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Reprinted from ANNALS OF THE NEW YORK ACADEMY OF SCIENCE
Vol. 54, Art. 3, Pages 347-361, 1951

THE PHARMACOLOGY OF DECAMETHONIUM

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The main features of the pharmacology of decamethonium are already well known,[20, 5] and there is no need to review these here in detail or to comment on its remarkable specificity of action. The recent analysis, however, by Burns and myself,[3] of the action of decamethonium at the end plate, throws considerable light on the numerous contrasts which have emerged, from the earliest experiments onwards, between decamethonium and those other substances causing neuromuscular block (of which I shall take d-tubocurarine as representative). In this paper, therefore, these differences will first be critically reviewed, and then related to the modes of action of the two drugs.

The Differences between Decamethonium and d-Tubocurarine. In TABLE 1 are tabulated the responses observed under different conditions with the two compounds. They fall naturally into several groups. First are the differences in the incidence of effect on different muscles. These appear not only between species (for instance, compare the rat and the cat), but also within species, as our results with the soleus and tibialis of the cat showed.[20, 22] It seems that even in man the same thing appears, in that decamethonium affects the pharyngeal, laryngeal, facial, and sometimes respiratory muscles less intensely in relation to the muscles of the trunk than does d-tubocurarine, and the muscles of the hand may also differ in their relative sensitivity to the two agents.[7, 11, 16, 21, 26] These differences in muscle sensitivity are confusing and are still completely unexplained. There is, however, one general feature about them. This is the inverse relationship between sensitivity to decamethonium and sensitivity to d-tubocurarine. Thus, the rat is more sensitive than the cat to the latter, but much less sensitive than the cat to decamethonium. Soleus and tibialis in the cat show the same relationship. Even in man, the exceptional sensitivity of ocular and pharyngeal muscles to d-tubocurarine, relative to the other muscles, is less when the paralysis is induced with decamethonium.

One can put the case in general terms. If the ratio "sensitivity of muscle a/sensitivity of muscle b" is, with d-tubocurarine, raised above unity, then decamethonium will reduce it, often to far less than unity. Taking the cases already quoted, the ratio, "rat sensitivity/cat sensitivity," is 2 for d-tubocurarine and 0.005 for decamethonium, and that for "cat soleus/cat tibialis" is roughly 1.6 for d-tubocurarine and 0.7 for decamethonium. It is unlikely that this inverse relation holds invariably. I know of no exception to it so far, however, and it helps to introduce some order into the observations. Further, as we shall see, something of the sort would be expected from the contrasting ways in which the two compounds produce their effects.

Second, we may take the effect of substances which raise the end-plate threshold to acetylcholine. Here again, we have the same inverse relation,

that, in so far as these various conditions favor d-tubocurarine, they antagonize decamethonium.[5, 9, 20, 22] We were so struck by the inverse relationship between the two drugs that we suggested[21] that the myasthenic patient might not be hypersensitive to decamethonium, as he is to d-tubocurarine. Sellick[25] was the first to bring evidence that this is the case, and recently Churchill-Davidson and Richardson,[6] studying the muscle action potentials of the abductor digiti minimi obtained by stimulating the ulnar nerve at 10 shocks per second, have also found that patients suffering from myasthenia gravis exhibited tolerance to decamethonium.

TABLE 1

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, Flaxedil, pentamethonium, ether anesthesia).	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
Chick Test	flaccid paralysis	spastic paralysis
(4) Tension during a tetanus of the motor nerve	rapid decay	sustained
(5) Miscellaneous		
(1) potassium	antagonism	no effect
(2) previous tetanization of motor nerve	antagonism	no effect
(3) phenol	antagonism	no effect
(4) anticholinesterases	antagonism	little effect, occasionally feeble potentiation or antagonism
(5) *m*-OH-phenyldimethylethyl ammonium (Ro 3198)	antagonism	no effect, or potentiation
(6) Effect in myasthenia	hypersensitivity	normal sensitivity or resistance

Third, we have the stimulant actions of decamethonium. These are

entirely lacking with d-tubocurarine. It is here, perhaps, that the similarity of decamethonium to acetylcholine is most easily visible, for all those myographic and electrical tests with which the stimulant action of acetylcholine can be demonstrated reveal a qualitatively identical stimulant action by decamethonium. Furthermore, as with acetylcholine, denervation changes the reaction of mammalian muscle to decamethonium from a twitch-like response to the phylogenetically more primitive contractural reaction.[4, 20, 28]

Fourth, is the difference between the flagging response of a muscle poisoned with d-tubocurarine and the sustained contraction with decamethonium during the application of a tetanus.[20]

Fifth, is the reaction to a diverse group of agents which share the ability to relieve or diminish block by d-tubocurarine. None of them, however, relieves block by decamethonium, and some may increase it.[3, 8, 17, 18, 20, 24, 27] Taking the responses of a muscle to a tetanus and to these agents into consideration together, one can summarize them by saying that, while block by d-tubocurarine is characteristically labile, that by decamethonium is characteristically stable and can be neither antagonized easily nor, as during a tetanus, readily deepened.

