ON SOME POINTS IN THE INNERVATION OF THE MAMMALIAN HEART.

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ALTHOUGH a large amount of work has been done on the nerves acting on the mammalian heart, yet it is only in a few cases that the method of direct registration of the movements of auricles and ventricles has been used (McWilliam[1], Roy and Adami[2]). This fact is probably largely responsible for the numerous gaps in our knowledge of the subject, as compared with the exact knowledge we have of the actions of the nerves in the cold-blooded animals, frog, tortoise, etc. (Gaskell[3], Heidenhain and others).

In a former paper[4], we showed that the electrical events accompanying the contraction of the mammalian heart were exactly analogous to those occurring in the frog and tortoise; and we started this present research with a view to determining how far this analogy extended to the innervation of the heart in these two classes of animals, and especially with regard to the influence of the two sets of cardiac nerves on conduction between auricles and ventricles. After we had written the rough draft of this paper, an abstract of a communication by Roy and Adami to the Royal Society has appeared[5], in which these authors, using their ingenious myocardiograph to record the ventricular and auricular contractions, point out that both vagi and accelerator nerves may affect rhythm or force or both together. As will be seen, our work confirms most of their results, so far as we treat of the same subjects. They have not, however, considered the influence of the nerves on

[1] Mc William. This *Journal.* Vol. IX. p. 167.

[2] Roy and Adami. *Practitioner*, 1889.

[3] Gaskell. "Innervation of the Heart." This *Journal.* Vol. IV. p. 43, and other papers.

[4] "On the Electromotive Phenomena of the Mammalian Heart." *Proc. Roy. Soc.* Vol. IV. p. 211.

[5] *Brit. Med. Journ.* Feb. 27, 1892.

propagation across the auriculo-ventricular groove, which is the chief object of this paper.

The researches of Wooldridge[1], Tigerstedt[2] and McWilliam[3], have shown that the normal sequence of the contraction of the heart-cavities is intimately dependent on the functional connexion of auricles and ventricles. If this be destroyed by crushing the auriculo-ventricular groove (Wooldridge) or by a section across the groove by means of Tigerstedt's atriotome, the normal sequence is abolished, the auricles and ventricles beating with independent rhythm. In most of Wooldridge's experiments the rhythm of the ventricles was markedly slower (one-third) than that of the auricles. We have found however that this is by no means invariably the case, but that the ventricles may beat almost as rapidly as the auricles, although their rhythm is quite independent. This effect cannot be produced by division of the auricular septum or of the chordæ tendinæ, nor by emptying the heart of blood, by clamping the great veins—showing that the ventricular beat is caused by an excitatory process started in the auricle and transmitted across the auriculo-ventricular groove.

In our work, we have chiefly concerned ourselves with studying the conditions affecting conduction from auricles to ventricles. McWilliam has already investigated the effect of stimulation of the vagus on the propagation of this excitatory process, and has shown that stimulation of this nerve is able to give rise to a block, just as in the case of the heart of the frog or tortoise. We have sought to continue these observations on the vagus and to extend them to the accelerator nerves.

Experimental methods.

In our experiments, we have confined ourselves to dogs, which were anæsthetised with chloroform and a large dose of morphia (3 to 5 grs.). Tracheotomy being performed, an injection of curare was given in the jugular vein and the vagi on both sides were exposed for stimulation. The left vagus was cut; the right vagus was left intact, to be divided, if need were, later. An incision being made in the median line of the thorax, the chest was opened with bone-forceps as nearly as possible through the middle of the sternum. By keeping accurately in the middle line, it is easy to avoid cutting any large vessels, so that the operation can be rapidly performed with little or no hæmorrhage. The left innominate vein was then cleared, ligatured in two places, and

[1] *Du Bois' Archiv*, 1883. [2] *Du Bois' Archiv*, 1884. [3] *Loc. cit.*

divided. A little dissection then brought to view the left inferior cervical ganglion, with its cardiac branches and the annulus of Vieussens lying on the subclavian artery. The anterior loop of the annulus was prepared for stimulation. The thoracic walls were now dragged apart with hooks, the pericardium incised and its margins stitched to the edges of the thoracic parieties. By this means the heart was raised well out of the chest, so that it was unaffected by the movements of the lungs.

