MODERN

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MODERN TRENDS

IN

ANAESTHESIA

Edited by

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PREFACE

MEDICINE has been called by Virgil a "Quiet Art"—yet so rapid has been its development of recent years that one may with justification wonder when is the opportunity of quietness presented. The daily round, the common task, gives little chance for the practitioner in any branch to keep abreast of the phenomenal rate of expansion and accumulation of new knowledge, let alone to reflect in peace and quiet on the direction in which we are moving. The average specialist can only manage to glance through the technical journals of his immediate interest and even this must be done at the end of a tiring and exacting day. Recent technical advances, however, can seldom be safely practised without some knowledge of the basic facts upon which they are based and these are to be found dispersed throughout journals and volumes outside the usual field of reading of the clinician.

In this book it has been our aim to present a review of new knowledge covering a wide area of theory as well as practice. We have asked our authors also to scan the horizon for signs of the direction in which we are moving and to indicate the lines upon which we must work to advance further. We had hoped that facts would be laced with a stimulating source of justifiable speculation and so put our readers in line with the most recent thoughts in this most absorbing field of medicine. It is a first attempt to do this for anaesthesia in book form and, if we have only been partially successful, that is no fault of those who have contributed; the fault must be laid at our door and attributed to our inexperience in this, we believe, new type of review.

Francis Bacon gave some good advice:

> Reade not to contradict and confute; Nor to Beleeve and Take for granted; Nor to find Talke and Discourse; But to weigh and Consider. Some Bookes are to be Tasted, Others to be Swallowed, and Some Few to be Chewed and Digested.

It is our hope that this volume might be counted worthy to be subjected to the latter treatment.

Our thanks must be expressed to all those who have given up their valuable time to contribute to these pages; to our Publishers for their patience, forbearance, advice and criticism; to Miss Finlayson, Secretary to the Department of Anaesthesia in the University of Liverpool, for a deal of secretarial assistance with the manuscripts; to those who have permitted us to reproduce illustrations from their pages, to whom we have made an acknowledgement in the captions.

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FRANKIS T. EVANS
T. CECIL GRAY

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March, 1958

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THE RELAXANT DRUGS

W. D. M. Paton

INTRODUCTION

The most striking feature of the development of anaesthesia in the last twenty years has been the progressive assumption by the anaesthetist of responsibility for the control of functions of the body normally exerted by the body itself. Originally, anaesthesia did little more than produce unconsciousness with the resultant abolition of the sense of pain. But now the anaesthetist may breathe for a patient (having paralysed the muscles with relaxants), may control the patient's blood pressure (having paralysed the normal autonomic control), may control the body temperature (by artificial thermal exchange as well as by autonomically active drugs) and may even interfere quite substantially with the electrolyte balance of the *milieu interne*. The first step in this progressive mastering of the physiology of anaesthetized patients came when curare preparations were shown to be clinically useful in surgical anaesthesia. The success of such substances, in rendering surgery quicker and more efficient, has been a stimulus not only to the development of other relaxants, but to the closer study of their action and to a general interest by anaesthetists in using drugs.

THE MECHANISMS OF NEUROMUSCULAR TRANSMISSION

It is now generally accepted that transmission at the neuromuscular junction takes place by chemical means: that is, that a propagated impulse down a motor nerve causes the release at its terminations of acetylcholine, which then excites the specific receptor area underneath the nerve endings to elicit an "endplate potential"; this in turn excites the rest of the muscle fibre electrically. Recent electrophysiological work on the neuromuscular transmission has added some new interesting items of knowledge (*see* del Castillo and Katz, 1956, for a valuable review in which the principal references will be found).

