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MODE OF ACTION OF NEUROMUSCULAR BLOCKING AGENTS*

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TEN years ago, it would have been fairly easy for a pharmacologist to give an account of how drugs act which produce neuromuscular block. But two main developments have made the story more complicated. First, among such drugs, substances of different and indeed of diametrically opposed action are now known. Secondly, with the clinical exploitation of curare and similar compounds, the anaesthetist now asks much more searching questions, such as why a paralysis is sometimes abnormally prolonged, what happens when different relaxants are combined, or how different clinical conditions influence their action. This paper, therefore, will discuss some of those results or lines of investigation in the laboratory which throw most light, or may come to throw light, on these everyday practical demands.

COMPETITION AND DEPOLARIZATION BLOCK

Our picture of neuromuscular transmission, now, is the following: the nerve impulse releases acetylcholine at the nerve endings; the acetylcholine then depolarizes the endplate region simply by making a sort of physiological "short circuit" across the membrane there (Fatt and Katz, 1951); the local negativity so set up then excites the adjacent muscle membrane, leading to a propagated action potential and to muscular contraction; the acetylcholine is meanwhile rapidly destroyed by the cholinesterase present, so as to prepare for the next impulse. Substances such as curare simply act by being sufficiently like acetylcholine to have an affinity for the specific receptors normally receiving acetylcholine, but so unlike acetylcholine that they cannot activate the receptors. They thus "compete" with acetylcholine, just as (to use a frivolous analogy) a very fat man in a revolving door, with an "affinity" for the door yet incapable of passing through it, prevents those of more normal size from using it. Such a view of curare's action is very satisfactory: it explains all the forms of curare's antagonism to acetylcholine, the effects of anticholinesterases, and why quaternary salts almost always have a neuromuscular action.

But the picture became more complicated again when it was recognized that another type of neuromuscular block existed, which can now be termed block by depolarization. This was, indeed, indicated many years ago, when eserine and neostigmine were first studied. But it

* A paper given at the World Congress of Anaesthesiologists, Scheveningen, Holland, in September 1955.

became important with decamethonium; and the clinical usefulness of such block is now fully established with suxamethonium. The first analysis of depolarization block was made using decamethonium; although it is now less commonly used than suxamethonium, it is in some ways more convenient to study, since its destruction in the body does not complicate the experiments. But precisely analogous findings have been made with suxamethonium and with acetylcholine itself.

Depolarization block can be introduced in a general way by listing (table I) the differences which were found to exist between d-tubocurarine and decamethonium (reviewed by Paton and Zaimis, 1952). It was disconcerting to find two substances, both neuromuscular blocking agents in the classical sense, and therefore presumably both acting within the same extremely restricted area, which yet differed in almost every detail. The most fundamental of these differences seemed to be that decamethonium, like acetylcholine, could specifically depolarize and excite the motor endplate. It is rather remarkable

TABLE I

Test	d-Tubocurarine	Decamethonium
(1) Muscle selectivity:		
(*a*) among species	Sensitivity of rat > mouse > rabbit > man and cat.	Sensitivity of man and cat > rabbit > mouse > rat.
(*b*) within species:		
cat	Respiration and soleus more sensitive than tibialis.	Tibialis more sensitive than respiration and soleus.
man	Laryngeal, pharyngeal, and ocular muscles outstandingly sensitive compared to skeletal muscles.	Laryngeal, Pharyngeal, and ocular muscles only moderately sensitive, compared to skeletal muscles.
(2) Effect of substances raising threshold of end plate to acetylcholine (d-tubocurarine, gallamine, pentamethonium, ether anaesthesia).	Potentiation.	Antagonism.
(3) Muscle stimulation.	Nil or trivial in all species tested.	Fasciculations, with repetitive firing, in cat muscle and in human muscle. Contractures of denervated cat muscle and avian and frog muscle.
(4) Tension during a tetanus of the motor nerve.	Rapid decay.	Sustained.
(5) Miscellaneous:		
(*a*) potassium	Antagonism.	No effect.
(*b*) previous tetanization of motor nerve	Antagonism.	No effect.
(*c*) anticholinesterases	Antagonism.	Little effect, occasionally feeble potentiation or antagonism.
(*d*) m-OH-phenyldimethylethyl ammonium (Ro 3198; Tensilon)	Antagonism.	No effect or potentiation.
(*e*) effect in myasthenia.	Hypersensitivity.	Normal sensitivity or resistance.

how the spatial distribution of the endplate depolarization in a muscle after decamethonium is indistinguishable from acetylcholine (fig. 1).

But the discovery that decamethonium can stimulate a muscle does not, at first sight, explain how it produces neuromuscular block. One might think, indeed, that it would tend to prevent block and to help acetylcholine perform its tasks more effectively. Two immediate theories might be made.

