# XXI. *The Direct Influence of Gradual Variations of Temperature upon the Rate of Beat of the Dog's Heart.*

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[Plates 48, 49.]

## *Introduction.*

In the year 1881 I briefly described (1) a method of experimenting by which the heart and lungs of a Dog or Cat could be completely isolated physiologically from the remainder of the body of the animal, and kept alive some hours for study in an apparently normal condition, the heart beating regularly and maintaining a good arterial pressure. Since then I have been at work investigating the influence of various conditions upon the pulse-rate of Dogs' hearts so isolated; while under my supervision several of my pupils have been engaged in studying the work done in a unit of time by such hearts under different external conditions.

As regards the effects of variations of arterial pressure upon the pulse-rate of the isolated Dog's heart, my results have already been published (2); and detailed observations as to the influence of variations in venous pressure will shortly be printed. But in so far as the influence of temperature variations upon the cardiac rhythm is concerned, only a brief preliminary announcement (3) has been made. In the present paper I propose to give a full account of my experiments upon this subject, which is one that, apart from and in addition to its purely physiological interest, has considerable practical importance in connexion with inquiries as to the immediate cause of the quick pulse so constantly found in warm-blooded animals suffering from fever.

Almost all that we have hitherto known concerning the direct influence of temperature changes upon the cardiac rhythm is derived from experiments made upon cold-blooded animals, especially Frogs. As regards these animals all observers are agreed that as the temperature of the heart is gradually raised from near zero to about 40° C., its beat is quickened. It is clear, however, that we can only argue with



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much reserve from the heart of the Frog to that of the Mammal when the direct effect of temperature variations is concerned. The Frog can hardly be said to have any normal temperature, and has but slightly developed temperature-regulating physiological mechanisms; its healthy temperature varies from a very low point in midwinter to 32° C. or above on a Baltimore summer day. The Mammal, on the contrary, is constructed to maintain a definite normal temperature, which does not vary beyond very narrow limits; a departure of even a couple of degrees from this normal is always the sign or the cause of pathological processes. We find the Mammalia, accordingly, provided with highly complex temperature-regulating mechanisms, in possessing which they differ very sharply from the Amphibia. While it might therefore be expected *à priori* that the Frog's heart is so constructed as to work better at those warm temperatures at which the general nervo-muscular apparatus of the animal is most active, and the calls upon the organs of nutrition greatest, the discovery that such is actually the case and that the warmed hearts of Frogs beat quicker than cold, does not justify us in forthwith concluding that the Mammalian heart, placed in and adapted to the needs of an animal with only one healthy temperature, would behave in like manner. This doubt concerning the validity when extended to warm-blooded animals of arguments based on experiments made with the hearts of Frogs is increased when we call to mind the fact that an elevation, within physiological limits, of the temperature of the medium to which a cold-blooded animal is exposed increases its tissue metamorphoses, as evidenced by a greater excretion of carbon oxide, while exactly the reverse is the case in respect to the Mammal. Recalling the wonderful physiological adaptation of the organs of animals to the conditions under which they live, we might almost expect that increased temperature (not reaching pathological limits) of the blood carried to it would lead to a slowing of the beat of the Mammalian heart in correlation with the diminished oxidations then occurring in the body generally, and its consequently diminished nutritional demands.

There are still other reasons why the direct application to the Mammalian heart of the results of experiments upon Frogs is unsatisfactory. It has been shown (4) that the muscular tissue of the Amphibian heart differs considerably in histological characters from that of the Mammalian: with this difference in minute structure quite important functional differences may be associated. Moreover, the Mammalian heart is known to be far more under the control of extrinsic nerve centres than is that of the Frog. Though the heart of the latter animal receives cardio-inhibitory fibres through the vagus, their centre of origin is not usually in action, as shown by the fact that cutting the vagi does not lead to pulse-quickening; exactly the reverse and to a very marked extent is the case in the Dog (see especially V. Bezold) (5), and also in Man as shown by the phenomena observed in cases of atropin poisoning. In addition, the Mammalian heart receives from the cerebro-spinal centre accelerator nerve fibres, and the existence of any such pulse-quickening fibres in connexion with the Frog's

heart is at present doubtful. Consequently, bearing in mind that greater division of physiological duties which characterises the higher animal, we may justifiably doubt whether the simple relation of higher temperature (within limits) and quicker pulse found in the Frog and dependent only on the properties of the heart itself, may not be entirely absent in the isolated heart of the higher animal, which we know to have its rate of beat under normal circumstances controlled by a highly specialised set of extrinsic nerve centres.

The above considerations, taken in connexion with the fact that "fever" can hardly be said to exist in an animal with so variable a normal temperature as the Frog exhibits, made it very desirable to study directly the influence of temperature variations upon the pulse-rate of the Mammalian heart.

The experiments hitherto made upon Mammalia do not really solve the question whether the quicker pulse of the warmer animal is due to a direct or an indirect action (*i.e.*, one exerted by extrinsic nerve centres) upon the heart. BERNARD, WALTHER, HORWATH, and no doubt others have found a slow pulse in artificially cooled animals; the same phenomenon has been observed in hybernating Mammals during their winter sleep. As regards the effect of heightened temperature upon the pulse-rate, BRUNTON (6) has showed that when Rabbits are heated the heart beats quicker. But when a whole animal is warmed or cooled we are not justified in concluding that because the heart beats quicker or slower therefore the temperature change has directly influenced the rhythm of that organ. Not only may temperature changes indirectly affect the heart through its extrinsic nerves, but they may also so alter tissue metamorphosis in various organs as to essentially modify the composition of the blood flowing through the heart; and we know that very slight alterations in the chemical composition of that liquid may profoundly influence the heart. Before we are entitled to state positively that changes of temperature directly influence the rhythm of the heart of the warm-blooded animal, we must have data based on experiments made with the hearts of such animals cut off from all possible control through extrinsic nerve centres, and supplied with nutriment of constant composition. The only experiments known to me which approach the fulfilment of such conditions are those made by several observers (SCHENK (7), WERNICKE (8), CLELAND (9)) on the influence of temperature changes upon the rate of pulsation of the hearts of embryo Chicks during the first three days of incubation. Such experiments afford, however, even a less safe ground for conclusions as to the adult Mammalian heart than do the experiments upon Frogs' hearts above referred to. The heart of three-day Chick embryos is but a protoplasmic mass, little differentiated, presenting neither definite muscular or nervous tissue, and without any developed controlling extrinsic nerves. From the fact that such a mass of hardly-differentiated embryonic cells contracts more frequently when warm than when cold, we cannot safely conclude that the adult heart, with its fully developed muscular and nervous tissues, and placed under the

governance of nerve centres located outside it in the body, would, if isolated, respond in like manner to similar temperature changes.

While experiment upon the isolated hearts of Frogs, Fishes, and Bird embryos, combined with the changes in the pulse-rate observed when Mammals are heated or cooled, have led to a general consensus of opinion among physiologists that gradual and moderate increases of temperature quicken the Mammalian pulse by direct action upon the cardiac tissues, and moderate diminutions of temperature similarly slow the pulse, the proof that the action of such temperature changes was exerted directly upon the heart itself did not seem satisfactory, for the reasons above stated. Hence the investigation described in the following pages was undertaken.

### *The method.*

The fundamental idea upon which all my work on the isolated Mammalian heart has been based is to occlude all vessels of the systemic circulation except those supplying the heart itself, while leaving the pulmonary circulation intact. The heart and lungs being supplied with blood alone retain their vitality; all extraneous nerve centres getting no blood soon die with the remainder of the animal. Moreover, the blood supplied to the heart passes through no organ of the body but the lungs, and in these it undergoes simple and well understood changes; no sudden chemical alteration in it due to the products of the abnormal activity or commencing death of muscle, gland, or brain is possible. As the blood flows around through heart and lungs time and again, it no doubt experiences a gradual deterioration due to loss of foods and gain of wastes from those organs; but this change is gradual and uniform, and if a sufficient quantity of blood be used, the accumulation of wastes (carbon dioxide being carried off by the lungs as in normal conditions) and the deterioration in nutritive quality do not for some hours alter its constitution to an extent which in any way interferes with the forcible, regular, and normal beat of the heart. The means adopted for renewing the blood circulating through heart and lungs, as also for maintaining constant arterial and venous pressures and for regulating the temperature of the blood not having as yet been published in detail, and the method also having been much modified since the preliminary account was published, it is necessary to describe with some minuteness the operation of isolating the heart and the apparatus employed for subsequently keeping it alive under approximately normal and readily controllable conditions. I do this the more readily as the present form of the apparatus is the result of more than a year's experience and the accumulated improvements suggested by several workers (among whom special acknowledgment is due to my friends and pupils W. H. Howell and F. Donaldson), so that it now leaves little to be desired in the convenience with which it admits of keeping a heart under conditions in which venous pressure, arterial pressure, and temperature are readily ascertained and controlled. So far as the present series of experiments (those relating

to the effect of temperature changes upon the pulse-rate of the isolated heart) is concerned, Dogs only have been used, and defibrinated strained Calf's blood has been the medium employed to nourish the isolated heart.

