XXIII. The Croonian Lecture.—*On the Rhythm of the Heart of the Frog, and on the Nature of the Action of the Vagus Nerve.*

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[Plates 66–70.]

In all investigations upon the causation of the beat of the heart, one question stands forward prominently before all others, viz.: What is the relative share taken by the ganglion cells and the muscular tissue respectively in the production of its spontaneous rhythmical beats? And in any discussion upon the action of the cardiac nerves, the most important question always is, How far do they act on the ganglion cells, how far on the muscular tissue directly?

In recent times a variety of investigations have pointed unmistakably to the conclusion that rhythmical action can occur in muscular tissue under the influence of a constant stimulus without the intervention of ganglion cells, or at all events of any well-defined recognisable nerve-cells; in other words, certain kinds of muscular tissue possess the faculty of transforming the effects of a continuous stimulus into a discontinuous result.

Again, there can be no doubt whatever that in the heart of the Frog the rhythmical beat is markedly associated with the presence of certain ganglion cells, especially the cells of Remak's ganglia, so that the first question which it is absolutely necessary to answer is, Does the normal rhythm of the heart as a whole depend upon separate rhythmical impulses passing from certain motor ganglia to the muscular tissue, each of which impulses causes a contraction, so that the rhythm is due to the nerve cells, and the muscle simply gives expression to it, or do the motor cells send to the muscles a continuous series of subminimal impulses, the effects of which the muscle sums up, so as to produce from time to time a single beat; in other words, Is the rhythm due to the muscle, while the nerve cells supply the constant stimulus?

Further, before it is possible to consider the action of the cardiac nerves, it is necessary to come to some conclusion respecting the different attributes of the cardiac muscle apart from the question of rhythm, and it seems to me that the three which especially demand attention are the following:—

1. Contraction-power, as measured by the extent of the contraction.
2. Excitability, as measured by the response or non-response of the muscle to the stimulus.
3. Tonicity, as measured by the extent of the relaxation of the tissue at the commencement of each contraction.

I propose, then, to discuss in the first part of this paper not only the nature of the normal rhythm of the heart, but also certain variations in the three above-mentioned attributes of the cardiac muscle, together with their relations to each other. Afterwards I will proceed to the second part and endeavour to determine the respective actions of the vagus nerve upon the ganglion cells and the cardiac muscle.

In order to investigate the different problems suggested above, it is clearly necessary to employ the graphic method, and at the same time it is very advisable to obtain a method which shall register simultaneously as many of the different factors involved as possible.

As far as the question of tonicity is concerned, I have chiefly made use of the arrangement described in my paper* "On the Tonicity of the Heart and Blood-vessels," and those experiments I propose to consider later on; there are, however, considerable difficulties of interpretation in using this method for the determination of the force of contraction of different parts of the heart. I therefore resolved to investigate the nature of the cardiac contractions in the bloodless heart after the same plan as has been used with such marked success in the case of ordinary striped muscle and its nerve.

The vagus nerve, usually on the left side, is dissected out so as to be as long as possible, and a ligature attached to one end; the two aortic trunks are cut close to the bulbus, and a thread is tied to the extremity of the loose auricular flap, at the junction of the two auricles, which is exposed by the removal of the aortic trunks; another thread is attached to the extreme apex of the ventricle, and the heart with a piece of the œsophagus and trachea behind it, and with the vagus nerve intact, is removed from the body. In taking the heart out the lungs are cut away, and the venous sinus carefully left intact. One of KRONECKER's forceps is now made to clip the free end of the œsophagus and trachea, and held tight in a suitable holder (Plate 66, F). The thread attached to the auricles is fixed by means of a small hook to a lever A, which is capable of movement in a vertical plane, while that attached to the ventricle is fixed in a similar way to another exactly similar lever B, which can slide up and down on the same support below the lever A. The upper lever to which the auricles are attached is drawn up above the horizontal position by means of an elastic thread fixed to it near the fulcrum, and also fixed to the support above it, as is seen at C in the figure. In this way the heart is suspended between the two levers A and B, the lower one of which is drawn upwards by its contraction, the upper one downwards. Between the two a clamp D is now placed so as just to hold the tissue tight in the auriculo-ventricular groove, and the two levers are adjusted so that they are parallel and horizontal. The clamp is made of two limbs of strong but thin metal with carefully rounded edges, which are capable of being approximated to each other by means of a fine micrometer screw. The levers are provided with aluminium-foil points, and are adjusted so that the two writing-points are exactly in the same vertical line when the levers are horizontal. By

* Journal of Physiol., vol. iii., p. 48.

means of a drum the two levers write at the same moment upon the blackened paper, and the upper lever moving downwards records the contractions of the auricle, while the lower lever moving upwards traces those of the ventricle.

The vagus nerve is now laid upon a pair of platinum electrodes E, and kept moist by laying over it a piece of filter paper dipped into normal saline solution. The electrodes are in connexion with an ordinary induction coil driven by a single DANIELL cell, the interruptor of which is a tuning-fork instead of the usual hammer. In addition to the two tracings described above, the usual time and stimulation markers write on the blackened paper.

In the description just given I have spoken of the clamp as being placed in the auriculo-ventricular groove, so as to register the auricular and ventricular contractions simultaneously; it can, however, be placed across any portion of the heart, for example between the sinus and auricles, so as to register the sinus and auricular contractions; midway between the base and the apex of the ventricle, so as to register the contractions of the base and apex simultaneously, &c.

Besides the advantage obtained by the power of registering at will the contractions of any two contiguous parts of the heart, the clamp enables us to study the effects of compression at different points much more delicately than the old plan of ligaturing, for it is possible either just to hold the tissue so as not to injure it physiologically or to compress it up to any required amount by the simple movement of the micrometer screw.

Further, it is possible to cut the ventricle open from base to apex, and to apply poisons or fluids of any kind to that part of the heart which is situated below the clamp without any chance of their reaching the parts above the clamp (the latter being provided with a flange on each side to prevent the fluids passing over it). Also the parts on the one side of the clamp can be heated or cooled independently of the parts on the other side, and under all these different conditions the effect of stimulation of the vagus nerve can be studied. Throughout the course of each experiment the heart is kept moist by the application of salt solution.

PART I.

ON THE RHYTHM OF THE HEART.

If we imagine a portion of muscle made to contract rhythmically by the action of certain cells situated at a distance from it, then it is clear that the rate of rhythm will be independent of any increase in the excitability of the muscle, if the rhythm is due to separate impulses passing from the cells to the muscles, each of which is able to cause a contraction; on the other hand, an increase in the muscular excitability must cause a quicker rate of rhythm, if the rhythm is dependent upon some process of summation of stimuli taking place in the muscle itself.

Now, by the method described above it is possible to influence in different ways either the ventricle alone on the one side of the clamp without affecting the sinus and auricles on the other side, or only the auricles and other parts on that side of the

clamp without touching the ventricle; so that it is possible to increase or diminish the excitability of the ventricular muscle without affecting the discharges from the motor ganglia, or to act upon the motor ganglia without altering the excitability of the ventricle. Of the various means for effecting this object, it will be sufficient to give examples of the action of heat, atropin and muscarin.

When the whole heart is heated the rate of rhythm is always greatly increased, and the same, as is well known, is true in the case of either the ventricle or apex when isolated and beating spontaneously. In this latter case the greater rapidity of rhythm is partly, at all events, to be ascribed to the increase of excitability in the muscle due to the heating.

Suppose, now, in the heart suspended as described above the ventricle alone be heated, then its excitability will be increased* while that of the auricles will remain the same as before, and therefore if the rhythm be dependent upon the muscular tissue, as in the case of the isolated apex, the ventricle ought to beat at a quicker rate than the auricles whose excitability has not been altered. On the other hand, if the rhythm is due to discrete impulses passing from the motor ganglia to the ventricle, then no increase in the excitability of the latter ought to make the smallest alteration in the rate of the beats, because upon that view the ventricle does not contract except when an impulse reaches it, and the motor ganglia remaining outside the range of the heating the rate at which their discharges take place remains unaltered and is unaffected by any alteration in the excitability of the ventricular muscle. Of these two views experiment proves that the latter is the true one.

If the clamp be placed in the auriculo-ventricular groove and be tightened so as just to hold the tissue firmly, then both auricles and ventricle continue to beat with perfect regularity for hours, each ventricular beat following in orderly sequence upon each auricular. In order to heat the parts of the heart on one side of the clamp without heating those on the other side I have used a spiral of thin platinum or copper wire which is placed round either the ventricle or the auricles and sinus and is in connexion by means of a key with a battery of two or three GROVE cells. When the ventricle alone is to be heated it is placed in connexion with the upper lever and the auricles with the lower; if the heating is intended to affect only the sinus and auricles then the arrangement is reversed. That this method works well is shown by the fact that whereas a thermometer suspended within the spiral may show a rise up to 50° or 60° C. under the heating influence of three GROVE cells, yet a thermometer placed against the tissue just below the clamp does not show any rise at all, when the spiral is in position round that part of the heart which is situated above the clamp.

Heating the sinus and auricles alone in this way causes a most marked increase in the rate of rhythm both of the auricles and ventricle, with other phenomena which will be mentioned presently (Plate 67, fig. 1), showing that the method of heating is effective. On the other hand, when the ventricle alone is heated no alteration *in the*

* KRONECKER, "Das charact. Merkmal der Herzmuskel-Beweg." LUDWIG's Festgabe, 1874.

rate of rhythm either of ventricle or auricles is produced; the rate of the auricular beats continues the same; the ventricular beat follows upon each auricular with the same regularity as before, and, in fact, as far as the rhythm is concerned the ventricle might not have been heated (Plate 67, fig. 2). That the heating was effective, however, the figure clearly shows, for the force of the ventricular contractions is markedly diminished during the time that the muscle was heated: a fact of considerable importance, as proving that heat acts upon the muscular tissue of the heart in such a way as to diminish the force of its contractions apart altogether from the rapidity of the rate of rhythm of those contractions.

This experiment seems to me positive proof that in the whole heart the rhythm is due to discrete impulses proceeding from certain motor ganglia to the muscular tissue, each of which impulses causes a contraction of that tissue. Further evidence to the same effect is given by a series of results which may be generalized as follows :--

Any influence which, applied to the auricles and sinus alone, causes an alteration in the rhythm of the auricles, affects the rate of the ventricular beats synchronously, while the same influence, applied to the ventricle alone, causes no initial alteration in the rhythm either of ventricle or auricles.

Thus cold slows both the auricular and ventricular beats when applied to the auricles and sinus, while the same amount of cold produces no effect on the rhythm when applied to the ventricle alone. Atropin sulphate (1 p.c. solution) dropped on to the auricles and sinus slows the rate of beating of the whole heart most markedly (Plate 70, fig. 26 B) while the same solution applied to the cut-open ventricle produces no initial effect upon the rhythm. So, too, with muscarin sulphate, a marked slowing when applied to the auricles and sinus; no alteration of rhythm, for some time at all events, when confined to the ventricle. (See Plate 70, figs. 26 A, 27.)

Many more instances of the same kind might be given, but enough has been said already to permit us to formulate the following proposition :—

The rhythmical contractions of the heart as a whole are caused by discrete impulses which proceed rhythmically from certain motor ganglia to the auricles and ventricle.

The apparent discrepancy between this assertion and the rhythmical phenomena exhibited by the isolated ventricle and apex will be discussed at the end of this part of my subject.

On the want of sequence between the ventricular and auricular contractions.

If, however, we conclude that separate impulses pass from the motor ganglia to the ventricle, the further question arises, What conditions are necessary so that each one of these impulses should cause a contraction of the ventricular muscle?

In the ventricle or apex alone we know, from the experiments of KRONECKER,* that

* *Op. cit.*

a series of single induction shocks of sufficient strength, sent through the muscle at a definite and invariable rate, will cause a synchronous series of contractions; and that if then the muscle be cooled down, the same series of single stimuli will cause a series of contractions synchronous not with every stimulus, but with every second stimulus. Again, v. BASCH* has shown that a series of single stimuli of the same strength may cause a series of contractions synchronous with every second stimulus when each stimulus is so weak as to be unable to cause a contraction by itself.

From these two observations we may draw the conclusion that a definite relation between the strength of the stimulus and the excitability of the ventricular muscle is necessary, in order that the muscle should contract synchronously with the series of artificial stimuli; and also that the muscle may be made to respond synchronously to every second stimulus, instead of to every stimulus, either by lowering the excitability of the muscle, the strength of the stimulus remaining unaltered, or by lessening the stimulus, while the excitability remains the same.

In his latest paper,† v. BASCH suggests as an explanation of this half-rhythm that a stimulus which is insufficient to cause a contraction increases the excitability of the muscle, so that a subsequent stimulus of the same strength is thereby enabled to produce a contraction.

These observations of KRONECKER and v. BASCH may be taken as evidence that the ventricular muscle is able to sum up the effects of two or even more artificial stimuli; but so far we have no proof that it is able to act in the same way towards the normal impulses coming from the motor ganglia.

This evidence I have been able to supply by my method of experimentation, and have come to the conclusion that a definite relation between the strength of the impulses from the motor ganglia, and the excitability of the ventricular muscle, is requisite to ensure the occurrence of a series of ventricular beats synchronous with the impulses coming from the motor ganglia. Here, too, just as in the case of the artificial stimuli, a certain number of the impulses prove inefficient to cause a contraction when the excitability of the muscle is lowered sufficiently; here, too, a diminution in the strength of the impulses below a certain limit causes the ventricle to beat synchronously with every two, three, or more impulses, instead of with every impulse, although the excitability of the muscle remains the same.

In this case, then, as well as in the case of artificial stimulation, the probable explanation of the half-rhythm observed is to be found in the following extension of the suggestion made by v. BASCH, viz.: *when the relation between the strength of the impulses coming from the motor ganglia and the excitability of the ventricular muscle is such that each separate impulse is not able to cause a beat of the ventricle, then the ventricle does not necessarily remain quiescent, but beats synchronously with every second*

* Sitzber. d. k. Akad. d. Wiss. (Wien.) Bd. lxxix., III. Abth.

† Arch. f. Anat. u. Physiol. (Physiol. Abth.). 1880, S. 283.

impulse, because each impulse, though unable to cause a contraction of the muscle, may increase its excitability to the height necessary for the production of a beat by the time the next impulse reaches the tissue.

The proof of these assertions depends upon the fact that, by the method of clamping, it is possible to alter the relation between the strength of the impulses and the excitability of the ventricular muscle without affecting the relation between the motor ganglia and the auricular muscle. The rate, therefore, at which the impulses are sent out from the motor ganglia is indicated by the rate of the auricular beats, and the extent of synchronism between them and the beats of the ventricle determines the number of impulses that have been made inefficient, as far as the causation of a ventricular beat is concerned, by the action of each special operation.

This want of sequence between the auricular and ventricular contractions can be obtained by three different methods.

1. By tightening the clamp in the auriculo-ventricular groove.
2. By heating the auricles and sinus without heating the ventricle.
3. By the application of various poisons to the ventricle alone.

By the use of the micrometer screw attached to the clamp it is possible to compress the tissue so slightly, and yet to hold it with sufficient firmness, that the sequence of ventricular upon auricular beats continues without alteration or interruption; it is possible also to compress it so strongly that the motor impulses can no longer reach the ventricle, and therefore the ventricle remains quiescent, while the auricles continue beating with unaltered rhythm; and it is possible to compress it to any extent intermediate between these two extremes, and to observe the alteration in the ventricular rhythm so produced. This latter case is that with which we are specially concerned at present, and in every instance I have found that with gradual tightening of the clamp the ventricle does not pass abruptly into a state of quiescence, but that the increased compression always causes the ventricle to beat slower than the auricles. This slower rate of beating is never independent of the auricular rate, but is connected with it in such a way that the ventricle, instead of beating synchronously with each beat of the auricles, beats synchronously with every second, third, fourth, or more auricular beat. The commonest effect by far, and the one which is most permanent, is that in which the ventricle beats synchronously with every second beat of the auricles; and, indeed, by careful manipulation of the micrometer screw, it is always possible to bring about this particular kind of rhythm, and in many cases to make the ventricle beat permanently with this rhythm for the rest of the experiment. In other cases this rhythm may last for a considerable length of time, and then the ventricle return to a rate synchronous with that of the auricles. So, too, when the clamp is first tightened the half-rhythm may be caused immediately, or the ventricle may cease to beat for a short time, and then commence to beat with intervals between the beats, corresponding to a large number of auricular beats, such as 1 ventricular beat to 6 auricular; quickly passing

through such intermediate stages as 1 ventricular to 5 auricular, 1 to 4, 1 to 3, it settles down to the rhythm 1 to 2, at which it remains permanently, or ultimately returns to a rate synchronous with the auricular (Plate 67, fig. 3).

In some cases the rhythm of the ventricular beats has remained for a long time synchronous with every third beat of the auricles, instead of every second, as in Plate 68, fig. 14, and in other cases, for a shorter time, with every fourth beat. This latter rate of rhythm occurs frequently in the apex of the heart when the clamp is placed across the middle of the ventricle and the beats of the apex and base of the ventricle are compared (see Plate 69, fig. 16); here, too, however, the more permanent rate caused by the compression of the clamp is that in which the apex beats synchronously with every second beat of the base.

These facts show that direct compression of the tissue between the motor ganglia and the ventricle causes a certain number of the impulses to be ineffective as far as the causation of a ventricular beat is concerned, although, as shown by the auricular beats, that compression has not interfered with the rate of discharge from the ganglia. Either, then, the compression of the clamp in the auriculo-ventricular groove has caused a diminution in the excitability of the ventricular muscle without altering the strength of the impulses coming to it, or it has diminished the strength of the impulses to the muscle and so caused it to respond to every second instead of to every impulse. Which of these two solutions is the most probable will be better discussed after the consideration of the effects upon the ventricular rhythm of heating the auricles and sinus only, and of the application of poisons to the ventricle alone.

When by the method described above the auricles and sinus alone are heated, any variations which are noticed in the rhythm of the ventricle must be due to the action of the heat upon the motor impulses before they have reached the ventricular muscle and not to any alteration in the excitability of the muscle itself, for the latter is out of the range of the heating.

In many respects there is a decided resemblance between the action of the clamp and the effect of heating the auricles and sinus upon the rhythm of the ventricle. Thus, if the heating has been sufficient only slightly to accelerate and diminish the auricular contractions, then it is found that the ventricle is able to beat synchronously with the accelerated auricular beats, just as a slight compression of the clamp does not interfere with the regular sequence of ventricular upon auricular beats. If the heating continues the auricular beats become weaker and more rapid, and the curves then show that the ventricle is unable to respond with the same rapidity, and ceasing suddenly to beat synchronously with the auricles, it answers with a single contraction to every two contractions of the auricles. When the heating is removed and the auricles begin to beat less frequently, the ventricle again alters its rate so as to beat synchronously with the auricles with the same suddenness as in its original alteration of rhythm. So, too, an increase in the tightness of the clamp makes the ventricle beat

synchronously with every second beat of the auricles, and upon loosening the clamp the original sequence of beats returns.

Finally, in some cases heating the auricles and sinus causes the ventricle more or less suddenly to cease beating and remain quiescent in the relaxed condition, although, as will be shown hereafter, we have reason to think that the motor impulses are still passing to the muscle; similarly, when the clamp in the auriculo-ventricular groove is tightened sufficiently the ventricle remains quiescent, even although there is proof that the impulses have not been entirely prevented from reaching the muscle (see Plate 69, figs. 17 and 18).

Again, it is to be noticed that when the ventricle is made to beat synchronously with every second beat of the auricles, either by heating the auricles and sinus as in Plate 67, fig. 1), or by tightening the clamp as in Plate 67, fig. 3, the slower contractions are always larger than the previous ones, and this greater force of the contraction is only partly, at all events, due to the fact that with a slower beat the muscle contracts from a position of greater relaxation than with a quicker one. The figures, it is true, show that the lever does fall lower between the contractions when the ventricle is beating slowly than when it is beating quickly—a fact which proves that, with the ordinary rate of beating, the ventricle has not time to relax to its full extent before another contraction commences—but they also show that the lever rises above the level of the previous quicker beats; in other words, the slower beats are accompanied by an increase in the force of the contraction as well as by an increase in the relaxation of the muscle between the beats.

The similarity between the effects of clamping and those of heating the auricles and sinus upon the rhythm of the ventricle is so marked and consistent, that we may fairly conclude that any explanation which is sufficient for the one phenomenon must also resolve the other.

What factors, then, can be conceived as common to these two methods by which such similar results may be produced?

In the first place, it may be argued that the excitability of the ventricular muscle has been diminished by the clamping, and therefore the ventricle can only respond once to every two impulses. The possibility of such a causation for the production of the half-rhythm is shown by the fact that curare or muscarin, when applied to the ventricle alone, does ultimately cause that muscle to beat synchronously with every second auricular beat, without any alteration of the rate of the auricular contractions.

It is, however, to be noticed that these poisons never produce this effect until they have acted so powerfully upon the muscular tissue of the ventricle as markedly to lower the strength of its contractions; that, in fact, as one would expect, any method by which the excitability of the muscle is lowered to such an extent that it is only able to respond to every second impulse, must at the same time greatly diminish the strength of the contractions of that muscle.

This fact that a diminution of the contraction force accompanies the production of

the half-rhythm when it is clearly due to a diminution in the excitability of the ventricular muscle, points unmistakably to the conclusion that the half-rhythm caused by clamping, in which, as has been shown, the ventricle contracts with greater force than before the clamp was tightened, is not due to any diminution of muscular excitability caused by the action of the clamp. This is further shown by the following facts :—

1. The effect of tightening the clamp upon the rhythm of the ventricle is the same in kind, whether the clamp be near the ventricle, as in the auriculo-ventricular groove, or far from it, as at the junction of the sinus and auricles ; *i.e.*, whether the clamp be in a position where it might possibly lower the excitability of the muscle by direct injury, or so far removed as to make it impossible to affect the muscle directly.

2. When the clamp is placed across the middle of the ventricle the base may continue to beat with the same rhythm as the auricles, while the apex beats synchronously with every second, third, fourth, or more beats of the base; and it seems impossible to imagine that a direct mechanical injury across the middle of a muscle should so markedly lower the excitability of one side without perceptibly diminishing that of the other.

3. It frequently happens, as already mentioned, that a standstill of the ventricle occurs immediately upon the clamp being tightened, but that after an interval the ventricle commences to beat again ; if, therefore, the clamp acts by diminishing the excitability of the ventricular muscle, this recommencement of the beats must be due to a gradual recovery of that excitability from the first depressing effect of the increased compression ; this recovery of the excitability ought therefore to be capable of measurement by the method of sending single induction shocks through the muscle at regular intervals, after it has been rendered quiescent by tightening the clamp in the auriculo-ventricular groove. I have made this experiment, and with single shocks sent through every 3 or 5 seconds with the secondary coil carefully regulated so as just to give a contraction at every shock, I could find no evidence whatever that a weaker stimulus was sufficient to produce contractions synchronous with the stimuli, even after a length of time much greater than is ever seen between the time of tightening the clamp and the recommencement of spontaneous beats.

For these different reasons, then, it is most probable that the compression of the clamp does not alter the rhythm of the ventricle by lowering the excitability of its muscular tissue, and we may infer that the same conclusion holds good in reference to the effect of heating the auricles and sinus. Another explanation must therefore be found.

Since the experiments of MAREY and others it is recognised as a fact that every contraction of the ventricle is accompanied by a marked diminution of the excitability of the muscle, so that if minimal stimuli be applied to the ventricle at too rapid a rate the muscle will not be able to contract to each stimulus, because it has not had time to recover sufficiently from the loss of excitability caused by the previous contraction. For this reason, then, we can conceive that any influence like heating the auricles and

sinus only, which causes the motor ganglia to send out impulses at a much quicker rate without increasing the excitability of the ventricle, may cause the ventricle to respond synchronously to every second of these quicker impulses, instead of to every impulse.

Now, although this explanation may be sufficient in the case of the half-rhythm produced by heating the sinus and auricles only, it is clearly inefficient to explain the action of tightening the clamp, for in this latter case no alteration in the rate of the auricular contractions occurs.

Since, therefore, the compression by means of the clamp in the sulcus does not produce its effects upon the ventricle by lowering its excitability, or by altering the rate of the impulses from the motor ganglia, it is most probable that it does act by weakening the strength of the impulses in the same way as suggested by v. BASCH, in order to explain the half-rhythm caused by the use of sufficiently weak electrical stimuli.

Further, the similarity between the effects of tightening the clamp and of heating the sinus and auricles alone, is sufficiently great to suggest that in both cases the effects are produced in the same way, and therefore the main reason why heating the sinus and auricles caused the observed alteration in the rhythm of the ventricle is to be found in the fact that, when the motor ganglia are heated, not only is the rate of discharge of the impulses quickened, but also the quicker impulses are of necessity weaker than before.

To sum up the conclusions arrived at so far, we have the following propositions :—

1. The rhythm of the heart is caused by discrete motor impulses passing to the muscular tissue from certain motor ganglia.

2. Each one of these impulses produces a contraction of the ventricle only when a due relation exists between the strength of the impulses and the excitability of the ventricular muscle.

3. When each impulse is inefficient to cause a contraction of the ventricle, the ventricular muscle has the power of summing up the effects of two or more of these inefficient impulses, and so continues to beat rhythmically, though no longer synchronously with every impulse.

4. The easiest explanation of this summation process is as follows : Every impulse which is inefficient to produce a muscular contraction increases the excitability of the muscle, and therefore makes it easier for a second similar impulse to cause a contraction.

5. The impulses can be made inefficient to produce contractions synchronous with them by lowering sufficiently the excitability of the ventricle, as is seen in the action of poisons, even although the rate and strength of the impulses remain unaltered.

6. The impulses can also be made inefficient when the excitability of the muscle is unchanged by diminishing the strength of the impulse, as is seen in the effects of compressing the tissue between the ventricle and the motor ganglia or of heating the auricles and sinus without heating the ventricle.

7. There is a limit to the extent to which a series of inefficient impulses can raise the excitability of the muscle so that the ventricle can remain absolutely quiescent, even although the impulses still pass to it, when those impulses are sufficiently weakened, as will be shown in the second part of this paper.

The assertion that the rhythm of the heart is normally due to separate impulses discharged from the motor ganglia in the venous sinus, each of which causes a contraction of the cardiac muscle, is not intended to imply that these impulses necessarily travel along simple nerve fibres without passing through one or more interpolated ganglion cells, but only that whatever the nature of the path of the conduction of the nervous impulse may be, separate discharges from the motor ganglia at one end of the path reach the muscle as separate impulses at the other end.

So, too, I have spoken of the motor ganglia in the venous sinus without meaning thereby to assert that these ganglia may not extend slightly beyond the sinus into the auricular septum as asserted by LÖWIT* (for as a matter of fact experiments which I have made expressly for this purpose have convinced me of the truth of his assertion), or that the other groups of ganglion cells found in different parts of the heart may not upon occasion perform motor functions.

The whole question of the action of these different groups of nerve cells deserves separate discussion. In this paper I have purposely abstained from that discussion because my object is to describe certain definite well established facts rather than to enlarge upon all the various topics connected with the theory of the heart's action.

In this first part of the paper, therefore, I have confined myself to the question of the relation of the muscular tissue to the impulses coming to it, and have attempted to prove not only that the normal beat of the heart is dependent upon separate impulses coming to the cardiac muscle, but that, in addition, the muscular tissue is of such a character that if from any cause the impulses discharged from the motor ganglia should become too weak to cause a contraction, the rhythmical action of the heart can still continue though at a slower rate, because each of these impulses, abortive though it is to produce a contraction, increases the excitability of the muscle, and therefore the latter responds rhythmically to every two or three of the impulses coming to it.

This relation between the stimulus and the excitability of the muscle, which in the whole heart is to be regarded as a special safeguard for the maintenance of its rhythmical action and not the prime cause of that action, is on the other hand the chief factor in the causation of the rhythm of the isolated apex of the ventricle.

The large number of investigations on this subject which have been made of recent years may, as far as the rhythm is concerned, be summed up by saying that the muscular tissue of the apex contracts rhythmically under the influence of a sufficient continually acting stimulus, whether that stimulus be electrical, chemical or mechanical. Thus spontaneous rhythmical contractions occur when the constant current or a weak tetanizing current is sent through the tissue, and the rapidity of the rhythm varies

* PFLÜGER'S Archiv, Bd. xxiii., S. 313.

directly with the strength of the current; also fluids containing different chemical substances, especially alkaline substances like sodium hydrate and sodium carbonate, which according to BIEDERMANN* increase most markedly the excitability of the striated muscular tissue, produce when supplied to the apex more or less rhythmical contractions. Further, nutritive fluids alone, such as the blood of the animal itself, cause the same effect, provided that in addition a certain pressure exists within the apex cavity; and the effect of this distension of the walls by pressure, which is the *essential point* in this method of producing rhythmical apex contractions, may fairly be classed as a continuous mechanical stimulation. Here, also, according to LUDWIG and LUCHSINGER,† the rapidity of the rhythm varies directly with the extent of this pressure.

The facts which have just been urged show that the ventricular muscle has the power of summing up the effects of two, three, or more impulses so as to produce a contraction though each of those impulses is inefficient of itself to cause the muscle to contract. In the same way it is possible to conceive that the muscle should be able to sum up the effects of a series of stimuli which follow one another so closely as to deserve the title of a continuous rather than a discontinuous stimulation. If, then, we have reason to suppose that in the first case the discontinuous stimuli ultimately produce a contraction by increasing the excitability of the muscle, so in the second case we may suppose that a continuous stimulation causes a rhythmical series of contractions by acting in the same way. The difference between the two cases would consist in the extent to which the excitability was increased; in the one, the muscle is not rendered sufficiently excitable to contract without the assistance of a distinct separate stimulus; in the other, the excitability is increased so much that no separate stimulus is required: the muscle, in fact, can be spoken of as capable of spontaneous contraction.

