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The Influence of Temperature and of Endocardiac Pressure on the Heart and particularly on the action of the Vagus and Cardiac Sympathetic Nerves.

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Section I. The Influence of Temperature on the activity of the Cardiac nerves in the Frog and Toad.

Through the recent researches of a great number of observers, and particularly of Gaskell (On the Rhythm of the Heart of the Frog and the Action of the Vagus Nerve – Phil. Trans. 1882, p. 993; Journal of Physiology III, Nos 5 & 6; Brit. Med. Journ. 1882, p. 572; Proc. Camb. Phil. Soc. Vol IV, Pt. V.; Journ. of Physiology IV p. 43.; &c) 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 the chief cardiac poisons,

notably atropia and muscarin, is, according to this view, essentially an alteration of the muscular fibres, (although the nerve fibres in the cranial can also be affected, especially by atropia) an alteration which manifests itself in various ways, but most strikingly in the changed relations of the cardiac muscle to the cardiac nerves. (Gaskell, Journ. of Physiology IV loc. cit.; VIII p. 404)

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 conditions are still physiological. Further, by altering the temperature it is possible to alter the rate of physiological change in tolerably strict gradation. It is besides easy to hit this or that stage again when it is desired to repeat an observation. And, although it is not possible to confine the action to any particular tissue, 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.

For these reasons, among others, it seemed desirable to make a systematic series of observations on the influence of the vagus and sympathetic nerves 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 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.

A. The Influence ~~Effect~~ of temperature on 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 II).

Schelske (Ueber die Veränderungen der Erregbarkeit durch die Wärme, Heidelberg, 1860) observed that when the frog's heart is heated to 28°–35° C it beats more quickly, and then stands still; and now stimulation of the vagus by the interrupted current causes a tetanic condition, while single induction shocks are followed by single contractions.

Hoffmann (Beiträge zur Anatomie u. Physiologie des N. vagus bei Fischen, 1860; Diss. Giessen, 1860) tried Schelske's vagus experiment on the carp, but failed to get his result. In the frog in one or two cases stimulation of the vagus by induction shocks caused strong pulsations, first of the auricle then of the ventricle., ~~which~~ These pulsations stopped when the current was shut off.

Cyon (Sächsische Berichte, 1866 pp. 302, 303; Arbeiten aus der physiol. Anstalt zu Leipzig, 1867, p. 118) 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 during stimulation of the vagus at the normal temperature. This continued one to two 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 apparatus in the heart. But in gradual warming Ludwig and Cyon concluded that the retarding factors failed before the motor factors.

Eckhard (Experimentalphysiologie d. Nervensystems, 1865, p. 200; Beiträge z. Anat. u. Physiol. VII, 1873, pp. 3–6) 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 (Das Hemmungsnervensystem d. Herzens, Berlin 1869), 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 standstill by the vagus.

Aristow (Arch. f. (Anat. u.) Physiol., 1879, p. 198) investigated, under Ludwig'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). 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 ~~special~~ experiments on the ~~point~~ cardiac nerves, he concludes from his general results that the inhibitory apparatus is attacked, as the temperature rises, sooner than the

motor centres, "was dadurch bewiesen werden kann, dass man ohne den Herzstillstand in Folge der Einwirkung höherer Temperaturgrade abzuwarten in Moment, wo die Herz: contractionen stark vermehrt sind, das Herz elektrisch reizt. Man erhält anstatt Ver: langsamung oder Stillstand in Diastole noch stärkere Beschleunigung der Herz: schläge."

I quote this passage verbatim because, as will be seen, it does not at all support the conclusion which is built on it.

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 intra-cardiac inhibitory apparatus also suffers paresis when the temperature is low. The beats are then quickened by electrical stimulation of the ~~heart~~ Vagus.

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

Luchsinger and J. M. Ludwig (Pflüger's Archiv Bd. 25, p. 211, 1881) repeated the older experiments on the effect of temperature on the vagus, still only by the method of simple

inspection. 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. Not having used a graphic method, their ~~observations~~ could only take account of the changes in the rate of the heart, and not of ~~which is~~ the even more important, ~~the~~ changes in the force of the contractions, brought about by stimulation of the vagus.

