On the Occurrence of Post-tetanic Tremor in Several Types of Muscle.

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Part I.

In 1901* I discovered that a frog's gastrocnemius which had been kept in complete tetanus, either by direct or indirect stimulation, would, if the stimulation were continued until fatigue had begun to manifest itself, fall into a state of obvious tremor. This tremor, whose average periodicity in

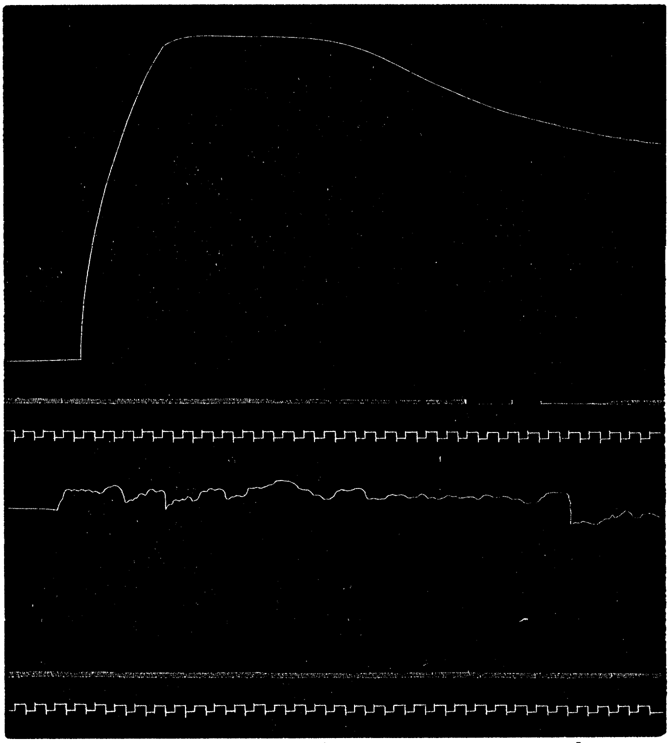

Fig. 1.—Gastrocnemius, frog. Indirect stimulation. 5 grammes close to axle of lever giving amplification of 14. Upper tracing, "complete tetanus" for about 25 seconds; lower tracing shows point of commencement of post-tetanic tremor. Periodicity at first 6 a second. Stimulation (Neef's hammer) is recorded above time in half-seconds. (Reduced to $\frac{1}{2}$.)

* D. F. Harris, 'Phys. Soc. Proc.,' March 1, 1903.

the frog's gastrocnemius is four to six a second, can be maintained unaltered as to its time-relations, but of slowly declining amplitude, for a relatively long time (half an hour).

Fig. 1 shows the smooth line of complete tetanus, breaking off into the post-tetanic tremor in the frog's gastrocnemius stimulated indirectly.*

On investigating as many animal types as I could procure, I found that a post-tetanic tremor could be demonstrated in man, cat, kitten, rabbit, pigeon, and frog, both with and without intact circulation, the mean periodicity of the tremor in all types being between two and six or eight per second.

An analogous tremor is elicitable in muscles of fish and lobster.

Fig. 3 is a facsimile of the tracing obtained by stimulating the human flexor sublimis digitorum by rapid induction-shocks.

After the time of complete tetanus is over, the muscle falls into a state of irregular tremor which in my own arm I caused to be maintained for half an hour, during which time it did not alter either in intensity or in average periodicity.

Sponge-electrodes were placed on two spots, an upper and a lower, on the fore-arm over the flexor sublimis digitorum. The middle finger had a ring slipped over its terminal phalanx, and from this a thread passed over a pulley to the spring of an ergograph.†

The interruptions here were 60 per second (30 makes and 30 breaks); and as there was previous independent evidence to show that the makes were subliminal, I may take it that 30 break shocks per second constituted the "stimuli."

The responses occurred with an average periodicity of four per second. The ratio of stimuli to responses is then 30 : 4 or 7·5 : 1, *i.e.*, 1 in 7·5 may be said to be the figure of physiological insusceptibility in this case. Obviously the muscle had its circulation intact.

[I may say that at the end of half an hour I experienced no sensation of fatigue in the muscle, but in the above and in all similar experiments on my own muscles the sensations of "the muscular sense" were quite distinct. A thrill corresponding to the rate of stimulation was perceptible.]

The next type of muscle I investigated was that in the cat. In one experiment, a young cat was pithed under a dose of A.C.E. mixture and artificial respiration done. The Tendo Achillis was fastened to a bell-crank lever, a 50-gramme weight being attached as near the axle as possible.

Direct stimulation of a muscle with intact circulation was kept up for

* The current in the primary circuit that was usually employed for tetanic stimulation was one of about 3·8 amperes (voltage 4·2).

† The "period" of this spring was 40 to 42 per second.

half an hour, at the end of which time, while the muscle was still irritable, it was so feeble that a weight of 20 grammes had to be substituted. The average periodicity of the tremor is three to five per second.

