The present experiments represent an attempt to throw further light on the origin of the spontaneous miniature end-plate potentials and on their relation to the transmitted response (see Fatt & Katz, 1952, 1953; Castillo & Katz, 1954c-e). In particular, it was of interest to investigate whether the rate of the spontaneous discharge is controlled by the membrane polarization of the nerve endings. By passing polarizing currents through the terminal portion of a motor axon and studying their effects from the other side of the synapse, it was hoped to get further information on the neuromuscular mechanism.

**METHODS**

The technique described in previous papers (Fatt & Katz, 1951; Castillo & Katz, 1954c-e) was modified to provide means of influencing the membrane potential of the pre-synaptic nerve terminals. The m. ext. i. dig. IV of the frog was used as before, but nerve-muscle junctions were selected in the neighbourhood of the nerve entry, so that the intramuscular path of the motor axon was short. In many experiments a branch of the nerve was followed by dissection beyond the point of the main nerve entry to a region where it terminated on a group of muscle fibres.

In mounting the preparation the nerve was lifted above the muscle and supported by a glass hook to hold it taut. The Ringer solution was drained from the chamber until the fluid level reached the surface of the muscle, and the nerve was covered with a layer of liquid paraffin. The electrode arrangement is shown in Fig. 1. In addition to the stimulating and the internal and external recording electrodes, a pair of non-polarizable electrodes was used to pass d.c. through the terminal part of the nerve. The most convenient way of applying them was to place one electrode on the peroneal nerve and the other in the Ringer bath. The current lines converge at the point where the nerve twigs emerge from the muscle and cross the saline/oil interface. The advantages of this procedure are that the thinnest part of the nerve need not be touched and the polarizing electrodes do not interfere with the manipulation of the internal recording electrode. A disadvantage is that a p.d. (usually a fraction of a mV) is recorded due to current flow in the Ringer bath. The magnitude of this p.d. depends on the exact position of the microelectrode, for the greater part of the potential drop is localized, due to convergence of current lines, at the point of emergence of the nerve. The p.d. could be made negligible by removing the polarizing electrodes from the bath and applying it to the nerve itself, or by working with very fine nerve twigs which require a correspondingly low current strength, and inserting the recording electrode a little distance away from the nerve entry (cf. Fig. 4d).

**RESULTS**

**A. Effect of polarizing currents on the spontaneous activity of motor nerve endings**

The experiments described in this section were made by passing prolonged electrotonic currents through the terminal part of the motor nerve and recording changes in the local discharge of miniature e.p.p.’s. Care was taken, by increasing the current gradually, to avoid the initiation of a nerve impulse.

The experiment depended upon a selection of end-plates near the entry of the polarized nerve branch. The farther the junction and the longer the intramuscular portion of the supplying axon, the more remote become the chances of producing electrotonic effects at the terminals. Moreover, if an attempt is made to obtain electrotonic effects on a distant junction, there is the risk of damaging the nerve by using excessive current strength. Once these difficulties are realized, reproducible results can readily be obtained in most preparations.

1. **Cathodic currents.** When a strong enough current is passed through the motor nerve, with the cathode near the intramuscular endings, the rate of firing of miniature e.p.p.’s increases well above the spontaneous background activity. The effect is graded according to the strength of the current and
Fig. 2. Electrotonic effects on the discharge of miniature e.p.p.'s. a-f, cathodic; g, h, anodic polarization of nerve endings. Direction and relative strength of current (passing through nerve) are registered by second oscilloscope beam. Downward deflexion means descending current. Voltage scale applies to miniature e.p.p.'s recorded with intracellular electrode.

Electrotonus at motor nerve endings

ceases as soon as the current is withdrawn. Examples are shown in Fig. 2, and the relation between changes in firing rate and current intensity is illustrated in Fig. 5. It is of interest that this relation is of the same non-linear type as that found for the cathodic local response of nerve fibres (Katz, 1937; Hodgkin, 1938; Castillo & Stark, 1952).