PART II.

ON THE ACTION OF THE VAGUS NERVE.

Ever since the brothers WEBER discovered that stimulation of the vagus nerve caused the heart to stand still, physiologists have been incessantly endeavouring to discover the reason of this standstill, with the result that an enormous mass of facts in connexion with the action of the nerve has been accumulated, and a variety of hypotheses have been suggested to explain these facts.

Thus it was found that the vagus at one time causes complete stoppage, at another only slowing of the heart's rhythm; this fact has led to the view that the complete cessation of beats is simply a prolonged slowing, and therefore that the nerve by its direct action upon the motor ganglia causes the discharges from the ganglia to take place at a slower rate.

itzungsber. d. k. Akad. d. Wiss. (Wien). Bd. lxxxii., 1880.

† PFLÜGER'S Archiv, Bd. xxv., S. 211.

Another view, which largely depends for its support upon the action of various poisons, is, that the nerve does not produce standstill by direct interference with the motor ganglia, but because it excites some inhibitory mechanism which is interpolated between these ganglia and the muscular tissue. Both these views have one hypothesis in common, viz.: that the inhibitory action of the nerve is due to the prevention of the discharges from the motor ganglia from reaching the muscular tissue, and not to the action of the nerve upon the muscle itself. In pharmacological literature especially this hypothesis has become so predominant that again and again the statement is made that such and such a poison paralyses or stimulates some part or other of the vagus nerve, when the facts only show in the first case that the vagus is no longer able to produce standstill, and in the second that the poison has by its action caused the heart to beat slower.

Again, a number of observers, notably SCHIFF,* have asserted that stimulation of the vagus nerve of the Frog under certain circumstances always causes acceleration of the heart's rhythm, and not slowing: a result which, conjoined with the action of atropia, has led to the supposition that the Frog's vagus contains accelerator as well as inhibitory fibres, and a fresh set of hypotheses has been made with respect to the relative vitality of these two sets of fibres.

Finally, it has been long known that the contractions which immediately follow the standstill caused by vagus stimulation are much weaker than the normal contractions, and NUËL† has shown that stimulation of the nerve weakens, at all events the auricular contractions, even without a preliminary standstill.

We have, therefore, according to present views at least, three sets of fibres in the Frog's vagus, viz.: fibres which are capable of slowing or entirely preventing the discharges from the motor ganglia; fibres which accelerate those discharges; and fibres which *in some way or other* diminish the force of the cardiac contractions. In addition, we have various statements that sometimes only one vagus is active, that at certain times of the year the vagus loses all power, &c.

The literature of the subject then affords ample evidence of considerable discrepancy not only as to the explanation of the action of the vagus, but also as to observed facts connected with that action. The reason of this confusion will appear in the following pages, and I will say at present that it is based upon a view of the nature of the action of the vagus, which appears to me to be too much one-sided. Too great prominence has hitherto been assigned to the action of the nerve upon the motor ganglia—too little to its action upon the muscular tissue.

The most striking feature of vagus stimulation is a more or less prolonged standstill of the heart. There is no reason *à priori* to assign this standstill to the action of the nerve upon the rate of the discharges from the motor ganglia rather than to its action upon the muscular tissue of the heart. Either conception is perfectly possible, and its truth can be tested directly by experiment.

* PFLÜGER'S Archiv, Bd. xviii., S. 172.

† Ibid., Bd. ix., S. 83.

Thus if standstill is invariably due to a slowing of the rate of the discharges from the motor ganglia, experiment ought naturally to show that the beats which first occur after the standstill are more infrequent than before the nerve was stimulated, and that the subsequent recovery of the rhythm up to or beyond the original frequency takes place gradually and not abruptly. Also a stimulation which is unable to cause complete standstill ought to produce the effect nearest to standstill, viz.: a greater or less slowing of the heart independently of any alteration in the force of the contractions.

If, on the other hand, standstill is invariably caused by the action of the nerve upon the muscular tissue, so that the latter does not respond to the impulses coming to it, then we should expect to find (in accordance with the law of BOWDITCH* that the force of the contractions of the ventricle is not dependent upon the strength of the stimulus); that the first beats which occur after the standstill are very small, that the force of the contractions gradually increases up to or beyond the orignal force, and that the rate of rhythm after the standstill is not necessarily slower than before the stimulation of the nerve. Also a stimulation which is unable to cause complete standstill ought to produce the effect nearest to standstill, viz.: a more or less marked diminution in the force of the contractions independently of any alteration of rhythm.

The majority of physiologists have hitherto accepted the first of these views as the *invariable* explanation of the standstill of the heart caused by the action of the vagus nerve, and in accordance with this view always speak of the vagus as causing *inhibition* of the heart's action.

In this present paper I propose to give evidence that, at all events in the heart removed from the body, the second view is the true one, and in accordance therefore with this conception I have throughout spoken of the vagus as causing *quiescence* of the heart.

It is of course possible and indeed probable that both these views may be true, and that therefore the vagus may cause standstill sometimes by the one action and sometimes by the other. Whether this is so or not I am not at present able to judge; I can only say that in the suspended heart I have never as yet seen any reason to suppose that the vagus is capable of producing such a prolonged slowing of the rate of the discharges from the motor ganglia as to entitle that slowing to the name of standstill of the heart; while on the other hand the quiescence of the heart produced by the action of the nerve upon the force of the muscular contractions may last for a considerable time.

Again, physiologists and pharmacologists have hitherto considered that the inhibitory action of the nerve is abolished when its stimulation no longer causes standstill or slowing of the heart. This view will clearly require modification if the quiescence of the heart is due to the action of the nerve upon the force of the contractions rather than upon the rate of the discharges from the motor ganglia. Indeed, it will be no

* LUDWIG'S Arbeiten, 1871, S. 139.

longer possible to speak of the inhibitory action of the nerve apart from its whole action. In every case, then, it will be necessary, before we can assert that its action is abolished, to determine that the vagus is no longer able to cause any alteration, not only in the rate of rhythm, but also in the strength of the cardiac contractions.

I use the term *alteration*, rather than *diminution*, of the force of the contractions advisedly, for it will not be sufficient to show that the vagus is no longer able to cause any diminution; it must also be shown that it is unable to cause any *increase* of the force of the beats, because, as will be seen, the most permanent and invariable function of the vagus (in the heart removed from the body, at all events) is to *increase the strength* of the muscular contractions.

Before describing the results of the experiments upon which the assertions made above are based, it is desirable to say a few words about the conditions under which they were conducted. In every case the vagus nerve was carefully dissected out nearly or quite up to its ganglion and placed on the electrodes, so that there was about a quarter of an inch of free space between the electrodes and the nearest tissue. The experiments were made in the months of February, March, April, May, June, and July of this year, and the animals used were Toads or large, in most cases freshly caught, specimens of *Rana temporaria*. The left vagus was invariably used, and I can safely assert that in no single instance has its stimulation failed to produce some effect upon the heart, although, as will be seen, that effect is not always the same.

In my first experiments the heart was suspended by means of KRONECKER'S forceps attached to the bulbus aortæ, the ventricle was slit open from base to apex, and the contractions of the ventricle alone were registered by means of a lever which was attached by a thread to the very apex. The typical effect of vagus stimulation under these circumstances is seen in Plate 67, fig. 4, which shows that by this method complete inhibition can be obtained; that when the ventricle begins to beat again the first beats are very small, but that they soon begin to increase in size and shortly after the end of the stimulation reach a maximum which is very muchgreater than be for the stimulation. From this maximum the force of the contractions very slowly diminishes to the original size.

I give this curve simply to show that the nature of the phenomena seen upon vagus stimulation when the clamp is used cannot be ascribed to the use of the clamp, for, as the subsequent curves will show, there is no essential difference between the curves produced whether the clamp is absent or present. As, however, the results are much more interesting when the auricular and ventricular beats are simultaneously recorded, I will proceed at once to describe the effects of stimulating the nerve when the clamp is in the auriculo-ventricular groove and is tightened so as just to hold the tissue; the ventricle is therefore beating synchronously with every beat of the auricles.

As the large majority of my experiments have been made with the clamp in this position, I am enabled to draw conclusions from a very great number of curves, each one of which represents a separate stimulation of the vagus nerve. Upon examination

of these curves taken as a whole it is seen that although stimulation of the vagus produces different effects at different times, these effects can all be reduced to the three following types :—

1. Complete quiescence of both ventricle and auricles, followed by contractions which at first are scarcely visible, but which rapidly increase in size until at the maximum they are much greater than before the stimulation of the nerve ; from this maximum they very gradually decrease until the original force of contraction is again reached (Plate 67, fig. 6, curve B).

2. During the stimulation no quiescence of either ventricle or auricles, but simply a diminution of the size of the contractions, followed by a rapid and marked augmentation of the contraction curve beyond the original height, and then a slow gradual diminution to the size before the nerve was stimulated (Plate 67, fig. 6, curve A ; Plate 68, figs. 8, 9, &c.).

3. No primary diminution, but from the commencement of the stimulation the beats increase in force, and after a time gradually return again to the original size (Plate 68, fig. 10). Between these three types every conceivable variation may occur, so that a series of curves may be selected in which no line of demarcation can be drawn between complete primary quiescence, or to use the usual term, inhibition, on the one hand, and a simple primary augmentation of the contraction force on the other. Such a series is to a certain extent represented by Plates 67, 68, figs. 6, B, 6, A, 8, 9, 10.

Further, the curves show that not only does the height of the contractions vary in a graduated series from the null point on the one side up to a height much greater than before the stimulation on the other, but also that this variation is independent of the rate of rhythm. In the majority of experiments the rhythm is seen to be decidedly accelerated by the stimulation of the nerve, in others no alteration of rhythm can be perceived. Thus in Plate 67, fig. 6, B, as soon as beats appear after the primary quiescence they show a slight acceleration of rhythm ; so, too, in such figures as Plate 68, figs. 9, 10, where the nerve stimulation produced a primary diminution and a primary augmentation of the force of the contractions respectively, the rhythm is seen to be accelerated or unaltered from the commencement of the stimulation.

In all cases where acceleration occurs, the return to the original rate is slow and gradual, in the same way as the return to the original contraction force.

Another proof that this quiescence, which is caused by stimulation of the vagus, is not due to any interference with the rate of discharge from the motor ganglia, is most markedly shown by the fact that stimulation of the nerve often reduces the ventricle to a state of complete quiescence, while the auricles not only continue beating but beat with greater rapidity than before. Thus we may have complete quiescence of the ventricle with the auricles so nearly quiescent that their accelerated contractions are barely visible on the curve (Plate 67, fig. 7), in other cases with the auricular contractions more and more plainly visible (Plate 67, fig. 5), until finally we may obtain curves in which the ventricular beats are diminished down to complete quiescence, while the

auricular are, from the commencement of the stimulation, augmented in force (Plate 67, fig. 11). The reverse, however, never occurs—I have never seen quiescence of the auricles with simultaneous primary augmentation in the force of the ventricular contractions.

A careful examination of the large number of curves which I possess will, I venture to think, afford clear evidence of the truth of the following statements :—

1. The effect of stimulation of the vagus nerve, which is most constant, is an augmentation of the force of the contractions, both of the auricles and ventricle; an augmentation which cannot be regarded as a mere rebound, so to speak, from a previous diminution of the force of the contractions.

2. In the case of both auricles and ventricle a series of curves can be obtained which show that stimulation of the vagus is able to produce a perfect gradation of effects upon the strength of the contractions irrespectively of the rate of rhythm : a gradation which extends from a simple augmentation of the force of the contractions as the result of the nerve stimulation, down to so great a primary diminution of that force that the contractions are no longer visible, and therefore quiescence results from the stimulation of the nerve.

3. The auricles and ventricle may be in different phases of this gradation at the same moment, with the qualification that, if quiescence be called the lowest and primary augmentation of the force of the contractions, the highest term of the series, the ventricle, is always in a lower phase than the auricles.

The auricular curves are different from the ventricular in one or two other details ; thus the maximum effect on the force of the contractions is reached more quickly after the end of the stimulation in the former than in the latter, so that the auricular beats have already reached their maximum, while those of the ventricle are still increasing. (Plate 68, figs. 9, 10). The auricles also return to their original force of contraction much more quickly than does the ventricle ; as is seen in Plate 68, figs. 9, 10. The same figures show another peculiarity of the auricular curves, which is especially characteristic of the Toad's heart, viz.: after the maximum force of contraction has been reached, the contractions gradually diminish to a height less than before the stimulation, and then again increase up to or slightly beyond their original height : a peculiarity which I have never as yet observed in the ventricular curves.

I have already said sufficient to justify the assertion which I made above, that the vagus is never absolutely inefficient ; it always produces some effect or other upon stimulation, and I have described a variety of the effects which it does produce. Hitherto I have considered the curves as a whole, and have shown that the different effects seen when the nerve is stimulated—as far at least as the action of the nerve upon the force of the contractions is concerned—can all be arranged in a graduated series in which no line of demarcation can be drawn separating one especial effect from another. It remains to be seen whether a similar gradation can be produced

by a series of stimulations in each separate experiment, and, if so, what conditions are necessary for its production.

In the first place, stimulation of the vagus is much more likely to reduce the force of the contractions down to complete quiescence immediately after removal of the heart from the body, than after it has been suspended for some time; and, indeed, a variety of facts can be brought together which all point in one direction, viz.: that the production of quiescence by stimulation of the nerve stands in intimate relation with the existence of a suitable nutrition of the heart. Thus it frequently happens that typical inhibition can be obtained before the heart is removed from the body, although after it has been suspended it is impossible by any strength of stimulation to reduce the strength of the contractions to such an extent as to cause standstill.

Again, experiments made in June for this express purpose show that if the heart be suspended as quickly after removal as possible, and the circulation be kept intact till the last moment, then, with a certain strength of current the first stimulation caused absolute quiescence; the next, although of the same strength and length, only a primary diminution of the force of the contractions, and with succeeding stimulations of the same strength and the same length and following upon one another at as nearly as possible the same intervals of time, there was a decided tendency for the primary diminution of the contraction force not only to diminish in extent, but also to affect a smaller number of beats, until at last the stimulation caused an increase in the force of the contractions with a previous diminution of only one or two or even no beats at all (see Plate 68, fig. 9).

Indeed, it can be said that in the course of each separate experiment the successive stimulations of the nerve tend to show the same gradation of effects from complete quiescence followed by augmentation on the one hand, up to a simple primary augmentation of the force of the contractions on the other, as has already been pointed out from the consideration of the whole number of curves.

In the second place, the examination of my curves indicates that the nature of the special nutritive condition of the heart, upon which the phenomenon of vagus standstill depends, may possibly be given by the chemical examination of a large number of hearts at different times of the year, for as far as I can judge from this first series of experiments, standstill is more likely to occur upon vagus stimulation, after the heart has been cut out and suspended, in the early spring months of the year than in the summer months. Indeed, in some cases in March, stimulation was still able to cause quiescence even after the heart had remained suspended for nearly two hours.

In Plate 68, fig. 12, curve A, I give an example of quiescence of the auricular contractions caused by vagus stimulation, which was obtained about an hour and a half after removal of the heart from the body, during which time the vagus had been stimulated nine times. In curve B of the same figure, which is a continuation of curve A (except that between A and B the vagus was stimulated so that the beats at the commencement of the curve B represent the maximum contractions due to that stimulation) the vagus was stimulated with the same strength of current at frequent intervals, so that the auricle was not allowed to reach the maximum of its contractions. The curve shows well not only that quiescence was at first produced, but also the resolution of that quiescence into barely visible rhythmical contractions.

From these experiments the conclusion can be drawn that the impairment of the nutrition of the heart caused by the removal of the circulation is not of itself sufficient to take away from the vagus the power of reducing the force of the contractions to the null point; but rather that, in addition, some unknown factor, upon which this diminution of the beats depends, is more powerful at one time than at another.

In all that has been said hitherto, no evidence has been given that the vagus is able to cause any slowing of the rate at which impulses are discharged from the motor ganglia, but, on the contrary, clear evidence that it is able to accelerate that rate, and although the large majority of my curves point directly to that conclusion, yet occasionally a curve is obtained in which an undoubted slowing has taken place. In some cases it is possible that the slowing may be due to the failure of certain impulses to produce a contraction as is undoubtedly the case in the slower ventricular beats seen in Plate 69, fig. 15, where the stimulation of the vagus caused the ventricle to beat for a time synchronously with every second auricular beat. On the other hand, such slowing as is seen in Plate 67, fig. 13, where the recovery of the rate of rhythm after the end of the stimulation was gradual both in auricles and ventricle, cannot be explained, except upon the supposition that the nerve stimulation had slowed the rate of the discharges from the motor ganglia.

Indeed, the fact that the vagus is able to cause a slowing of the heart's rhythm is so well established as not to admit of doubt; all I contend for is, that that slowing is not always a *sufficient* explanation of the phenomenon known as vagus inhibition.

Further, I venture to suggest that the hypothesis that the vagus contains two sets of fibres going to the motor ganglia, of which the one causes upon stimulation acceleration, the other a slowing of the rate of discharge from the motor ganglia, is no more necessary than the similar supposition that the nerve contains two sets of fibres supplying the muscular tissue, of which the one causes a diminution, the other an increase of the force of the contractions.

The experiment from which Plate 67, fig. 13, is taken shows clearly the rapid diminution of the power of the vagus to produce a slowing of the heart when the heart is removed from the body, and suggests that that removal affects the action of the nerve upon the rate of rhythm in the same direction as it affects its action upon the force of the muscular contractions. Thus, in Plate 67, fig. 13, the effect of the first stimulation of the nerve immediately after the heart was suspended, is given. The second stimulation, about a minute after the first, still caused a decided slowing, but very much less marked in extent than before. The third stimulation showed that the nerve was no longer able to produce any slowing, although the effect upon the force of the contractions was as great as in the previous stimulations.

On the influence of the vagus nerve upon the excitability of the ventricular muscle.

Seeing that the vagus acts so powerfully upon the force of the muscular contractions, it is natural to expect that it also has an influence upon the excitability of the muscular tissue. The nature of this influence can be determined by the following considerations.

In the first part of this paper I have attempted to prove that the ventricle beats synchronously with the auricles when a due relation subsists between the strength of the impulses from the motor ganglia and the excitability of the ventricle. When, however, the strength of the impulses is diminished either by clamping or by the action of heat upon the motor ganglia, this due relation is destroyed and the ventricle either beats synchronously with every second, third, or more contractions of the auricles or else does not beat at all. If under these circumstances the excitability of the ventricular muscle be increased, then the relation between the strength of the impulses and the muscular excitability, which is necessary for synchronous contractions, will be restored, either fully or partially, according to the extent to which the excitability is raised. On the other hand, if the excitability be lowered then that due relation will be still further destroyed, and each beat of the ventricle will follow upon a still larger number of auricular beats than before.

In accordance with this method of testing the excitability, experiment proves that the vagus may cause a diminution of the excitability of the ventricle during the first part of its action, during, therefore, the period when it is known to diminish the force of the contractions; and may cause an increase of excitability when it augments the force of the contractions.

I will now proceed to give the facts upon which the truth of this proposition depends, and will first examine the action of the nerve when the clamp in the auriculo-ventricular groove is tightened so as to make the ventricle beat synchronously with every second or third beat of the auricles.

In this case the most striking effect of stimulation of the nerve is the alteration which is produced in the rate of the ventricular rhythm rather than the variations in the force of the ventricular contractions. It is true that the nerve stimulation may still cause the force of the ventricular contractions to be diminished and augmented in the same way as already described, but neither the diminution nor the augmentation are so manifest as when the ventricle is beating synchronously with every auricular beat; this is doubtless largely owing to the greater size of the ventricular contractions in consequence of their slower rate of rhythm. This is, however, not the main distinction between the two cases.

When the ventricle is beating synchronously with every beat of the auricles we have seen that this synchronism continues during the period of diminution as well as during the period of augmentation of the force of the contractions; when, however, the ventricle is beating synchronously with every second beat of the auricles the same law does not necessarily hold; in many cases stimulation of the nerve causes a sudden alteration in the relation of the ventricular to the auricular rhythm.

In the first place the rhythm of the ventricle becomes synchronous with that of the auricles for a longer or shorter period. This period of synchronism corresponds to the time when the contractions would have been greatest if the ventricle had been beating in due sequence with the auricles; it may therefore occur sometimes during the stimula-

tion, at other times some considerable time after the end of the stimulation. Thus in Plate 68, fig. 14, the ventricle was beating synchronously with every third beat of the auricles ; for a definite period after the end of the stimulation of the vagus its rhythm was changed so that it beat synchronously with every second instead of with every third auricular beat. Similar figures might be given to show how the vagus causes the ventricle to beat synchronously with every beat of the auricles instead of with every second beat.

These curves show that stimulation of the vagus increased the excitability of the ventricle sufficiently to enable it either wholly or partially to recover for a time the normal sequence of its beats upon those of the auricles, and also that increase of excitability took place at the same time as the maximum increase in the force of the contractions.

In the second place, stimulation of the vagus may cause a primary slowing of such a character that a variable number of auricular beats are dropped out from the ventricular curve, and then afterwards the ventricle may regain its original rhythm or even become synchronous with every beat of the auricles (Plate 69, fig 15).

Further, this slowing of the ventricle may not only be coincident with an acceleration of the auricles, but in fact is more likely to occur when stimulation of the nerve causes a marked auricular acceleration. This, at first sight paradoxical, assertion follows necessarily upon the arguments put forward in the first part of this paper, if it be assumed that the vagus diminishes the excitability of the muscle at the same time that it depresses the strength of the contractions ; for the greater rapidity of the auricular contractions denotes not only quicker but also weaker impulses from the motor ganglia ; and it is clear that, if the impulses be weakened at the same time that the excitability is lessened, a larger number of impulses will require to be summed up in order to produce a contraction, than if the excitability only is diminished.

Again, if the clamp be placed across the middle of the ventricle, and the contractions of the base and apex of the ventricle be registered, the same diminution of excitability can be observed. Thus, when the apex is beating synchronously with every second or, as in Plate 69, fig. 16, with every fourth beat of the base, then coincident with the diminution and acceleration of the contractions of the base, which occur during the stimulation of the nerve, the beats of the apex take place at a slower rate than before, because each apex contraction corresponds to a larger number, and therefore probably to a longer series of base-contractions than before the stimulation.

Thus in the instance given (Plate 69, fig. 16) I have marked the corresponding contractions on the two sides with the same numbers, and it is seen that before the stimulation of the vagus the relation between the rhythm of the apex and the base was such that each apex-contraction corresponded to four base-contractions. During the stimulation the beats of the base became weaker and more frequent, while those of the apex were so much slower that only two beats took place, of which the first corresponded to twelve beats of the base and the second to eight beats. After the stimulation the original relation between the rhythm of the apex and base was restored, so that each apex-contraction again corresponded to four base-contractions. Curves similar to this are those most frequently obtained with the clamp in this position.

These facts alone make it probable that the vagus lowers the excitability of the muscle at one time and increases it at another. Now although this diminution of excitability occurs at that period of the vagus action when the stimulation of the nerve is known to cause a diminution of the force of the contractions, yet it is clear that the connexion between the two is relative and not absolute. As has been seen, when the contractions are synchronous with the impulses, stimulation of the nerve is able to reduce the force of the contractions to the vanishing point, and yet up to the last moment of visible contractions every impulse is followed by a contraction—*i.e.*, the excitability does not in this case fall sufficiently, in relation to the strength of the impulses, to prevent the muscle from responding to every impulse, even although the contractions become so small as to be almost invisible. Since, therefore, we have reason to suppose that the vagus stimulation does diminish the excitability at the first period of its action—*i.e.*, at the time when it diminishes the force of the contractions—and yet leaves the cardiac muscle still able to respond synchronously to the impulses, provided that the latter have not been diminished in strength, the inevitable conclusion is, that normally the excitability of the muscular tissue is greater than is necessary to enable it just to respond to every impulse. In other words, a range is allowed within which the excitability may fluctuate without thereby preventing the synchronous response of the muscle to the impulses, as long as the strength of the impulses does not diminish. As a rule the lower limit of this range is not passed, in consequence of vagus stimulation, when the strength of the impulses is not interfered with; and therefore in these cases the diminution of excitability caused by the vagus is not rendered visible. This diminution can, however, be made manifest by first reducing the excitability of the muscle to some extent. Thus if muscarin be applied to the ventricle alone, when it is beating synchronously with every beat of the auricles, and the vagus be stimulated when the muscarin has, without altering the synchronism, greatly reduced the force of the ventricular contractions, then the stimulation may cause the ventricle to beat synchronously with every second auricular beat for a short period, showing that the stimulation of the nerve, added to the effect of the muscarin, has reduced the excitability of the ventricle to a greater extent than the muscarin alone had done.

Hitherto I have chiefly spoken about the *diminution* of excitability caused by the vagus, and will therefore now proceed to give further proofs that the vagus increases the excitability of the muscle at the same time that it augments the force of its contractions. The most striking proof of this fact, in addition to what has been already said, is given by the effect upon the ventricle of stimulation of the nerve when the ventricle is rendered quiescent either by heating the sinus and auricles or by tightening the clamp in the auriculo-ventricular groove.

In both cases the effect is the same, and is well exemplified in the series of Plate 69, fig. 17, curves A, B, C, D, which represent the effects of vagus stimulation in a single

heating experiment. Plate 69, fig. 18, shows the corresponding effect when standstill is produced by clamping.

A consideration of these and similar curves shows that when, whether from the effect of clamping alone or from the combined effects of heating the motor ganglia and clamping, the ventricle is not beating, stimulation of the vagus causes a series of ventricular beats which commences as a rule some little time after the end of the stimulation. These contractions last for a certain time, and then the ventricle again becomes quiescent, until, with a new stimulation of the nerve, a new group of contractions is produced. Again, the contractions in each of these series are synchronous with the auricular contractions, and are strong vigorous contractions such as would have been produced had the ventricle been beating when the nerve was stimulated. This shows that the beats in each of these series, as far as their mere occurrence is concerned, are due to motor impulses which pass to the ventricle at the same rate as to the auricles, and therefore that during the previous quiescence the motor impulses were still passing to the ventricle, but were not able to produce any contractions. Again, these series of contractions do not as a rule take place during the stimulation of the nerve, but some time after the stimulation, and the position of each series corresponds closely to the position of the maximum contractions seen after the end of the stimulation of the nerve in the ordinary curve of vagus stimulation. An explanation, therefore, of this action of the vagus is clearly given by the supposition that by the action of the nerve the excitability of the ventricular muscle is increased at the same time that the force of the contractions is increased. Hence as soon as the excitability is sufficiently raised the motor impulses which have been rendered inefficient by the action of the clamp, or by the action of heat upon the motor ganglia, are able to cause contractions: and these contractions last until by the passing off of the vagus influence the excitability has again sunk too low for the impulses to be able to cause a contraction.

The beats in each series are not necessarily synchronous with every impulse from the beginning to the end of the series. As far as I have seen they are usually synchronous in the middle beats of each group, but the series may begin and end with one or two beats which are synchronous with every second auricular contraction instead of with every one. This latter form of curve simply denotes that the rise and fall of the excitability has not been so abrupt as in the first case, as can easily be seen by drawing a diagram to represent the curve of excitability in relation to the strength of the impulses.

Further, it was noticed in the course of the experiment from which Plate 69, fig. 17, is taken, that after a while the same strength of stimulation caused a series of ventricular contractions when the auricles and sinus were not heated, and no effect whatever when the nerve was stimulated during the time of heating; in other words, when the strength of the impulses was made still weaker by the heating, the rise of excitability caused by the vagus stimulation was not sufficient to make those impulses efficient to cause ventricular contractions.

Also (as is seen in Plate 69, fig. 17, B, C, D) during the course of the experiment each series of ventricular contractions lasted on the whole a shorter and shorter time, and commenced later and later after the end of the stimulation—a fact which is to be explained by the progressive exhaustion of the whole heart.

On the action of the vagus upon the ventricular muscle when that muscle is beating with alternately strong and weak beats.

When the heart is suspended in the manner already described and the ventricle is beating in due sequence with the auricles, it frequently happens that, although the auricular contractions are all equal in force, the ventricle is seen to be beating with alternately weak and strong contractions, as is shown in Plates 67, 69, figs. 7, 19, 21. If, now, the vagus be stimulated, this alternation in the size of the ventricular contractions disappears simultaneously with the increase in the force of the contractions caused by the nerve stimulation, and reappears again as the contractions return to their original size; and if the nerve be stimulated a second time, while the contractions are still equal in force, then with the primary diminution in force caused by the stimulation the alternately weak and strong beats again appear, and again give way to beats of equal force with the subsequent augmentation of the force of the contractions. This is well shown in Plate 69, fig. 19.

It is difficult to come to any final conclusion upon the causation of this alternation in the strength of the ventricular contractions, though it is possible to somewhat limit the area of discussion. In the first place, they are clearly local in origin, for by clamping across the middle of the ventricle the same alternation in strength is sometimes seen in the beats of the apex, while those of the base of the ventricle remain of the same strength throughout (Plate 69, fig. 20). Here, too, the vagus removes this alternation in the same way as in the case of the whole ventricle. Also, as far as I have seen, this phenomenon is confined to the ventricle. I have never seen any appearance of this alternation of contraction-force in the auricular beats. In the second place, they are not necessarily due to the clamp, for the same alternation may occur when the ventricle alone is suspended and no clamp is used.

