ON THE TONICITY OF THE HEART AND BLOOD VESSELS[1].

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THE tendency of physiologists of the present time to attribute to nerve cells the chief agency in the causation of rhythmical phenomena has led to the generally received hypothesis that the beat of the heart is brought about by the action of certain ganglion cells situated in the heart itself, while the cardiac muscular tissue is credited with the purely subordinate *rôle* of responding to the impulses generated in these nerve cells; and, further, that the muscles of the smaller arteries are kept in a state of semi-contraction, that is, of tonicity, by the influence of the nerve cells of the vasomotor centre.

In accordance then with these views the action of the vagus, as well as of all influences which act similarly to the vagus, is explained by the supposition that that process going on in certain of the cardiac ganglion cells which manifests itself in a beat, is interfered with either indirectly through the operation of a special inhibitory ganglionic mechanism, or directly, whenever the vagus is set in action.

Also, when it was found that certain nerves possessed the property of causing the blood vessels to dilate, and that after separation from the central nervous system the tonicity of the smaller arteries was lost only for a time, the same predominating idea necessitated the hypothesis of a local peripherally situated ganglionic vasomotor mechanism which was able to take on the functions previously held by the centrally situated nerve cells; and, therefore, dilation of the arteries could be brought about by the action of certain "vaso-dilator" nerves interfering with the processes going on in these hypothetical peripheral ganglion cells.—Thus harmonizing, on the one hand, the conception of the causation of the tonicity of arteries and of the rhythmical beat of the heart, and on the other hand, the action of the vaso-dilator nerve and the vagus.

This view, however, has required a still further extension, since it has been found that the lower two-thirds of the ventricle of the frog's heart

[1] An abstract of this paper was read before the Royal Society, March 11, 1880.

will beat rhythmically, either by the action of the constant current or by supplying it with an artificial blood solution, as in the experiments of Merunowicz[1]. If, therefore, one is still to attribute to the muscular tissue of the heart the subordinate part usually assigned to it in the causation of the beat, one must assume that in this part of the ventricle there is some nervous mechanism which has as yet escaped notice, although it has been examined so carefully and so often that one can say with absolute certainty, that there are no ganglion cells here in the smallest degree resembling those found in other parts of the heart, *i.e.*, resembling the nervous mechanism upon which the normal beat of the heart is supposed to depend. Seeing then how insecure is the hypothesis of the existence of automatically acting nerve cells, both in the apex of the frog's heart, and in, or in the neighbourhood of the muscular tissue of the smaller arteries, it is well worth while to consider whether the phenomena in question may not be explained by the properties of the muscular tissue *per se*.

Now, however, we attempt to explain the fact, that a constant continual stimulus is able to bring about a rhythmical result, whether in the case of nervous tissues by Rosenthal's well known resistance theory, or in the case of muscular tissues by Romanes' exhaustion theory[2], it is clear that our views of the manner in which modifications of the rhythm are produced will be most closely connected with the hypothesis we happen to hold ; thus, as is natural, according to the present view the alterations not only of rate of rhythm, but also of the character of the beat which occur under different circumstances, are, as a rule, discussed on the supposition that it is the variation in the stimulus, rather than an alteration in the receptivity of the muscle to the stimulus, to which the effects produced are due ; while on the other hand, on the hypothesis that the cardiac muscle itself responds rhythmically to a constant stimulus, the attention is naturally directed towards variations in the receptivity of the muscle rather than to variations of the strength of the stimulus.

In this paper, then, I propose to examine into the alterations of the character of the heart's action, and of the tone of the arteries produced by alterations in the nutritive condition of the muscular substance, on the assumption that the apex of the heart and the muscles of the smaller arteries are free from nerve cells.

As in the experiments upon the action of the heart, I was desirous

[1] Ludwig's *Arbeiten*, 1875, p. 132.
[2] *Phil. Trans.*, Part I., 1880, p. 161.

of comparing, under the same conditions, the effect of different fluids (1) upon the whole heart, with vagus attached; (2) upon the ventricle; and (3) upon the apex, I have made use of Roy's tonometer[1], modified in the following way:—

The heart is suspended in a glass bottle of size sufficient to hold the whole heart with cannulæ fixed into one superior vena cava and aorta, as well as electrodes for the vagus. This bottle can be filled with oil, or normal saline solution, or any other fluid that may be deemed advisable, and from its shoulder a German silver tube passes to a cylindrical reservoir, also made of German silver, within which the piston of Roy's tonometer can move vertically up and down. The upper extremity of this reservoir is closed by a stop-cock, so that the reservoir and tube connecting it with the glass bottle can be filled with oil, and at one side of the reservoir is a tap for the purpose of running out the oil and so raising the lever, as in Roy's tonometer. The glass bottle possesses two stoppers, the one fitted with the ordinary perfusion cannula for the ventricle or apex, and the other fitted with cannulæ for the whole heart and electrodes. The whole apparatus is air-tight, and the smallest variation in the capacity of the ventricular cavity is magnified and registered by means of a lever. The tracing is made on the continuous paper of the kymographion by means of a fine camel's hair brush attached to the extremity of the lever.

In order to compare the action of different fluids under precisely the same conditions, it is necessary to insure that they pass through the heart at the same pressure, and at the same time to arrange so that any one solution can be sent through during any period of the action of any other solution. To effect this I use three funnels arranged on a stand, which can be raised or lowered to any height required; the funnels communicate by means of three india-rubber tubes and three three-way taps with the inflow cannula, so that by simply turning any one of the three taps any particular solution can be sent through the heart. The funnels are filled with different solutions, and the level of the fluid in each funnel kept constant by means of a Marriotte supply flask placed on the stand, and containing the same solution as that in its respective funnel.

The defibrinated blood solutions of which I have made use have been either one part blood (sheep's, bullock's, or rabbit's) to four parts 0·75 p. c. salt solution, as recommended by Merunowicz, or one part blood to two parts salt solution, as used by Roy.

[1] *Journal of Physiol.*, Vol. I., p. 452.

I. *It is not the foreign nature of the blood supply, as Bernstein thought, which is the reason why the apex of the frog's heart beats when supplied by a mixture of blood and salt solution.*

Bernstein[1], and confirming him, Bowditch[2], have shown that, if the lower two-thirds of the ventricle be separated physiologically from the upper third and auricles by nipping the ventricle by means of a fine wire forceps, then the apex will remain quiescent indefinitely, although supplied with the frog's own blood by the beating auricles and upper part of ventricle. This is true enough; but what is not true, is the supposition that the frog's own blood cannot bring about a separate series of beats in the physiologically isolated apex. As Dr. Foster has shown me, and as I have often seen for myself, if, after the ventricle has been nipped, and the apex thus reduced to quiescence, the aortic branches be clamped, and the outflow from the heart thereby prevented, then, by the continual beating of the upper part of the heart, the pressure in the apex is increased, and the apex, though only supplied with its own blood, will beat spontaneously. The rate of beat of the apex is entirely independent of that of the upper part of the ventricle and auricles, being always very much slower. The beats do not, as a rule, commence immediately after the closure of the aorta, but even as long a time as two minutes may elapse before a single beat takes place; for a variable time after the nipping of the ventricle clamping the aorta is unable to produce beats. It will be remembered that, according to Merunowicz, it was necessary to wait for even as long as sixty minutes after the blood solution had begun to pass into the apex before any beats took place. As soon as the aorta is unclamped, or very quickly afterwards, the apex returns to its former state of quiescence, and will remain without beating, unless the pressure be again increased by clamping the aorta. This experiment seems to show that the spontaneous apex beats depend rather upon the pressure in the cavity than upon the nature of the blood supply.

The reverse experiment shows this. In a pithed frog the heart is exposed, and the frog's own blood replaced by a mixture of sheep's blood and salt solution—1 part blood to 4 parts 0·75 p. c. salt solution—by

[1] *Centralb. f. d. Med. Wiss.*, 1876, pp. 385, 435.
[2] *Journ. Physiol.*, Vol. I., p. 104.

means of a cannula in the abdominal vein, the lower end of the vein being left open. As soon as all the frog's own blood has been removed the flow through the cannula is stopped, and directly afterwards, when the heart has regained its natural size, the lower end of the vein is ligatured. The frog is thus supplied with the artificial blood solution instead of its own blood, and the heart continues to beat strongly and regularly. The ventricle is now nipped, and immediately the apex remains quiescent, as in Bernstein's experiment. The upper part of the ventricle and auricles beat vigorously, and keep the lower two-thirds of the ventricle well supplied with the artificial blood solution; yet, although the apex be observed for hours, it will not beat. As soon, however, as the blood solution is allowed to flow at a slight pressure into the cannula, which is tied into the upper end of the abdominal vein, the lower end being still tied, the heart becomes distended with blood, its upper portion beats exceedingly vigorously, and almost immediately, or in a very short time, the apex commences to contract regularly and strongly, emptying itself at each contraction. The rate of beat is slower than, and independent of, that of the upper third of the ventricle. If the increase of pressure due to the passing in of the blood solution is not sufficient to bring about these spontaneous apex beats, then it is only necessary to clamp the aorta as well in order to obtain a series of strong apex contractions. In either case, upon the removal of pressure, by unclamping the aorta or stopping the inflow of blood, and at the same time opening the lower end of the abdominal vein, as soon as the heart returns to its original volume, the apex returns to its normal condition of absolute quiescence.

These experiments prove conclusively that the difference between the action of an artificial blood solution and the frog's own blood, as far at least as the causation of the spontaneous apex beats is concerned, is an unessential one, and at the same time show how important a factor for their production is the amount of pressure within the apex cavity.

Note.—Since the above experiments were performed a short notice of a paper by Ludwig and Luchsinger appeared in the *Centralblatt f. Med. Wiss.*, 1879, p. 404, in which the authors state that the spontaneous apex beats obtained by Merunowicz depend in part upon the pressure in the apex cavity.

II. *On the action of dilute alkaline solutions upon the cardiac muscle.*

The experiments of Merunowicz[1], Stiénon[2], and Gaule[3] have all shown how the apex of the heart, after being reduced to rest by washing out with salt solution, can be made to beat again by sending through a dilute alkaline salt solution. None of these observers, however, seem to attribute any definite action upon the muscular tissue to the alkaline fluid, they rather conclude that the alkali causes beats to reappear because it removes some obstruction, probably acid in nature, which has been accumulating in the heart and which has prevented its pulsations; the beats then are supposed simply to be set free by the action of the alkali, and after a time that action ceases to have any effect and the apex again stops beating because the substance upon which its contractile power depends requires renewal. In this second standstill, after the alkali solution has for some time been passing through the heart, nothing is said to lead one to suppose that the standstill is in any way different to that caused by the salt solution alone, that is, a standstill in full diastole. This, however, is not the case. If the ventricle or apex, placed in Roy's tonometer as described above, be made to beat with an artificial blood solution and then be washed out with a continuous stream of a 0·75 p. c. salt solution at a constant pressure of 20 c. m. until the beats have entirely ceased and the ventricle remains motionless in diastole, then, upon sending through a dilute alkaline solution (of the strength recommended by Gaule, viz., one part sod. hydr. to 20,000 parts salt solution) at the same pressure, a series of beats takes place and again the ventricle stops beating, but no longer in the condition of diastole, the standstill which now occurs is always a systolic rather than a diastolic one.

The genesis of this systolic standstill can be better shown by sending the alkaline solution through the ventricle when beating under the influence of the artificial blood solution.

In Fig. 1, Pl. I., I have endeavoured to depict the principal points in the curve that are invariably obtained under these circumstances.

[1] *Loc. cit.*
[2] *Arch. f. Anat. u. Phys. (Physiol. Abth.)*, 1878, p. 263.
[3] *Arch. f. Anat. u. Phys: (Physiol. Abth.)*, 1878, p. 291.

