LETTERS TO THE EDITORS

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Motor End-Plate Differences as a Determining Factor in the Mode of Action of Neuro-Muscular Blocking Substances

In consequence of the results obtained with decamethonium in the cat[1,2] and in human beings[3], we felt justified in putting forward the thesis that decamethonium produced a neuromuscular block in mammals only through a persisting depolarization of the motor end-plate. But work undertaken with other mammalian species (monkeys, dogs, hares) during the past few months reveals that decamethonium can produce in these three a neuromuscular block which differs in many ways from the block produced by pure depolarization. Thus in these species the tetanus is poorly sustained, and antagonizes the block, which is also antagonized by anticholinesterases. The white muscles show an acute decreasing sensitivity to decamethonium, a second injection of a dose which at first produced almost complete paralysis failing to produce any effect. If one records simultaneously from a red muscle and a white one[4], a transition from a depolarizing type of block to a block by competitive inhibition is seen.

Succinylcholine, a pure depolarizing substance, when used on the cat, gave similar results to decamethonium on the monkey and the dog. These findings clearly indicate that decamethonium and succinylcholine can no longer be described as purely depolarizing substances in these species. What, then, are they ? Undoubtedly they are not just competitive inhibitors, because in the first place they produce features of a depolarizing substance, and in the second place the muscles of the species under consideration show an acute decreasing sensitivity to decamethonium and to succinylcholine. Such a result is never obtained from a competitive inhibitor like *d*-tubocurarine. The impression resulting from the study of these facts is that the picture obtained in the monkey and the dog is similar to that obtained in the cat when an injection of *d*-tubocurarine is interposed between the first and subsequent doses of decamethonium.

A tentative suggestion I should like to put forward is that there may be a dual mode of action of decamethonium and succinylcholine upon the muscles of these animals. It seems possible that, while the molecules at first adhere in the specific way necessary to produce a depolarization at the end-plate, their grip eventually changes, with the result that from depolarizing substances they become competitive inhibitors.

This idea is strengthened by two other observations. A higher member of the same series as decamethonium, tridecamethonium, produces in the cat a similar picture to that produced by decamethonium in the monkey and in the dog. This shows that if the polymethylene chain is lengthened, the molecule loses the specific property required to produce a neuromuscular block by pure depolarization even in the cat. The other observation relates to the action of these substances on avian muscle[5]. In birds, *d*-tubocurarine produces the usual paralysis, whereas decamethonium and succinylcholine produce a pure contracture characterized by extension of the limbs and retraction of the head[5]. If the dose is small, recovery is abrupt ; if large, the animal dies in contracture and never exhibits paralysis. But when an injection of tridecamethonium is given, a completely different picture is produced. First contracture appears ; but slowly, while the legs are still extended, the head drops forward in paralysis and finally the paralysis extends to involve the muscles of the leg so that the whole animal becomes flaccid. In the bird, as in the monkey, we start with a decamethonium picture and finish with a *d*-tubocurarine one.

Hitherto it has generally been assumed that results obtained from experiments upon one mammal could safely be regarded as typical for mammals in general. It is now clear that results obtained from the muscle of any one mammalian species are valid only for this species, and perhaps for the particular muscle upon which the experiment was made.

These findings seem to provide an explanation for the varying sensitivity of different species to decamethonium. In species where depolarization is the only mode of action of decamethonium, sensitivity is great. But immediately the dual mode of action comes into play, the muscle becomes more resistant to decamethonium, most probably because these two modes of action are antagonistic.

The variations of the cat, monkey and dog muscles in response to substances like decamethonium and succinylcholine show that there must be distinct physical differences between the muscle membranes of these mammalian species, in spite of the similarity of their reaction to acetylcholine—a fact revealed so far only by such pharmacological analyses. These normally occurring differences in certain species may appear as pathological changes in the muscles of any one species. Taking into consideration results obtained by Churchill-Davidson and Richardson (see succeeding communication), we may reasonably conclude that the myasthenic syndrome is due to changes developing at the motor end-plates of these subjects ; these changes make them react to their own acetylcholine as if acetylcholine were a competitive blocking substance.

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[2] Zaimis, E. J., *J. Physiol.*, **112**, 176 (1951).
[3] Churchill-Davidson, H. C., and Richardson, A. T., *Proc. Roy. Soc. Med.*, **45**, 179 (1952).
[4] Paton, W. D. M., and Zaimis, E. J., *J. Physiol.*, **112**, 311 (1951).
[5] Buttle, G. A. H., and Zaimis, E. J., *J. Pharm. Pharmacol*, **1**, 991 (1949).

The exact mechanism responsible for the muscle weakness and rapid fatigue characteristic of myasthenia gravis remains unknown, although it has long been recognized to be associated with a failure of neuromuscular transmission. Three main factors have been suggested as the possible cause of this neuromuscular block : first, a reduction in the amount of acetylcholine liberated at the myoneural junction ; secondly, an excessive rate of its destruction due to increased esterase activity ; and thirdly, the prevention of its depolarizing action on the motor end-plate by a curare-like substance.

There is no adequate evidence to indicate an abnormality in the production or destruction of acetylcholine in myasthenia, and one could not