The contractions of the auricles were registered by means of a thread attached to the tip of the right auricular appendix which pulled on the lever of a tambour; the contractions of the ventricles by means of a modification of the *pince myocardiographique*. The levers of the receiving tambours were arranged to write in the same vertical line on the smoked paper of a Huertle's kymograph. Three time-markers below served to record the stimulation of accelerators, stimulation of vagus or of heart and the time (seconds). In investigating the conditions of propagation of the excitatory process, it is very necessary to know the exact moment at which the process is started; and to this end, as in our previous experiments on the electromotive phenomena of the heart, we have used the method of inducing an artificial rhythm by stimulating some part of the auricles or ventricles by means of induced currents, at a greater rate than the normal rhythm. For this purpose we used either von Frey's rheotome, arranged as a simple interrupter, or the inductorium, as modified by Ewald of Strassburg, in which the rate of the interrupter can be varied at will, from once in two seconds to 50 times a second.

A fundamental fact in connection with the question of propagation is that first pointed out for the mammalian heart by McWilliam, viz. that it is possible by stimulating the ventricle at a greater rate than the normal rhythm to obtain a reversed beat. The fact that this reversed sequence is abolished by the Wooldridge ligature and may be excited in the bloodless excised heart shows conclusively that it is subject to the same conditions and brought about by the same mechanism as normal sequence. At the same time there is no doubt that there is a greater resistance to impulses passing across the auriculo-ventricular junction in the reversed than in the normal direction.

In many cases this reversed contraction does not succeed. We stimulate the ventricles 3 or 4 times per sec. and the auricles either continue beating at the same rate as before or they follow the ventricle only partially, dropping one beat out of every three or four. There

seems also to be a difference in the rapidity of propagation of the excitatory process in the two directions. The time that elapses after stimulation of the auricle before the ventricular lever rises is from ·15″ to ·16″. In the reversed direction the interval is longer, ·19″ to ·22″. These numbers however are the result of only a few observations, since we are not certain that our methods of recording can give accurately enough the exact times at which the contractions of the auricles and ventricles begin. We hope to investigate the subject more fully, taking the first electrical change as the index of the arrival of the excitatory process. By photographing the electrical changes, with the help of a capillary electrometer, we hope to come to a certain conclusion on the subject.

Action of Vagi.

A. *On Auricle.* The action of the vagus on the auricle is fairly familiar from the work of Johansson and Tigerstedt[1], McWilliam, Roy and Adami on the subject. As in the tortoise's heart, it may act either on force or rate of contraction; or, as in the majority of cases, both these effects may be combined. The effect on force however is by far the most marked. We have frequently obtained tracings in which the rhythm was unaltered, although the strength of the auricular contractions was markedly diminished. On the other hand, we have never obtained a tracing presenting an effect on rhythm alone, although this is often affected before the strength of contraction. Depression of the auricular beat under vagus excitation may occur to such an extent that it is exceedingly difficult to be certain whether the auricle is beating or not—the beats in fact seem to be reduced to invisibility. Thus we have often, under strong vagus stimulation, thought that the auricles had entirely ceased beating and that the ventricles were beating with their own proper rhythm. But on screwing the auricular lever away from the drum, so as to avoid the least possible friction, a tiny movement of the lever was so seen immediately *preceding* each ventricular beat, although the auricles themselves, as observed by the eye, seemed perfectly motionless. In fact, we should say from the results of our experiments that it is extremely difficult, even using strong vagus stimulation, to cause complete cessation of auricular contraction. It seems possible that an excitatory process may occur in the auricle and may be transmitted thence to the ventricle, without causing any appreciable (i.e. registrable) contraction of the auricle itself.

[1] Johansson and Tigerstedt. *Hygieia Festband*, 1889.

