WAVE-LIKE VARIATIONS IN MUSCULAR FATIGUE CURVES

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(*From the Wellcome Physiological Research Laboratories.*)

FROM time to time there have been noticed in muscular fatigue curves certain oscillations of the summit line, for which no definite reason could be assigned. The present work was undertaken in consequence of the accidental discovery of a means by which such oscillations could be produced at will.

When the work had been practically completed it was noticed that Robert Müller[1], following Wedenski, had observed certain variations, somewhat similar to the present ones, in frogs' muscle fatigue curves, when short periods of tetanus were used. No other reference has been found in the literature on the subject to any similar phenomenon in fatigue curves.

Method. In most cases the gastrocnemius muscle of the frog was used. The animal was pithed. A pin was passed through the knee-joint and formed one of the electrodes, and also served to fix the muscle to the frog-board. The other electrode consisted of a very fine flexible copper wire, sewn through the tendo Achillis; this gave perfect freedom of movement to the lower end of the muscle. A thread was tied to the tendon, and passed round the larger wheel of a vulcanite pulley lever; the weight was hung on a smaller wheel on the same axle. In this way the tension on the muscle was very approximately constant at each stage of the contraction and relaxation.

If the muscle was to be treated as isolated, the femur and overlying muscles were cut through and the tibio-fibula also severed a short distance below the knee-joint, leaving the gastrocnemius muscle alone covered with a "trouser" of skin.

If the muscle was to be left in the "circulation," the foot was fastened by passing a pin through it into the frog-board. The lever was not supported, and usually the whole tension on the muscle, including

[1] Robert Müller. *Pflüger's Arch.* CVII. p. 297.

the weight of the lever, was 20 grms, and the magnification about 15 times; the reduction of the figures is given in linear measurement.

In most cases one dry cell (about 1·3 volts) was used for the electrical stimulation. Break induction shocks at regular intervals were obtained by means of a Brodie sector interrupter[1], rotated by an electric motor. From this the secondary wires led to a du Bois key, which could be used to short circuit the stimuli, when necessary. The induction coil was of the ordinary type.

By these means it was possible to obtain a series of stimuli of the same intensity and at regular time intervals, which could be varied at will. An uninterrupted series of contractions of a frog's gastrocnemius muscle under such conditions with constant temperature, showed a very smooth, regular, summit line.

When any experiment was made under special temperature conditions, the requisite temperature was maintained by arranging the muscle in a cardboard box, waxed with paraffin, and warmed inside by means of water flowing through glass tubes: a small hole allowed the thread to pass out to the lever. A similar arrangement was used when the experiment was to be made with gases other than air, a stream of the gas being driven into the box more than sufficient to counteract any escape of gas or inlet of air at the hole where the thread passed out to the lever.

The phenomenon in its most typical form is seen when a muscle is stimulated directly with break induction shocks, interrupted at regular intervals. With stimuli at the rate of about 20 per minute and short-circuiting of 6 stimuli after each period of 30 efficient maximal stimuli, whilst the muscle is still fresh and unfatigued, the first contraction after a pause is smaller than the last one before the pause, and during the period of excitation the summit line gradually rises. But after the top of the ordinary treppe has been reached, *i.e.* after about six such periods of excitation, the first contraction after a pause becomes somewhat larger than the last one before the pause; then the summit line dips down slightly and then rises again. After this at each successive period of excitation the initial height after a pause becomes more marked, and there is not only one trough, but crest and trough succeed one another in gradually decreasing size whilst the excitation continues.

During the subsequent periods of excitation the first "wave" grows in comparison with succeeding ones until eventually when the muscle

[1] This *Journal*, XIX. *Proc. Phys. Soc.* p. x. 1896.

is much fatigued, the initial increase in height and the first wave alone are visible.

During the latest stage of fatigue, the only evident effect of the pause is the initial increase.

One experiment given in detail will suffice to give some idea as to the time relations (Fig. 1): gastrocnemius muscle in circulation, arrangement as described above; break induction shocks at intervals of 2·6 secs. giving maximal contractions; recorded on slow-moving drum; six stimuli short-circuited after each period of 30 contractions. Twelve preliminary contractions recorded to determine adjustment; then proper record started.

1st Period. The summit line is rising slightly; base line falling rather more rapidly; rapid contraction and relaxation.

2nd Period. First contraction somewhat smaller than last of 1st period; summit line rising; base line still gradually falling; contractions rapid.

3rd Period. Same as 2nd period; but rise in summit line less marked; relaxations becoming slower at end of period.

Base line falls slightly during interval.

4th Period. Summit line practically level; relaxations becoming somewhat slower. Base line falls distinctly during interval.