(*a*) The first, which one can call the "concealed competition" theory, is that, although the depolarization is of interest, yet the fundamental action of decamethonium is still one of competition, preventing acetylcholine from producing at the endplate region a response (endplate potential or e.p.p.) big enough to excite normal muscle. Such a theory is intrinsically unlikely, for it would require the drug (already known to be acetylcholine-like and to summate with acetylcholine) to have at the same time an antagonism to acetylcholine; and this antagonism must be sufficient not merely to reduce the endplate potential as far as curare does, but a good deal further, so as to overcome the assistance which decamethonium, by partially depolarizing the endplate, has already given to the endplate potential.

(*b*) It might be proposed, on the other hand, that when neuromuscular block is established by decamethonium, then the endplate is so profoundly depolarized that acetylcholine released by a nerve impulse can do nothing more (the "total depolarization" theory). Again, there is at once a difficulty; for, if this were the case, why does not the muscle fibre become continuously activated by such a maximally excited endplate? Yet we know that, in fact, the stimulant phase of the action of such drugs is transient.

The problem has been analysed electrophysiologically in some detail (Burns and Paton, 1951); but we need not discuss the full evidence. A single observation disposes of both these suggestions, and provides a key to the true explanation (fig. 2).

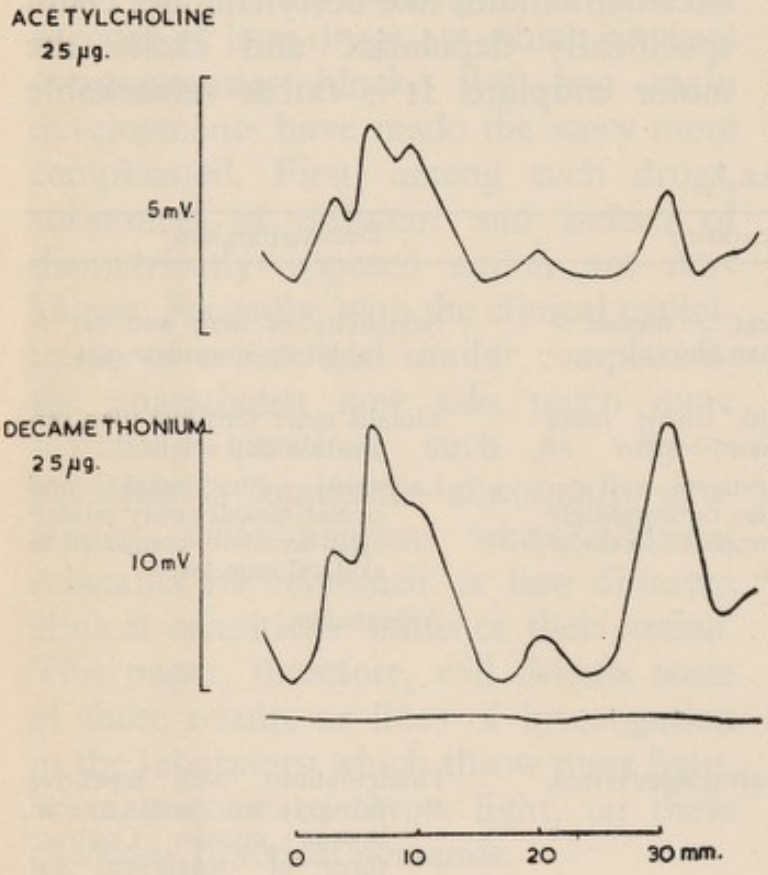

FIG. 1

Records of the distribution of potential along brachioradialis muscle in the cat (a) normal (lowest tracing); (*b*) after 25 µg decamethonium intra-arterially (middle tracing); (*c*) after 25 µg acetylcholine intra-arterially (top tracing).

This muscle has a complicated system of endplates, which is mapped out by the depolarization produced by the two drugs. Although acetylcholine has a less intense depolarizing action than decamethonium, because it is destroyed by cholinesterase, the selective actions of the two drugs on endplate regions are exactly parallel.

(From Burns and Paton (1951) by permission of the *Journal of Physiology*)

