THE ROLE OF ACETYLCHOLINE IN SYNAPTIC TRANSMISSION: A CRITICAL REVIEW

BY

D. WHITTERIDGE

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The nature of the mechanism of synaptic transmission has occupied a central place in physiological investigation for the last fifteen years; and, although there are now fewer disputed observations, the interpretations placed on the data seem to be as widely divergent as ever. In his valuable review of the evidence on the mode of action of acetylcholine (subsequently abbreviated as ACh) on the central nervous system, Feldberg (1945) spoke of the problem as "almost solved." A little later Gerard (1946), summing up the symposium on the physico-chemical nature of nervous activity, concluded that "ACh is not critically involved in nerve conduction and we must be reserved in assigning to it a role in junctional transmission particularly within the nervous system." Some new evidence which has appeared in the last few years now helps to define the points at which current views of the action of ACh are almost certainly wrong, and brings into relief earlier observations which support an alternative view.

Action of Acetylcholine in Excitation of Nerve and Muscle

In the central nervous system, exact information about events at single synapses is so difficult to obtain that the habit of arguing by analogy from the peripheral nervous system is ingrained and often profitable. It is, therefore, worth considering what is known of the mode of action of ACh and other mechanisms in the excitation of nerve and muscle.

Depolarization by Acetylcholine.—As soon as it was realized that there is some evidence for the liberation of ACh during excitation along the whole length of nerve fibres, it was suggested that this substance was responsible for the depolarization of the nerve fibre, and that by spreading forward it was responsible for the spread of the impulse. This view is ruled out by the salt bridge experiment of Osterhout and Hill (1930), and by the corresponding experiments on nerve (Hodgkin, 1939). These experiments establish that the local circuits set up between an active and an inactive point on the nerve are themselves sufficient to depolarize and therefore activate the distant point. Spread of the impulse can occur in the absence of the diffusion of any chemical substance. The view of the mode of action of ACh was therefore modified by the suggestion that the principal effect of ACh was to increase the permeability of the cell membrane, and that the effect of electrical excitation of the cell membrane was to produce the liberation of ACh. This was said to permit the depolarization of adjacent points by local flow of current, which again liberates ACh. The transmitting agent is the flow of current, but the current is generated by the release of ACh (Nachmansohn, 1945). If this is interpreted to mean that an increase of permeability due to ACh permits the flow of current generated by some unknown source of E.M.F., this view would at first sight seem to be tenable.

The strongest support for the view that ACh is intimately concerned with processes leading to depolarization comes from the nerve-muscle junction. Cowan (1938) showed that the sartorius muscle could be depolarized to a considerable extent by immersing it in a solution of ACh, and that this depolarization could be prevented by the previous application of curarime. Kuffler (1943) applied ACh locally to the end-plate region in his single nerve-muscle junction preparation, and succeeded in showing that its depolarizing effect is limited to the end-plate region. It neither depolarizes nor sets up nerve impulses on the surface of the muscle itself. Potassium however sets up impulses most readily at the end-plate region, but depolarizes both the muscle fibre and the end-plate.

Action of Anticholinesterases and ACh on Nerve.—The nerve muscle junction and probably the electric organ provide the only established cases of the depolarization of undamaged tissue by ACh, and it is therefore a doubtful assumption to ascribe all excitatory effects of ACh elsewhere to a depolarization.
The main reasons for believing that ACh plays an essential part in the initiation of nervous impulses in peripheral nerve have been summarized by Nachmansohn (1946). In the motor nerves of vertebrates, ACh is liberated by the passage of nerve impulses, conduction is blocked by anticholinesterases, cholinesterase is present in nerve and is highly specific, and choline acetylase, an enzyme system which synthesizes ACh, is also present and active. Much argument has taken place over the second proposition, the question at issue being whether the inhibitory effect of anticholinesterases, particularly disopropyl fluorophosphate, or DFP, on the enzyme system is exerted pari passu with its effects on the blocking of impulses. The results of Bullock, Grundfest, Nachmansohn, Rothenburg, and Sterling (1946) suggest that these two effects do in fact run parallel. The essential step in this argument, however, in order to establish that ACh plays some part in the initiation of the impulse, is to show that DFP blocks the conduction of the action potential because it gives rise to signs of persistent activity such as a reduction in the resting potential. Such an effect is produced by potassium, though the two actions do not run parallel (Steinbach, 1944). Recent work by Toman and others (1947) has made it clear that potassium and DFP can both block conduction, but that they do so by totally different mechanisms. When frog sciatic nerve is exposed to increased concentration of potassium, the action potential is abolished when the resting potential has been reduced by 20 to 30 per cent. In the early stages of this process the threshold to stimulation is reduced and the conduction rate is increased. The action of DFP, however, is to maintain the resting potential or increase it slightly, to reduce the conduction rate, and to increase the threshold. It has been known for some time that the local anaesthetics also block conduction in nerve fibres while maintaining the resting potential. Lorente de No (1944) showed that ACh and eserine up to a concentration of 0.001M did not block conduction but maintained the resting potential. They shared with added magnesium the property of delaying the fall in resting potential produced by asphyxia of the nerve. Eserine, in concentration of 0.01 M or over, blocked conduction, but also decreased the resting potential. If, however, blocking of conduction and inhibition of cholinesterase can occur with DFP but without change in the resting potential, it is difficult to ascribe this effect of eserine to its anticholinesterase activity.