5th Period. First contraction still somewhat smaller than last one of previous period; summit line rises at first but towards the end of the period commences to fall slightly; marked slowing of the end of relaxations.

Base line fall during interval is becoming more marked.

6th Period. First contraction is slightly larger than last before interval; gradual fall during first four; after fourth there is a slight rise and then a gradual fall till the end of the period; end of relaxations slow.

7th Period. First contraction markedly higher; gradual fall to 4th, which is the smallest; then gradual rise for four; then a more gradual fall.

8th Period. The initial height after rest and the gradual fall to the 4th summit are more marked, but after the next rise there is a second smaller fall and rise.

9th Period. Initial height becoming more marked, as also the fall to 4th summit; and four subsequent rises with intervening falls are noticed, the last crest being reached at the 30th contraction.

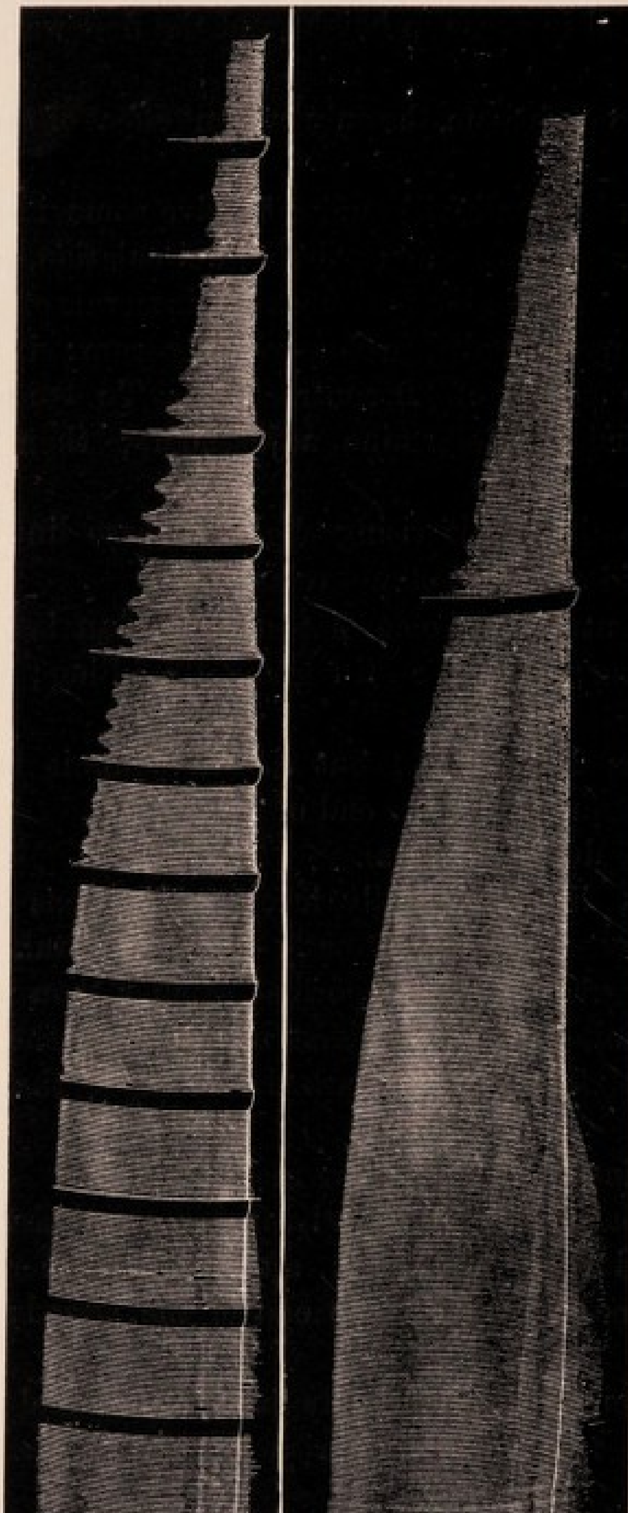


Fig. 1. Reduced × ⅓. Frog's gastrocnemius in circulation; direct stimulation at intervals of 2·6 secs.; isotonic lever giving about 15 times magnification; total load 20 grms.: six stimuli short-circuited after each period of 30 contractions.

Fig. 2. Reduced × ⅓. Corresponding gastrocnemius from other leg of frog used in Fig. 1; same conditions of fatigue but no short-circuiting until after 365 contractions, then six stimuli short-circuited.

10th Period. Same as 9th, except that the waves are still more marked.

11th Period. Excitation continued for 33 contractions, the initial height has become very marked, the waves are slightly slower than during earlier periods; the base line shows some variation due to contraction remainder.

12th Period. Initial height is still more marked; the waves grow markedly smaller after the first one.

