On the peculiarities of excitability which the fibres of cardiac muscle show[1,2]

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From the Physiological Institute at Leipzig, introduced by the scientific member C. Ludwig (With 22 wood engravings)

The excised frog heart can be filled with fluids of various compositions and the cavity changes can be examined by a manometer to determine the number and the range of its beats. This preparation therefore seemed to me to be very suitable for the study of the conditions under which the excitation processes of the heart fatigue and recover. During the execution of this project, it very soon became evident that this purpose could only be realised if the peculiarities of fatiguing and recovering cardiac muscle could be known to a more precise extent. To the solution of this limited task, for which I had the kindhearted support of Professor C. Ludwig, I first had to direct my attention.

The preparation which I needed for my experiments, I procured by putting a glass cannula in the cavity of the ventricle, advancing it from the auricle of the excised heart and tying it approximately at the border of the upper third of the wall of the ventricle. In this way, the muscle fibres of the lower two-thirds of the chamber, which I shall call in short, 'The Apex of the Heart', could be severed from its living connection with the auricle (and from the ring of the ventricle bordering the atrio-ventricular groove) and thereby, as known, could be deprived of the control of endogenous cardiac stimuli. It was necessary to fill the cavity of the apex of the ventricle (via the cannula) with fluid and to connect it to a manometer. The extent of its contractions could be measured in the same way as is done in the intact heart, by movement of the amount of fluid in the manometer. In using the great advantages which this sensitive way of determining the twitches allows, one should not forget that there are also shortcomings and that it is not free from special difficulties.

[1] Originally published in 1871 in German as: 'Über die Eigenthümlichkeiten der Reizbarkeit, welche die Muskelfasern des Herzens zeigen'.

[2] A historical note about the work follows on pp. 31–39.

Its first flaw is that nothing else is known to us about the relation between the linear shortening of the muscle and the volume of the ejected fluid. We could assume that volume is related to the linear muscle dimension cubed, so that the curve of the ejected volumes plotted versus the increasing shortening of the muscle fibres (abscissa) is concave toward the abscissa.

At this stage of our insight we are forced to measure twitches of the apex of the ventricle (which we want to compare with each other) with exactly the same filling of its cavity. Only with this precondition does the height of the manometer displacement accurately register the size of the twitch.

The manometer introduces another blemish, in that, with progressing twitches and the consequent increase of fluid in the manometer arm, the weight which has to be lifted by the heart is changed (see Fig. I). Therefore,

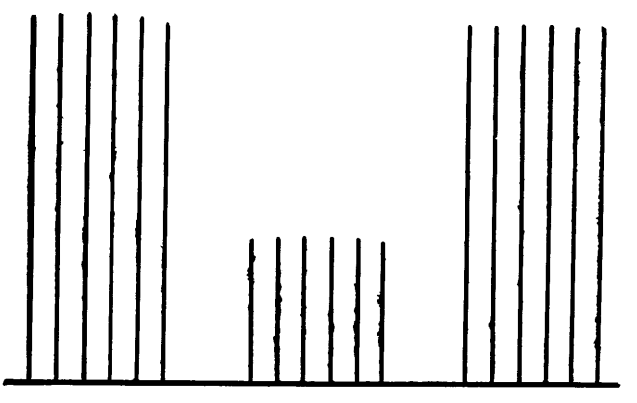


Fig. I. Water- Mercury- Water-Manometer

all series of experiments for which the constancy of the weight is a necessity have to be excluded. The influence of the weight on the recorded amplitude of the cardiac twitches becomes evident if the same preparation (in spite of the fact that it had been brought to the same degree of filling and had been stimulated in precisely the same way) would eject quite unequal volumes when the specific weight of the fluid, with which the manometer had been filled, was changed.

In the recordings illustrated in Fig. I, the excursion of the water-manometer ($=17$ mm) is more than twice that in the mercury-manometer ($=7$ mm). The increase in pressure, which in the latter case is produced by the mercury column (which is lifted above the position of equilibrium),

is more than ten times as high as the one present in the water manometer ($=2 \times 7 \times 13.6$). In spite of the foregoing considerations, I still gave preference to the mercury-manometer. I did so because it is easier to handle and because in the subsequent series of experiments, the interrelationship of the lifting height to the carried weight did not matter.

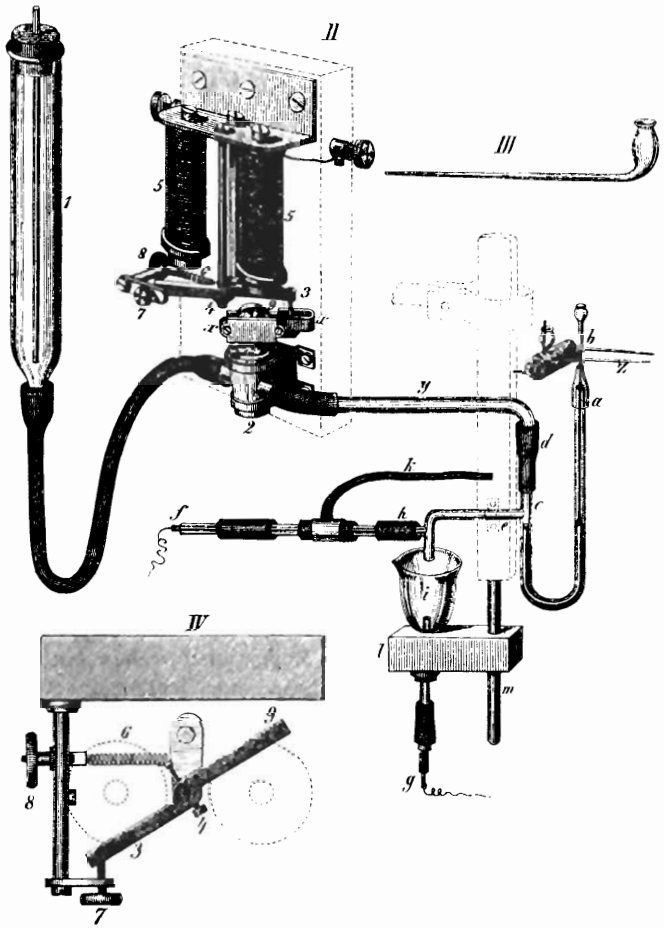
It was necessary to expose the apex of the heart to easily graded stimuli which could be delivered at arbitrary but regular intervals. To this end, an apparatus served me which was built according to the model which had been put together and successfully used by K. Kronecker, consisting of

1. The recording manometer which was writing the variable positions of its mercury column with light liquid ink (solution of aniline blue) on the
2. paper of a rotating drum. To facilitate the observation and to save paper, the cog of the clockwork was stopped after each half revolution, so that the drum itself was standing still during the twitch, but moved on for approximately 2 mm after completion of the twitch.
3. A small bottle as proposed by Mariotte which kept the filling of the apex of the heart constant during the duration of the experiment. In the tube which connected the cavity of the bottle with that of the cardiac apex,
4. a stopcock of glass was inserted, which could be closed during the twitch and opened again afterwards with the help of an electromagnet.
5. Electrodes which could not be polarised and which
6. conducted only the opening pulse (shock) to the ventricle using a sliding apparatus.
7. A cogwheel on a clockwork which would interrupt the electrical current which went through the primary spiral of the inductor at regular but arbitrarily changeable intervals.
8. A relay to make the main current independent of the contacts of the clockwork.