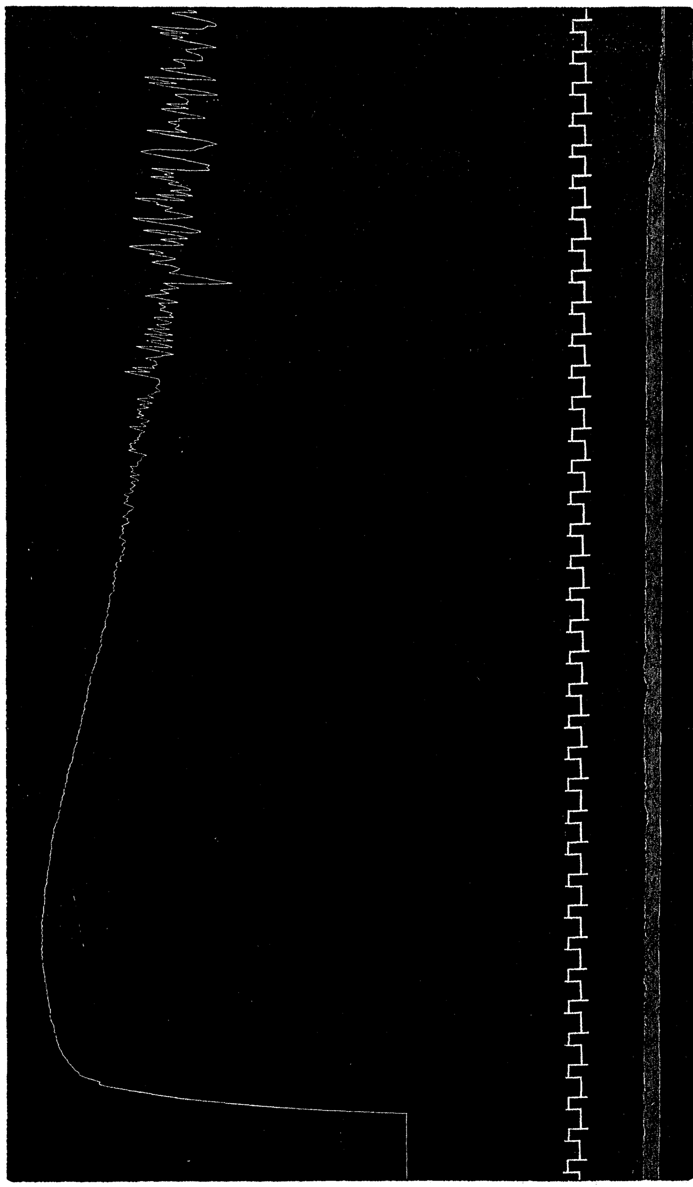

Fig. 2a.—Gastrocnemius, kitten. 10 grammes, same lever as in fig. 1. Stimuli from 100 a second tuning-fork in primary circuit, recorded below time in half-seconds. Onset of coarse tremor, 8 seconds from commencement of tetanus. Periodicity, 8; later, 5 to 6 a second. (With a lens a tremor can be seen during the complete tetanus, of periodicity 16 to 18 a second.)

In only one case, in mammalian muscle, did I obtain a rate slower than three to four per second, viz., one to two a second (fig. 4). Here the

gastrocnemius was attached in the usual way to a bell-crank lever which carried a 10-gramme weight.

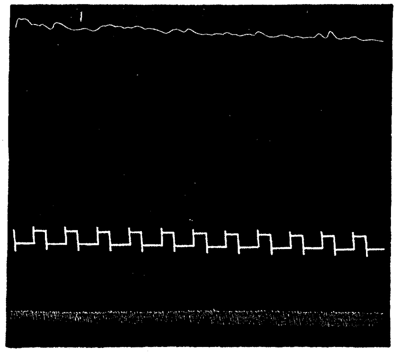

Fig. 2b.—Portion taken from middle of record of post-tetanic tremor several minutes after commencement. (Facsimile.)

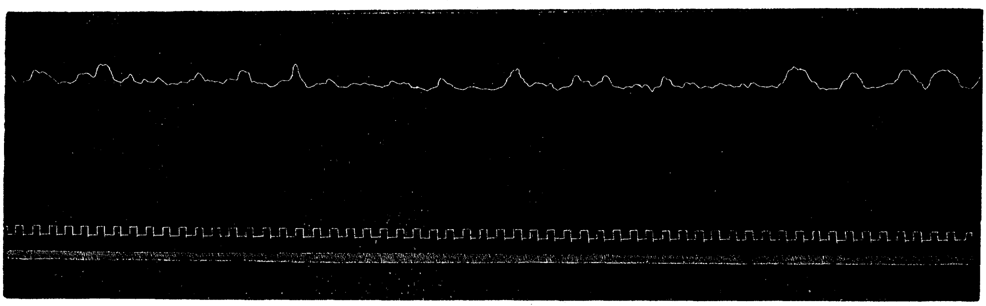

Fig. 3.—Flexor sublimis digitorum (homo); sponge-electrodes. Neef's hammer. Helmholtz side-wire in primary coil. Porter's ergograph-spring as recorder. Stimulation recorded below time in half-seconds. Tremor maintained for 30 minutes. Average periodicity 5 to 6 a second. (Facsimile.)