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 (Pflüger's Archiv Bd. 27, p. 383) that he was never able to demonstrate any action of the vagus on the heart in heat standstill, other than the ordinary inhibitory action; and an experiment of Petris (Beitrag zur Lehre von den Hemmungsapparaten des Herzens, Bern 1880) in which

he shewed that the muscarin standstill was removed by heating the heart to 42°C, but returned again at 17° C.

It will be seen that hitherto there has been no systematic examination by a suitable method on the influence of temperature on the vagus function in the frog. The still scantier results for warm-blooded animals, and for one or two other cold blooded animals will be referred to later on. Practically the only workers who have done more than skim the surface of this subject are Luchsinger and Ludwig for the frog, and Baxt (Ueber die Stellung des Nervus vagus zum Nervus accelerans cordis. — Ludwig's Arbeiten 1875) for the dog. The result of Baxt was negative. He could find no influence of temperature on the activity of the vagus. But his only test for that activity was a change in the rate of the heart.

The only criticism I have to make upon the work of previous observers 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 beat was slowed or standstill produced by stimulation of the nerve.

Since Gaskell's work on the heart 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 nor perhaps the least ambiguous. The masterly analysis of Gaskell (Phil. Trans 1882, loc. cit.) has shewn us that the diminution in the force of the individual beats, with or without an alteration of rhythm is, in the frog at least, the most constant and characteristic inhibitory effect of vagus stimulation. Coats (Sächsische Berichte, 12th. Dec. 1869) and Nüel (Pflüger's Archiv Bd 9, p. 183) had previously to Gaskell, and Heidenhain almost simultaneously with him (Pflüger's Archiv Bd. 27, p. 383, 1882) pointed out this effect. Further, the different parts of the heart are not necessarily affected in the same way or to the same extent by the action of the

vagus. There are, besides, important effects on the sequence of the contractions in the different parts of the heart. It is, therefore, impossible to make a satisfactory study of the vagus action, unless we can analyse the total effect by the aid of a graphic method which records the contractions of the auricles and ventricle separately and simultaneously.

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. (References & letters in Fig 1. required here.

On the same stand were arranged two writing levers supported by elastic bands in the ordinary way, a holder carrying a 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 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 &c 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 oesophagus, 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. ~~This clamp~~ 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 bought 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 was 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 ~~in the~~ when the solution covered the heart.

Two pairs of fine electrodes 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 electromagnetic marker which recorded the beginning and end of stimulation. ~~In this way either~~ 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, but not through both at the same time. There was besides the usual time-marker, marking two-second intervals in nearly the whole of the tracings.

Figure 1 gives a diagram of the arrangements.

Instead of using the pulley, I used,

in a few Experiments, a lower lever of such a form that the point of attachment of the ventricular thread was near the bottom of the glass vessel, so as still to allow complete immersion of the heart. (Fig. 2) For this purpose it was necessary to immerse the axis of rotation of the lever, and not merely to make a rectangular bend in the length of the lever, 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. 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 worthwhile to change, and most of the tracings have been got by the pulley method.

One point I must, in justice to myself, mention here. It will be noticed that in a good many of the tracings the drum 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 ~~that is~~

artificial. The time trace will, however, prevent error. The clockwork was in exceedingly bad order, but it was the best I had at my disposal. If I could have afforded better, the tracings would have been prettier.

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 clamps, 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. In a few of the earlier experiments with the clamps only the auricular contractions were recorded.

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, 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 temperature of the room. 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, 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. ~~As to the~~

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 the close dependence of the ventricular upon the auricular rhythm in the normal heart of the frog complicates the mere effect of temperature.

The results of the 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 (Arch. f. physiol. Heilkunde VIII. p. 183, 1849); Ludwig and Hoffa (Zeitschrift f. rat. Med. Bd. 9, p. 107, 1850); 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 or in both rate and strength. It was afterwards obsened by Schiff (Moleschotts Untersuch. 1865, p. 58; 1873, p. 189), Rutherford (Journal of Anatomy and Physiology, III p. 408, 1869), Schmiedeberg, and others that this is 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 (Pflüger's Archiv, Bd. 27 loc. cit.), and Gaskell (Journ. of Physiology V, p. 46, 1884; Proc. Physiol. Soc., June 7, 1884, Journ. of Physiology V, p. xiii) that there are two sets of fibres in the vagus of the dog which produce opposite effects upon the heart, the true vagus fibres and the sympathetic fibres. When the word "vagus", without qualification, is used 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 dogs, 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 (Sächs. Berichte 1873, pp. 158–179), and especially of Baxt (loc. cit.) on the mammal that the effect of simultaneous stimulation 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 its components, but is shown 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 this 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. 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 now been carried out except the electrical stimulation of the intra-cranial vagus, for which frogs of suitable size have not yet been obtained. One or two questions of some interest remain unanswered till these Experiments are completed.

