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THE "ALL-OR-NONE" LAW IN SKELETAL MUSCLE AND NERVE FIBRES

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1. THE ORIGIN OF THE "ALL-OR-NONE" PRINCIPLE

In 1903 Keith Lucas came back to Cambridge after two years spent in New Zealand to collect fauna from the lakes. He was made a Fellow of Trinity in 1904 and began his experimental work at the Physiological Laboratory. In these days the Laboratory reckoned many distinguished physiologists such as Archibald V. Hill, George Ralph Mines and John Newport Langley, which allowed Lucas to have a working room. Besides the room at his disposition in the University Laboratory, he had a personal workshop at his house. Lucas's mechanical skills are renowned: he gained an exceptional knowledge of mechanical principles and of the right use of tools. For example, he was able to record the electric responses of the sciatic-gastrocnemius preparation (or of the sartorius muscle) of the frog (*Rana temporaria*) with the capillary electrometer. This instrument was chosen rather than the string galvanometer, because admirably adapted to follow the rapid changes in striated muscles by casting the shadow of a column mercury in a capillary tube.

In these years, Lucas was interested in the properties of muscle and nerve. Working on the muscle nerve preparation (usually of the frog), physiologists of the late nineteenth century observed stricly localized changes at all point of the nerve fibre's length set up by a "disturbance" which propagated along the fibre itself. Consequently they discussed whether the so-called propagated disturbance was the real nervous impulse or a simple manifestation of it.

In particular, Lucas was engaged in the question posed by physiologists for a hundred years: "What kind of change takes place in our muscles to make them contract and what signals are sent down through the nerve fibres from the brain to order the contraction of the muscles?" In the study of the muscular contraction and relaxation, Lucas employed a photographic method to obtain a truthful record of the curve of the movement followed by a few fibres of the muscle. This evidence could be obtained cutting down a small muscle (usually the *cutaneus dorsi* of the frog, which contains 150-200 fibres) until only a few fibres were left in it.

At first, Lucas's investigation dealt with the *gradation* of the contraction in a skeletal muscle fibre. He recorded contractions at intervals of 30 seconds with small successive increases of stimulus and observed that, as the strength of the stimulus increased, also the magnitude of the contraction increased, not continuously, but in a series of distinct and definite (*abrupt*) steps.

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In that time, physiologists reputed that contraction was discontinuous either by gradation in *each single fibre* or by variation in the *number of the fibres* used in the preparation. According to the first conception, each excitable element composing the tissue was the seat of a process varying in intensity with the amount of electrolytic change produced by stimulus between two limiting points: a minimal point below which the change is not able to excite a response, and a maximal point above which the change is unable to increase the amount of the active response. According to this point of view, each element would give by itself all grades of submaximal responses corresponding to grades of the intensity of the stimulus.

A second conception emphasized the number of fibres which were simultaneously thrown into activity. In this regard, Paul Grützner in 1887 and, more recently, Francis Gotch from the Physiological Laboratory in Oxford supported the hypothesis that the *number* of fibres was the only means of grading. In 1902 Gotch observed that such tissues as nerve trunks and voluntary muscles (for example the gastrocnemius of the frog) are composed of a large number of excitable elements, each physiologically so distinct from the others that the active state in anyone of them cannot spread into the neighbour ones. Thus the submaximal responses occurred if the active process was confined to a limited number of available structures; but, as the exciting current of the stimulus increased in intensity, the response increased because more fibres were seen to be involved in producing the contraction. Finally, the response could reach its maximum when all the elements were aroused.

However, Gotch's paper in 1902 had not attracted much attention, "as it contained a suggestion rather than a proof". Furthermore, the whole subject was not clear for two reasons: 1) terms such as "stimulus", "excitation", "conductivity" were often used with different meanings; 2) nerve and muscle were assumed as a single unit and not as a collection of distinct fibres. Besides, the classical method (constituted of the du Bois-Reymond induction coil for stimulation and the smoked-paper drum for recording muscular contraction, applied on the gastrocnemius-sciatic nerve preparation of the frog) was not exempt from artifacts.

Three years later, in his famous experiment on the *cutaneus dorsi* of the frog, Lucas showed that the number of the steps of the increasing contraction was irregular, but always *less* than the number of the muscle fibres involved in the preparation. For Lucas the hypothesis that contraction of each single fibre increased discontinuously could not be accorded with any experimental fact. On the other hand, if the steps marked the progressive addition of new fresh fibres to the number of those previously excited, this behavior of the skeletal muscle fibres preparation could accord with the activity of the ventricular ones. And relatively to heart muscle, since 1871 there was solid evidence that fibres obey a precise law.