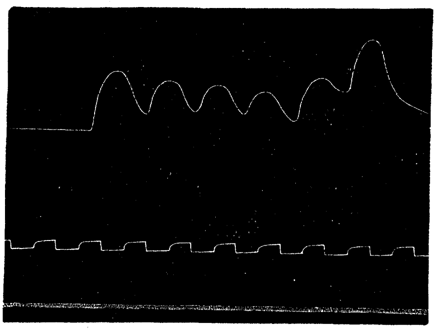

Fig. 4.—Gastrocnemius, kitten (pithed, artificial respiration). Complete tetanus (on direct stimulation) suddenly breaking off into post-tetanic tremor.

The animal was pithed, artificial respiration was used, and very little blood lost in preparing the muscle. With indirect stimulation, the muscle exhibited

complete tetanus for an unusually long time; several minutes after the stimulation had been made direct (owing to the onset of end-plate fatigue)

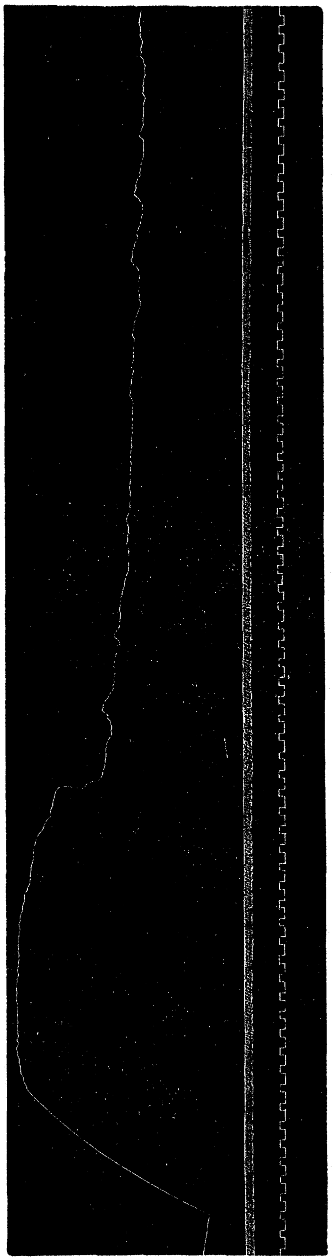

Fig. 5.—Extensor longus digitorum, pigeon, pithed. 20 grammes near axle. Lever as in fig. 1. Stimulation direct. Stimulation by Neef's hammer (side-wire), recorded above time in half-seconds. Tremor recorded for 20 minutes. Periodicity, 3 to 5 a second.

the tetanus was still complete, but after a few seconds more the muscle quite suddenly broke off into a tremor with a periodicity of about one or two per

second which, becoming rhythmic, was maintained of singularly constant intensity.

To investigate the post-tetanic tremor in the bird, I used the pigeon (pithed). The extensor of the toes was the muscle chosen: a cord from the tendon for the toe passed to a hinged lever weighted with 20 grammes quite close to the axle. Direct stimulation was maintained for 20 minutes; portions of the tremor during this time are reproduced in fig. 5. The average periodicity of the tremor is three to five a second.

In the case of the muscles of the fish, in some experiments I used those of the tail of the plaice or "spotted flounder" (*Pleuronectes platessa*), the fish being pithed. Considerable difficulty was encountered in fixing the very soft-fibred muscles to the recorder.

Using the hammer as interruptor, and direct stimulation, I obtained a tremor of about one per second, which could not, however, be maintained indefinitely; fatigue seemed to supervene with considerable rapidity; I found great difficulty in bringing out smooth complete tetanus at all: the tendency to tremor was present from the first.

When we used the muscles that close the jaw we obtained a tremor of a very slow periodicity, a shortening lasting about 1 second and occurring at irregular intervals of 3, 4, 5, or 6 seconds each.

In the case of the lobster (*Homarus vulgaris*), we used one of the flexors of the abdominal somites. The preparation was fixed by clamping a portion of the carapace in muscle-forceps and attaching the fibres of the muscle to a horizontal lever with a weight (10 grammes) very near the axle. The stimulation was, of course, in all cases direct, fine wires being led from the short-circuiting key in the secondary circuit directly into the muscle substance.

On submitting the muscle of the lobster to stimulation similar to that employed in most of the other types of muscle (viz., stimuli given by Neef's hammer, with side-wire), I failed entirely to produce complete tetanus; in other words, the muscle fell into a state of tremor from the very beginning of the stimulation.

This is very well seen in fig. 7, where, using a quite fresh flexor of abdominal somite, a violent tremor is elicited without any preliminary period of complete tetanus.

The periodicity of this tremor in the first second was nine a second, but, as fatigue set in, it fell to three a second.