The nature of the change in the endplate membrane

Katz and his colleagues, in elegant experiments with micro-electrodes, have shown that acetylcholine produces at the endplate receptors a particular type of change of membrane permeability. They describe it as being equivalent to a "short circuit"; they mean by this that there is no *specific* increase in permeability to the ions either side of the membrane but that, so far as they could detect, the membrane becomes permeable to all ions indifferently. If this happens at a membrane, then

1—M.T.A.

the potential which will come to be recorded across it will be that seen when two solutions of the same compositions as the extracellular and intracellular fluids come into contact. This so-called "junctional potential" is fairly small (not more than 15 mV, inside negative). Whenever acetylcholine acts at the endplate, therefore, it will, by means of this "short-circuit" action, tend to "pull" the membrane potential to this level. Thus, when it acts on a resting muscle fibre, the endplate region is depolarized, that is it becomes negative relative to the rest of the fibre, and excites it. But an even more interesting effect can be produced (Fig. 1). Suppose that the fibre is excited by stimulating the muscle directly, away from the
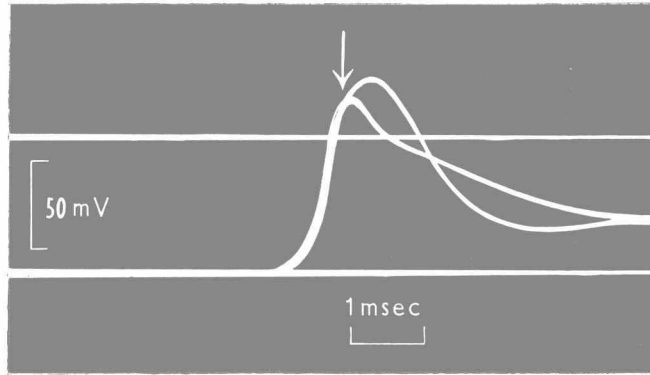

FIG. 1.—Effect of the transmitter released during a directly excited muscle action potential. Intracellular recording from endplate of frog's sartorius. Temperature 19° C. The larger of the two records is a simple *M* spike. Arrow indicates commencement of *N* response, just before the crest of the *M* spike. Upper horizontal trace, zero membrane potential, lower horizontal trace, resting membrane potential.
(*After del Castillo and Katz (1954b), by courtesy of J. Physiol.*)

endplate (*M* response). Then an action potential will sweep over the endplate region, and the usual "overshoot" of membrane potential (due to the very high sodium permeability during the action potential) will be seen. Now, suppose further that we time a shock to the nerve (*N* response) so that endplate activation by released acetylcholine coincides with the passage of the directly stimulated action potential. Again, acetylcholine's action is to short-circuit the membrane; but now it shows itself by cutting down the overshoot, tending again to "pull" the membrane to the junctional potential—this time from the opposite direction. This work has been supplemented by the remarkable observation that the transmitter will produce its effect even in the absence of any standing resting potential across the membrane. If a muscle is soaked in potassium sulphate (which completely depolarizes it), action of the transmitter can still be shown by the fall in membrane resistance which it elicits. It seems, therefore, that the action of acetylcholine, and drugs like it, at the motor endplate consists of a generalized increase in permeability which does not depend on any other particular ions being present, nor even on a membrane potential being present. It is interesting that an action of the same sort seems to be exerted by the chemical transmitter in the spinal

cord which activates motoneurones (Eccles, 1957) although we know that it is not acetylcholine.

The site of acetylcholine receptors

Del Castillo and Katz, using micro-injection techniques, have also proved that the receptors for acetylcholine are only on the outside of the endplate membrane. They used micro-electrodes filled with acetylcholine, from which brief "pulses" of acetylcholine could be discharged by passing current through the electrode; and they recorded the effect by means of intracellular electrodes. They found that typical endplate potentials can be produced more and more readily as the "syringe" approached the endplate membrane, until the point at which the membrane was actually penetrated. From this point onwards, acetylcholine was neither effective itself, nor did it modify the effect of acetylcholine administered