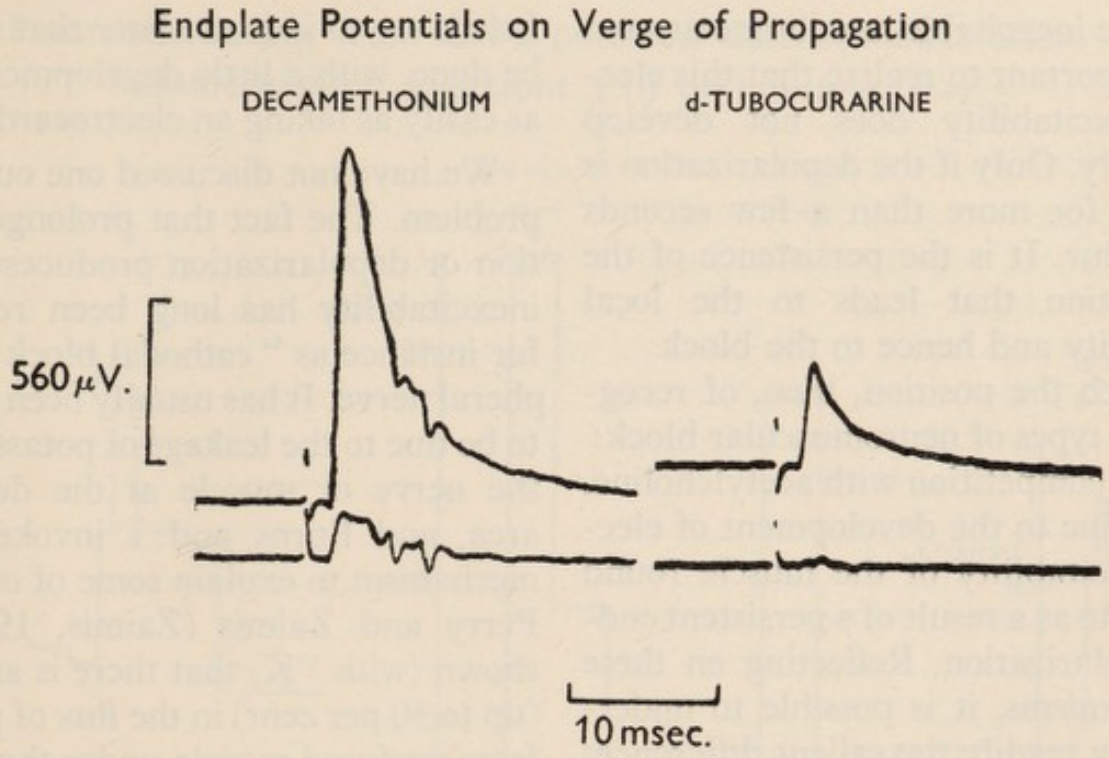

FIG. 2

Records of endplate potentials in response to excitation of the motor nerve of the cat's gracilis. In each tracing, the upper record is taken with an electrode directly over the endplate, the lower record with an electrode 2 mm away; the lower record serves to show that the muscle is just on the verge of being excited by the endplate potential, as indicated by the irregular abortive "spikes".

The lefthand tracings were obtained by allowing a muscle to recover from a large dose of decamethonium until the verge of propagation was reached. The righthand tracing was obtained after full recovery from decamethonium, using the same method on the same endplate region with d-tubocurarine.

(From Burns and Paton (1951) by permission of the *Journal of Physiology*)

It depends on finding, at the endplate region, the size of endplate potential which is just on the threshold of exciting the muscle fibre. d-Tubocurarine does not affect the muscle membrane electrically, so that the e.p.p. obtained with it measures the normal "propagation threshold". With decamethonium, however, even though the endplate potential starts from a raised "base-line" of pre-existing depolarization, yet it has to be up to three times greater to excite the muscle than with d-tubocurarine. If bigger endplate potentials can be seen after decamethonium, then we must abandon the theories that it acts like d-tubocurarine (which would require the same sized potentials or even smaller ones, according to the degree of endplate depolarization), or that the endplate is totally depolarized (which would abolish the potentials). Further, we have a demonstration of the main cause of block. It is that, after decamethonium, the muscle fibre has become refractory to electrical stimulation, either by the endplate potential or by externally applied shocks. Hence an endplate depolarization, which in the normal or curarized muscle would be fully adequate to excite, comes to be ineffective, since it cannot stir into

activity the inexcitable membrane around it. It is important to realize that this electrical inexcitability does not develop immediately. Only if the depolarization is prolonged for more than a few seconds does it occur. It is the persistence of the depolarization that leads to the local inexcitability and hence to the block.

We reach the position, then, of recognizing two types of neuromuscular block: one due to competition with acetylcholine, the other due to the development of electrical inexcitability of the muscle round the endplate as a result of a persistent endplate depolarization. Reflecting on these two mechanisms, it is possible to understand fairly readily the salient differences of detail between d-tubocurarine and decamethonium (Paton, 1951).