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 Sinus, 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 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.

"Medium" or "starting temperature" means the temperature of the room, which varied between 11° and 16° C on different days.

1. The Effect of temperature on the inhibitory action of the vagus. (Tracings 95 + 96 and many others 97 + 98)

(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 nerve is augmentor at the medium temperature, it is also augmentor at any other temperature at which there is any action at all.

Tracing 93 is an example of primary

augmentation caused by the vagus. Many of the tracings illustrate the statement as to primary inhibition.

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. We might have supposed a priori that if it is really the state of the muscular tissue of the heart, which determines 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, and as he still apparently thinks with regard to the atropinized heart, 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, and dilatation if it has been cooled — (Lépine, Mémoires de Société de Biologie, March 4th, 1876; Bernstein, Pflüger's Archiv Bd. 15, p. 575), — 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, according to the temperature.

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 determined before the impulse reaches the muscle, yet it is the state of the muscle itself which determines how the "general idea," so to speak, 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 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. But then it is found that when the heart is again brought to the temperature at which the action was originally inhibitory, or tested at any other higher or lower temperature,

the primary action is now augmentor, i.e. the inhibitory action has been permanently destroyed. This may apparently happen in two ways:

(1) the two sets of nerve fibres near the cut end of the vagus trunk do not seem always to die at the same rate. For it is occasionally found that whilst the primary action of the vagus has become augmentor, if a fresh piece of the nerve below the previous position of the electrode be stimulated, the primary inhibitory action may be again got. Of course it must here be kept in mind that the nearer the point of stimulation is to the heart, the greater is the chance of directly stimulating the fibres.

(2) More frequently it is impossible by stimulating any part of the nerve trunk to obtain primary inhibition. Here ~~either~~ the inhibitory fibres in the whole of the nerve trunk have deteriorated sooner than the sympathetic fibres, or the hypothetical nerve endings, or the still more hypothetical intermediate mechanisms have been differently affected; or, finally, the cardiac muscle has become permanently changed so as to be no longer able to respond to the inhibitory fibres while still responding to excitation of the augmentor fibres.

The main point is that the fundamental type

of the action of the cardiac nerves cannot be temporarily changed by change of temperature.

(2) Effect of lowering the temperature of the heart on the inhibitory action of the vagus.

As the temperature is lowered from the medium temperature, the inhibitory activity of the vagus is diminished, by whatever criterion that activity is estimated. (Tracing 44.

(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 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 size of the auricular beats, accompanied at first, perhaps, with a diminution in the size of the ventricular beats. As the temperature is lowered still further, the effect upon the size 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.

In this way it may often be shewn that the standstill caused at the ordinary temperature is really "quiescence" in Gaskell's sense, i.e. is due to diminution in the size 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 maximum, 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 seen the truth 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 ~~marked~~ indication, before or after the standstill, of a marked change of rate.

Since at low temperatures the power of the vagus

to cause complete standstill ~~or modified slowing of the beat~~ 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 size of the auricular beats, not amounting to 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 vagus 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.

(See Tracings 55 & 56, & 28.)

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.

(c) 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 of 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. (Phil. Trans 1882, loc. cit.)

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

want to point out is that even when the ventricle is at a low temperature, stimulation of the vagus may be able to restore the normal sequence of ventricular on auricular beat. This may happen without any previous diminution of the size of the ventricular beat, but it occurs after the diminished auricular beats have again begun to increase, and, therefore, properly belongs to the stage of secondary augmentation.

Apparently here the increase of conductivity of the auriculo-ventricular junction is alone concerned in bringing about the regular sequence. The ventricle apparently, though cooled, is able to beat regularly with the auricle, if only every auricular contraction is able to spread beyond the junction. In other words, the conductivity of the muscle at the auriculo-ventricular junction may be more depressed by cold than the excitability of the ventricle, ~~the contract~~. 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 for 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 greatly 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 size. 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, the ventricle being at the ordinary temperature.