The absolute current intensities at which these effects were observed (usually less than 1 μA) are of little significance, as they depend on the thickness of the nerve branch and the proximity of the endings. To obtain appreciable changes in firing rate the current had to be increased usually above the strength at which local anodic block was produced, though in some cases weaker current gave clear effects.

The frequency of the discharge rose while the current increased and sometimes continued to rise slowly after the current strength had reached a steady level. Unless excessive intensities were used which caused irreversible damage, there seemed to be little or no accommodation to the cathodic current; the discharge remained at high frequency for many seconds while the current was flowing and promptly declined when the current was discontinued.

(2) Anodic currents. It would be natural to suppose that the spontaneous activity, in the absence of polarizing currents, and the increased random activity elicited at the cathode have the same origin, in other words that the rate of spontaneous discharge is controlled by the level of the resting potential and increases when the nerve endings become depolarized. One would, therefore, expect that hyperpolarization, at the anode, would reduce or suppress the spontaneous activity.

Anodic polarization produced, however, an entirely unexpected result. With weak currents no effect was observed. Above a certain threshold strength, a prolonged outburst of miniature potentials occurred. With intermediate intensities, brief bursts were observed appearing after a variable delay. The effect is illustrated in Figs. 2–4 which show several other characteristics of the ‘anodic burst’. The discharges were of high frequency and commenced suddenly; once started, their further course seemed almost uncontrolled by the current; in some records, intermittent bursts were seen while the current was on, in others the firing continued for many seconds after the current had been withdrawn and gradually died down.

The phenomenon had in many ways the character of a triggered, ‘dielectric breakdown’ effect which might indeed be imagined to occur if the membrane were subjected to too high a voltage.

While the effects on the frequency of the discharge were easily observed, the size of the miniature potentials did not seem to be greatly altered by currents of either direction. Unfortunately, amplitudes of individual potentials cannot be measured at high rates of discharge, and the information on this point is therefore incomplete. There was no significant change in size pre-
coding or following anodic bursts, the mean difference in nine experiments being nil. During cathodic currents, eighteen out of twenty-one experiments showed no significant change. In three experiments there was an increase in mean size, but there was reason to suspect this to be due to accidental factors; in two experiments, the apparent increase in size probably arose from the greater chances of 'multiple coincidence' at the higher rate of firing (cf. Fatt & Katz, 1952, p. 125); in the third experiment, the 'resting' discharge was extremely infrequent and the sample probably inadequate. The average effect in twenty-one cathodic experiments, including these three, was a 5% increase of amplitude.

The fact that anodic as well as cathodic currents caused an increased rate of end-plate activity seemed so strange that a careful search for artifacts had to be made. We suspected that the current might have caused the muscle to contract and the increased activity might have been due to mechanical stretch of nerve endings (see Fatt & Katz, 1952, p. 122). Although it was difficult to see how the muscle could have been stimulated in the Ringer bath, nor had any electrotonic potentials been detected inside the muscle fibres, more direct tests were necessary to rule out contraction artifacts. The following observations are relevant to this point: (i) When the distal polarizing electrode was taken out of the bath and placed on the nerve itself, passage of current through the muscle bath was eliminated without in any way altering the result of the experiment. (ii) The observed changes in activity vanished when the distal polarizing electrode (or the fluid level, with the electrode immersed) was moved along the nerve several millimetres away from the muscle. (iii) Changes of activity were only recorded from end-plates whose nerve supply was intact, not from junctions whose axons had been severed at the entry into the muscle. (iv) In prostigmine-treated muscle, the 'anodic bursts' produced a large enough depolarization to give rise to spikes and twitches. Even when such vigorous mechanical disturbances occurred, no change in activity was observed at junctions whose axon supply had been cut near-by. In view of all these observations, mechanical artifacts could be safely dismissed.

There remains then the peculiar fact that, independent of its polarity, an applied current increases the spontaneous discharge of miniature potentials,
but cannot reduce it. Nevertheless, the character of the anodic burst is quite distinct from the graded cathodic effect, and it is very probable that different mechanisms are involved.