Because the items which are mentioned under the first six numerals (except the electric magnetic stopcock), have been described in these transactions before, I can confine myself to the apparatus depicted in Figures II, III and IV and a short explanation.

The known frog manometer (Fig. II) carried at its free end, a perforated glass cap in order to guide the light floater made of a fine straw: at the upper end of the latter, a very fine glass spring (b) was lacquered on, filled with an aniline-solution which inscribed the reading of the manometer

Fig. II. III. IV.



on the smooth paper of the drum. Fig. III shows the spring at its natural size. The second shaft of the manometer opens at (c) and (d). The opening (c) leads into the rectangularly bent tube (e), on the descending shaft to which a rubber tube connected the ventricular cannula. The electrodes which led the induction-current to the heart ended in the apparatus at (f) and (g); these consisted (according to the directions given by du Bios) of glass tubes in which a zinc amalgam rod was put, which was surrounded by a solution of sulphate acid zinc oxide. At their cardiac ends, the tubes were closed by a stopper made of cotton which had been submerged into $\frac{1}{2}\%$ NaCl solution. At their other end, a tube of flexible rubber connected them to the zinc rod. The electrode (f) was in connection with the fluid contents of the heart apex by the tubule (h) which had been connected

to the descending shaft of the rectangular tube. The electrode (g) led to the bell shaped glass (i); the latter was filled during the experiment with serum to such an extent that it reached to the upper rim of the small glass bell (i); thereby, it was possible to keep the height of the serum always the same, because every drop that had been filtered through the cardiac wall had to run through the spout.

The electrode (f) was kept in its position by the wire (k): the small glass bell (i) rested on the perforated prism made of cork (l), which could be moved on the rod (m). The apparatus which controlled the degree of filling consisted in the beginning, of a small Mariotte bottle (1), which would be brought to the desired height by a holding device (not depicted in the drawing). The lower part of the bottle was connected with the glasscock (2) by the tube of flexible rubber. The stopcock could be opened and closed by means of a small spiral spring and an electromagnet. The time in which the one or the other occurred, had been chosen in such a manner that the pressure bottle was shut off from the ventricle when the latter was contracting. However, there was an open communication between both of them when the ventricle was limp. The necessary guidance for the cone of the stopcock was achieved by the armature (3) which is shown in Fig. II from the side and in Fig. IV in plan view. The rodshaped armature (3) rotated in the horizontal plane around the vertical axis (4). If the magnetism in the iron cores (5, 5) was developed, the rod lay parallel to the line which connected the centre of the bases of both iron cores. If however, the magnetism disappeared in the latter, the rod (3) was pulled by the spiral spring (6) (Fig. IV) into the position which it shows in this figure. The excursion which the rod could reach by the pull of the spring, was limited by the screw (7), which was located in a small crossbeam on a brass column on which the screw (8) was located (Fig. IV): this served to increase the tension of the spiral spring. The movement which the armature (3) exerted was transferred by means of a small pivot (9) to the clamp (x), which embraced the cone of the stopcock (2). The pivot (9) had (within the clamp (x)) some room to move, as can be seen in Fig. II. Beyond the stopcock, there was a small tube (y), which led (after a rectangular bend) to the opening of the second manometer tube. To mark the position of equilibrium of the mercury-column in the manometer, there was a glass spring (z) which was fixed by a cork at the rack to which the manometer was fixed. Since the spring which was floating on the mercury had been brought to the height of mercury equilibrium before fixation on the ventricle, and because it was kept in this position during the total rotation of the drum, it was possible to find (at any optional section of

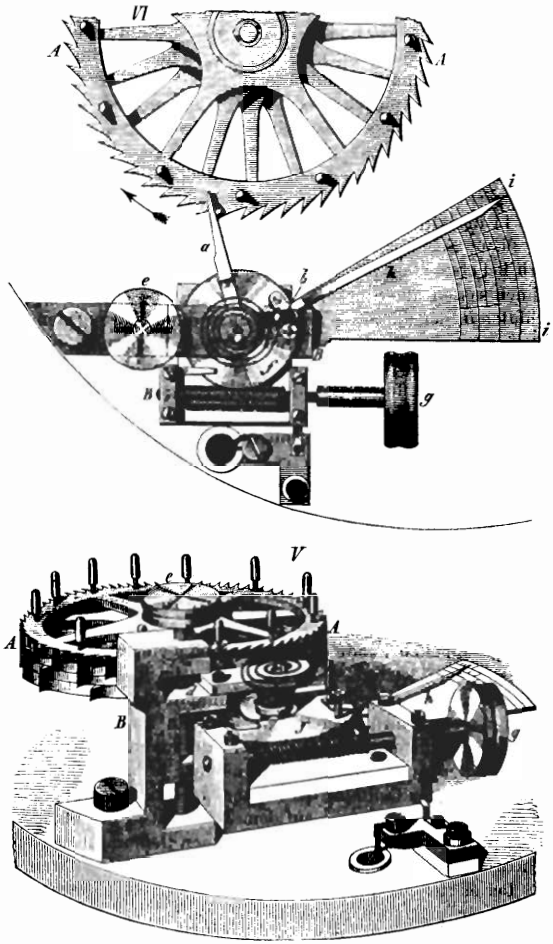
the cardiac curve) the height by which the curve had risen above the position of the mercury equilibrium.

The wheel, which is referred to as a contact breaker and which is listed under number (7) in the table of my instruments, was driven by clockwork supplied with a centrifugal pendulum. The contact breaker should open and close the electrical current at regularly recurring intervals in such a way that one could choose optionally between the intervals of 1, 2, 3, 4, 5, 10, 15, 20, 30 and 60 seconds. Furthermore, if one desired, the current could be opened immediately after its closure, or closed during a longer interval of time. The contact breaker, which achieved this, was constructed and executed by the watchmaker B. Zachariae in Leipzig; it consisted of a wheel being driven by clockwork on the rim of which were cut multiple rows of teeth. There was an adjustable angular lever, one of whose arms was leading to the cog-wheel, whilst the other was in contact with a knob of platinum (Figs. V and VI). The exact description of the apparatus may begin with the angular level. Both of its arms (a) and (b) which were inclined at a sharp angle (Fig. VI in plan view) were revolving around a vertical axis. The arm (a) was pointing to the cog-wheel (A) at the rim of which it could drag. The arm (b) was connected to a spiral spring which pressed it against the small button (c), provided that the arm (b) was not kept fixed by a higher force. Because one of the terminals of the battery ended in the small button (c) and the other one in the lever-arm (b), the flow of the current depended on their mutual contact. At times when a tooth of the wheel (A) pushed the arm (a) in front of itself (and in consequence also pulled arm (b) behind), the current was interrupted. If arm (a) slid down from the progressing tooth, the spiral spring drove back arm (b) in the opposite direction to the stop at the small button (c).