Thus, although we cannot use the term "post-tetanic" of the tremor which appears in the muscle of the fish or of the lobster in consequence of stimulation by rapidly recurring (tetanic) stimuli (30 to 70 a second), never-

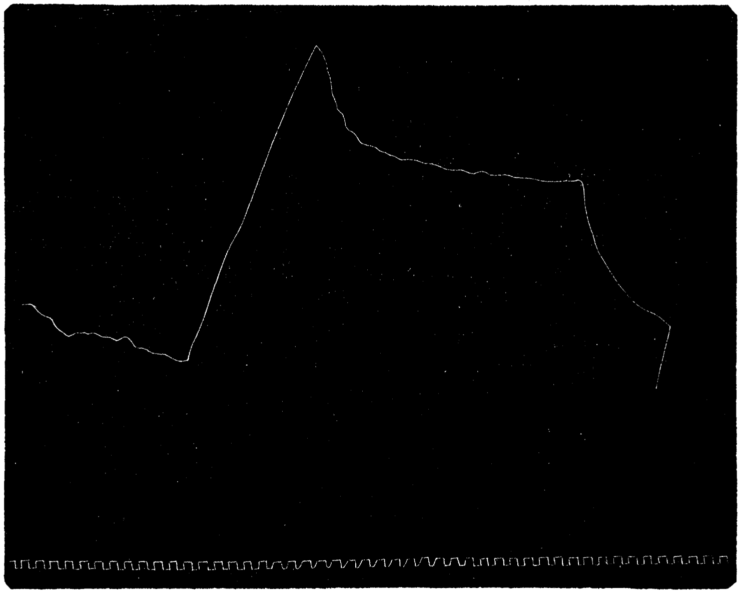

FIG. 6.—Tail-muscle of *Pleuronectes platessa.* 5 grammes near axle. Lever as in fig. 1. Neef's hammer, side-wire. Stimulation direct. Time in half-seconds. No complete tetanus. Tremor of periodicity, 1·5 to 2 a second.

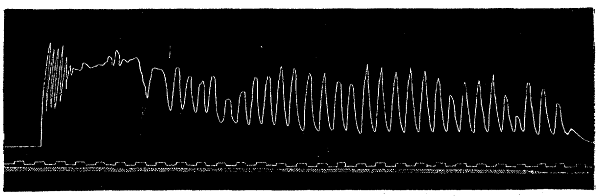

FIG. 7.—Muscle of abdominal somite, *Homarus vulgaris.* Lever as in fig. 1. Stimulation direct. Break-shocks only. 10 grammes near axle. Stimulation, given by Neef's hammer (side-wire), recorded below time in half-seconds. Tremor from commencement. Periodicity at first 9 a second, soon becoming 3 a second. (Tracing reduced to one-half.)

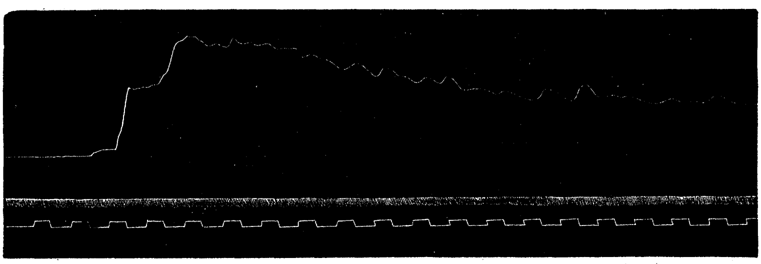

FIG. 8.—Tremor in a not quite so fresh muscle of lobster, average periodicity 4 to 5 a second. Stimuli at least 70 a second recorded above the time in half-seconds. Conditions as in fig. 7. (Facsimile.)

theless the time-relations of this tremor are comparable with those of the post-tetanic tremor of the higher muscular types.

Crustacean muscle is no exception to the universality of this phenomenon of slow tremor appearing in muscles subjected to "tetanising" stimuli; it possesses, in common with mammalian, avian, and amphibian muscular protoplasm, that property of functional insusceptibility in virtue of which it avoids exhaustion by falling into a state of comparatively slow "rhythmic" contractions.

Part II.—Analysis of Results and Theoretical.

(1) The first point that may be noticed here is that the tremor of post-tetanic onset is in its average periodicity *not* that of the tremor of the same muscle about to pass from incomplete to complete tetanus. *E.g.*, in frog's gastrocnemius the maximal rhythm of the incomplete tetanus (just before fusion to complete) is something between 25 and 28 per second,* while the "rhythm" of the tremor that follows spontaneously on a period of complete tetanus is about four to six a second. Instead of 25 to 28 responses per second, the muscle can now exhibit no more than five to six, or about one-fifth of the former.

Obviously, fatigue is the cause of this physiological insusceptibility; fatigue which, by preventing responses at anything like the rhythm of the stimuli (30 to 100 per second), prevents the early onset of complete *exhaustion.* This physiological insusceptibility may be taken as a protective mechanism against the fatal effects of full fatigue.

