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Review

Nerves, alcohol and drugs, the Adrian–Kato controversy on nervous conduction: deep insights from a "wrong" experiment?

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Abstract

Edgar Douglas Adrian, a dominating figure of 20th century electrophysiology, published in 1912 a study on the effects of the conduction block induced by application of alcohol vapours to small segments of nerves from which he derived the conclusion that nerve signals regenerate along the nerve fibre during the conduction process. This conclusion was based on results of experiments in which the time required to produce a conduction block was found to decrease as the length of the nerve segment treated was increased. These results could not be confirmed when similar experiments were performed about 10 years later by Gen'ichi Kato, a leading figure of Japanese physiology and founder of one of the great schools of Japanese electrophysiology. Directly or indirectly, the Adrian–Kato controversy was at the inception of two of the most important advancements of 20th century neurophysiology: the elucidation of the mechanism of nervous conduction in squid giant axon by Hodgkin and Huxley and the discovery of the saltatory conduction in myelinated nerve fibres by Tasaki, Takeuchi, Huxley and Stämpfli. This controversy is also interesting for its epistemological aspects, which is important now to re-evaluate.

Theme: Excitable membranes and synaptic transmission
Topic: Nervous conduction impairments

Keywords: Nerves, alcohol and drugs; Adrian–Kato controversy; Nervous conduction

> A disturbance, such as the nervous impulse, which progresses in space must derive the energy of its progression from some source; and we can divide such changes as we know into two classes according to the source from which the energy is derived. One class will consist of those changes which are dependent on the energy supplied to them at their start. An example of this kind is a sound wave or any strain in an elastic medium which depends for its progression on the energy of the blow by which it was initiated [...]. A second class of progressive disturbance is one which depends for its progression on the energy supplied locally by the disturbance itself. An example of this type is the firing of a train of gunpowder, where the liberation of energy by the chemical change of firing at one point raises the temperature sufficiently to cause the same change at the next point. Suppose that the gunpowder is damp in part of the train; in this part the heat liberated will be partly used in evaporating water, and the temperature rise will be less, so that the progress of the chemical change may even be interrupted; but if the firing does just succeed in passing the damp part, the progress of the change in the dry part beyond will be just the same as though the whole train had been dry. The recovery of the nervous impulse after its reduction in a narcotised tract of nerve suggests that the disturbance transmitted may be of the second type, depending for its progression on the local supply of energy from a source distributed along the nerve fibre.

In these words there is a clear and vivid recognition of a fundamental property of nerve signal conduction, i.e. its regenerative character and its dependence for signal progression on an energy locally distributed along the propagation line. The passage quoted marks the beginning of a chapter of *The conduction of the Nervous Impulse*, a

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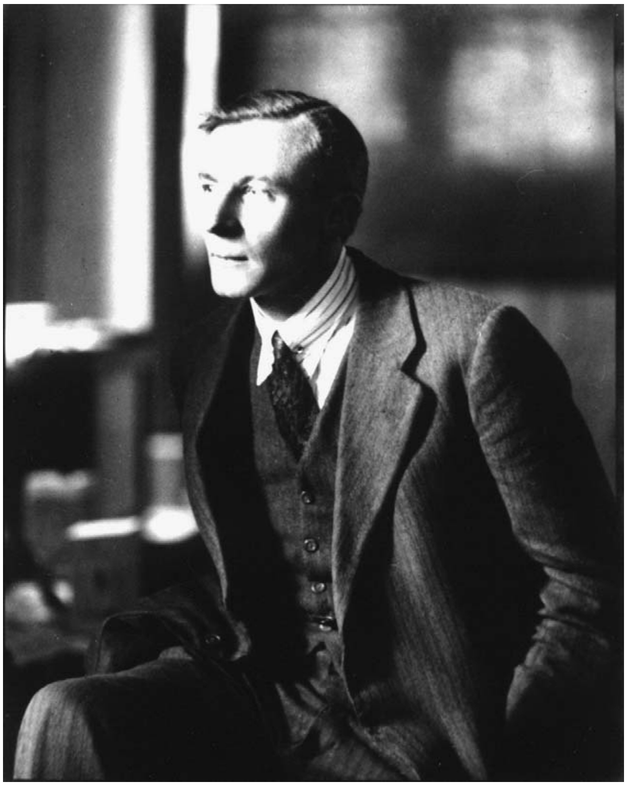

Fig. 1. Edgar Douglas Adrian at the epoch of his first electrophysiological studies (by courtesy of the Library of the Trinity College, Cambridge).

landmark book in the history of physiology. This was the book that Keith Lucas (1876–1916), an eminent British physiologist, was writing in July 1916, a few months before he lost his life in an airplane accident connected to the first world war. It was edited and published in 1917 by Lucas' pupil, Edgar Douglas Adrian (1889–1977), a name bound to become famous in the annals of 20th century science [47].