The situation in these experiments is more complicated than, for instance, at the sensory nerve endings of a muscle spindle, whose discharge can be increased in frequency by cathodic and lowered by anodic polarization (unpublished experiments by C. Edwards). In the case of these sensory endings, the rate of firing appears to be directly controlled by the level of the membrane potential (cf. Katz, 1950), while in the present experiments the absence of an anodic reduction makes it doubtful whether the spontaneous activity depends on the membrane potential in any simple way. It is more probable that electrotonic potentials produce increased activity at the motor nerve terminals by indirect means, for instance, by altering their membrane permeability. Such an indirect effect may well have a threshold, or be related to current intensity in the non-linear fashion observed with cathodic polarization.

In the terms of a previously discussed hypothesis (Castillo & Katz, 1954c), the miniature potentials are said to be due to the activation, in the nerve terminals, of specific carrier molecules (\(X^\prime\)). They may originate in different ways and from different inactive precursors; it was suggested that one of these is a calcium compound CaX, activated specifically by the nerve impulse. Another type of precursor may reach the excited state by thermal activity and so give rise to spontaneous discharges. This hypothesis was put forward to account for the facts that Ca deficiency (or addition of Mg) blocks the response, but not the spontaneous activity of miniature units.

One may suppose that cathodic currents produce their effect via a local-response mechanism, operating in a manner analogous to the nerve impulse. In other words, the firing at the cathode might be a maintained and attenuated form of normal response.

On the other hand, the anodic bursts which are often followed by uncontrolled after-discharge bear a resemblance to a breakdown phenomenon rather than to a physiological response. They might be due to a much more drastic disturbance of the membrane, e.g. ionizations caused by excessive voltage, in the course of which large numbers of active \(X^\prime\) molecules may be liberated.

With these suggestions in mind, the effects of Mg and Ca on the polarization phenomena were investigated. If the cathodic effect depends on the normal response mechanism of the nerve endings, one would expect it to be strongly inhibited by Mg, \((a)\) because of the specific synaptic blocking action of Mg, and \((b)\) because of a rise in the threshold of electric excitation. The effect of Ca is more difficult to foresee because its two actions would tend to cancel rather than potentiate. If the anodic effect is due to a physical 'breakdown' phenomenon, it would presumably remain unchanged by either of these ionic influences. These predictions were indeed borne out by the results of ten experiments, examples of which are shown in Figs. 5 and 6. Although the experiments were not accurate and often suffered from a gradual decline of the cathodic 'response', it was clear that with a given current, the cathodic effect was greatly reduced, and often became insignificant, when a high Mg (14 mm) and low Ca (0.9 mm) concentration was used. On the other hand, there were no obvious changes in the anodic effects; high-frequency bursts and prolonged after-discharges were still observed at the usual current intensities. In an experiment in which the Ca concentrations alone was changed to \(\frac{1}{4}\) and 4 times the normal level (1.8 mm), no clear effect was obtained. On the other hand, when the cathodic effect had been reduced or suppressed by 10 mm-Mg, PH. CXXIV.
addition of 6 mM-Ca restored the cathodic firing rates, at least at some junctions, to nearly their original value (cf. Fig. 6). One may conclude, therefore, that the mechanism of the cathodic firing is influenced by Ca and Mg in the same antagonistic manner as the response to a nerve impulse.

Fig. 6. Effect of Mg and Ca on the cathodic increase in random firing. Plotted as in Fig. 5, ordinates showing increments in discharge rate (resting rate was 1–2 per sec), abscissae relative current intensities. Five successive runs were made, in the following order: 1, normal Ringer (hollow circles); 2, 10 mM-Mg (hollow triangles); 3, 10 mM-Mg + extra 6 mM-Ca (full circles); 4, 10 mM-Mg, as in 2 (full triangles); 5, 10 mM-Mg + extra 6 mM-Ca, as in 3 (crosses). Prostigmine, 10⁻⁴ (w/v), was used throughout.

Anodic breakdown phenomena in medullated axons

In order to find out more about the nature of the anodic effect, the reaction of isolated nerve fibres to large anelectrotonic potentials was studied. It had previously been shown by Hodgkin (1947) that the membrane of a non-medullated axon suffers a gradual loss of resistance when it is subjected to an excessive anodic potential. It was of interest to repeat the experiment on a small, confined area of axon membrane, e.g. at a node of Ranvier, where the situation might simulate that of the nerve endings a little more closely.