Owing to the length of the original curve, I have thought it best to give pieces of it taken at intervals during the action of the alkaline solution rather than such another length of curve as is represented in Fig. 3, Pl. II. The details of this particular experiment were as follows:—

March 1, 1879. Frog's ventricle on cannula; three funnels containing sheep's blood solution (one part to two parts salt solution), alkaline solution (one part sod. hydrate to 20,000 parts salt solution), and acid solution (one part lactic acid to 10,000 parts salt solution) respectively were placed in connection with the inflow cannula. The level of the fluid in the funnels was kept constant at a height of 20 c. m. above the ventricle. The extremity of the outflow tube was fixed at a height of 6 c. m. below level of fluid in the funnels. The blood solution was first allowed to run through the ventricle, and after it had been beating for some time with the regularity and force represented by the first part of the curve, *a*, the alkaline solution was made to run through at the point marked by the arrow. The curves, *b*, *c*, *d*, and *e*, represent pieces of the whole curve obtained, taken at the following intervals:—

Between the end of	*a*	and the beginning of	*b*	there were	39	sec. and	14	beats.		
„	„	*b*	„	„	*c*	„	91	„	39	„
„	„	*c*	„	„	*d*	„	44	„	18	„
„	„	*d*	„	„	*e*	„	22	„	6	„

The gradation from the normal beat at *a* to the alkaline standstill at the end of *e* was in the original curve perfectly gradual.

Upon examination of the figure as a whole two facts are very clearly seen. In the first place, the height to which the lever is raised above the abscissa line at each beat remains the same; in other words, the force of each separate contraction has not been diminished by the action of the alkali—the cavity of the ventricle is closed during each systole throughout the whole curve as completely as with the artificial blood solution. In the second place, there is a gradual rise in the height of the lever above the abscissa line during each diastole, that is to say, the extent of the relaxation of the ventricle between successive beats is progressively diminished by the action of the alkaline solution. Further, if instead of examining the figure as a whole each separate contraction be noticed, it is seen that coincident with the increasing imperfection of the relaxation during the diastole there is a progressive lengthening of the time of full contraction during each systole. With the blood solution alone, each beat as traced by the lever presents a slightly rounded apex, showing that the ventricle remained only for a fraction of a second in the position of full contraction,

while with the alkali solution the tracings become more and more flat-topped, the cavity of the ventricle remains closed for a longer and longer time. The ultimate effect of the increasing difficulty of relaxation is to cause the lever to draw a straight line at the height of full contraction. The systolic standstill which is thus brought about, does not necessarily prove that the ventricle is no longer beating, but simply that the contractions are no longer capable of being registered, because the action of the alkali has put the tissue into such a condition that the cavity is closed during both the systole and diastole.

If, as is possible, the ventricle can contract beyond the complete closure of the cavity, then invisible beats may in reality occur, although by the method used it would be impossible to register them. Whether this be the case or not, it is clear that the standstill produced by the alkali solution is not of the nature of a tetanus, but rather that there is some gradual change in the condition of the muscular tissue independently of the beats of that tissue, a change corresponding to what has received the name of "idio-muscular contraction." The standstill is not caused by such a rapid increase in the rate of pulsation that there is no longer time for relaxation to take place, for the rate of rhythm is slower rather than quicker at the end of the curve than at its commencement, but by a gradual alteration in the condition of the tissue itself, which becomes, so to speak, more and more tightened up, until at last the cavity is closed during the whole cycle of the beat. It is in consequence of this alteration of the tissue that the separate beats are changed in character, and not the variation of the beat which produces the standstill.

This view is confirmed by observations of the action of the alkali solution on the non-beating apex.

If, instead of supplying the apex with an artificial blood solution, its own blood be washed out with 0·75 p. c. salt solution, it will frequently remain without beating, and it is possible to supply this non-beating relaxed apex with normal saline solutions containing alkali, acids, &c., without the necessary occurrence of a single spontaneous beat.

In this way it can be shown that the dilute alkali solution causes the apex to pass very slowly from the position of extreme relaxation to that of full contraction.

Thus, in an experiment on Oct. 25, 1879, normal saline solution was sent through the non-beating apex for six minutes, at a constant pressure of 22 c. m., during which time the apex remained relaxed without a single spontaneous pulsation, and then the alkaline solution (1 part sod. hydrate to 20,000 parts

salt solution) was sent through at the same pressure. During the whole time that the alkaline solution was flowing, the lever was very steadily and very slowly rising, so that in eleven minutes from the time when the alkali solution was sent through it had risen 16·5 mm., a rise corresponding very nearly to the full contraction of the apex. During this gradual rise only two spontaneous beats took place.

It is clear, then, from these two sets of experiments, that a dilute alkaline solution acts upon the muscular tissue of the heart in such a way as to bring it from a position of relaxation to one of contraction, and that, according to the stage reached in this alteration of the contractile tissue, so will be the nature of the beat produced by the ventricle; the more the muscle is drawn together by the action of the alkali, the longer is the time of full contraction in each beat—meaning by the term full contraction, the complete closure of the ventricular cavity.

III. *Dilute acid solutions act on the cardiac muscle in the opposite direction to dilute alkaline solutions.*

At present I have made use of only two acid solutions, viz., 1 part lactic acid to 10,000 parts salt solution, and 1 part lactic acid to 20,000 parts salt solution. These were sent through the ventricle or apex in the same way as the alkaline solution, and to show the invariable effect of the lactic acid, I give in Fig. 2, Pl. I., an example, taken, for the sake of comparison, from the same experiment as Fig. 1. After Fig. 1 had been obtained, the artificial blood solution was sent through, and after it had been flowing for seven minutes the lactic acid solution (1 lactic to 10,000 salt solution) was turned through the ventricle, and Fig. 2 obtained. From the figure it is seen how the lactic acid solution, which was sent in at the point marked by an arrow, quickly brings the ventricle to standstill in the position of complete relaxation; how, as the action continues, the height of each beat is lowered, and at the same time the beats assume a more pointed character than with the artificial blood solution. The effect, in fact, is exactly the reverse of what took place with the alkaline solution. Another point may also be noticed by a comparison of Figs. 1 and 2, and that is, that in each case the beats produced by the artificial blood solution are the same in strength and character; in

other words, the systolic standstill caused by the alkali solution is not due to any permanent injury to the muscular tissue; and in the same way, it is clear that the diastolic standstill produced by the lactic acid solution is also not a sign of any lasting paralysing injury; for, in either case, the blood solution is able to produce pulsations in no way differing from those that are normally produced before either the alkali or acid solutions are sent through. If, instead of a solution of the strength 1 in 10,000, one of the strength 1 lactic to 20,000 salt solution had been used, the resulting curve would have been of precisely the same description, except that the diastolic standstill would have taken rather a longer time to be developed. With the beating apex instead of the ventricle the curve obtained is of the same character.

IV. *The action of the acid and alkali solutions are antagonistic.*

When, by means of an acid solution, the beats of the ventricle have been very much lowered in force, then the alkaline solution brings back the force of the beat to its original height, and then produces its own characteristic effect, and upon again sending through the acid solution the action of the alkali is gradually overpowered and the ventricle slowly falls from a position of full contraction to one of extreme dilation. This is well shown in Fig. 3, Pl. II.

Again, if the acid solution has brought about a condition of nearly absolute diastolic standstill, then removal of the acid by normal salt solution does not improve the beats, and the position of the lever during the diastole remains the same, but immediately the alkaline solution is sent through the lever rises during the diastole, and at the same time the beats are strengthened until the ventricle passes into the condition of systolic standstill.

The reverse case is also true. Although salt solution alone after the alkali solution will very gradually bring the ventricle from the contracted to the dilated condition, yet the addition of lactic acid to the salt solution is able to produce the same effect with much greater rapidity.

V. *Certain poisons act upon the muscular tissue of the heart like alkalies, others like acids.*

At present I have not had time to investigate the whole series of so-called heart poisons, and cannot, therefore, say whether in all cases where a systolic or diastolic standstill is produced, the muscular tissue of the heart is affected in the same way as in the case of alkalies and acids respectively. I have, however, made a sufficient number of experiments with antiarin, digitalin, and muscarin to be able to assert that their action closely resembles that of the dilute alkaline and acid solutions respectively.

Thus, antiarin and digitalin solutions produce an alteration in the condition of the muscular tissue of the apex irrespective of its pulsations, of the same nature as already described in the case of the alkali solution, and at the same time cause a gradual lengthening of the time of full contraction in each beat when supplied to the beating apex or ventricle. On the other hand, a blood solution containing muscarin gradually lowers the height of each contraction in the case of the beating ventricle, and the tracing of each beat shows the pointed apex characteristic of the action of the lactic acid solution.

The following experiments will serve as examples of the action of these drugs:—

Oct. 27, 1879. Frog's apex tied on cannula, and 0·75 p. c. salt solution sent through at 22 c. m. pressure at 3.49 p.m. The apex did not beat spontaneously, and at 3.57 a solution of antiarin in salt solution (one part antiarin to 2,000 parts salt solution) was sent through at the same pressure. The lever rose steadily and slowly, reaching its highest point at 4.28, after the solution had been passing through for 31 minutes, during which time only a single spontaneous contraction had occurred. Judging from the height to which the lever was raised by this spontaneous contraction, the maximum "idio-muscular contraction" due to the antiarin was, in this case, much less than the full contraction of the apex, for at 4.28 the lever had risen only 9 mm., while the spontaneous beat caused it to rise 25 mm. above its original position. By a single sharp compression of the outflow tube between the finger and thumb a single artificial contraction could always be produced. Fig. 4, Pl. I., shows the effect of the antiarin salt solution upon these artificial beats. The smaller of the two contractions figured was obtained directly after the apex had been tied on, when the salt solution alone was passing through; the other one, when the antiarin solution had been flowing for 22 minutes.

Oct 21, 1879. Frog's apex on cannula. Solution of defibrinated rabbit's blood (one part blood to four parts salt solution) sent through at 20 c. m. pressure. The apex began to beat in 9 minutes, and continued beating with the blood solution, not regularly, but in small groups of beats. Thirty-six minutes after the apex was tied on the cannula an antiarin blood solution (one part antiarin to 1,000 parts of the rabbit's blood solution) was sent through at the same pressure. In the original curve the gradual change in the character of each beat, together with the gradual production of the systolic standstill, was well shown. In Fig. 5, Pl. I., I have reproduced pieces of the original curve.

At the arrow in the curve, *a*, the antiarin blood solution was turned through.

Between the end of *a* and beginning of *b* there were 80 sec. and 33 beats.

„ „ *b* „ *c* „ 51 „ 10 „

„ „ *c* „ *d* „ 72 „ 5 „

„ „ *d* „ *e* „ 58 „ No beats, [but a gradual rise of the lever.

Feb. 12, 1880. Apex on cannula. Bullock's blood solution (1 to 2 salt solution) sent through at 10 c. m. pressure, and after 28 minutes the apex began to beat. It beat, however, only for two minutes, and although the pressure was raised to 20 c. m., it would not beat again, but remained quiescent in the relaxed condition. A muscarin blood solution was then sent through (1 part musc. sulph. to 2,000 parts blood solution) at 20 c. m. pressure, and continued to flow through for 30 minutes. Throughout the whole time the apex remained completely relaxed without beating, the lever falling very slightly. A digitalin blood solution was then sent through (1 part digit. to 4,000 parts blood solution), and the capacity of the apex began slowly and steadily to diminish. After this solution had flowed through for 23 minutes, at which time the cavity of the apex had become nearly closed without a single beat having taken place, the muscarin solution was again sent through. The apex gradually relaxed, and in 17 minutes was again fully dilated. The digitalin solution was turned on, and again a gradual, steady rise of the lever was seen, followed by a steady fall to the position of relaxation upon again sending through the muscarin solution.

Feb. 12, 1880. Frog's ventricle on cannula. Three solutions prepared, blood solution (1 part bullock's blood to 2 parts salt solution), muscarin blood solution (1 part musc. sulph to 2,000 parts blood solution), digitalin blood solution (1 part digitalin to 4,000 parts blood solution). Height of fluids above ventricle, 10 c. m. Height of outflow, about 3 c. m. below level of fluids in funnels.

Blood solution through at 3.20 p.m. Ventricle beat strongly. The character of the beat is represented in the first beat of Fig. 6, Pl. III. The muscarin blood solution was sent through at 3.34, and, as is shown in curve *a*, Fig. 6, the character of the beat began immediately to alter. The gradual alteration in the force and nature of the contractions as the muscarin solution continued to flow through, is represented in the first line of Fig. 6. The

separate curves, *a, b, c, d, e, f,* are samples of the original curve taken at the following times : *a* at 3.34 (the arrow shows when the muscarin solution began to flow through), *b* at 3.37, *c* at 3.41, *d* at 3.46, *e* at 3.54, *f* at 3.57. The change in the original curve from *a* to *f* was perfectly gradual, as far as the character of each contraction is concerned.