The ability to change the time interval between two consecutive current flows was achieved as follows: The circumference of the wheel (A) rotates four rows of teeth (of 60, 30, 20, and 15 pieces each) once a minute. In addition, 12 small pins are located on the upper plane of the wheel (A). At the moment at which arm (a) was opposite the pins or rows of teeth, the flow of the current recurred after 1, 2, 3, 4, or 5 seconds. To prolong the interval beyond this period, one removed 6, 8, 9, 10 or 11 pins, by which intervals of 12,[3], 15, 20, 30 and 60 seconds were made possible. The rows of teeth could also be set against arm (a) at will, by locating the contact pieces on slider (B), which could be elevated by the

[3] Apparently a misprint or miscalculation has occurred here, because removing 6 pins would give an interval of 10, not 12 seconds.

Fig. V. VI.



screw (e) and the guiding plate (d). The fulfilment of the second requirement (optional distribution of the total time for an interval between the flow and the interruption of the current), was realised because the arm (a) could be held by the tooth which was grabbing it for different periods of time. If this happened, the arm (when it had glided down) was momentarily taken up again by the succeeding tooth, the duration of the flow of current dropping to a minimum. In the other case (where the grabbed tooth was released instantaneously), the duration of the interruption was minimised. To achieve this, the device which was enabling contact with the slider (B) was set on the disc (f), itself geared with its toothing

rim into the screw (g). Screw (g) could change the direction by which arm (a) pointed to the circumference of the wheel (A). Because the duration of current flow, or the interruption of the current, depended on the position of the disc (f), it was very convenient to mark the position of the arm (a) by a pointer (h) on the clockface (i–i); these positions were equivalent to a certain duration of flow interruption. This could be achieved at any time very easily and reliably.

The electrical current for which this contact breaker had been constructed produced the stimulating induction current and, in addition, magnetised two pairs of iron cores, namely the one at the glass-stopcock and the other one at the blade of the device rotating the drum. In order to achieve this, a strong current of high amperage was necessary which could not conduct through the contact breaker; the need for a relay became evident. By this, the main current could be kept flowing whereas the current of the relay was interrupted by the contact breaker. I adjusted the latter in such a way that the duration of the contact breaker amounted to 0.5 seconds.

According to the positioning of my apparatus, if the main current was flowing, the blade of the rotating drum was released, the electromagnetic stopcock opened and an induction beat was produced, being made ineffective by attenuation. The time of 0.5 seconds was sufficient to bring the contents of the heart to the pressure of the filling bottle, and to make the drum perform a rotation which would lead to a displacement of the paper by approximately 1 to 2 mm. If after this the main current was interrupted, the blade was held fast, the stopcock was closed and an interrupting induction beat was sent through the heart. This, because of its long latent stimulation, triggered a twitch only after the stopcock had been closed.

For the understanding of the experiments and the full assessment of the apparatus, a few more remarks should serve. The application of the ink facilitated the experiment extraordinarily. Its use was more accurate than that of smoke as its easily flowing solution wrote on smooth English paper. The sliding pen which was in use had been made according to the description of A. Fick (1869). The specifications on the strength of stimulation in the following paper accordingly do not describe the distances of the coils, but the size of the induction intensity; the maximum strength that could be reached was estimated to be 1000.

The stimuli which were conducted to the apex of the heart shorted to the wall of the ventricle; accordingly the stimuli must also have stimulated the muscle and not only the nerves. Because the electrode, reaching into

the glass bell filled with serum, was vertical, special caution was needed to avoid the accumulation of small air bubbles under the stopper made of cotton. I do not think it unnecessary to point out that I was aware of this source of error. I start the description of my experiments with the chapter:

1. that deals with the **relation between the numbers of stimuli and the number of cardiac twitches**.

If the apex of the heart is stimulated at regular intervals by equal induction pulses, it either contracts after each stimulus or the number of the twitches is larger or smaller than the number of the stimuli. These three different kinds of response will be called: the regular, the supernumerary, and the discontinuous pulse or beat sequence.

The supernumerary sequence of beats occurred in my experiments rarely, and only then if the ventricle had not been ligated deep enough. Since this seems to be a fault of my experiments, I shall not take it into consideration further. This, of course, does not mean that the supernumerary sequence of beats is not worthy of special consideration. On the contrary, I consider that the relationships between this phenomenon and those which we are dealing with in this paper are very close. If the ventricle is tied deep enough, discontinuous and regular pulses can be produced at will by mere changes in the strength or sequence of the induction pulses.

First, I shall speak about the dependence of the sequence of pulses on the strength of the induction shock. If the strength of the induction shocks is gradually increased from low values, quite soon a point is reached at which the stimulation induces a twitch. If one maintains this strength and allows the induction pulses to follow at regular intervals, not every one of them will lead to a contraction. Thus, the number of stimuli exceed the number of pulses significantly. If, however, the strength of the induction shocks is increased further and further, the number of contractions also grows, without however equalling that of the stimuli. Little by little, one is reaching a value at which the sequence of pulses is becoming regular, i.e. that each stimulus is followed by a twitch. Occasionally, however, it happens that, in spite of a great intensity of the induction currents, no regular sequence of pulses can be obtained. When this occurred, the relation between the number of contractions and the number of stimuli approached unity. In order to document these communications, I shall give some examples: see over.

The discontinuous sequence of pulses may be transformed into a regular one, by increasing the interval between two stimuli of unchanged strength (but also by the fact that with unchanging strength of the stimulus, the

Intervals between two stimuli = 6 seconds.

strength of the stimuli	100	105	110	120	130	140
number of twitches/ number of stimuli =	0.0	0.07	0.10	0.20	0.66	1.00

Intervals between two stimuli = 4 seconds

strength of the stimuli	100	110	90	80	90	110	130	150
number of twitches/ number of stimuli =	0.04	1.0	0.17	0.30	0.88	0.77	0.82	1.0

Intervals between two stimuli = 6 seconds

strength of the stimuli	200	207	215	222	230	237
number of twitches/ number of stimuli =	0.0	0.7	0.14	0.24	0.59	0.87

interval between two of them is increased). In the examples below, the intervals were changed in an ascending and descending order.

Strength of the stimulus = 140

Interval in seconds		4	6	4				
number of contractions/ number of stimuli =		0.58	1.00	0.57				

strength of the stimulus = 150

interval in seconds	5	10	5	4	3	4	5	10
number of contractions/ number of stimuli =	0.74	0.97	0.87	0.71	0.73	0.80	0.95	1.0

Instead of searching for a given intensity of the induction current which at a particular interval would generate the regular sequence of pulses, one can also proceed vice versa, i.e. one can ascertain the threshold current at which (for varying intervals) the pulses are just still regular. In the execution of these experiments, one expects that with increasing length of the interval, the intensity of the stimulus could appreciably decrease before the regular sequence of pulses became a discontinuous one. This only happened in a very limited fashion. One may therefore conclude that large differences of the interval may be compensated for, by small changes of stimulus strength. A few examples may serve as an illustration. For the understanding of these examples, one has to note that, with the mentioned

intensities of the induction current which are listed after the rubric 'strength of stimulation', the pulse sequence becomes regular when the induction pulses occur at the given intervals.

interval (in seconds)	10	3	4	4	3
strength of stimulation	42	43	41	45	46

and at another heart apex:

interval (in seconds)	3	4	3	5
strength of stimulation	80	74	74	68

Should one not feel urged by these and similar series of experiments to regard the above mentioned assumption as a well-founded fact, one should nevertheless be careful not to see a refutation in its imperfect confirmation. In the properties of the heart itself lie the reasons which make it difficult, yes even impossible, to furnish the proof.