The idea of a possible similarity with the cardiac tissue had been advanced also by Gotch. In fact, for Gotch the causal factor in the production of submaximal effects in nerve and muscle could be the "partial" stimulation, i.e. the circumstance that the excitatory process was limited to a small portion of the available elements. But – he observed – in the case of the cardiac tissue, such a limitation was improbable because the elements are all in "physiological connexion". For example, in the frog's heart no variation in the magnitude of the response as dependent on the stimulus intensity might be recorded. This tissue is constructed in manner that no partial stimulation is possible, and so it always gives the maximal response as regards the number of aroused fibres provided that the stimulus excites it at all. Lucas also agreed on the fact that in amphibia the fundamental difference between skeletal and ventricular muscle had to lie rather in the functional connexion of the muscle fibres than in their individual behavior. In fact, cardiac cells and fibres are connected one with another, whereas skeletal muscle cells are isolated by sarcolemma. Moreover, in a footnote to his article, Gotch referred that, as regard the frog's heart, "the 'all or none' principle is founded on the observations of Bowditch" exposed in the "Arbeiten aus der physiologischen Anstalt zu Leipzig" in 1871.

After studies of comparative anatomy and physiology at the Harvard Medical School, Henry Pickering Bowditch went in Europe in 1868-72 and studied firstly in Paris with Claude Bernard, Louis-Antoine Ranvier and Étienne Jules Marey, then in Bonn with Wilhelm Kühne and Max Schultze. Finally, he worked in Leipzig with Carl Ludwig, representative of the so-called physico-chemical school in Germany. In experimenting on the physiologically severed apex of the heart, Bowditch investigated the irritability of its muscular fibres and in particular the contraction and the relation of response to stimulus. He observed that an induction shock produced a contraction or failed to do so according its intensity ("An unserem Object bewirkt der Inductionsstrom entweder eine Zuckung oder er vermag dieses nicht").

In 1909 Lucas made another experiment stimulating the *cutaneus dorsi* of the frog through a nerve containing only eight or none motor fibres, each of which innervated on the average about twenty muscle-fibres. Then he hypothesized that, as the strength of the current exciting the nerve increased, the muscle fibres innervated could come in action one after another. He found that only four or five steps occurred in response to the stimulus, and that the number of the steps was never greater than the number of the motor fibres. Thus each nerve fibre induced contraction in all the muscle fibres which it innervated. Since the passage from a step to another occurred without intermediate contractions, it meant that the fibres usually contracted *either or not at all* to a nearly maximal magnitude, regardless of the strength of the stimulus which excited the nerve fibre.

2. CONDUCTIVITY AND GRADING

Nevertheless there were some cases in which the intensity of the effect seemed to be *graded* by grading the intensity of the stimulus. In his seminal work on the integrative action of the nervous system (1906), Charles Sherrington quoted a vaste literature according to which a proportion could be established between the increment of the stimulus and the response of the muscle. As regards the correspondence between intensity of the stimulus and reflex end-effect, Sherrington observed that it was often stated that reflex reactions resemble as to intensity the "all-or-nothing" principle of the cardiac beat. However, he was persuaded that "graded intensity of reflex-effect does occur". In particular, in the scratch-reflex a grading of the intensity of the reflex was easily obtainable by grading the intensity of the stimulus. He noticed the greater amplitude obtained in the individual beats of the rhythmic contraction of the hind limb of a spinal dog in correspondence with the increase of intensity of stimulus. In effect, the increase of intensity of response did not reveal itself in increase in frequence of the rhythm of the scratch-reflex, which was relatively immutable; but it was possible obtain a dozen grades of amplitude in a dozen successive examples of this reflex. And the beats of the contraction in response to a strong stimulus could be six times greater than the beats evoked by a weak.

Thus Sherrington could stress the difference between these two kinds of reaction: the reflex differs from the heart beat because its intensity follows the change of intensity of the stimulus, and he might conclude that the scratch-reflex "does not observe the 'all-or-nothing' principle". But Sherrington went further and tried to formulate a physiological explication of this different behavior. In the heart it was important to apply a pressure on the contents of the ventricle higher than that in the aorta. When this object is gained, any further amount of pressure is useless or even detrimental for the cardiac muscle, which is more closely associated with its internal conditions than with the properties (such as intensity) of the external stimuli. On the contrary, it is natural that a strong scratch-reflex may remove an irritation more easily than a weak response.