Another point could be noticed in the action of the muscarin solution. The rate of rhythm during the time that the muscarin solution was passing through was quicker than with the blood solution alone, until the force of the contractions had diminished so much that the diastolic standstill was imminent. Also at first there was a strong tendency to grouping in the beats, as is shown at curve *b*. This gave way, however, to a perfectly regular rhythm between *c* and *d*, so that *c* represents a portion of one of the last of the groups, while *d, e,* and *f* show the regularity of the rhythm at the times when they were taken.

The blood solution was then sent through, and the strength of the contractions gradually recovered, until at 4.23 the ventricle was beating as represented in the curve *g*. As is seen, the force of the contraction is nearly as great as with the blood solution originally, while each beat possesses a somewhat more pointed character than the original beats with the blood solution. At the end of the curve *g* the digitalin blood solution was sent through, and the pieces of curve, *h, k, l, m, n,* are samples taken every minute to show the gradual action of the digitalin solution. Thus the curve *h* begins one minute after the end of the curve *g*, *k* two minutes after the end of *g*, &c. The third row of Fig. 6 is the direct continuation of the curve *n*, and is given in full in order to show the mode of formation of the digitalin standstill, and also the way the beats return upon sending through the artificial blood solution at the point marked by an arrow. Just as the muscarin leaves behind it a beat with a more or less permanently pointed character, so the digitalin leaves its impress upon the nature of the contraction. Thus, after the blood solution had been passing through for $5\frac{1}{2}$ minutes, the character of the beats was as represented in the curve *o*. The muscarin blood solution was then sent through, and the curves *p* and *q* show the nature of the beats 40 seconds and 7 minutes after the commencement of the flow of muscarin blood. The digitalin blood solution was then again turned through at the arrow in the curve *q*, and, as is seen, the digitalin quickly began to produce its characteristic effect. Again the muscarin blood solution was sent through, and the beats changed steadily from the flat-topped to the pointed character, as is seen in curve *r*, which represents the contractions after the muscarin solution had been passing through for $1\frac{1}{2}$ minute. At the arrow in the curve *r* the digitalin solution was again sent through, and in $1\frac{1}{2}$ minute the contractions were as represented in the curve *s*.

As far as can be judged from this experiment, the digitalin and muscarin blood solutions act in directions opposed to each other much in the same way as the sod. hydrate and lactic salt solutions.

From these experiments and from those of Bowditch[1] and Ringer and Morshead[2] it seems clear that muscarin produces its effect upon

[1] Ludwig's *Arbeiten*, 1871.
[2] *Journ. Physiol.*, Vol. II., p. 235.

the heart by its action upon the muscular tissue, rather than by the excitation of any inhibitory apparatus, and the last two experiments point to the conclusion that digitalin and muscarin are antagonistic in their action to the same extent as dilute alkaline and acid solutions. Further experiments must prove how far such an antagonism really exists, as at present my experiments are too few to justify me in expressing a decided opinion on this point. So, too, with respect to pilocarpin and atropin, I have as yet only made isolated observations upon their action on the muscular tissue of the apex, and, therefore, can only say that pilocarpin appears to resemble muscarin, while atropin acts in the same direction as an alkaline solution, but apparently much less powerfully. As instances of the nature of the atropin action upon the beating and non-beating apex when compared with salt solution alone, I give the two following examples:—

Nov. 4, 1879. Frog's apex on cannula; salt solution (0·75 p. c.) and atropin salt solution (1 part atrop. sulph. to 1,000 parts salt solution) placed in funnels, and level of fluid kept constant at 20 c. m. above heart.

Salt solution allowed to flow at 3.45 p.m. At 3.58 apex began to beat spontaneously with the salt solution alone; the spontaneous beats were few and far between; at 4.2 the atropin solution was sent through, the lever rose slightly and a series of spontaneous beats took place. At 4.17 the salt solution was turned through, the lever began immediately to fall and spontaneous beats of the type shown in the first part of Fig. 7, Pl. III., were obtained. At 4.20 the atropin solution was again sent through, the lever immediately rose and the nature of the beats, as well as the rise of the lever, is shown in the second part of Fig. 7, Pl. III. Again the salt solution flowed through, and immediately the lever fell and the beats became more pointed; and lastly the atropin was again sent in, and the lever rose as before and the separate contractions became more flat-topped.

Nov. 18, 1879. Apex of frog's heart on cannula; frog had been pithed some time, heart was large, distended with venous blood, scarcely beating. Salt solution (0·75 p. c.) and atropin salt solution (1 part atropin to 5,000 salt solution) in funnels, with level of fluid constant at 13 c. m. above heart. Salt solution sent through at 1.20 p.m., apex remained fully distended and motionless. At 1.42 the atropin salt solution was allowed to flow through, and the lever rose very slowly and steadily, so that at 2.6, *i.e.*, in 24 minutes, it had risen 8·5 mm. without the occurrence of a single beat. Upon then turning the salt solution through the lever slowly fell, and at 2.16 had reached its original level. Again the same atropin solution was allowed to flow through, the lever again slowly rose, and at 2.34 had risen very nearly the same amount as before, *i.e.*, 8 mm. During this 18 minutes 3 spontaneous beats took place. If one can at all judge from the height the lever was raised by these contractions the diminution in size of the apex cavity due to the atropin was less than half the complete closure of the cavity.

VI. *Alkaline and acid solutions act upon the muscles of the smaller arteries in the same way as upon the cardiac muscle.*

Again, I have made use of the same two fluids, viz., one part sod. hydrate to 10,000 or 20,000 parts salt solution, and one part lactic acid to 10,000 or 13,000 parts salt solution, to prove the above proposition. The experiments were mainly conducted on the arteries of the mylohyoid muscle, but were confirmed by the action of the fluids on the mesenteric arteries and the vessels of the whole leg of the frog.

In the case of the mylohyoid, the method of investigation was as follows:—The frog was pithed, the heart exposed, and the right mylohyoid muscle placed under the microscope in the way described in my former paper[1]; a cannula in connection with the same arrangement of funnels as described above was then tied in the right systemic aorta, the left aortic arch ligatured, and the abdominal vein cut, or an incision made in the sinus venosus to allow the escape of the fluids sent through. In this way the different solutions were sent through the muscle at a constant pressure, while at the same time the modification of the heart's action caused by any particular solution was prevented from having any effect upon the calibre of the blood vessels. The level of the fluid in the funnels was, in the majority of the experiments, 25 c. m. above the cannula in the aorta; normal saline solution (0·75 p. c.) was always first sent through in order to remove the frog's own blood, and to make sure that the fluid flowed freely through the muscle. The mylohyoid nerve was usually cut, in addition to the operation of pithing, in order to be certain of the removal of all central nervous influence. Besides the measurement of the size of the arteries in the muscle, a rough estimate of the comparative dilation or constriction of the vessels throughout the body could be obtained by observing whether the drops that fell from the stand on which the body of the frog was laid followed one another more quickly at one time than another. From a large number of experiments that I have made in this way I find that

1. The salt solution alone produces no absolutely definite effect. In the majority of cases the calibre of the artery observed diminished as the solution removed the blood in the vessels (owing to the previous

[1] *Journ. Anat. & Physiol.*, XI., p. 720.

operations, the vessels are usually somewhat, in many cases considerably, dilated at the beginning of the experiment). In other cases the calibre remained unaltered, or might even enlarge slightly as the solution passed through.

2. With the lactic acid solution the calibre was always enlarged, and the fluid dropped more freely from the body of the animal.

3. With the alkaline solution the artery always diminished in size, usually to absolute closure, and at the same time the fluid dropped very much more slowly; sometimes, indeed, the arterial constriction throughout the body was so great that the fluid entirely ceased to flow. This universal constriction was, I think, often, if not always, due to a complete closure of the larger arterial trunks, for I have occasionally noticed that, when the alkaline solution is sent through after the salt solution alone the circulation in the muscle suddenly ceases while the smaller arteries are still open, and stray corpuscles are seen moving from the veins to the arteries, as though some obstacle to the circulation existed between the cannula and the muscle.

The following is a typical example of the behaviour of the muscle arteries with the acid and alkali solutions. The figures denote the divisions of the scale of the micrometer eye-piece, and with the power used each unit corresponds to an actual size of $\frac{1}{120}$ mm.

Dec. 9, 1878. Frog pithed, heart exposed, right mylohyoid muscle under the microscope. Circulation in muscle very good, vessels clear, somewhat dilated. A place was chosen where an artery divided into a small and large branch, both branches were observed, the small one only measured. It measured 5, with a vigorous circulation in it.

The cannula, in connection with three funnels containing 0·75 p. c. salt solution, 1 sod. hydrate to 10,000 salt solution, and 1 lactic acid to 13,000 salt solution, was then tied into the right systemic aorta; the left aortic arch was tied, and an incision made in the sinus venosus. The height of the fluids in the funnels above the cannula was 25 c. m.

The salt solution was sent through at 3.8 and the blood in the muscle was seen to be washing out well.

Fluid.	*Time.*	*Size of Artery.*
Salt solution.		
	3.11	5
	13	4 All corpuscles gone.
	14	3 Edges uneven.

Fluid.	*Time.*	*Size of Artery.*
Lactic solution was now sent through.		
	3.15	Opening.
	15.5	5
	16	5·5
	17	6
	18	6
	19	6
	20	6
Salt solution was turned through.		
	20.5	6
	21	6
	22	6
	24	5·5
	27	5
Alkaline solution was sent through.		
	28	4
	29	4·5 Uneven edges.
	32	Closed.
Salt solution through.		
	34	Closed.
	35	Nearly closed.
	36	Under 3 nearly closed.
	37	do.
	38	do.
	39	do.
	40	do.
Lactic through.		
	41	4
	42	5
	43	5·5
	44	5·75
	45	5·75
Salt solution through.		
	46	5·5
	49	5·75
	50	5·5
	52	5·5

Fluid.	*Time.*	*Size of Artery.*
Alkaline solution through.		
	3.53	4
	54	Barely 3.
	55	Closed.
	56	Closed.
	57	Closed.
Salt solution through.		
	58	Closed.
	59	Closed.
	4.1	3·5
	2	4 nearly.
	3	
	4	4
Lactic through.		
	5	4·5
	5.5	5·5
	6	
	8	6
	9	6
	10	6
	11	Nearly 7.
	12	Over 6.
Salt solution through.		
	13	6
	14	6
	18	6
	20	6
	21	6

The larger branch behaved in exactly the same way as the one measured, being absolutely closed with the alkaline and fully dilated with the acid solution. At the same time the fluid dropped freely from the frog when the acid solution or salt solution after the acid was passing through, and very slowly with the alkaline solution or salt solution after the alkali.

This experiment shows clearly that the muscles of the smaller arteries react to these very dilute acid or alkali solutions in precisely the same way as the cardiac muscle. In each case the acid solution produces a condition of relaxation which is not recoverable by the action of salt

solution alone, and a condition of constriction with the alkali solution which is only slowly removed by the salt solution, but much more rapidly and completely by the acid.

As might have been concluded from the different rates of flow from the body of the frog when the different solutions were sent through, other methods of experimentation give precisely similar results: thus, if the fluids be sent through the legs of the frog by means of a cannula in the abdominal aorta just above its bifurcation, and, the rest of the body being cut away, the rate of flow be measured by counting the number of drops per minute that fall from the open abdominal and pelvic veins, it is always found that the rate is much diminished by the alkaline and increased by the acid solution; so, too, if the mesentery be spread under the microscope, and the fluids be dropped on to it, the arteries are seen to constrict with an alkaline fluid, and to dilate again with an acid solution.

With respect to the action of other acids, I have as yet made only a single experiment with acetic acid (1 acetic acid to 10,000 salt solution), and in this experiment the arteries of the mylohyoid muscle dilated fully as the acid passed through, in the same way as with the lactic acid solutions.

Conclusions from the foregoing experiments.