I would like to digress here for a moment on to the problem of how to diagnose what type of block exists. For some time what one can call the general "clinical" picture has often been used. But I am coming to suspect that this is not good enough, particularly if one or two signs alone are taken. Suppose one draws an analogy between assessing the state of the neuromuscular junction and, for example, diagnosing a case of thyrotoxicosis; then features such as the tetanic response, or the proportionate effect on the respiratory muscles, or the sensitivity to anticholinesterases correspond to suggestive (but not decisive) signs such as loss of weight or shaky hands. But the *specific* diagnosis of thyrotoxicosis, especially in doubtful cases, rests on the basal metabolic rate and on the iodine uptake by the gland; so also the *specific* diagnosis of the neuromuscular state rests on determining the electrical conditions at the endplate. I shall try to indicate later that this could be done, with a little development, almost as easily as taking an electrocardiogram.

We have not discussed one outstanding problem. The fact that prolonged excitation or depolarization produces electrical inexcitability has long been recognized, for instance as "cathodal block" of peripheral nerve. It has usually been presumed to be due to the leakage of potassium from the nerve or muscle at the depolarized area, and Burns and I invoked such a mechanism to explain some of our results. Perry and Zaimis (Zaimis, 1954) have shown (with ^{42}K) that there is an increase (up to 30 per cent) in the flux of potassium from perfused muscle under the influence of decamethonium. But such an experiment only measures the traffic in one direction, and two important questions remain. Does the muscle actually *lose* significant amounts of potassium; for instance, is the loss big enough to produce a rise in blood potassium? And do local circulatory conditions, which might influence its accumulation in the tissue spaces, influence depolarization block? In some recent experiments, measuring the absolute amounts of potassium in the blood and in the effluent from perfused muscles, I have found that substantial amounts of potassium are mobilized. With the cat's isolated perfused gastrocnemius (fig. 3) the release amounts to about 1 per cent of the potassium in the muscle. It tends to fall away with repeated injections, or during a continued infusion. If the flow of perfusate is very fast, the rise in concentration of potassium in the effluent is correspondingly reduced; if the flow is slowed, it rises, although it does not rise above a certain limit. These experiments