Further, the sizes of these alternately weak and strong contractions are clearly dependent upon each other, so that, other things being equal, the more marked the diminution in the weak contractions the more marked also is the increase in the strong ones which alternate with them; therefore if, as sometimes happens, the alternation disappears, temporarily though it may be, when the ventricle is moistened with normal saline solution, then the size of the equal contractions is intermediate between the size of the alternately weak and strong ones. This relation is beautifully seen when, as is apt to occur, a secondary rhythm appears in these contractions, as is shown in Plate 69, fig. 21. Here it is seen that the weak contractions increase to a maximum while the strong contractions diminish simultaneously to a minimum, and *vice versâ*, the minima of the weak correspond to the maxima of the strong.

Now we know from the experiments of BOWDITCH* that the force of the ventricular contractions is independent of the strength of the stimulus. The explanation, therefore, of this alternation in the force of the contractions must be sought for in the

* *Op. cit.*

muscular tissue itself, and it seems to me that the most probable explanation is that a larger amount of tissue contracts when the beats are large than when they are small, and that, therefore, in all probability, certain portions of the ventricle respond only to every second impulse, while other portions respond to every impulse. The observations of AUBERT * show that by the direct action of a blow a circumscribed area of the ventricular muscle can be made to remain quiescent, while the rest of the ventricle is contracting rhythmically. I am inclined, therefore, to suggest that, owing to some cause in the manipulation, such as cutting open the ventricle, or some other cause which affects the ventricle unequally, the excitability of the ventricular muscle is at the time not absolutely the same throughout, so that, although the impulses remain the same in strength, yet certain parts which possess a lower excitability are able to respond only to every second impulse, while the rest of the tissue responds to every impulse. In this way, if the strength of the contractions depends upon the amount of tissue contracting, we see not only that every second beat must be larger, but also that the size of each strong contraction must vary inversely as the size of each corresponding weaker contraction.

Upon this assumption the action of the vagus admits of easy explanation, for it is evident that the alternation disappears during the time when we have reason to suppose that the maximum rise of excitability caused by vagus stimulation is produced, and reappears when the normal excitability is regained, or when the excitability is lowered below the normal by the action of the vagus. If, therefore, we look upon this alternation in the strength of the contractions as due to a local lowering of excitability, so that certain portions contract once only to every two contractions of the rest of the ventricle, then it is clear that as soon as the excitability of these parts is raised sufficiently for them to respond to every impulse, every contraction must become as strong as every other contraction, for every part of the ventricle will contract to every impulse. On the other hand, if the general excitability is lowered there must be a greater tendency for this alternation to occur ; thus, it sometimes happens that when the ventricle is beating with contractions of equal height, stimulation of the vagus causes not only a lowering of the height of the contractions, but also a temporary appearance of alternately strong and weak beats.

Also, when there is a great difference in size between the consecutive contractions, it is possible for the stimulation of the vagus to fail in increasing the excitability of all portions of the ventricle to an extent sufficient to cause them to respond synchronously with every impulse, so that the alternation does not entirely disappear in any part of the curve, although the difference in height between consecutive beats is not so great during the period of augmentation of the force of the contractions as before the stimulation ; in other words, the nerve stimulation has sufficiently increased the excitability of some portions of the affected area, though not of the whole of it.

* PFLÜGER'S Archiv, Bd. xxiv., S. 357.

On the action of the vagus nerve upon the tonicity of the heart.

The question whether any particular influence upon the heart causes the relaxation of the tissue to become greater or less than the normal, is always attended with the difficulty that it is impossible to say what the normal amount of relaxation really is. Thus with the ordinary rate of rhythm the amount of relaxation is always greater with a slower beat than with a quicker one, a fact which is to be explained by the simple supposition that the condition of contraction has not absolutely passed away when the next contraction takes place unless the contractions follow at a slower rate than the normal; so that for this reason alone a greater relaxation must occur if the vagus causes a slowing of the beats and a less relaxation if the beats are made more frequent. On the other hand, if the tissue is relaxed when the rhythm of the beats is accelerated or unaltered, we may then fairly speak of an increased relaxation of the tissue, and if the relaxation is less, when the rate is the same or slower, then we may speak of a diminished relaxation of the tissue. Thus, for instance, every experiment shows that muscarin and lactic acid truly increase, while sodium hydrate and digitalin truly diminish the normal relaxation of the tissue.

Now in endeavouring to estimate the extent of relaxation in a hollow muscle like the ventricle, it is clear that the measurement of its capacity will afford a better chance of obtaining a visible amount of relaxation than any mere linear measurement such as is given by the method described above. I have therefore endeavoured to find out whether the vagus really causes any relaxation of the ventricle by the following method :—

The instrument which I have used is a modification of Roy's tonometer* and is represented in Plate 70, figs. 22, 23. The glass chamber A is in connexion by means of a metal tube with the recording chamber B, to the lower end of which the membrane used by Roy is tied and within which the piston attached to this membrane is able to move up and down and so to cause corresponding movements of the lever. The funnel and tap on the top of the metal chamber B is for the purpose of filling this chamber and the connecting tube C with oil. The tap in the tube C enables us to free this tube from air; and somewhat below the middle of the chamber B is a tap which allows oil to be drawn out of the apparatus by means of the indiarubber tube D, and so to exhaust the pressure within the whole apparatus and raise the lever to the horizontal position as described by Roy in the original description of his tonometer. The glass chamber A is provided with a vulcanite stopper which fits absolutely tight, so that any variation in the contents of the chamber A must be transmitted to the chamber B through the tube C, and cause a corresponding variation in the position of the lever. There is no necessity that the chamber A should be filled with oil; it may be filled with normal salt solution or any other fluid without preventing the working of the membrane, because the lower extremity of the chamber B is on the same level with the top of the chamber A, and therefore the oil in the chamber B will not be contaminated by the salt solution in A.

The vulcanite stopper, of which a separate drawing is given on Plate 70, fig. 23, contains five holes of exactly the same diameter; small portions of a piece of metal tubing which has been ground accurately to fit these holes can be inserted into one or more of them, according to the requirements of each experiment, and those

* Journal of Physiol., vol. i., p. 452.

holes which are not required can be closed absolutely by vulcanite plugs, of which one is represented in the drawing.

Different instruments can be fixed into any of these pieces of metal tubing, and so the apparatus be made available for a variety of experiments, either upon the whole heart or on the ventricle or apex alone.

In the figure the vulcanite stopper is represented when fitted up for the purpose of investigating the action of the vagus nerve upon the whole heart when an artificial solution of blood is flowing into it.

The metal cannula E, which fits tightly into any one of the pieces of metal tubing, is tied into the commencement of the venous sinus—the small glass cannula in the middle is fixed into one of the aortic trunks; the plate F is a cork plate fixed on a piece of thin metal, which is soldered to its corresponding piece of metal tubing. This piece of tubing can either be sealed hermetically or be left open and attached to a manometer, in order to observe the pressure within the apparatus. The glass tube G, which is hermetically sealed at both ends, carries within it a pair of platinum electrodes, bent at their extremities into the form of a loop. Two very small holes are blown exactly opposite to each other in the middle of this tube, and the electrodes are fixed within it so that the line joining the two holes is just below the lowest point of the electrodes. Through these holes the vagus nerve can be drawn by a thread attached to its extremity, and by pinning the end of the thread on to the cork slab F, the nerve will remain always in contact with the electrodes. Since the glass tube which contains the electrodes is closed both above and below, the air within it does not escape, and therefore the part of the nerve which lies on the electrodes is during the whole time of the experiment surrounded by air, although the heart itself is plunged in normal salt solution. In this way all escape of current is avoided.

While the heart is still within the body the arterial cannula is tied into the right aortic trunk, and the metal venous cannula into the commencement of the venous sinus (this cannula has an internal diameter of fully 3 millims.). The two superior venæ cavæ are tied without injuring the vagus nerve on the left side, the roots of both lungs and the left aortic trunk are ligatured, the lungs are cut away, and the heart with the left vagus intact is removed from the body. The cannulæ are then filled with blood solution and slipped on to their respective pieces of metal tubing; the heart is fixed in its place by means of pins stuck through the œsophagus and surrounding tissue into the cork slab F. The vagus nerve is then gently drawn through the glass tube over the electrodes and fixed by means of a pin through the thread attached to its extremity.

The vulcanite stopper is now placed in position in the chamber A, and the superfluous salt solution allowed to escape through that hole, which is afterwards closed by the vulcanite plug, as shown in the figure. The oil is now allowed to run out of the indiarubber tube D until the lever is horizontal, and the tracing can then begin.

The arrangement for keeping constant the pressure of the fluid sent into the heart is the same as already described in my former paper.* When the lever is made horizontal by the running out of the oil, it is found that the negative pressure in the chamber A amounts to 5 centims. of water. Therefore the pressure of the fluid in the venous side of the heart is 5 centims. of water, when the level of the blood solution is the same as that of the extremity of the cannula in the venous sinus.

The curves obtained by this method (Plate 70, fig. 24) are sufficiently striking, but unfortunately not easy to interpret. From the nature of the arrangement it is clear that the beats in the curves represent the changes in volume of the whole heart when beating with a blood supply at a constant pressure. Therefore when the auricle contracts that contraction ought not to be registered at all, for it causes simply a transference of fluid from one part of the heart to another, unless by the contraction a certain amount of fluid is thrown backwards along the inflow tube. Again, when the ventricle

* *Op. cit.*

contracts the curve registers not the amount of fluid thrown out by that contraction, but the difference between that amount and the amount which has flowed into the auricles during the time of that contraction; and this latter amount will depend upon the extent to which the auricles have completed their relaxation when the ventricle begins to contract. It seemed to me, therefore, impossible to come to any satisfactory conclusions when auricles and ventricle were both beating. In consequence, I have attempted to prevent the auricles from beating by raising the pressure of the blood solution flowing into them sufficiently high, and as Roy* has asserted that a pressure of 15 centims. is almost sufficient to prevent their contracting, I have always used a higher pressure than this, and have always carefully observed that there were no movements of the auricles visible to the naked eye or registered on the tracing before I proceeded to stimulate the vagus nerve. In this way I have seen most distinct relaxation of the ventricle upon vagus stimulation without any slowing of the rate of rhythm. Thus Plate 70, figs. 25 A and B, represents two cases taken from the same heart as fig. 24; the pressure within the auricles was 28 and 29 centims. of water respectively, and as is seen by the gradual slope of the curve in fig. 25 B as a whole, there was a slight amount of leakage from some part in consequence of the high pressure; still the curves show clearly enough that the contractions which occur when the nerve is stimulated start from a lower level of the lever; and as no variations in the condition of the auricles was to be noticed, it seems to me that the only explanation of such curves as these is that the vagus causes a true relaxation of the muscular tissue of the ventricle, and in all probability of the auricles as well.

If, now, we turn to the consideration of the curves obtained by the method of suspending the heart, we see decided indications of the same fact; in many of the curves it can be noticed that with the diminution of the beats caused by vagus stimulation, the diastolic line formed by joining the points of greatest relaxation falls very slightly nearer to the abscissa than before the stimulation (Plate 69, figs. 15, 17 A, &c.).

Another peculiarity can be seen in many of these curves, which is sometimes much more pronounced than at other times, viz.: that with the increase in the force of the contractions, the diastolic line is raised higher above the abscissa; this is well shown in Plates 68, 69, figs. 10 and 17 A. This diminution of relaxation between the beats may be due to an increased tonicity of the ventricle, coincident with the increase in the force of the contractions, or it may be caused mechanically by the arrangement of the apparatus. Thus, when the clamp is not very tight the movements of both auricle and ventricle are transmitted mechanically through the clamp to the other side, so that the contraction of the ventricle not only pulls the lower lever upwards but also slightly moves the upper lever downwards, and the reverse with the contractions of the auricles; therefore, if the ventricular contraction comes before the auricular lever has reached its lowest position of relaxation, then the pull of the ventricle will not only prevent the auricular lever falling any lower but will also increase the size of the next auricular contraction. This mechanical influence of the ventricular contractions is seen in such cases as Plate 68, fig. 14, where the ventricular beats have produced the appearance of strong and weak beats in the auricular curve. It is possible then to explain the rise in the diastolic line, both of auricles and ventricle, which often occurs after stimulation of the vagus nerve by the fact that owing to the increase in the force of the contractions, a stronger mechanical effect is produced upon the contractions of that part of the heart

* *Op. cit.*, p. 469.

which is situated on the opposite side of the clamp. That this will help to explain many of the cases of diminished relaxation after vagus stimulation there can be no doubt. Still, I have seen cases in which such an explanation does not seem sufficient, especially when the ventricle is beating with alternately strong and weak beats.

Further, such an explanation will not account for the peculiar shape of the diastolic line in the series of ventricular beats which occur as a consequence of vagus stimulation when the ventricle has been reduced to standstill either by tightening the clamp or heating the auricles and sinus. The series of curves given in Plate 69, figs. 17 and 18, show, firstly, that when the ventricle is made to beat with the same rhythm as the auricles the relaxation between the beats is very much less than that of the quiescent ventricle; and, secondly, that the muscle relaxes less between consecutive beats near the commencement of each group of beats than later on in that group, although as is seen in curve C, fig. 17, the rate of rhythm has remained the same throughout the series of beats. This diminution of relaxation at the commencement of each group is clearly not due to any mechanical action of the auricular contractions; for, as is seen in all the figures, and especially in fig. 18, where the maximum contractions of the auricles occurred before the ventricle began to beat, those contractions caused no appreciable effect upon the position of the ventricular lever.

I am inclined, therefore, to think that it is possible that the increase of the contraction force caused by the action of the vagus nerve may be accompanied by an increase of tonicity, and that the diminution in the contraction force is certainly accompanied by a diminution of tonicity. I am the more emboldened to consider this a possibility by the fact that AUBERT* has already, from observations on the action of the Dog's heart, suggested that cardio-tonic nerves for the heart exist, and by their action cause the greater relaxation which exists during the stimulation of the vagus and the diminution of relaxation which he noticed after the end of the stimulation of the nerve.

The effect of atropin, muscarin, and curare upon the action of the vagus.

Before mentioning the effect of these poisons upon the vagus action, I will endeavour to sum up briefly their actions upon the motor ganglia and the muscular tissue respectively, as far, at least, as can be judged from these present experiments.

Atropin applied to the ventricle alone does not alter its rate of rhythm or the force of its contraction except after repeated applications. From this we can say that atropin does not prevent the muscle from contracting to its full extent or diminish its excitability except in extreme doses.

Muscarin applied to the ventricle alone rapidily diminishes the force of its contractions without altering the rate of rhythm, and may ultimately make the ventricle beat synchronously with every second auricular beat. Muscarin, therefore, prevents the full contraction of the muscle and diminishes its excitability.

Curare applied to the ventricle alone produces at first no alteration in the force of its contractions or in its rhythm; after repeated doses it diminishes the contraction force and often causes the ventricle to respond once only to every two auricle contractions. Curare, therefore, ultimately prevents the full contraction of the muscle and lowers its excitability.

Atropin applied to the sinus and auricles only, slows the rhythm both of auricles and ventricle. With this slowing it causes the ventricle to beat synchronously with

* PLÜGER'S Archiv, Bd. v., S. 621.

the auricles, if it has previously been beating with half-rhythm, and increases the strength of the contractions both of auricles and ventricle. Also as long as the auricles are beating, the ventricle beats synchronously with them. From these facts I conclude that atropin slows the rate of the discharges from the motor ganglia without making them weaker; with the slower rate the impulses are therefore stronger than before, and the contractions must also be stronger, up to a certain extent of slowing, because with a certain slow rate of rhythm the maximum contractions of the heart are obtained. Whether the strength of the impulses is absolutely increased apart from the presumably beneficial effects of the slower rate I cannot say positively, though I am inclined to think they may be, as in some cases it has seemed to me that after atropin has been given it is necessary to screw the clamp up tighter than usual in order to cause the ventricle to remain quiescent.

Muscarin applied to the auricles and sinus only, slows the rhythm both of auricles and ventricle, weakens the auricular contractions, and may cause the ventricle to beat with half-rhythm or to remain quiescent, before the auricular contractions have ceased. This shows that muscarin not only slows the rate of the discharges from the motor ganglia but also weakens the strength of the impulses.

Curare applied to the auricles and sinus only, produces at first hardly any effect; it soon, however, slows the rhythm and may ultimately cause the ventricle to beat with half-rhythm. It therefore slows the rate of discharges from the motor ganglia and ultimately weakens the strength of the impulses.

If the heart be suspended with the cut-open ventricle downwards and muscarin be applied to the ventricle alone, then the ventricular beats are weakened without altering the rhythm, as in Plate 70, fig. 26, curve A. If the preparation be now turned over without loosening the clamp, so that the auricles are downwards, atropin can be applied to the auricles and sinus alone without any chance of its reaching the ventricle. Then, as is seen in Plate 70, fig. 26, curve B, where the atropin was applied to the auricles and sinus at the point denoted by the arrow, the rhythm both of auricles and ventricle is slowed, and in consequence the ventricular as well as the auricular contractions are slightly strengthened in force. If, now, atropin be applied to the ventricle, the ventricular contractions immediately increase very greatly in strength, as is shown in Plate 70, fig. 26, curve C, which is the direct continuation of the curve B. This shows that atropin removes the weakening effect of muscarin on the muscular tissue itself.

Again, if the heart be beating slowly in consequence of the application of muscarin to the sinus and auricles alone, then atropin applied to the tissue on the same side of the clamp does not quicken the rate of rhythm, although it may cause the auricular beats to become stronger. Atropin, however, may undoubtedly cause the heart to beat again when it has ceased beating from the application of muscarin.

We are now in a position to consider the effects of these three poisons upon the action of the vagus nerve, and I will take first the case of atropin upon the whole heart.

Atropin when applied to the whole heart ultimately removes all the different effects

of vagus stimulation, it prevents any diminution of the force of the contractions, and *à fortiori* any standstill, it prevents any increase of the contraction force and it prevents any acceleration. Examination of the various atropin curves which I possess shows that the first effect of atropin is to lessen the extent of the diminution of the force of the contractions caused by the stimulation of the nerve, so that in this stage the vagus finally produces acceleration* and augmentation of the beats only. In the further stage with the slow vigorous contractions characteristic of the atropinized heart, less and less acceleration and less and less augmentation of the force of the beats occurs, until at last stimulation of the nerve, even with the strongest current, is absolutely ineffective.

This experiment not only proves that atropin prevents the action of the vagus, but it also does away with an objection that might by some possibility be made against such results of vagus stimulation as I have recorded, viz.: that they are due, in part at all events, to escape of current, an objection which I believe has already been urged against SCHELSKE'S† assertion that in certain cases where the heart was not beating, he was able to make it beat again by stimulation of the vagus. I have, however, satisfied myself, apart from the action of atropin, that the effects seen are due to the vagus stimulation alone, and not to any escape of current. Thus the space between the electrodes and the tissue is considerable, and great care was always taken that there should be no communication between the electrodes and the heart except by means of the bare nerve. Again, if the thread to which the nerve is attached be first well moistened and then placed on the electrodes instead of the nerve, no effect whatever is produced upon sending the current through, although upon gently drawing the nerve on the electrodes which have throughout remained in the same position, the characteristic effect is immediately produced on stimulation. Also if the electrodes be placed directly upon the tissue between the heart and the forceps which hold the œsophagus, no effect whatever is produced on the heart with a current of the same strength as is sufficient to cause all the effects which are seen when the nerve is stimulated.

Since the vagus acts both upon the motor ganglion and the muscular tissue, and atropin is able to remove the whole effect of the action of the nerve, it naturally follows that by the local action of poisons it may be possible to abolish the vagus action in one part of the heart while leaving it intact in another. With this view I have applied the poisons either to the ventricle alone or to the sinus and auricles alone, and have obtained certain somewhat striking results; at the same time the number of these experiments is hardly sufficient as yet to allow me to say that these results are in every case so constant as to be entirely due to the action of the poison upon the sinus and auricles in one case or the ventricle in the other.

Thus, for instance, in Plate 70, fig. 27, muscarin had been applied to the sinus and auricles only, until, as is seen, the auricular beats had become slow, irregular, and somewhat weaker. The vagus was stimulated between the two vertical lines, and, as the figure shows, no effect was produced either on the rhythm or on the force of the auricular contractions (although previous to application of the muscarin the auricular contractions were augmented in force by the nerve stimulation); while on the other hand the ventricular contractions were increased in force to as great an extent as at the beginning of the experiment. Also the

* SCHIFF, Molesch. Unters., 1865, S. 58.

† Ueber die Veränderungen der Erregbarkeit durch d. Wärme, S. 20. Heidelberg, 1860.

fact that the ventricular rhythm was throughout the same as the auricular shows that the muscarin had caused the slowness and irregularity of the rhythm by its action upon the motor ganglia, and not because it had rendered the auricular muscle unable to respond to every impulse. The curve affords, too, a good proof that separate and not continuous impulses pass from the ganglia to the ventricle, otherwise it is impossible to conceive that with the increased excitability of the muscle caused by the vagus action it would be obliged to contract in the same slow irregular manner as the auricles.

Very soon after this curve was taken the muscarin caused the action of the motor ganglia to cease altogether, and then it was found that stimulation of the vagus was unable to make either ventricle or auricle beat.

This shows that the vagus is *not a motor* nerve to the muscle, for if it were so it must have caused contractions of the ventricle, seeing how powerfully it had been able to affect the ventricle a very short time before.

Again, cases occur where the curves show that muscarin applied to the auricular side only had very greatly reduced the size of the auricular beats, somewhat slowed the rhythm, and by its weakening action on the strength of the impulses caused the ventricle (which had previously been beating synchronously with the auricles) to remain quiescent. Stimulation of the nerve produced only a slight quickening of the auricular beats, and after the end of the stimulation a series of ventricular beats similar to what has already been described when the ventricles were reduced to standstill either by clamping or heating the auricles and sinus.

Muscarin, then, is apparently able to prevent the action of the vagus upon the auricles when applied to the auricles and sinus alone, without thereby preventing the action of the nerve upon the ventricle.

When atropin is applied to the sinus and auricles alone, then, simultaneously with the appearance of the slow vigorous beats thereby caused, the action of the vagus both on the rate of rhythm and upon the force of the ventricular as well as the auricular contractions entirely disappears. In fact, atropin applied to the sinus and auricles alone is as effective as when applied to the whole heart.

Curare applied to the auricles and sinus alone is able to prevent the action of the vagus nerve upon the auricular muscle, as far, at all events, as the diminution of the force of the contractions is concerned, without, as in the case of muscarin, greatly diminishing the force of the auricular contractions, while at the same time it leaves intact the action of the nerve upon the force of the ventricular contractions.

When any one of these three poisons is applied to the ventricle alone, the action of the vagus upon the force of the ventricular contractions is gradually removed without affecting its action upon the rhythm of the heart or upon the force of the auricular contractions. The usual sequence of events is as follows :—Soon after the application of the poison the nerve stimulation is no longer able to cause any diminution of the force of the contractions of the ventricle, so that in this stage it causes simply an increase of force with acceleration, if the auricular beats are accelerated. The maximum of this increase is less, and takes place later after the stimulation than before the application of the poison. As the action of the poison continues, the ventricular beats become smaller and smaller, and the augmentation of their contractions due to the vagus stimulation becomes less and less marked, until at last the

vagus produces no alteration in the size of the contractions, but only an alteration of rhythm in accordance with the alteration of rate of the auricular contractions.*

Conclusion.

The curves and arguments given in this paper show clearly that the vagus nerve exercises a powerful influence upon the muscular tissue of the heart as well as upon the motor ganglia. That it acts upon the muscular tissue is proved by the fact that its stimulation causes a profound alteration of the force of the muscular contractions, together with corresponding variations in the excitability and tonicity of the muscle, without necessarily altering the rate of rhythm.

Its action upon the force of the contractions may be in the direction of diminution or of augmentation, so that the nerve sometimes causes a diminution of the force of the contractions followed by augmentation, sometimes augmentation alone without any previous diminution.

This diminution may vary greatly both in extent and duration ; it may be very slight or so great that the contractions disappear altogether, so that in this way complete quiescence may be caused ; it may be that the first few beats only after the beginning of the stimulation are affected or the effect may continue until some little time after the end of the stimulation.

The extent of this diminution is in close connexion with the nutritive condition of the heart, so that quiescence followed by augmentation is more likely to occur when the heart is first suspended ; and augmentation alone, without previous diminution, after the heart has been removed from the circulation for some time.

Augmentation, therefore, without a previous diminution, is that effect of the stimulation of the vagus upon the muscular tissue which is the most enduring ; and in accordance with this, poisons which gradually prevent the whole action of the vagus upon the muscular tissue always remove first the power of the nerve to cause a diminution of the force of the contractions, and *à fortiori* quiescence, and afterwards its power to cause augmentation of that force.

The vagus, also, in all probability acts upon the motor ganglia in the same direction as upon the muscular tissue. It is able at one time to cause slowing, at another acceleration without a previous slowing. The slowing is more likely to occur before removal of the heart, or immediately after the heart has been suspended ; acceleration alone or no effect at all after the removal of the circulation or after the heart has been suspended some time.

So, too, poisons which entirely remove the action of the vagus first prevent the nerve from causing slowing, and only finally prevent the causation of acceleration.

If, then, we compare slowing of the rate of the discharges from the motor ganglia to

* N.B.—The hearts of Toads are apparently less susceptible to the action of all three of these poisons than those of Frogs. For instance, it takes much longer time to remove the whole effect of the action of the vagus by means of atropin (1 p. c. solution) in the case of the former than in the case of the latter.

diminution of the force of the contractions of the cardiac muscle, and acceleration of that rate to augmentation of that force, we can say that the action of the vagus upon all parts of the heart is similar; and that the difference of its action at different times depends not upon a multiplicity of nerve fibres, each possessing different functions, but rather upon the different effects produced by the same nerve in consequence of variations in the condition of nutrition of the heart as a whole—variations of nutrition to which naturally the more delicately-organised ganglion cells would prove more sensitive than the comparatively coarser muscular fibres.

How, then, can we imagine to ourselves the action of the nerve upon the heart? In the first place, it is clear that the nerve cannot be considered as the motor nerve of the muscle in the sense in which the words motor nerve are ordinarily used. The nerve itself cannot upon stimulation cause a contraction of the cardiac muscle; but causes such a modification in the chemical processes going on in the muscle as to modify the force of the contractions which take place when the impulses from the motor ganglia reach the muscle. In fact, two distinct processes are going on—the one, *motor*, represented by the impulses from the motor ganglia, and corresponding to the blow by which such an explosive substance as nitro-glycerine, for instance, is exploded; the other, *trophic*, represented by the action of the vagus upon the muscular substance, and corresponding to something affecting the nature or properties of the explosive substance itself.

The problem, then, to be explained is, what conception can be formed of the nature of the changes caused in the muscle by the action of the nerve, which shall satisfy the conditions that the same nerve can produce in different cases a graduated series of different effects extending from a simple increase in the force of the contractions on the one side down to diminution of force even to complete standstill on the other?

In trying to form a theory to explain new facts, it is always advisable to see if any theory which has been devised to explain somewhat similar facts will apply to this case also. With this consideration I cannot help thinking that the recent views which have been put forward to explain the changes going on in gland cells in a condition of rest and activity may help in the conception of the changes going on in the cardiac muscle cells under the influence of such a nerve as the vagus. In all secretory glands it appears to be the fact that the formation of the ultimate products of secretion is a gradual process, three stages of which can be recognised, viz.: the growth of the protoplasm, the formation of zymogen from the protoplasm, and the formation of the ultimate products from the zymogen; and according to LANGLEY* these three processes not only go on at the same time, but also there may be, under different circumstances, a difference in the relative rates at which they proceed.

If, then, we imagine in the cardiac muscle an initial or ground substance, or, in correspondence with the gland cell, a muscle protoplasm and a final or explosive substance which is not self-explosible, but requires a stimulus to fire it off, then we may conceive

that the protoplasm does not form the explosive substance directly, but that there are intermediate stages corresponding to the zymogenic stage in the gland. According to this view there would be in the cardiac muscle during its normal activity three processes going on: the growth of the protoplasm with the aid of the raw material from the nutritive fluid surrounding the muscle fibres; the transformation of the protoplasm into intermediate products, which are non-explosible, or at least explosible with difficulty; and the formation from these of easily explosible material; in fact, a gradual succession from stable to more and more unstable combinations. If, then, the formative activity of the muscle be distributed over these three stages in the right proportion, it follows that impulses passing to the muscle at equal times must all cause contractions of equal force. If, however, that activity be exclusively directed towards the formation of the muscle protoplasm or the intermediate non-explosible substances it is conceivable that no contractions should be able to take place, because no suitable material was ready for the impulses to act upon, though as a natural consequence of this greater activity in the formation of the intermediate substances the ultimate effect would be that the subsequent contractions would be very much greater than before. On this view, then, the force of the contraction at any time depends upon the relative rates at which these three processes proceed.