From what I have already proved, certain conclusions of great importance for the explanation of various problems connected with the vascular system seem to me to be deducible. Hitherto one has always looked upon the condition of the heart and the tonicity of the smaller arteries as chiefly regulated by the action of various nervous mechanisms, without paying much attention to the nature of the fluid surrounding their muscular fibres. The results recorded above would seem to show that this latter cannot be neglected, and that one factor upon which the state of constriction of the muscles both of the heart and arteries depends is the extent of the alkalinity of the fluid surrounding them. Now since a very dilute alkaline solution produces a constrictive effect upon the muscular tissue of the heart and arteries, which lasts as long as the solution is in contact with those tissues, one may advantageously speak of the action of the alkali as the production of a "tonic" condition of the contractile tissue; while, on the other hand, the dilute

lactic acid solution causes an "atonic" condition of that tissue. The expression "tonic condition" seems to me preferable to the term "idio-muscular contraction," because it does not prejudge the question of the nature of the phenomenon expressed by it to the same extent as the latter. In the case of ordinary striated muscle, as well as of the muscles of the smaller arteries, the word "tone" is used to express something which in many respects is different to what is meant by the term "contraction." One can then say that the presence of an alkaline fluid must tend to keep the cardiac and arterial muscles in a state of tonicity, and that upon the extent of the alkalinity the amount of tonicity will, in part, at all events, depend.

Now in all the organs of the body we are confronted with two invariable facts—the one, that the lymph fluid of all tissues in the condition of inactivity is alkaline, and the other, that the natural activity of an organ is invariably accompanied by a dilation of its blood vessels. This latter fact has always been explained as due to a reflex action of the nerves governing the blood vessels, although, as pointed out by Huizinga[1], this view leads directly to the assumption that the hypothetical peripheral ganglia supposed to be situated in the blood vessels can themselves be the seat of the reflex action.

Before ascribing to these possibly non-existent ganglion cells functions which can hardly yet be considered as satisfactorily proved to be the property of any sporadic ganglion cells (for the reflex function both of the heart ganglia and of the submaxillary ganglion is, to say the least of it, decidedly doubtful), it is surely worth while to see whether it is not possible that the chemical changes going on in the organ itself may not directly bring about a dilation of the blood vessels of that organ, and so, without the intervention of the nervous system, regulate its own blood supply according to its own needs. In other words, is it possible that the chemical changes occurring in the organ itself during its activity may affect the state of its blood vessels; and if so, how can we conceive such action to take place?

We know that the interchange of material between the blood and the tissue cell is continually going on, not only during the activity of the tissue but also during the state of rest; new material is being formed, old material broken up, and, in the shape of what are called the waste products of the tissue, discharged from it. There must, then, be in continual operation throughout the body, not only a process of

[1] Pflüger's *Arch.*, XI., p. 207.

reparation, but also a process of excretion; and the activity of the tissue which denotes an increased metabolism in that tissue must therefore be characterized by a greater formation of these waste products, and consequently the amount of them discharged during a state of activity must be greater than during the state of rest. If these products are to be removed, they must necessarily pass into the fluid which bathes all the tissue elements of the body, into, that is to say, the commencement of the lymph system of the particular organ in question; from this fluid they may pass away in two directions, either through the capillaries into the blood system direct, or else with the lymph fluid into the larger lymphatics, and so ultimately into the blood. It is then, it seems to me, not unreasonable to assert that, in every case of activity of an organ, the lymph fluid of that organ must be modified in composition by the access of these decomposition products. The question, therefore, arises, Is this modification of the tissue fluid likely or able to influence the calibre of the blood vessels of the tissue in question?

With respect to the capillaries Severini[1] answers in the affirmative, and argues that the CO_2 formed by the activity of the tissue brings about such an alteration of shape in the nuclei of Golubew as to cause an enlargement of the calibre of the capillaries, while, on the other hand, the action of O is just the reverse, the nuclei become more spherical, project to a greater distance into the lumen of the capillary, and so the calibre is lessened. According to him the amount of dilation depends upon the relative proportions of O and CO_2 in the blood at the time. However this may be, it alone is clearly insufficient to account for the dilation of the vessels of any organ during its activity, and its insufficiency is plainly shown by my observation that the smaller arteries of the mylohyoid muscle dilate when the muscle contracts. Any satisfactory explanation of the vascular dilation accompanying the activity of an organ that is based upon the action of the excretory products of the tissue itself, must deal with the enlargement of the smaller arteries and not only with the calibre of the capillaries. Is there then any likelihood that the muscles of the smaller arteries should be affected by the nature of the lymph fluid of the tissue they supply? From what is known of the structure of the arterioles it seems highly probable that such must be the case. We find in them an inner elastic membrane intervening between the blood stream and the well developed muscular layer, while the outer elastic layer is absent, the adventitia lying immediately against

[1] *Innerv. d. Vas. Sang.* Perugia, 1878.

the muscular coat. This adventitia is composed of loosely compacted fibres containing spaces within their meshes which are in all probability continuous with the lymph spaces of the tissue itself. With such an arrangement as this it seems highly probable that the naked muscular fibres of the smaller arteries must be continually bathed by the lymph fluid of the tissue they supply, and that it is the constitution of this fluid which must influence them rather than that of the blood circulating in their interior.

Now, in all organs during the state of rest the muscle fibres of these smaller arteries are in a state of tonicity due to the influence of the vasomotor centre, and also from what I have already proved to the alkalinity of the lymph fluid. One cause then which would necessarily bring about a diminution of this tonicity, *i.e.*, a dilation of the artery, must be any diminution in the alkalinity of the lymph fluid, and the dilation from this cause would be the greatest possible if the fluid were to become acid instead of alkaline.

That such a diminution of alkalinity must occur in the case of ordinary muscular contraction seems in the highest degree probable. With respect to other organs the production of an acid during the activity of the organ is not so definitely proved as in the case of muscle, although from the similarity between the essential phenomena manifested by the protoplasmic substances of the body, it would be more reasonable to expect that such a production did take place than not. In the case of the grey matter of the central nervous system an acid—apparently lactic acid—is set free very readily, and in the case of the pancreas an observation of Heidenhain points strongly to the production of some acid during the activity of the gland, for he shows that the presence of an acid is favourable to the conversion of zymogen into ferment, which naturally leads to the suggestion that the activity of the gland cell, like that of the muscle cell, is characterized by the formation of an acid, and that the presence of this acid assists in the production of the ferment. If this is true in the case of the pancreas it is probably true of other glandular organs, so that this observation lends great weight to my supposition that a diminution of alkalinity takes place in the lymph fluid of all tissues when the tissue is in a state of activity.

Again, according to recent experiments by Klug[1], the presence of oxygen is favourable to the normal vigorous pulsations of the ventricle, while a superabundance of carbonic acid in the blood used quickly

[1] *Arch. Anat. u. Phys. (Phys. Abth.)*, 1879, p. 435.

reduces the height of the pulsations and brings about a diastolic standstill; and, further, according to Adamkiewicz[1], the oxydation processes throughout the body are greatly assisted by the alkalinity of the tissue fluids. Throughout the whole vascular system, then, there is evidence to show that its normal tonicity and rhythmical action are dependent in part upon the due oxygenation and alkalinity of the fluid supplied to its muscular tissues, while, on the other hand, the tonicity cannot be maintained or the rhythmical action continued when that fluid is overcharged with such products of tissue metamorphosis as lactic and carbonic acids.

Further, in the case of the heart one would suggest that the normal beat depends partly upon the maintenance of a due tonic condition of the muscular tissue. That tissue is capable of variation between two extreme conditions, that of extreme "atonicity," which gives rise to the phenomenon known as "diastolic," or I should prefer to call it "atonic," standstill, and that of extreme "tonicity," characterized by the "systolic" or "tonic" standstill. Between these two extremes the muscular tissue is capable of spontaneous visible pulsations, which vary in character, according as the condition of the muscle approaches the one or the other extreme. Thus, if one considers that the normal condition of the ventricular muscle is such that the relaxation between the separate contractions is nearly complete, and the cavity of the ventricle is absolutely closed for a definite time during each contraction, then, with a greater tonicity of the muscle, the cavity of the ventricle would be closed for a longer time during each systole, and the relaxation would be less complete during each diastole. On the other hand, with a more atonic condition, the force of each contraction would be diminished, the cavity of the ventricle no longer closed, while the relaxation during the diastole would be as great or even greater than in the normal condition. Conversely, one might argue that an "atonic" condition of the cardiac muscle has been produced, when, in consequence of some operation, the tissue remains completely relaxed and incapable of spontaneous pulsations, although still able to contract upon artificial stimulation. According, then, to this view, it would be possible to say that the effect of the ligature round the ventricle when the apex is tied on the cannula is to inhibit the natural spontaneous apex beats by the production of such a complete atonic condition of the muscular tissue of the apex, and the effect of the alkaline blood solution is to gradually

[1] *Arch. f Anat. u. Phys. (Phys. Abth.)*, 1879, p. 370.

improve the tonicity, until at last the muscle is able to respond to the combined action of the blood solution and the pressure within the cavity, and spontaneous pulsations result.

If this hypothesis is true, experiment ought to confirm it in two ways. Firstly, from the time of tying on the apex until some time after pulsations have commenced the lever ought steadily to rise, owing to the improvement in the condition of the tissue by the blood solution; and secondly, the first pulsations should be feebler, and present a more pointed appearance, than those that occur later.

Now both these phenomena do occur: in the majority of cases the lever does rise slightly as the blood flows through, and the first beats that occur, whether spontaneous or artificially produced (by a single sharp compression of the outflow tube), are less forcible and more pointed in character than subsequent beats. At first sight, then, it would appear that experiment fully bears out the hypothesis suggested; another possible explanation of the slight rise of the lever observed has, however, quite recently occurred to me, viz., that it might be due to a very slight cooling down of the oil in the apparatus, and not to any variation in the capacity of the apex cavity, and upon investigation I find that the whole apparatus is extremely sensitive to changes of temperature: a slight variation in the temperature of the room, the heat of the hand placed for a very short time on the outside of the bottle in which the heart is suspended, &c., all cause a distinct slight movement of the lever in the upwards or downwards direction, according as the oil contracts or expands. At present, therefore, I prefer to leave it doubtful whether any such rise of the lever is in reality due to the tonic action of the blood solution; at the same time, that such an action does truly exist seems highly probable from the circumstance that the beats do alter in character under the influence of the blood solution in the same direction as during the tonic action of the alkali solution. This alteration in the character of the beat is seen in Fig. 8, Pl. I., where the lower of the two beats was artificially produced by compression of the outflow tube at 1.43 p.m., *i.e.*, eighteen minutes after the apex had been tied on; and the upper one was caused in the same way at 2.20 p.m., after the blood solution had passed through for fifty-five minutes. As the curves are drawn to the same abscissa line, they show not only the greater height and longer systole of the second contraction, but also the rise of the lever as the blood passed through. The change in the character of the natural pulsations is most evident in those cases where the whole ventricle has been tied on the cannula, and, in consequence

of the operation, has remained for a time quiescent in the relaxed condition similar to what always occurs when the apex alone is tied on. The following is the most marked instance that I have seen :—

21st Nov., 1879. Ventricle on cannula. Sheep's blood solution (1 part to 2 parts salt solution) in funnel; the level of the fluid kept constant at 8 c. m. above ventricle. Ventricle not beating when placed in the oil at 2.35 p.m. Tracing began immediately, and at 2.37 the first contraction occurred; the first tracing in Fig. 9, Pl. III., represents this beat. As the blood solution continued to flow through, the lever rose steadily, and the beats improved in force. The second tracing represents the amount of the rise of the lever and the nature of the contraction at 2·40. Between the first and second tracing six beats had occurred. The last tracing in Fig. 9, Pl. III., shows the ultimate rise of the lever and the ultimate force and character of the beat attained.

As I have already said, I have used the term "tonic condition" to express the action of alkalies, digitalin, antiarin, &c., upon the muscular tissue of the heart and arteries, simply for want of a better.

What the exact nature of this action is, it is impossible to say. There are, as far as I can find, at present three separate views of the production of a systolic standstill. Thus, to take the case of digitalin :—

1. The digitalin may act as a stimulus to the contractile tissue, and so cause an idio-muscular contraction. According to this view, the "tonic condition" would be strictly a condition of greater or less contraction.