The heart-muscle itself has the remarkable peculiarity that its sensitivity to stimulus strength changes as the result of the twitches which it has executed. Thus, after a longer series of contractions, a weaker stimulus than before this series suffices to trigger a regular sequence of pulses.

One's attention to the influence which the preceding twitches exert, is drawn if one uses the same stimulus with the same interval multiple times successively. Under these circumstances, the quotient of the number of twitches over the number of stimuli grows in size gradually. It may equal unity, so that a stimulus, the intensity of which did not suffice originally to induce a regular sequence of pulses, gradually becomes sufficient. For instance, I shall refer to the following observations: If the apex of a heart was stimulated by an induction shock of intensity 52 at intervals of 6 seconds, 100-times successively, the apex of the heart contracted in consequence of the first to the tenth stimulus twice, of the 11th to the 20th stimulus twice, of the 21st to the 30th stimulus twice, of the 31st to the 40th 6 times, of the 41st to the 50th stimulus 7 times, of the 51st to the 60th stimulus 6 times, of the 61st to the 70th stimulus 5 times, of the 71st to the 80th stimulus 9 times, of the 81st to the 90th stimulus 10 times, of the 91st to the 100th stimulus 10 times. Thus, the ratio of the twitches to the stimuli had increased from 0.2 to 1.0 with some variations.

In another case, in which the intensity of the strength of stimulation amounted to 52 also, and the interval to 6 seconds, the ratio grew during 40 stimuli for each 10 of them from 0.2 to 0.4, to 0.8 and finally reached 1.0. The growing sensitivity which the heart apex gains after many successively executed twitches is substantiated by the observation that the intensity of the induction current which is necessary to induce a regular sequence of pulses may decrease, in the course of a longer series of experiments. As an example, the following may serve:

Interval 5 seconds

strength of stimulation	200	300	200	150	100	110	115
number of twitches/ number of stimuli	0.0	1.0	1.0	1.0	0.27	0.8	0.9

If, thereafter, the same heart apex was stimulated at intervals of 10 seconds, the strength of stimulation was related to the ratio between the number of stimuli and the number of twitches as illustrated by the following numerical series. In the upper line I have listed the strengths of stimulation and, in the second, the respective proportional numbers:

115	90	110	115	105	100	90	80	70	65
0.0	0.6	1.0	1.0	1.0	1.0	1.0	1.0	1.0	0.7

70	68	66	60	55	50	46	42	38	42	40	42
1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	0.0	0.9	0.2	0.7

Observations such as these speak quite expressively for the fact that the sensitivity of the apex of the heart is increased by the executed twitches, because the same strength of stimulation alternately leads to either a discontinuous or to a regular sequence of pulses, depending on the preceding response. In the discontinuous sequence of pulses, the twitches (without following a special rule), may either appear or fail to appear; I think it necessary to point out this behaviour and to illustrate it by the reproduction of some recordings, see Figs VII and VIII.

After having looked at these figures, one will see how difficult it is to describe their contents by word precisely; to use a quotient can merely be a stopgap. Its application is solely excusable because it was only thereby possible to come closer to the understanding of some very peculiar facts.

Fig. VII.

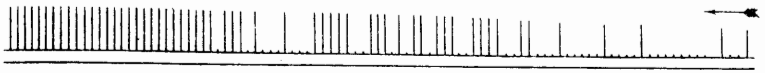
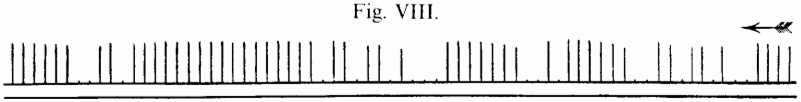


Fig. VIII.



Every dot on the baseline marks an induction shock

If one envisages the heights to which the twitching apex of the heart is able to drive the mercury, it is immediately evident that the extent of the twitch does not show any dependence on the mode of its recurrence.

In both series of experiments, the twitch may be equal or unequal, and if the latter occurs, the twitch can be greater or smaller in the discontinuous series than in the regular one. From this behaviour one can infer that the stimulus which induces a discontinuous series is sufficient to elicit the maximum twitch of which cardiac muscle is capable. However, since this cannot be done all the time, we are forced to give this phenomenon, in contrast to the stimulus which can achieve it, a special name. I shall call the stimulus which always induces a twitch as often as it occurs, the *unfailing* stimulus, whereas the one which can induce the maximal twitch only occasionally may be called the *adequate* stimulus.

That the adequate stimulus is not an unfailing one cannot be due to a fatigue of the muscle mass. Such exhaustion would not explain why the twitch, if it occurs in a discontinuous series, is not smaller than in the regular one. Even less could it be reconciled with the assumption that the frequent repetition of the same stimulus (in the same interval) could change an initially adequate into an unfailing stimulus.

If the heart muscle reacts to natural stimuli in a similar way, we would have found a new reason for the intermittent pulse especially found in those hearts whose inhibitory nerves are out of action. If, at the moment, I hesitate to apply the phenomena which the apex of the heart are showing to the intact heart, it is because of the ligature which has been put around the musculature to ensure the fixation of the cannula. Why should the ligation of the ventricle not act similarly to the one in the atrium? And if this would be the case, an inhibitory stimulus would be present which is lacking in the intact heart. This hypothesis receives some confirmation by an observation which I made incidentally but did not follow (unfortunately). It is that the strength of the stimulus which will induce a regular

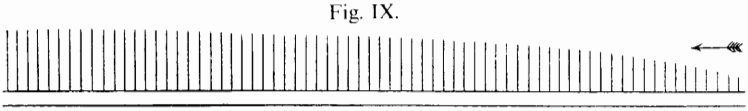
sequence of pulses has to increase considerably if one adds a new ligature to the existing one; this sometimes has to be done if the first tie around the cannula was not tight enough.

Sometimes the introduction of fresh serum into the cavity of the apex of the heart is effective in the opposite way to the ligature. Quite often one can lower the strength of the stimulus considerably after such a change, without losing its character of being unfailing.

2. **On the extent of the cardiac twitch.** For the size which the twitch can reach, the time which passes between it and a preceding contraction is of such importance, that above all it is necessary to consider its effect. Here, it is always presupposed that the cavity of the cardiac apex is filled with fresh reddish serum of rabbit blood, and that the stimulus which is effective at regular intervals, is not only maximal but that its strength is unfailing.