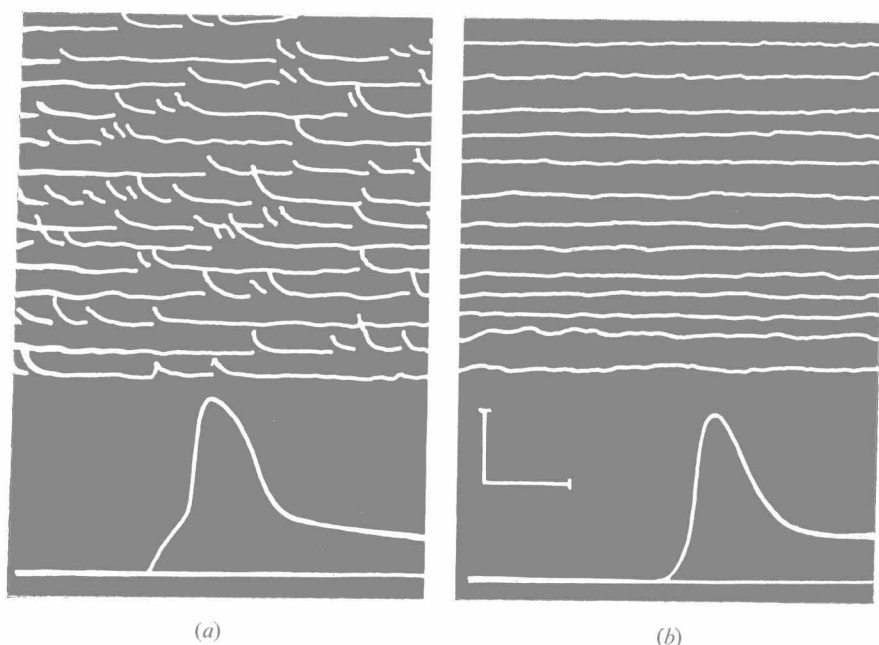(a)   (b)

FIG. 2.—Spontaneous miniature endplate potentials in frog muscle: intracellular recording. In (a) the micro-electrode was inside the muscle fibre at the endplate region; in (b) 2 millimetres away in the same fibre. The upper part of (a) shows the miniature endplate potentials, recorded at high amplification and slow speed (calibration 3·6 mV and 47 msec); the lower part the response to a nerve impulse, at low amplification and higher speed (calibration 50 mV and 2 msec). The responses in (b), recorded in the same way, show that the miniature endplate potentials are hardly detectable 2 millimetres away from the endplate; and also show the pure muscle action potential, delayed by propagation from the endplate 2 millimetres away.

(After Fatt and Katz (1952), by courtesy of J. Physiol.)

from the outside. This means that the receptors on which acetylcholine acts are only on the outer side of the membrane. It renders highly improbable a theory which postulates any action for acetylcholine within the muscle fibre, so far as changes in membrane potential are concerned.

They have extended this work (del Castillo and Katz, 1957) to show that the receptors for d-tubocurarine, decamethonium and suxamethonium occupy the same external site as those for acetylcholine, and have compared on frog muscle the actions of these agents.

The quantal behaviour of the motor nerve endings

When Fatt and Katz first came to penetrate with micro-electrodes the endplate region, they found that even when the nerve was not being stimulated the membrane was not completely quiescent, but was the site of continuous small fluctuations of potential (Fig. 2). These potential changes resembled miniature endplate potentials, being of the same shape but about 1 per cent of the normal
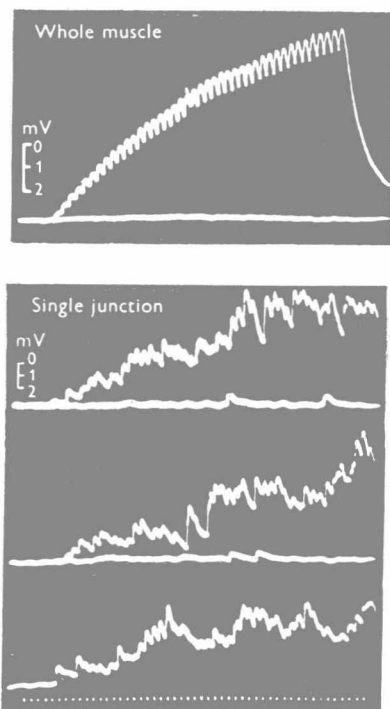