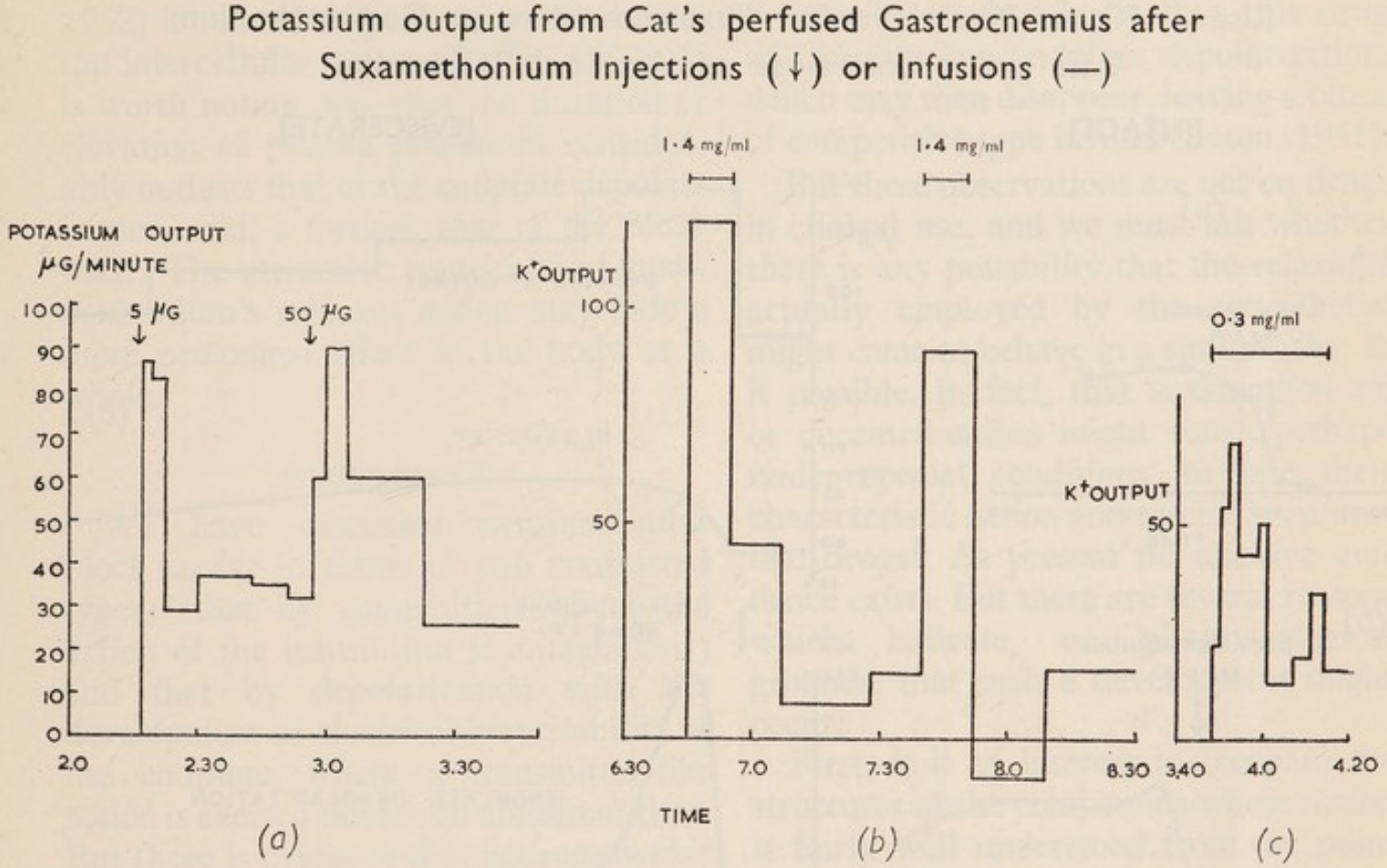

FIG. 3

Results of experiments on the output of potassium from an isolated perfused gastrocnemius muscle of the cat.

In (*a*) single injections of 5 μg and 50 μg suxamethonium were given.
In (*b*) an infusion of suxamethonium, 1.4 mg/ml, was given twice, for 10 minutes each time.
In (*c*) an infusion of suxamethonium, 0.3 mg/ml, was given for a period of 30 minutes.

show that release takes place unequivocally from the muscle itself.

In the whole animal the total release is sufficient to raise the plasma potassium levels very substantially (fig. 4).* Since potassium release can occur with other conditions, notably sympathetic activity or adrenaline release, it is necessary to keep the animal on artificial respiration to prevent asphyxia. Further, when using suxamethonium, it might be objected that the rise in plasma potassium was due to its ability to stimulate sympathetic ganglia (although this is only a feeble action). This can be excluded in two ways. Firstly, decamethonium, which lacks any ganglion-stimulant action, is as effective in raising the plasma potassium. Secondly, if the animal is eviscerate (so removing the liver from which adrenaline mobilizes potassium), suxamethonium is still effective. Indeed, it is highly potentiated, so that a several times smaller dose is required to produce the same neuromuscular effect as in the normal animal.

* Since this work was done, the paper by H. Klupp et al. (*Arch. int. Pharmacodyn.*, **98**, 340–354, 1954), was drawn to my attention. These authors found that in dogs, suxamethonium and decamethonium could increase the plasma potassium by up to 30 per cent; that d-tubocurarine (except in large doses) was free of this action, but could antagonize potassium release by suxamethonium and decamethonium; and that potassium release from perfused hindlimbs could be achieved.