The Mechanism of Action of Decamethonium. A muscle paralyzed by d-tubocurarine is electrically normal. Its membrane potential is at all points the same as in the untreated muscle, and its direct electrical excitability is everywhere the same, being indistinguishable from that of the normal muscle fiber. A muscle paralyzed by decamethonium is quite different. The muscle membrane is now depolarized, not generally, but only at the regions containing motor end plates. If an electrode is swept along a muscle fiber, to record the potential along it with respect, say, to an electrode placed on the fiber tip, this localized depolarization of the end-plate region can readily be demonstrated, although the normal muscle showed no potential differences at all along its surface.

The properties of this depolarization and its relation to neuromuscular block have been analyzed in some detail by Burns and myself on the cat,[3] as well as by Jarcho *et al.*[13] on the rat. The two animals have not yielded entirely similar results, and I will confine myself to those on the cat, about which we know more, and which corresponds more closely to man in its reactions.

First, the depolarization is not static but spreads slowly a little way along the muscle fiber with lapse of time. This spread is never to the whole muscle fiber, but is such that the fall in membrane potential of a point, say, 3 mm. away from the end plate may at first be negligible but 20 minutes later is easily detectable. This spread is not due to diffuse action of the drug. It is a consequence of any localized depolarization and it can be mimicked by injuring the muscle fiber in various ways, by other depolarizing drugs, and even by simply applying a negative electrode to the surface of the muscle for sufficiently long to produce a persistent reduction in membrane potential.

This region of localized depolarization is also one of electrical inexcitability. This inexcitability does not come on at once. If recorded continuously, it is found that, during the early stages of depolarization, the

excitability of the end-plate region is actually increased, and then it passes over (in a time depending on the dose of decamethonium) into a depression of excitability. This inexcitability can be demonstrated in another way: by exciting the muscle directly to one side of the end-plate region and recording action potentials either side of the end plate. In a completely curarized muscle, propagation of such action potentials proceeds along the full length of muscle fiber, crossing the end-plate region without alteration. With decamethonium, however, the end plate now represents a region of block across which the action potential is unable to excite the muscle membrane beyond.

This evidence shows that the depolarization of the end plate leads to an inexcitability of the end-plate region adequate to cause neuromuscular block. We found, in addition, that block, for a given degree of depolarization, was greater the longer the depolarization had lasted. This naturally follows from the spread of depolarization and of inexcitability, which will create, with lapse of time, a widening barrier of inexcitable tissue between the end plate and normal muscle.

There is some evidence, however, that another mechanism may also be involved. Particularly after a large dose of decamethonium, it seems probable that the drug reduces the end-plate potential by diminishing the remaining possible depolarization. Since the end plate is already well depolarized, further discharge of acetylcholine on to the end plate can only elicit a small electrical response.

We have, therefore, two mechanisms by which the depolarization evoked by decamethonium can block neuromuscular excitation: the development of electrical inexcitability of the membrane, and a reduction of the end-plate potential by reason of the already existing end-plate depolarization.

It might be argued, however, that these processes were merely subsidiary to some other form of neuromuscular block. Although there is no evidence at all to support such an idea, the experiments quoted do not completely exclude it. One can bring against it additional experiments of another kind, however, in which polarizing currents are applied to the end-plate region. As is well known, if a curarized end-plate region is depolarized by applying a cathode to it, transmission returns. Conversely, making the end plate of a curarized muscle positive, by applying an anode, deepens the failure of transmission. If a muscle under decamethonium is tested in the same way, however, one obtains precisely the opposite results. Transmission is promptly restored with an anode; a cathode merely serves to deepen it. There seems no conceivable way in which this result could come about, unless the depolarization of the end plate was actually causing the block.

It seems inescapable, therefore, that the depolarization is not incidental to a normal, true curare-like action, but that it is actually responsible for the blocking action of decamethonium.

Evidence of the same kind has been obtained for the block obtained with acetylcholine, when given either in large doses or in the presence of anticholinesterases. One obtains a depolarization of the end plate which is in-

distinguishable from that due to decamethonium, and sums with it, together with inexcitability of the end-plate region. The neuromuscular block is reversible in the same way by anodal current.

There is one further point about block by depolarization on which I have only touched. One might ask how it comes about that depolarization of the muscle membrane, which is used in an ordinary class experiment for purposes of exciting muscles, can cause inexcitability and block. The reason for this lies in the persistence of the depolarization. It is true that transient applications of depolarizing drugs cause only excitation. The effect of acetylcholine released in normal transmission is typical of this. If the depolarization is prolonged for more than a brief period, however, (depending on the intensity of depolarization), depression follows. Such a sequence can be shown quite simply by applying a cathode to a normal, or still better, a curarized muscle. As soon as the current is switched on, transmission is increased and remains greatly augmented for a brief period. Then it begins to fail again, and it is ultimately reduced by the persistent depolarization to a lower level than that at which it started. Allowing for variations in time scale, this sequence typifies the course of decamethonium block, in that such block arises from the persistence of an excitatory process, and always shows, during its early stages, some sign of excitation or increased excitability before the block itself ensues.