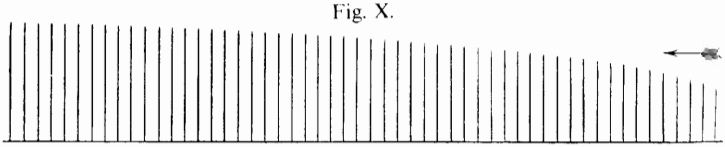
If before the beginning of a series of consecutive, equally intensive, stimuli with intervals of approximately 4 to 6 seconds, the apex of the heart had been in perfect rest over several minutes, a series of twitches is induced as depicted in Figs IX and X. The records come from two different hearts; IX worked with a mercury-manometer, X with a water-manometer.

Fig. IX.



Mercury-manometer

Fig. X.



Water-manometer

The first twitch, elicited after a minute-long pause, is the smallest, and each following one increases in size in such a way that with the rising number of twitches, the amount of increase gets smaller and smaller until it completely vanishes. The subsequent twitches have the same size. I call such a sequence of twitches a *Treppe* (*staircase*). The steps of different *Treppen* obtained in the same heart show various deviations with respect to their minimal and maximal sizes, as well as to their connecting links. Therefore, the next task was to look at the reasons for these variations

and especially the dependence on strength, direction and interval of the stimulating induction current.

It is evident that the shape which the *Treppe* takes is absolutely independent of the direction and strength of the induction current. This was expected from the very beginning, because the stimuli applied were maximal. I nevertheless have convinced myself by the most thoroughly executed experiments, that the extent of the first, the increment of the next and the size of the maximal twitch were not influenced by the aforementioned properties of the stimulus.

If one lets at least five minutes pass between two consecutive series of experiments, all twitches are small or completely equal, or only deviating within the limits of error of the measurement. This, in spite of the fact that the direction of the currents is sometimes ascending, sometimes descending, and of different intensities.

In order to obtain a number of comparable observations, I rested the apex of the heart for 5 minutes and then stimulated it by two stimuli, of which the second followed the first by an interval of some seconds. Thereafter the apex of the heart was rested again for another 5 minutes, and again a pair of stimuli was given with a similar interval and so forth. Whereas the pauses and the intervals between the stimuli stayed the same, the intensity of the current was manifoldly changed. Twelve pairs of twitches were obtained which are listed in the following table (see over).

To appreciate the exactness with which these numbers depict the independence of the growth of the twitches from the properties of the stimulus, one has to realise that the twitch height (because of the known properties of the manometer) could only be recorded at half the real amplitude. Since the numbers reflect the full value of the height, the error of measurement is doubled. Because upstrokes with values of 0.1 mm recorded by ink on the paper, undoubtedly fall in the range of error, differences of less than ± 0.2 mm between a pair of observations cannot be taken as significant. Thus the agreement between the differences which consecutive pairs of twitches show is very great indeed. However, the upper four pairs are equal among themselves but show a 0.4 mm difference from the four last ones, which also are equal among themselves. This may indicate that with the passage of time the muscle mass of the apex of the heart could experience marked changes in its characteristics. If this is accepted and observations are only compared when they were obtained with intervals which are not too far apart, the conclusiveness of the results does not leave much to be desired. All experiments which I performed according to this plan have yielded the same result.

Treppe Number	Twitch Number	Height of manometer column lifted (mm)	Strength of induction shock	Difference in manometer heights (mm)	Direction of induction current
I	1	11.0	90	1.4	Rising
	2	12.4	90		
II	1	11.0	90	1.4	„
	2	12.4	100		
III	1	11.0	90	1.4	„
	2	12.4	90		
IV	1	11.0	90	1.4	„
	2	12.4	120		
V	1	10.4	90	1.8	„
	2	12.2	120		
VI	1	10.2	90	1.2	„
	2	11.4	130		
VII	1	11.0	90	1.4	„
	2	12.4	90		
VIII	1	11.0	78	1.6	„
	2	12.6	78		
IX	1	11.0	90	1.8	„
	2	12.8	90		
X	1	11.0	90	1.8	„
	2	12.8	150		
XI	1	11.0	90	1.8	„
	2	12.8	90		
XII	1	11.0	90	1.8	Falling
	2	12.8	90		

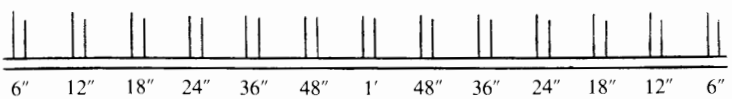
We have seen that the size of the smallest twitch and the increase between two consecutive twitches at the same interval are independent of the strength and the direction of the stimuli. The same proof is left for the maximum of the twitches. However, this has already been confirmed during the extensive series of observations (which have been performed on the adequate and unfailing stimulus), mentioned on page 14 in this manuscript.

However, the effects are quite different if the interval which separates two consecutive beats is changed. Because the stimuli can be regarded as useless without twitches, it would be more correct to speak of an interval between twitches instead of between stimuli. The latter expression can

therefore only be justified as long as one speaks of unfailing stimuli. In order to portray the dependence of twitch amplitude on the interval between the stimuli, one can proceed in different fashions.

a. After a pause of two to five minutes, one lets two consecutive twitches follow each other. The interval which separates one pair of twitches from another should be made variable following a certain rule. For instance, the interval can last 4 seconds between the first pair, 6 seconds between the second and so forth, up to a minute, and then one decreases the interval again in a descending fashion to 4 seconds. An experiment which is performed in such a manner shows that the first contractions of all pairs are almost if not completely equally large. The second twitches of the pair however, are unequally large; and in general larger than the first twitches. The amount by which they exceed the height of the first twitch is related to the length of the interval between the twitches that belong to one pair. The picture to which such a series of observations leads is in the following figure (XI).

Fig. XI



b. As with the increase between two consecutive beats, so also the highest step the *Treppe* can obtain is determined by the interval of the stimuli. This assertion can easily be proven in the following way; one sends unfailing stimuli with a given interval to the apex of the heart until the height of the twitches no longer increases. This is done for a series of different intervals. It is desirable to change the duration of the interval according to a certain rule in an ascending and a descending fashion. As examples of this kind, I want to emphasize two which have been obtained with different apexes of heart. In the upper row of numbers, the intervals are listed in seconds, in the lower row, the maxima of the height of the twitches. Below each interval the greatest height is listed which could be obtained by its application (see over).

From these rows it can be seen, that the greatest height which the apex of the heart (which had been filled with pure serum) can generate is apparent with an interval between 4 to 5 seconds. If the interval is prolonged the height will decrease continuously, until it (according to the individuality of the heart) reaches a minimum at a pause of five minutes; it does not fall further after a longer period of rest. Nonetheless, the extent

I.

seconds	60	30	15	10	5	4	3	2	4	5	15	60
mm	12.0	14.0	16.0	17.0	18.0	18.0	16.4	14.4	15.2	15.2	14.4	10.0

II.

seconds	5	60	30	20	5
mm	24.4	10.6	15.4	17.6	23.2

of the twitches does decline if the interval is shortened from four to two seconds. I rarely went to shorter intervals because the twitches either merge to a tetanus or do not become more frequent. The behaviour of cardiac muscle towards quickly successive stimuli needs a special study, which considers changing excitability depending on the season of the year.