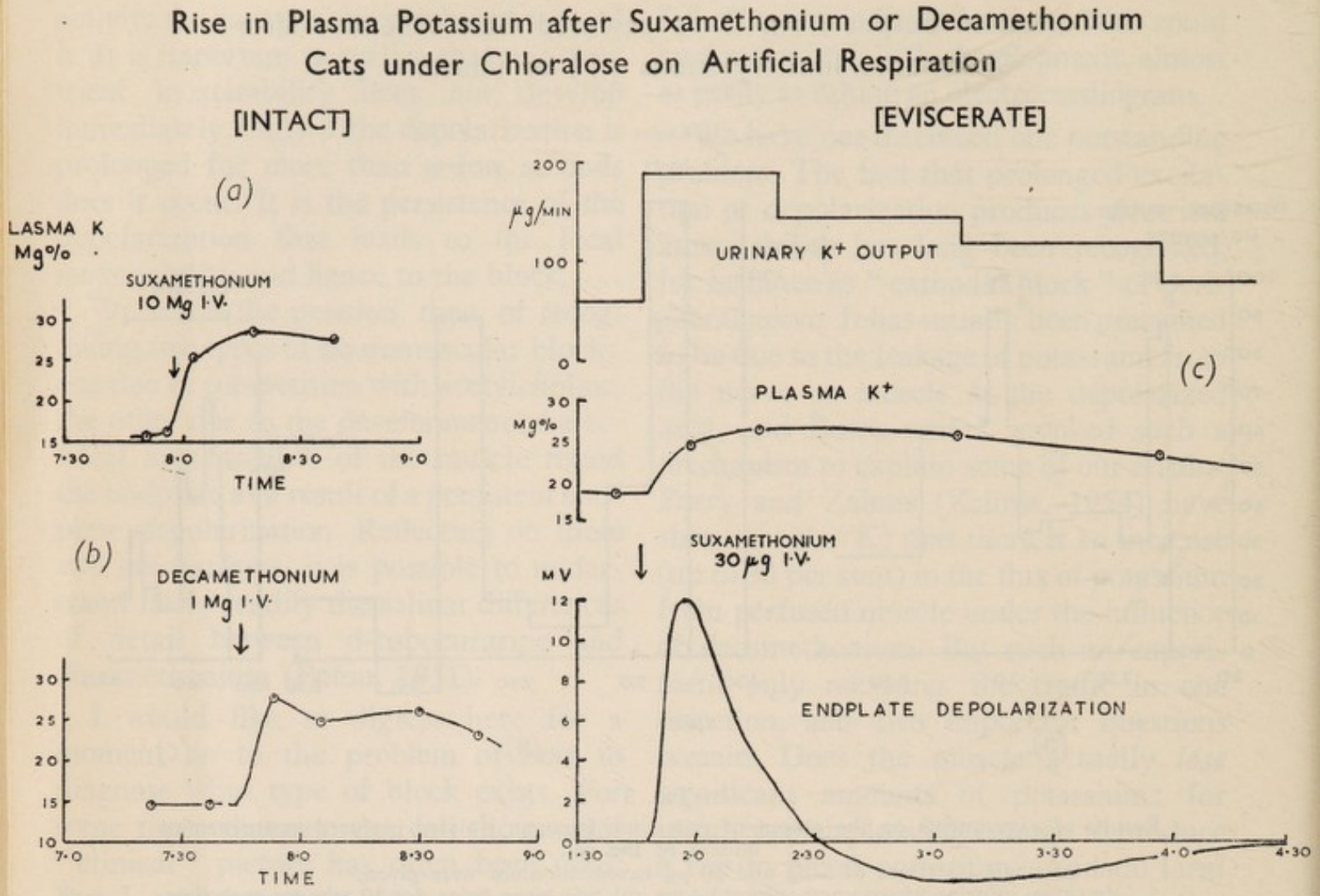

FIG. 4

Results of experiments on the change in plasma potassium concentration in cats anaesthetized with chloralose and on artificial respiration after decamethonium or suxamethonium.

(*a*) Effect of 10 mg suxamethonium on plasma potassium level.

(*b*) Effect of 1 mg decamethonium on plasma potassium level. The response is as great, although decamethonium is totally devoid of any sympathetic stimulant action.

(*c*) Effect of 30 µg suxamethonium in a cat eviscerated to exclude participation by the liver in the mobilization of potassium. The middle tracing shows the changes in plasma potassium, which outlast considerably the endplate depolarization (lower tracing). In this animal there was a satisfactory urine flow, and the increase in urinary potassium (upper tracing) corresponded with the rise in plasma level.

This suggests that defect of liver function may influence considerably the destruction of suxamethonium in the body.

The fact that these ionic movements are so big means that during, and after, a block by a drug depolarizing the endplate, the ionic concentrations either side of the muscle membrane must be significantly altered. The implications of this for the state of block are not simple, but it is clear that the reaction of the endplate and of the muscle membrane adjacent will be radically conditioned by them. Their existence supports, in addition, the suggestion made some time ago that the relationship between bloodflow and neuromuscular block with decamethonium (Churchill - Davidson and Richardson,

1952) is related to potassium release into the intercellular spaces (Paton, 1952). It is worth noting, too, that the duration of elevation of plasma potassium considerably outlasts that of the endplate depolarization, and, a fortiori, that of the block itself. The attractive transience of suxamethonium's relaxant action may hide a more prolonged effect in the body as a whole.

MIXED BLOCK

We have discussed neuromuscular block so far in terms of two contrasted types: that by competition where the action of the transmitter is antagonized; and that by depolarization with the development of electrical inexcitability at the endplate, where a transmitter-like action is exerted but for an abnormal time. But there is evidence that neuromuscular block of an intermediate kind may exist, in which a depolarization may take place initially and pass off, leaving nevertheless a state of block, now competitive in character. Drugs which first stimulate and then desensitize the tissue both to their own action and to that of similar substances have been known since Straub (1907) first showed the phenomenon for the action of muscarine on Aplysia heart. Nicotine, in its action on autonomic ganglia, is a notable example; and many sympathomimetics amines have the characteristic sequence of sympathomimetic followed by sympatholytic action. Among drugs active on the endplate a similar type of action is described for some of the aliphatic quaternary salts studied by Dallemagne and Phillipot (1951), Ginzel et al. (1952) and Zaimis (1953). With decyltrimethylammonium it has, indeed, been verified electrically that this drug will produce an endplate depolarization, which may then disappear, leaving a block of competitive type behind (Paton, 1951).

But these observations are not on drugs in clinical use, and we must ask whether there is any possibility that the relaxants actually employed by the anaesthetist might come to behave in a similar way. Is it possible, in fact, that suxamethonium or decamethonium might come, perhaps under special conditions, to lose their characteristic action and resemble curare-like drugs? At present no decisive evidence exists. But there are several reasons which indicate, on pharmacological grounds, that such a development might occur.