13th Period. Excitation continued for 55 contractions; initial contraction is 29 mm. in height, whereas the fifth is only 14 mm., the largest of the whole series produced by the muscle being 40 mm. The gradual subsidence of the waves is also marked, the fifth crest being only just visible.

14th Period. Large initial contraction, but all waves are very small; the general height of the summit line is constant.

15th Period. The size of the initial contraction is still remarkable; but the waves have almost completely disappeared. Record stopped.

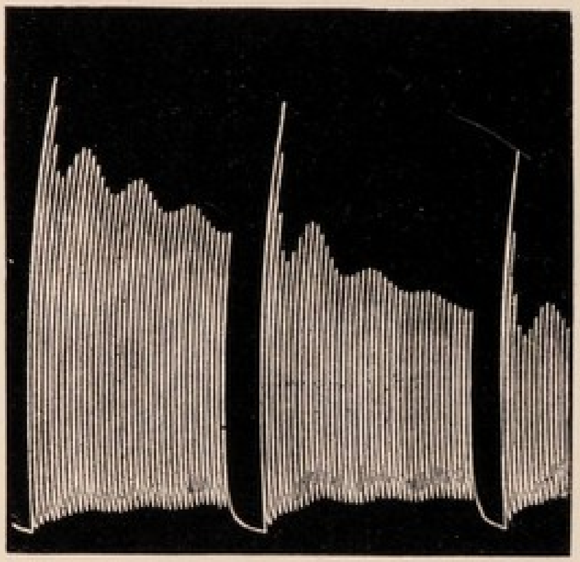
The muscle from the opposite leg of the same frog was subsequently prepared and stimulated in exactly the same way by the same apparatus but no pause was made until 365 contractions had been recorded. At this time the summit line had fallen considerably (Fig. 2) and there was the usual slowing at the end of relaxation, leaving some contraction remainder. The summit line had so far shown no rapid variations. At this stage a pause was made for a period of six stimuli. After renewal of excitation the initial contraction was 32 mm., whereas the last one before the pause was 24 mm. The subsequent waves were produced as in the other muscle, four crests being visible, showing gradual decrease in size. After the fourth, which was very small, the summit line again became smooth and gradually sank.

Thus if instead of the pause being repeated, the excitation be continued without further interruption when once the waves are produced, it is seen, as in Fig. 2, that the waves gradually become smaller and disappear; but a second pause will evoke them again.

Fig. 3 shows a small portion of an interrupted curve, giving waves in greater detail. In certain cases of curves which have been interrupted for short periods at regular intervals, the base line, during the short-circuited periods, rises at first, and later in the fatigue becomes horizontal, and then, still later, gradually falls. The waves in these cases begin to appear at the time when the base line during rest begins to fall, and become more pronounced when the fall becomes more rapid.

The independence of the phenomenon from any possible rhythmical changes in the exciting stimuli is shown by interposing a corresponding muscle for short-circuiting purposes, instead of using the du Bois key; and also by recording the contractions of two muscles at different temperatures, stimulated in series. In the second case, as will be seen later, the waves are produced at different rates in the two curves.

Interference with the circulation appears to have no effect on the production of the waves, since experiments with a pair of muscles, one in circulation, and the other isolated, give results which resemble one another in almost every detail.



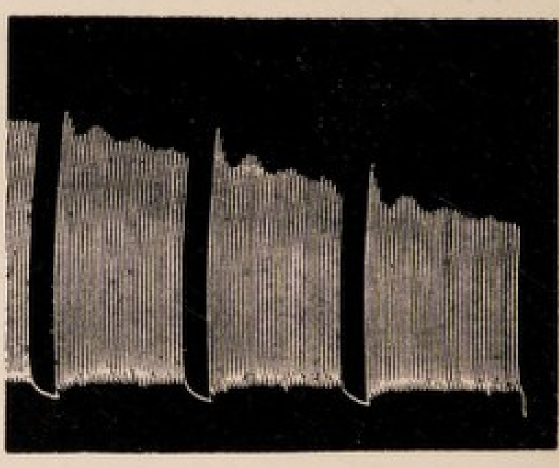


Fig. 3. Small portion of curve produced under similar conditions to those in Figs. 1 and 2.

Fig. 4. Frog's gastrocnemius in circulation: indirect excitation by means of the sciatic nerve: other conditions as in Fig. 1.

It was next shown that the waves could be produced equally well after sufficient curare had been administered to paralyze the nerve-endings completely: thus the phenomenon is certainly muscular or is shown by some structure which is peripheral to the seat of curare-action, though, as before mentioned, it can be evoked during excitation of the muscle through the nerve. This latter method does not however yield good results, as it has not been found possible to obtain the necessary regularity in the summit line, owing probably to variations in the nerve or nerve-ending. Fig. 4 however shows an exceptionally good result obtained with indirect excitation.