We may, therefore, contrast the blocks by these two agents as follows: that by d-tubocurarine is due to a reduction in action of the chemical transmitter; that by decamethonium follows an abnormally prolonged transmitter-like action, in which initial excitation passes over into inexcitability.

Correlation of Differences between Decamethonium and d-Tubocurarine with Their Modes of Action. The differences described earlier can be summarized in three statements: (a) decamethonium has a stimulant action on skeletal muscle which d-tubocurarine lacks; (b) there is an inverse relationship between the conditions for sensitivity to decamethonium and those for sensitivity to d-tubocurarine; (c) neuromuscular block by d-tubocurarine is labile, that by decamethonium is stable. We have now to see how these can be related to the actions of the two drugs.

(a) The stimulant properties of decamethonium clearly flow at once from its depolarizing action. The fasciculations observed by many workers in unanesthetized man are thus qualitatively identical with a normal voluntary movement, although profoundly modified in detail by the slow access of decamethonium to the end plate, since it must be carried thither by the blood stream. It is worth mentioning here incidentally that, if in an investigation of a new substance it is desired to see how far it has a specific depolarizing action at the end plate, probably the simplest test is to seek for one of these stimulant actions on skeletal muscle. Two are particularly convenient, and may be made quantitative: eliciting of a contracture from the frog's rectus, and testing for the production of opisthotonic spastic paralysis in the bird.[4] For any extended study, the danger of being misled

by species difference, particularly on the quantitative side, makes it important also to try the action on mammalian muscle, preferably on that of a cat.

(b) The inverse relationship between the activity of decamethonium and d-tubocurarine under various conditions is at present only partially explicable. We do not know why different muscles should differ in their reactions to drugs. The suggestion that it is related to their "redness" or "whiteness,"[22] and so, perhaps, to their phylogenetic status, may help to order the observations but does not throw much light on the actual source of the difference. Given such varying sensitivity, however, one would in

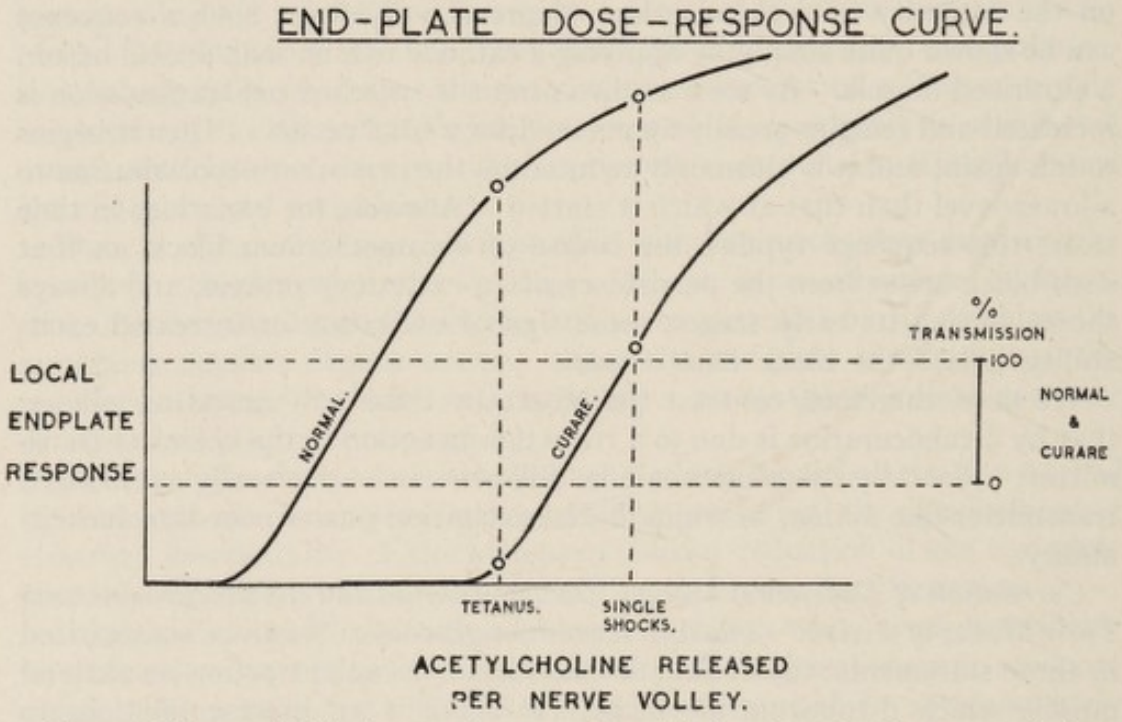

FIGURE 1. Diagram of relation between the amount of acetylcholine released at the nerve terminations, with single shocks or during a tetanus, and the local response (depolarization) elicited by the acetylcholine at the end-plate region. To the right of the diagram is given the range of thresholds, from zero to 100 per cent transmission from end plate to muscle fiber. Left-hand curve, normal muscle; right-hand curve, curarized muscle.

fact expect depolarizing drugs to behave inversely with curarizing drugs. Any relative change in sensitivity of an end plate can do only one of two things: it may increase its response to acetylcholine (and therefore to decamethonium), but this will reduce the effectiveness of d-tubocurarine; or it may decrease the response to acetylcholine (and likewise decamethonium), which will allow d-tubocurarine to operate at greater advantage. Whatever change in sensitivity of the end plate takes place, it cannot increase sensitivity both to d-tubocurarine *and* to decamethonium.

