Experiments I.—IV. are examples of this part of the work.

Note. When the uninjured tissue becomes more positive relatively to the injured apex, the deflection is to right. The graduation of the scale is from right to left. The zero is taken at 250.

Experiment I.

Frog. Vagus prepared. With heart at temperature of air, deflections are nearly from end to end of scale. Heated heart. It beats very quickly but image does not come quite to rest. Mean point of swings 175. Now stimulated vagus. Short interval in which no effect on galvanometer. Then large swing to right coming to rest at 130, i.e. 45 to right of previous mean. On continuing stimulation no increase of this was got, nor on strengthening the stimulus from 60 to 0 (i.e. from distance 60 mm. between coils to coils close up). Heart allowed to cool. Mean point 177.

Heated again. Vibrations become less and quicker, and mean point shifts to 165, i.e. 12 to right. Then comes a sudden deflection to right, settling at 130, and accompanied with standstill of heart. This deflection is not altered by stimulation of vagus with coils at 60. Strengthened stimulus,

At first no effect; then small movement to left, accompanied with beating of heart, which continues, as do the vibrations of the image. Allowed heart to cool. Mean point 178.

Stimulated vagus. Vibrations at first increased in size and slowed (the increase in size would of course be due to the slowing, as the galvanometer would have more time to follow out the swing); then image comes to rest at 150, and no difference caused by further stronger stimulation.

Note that with the heart at the temperature of the air (8° C.) the deflection when the heart is brought to rest by the vagus does not go so far to right as in the case of the heated heart when stopped by the vagus or in heat standstill, *i.e.* the uninjured point does not become relatively so much more positive to injured in cold as in heated heart. This quite corresponds with the smaller relaxation in the cold. In this experiment the small deflection to right might be due to deterioration of heart and diminution of the demarcation current; but the same thing has been sometimes noticed in fresh hearts.

Experiment II.

Toad. Sympathetics prepared. Heated heart, by water at 40° C. through worm. Sudden swing to right coming to rest at 232, accompanied with standstill. The mean of three consecutive swings was taken in this experiment.

Allowed to cool. Swings 282, 210, 280. Mean, 257.

Water at 35° C. Standstill; deflection comes to rest at 238.

Sympathetic stimulated; no effect, except when heart begins to beat.

Soon after heart has resumed beating, and while the beats are still quick, swings are 230, 272, 230. Mean, 244.

Painted with 1% solution of atropia without touching neighbourhood of electrodes. Swings are soon much increased in size and difficult to read exactly, 350, 170, 350. Mean, 290?

Water at 40° C. Causes standstill very rapidly, but no sudden swing to right. Image comes slowly to 245, zero being 250.

Cooled to temperature of air. Swings again large. Water at 35° C.; first increase in size of swings, then increase in rapidity and diminution in size, and then a rather sudden swing at standstill, coming to rest between 240 and 250.

Experiment III.

Frog. Both sympathetics prepared. Water at 50° through worm; vibrations quickened, but no standstill. Mean point changes from 220 to 214 and then to 202 as heating goes on. Stimulation of sympathetic now causes gradual movement of 15 divisions to left, but there is evidently slight escape of current. The beat is quickened at the same time.

Arranged stimulating electrodes so as to be properly insulated. Water at 50° C. Standstill. No effect on stimulation of the sympathetic.

Experiment IV.

Frog. Both vagi prepared. Swings right off scale to either side. Water at 50° C. Vibrations soon get very small; mean point 180. This gradually shifts to 165, and then the image moves suddenly to 112. Heart is now in standstill. Now stimulated one vagus. Small gradual movement of about 5 divisions to left; then suddenly large swing to left, and then rapid small vibrations. Heart began to beat simultaneously with the large swing.

Water at 45° C. Standstill soon comes on, accompanied with sudden deflection to 134. Water run off. Deflection remains for $1\frac{1}{2}$ minutes steady at 134. Then small gradual movement to left of about 5 divisions; then sudden jump to left accompanied with a beat of the heart, and then rapid vibrations as before. Everything is exactly like the previous observation when vagus was stimulated.

A few experiments were made without reference to the action of the cardiac nerves. Of these Experiment V. is an example.

Experiment V.

Toad. Vigorous heart. Water at 55° C. Vibrations much quickened, range only 3 or 4 divisions; mean point 260. This range and mean point are long maintained, the temperature of the water being kept constant.

Now allowed heart to cool. In 5 minutes after, the swings are

290 } Range, 58.
232 } Mean, 261.

Painted with atropia, avoiding electrodes. In one minute after, swings are 372 } Range, 228.
144 } Mean, 258.

Water at 60° C. Vibrations get very quick; almost but not quite stationary at 260. Then image passes with moderate quickness to 236, where it remains for a very short time; then passes back to 250 where it remains permanently.

Passed cold water through worm. No effect. Heart is seen to be dead.

Note. Here there is no doubt that the movement from 260 to 232 was coincident with heat standstill of the heart, which rapidly passed on to heat rigor, when the deflection came back to 250 (zero) and remained there. This quite corresponds with Sanderson and Page's experiment on local heating in the resting heart when the heating was excessive, except of course in the important point that here the heart was beating, though feebly, up to the time of the positive swing.

The object of putting on atropia was to test independently Cyon's idea of the stimulation of an inhibitory mechanism in heat standstill, by seeing whether there was any difference in the suddenness of the electromotive change connected with the heat standstill in the atropinised heart. Sometimes the change did seem to be more gradual than in the unpoisoned heart, but sometimes it was quite as abrupt.

The effect of atropia in slowing and strengthening the beat is very strikingly seen on the galvanometer; and indeed exaggerated if the needle is already unable to follow altogether the changes in the normal heart. On this account I may perhaps be allowed to quote one other experiment.

Experiment VI.

Frog. Vagus prepared. At ordinary temperature, swings

320 } Range, 140.
180 } Mean, 250.

Keep steadily at this. Painted with atropia at temperature of room, keeping far from electrodes. No difference at first. In 1 minute after, swings are getting larger. 340 } Range, 180.
160 } Mean, 250.

In 3 minutes 480 } Range, 440.
40 } Mean, 260.

In 3 minutes more, 350 } Range, 210.
140 } Mean, 245.

Range is now decreasing markedly.

In 3 minutes more, 325 } Range, 157.
168 } Mean, 246.

In 2 minutes more, 320 } Range, 140.
180 } Mean, 250.

As control painted heart in same way with water at temperature of room. No change in swings. Decrease still goes on.

In 15 minutes 284 } Range, 54.
230 } Mean, 257.

Water at 55° C. through worm. Heat standstill and sudden jump from 235 to 200.

Stimulated right vagus. Gradual movement of 8 divisions to right, which increases a little after stimulation stopped. The beating begins again.

Water at 45° C. Sudden movement from 225 to 200, and standstill of heart. On stimulation of vagus no effect; but heart begins to beat soon after.

Water at 60° C. Successive slow movements to right and quick vibration for a short time at each new position; then a small sudden jump to right, and standstill of heart. Before standstill stimulation of vagus causes slight movement to left and quick vibrations around the new mean point. Then a further stimulation caused a further movement to left; in fact a sort of inverse process to what happened during the heating.

The electromotive phenomena of the heart beating under a high endocardiac pressure.

The heart was arranged as described in Section IV., except that a heat section was made on the apex of the ventricle. I did not make quite so many experiments on this part of the subject as on the electrical phenomena of the heated heart. The cardiac nerves were only stimulated when the heart had been reduced to standstill by sudden lowering of the pressure.

In spite of the short-circuiting which the saline solution with which the heart is filled must cause, and which might be avoided by using oil, the deflections were fairly marked. When the heart was led off from the auriculo-ventricular or the auricle and the apex of the ventricle, even the auricular beat was clearly shewn on the galvanometer although there was only a mere film of tissue separating the auricular electrode from the solution. This is, of course, not more astonishing than that in Waller's beautiful experiment[1] the electromotive changes of the mammalian heart, filled with blood as it is and deeply buried among conductors, should be quite in evidence on the surface of the body.

But in most cases the ventricle only was led off, one electrode being on the apex and the other near the auriculo-ventricular groove but wholly on the ventricle. A peculiarity of the vibrations which is worth noting was their extreme slowness, corresponding with the long, labouring contraction and slow relaxation of the distended ventricle. Evidently the electrical change is not hurried over as a mere preliminary to the mechanical change, but has the same slow, deliberate character.

[1] *Phil. Trans.* 1889, *B*, p. 169.

No distinct evidence was got of any electromotive change being caused in the ventricle by stimulation of the vagus or sympathetic which was not associated with mechanical changes.

Experiments VII.—IX. are examples.

Experiment VII.

Frog. Heart under pressure (29 c.m. of normal saline). Apex ligatured. Led off from apex and upper part of ventricle. The deflection accompanying the systole is very slow compared with that in normal heart, and so is the return.

In the standstill caused by sudden diminution of pressure to 7 c.m. vagus was stimulated with pretty strong current (distance 40 mm.). Caused deflection of 12 divisions to left, i.e. as if uninjured surface had become more negative relatively to injured apex. This deflection returns at once on shutting off current; and is reversed in direction by reversing current in primary coil. It is, therefore, due to bad insulation. The mean point of the swings shifted far to left (120 divisions) as the pressure was again increased (increasing negativity corresponding to the increasing tone of the ventricle?).

Experiment VIII.

Frog. Sympathetic on one side and vagus on other prepared. Heat section on apex. One electrode on apex, other on ventricle near auriculo-ventricular groove. Pressure 39 c.m. Large deflections. Movements of image are very gradual, and remain long at the maximum, corresponding to the long systole; and the backward movement is also gradual.

Standstill produced by suddenly lowering pressure. Stimulation of sympathetic is followed by a deflection to left, but this returns to right; and it is seen that the heart has begun to beat.

Experiment IX.

Frog. Heat section on apex of ventricle. Led off from apex and auriculo-ventricular junction. By mistake the pressure was not accurately read. It must have been less than 10 c.m. Deflection broken up into auricular and ventricular part,

$$246\underset{\smile}{\text{—}}284\overset{\frown}{\text{—}}270\underset{\smile}{\text{—}}286\overset{\frown}{\text{—}}246.$$

AD over 284—270; VD over 286—246; AS under 246—284; VS under 270—286.

AS, VS = auricular and ventricular contraction respectively.

AD, VD = relaxation.

The auricular contraction can be seen, by observing the heart, to be distinctly separated from the ventricular.