2. It may act by its mere presence in such a way as to alter the elasticity of the contractile material, although at the same time it does not enter into combination with that tissue (Schmiedeberg).

3. It may alter the contractile material by entering into combination with it, and so forming a new substance of different molecular constitution, which yet possesses the power of contraction. It is impossible definitely to decide between the first two theories, because there is no satisfactory test capable of deciding between an increased elasticity and a contracted condition of the cardiac muscle. Roy[1] has already discussed the question, and concludes that for digitalin the evidence is in favour of an "idio-muscular contraction," rather than an increase of elasticity. I have attempted by the same method to decide the question for the

[1] *Loc. cit.*

"tonic condition" caused by sodium hydrate, antiarin, and digitalin, but hitherto without success. The results were too variable to draw any definite conclusions from them, and all one can say is, that there is this amount of resemblance between the contracted and "tonic" conditions of the ventricular muscle, viz., in each case the maximum increase of distension caused by equal increments of pressure occurs between two pressures decidedly higher than the two which give the maximum increase of distension in the relaxed condition of the ventricle.

The third theory is a very attractive one, although at present it can only be looked upon as the merest hypothesis; the argument would be of the following description :—

The contractile tissue of the whole vascular system possesses a constituent which is capable of entering into a more or less stable combination with two groups of substances, of which alkalies and acids are the respective types. Further, the physical peculiarities of the contractile tissue vary according to the nature and extent of such combination, while the power of contraction is not lost until certain limits in either direction are overpassed.

Schmiedeberg[1] argues, in the case of digitoxin, against the hypothesis of a direct combination of the alkaloid with the muscular tissue of the heart, that the amount of digitoxin which is capable of producing a tonic standstill is so exceedingly small that one cannot imagine it sufficient to combine with the whole muscular tissue of the heart. His experiment is that if 0·1 mgrms. of digitoxin be injected under the skin of the frog, that amount is sufficient to produce systolic standstill. Therefore, dividing this equally over the body, we have only 0·0005 mgrms. for the heart, an amount so small in comparison to the muscular tissue of the heart that one cannot imagine its effect is produced by combination with that tissue. Clearly, however, the argument is erroneous, for the whole of that amount injected which passes through the tissues at all must first pass through the heart, and, therefore, the heart must be affected by the poison to a much greater extent than the other tissues.

A more important objection can be urged from the recent experiments of Rossbach and v. Anrep[2]. According to them, sodium compounds produce no "tonic condition" of the ordinary striated muscle, while digitalin produces a lengthening rather than a shortening of the muscular fibre. If these experiments are confirmed, the arguments in favour of a

[1] Ludwig's *Festgabe.*

[2] Pflüger's *Archiv*, Vol. XXI., p. 240.

direct combination of digitalin with the contractile material would lose a good deal of weight, for one cannot conceive that the cardiac or vascular muscle should be able to form a compound possessing physical peculiarities diametrically opposed to the compound formed in ordinary muscle under similar circumstances.

My chief object in writing this paper has been, however, not so much to discuss the meaning of the systolic standstill as to draw attention as strongly as possible to the "tonic" and "atonic" condition of the whole vascular system produced by very dilute solutions of alkalies and acids respectively. How far the facts and suggestions of this paper may modify the present views of the action of the inhibitory nerves of the vascular system, of the nature of the recovery of tonicity after removal from the central nervous system, and of the action of alkaline medicines and digitalis in the febrile state, I must leave to another paper which I hope before long to be able to publish.

DESCRIPTION OF FIGURES. PLATES I., II., III.

All the parts of all the figures are drawn to the same abscissa line with the exception of Fig. 4. The divisions on each abscissa line correspond to intervals of 5 seconds.

Fig. 1. March 1, 1879. The formation of the alkaline standstill. The sodium hydrate solution was sent through the beating ventricle at the place marked by an arrow.

Fig. 2. March 1, 1879. The formation of the lactic acid standstill. The acid solution was sent through at the point marked by an arrow.

Fig. 3. March 15, 1879. The antagonism between the alkaline and acid solutions upon the beating ventricle. The conditions of the experiment were the same as in Figs. 1 and 2, except that the strength of the lactic acid solution was 1 part lactic acid to 20,000 parts salt solution.

Fig. 4. Oct. 27, 1879. The action of antiarin upon the artificially produced apex contraction.

Fig. 5. Oct. 21, 1879. The formation of the antiarin standstill in the case of the beating apex.

Fig. 6. Feb. 12, 1880. The formation of the muscarin and digitalin standstills in the case of the beating ventricle.

Fig. 7. Nov. 4, 1879. The action of atropin upon the apex when beating under the influence of salt solution alone.

Fig. 8. Nov. 5, 1879. The alteration in the capacity of the apex cavity and in the character of the artificially produced apex contraction under the influence of the artificial blood solution.

Fig. 9. Nov. 21, 1879. Shows the alteration in the spontaneous ventricular contractions, caused by the artificial blood solution.

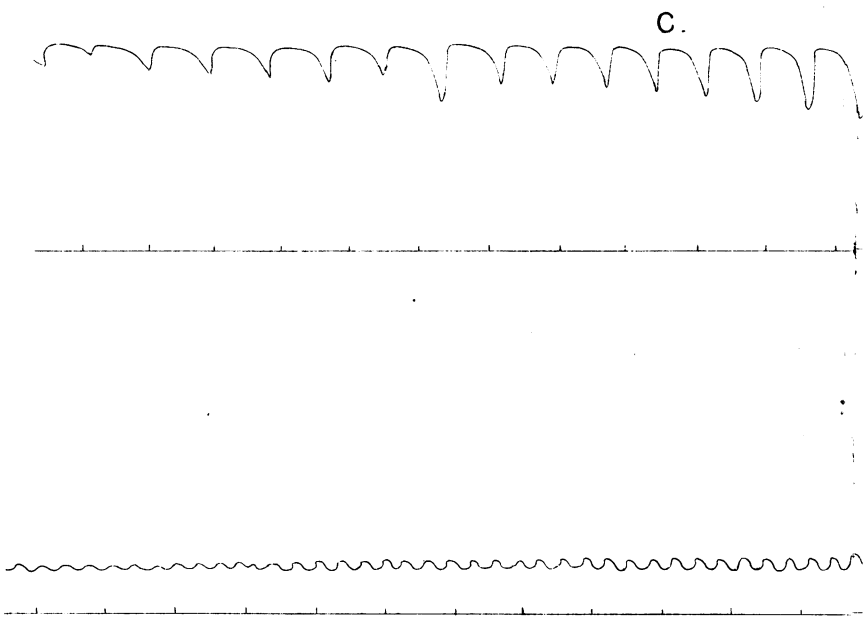
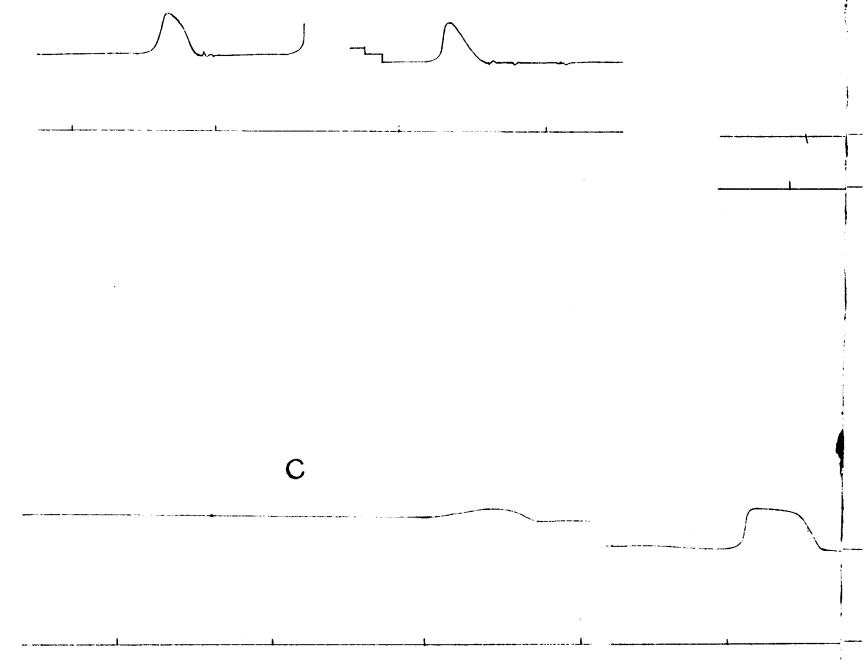
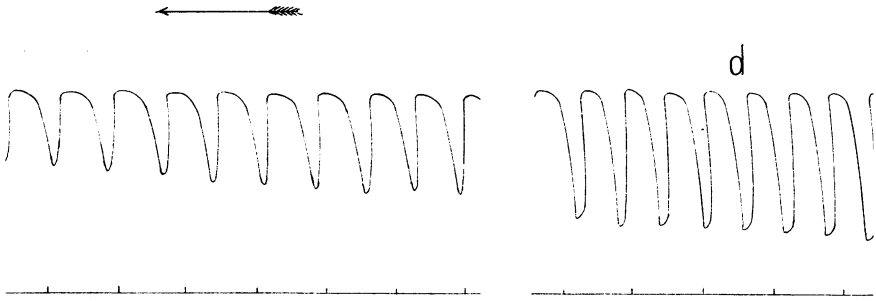
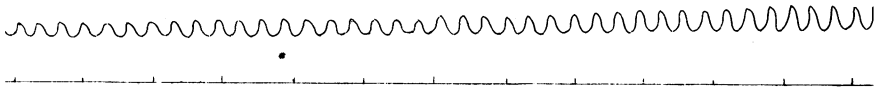
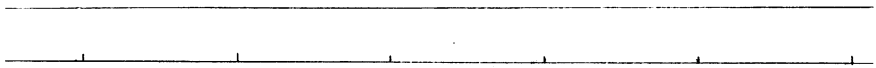


FIG 8.









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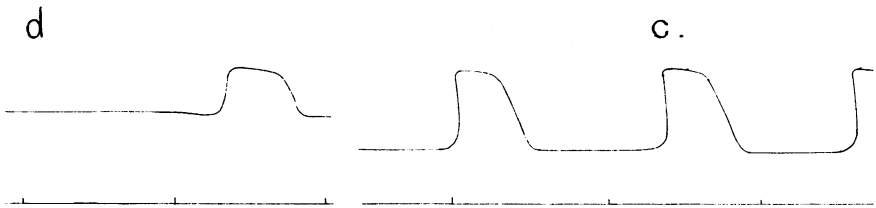


c.

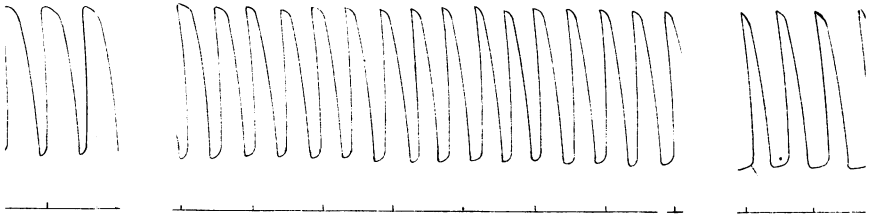
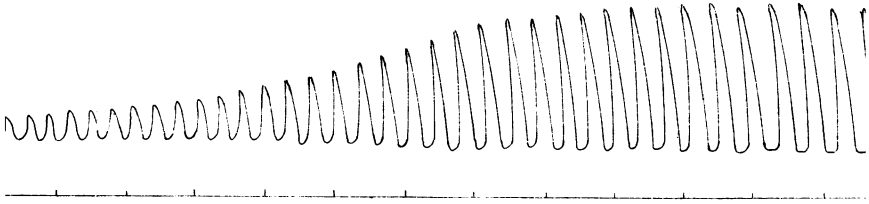


FIG 2.