The animal having been placed under the influence of chloroform, ether, morphia, or curaré, the further course of an experiment was as follows :—

After tracheotomy the pneumogastro-sympathetic trunks were divided on each side of the neck with the object of saving the heart from the results of the powerful excitation of the cardio-inhibitory centre in the medulla oblongata, which usually occurs later, when the blood-supply of the brain is cut off. A cannula was also placed in the cardiac end of each common carotid artery, the arteries being clamped on the cardiac sides of the cannulæ. Next, the first pair of costal cartilages and the bit of sternum lying between them were cut away, and artificial respiration commenced; then the internal mammary arteries were tied as they pass forwards from the subclavians to the breast bone. The whole front and sides of the thorax were next cut away, and the right subclavian artery dissected out and tied just above the point at which it separates from theright carotid. The superior vena cava was then prepared, and ligatures placed loosely around it ready for subsequently occluding the vessel and tying in a cannula.

Proceeding now to the left side of the chest, the subclavian artery is ligated, and, the left lung being gently held aside, the aorta is isolated and cleared near the diaphragm. A ligature is placed loosely around the vessel, just beyond its arch, and a strong clamp tightened on it to the distal side of this ligature. An aperture having been made in the thoracic aorta, near its posterior end, a cannula of the form represented in Plate 48, fig. 4, and filled with defibrinated strained Calf's blood, is inserted into the vessel, and, the aortic clamp being removed, is pushed up to the left end of the aortic arch, where the ligature above-mentioned is tied tightly around it. These aortic cannulas are made of thin brass tubing, and are kept at hand of several sizes, so that one can always be found which fits tightly into the aorta of the animal, and is closely clasped by the elastic walls of that vessel. The cannula has on its distal end the bit of rubber tubing, *v*, on which is the clamp, *w*, which is screwed tight when the tube is filled with defibrinated blood before its insertion into the artery.

So far all the systemic arteries but the coronaries of the heart are occluded. Each common carotid has a cannula in it; both subclavians are ligated below the point at which they give off any branch, and the aortic cannula is tied in at a level of the vessel, just beyond its arch, at which it has given off no bronchial or intercostal branches.* As one consequence, violent dyspnœic symptoms usually occur in spite of the steadily maintained artificial respiration, being of course due to the want of a

* Sometimes in young Dogs a minute branch is given off from the innominate artery to the thymus. This was sometimes tied, but usually neglected, as it is difficult to get at, and the amount of blood drained off by it is trivial, and when both venæ cavæ are tied cannot get back to the heart.

supply of fresh blood to the respiratory nerve centre. To complete the preliminary operation the inferior vena cava is tied above the diaphragm, and the right lung being pushed towards the median line, the vena azygos is ligated near its junction with the superior cava; the latter vessel is then tied below the point where the innominate and internal mammary veins join it by tightening one of the ligatures already described as placed loosely around it.

The next step is to wash out the blood contained in the heart and lungs, and replace it by defibrinated blood. For this purpose the cannula *z* (Plate 48, fig. 3), connected with the MARIOTTE flask U, filled with defibrinated Calf's blood at the temperature 38° C., is inserted into the cardiac end of the superior cava, and tied there. The clamp on the tubing connecting the flask with the cannula is opened, and blood from the flask allowed to enter the right auricle. The clamps on each carotid, and on the aortic cannula, are then opened in turn for a short time so as to wash out all blood already in heart and lungs, and replace it with the defibrinated blood.

This having been done, and the clamps again closed, the animal, still tied on the dog-holder, is transferred to the warm moist chamber represented in outline in Plate 48, fig. 1; in this chamber it is thenceforth fed steadily with defibrinated blood of known temperature, supplied at a known and controllable pressure, and from the chamber it pumps out blood against a known and readily varied aortic resistance. The structure, contents, and preliminary preparation of the warm chamber have next to be described. It is 125 centims. long, 65 centims. wide, and 65 centims. high. It has no bottom, but when in use sits in a shallow iron trough (not represented in the figure) filled with water, and raised on supports which admit of BUNSEN burners being placed under it, by whose means the air in the chest is kept moist and warm. The roof, sides, and the end, A, are glazed; the end, B, is of wood, and perforated by apertures through which several tubes pass. The object of glazing most of the walls of the chamber is to enable a ready view to be had of what is going on inside it; this is apt to be interfered with by condensation of water on the glass during the course of experiment; this drawback may, however, be nearly entirely obviated by smearing the inside of the glass with glycerine.

In the chest are two MARIOTTE'S flasks, C and D, each of a capacity of about four litres. The flasks are entirely similar in all respects, but for the sake of clearness in the diagram the tubes only have been represented in connexion with C, while the water-jacket which surrounds each flask is only indicated with D. This jacket, E, is merely a cylindrical tinned-iron bucket, somewhat wider than the flask. It is filled with water, and has, in connexion with it, a syphon by which it can be readily emptied, and a supply tube through which it can be filled. The syphon and supply tube have been omitted in the figure. Their ends pass outside the warm chamber, so that the water in the jackets can be changed without opening the box. As the flask empties of blood when in use, it tends to float up in the water of the

vessel E. This is prevented by the collar *a*, which fits round the neck of the flask, and is attached by the bars *b*, *b*, to the upper edge of E.

In connexion with C are shown the tubes which pass through the air-tight cork of each MARIOTTE'S flask. These are four in number. Two (*c*, *d*) are used when the flask is to be filled with blood; the other two (*e*, *f*) are employed when the flask is at work supplying the heart. When C is to be filled, the tubes *e* and *f* are closed by clamps or stopcocks put on the pieces of rubber tubing attached to their upper ends. The clamp *g* on the rubber tube attached to the upper end of *d* (which tubing, as shown in the figure, passes through an aperture, G, in the roof of the chamber) is opened, as is also the stopcock *h*, which is placed on the course of the tube leading from *c* to the funnel F. Meanwhile the corresponding stopcock *h'*, on the tube leading to the flask D, is closed. Defibrinated blood poured into F then enters the flask C through *c*, and the air which it displaces is driven out through *d*. C having been four-fifths filled, the stopcock *h* and the clamp *g* are closed, and the clamp *i* opened.

From the tube *f*, which dips deepest into the flask C, leads the rubber tube *k*; this passes through the end B of the warm chamber, and the next part of its course is shown in Plate 48, fig. 2, where *k* is seen to lead to the stopcock *l*, which is connected with one limb of the Y-piece *m*, another limb of which is attached to the corresponding tube *k'*, leading from the flask D. The remaining limb of the Y-piece leads to the rubber tube *n*, which is seen again in fig. 1, after entering the warm chamber. There *n* is seen to be continuous with the T-piece *o*, in the vertical limb of which is the thermometer *p*. Beyond the T-piece is the stopcock *q*, which ends in the rubber tubing *y*.

The flask C having been filled, we next go to the flask D, in connexion with which much of the details of the tubing have been omitted; but in all respects the flasks C and D and their connexions are similar. In the lettering of the figures whenever a connexion of C is indicated by a letter, the corresponding connexion of D is indicated by the same letter with a dash: *h* of C answers to *h'* of D; *d* of C to *d'* of D; *i* of C to *i'* of D, and so forth; so that a detailed description of the tubes connected with D is unnecessary.

To fill D the stopcock *h* is closed, and *h'* opened, as is also *g'*, while *i'* and *k'* are closed. Defibrinated blood poured into F then enters the flask D, and is added until that flask is about one-fourth filled. Then the stopcock *h'* is closed, the clamp *g'* screwed up, and the clamp *i'* opened. The further course of *k'* is seen in Plate 48, fig. 2, where it is shown as joining *k* at *m*; it therefore ends also in the stopcock and rubber tubing *q* and *y*.

So far we have got the flask C four-fifths full of defibrinated blood and the flask D one-fourth full. It remains to fill the tube *f* and its fellow, and the system of tubes leading from both of them to the stopcock *q*, which during an experiment is connected with the superior vena cava, and has to supply the heart steadily with defibrinated blood. The tube *f* and its fellow have to act as syphons, and therefore the lower ends

of $f$ and $f'$ must be above the level of the exit of $q$. To secure this, both flasks, C and D, are suspended by cords $r$, $r'$, which support each flask and its water-jacket. These cords pass over pulleys borne on a framework, H, I, J, K, attached to the roof of the warm chamber, and each passes at its distal end round a fastener, $s$; by means of these cords the MARIOTTE'S flasks can be raised and maintained at any desired level within the warm chamber. In the series of experiments here described both flasks were raised to the same height, although in fig. 1, C has been drawn lower than D for the sake of showing their connexions more clearly in the drawing.

To fill the syphon connected with C, the stopcock $h$ and the clamp $g$ are closed; the clamp $i$ is left open, as is the stopcock $l$ (Plate 48, fig. 2), while $l'$ is kept shut. Then $q$ (fig. 1) is opened, and suction applied to the end of $y$; blood then flows out of C through $f$, while air enters through $e$; and this blood is supplied to $y$ under constant pressure.