When pressure increased, the rightward movement corresponding to *AD* is greater than at lower pressure, and it can be seen that the interval between the auricular and ventricular contraction is increased. The rightward movement *AD* is always more gradual than *VD*.

When pressure increased, the mean point moves somewhat to left.

$$\overset{AD}{\frown}\qquad\overset{VD}{\frown}$$
$$255\text{—}288\text{—}276\text{—}284\text{—}255.$$
$$\underset{AS}{\smile}\qquad\underset{VS}{\smile}$$

The general result of Section VI. is negative, so far as changes analogous to those observed by Gaskell are concerned. And, of course, when one has to be content with a negative result there is always the possibility that some more fortunate or more skilful observer may afterwards find a positive one. Indeed the conditions of my experiments cannot be considered favourable either to the production of Gaskell's electromotive effects, or to their detection if only feebly developed.

Gaskell found that, when the quiescent auricle of the tortoise is led off to the galvanometer from a heat section on the apex and an uninjured point, stimulation of the vagus caused the uninjured tissue to become more positive relatively to the heat section, although no mechanical change could be detected[1]. He also found that when the ventricle of the toad, which has been brought to rest by the careful application of muscarin to the sinus or by tightening the clamp in the auriculo-ventricular groove, is led off to the galvanometer, and the sympathetic is then stimulated, an electromotive change is caused by which the uninjured tissue of the ventricle becomes more negative relatively to an injured spot.

Sanderson[2] found that in inhibition the uninjured surface of the tortoise auricle in the beating heart and of the ventricle of the entire frog's heart or of the stannius' heart, when stimulated artificially at regular intervals, is somewhat more positive relatively to an injured surface than in diastole. As regards ordinary diastole the meaning of this is that there is a remainder of excitation which lasts till the next contraction.

Gaskell considered that his experiments favoured the view that the vagus causes a constructive, and the sympathetic a destructive, metabolism, which may take place without leading to any mechanical change. It is not by any means certain, so far as I can see, however,

[1] This *Journal*, VII. p. 451; VIII. p. 404; *Ludwig's Festschrift*, 1887.

[2] *Proc. of Physiol. Soc.* July 2, 1887. This *Journal*, VIII. p. xxvii.

that general metabolic changes must be associated with electromotive effects of the same order of magnitude as those associated with the functional activity of the excitable tissues. We do not know definitely even in the case of the salivary glands, retina or electrical organ, much less in the case of muscle or nerve, that it is a chemical change associated with excitation which causes the electromotive change. Still less do we know what the effect of any chemical change, not directly and immediately connected with the functional activity of a tissue, on the electromotive properties of that tissue may be.

If an active destructive metabolism is always associated with a marked negative change, it is difficult to see why the surface even of a resting uninjured muscle, should not be always at least feebly negative to its tendon or why muscle warmed to a moderately high temperature should become positive to muscle at the ordinary temperature. The production of carbonic acid increases with the temperature for a very considerable elevation, yet the uninjured surface of the heated ventricle of the frog's heart becomes gradually more positive to the injured apex as the contractions decline in force, and the stopping of the feeble beats of the heart just about to go into heat standstill is shewn by a marked positive swing. In fact the weakest contraction or the slightest relaxation seems to have far larger electromotive accompaniments than any increase or decrease of general metabolism which a change of temperature can produce.

Again, the localised heating of the resting heart is accompanied with a positive change which becomes a negative change only when the heating produces that permanent local injury which seems to be connected with lasting local excitation. Du Bois-Reymond, indeed[1], found that a finger at 0° was strongly positive to a finger at 15°—30°, but far less strongly positive to a finger at 45°; while a finger at 15° was weakly positive to one at 30°, but strongly negative to a finger at 45°. But this does not prove that it is the excess of the general destructive metabolism at 15°—30° over that at 0° or 45° which determines the electrical behaviour; for in all probability du Bois-Reymond's current was a secretion current depending on the sweat glands, and the variations of temperature would affect the electromotive behaviour as they affected the functional activity of the excitable glands. That is to say the marked electrical changes here too are probably associated not with general chemical processes but more immediately with the

[1] *Thierische Electricität*, Bd. II. p. 206, &c.

specialised changes which we recognise as belonging to the "excited" state. One would, therefore, look first of all for the explanation of Gaskell's experiments in slight functional changes produced by the cardiac nerves, or in a tendency to the production of such changes which is hindered in some way from outward expression. I do not say for a moment that the quest is likely to be successful. But there seem to be at least two possible explanations of Gaskell's positive variation in the tortoise auricle without going beyond what we already know.

(1) We know that when a skeletal muscle is stretched so that it cannot contract, the negative variation still occurs on stimulation; the tendency to, or attempt at contraction determines the electrical change. Now in Gaskell's experiment the auricle was stretched to some extent mechanically; and stimulation of the vagus might cause a physiological relaxation corresponding to the amount of stretching or to part of it; and although no change of form might be seen, this ought to be accompanied with the ordinary electrical change associated with relaxation, a positive effect, namely. The diminution of tone which according to several observers, including Gaskell himself, stimulation of the vagus may cause also occurs to one, especially in connection with Sanderson's results in the beating heart. Or the hindrance to the visible change might be due to something in the state of the tissue, which rendered increased relaxation difficult, analogous to the hindrance which in the exhausted mammalian heart, sometimes renders the contractions difficult or impossible, but nevertheless allows the corresponding action currents to be developed[1].

(2) The injury caused by the separation of the auricle from the sinus and by the heat section might produce a latent excitation spreading even to the neighbourhood of the electrode on the uninjured tissue. Now if the action of the vagus, whatever it be, lessens excitation, it would cause this tissue to become more positive, although it might not be able to spread into the injured zone, which would accordingly remain at its old potential, and the total result would be a positive change.

This discussion does not at all call in question the possibility or probability that the vagus may influence the constructive metabolism of the cardiac tissue. The question now is whether an action of this sort, entirely unconnected with mechanical change or tendency to such change, is associated with the well-marked electromotive effects

[1] Waller and Reid. *Phil. Trans.*, 1887, Part *B.* p. 215, &c.

hitherto observed only as immediately following, or preceding, or accompanying excitation. It may be said that the action of the vagus is really a negative excitation; that its trophic effects are as much excitatory as the motor effect of excitation of a skeletal muscle by its nerve is trophic. The whole point and core of the question, it seems to me, is whether the vagus action or rather the part of it which is associated with Gaskell's electromotive change, is a "diffuse" action, so to say, like the slow processes of general nutrition, and placed far back in the metabolic sequence of which rhythmical contraction is the normal outcome, or a short and concentrated "impulse," immediately related to mechanical relaxation or tendency to such, and carrying, it may be, slow nutritive effects in its train. Now Gaskell found that the deflection might begin to give way again in a very short time, even when stimulation of the vagus was continued. So that the duration of this latent effect seems to correspond with that of the mechanical changes succeeding stimulation of the vagus under ordinary conditions.

Gaskell's negative variation in the ventricle of a heart stopped by the application of muscarin to the sinus or by the clamp, might be explained as an attempt of the heart or of the ventricle to contract which was prevented by some resistance from succeeding, but was, nevertheless, accompanied by an electrical change like that in a stretched skeletal muscle, or still more like the variation observed by Waller and Reid above referred to. In the case of the clamped ventricle it would be necessary to enquire whether the variation means anything more than that the "impulse" from the auricle, favoured by the action of the sympathetic, reaches the ventricle, although it is not able to cause a contraction. It would be necessary further to know whether there was absolutely no change of "tone" in the muscarin standstill or in the clamped ventricle after stimulation of the sympathetic, as it would seem that in the normal heart such stimulation causes an increase of tone which persists for some little time. Such a change would, of course, explain the persistence of Gaskell's effect after stimulation of the sympathetic.

In concluding this paper I have to acknowledge my indebtedness to Dr Gaskell for his kind advice on several occasions, and to Mr Langley for criticism no less kind after the paper was in manuscript.

The above paper was sent in as a Thesis to the Medical Faculty of the University of Edinburgh, 14th May, 1891.

TABLE I.

Acceleration caused by sympathetic.

I Temp.	II Strength of stimulus given as distance between coils in mm.	III Rate before stimulation calculated as the number of beats in 100″.	IV Maximum rate after stimulation calculated as the number of beats in 100″.	V Ratio of rate after, to that before stimulation.	VI Remarks.	VII Number of Tracing.
16°	40	45	53	1·18		42 & 43
10°	40	26	32	1·23		,,
13·5°	40	40	41	1·02		,,
15°	20	56	57	1·0	Considerable increase in force	,,
*9·5° ice	10	—	—	1·00	No effect	,,
16°	20	50	54	1·08	Marked increase in force	,,
12°	100	—	—	1·00	No effect	48, 49 & 50
12°	10	35	48	1·37		,,
13·5°	10	36	50	1·39		,,
19°	10	42	62	1·48		,,
11°	10	36	46	1·28		,,
8°	10	30	40	1·33		,,
9°	10	31	36	1·16		,,
ice	10	—	—	1·00	No effect	,,
9·5°	30	53	60	1·13		52
15°	40	15	24	1·60		55
10°	40	—	—	1·00	No effect	,,
14°	20	15	40	2·66		58 & 59
26°	20	28	71	2·53		,,
27°	30	55	59	1·07		,,
34°	30	61	87	1·42		,,
18°	30	26	50	1·92		67
14°	40	21	44	2·09		70–75
1·5°	40	15	17	1·13		,,
14°	40	40	57	1·42	Note increase in rate at ord. temp.	,, (Tr. 70)
6°	40	27	33	1·22		,,
6°	40	26	33	1·27		,, (Tr. 72)
3°	40	20	22	1·10		,,
8°	40	31	40	1·29	Size of beats little affected.	,, (Tr. 73)
11°	40	33	45	1·36		,,
17°	40	48	63	1·31		,,
14°	40	34	42	1·23		,, (Tr. 74)
19°	40	47	59	1·25		,,
12·5°	40	36	48	1·33		,,
14°	40	29	33	1·14	Little acceleration but great increase now in force	,, (Tr. 75)
14°	40	14	28	2·00		76–81 (Tr. 76)
14·2°	40	11	42	3·82		,, (Tr. 77)
14·2°	40	12	25	2·08		,,
2·4°	40	12	15	1·25		,,
4°	40	19	21	1·10		,, (Tr. 78)
8·2°	40	28	33	1·18		,,
11·8°	40	44	46	1·04		,,
11·8°	40	42	50	1·19		,, (Tr. 79)

* The word "ice," preceded by a temperature, means that ice was added to salt solution of the given temperature while the heart was immersed in it, and allowed to come in contact with the heart, the actual temperature of which would, therefore, be lower than the thermometer reading.