(f) Stimulation of the Sinus is generally effective in causing inhibition at a lower temperature than stimulation of the vagus trunk.

According to Cyon and others stimulation of the Sinus in the cooled heart does not cause standstill, but at most deepthening of the pause. I have found by the graphic method 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. (Tracings 82, 83, 84, 85)

Stimulation of the auricle caused similar effects, although less marked for the same strength of stimulus and more strictly confined to the auricular contractions. When the stimulus for the Sinus was made just strong enough (Sin. 100 in Tracings) 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 size. This slowing was preceded by a premature beat due to direct motor stimulation. At temperatures a little higher the same stimulus caused

diminution of the size of the auricular beats.
With the heart in situ I have seen long continued standstill caused by stimulation of the vagus when the heart was surrounded by ice, and after the vagus had ceased to have any effect.

(3) The Effect of increase of temperature 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. 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 be now raised, complete standstill can be obtained with this strength of stimulus. (Tracings 95 & 96, and many others)

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 minimum Stimulus fixed in this way was at 21°C that at which the distance between the primary and secondary coils was 170 mm.; at 31°C the distance was 176 mm.; at 35°C 188 mm. In another Experiment, at 31°C, 149 mm; at 39°C, 160 mm.

(8) 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 almost invariably 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, and is only seen when the vagus at the ordinary temperature has no action of any kind, but not when the primary effect at the ordinary temperature is augmentation.

Gaskell never found the vagus in the frog without action of some kind. This of course refers to

the ordinary temperature. Whatever the reason may be, I have not been so uniformly successful in avoiding preparations in which the vagus was totally inactive. Such preparations were not common, and very possibly some of them were due to faulty manipulation; but the two or three cases in which a totally inactive vagus at the ordinary temperature, came to have a certain amount of inhibitory action at higher temperatures shew that this was not always the cause.

(c) At very high temperatures (35°C and upwards) the vagus is 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 tetanus more or less complete. Ariston (loc. cit.) 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 (d) Tracings 82-85.

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; 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 now let us consider how the muscular element affects the total result. Direct stimulation of a skeletal muscle causes contraction, a purely motor effect so far as we know, except perhaps under very special circumstances as in Weber's overloaded muscle. Direct stimulation of the cardiac muscle, as Gaskell has shewn, with a weak interrupted current, may cause not motor but inhibitory effects, resembling to all intents and purposes the effect of vagus stimulation. And the results of Foster and Dew-Smith in the

Snail's heart, along with evidence accumulating of late years from many quarters, have made it at least probable that the cardiac muscle, at any rate, can respond to stimulation either by relaxation or by contraction; and that it depends on various circumstances, among others on the strength and character of the stimulus, which of these effects shall appear. Further, the condition of the muscle can be so altered by artificial means, by atropia E.g., that the power of responding by inhibitory effects may be lost, and only the motor response remain.

But it is clear that to alter the temperature is practically to change the strength of the stimulus. This is not the whole effect of altering the temperature, but it is evidently one effect. A stimulus which would be strong in the heated heart relatively to the excitability of the muscle, might be weak in the cooled heart. For this reason alone a stimulus suited to bring out motor effects at a high temperature would be suited to bring out inhibitory effects at a low. But it may well be that, for other reasons, the muscle at the lower temperature is relatively more excitable for the inhibitory than for the motor effect when

directly stimulated, just as we shall see it to be more readily affected indirectly through the inhibitory than through the augmentor nerves.

The visible result of direct stimulation of the sinus will, therefore, depend on the relative activity of three factors, the inhibitory power of the vagus fibres, the tendency of the muscle to the inhibitory state when directly excited in relation to the strength and kind of stimulus employed, and the motor excitability of the muscle. The sympathetic fibres need not be enumerated among these factors because we know that the inhibitory fibres of the vagus always take precedence over these in point of time at the higher temperatures, as at the lower.

The tendency to inhibition may be overborne by the motor activity of the directly excited muscle, just as we know that during the vagus standstill a direct stimulus is succeeded by a beat. For although the inhibitory action of the vagus can temporarily repress the effect of the augmentor nerves, it cannot repress the contraction provoked by direct stimulation, any more than the tendency to inhibition of the cardiac muscle under the influence of a weak interrupted current can repress the tendency to contraction when the

current is stronger.