(2) The post-tetanic tremor is a myogenic phenomenon. It occurs in muscle directly stimulated, whether curarised or not, and a tremor indistinguishable from it is given by, *e.g.*, the dying diaphragm (fig. 10). For tremors of directly stimulated muscles, see figs. 2B and 3. For tremor of curarised muscle (toad), see fig. 9.

The so-called "spontaneous" tremor I was able to record for three quarters of an hour in the dying diaphragm of a pithed rabbit which had its phrenics cut. It is a tremor of about six per second average periodicity and, therefore, quite similar in time-relations to the post-tetanic.†

(3) While the periodicity of the post-tetanic tremor is rarely, during long periods, more than six per second, it is not of the same periodicity in all the muscles even of the same animal.

* T. G. Brodie, 'Elements of Experimental Physiology,' pp. 62, 63. London: Longmans, Green, and Co., 1898.

† D. F. Harris, "On the Time-relations of the Spontaneous Tremor of the Diaphragm," 'Phys. Soc. Proc.,' January 26, 1907.

Thus, while in the frog's gastrocnemius it is about six per second, in the hyoglossus it is only 2 to 2·5 a second; ratio 3 : 1.

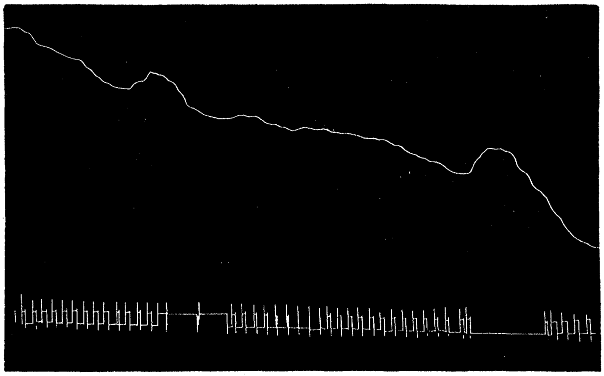

FIG. 9.—Gastrocnemius, toad, curarised. 5 grammes. Bell-crank lever. Stimuli by Neef's hammer (side-wire). Time in half-seconds. Tremor maintained for 15 minutes. Average periodicity, 2·5 to 3 a second. (Facsimile.)

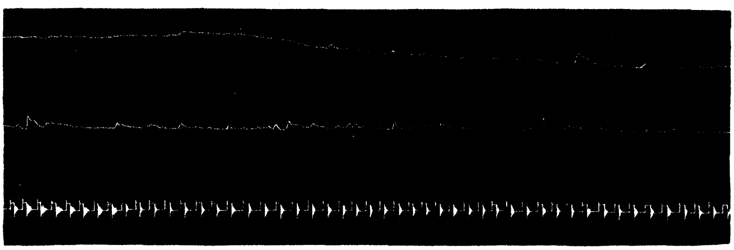

FIG. 10.—Diaphragm, rabbit (pithed, phrenics cut). "Spontaneous" tremor recorded for ¾ hour. Time in half-seconds. Lever as in fig. 1; no weight. Periodicity at first 10 a second; later, 5 a second. (Facsimile.)

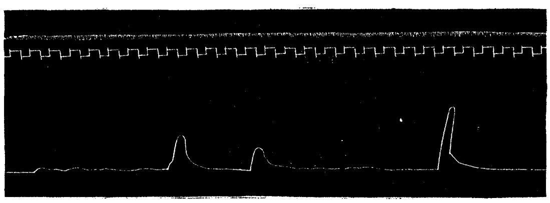

FIG. 11.—Hyoglossus, frog. Direct stimulation; no weight. Neef's hammer (side-wire). Time in half-seconds. Tremor. Periodicity, 2 to 3 a second.

This difference is interesting in the light of the well-known difference in the number of stimuli necessary to cause complete tetanus in the gastrocnemius and in the hyoglossus respectively, viz., 30 and 10 respectively, ratio 3 : 1.

The post-tetanic tremor, no less than the genesis of their tetanus, proclaims

the differences in molecular mobility between the gastrocnemius and the hyoglossus muscles.

Similarly, a poison like curare, which diminishes protoplasmic mobility, brings down the periodicity of the post-tetanic tremor from the six per second of frog's normal gastrocnemius to 2·5 to 3 per second in the curarised gastrocnemius (*cf.* fig. 9).

In other words, the physiological insusceptibility is now about three times as great as in the normal frog muscle; or, again, the curarised gastrocnemius becomes reduced, as regards molecular mobility, to the level of the less mobile hyoglossus.

(4) The post-tetanic tremor is characteristically irregular in intensity from moment to moment.

Previously to my publishing the first note on the periodicity of this tremor, Dr. Bayliss was good enough to suggest, in a private communication, that the irregularity in the record of the tremor was due to irregular variations in the intensity of the various members of the series of stimuli given by Neef's hammer, that is to say, that the stimuli varied from submaximal to maximal and *vice versâ*. I had eliminated this possibility, by noticing that post-tetanic tremor could be produced at all distances between the primary and secondary coils, both when the stimuli were submaximal and when they were maximal.