(c) We turn now to the contrast between what I have termed the lability of d-tubocurarine block and the stability of that produced by decamethonium. To clarify the discussion of this, I have drawn up a schematic dose-response curve for the motor end plate's response to acetylcholine released at the nerve terminations (FIGURE 1). This may indeed, be a premature infant. As is so often the case, however, its gestation has proved

very enlightening, if only in revealing one's ignorance on the quantitative side.

First let us consider a normal muscle. Kuffler's work[14] enables us to say that there is a graded local response by the end plate (in the form of a depolarization of this region) to graded doses of acetylcholine. One may reasonably postulate, therefore, that the dose-response curve is of the S-shaped type so common in pharmacology, such that a definite amount of acetylcholine is needed to produce a threshold effect and that the response flattens off with the larger doses of acetylcholine.

We know little more about acetylcholine output to nerve stimulation than that it occurs. The experiments of Brown[2] suggested that the amount of acetylcholine released by single shocks is considerably more than necessary for exciting the all-or-none response of the whole muscle fiber. Burns and I found that in a normal muscle, with tetanization of the motor nerve, a small depolarization of the end plate persisting between the shocks could be recorded, but that, even during the tetanus, this dwindled to almost undetectable levels quite rapidly. This depolarization was greatly increased and prolonged by anticholinesterases and must have been due to the action of acetylcholine released by the nerve impulses. It follows, therefore, that the amount of acetylcholine released per shock falls during a tetanus, and, further, since transmission did not fail during the tetanus, that the amount of acetylcholine released was greatly supraliminal during the earlier shocks of the tetanus. The view that the acetylcholine output falls with closely succeeding shocks is also supported by the known waning output observed with a perfused superior cervical ganglion subjected to continuous stimulation. On the basis of all this evidence, we can, therefore, mark off two points on the scale of acetylcholine release: one for that by single shocks and one (arbitrarily placed and of smaller magnitude) for that during a tetanus (which will obviously change its relative position according to the frequency). At the same time, we set a value for the threshold of the muscle fiber (*i.e.*, that magnitude of the end plate's local response which excites a propagated impulse along the whole fiber) or rather for the range of thresholds, since we are, in practice, concerned with the responses of a population of end plates. We set this threshold range so that it is well below the local response evoked by a single nerve volley, and also below that evoked by each shock of a tetanus.

With *d*-tubocurarine, there can be little doubt as to how the schema must be modified (FIGURE 1). By many tests, ranging from Kuffler's single muscle fiber to experiments on the contractions and contractures of amphibian and mammalian muscle, it is established that d-tubocurarine raises the threshold of the end plate to acetylcholine. We therefore draw a parallel curve, shifted sufficiently to the right to bring the region of local responses to single shocks and to tetani into the zone of failing transmission. Since it is known that the electrical excitability of the muscle is unchanged, the propagation threshold remains in the same position as with normal muscle.

Such a picture provides at once an explanation for the lability of block due to d-tubocurarine, for the characteristic feature of the transmission diagram is that the physiological range of end-plate responses is now so

placed relative to the thresholds for propagation that small changes in the local response readily reflect themselves in significant changes in transmission. A reduction of acetylcholine output, during a tetanus, must at once lessen transmission. The effects of potassium, anticholinesterases, and a preceding tetanus are all easily explained by supposing that these, in various ways, increase (even by quite small amounts) the end-plate response to acetylcholine in the curarized muscle. The lability of d-tubocurarine block, then, may be regarded as due to the reduction of the local response, so that the physiological range of responses is no longer supraliminal but has moved on to the sloping and discriminating part of the dose-response range.