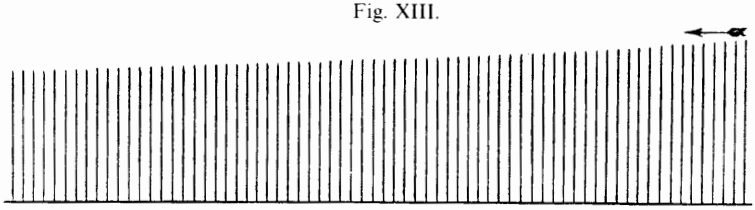
With knowledge of the inherent properties, it is not difficult to predict if a twitch of the apex of the heart will be greater or smaller than a preceding or later one, if the succession of the stimuli is known. Only comparison of two twitches which are not separated by a larger number of contractions is legitimate, because under this condition new influences come to bear.

The interdependence between twitch height, number and sequence is not completely described by the expression which is derived from the *Treppe*. This is not quite self-evident because the apex of the heart, as every other muscle, loses working capacity in the course of the performed work. A greater number of unfailing stimuli causes the contractions to decrease gradually until they finally disappear. On the way in which this fatiguing occurs, I can say the following: if one plots the heights of contractions following the descriptions of H. Kronecker, one sees that the line is either straight or descending to the abscissa by a convexity which is directed towards the abscissa. In skeletal leg muscle, the curve of fatigue would have pointed its concavity towards the abscissa, so that the decrease in the extent of the twitches during fatigue would have been the contrary picture to its ascending character in the *Treppe*. About the reason for the apparent extent of fatigue of cardiac muscle decreasing with the growing number of contractions, I dare not speculate because of a lack of experiments. The interval of the stimuli exerts a visible influence on the steepness with which the curve of fatigue declines. Also on this aspect I have to refrain from an extensive explanation and can only restrict myself to the presentation of two of my pertinent observations (Figs XII and XIII).

Fig. XII.

Interval 2 seconds

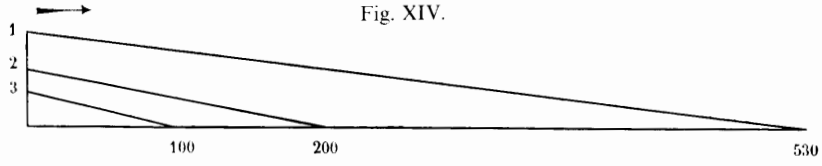
Fig. XIII.



Interval 4 seconds

If in consequence of fatigue, the twitches of the apex of the heart finally get too small to lift the mercury visibly, one can make a comparison with fatiguing skeletal muscle by replacing the serum with which the ventricle has been working up until now by new serum. The working capacity which the heart thereby gains is not insignificant, but it is far less than was present originally. If the apex of the heart is fatigued for the second time by the executed twitches it can recover again following a new change of the serum, but the efficiency attainable will be smaller than that produced by the first change in serum. If one continues in this way with the fatiguing and the exchange of the serum, a point will finally be reached at which the addition of new serum is completely ineffective. The following wood engraving may serve as an example for this, in many aspects, remarkable behaviour. In order to understand this, it is necessary to observe that instead of the recorded twitches only the decline of the line of fatiguing has been drawn, and the abscissa across which it runs has been shortened. Its length has been taken as proportional to the number of twitches which have been performed from the maximum to their disappearance.

Fig. XIV.



The uppermost of the three lines depicts the decline of the fatiguing of the fresh apex of the heart; the length of the abscissa corresponds to 530 twitches; the second line shows the fatiguing after the first change in serum; the length of the abscissa represents 200 twitches; the third line finally shows the fatiguing after the second change in serum; the length of the abscissa corresponds to 100 twitches. By comparison of the lines of fatiguing, it is evident that, with each new recovery, not only the maximum of the twitch gets smaller, but that the steepness of its decline increases.

In addition to the insights which can be gained from skeletal muscle, the apex of the heart offers a new one, which relates to the importance which the qualities of the serum have in regard to the muscle which is fatigued to various degrees. The same amount of identical quality serum made possible at first 500, then only 200 and finally only 100 twitches. Thus, less than half the number of twitches which the muscle executed after the first recovery either changed the serum as much as the ones which the fresh apex of the heart had performed or, if this is not the case, the serum has to be richer in recuperating substances if it has to restore a fatigued instead of a fresh muscle. Also on this important alternative further experiments have to decide.

Apart from the endurance and the size of twitch, fatigued muscle does not differ from fresh; namely, the inherent stepwise increase of the height of the twitches and the dependence of the latter on the stimulus interval are retained.

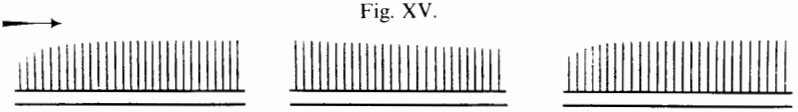
The excitability of the heart becomes quite different if its cavity is filled with other fluids instead of with pure serum, or if poison is added to the serum. Because the new phenomena explain the hitherto mentioned observations, their description will follow immediately.

A. A solution of 0.5 g NaCl and 4.0 g gum arabic in 100 parts of water

I tried this fluid to save some of the serum. The most striking deviation by the heart that was filled with this gum was shown by its behaviour after a longer period of rest. If after this period of rest the regular sequence of stimuli was reintroduced, the stepwise increase of successive twitches would be missing. The same apex of the heart was alternately filled with serum, with gum solution and again with serum. Fig. XV shows the result of an experiment.

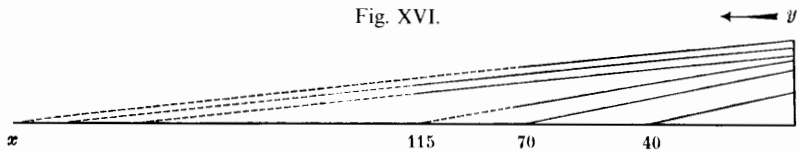
In other experiments, a maximum was reached after only one or two twitches. Such aberrant *Treppen* occurred more often after very long than after short pauses. Normally with lengthing of the resting period, the first

Fig. XV.



of the twitches to be triggered decreased, but with gum solution, the first of the triggered twitches increased according to the duration of the resting period, and this to a not insignificant degree, if one allowed the aforementioned time to extend to 10 minutes. Consequently, the apex of the heart behaves like any other cross-striated muscle, but it seems only qualitatively, since the recovery was much more powerful than in skeletal muscle, which I have seen perform work in the experiments of my friend Kronecker. The capacity of work performance which had been gained during the resting period did not decline as rapidly as in ordinary skeletal muscle. In the following figure (XVI), the heights of the twitches are

Fig. XVI.



depicted on the y axis while the lengths on the x axis are proportional to the numbers of executed twitches. Each of the 6 lines corresponds to a series of contractions which started 7 to 10 minutes after the conclusion of the preceding ones. The drawn part of this line has been constructed according to the number of actually performed beats, whereas the dotted part has been drawn under the premise that the decline in the height of the twitches would continue in a linear fashion. The numbers below the abscissa indicate the beat number corresponding to that point.