As I had already used the Helmholtz side-wire equaliser, and did not consider that the vibrating reed gave stimuli of sufficiently uniform intensity, I decided to test the point by (1) using a 100 a second electro-magnetic tuning-fork as interruptor in the primary, and (2) by using as interruptor, in the primary circuit, a metallic rotating wheel provided with teeth which dipped into a pool of mercury, and was driven at varying speeds by a small air-engine.

By neither of these methods was the irregularity abolished; and in the case of certain muscles was not in any obvious manner diminished (notably fig. 2, muscle of kitten, where the 100 a second fork was used).

While freely admitting it possible that a series of stimuli of absolutely equal physical intensity would give the least irregular form of post-tetanic tremor, yet I am compelled, from a study of a large number of these tremors through long periods during which the stimuli were as constant in energy as possible, to believe that the irregularity of the post-tetanic tremor is inherently characteristic of it.

It seems to me that the irregularities can be explained by:—

1. Non-simultaneous onset of fatigue in the several fasciculi or fibres of the muscle; so that when we use even physically equal stimuli, a stimulus which is effective for one fibre or fasciculus may not be so for another, or if effective

for one fibre, etc., at one moment, may not be so for that same fibre at the next moment.

All the fibres are not equally fatigued after the same duration of stimulation, and, through their irresponsiveness, certain fatigued fibres rest, to recover their irritability later on, so that a stimulus sub-liminal for a given fibre at one moment may be liminal or supra-liminal for it after a short interval.

2. In the next place, it is not probable that all the fibres composing the depths of a muscular mass receive either in indirect or in direct stimulation their stimuli at absolutely the same instant through the entire muscle—the so-called "non-instantaneous innervation;" and, further, it is known that certain fasiculi have more component fibres than others, more fibres to be innervated.

It rarely happens that all the fibres contract simultaneously, but when they do, we obtain a result as in fig. 4—a series of large waves of quite slow rhythm, 1·5 to 2 a second—reminding one strongly in some respects of a cardiac rhythm as seen in fig. 12, which is a record of the so-called "heat-tetanus" of the ventricle of the heart of a rabbit.

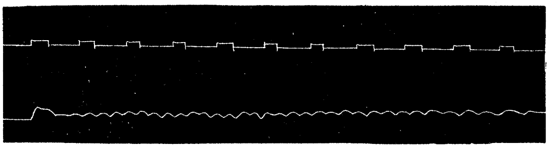

FIG. 12.—Ventricle of heart (rabbit), immersed in continuously heated 1-per-cent. NaCl. Lever same as in fig. 1. 5 grammes weight. Time in half-seconds. Maximal periodicity, 6 to 7 per second.

In this case the gastrocnemius muscle had its circulation intact (kitten pithed, artificial respiration); the stimuli were from a tuning-fork in the primary, *i.e.*, as physically uniform as possible; stimulation was direct. Here I conclude that the onset of fatigue was simultaneous throughout, practically, all the fibres of the muscle, a condition, for several reasons, very rarely met with (fig. 4).

Here, if anywhere, the conditions were such as to favour the simultaneous onset of fatigue in the fibres, for the stimuli were as equal in intensity as was possible, and any conditions due to varying degrees of neural fatigue were eliminated by the previous fatigue of the motor end-plates; all the fibres were still supplied with oxygenated blood, *i.e.*, were under the same conditions as regards nourishment and removal of waste-products, so that there was maximum uniformity of both the physical and metabolic conditions.

Except for a second or two, I have seen none but irregular tracings of

post-tetanic tremors, and this irregularity also characterises even those tremors which are produced by the so-called "constant" stimuli and also certain tremors of "spontaneous" origin.

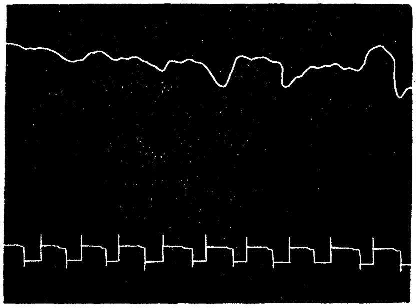

FIG. 13.—Gastrocnemius, frog. Sciatic nerve drying. Bell-crank lever; no weight. Time in half-seconds. Periodicity of tremor, 4 to 6 a second. (Facsimile.)

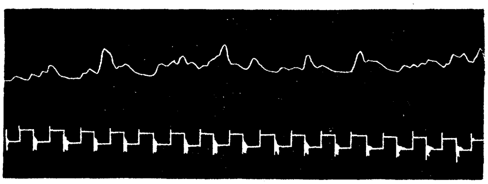

FIG. 14.—Gastrocnemius, frog. Solid NaCl placed on sciatic nerve. Bell-crank lever; no weight. Time in half-seconds. Periodicity of tremor, 5 to 7 a second. (Facsimile.)