It is, however, pointed out by Steinbach (1944) that “the injury potential should be regarded as a measurable force (or quantity since some current must be flowing) which may reflect drastic weakening of the membrane... Rectification may be a better measure of conditions at the surface of a cell; it in turn is probably considerably less sensitive than the action potential or impedance changes measured by Cole and his collaborators.”

It has also been shown that although added potassium does decrease the membrane resistance of unmyelinated giant fibres, ACh has no such effect even in very high concentrations (Hodgkin, 1947). Most of the work on the effect of DFP on the blocking of the action potential has been carried out on these fibres (Bullock, Nachmansohn, and Rothenburg, 1946), and it seems clear that as far as these fibres are concerned Nachmansohn’s view of ACh as an agent which increases membrane permeability is therefore not really tenable. The persistence of ACh seems to be associated with an increased stability of the cell membrane. There may be some important differences between giant fibres and frog sciatic nerve fibres, since the threshold of the former is increased by added potassium, (Hodgkin, 1947; Toman and others, 1947), whereas the threshold of frog sciatic nerve fibres seems to be lowered. No significant difference in the action of ACh or of DFP on these fibres has yet come to light.

**ACh and Heart Muscle.**—In spite of much conflicting evidence, it now seems clear that neither ACh nor vagal inhibitory impulses have any effect on the resting potential of heart muscle. This seems to be established for the frog’s heart which has been arrested (Segers, 1945). With a slowly beating heart the effect of ACh is to reduce the refractory period (Drury and others, 1920), and to abolish the negative after-potential which follows each beat (Segers, 1945). If the heart is beating fast the negative after-potentials will sum, and the effect of suddenly arresting the heart by any means involving ACh or otherwise will be to produce an apparent positivity, the so-called Gaskell effect. The work of Eccles and Brown (1934) suggests that ACh produces a prolongation of the process of recovery of the pacemaker, a process unaccompanied by any detectable surface potential changes. There is, however, some evidence that ACh may depolarize an injured but incompletely depolarized point (Segers, 1945).

**Saline Models.**—Another argument for an effect of ACh in producing surface potential changes and in decreasing membrane resistance is derived from the work of Beutner and Barnes (1942) on models consisting of saline solutions separated by lipid interfaces. It is not clear that these models have enough features in common with nerve cells to have any relevance to the present problem.

**Artificial Synapses.**—The position of a purely
“electrical” theory of junctional transmission has been strengthened by the discovery and analysis of a number of artificial synapses, in which an impulse from one nerve cell can excite a second in the absence of any specialized chemical transmitter mechanisms. The first of such systems to be discovered was that of Jasper and Monnier (1938), but as their synaptic delay was about 20 msec, the processes involved were probably complex. Katz and Schmitt (1939) showed that an impulse in an unmyelinated giant fibre could cause a reduction in the threshold of an adjacent parallel fibre of about 20 per cent., and that this change in threshold was related to local current flow set up in the second fibre by the impulse in the first. This change was insufficient to excite, but by arranging the fibres so that the impulse never receded from the area of contact, and by making the fibres hyperexcitable by soaking in citrate, Arvanitaki (1942) was able to make the impulse in the first fibre set up an impulse in the second. Subsequently it was found that an artificial synapse could be set up between motor and sensory fibres at the cut surface of a mammalian nerve trunk (Granit and others, 1943). A similar effect whereby impulses could be synchronized was described much earlier by Adrian (1930) at the cut end of a mammalian nerve trunk in vitro. A theoretical treatment of the relation between anatomical arrangement and changes in current flow has been given by Eccles (1946b).