The cock $q$ is now closed, as also $h'$ and the clamp $g'$. The clamp $i'$ is left open, the stopcock $l$ (Plate 48, fig. 2) closed, and $l'$ opened. When $q$ is now once more opened and suction applied to $y$, blood from D passes out by the tube $k'$ and reaches $q$ through the tube $n$ (fig. 1). D now, like C, behaves as a MARIOTTE'S flask, and supplies blood to $y$ under a constant pressure. If both flasks be raised to the same height above the level of the superior vena cava, with which $y$ (as will be described immediately) is connected, we can supply a heart with blood from either flask at will. When the stopcock $l$ (Plate 48, fig. 2) is open and $l'$ closed, the heart is fed from the flask C; when $l$ is closed and $l'$ opened, the blood is derived from D.

The flasks and the syphon tubes are filled as above described before the operation on the Dog is commenced, and the stopcocks so arranged ($l$ open and $l'$ closed) that on opening $q$ blood will be drawn from C.

The water-jackets around each flask being filled, the gas burners under the trough which supports the warm chamber are lighted. From time to time $q$ is opened, and blood from C let flow through it. When the temperature of this blood, as indicated by the thermometer $p$, is about 37° C., the gas is turned low and the operation on the Dog, described above, is proceeded with. While the flasks are warming $g$ and $g'$ are left open to allow some of the air in each flask to escape as it becomes expanded by the heat. Just before transferring the animal to the warm chest, $g$ is screwed up, but $g'$ left open; $h'$ is also opened, and care is taken that $h$ is shut. Under these circumstances C supplies blood to $y$ when $q$ is opened, while D (only one-fourth filled) is cut off from all connexion with $q$ but is ready to receive any blood poured into it from the funnel F, or flowing to it through the tube L.

When the animal is transferred to the chamber the portable MARIOTTE'S flask (Plate 48, fig. 3) is carried along with it by an assistant, and still supplies the heart with blood. A bit of brass tubing, $u$ (fig. 1), inserted into the lower end of the tube, $t$, is now connected with the distal end of the piece of rubber tubing, $v$ (Plate 48, figs. 1 and 3), attached to the distal end of the aortic cannula. The clamp $w$ is then opened

wide and the left ventricle pumps into and fills the tube $t$, from whose distal end the blood enters the funnel $x$; from this funnel it passes along L to the stopcock $h'$ and thence to the flask D. The tube $t$ has a bore at least as wide as that of the thoracic aorta of the animal, so that the heart pumps freely into it.

Next, the superior vena cava cannula $z$ (Plate 48, fig. 3) is slipped out of the rubber tube connecting it with the portable MARIOTTE'S flask U, and quickly inserted into $y$ (fig. 1), care being taken that $y$ is first filled with blood. The stopcock $q$ being then opened, the heart is steadily supplied with blood from C. This blood, after traversing the lungs, is driven out of the left ventricle through $t$, and flows back to D, where it collects; accordingly as C empties D fills. When C is nearly exhausted the stopcock $h'$ is closed, and also the clamp $g'$; $i'$ is opened, as is also the stopcock $l'$ (Plate 48, fig. 2). Simultaneously $h$ and $g$ are opened, and $i$ and $l$ closed. D now becomes the feeding and C the recipient flask. When D in turn is empty and C full the reverse steps to those above described make C the supplying and D the receiving flask; and so on as often as necessary in the course of an experiment. As all the clamps and stopcocks lie outside the warm chamber the connexion of the flasks with the heart can be changed when desired without opening the chamber. During an experiment the tube L and the part of $t$ outside the warm chamber are kept wrapped in raw cotton, as also the funnel $x$; and the openings G and G′ are loosely covered with damp cloths.

To return to the steps immediately following the placing of the animal in the warm chest: $y$ having been connected with the superior vena cava, the bellows hitherto used are disconnected from the tracheal cannula, and over this is slipped the delivery tube of one of the convenient respiration engines, driven by water pressure, manufactured by the Cambridge Scientific Instrument Company; this engine henceforth maintains uniform artificial respiration: its delivery tube is not represented in the figure, but enters the warm chest through an aperture in its back. Next a clamp is placed on the left subclavian artery, close to its origin. The vessel is opened between this and the ligature previously placed on it, and the bulb of a thermometer inserted into the artery. The clamp being removed, the thermometer is pushed down until its bulb projects into the aortic arch, and is then firmly tied in that position.

Finally the cannula M is placed in the right carotid of the Dog and the cannula N in the left, and the clamps on those vessels removed. These cannulas are in connexion with the lead tubes O and P, which pass out through the end B of the warm chamber, and are connected with manometers. One manometer is a FICK'S spring manometer, and is used for indicating the pulse-rate; the other is a mean pressure mercury manometer, after MAREY, having in its bend a stopcock which is nearly closed, so that each pulse-beat is hardly visible on the tracing, but the mean pressure at any time in the carotid is indicated.* The pens of both manometers write over

* In some of the earlier experiments only a mercury manometer was used. Owing to the doubts

one another on the paper of a LUDWIG's large kymograph. Below them, in the same vertical line, a chronograph pen inscribes seconds.

As soon as the carotid cannulas are inserted the front of the warm chamber (which had been removed to admit of placing the animal inside and performing the above described manipulations) is replaced. The gas burners below the trough supporting the warm chamber are turned up, and a pause made before beginning observations until the air in the chamber, which has been much cooled while the front was away, is again heated up to about 38° C.; and also until at least twenty minutes have elapsed since the complete occlusion of all the systemic circulation except that through the coronary vessels. Before the lapse of this time all signs of any activity of the extra-cardiac nerve centres cease, and the physiologically isolated heart is ready for experiment under conditions in which venous pressure, arterial pressure, and the temperature of the blood flowing through it are under very complete control.

By raising or lowering the MARIOTTE's flasks, C and D, venous pressure (*i.e.*, the pressure under which blood enters the right auricle) can be varied within wide limits. In the experiments described in the present paper it was always kept at that exerted by the weight of a column of defibrinated Calf's blood 15 centims. in height, except when the contrary is expressly stated. Aortic pressure can be varied by sliding the support Q, which carries with it the exit of the aortic outflow tube, up or down the vertical rod R. Only the lower part of this rod is represented in the figure; its upper end reaches to the ceiling of the room. In most experiments the height of Q was arranged so that the mean pressure in the carotid was about 100 millims. of mercury. I had supposed before trial that I could in this way keep mean arterial pressure absolutely constant. But in spite of the small resistance offered by the wide aortic cannula and the wide system of tubes leading from it to the outflow point S, it turned out that the pressure as measured in the carotid (and therefore in the aortic arch) did not depend entirely and simply on the difference of level between the root of the aorta and the aperture of S. The left ventricle pumped out so much blood as to get up some elastic tension in the aortic arch and the arterial stumps still connected with it, and the pressure due to this was added to that dependent on the height of the column of blood against which the heart worked and on friction in the outflow tubes through which it was driven. So long as the heart works with sufficient force to pump blood up to and out of S the resistance due to the weight of the column of blood to be lifted remains the same; if the rate of flow be slower, the resistance, and therefore the increased pressure due to friction, will be diminished, but in such wide tubes probably only to a trivial extent. When, however, any cause, such as change in temperature, deterioration in quality of the blood supply, impediment in the pulmonary flow, or gradual death of the isolated heart, influences the amount of blood pumped out in the unit of time by

which have been cast upon the accuracy of this instrument when a very slow or a very quick pulse is to be recorded, the FICK manometer was subsequently added. It turned out, however, that this was unnecessary; the pulse-rate recorded by both manometers was exactly the same.

the left ventricle, then the elastic reaction due to distension of the stumps of the great arteries is altered. Hence, even while a heart is pumping blood freely out through the exit S, kept at a constant height, variation of arterial pressure, as measured in the carotid, may occur to the extent of 10 millims. of mercury pressure. Such variations will be noticed in some of the protocols of experiments given in this paper; but fortunately they in no way affect the question here considered, viz.: the influence of changes of temperature upon the rate of beat of the isolated heart. I have previously shown (2) that slow variations of arterial pressure between the limits of 30 and 150 millims. of mercury do not in the least influence the pulse-rate of the isolated Dog's heart, provided venous pressure and the composition and temperature of the blood be kept constant.

Venous pressure and, approximately, arterial pressure being kept uniform the temperature of the blood alone was altered in the experiments below described. The variation was effected in two ways. First by pouring a little heated (50° C.) or cooled (10° C.) blood into the funnel F from which it entered the flask not in use at that moment, and warmed or cooled the blood already in it. Then this flask was used to feed the heart and the other as the recipient, by opening and closing the proper clamps and stopcocks. This method was rarely used, as it sometimes produced secondary effects, due to the comparatively sudden changes of temperature in the blood supplied to the heart. A more gradual and uniform alteration in the temperature of the blood was secured by changing the water in the jackets around the MARIOTTE'S flasks. Some hot water and some water cooled by ice to 5° or 10° C. were always kept at hand during an experiment. If a series of heating observations was to be made, some of the water already in the jackets was syphoned off, and replaced with warm, care being taken that the temperature never rose above 60° C., so as to avoid all risk of coagulating any of the proteids of the defibrinated blood: more hot water was added from time to time if necessary. To initiate a series of observations as to the effect of cooling, the iced water was of course employed. The best results were obtained when the temperature of the water in the jackets did not differ by more than 20° from the temperature of the blood in the flask. When either MARIOTTE'S flask was in use the rapid bubbling through its contents of the air entering by the tubes *e* and *e'* ensured their thorough mixture.