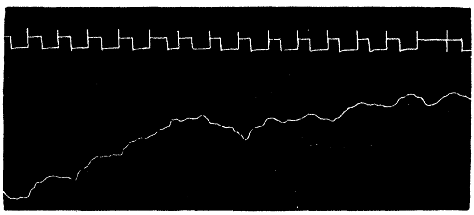

FIG. 15.—Gastrocnemius, frog. Sciatic nerve pinched. Bell-crank lever; no weight. Time in half-seconds. Periodicity of tremor, 6 a second. (Facsimile.)

With regard to tremors due to "constant" or "single" stimuli, we have the tremors from (1) drying of the nerve; (2) chemical stimulation of the nerve, *e.g.*, by NaCl; (3) pinching the nerve; (4) heat suddenly applied to the nerve; and (5) the disappearance of anelectrotonus from the nerve: while the tremor of the dying diaphragm is an example of the "spontaneous" kind (*cf.* fig. 10).

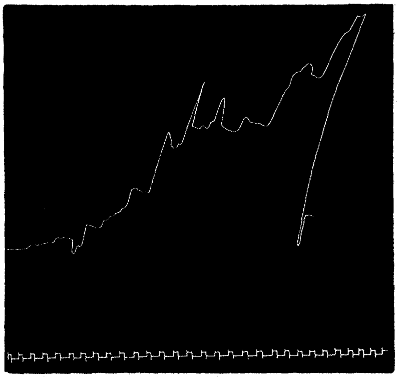

FIG. 16.—Gastrocnemius, frog. Sciatic nerve suddenly heated by hot NaCl 75-per-cent. solution. Bell-crank lever. Time in half-seconds. Periodicity of tremor, 4 per second. (Facsimile.)

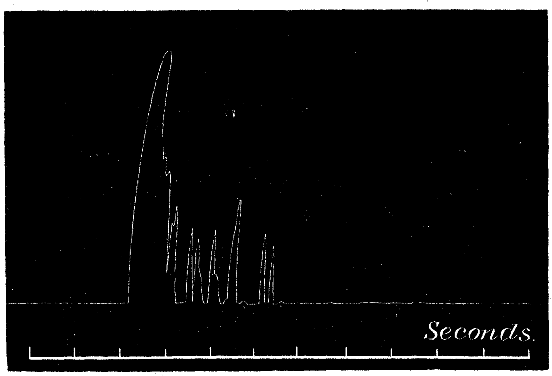

FIG. 17.—Gastrocnemius, frog. Ritter's "opening tetanus." Bell-crank lever; no weight. 1 cm. of sciatic nerve had "constant" current ($5{\cdot}4 \times 10^{-5}$ ampere) ascending for 5 minutes through non-polarisable electrodes. To be read from left to right. Time in seconds. Periodicity at beginning of tremor, 5 to 6 a second. (Facsimile.)

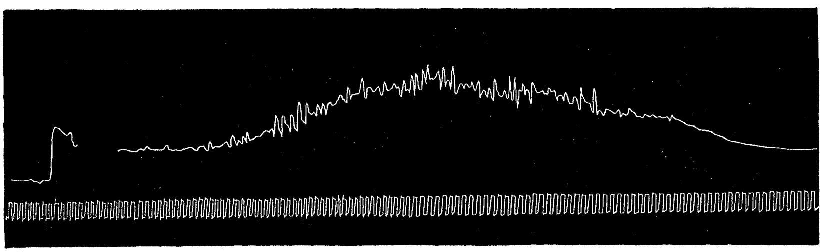

FIG. 18.—Sartorius, frog, completely immersed in Biedermann's fluid. To be read from left to right. Time in half-seconds. Average periodicity, 4 per second. (Facsimile.)

All of these tremors are more or less irregular.

Now all these tremors are, as to average periodicity, of the same order as

the post-tetanic (three or four to six a second), and as the coarse tremor brought on by fatigue in, *e.g.*, the human deltoid (fig. 19).

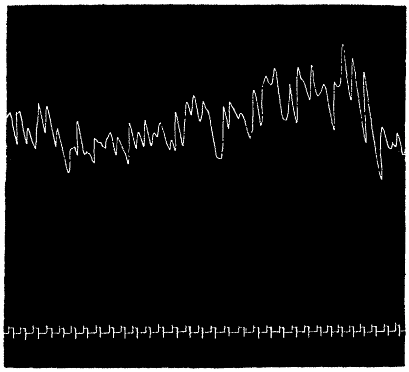

FIG. 19.—Deltoid, human, coarse fatigue tremor of. Arm held out horizontally with 1 kilo. in hand; cord from middle finger to button of cardiograph (Marey's). Tracing by a recording tambour. Time in half-seconds. Periodicity of tremor, 5 per second. To be read from left to right. (Facsimile.)

In these cases we may say that *inco-ordination* of fibres or of fasciculi is the element common to all, whether this has been brought about by "non-simultaneous innervation" or by repeatedly varying degrees of the excitability of the fibres brought on either by fatigue or by some hitherto unexplained state of inaccessibility to certain stimuli.