The concept of excitation by local circuits has been extended to the activation of cells in the central nervous system by electrical fields due to synchronous activity of large numbers of cells. The evidence for this phenomenon is very strong in the case of the frog's brain in which the synapses are poisoned with nicotine (Libet and Gerard, 1939). If now large slow electrical waves are set up by treatment with caffeine, not only can these waves spread across the whole of the cerebrum, but they can also cross a clean section of the brain, if the severed surfaces be again placed in apposition. Similar synchronization of large slow waves across a cut surface can occur when the spinal cord is strychninized, a few segments are cleanly divided, and the cut surfaces are put back into apposition (Bremer, 1941). For our present purposes we are merely concerned to establish that synchronous activation of nerve cells may occur by electrical means, in the absence of specific synaptic mechanisms.

**Junctional Potentials.**—Other far-reaching results of investigation of the electrical changes and the corresponding changes in the excitability of tissues have been the discovery of junctional potentials, of the end-plate potential of striated muscle, of the synaptic potentials of sympathetic ganglia (Eccles and Kuffler, 1941) and of motoneurones of the spinal cord (Brooks and Eccles, 1947). These junctional potentials are localized but spread decrementally; they have a rapid rising phase and an exponential decay, with a total duration of from twenty to fifty times the duration of the action potential in the afferent fibre. They seem to give rise to impulses in the muscle fibre and the nerve cell during their rising phase, but throughout their course they also exert a facilitatory effect on the cell. In the nerve muscle junction, the end-plate potential is believed to behave in all respects like a brief cathodal polarization (Eccles and Kuffler, 1941). Assuming that the end-plate has similar properties to the nerve membrane it is possible to obtain some estimate of the time course of the transmitter agent responsible for this cathodal polarization, using Hill's (1936) equations for nerve. The transmitter agent, which may well be ACh, has an initial brief "spike" and a prolonged "tail." The spike is unaffected by anticholinesterases, but the tail is greatly increased. Although there is some evidence that the muscle fibre may accommodate to the presence of the end-plate potential, it may be large enough in the presence of anticholinesterases to give rise to repetitive responses of the muscle fibre. All the evidence is consistent with the view that the end-plate potential is an essential intermediary in the transmission from nerve to muscle.

**Sympathetic Ganglia.**—The situation in the sympathetic ganglia is in many points similar to that at the nerve muscle junction. A preganglionic volley can set up a synaptic potential which can be shown to precede the setting up of postganglionic impulses in the partially curarized ganglion. The synaptic potential seems to be due to a transmitter agent which is likewise removed by fast and slow processes, only the second of which is delayed by anticholinesterases. There is, however, still some doubt about the process responsible for the early part of the synaptic potential, a doubt which has been reinforced by recent work of de Castro (1942). He has taken the vagus nerve, and cut it above the nodose ganglion. Its central end, which after degeneration contains only sensory fibres, is then anastomosed to the lower end of the superior cervical ganglion. Contrary to expectations based on interpretations by Dale of the work of Langley and Anderson (1904), in 30 per cent. of cases the vagal sensory fibres which, like all other sensory fibres, are presumed to contain no ACh, yet succeed in establishing functional connexion with the ganglion cells. De Castro has shown that the addition of eserine does not in any way modify transmission across this ganglion. This is in striking contrast with the effects of eserine in the normal ganglion, in which eserine produces a considerable after-discharge.
to a preganglionic tetanus. If, however, the cholinergic centrifugal fibres from the lower end of the nodose ganglion are anastomosed with the superior cervical ganglion, these junctions give an after-discharge on treatment with eserine. If these findings are to be relied upon, and it has been pointed out that fibres of unexpected origin frequently appear in degenerating nerve trunks, there are two far-reaching implications; firstly that the rule that only cholinergic fibres can replace cholinergic fibres is not of general application, and secondly, and much more important, that there may be an excitatory effect common to all nerve fibres irrespective of their chemical affiliations.