Curiously, in referring to the "all-or-nothing" principle of the cardiac beat, Sherrington quoted Wilhelm Wundt, Professor at the University of Leipzig. It was not the first time that physiologists made reference to Wundt on this subject. Yet in 1880, in a research on the influence of the strychnin on the reflex movements of the frog, Geo. L. Walton of Boston revealed the altered relation of contraction to stimulus during strychnin poisoning and noticed that it had been pointed out by Wundt (and confirmed by himself) that "a stimulus which is strong enough to produce any reflex contraction in a muscle produces a maximal contraction, and the muscle will not react more strongly if the greatest possible stimulus is applied".

Indeed, in 1876, in his work on the *Mechanik der Nerven*, and precisely in a chapter dedicated to the changements of irritability in the reflex movements under toxic substances, Wundt had observed that with the supply of small or great quantities of poison, the development of contraction changed into a continuous tetanus, i.e. in a sustained contraction constituted by the fusion of individual twitches. Started in the presence of weak excitations, this convulsive phenomenon increased in strength; however, when the stimulations became stronger, it increased "nur wenig". So, provided that a stimulus was *stark genug*, a maximal excitation supervened.

3. THE EMERGENCE OF THE TIMING

In repeating Wundt's experiments on the relation between the contraction and the strength of the stimulus, Walton found that another factor could be taken in consideration in order to show that in poison convulsions the muscular contractions are not in relation to the strength of the stimulus. This new factor was the *time span* between successive stimuli. Indeed, Walton noticed that, given a series of stimuli capable of producing a contraction, a stimulus was able to call out a maximal response provided a certain period of time had elapsed since the previous stimulus of the series. On the other hand, if the following stimulus was given without allowing this period of time to elapse, the contraction varied in accordance to the strenght of the stimulus.

The role of the *temporal factor* in the conduction of the nervous impulse was coming out. In an essay on the locomotor system of Medusae presented in 1877 to the Royal Society, George Romanes exhorted to notice the great similarity between the recordings of the successive increments of the responses to successive induction-shocks obtained in the fibres of the umbrella of *Aurelia* and the records published in the paper of Bowditch. He remarked that, in spite of the wide separation of the tissues in the animal scale between the muscle fibres of the heart and those of the Medusae, nevertheless towards stimulation these structures behaved in a similar manner, and reputed this phenomenon "a fact of great interest". However, he could not fail to put in evidence a difference between them: in the case of Medusa, if a pause of ten seconds elapsed in a series of stimuli and then the stimulation commenced again, the first response was not of maximum intensity. Moreover, if a whole minute elapsed between the maximal effect of a series of stimulations and the first of a new series, the tissue appeared to have completely forgotten the occurrence of the previous series so that the next one seemed to begin anew from the first step. On the contrary, in the case of the heart, an interval of five minutes had to intervene between the two series of stimuli before the effect of the first on the second was totally eliminated. This peculiarity induced Romanes to employ the metaphor that the "memory" of the cardiac tissue is about five times as long as that of medusoid fibres.

Obviously, the observations reported by Walton and Romanes dealt with the phenomenon of alteration of irritability *during and after* excitation. Since 1871 Marey observed that, in response to an artificial stimulation, heart showed a reduced irritability during the systole and that recovery could occur during the following diastole. Marey called this period of diminished excitability "phase réfractaire" and this phenomenon was a subject of great experimental interest. Soon an analogous refractory period (i.e. the state which must pass away before another complete wave of activity can occur) was discovered for the motor centers of the cerebral cortex (of the dog) and for many reflexes. In 1899 Gotch and G.J. Burch showed a refractory period of short duration in the nerve. In the same year Arthur E. Boycott remarked that two stimuli separated by a certain time interval produced a summated contraction of the muscle connected with the nerve. But if the interval between the two stimuli was shorter, the contraction was of the same size as that produced by the first stimulus alone. There was evidence that a second stimulus occurring very soon after the passage of an impulse was unable to set off a second impulse or a second twitch in the muscle. In fact, the nervous fibre entered a refractory phase.