B. *Action on Ventricle.* Johansson and Tigerstedt have divided the action of the vagus on the heart into three stages, according to the strength of the stimulus applied. Weak stimuli, according to them, affect primarily the auricles, diminishing rate and contraction, and only secondarily, the rate of the ventricle. Stronger stimuli stop the auricle altogether, the ventricle beating with its own rhythm, the height of the contractions being almost unchanged. The strongest stimuli affect also the ventricles in the direction of inhibition. Roy and Adami came to practically the same results. Our experiments bear out for a great part these conclusions; but we must make one reservation with regard to the point we have mentioned above, i.e. the difficulty of being quite certain that the auricles have really ceased beating and that the ventricles are beating with their own proper rhythm. There is no doubt however that the ventricles are much less subject to vagus influence than the auricles. The direct action of the vagus on the ventricles can be indubitably shown when, under moderate stimulation, the normal rhythm is reversed, and the auricles are beating extremely feebly after the ventricles. Instances of this we have observed a few times, and have then noticed that strengthening the vagus stimulation causes further slowing or stopping of the ventricular beat and the same result is invariably obtained in the common case of apparent complete auricular inhibition.

The direct action of the vagus on the ventricle is further shown by the old observation of Einbrodt, which we have confirmed, that it requires much stronger induced currents to send the ventricle into delirium under vagus excitation than under normal conditions.

It is more difficult to be certain of the direct effect of the vagus on the force of the ventricular beat. Tracings taken by Roy and Adami with their myocardiograph show no diminution of the ventricular beat during vagus excitation. We have found that, although moderate stimuli have no effect in diminishing the strength of the ventricular contraction, yet if the stimulus be largely increased, there is a slight diminution in the strength of contraction, as recorded by our methods. We do not think, however, that we are justified in arguing from this slight diminution in strength of the contraction, a direct depressor effect of the vagus on the ventricle. Under prolonged vagus excitation, the increasing asphyxia of the cardiac muscle and distension of its cavity would sufficiently account for it, without assuming any special depressor action of this nerve. So we would conclude that the vagus has a direct effect on the ventricular rhythm, but that it is unable to affect the

strength of the ventricular beat—a marked contrast to what obtains in the auricles.

C. *Effect of vagus on conducting power of auriculo-ventricular junction.* This may be studied on the heart beating normally or on hearts excited to contract by means of stimuli applied to auricle or ventricle. The effect of the vagus in producing a block to the passage of normal impulses from auricle to ventricle was pointed out by McWilliam (*loc. cit.*). A very common effect of stimulation of this nerve is that the auricle goes on beating at rather slower rate and with gradually diminishing strength, while the ventricle stops dead for some time, or only responds every now and then to the auricular beat. In many cases it is possible, by adjusting the strength of the stimulus, to obtain a tracing showing that the ventricle responds only to every second auricular contraction—an effect exactly analogous to that produced by Gaskell in the tortoise and frog by incision or clamping of the auriculo-ventricular groove.

In artificially excited hearts, the blocking effect of the vagus on conduction in either direction can be easily shown. If the auricles are excited 3 or 4 times per sec., the ventricle as a rule responds regularly to every auricular beat. If then the vagus is stimulated with a weak induced current, the ventricle may drop every other beat, or may for a short time cease to respond at all to the auricular contractions.

The auricular contractions are at the same time diminished in size from the direct action of the vagus on the auricles; and it might be argued that the defective propagation was due to depression of the excitatory process at its starting-point. But we know already from study of hearts under vagus excitation, that a beat of the auricle which is almost inappreciable, can cause contraction of the ventricles; so that we are forced to conclude that the effects are due to a diminution of conducting power and not to the depression of the excitatory process in the auricles. The fact that these blocking effects can be produced with weak currents shows that they are not due merely to lowered excitability of the ventricular muscle, for it needs a strong stimulation of the vagus to produce a slowing effect on the *ventricular* rhythm, or any appreciable diminution of its excitability.

A vagus block is still more easily produced when the ventricles are being excited and so are initiating the contractions. This fact is what one would expect from the depressing action of the vagus upon the auricles (the receiving tissue) and would not by itself afford any evidence of interference with the mechanism of propagation. But probably in

this case both factors are involved in preventing the transmission of the contractions from ventricles to auricles.

Action of Accelerator Nerves.