TABLE I. (*continued*)

I Temp.	II Strength of stimulus given as distance between coils in mm.	III Rate before stimulation calculated as the number of beats in 100″.	IV Maximum rate after stimulation calculated as the number of beats in 100″.	V Ratio of rate after, to that before stimulation.	VI Remarks.	VII Number of Tracing.
4°	20	22	29	1·32		76–81 (Tr. 80)
2°	20	18	21	1·16		,,
15·2°	40	13	42	3·23		87
11·5°	50	33	49	1·48		91 & 92
11·5°	70	24	48	2·00	Fresh piece of nerve stimulated	,,
11·5°	100	23	35	1·52		,,
11·5°	120	—	—	—	No effect	,,
23·2°	120	—	—	—	No effect	,,
23·2°	100	77	83	1·08	Some increase in force	,,
22·2°	70	62	100	1·61		,,
11·5°	70	45	60	1·33		,,
18°	70	43	66	1·54		,,
14·1°	vagus 70	36	50	1·39	Primary augmentation by vagus	93
6°	vagus 70	15	16	1·06		,,
air 14°*	70	45	50	1·11		101–104 (Tr. 101)
air 14°	50	45	50	1·11		,,
12·1°	50	42	50	1·19		,,
4°	50	20	24	1·20		,, (Tr. 102)
4°	30	24	23	0·95		,,
19·2°	30	71	87	1·22		,,
14°	70	38	55	1·44		,, (Tr. 103 *b*)
4·6°	50	20	27	1·35		,, (Tr. 104)
4·6°	20	25	27	1·08		,,

* When the word "air" precedes the temperature it signifies that the heart during the observation was not immersed in solution. When the temperature is given without this prefix it means that the heart was immersed in solution at the given temperature.

TABLE II.

Latent period of sympathetic.

(Only measured in a few of the tracings.)

Temperature.	Latent period in seconds.	Tracing.
13·5°	5·5	48–50
19°	4	,,
6°	6	70–75
6°	8	,,
3°	10	,,
8°	6	,,
17°	4	,,
11°	6	,,
19°	4	,,
12·5°	5·5	,,
4°	11	80

EXPLANATION OF PLATES.

PLATE III.

Fig. 1. *G*, the vessel containing the salt solution in which the heart is immersed; *C*, the clamp; *P*, the pulley round which the thread attached to the ventricle passes; *R*, the inflow tube connected with the reservoir of salt solution; *O'*, the outflow tube and *O*, the overflow tube, passing to the vessels *B'* and *B*; *L* and *L'*, levers; *T*, thermometer.

Fig. 2. *G*, vessel containing heart; *L'*, bent lever for ventricle. The fulcrum of the lever is at *F*. The counterpoise is suspended at *H*.

Fig. 3. *A* is the curve representing in one experiment the rate of the heart before stimulation of the sympathetic, and *B* the maximum rate after stimulation, the number of beats per 100″ being laid off along the vertical, and the temperature along the horizontal axis.

C is the curve shewing the ratio of the frequency after, to that before stimulation of the sympathetic. It is put with the others to save space, although its ordinates are of course in arbitrary units.

D shews the absolute amount of acceleration at the various temperatures, the ordinates being the excess of the rate before, over that after stimulation.

PLATES IV. V. VI.

Figs. 1—45, except Fig. 27, and 65—69 are to be read from right to left, Figs. 46—64 and Fig. 27, from left to right.

The temperatures are marked on or above the signal line for the time of stimulation. The strength of stimulus (distance of secondary from primary coil in mm.) is marked on the same line. *V* means vagus, *S* sympathetic.

In a good many tracings the auricular part only is reproduced in order to save space, and in a few, only the ventricular part is given. Where both curves are given the upper is the auricular, the lower that of the ventricle. Where one part is alone given it is marked *A* (auricle) or *V* (ventricle).

Figs. 1—6 (Tr. 44)[1]. Vagus. Temperature diminished from the air temperature (15°·5) to 8° (Fig. 2), and then below 8° (Figs. 3 and 4) by

[1] All the tracings in the series of experiments covered by this paper were numbered consecutively, each drum paper kept being called a "tracing." The numbers are put here in brackets merely for reference, and have no relation to the numbers assigned to the figures in the plates, which are arranged in the order convenient for illustrating the text. No single "tracing" contains records from more than one preparation, but frequently the same preparation runs through more than one tracing. Each *group* of figures (Figs. 1—6 e.g.) is from a single preparation. It would be risky to make comparisons in any other way.

addition of ice. In Fig. 5 the stimulus was strengthened to 30, but there is a much smaller inhibitory effect than with *V*78 at ordinary temperature or at 13° (Fig. 6).

Figs. 7—12 (Tr. 62). Vagus. Temperature first diminished from the air temperature, 11° (Fig. 7) to 4°·5 (Fig. 8), below this (Fig. 9); then raised to 8° (Fig. 10) and 18° (Fig. 12).

The effect on the ventricle disappears at the lower temperatures before that on the auricle (Figs. 8, 9).

Figs. 13—16 (Trs. 95 and 96). Vagus. Two strengths of stimulus (*V*70 and *V*90) used at two different temperatures, air temperature, 12°·7 (Figs. 13 and 14), and 4°·1 (Figs. 15 and 16). *V*90 is ineffectual at 4°·1; *V*70 has still some effect on auricle, but little on ventricle.

Figs. 17, 18 (Trs. 97 and 98). Vagus. Considerable secondary augmentation at 24°·2 (Fig. 18), none at 3°·9. In an intermediate tracing taken at 13°·1, but not shewn here, there was slight but distinct secondary augmentation.

Figs. 19—25 (Trs. 82—84). Direct stimulation of auricle at air temperature, 11° (Fig. 19), and at 2°·3 (Fig. 21); and direct stimulation of sinus at 11°·2 (Fig. 22), 9°·8 (Fig. 23), 1°·8 (Fig. 24) and 3° (Fig. 25). The auricles are almost alone directly affected by their stimulation, while with stimulation of the sinus the ventricles are also directly influenced. In both cases distinct inhibitory effects are still seen at very low temperatures. Fig. 20 shews the effect of a low temperature on the tone, especially of the ventricle.

Fig. 26 (Tr. 86 II.). Effect of stimulation of the sympathetic (*S*30) during complete heat standstill at 28°·5, and of the vagus (*V*70) when the ventricle has nearly again passed into standstill. The extent and rapidity of movement of the ventricular lever were so great that it was difficult to keep the writing point properly on the paper.

Fig. 27 (Tr. 155). Effect of stimulation of the vagus (*V*50) during complete heat standstill at 33°. Here there was no marked secondary augmentation at the air temperature or at temperatures below that of heat standstill. Accordingly, the beats are not particularly strong or rapid when the heart is roused from the standstill.

Stimulation of the sympathetic (same stimulus, *S*50) during standstill was followed by a very similar curve (not reproduced here).

Figs. 28, 29 and 30 (Tr. 33). Auricle alone. Sympathetic stimulated at 12°, 23° and 8°. The *relative* augmentation at 23° is very great because the heart is beating feebly before stimulation. The *absolute* force of the augmented beat at 12° is at least as great as at 23°. At 8° the heart is beating very strongly, and stimulation of the sympathetic causes little, if any, increase in force and only a very slight increase in rate.

Figs. 31—34 (Trs. 58 and 59). Only auricular tracing reproduced.

Fig. 31 shews a heart beating very strongly at the ordinary temperature, 14°; and in this case little, if any, increase of force is caused by stimulation of the sympathetic.

At higher temperatures, 26° (Fig. 32), 34° (Fig. 34) the beat of the auricle still continues abnormally strong for those temperatures, and the usual marked increase of force is absent here too. Fig. 33 shews a great diminution of tone caused by a rise of temperature from 14° to 27°. In Fig. 34 the rise of temperature to 34° causes a greater acceleration than stimulation of the sympathetic at that temperature later on, probably because the heart gets rapidly exhausted at the high temperature, as is shewn by the great slackening of the rate just before stimulation. Fig. 32 shews how stimulation of the sympathetic abolishes for a time the grouped beating, enabling the heart to fill up the intervals.

Figs. 35—38 (Trs. 70, 72, 74 and 75). Sympathetic. Only auricular tracing reproduced except in Fig. 35. This series shews how the effect of stimulation of the sympathetic varies with the strength of the heart's action when this is altered in other ways than by change of temperature.

These tracings were all taken from the same heart at different periods in the course of a long experiment, but all at practically the same temperature, that of the air. When the heart is still beating very strongly (Fig. 35) the augmentation takes the form of acceleration; as it grows weaker (Figs. 36—38) it takes more and more the form of increase of force, it may be along with some acceleration.

Figs. 39—41 (Trs. 91 and 92). Sympathetic. Auricular tracing only reproduced. Increased force of beats specially characteristic of augmentation at higher temperatures, 22°·2 (Fig. 40), acceleration at lower, 11°·5 (Fig. 39). Fig. 41, at 18°, is intermediate. Note increase of tone during augmentation, especially in Figs. 39 and 40.

Figs. 42—45 (Tr. 42). Auricle only. Stimulation alternately of sympathetic and vagus as the temperature is reduced. Figs. 42 and 43 at 15° (temperature of air). Then solution exchanged for one at 9°·5. *S*40 has now scarcely any effect. *V*100 has still some effect, causing diminution in force of beat of auricle. Strengthened stimulus for both nerves; and cooled further by adding ice to solution. *V*60 causes distinct inhibition (Fig. 45); *S*10, no effect.

Figs. 46—48 (Tr. 172). Effect of secondary alteration of temperature on the inhibitory action of the vagus. In Fig. 46 the temperature of 19°·7 (that of the air) was maintained throughout. In Fig. 47 this temperature was suddenly exchanged at the end of stimulation of the vagus for one of 4°. In Fig. 48 the temperature of 4° was maintained throughout, and the stimulation has no effect.

Figs. 49—51 (Tr. 161). Effect of secondary alteration of temperature on

the action of the sympathetic. Only auricular tracing recorded. In Fig. 49 the initial temperature, 22°·2, was exchanged at the end of stimulation for 29°·2, and in Fig. 50 for 28°·7. In Fig. 50 the change was made nearer the beginning of the augmentation, the period of stimulation being shorter than in Fig. 49. In Fig. 51 the initial temperature of 22°·6 was maintained throughout.