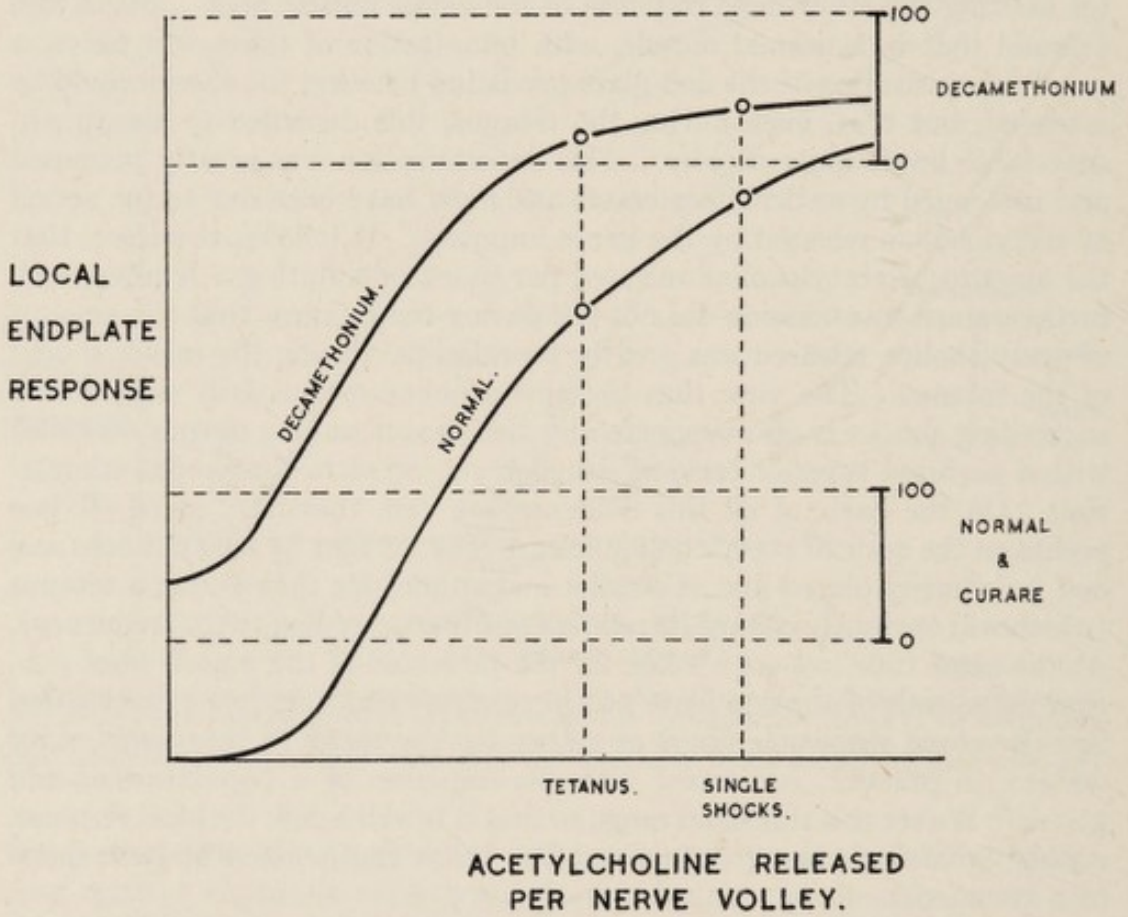

FIGURE 2. As FIGURE 1. Right-hand lower curve and lower range of thresholds, normal muscle; left-hand upper curve and upper range of thresholds, muscle treated with decamethonium.

With decamethonium, the situation is reversed (FIGURE 2). The end plate is already the site of some degree of local response. In the figure, I have drawn this above the normal threshold, so that it will have caused the initial stimulant action that we have already discussed. This local response now sums with that to acetylcholine, so that the whole curve is raised. The advantages to transmission conferred initially by this are lost, because, as we have seen, such a local response, if it is persistent, causes electrical inexcitability, and the propagation threshold rises. Now, however, another aspect of the difference from d-tubocurarine appears. The summation of

the local response to locally released acetylcholine with that to the circulating decamethonium will raise the physiological range of local responses much nearer the maximum response and, therefore, on to a flatter part of the dose-response curve. The result is, of course, that the size of local response can be influenced much less by variations in acetylcholine output or in sensitivity of end plate to acetylcholine. Accordingly, we should expect to find, as we do, that a tetanus is well sustained at a tension not far short of that given by a twitch, and that the facilitations to which d-tubocurarine block yields so readily are here relatively ineffective.

The results of this analysis show, therefore, that the exaggerated transmitter-like action in decamethonium block accounts readily for the initial stimulant aspects and for the stability of the block; the depression of transmitter action by d-tubocurarine explains the absence of stimulation during d-tubocurarine block and for its lability; and the contrasting nature of the actions of the two drugs accounts for the inverse relationship between the conditions favoring one or the other. We can, in short, form a reasonably coherent picture of the behavior of these compounds, on the basis of their respective actions at the neuromuscular junction.

Further Considerations. (1) *Nomenclature of Drugs Causing Neuromuscular Block.* The terms "curarizing" and "curariform" are in danger of becoming meaningless. They are applied not only to the actions of the whole range of natural alkaloids, but also to the actions of decamethonium, ether, myanesin, and botulinum toxin, becoming sometimes virtually synonymous with "relaxing." It may be argued that this does not matter greatly in practice, if the final physiological effect looks the same. I do not think that this argument can be sustained. In the first place, there are important practical differences, for instance, between decamethonium and curare, in their response to antagonists and in the occurrence of hypersensitivity to them. Any nomenclature which may disguise such differences and so tend to clinical confusion can only be regarded as unsatisfactory. At the moment, perhaps, there are not too many drugs in this field for one to be able to master their properties fairly readily. There can be little doubt, however, that many more, like d-tubocurarine, or like decamethonium, or with intermediate properties, or with new properties, are going to be developed and used as relaxants, antidotes, or research tools in years to come. A continuation of the rate of progress observable over the last few years into the future seems to me likely to yield clinical chaos unless there is some revision and clarification of nomenclature.