Having waited, then, for the death of extrinsic nerve centres, and until the thermometer *p* had during some minutes indicated a tolerably even temperature, the water around the MARIOTTE'S flasks was cooled or heated, and a series of observations commenced. The initial temperature usually lay between 37° and 38°, but, as will be seen in the experiment protocols which follow, was sometimes higher or lower. Tracings of arterial pressure and pulse-rate were taken at intervals varying from one to five minutes. When the tracing was completed an assistant immediately opened a small door in the front of the warm chamber, and read off the temperature of the blood flowing through the heart.

As regards this temperature, the question arose which thermometer to use; that, *p*, in the inflow tube, or that pushed down the left subclavian to the aortic arch. The former gave the temperature of the blood flowing through the cavity of the right heart; the latter the temperature of the blood in the left auricle and ventricle and aorta, and accordingly in the coronary arteries supplying the cardiac capillaries. *A priori*, there seemed little doubt that it would be the temperature of this latter blood, brought as it was into close relation with every muscle fibre and ganglion cell in the heart, which would exert an influence on the cardiac rhythm, if any did. Experiment soon confirmed this. Both thermometers were read in several experiments, and it was always found that the pulse-rate changes followed much more closely the variations of temperature indicated by the instrument in the subclavian. In most cases, accordingly, only the reading of this thermometer was undertaken, as it was very desirable to reduce to a minimum the time during which the door of the warm chamber was open.

The temperature observed was written on the kymograph paper over the tracing, along with the time at which the latter had been taken. After a pause, another tracing was taken, time and temperature noted as before, and so on throughout the experiment, which was usually continued until the heart began to show symptoms of weakened or abnormal action.

The roll of tracings was subsequently gone over carefully, and on the graphic record of each observation periods of twenty seconds marked out; the pulses during that time were counted, and the mean arterial pressure measured. The results were then put in tabular form, the actual pulses counted being multiplied by three, so as to give the rate per minute instead of the number of beats in twenty seconds. In the "detailed results" given below, six such tables are printed; as curves present very quickly and accurately to the apprehension the general outcome of long columns of figures, charts have also been constructed (Plate 49) giving the curves of temperature variation and pulse-rate change during two of these experiments.

### *Detailed results of experiments.*

Before proceeding to the following tables, which give the actual figures as to pulse-rate and temperature for several experiments, a few words of explanation are desirable with reference to some three or four points.

First, it will be noted that for normal temperatures (38-39° C. in the left ventricle of the Dog, according to CLAUDE BERNARD) (10) the pulse is very fast. This is undoubtedly due to the section of both pneumogastrics, cutting off the heart from control by the extrinsic cardio-inhibitory centre, which is normally very active in the heart of the Dog. Upon atropin paralysis of the peripheral pneumogastric connexions with the heart V. BEZOLD and BLŒBAUM (5) found in this animal the pulse-rate

sometimes increased 80 per cent. An increase of 80 per cent. above the average will more than account for the quickest pulse observed by me at normal temperatures.

Second, it will be seen that, quite independent of any changes of temperature, the heart beats slower towards the end of an experiment than it did at the beginning, although its action may still be regular and each pulsation powerful. This is undoubtedly due to altered nutrition resulting from the use of Calf's blood, as it was not observed, or at least not until much later in my earlier experiments (2), when Dog's blood was employed. In consequence of this gradual and progressive slowing of the pulse it might be objected in a cooling experiment that any observed diminution of the rate of heart-beat was dependent on other conditions than cooling of the organ. To meet this objection, in most instances after a series of cooling observations a series of heating has been made on the same heart, and these show that in every case the heart beats much quicker when again warmed. This makes it clear that the slow pulse previously observed was not due merely to progressive malnutrition of the isolated heart, but was mainly dependent on the lower temperature to which the organ was exposed. Taking for example Experiment I., we find that at $1^h\ 34^m$ P.M. the heart beat 246 times a minute at the temperature of 37°·8 C. Forty-three minutes later (at $2^h\ 17^m$ P.M.) it beat only 217 times per minute at the temperature 38°·1 C; but meantime the pulse-rate, at $1^h\ 57^m$ M.P., had been down to 73 per minute, the temperature being 27°·8 C. This slow pulse being followed twenty minutes later by one nearly three times as fast cannot of course have been conditioned by any progressive diminution of functional capacity dependent on the prolonged use of Calf's blood; this becomes still more obvious when, later on in the same experiment, we find a second cooling accompanied by a slower pulse, and a second heating by a quicker.

Third, it may be noted that in no case does any one of the experiments given last longer than two hours, and that, with one exception (Experiment VI.), it is stated that the observations had ceased because of some obvious abnormality in the heart's action. In my earlier experiments with isolated hearts a practically normal beat often lasted for four hours or longer. They were however carried out on a different plan, which allowed of the use of defibrinated Dog's blood to nourish the heart. Instead of permitting the left ventricle to pump blood out through a wide aortic cannula, the only exit left was through a narrow cannula in one carotid, and, in correspondence with this fact, the tube supplying the superior cava was also narrow. In the present series of experiments the widest possible cannulæ was placed in the aorta and vena cava, and all the tubing attached to these, and the stopcocks upon it, had a bore as wide as that of the cannulæ. Under such circumstances the heart pumps round three or four litres of blood in a very few minutes, and with a smaller amount the stopcocks and clamps used to make the flasks C and D alternately feeding and recipient, would have to be changed at such short intervals as to make it impossible to carry on any uniform series of consecutive observations. With the original method 1000 to 1500 cubic centims. of whipped blood was enough for convenient use, and

this quantity it was possible to obtain from Dogs. When four litres or more of blood are wanted it becomes practically impossible to use Dog's blood, and so some other had to be selected. After several trials Calf's blood was chosen. This blood, however, nourishes the heart less satisfactorily, and hence the earlier indications of commencing death.

With respect to the choice of blood I add a few words which may be of aid to any one desirous to repeat my experiments. It is important to have it from quite young Calves; that is to say, from animals which are still suckling: a point of itself of some interest when considered in connexion with the well known fact that the chemical composition of the urine of the nurslings of Herbivora shows that their nutritional processes agree in the main with those of adult Carnivora, and differ essentially from those of the adults of their own species. In spite of all care I used to be frequently disappointed by the death of the isolated heart before any satisfactory number of observations could be carried out upon it, even in cases when I could think of no cause for the failure. Light broke upon me when the laboratory attendant, whose duty it was to bring the blood from the slaughter-house, remarked one day that it seemed to him that we nearly always got on better when he did not get the blood from "wharf calves." On questioning, I found that "wharf calves" was the term employed by Baltimore butchers to indicate animals which, though still young enough to yield veal, were of such age that they had long ceased to live on milk. Since the blood of such Calves has been rejected the percentage of failures has considerably decreased. It is hardly necessary to add that care must be taken that no extraneous matter enters the blood during its collection. Baltimore butchers stun the Calves and then cut their throats, and while the blood flows out vomiting frequently occurs and sends the contents of the stomach into the collecting pail. The blood from each animal has therefore to be collected separately, so that the quantity already obtained may not be rendered unfit for use by admixture with matters from the stomach of another animal.

Even with the best obtainable Calf's blood, however, the results are not as satisfactory as with Dog's blood. Not only does the heart die sooner, but other changes occur which shorten the time during which an experiment can be carried on. The most marked of these is lung œdema, which nearly always takes place in the course of an hour and a half, to such an extent as to seriously impede the pulmonary circulation and the æration of the blood in the lungs. In consequence, the supply of blood to the left heart is hindered, and the right heart becomes gorged, and its auricle finally paralyzed; and this, of course, puts an end to an experiment. Another trouble which is apt to occur when Calf's blood is used is considerable pericardial exudation, often to such an extent as to seriously interfere with the beat of the heart. This difficulty may, however, be readily avoided by cutting a small hole in the pericardium as soon as the heart is placed in the warm chamber. A third difficulty met with when Calf's blood is employed is more serious. Many observers have noted on the isolated Frog's

heart, supplied with various nutrient liquids, a gradual increase in the bulk of the organ in the course of a prolonged experiment; this increase being due, apparently, to an alteration in the elastic modulus of the cardiac muscle. The same phenomenon is observed when a Dog's heart is fed with Calf's blood. Gradually the systolic size of the organ increases, until at last, even at the height of its systole, the heart very nearly fills the pericardiac sac. During the subsequent diastole there is, therefore, but little opportunity for the organ to expand and receive blood. When this state of things takes place, one sees on the tracings that a good arterial pressure is still maintained, and that the heart rhythm is regular, but the height of each pulse curve is much diminished; and on looking at the exit (Plate 48, fig. 1, S) of the aortic outflow tube, it is seen that the quantity of blood expelled at each systole is markedly decreased. If the heart be then examined it will be found so distended as to tightly fill the pericardium, and if the latter be carefully cut away the pulse-rate remains unaltered; but the heart now does again nearly, or quite, its original work: the pulse-curves on the tracing regain their previous extent, and the gush from the aortic outflow tube at each systole becomes as great as it was before the occurrence of the distension of the heart. The impediment to the heart's action, due to this expansion, may be avoided either by cutting away the pericardium before beginning a set of observations or by removing it later when it begins to interfere with the heart's action. Both methods have been used in the course of the experiments whose results are given in the present paper. In selecting special examples for publication it seemed best, however, to include, mainly, cases in which the normal state of things had been interfered with as little as possible; and in none of the tables which follow was the pericardium cut away before the commencement of the observations, and in only two cases (Experiments II. and IV.) during their progress. It seemed desirable to include these for the purpose of showing that, although the heart's effective work is much diminished when it has become so distended as to fill the pericardium, yet its rate and force of beat are unaltered.