Figs. 52—57 (Trs. 137, 139 and 140). Stimulation of the vagus during augmentation produced by the sympathetic. Ordinary temperature. Fig. 52, vagus alone, strong stimulus, (*V*60).

Fig. 53, sympathetic (*S*50), then vagus (*V*60).

Fig. 54, vagus alone, with weaker stimulus, (*V*80); Fig. 55, sympathetic with strong stimulus (*S*25), then vagus (*V*80).

Fig. 56, vagus alone, with minimal stimulus (*V*150); Fig. 57, sympathetic with strong stimulus, (*S*25), then vagus (*V*150). Only auricular tracing reproduced in Figs. 54—57.

Note. In all this series the vagus readily causes complete standstill of the unaugmented heart, and where this is the case it also readily causes standstill of the augmented heart, except perhaps with truly minimal stimuli.

Figs. 58—62 (Trs. 127 and 128). Here the vagus causes complete standstill of the unaugmented heart only with difficulty (strong stimuli) if at all. In the augmented heart it only causes a certain amount of diminution of force, and in general has more effect on the auricle than the ventricle.

Fig. 63 (Tr. 126). Only the auricular tracing reproduced. This shews how the curve of augmentation may be permanently modified and not merely interrupted. Here the inhibition takes the form of slowing of the rhythm with some diminution in force. The beats then increase again in force, and overtop the maximum reached during the preceding part of the curve of augmentation, while at the same time the rate remains much slower. Incidentally the tracing shews that the inhibitory power of the vagus which had disappeared in Tr. 125, taken with the same preparation, has now been restored. This was still better shewn in a tracing from the unaugmented heart (not reproduced). Originally the vagus had a primary inhibitory action.

Fig. 64 (Tr. 125). Here the vagus causes primary augmentation, although in a previous tracing it had caused primary inhibition. The slight diminution of the force of the auricular beat is plainly related to the acceleration, for in a tracing taken immediately after this one but with stimulation of the sympathetic instead of the vagus, with the same strength of stimulus, the curve figured was almost exactly reproduced. Note that the auricle is beating strongly, and the augmentation takes the form of acceleration for a few beats and is then apparently over. In the ventricle, which is beating

feebly, the beats are greatly increased in force, as soon as the acceleration is over or nearly over, and this augmentation continues long although the auricular contraction is scarcely at all strengthened. In fact the ventricular augmentation seems quite independent of the auricular, and is evidently related to the previous feebleness of the ventricle.

Figs. 65 and 66 (Tr. 49). The antagonism of vagus and sympathetic at different temperatures. This subject has been only very slightly studied in the paper. The two curves reproduced here (auricle alone) shew that at 9° (Fig. 66) the vagus cuts down the previous augmentation proportionately about as much as at 19° (Fig. 65).

Figs. 67—69 (Tr. 61). Here a ventricle beating with an independent rhythm at 14° beats more quickly at 25° (Fig. 67) but soon stops. It is roused from this standstill by raising the temperature to 30° (Fig. 68), but soon stops again, to be again roused by a temperature of 36°·5 (Fig. 69).

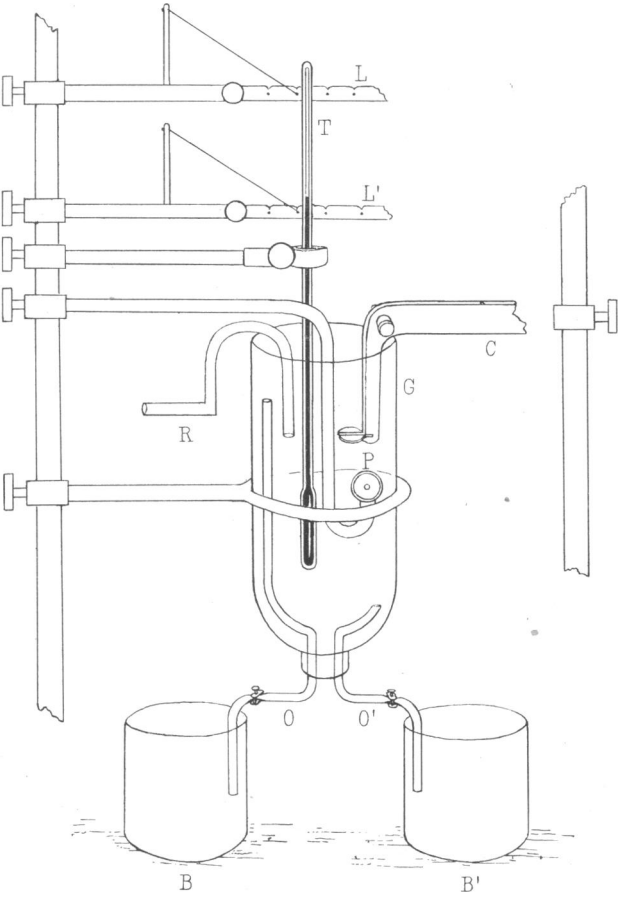

Fig. 1

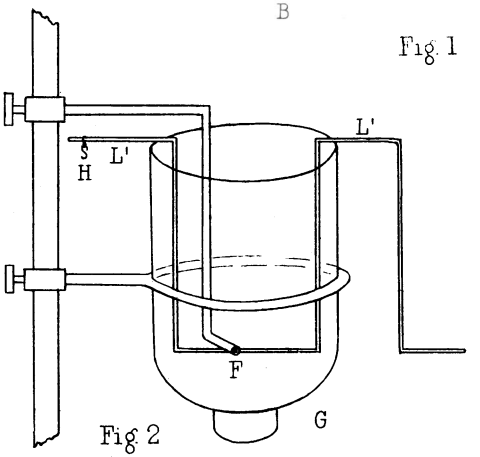

Fig. 2

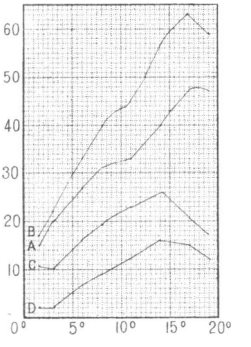

Fig. 3.

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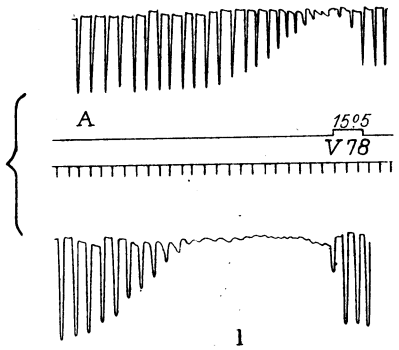

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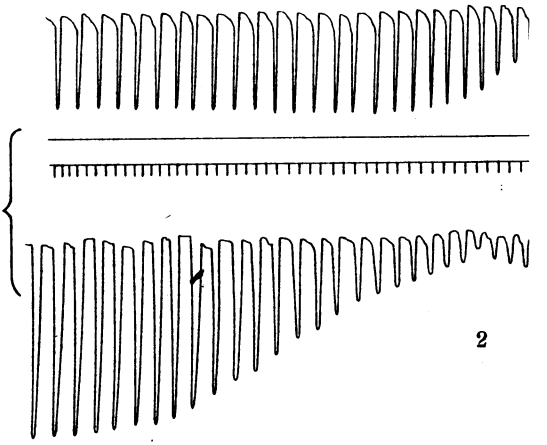

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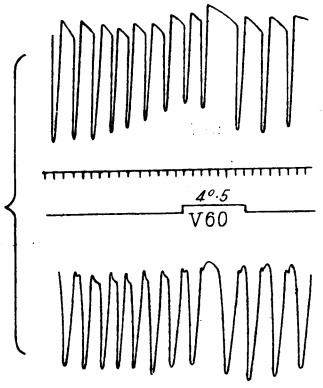

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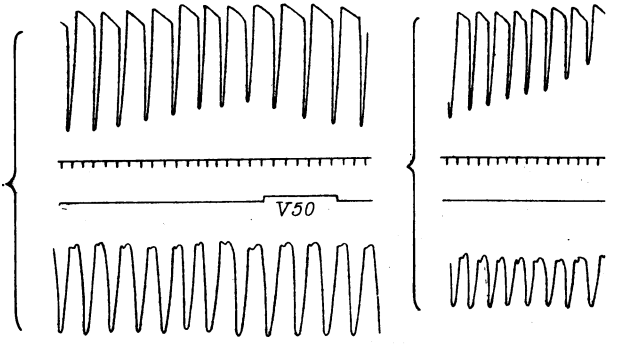

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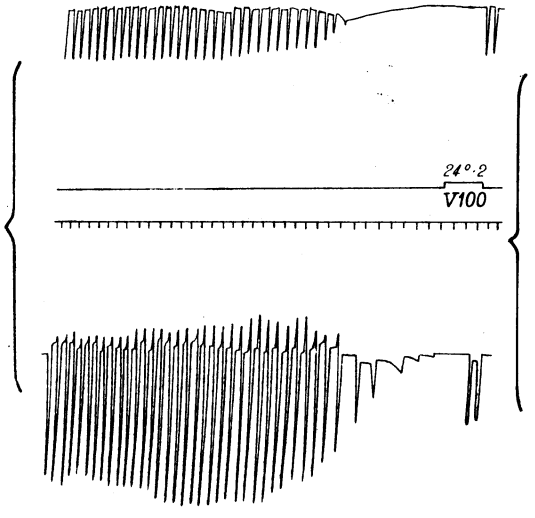

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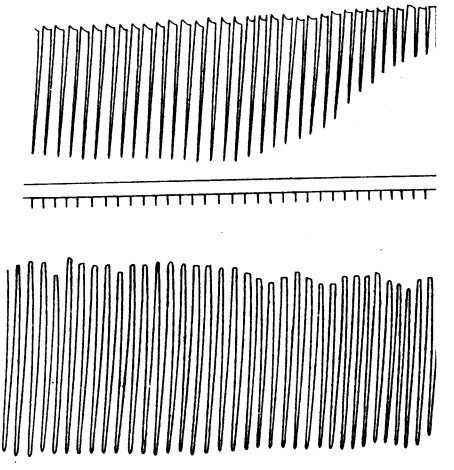