In addition, however, and possibly more important, is the need of clear terminology in pharmacology itself. It is almost trite to say that quantitative comparisons of intensity of action are valid only when the actions compared are themselves of a similar nature. Yet, how many comparisons of "curarizing" compounds there have been and how fertile and far-reaching are the speculations based on these comparisons, without any verification of such qualitative resemblance.

The task of finding better names is not an easy one, however, and no doubt they will be found by gradual evolution rather than created deliberately. Nevertheless, I should like to venture a few comments. It is

clearly convenient to retain the term "curare" and its derivatives for *some* sort of use. If this is done, such terms belong naturally, and now rigorously, to those compounds alone which raise the threshold of the motor end plate to acetylcholine. There seems to me real danger in trying to create fresh distinctions within a "curare" framework, such as between "curarizing" and "curariform," or (with deference to Professor Bovet) between "pachycurare" and "leptocurare." The mere introduction of the "curare" radicle seems to me to introduce confusion, infecting the meaning of such terms with the whole history of the natural alkaloid. The truth is that a word, phonetically corrupted from the dialect of the South American Indian, is no longer suited (save perhaps in the diversity of the twenty odd ways it has been spelled) to the requirements forced on us by modern synthetic pharmacology. How then may one conveniently refer to the action of decamethonium? A simple solution is to use the terms "depolarization," "depolarizing drug," "depolarization block," and, when a distinction from, say, potassium is required, to add "specific" or "end plate." But probably the best term remains to be found. It might be that such a name as "perexcitatory" would be better, expressing the fact, in a more general way, that decamethonium produces block not simply by causing a depolarization, but because this excitatory process persists beyond normal limits.

These are awkward points, and I have no qualifications to speak on them. I would like to add my voice, however, to those who wish for clarity.

(2) *Recent Anticurare Substances.* Attention has recently focused on a certain group of substances which can relieve block by curare-like substances, although they lack marked anticholinesterase activity. This group includes those studied by Wescoe and Riker,[27] Randall and Lehmann,[24] and Depierre and Funke,[8, 10] notably the m-hydroxy-phenyl-alkylammonium compounds. Now the properties of the latter compounds bear certain striking similarities to those of decamethonium, *viz.*; the potentiation of the nerve-excited twitch of normal mammalian muscle, contracture of denervated mammalian muscle, and contracture of frog's rectus with sensitization to acetylcholine. There can be little doubt that they possess some of that specific depolarizing activity at the motor end plate which acetylcholine and decamethonium display in intenser form. This view is strengthened by the observation that decamethonium itself can reverse block produced by Flaxedil[9] or by d-tubocurarine (Hutter, 1951: unpublished). Acetylcholine, of course, has long been known to do this (see 12 for references).

Given, therefore, that these anticurares can depolarize, and that a depolarizing drug can also reproduce their effects, it seems possible that a part, at least, of their activity in antagonizing d-tubocurarine rests on their ability to produce this depolarization. One can fairly readily, on the same lines as before, construct an end-plate response curve (FIGURE 3) demonstrating how such an effect might be brought about, the main assumption (for which there is some evidence) being that inexcitability does not result from small depolarizations.

There is, therefore, both reasonable evidence for supposing that anticurares possess depolarizing activity and a reasonable basis on which to explain this association. If this is so, then we may look for some of the

other properties of decamethonium in them. Three such properties immediately come to light. (a) Artusio *et al.*[1] have already commented on the lessened effectiveness of the m-OH-phenyl dimethylethylammonium compound as a curare antagonist in ether anesthesia or with deep curarization. (b) Others besides myself have found that it does not antagonize decamethonium. Far from antagonizing, it potentiates strongly. Thus, on a cat's tibialis, I found that, if given with 1 mg. Ro 3198, only 6 μg./kg. of decamethonium were needed to produce a 95 per cent block. (c) Depierre[8] has described a failure by m-hydroxyphenyltrimethylammonium to restore the respiration depressed by Flaxedil (although she also showed that this was