In view of the results with curare it was considered unnecessary in subsequent work with direct excitation to administer this drug.

A considerable number of experiments were made with the conditions as in Fig. 1, *i.e.* with stimuli at the rate of about 20 per minute and a pause for a period of six stimuli. But such a pause and such a rate of stimulation are not essential. If only one stimulus be omitted, the waves are quite evidently shown (Fig. 5) without appreciable alteration of wave length.

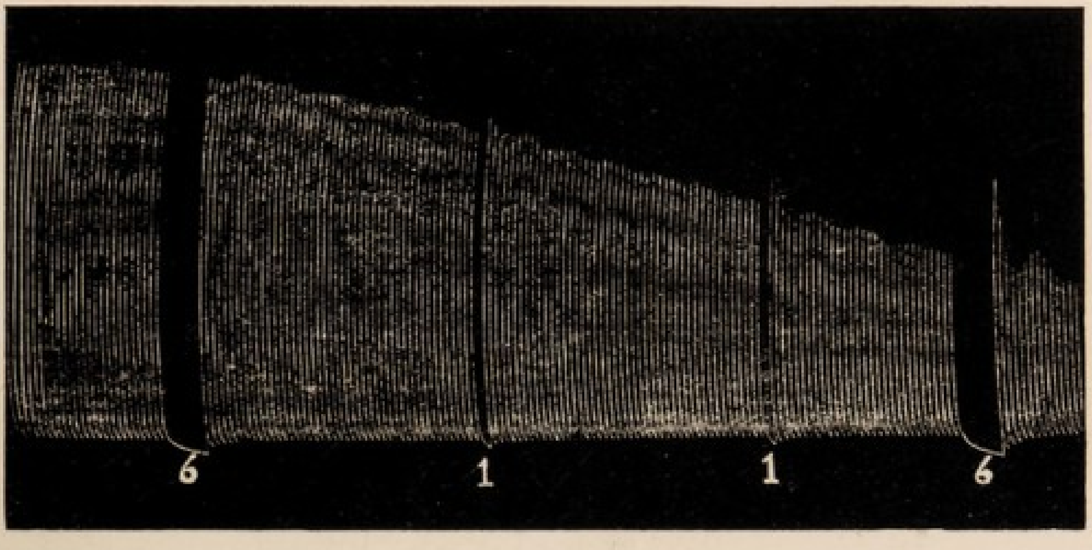


Fig. 5. Isolated frog's gastrocnemius; direct stimulation; stimuli short-circuited for different periods as marked.

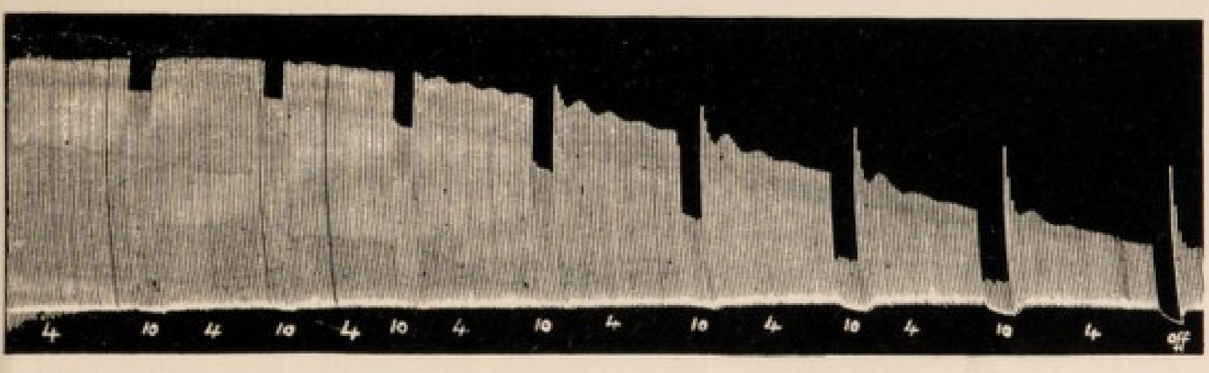


Fig. 6. $\times \frac{2}{3}$. Isolated frog's gastrocnemius; direct stimulation; position of secondary coil as indicated, the numbers giving the distance in cm. between secondary and primary coils; the intervals at 10 cm. represent sub-maximal contractions; those at 4 cm. were maximal when the muscle was fresh.