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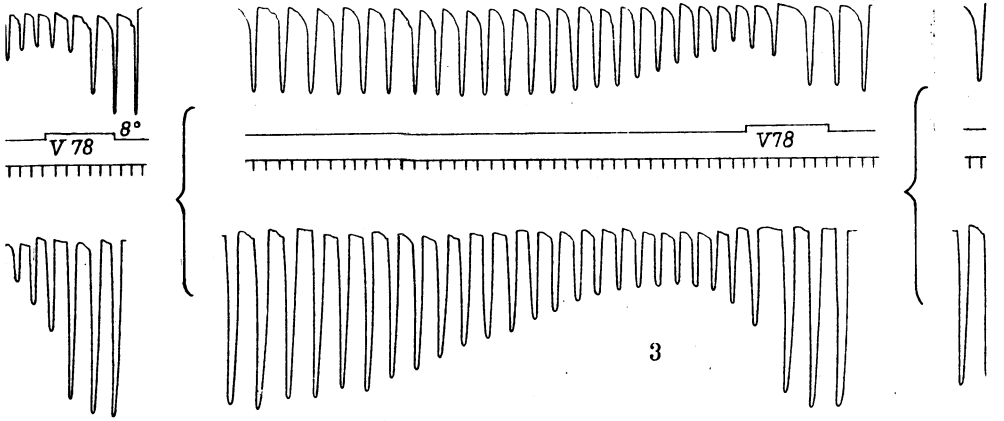

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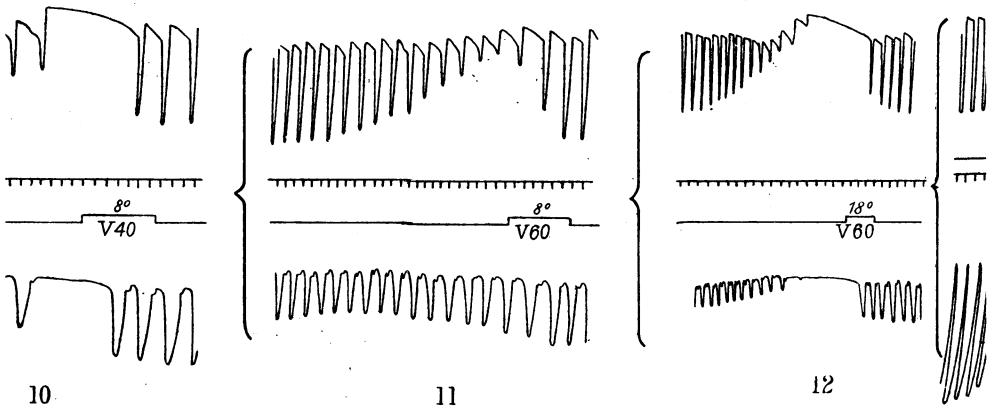

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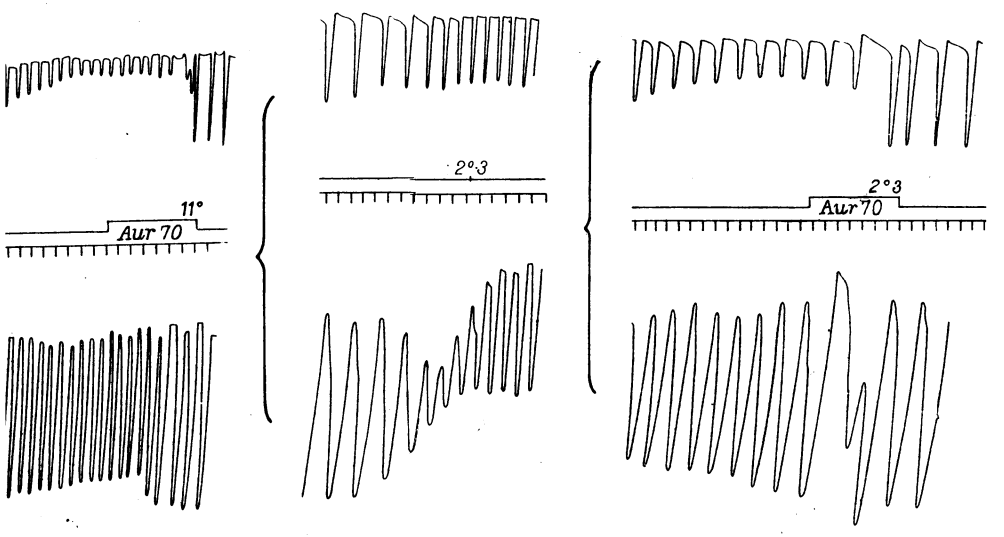

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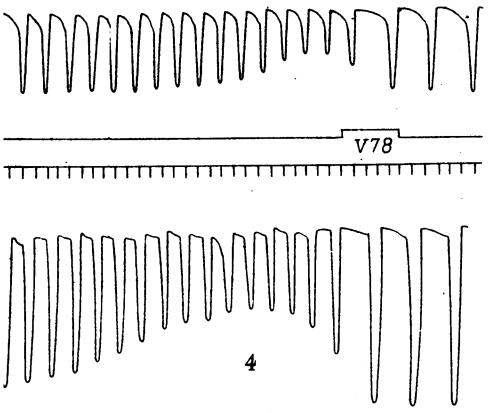

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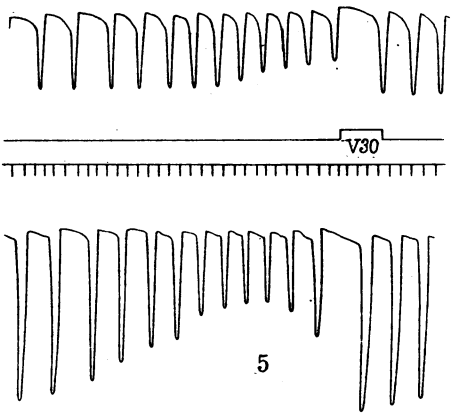

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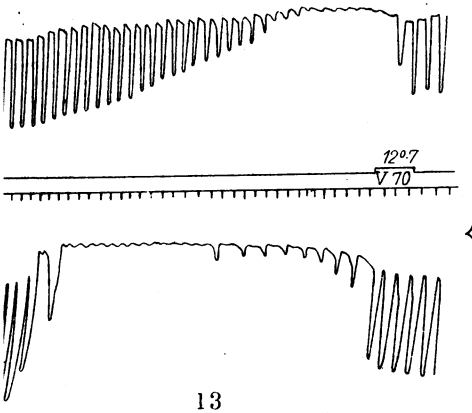

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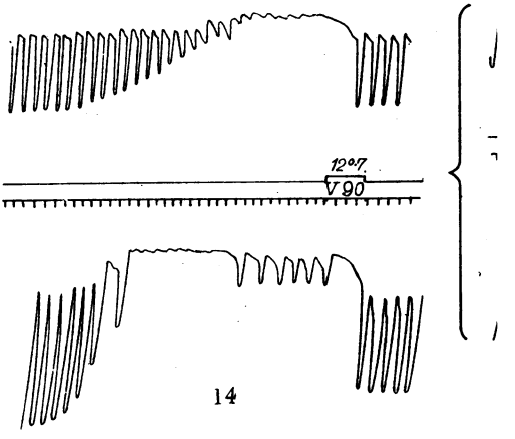

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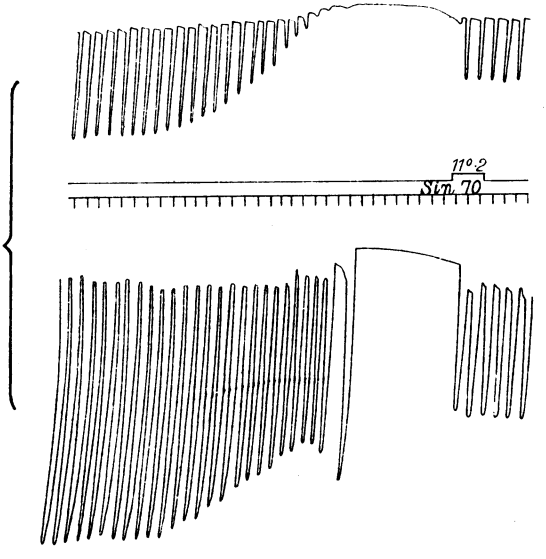

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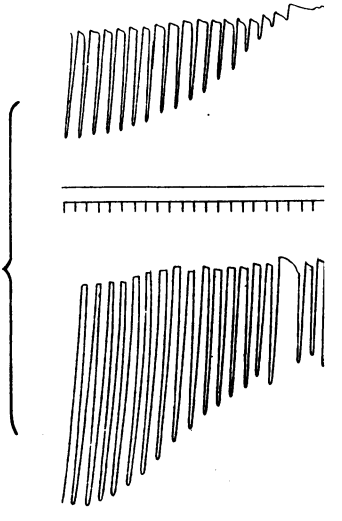

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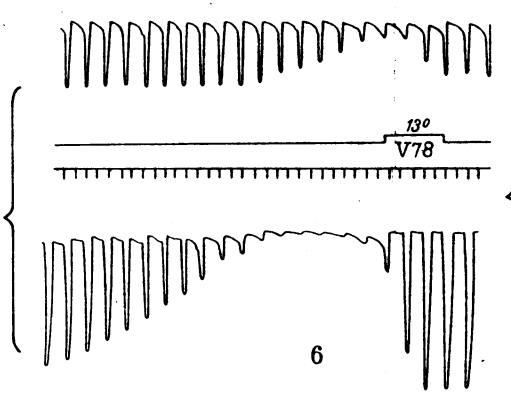

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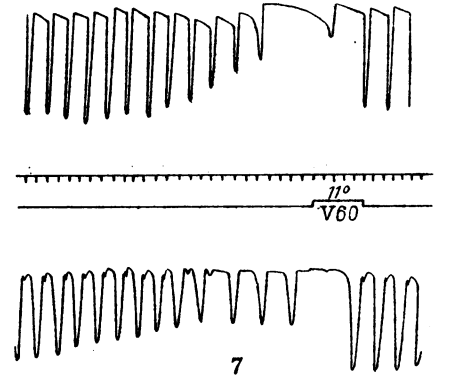

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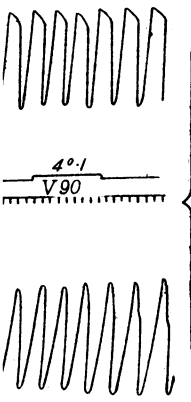

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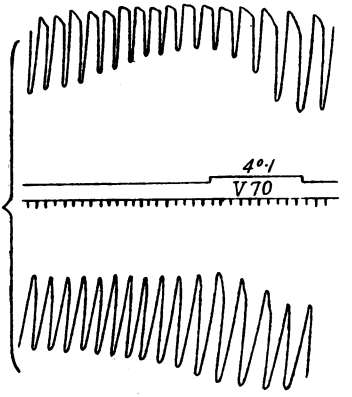