In this way I can imagine standstill to take place, and it is also quite conceivable that in certain conditions of nutrition of the heart it may occur more easily than in others; thus, as we have seen in the heart cut out and suspended, complete quiescence may in some cases be easily obtained, in others not at all; so, also, in the heart through which salt solution is flowing I have often obtained standstill upon stimulation of the vagus, thus confirming LUDWIG and LUCHSINGER,* while in other cases I have only obtained acceleration, thus confirming SCHIFF.†

Again, if the whole heart or the ventricle alone be beating in the apparatus described on page 1019, while salt solution is flowing through it, it will beat regularly and well for a long time with the salt solution, and if while it is still beating, whether strongly or weakly, blood solution be sent into it under the same conditions of pressure, &c., as the salt solution, then it often happens that as soon as the blood is seen to reach the heart or the ventricle the heart stops still in the relaxed condition, sometimes for a considerable length of time, and subsequently begins again to beat with the improved beats due to the blood solution. In the same heart this experiment may be repeated again and again; in other hearts the sudden supply of nutrient material contained in the blood does not cause any stoppage whatever, but a simple gradual improvement in the contractions. Upon the hypothesis suggested above this means that in consequence of the sudden supply of blood the whole energy available is in the one case engaged in the growth of the protoplasm from the raw material, so that no contractions can take place, while in the other it is distributed more equally over the different processes going on in the muscle.

* *Op. cit.* † *Op. cit.*

As a conceivable hypothesis, then, it seems to me we may say—the vagus increases the activity of the formative processes going on in the muscle, and it will produce therefore augmentation of the force of the contractions alone, or diminution followed by augmentation, or even standstill followed by augmentation, according as that activity is more or less equally distributed over the different stages of the process, the ultimate end of which is the formation of the final contractile substance.

Again, although I am not prepared at present to offer any definite theory to explain the action of the nerve upon the motor ganglia, yet still it is impossible to help being struck with the apparent resemblances between its action on these cells and on the muscle cells; thus just as in the case of the muscle the nerve may at one time cause diminution followed by augmentation of the contractions, at another time augmentation alone without any previous diminution, so in the case of the motor nerve cells, the vagus may under certain conditions cause a slowing of the rate of discharge of the impulses followed by acceleration, under other conditions acceleration alone without any previous slowing.

I venture, therefore, to suggest that—

> The vagus is the trophic nerve of both the muscular tissue and the motor ganglia, meaning thereby that it increases the activity of the various formative processes going on in both these kinds of tissue, and it produces all its effects by virtue of this quality.

In all that I have hitherto said I have been speaking entirely of the hearts of Frogs and Toads, and so far as these animals are concerned I venture to think that my views are in harmony with an experiment of FOSTER and DEW-SMITH,* who showed that although the constant current was able to cause rhythmical contractions in the isolated and quiescent apex or ventricle, or in the whole heart when rendered quiescent by the STANNIUS ligature, yet it was unable to do so when the heart was reduced to standstill by the stimulation of the vagus. This remarkable experiment, which, as far as I know, has never been disputed or explained, seems to me to follow naturally from the experiments and conclusions put forward in this paper.

As yet I have not made any experiments upon the hearts of warm-blooded animals, and cannot therefore assert from my own observations that the vagus acts in a similar way upon them; there are, however, certain experiments recorded which render this conclusion more or less probable. Thus PANUM and GIANUZZI† have both observed that in Rabbits with weakly-beating hearts, stimulation of the vagus causes the beats to become much stronger. TRAUBE‡ has observed that in a curarised animal the heart beats for a longer time after the cessation of artificial respiration with the vagi intact than when these nerves have been previously cut; and BROWN-SEQUARD§ has quite

* Journ. Anat. and Physiol., vol. x.

† HERMANN'S Handbuch der Phyiol., Bd. iv., S. 384.

‡ Allgem. Med. Centralzeitung, 1864, N. 42.

§ Gaz. Med. de Paris, 1880, p. 391.

recently noticed that if two Rabbits are killed at the same moment by cutting open the aorta, and if in the one the vagus has been strongly stimulated just before the aorta is opened and not in the other, then that heart which has been affected by the nerve stimulation will beat stronger and continue to beat a longer time than the heart of the Rabbit in which the vagus had not been stimulated.

These experiments render it probable that the action of the vagus on the warm-blooded is similar to its action on the cold-blooded heart.

Evidence of another kind is given by the observations of EICHORST* and ZANDER,† who find that the death which results from section of both vagi is not entirely due to inanition, but partly to degenerative changes in the heart itself; they therefore conclude that the vagi nerves exercise a trophic influence on the heart.

Hitherto I have tacitly assumed that the vagus acts directly upon the muscular tissue and the motor ganglia respectively, and not through the aid of some intermediate apparatus. Now although the experiments with muscarin and curare which I have just mentioned tend to confirm this view, for in each case the local application produced only local results whether upon the muscle or on the motor ganglia, yet the action of atropin is difficult to explain on this hypothesis. If atropin acts directly upon the muscular tissue and the motor ganglia, so as in each case to slow the rate at which the formative processes are going on, without at the same time diminishing the extent of those processes, then it is possible to conceive it as acting in direct opposition to such an influence as the vagus nerve which I have supposed to act by expediting those same formative processes; were this the whole of its action, however, it ought to prove as local in its effects as muscarin or curare. Since, however, atropin removes the whole action of the vagus nerve upon the ventricle when it has been applied to the sinus and auricles only, the question naturally arises, how is this to be explained? Is there a trophic centre for the ventricle which is situated either in the auricles or venous sinus, upon which both atropin and the vagus act? At present I do not see any absolute necessity to draw such a conclusion from this action of atropin, and therefore prefer to leave this question entirely undecided in the hope that further researches may enable me to come to some definite conclusion upon the matter.

In conclusion, I desire again to call attention to the fact that the action of the vagus upon the muscular tissue of the heart is characterised by two different sets of effects.

1. Diminution of contraction force associated with a diminution in the excitability and a diminution of the tonicity of the cardiac muscle.

2. Increase of contraction force associated with an increase in the excitability and possibly also with an increase in the tonicity of the cardiac muscle.

Upon the view put forth above that a series of substances are formed between the muscle protoplasm and the final explosive substance, it follows that the chemical combinations which are formed in the lower part of this series possess less explosive

* 'Die trophischen Bezichungen der Nervi Vagi zum Herzmuskel.' Berlin, 1878.

† PFLÜGER'S Archiv, Bd. xix., S. 263.

energy, are less excitable, and less compact than the combinations which occur in the higher part of the series. Finally, I cannot help being struck with the fact that alkaline substances such as sodium hydrate or sodium carbonate increase the excitability, increase the tonicity and increase the force of the contractions in weakly-beating hearts; while, on the other hand, such substances as lactic acid diminish the excitability, diminish the tonicity and diminish the force of the contractions of the cardiac muscle. Whether the resemblance in these two cases is purely fictitious, or whether the trophic action of the vagus nerve is connected with some such action of acids and alkalies I cannot say, and only put forward the resemblance in the hope that a possible clue may thus be found to the chemical action of the vagus upon the muscular substance of the heart.

Postscript.

(Added July 3rd, 1882.)

Throughout this paper I have spoken of impulses proceeding from the sinus to the ventricle without attempting to define the nature of the stimulus which causes the ventricle to contract, or the path along which the impulse travels. Subsequent investigations which I have made upon the hearts of Tortoises have thrown new light upon the cause of the sequence of the ventricular upon the auricular beat, and point to a possible explanation of the want of sequence observed under different circumstances which is somewhat different to that suggested above.

The heart of the Tortoise is removed from the body and suspended between two levers in the manner above described; no clamp is used, but the aortic trunk is held firmly in a suitable holder. By means of section of the auricle in different directions and to different extents I find that—

1. The sequence of the ventricular upon the auricular contractions is associated with the passage of a wave of contraction along the auricular muscular fibres to the auriculo-ventricular groove, and is not dependent upon the integrity of the large nerve trunks between the sinus and the ventricle.

2. By means of section of the auricle the passage of this wave can be *blocked* and the ventricle in consequence remains quiescent.

3. If the section be severe the block will be complete; no contractions will pass. If less severe, the block will be partial and then *every second* contraction will pass, and as soon as it reaches the auriculo-ventricular groove will cause a contraction of the ventricle.

In this way by hindering the passage of a contraction wave to the ventricle, the ventricle can be made to beat with every second contraction of the sinus and that part of the auricle in connexion with the sinus, in precisely the same way as by tightening the clamp between the sinus and ventricle of the Frog. The probability therefore is strong that the clamp produces the half-rhythm observed because it blocks

the passage of a contraction wave to the ventricle, and not because it weakens a nervous impulse from the sinus to the ventricle.

Again, when by section of the auricle of the Tortoise only every second contraction passes the block and induces a contraction of the ventricle, stimulation of the vagus is able to cause every contraction to pass, in a manner similar to that observed in the case of the Frog when the clamp was tightened. This, then, would seem to show that in this latter case too the vagus produced this effect, not so much by its influence upon the excitability of the *ventricular* muscle as by its power to remove the blocking of the *auricular* contractions caused by the pressure of the clamp upon the auricular fibres at their termination in the auriculo-ventricular groove.

Lastly, I find that with a section of the auricular muscle, such that every contraction is able to pass at a certain rhythm, only every second contraction passes at a quicker rhythm; *i.e.*, the time required for the auricular tissue to recover itself after a contraction is much longer at the blocking point than at other parts of the auricle. In this way many cases of half-rhythm which are coincident with an increased rapidity of rhythm are to be explained.

Description of Figures.

In all the figures the divisions on the line traced by the time marker correspond to intervals of two seconds. The duration of the vagus stimulation is in all cases marked by two thin vertical lines. All the curves read from left to right.

PLATES 66–70.

Fig. 1. March 17, 1881. Frog. Auricles and sinus alone heated between the two vertical lines.

Fig. 2. March 28, 1881. Toad. Ventricle alone heated between the two vertical lines.

Fig. 3. June 17, 1881. Frog. Clamp in auriculo-ventricular groove tightened at the place denoted by the arrow.

Fig. 4. Feb. 16, 1881. Frog. Stimulation of vagus. Sec. coil at 13 centims. No clamp. Ventricular beats only registered.

Fig. 5. March 17, 1881. Frog. Stimulation of vagus. Sec. coil at 10 centims. Auricles and sinus were heated. In consequence, auricles are beating very rapidly, and ventricle does not respond to every auricular beat.

Fig. 6. March 15, 1881. Frog. Stimulation of vagus. Sec. coil at 8 centims. The stimulation was probably weaker for some reason in curve A than in curve B.

Fig. 7. March 8, 1881. Frog. Stimulation of vagus. Sec. coil at 10 centims. The auricular contractions are just visible during the ventricular standstill.

Fig. 8. June 23, 1881. Toad. Stimulation of vagus. Sec. coil at 10 centims.

Fig. 9. June 20, 1881. Toad. Stimulation of vagus. Sec. coil at 10 centims.

Fig. 10. April 11, 1881. Toad. Stimulation of vagus. Sec. coil at 5 centims. The ventricle was unable to register the maximum of its contractions, as the upper and lower levers came in contact.

Fig. 11. March 1, 1881. Frog. Curve B. Stimulation of vagus. Sec. coil gradually pushed from 15 to 8 centims.

Fig. 12. March 15, 1881. Frog. Stimulation of vagus. Sec. coil at 5 centims. Auricular beats only shown. Curve B is the continuation of curve A, except that the vagus was stimulated between the two curves.

Fig. 13. March 10, 1881. Frog. Stimulation of the vagus. Sec. coil at 10 centims.

Fig. 14. May 12, 1881. Toad. Stimulation of vagus. Sec. coil at 8 centims. Ventricle beating once to every 3 auricular beats.

Fig. 15. April 11, 1881. Toad. Stimulation of vagus. Sec. coil at 10 centims.

Fig. 16. Feb. 25, 1881. Frog. Stimulation of vagus. Sec. coil at 8 centims. Contractions of base of ventricle, upper curve; of apex, lower curve.

Fig. 17. March 17, 1881. Frog. Curves A, B, C, D. Series of curves to show effect of vagus stimulation, when the ventricle is rendered quiescent, by heating the auricles and sinus.

Fig. 18. June 6, 1881. Toad. Stimulation of vagus. Sec. coil at 7 centims. Clamp tightened so as to render ventricle quiescent.

Fig. 19. May 9, 1881. Frog. Stimulation of vagus. Sec. coil at 9 and 8 centims. Ventricle beating with alternately strong and weak contractions. Intermediate part of the curves indicated by the dotted lines.

Fig. 20. Feb. 23, 1881. Apex and base of ventricle. Apex beating with alternately weak and strong contractions. Base upper, apex lower curve.

Fig. 21. June 16, 1881. Frog. Secondary rhythm in the alternately strong and weak contractions of the ventricle.

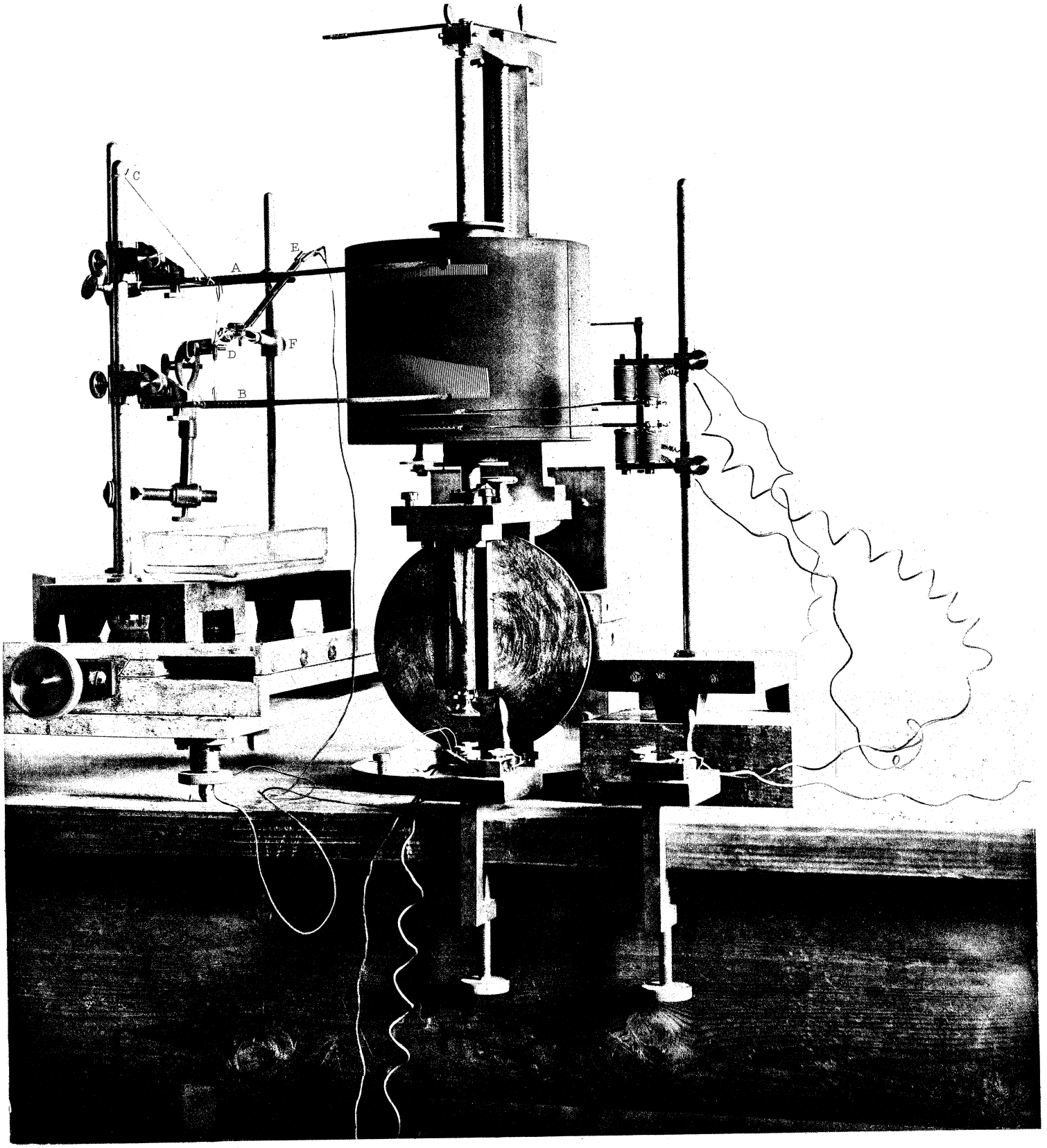
Figs. 22 and 23. Apparatus as described on page 1019.

Fig. 24. Nov. 4, 1880. Toad. Stimulation of the vagus. Sec. coil at 6 centims. Heart in modified Roy's tonometer. Pressure of blood solution 5 centims.

Fig. 25 A and B. Nov. 4, 1880. Stimulation of vagus. Sec. coil at 4 and 3 centims. Pressure of blood solution 28 centims. in A, 29 centims. in B.

Fig. 26. May 19, 1881. Frog. Curve A. Muscarin sulphate, 5 per cent. solution applied to the ventricle at the point marked by an arrow. Upper curve auricle, lower curve ventricle. Curve B. Atropin sulphate, 1 per cent. solution applied at arrow to the auricles and sinus only. Upper curve ventricle, lower curve auricle. Curve C. Atropin sulphate applied to ventricle at the arrow. Upper curve ventricle, lower curve auricle.

Fig. 27. July 16, 1881. Toad. Stimulation of vagus. Sec. coil at 10 centims. Muscarin sulphate, 5 per cent. solution had been applied to the auricles and sinus only.



Cambridge Scientific Instrument C.º Phot. *Heliog. Dujardin*

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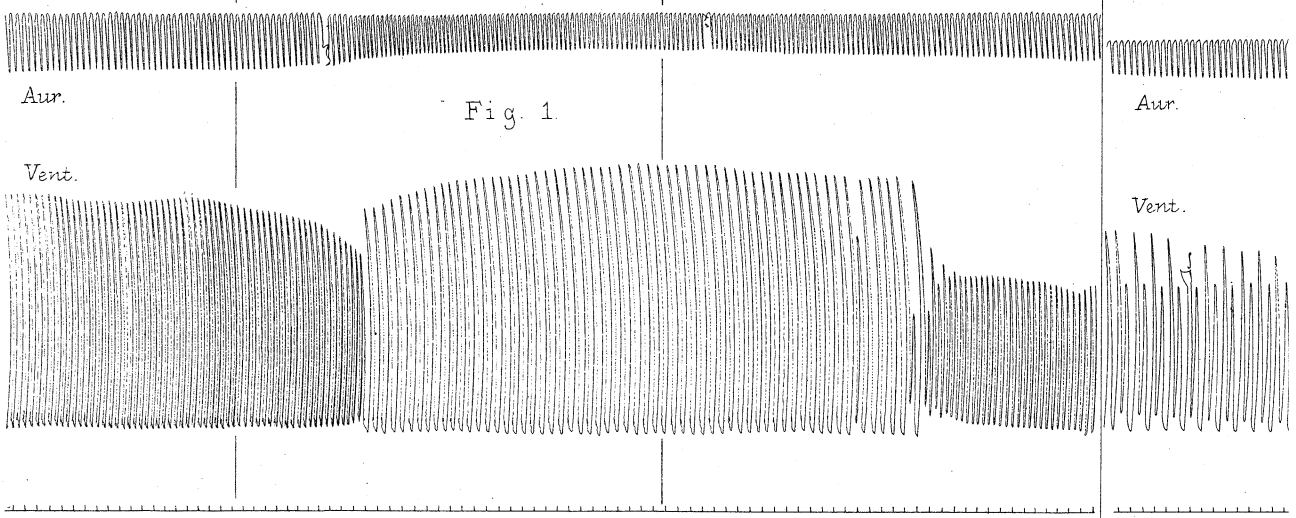

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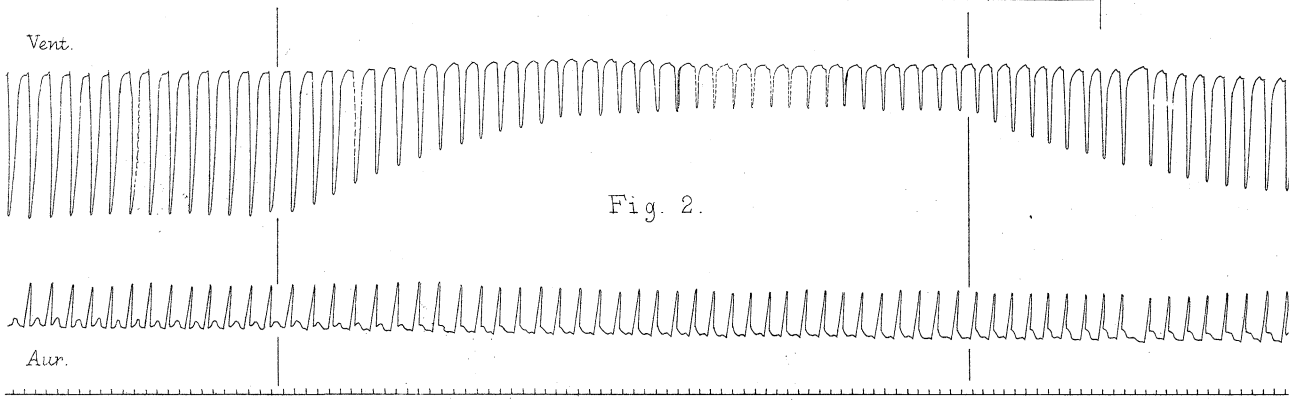

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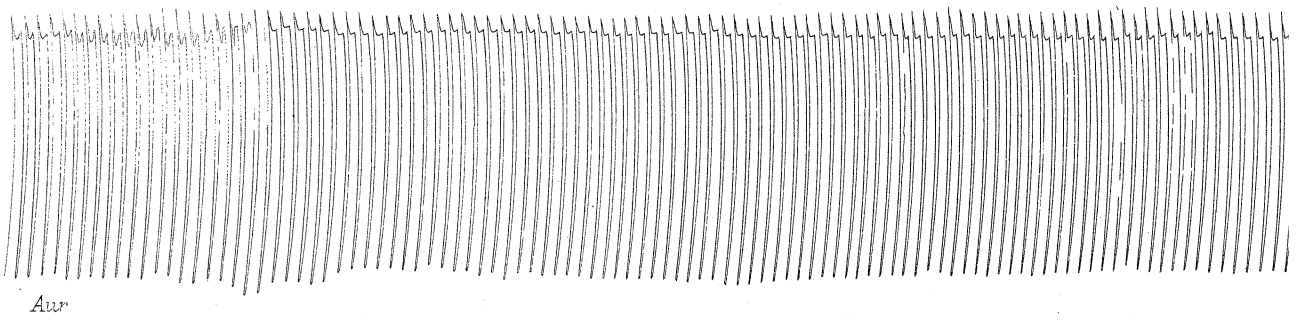

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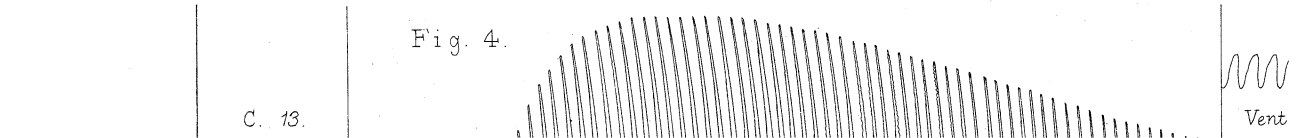

C. 13.

Fig. 4.

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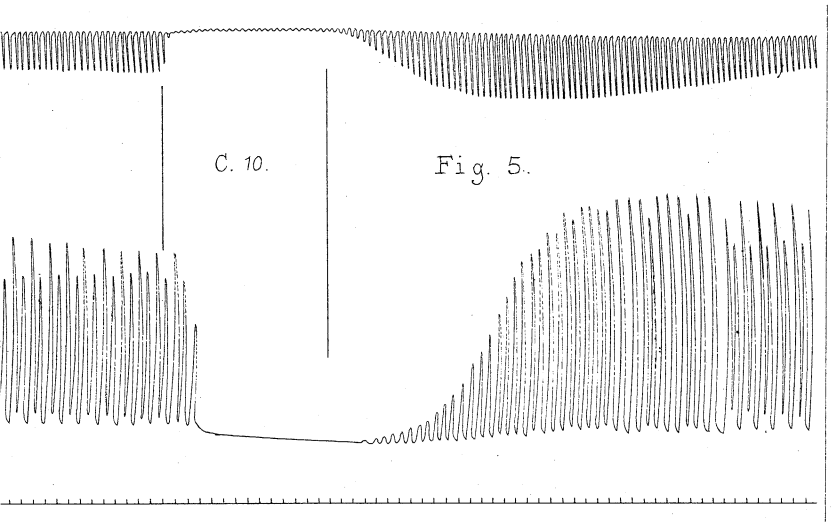

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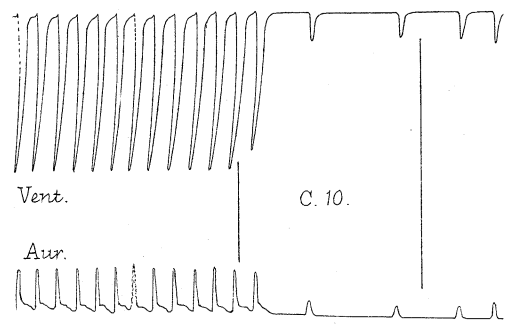

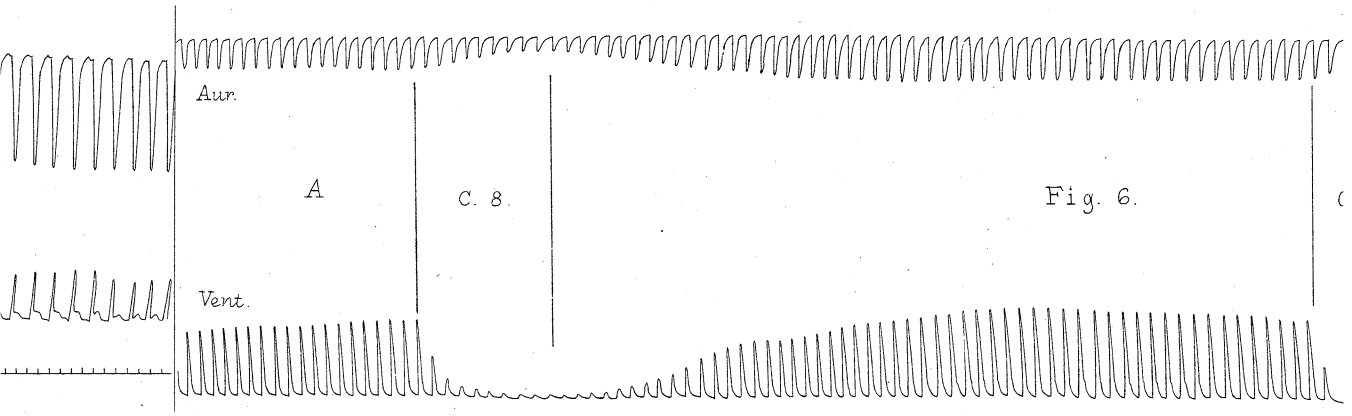

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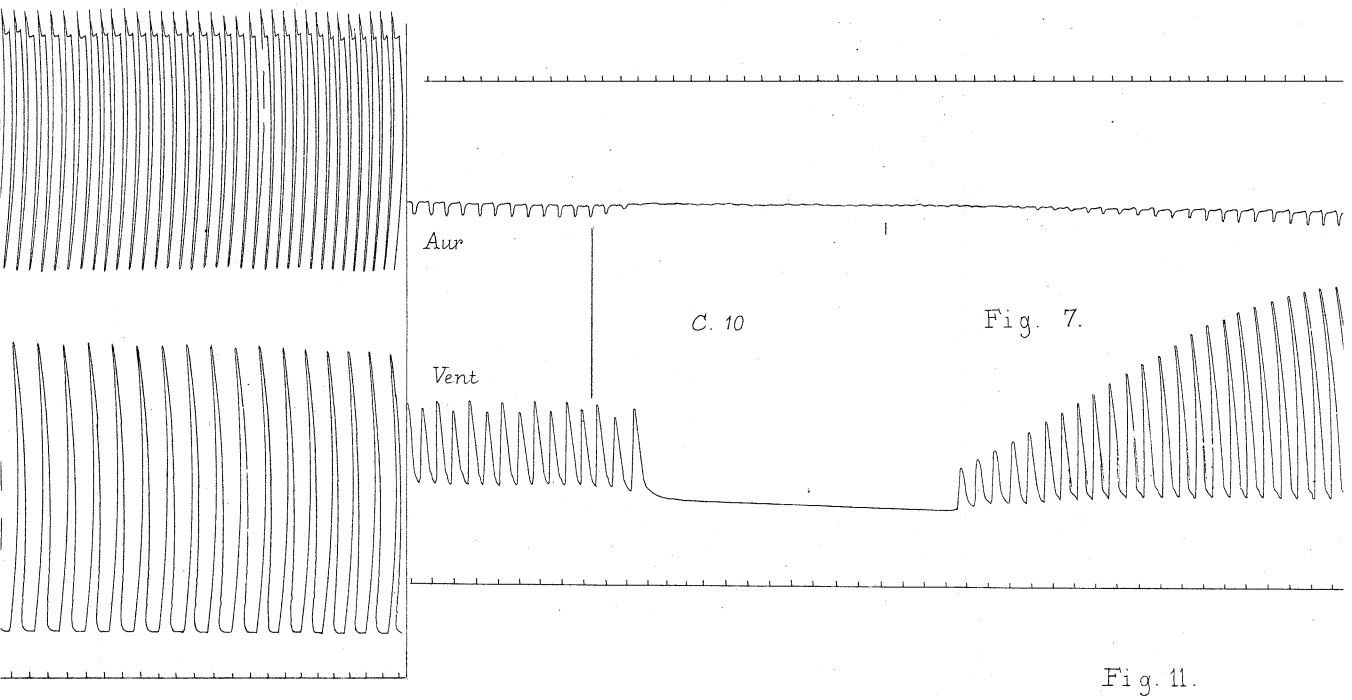
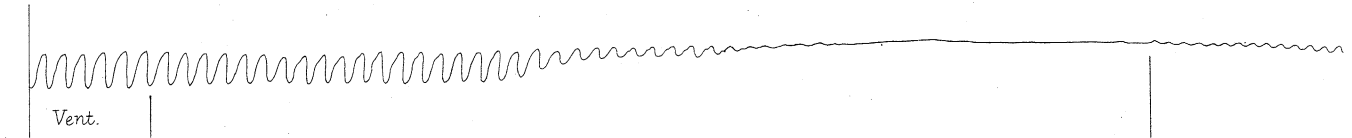
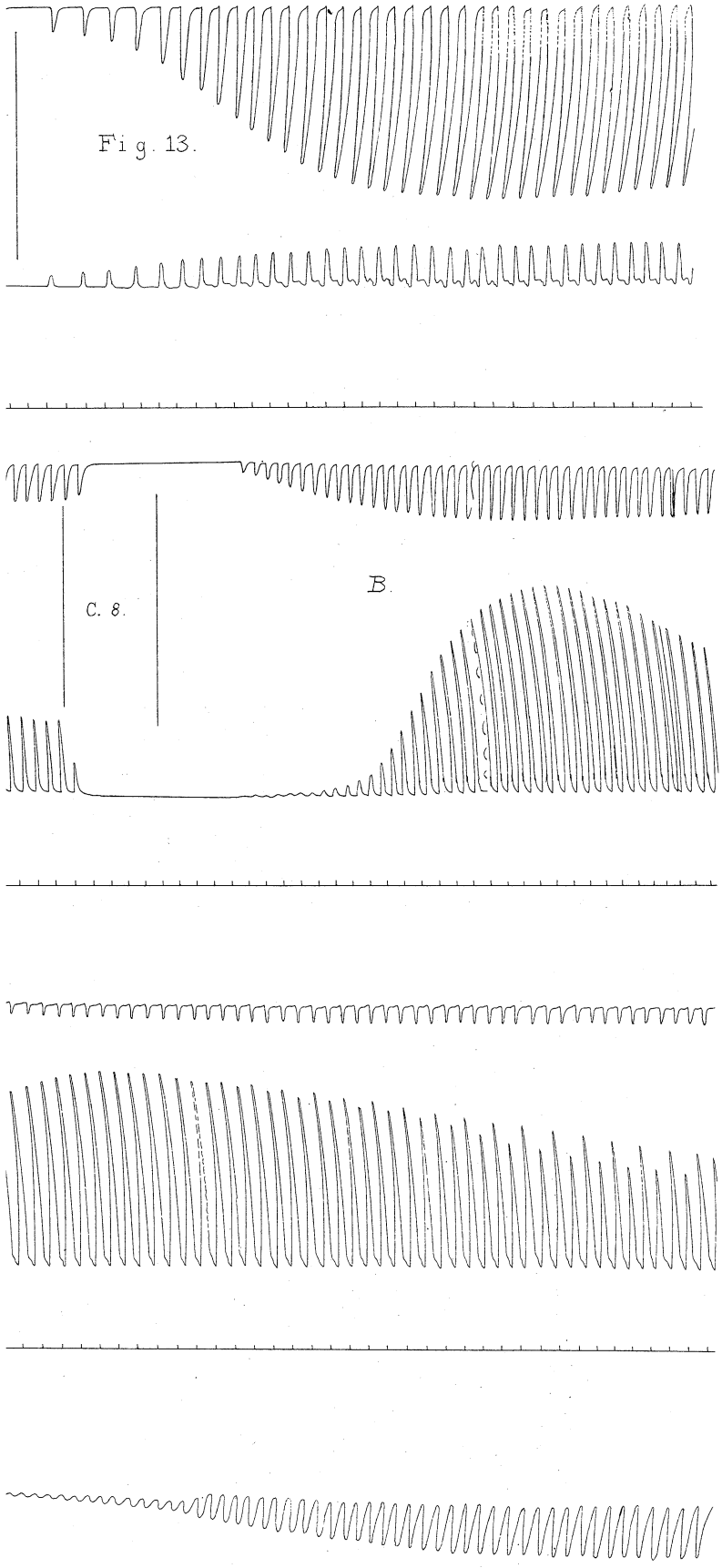


Fig. 7.