Medullated fibres were isolated from frog sciatics and mounted on ‘ridge insulators’ (Methods, Fig. 7). Polarizing currents were applied between electrodes 1 and 2 and potential differences recorded between 3 and 4, using a duplicate channel in which rapid fluctuations were selectively amplified. Figs. 8 and 9 show anodic ‘breakdown effects’ which occurred when the electrotonic potential became excessive. The abrupt and fluctuating character of the phenomenon is clearly seen. When the polarity of the current was reversed, a breakdown took place at the adjacent node in pool A, resulting in a sudden increase of the recorded p.d. The breakdown occurred when the applied p.d. between pools A and B exceeded a few tenths of a volt (observed range 150–400 mV), and the size of the electrotonic p.d. (recorded between pools B and C) approached that of the spike. In some cases (e.g. Fig. 9, record 5) the electrotonic p.d. collapsed almost completely, followed by a

Fig. 7. Medullated axon mounted on vaseline ridges which separate three pools of Ringer solution, A, B and C. Nodes of Ranvier indicated by gaps 1 and 2, polarizing; 3 and 4, recording electrodes.

Fig. 8. Action currents (a, b) and electrotonic currents (c–e) recorded from medullated axon. Recording electrodes shunted with 3 MΩ. Records a and b, response to stimulation at central end of nerve obtained before and after records c–e. c–e, effect of polarizing current. Current was applied and withdrawn gradually (time constant about 1 sec). Final voltage between polarizing electrodes approximately 0.25 V. Pool B was anodic in c and d, cathodic in e.

partial recovery and continued fluctuations; in other instances, the changes in amplitude were relatively small. When the current was withdrawn, the ‘breakdown noise’ gradually died out. It is of interest that the effect was still obtained in axons which had been paralysed by 1% procaine or by substituting choline for sodium. The effect of strong polarizing currents used in these experiments was not immediately injurious; thus the spike records in Fig. 8
obtained before and after a series of local 'breakdowns' did not show much change; but eventually irreversible damage resulted.

There is much resemblance between the anodic effect in the axon and the bursts of activity observed at the nerve-muscle junction. There are, however, some important points of difference. The voltage fluctuations of the axon show no distinctive standard component comparable to the miniature e.p.p. and during their subsidence merge imperceptibly into the base-line noise. It is uncertain, however, whether this difference has much significance, for it might result merely from unfavourable recording conditions. (A similar picture is indeed obtained at curarized end-plates where individual miniature potentials are too small to be distinguished, while anodic bursts can still be recognized by a suddenly intensified 'noise'.) It should also be remembered that the electric activity which one records at the end-plate must represent a 'filtered' version of the events in the nerve endings: for pre-synaptic disturbances which are not specifically connected with ACh-release are probably not transmitted.

A more significant difference is that the large anelectrotic potential which precedes and initiates the disturbances in the nerve membrane, fails to appear in the post-synaptic record (Castillo & Katz, 1954a). Any steady deflexions which were observed (e.g. Figs. 2g and 4a) were external p.d.'s due to current flow in the Ringer bath. They did not exceed a fraction of a millivolt and were eliminated by placing the distal polarizing electrode on the nerve (see Methods).

The absence of any electrotonic transmission across the nerve-muscle junction is of great interest, especially as these experiments provide positive evidence that electric changes in the nerve endings, other than impulses, can elicit local transmitter activity. The firing of miniature e.p.p.'s induced by the passage of a steady current through the nerve can only mean that electrotonic potential changes have reached the nerve terminals, or at any rate the points at which release of ACh and the initiation of miniature e.p.p.'s take place. The anodic effect, in particular, appears to be the result of an excessive hyperpolarization of the nerve endings, and yet no detectable trace of such hyperpolarization is transmitted to the muscle fibre. These results confirm the findings of Kuffler (1949), who, in various careful attempts, failed to observe transmission of electrotonic potentials across the myoneural junction or to influence the synaptic delay by varying the strength of the stimulus applied to the terminal portion of the nerve. It has been suggested (see Bullock, 1951) that the failure might have been due to excessive attenuation of electric signals in the nerve endings rather than across the synapse, but it would be difficult to maintain this argument against the present evidence, viz. that firing of miniature e.p.p.'s can be induced by pre-synaptic currents which themselves fail to be transmitted. In conjunction with Kuffler's (1949) findings, therefore, the present experiments strongly support the view that propagation of signals by local circuit action comes to a halt at the nerve-muscle junction and takes no direct part in the synaptic transmission process.