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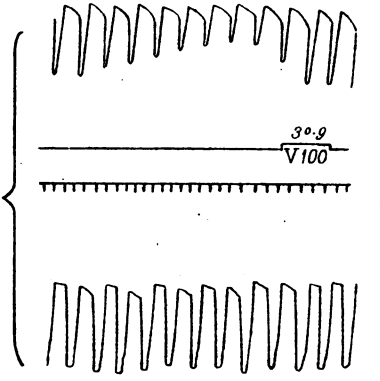

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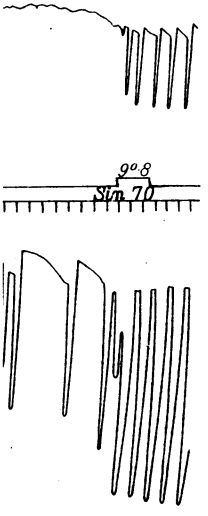

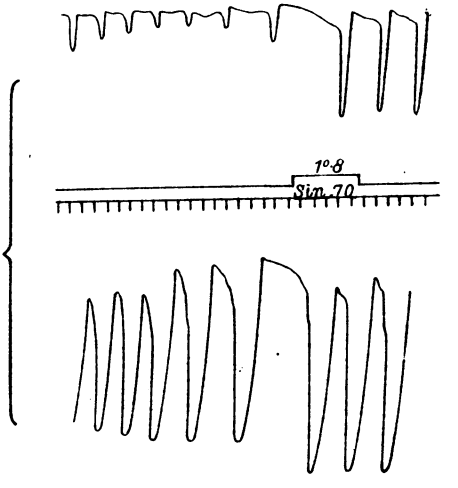

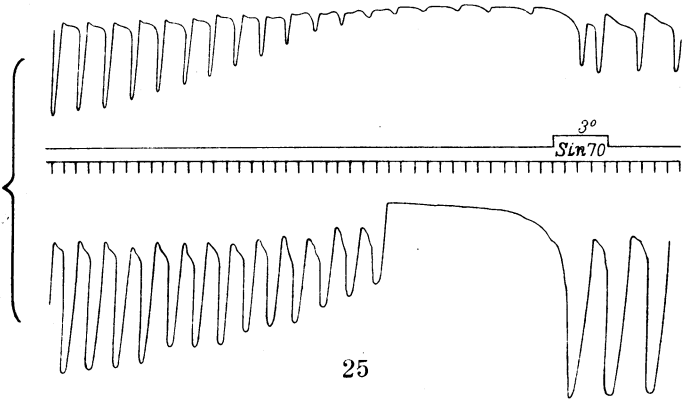

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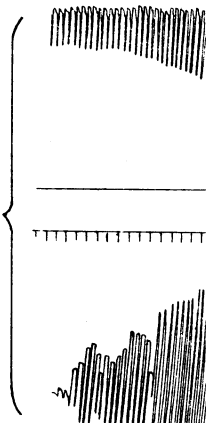

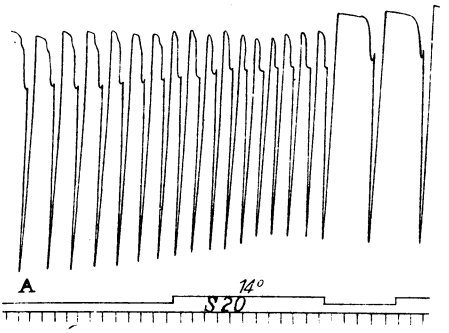

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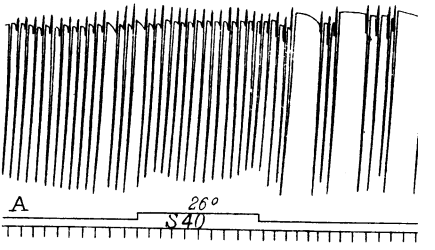

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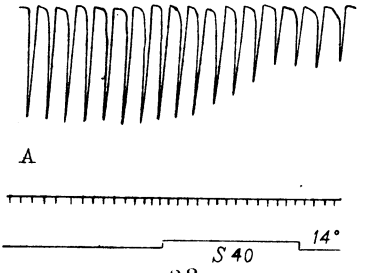

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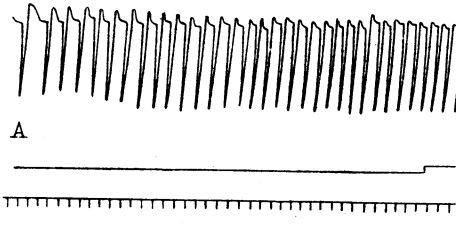

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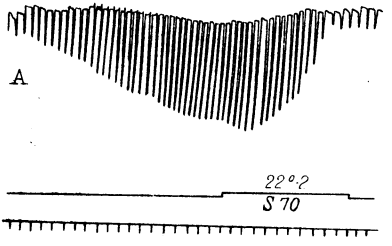

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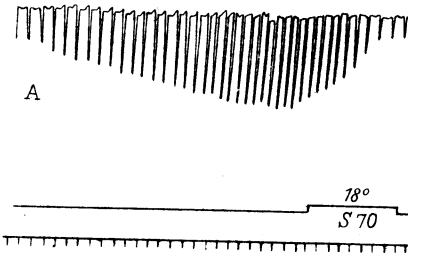

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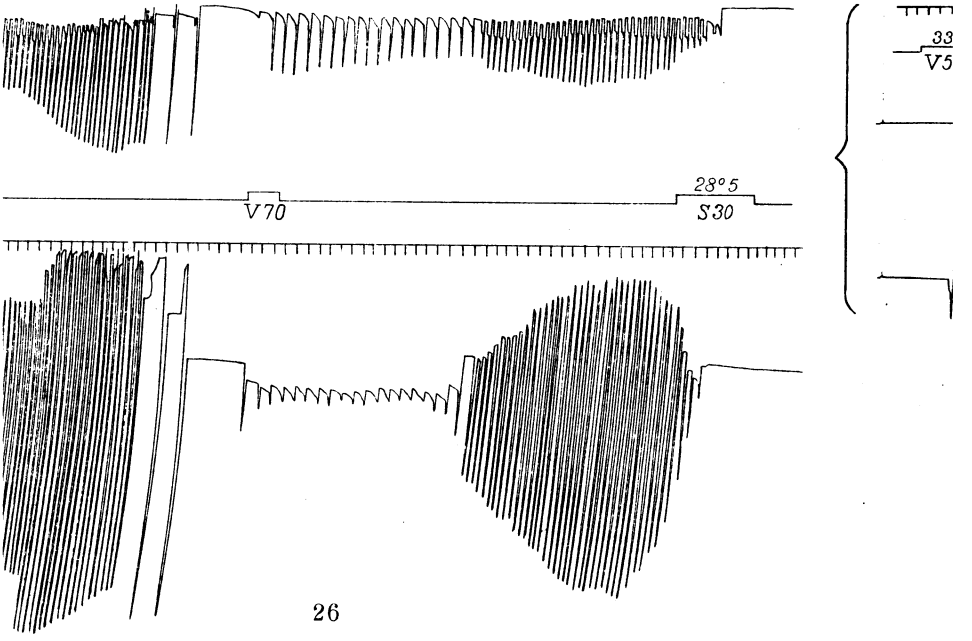

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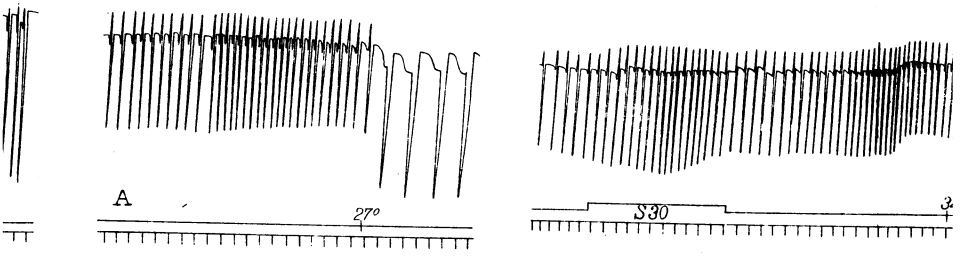

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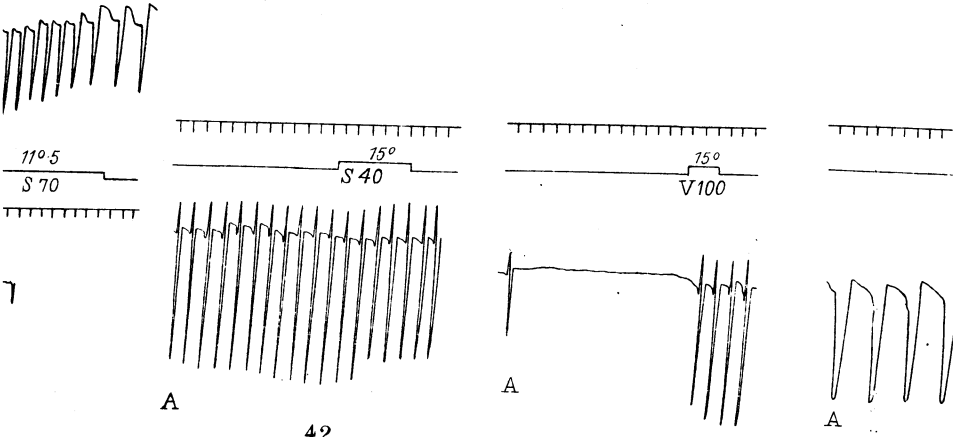

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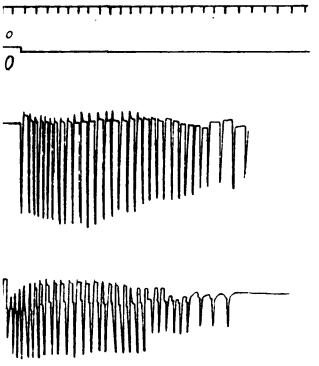

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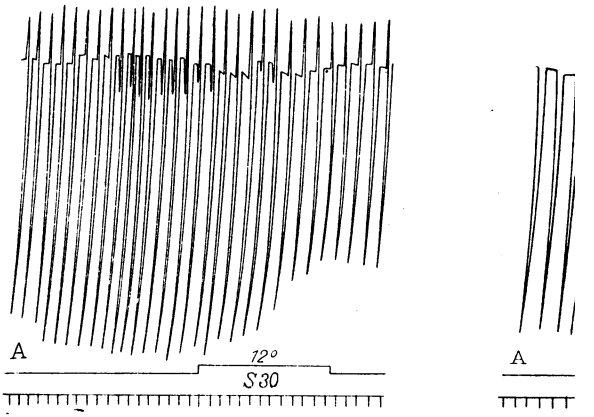