Fig. 11.

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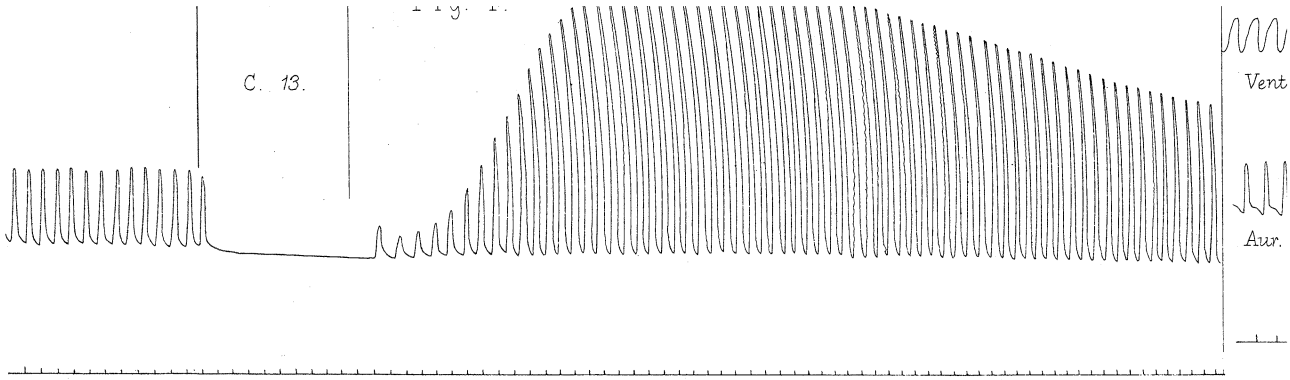
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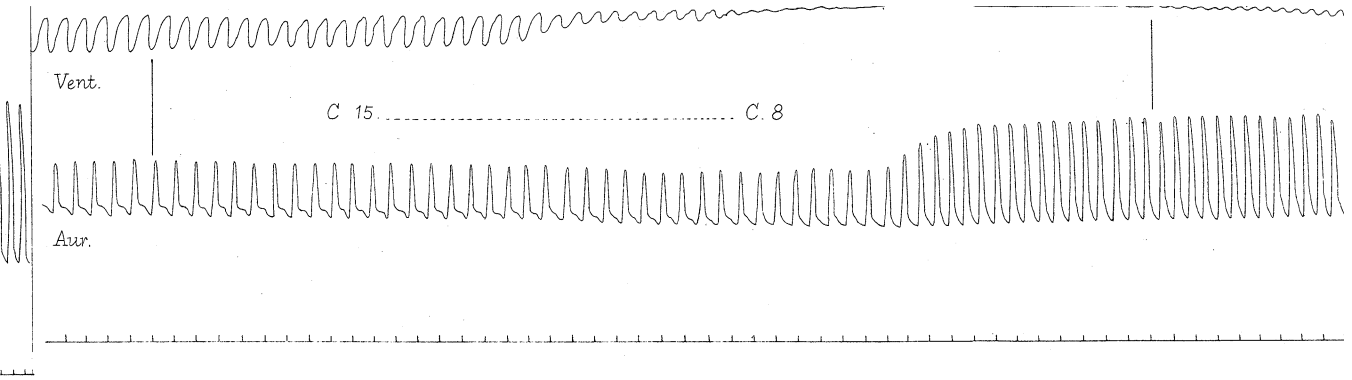
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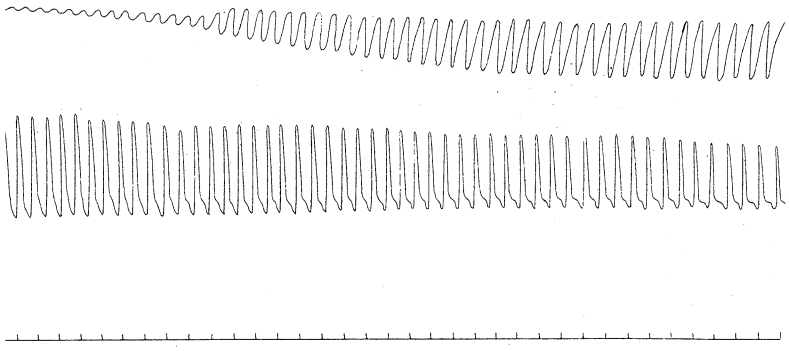

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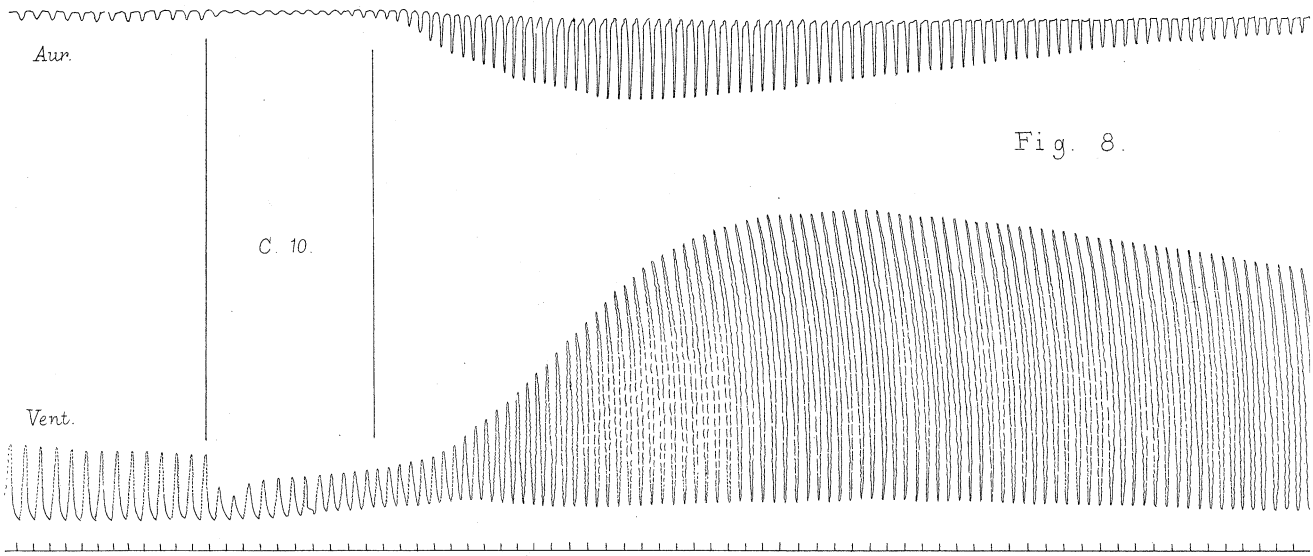

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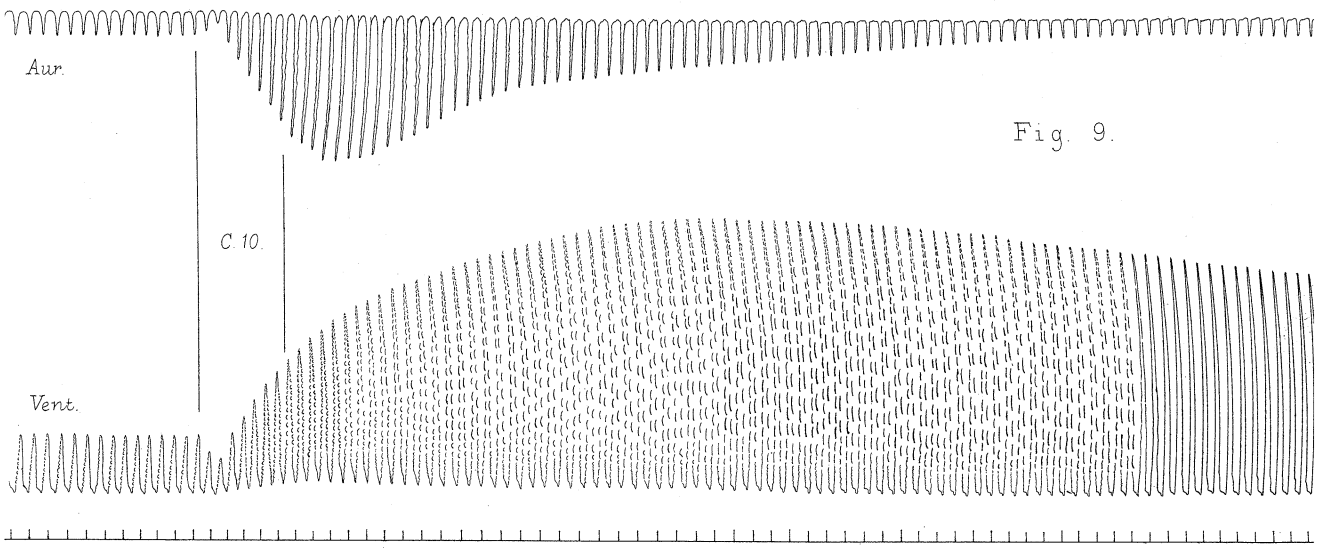

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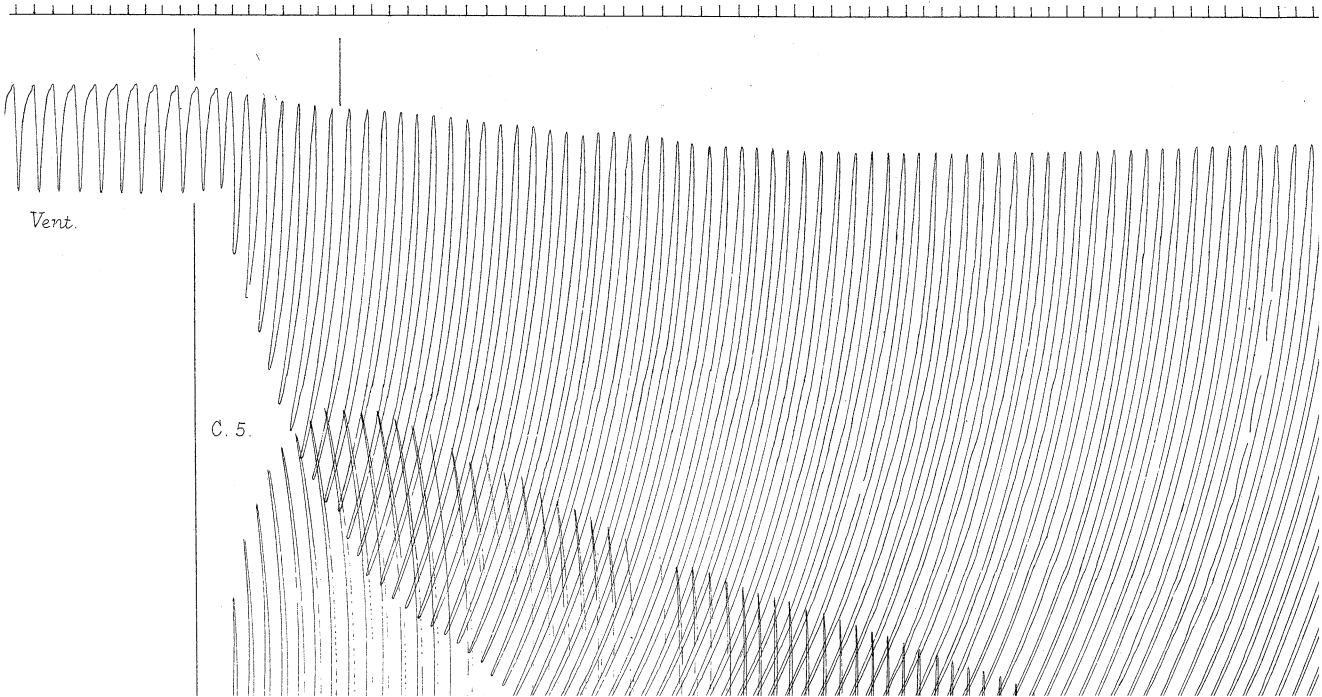

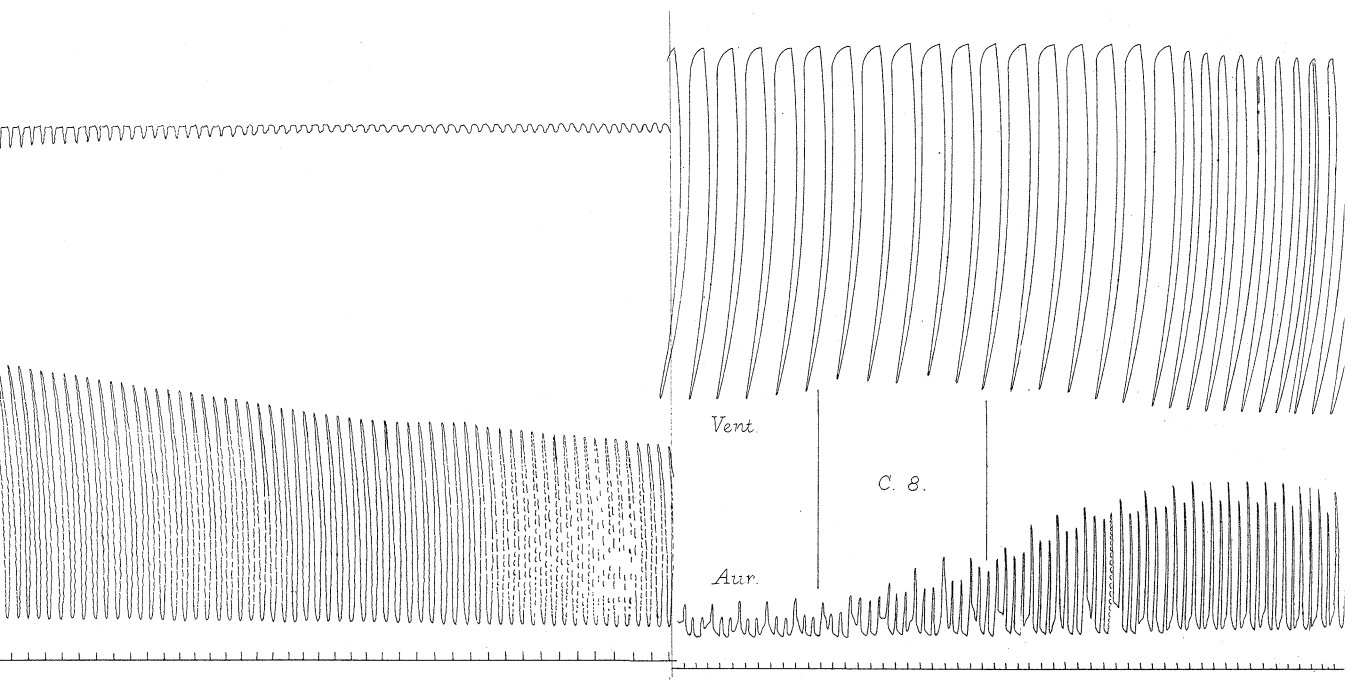

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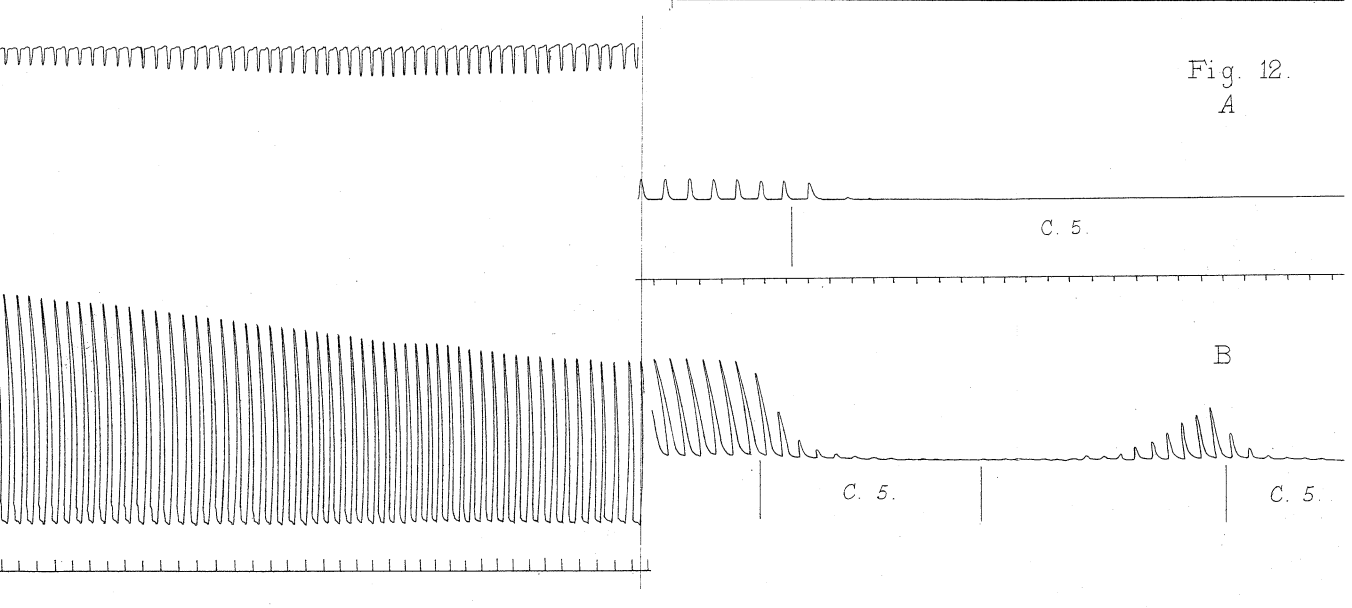

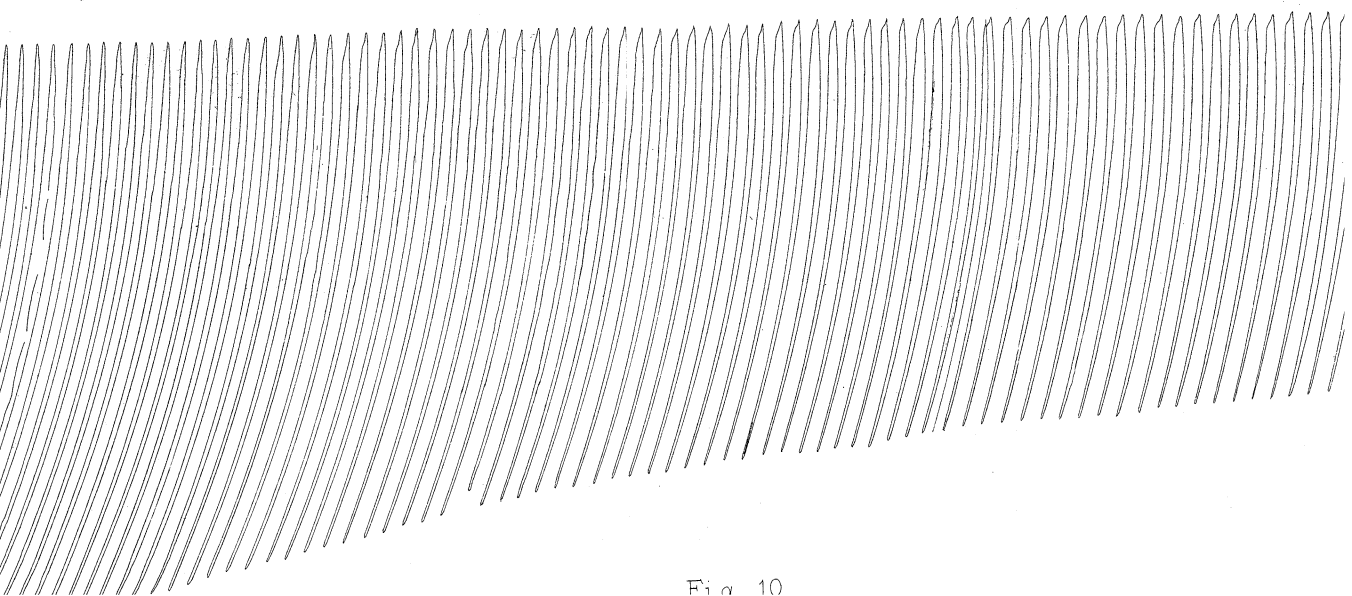

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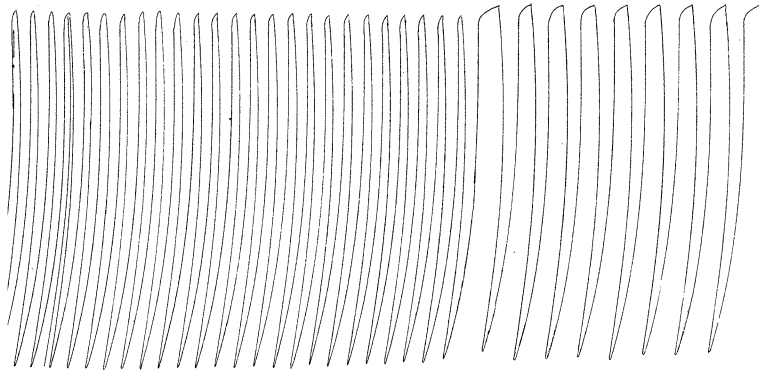

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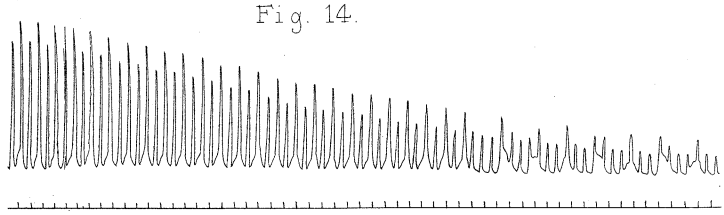

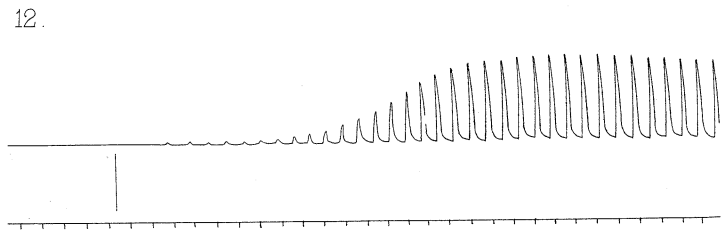

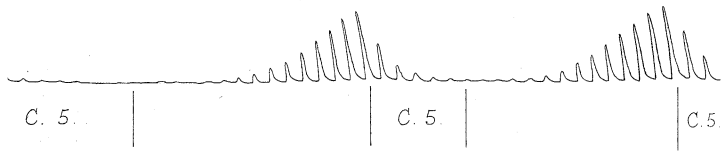

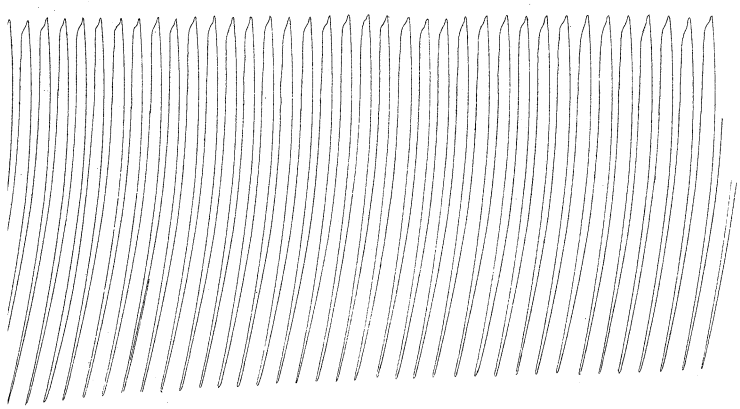

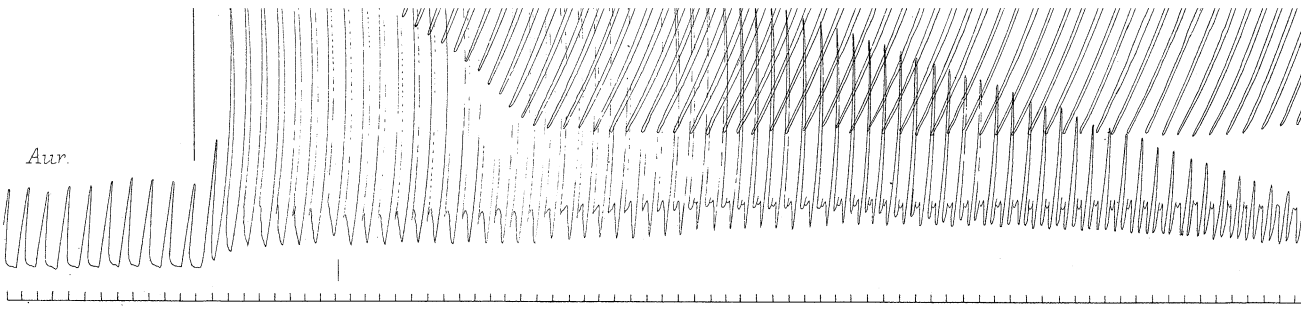
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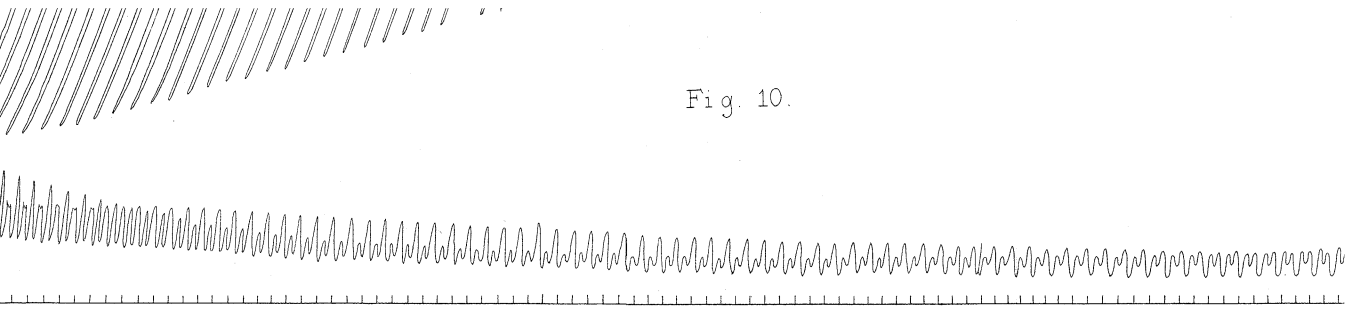

Fig. 10.