The ill results of pulmonary œdema above described may be obviated to a great extent by pricking numerous holes in the lungs with a fine needle. This allows the liquid collected in the air cells and small bronchial tubes to escape, and relieves the pressure on the pulmonary capillaries, while it also allows air to reach the air cells. This operation in no way affects the general result so far as pulse-rate is concerned, the chief objection to it being the loss of blood due to trickling from the wounds. To avoid objections, only one case (Experiment IV.) in which the lungs were so pricked is included in the experiments detailed in the present communication.

Before leaving this question of the troubles attending the use of Calf's blood, I may state that some considerable experience has led me to the conclusion that the drawbacks more than balance the advantages, at least in so far as most experiments are concerned. If I had to repeat the investigation here described, I should certainly tie the aorta just beyond its arch, and connect the outflow tube $t$ with the left

carotid instead of with the aorta; pulse-rate and mean pressure could then be recorded by manometers placed in the right subclavian and carotid arteries, and in correlation with the narrowed outflow orifice, the feeding tube, *n*, of the heart could be narrowed. Under such circumstances much less blood would be pumped around in a given time, and it would be possible to obtain the quantity requisite for carrying on an experiment from Dogs instead of from Calves. Pulmonary œdema and loss of cardiac elasticity would then occur much later. Of course in other cases, as when, for example, the greatest amount of blood which could be forced out from the left ventricle in a systole was to be sought, or the work done by the left ventricle under varying conditions, it would be necessary to use the wide tubes and stopcocks which I have above described, and these would almost necessarily lead to the use of other than Dogs' blood for the nourishment of the isolated heart.

Fourth, as a final remark before proceeding to give experiment protocols, I call attention to the fact that in the following tables it will be seen that now and then a slight rise of temperature occurs in the course of a cooling experiment, or a slight fall in the course of a heating. Such breaks were nearly always due to the necessity of changing the feeding MARIOTTE'S flasks from time to time. While C is emptying and D filling, it is not possible to ensure that when D is in turn connected with the heart, the blood in it shall always be exactly of such temperature as to fit into the series of cooling or heating observations which had been carried on with C. An endeavour was always made to make the observations with the alternate flasks regularly consecutive as regards changes of temperature, and it will be seen that, in most cases, this was attained. When it was not, the resulting temporary rises or falls of temperature serve only to verify the general result; a slight and transitory heating in the course of a general cooling experiment quickens the pulse, and *vice versâ*.

I now give, in tabular form, the results of six experiments.

### *Experiment I.*

April 24, 1882.—The Dog used weighed 5790 grms. and was chloroformed during the operation of isolating the heart. Venous pressure throughout equal to that exerted by a column of defibrinated Calf's blood 15 centims. in height. Arterial pressure, measured in the right carotid, varied between 97 and 104 millims. of mercury. All the systemic vessels but those of the coronary system of the heart were occluded at $12^h\ 50^m$ P.M.

| Number of observation. | Time, P.M. | Temperature, centigrade, indicated by thermometer passed through left subclavian to aortic arch. | Pulse-rate per minute. | Remarks. |
|---|---|---|---|---|
| | h. m. | | | |
| 1 | 1 33 | 37·5 | 240 | |
| 2 | 1 34 | 37·8 | 246 | |
| 3 | 1 38 | 35·5 | 204 | |
| 4 | 1 40 | 34 8 | 191 | |
| 5 | 1 42 | 33·8 | 178 | |
| 6 | 1 44 | 32·0 | 153 | |
| 7 | 1 46 | 31·5 | 148 | |
| 8 | 1 48 | 30·5 | 129 | |
| 9 | 1 50 | 29·9 | 119 | |
| 10 | 1 52 | 29·0 | 105 | |
| 11 | 1 54 | 28·0 | 82 | |
| 12 | 1 57 | 27·8 | 73 | |
| 13 | 1 58 | 28·3 | 79·5 | |
| 14 | 2 01 | 29·0 | 83 | |
| 15 | 2 04 | 29·6 | 88 | |
| 16 | 2 06 | 31·1 | 129 | |
| 17 | 2 07 | 33·0 | 155 | |
| 18 | 2 08 | 33·9 | 168 | |
| 19 | 2 10 | 35·5 | 190 | |
| 20 | 2 11 | 37·0 | 207 | |
| 21 | 2 13 | 37·9 | 223 | |
| 22 | 2 14 | 36·8 | 203 | |
| 23 | 2 15 | 37·3 | 209 | |
| 24 | 2 17 | 38·1 | 217 | |
| 25 | 2 19 | 39·5 | 233 | |
| 26 | 2 20 | 40·5 | 240 | |
| 27 | 2 22 | 39·8 | 225 | |
| 28 | 2 26 | 39·5 | 219 | |
| 29 | 2 28 | 38·0 | 198 | |
| 30 | 2 30 | 36·8 | 181 | |
| 31 | 2 31 | 36·0 | 179 | |
| 32 | 2 34 | 34·5 | 159 | |
| 33 | 2 36 | 34·5 | 160 | |
| 34 | 2 38 | 32·8 | 131 | |
| 35 | 2 39 | 31·8 | 114 | |
| 36 | 2 41 | 30·8 | 87 | |
| 37 | 2 43 | 30·3 | 84 | |
| 38 | 2 45 | 30·5 | 80 | Irregular. |
| 39 | 2 46 | 30·8 | 81 | Regular. |
| 40 | 2 47 | 31·3 | 84 | Slightly irregular. |
| 41 | 2 49 | 31·5 | 87 | Regular. |
| 42 | 2 51 | 32·1 | 118·5 | |
| 43 | 2 53 | 32·5 | 126 | |
| 44 | 2 55 | 33·1 | 135 | |
| 45 | 2 59 | 36·5 | 184 | |
| 46 | 3 00 | 36·3 | 160 | |
| 47 | 3 02 | 35·8 | 167 | |
| | | | | The pulse now became very irregular, and its rate fell rapidly in spite of a supply of warmer blood to the heart. |

The results of Experiment I. are represented graphically on Plate 49. Each division along the abscissa corresponds to two minutes of time. The level of the abscissa line answers to a temperature of 25° C. and to a pulse-rate of 60 per minute. The continuous curve represents the pulse variations during the experiment. Each division on the height of ordinates drawn from any point of the pulse curve to the abscissa answers to ten pulse beats more than 60 per minute. The dotted curve represents the temperature variations. Each division of height in ordinates drawn from it to the abscissa represents one degree centigrade above 25°. It will be observed that the curves of temperature and pulse-rate fall and rise together throughout the experiment.

*Experiment II.*

April 27, 1882.—The Dog weighed 5550 grms. Chloroform and ether administered during the operation of isolating the heart. Venous pressure that exerted by a column of defibrinated Calf's blood 15 centims. in height. All the systemic vessels but those supplying the heart itself were ligated at $3^h\ 10^m$ P.M. The animal was transferred to the warm chamber at $3^h\ 15^m$ P.M., and then decapitated and a stout wire run down the spinal canal as far as the lumbar region before any observations as to pulse-rate were made.

| Number of observation. | Time, P.M. | Arterial pressure in left carotid, in millims. of Hg. | Temperature in aortic arch. | Pulse-rate per minute. | Remarks. |
|---|---|---|---|---|---|
| | h. m. | | | | |
| 1 | 3 30 | 100 | 38·0 | 237 | |
| 2 | 3 33 | 102 | 37·9 | 234 | Since last observation one carotid cannula had slipped out and been replaced. |
| 3 | 3 40 | 99 | 38·5 | 241·5 | |
| 4 | 3 42 | 98 | 38·5 | 244 | |
| 5 | 3 44 | 98 | 41·5 | 273 | |
| 6 | 3 46 | 101 | 40·5 | 258 | |
| 7 | 3 47 | 99 | 40·9 | 261 | |
| 8 | 3 48 | 100 | 42·0 | 267 | |
| 9 | 3 52 | 100 | 42·0 | 265·5 | |
| 10 | 3 53 | 99 | 42·5 | 265·5 | |
| 11 | 3 54 | 100 | 42·5 | 250 | |
| 12 | 3 55 | 97 | 39·5 | 222 | Flask changed since last observation; hence the rapid alteration of temperature. |
| 13 | 3 57 | 97 | 37·0 | 198 | |
| 14 | 3 58 | 97 | 36·0 | 189 | |
| 15 | 3 59 | 97 | 35·5 | 175·5 | |
| 16 | 4 00 | 98 | 34·7 | 169 | |
| 17 | 4 01 | 97 | 34·0 | 162 | |
| 18 | 4 02 | 98 | 34·0 | 165 | |
| 19 | 4 04 | 98 | 33·9 | 153 | |
| 20 | 4 05 | 99 | 32·9 | 144 | |
| 21 | 4 06 | 100 | 32·5 | 140 | |
| 22 | 4 09 | 98 | 31·7 | 124·5 | |
| 23 | 4 11 | 100 | 30·1 | 105 | Pericardium cut away since last observation. |
| 24 | 4 12 | 100 | 30·0 | 105 | |
| 25 | 4 15 | 101 | 29·9 | 97 | |
| 26 | 4 17 | 101 | 29·5 | 88 | |
| 27 | 4 19 | 101 | 29·0 | 84 | |
| 28 | 4 21 | 103 | 28·5 | 76 | |
| 29 | 4 23 | 104 | 27·5 | 75 | |
| 30 | 4 26 | 108 | 27·3 | 66 | |
| 31 | 4 27 | 112 | 28·0 | 66 | |
| 32 | 4 30 | 108 | 28·1 | 69 | |
| 33 | 4 32 | 108 | 29·5 | 111 | |
| 34 | 4 33 | 108 | 31·5 | 129 | |
| 35 | 4 34 | 107 | 32·5 | 162 | |
| 36 | 4 35 | 109 | 34·0 | 183 | |
| 37 | 4 36 | 105 | 35(?) | 150 | |
| 38 | 4 37 | 107 | 34·1 | 144 | |
| 39 | 4 39 | 105 | 33·5 | 135 | |
| 40 | 4 41 | 106 | 33·5 | 133·5 | |
| 41 | 4 43 | 105 | 34·0 | 135 | Pulse irregular. |
| 42 | 4 44 | 102 | 34·7 | 117 | Pulse regular. |
| 43 | 4 46 | .. | .. | .. | Heart's beat now became very irregular and experiment was discontinued. |