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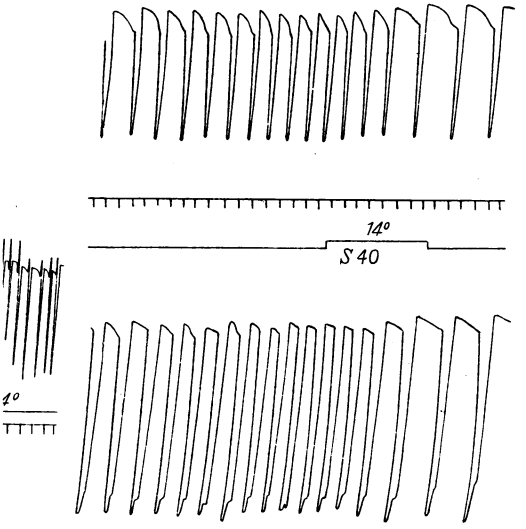

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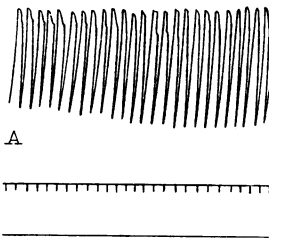

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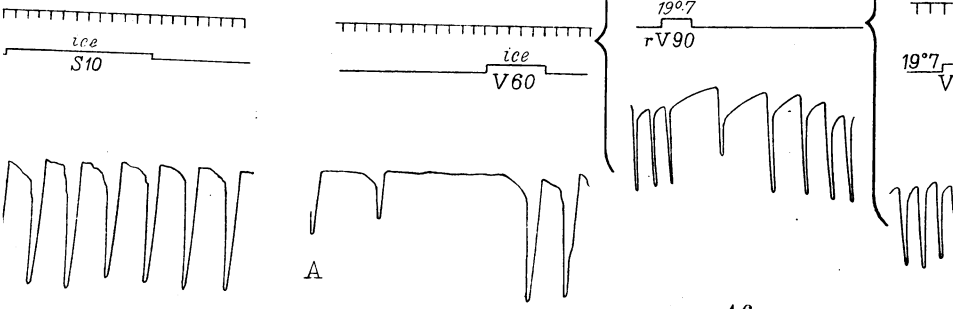

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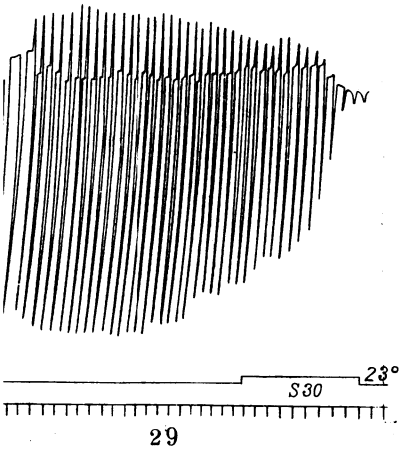

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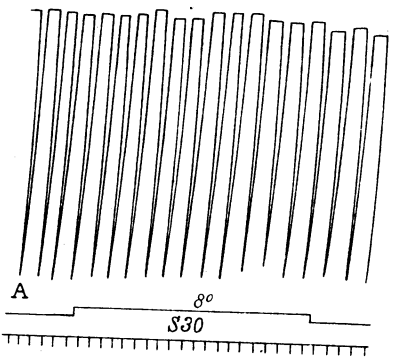

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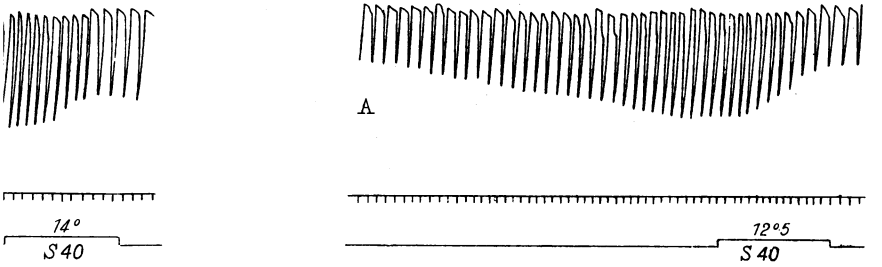

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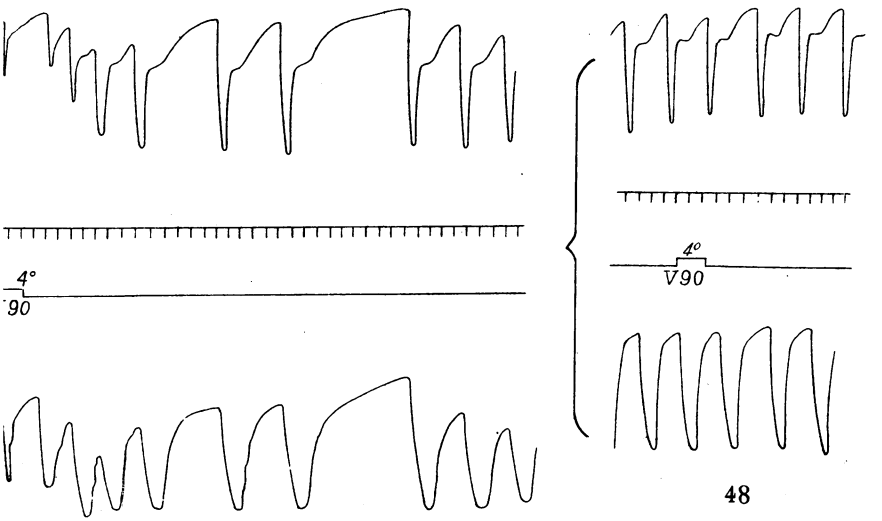

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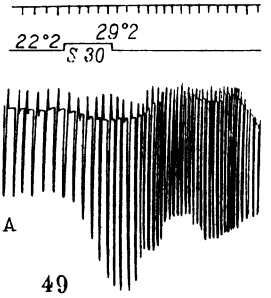

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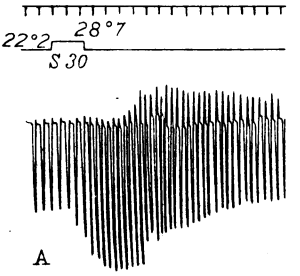

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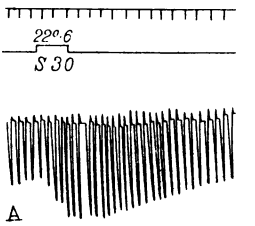

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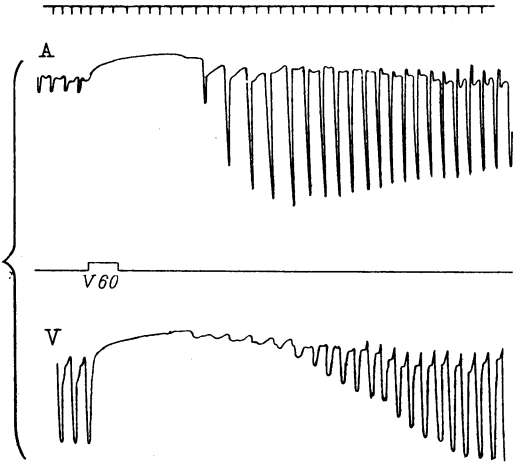

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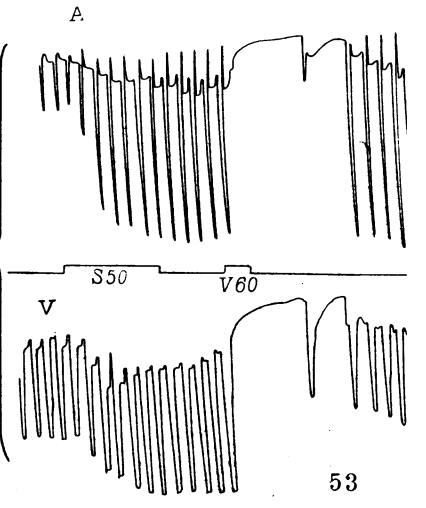

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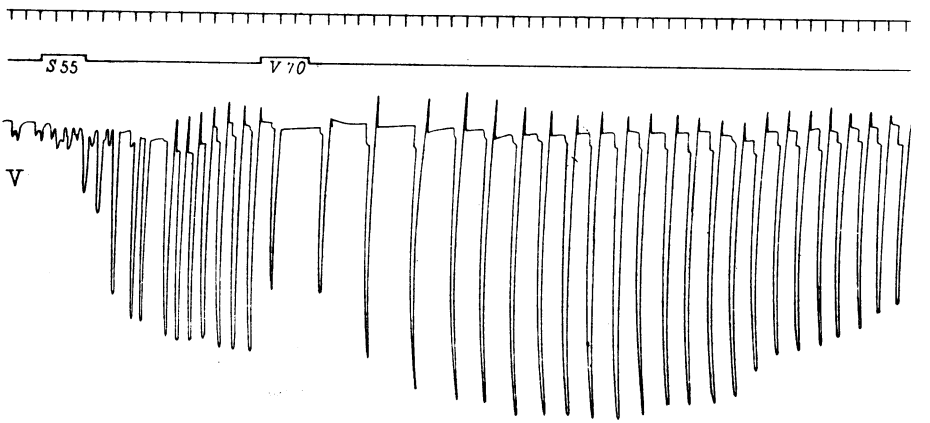

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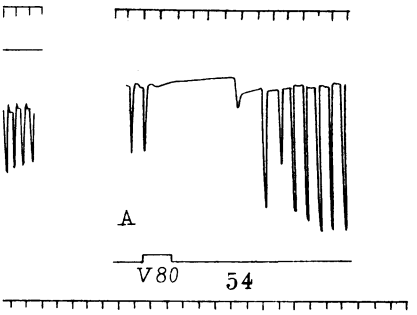

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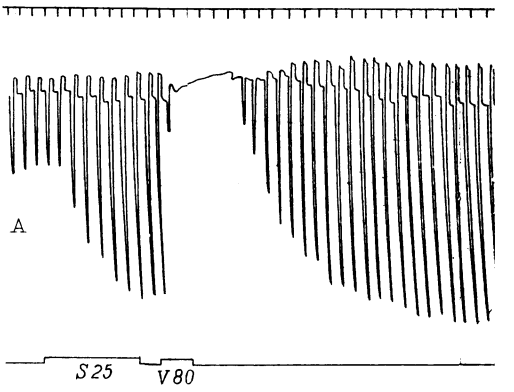