The last sentence of the citation shows that Lucas' (and Adrian's) conclusions on the nature of nerve signal progression were derived from experiments on the effects of narcotics on localised portions of nerves. These experiments were the most recent developments of a long research endeavour on excitable tissues initiated by Lucas at the beginning of the century, which had led, among other things, to a clear demonstration of the "all-or-none" character of muscle and nerve response ([42–44,46] and see also Refs. [13,14] and [3,8]). The localised application of agents capable of interfering with nerve conduction was based on a technique indicated as the "gas chamber", first introduced by Grünhagen in 1872 with the purpose of investigating nerve function impairments brought about by treatment with carbon dioxide [20]. Since then, it had been used for the treatment with a variety of agents, such as alcohol, ether, chloroform, local anaesthetics, following a diversity of experimental protocols.

A particularly striking application of the technique was made in 1912 by Adrian (then a 23-year-old student of the Trinity College, see Fig. 1). Adrian set up three different frog nerve-muscle preparations and submitted them to alcohol vapours using a modified "gas chamber" that allowed for simultaneous test and control experiments (Fig. 2A). He estimated the time necessary to induce complete nerve conduction block (or "extinction time"), revealed by the absence of muscle contraction in response to nerve electrical stimulation, when the treatment was applied to different segments of the nerve, namely a large 9-mm

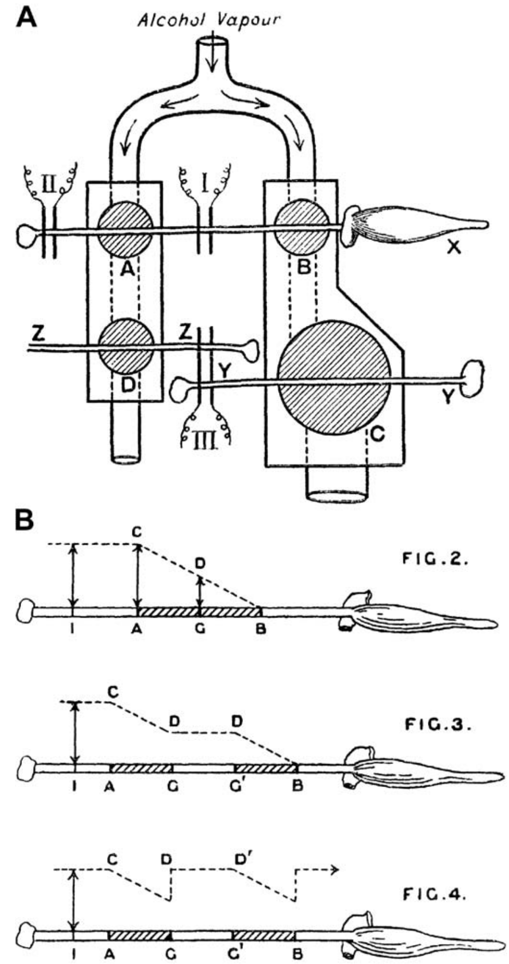

Fig. 2. (A) The apparatus used by Adrian to apply alcohol vapours (and other "narcotics") to segments of the frog nerve. The conduction is monitored by the muscle response produced by electric stimulation in various regions of the nerve as indicated. The apparatus allows for the simultaneous application of alcohol vapours to different segments of the nerve. (B) Schemes illustrating Adrian's interpretation of nerve conduction experiments based on the hypothesis that conduction occurs in a decremental way in the narcotised nerve segment. The upper panel shows why, according to Adrian, a nerve would be blocked more easily if the narcotic is applied to a long segment. The middle panel shows that a similar situation should apply to the condition of application to two short segments separated by an untreated zone, in the case the signal did not regenerate after passing through the first segment (a possibility that Adrian rejected). The lower panel illustrates the way Adrian interprets the course of the nerve signal in the experiment of application to two short segments separated by an untreated zone (from Adrian 1912, [1]).

tract in one preparation, a small 4.5-mm tract in a second one and in a third preparation, two 4.5-mm tracts separated by a 4.5 untreated zone. In the case of the treatment restricted to the single small tract, Adrian observed that it took about twice the time to achieve the block compared to the condition of alcohol application to the large tract (19 versus 11.5). Moreover (and surprisingly), there was no significant difference in the extinction time when alcohol was applied to two separated short segments compared to the single tract experiment [1].