First, it is of interest to compare the structures of the compounds whose action is fairly well understood from the point of view of their lipophilic tendency. Data do not exist, and indeed are not easy to obtain, giving quantitative measurements of this sort. But one can estimate it in a simple way by enumerating the carbon atoms in each molecule (lipophilic) and comparing them (table II) with the number of quaternary groups (hydrophilic). One can then see how, with increasing proportions of hydrocarbon to hydrophilic material, the mode of action moves from depolarization through mixed action to pure competition. The point is, of course, one which Bovet (1951), in his classification of lepto- and pachycurares, has already taken up. But here I am trying to estimate, not the shape of the molecule, but its tendency to be fixed in a fatty or a watery phase—i.e., its partition coefficient. The scheme suggests that drugs with some measure of hydrocarbon loading may

TABLE II

Relation between type of neuromuscular action and ratio of lipophilic atoms (carbon) to hydrophilic atoms (nitrogen).

(Data from Ginzel et al., Dallemagne and Phillipot, Zaimis, and unpublished)

Compound	Action		C atoms
	Depolarization	Competition	N atoms
T.M.A. (tetramethylammonium)	++		4
Acetylcholine	++		5
Suxamethonium	++		5
Decamethonium	++	(±)	8
Amyltrimethylammonium	++		8
Decamethonium (Me 2 : Et 1)	++	+	9
Decamethonium (Et 2 : Me 1)	++	++	10
Tridecamethonium	+	+	9.5
Gallamine	±	++	13
d-Tubocurarine	±	++	19
d-Tubocurarine methyl ether	−	++	20
Neostigmine	++	+	5.5

(through their lipoid affinity) develop an attachment to the membrane of a kind different from, additional to, and interfering with, the attachment which leads to endplate activation. For instance it might be essential, for normal activation, that a chemical bond involved be rapidly made and broken, or that the molecule has to move across or through the membrane; fixation of the molecule by its hydrocarbon content to adjacent lipoid regions of the membrane could well interfere with such a process. Now although suxamethonium and decamethonium are less lipophilic than the other compounds, they are not much less so. It seems possible, therefore, that a latent competitive element in their action might develop, particularly if their action were sufficiently prolonged, or if they were given in large doses, so that lipoid fixation could occur.

Secondly, we may note that continuous exposure even to normal naturally occurring molecules such as histamine, adrenaline or acetylcholine, may induce "accommodation" to their effects such that a state of relative refractoriness to excitation by them develops (Barsoum and Gaddum, 1935; von Euler, 1955; Douglas and Paton, 1954). Whether Straub's (1907) explanation (that the action of such drugs depended on the ratio between extracellular and intracellular concentrations, and hence could be diminished by passage of the drug inside the cell) is correct we do not know; but again it would lead us to expect a change in the character of the action of endplate stimulants with passage of time.

The possibility for explaining this accommodation that now interests me is that it is changes in potassium (and perhaps sodium) concentrations at the endplate region which can alter the responses of the endplate. We know that raised potassium levels can render tissues inexcitable, and there are indications that low potassium levels can increase the stimulant effect of some ganglion-blocking drugs (Perry and Reinert, 1954). The ionic consequences of a long-continued depolarization might well condition the endplate so that the

response to acetylcholine diminished, and propagation became more difficult.

Thirdly, we must remember that when depolarizing drugs are given after a previous dose of a competitive drug (for instance suxamethonium after d-tubocurarine) they lose some of their characteristics and come closer to being competitive in type.

It seems possible, therefore, from the purely pharmacological standpoint, that the depolarizing drugs, particularly if given (*a*) for a long time, or (*b*) in big doses, or (*c*) in conjunction with competitive drugs, may themselves lose some of their characteristic features and come to behave as being at least in part competitive, or may come to alter the responses of the motor endplate to other drugs.

Now from the practical point of view it is obviously impossible to predict what will happen. Would it be possible to assess the neuromuscular state of a patient during surgical anaesthesia? Until recently this might have been thought impracticable. But in fact the electrical changes in a muscle, produced by the localized endplate depolarizations throughout it, are quite gross and can be picked up by a diffuse nonpolarizable electrode placed, not accurately on an endplate region, but anywhere on the main body of a muscle, and recorded on a simple galvanometer. Unfortunately percutaneous recording in man is complicated by potentials existing in the skin. But these can be countered, or non-polarizable electrodes suitable for hypodermic use can be developed. Figure 5 shows the type of record obtained, with graded doses in the cat. There is no reason