Following these investigations, in the years between 1909-1912, Lucas determined the refractory phase for the sartorius of the frog. Recording the action currents by the capillary electrometer, Lucas showed that in a series of two induction shocks the second stimulus was ineffective for 005 seconds after the application of the first stimulus. It was clear that some time delays occurred for the restitution of irritability in nerve as in the heart, and Bowditch found that, after a discharge, the irritability in response to strong stimuli reappeared more rapidly than for weak, and the weaker the stimuli the longer had to be the intervals between them. Lucas arrived to the conclusion that an "abnormally long delay" in the response to stimuli falling just after the refractory period was a phenomenon common to different excitable tissues, and it was due to the temporary modification of the tissue by the passage of the propagated disturbance. He could map the entire process from excitation to the state in which the nerve is unable to respond to a second stimulus, due to a nerve impulse passing through a fibre. This phenomenon constituted the *absolute* refractory period. This phase is followed by a *relative* refractory period characterized by the fact that excitability gradually returns to normal. Finally, during the third period, the nerve is "actually more excitable than it is while at rest". Such a period of increased excitability was defined "supernormal phase".

This analysis of the refractory phase could help to explain the correlated phenomenon of "summation", that is the improved conduction of a second impulse. After a nervous impulse has passed in a decremental region in which it is eventually extinguished, this region passes through a course of recovery including a period of supernomal conduction. So a second impulse falling within a supernormal period of the previous disturbance is conducted further and passes through the decremental region or it allows the next impulse, which is still in its supernormal phase, to pass further.

The timing showed itself relevant in the return of excitability and generally in the conduction of the nerve impulses. Moreover the temporal factor seemed to imply important consequences also for the application of the "all-or-none" principle.

4. THE FORTUNE OF THE "ALL-OR-NONE" PRINCIPLE

From the finding of Gotch and Lucas in 1902-1905 many British and German physiologists worked to confirm that not only muscular fibres, but also nerve fibres obey the "all-or-none" principle: in a single fibre, "if the stimulus is strong enough, it produces a full-sized mechanical twitch, but below a certain threshold it gives nothing at all".

Again in 1912 Julius Vészi, a Hungarian scholar of the so-called German School of Max Verworn, at the Friedrich-Wilhelms-Universität in Bonn, remarked that in most of organic forms the intensity of the excitation depends on the strength of the stimulus. This relation, however, seemed not valid for all the living substances and yet in past times some cases were known that the magnitude of the stimulus effect did not depend on the stimulus strength. Such a behavior became well-known as regard to the cardiac muscle. In this connection, Bowditch succeeded in establishing for the first time the "Alles-oder-Nichts Gesetz" for the heart, i.e. that each stimulus, provided that is effective, excites a maximal contraction. Successively, – Vészi added – Hugo Kronecker and John McWilliams gave evidence to the fact that the size of the effect is independent on the intensity of the stimulus.

Verworn, who directed also the laboratory of Göttingen, with the contribution of some students and co-workers such as Friedrich Fröhlich and Edward Lodholz, proved "apparently without doubt" the validity of this law for medullated nerves. Being interested in the fundamental properties of living systems, he conceived irritability as a specific property of the organism and conduction as a manifestation of the primary process of excitation. To analyse the conditions of conduction, he compared two extreme cases, Rhizopodes, i.e. a type of protozoans, and nerves. Rhizopodes such as *Difflugia* possess pseudopodes, rudimentary kinds of conducting tissues used in locomotion and digestion, characterized by weaker or stronger responses according to the strenght of stimulation. On the other hand, also the nerve is a form of living substance in which irritability "has reached a high degre … and consequently the property of the conductivity in the nerve reaches the state of highest development of all living structures". In the normal nerves, Verworn observed, the weakest as well the stronger stimuli produce excitations of equal intensity: that is "the 'all-or-none law' is valid for the nerve". But when irritability was artificially reduced or altered, the nerve approached more and more the series of living substances, in which pseudopodes of Rhizopodes with their minimal capability of reaction seemed to be at the other extreme. Yet, between these two extreme forms of life, i.e. the medullary nerve with its maximal excitability, and the pseudopodes with their minimal irritability, it was possible to find many gradations. According to Verworn, further investigation was required as to whether these kinds follow the all-or-none principle.