This method of pauses provides the muscle with time for recovery between each active period, and as the contractions during activity were maximal, it was thought that, by replacing the pauses by periods of sub-maximal contractions, the waves could still be produced. This was shown to be the case, and not only did the waves appear during the maximal periods, but also showed signs of appearance during the sub-maximal periods (Fig. 6). An attempt to carry through the whole fatigue with sub-maximal stimuli and to produce the waves by pauses in such a series was unsuccessful, as it was found impossible to maintain a regular summit line, the irregularities being presumably due to variations in the actual muscle fibres which were excited and so fatigued, some being involved in the case of one stimulus and escaping at the next. Furthermore, if, instead of pauses, the weight lifted by the muscle be reduced for definite periods, waves appear in the summit line at the usual stage of fatigue both during the light and the heavy work periods, but tend to disappear first from the former (Fig. 7).

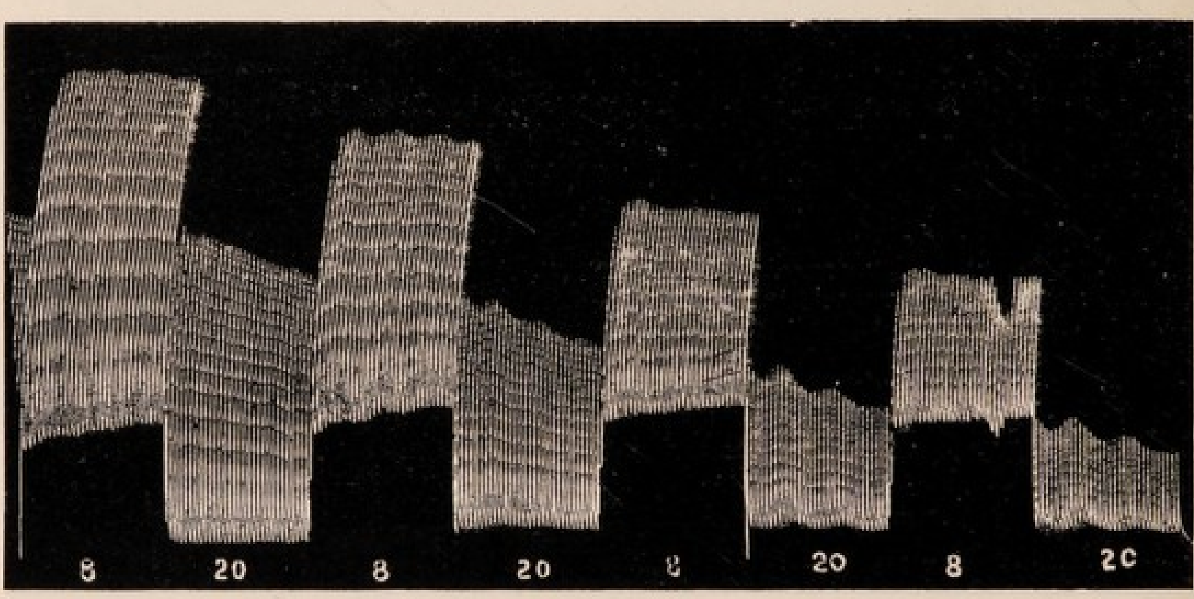


Fig. 7. Isolated frog's gastrocnemius; direct stimulation at intervals of 2·5 secs.; contractions maximal; periods of 30 contractions with load of 20 grms. between similar periods with load of 8 grms.

In the above cases an alteration in the amount of work done by the muscle in a definite time evoked the summit line variations.

If the same alteration be made by increasing the number of contractions in a definite time, the same effect is produced. For example, if one minute periods of stimuli at intervals of 1·1 sec. be alternated with one minute periods of stimuli at intervals of 2·1 secs., waves appear on the summit line at both rates of stimulation, varying in wave length, as will be seen later, with the rate of stimulation (Fig. 8).

From the fact that in these cases the waves appear on the summit line of both periods, it was natural to conclude that the mere alteration from one rate of work to another, without return to the original rate, was sufficient to evoke the waves, and on experiment this was found to be the case. A muscle was fatigued with a weight of 15 grms.

until the stage was reached when waves could be produced if a pause were made; then a 10 grm. weight was removed and the muscle was allowed to contract with the lighter load. Waves at once appeared in the summit line.

This fact, that mere alteration from one condition to another is sufficient, may perhaps account for the occasional occurrence of the waves on the summit line of a fatigue curve produced under apparently constant conditions. It seems possible that at a late stage in the fatigue an unnoticed alteration takes place in the rate of stimulation and so evokes the variations.