A. *On Auricles.* Stimulation of the accelerator nerves, commonly so-called, may have one or both of two effects—augmentation and acceleration (cp. Roy and Adami, *loc. cit.*). This double function of these nerves is well-defined. The most common effect is a combination of these two; that is to say, the auricle beats much faster and the beats are increased in amplitude. But it is by no means rare to obtain either augmentation or acceleration separately. In some cases, excitation of the large internal cardiac nerve (Pawlow[1]) on the right side produced marked acceleration of the auricular rhythm, accompanied by a depression of the strength of its beat. The depression was no doubt due to stimulation of admixed inhibitory fibres, but the fact that acceleration may be accompanied by depression shows conclusively, we think, that the two functions of augmentation and acceleration may be to a large extent independent of one another.

On the other hand, augmentation without acceleration is a not infrequent result towards the end of an experiment, when the auricles are beating quickly and feebly.

B. *On Ventricles.* Till recently, a direct action of accelerators on the ventricle had not been demonstrated. There are manifestly difficulties in the way. The beat of the ventricles is so largely determined both in rhythm and power by that of the auricles that it is difficult (with the means used in investigating the action of cardiac nerves by von Baxt, Boehm, Pawlow and others, it would be impossible) to be certain that any given result is not indirectly effected through the intermediation of the auricles. Roy and Adami have recently shown however that the accelerator (or augmentor) nerves may have a distinct effect on the ventricles in increasing the force of their contractions. We have confirmed this and have also been able to demonstrate an accelerator effect of these nerves on the idio-ventricular rhythm.

1. *Augmentor Effects.* The augmentation of the ventricular beat normally seen as the result of stimulating the sympathetic cardiac nerves, may be fairly ascribed to an increased inflow of blood at each augmented auricular beat. A difference in the strength of the excitatory process as it reaches the ventricle from the auricle would not by

[1] *Du Bois' Archiv*, 1887.

itself cause any augmentation of the ventricular beat, since the ventricle always responds to an efficient stimulus with a maximal contraction.

We have however obtained tracings of ventricular and auricular contractions before, during, and after stimulation of the anterior loop of the right annulus of Vieussens. In these it can be seen that, although the auricular beats are unaffected in strength (or, if anything, they are slightly diminished), there is nevertheless a marked augmentation of the ventricular beat. The same augmentor effect on the ventricle may be sometimes observed when the sympathetic cardiac nerves are stimulated during a vagus excitation sufficient to annihilate the auricular contractions. In neither of these can the augmentation be due to an increased inflow of blood during diastole, and so must, we take it, be ascribed to a direct action of these nerves on the ventricular muscle itself.

2. *Accelerator Effects.* Here again we have obtained distinct evidence of direct action of the accelerator nerves on the ventricles. Acceleration of the ventricular beat is often to be observed if the accelerator nerves are stimulated simultaneously with the vagi, the strength of the vagus excitation being adjusted so as to annihilate the auricular contractions. But the possibility of an excitatory process occurring in the auricles unaccompanied by any contraction that can be recorded by the means at our disposal, prevents us from drawing any conclusions from these results. In one or two cases however, during vagus stimulation, a very faint auricular beat followed the ventricular beat. The stimulation of the accelerator nerves in these cases caused acceleration of the ventricular beat. As the ventricles in these cases were initiating the beat, it is clear that the accelerator effect could not be due to the quickening of any invisible contractions occurring in the auricles. (The records were obtained on a slowly-moving surface. To be certain however of the sequence of contractions, the drum was put on to the fast rate, for a few seconds, just before exciting the accelerators and just afterwards; and we only accepted as reliable those tracings which showed a slight auricular contraction immediately *following* the ventricular. This sequence could be easily made out on the part of the curve taken at the fast rate.)

C. *On Conduction.* The improving effect of stimulating accelerator nerves on the conduction across the auriculo-ventricular junction can be easily and invariably demonstrated when the contraction-wave is made to travel in reverse direction by artificial excitation of the ventricles. The ventricles are excited rhythmically, and the rate of

excitation is gradually increased until it is seen that the auricles no longer beat in response to every ventricular contraction. If one vagus be intact in a morphinised animal, a rate of 3 per sec. is generally sufficient. If both vagi however are divided before the experiment, the ventricles may have to be excited 4, 5, or 6 times per sec., before the auricles refuse to follow. When we have determined the rate of ventricular contraction which is just too much to be transmitted to the auricles, the ventricle is excited at this rate and the accelerators then stimulated. In every case, stimulation of the accelerators removes the block, and the auricle beats during, and for a short time after the stimulation at the same rapid rate as the ventricle. (See Fig. 1, Plate XI.)