In other aspects, everything which has been observed concerning the adequate and unfailing stimulus is also completely valid in gum solution.

B. Solution of muscarine in rabbit serum

This poison which has become famous through the investigations of Schmiedeberg was added to the serum of rabbit blood which filled the cavity of the apex of the heart. The preparation was exposed to a series of stimuli before the poisoning. It hereby was evident (Fig. XVII), that during the stepwise increase of the twitches, the minimal and maximal

Fig. XVII.

twitch, and also the increase from one beat to the next became distinctly smaller during the poisoning.

From this it follows that with stimuli of equal intervals, the maximum of the twitch is always greater in the unpoisoned heart than in the one that had received muscarine. With intervals shorter than 4 seconds, the height of the twitch increases further with decreasing interval, so that the greatest beat appeared when the stimuli occurred every two seconds. Because with this short interval the twitches increase very significantly, the possibility cannot be excluded that the maximum of the twitch which a poisoned heart may reach after a 1 second interval is larger than the one that would be reached under the same circumstances in the unpoisoned heart. These effects become evident if at least 10 minutes have passed. If the poisoned heart is forced to perform numerous twitches, then the effect of the muscarine disappears gradually in the course of 1–2 hours; if this has happened, the apex of the heart can be poisoned again by a new dose of muscarine.

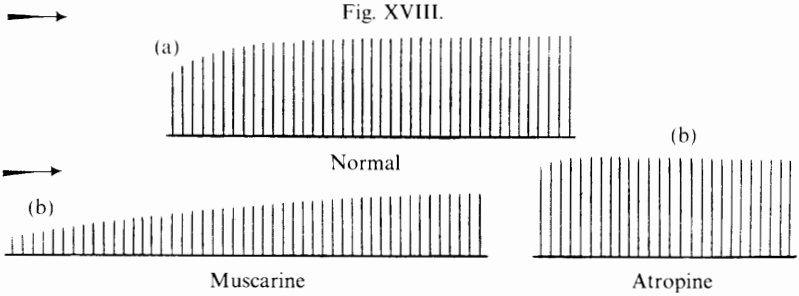
Because the possibility is conceivable that the muscarine is lowering the elastic coefficient of the cardiac wall, and since if this happened the smaller extent of the twitch of the apex of the heart may have been due to a lessened elastic tension of the wall, I increased the latter by filling the resting heart with a higher pressure than usual. This increase in pressure, however, did prove to be quite ineffective as to the extent of the twitch; the latter one stayed unchanged, and additionally was not altered if the resting heart was under 30 or 100 mm water column. With the exception of the aforementioned, the muscarine poisoned apex of the heart behaved in all aspects like the unpoisoned.

C. Solution of atropine in rabbit serum

Atropine was employed here as an antidote to muscarine. In Fig. XVIII, series of twitches were obtained in three different states: (a) has been produced by the unpoisoned heart, (b) by the one that was poisoned by muscarine, (c) by atropine.

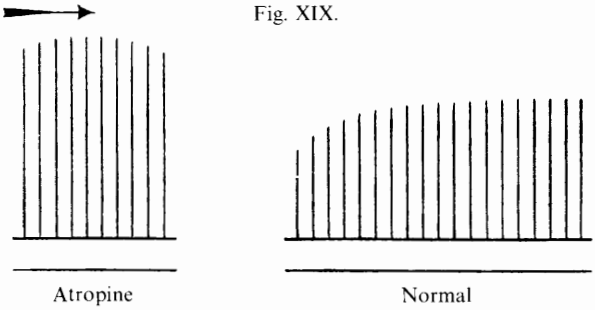
With atropine, the stepwise increase of the twitches could be abolished, whereas with muscarine it was prominent to a greater degree.

Fig. XVIII.



The absolute heights of the twitches during poisoning with atropine are greater than in the unpoisoned state. How large the difference can be, is shown in the following records, of which (a) was obtained before, and (b) after the poisoning with atropine (Fig. XIX).

Fig. XIX.



The dosages of atropine which are necessary to achieve these effects have to be called large (0.6 mg) in comparison to those which one has to use, according to Schmiedeberg, in the intact heart. In all other respects the atropine-poisoned heart behaved like the unpoisoned one.

D. Solution of Delphinin in rabbit serum[4]

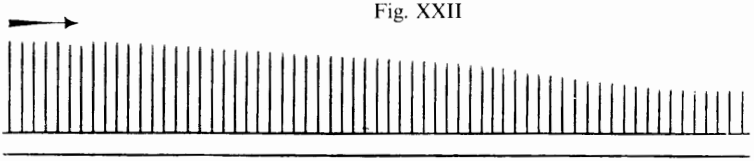
[4] Bowditch reported at length on the arrhythmogenic properties of this alkaloid, and on its effects in raising the electrical threshold for stimulation and eliminating the *Treppe*. In view of its limited interest this material, together with two figures has been excluded. The cardiac actions of delphinin can be found in: Bowman, W. C. & Rand, M. J. (1980). *Textbook of Pharmacology*, Blackwell Scientific Publications, Oxford. Second edition, p. 2254. The deleted text and figures are contained in the original translation (see footnote p. 31).

E. Changes of temperature

In earlier experiments, especially of those of Cyon (1866) it is known that with increasing temperature, the extent and working capacity of ventricular systole in the intact heart decreases. Whether this is due to a change in the natural endogenous cardiac stimuli, or the excitability of the muscular substance is unknown. From a study of the apex behaviour of the heart under the application of a constant and maximal stimulus, the opportunity arose to try and prevent the usual decrease of the twitch caused by atropine.

With increased temperature, the twitches decreased in height in spite of the maximal stimuli. The rule according to which this occurs resembles the one which is underlying the increase in the extent of the twitches with the staircase. A line which is connecting the upper points of the consecutive twitches results in a slightly bent curve which turns its concavity towards the abscissa, see Fig. XXII.

Fig. XXII



Application of atropine had no positive effect. During temperature increase, the heart that had been poisoned by atropine behaved exactly like the unpoisoned one. Measurements in the warmed heart are more difficult as the serum loses its recuperating property. In a series of experiments in which one started with a low temperature, increased the temperature and returned to the original one, the result is that the twitch with the renewed cooling of the apex of the heart, does not return to the same height which it showed before the warming. The twitch reaches its former height only if the old serum has been replaced by fresh.

F. Ligature of the atrium

From the experiments of Coats (1869) it is already evident that electrical stimulation of the ventricle during excitation of the vagus leads to smaller twitches.