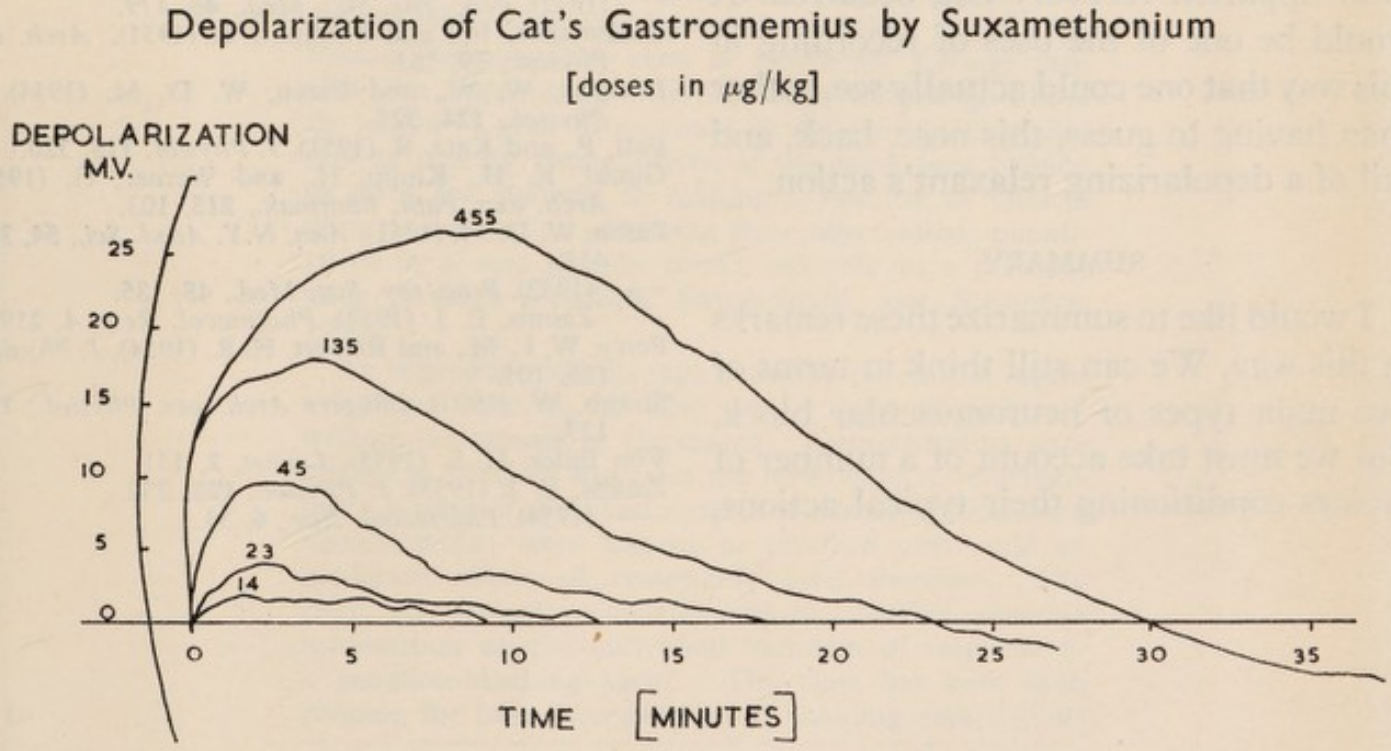

FIG. 5

Records of the depolarization of the gastrocnemius muscle of a cat anaesthetized with chloralose. The records were obtained with an electrode placed on top of a small saline-filled swab of cotton wool placed on the belly of the muscle, without localizing the endplate regions. The doses of suxamethonium, given intravenously, are marked opposite the corresponding tracing.

why an anaesthetist should not record for himself, if he wishes, similar tracings during an operation.

The figure allows me to bring out one last point. Study of muscular activity alone gives an incomplete picture of the course of events at an endplate. Before block begins, changes occur; when paralysis of transmission is complete, the drug's fundamental action can still be made more intense; and after recovery, there is a considerable interval before the endplate is normal. If one has then a record of (say) paralysis and recovery of the respiration, one must imagine also on the record a short "nose" corresponding to the beginning of the drug's action, a big "back" corresponding to the course of its action during the period of complete paralysis, and a long pharmacological tail after apparent recovery had occurred. It would be one of the uses of recording in this way that one could actually see, rather than having to guess, this nose, back, and tail of a depolarizing relaxant's action.

SUMMARY

I would like to summarize these remarks in this way. We can still think in terms of two main types of neuromuscular block. But we must take account of a number of factors conditioning their typical actions, of which perhaps the most important, because least studied, are:

(1) the ionic environment;
(2) the tissue blood flow; and
(3) the interaction together of different drugs.

Clinically, unpredictable and sometimes complex conditions must arise. But there is a real hope that simple electrophysical methods in the hands of anaesthetists might help to solve immediate problems. In addition it would throw further light on human pharmacology, to which (if one may say so) anaesthetists are making so great a contribution.

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