The same objection however as in the case of the vagus prevents us regarding this effect as a mere improvement of conduction. The paramount influence of the accelerators on the auricles would justify us in explaining this result as due to an increased excitability of the auricular muscle. We can however produce a block in the mammalian heart, as in the tortoise heart, by partial crushing of the auriculo-ventricular groove. In one experiment the auricles responded perfectly when the ventricles were excited about 3 times per sec. The auriculo-ventricular junction was then partially crushed by means of a ligature. When the ligature was relaxed, the ventricles at first beat with a different rhythm to the auricles; but after about 10 minutes the normal sequence of contraction was restored. It was now found that artificially induced ventricular contraction at the same rate as before was not transmitted to the auricles—that is to say, we had produced a block by the ligature. On stimulating the accelerators, this block was removed, and the auricles beat at the same rate as the artificially excited ventricles.

In the same way, it is possible to excite the auricles to contract so rapidly that the contractions are not all transmitted to the ventricles. The ventricles beat irregularly or else respond to every second auricular beat. Here we have produced a block—not by lowering the conduction-power of the tissue, but by raising the demands on the conduction-power of that tissue. This block can in like manner be removed by stimulation of the accelerator nerve. This effect cannot be so invariably demonstrated as the effect on the reversed beat. In many cases, the ventricle will respond to as many stimuli as it is possible to apply to the auricles—further increase of stimuli to the auricles only serving to send these organs into delirium. One experiment of this sort, in which we obtained this result again and again, was interesting from the fact that

towards the end of the experiment, stimulation of the accelerators (for the twelfth time) was absolutely without effect on the auricular beat. Almost immediately after this record was taken, the auricles were again stimulated about 5 times per second—the contractions not being followed by regular contractions of the ventricle. Stimulation of the accelerators now had the power of removing this block, as in the previous eleven observations (Fig. 2, Plate XI.). This experiment shows that the fibres which improve conducting tissue may retain their excitability after the accelerator fibres to the auricles have lost their effect, and that they are therefore probably distinct from the latter fibres.

Stimulation of the accelerators seems to quicken the rate of propagation of the wave from auricles to ventricles. Thus in one day, the times that elapsed between stimulation of the auricle and rise of the ventricular lever were, in a series of measurements, taken from several different experiments,

Before stimulation of accelerators:

·15″, ·15″, ·15″, ·16″, ·16″, ·16″, ·16″, ·15″, ·16″, ·17″, ·15″.

During stimulation of accelerators:

·14″, ·135″, ·13″, ·13″, ·13″, ·13″, ·13″, ·125″.

We shall investigate this question more fully with the help of the capillary electrometer.

Thus going to the dog's heart, as to the heart of the tortoise, there are two sets of fibres, each of which has an improving or depressing effect on rhythm, contractility and conducting power. The analogy is the more striking, since it is stated that there is no muscular continuity between the auricles and ventricles of the mammalian heart. If this be really the case, it would seem to be quite a matter of indifference to these phenomena—blocking by clamping of vagus, removal of block by stimulation of accelerators—whether the transmission of the excitatory process is effected by muscle or nerve. The phenomenon of reversed contraction also, if carried out by a nervous connection, is, as Prof. Gotch has pointed out to us, an absolutely new fact in muscle and nerve physiology. For here we should have nerve-fibres with a motor termination (or what corresponds to motor termination) at both ends, and capable of being excited at either end. No doubt many of our results on conduction might be explained by ascribing them to heightening or lowering of the excitability of the receiving tissue. But we think the considerations we have already adduced in discussing the

action of the vagus on conduction and those brought forward by Mc William (*loc. cit.* p. 369) rather point to our first interpretation.

We would conclude then that there is no essential difference between the hearts of the mammal and of the cold-blooded animals; and that each is subject to the same varieties of nerve-influence.