Nevertheless, following a current approach in Germany, Verworn sustained a "metabolic-cellularistic" point of view, according to which living substance contains elements organized in a characteristic manner and life processes consist in the metabolism of proteids. Consequently he was inclined to explain these vital processes on a *molecular* basis. He believed that in the course of excitation (and conduction) the same number of specific molecules capable of disintegration was broken down at any cross section of the fibre as at the point of stimulation, so that an equal amount of energy was set free. This hypothesis of a homogeneous molecular structure constituted a possible explanation of the all-or-none law. The nerve appeared to behave differently from e.g. the ganglion cell because the nervous fibre does not obey the summation principle even under stimuli in rapid succession. This fact was a clear consequence of the application of the same principle: the weakest effective stimulus produces maximal excitation and the response cannot be further increased. So the nervous fibres constitute tissues in which such an alteration in the highest degree of the excitation is not possible. In order to distinguish the different types of organisms, Verworn employed the terms of *heterobolic* and *isobolic* living systems: while the former could exhibit various degree of discharge depending on the intensity of the stimulus, the latter, which are not capable of summation, display a constant discharge set up by stimuli of different intensity. The existence of these specific properties do not prevent the isobolic systems from assuming a heterobolic character, for example during the refractory period and before the return to the primitive isobolic state with the recovery of the equilibrium of metabolism. These observations induced Verworn to declare the "only relative validity" of the all-or-none principle. However, a system may lose its isobolic character to become heterobolic in such states as fatigue, asphyxia, cooling, narcosis etc., i.e. when the refractory period is prolonged.

5. DECREMENT AND CONDUCTION

In these years, nervous conduction (and the relation between stimulus and response) was often examined and measured reducing the impulse to subnormal intensity, eventually inducing extinction in it. Introduced by Alfred Grünhagen in 1872, this method consisted in passing a portion of the nerve of the muscle-nerve preparation through a gas-chamber or a region of low temperature.

Employing this technique, also Vészi arrived to conclusion that – in condition of impaired conductivity – the magnitude of the propagated disturbance cannot be invariable, because it must depend on the distance travelled in the altered region. In the same period Edgar Adrian, one of the most promising pupils of Lucas at Trinity, applied the same method to verify whether the impulse could recover after the passage through a decremental region, emerging into a tract of normal nerve. If an impulse was able to overcome extinction, then it would recover its normal size when emerging from the affected area. But in a region of decrement, Adrian noticed, the all-or-none principle could not hold, because the size of the disturbance at any point of the nerve trunk varied with the distance travelled in the altered region. So a measure of the intensity of the impulse could be obtained in terms of its ability to travel and to go beyond the region of impairment. Again in 1914 Lucas and Adrian thought it was not possible to express this intensity in any physical or chemical variable. Nevertheless, they asserted that at the present state of knowledge the only thing important to the study of the nervous transmission was the *chance* that the impulse be successfully conducted.

In reaching the conclusion that, although reduced in magnitude by passing through a decremental region, a propagated disturbance can regain its original size emerging into the normal tissue, Adrian noticed that no assumption had been made with regard to the relation between the disturbance and the strenght of the stimulus. Therefore, his conclusion was that the relation is "all-or-none": a small disturbance called up by a weak stimulus increased in size in exactly the same way as a disturbance which was started by a stronger stimulus, and reduced in its passage down the fibre.

These observations moved Adrian to conceive that the size of the propagated disturbance at any point in a nerve fibre only depends on the *local conditions* of the fibre "at that point and not on the previous history of the disturbance before it arrived there". In particular, Adrian intended that these conditions cannot be altered by the nature of the stimulus or the conditions of the path through which the impulse travelled: in other words, there is no stage in the process at which a stronger stimulus may affect the muscle when the "normal threshold stimulus" cannot do so.

At this point, it was necessary to reach an agreement on the meaning of the concept of conductivity. Generally, the conductivity of a nerve was assumed to mean its ability to conduct, i.e. as inversely proportional to the least size of the disturbance travelling without extinction. So German physiologists were accustomed to measure it in terms of the strength of the stimulus necessary to affect the muscle. And this interpretation implied that the size of the propagated disturbance had to vary with the stimulus strength. But, since it was difficult to explain the mechanism of conductivity under normal conditions, they often introduced an element of disturbance, and the strategy of comparing (and measuring) the "normal" state (in this case, the normal tract of a nerve) with the "pathological" or "affected" one (the region of decrement) was typical of the physiological approach of that time.

Another of the unresolved difficulties of sensory physiology in the nineteenth century concerned the possible difference between sensory and motor fibres. In his posthumous collection of lectures delivered in the spring of 1914 and edited by Adrian, Lucas admitted that experimental work on grading had been confined to the motor nerves (of the frog), and it was perhaps an unjustified assumption to extend it to cover sensory nerves as well. Nevertheless he thought that it was unlikely that the processes of conduction were radically different in the two kinds of nerves.

Following the zoological observations of Verworn, Adrian and the American physiologist Alexander Forbes agreed that the "gradual dying out" of the impulse seemed the normal occurrence in some primitive forms of life and conducting tissues, such as the sea anemone and *Difflugia*. But in the vertebrate motor nerve fibres, the mechanism of conduction had become "more efficient", so an impulse could travel without changing size.