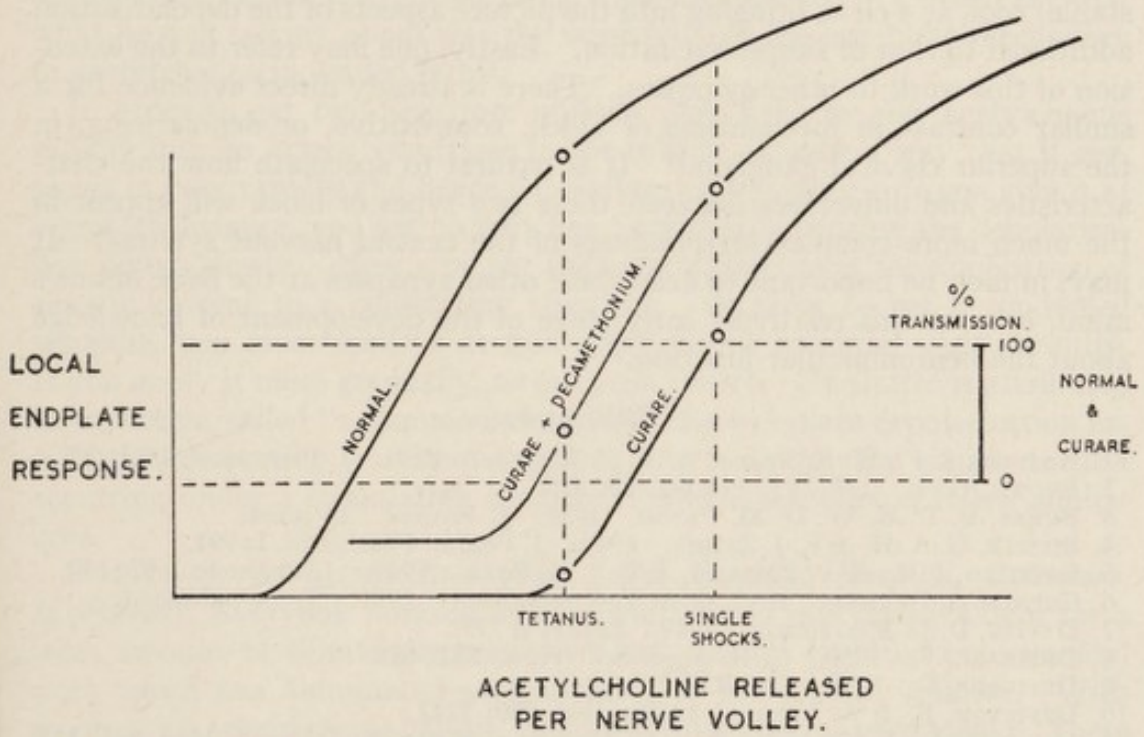

FIGURE 3. AS FIGURE 1. Left-hand curve, normal muscle; right-hand curve, curarized muscle; middle curve, curarized muscle treated with decamethonium.

not due to a failure to restore phrenic-nerve-diaphragm transmission). We have therefore, for this compound, an antagonism to it by ether and d-tubocurarine, a potentiation by it of decamethonium, and a possible refractoriness to it of respiratory muscles—all features typical of the action of decamethonium. Finally, one might remark that the transience of action of these drugs may be, indeed, not due to their rapid destruction (for which Unna and his colleagues[26] failed to find evidence) but to the succession of the end-plate facilitation by a later rise in propagation threshold.

It is not my purpose now to press the argument that these phenylalkylammonium compounds act wholly by virtue of their resemblance to decamethonium. I feel, indeed, fairly confident that this is not true, but that, like many other drugs, they have a complex action. I wish only to suggest that, in analyzing their mode of action, it is worth while, before embarking on complex *ad hoc* drug-receptor theories, to consider the simpler possibility that part of such action may be simply facilitation of neuro-

muscular transmission due to a limited depolarization of the end plate. Our knowledge of the actions of acetylcholine at the end plate, by extrapolation from those of decamethonium, now allows us to test such a theory quite rigorously.

(3) *Further Work.* Certain lines of future investigation appear to derive added interest from this analysis of the properties of depolarizing and curarizing drugs. There is, for instance, the peculiarity of the rat's neuromuscular junction, if its insensitivity to decamethonium is taken (as I think it must be) as an indication that it is also very insensitive to acetylcholine. Again, in the more fundamental problem of how acetylcholine effects its specific depolarization, decamethonium may well be a useful (because more stable) tool, as well as bringing into the picture aspects of the depolarization additional to that of simple excitation. Lastly, one may refer to the extension of this work to other synapses. There is already direct evidence for a similar contrast in mechanisms of block, competitive, or depolarizing, in the superior cervical ganglion.[19] It is natural to speculate how the characteristics and differences between these two types of block will appear in the much more complex surroundings of the central nervous synapse. It may, in fact, be important to keep these other synapses at the back of one's mind, even at this relatively early stage of the development of knowledge about the neuromuscular junction.

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Discussion of the Paper

Doctor George Acheson (*University of Cincinnati College of Medicine, Cincinnati, Ohio*): I heartily agree with Doctor Paton's insistence on sound terminology. We need clear words for the clearer analysis and understanding of the mechanisms we study. I would quibble with the term "threshold to acetylcholine," since I believe Doctor Paton is considering the action of acetylcholine by depolarization of the end plate. He is not dealing primarily with an all-or-none effect, and I believe that the term "threshold" should be reserved for all-or-none stimulation. The threshold is like the doorstep: either you step up or you don't step up. The acetylcholine effect on the transmission mechanism is a graded phenomenon. I would say that what he was talking about was the sensitivity of the end-plate mechanism to acetylcholine in graded terms.