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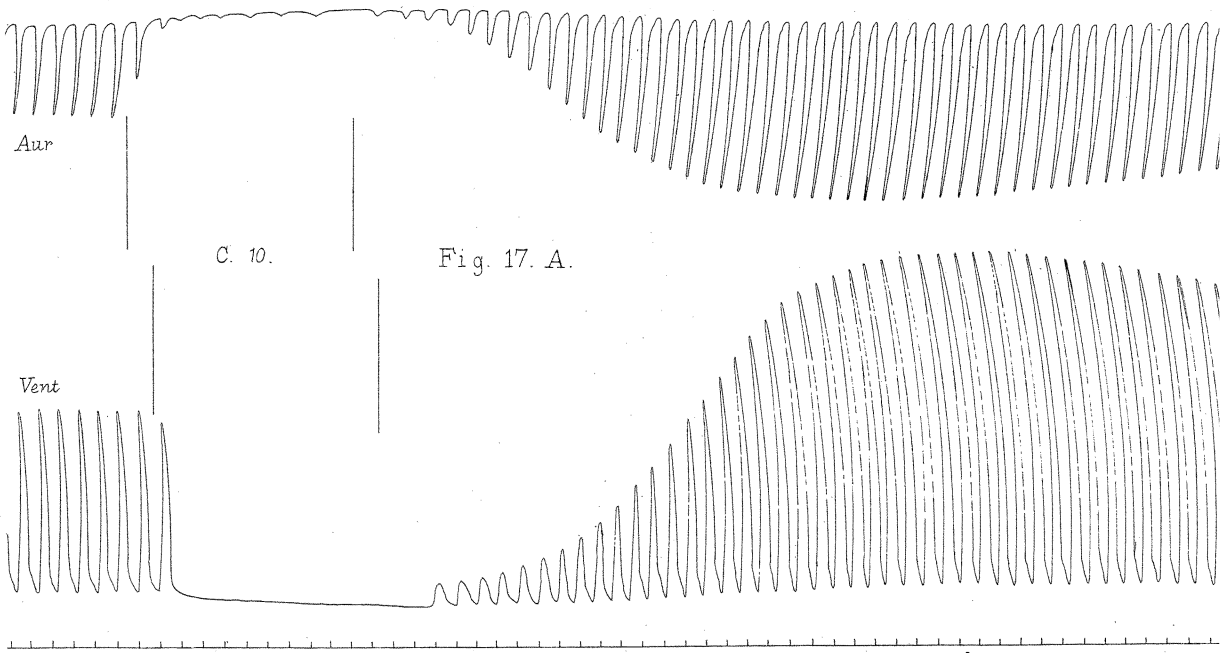


Fig. 17. A.

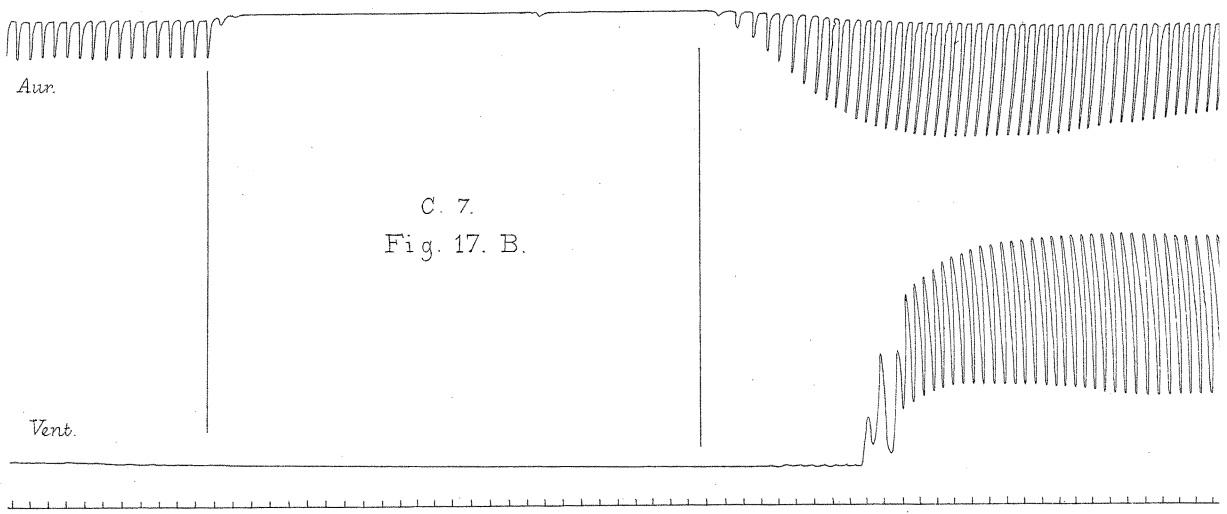


Fig. 17. B.

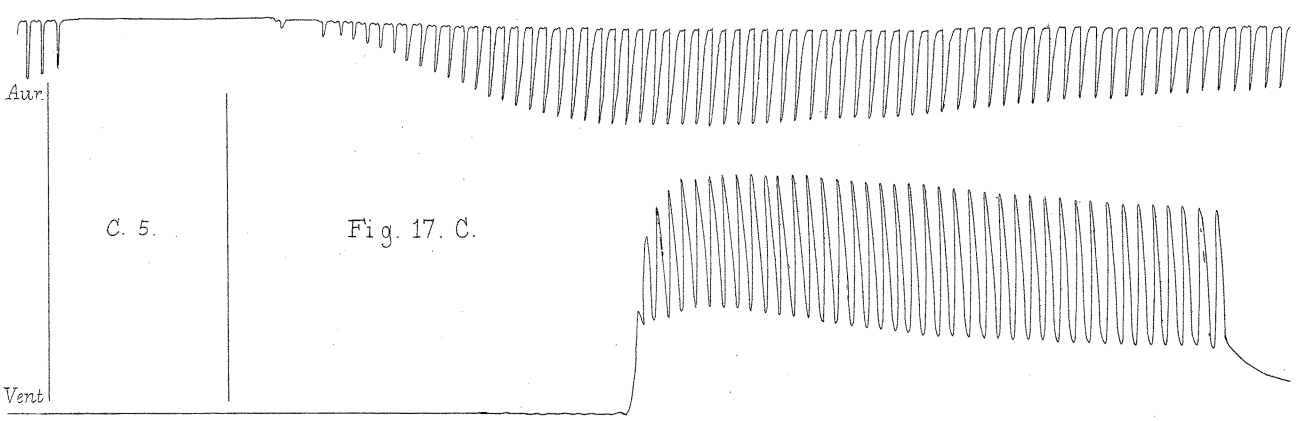
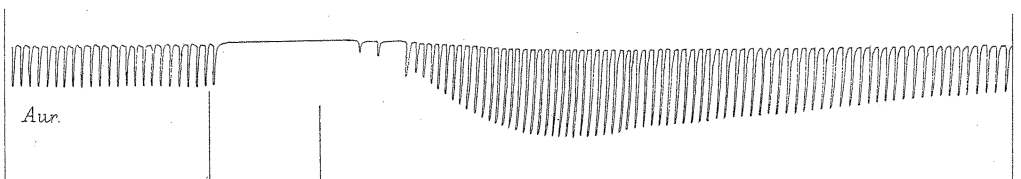


Fig. 17. C.



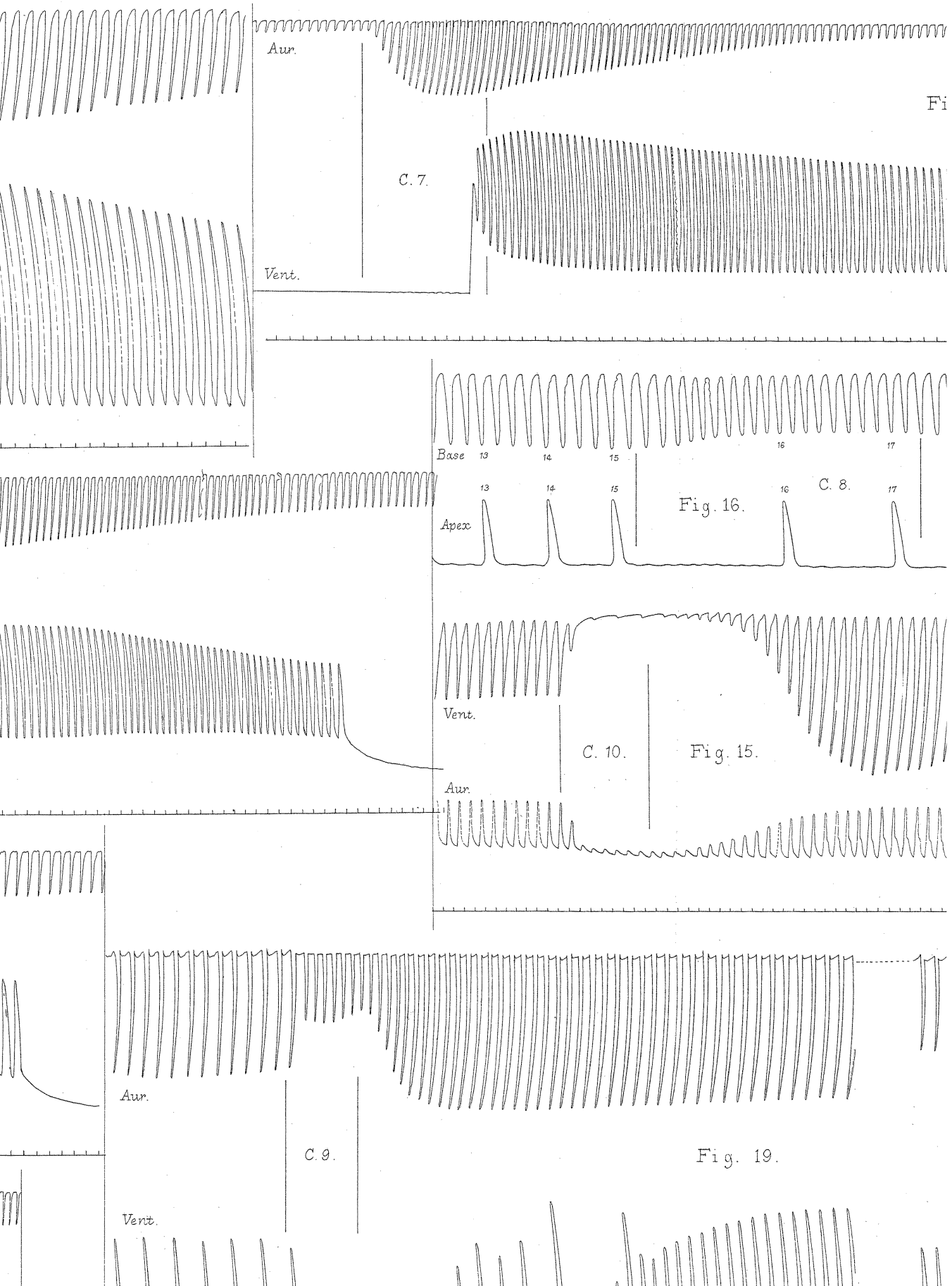
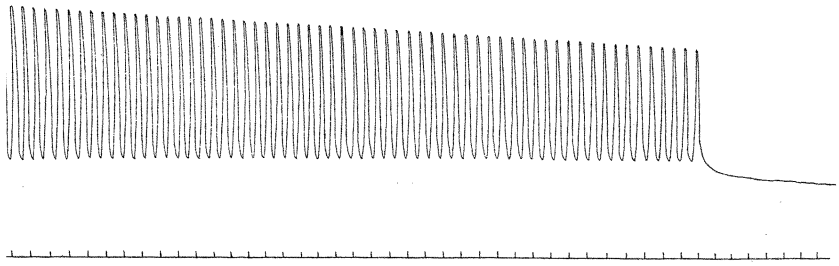
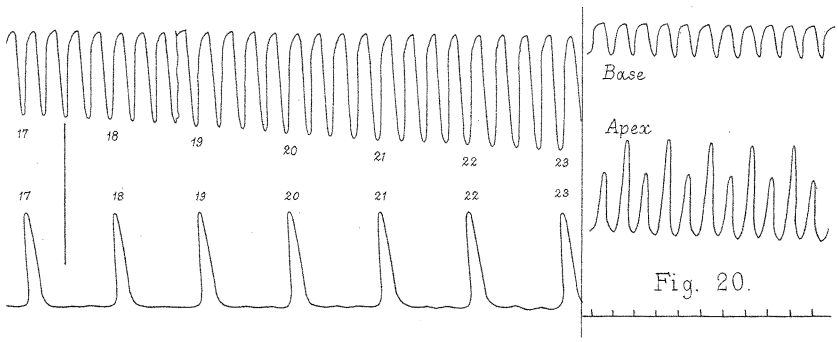

Aur.
C. 7.
Vent.
Base
13
14
15
16
17
Apex
C. 8.
Fig. 16.
Vent.
C. 10.
Fig. 15.
Aur.
Aur.
C. 9.
Fig. 19.
Vent.

Fig. 18.





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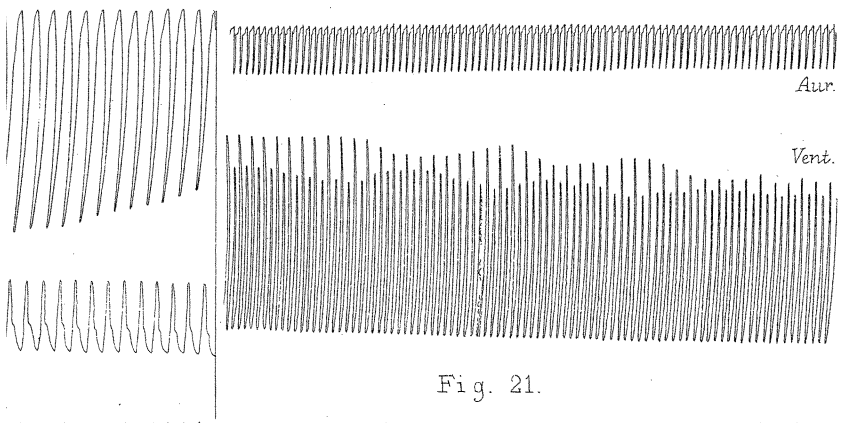

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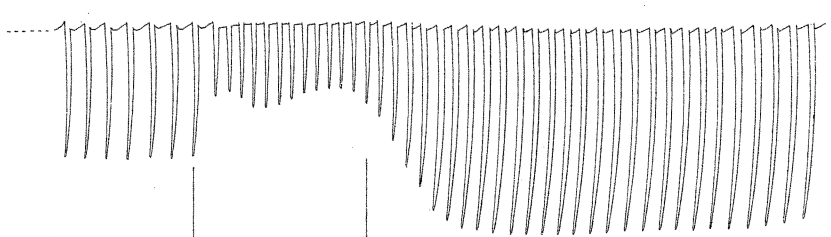
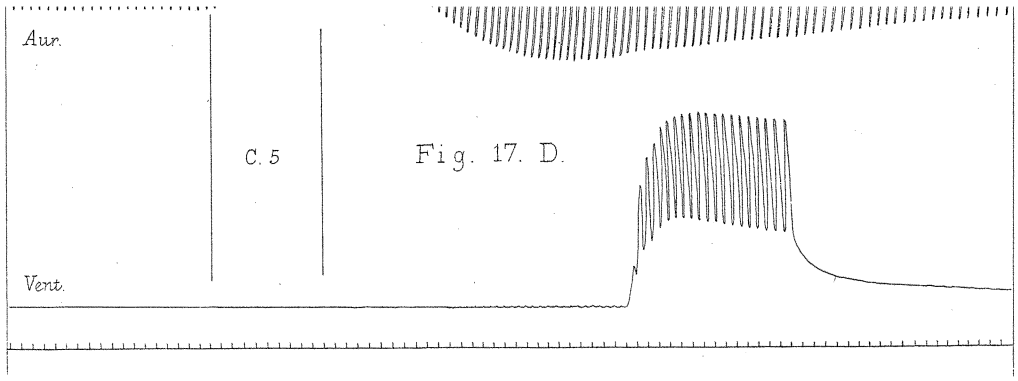


C. 8.



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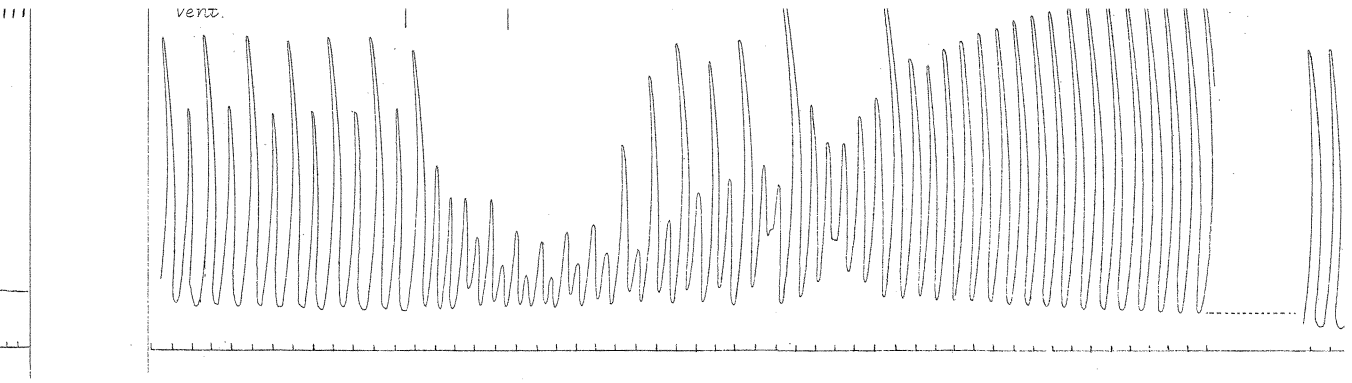
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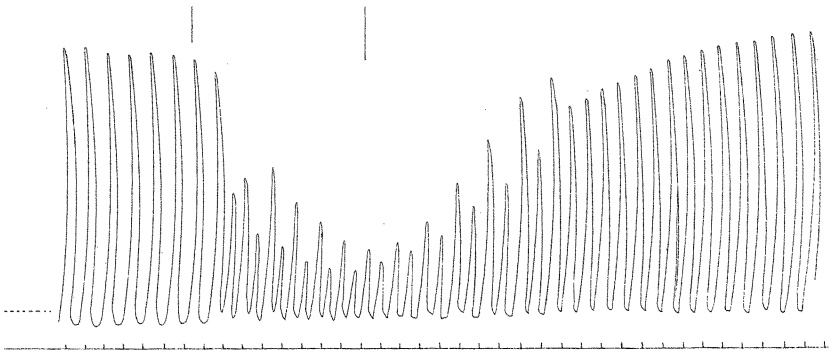

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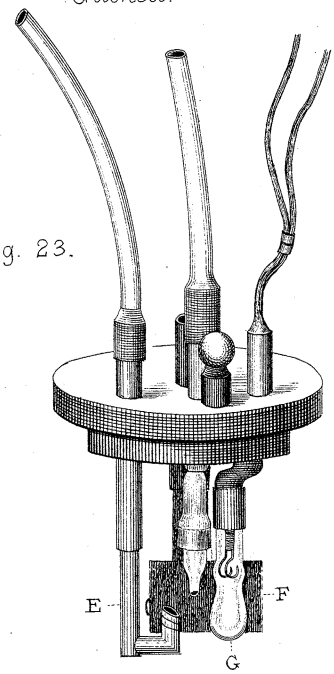

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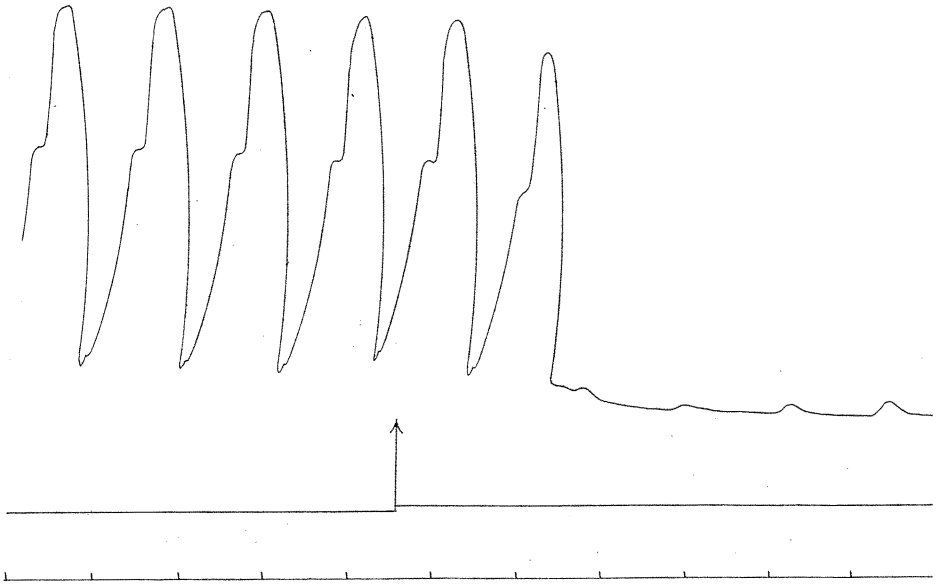

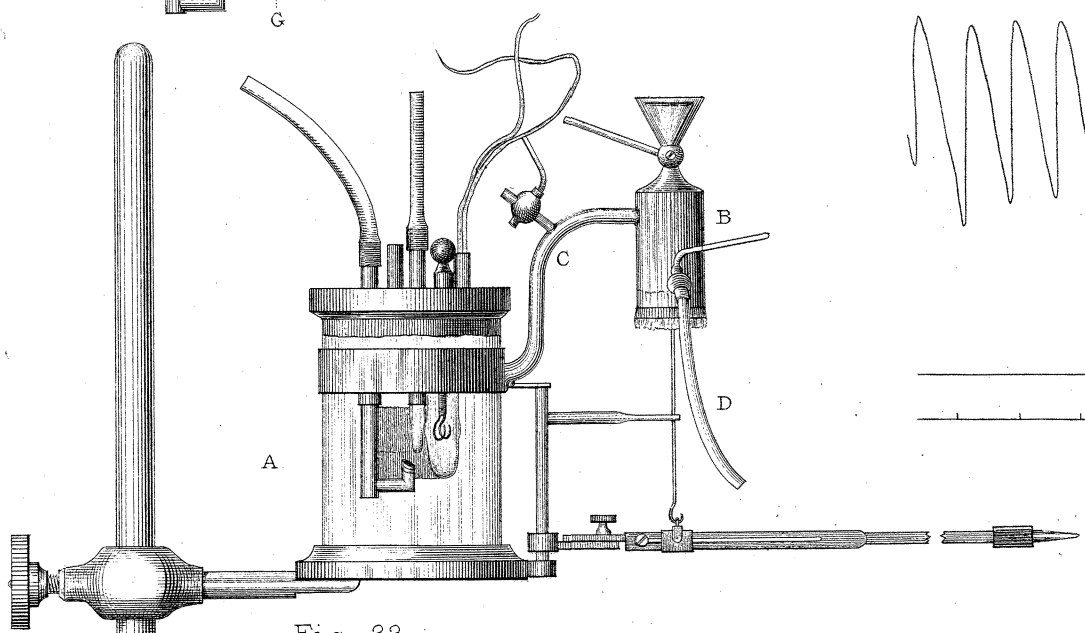

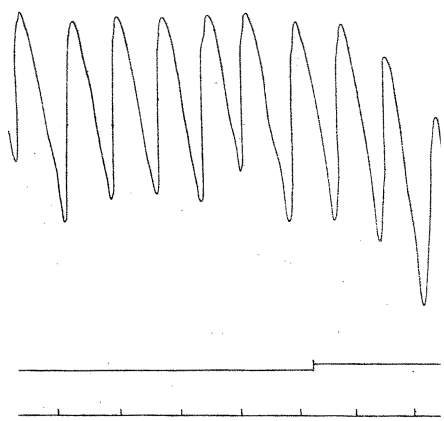

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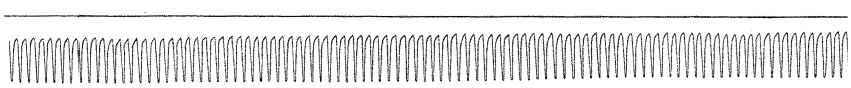

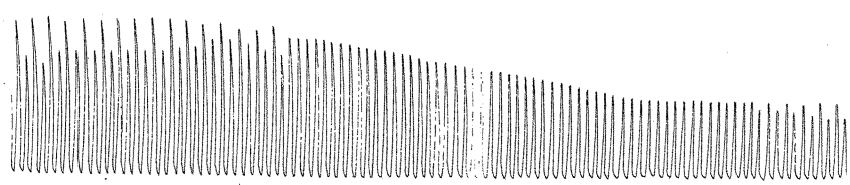

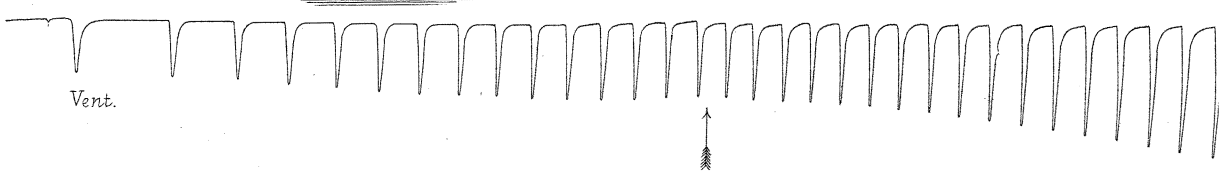

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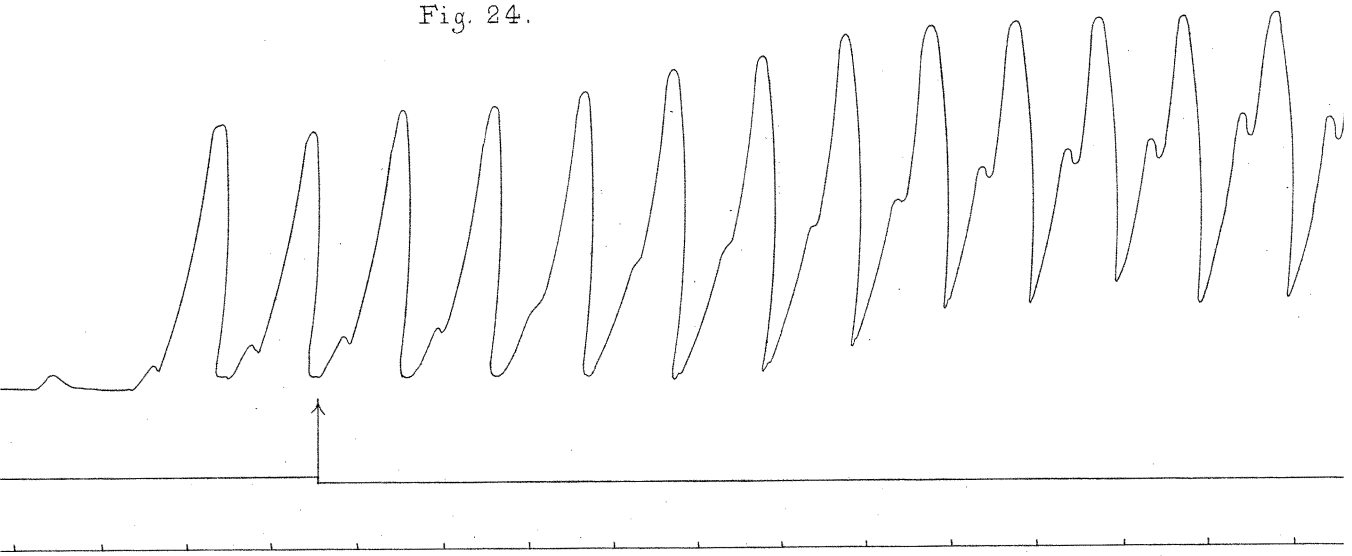
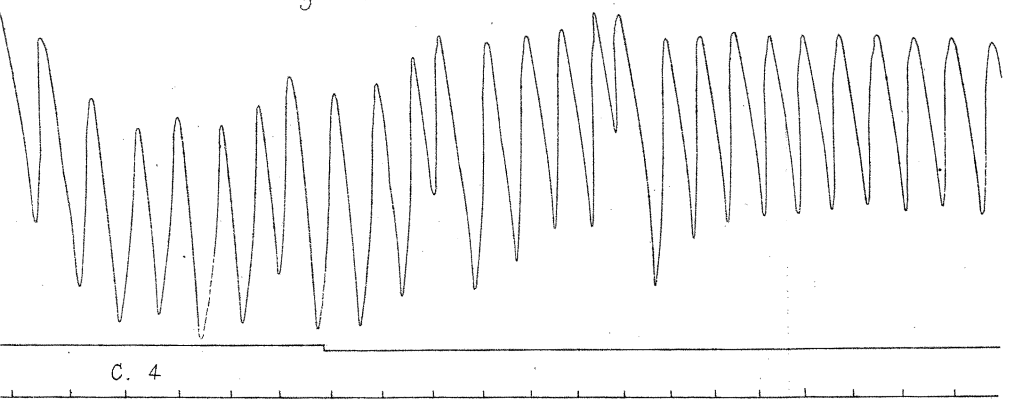
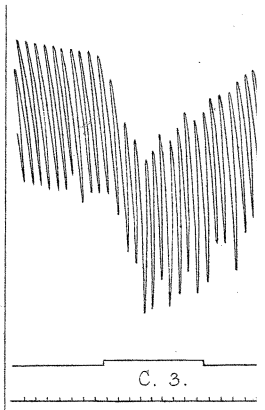


Fig. 25. A.