FIG. 3.—Records from whole muscle (*above*) and from a single fibre with intracellular electrode (*below*), after treating preparation with solutions of raised magnesium and reduced calcium content, during stimulation of the nerve at 100/sec. In the record from the whole muscle, the responses from some hundreds of endplates are averaged. But in the record from a single fibre, the "quantal" make-up of the response can be seen. The horizontal traces are taken in the resting state (note miniature potentials occasionally); the nerve stimuli are indicated by dots.
(*After del Castillo and Katz (1954a), by courtesy of J. Physiol.*)

endplate potential. Further, it was found that these miniature endplate potentials were always quantal, that is, of a particular size or some higher multiple of that size, the quanta often being superimposed obviously one on another. By calculating the electrical charge which was associated with these potential changes, and on other grounds, it was concluded that they could be produced only by many thousands of molecules of acetylcholine and not by single molecules. Thus far, of course, the miniature endplate potentials might not necessarily bear any important relationship to normal transmission. With the ordinary, full sized, endplate potential resulting from nervous excitation, the potential change is so large that, even if individual miniature potentials are involved, they could not be

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identified. But if neuromuscular transmission is impaired by raising the magnesium and diminishing the calcium of the surrounding fluid, then the endplate potential can be progressively reduced until it can be seen to be "fragmented", and to be built up of miniature units, quanta, comparable to those seen during the spontaneous activity just described (Fig. 3).

This is important for the theory of acetylcholine release. It had usually been supposed that the acetylcholine was in some way mobilized at the nerve ending and then diffused, molecule by molecule, out of the nerve endings towards the receptor area. On the contrary, it appears that the acetylcholine must be aggregated in packets in the nerve ending, and that it is these packets which escape from the nerve ending, there presumably breaking up and producing the discrete changes
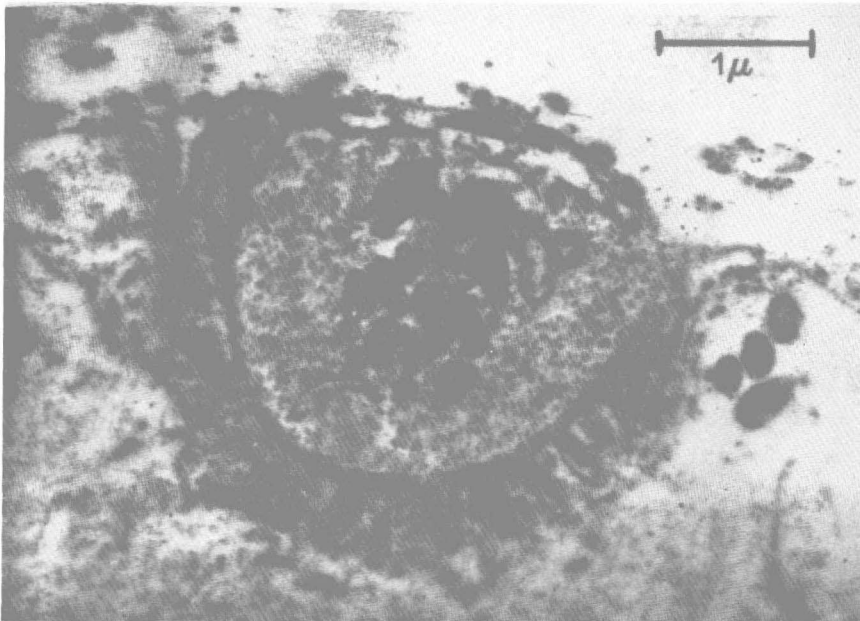

FIG. 4.—Electron micrographs of a reptilian neuromuscular junction. The nerve ending indents the sarcoplasm, and fine junctional folds project from it. The ending contains, in addition to mitochondria (large dark particles), many small globules less than 0.1μ in diameter.

(*After Robertson, cited by del Castillo and Katz (1956), by courtesy of Pergamon Press*)

of endplate activity just described. It is interesting that electron microphotographs of the nerve-terminals show, in addition to mitochondria, a mass of small vesicles, which might be imagined each to contain the acetylcholine-packet postulated (Fig. 4). The practical implication of this, of course, has still to emerge: although drugs active against acetylcholine release are known, they are not yet of any obvious use. But it makes all the difference to theories of acetylcholine release whether it is to be conceived as diffusing out of a transiently permeable membrane, or as a process whereby relatively large conglomerates must be allowed to escape.