B. Effects of polarizing currents on neuromuscular transmission

In the preceding experiments, the influence of a 'pre-synaptic' electrotonus was studied on the random activity of the nerve-muscle junction, in the absence of a nerve impulse. It remained to be investigated whether the end-plate response to an impulse could be modified by electrotonic currents in the terminal parts of the nerve axon.

This experiment is more difficult to perform because electrotonic block occurs in the axon at a relatively low current strength, and the usable range of intensities is therefore much smaller than in the previous work. Moreover,
the experiments are complicated because the polarizing current may modify the transmitted response at several stages: (i) by electrotonic changes in the amplitude and duration of the pre-synaptic spike (cf. Lorente de Nó, 1947); (ii) by direct activation, or by altering the chances of response, of the terminal units (cf. Section A); and finally (iii) by partial blockage of the nerve impulse in its terminals when the current becomes too strong. A variety of effects have indeed been observed which may be attributed to these different causes, but some of which are difficult to interpret. They will be described in the order of regularity with which they have been observed.

The success of these experiments, even more so than in the previous section, depended upon a close proximity between end-plate and nerve entry into the muscle bath, and at many junctions, no effect could be obtained except axon blockage and disappearance of the e.p.p. To reduce the risk of mechanical damage, with the internal recording electrode, all the experiments were made on reduced, subthreshold, e.p.p.'s, transmission having been blocked by curarine, Mg, or previous stimulation, as stated below.

(1) ‘Anodic facilitation.’ This was a clear effect observed at many junctions. It consisted of an appreciable increase in the size of the e.p.p. when the nerve endings were subjected to moderate anodic polarization. Examples are shown in Fig. 10, from preparations blocked by curarine (records 2–4) or by prolonged previous stimulation of the nerve (records 1). The relation between current strength and e.p.p. amplitude is illustrated in Fig. 11. The maximum observed increase of the e.p.p. was 85%.

It should be noted that this effect is in no way related to the increase of the e.p.p. which accompanies post-synaptic hyperpolarization (Fatt & Katz, 1951, p. 557). In the present experiments, the resting potential of the muscle fibre remained unaltered, and the change in the e.p.p. must have been due to an increased power of transmission by the nerve impulse (cf. Lloyd, 1949; Castillo & Katz, 1954b).

It has previously been shown (p. 589–590) that the size of the individual miniature potentials is not affected by anodic polarization of the nerve; hence the increase of the e.p.p. is probably due to a recruitment of additional ‘quanta’ (see Castillo & Katz, 1954e).

The phenomenon of anodic facilitation is not entirely new nor unexpected. It appears to be related to the known fact that the amplitude of a nerve or muscle spike increases during a period of hyperpolarization (cf. Lorente de Nó, 1947; Lloyd, 1949). The present results suggest, indirectly, that the size of the action potential in the nerve endings is one of the factors which controls ACh release, and that it can do so in a ‘quantal’ manner.

(2) Other effects. The influence of stronger currents and of cathodic polarization was not clear-cut and will be described very briefly. We failed to observe a significant depression of the e.p.p. with moderate cathodic currents, cor-
The procedure was to stimulate the nerve at a low rate (twitches having been abolished by Mg), then to apply increasing anodic polarization and discontinue it when an outburst of miniature potentials had been produced.