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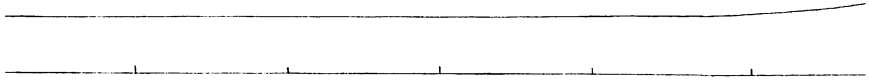
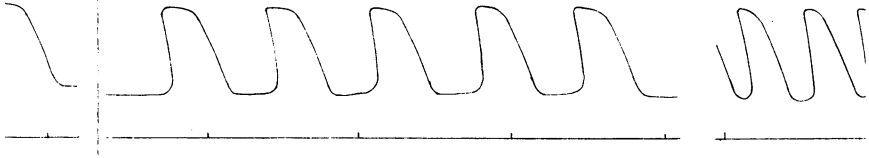
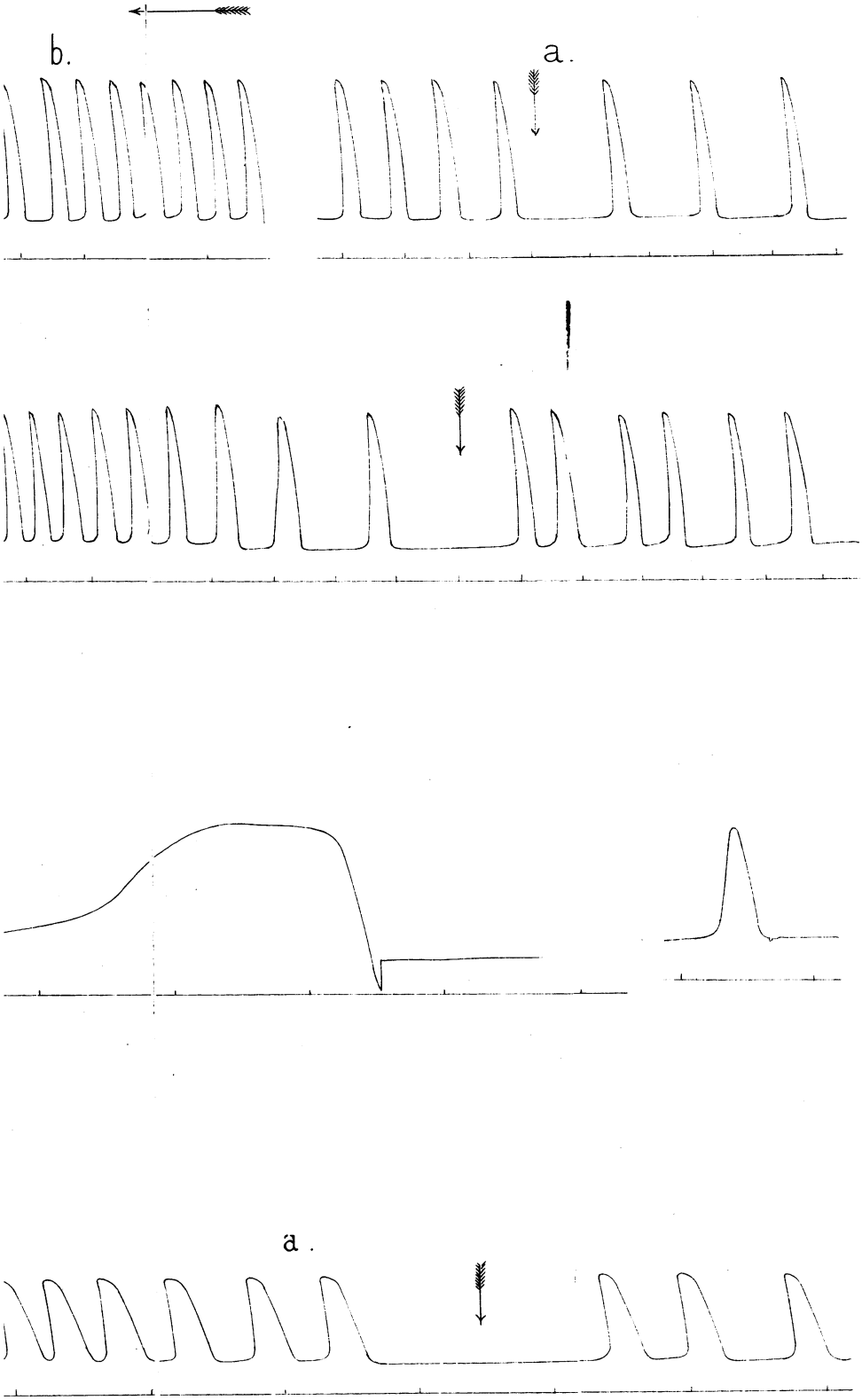


IG 5.

b.

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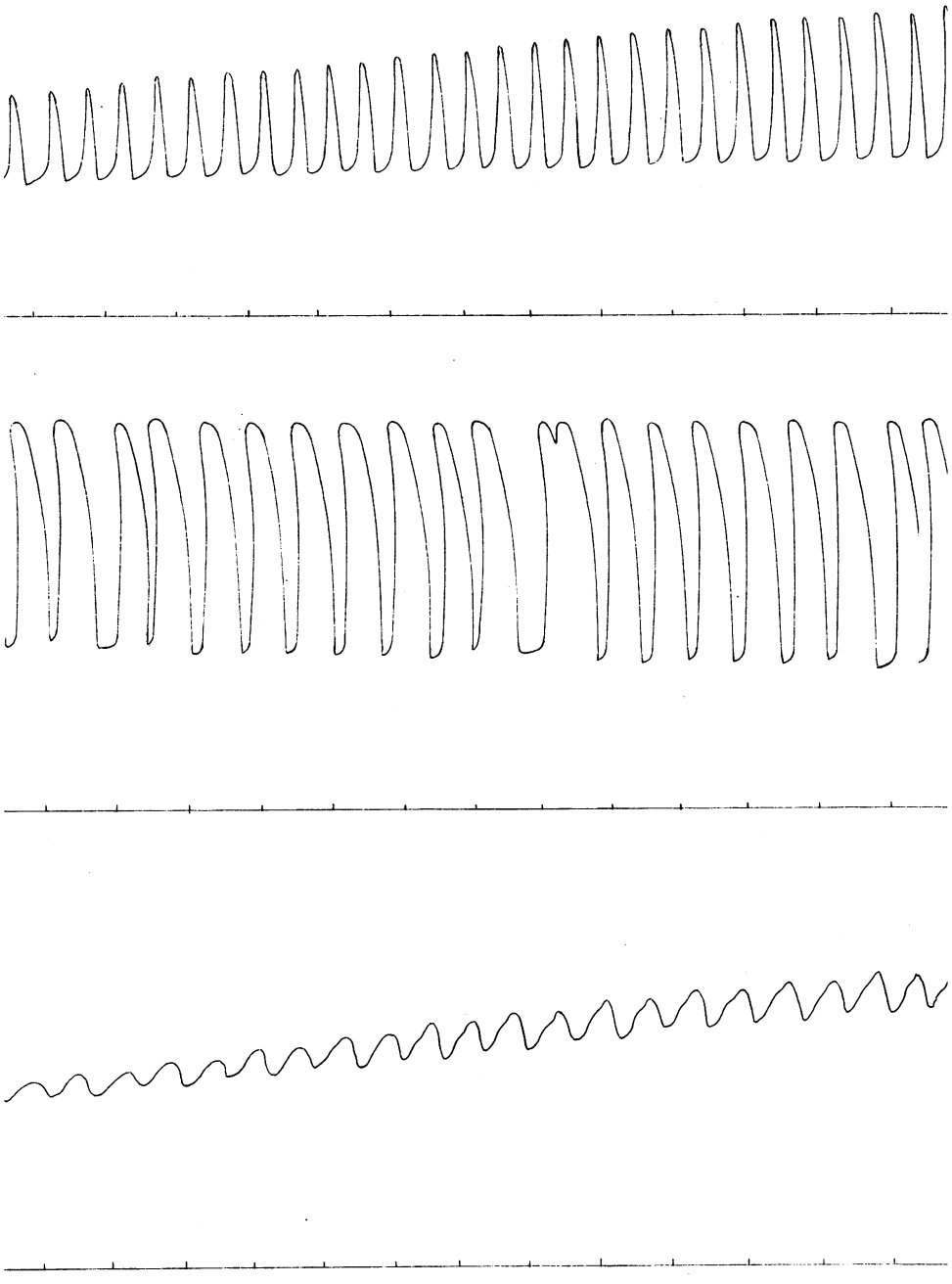