It is, therefore, possible by direct stimulation of the sinus, without changing the strength of the stimulus, to range from a typical inhibition to an apparently typical augmentation of the action of the heart merely by raising the temperature. So that here the change of temperature causes a change analogous to that caused by atropia, so far as direct stimulation of the sinus goes, but differing in this, that stimulation of the vagus trunk not only still causes primary inhibitory effects but causes them even more readily than before.

It is not, however, an invariable rule that at high temperatures stimulation of the sinus no longer causes inhibition. (T. 90) It depends to a certain extent on the strength of the stimulus. Inhibition may sometimes be got just before the heart goes into heat standstill. On the other hand a tetanic 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 only of the auricle, or in slowing of the rhythm without or without alteration in the size 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 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. When stimulation of the nerve has failed in the cooled heart, direct stimulation of the fibres 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 cooled frog's heart is like the normal tortoise heart, the auricles alone being directly influenced by stimulation of the nerve.

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 still active, still active when the heat standstill is just passing away. In a later section we shall try to follow it into the heat standstill itself.

2. The effect of temperature on the secondary augmentation caused by stimulation of the vagus.

Since the secondary augmentor action of the vagus is due, chiefly at all events, to the sympathetic fibres, this section might more logically be placed after 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 Section I.B, 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 a further proof that the two effects are due essentially to the same cause, and that, as in the mammal, the augmentor effect follows its own law independently of simultaneous stimulation of the inhibitory fibres, although not till the inhibitory action has completed its curve.

The secondary augmentation is generally much greater at the higher than at the lower

temperatures, especially as regards the ratio of the force of the beat after and before stimulation; generally, but not so constantly, greater also as regards the ratio of frequency of the beat after and before stimulation.

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 very high temperatures, with a rapidly beating heart, the augmentation is prone to shew itself by increase in the force of the beat without marked change of rate.

There is one of the interesting points 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 still seen at the low temperature. A secondary acceleration can apparently be got after stimulation of the vagus with a moderately strong stimulus at 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

obscure

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 perhaps that the true vagus fibres themselves may 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 (Pflüger's Arch. Bd. 27, loc. cit.), indeed, generally got only inhibitory effects by chemical stimulation of the medulla oblongata, and the beats did not usually regain their original strength. And Gaskell (Journal of Physiology V loc. cit.) stated that the true vagus fibres are altogether inhibitory, while the sympathetic fibres in the vagus trunk are altogether augmentor. "Stimulation of the intra-cranial vagus was shewn to cause purely inhibitory effects, both the rate of rhythm and the strength of the contractions being markedly diminished not only during the stimulation but permanently." Again, in

a description of an experiment of Gaskell's it is said, "When the beats did appear they were neither stronger nor quicker than before, but, on the contrary, after each successive stimulation a permanent weakening was observed, so that before very long the heart was reduced to a condition very near that of death." Foster (Textbook of Physiology Part I, 1888), however, states that "the inhibition" (caused by stimulation of the intra-cranial vagus) "when it ceases is often at all events followed by a period of reaction, during which the heart for a while beats more vigorously and rapidly than before. Indeed the total effect of stimulating the vagus fibres is not to exhaust the heart but rather to strengthen it, and by repeated inhibitions carefully administered a feebly beating heart may be nursed into vigorous activity."

I am not quite able to reconcile the statements of Gaskell and Foster, but I have only been able to see Gaskell's preliminary papers. I presume, therefore, that Foster's description is founded on later work, and that we may consider a certain amount of augmentation as a normal, or at least a common secondary result of stimulation of the pure vagus fibres, but of subordinate importance to the augmentation

which is caused by the sympathetic fibres under conditions favouring their activity.

Bayt, too, 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.

In this connection it is of interest that the secondary acceleration following stimulation of the vagus should persist at lower temperatures than ~~that~~ the acceleration caused by the sympathetic.

What degree of constancy this result may have the experiments on the effect of temperature on the action of the intra-cranial vagus will give us the means of deciding, when they are completed.