In order to account for the shorter extinction time with long segment application (compared to the case with the single short segment), Adrian assumed (as proposed by many previous authors [15,16,53] and strongly advocated particularly by Max Verworn, a leading figure of German physiology, see Ref. [58]) that in the narcotised region, conduction occurred in a spatially decremental way. Moreover (and importantly), the similarity of the extinction time when alcohol was applied to a single tract or to two short segments was considered as evidence that the signal could recover its full amplitude after passing through a zone of partial block if, in the course of its propagation, it encountered a sufficiently long tract of untreated nerve (see Fig. 2B, lower panel). The general conclusion (discussed at length in the 1917 book) was that the nerve signal regenerated in the course of its propagation because it depended, for its progression, on a local energy available along the conduction line. In this respect, it was thus somewhat like the firing of a train of gunpowder, according to a metaphor that had been evoked long before, at the time when Hermann von Helmholtz first measured the nerve conduction speed [21,51].

Through the work of Adrian and Lucas the regenerative character of nerve signal was thus fully recognised. This ideally opened the way to the modern phase of investigation on the mechanisms underlying the generation and propagation of nerve that culminated in epochal studies on squid giant axon published by Alan Hodgkin and Andrew Huxley in 1952 (partially in collaboration with Bernard Katz, see Refs. [30–34]). This modern phase began at around 1934, with initial experiments performed by Alan Hodgkin, at the time a young student of Adrian at the Trinity College (see Refs. [22–25] and [27]). As with Adrian, Hodgkin also published his first paper in the *Journal of Physiology* at the age of 23. As we shall see, the early experiments of Hodgkin are in some way a continuation of the work that Adrian (and Lucas) was doing about 30 years before. The ideal path that goes from Lucas' and Adrian's experiments to Hodgkin's research represents one of the main developments of the 20th century nerve physiology. It is, however, far from representing a simple and straightforward line of scientific progress, as it might appear at first view.

Some years after the publication of Lucas' book, nerve block experiments were pursued in Japan in the laboratory of Gen'ichi Kato (1890–1979) at Keio University. Kato [37] was not able to confirm the basic observation on which Adrian and Lucas had founded the interpretation of their experiments, namely the dependence of the extinction time of nerve conduction on the length of the nerve segment treated. According to the Japanese group, this time remained essentially the same, irrespective of the length of the nerve region exposed to narcotics. The experiment was repeated with great accuracy using a large variety of arrangements (see Fig. 3) and a great diversity of narcotising agents (alcohol, chloroform, urethane, chloral hydrate, cocaine): the time to achieve the conduction block (measured by recording muscle contraction or the amplitude of the electric response downhill away from the treated zone) was the same when nerve segments of different length were treated. In contrast to Adrian's and Lucas' interpretation, Kato accounted for these experiments by assuming that, as in normal nerves, the signal is conducted without decrement also in the nerve trunks exposed to narcotics, and that there was no summation of the effects induced in adjacent tracts of nerves (in spite of the fact that treatment could reduce the amplitude of the signal and reduce its progression speed).

Kato first presented these results at the meeting of the Japanese Physiological Society held in Fukuoka in April 1923 (see Refs. [9,12,40,41]). Afterwards, he planned to attend the XII International Congress of Physiological Sciences, to be held in Stockholm in 1926, in order to give a public experimental demonstration capable of convincing

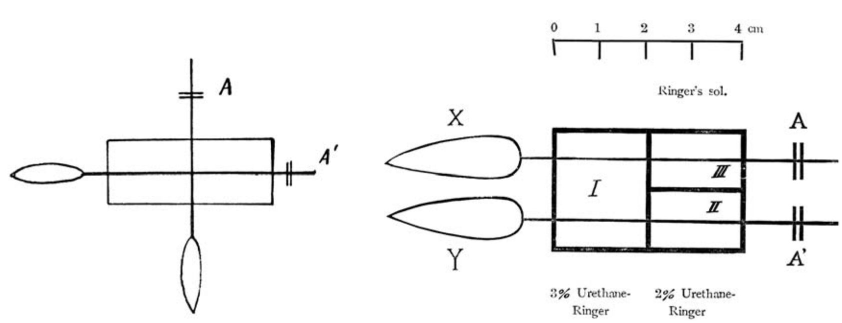

Fig. 3. Two of the arrangements used by Kato and his collaborators in order to study the effects of narcotics on nerve conduction. On the left, the setup used to apply, using a single chamber, narcotics to different lengths of two nerve trunks (usually from the same animal). On the right, a multi-chamber arrangement used to investigate the effects of different treatments applied simultaneously to various portions of the nerve (from Kato 1924, [37]).