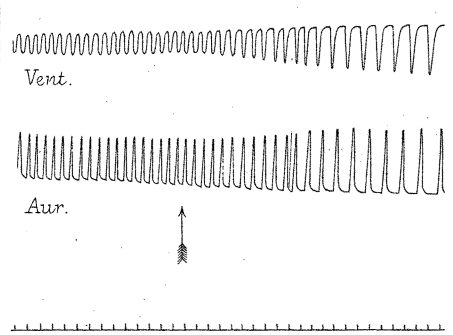
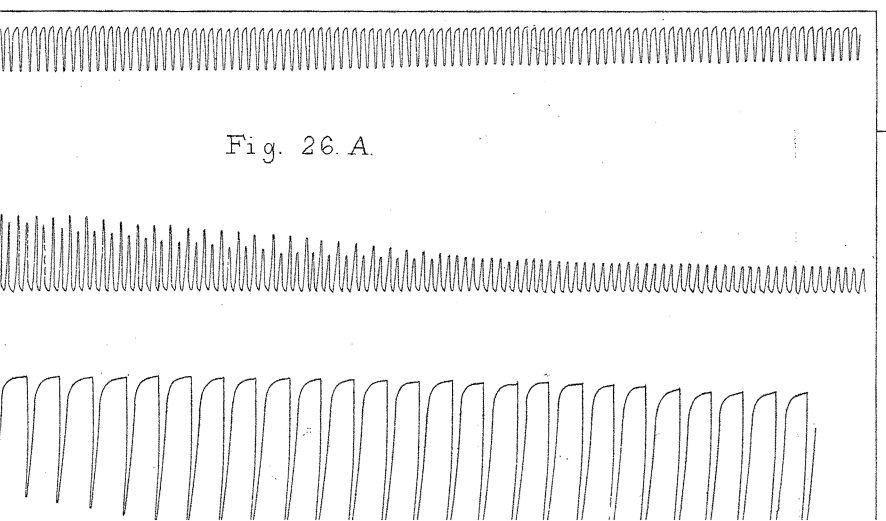


Fig. 26. A.



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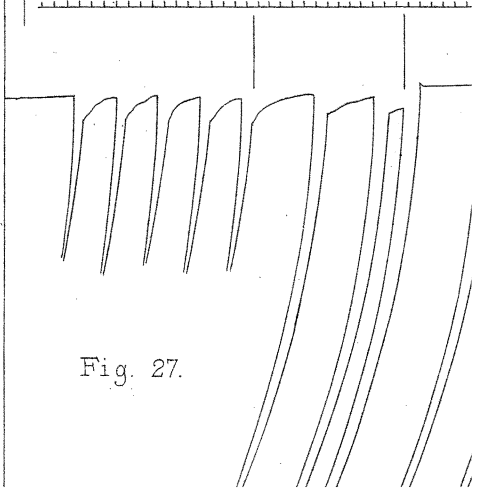

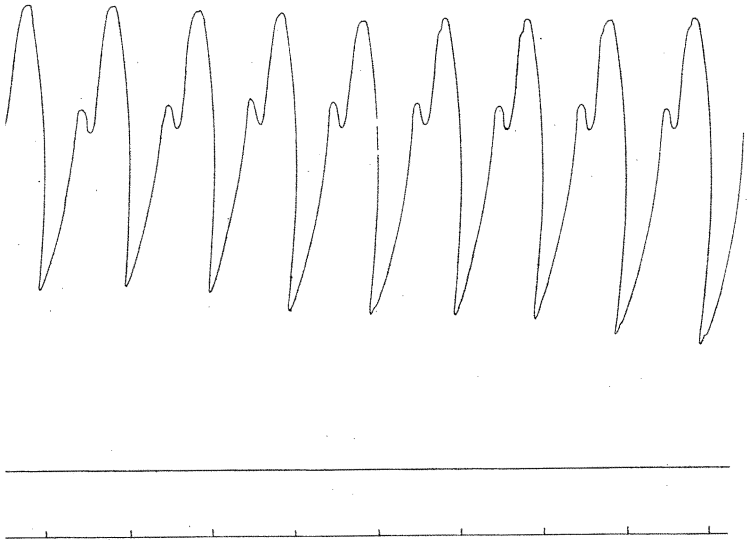

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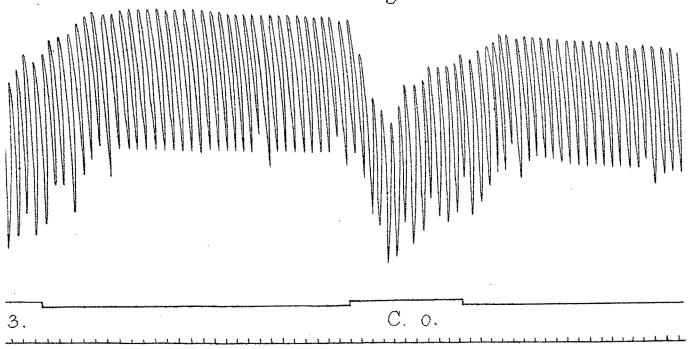


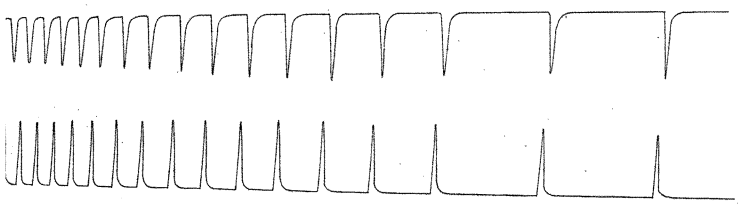
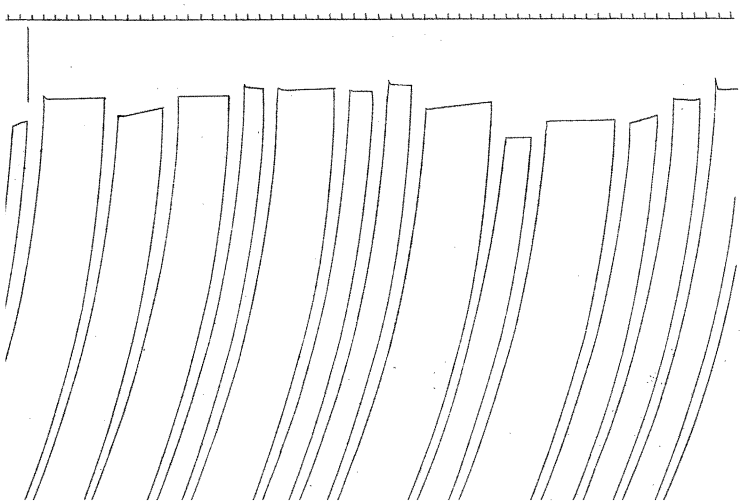


Fig. 26. B.



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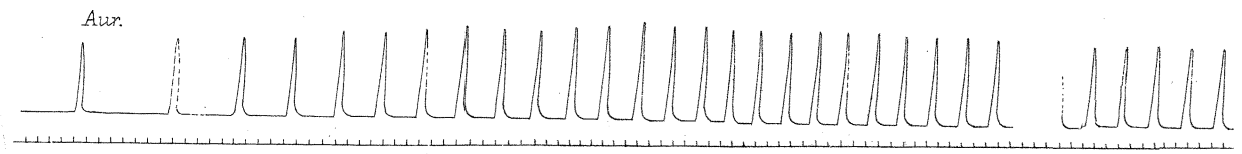

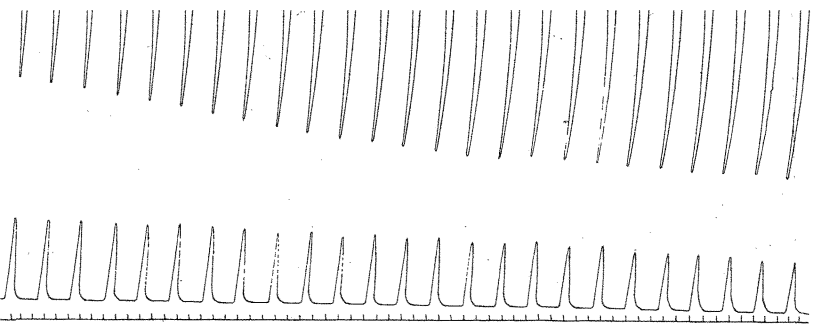

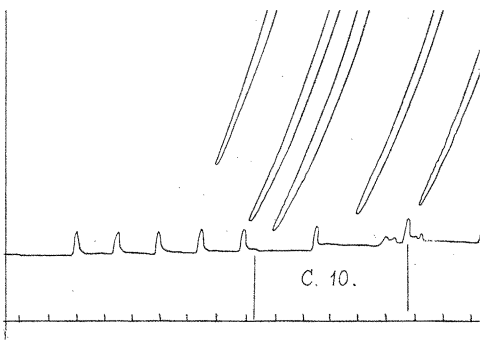
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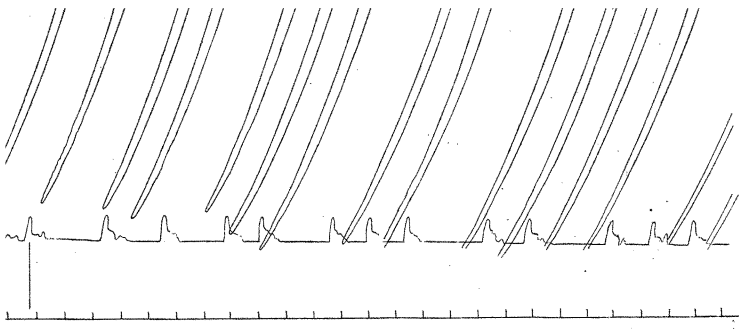

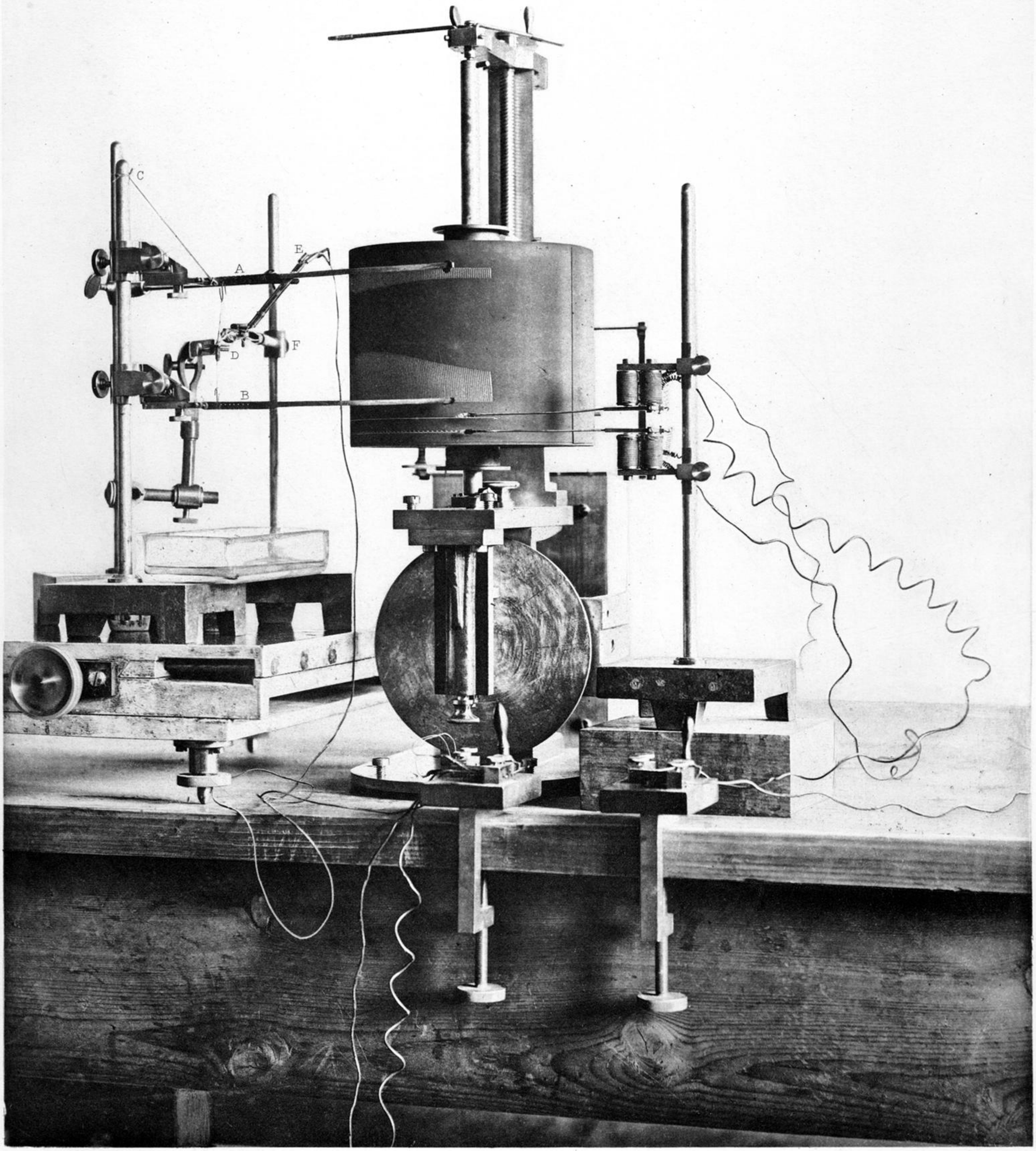
C
A
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Gaskell.

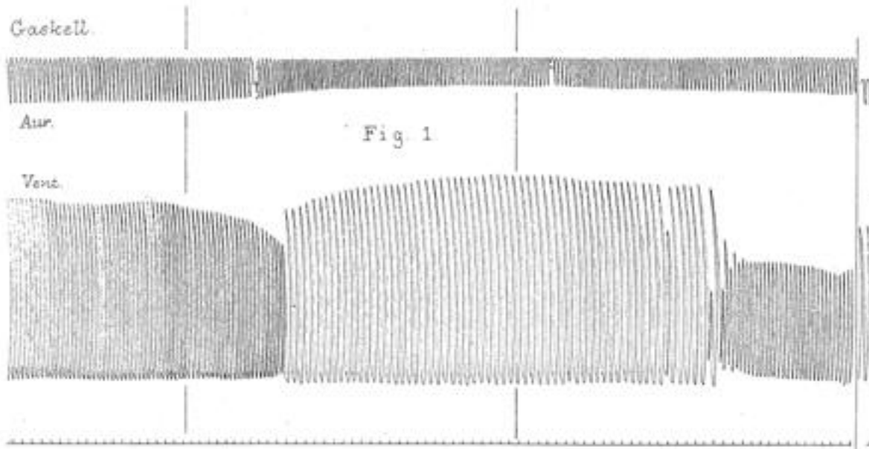
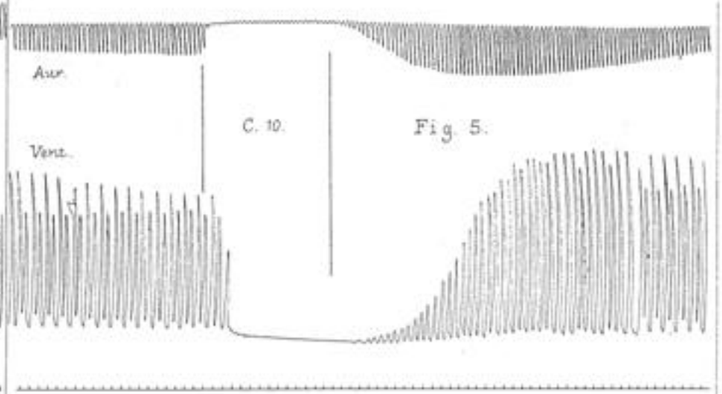


Fig. 1



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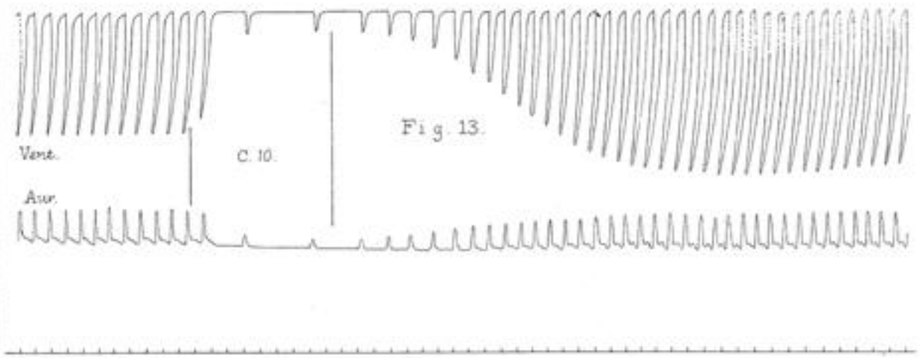

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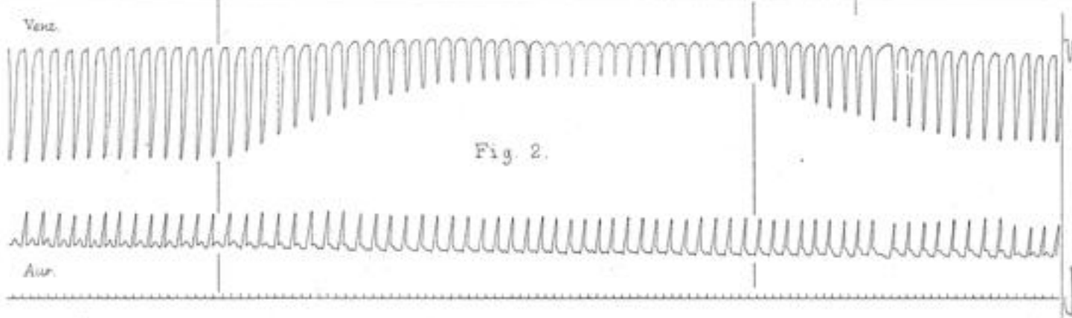

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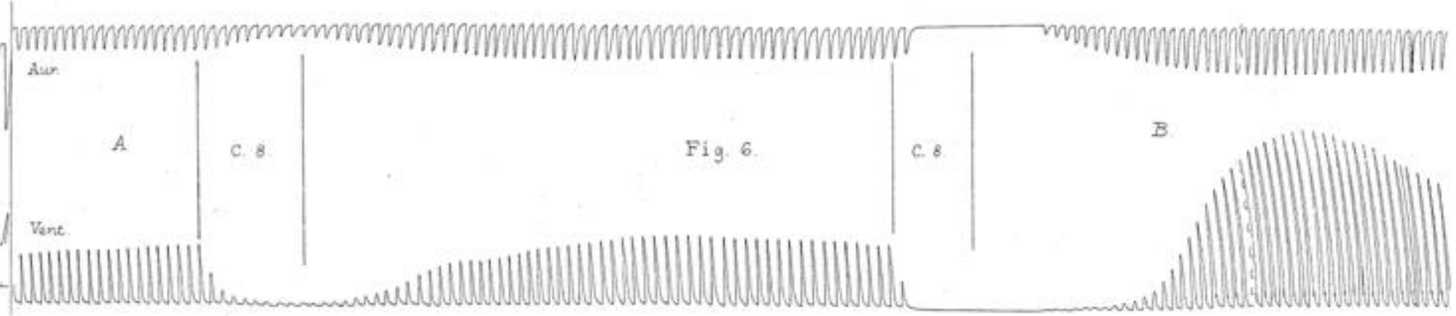

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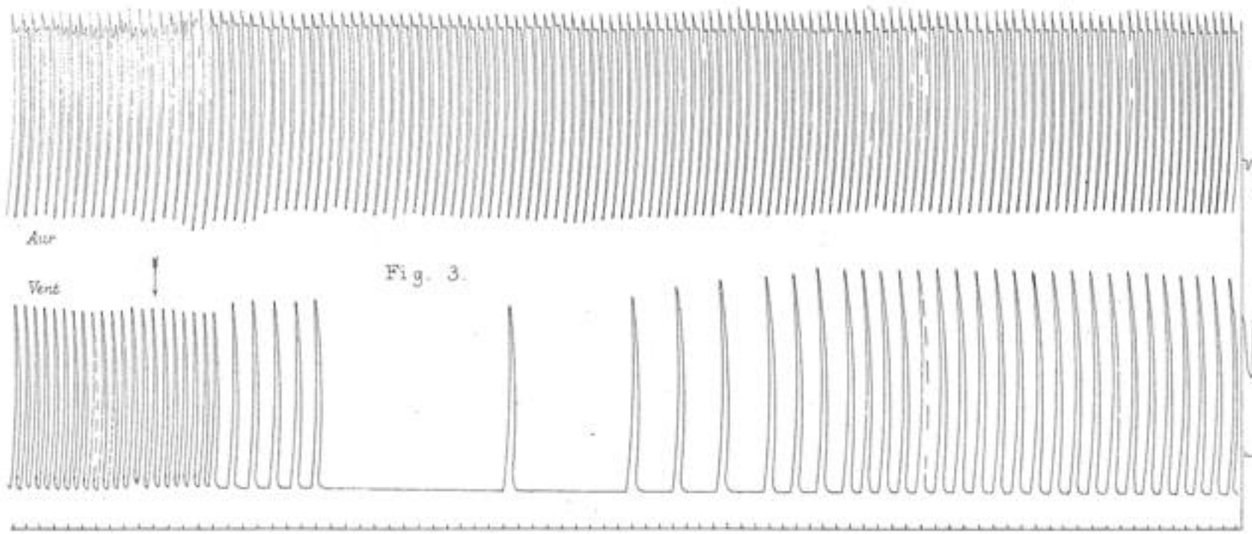

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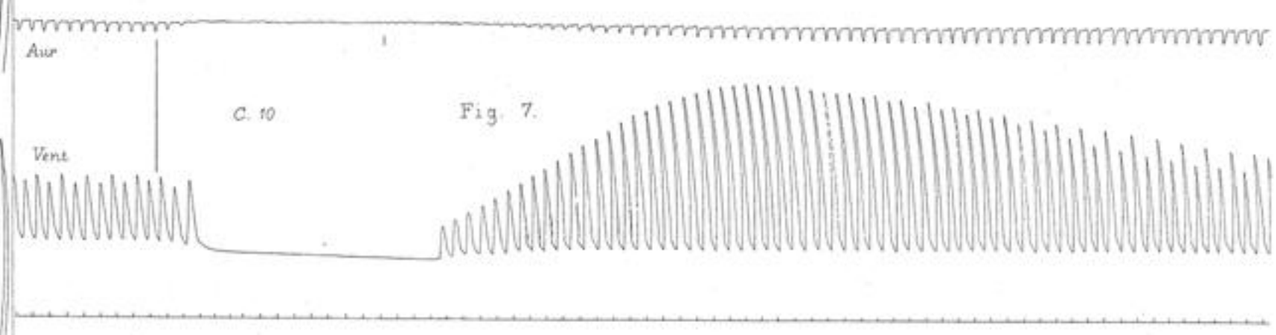

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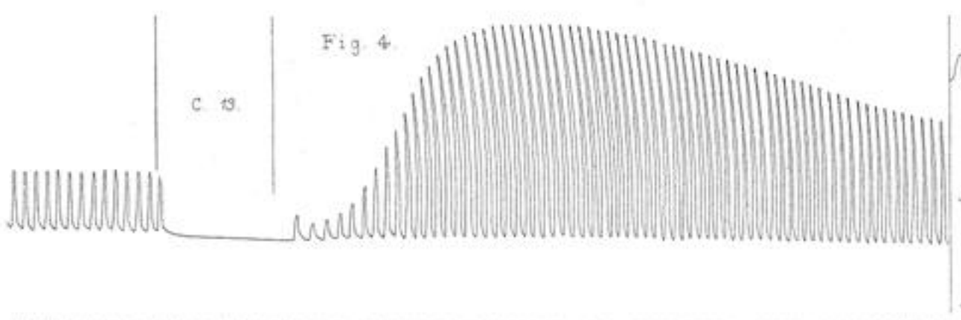
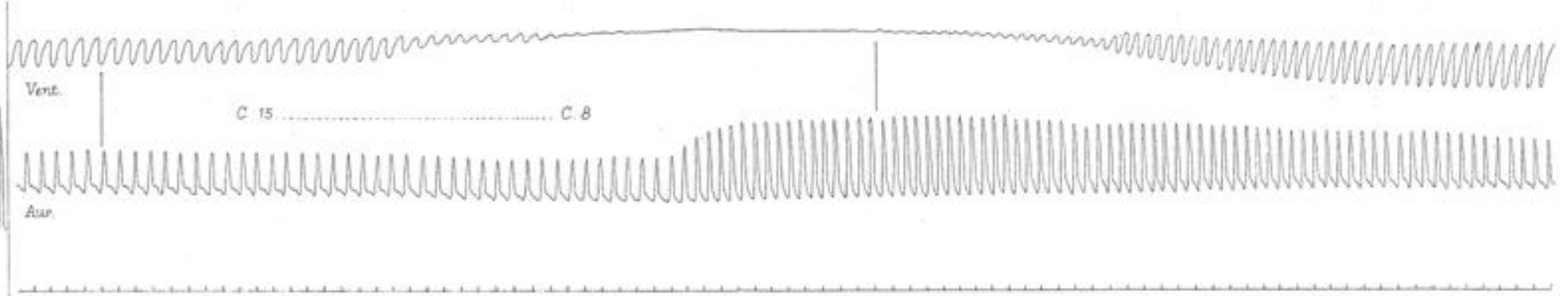


Fig. 4.

Fig. 11.