3. The effect of stimulation of the Vagus on the heart in heat standstill. (Tracing 86, 88, 39)

I find that when the heart has entered into heat standstill, stimulation of the vagus can still in some cases, (particularly when the standstill has been obtained at a comparatively low temperature or has only lasted a short time) cause the heart to execute a series of beats. This confirms a statement made by Schelske (Op. cit.) long ago, but which has been contradicted by many observers (Eckhard, Meyer, Ludwig and

and Luchsinger and Heidenhain) 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, a "Wogen oder Wühlen", was caused, which 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 obtained, 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 begin, if the stimulation is short, till after the current is shut off. 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 overheated 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 observed it in the course of experiments not directed specially to this point, and have made only a comparatively small number of special experiments, the proportion of cases in which a positive result can be obtained may be larger than I suppose. One condition which undoubtedly favours a positive result is that the heat standstill should be obtained at as low a temperature as possible, and we shall see in Lection II 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 the standstill takes place must of course be maintained during the experiment. When this is done the heart seldom or never begins beating of itself. When it is roused to activity by the stimulation of its nerves, it does not go on beating indefinitely in a solution of constant temperature. On the contrary, after a longer or shorter group of beats it relapses into standstill, from which it may be again roused by a second stimulation of the nerves, or even by a third or fourth stimulation. Ultimately, however, if the temperature at which heat standstill was originally got is still 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 if 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 again to beat 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 very striking at high temperatures just before and just after heat standstill. If, then, the augmentor function of the vagus, i.e. practically of the sympathetic fibres in it, is not paralysed the very moment the heart stops in heat standstill, 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. (Löwitt, Pflüger's Archiv Bd. 27, p. 333) Gaskell has shewn that stimulation of the sympathetic has the same effect in the toad's heart. (Journal of Physiology VIII, 1887, p. 404) If the dose be increased, this effect is no longer obtained.

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 the ventricle to recommence beating. If the clamp be made tighter, this action will not occur. In another form of standstill to be described later on the vagus or sympathetic can also cause the heart to begin beating again. So that the mere fact that the heart is in standstill does not make it impossible or even improbable that its nerves may be still active. We have therefore to consider whether there is any peculiarity in the last standstill which makes it impossible that the activity of the nerves should remain.

A very high temperature of course can not only temporarily but permanently paralyse both the heart and its nerves. With a temperature so high we have nothing to do. The heart 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. There is no known reason why a temperature which is just sufficient to depress the rhythmical power of the ~~heart~~ sinus to the point at which it must stop should necessarily at the same moment paralyse the activity of the cardiac nerves.

Whenever the conditions of the cardiac tissue on which the rhythmical beat depends are restored the heart will beat. These conditions may be restored in various ways. Lowering the temperature is one way. 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. The properties of the cardiac muscle on which the rhythmical beat depends are altered in a great variety of circumstances by stimulation of the mixed vagus trunk or of the sympathetic. In the midst of external conditions which previously hindered

the heart or a part of it from beating, and without any change in these conditions, the cardiac nerves by producing internal changes can cause the heart to beat. There is no reason whatever why this particular condition of a high temperature should be an exception. And as my tracings show, it is not an exception. The vagus occasionally, the sympathetic I think more frequently, can rouse the heart from heat standstill; and when this happens the beats are sometimes of great size and rapidity.

It is not unfrequently seen that when the ventricle alone is in heat standstill while the auricles continue beating, stimulation of the vagus which produces its ordinary effects, primary inhibition secondary augmentation, on the auricle, may rouse the ventricle for a time to contraction, which begins during the time when the auricular beats are augmented. In Gaskell's phraseology the katabolism of the ventricle or the conductivity of the tissue at the auriculo-ventricular junction, which has been reduced by the high temperature is restored at that temperature by the action of the augmentor nerves.

It may be asked why the vagus does not in every case rouse the heart from heat standstill. The question is somewhat* the same as to ask why the cardiac

nerves do not always rouse the heart which has been brought to standstill by muscarin applied without any regard to the dose, or the ventricle which has been brought to standstill without any care as to the amount of pressure used, except that the ventricle must still be able to beat, however feebly, when the clamp is removed. In these circumstances the cardiac nerves could occasionally be found active, but generally not the reverse. Heating the heart to the temperature of standstill is a severe strain on the heart and its nerves. If it is done without any careful trial of the minimum temperature which will suffice, the tissue will generally be so much depressed that it cannot be improved by nervous action or cannot be improved sufficiently to be able to beat rhythmically. Again, it is possible that at a certain temperature the nerve fibres in the heart or their ends may suffer temporary paralysis, but there is no reason which can be given why this temperature should be precisely that at which the heart ceases to beat. On the old hypothesis of motor ganglia and ganglionic mechanisms intermediate between the muscular tissue and the nerves, a simultaneous paralysis of rhythmical contraction and of the activity of the cardiac nerves would be very likely.