I take it that this inco-ordination or non-simultaneousness of innervation is what Dr. Haycraft alludes to when, discussing normal voluntary tetanus, he writes . . . "muscles exhibit fascicular or other *local* movements."*

If this be true as regards normal voluntary tetanus, the record of which is very regular compared with the tremors under study at present, it must apply with increased force to those tremors of muscles in which fatigue has set in.

While fatigue, inducing fascicular inco-ordination, can be held to explain the irregularity of the post-tetanic tremor and the spontaneous tremors of dying muscle, it is difficult to see how fatigue can be the main factor producing the irregularity of such tremors as those from chemical, mechanical, or thermal stimulation or from anelectrotonus, seeing that the irregular contractions are present from the very first when fatigue obviously cannot have set in.

The probability is that those stimuli called "single" or "constant" are, as regards nerve-molecules, anything but constant in their stimulating power.

* J. B. Haycraft, "Voluntary and Reflex Muscular Contraction," 'Phys. Journ.,' vol. 11, 1890, p. 366.

Drying of nerve in air, abstraction of water by NaCl, increase of temperature, even pinching the nerve cannot be assumed to be respectively uniform in their modes of being stimuli; in fact, physically they represent stimuli varying considerably in intensity from moment to moment. They introduce intra-molecular disturbances of various potentials and of varying disruptive powers as regards the biogens of the nerve. These disturbances "act" like discrete stimuli of varying intensities.

Theoretical Explanation of the Meaning of the Post-tetanic Tremor and Tremors of Similar Periodicity.*

The property of functional inertia of muscular protoplasm expressed here as a physiological insusceptibility to certain stimuli seems to me to furnish the key to the meaning of the post-tetanic tremor. I regard it as a protective mechanism which, by permitting the establishment of this fatigue-rhythm of low periodicity, averts for a time the physiological calamity of full exhaustion.

If there *could* be responses to such high rates of stimulation as 30, 40, or 100 per second, the muscle would very soon be utterly tired out and incapacitated for a long time from activity. But, owing to the possession of the property of physiological irresponsiveness (functional inertia), the muscle subjected to continued stimulation responds only to some of the stimuli in the rapid series (every fifth, seventh, or tenth), or responds at a rhythm very much lower than that of the stimuli, thus substituting chronic fatigue for acute exhaustion.

Here, in virtue of functional inertia, the living matter preserves itself from that destruction which would overtake it were it possessed of affectability alone. The two properties are co-existent in the living matter: resting muscle has much affectability, but little functional inertia; as activity proceeds, the affectability diminishes and the functional inertia increases towards the continued stimulation, until a point is at last reached when the ratio between the two properties is such that only every 1 in 7 or 10 stimuli is responded to, the others being functionally disregarded. This state of matters can be exhibited for a long time, biologically speaking, viz., half an hour, as in the post-tetanic tremor of the human flexor sublimis digitorum with intact circulation.

The biotonic state at any moment depends on the ratio of the degrees of possession of these two properties; were affectability alone present we

* D. F. Harris, "Functional Inertia, a Property of Protoplasm," 'Roy. Soc. Edin. Proc.,' vol. 24, p. 196; and D. F. Harris, "Affectability and Functional Inertia as *the* two Properties of Protoplasm," 'Scot. Micros. Soc. Proc.,' vol. 4.

would have, as a result of perfect response to all stimuli, a maximum uncontrollable activity, and the rapid end of things in death; were functional inertia alone present, we would have complete irresponsiveness to all stimuli.

But a condition of functional compromise between the two biotonic extremes is set up, and thus a mean condition, known as "fatigue," established. I take the existence of the post-tetanic tremor as one more expression of the physiological significance of fatigue and of rhythm.

In those tremors arising from a single stimulus (figs. 15, 16, and 17), or from continued stimulation (figs. 13 and 14), or spontaneously (fig. 10), we have the property of functional inertia of the muscular substance contributing to the explanation of the feature common to them all, the *want* of correspondence between the character of the responses and the nature and mode of application of the stimuli.

Tremors of the same average periodicity, 3 to 6 a second, are elicited by stimuli physico-chemically the most varied, and may be seen characterising cases so far apart physiologically as the dying diaphragm and the maximal rate of beat of the heart ventricle.

This non-correspondence or lack of parallelism between stimulation and response seems to be due to the stimulus-disregarding property of functional inertia in the muscle-substance, the same property which, in the case of long-continued rhythmic stimulation, expresses itself in the post-tetanic tremor.

Through affectability muscle responds to any stimulus by contracting, but through functional inertia the nature, the mode of application, and even the rhythm of the stimulation is *disregarded*, and to the most varied kinds of stimulation the response becomes the same—a tremor whose component events recur with the same slow average periodicity.

"It seems," writes Professor Biedermann,* "to be an almost universal property of muscular substance to fall, under certain conditions, with all prolonged stimuli into a state of visible rhythmical excitation." The above data, I submit, are an experimental and statistical verification of this statement.

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* 'Electro-physiology,' vol. 1, p. 107. London: Macmillan, 1896.