Experiment II. presents two points of special interest: in the first place the brain was removed and the cervical and dorsal spinal cord destroyed before the observations commenced, so that an additional security was obtained that no cerebro-spinal centres were influencing the pulse rate. In the second place it is one of the cases in which the heart became considerably distended during the course of the experiment, so that the pericardium had to be cut away. As will be seen, this did not at all affect the general result.

*Experiment III.*

May 3, 1882.—Dog weighed 6000 grms. Narcotised by subcutaneous injection of acetate of morphia before the operation of isolating the heart was commenced. Venous pressure at first that due to a column of whipped blood 10 centims. high, and afterwards to a column 15 centims. in height. Heart isolated at $12^h\ 55^m$ P.M.

| Number of observation. | Time, P.M. | Carotid pressure in millims. of Hg. | Temperature. C.° in aortic thermometer. | Pulse-rate per minute. | Remarks. |
|---|---|---|---|---|---|
| | h. m. | | | | |
| 1 | 1 20 | 110 | 34·5 | 151·5 | Venous pressure 10 centims. |
| 2 | 1 23 | 110 | 34·9 | 162 | |
| 3 | 1 25 | 110 | 36·1 | 185 | |
| 4 | 1 27 | 110 | 36·1 | 186 | |
| 5 | 1 29 | 110 | 37·9 | 211 | |
| 6 | 1 30 | 110 | 39·3 | 225 | |
| 7 | 1 31 | 110 | 40·0 | 232·5 | |
| 8 | 1 33 | 111 | 40·5 | 235 | |
| 9 | 1 35 | 110 | 40·3 | 222 | |
| 10 | 1 38 | 110 | 38·5 | 202·5 | |
| 11 | 1 41 | 109 | 37·0 | 184·5 | Venous pressure raised to 15 centims. between observations 10 and 11. |
| 12 | 1 43 | 110 | 36·9 | 195 | |
| 13 | 1 45 | 110 | 35·5 | 168 | |
| 14 | 1 46 | 112 | 33·9 | 152 | |
| 15 | 1 49 | 110 | 33·5 | 156 | |
| 16 | 1 51 | 110 | 32·7 | 142 | |
| 17 | 1 53 | 110 | 32·1 | 129 | |
| 18 | 1 55 | 111 | 30·0 | 102 | |
| 19 | 1 57 | 111 | 29·1 | 94·5 | |
| 20 | 1 58 | 110 | 28·9 | 87 | |
| 21 | 1 59 | 96 | 28·0 | 67·5 | Heart weakens and ceases to pump round before next observation. |
| 22 | 2 06 | 42 | 31·5 | 63 | |
| 23 | 2 08 | .. | .. | .. | Heart beat irregular and experiment discontinued. |
| 24 | 2 10 | .. | .. | .. | |

*Experiment IV.*

May 10, 1882.—Dog weighed 10,300 grms. Narcotised by subcutaneous injection of acetate of morphia before commencing the operation of isolating the heart. Venous pressure that due to a column of defibrinated Calf's blood 15 centims. in height. Heart isolated at $12^h\ 25^m$ P.M.

| Number of observation. | Time, P.M. | Carotid pressure in millims. of Hg. | Temperature in aortic arch. | Pulse-rate per minute. | Remarks. |
|---|---|---|---|---|---|
| | h. m. | | | | |
| 1 | 12 45 | 118 | 34·1(?) | 158 | It seems almost certain that the reading of the thermometer in observation 1 was a degree out, and should be 35·1°. |
| 2 | 12 47 | 117 | 34·5 | 151 | |
| 3 | 12 49 | 116 | 35·1 | 157 | |
| 4 | 12 51 | 116 | 35·5 | 156 | |
| 5 | 12 53 | 116 | 37·1 | 183 | |
| 6 | 12 54 | 116 | 39·0 | 195 | |
| 7 | 12 55 | 116 | 38·0 | 180 | |
| 8 | 12 56 | 116 | 38·3 | 181·5 | |
| 9 | 12 58 | 116 | 38·5 | 184·5 | |
| 10 | 12 59 | 116 | 38·5 | 183·0 | |
| 11 | 1 00 | 116 | 38·0 | 172·5 | |
| 12 | 1 02 | 112 | 37·5 | 166·5 | |
| 13 | 1 03 | 113 | 36·5 | 157·5 | |
| 14 | 1 05 | 112 | 35·0 | 137·0 | |
| 15 | 1 06 | 114 | 34·0 | 127·5 | |
| 16 | 1 08 | 114 | 33·5 | 126·0 | |
| 17 | 1 09 | 112 | 33·5 | 126·0 | |
| 18 | 1 11 | 111 | 32·7 | 114 | |
| 19 | 1 13 | 110 | 31·9 | 108 | |
| 20 | 1 14 | 111 | 31·5 | 102 | |
| 21 | 1 15 | 113 | 31·0 | 99 | |
| 22 | 1 17 | 113 | 30·5 | 92 | |
| 23 | 1 20 | 112 | 31·5 | 110 | |
| 24 | 1 22 | 112 | 32·5 | 119 | |
| 25 | 1 24 | 110 | 33·9 | 133·5 | |
| 26 | 1 27 | 110 | 34·0 | 129 | Lungs pricked since last observation. |
| 27 | 1 30 | 113 | 34·5 | 139·5 | |
| 28 | 1 32 | 114 | 35·0 | 140 | |
| 29 | 1 34 | 114 | 35·5 | 148 | |
| 30 | 1 37 | (?) | 36·5 | 179 | Pericardium cut away since last observation. |
| 31 | 1 38 | 101 | 38·0 | 192 | |
| 32 | 1 39 | 105 | 39·0 | 198 | |
| 33 | 1 40 | 107 | 39·6 | 199 | |
| 34 | 1 42 | 108 | 39·0 | 189 | |
| | | | | | After this the heart suddenly ceased to pump round, and its right auricle was seen to be paralysed. The lungs were extremely œdematous. |

The chart on Plate 49 represents graphically the results of the preceding experiment.

*Experiment V.*

May 22, 1882.— Dog weighed 5605 grms. Chloroform administered while the heart was being isolated. Venous pressure at first that due to a column of defibrinated Calf's blood 10 centims. in height, then doubled. Temperatures taken both in inflow tube (by thermometer *p*, Plate 48, fig. 1) and in the aortic arch by a cannula thrust down the left subclavian artery. Heart isolated at $1^h\ 30^m$ P.M. The mean temperature given in the sixth column is obtained by adding together the inflow and outflow temperatures and dividing by 2. It does not really represent the mean temperature of the heart, as while the inflow temperature is that of the blood in right auricle and ventricle, and the outflow (aortic) temperature that in left auricle and ventricle, the latter is also the temperature of the blood circulating in the walls of the heart itself.