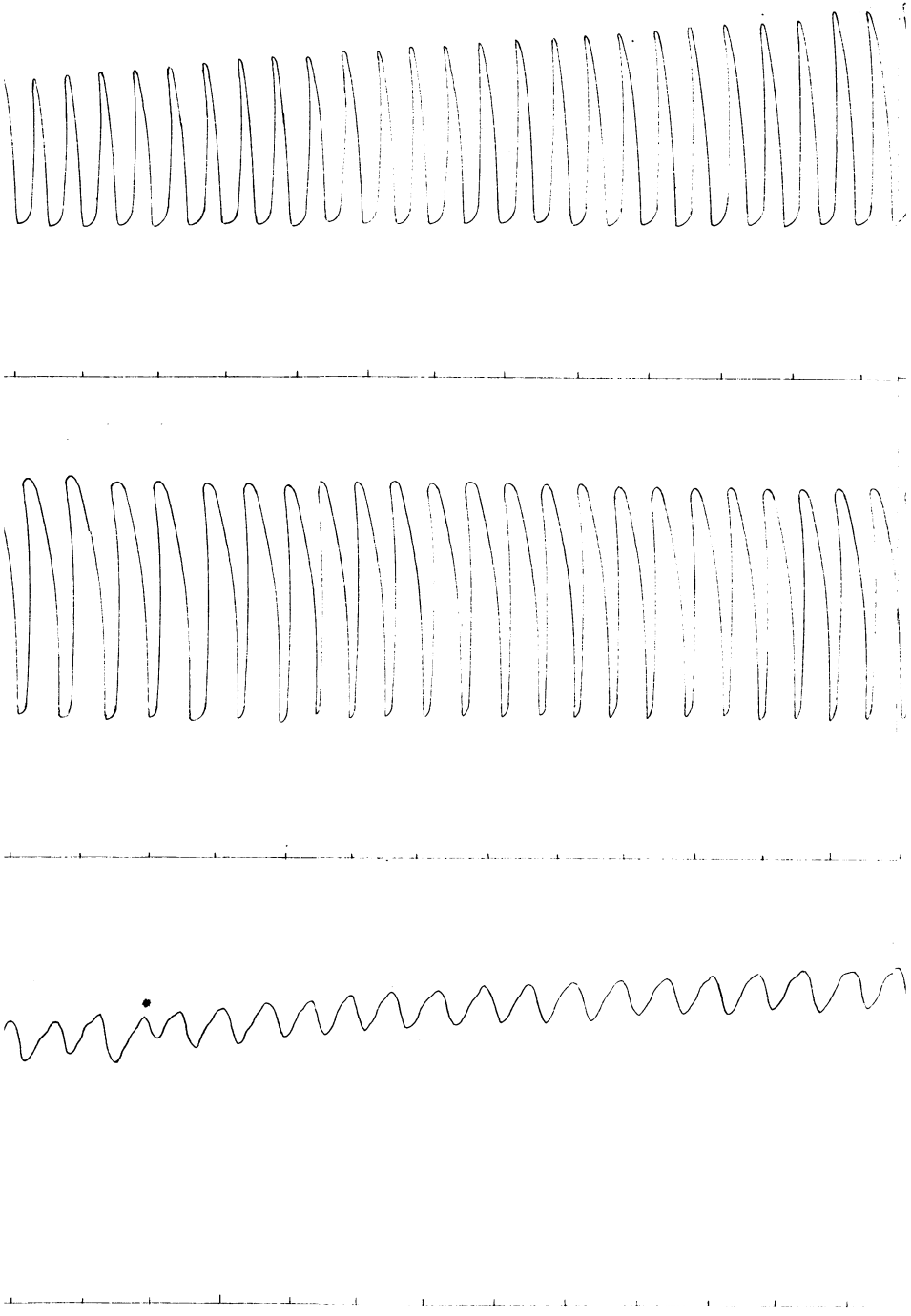
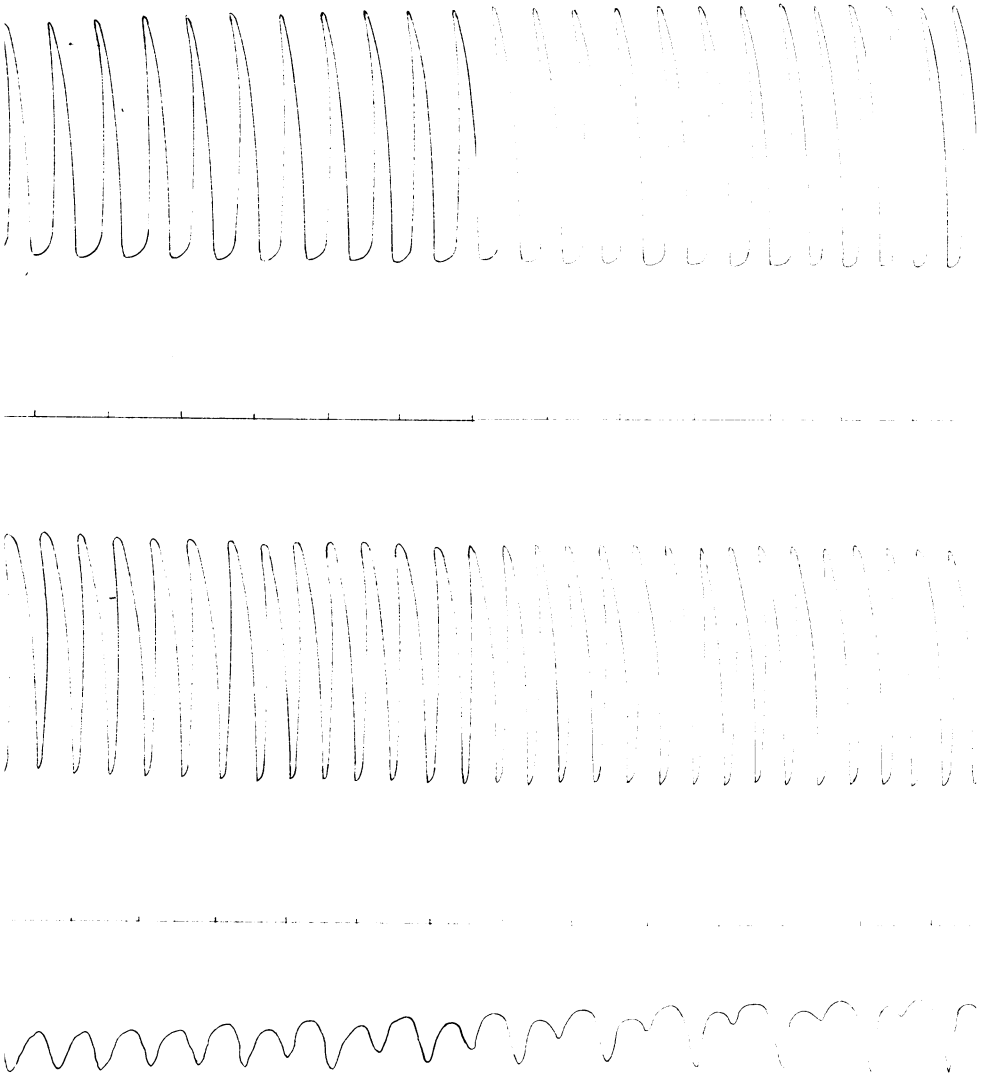
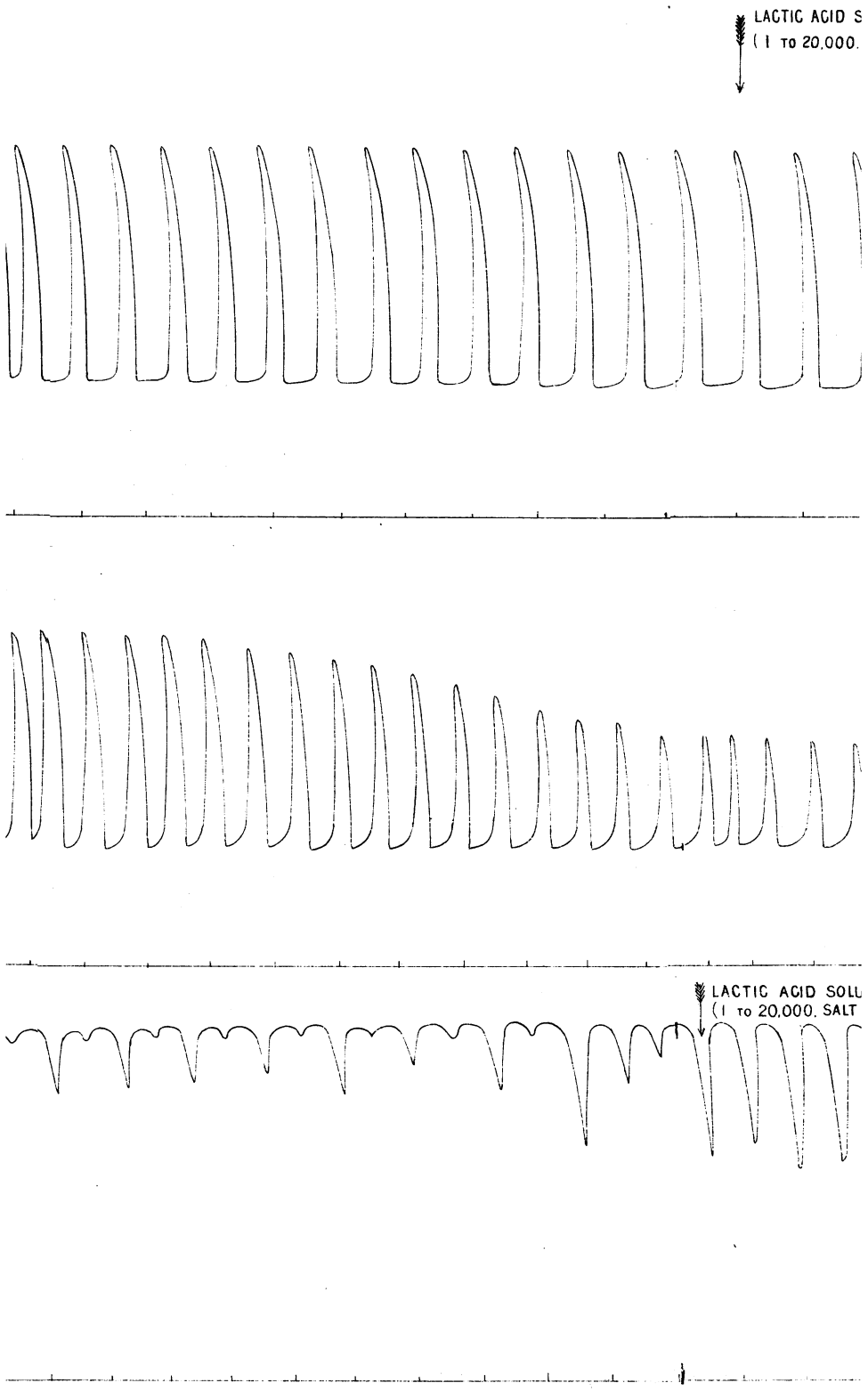


FIG 3.

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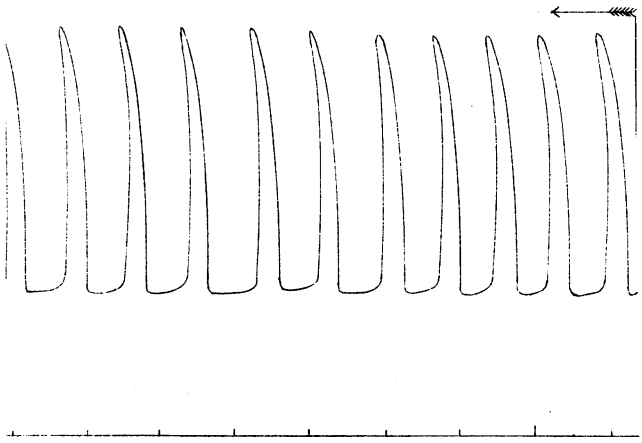
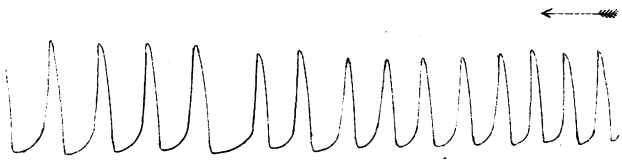
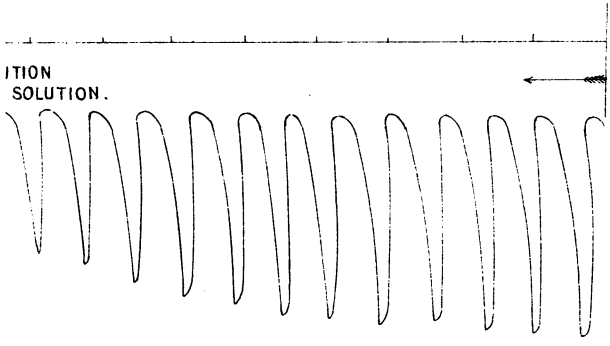
BLOOD SOLUTION.

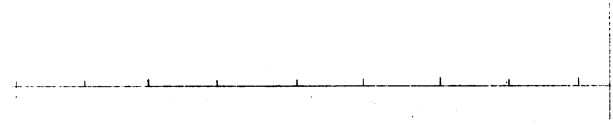


SODIUM HYDRATE SOLUTION.
(1 TO 20.000, SALT SOLUTION)



ITION
SOLUTION.