The Central Nervous System.—In the central nervous system the important advances of the last ten years have been due to the analysis of the so-called "simple reflex" by limiting the stimulus used to fibres of the same function, instead of the blunderbuss stimulation of whole nerve trunks, and also to the study of the behaviour of as few neurones as possible by micro-electrode methods. In these ways it has been possible to separate two-neurone from multi-neurone reflex arcs and to distinguish between their properties. Just as central reflex time has had to be split into nuclear delay, the time needed to excite an internuncial pool, and synaptic delay proper, the time needed to excite the motoneurone (Lloyd, 1944), so it is necessary to distinguish between the components of central excitatory state due to internuncial reverberation and repetitive activity, and the residual facilitation which can be detected on motoneurones in a two-neurone arc (Lloyd, 1946; Eccles, 1946a). Central inhibitory state also seems to consist of a direct inhibition exerted on motoneurones, without measurable latency and reaching its maximum in 1 msec. (Lloyd, 1941) and much longer lasting processes occurring in interneurones probably due in part to the summation of subnormality (Lorente de No, 1939).

In order to obtain a volley of impulses in fibres of the same function, Lloyd (1946) used very weak stimuli applied to afferent nerve trunks from muscle, and recorded from the corresponding anterior roots. Such stimuli which will only excite the large proprioceptive fibres have been shown to produce a brief "residual facilitation" of motoneurones with an extreme duration of 10 or 15 msecs. The failure of Lorente de No (1939) to observe the phenomenon was probably due to the stimulation of mixed inhibitory and excitatory fibres by shocks applied to the posterior longitudinal bundle. Brooks and Eccles (1947a) have put forward a view of direct inhibition which is essentially similar to the decrease in excitability due to anodal polarization seen at an artificial synapse ahead of the advancing impulse (Katz and Schmitt, 1939). They suggest that Golgi cells with short axons may produce such an effect as long as excitation of the soma does not give rise to an impulse in its axon.

The Synaptic Potentials of Motoneurones.—Observations of the activity of motoneurones with micro-electrodes have confirmed and extended earlier observations on the potentials conducted decrementally down the anterior roots (Barron and Matthews, 1938). The synaptic potential begins about 0-3 msecs. after the arrival of the impulses at the motoneurone, reaches its peak after 1 msec, and decays over the next 10 msecs. The increase in the excitability of the motoneurone begins a little before the first sign of the synaptic potential, and rises very rapidly so that impulses are set up during its rising phase. The fall in synaptic potential goes parallel to the period of residual facilitation, and Eccles suggests that the synaptic potential is the electrical sign of the central excitatory state. The parallelism between the course of the summation of two synaptic potentials with the resulting outbursts of facilitated impulses as observed by Eccles (1946a) and the diagram of the presumed time course of the central excitatory state from the shortening of the central delay of the flexor reflex (Eccles and Sherrington, 1931) is particularly striking.

Any particular reflex usually makes use of pathways of various degrees of complexity. The knee jerk utilizes primarily two neurone pathways, but the after-discharge—which may be conspicuous in the toad, for example—is due to internuncial activity. The flexor reflex is mediated entirely by multi-neurone paths when unfacilitated; but, when preceded by a facilitatory volley, its central delay is reduced to about 1-0 msecs., perhaps because three neurone paths are now able to excite the motoneurones.

Action of ACh and Anticholinesterases on the Central Nervous System.—When we turn to a survey of our present state of knowledge of the action of ACh and anticholinesterases on the central nervous system it is at once obvious that these analytical methods have not yet been fully applied. While all the recent advances in neurophysiology have been due to the precise delimitation of the unit activities studied, work on these drugs has been based on their effects on "simple reflexes" with techniques that are not capable of analysing the results in temporal, spatial, or functional terms.

The most notable exception is the work of Bremer (1937), who pointed out that the effect of 0-1 μg. ACh injected intra-arterially in his preparation of the encéphale isole was exerted solely on the after-discharge to a sensory stimulus, not at all on the
primary wave. This contrasts with the effect of strychnine, which amplifies the primary wave and depresses the after-discharge. Nembutal has a selective depressant effect on the after-discharge. Exactly similar phenomena were observed in the spinal reflexes of the toad, in which after-discharge is conspicuous and long-lasting. The after-discharge was greatly increased by 0.25 µg. ACh injected intra-arterially, with little change in the primary reflex discharge. The anticholinesterases had similar selective effects (Bremer and others, 1942). Few comparable data are available for mammalian spinal reflexes, since most observations have been made with mechanical myographs of low natural period which are incapable of recording separately the much briefer initial reflex responses and after-discharges. When electrical recording methods have been used, they have recorded the summed electrical activity of a muscle and do not usually permit the observation of the evolution of the discharge in a single motor unit. The observations of Wikler (1945), however, have been made with a technique similar to that of Lloyd. He finds that eserine (0.25 mg/kg) does augment two neurone arcs in the spinal cord of the cat.