western colleagues of an observation that disagreed the generally held view. One of the reasons of this decision was the strong opposition that these results met in Hidezurumaru Ishikawa, Kato's former teacher and an influential figure of Japanese science. Meanwhile, Kato and his collaborators had confirmed and extended their investigations using a variety of experimental strategies and applying various narcotics or asphyxiants or other procedures (heating, cooling) to produce block in many nerve types (motor, sensory, sympathetic and parasympathetic) of different animal species in order to match any possible objection to their validity and interpretation [37,38].

In a biographical sketch published in English about 30 years ago [41] (which summarises a longer narration in Japanese published in 1957, see Ref. [40]), Kato outlines in a vivid way the 1-month odyssey through the trans-Siberian railway of four Japanese physiologists (Kato himself accompanied by three collaborators, see Fig. 4) bringing, in their passenger car, giant Japanese toads (more that 150 in number) necessary for the experimental demonstration. Notwithstanding the care used for the transportation (the toads were put in special multi-compartment refrigerated boxes), all the animal died before the demonstration in Stockholm. The journey was particularly rich of vicissitudes, also because of the events associated to Lenin's uprising. Most of the railway stations were occupied by revolutionary workmen. The journey might have had dangerous consequences also for the four scientists if they were not given by the Russian authorities a providential "protection certificate".

In spite of all these difficulties, the planned experimental demonstration of nerve conduction block could be made anyhow by using frogs eventually obtained from Holland. The way Kato narrates the Stockholm events is particularly solemn and gives the impression that the attendants were really witnessing an epochal event of science history. Friedrich Fröhlich, one of the supporter of the "decremental" hypothesis, was particularly attentive, but the results left no room for doubts: it took 24 min and 16 s to block the conduction when the treatment was applied to the short (1.5 cm) segment and 24 min and 15 s in the case of the long (3 cm) segment (both nerves were from the same frog). One of the demonstrations was considered so important that one of attendants commented it by crying (in German) "Revolution der Physiologie".

It is possible that in narrating these episodes more than 30 years after their occurrence, Kato overstated their relevance. Positive evidence, however, underlines the importance attributed to his experiments both by the scientific community of those days and by the general public too (Kato's performance also receiving attention in important newspapers). In 1930, Fulton included a passage from

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Fig. 4. Gen'ichi Kato and his collaborators at the epoch of the trans-Siberian journey from Tokyo to Stockholm to demonstrate nerve conduction block experiments (Kato is the person seated in the centre of the picture). The collaborators around him are (from left to right): Ryouichi Miyake, Ryoukichi Maki and Ryouji Uchimura (from Kato 1957, [40]).

Kato's work in his *Selected Readings in the History of Physiology* [17]. A few years later, Kato received a "Guest of Honour" invitation to demonstrate some of his recent results at the XV International Physiological Congress to be held in 1935 in Moscow. In order to push him to attend the Congress, the Russian Government assured Kato of a series of favourable conditions which made the second trans-Siberian journey favourable for the party of scientists (an escort with English-speaking interpreters accompanied them during the passage through the Soviet regions) and for the toads as well.

From the point of view of the author, the importance of the events is also attested by the publication of two short books in English (one in 1924 and another in 1926, Refs. [38,39]) which provide a detailed account of the various experiments performed by the Japanese team in support of their theory of decrementless conduction in narcotised nerves. These books have historical interest also because they are among the first neurophysiological monographic volumes issued in English by a Japanese publisher (the pioneer character of the endeavour is attested by the somewhat low printing quality and by the presence of imperfections of the English). Curiously, in the 1924 book, Kato not only criticizes Adrian's (and Lucas') interpretation of the experiment on the decremental character of nerve conduction in a narcotised nerves, but also addresses the "metaphorical" argument of the progression of firing along an inflammable tract in a direct and surprising way. He reports an experiment made by one of his collaborators (Ryoukichi Maki) in which firing progression was studied in a stick of Japanese incense (instead in a gunpowder tract, whose combustion was considered too fast to be studied): selected segments of the stick were treated in such a way to diminish combustibility (to parallel the action of narcotics on nerve trunks).