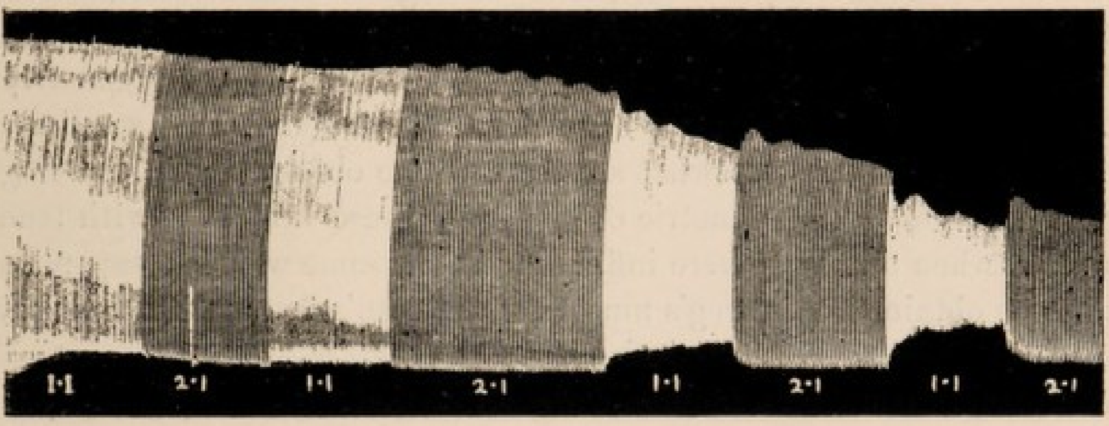


Fig. 8. ×¾. Isolated frog's gastrocnemius; direct maximal stimulation; periods of stimulation at intervals of 2·1 secs. between periods at intervals of 1·1 sec.

It was found rather difficult to ascertain whether mere alteration in temperature would be sufficient to produce the variations, since any such alteration in the temperature of the muscle itself must be gradual, and alteration in the other conditions, to be effectual, must be fairly rapid. But evidence was obtained which showed that the momentary application of 0·6 % saline at 40° C. to the surface of the muscle would evoke the variations in some slight degree.

A repetition of Müller's method of stimulation by means of short periods of tetanus produced similar results to those obtained by him, except that in these cases the wave time was shorter than in his curves. This was to be expected since these experiments were done in summer at ordinary room temperature, whereas he used cold frogs. He states that with warm frogs he was unable to obtain the required result, merely obtaining a slight indication. Also for the same reason as above he was unable to see more than one or at most two waves, whereas with warm frogs several can be produced in succession.

Under isometric conditions, using an ordinary isometric lever and the usual rate of stimulation with pauses, the waves are again clearly shown, though perhaps in a somewhat less marked degree.

Other muscles of the frog, besides the gastrocnemius, have also been used. The gracilis-semi-membranosus preparation gives the same result as the gastrocnemius. But no result has been obtained with sartorius or hyoglossus. The former merely gives an initial rise in the summit line after each pause. As the heart showed the treppe so clearly it was thought possible that a positive result might be obtained with this muscle. But no result was obtained with an isolated quiescent ventricle preparation from the frog.

In most of the experiments summer frogs have been used, but the variations have also been obtained with muscles from winter frogs in March and November. The toad's gastrocnemius has also been tried. In most cases no waves were obtained: but in some cases small slow variations appeared, somewhat similar to those obtained with the frog's gastrocnemius under isometric conditions. These variations with toad's muscle, when obtained, were influenced in the same way by temperature as those obtained with frog's muscle. The toad's sartorius did not give any evident signs of the variations.

Certain mammalian muscles have been tried; guinea pigs and rats, under urethane or pithed, were used. But it was found somewhat difficult to get a smooth summit line. However, in one case, with a gastrocnemius muscle from a pithed rat, fatigued in the usual way, definite traces of waves were obtained.

The best results were always obtained by using the gastrocnemius of the frog and the method of pauses. Hence these means have been used to investigate in greater detail the production of the waves in relation to temperature, rhythm, and various reagents.

With constant temperature, tension and rate of stimulation, the time for one wave-length is approximately constant for each particular stage of the fatigue curve. There is a considerable tendency for the waves to become slower in the later stages of fatigue, especially when the muscle is under abnormal conditions such as an atmosphere of carbon dioxide.

With increasing temperature the wave-time decreases, until at about 30° C. no waves can be evoked. The following figures are from some experiments in which the temperature variations were carefully measured, the initial wave after a pause being the only one reckoned in each case.

From the figures given it will be seen that for any particular rate of stimulation the wave-time decreases as the temperature rises.