In 1913-15, in agreement with the experiments of Grünhagen, Lodholz and Ernst Rehorn had applied stimuli in a region of decrement. This was done under narcosis, so that the required strength of the stimulus to trigger an impulse strong enough to reach the muscle increased with the distance the impulse was to travel in the region. Thus an impulse set off by a weak stimulus could travel only a short distance, while a stronger stimulus could set off an impulse able to travel further. In 1922 Adrian and Forbes replicated the experiment made by Lodholz and Rehorn, and their conclusions confirmed the one of the German electrophysiologists. Evidence was gained that in a decremental region the nerve does not react according to all-or-none principle. Then Adrian and Forbes intended to examine the effect of decrement also in the mammalian sensory fibres, and verify whether the conduction differs radically in afferent and efferent fibres. To this purpose, they chose the internal saphenous of the cat – in that this nerve does not contain any motor fibre – and measured the magnitude of the electric response set off by an impulse which travelled some distance before eventually fading away. Their purpose was to determine the stimulus strength required to give a minimal and a maximal electric response at different stages of narcosis until complete failure of conduction. As the electric response became smaller, the strength for a minimal response remained constant or rose, but the strength required for a maximal response fell. Thus the stimulus which was effective before the complete failure was originally "only just strong enough to produce any effect at all". This conclusion revealed that the size of the impulse does not depend on the strength of the stimulus and the sensory fibres do not differ from the motor ones relatively to the all-or-none relation.

6. THE SUPERVENIENCE OF THE FREQUENCY

Soon the results achieved by Adrian appeared to have important consequences on the development of the investigation on nervous conduction. More precisely, he confirmed the conclusions advanced by Gotch and Lucas: when a motor nerve is artificially excited by stimuli of various strengths, the graded contraction of the muscle results solely from variation in the number of fibres implied. Since a weak stimulus may be sufficient to excite a nerve, when the strength of the stimulus is varied, the only variable which must be introduced is the *numerical factor*, that is the number of the fibres brought into action. Intensity of sensation and size of the impulse do not depend on the strength of the stimulation both in the sensory and in the motor fibres.

So far the experimental work showed some different phenomena. Relative to the statement "A nerve fibre obeys the all-or none principle", Adrian recognized that it could be open to at least two interpretations: it might mean that the size of the propagated disturbance at any point in the course of the conduction is independent of the strength of the stimulus, but also that the magnitude is invariant or dependent on the local conditions only. To start a propagated disturbance, a stimulus has to induce some change in the local conditions. Thus two distinct events take place: a local irritation or excitatory disturbance, and – when the propagated disturbance is started – a refractory state which prevents any local change. Adrian was sure that the all-or-none relation did not show anything about the local excitatory process either on the nature of the propagated disturbance or on the mechanism of the conduction. Neverthless, as Lucas noticed in 1912, the experiments based on the narcotising chamber allowed to differentiate irritability from conductivity, since in the narcotised tract excitability – not conductivity – appeared suspended.

Furthermore, the "all-or-none" seemed the normal reaction of the motor fibre. Yet it was not the only reaction the fibre was capable of. Especially under artificial conditions it was likely to obtain a state of the fibre in which the intensity of the impulse was *variable*. In a first time, Lucas and Adrian supposed that conduction with decrement induced by artificial means could throw light on the knowledge (and measure) of the nervous impulse. Since 1912-14 they came to the conclusion that decrement was probably a *normal* event in certain structures of the central nervous system. In fact, they observed that in the junction between motor nerve and skeletal muscle the impulse seemed to behave in the same way as in the decremental tract.

Successively also Adrian and Forbes assumed that the case of decremental conduction, when the impulse becomes smaller and smaller and less able to travel as it traverses a trunk of fibres treated with narcotics, might be the normal condition of the sensory nerve fibre. In this case the size of the impulse depended not only on the local conditions, but also on the short (or long) distance travelled in the affected region. Although with decremental conduction the size of the impulse depended on the distance travelled, yet from this observation it did not follow that it depended on the strength of the stimulus.

While working on mammalian sensory nerves, Adrian and Forbes observed "just very little grading" in the initial impulse size, which was of scarce value in the whole activity of the central nervous system. However physiologists usually experienced a grading of sensation: Lucas noticed the wide variations in the intensity of sensations and Sherrington asserted that the scratch-reflex did not obey the "all-or-none" principle. The grading of the intensity of the reflex was "easily obtainable" by grading the intensity of the stimulus. Finally, Forbes and his colleague Alan Gregg quoted the rich literature of research in which gradation of magnitude was assumed. In particular, in the case of luminous and acoustic sensations we can experience the subtlest variety of graded intensity, and a grading depending uniquely on the number of the fibres set in action appeared too simplistic and inadequate to the very proponents of this explanation.