On the more modern view which places the cause of the rhythm in the muscle itself there is no such possibility.

Section I. B.

The influence of the temperature of the heart on the activity of the cardiac sympathetic nerve. (Tracings 48, 49, 50; 58, 59; 67–69; 70–75.

The sympathetic was prepared in the usual way by isolating it, tying 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.

(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, it may be said that in general 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 usually 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 ~~rarely does~~ 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 ~~only~~ 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 its 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 of the beats is alone present.

Tracing 49 at 8° and Tracing 50 at 9° are exceptions. Here at the lower temperature the increase in size of the beat is relatively greater than at the medium temperature. But it is instructive to note that precisely in these two cases the size of the beats before stimulation, especially in Tracing 50, is smaller at the lower than at the medium temperature instead of being as large or larger, as is normally the case. In Tracing 50 the heart is plainly becoming exhausted; and the sympathetic action, as we shall see, limits itself to the state of the heart, causing chiefly an increase in the size of the beats when these are small as in the heart at very high temperatures, and

chiefly an increase in the rate of the beats when these are large, as in the cooled heart they normally are.

(C) When the activity of the sympathetic is estimated by the alteration which it produces in the frequency of the beats — say by the ratio of the frequency before, and 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. Ultimately, with still falling temperature, the curve again bends towards the abscissa axis, until it cuts it at the temperature at which 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 size 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. It is astonishing, however, at what low temperatures the sympathetic can still shew a distinct influence. Baxt (Op. cit.) found that the power of the accelerans in the dog to quicken the beat of the heart even at 27° – 30° C was greatly lessened, suggesting that a further ~~extraordinary~~ 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 in 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.

In the dog I have found considerable acceleration caused by the sympathetic at 4°, and a distinct effect at 3° and even at 1°.5. Of course it differs greatly in different hearts. Naturally we cannot expect anything of this sort in the warm-

blooded heart. 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 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 mechanism. But while Bayt 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. (Tracings 42 & 43) 55, 56 & 57. 76–81, 87, 88.

But it has sometimes not been possible to say that the sympathetic in the frog failed before the vagus. (Tracing 62) Since, however, the vagus has not been found to fail before the sympathetic, unless when 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 in this paragraph on the differential action of lowered temperature on the two nerves is justified.

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 vagus trunk instead of the intracranial vagus roots 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 trunk 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 cooling the nerve alone the activity of the sympathetic fibres might be altered relatively to that of the vagus fibres, and that by heating or cooling the effect of either set might be made to preponderate. Bayt took no account of any possible effect of temperature on the accelerans and vagus fibres themselves. They were necessarily, with this 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.

(a) 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 that 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, and this is true even where at the medium temperature the chief or sole effect is increase of

the rate. The limit 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 20–25° 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 20°–25° C, and even up to the temperature at which the heart goes into heat 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 Bayliss curves shew such a limit for the accelerans, although his highest temperatures were only two or three degrees above the normal, and although we should perhaps expect the warm-blooded heart to be more plastic in this respect than that of the frog. The highest rate I have

counted in any of my Experiments was 80 beats per minute after stimulation of the sympathetic 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.

(Tracings 48, 49 & 50; 90–95)

Tracings 91 and 92.

(c) The curve of activity of the sympathetic, when the activity is estimated only from the maximum acceleration, rises at first rapidly as the temperature is increased from the medium temperature, then more slowly, reaches a maximum, and may even decline with further increase of temperature. When the activity is estimated from the maximum increase in the amplitude of the beat, the curve rises at first slowly, then more rapidly, and it is doubtful whether it reaches a maximum.

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

(d) It has already been incidentally mentioned in describing the occasional effect of stimulation of 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

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 if 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 sympathetic. But I have seen

it in fresh and vigorous hearts, in which standstill did not take place till 36°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 even for the same heart, but can ~~always~~ 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.

(c) Sometimes when the heart is at a high temperature and the ventricle is beating feebly, stimulation of the sympathetic, while greatly

increasing the amplitude & to some extent the rate of the auricular beats, may conceal the same time diminution in the size of the ventricular beats.

I suppose that 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 & maintain the force of its contractions at the same time, just as the normal heart gradually beats less strongly when rise of temperature compels it to beat more quickly.