With my improved equipment it seemed of interest to me to study if, by means of the regularly recurring electrical stimulus in a heart whose inhibitory nerves were excited, the phenomenon which we called *Treppe*

could be induced. I suppressed the inherent twitches of the heart by a ligature around the atrium and stimulated the ventricles at regular intervals. *Treppe* could be produced which was similar in appearance to that in the muscarine-poisoned heart. In one case for example, it required 54 beats, at 2 second intervals, to increase from an initial twitch of 2 mm to the maximum of 17 mm. I could not follow this promising experiment any further because of lack of time.

To what extent are the results described above suitable to advance our thinking about the processes in the inside of muscle fibres and especially in those of the heart?[5]

1. The interdependence of the size of a cardiac twitch on the number of the preceding contractions, and on the interval between it and the preceding twitch, (the phenomenon of fatigue by work and its recovery by rest) is similar to findings in other muscles, if the heart is either filled with sodium-chloride gum solution or has been poisoned with atropine. This could be explained by the supposition that in the surviving muscle, there is a certain store of a substance from which, in the time between two twitches, a limited amount is transformed into such a state that on the introduction of a stimulus a twitch is produced, and that substance is used for work. Both the rate at which this alteration of the mass proceeds and the maximum force produced by this alteration, depends upon the stored amount of that transmutable substance, for not only does the extent of the twitches decline compared to previous twitches, but also, at longer intervals the original height of the twitch can no longer be obtained.

Such presuppositions do not suffice, however, to explain the characteristics which the ventricle shows when filled either with serum intoxicated with muscarine, or under vagal stimulation. But this very explanation is incompatible with the observation that, up to a certain limit, the size of the twitch declines with the duration of the interval. Since the heart muscle gains in its twitch capacity during a period of rest, one has to postulate for the observations during stimulation of the vagus nerve, poisoning with atropine, etc, that during the pause where there is no twitch (in contrast to the circumstances which increase the extent of contraction), factors develop which try to decrease the size of twitch. These later influences might be best compared with the influence of friction, because by their appearance, the occurrence of the twitch is not impeded, but only its

[5] In what follows (the 'Discussion'), we present as precise a translation as possible. Where ambiguities arise about which preparation is being referred to, they cannot be resolved from the original text.

excursion will be diminished. Hence, we could say each twitch would result from two directly opposing influences, an accelerating and an attenuating one.

Further information about this reduction in twitch height can be obained from regularly repeated stimulations. In an executed twitch, the attenuating circumstances will partly be destroyed, and in the recovery period be restored, so that the fatiguing and the recuperating influences are valid for the attenuating, as well as the accelerating influence, the difference being that the recovery of the first progresses more slowly than the latter; in consequence of this, the extent of the twitch increases with declining stimulation intervals. The strength with which the influence of the attenuation is brought to bear increases considerably under the conditions that are made probable, if not definite, by the support of a stimulation of a nerve; should this stimulation (similar to the one which leads to an increase of the excursion) be a triggered movement? If the conditions which produce an attenuation have developed to a great extent during a long period of rest, it can only be countermanded by a series of twitches to the size with which they are otherwise effective, at a given interval. This is a complete analogy to the time that the ordinary muscle needs to recover. If the cardiac muscle, due to continuously increasing number of twitches, is progressing towards death, the accelerating and decelerating influences will disappear to the same extent and the size of the twitches can be influenced in the same direction.

Because the development of the attenuating conditions in heart muscle can only be observed under certain circumstances, it remains doubtful on one hand, if the normal heart can develop them. Not all cross-striated muscles show them under certain conditions. Evidence for attenuation has been shown from the phenomena observed by Wendt (1859)[6] which have been described as secondary modification.

2. The induction current of the smallest strength which can evoke a cardiac twitch, does not cause the weakest of all twitches, and twitch height does not reach an unsurpassable maximum if the intensity of the stimulating current is increased. In our experiments, the induction current either induced a twitch or not; and if it did so, it provoked the most extensive twitch which that induction current could produce. The reason why the apex of the heart contracts to a different extent lies in the variable properties of the muscle fibre itself.

[6] This is a reference to a point which was (and is!) controversial, namely the influence of experimental conditions on the scale of force–interval effects.

3. If an induction current exceeds a so-called maximal limit, it will provoke a twitch in ordinary cross-striated muscle as often as it is applied; in the heart, however, this is only possible when the current is increased considerably beyond that needed to produce a twitch. One could say that, by the differences between the intensities of the adequate to the unfailing stimulus, the heart possesses some kind of a replacement property, which is that it can increase, within certain limits of the strength of current, from the minimal to the maximal extent of its twitch. By proposing such an analogy one has to beware of the fact that factors affecting the reliability of an induction current in producing a twitch are not simple. The present observations make it clear that a stimulus of only adequate strength, and at long intervals (seconds) was sometimes effective and sometimes not, but no external cause for these differences could be seen.

Therefore, we were left with the assumption that the excitability of the heart does not represent a state of equilibrium, but that it is a swiftly changing event, since the degrees of excitability towards the weaker stimuli can appear and disappear like waves, which rise and fall in an irregular sequence over the constant level of the unfailing stimulus. This variable sensitivity was in contrast to the reproducible effects produced by the unfailing stimulus. In these circumstances, the intensity of the induction current did not have to be increased, even when twitch height had decreased either due to poisoning with muscarine, or fatigue. The only change which occurred fairly frequently was when the unfailing stimulus was near the lower strengths of current, and the heart had performed a larger number of beats of equal intervals. With a longer period of rest, the sensitivity declined which was attenuated by a series of twitches. From these observations, the following consideration was proposed:

stimulation of the vagus, ligature of the atrium and poisoning with muscarine provoke in the intact heart, two series of phenomena: (i) a loss of contractions and (ii) a decrease of the size of those which can be generated. Can both of these have the same cause? The loss of the twitches can be explained in two different ways; either by the fact that the sensitivity of the muscle fibre to the stimulus is getting smaller, so that a stimulus which was previously unfailing becomes only adequate, or by the fact that the stimulus itself is losing strength. Since during poisoning with muscarine the induction current did not have to be increased in order to stay unfailing, it would appear that the second of the mentioned possibilities is more plausible. Notwithstanding this, we have to allow that the induction current as a stimulus has many properties, which are dissimilar

to natural cardiac stimuli, and furthermore, that in my experiments it was not possible to grade the stimuli finely enough.

4. Since the normal apex of the heart does not contract spontaneously, it is justified to assume that endogenous cardiac stimuli originate in the atrium or in the atrio-ventricular groove. In the delphinin-intoxicated heart, however, the apex of the heart shows inherent twitches, which seem to be similar to normal heart beats in terms of their energy and time course, and the more or less regular sequence. Therefore, it would appear that the apex of the heart, by incorporation of a trace quantity of delphinin, can be transformed into a 'normal heart'. Whether indeed, the endogenous stimuli which excite the delphinin-intoxicated apex of the heart are identical, or not, to those which originate from the atrium, cannot be decided. However, it is again evident that cardiac muscle is essentially different from the usual cross-striated muscle in so far that the cross-striated muscle will develop a long-lasting tetanus if poisoned by delphinin (Weyland, 1870), but will not show any kind of endogenously caused twitches.

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Weyland (1870), In Eckhard's contribution Vol. V, pp. 51 and 68.