Adrian and Forbes remarked that the extreme range of gradation of certain sensations and reflex responses could induce one to think that sensory fibres differ from the motor ones in that they possess *changes in frequency* as means of varying their response. If conduction with decrement might be a normal event in the sensory fibres, the gradation of the reflex activity could be explainable without using the all-or-none reaction. According to Verworn, besides, in the primitive networks the impulse seemed to vary with the stimulus. And the same effect appeared also in the medullated nerve fibre, when it was in a region of artificially induced decrement. On the other hand, impulses set up in the internal saphenous by stimuli of different strength appeared equally capable of traversing a narcotised region. If conduction failed, the failure occurred owing to impulses set up by both weak and strong stimuli.

To face the problems due to the wide variation in reflex response, Adrian and Forbes came to the conclusion that there are two ways of grading: by varying the number of fibres involved in the response and by the *frequency* of impulses brought in action by continuous or repeated stimulation. A single break shock of great strength was able to excite two or more successive impulses. So they proposed that such repetitive discharge constituted a possible mechanism for grading the reflex effect in response to supramaximal (or more than strong) stimuli. In 1922 Adrian and Forbes confirmed a suggestion advanced by Forbes and Gregg relative to deformed active current records which seemed produced by the passage of two or more impulses instead of one. However, seven years before Forbes and Gregg only discussed the theoretical reasons for the *possibility* that a powerful shock might initiate a second propagated disturbance. Now, on the contrary, for the first time in the history of electrophysiology, frequency was invoked to explain the intensity of sensation, and the brain was conceived as interpreting the rhythm of impulses as evidence of the intensity of peripheral stimulation.

7. "ALL-OR-NONE" AND SYNAPSES

Electrophysiologists in the late ninetienth century had to face at least three kinds of problems: (i) the nerve alteration under a nervous impulse; (ii) the ability of an impulse to be conducted through a region of decrement, and (iii) the possible dissociation between electric response and propagated disturbance. The difficult interpretation of these processes induced them to reserve particular attention to the elements of disturbance and, at a certain point, decrement and recovery after the condition of impaired conduction began to be investigated not only in the peripheral junction tissues, but also in the central mechanisms.

In this time, synapses were a process still largely unknown. Indeed, a region in which conductivity was impaired was a good model for synapses and junctions, and the explanation proposed for a blocked region of nerve might be transferred to the synapse or neuromuscolar junction. For Lucas and Adrian there was nothing special about synapses and neuromuscolar junction. Adrian thought that they constituted a critical zone in which conduction exhibits a decrement pattern. The resistance to conduction at a synapse was an expression of decrement. Synapses were decremental areas acting as valves that admit or exclude disturbances depending on their magnitude or time of arrival.

Following this suggestion, Forbes and Gregg tried to correlate the passage of two or more impulses with the action of the central nervous system. Assuming that dendrites and synapses have a shorter refractory period than afferent nervous trunks, it became possible to explain the central summation: a second impulse passing the afferent fibre in its relative refractory period may reach the centre during its state of supernormal conductivity. Forbes and Gregg believed that the central effect of two disturbances was different from that of one. In particular, it was relevant to see whether two impulses arrived in a closer temporal succession: the increased frequency explained the infinite gradation of the central effect. At this regard, though recognising their poor knowledge about the central nervous system, in 1922 Adrian and Forbes admitted that single impulses could be multiplied because they pass through many synapses and dendrites which converge towards motor neurons.

Adrian and Forbes on one hand, and Sherrington on the other hand, conceived two opposite views of the synapse. Sherrington postulated synapse as a "neuron threshold". He asserted that – to excite a neuron – it was necessary to "overcome" the synaptic threshold. Then, in a reflex arc with two synapses, from Sherrington's point of view, it would not be sufficient to excite the internuncial neuron to overcome the threshold of the whole arc, because the individual thresholds tend to sum. On the contrary, if a synapse acts a region of decrement, then all the impulse needs is to pass through it, regaining its normal size while emerging. Thus it is not true that the threshold of the whole reflex arc cannot be lower than the highest threshold in it. If the synapses behave as a region of decrement, a single impulse traversing synapses in its path will set off maximal impulses in every neuron of the arc, and to the total threshold it will be enough to have the numerical value of the threshold of the afferent fibre.