We cannot leave this subject without alluding to one statement of Roy and Adami, which is in direct opposition to all previous work on the matter, and which we have been quite unable to confirm. In describing the mode of interaction of the vagi and accelerators, these authors point out "that when the vagi are paralysed by section or atropin, the augmentores would seem to have no control over the cardiac rhythm and that, therefore, they can only act by inhibiting the influence of the vagi on the rhythmic centre of the heart." When von Baxt[1] made his classical researches on the accelerator effect of these nerves on the heart, he commenced *all* his experiments by dividing both vagi. All the numerous tables of the acceleration produced by stimulation of the accelerator nerves were results obtained from animals in which *both vagi* were divided. We have almost invariably obtained acceleration on stimulating these nerves when both vagi were cut. The few cases in which we did not obtain this effect were those in which the stimulation was tried at the end of a long experiment, and the animal was exhausted and the heart beating very rapidly—perhaps in consequence of reflex acceleration excited by the strong stimulation of sensory nerves. The usual acceleration we obtained in dogs with both vagi cut was from 7—9 to 11—13 in four seconds—an acceleration of about 50 %.

We have not tried the effect of stimulation of the accelerators after administration of atropin. Boehm however states that he obtained quickening of the beat on stimulating these nerves in cats poisoned by this drug.

DESCRIPTION OF CURVES. PLATE XI.

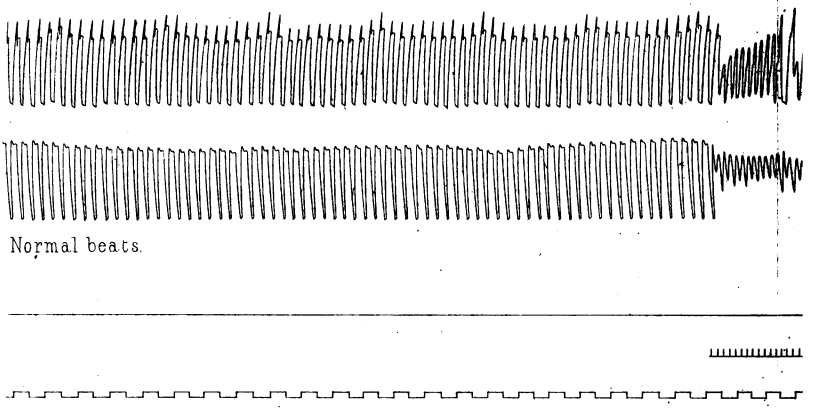
The curves are to be read from left to right. The upper tracing is the ventricular; the next, the auricular beat. The ventricular lever moves upwards, the auricular downwards with each contraction. Each double excursion of the time-marker represents one second.

Fig. 1. The ventricles were excited 14 times in 3 seconds. The auricles

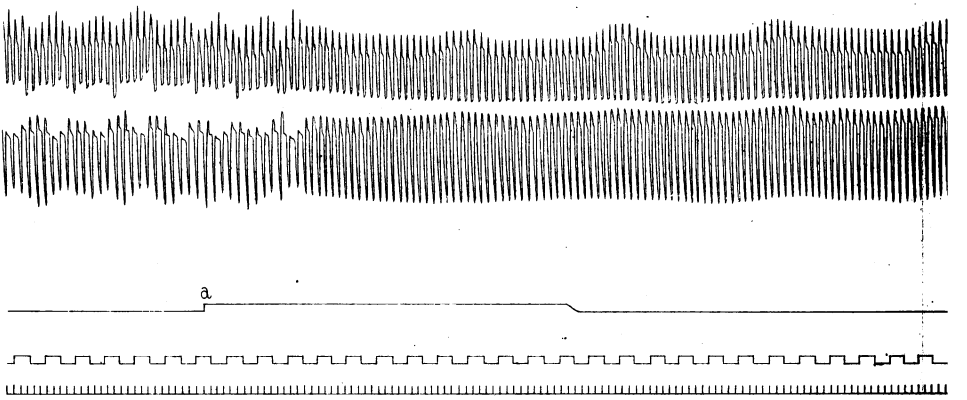
[1] *Du Bois' Archiv*, 1877, p. 521.

did not respond, but went on beating at their original rhythm of 11 in 3 seconds. Excitation of the accelerators at *a* and *b* caused the auricles to follow the ventricles. In the tracing, two stimulations of the accelerator nerve are shown; and in each case the block was removed some seconds after the current was thrown into the nerve, and the improved conduction lasted some time after stimulation of the nerve was discontinued.