Fully convinced, on the basis of his numerous experiments, of the decrementless character of transmission in narcotised regions of nerves, Kato accounted for Adrian's finding (on the dependence of extinction time on the length of the nerve segment treated) as a consequence of an experimental artefact mainly due to narcotic application to exceedingly short nerve tracts. According to the Japanese scientist, with segments shorter than about 6 mm, it was difficult to be certain that the concentration of narcotics in the treated portion really reached a local concentration in the nervous tissue similar to that attainable with longer tract application (see Fig. 5). Since in his studies Adrian compared segments of 4.5- and 9-mm length, it was possible to assume that such a "short-segment" artefact was responsible for the different extinction times observed in the two conditions.

If one follows the literature of the epoch, it is difficult to escape the conclusion that, in the controversy that opposed Kato to the supporters of decremental conduction in narcotised regions of nerves (principally Adrian), the Japanese scientist was the winner. Many scientists, and among them

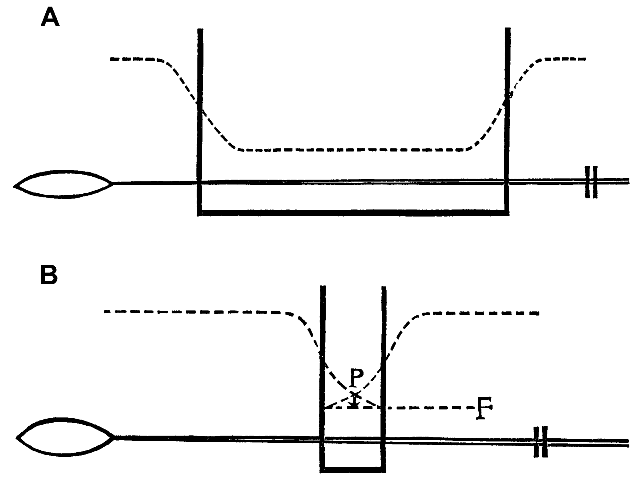

Fig. 5. (A) Scheme illustrating the main reason why, according to Kato, in the experiments of conduction block, narcotics should be applied to relatively long nerve segments in order to achieve a relatively uniform and reliable distribution. The dashed line above the schematic representation of the nerve muscle preparation plots the conductivity that is altered by the treatment applied in the central region of the nerve. In the case of a short segment (B) "border effects" would influence the spatial distribution of narcotics in the treated region and thus result in less conduction impairment (from Kato 1924, [37]).

also a former collaborator of Adrian (Alexander Forbes), confirmed Kato's results on the independence of extinction time from the length of the treated segment. Adrian's tendency to avoid a direct polemics with Kato and to open a different field of investigation (very successfully though) was probably due, at least in part, to his intimate conviction of the essential validity of the criticism of his Japanese antagonist (see Ref. [28]).

A retrospective insight to this now almost generally forgotten debate on the nature of conduction in "narcotised" nerves might serve to illustrate the complexity of a historical judgement on episodes of science progress, particularly when it implies the problem of a distinction between "truth" and "error". As already mentioned, the conclusions that Adrian and Lucas derived from their experiments were valid and far reaching because they established, at least from a phenomenological point of view, one of the most fundamental property of the progression of nerve impulse, i.e. the regenerative character of the process responsible for the renewal of nerve impulse during its propagation at the expense of an energy accumulated locally along the nerve fibre. We now know that, by depending on electrochemical energy due to asymmetric ion environments that exist at the two sides of the nerve fibre membrane, nature has been able to solve the formidable problem of conducting electric signals along long and thin nerve fibres. Due to their small diameter and to the poorly conductive nature of their constitutive materials (biological tissues have specific electrical resistances that may by 10^8 larger than good conductors like metals), nerve fibres may have resistance comparable to those of metallic cables many times the distance from the Earth to Saturn. This estimate which, in a highly suggestive way, illustrates the physical difficulties of nerve signal propagation, is taken from a book written in 1964 by Alan Hodgkin [26], whose title was (intentionally) the same of the Lucas' (and Adrian's) 1917 book (Hodgkin, personal communication).