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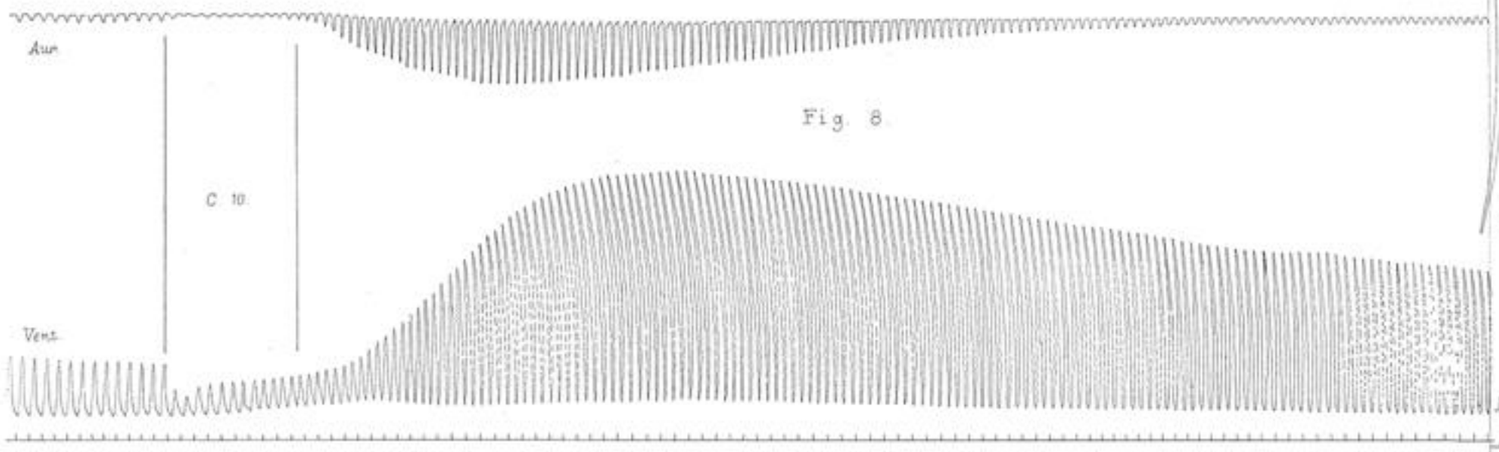

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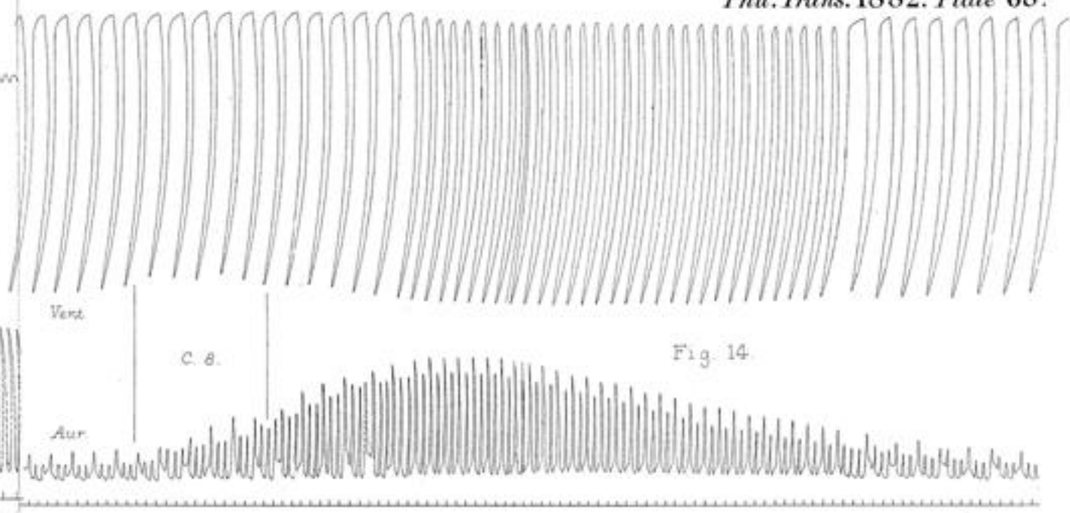

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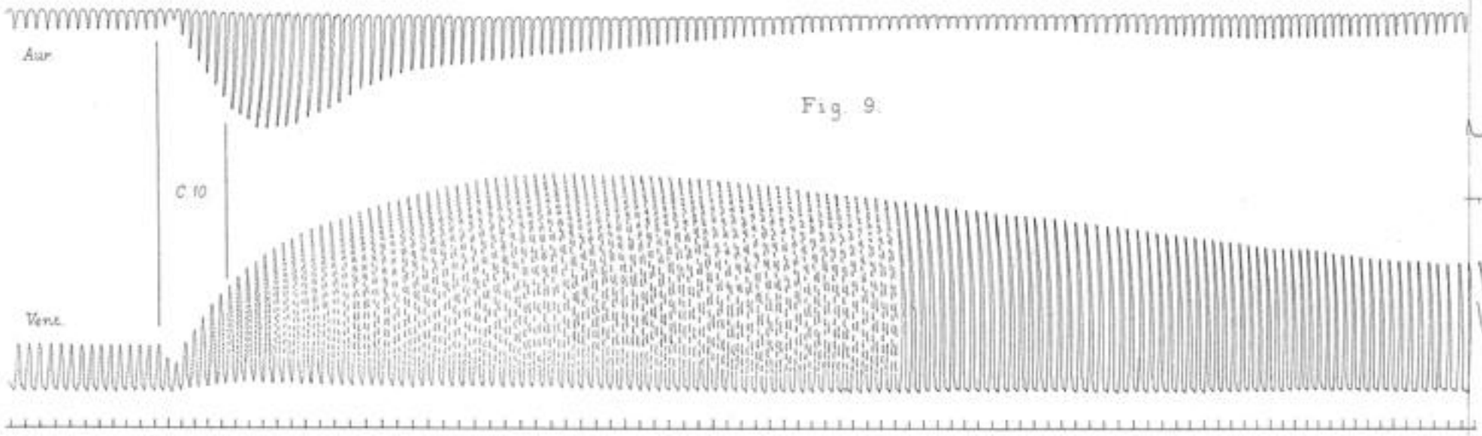

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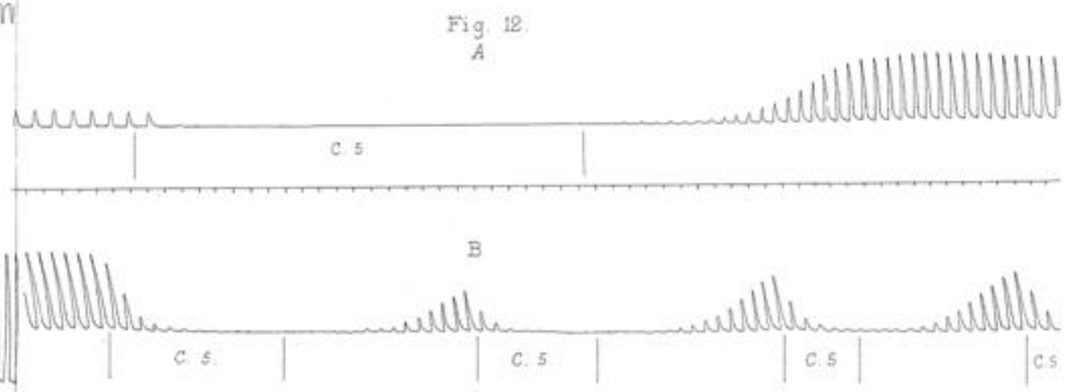

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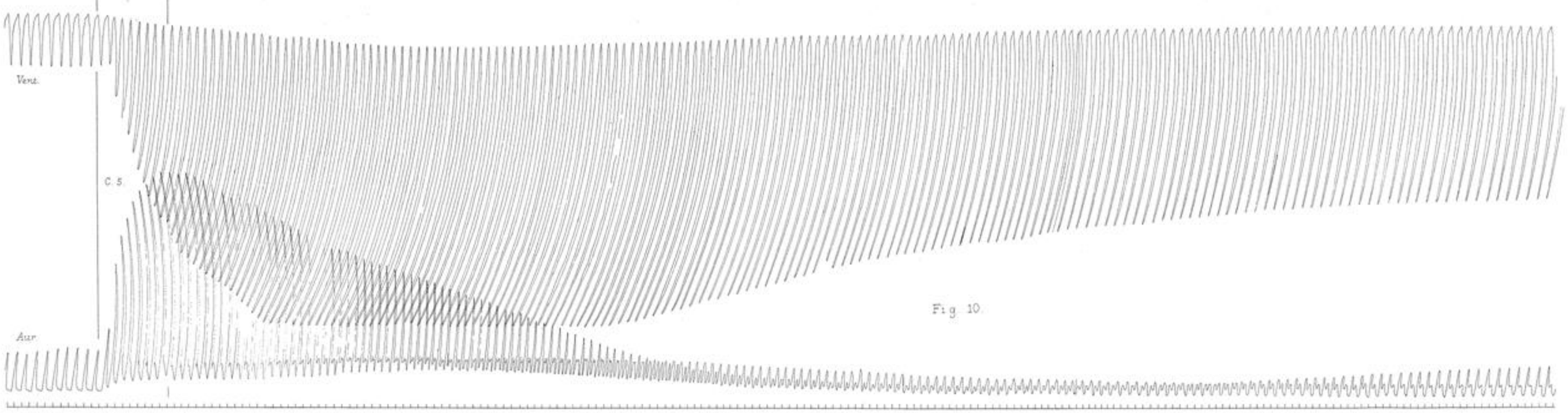

Fig. 10.

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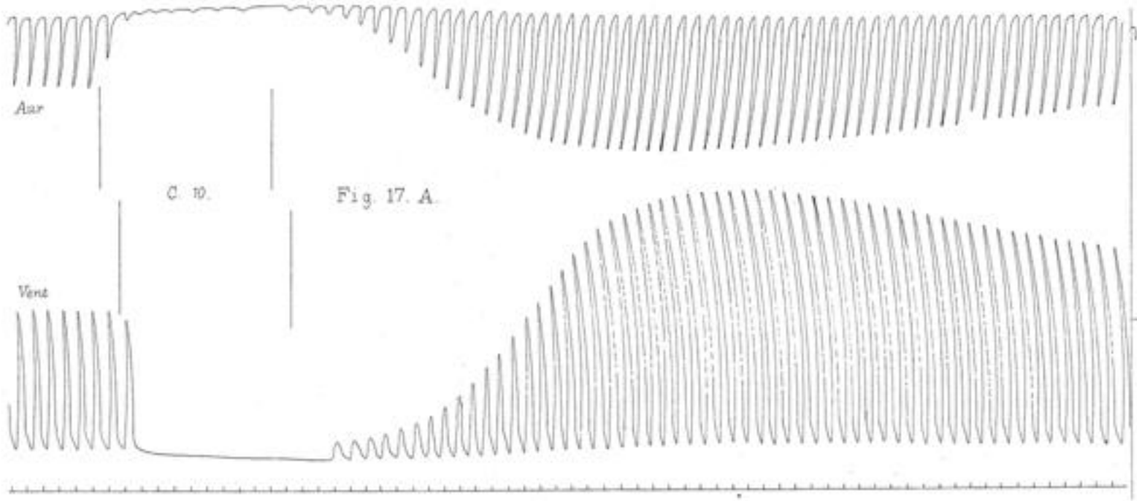

Fig. 17. A.

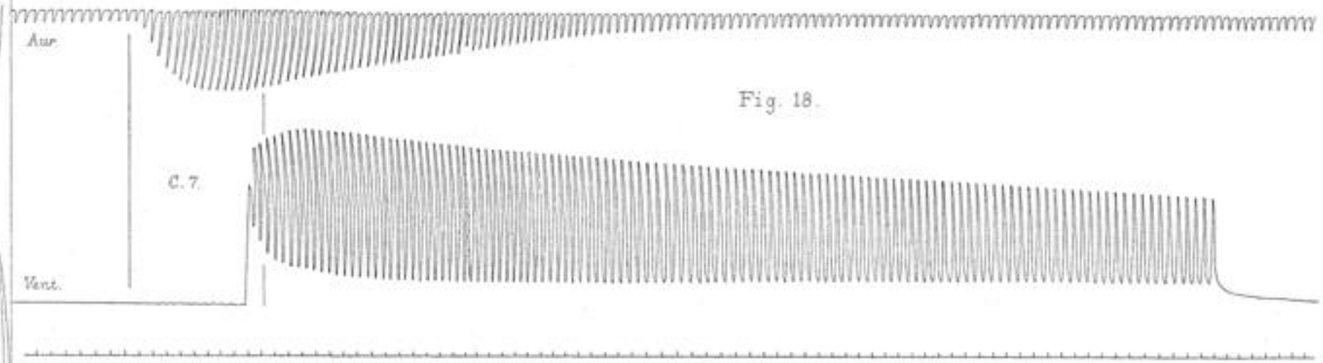

Fig. 18.

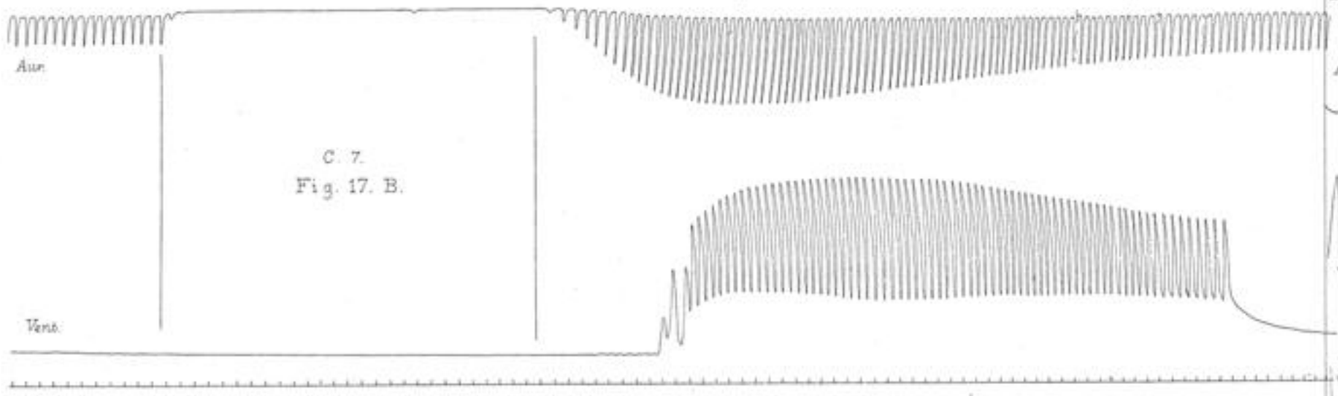

Fig. 17. B.

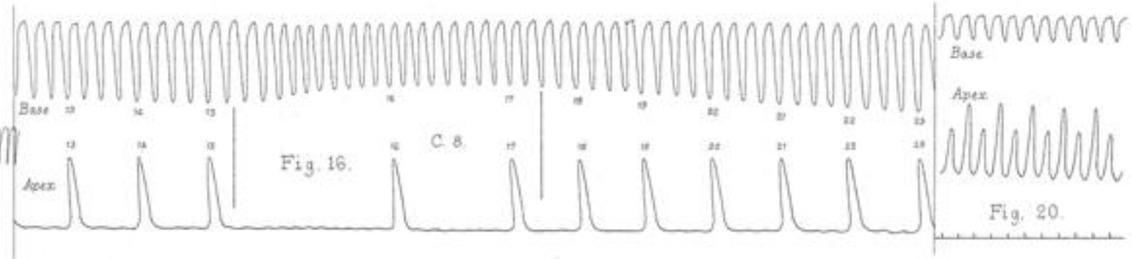

Fig. 16.

Fig. 20.

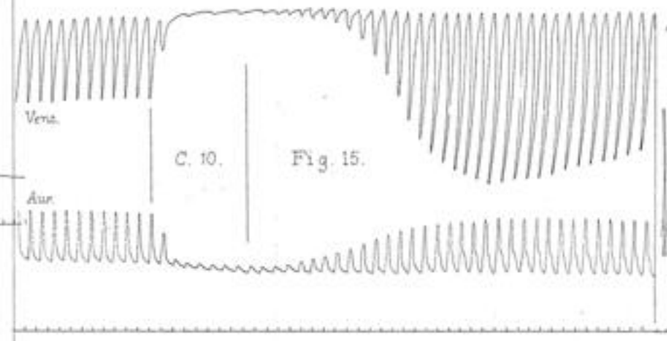

Fig. 15.

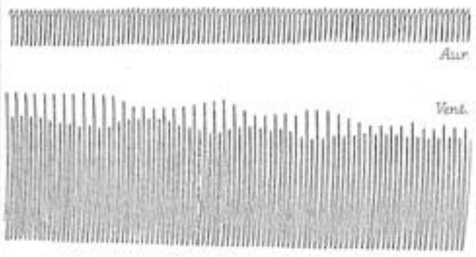

Fig. 21.

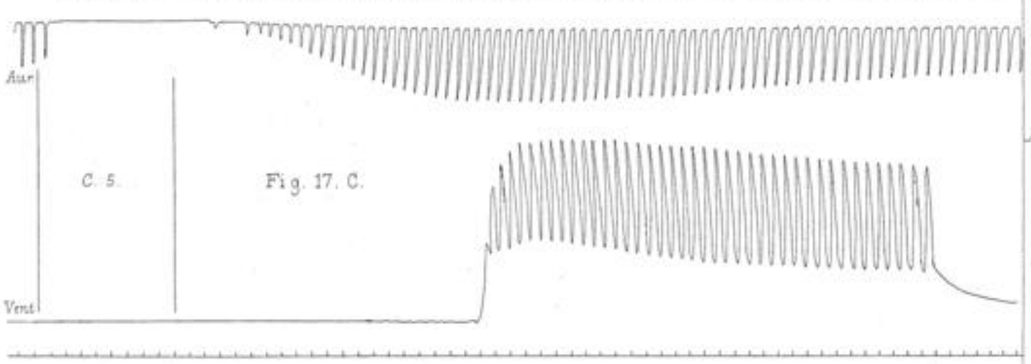

Fig. 17. C.

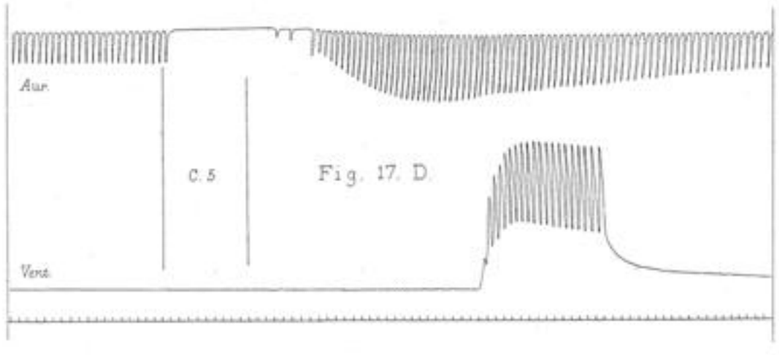

Fig. 17. D.

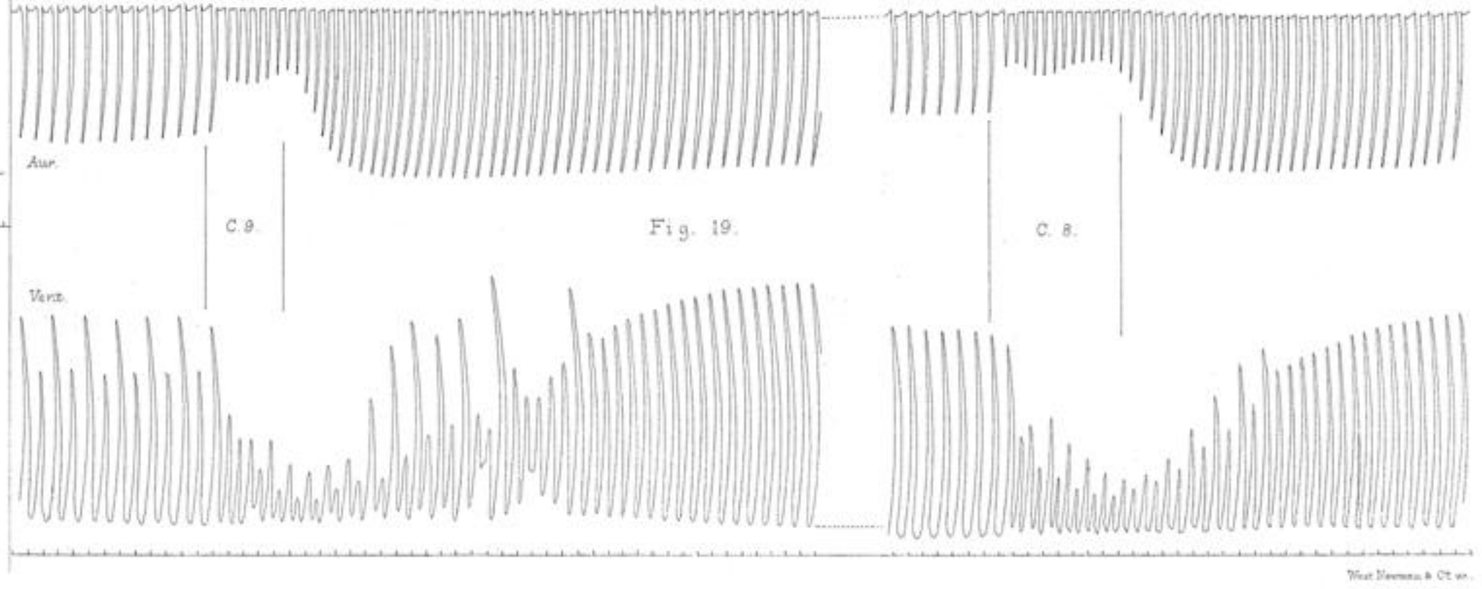

Fig. 19.

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Fig. 23.

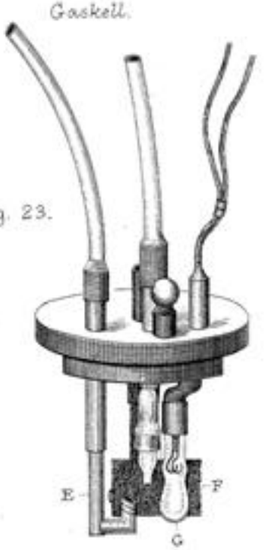
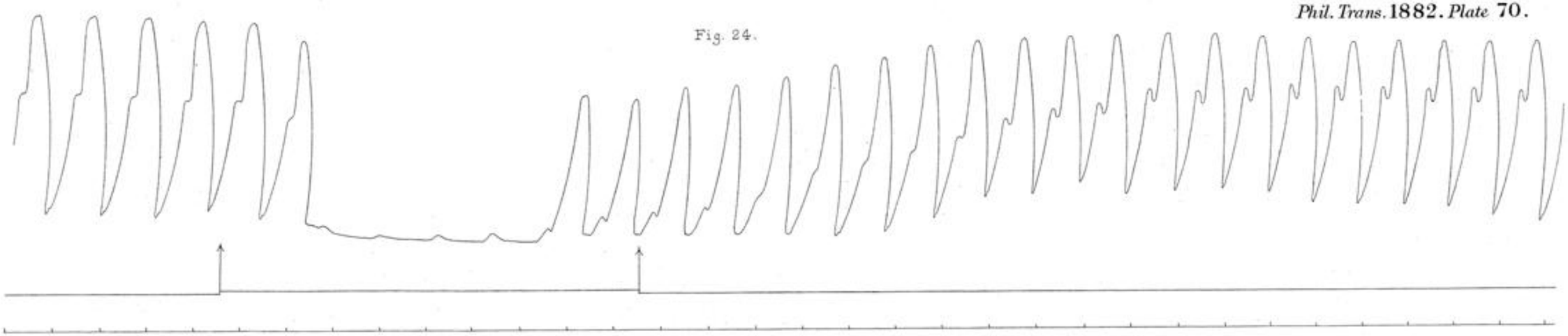


Fig. 24.



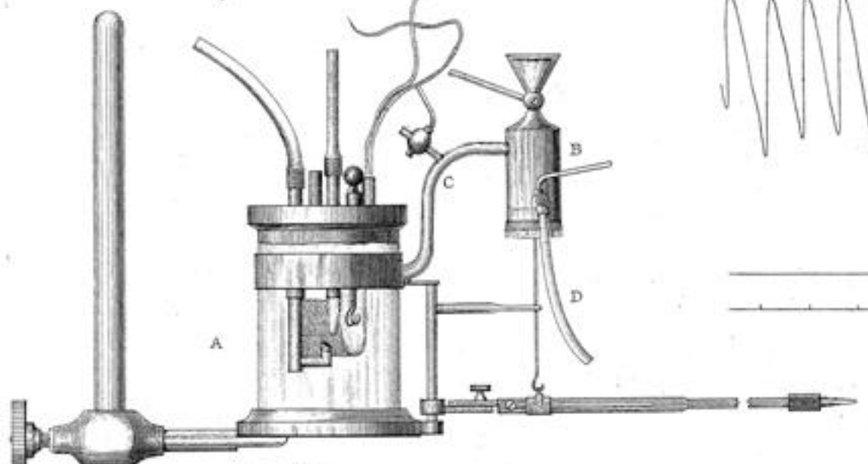


Fig. 22.

Fig. 25. A.

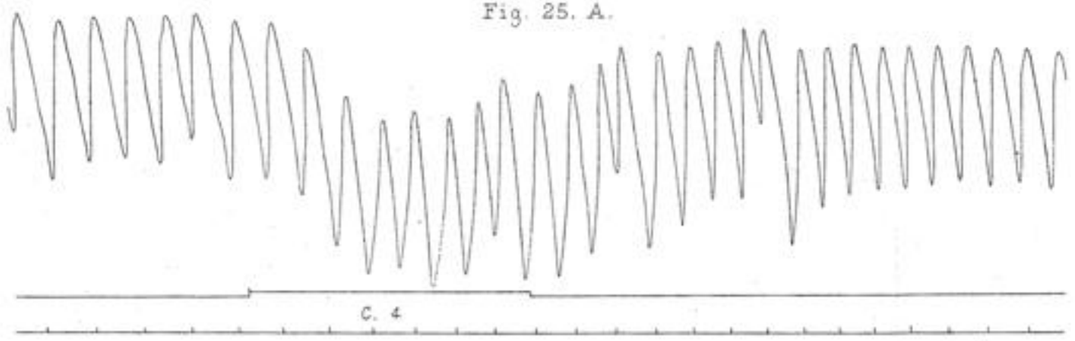
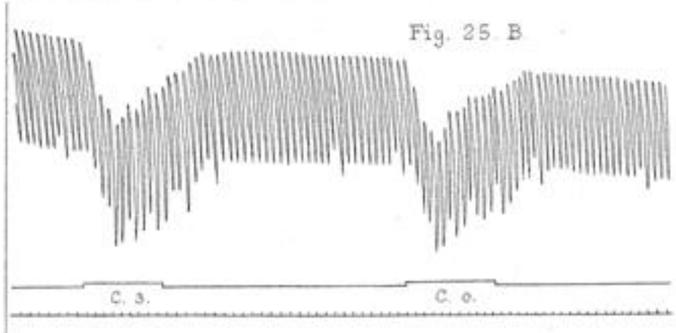


Fig. 25. B



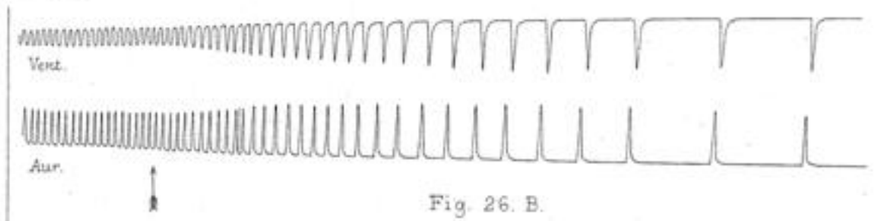


Fig. 26. B.

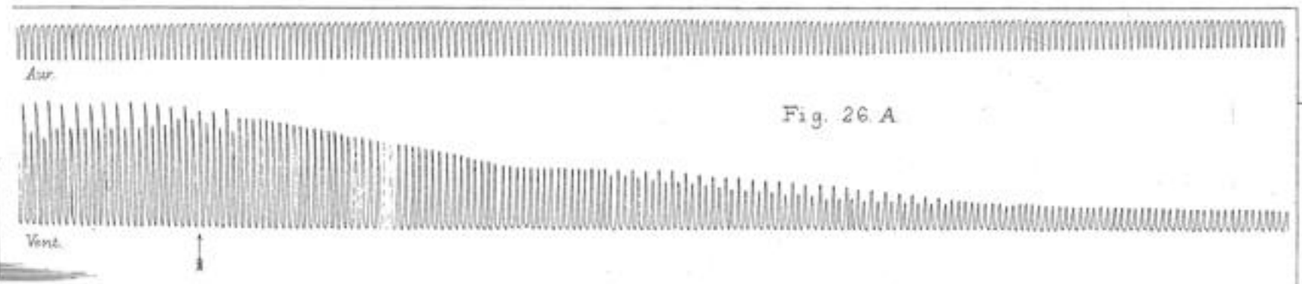


Fig. 26. A

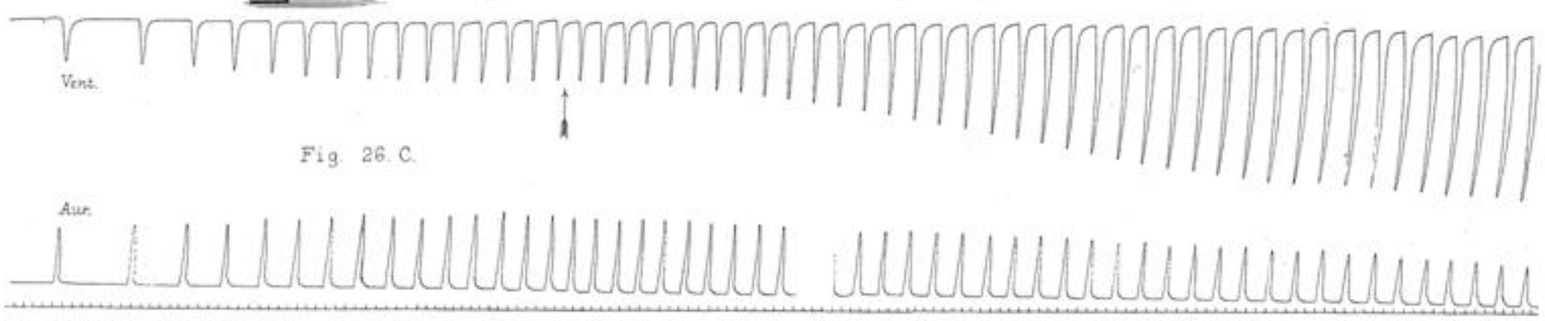


Fig. 26. C.

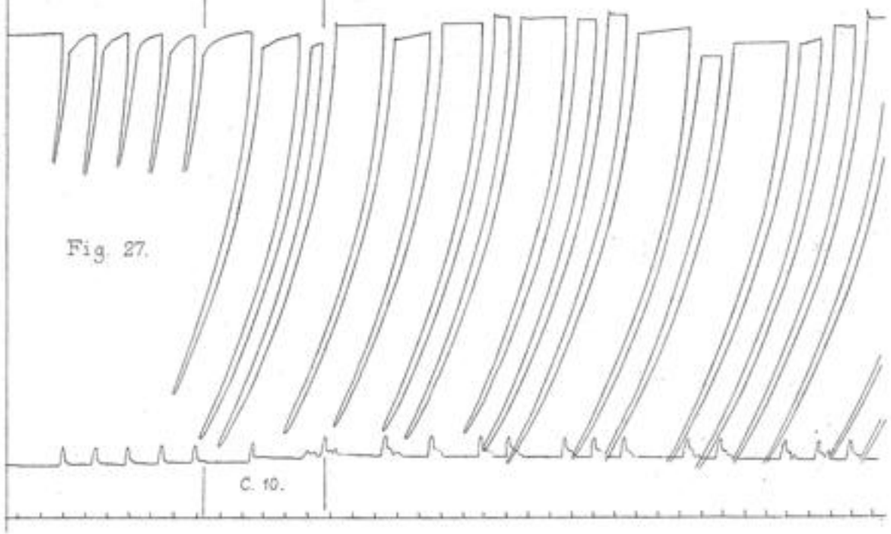


Fig. 27.