Fig. 2. The lowest line is the time-marking; the next shows the stimulation of the auricles, and the next the stimulation of the accelerator nerve (anterior loop of left annulus of Vieussens). On stimulating the auricles 5 times a second, the ventricles followed very irregularly, dropping one beat in every two or three. Eleven seconds after commencement of accelerator excitation, the block is removed and the ventricle responds to every auricular beat. This improvement in conduction lasts 13 seconds after excitation of the accelerators has ceased. This tracing is the one mentioned in the text, taken just after one which showed that the accelerator nerves had quite lost their power to affect the rhythm or power of the auricles.



Normal beats.



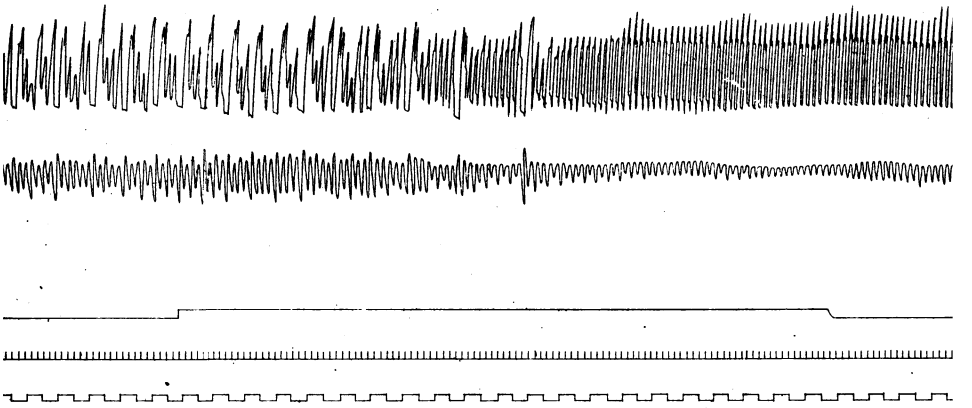


Fig 2.

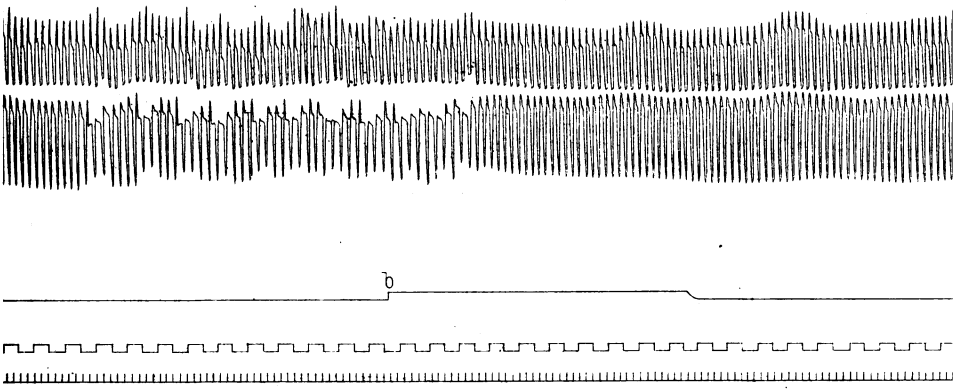
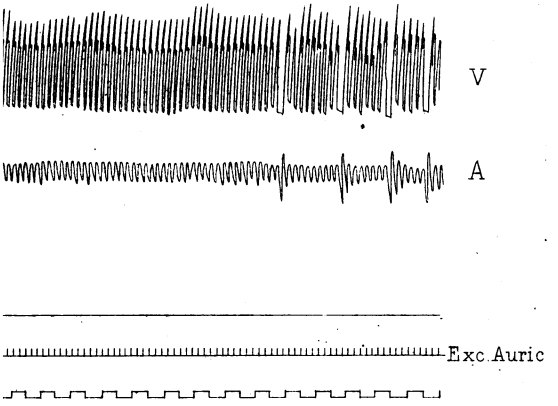


Fig 1.

Cambridge Engraving Company.


V
A
Exc. Auric
V
A
Exc. Accel.
Exc. Vent.