| Number of observation. | Time, P.M. | Carotid pressure in millims. of Hg. | Inflow temperature. | Outflow (aortic) temperature. | Mean temperature. | Pulse-rate per minute. | Remarks. |
|---|---|---|---|---|---|---|---|
| | h. m. | | | | | | |
| 1 | 1 55 | 94 | 36·3 | 36·5 | 36·4 | 227 | Venous pressure 10 centims. |
| 2 | 2 00 | 94 | 37·3 | 37·3 | 37·3 | 234 | |
| 3 | 2 05 | 94 | 37·3 | 37·5 | 37·4 | 238 | |
| 4 | 2 10 | 94 | 37·5 | 36·7 | 37·1 | 225 | |
| 5 | 2 12 | 93 | 38·5 | 37·5 | 38·0 | 231 | |
| 6 | 2 14 | 96 | 39·5 | 39·0 | 39·2 | 249 | Venous pressure raised to 20 centims. |
| 7 | 2 16 | 96 | 38·0 | 38·5 | 38·2 | 244·5 | |
| 8 | 2 18 | 96 | 38·5 | 38·3 | 38·4 | 238·5 | |
| 9 | 2 20 | 97 | 39·0 | 38·7 | 38·8 | 241 | |
| 10 | 2 23 | 94 | 39·1 | 39·0 | 39·0 | 244 | |
| 11 | 2 25 | 94 | 40·3 | 39·7 | 40·0 | 249 | |
| 12 | 2 27 | 95 | 40·7 | 40·1 | 40·4 | 252 | |
| 13 | 2 30 | 97 | 40·0 | 39·9 | 39·9 | 252 | |
| 14 | 2 33 | 92 | 40·0 | 39·7 | 39·8 | 243 | |
| 15 | 2 35 | 92 | 40·0 | 39·5 | 39·7 | 233 | |
| 16 | 2 38 | 52 | (?) | (?) | .. | 102 | Pulse very suddenly slowed and became somewhat irregular and experiment discontinued. |

## *Experiment VI.*

May 22, 1882.—Dog weighed 1140 grms. Chloroformed while the heart was being isolated. Venous pressure throughout that due to a column of defibrinated Calf's blood 20 centims. in height. Heart isolated at $3^h\ 40^m$ P.M.

| Number of observation. | Time, P.M. | Carotid pressure in millims. of Hg. | Temperature of aortic blood. | Pulse-rate per minute. | Remarks. |
|---|---|---|---|---|---|
| | h. m. | | | | |
| 1 | 4 05 | 101 | 37·5 | 173 | |
| 2 | 4 07 | 99 | 36·9 | 170 | |
| 3 | 4 09 | 98 | 36·7 | 163·5 | |
| 4 | 4 14 | 98 | 36·7 | 156 | |
| 5 | 4 17 | 97 | 36·0 | 145·5 | |
| 6 | 4 20 | 97 | 35·1 | 132 | |
| 7 | 4 22 | 98 | 34·6 | 126 | |
| 8 | 4 23 | 98 | 34·1 | 117 | |
| 9 | 4 25 | 99 | 33·5 | 114 | |
| 10 | 4 28 | 97 | 33·0 | 108 | |
| 11 | 4 30 | 97 | 32·3 | 105 | |
| 12 | 4 32 | 96 | 32·5 | 91 | |
| 13 | 4 33 | 98 | 31·5 | 85 | |
| 14 | 4 34 | 98 | 31·1 | 85·5 | |
| 15 | 4 36 | 96 | 30·5 | 73·5 | |
| 16 | 4 37 | 96 | 30·1 | 76 | |
| 17 | 4 39 | 98 | 29·9 | 68 | |
| 18 | 4 41 | 95 | 29·5 | 69 | |
| 19 | 4 43 | 98 | 29·3 | 61 | |
| 20 | 4 45 | 98 | 28·9 | 63 | |
| 21 | 4 47 | 96 | 28·7 | 55·5 | |
| 22 | 4 51 | 98 | 28·7 | 61 | |
| 23 | 4 55 | 94 | 28·5 | 54 | |
| 24 | 4 57 | 97 | 28·5 | 54 | |
| 25 | 5 00 | 97 | 28·3 | 48 | |
| 26 | 5 03 | 96 | 28·1 | 52 | |
| 27 | 5 05 | 96 | 27·7 | 43 | |
| 28 | 5 08 | 94 | 27·5 | 28 | Pulse irregular but each beat powerful. |
| 29 | 5 10 | 90 | 27·6 | 24 | |
| 30 | 5 12 | 90 | 27·6 | 24 | |
| 31 | 5 14 | 92 | 27·6 | 21 | |
| 32 | 5 16 | 82 | 27·3 | 19·5 | Heart ceases to pump blood to top of aortic outflow tube. |
| 33 | 5 18 | 67 | 27·3 | 21 | |
| 34 | 5 21 | 58 | 27·1 | 21 | |
| 35 | 5 23 | 52 | 27·3 | 18 | |
| 36 | 5 25 | 49 | 27·3 | 18 | |
| 37 | 5 27 | 51 | 27·5 | 21 | |
| 38 | 5 30 | 45 | 28·0 | 19·5 | |
| 39 | 5 35 | 70 | 28·0 | 40·5 | Pumps round again. |
| 40 | 5 37 | 92 | 28·3 | 48 | |
| 41 | 5 40 | 93 | 28·5 | 58 | |
| 42 | 5 42 | 94 | 28·7 | 66 | |
| 43 | 5 43 | 96 | 29·1 | 73 | |
| 44 | 5 45 | 95 | 29·9 | 76 | |
| 45 | 5 49 | 93 | 30·5 | 82·5 | |
| 46 | 5 51 | 93 | 31·5 | 99 | |
| | | | | | Experiment now discontinued. Heart still beating regularly and forcibly. |

The above experiment is remarkable for the very slow pulse observed throughout. Even at 37°·5 the pulse was only 173 per minute, whereas in most isolated hearts it is over 200 at that temperature. When the temperature was brought down to near 27° the extraordinary slow pulse of 18 per minute resulted; a pulse so slow that although each beat was powerful the left ventricle pumped out in each minute less blood than was drained off from the aorta by the coronary arteries, so that the level of the blood in the aortic exit tube fell lower and lower until the carotid pressure finally came down to 41 millims. of mercury. On again heating the blood supplied to the heart the organ regained completely its functional activity. Before the cooling (observation 13) the pulse rate at the temperature 31°·5 was 85 per minute, and pressure in the carotid was 98 millims. of Hg. After the cooling, on again heating, we find at the same temperature (observation 46) a pulse of 99 per minute and a carotid pressure of 93 millims. of mercury. It is unfortunate that the experiment was not continued, but the exceptionally slow pulse obtained was not recognised until the tracings were counted out the next day, and as it was the second experiment of the same date I was fatigued and stopped so soon as I had satisfied myself that reheating the blood had quickened the pulse, instead of going on as usual until the heart began to show signs of commencing death.

## *Conclusions.*

As regards the question which the preceding experiments were primarily designed to answer, their results are decisive. They make it clear that the Mammalian heart when quite cut off from all extraneous nervous control, and when supplied with blood which has not been altered in composition by products of abnormal tissue change, due to abnormal heating or cooling of other organs of the body, does beat quicker when warmer blood is supplied to it, and slower when it gets cooler blood. In this respect the heart of the Dog behaves quite like that of the Frog. In spite of the greater division of physiological duties in the body of the Mammal, and the greater subjection of the Mammalian heart to control from special extrinsic nerve centres, the Dog's heart in its own neuro-muscular apparatus is so constituted as to have its rate of periodic activity directly controlled by its temperature. To account for the quick pulse of fever we need therefore assume no paralysis of extrinsic cardio-inhibitory nerve centres and no excitation of cardio-accelerator. The warmed Mammalian heart beats quicker because of its own physiological properties.

In addition to the above main question, several subsidiary points have some light thrown upon them.

(1.) The rate of beat of the Mammalian heart does not directly depend upon the temperature of the blood reaching the right auricle, except in so far as this influences the temperature of the blood pumped out by the left ventricle and supplied to the coronary arteries. It is not the temperature of the blood in its cavities which influences

the rate of beat of the Dog's heart, but the temperature of the blood sent to its capillaries. In other words, temperature changes do not influence the pulse-rate by stimulating afferent nerves in the endocardium which then act upon cardio-motor ganglia, but they act directly upon the muscle fibres or nerve cells of the organ.

(2.) A second subsidiary fact illustrated by the preceding experiments is that the heart of the Dog can be nourished for some time and kept in a good state of functional activity when fed only with Calf's blood: but this blood is far less satisfactory than Dog's blood, its use soon leading to pulmonary œdema and alteration of the elastic modulus of the cardiac muscular tissue.

(3.) As a third point of interest it may be noted that no clotting takes place in defibrinated blood circulated for some hours through the living heart and lungs. Such blood contains an abundance of fibrino-plastin (paraglobulin) and fibrin ferment, together with the quantity of salines necessary for the formation of fibrin if fibrinogen were present. Fibrinogen, therefore, is produced in other organs of the body than heart and lungs. By further experiments in which the isolated heart shall be connected with various other isolated organs and pump blood through them I hope to discover in what organs fibrinogen is produced.

It would have added much to the interest of the research described in the preceding pages if determinations had been made as to the highest and lowest temperatures at which the Dog's heart would beat, and I had hoped when commencing the investigation to have discovered those temperatures. It turned out, however, that with the method of work described in the preceding pages this was not possible. When the heart is considerably cooled, for example, it pumps around so little blood that the amount sent out at each systole of the left ventricle is less than that carried off by the coronary arteries. Under these circumstances the coronary system is mainly supplied with warm blood derived from the column of liquid accumulated in the aortic outflow tube (Plate 48, fig. 1, *t*.) As a consequence, the blood in the right heart comes to be of a very different temperature from that circulating in the cardiac capillaries, and the result is irregular and inco-ordinate action of the right and left sides of the heart, and a total cessation of all circulation. Quite similar results follow warming of the blood supplied to the right auricle to near the death temperature. Consequently I have not been able to discover the temperature limits of the vitality of the Dog's heart. Some preliminary experiments, carried on in a different manner, lead me to hope that the question as to the highest and lowest temperature at which a Dog's heart will beat can be solved; but my work in that connexion is not yet ready for publication.