Some interesting conclusions may be drawn from the mechanical records available. Those of Bülbîring and Burn (1941) have the great advantage that they were made on dogs with the spinal cord separately perfused from the muscles used for recording, so that no doubt the effects concerned were central and not peripheral. They found that ACh injected intra-arterially in doses of 1 µg, produced contractions of muscles after a latency of 10 to 20 seconds. ACh without an anticholinesterase slightly augmented the flexor reflex, but had a slight transient depressant effect on the knee jerk. This difference was accentuated by anticholinesterases which depressed the knee jerk and augmented the flexor reflex. Rebound after inhibition of the knee jerk was greatly augmented by eserine. Calma and Wright (1944), have examined the effect of eserine by intrathecal injection on decerebrate and chloralosed cats. They occasionally find selective effects on the first recorded contraction and the after-waves, especially with small doses. When they obtain very large increases in tone of the quadriceps there is a fall in the peak tension of the knee jerk. This must represent a very large decrease in the excitability of the reflex centres to the afferent volley, since the knee jerk normally increases rapidly in size with increase of the initial tension in the muscle, owing to the excitation of additional stretch receptors. Up to four-fold increases in the height of the knee jerk were recorded in experiments in which the tension of the resting muscles apparently did not change much. They also find the crossed extensor and jar reflexes are increased by eserine, but the effect on the flexor reflex is variable. Inhibitory phenomena are not uncommon. Kremer (1942) obtained evidence of inhibition of the knee jerk and of spasticity in man following on the intrathecal injection of prostigmine and eserine. These results have recently been confirmed by Guttmann (1948) on patients with complete spinal transections. He finds that spasticity is abolished by prostigmine, as is the reflex emptying of the bladder, but the spinal vasomotor reflexes persist and, in a high proportion of patients, ejaculation takes place.

Selective Effects.—Crucial evidence for a selective effect on two-neurone and multi-neurone pathways can only come from preparations in which the motoneurones are not depressed by anaesthetics or narcotics, and are not subjected to an increased facilitatory bombardment from other parts of the cord. Such evidence is provided by Eccles (1947), who has observed the effects of ACh on the synaptic potential and on impulse discharge in the spinal cord. In the deeply anaesthetized cord he finds no effect whatever of ACh. In the unanaesthetized cord ACh has either no effect on the rising phase of the synaptic potential or it may cause a small decrease attributed to occlusion. The falling phase is obscured by irregular activity due to internuncial discharge, which begins after about 3 or 4 msecs. Eccles (1947) also points out that in the nerve muscle junction large amounts of ACh block the transmission of impulses and abolish the end-plate potential. A similar blocking of impulses and diminution of the synaptic potential can be demonstrated in the superior cervical ganglion. No such effect is demonstrable in the spinal cord. Even in the presence of very large amounts of ACh with an anticholinesterase, in the anaesthetized cord the synaptic potential is unaffected, and in the unanaesthetized cord it shows only a slight diminution. Unlike the junctional potentials in the nerve muscle junction and the ganglion, the synaptic potential of the cord is not prolonged by the action of anticholinesterases.

On the other hand, in view of the presence of preformed ACh, cholinesterase, and choline acetylase in the central nervous system, it is a little difficult to dismiss the excitatory effects of less than 1 µg. ACh as pharmacological actions. As there is some evidence for an action of ACh on recovery processes in the peripheral nerve, the possibility of a similar action on central neurones seems worth exploring.

Repetitive Activity.—There is good evidence of a selective effect of ACh on repetitive activity, particularly on internuncial cells. The evidence of Eccles (1947), Bremer (1937), Bremer, Bonnet, and Moldaver
(1942) strongly supports this view, and the work of Calma and Wright (1946) is consistent with it. It is unfortunate that the effect of close arterial injection of ACh was not observed in the elegant experiments of Wikler (1945).