The existence of spontaneous activity at the nerve endings (which occurs in

mammalian muscle also) (Boyd and Martin, 1956a) has the further consequence that the endplate is probably never at complete rest, even when tonic motor nerve activity is absent. The frequency of the miniature endplate potential discharge can be increased by previous tetanization of the nerve, by raised osmotic pressure of the fluid surrounding it, or by potassium; it is decreased by cold and by botulinum toxin. The size of the endplate potentials is raised only by anti-cholinesterase drugs; nothing else has been found to increase the effectiveness of the quanta of acetylcholine released. Correspondingly, a dose of a competitive blocking agent will reduce or abolish the size of the miniature potentials.

MECHANISMS OF NEUROMUSCULAR BLOCK

The interest taken in muscle relaxants, and the occurrence of rather puzzling situations after anaesthesia, have led to a good deal of speculation. It is worth recapitulating the basic features of neuromuscular block, although these have been fully described many times (see Foldes, 1957, for a recent review). In neuro-muscular block, firstly nervous transmission, and secondly muscular excitability and force, are intact. This may seem almost too elementary to mention. But in fact many cases of apnoea after surgical operation are attributed to the action of a muscle relaxant, without any test whether central nervous activity, nervous conduction or muscular power are impaired. Classical curare-like action is associated, thirdly, with a normal release of acetylcholine. There do not appear, as a matter of fact, to be any clinical situations, outside botulism, in which a depression of acetylcholine release might be anticipated. But drugs are being discovered which interfere with acetylcholine synthesis (and hence with acetyl-choline release), so that this will become an important distinguishing feature. These three criteria suffice to characterize the classical agents like d-tubocurarine and the alkaloids from calabash curare.

But the situation is different with drugs like decamethonium and suxamethonium. The classical requirements are still fulfilled, but when the action of the drugs is probed, it is found that they imitate the transmitter at the motor endplate. Thus, twitch of a mammalian muscle, the specific endplate depolarization, and the classical contracture of frog, avian and denervated muscle can all be produced. It may then be asked how neuromuscular block can be brought about. Argument proceeds about this (Foldes, 1957) and the writer wishes here only to emphasize one change which it is known takes place in the muscle fibre, but does not occur in the muscle under d-tubocurarine; this is the development of electrical inexcitability of the endplate region and its immediate surroundings. Fig. 5 shows measurements of the excitability of the endplate region under these conditions; the stimulus required to produce excitation by means of two closely spaced electrodes increases something like 25 times after the action of decamethonium. Burns and Paton (1951) concluded that this inexcitability was a direct result of endplate depolarization, and attributed it to an escape of potassium, through the reduction of the membrane potential at this point. Whatever may be said about the fluctua-tions of membrane potential in this vicinity, the fact that the membrane has become less excitable means that an endplate potential set up in this region must be larger than in the curarized muscle, if it is to excite the rest of the muscle fibre. In other words, transmission is going to fail with relatively large endplate potentials,

capable of exciting the normal muscle. This in itself is sufficient to account for the neuromuscular blocking action possessed by the compounds. It also accounts for the characteristic transience of the excitatory phenomena produced by drugs of this sort. It is a curious fact that, by injecting a depolarizing drug, a standing depolarization at the endplate is produced which, other things being equal, would be sufficient to throw the muscle fibre into a violent tetanus. It is only because the endplate region becomes less excitable that the muscle is protected from this presumably highly unphysiological and potentially exhausting state. Fig. 6 illustrates graphically the sort of sequence of events which one would reconstruct from the information available on mammalian muscles (Boyd and Martin, 1956b;