TABLE I. *Variations in wave time at different temperatures; isolated gastrocnemii of frog.*

No.	Temperature C. Air	Skin	Interval between stimuli	Wave-time
1.	23·5°	—	2·6 secs.	10·4 secs.
2.	20·0	—	2·6	16—18
3.	19·0	—	2·6	about 18·2
4.	—	14°	2·6	21—23
5.	—	13·5	2·6	26—28·5
6.	24·5	22·3	1·7	11·2—14·6
7.	22·2	19·5	1·7	12·9—16·3
8.	24	21·5	1·3	9·6
9.	21	18·5	1·3	11·7

If, however, the temperature be kept constant and the rate of stimulation altered, the wave-time appears to increase with an increase in the interval between the stimuli and decrease when the stimuli become more frequent. The figures given are as accurate as it was found possible to make them, but in estimating the position of the top of the crest it is not possible in most cases to say that it is exactly at the time of some particular contraction, and it seems more accurate to say that it is between some two or three contractions, and to take the mean time.

In this case two isolated gastrocnemii were taken from the same frog and stimulated in series. No. 1 was in a box warmed to 24·5° C., giving a temperature under the skin of 22° C., and No. 2 was in air at room temperature 21·5° C. and skin temperature 19° C.

TABLE II. *Variations in wave-time with different intervals between the stimuli; isolated gastrocnemii in series; No.* 1 *at* 22° *C.; No.* 2 *at* 19° *C.*

Intervals between stimuli	Wave-time No. 1	Wave-time No. 2
1·25 secs.	9·7 secs.	14·2 secs.
2·55	13·8	17·4
3·8	15·2	21·2
1·25	9·7	13·9
2·55	12·3	16·4
3·8	15·2	19·0
2·55	11·8	15·6
1·25	8·4	13·5

A number of experiments have been made in which the muscle was made to contract in various gases, namely oxygen, hydrogen, and carbon dioxide. In all cases the waves appeared as usual. With oxygen fatigue was delayed so that it was necessary to carry on the stimulation for a longer time before the proper stage of fatigue was reached. With carbon dioxide the waves appeared early and were at first small and rather abnormally rapid. The change in wave-time as the fatigue progressed was very marked. No experiment has been made with nitrogen, but in Fletcher's paper[1] on the oxygen-exchange of muscle during fatigue a tracing is given which shows a record of the contractions of a frog's gastrocnemius in pure nitrogen and there it is quite possible to see the first wave.

Attempts were made to modify the phenomenon by perfusing the muscle with various solutions. This was carried out by means of a cannula tied into the bulbus arteriosus, the gastrocnemius being left in the circulation and made to contract during perfusion. Before perfusion the other leg was tied off and its gastrocnemius used as a control.

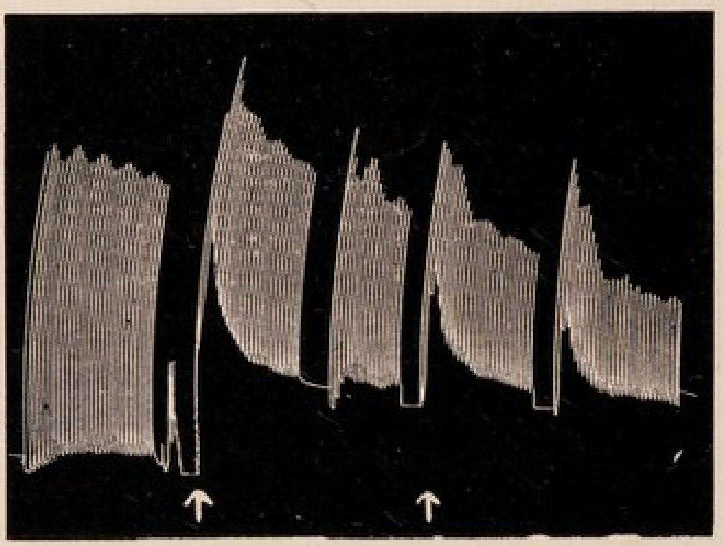


Fig. 9. $\times \frac{2}{3}$. Isolated frog's gastrocnemius; direct maximal stimulation; 0·1 % veratrine hydrochloride directly applied to the muscle at points marked with an arrow.

Perfusion with 0·05 % paralactic acid in 0·6 % saline appeared to hasten the onset of the waves as compared with the control leg; but this was to be expected since paralactic acid induces more rapidly the other evidences of fatigue. A similar result was obtained on perfusion with 0·1 % mono-potassium phosphate in 0·6 % saline.

The results obtained after the injection of veratrine are of interest. An injection of 0·1 mgm. of veratrine hydrochloride into the dorsal lymph sac of a frog produced a well-marked characteristic result in a few minutes. The animal was then pithed and the gastrocnemius on one side isolated. Stimulation was made at intervals of 2·6 secs. and

[1] This *Journal*, XXVIII. p. 490, fig. 7. 1902.

gave at first a typical veratrine contraction and then single fast twitches. The base line showed a very rapid rise and fall, but subsequently although fatigue was somewhat rapid the waves were shown very clearly.