Forbes and Gregg went further trying to make an analysis of the central activity: lateral reinforcements coming from other afferent fibres resulting from the arrangement of the branched ends would justify the ability of a *volley or train* of impulses in many afferent nerves to excite central neurons, while a smaller number of impulses would fail in this task. Some years earlier, it had been thought that impulses arrive at the centre not as volley, but as platoon fire. This metaphor reproposed the image used in 1877 by Ernst Brücke, and quoted by Nicholaj Y. Wedensky, "nicht nach Art von salven, sondern nach Art eines Pelottenfeuers".

Again in *The Basis of Sensation* (1928) Adrian observed that the different fibres composing the nerve trunk are independent units, excited or not by the strength of the stimulus. Although the impulses do not all travel at exactly the same rate in the different fibres, they are close together and it is possible to consider them as a single volley. Coming to the central network, the impulses do not seem to travel simultaneously, but in succession, thus a sum of propagated disturbances might occur. In any case, the *timing* of the arrival of the single impulses is meaningful, because – to be successful and produce summation – the impulses have to fall outside the refractory period of their predecessor.

8. CONCLUSION

Finally, in 1935, with regard to the "all-or-none" principle, Adrian recognised that it could be responsible for a great deal of confusion. He concluded it would be wiser not to refer to the compliance to this law, but more simply to a relation between the stimulus and the propagated disturbance. The simple fact was that a stimulus produces local effects on a nerve, or a muscle or a sense organ. These effects may vary in strength, but the "explosive waves" travelling away from the affected region cannot be altered in intensity by making the stimulus stronger or weaker. They depend at each point on the state of the fibre at that point, so they are not invariant. This was the key point.

For the sake of truth, it is necessary to add some historical considerations about further researches on the conduction with decrement and the fundamental problem of synapses. The views of Lucas and Adrian that the intensity of an impulse is independent of the strength of the stimulus were later criticized by Hallowell Davis and his colleagues at Harvard. In fact Adrian's experiments were hampered by the short lenghts of nerve with branching fibres. When longer lengths of unbranched nerve were employed (for example, the peroneal of the cat), there was sufficient room to stimulate at three sites within the narcotized region. Thus it was found no evidence of such a progressive decremental conduction. The alternative explanation given was that the narcotic caused successive failure of some portion of the fibres to account for the drop in the nerve impulse. The studies of Davis et al. in 1926 confirmed the outcome of the work of Genichi Kato in Japan, who showed in singles fibres of the amphibian (the longer nerves of the larger Japanese toad, *Bufo vulgaris*) that conduction along a narcotized region is also decrementless and obeys the "all-or-none" principle. The suspension time was the same in longer and shorter narcotized nerves.

So in the following decades the use of single fibre analysis and the recording of action potential discharges fully proved the "all-or-none" property of both motor and sensory fibres. As Alan Hodgkin observed, Adrian's idea of a continuous decrement in narcotized nerve was abandoned and replaced by the conception that, after a short transitional decrement, the impulse is conducted at a reduced, but constant amplitude, in a narcotized nerve.

Relatively to the synapses, in the first decades of the twentieth century, the hypothesis widely accepted was that transmission in the central nervous system and at neuromuscolar junction was *electrical*[1]. Thus the electrophysiologists looked for an explication closer to their own experience. Only after the second world war the modern concept of nerve conduction and the neurotransmitter action at the synapse were fully understood, and it was known that impulses get across synapses and neuromuscolar junctions by *chemical* transmission. But, as matter of fact, these further developments belong to a successive chapter of the history of neurophysiology.

ABSTRACT

In 1905 the Cambridge physiologist Keith Lucas extended the "all-or-none" principle (introduced by H.P. Bowditch for the cardiac tissue) to skeletal muscle and nerve fibres. Nevertheless, in a short time it was clear that nerve fibres obey this law, but also that frequency of discharge is another relevant factor in the nervous conduction.

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[1] Back in the twenties Otto Loewi demonstrated the action of a chemical substance as a neurotransmitter. In the thirties there was a neurophysiological debate on how the nervous system transmission works and, in particular, at the level of the neuro-muscular synapses. The school led by John Eccles asserted that the conduction of the action potential depends on passive currents directly diffusing from the pre-synaptical to the post-synaptical neuron. In contrast, according to a pharmacological point of view, Henry Dale argued that the transmission was due to a chemical mediator released by the pre-synaptic cell.

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