There is another consideration that one is led to make about the controversy on the nature of conduction in narcotised nerve that opposed Adrian and Kato about 80 years ago. Although the two scientists disagreed as to the decremental character of conduction in the nerve segment exposed to alcohol (or to other inactivating agents), there was no fundamental conflict for what concerned their view of conduction in normal nerve. From this point of view, the polemics may appear overstated and centred on secondary details of experimentation and of interpretation, but attest to the great importance attributed, decades ago, to scientific debates on aspects of basic research of apparently no immediate applied relevance.

One good issue of the matter was that, in order to overtake the difficulties connected to the interpretation of conduction block experiments of nerve trunks and prove in an unquestionable way his hypothesis, Kato and his collaborators (particularly Ichiji Tasaki) developed, at the beginning of the 1930s, a technique which allowed for the anatomical dissociation of a single living nerve fibre. This procedure provided a useful preparation for the study of "microphysiology" of nerves (as Kato called it in another book first published in 1934 [39]), and in particular for the investigation of the role of Ranvier nodes in the conduction of myelinated fibres. There is indeed a line of continuity between the first conduction block experiments (carried out on nerve trunks in Kato's laboratory in the 1920s), and the single fibre studies which, in the 1950s, led Ichiji Tasaki, Taiji Takeuchi, Andrew Huxley and Robert Stämpfli to establish the saltatory character of conduction in myelinated nerves (see Refs. [35,36,52,56,57]. Essential links in this path of investigation are the initial observations made by Kato's collaborators (and notably by Tasaki) that, in single nerve fibres, sensitivity to narcotics is restricted to nodal regions, and this localised sensitivity is paralleled by a higher electrical excitability of the nodal membrane compared to the internodal surface. In order to demonstrate that an inward current appears exclusively in the nodal region during nerve impulse progression, Tasaki developed an "air gap technique" that seems to be visually inspired by the multi-chamber techniques used in the experiments of narcosis carried out in nerve trunks in the first half of the 20th century, by Adrian, Kato and many others (see Refs. [54,55]).

The importance of the single nerve fibre technique for the study of nerve function goes beyond the nerve conduction block experiments. In appropriate experimental conditions, it could be used to establish the functional role of a particular class of nerve fibres (as for instance their role in a specific reflex response). For his achievements Kato received several nominations for the Nobel prize (among his sponsors was also Pavlov, his strong admirer, see Ref. [12]).

On his side, Adrian, although apparently abandoning the study of narcotics on nerve signal propagation, and more in general of the mechanisms of nerve impulse generation and conduction, was able to achieve the first recording of unitary activity in electrically excitable cells [5–7,9,11]. It is mainly from Adrian's work that we have learned that a pulse frequency modulation is the way nerve cells can code information as electrical signals. Moreover, the term "information" in a neurophysiological context was apparently first used by Adrian in 1928 to designate the message associated to nerve electrical impulses in sensory fibres [19].

From a certain point of view, a moral that we could draw from the Adrian–Kato polemics is that, in particular circumstances, controversies can stimulate scientific progress, because they may push the contenders to develop new experimental and logical arguments from which important achievements may derive. In a somewhat related context, a particularly emblematic case was the harsh debate that, more than two centuries ago, opposed Luigi Galvani to Alessandro Volta. From Galvani's studies we have derived the notion that an electric mechanism is involved in nerve function. On the other hand, Volta's researches led to the invention of one of the most extraordinary human invention, the electric (or Voltaic) battery [48–50].

As already mentioned, it is problematic to separate truth from error in science history, and, it is also difficult to evaluate the consequences that "correct" or "wrong" experiments may have on scientific development. We could perhaps say that science progress has greatly benefited from the conclusions that Adrian derived from a "wrong" experiment (not less than from Kato's "correct" experiments), as it has happened also in other circumstances.

Considering Adrian's case as an example of a "true" conclusion derived from a "wrong" experiment may not be, however, all the truth. As mentioned, Kato found that the independency of the extinction time from the nerve length held true only when using relatively large nerve segments. He dismissed Adrian's results as consequence of an artefact due to the shortness of the nerve tracts treated. Although Kato provides apparently sound arguments to justify his judgement of the flaws in Adrian's experiments (diffusion of the narcotic outside the treated region, physical spreading of current, etc.), it may be worth considering the problem more closely, and in particular try to understand why the "artefact" becomes especially critical with segments less than 6 mm in length.