If this facilitatory effect of ACh on repetitive activity be admitted, some idea of its mechanism seems to be necessary. It has been suggested by Lorente de No and Feng (1946) that a decrease in the L fraction of the membrane potential, which is normally responsible for a large fraction of the negative after-potential, is a necessary condition for the appearance of rhythmic activity in frog nerve. It has been shown that the appearance of ACh would increase the rate of recovery and increase the maximum rate at which the cell could discharge. This view would fit with the observations of Welsh and Hyde (1944), who find that the richness in ACh in various parts of the rat's brain varies with the resistance to asphyxia.

Excitatory and Paralytic Effects of Anticholinesterases.—A possible analogy for the reversal of effects with size of dose which occurs in the action of anticholinesterases on the central nervous system is provided by the so-called paralytic effect of overdose of prostigmin on the nerve muscle junction. Small doses of prostigmin increase the muscular contraction to a single volley by producing repetitive discharge. Large doses paralyze the muscle by allowing the accumulation of such large amounts of ACh that the end-plate remains permanently depolarized. In tissues which are not depolarized by ACh, some other explanation must be sought. If one regards the rhythmically active cell as a simple relaxation oscillator, it is clear that rhythmic activity can be abolished when the cell is permanently in either of its stable states, that is, for a nerve cell, when it is permanently polarized or depolarized. It is possible that acceleration of recovery processes might lead to the excessive stability of the cell membrane, with a resulting inexcitability. In this way ACh or an anticholinesterase might lead to increased inter-nervular activity in small doses, but might abolish activity in large doses.

Other complications are not lacking. It has been shown unequivocally that in giant nerve fibres eserine can penetrate the cell membrane and inhibit cholinesterase, whereas prostigmin cannot (Bullock, Nachmansohn, and Rothenburg, 1946). It was suggested by Schweitzer, Stedman, and Wright (1939) that the water and lipid solubility of tertiary and quaternary ammonium compounds with anticholinesterase activity might determine whether the substance had an excitatory or depressant effect. There seems now to be no reason why these hypotheses should not be tested on unitary activities under more rigid conditions.

Observations of the effect of these drugs on the cortex have been complicated by the unsuspected existence of a cholinergic vasomotor system activated by nerve fibres from the greater superficial petrosal nerve (Darrow and others, 1944). It is therefore possible that some of the effects of cholinergic drugs on the cortex may have been due to vasodilatation with an increased blood flow, with a resulting increase in the local pH and an increased local excitability of cortical neurones (Dusser de Barenne and others, 1937).

Electrical and Chemical Aspects of Synaptic Transmission.—At one time attempts were made to harmonize electrical and chemical aspects of synaptic transmission by pointing out that all current flowing in living tissues must be carried by ions, and that acetylcholine might be ionized in solution and have peculiar properties in moving from watery solutions into lipoid layers under the influence of potential gradients. No measurements of its ionic mobility have yet been made, and measurements under relevant conditions would be very difficult to make. Its limited effects on the electrical behaviour of nerve have not given much encouragement to this view, but it is by no means ruled out. It has not been suggested that adrenaline owes its excitatory effects to any electrical properties it may have, but it does show a variety of curious interactions with acetylcholine (Burn, 1945). Adrenaline is known to increase the negative after-potential in the heart, (Segers, 1945), and it is possible that these interactions between ACh and adrenaline take place at the point at which energy is made available by the enzyme systems for the rebuilding of the cell membrane. Recent work on the synthesis of ACh has established that it is related to adenosine triphosphate, to creatine phosphate, and, in fact, to the main lines of intra-cellular enzyme organization (Feldberg, 1945; Nachmansohn, 1945).

Summary

1. The evidence for the mode of action of acetylcholine on nerve and muscle suggests that, although it produces depolarization at the nerve muscle junction, it does not do so on nerve or on heart muscle.
Its first effect on heart muscle is to reduce the negative after-potential, and to reduce the refractory period.

2. Recent advances in neurophysiology have depended on the analysis of the so-called simple reflex by means of the stimulation of units of uniform function, by recording from as few units as possible and by the accurate analysis of events in time. These methods have as yet hardly been applied to the study of the effects of ACh and anticholinesterases on the central nervous system.

3. The data at present available suggest that the excitation of a motoneurone is due to the cathodal polarizing effect of the synaptic potential set up by the afferent volley. ACh seems to have no effect on this process. The main action of ACh in the central nervous system seems to be the facilitation of repetitive activity, particularly in interneurones. The mode of production of this interneuronal facilitation is at present a subject for speculation.

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D. Whitteridge

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