Results are illustrated in Fig. 12. The e.p.p. vanished (often after a transient increase of the kind described on p. 598), the nerve being blocked by the anodic current long before the 'bursting' threshold had been reached. When the current was withdrawn, the e.p.p. reappeared at once and was found to be significantly larger during the period of after-discharge than before. It is clear that, whatever happened in the nerve endings during the anodic burst, it did not leave behind conduction failure or reduced responsiveness of the terminal units, but rather an increased tendency to activation.

**Fig. 11.** Facilitation of e.p.p. by anodic polarization of nerve endings. Two experiments, showing up to 60% increase of the e.p.p. (curarized muscle). Ordinates: size of e.p.p. in relative units. Abscissae: polarizing current strength. Shaded area in the upper figure shows range of current intensities in which the response became irregular and intermittent failure (presumably due to anodic axon block) occurred.

**DISCUSSION**

The experiments of this paper are concerned with one main finding, namely, that post-synaptic events can be elicited and modified by local electrotonic changes in the pre-synaptic nerve endings, without involving nerve impulses. Two kinds of effects were observed: (i) the rate of random firing of miniature potentials, and (ii) the size of the transmitted response, more specifically the quantum content of the e.p.p., was changed.

While the general result is clear and needs little comment, the details are complicated, and the aim of the discussion is to try to find some order among the variety of phenomena which have been described. The main difficulty which confronts us is the fact that electrotonic influences alter the synaptic process at various points; for example, there is little doubt that the observed increases in the random discharge during anodic and cathodic polarization originate at different points of the system and involve different mechanisms.

In Table 1 observed changes in the size of response and the rate of random activity have been compiled. This summary merely shows that there is no simple correlation between the two types of synaptic activity, and yet the same unitary process appears to be involved in both, namely, a quantal release of ACh and the production of a miniature e.p.p.

In a previous paper (Castillo & Katz, 1964a) various alternative hypotheses were discussed to account for the origin of the spontaneous miniature potentials, their connexion with the activity elicited by nerve impulses, and the
differential effects of Ca and Mg on both. The scheme which seemed best suited then to fit the experimental results is reproduced below, and we may now consider whether it will also fit the observations of the present paper without additional assumptions:

\[
\begin{align*}
\text{Inactive carrier } X & \quad \text{Active carrier } X' \\
\text{Ca} + X & \rightleftharpoons \text{CaX} \\
\text{CaX} & \xrightarrow{N} \text{Ca} + X' \\
\text{Spont.} & \xrightarrow{X} X' \\
\text{CaX} + \text{Mg} & \rightleftharpoons \text{MgX} + \text{Ca}
\end{align*}
\]

On this hypothesis, the common step in ‘spontaneous’ as well as ‘evoked’ activity is the release of an active ‘carrier molecule’ X which transports, or allows the passage of, a large number of ACh ions and leads to the production of a miniature e.p.p. There are different ways in which X' can be formed: (i) from a CaX compound which is specifically acted on by the nerve impulse and transformed to Ca + X', (ii) from other inactive precursors (X) which may change to X' spontaneously, due to thermal activity. Only the first of these resources is blocked by Mg, or by Ca deficiency.

To explain the different electrotonic changes in random activity, one might suppose that the graded cathodic effect, which is sensitive to Ca and Mg, operates via channel (i), while the anodic effect is to release additional unstable precursor-molecules from the membrane. In other words, the cathodic effect would be classified as a weak form of response, while the anodic outburst is regarded as a sudden increase of the spontaneous type of activity (with the same degree of independence of Ca and Mg concentrations).

Once we accept a dual mode of origin of the miniature potential the scheme becomes so flexible that there is no great difficulty in fitting it to most of the phenomena which have been described. For example, if an additional quantity of X' is released from source (ii), this gives not only increased random activity, but also increased response, for the amplitude of the e.p.p. depends upon the number of available CaX molecules, and this becomes greater through the back reaction X' + Ca → CaX. In this way, the increase in e.p.p. associated with post-anodic firing of miniature potentials could be explained (Fig. 12). On the other hand, suppose that as the result of prolonged nerve stimulation the back reaction X' + Ca → CaX is slowed (in other words, the forward reaction becomes less reversible), then X' would accumulate and CaX progressively become depleted, and this could explain the failure of response during ‘fatigue’ and its association with an increased rate of random firing.