FIG. 5.—Cat, chloralose, gracilis. Graph of excitability measurements in (a) normal muscle; (b) 18 and 23 min. after 80μg/kg decamethonium intravenously; (c) after 0·7 mg/kg d-tubocurarine intravenously. Ordinates: volts required to produce standard action potential by direct stimulation. Abscissae: distance along muscle fibre of point of stimulation from centre of endplate zone at zero.
(After Burns and Paton (1951), by courtesy of J. Physiol.)
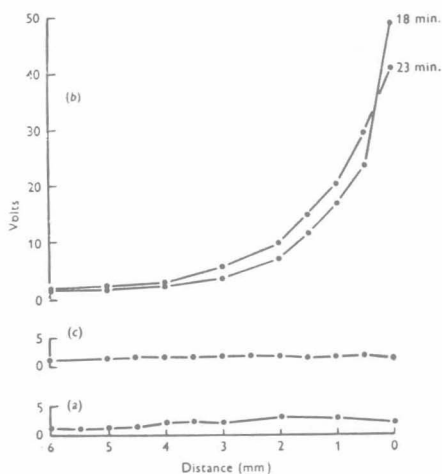
Burns and Paton, 1951). The writer believes that these are the principal mechanisms involved in the ordinary use of drugs of this type; some special conditions are discussed below. It may be noted that the fundamental cause of neuromuscular block by a depolarizing drug is not the depolarization itself (which would assist transmission) but the electrical inexcitability of the muscle resulting from it. In many respects the change of excitability of the muscle is a better sign of the nature of the block than a measure of the standing depolarization.

Accommodation to transmitter action

Although repeated cycles of paralysis and recovery can be produced with decamethonium or suxamethonium, it was early noticed that the depolarization produced in cat's gracilis muscle by successive doses dwindled somewhat (Burns and Paton, 1951). A similar phenomenon was seen in the depolarization of muscles produced by large doses of an anticholinesterase (TEPP) (Douglas and Paton, 1954): this may contribute to the resistance to cholinesterase poisoning described for certain phosphorus compounds; if an animal could be brought through a first poisoning, it was partially resistant to further doses (Barnes, 1953). A diminishing action by acetylcholine was also described on frog muscle (Fatt, 1950). In these instances, however, endplate depolarization never disappeared,

and the appearance was that of a depolarizing agent becoming less effective, rather than that of its action changing qualitatively.

Somewhat different was the phenomenon demonstrated by Zaimis (1953). On some muscles, for example of monkey, decamethonium on its first administration would have its usual action, but as doses were repeated it became less active, and came to exert actions very like those seen with d-tubocurarine. This could be detected even in the cat, if the soleus muscle was studied. These results were very similar to those found by Paton and Perry (1953) with nicotine on autonomic ganglia. In this case nicotine starts by exciting ganglia, with a well marked
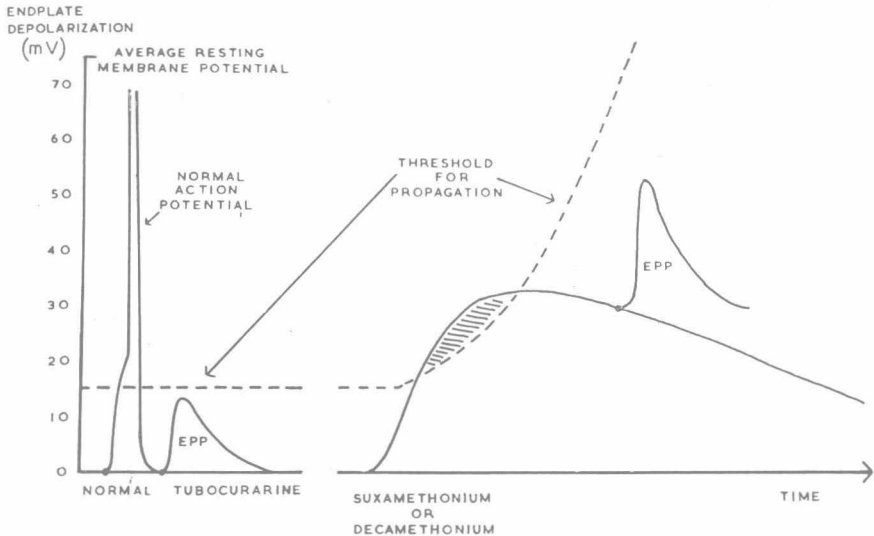