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Fig. 2.

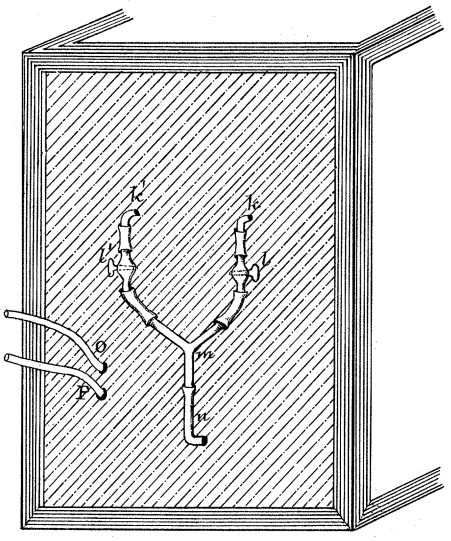



Fig. 3.

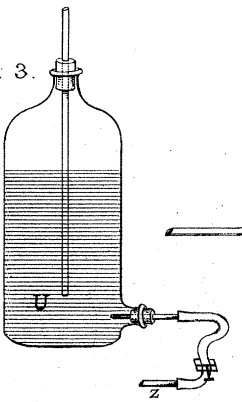
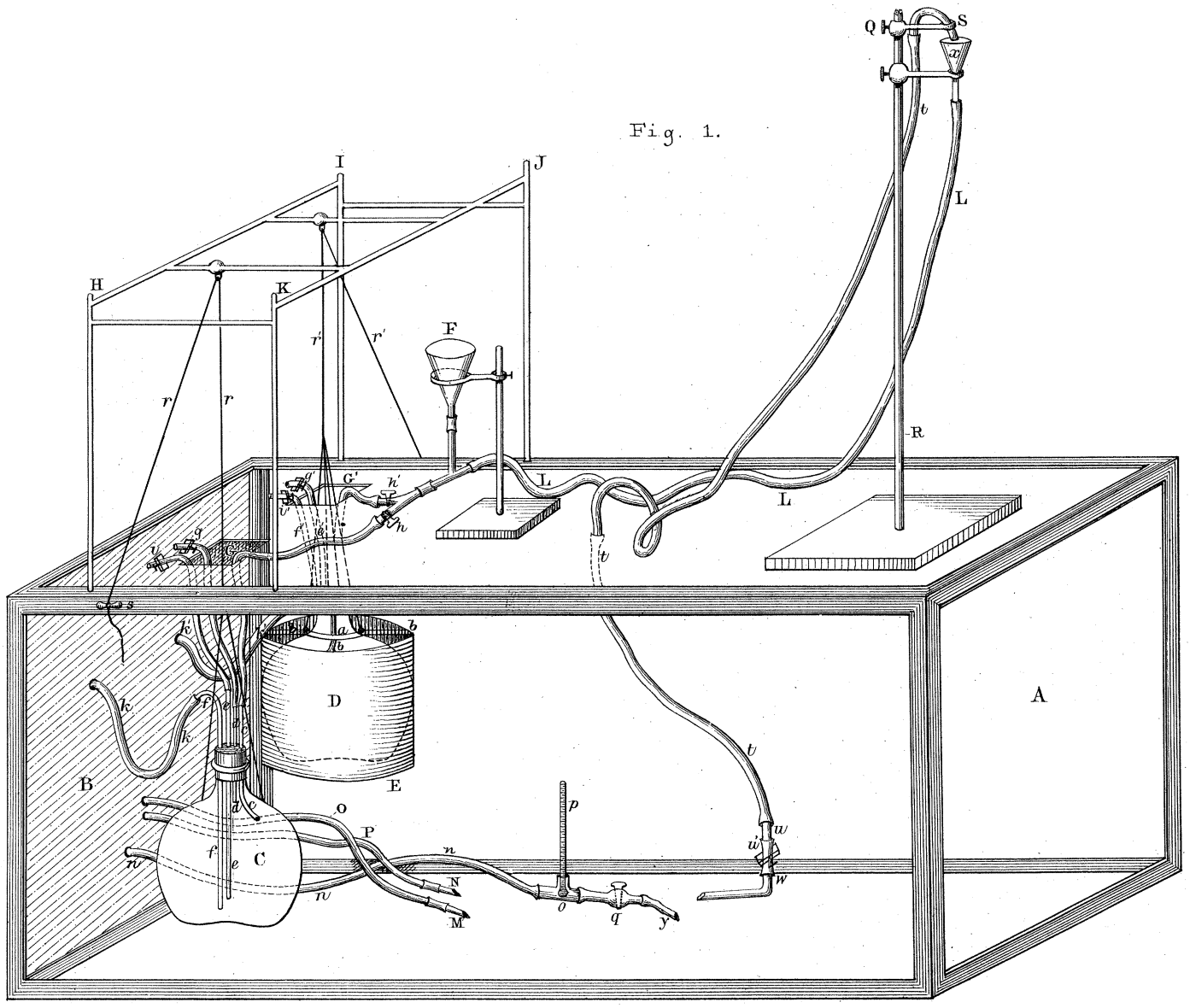






Fig. 4.

Fig. 1.

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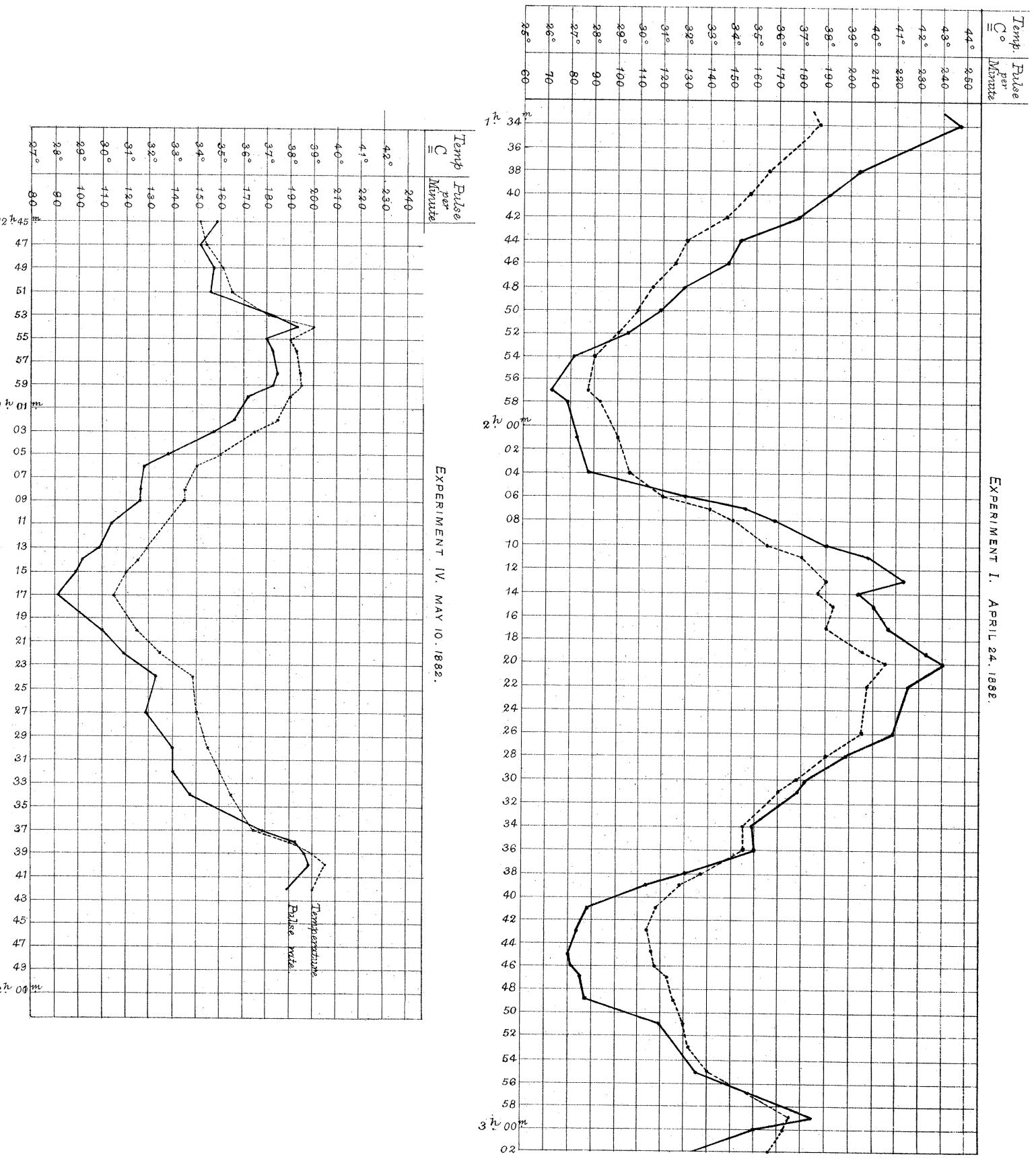


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