In another case the fatigue curve was started with the non-poisoned muscle and then a solution of 0·01 % veratrine hydrochloride in 0·6 % saline was applied at the stage of fatigue when waves were appearing. The base line rise took place, but at the same time the waves appeared at a different rate to the base line contraction and were superposed upon it (Fig. 9).

In certain cases where the rate of stimulation was rapid, the base line showed variations which had the same wave-time as the summit line variations, but occurred very slightly later than the latter, the summit line reaching the crest of a wave a few contractions in advance of the base line crest (Fig. 10).

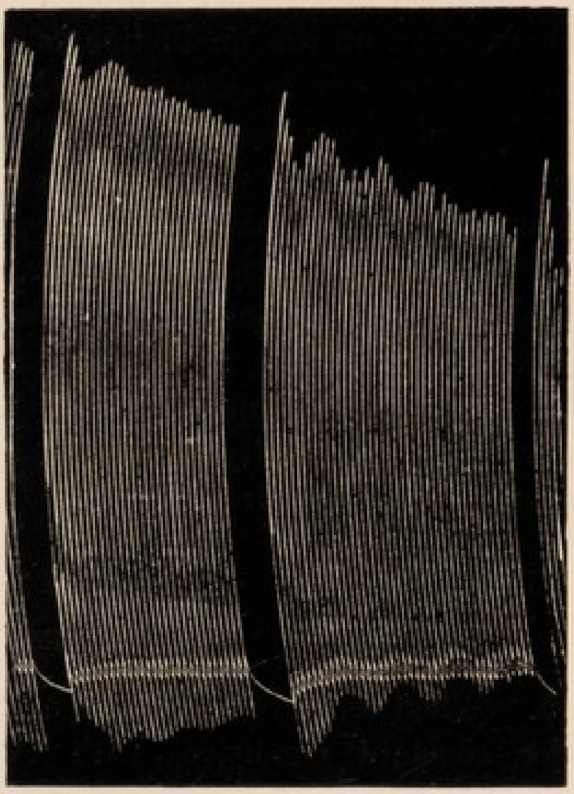


Fig. 10. Isolated frog's gastrocnemius; direct maximal stimulation at intervals of 2 secs.; showing waves in base line.

Fig. 11. Isolated frog's gastrocnemius; direct maximal stimulation; large magnification and small load; regular waves on throw-down line in spite of irregularities in summit line waves.

It might have been concluded that the summit line variations were due to varying amounts of contraction-remainder, causing a varying support of the lever at the beginning of each contraction. This seems hardly adequate to account for the change, since if the lever be supported at different levels by means of a stop, during the production of the waves no apparent change is induced. Also if a support be used throughout the interrupted series of contractions, a stage can be reached, at which the initial contraction after a pause is able to lift the lever a considerable distance, then in the first trough the summit line sinks below the level of the support, but the following crest may rise just above this level, so that the tracing shows a short period during which no contractions are recorded.

In some experiments where the waves appeared early in the fatigue, at a time when the relaxation was still rapid and when there was thus a considerable throw-down of the lever below its stationary relaxation level, waves appeared on the line formed by joining the lowest points to which the throw-down carried the lever (Fig. 11).

Injections of cocaine, atropine, or supra-renal preparations were without effect on the production of the waves, as were also ether and chloroform vapour in quantities which left the muscle still excitable. And, indeed, it was found that, in the case of any muscle which would produce the waves when fatigued under ordinary conditions, the influence of no external agent, except extremes of heat and cold, could prevent their occurrence. In certain frogs the gastrocnemius would not show the variations; and this was also the case when there were marked irregularities in the summit line at the beginning of an experiment. For the appearance of the waves in the most evident form, constancy and regularity of excitation, combined with some fairly rapid interruption, are essential.

Summary.

1. When certain frogs', toads', and mammalian muscles are fatigued under constant conditions with maximal break induction shocks, temporary wave-like variations can be produced in the summit line during the later stages of fatigue, by any alteration in :

(*a*) load, (*b*) rate of stimulation, (*c*) temperature, and also by introducing short periods of rest or of sub-maximal stimulation.

2. These variations can be evoked in the frog's gastrocnemius in winter as well as summer animals, whether the muscle be in the circulation or isolated, whether the stimulation be direct or indirect,

under both isometric and isotonic conditions, and are not abolished by large doses of curare or by any such reagents or conditions as will leave the muscle still excitable.

3. The onset of the stage of fatigue at which the variations can be evoked, is hastened by such conditions as will induce more rapid fatigue in the muscle.

4. The time relations of the individual variations vary with the temperature and the interval between the stimuli.