To such purpose we can use the data derived from the first studies on nerve conduction that Hodgkin started in 1934 and published in 1937. The then young student of Trinity College undertook to investigate the effects of signal conduction block obtained by cooling (or applying a pressure to) a short segment of frog nerve [22,23]. The continuity of Hodgkin's experiments with the investigation carried out in the same laboratory some 20 years before is not only logical and ideal, but also ''material'' as it attested by the use (at least in the initial phase of the work) of a similar frog nerve-muscle preparation—see Fig. 6A, a similar smoked drum device for monitoring muscle contraction and of an electric stimulator devised long before by Keith Lucas (Lucas' spring contact breaker). Only in the continuation of his study Hodgkin used more modern methods for monitoring the nerve conduction block (he recorded nerve electrical signals with the recently developed oscillographic technique, see Refs. [22,23,29]).

Hodgkin's experiments showed that, when conduction is blocked in a short nerve tract, a change of nerve activity can be detected in a limited segment outside the blocked region (and downstream with respect to the direction of propagation of the nerve signal). This change consists of an increase of excitability accompanied by (and due to) an electric response of small amplitude, and of similar polarity to the normal electric signal which propagates in the untreated region. In contrast with the normal impulse, however, both the excitability change and the electric response propagate in a decremental way, with a space constant of about 2 mm (both effects becoming practically undetectable after about 7 mm, see Fig. 6B).

As we now know well, the localised electric signal detected by Hodgkin in these experiments is the expression (in the particular conditions created by the block) of local circuit currents generated by the wavefront of the electric impulse that invades nerve fibre. In the untreated nerve, this signal is large enough to excite the tract of fibre ahead, and in this way, it plays a crucial role in the mechanism responsible for the ''regeneration'' and for the progression of nerve impulse. In nerve conduction block studies, due to the short space constant of its propagation, this signal can be detected experimentally only if the treatment is applied to a very short segment of the nerve. In Hodgkin's experiments, the cold block was usually applied to a 3.5-mm nerve tract. This distance is shorter than the 6-mm length considered by Kato as discriminating between a correctly planned experiment and a wrong one open to the short-segment artefact.

These considerations may help to throw new light on the scientific problem that was at the heart of the argument in the discussion between Adrian and Kato. No doubt, an electrical signal can propagate in a non-decremental way along a narcotised region (or in an otherwise impaired region) of the nerve (as Kato pretended, and as it might happen in ''natural experiments'' occurring in demyelinating diseases). A convenient way to show that is to expose a long nerve segment to the narcotic agent and to use a shallow narcosis. With present day techniques this experiment is easily done experiment (and is sometimes carried out as an experimental demonstration for didactic purpose).