Fig. 6.—Diagram of neuromuscular transmission and block. Under normal conditions, a nerve stimulus gives rise to an endplate depolarization; when this exceeds the threshold for exciting the muscle fibre, a propagated action potential arises from it. After tubocurarine in sufficient dose, the endplate depolarization does not reach the threshold required for propagation, and a pure endplate potential (EPP) is seen. After decamethonium or suxamethonium, the endplate is depolarized by the drug, and this depolarization may rise above the threshold. But the threshold for propagation also rises, cutting short the period over which the muscle can show stimulant effects (hatched area). If the nerve is stimulated now, an endplate potential large enough to excite under normal conditions can be obtained: it is ineffective because of the rise in threshold.

depolarization, but presently the excitant depolarizing action disappears totally, and although complete block may persist, it is now of a hexamethonium type. A similar sequence has been observed with decyltrimethylammonium on the motor endplate. Here we seem to have unequivocal evidence of a change in the character of the block, not merely of the intensity of action.

Recently Thesleff (1955, 1956), using micro-electrodes for internal recording of membrane potentials of frog muscles *in vitro*, made the remarkable observation that, if the muscle is exposed to depolarizing drugs including acetylcholine itself for a sufficient period (15 minutes or more), the endplate depolarization produced

by them not only dwindles but may totally disappear. The muscle now cannot be excited through its nerve, nor by added acetylcholine; nor will anticholinesterases restore transmission. He was able to demonstrate, in rat muscle, a similar phenomenon, although the endplate depolarization never sank below 30 per cent of its initial value. If the acetylcholine is washed out the muscle fairly slowly recovers its normal response to acetylcholine. Thesleff believes that his results show that acetylcholine and other depolarizing drugs exert a curare-like action. Zaimis (1953) has made a similar proposal, in applying her work to the genesis of myasthenia, suggesting that in these patients acetylcholine released at motor nerves may come to have a dual action, first stimulating, then blocking itself.

Churchill-Davidson and Richardson (1957) have put forward similar ideas on the basis of their work analysing the action of decamethonium and anti-cholinesterases in myasthenic patients. They noticed that a myasthenic patient deteriorated markedly whenever anticholinesterase therapy was continued, but improved under conditions of rest and withdrawal of anticholinesterase therapy, when anticholinesterases would become temporarily effective again. From observations such as this they concluded that her motor endplates were becoming resistant to acetylcholine (or its breakdown products) in proportion to the amount of acetylcholine released in their vicinity. If this was the case then her condition should be improved by "resting" the endplate from its chemical stimulation completely. They attempted to do this by curarizing her with *d*-tubocurarine for 8 days. Interestingly enough, her requirement for *d*-tubocurarine to produce a satisfactory degree of general neuromuscular block was in the normal range. At the end of this rest period, and after an interval during which the effects of the *d*-tubocurarine wore off, the patient returned to a stronger state than earlier. When anticholinesterases were administered, there was a dramatically satisfactory response, and for a period of several months she was stronger than she had been for a long time. This is only one case, but so far as it goes it bears out to the full the idea that in myasthenics at least the motor endplates can become refractory in one way or another, as a result of continued exposure to acetylcholine, so that a possible method of treatment is to diminish such exposure.

The writer finds the idea that acetylcholine can curarize the endplate a difficult concept, for two reasons. The first is the remoteness in structure between ordinary curarizing drugs and acetylcholine. All the active curare-like compounds have relatively large molecules; and simpler analogues are usually much less effective; thus as an agent expected to imitate, for instance, *d*-tubocurarine, acetylcholine is structurally improbable. Secondly, it seems unlikely that acetylcholine, acting at a site peculiarly rich in the enzyme specifically destroying it, could persist there after washing out, in the way required to block receptors. For this to occur would imply a combination with receptors unlike the normal combination, and of a type which dissociated extraordinarily slowly. Grob, Johns and Harvey (1956) find that in the myasthenic the response to choline is also changed, and this substance, normally "depolarizing" in type, comes to have an apparently "competitive" action. This would allow one to argue that it is choline, rather than acetylcholine, which may persist at the receptors and cause block. The main difficulty is that choline is about 1,000 times less active than acetylcholine, and it is doubtful whether enough choline would appear to exert a significant effect. The writer feels, therefore, that the change in response of the endplate to acetylcholine