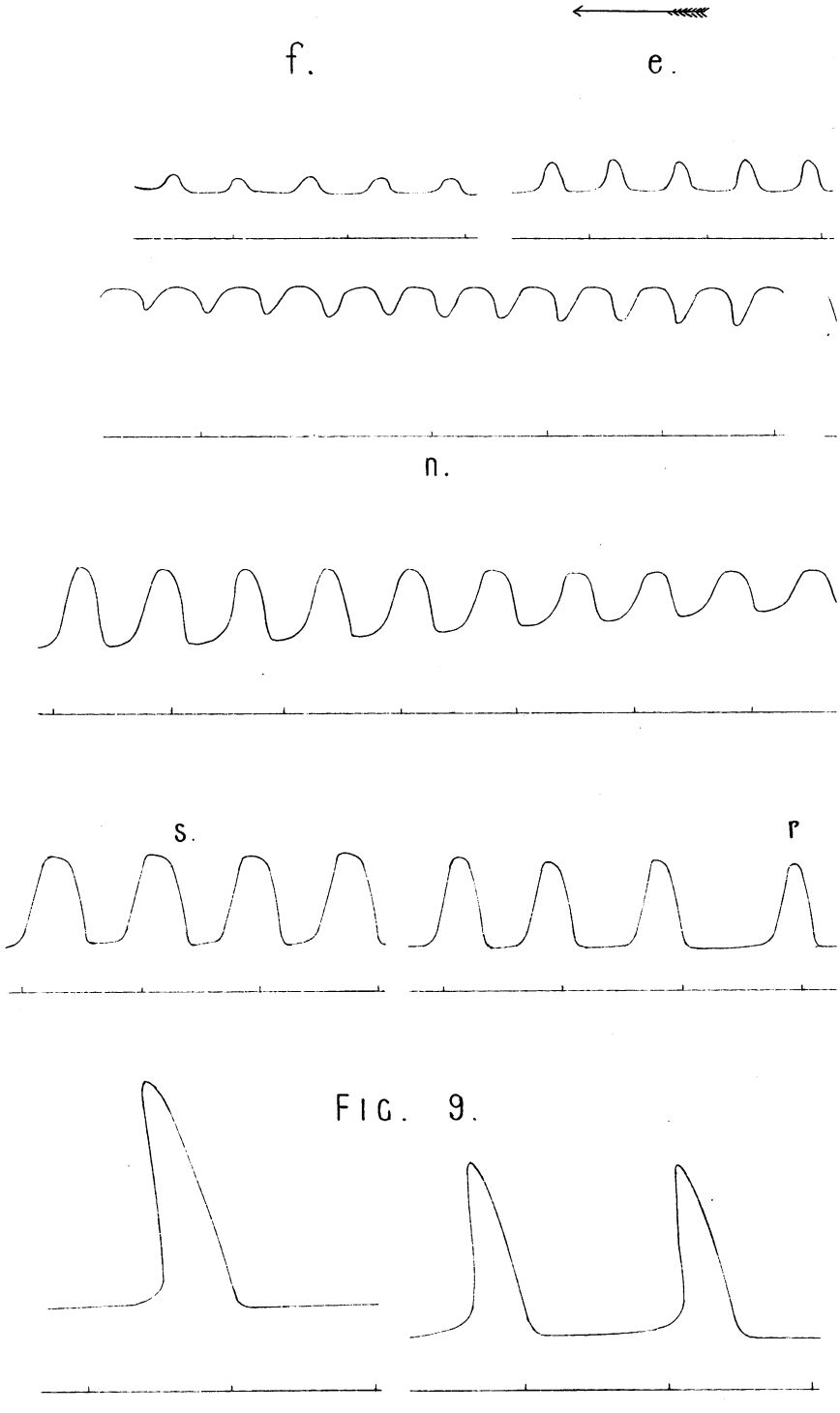
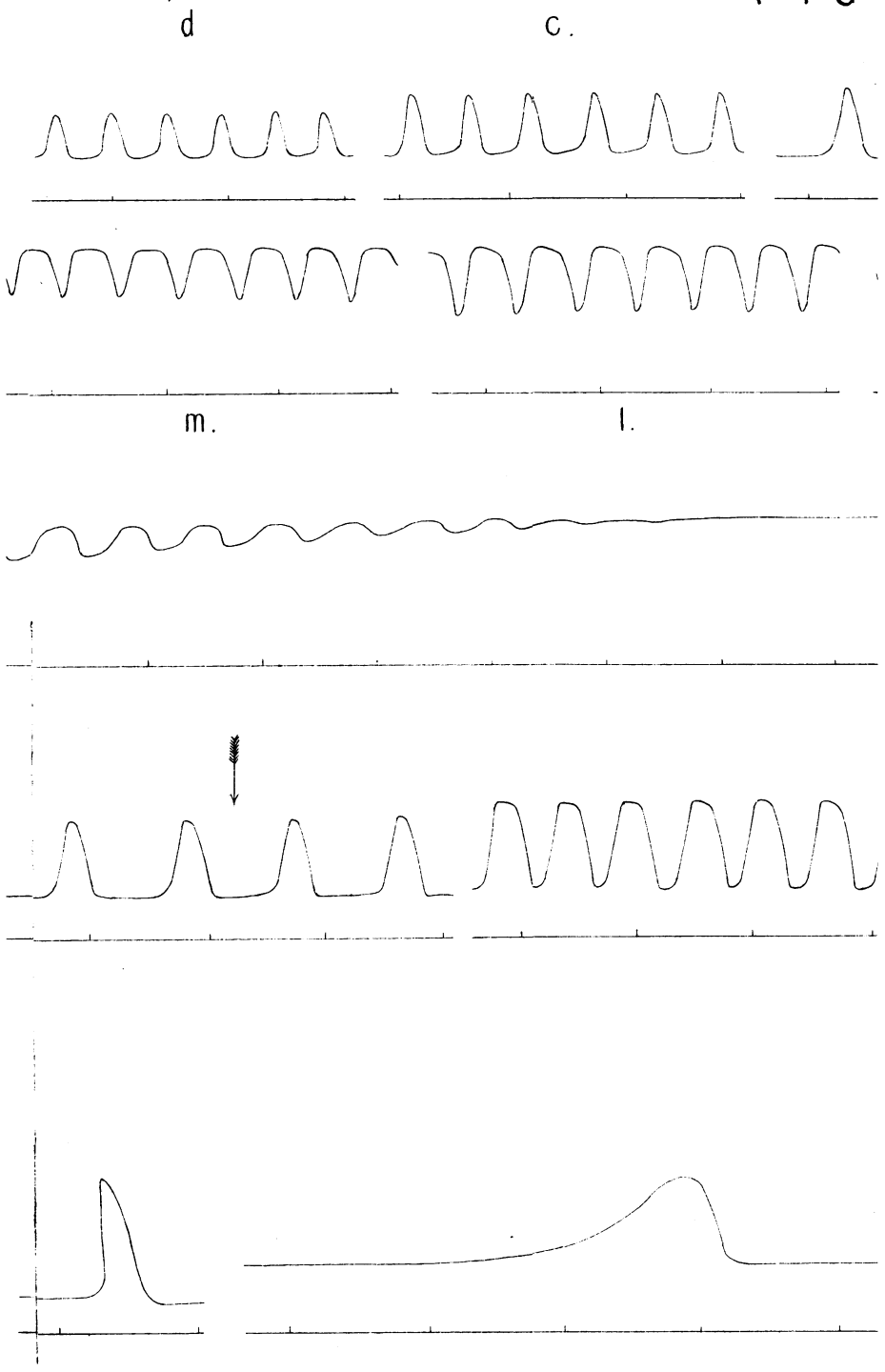


FIG. 9.

FIG



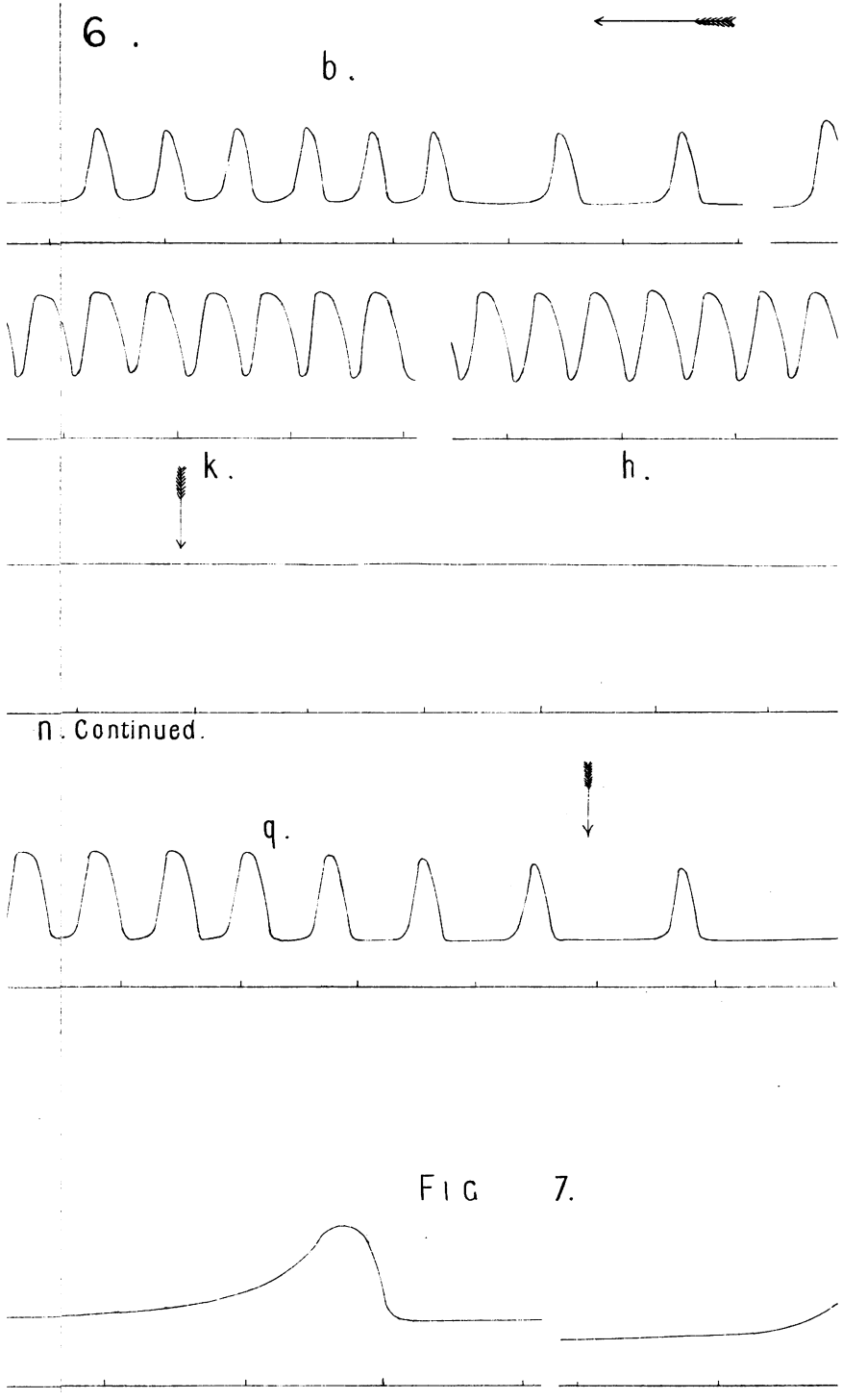
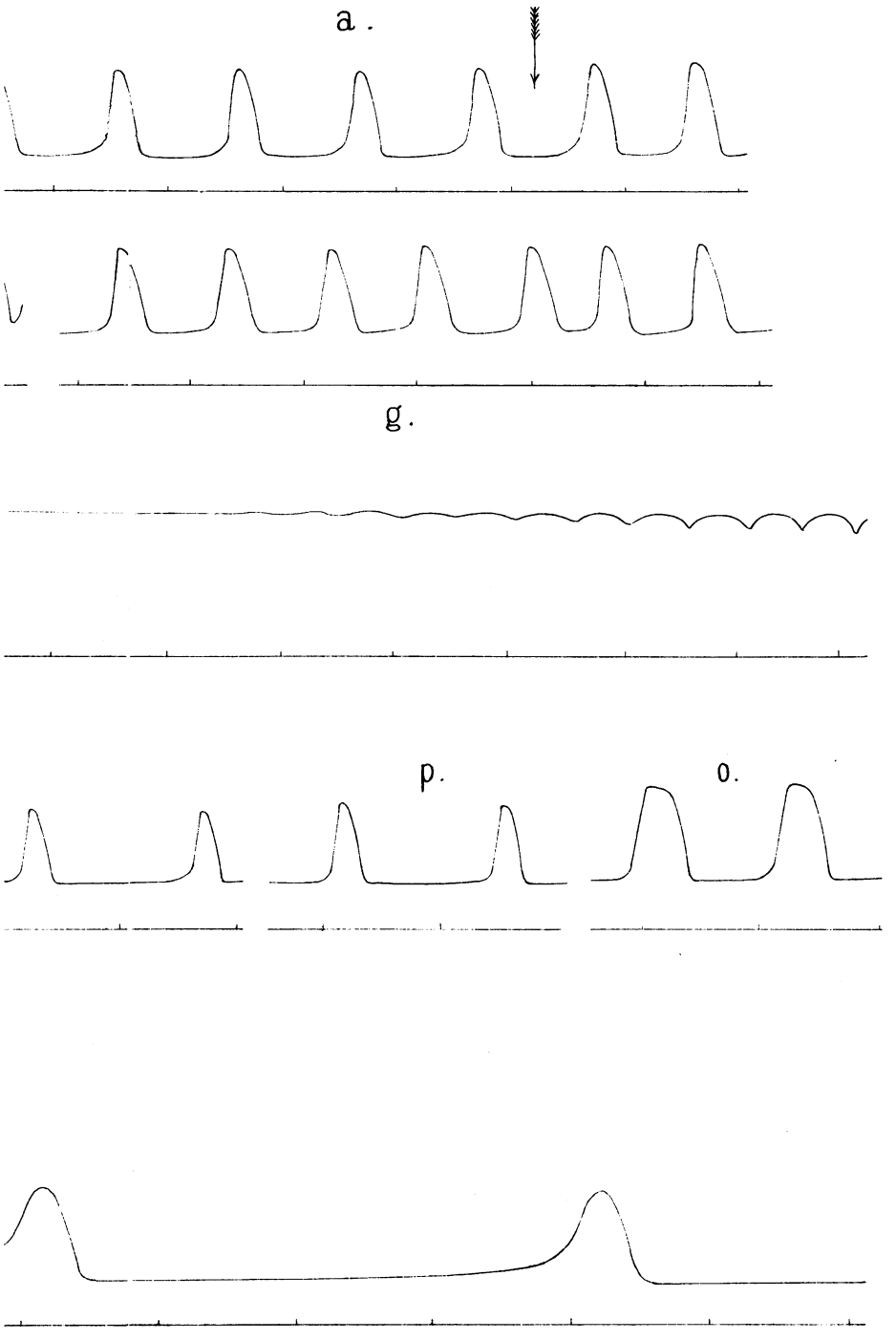


FIG 7.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