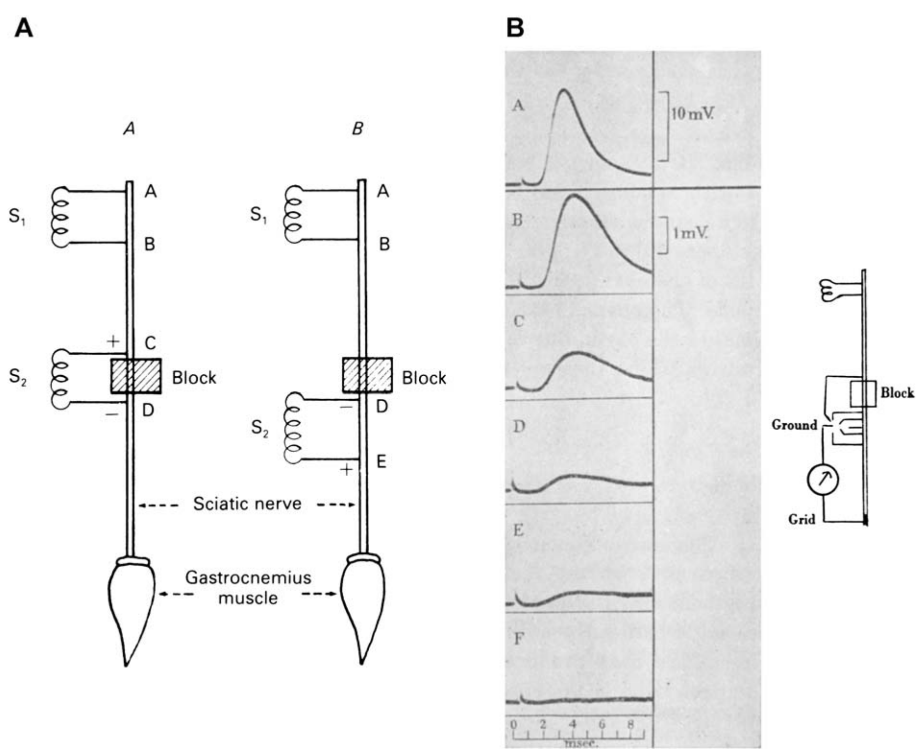

Fig. 6. (A) The initial Hodgkin's experiment of nerve conduction block by localised cooling in the frog nerve muscle preparation (from Hodgkin 1992, [29]). (B) Hodgkin's electric recording of the potential that propagated in a decremental way in a short nerve tract downhill after application of a cold block to a 3.5-mm nerve tract. In panel A is the extracellularly recorded action potential proximal to the block, B–F are the potentials distal to the block recorded at the same amplification (which is about five times greater than in A), at the following distances (the block): (B) 1.4 mm; (C) 2.5 mm; (D) 4.1 mm; (E) 5.5 mm; (F) 8.3 mm (from Hodgkin 1937, [23]).

On that regards, it is likely that the availability of giant Japanese toads, whose nerves might be more than 10 cm in length, might have represented a "material" bias to using long nerve tracts in the initial narcosis experiments carried out by Kato's collaborators.

On the other hand, if one aims at investigating the mechanism underlying the generation and propagation of nerve impulse, then an intense treatment, applied to a short region of the nerve, may provide deep insight into some of the fundamental processes involved. As mentioned, a localised application to a short nerve region was the strategy used by Hodgkin in his initial research which marked the dawn of the modern physiology of nerve conduction. In Hodgkin's experiments, the breakthrough was to investigate nerve conduction events in a localised normal region just outside the blocked tract. This avoided the intricacies of the modifications that conduction mechanism undergoes in the initial segment of the treated region, at the transition from normal regenerative progression to the decremental conduction (these modifications are complex and also specific for the treatments applied).

A particularly clear-cut demonstration that a narcotised nerve can conduct either in a decrementless and in a decremental way, depending on the way treatment is applied, was provided by Tasaki in single fibre nerve preparation of myelinated nerve (see Ref. [54]). The important point, of both physiological and pathological relevance, emerging from these studies is that signal progression in myelinated fibres occurs with a large safety factor. The signal which "jumps" from one Ranvier node to the next has an amplitude which is 5–7 times above the threshold necessary to activate a new impulse in the unexcited node ahead. In the narcotised fibre, conduction occurs in a decrementless way as far as the threshold for impulse generation in the nodal membrane is exceeded, and it turns to be become decremental with stronger narcotic action.

On the basis of the considerations above, it may be inappropriate to consider Adrian's experiment simply as a wrong experiment leading to a good conclusion.

In their investigation, Lucas and Adrian were convinced that besides (and in parallel to) the full amplitude and propagated nerve impulse (their "propagated disturbance"), nerve signalling involves a different process, mechanistically connected to the generation of the full blown impulse, but phenomenologically different from it (a process which is local and not propagated does not have the all-or-none character of the impulsive signal, and is instead capable of summation, see Refs. [1,2,4,10,43–45]). The results of Adrian's 1912 nerve block experiment were interpretable according to this view (and by no trivial reasons as we now know on the basis of subsequent Hodgkin's studies). This explains why Adrian concentrated his interest on the effects of treatments applied to short nerve segments (instead of using more extensive applications) and was ready to take his results as evidence capable of revealing the nature of local processes involved in the conduction of nerve impulse.

In the Adrian–Kato story, we can thus see another interesting aspect of scientific endeavour which may emerge in a particularly evident way in the occasion of controversies. A particular disposition, derived by both previous experimental investigation and logical elaboration (and by other more elusive factors as well), may not only orientate scientists in interpreting the results of their experiments, but can also direct them in choosing particular experimental arrangements and attributing special relevance to some of their findings, while discarding others as flawed (or of smaller interest). Although apparently performing the same experiment and trying to interpret the same phenomenon, Adrian and Kato were performing their conduction block experiments from a somewhat different perspective and with a somewhat different aim.

As Galileo has suggestively stated about four centuries ago in *Il Saggiatore*, in order to interpret the Universe, "this very great book that is continuously laid before our eyes", we need to know the characters it is written with. It can perhaps be said that, in conducting the experiments on the effects of narcotising agents on nerve conduction and in interpreting their results, Adrian and Kato were referring to somewhat different "characters" in their attempt to decipher some important pages of the book of Universe [18].

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