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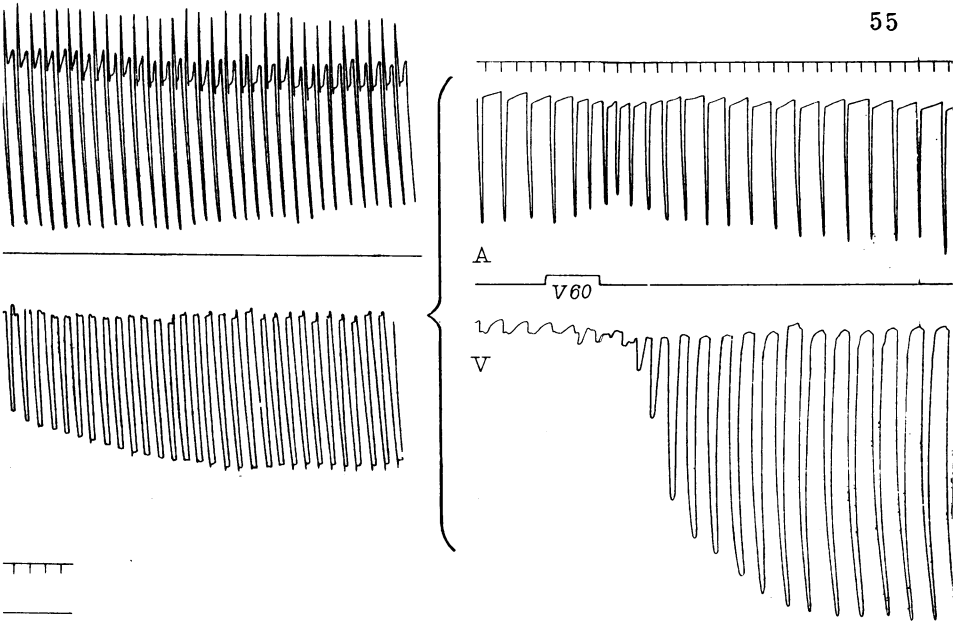

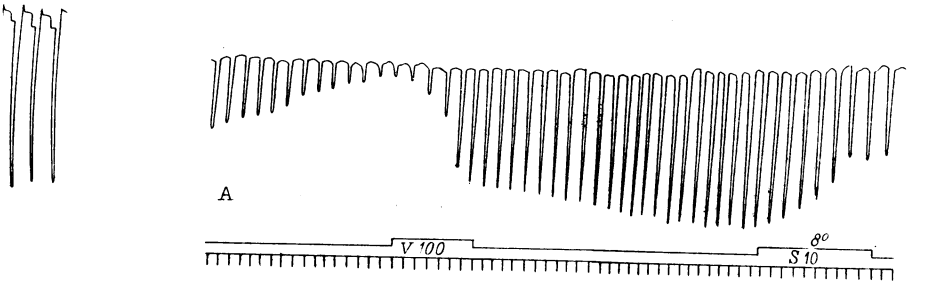

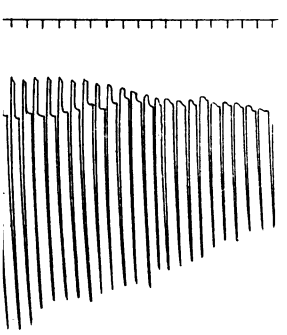

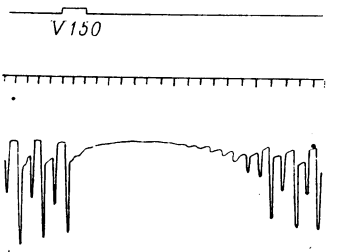

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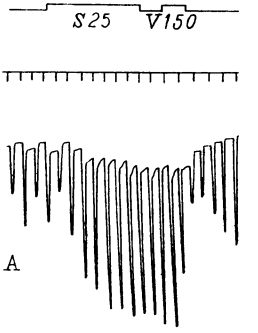

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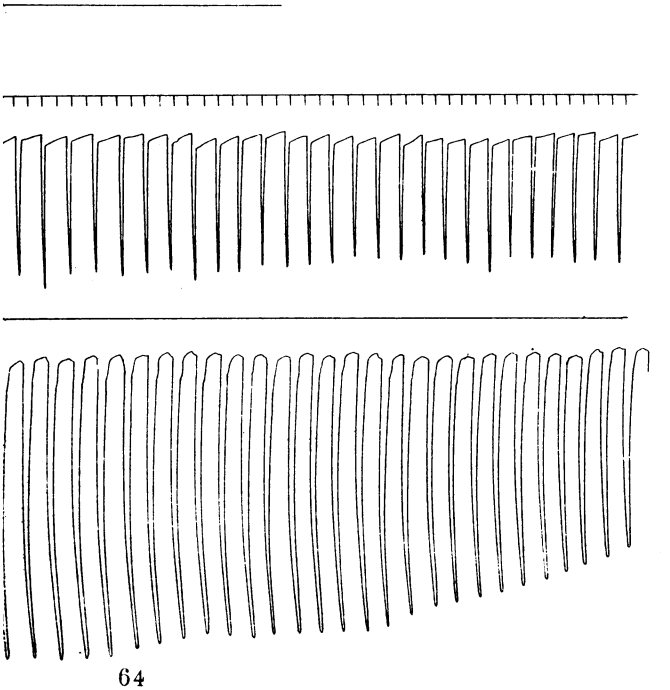

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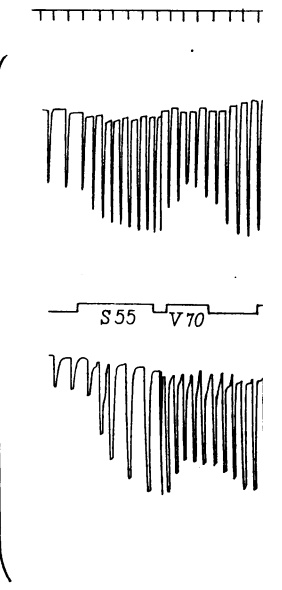

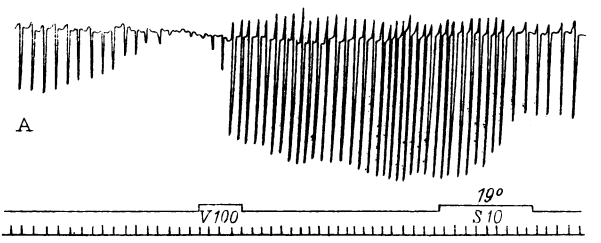

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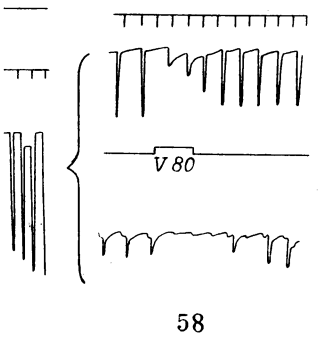

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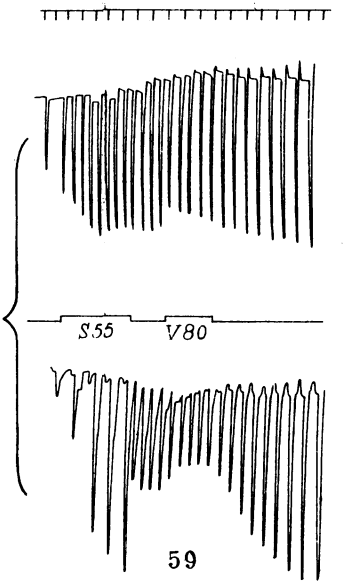

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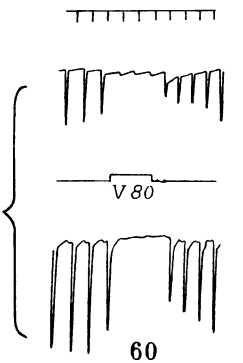

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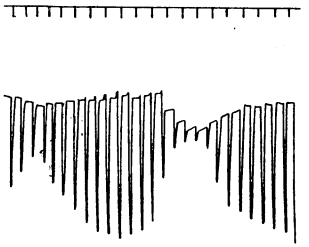

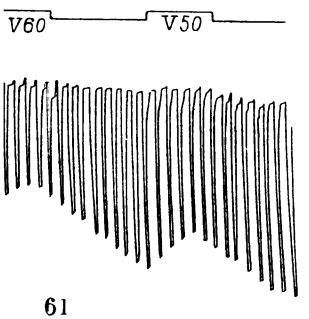

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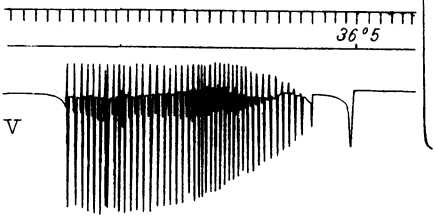

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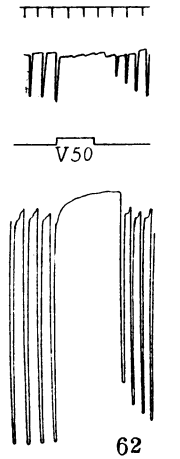

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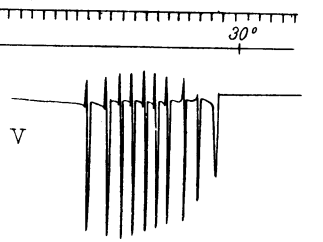

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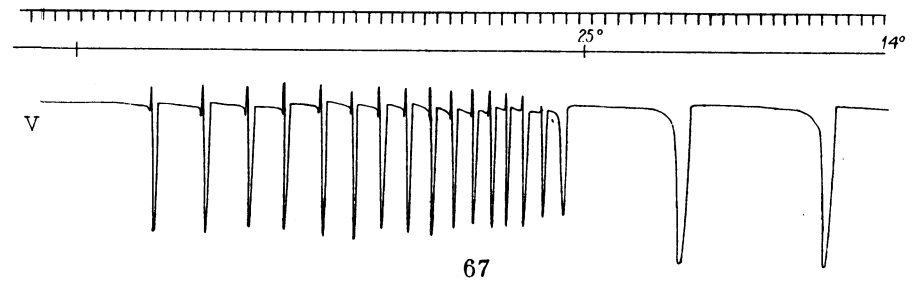

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