Finally, the facilitation of the e.p.p. (Castillo & Katz, 1954a), and the increase of the e.p.p. during moderate anelectrotonus of the nerve endings, may be tentatively ascribed to an increase in 'N' (the terminal amplitude of the nerve impulse), in conformity with known electrotonic effects on the axon spike and especially with recent observations of Lloyd (1949) on spinal reflex potentiation.

The present scheme has the virtue of helping to summarize an otherwise rather chaotic variety of phenomena. Whether the postulated X' molecules and their dual mode of derivation will survive further experimental tests is a matter of conjecture.

**SUMMARY**

1. The effect of a ‘pre-synaptic’ electrotonus on ‘post-synaptic’ activity was studied at the nerve-muscle junction, by passing polarizing currents through the terminal part of the motor axon and recording potential changes at the end-plate with an electrode inside the muscle fibre.

2. Cathodic polarization of nerve endings produces a graded increase of the rate of firing of miniature end-plate potentials.

3. Anodic polarization of low intensity has no effect on the random activity at the end-plate. When a critical current strength is exceeded an outburst of miniature potentials occurs at high frequency which may continue for some seconds after the current is withdrawn. An apparently related breakdown effect accompanied by rapid fluctuations of the electrotonic potential is observed in medullated axons when a node of Ranvier is subjected to an excessive anodic potential.

4. Although the rate of discharge of miniature e.p.p.'s can be changed by electrotonic alterations of the nerve endings, there is no direct transmission of electrotonic potentials across the nerve-muscle junction.

5. The cathodic effect is greatly reduced by high Mg concentrations, while the anodic burst of miniature potentials appears to be unaffected.

6. Different modes of action are suggested for cathodic and anodic increase of random activity. They are discussed in relation to the ‘responsive’ and ‘spontaneous’ mechanisms of acetylcholine release at the nerve-muscle junction.
7. The amplitude of the e.p.p. (in response to a nerve impulse) can be changed by passing electrotonic currents through the nerve. Among several phenomena which were observed, the most significant effect was an increase of e.p.p. during weak or moderate anodic polarization of the nerve endings.

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THE DURATION OF THE PLATEAU OF FULL ACTIVITY IN FROG MUSCLE

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When a muscle is stimulated there is an abrupt change from rest to activity (Hill, 1949). Because of the series-elastic component in muscle, the tension rises slowly, and in a twitch the tension developed is usually only a fraction of that developed in a tetanus; but Hill (1949, 1951) has shown that the intrinsic response of the contractile material is of the same magnitude in a twitch as in a tetanus and that it reaches its full extent immediately after the end of the latent period. Once elicited by a single stimulus, the active state of the muscle remains constant for a period, on a plateau, before it begins to decay.

The theoretical interest in the duration of this plateau has been discussed by Hill (1953a). The quick stretch technique which he used in his earlier experiments (Hill, 1949) did not allow him to assign any accurate value to the duration of this plateau. In his paper Hill (1949) gives a diagram where the time courses, in a single twitch, of the active state and the recorded isometric tension of the whole muscle are plotted together. The plateau of the active state curve seems to last for a little less than half the time taken by the muscle to reach its maximum tension; since the relaxation of the tension of the whole sartorius at 0° C in a single twitch can be taken to occur about 250 msec after the stimulus, the active state would have begun to subside by about 100 msec. The difference between these two times is another result of the presence of the series-elastic component, which causes a time-lag between the internal response and its external sign, the recorded twitch tension. When other more sensitive techniques were used, decay in the active state could be detected at 80–90 msec (Hill, 1953a); indeed, signs of it appeared at about 60 msec (Hill & Macpherson, unpublished). Recently, Macpherson & Wilkie (1953a) have measured the start of this decay by yet another method. They superimposed the isometric tension curves of a twitch and of a tetanus, and the moment at which the ascending phases began to diverge was taken to mark the onset of decay in the active state. This was found to occur at 50–60 msec after the stimulus and, in later experiments, at 44 msec (Macpherson & Wilkie, 1953b).