In order to get twitches from muscles, you have to give acetylcholine rapidly into an artery very close to the muscle, in such a way that it gets swept in very rapidly and hence depolarizes very rapidly. If you give it at a greater distance, you get no twitches, presumably because the depolarization occurs slowly. Now, you get the same difference in the application of electric current to a conducting structure. In order to get a conducted response, you must apply a certain difference of potential very abruptly. If you apply it more gradually, no response occurs. The latter is attributed to a process called "accommodation." If the end-plate depolarization excites the conducting system of the muscle by a mechanism similar to that occurring under a stimulating electrode, its behavior should follow similar laws.

Doctor J. L. Lilienthal (*The Johns Hopkins Hospital, Baltimore, Maryland*): Everyone working in this field is in Doctor Paton's debt for a large amount of beautifully conceived and cleanly executed experimental work which has illuminated several facets of the general problem. With much of his stimulating analysis, there will exist general agreement. There are, however, certain observations already described which suggest that the time, although always ripe for hypothesis, is perhaps not yet here for too rigid a classification. Some of the differences in phenomena described by Doctor Jarcho and by Doctor Paton might be attributed to differences in the species studied. If this be the case then one is confronted with the dilemma: is it the cat or the rat which represents the exception? I am sure I do not know, but it may place this question in a different light if I remind you that those who work with primates, human or sub-human, might consider both cat and rat to be distinctly second-class citizens in this hierarchy. It is always tempting to make observations on the tibialis muscle of the cat, then construct from these observations hypotheses applicable to all cat muscle, and finally to generalize about muscle in general. This natural series of steps is valuable only when we keep clearly in mind that such generalizations may later require considerable qualification in the light of observations on other forms of muscle.

Doctor Lawrence Stark (*New York Medical College, New York, N. Y.*): We have been working in Professor Brown's laboratory at the University College, London, on end-plate potentials from the frog sciatic-sartorius preparation. Using acetylcholine and prostigmine, we blocked neuromuscular conduction by depolarization, a mechanism similar to that described by Doctor Paton for decamethonium. We also noted the localization of depolarization to the anatomical end-plate region.

With reference to Doctor Jarcho's data on fibrillation of denervated muscle, I think it is important to remember that less is known about denervated muscle than about the usual nerve-muscle preparations. One should therefore not try to reason facilely from evidence concerning fibrillation to mechanisms of drug action. These fibrillations are occurring spontaneously—perhaps they are another sort of biological noise—and, presumably, no evidence for their origin from nerve endings is available. Thus, neuro-muscular transmission might not be directly involved in their production.

Doctor Paton: First, as to Dr. Acheson's points. I am afraid I wasn't sufficiently explicit in explaining the diagram of excitability around the end-plate region exposed to decamethonium. The ordinates were the voltage required to produce, by direct electrical excitation of the muscle at various points along it, an action potential of constant size recorded at the tip of the muscle. Thus, the muscle response was held constant.

His remarks about the use of the term "threshold" are entirely justified and acceptable. I wish I saw more clearly how the action of decamethonium was related to accommodation and adaptive phenomena. I think it is quite likely that in time a great number of these will ultimately all be explicable in terms of the properties of cathodal block. At the moment, however, we are a long way from being able to draw any general picture of this sort.

Doctor Lilienthal said some nice things about the work I reported. I should like to say in reply, as I could not in the paper, how much it owes to other people, particularly to my recent colleagues at Hampstead, G. L. Brown, F. C. MacIntosh, and Doctor Harold King, and to many people here both on the platform and off it. I am very conscious of the importance of the muscle and species variation, as raised by Doctor Lilienthal. I still think that the cat is the best animal to use, particularly since using it to predict the dose of decamethonium to be used in our first human trials turned out so successfully.

Finally, on the question of nomenclature of pharmacological effects—Sir Henry Dale's advice was extremely shrewd. I don't believe, however, that giving the name of a drug to an action entirely removes any supposition as to the method of its action, and it may introduce difficulties of its own. These are particularly well illustrated by the term "nicotine-like." We know that this action has at least four independent aspects: end-plate stimulation, neuromuscular block by competition with acetylcholine, ganglion stimulation, and ganglionic block, epitomized respectively by decamethon-

ium, d-tubocurarine, tetramethylammonium, and hexamethonium. If nicotine proves to have an important action on other structures, additional pairs of actions will have to be added to such a list. Nicotine itself is clearly no longer a specific enough drug to avoid confusion. Nor can we substitute other drugs for it until we have ones which are sufficiently specific and free of other actions. Under these conditions, I personally prefer a term such as "depolarizing," which can be qualified with respect to the structure involved, and which unambiguously, but not elaborately, indicates the mode of action of the drug in question.