THE RELATIVE SUSCEPTIBILITY OF THE DIAPHRAGM, AS COMPARED WITH THE LIMB MUSCLES, TO THE EFFECTS OF TUBOCURARINE CHLORIDE


In the classical accounts of the action of curare on the mammal, a definite order in which paralysis occurs in different muscles is agreed by all observers. The first to be affected are the short muscles of the toes with those of the eye and ear, then those in the limbs, next those in the trunk, and, finally, the diaphragm. In the earlier stages the paralysis of any muscle is not complete in that, at a time when no sustained tetanic contraction can be elicited, a response in the form of a "twitch" may still occur. It is the failure of the tetanic contraction which causes the poisoned animal to fall to the ground, although even then it may still be able to move its limbs.

Why there should be this sequence in the onset of paralysis, and why in particular the diaphragm should be the last muscle affected, is still unknown. Explanations have been offered for the relative insusceptibility of the diaphragm as compared with the limb muscles, but none seems entirely satisfactory. It has been suggested that the known difference between the diaphragm, a red muscle, and the limb muscles, chiefly white, is enough to account for the difference in susceptibility. On the other hand it may be argued that, while this difference undoubtedly exists, the action of tubocurarine is not upon the fibres themselves, but rather upon some undetermined point in a chain reaction occurring between the anatomical nerve ending, the end-plate, and the muscle fibre. So far as we are aware, little or nothing is known about any difference in that
chain reaction in red, as opposed to white, muscles. Again it has been argued that the diaphragm is a muscle of intermittent activity, and that the intervening short periods of rest are sufficient for the restoration of its function, while the limb muscles, or some of them, are required to be continually in action if the animal is to remain on its feet. This argument, however, applies equally forcibly to the limb muscles, as it has been shown conclusively by the Cambridge School that the absence of fatigue in these muscles is due to the fact that a proportion only of the fibres is in action at any time, and so the duty of maintaining posture is shared by all the fibres acting in groups, as it were in relays. There is, then, an intermittency in the activity of the limb muscles, as well as of the diaphragm.

It occurred to us that the difference in susceptibility of these muscles might be rather apparent than real. The needs of the body for gaseous exchanges through the lungs determine the extent of the respiratory movements, and so of the activity of the diaphragm. In an animal rendered immobile by curare or by an anaesthetic these needs will be reduced to a minimum, and it seemed not impossible that such minimal requirements might be met by a very greatly reduced power of movement of the diaphragm, in fact by a diaphragm which had been weakened to an extent comparable with that of the limb muscles when they became unable to sustain the weight of the body.

As we were unaware of any previous work in which a direct comparison of the effects of tubocurarine chloride on the power of the diaphragm and of the limb muscles had been made, this investigation was set on foot. When, however, this work was nearing completion, an account of an investigation with a somewhat similar line of approach appeared (Mushin, Wien, Mason and Langston, 1949). As the result of our observations, we have to admit that our original idea has been completely disproved, and that there is an inherent difference in susceptibility to the action of tubocurarine chloride between the diaphragm and the limb muscles.
Fig. 1

Cat, 4 kgm., decerebrate. Upper tracing, tibialis anticus; lower, diaphragm. Running through the latter is the blood pressure record. Next to bottom line indicates zero blood pressure. Bottom line, time tracing at 10 sec. intervals. In each of the first seven sections an injection of tubocurarine chloride in amounts as shown on the figure was made. Three injections of 0.05, 0.05, and 0.025 mg. of physostigmine and one of 1 mg. of atropine were given subsequently. For description see text.

G. & H.
Rabbit, 3.2 kgm., sodium pentobarbitone. Top record, diaphragmatic respiratory movements, the figures representing frequency per minute. Second record, blood pressure, steady almost throughout at 120 mm. Hg. Third record, contractions of gastrocnemius muscle. Lowest two lines, as Fig. 1. The figures at the injection points are total doses of tubocurarine chloride given. Before the first section an amount of 0.175 mg. had been given with atropine. A further 0.1 mg. was given between sections 5 and 6. For description see text.

G. & H.
EXPERIMENTAL METHODS

In one section of the work, rabbits lightly anaesthetised with sodium pentobarbitone were employed. The greater part, however, has been done on cats, either decerebrate or under light chloralose anaesthesia. At the commencement attempts were made to use the decapitate animal but these failed, owing as it seemed to the low systemic blood pressure, inevitable with this preparation, giving an insufficient supply to the muscles.

In the first section the thorax of the decerebrate cat was opened under artificial respiration and both phrenic nerves were cleared and cut as high up as possible in the chest. Sherrington’s preparation of the tibialis anticus muscle was adopted and its motor nerve also cut as high up as possible. The contractions of the two muscles were recorded by connecting the tendons to levers working against suitably adjusted springs, care being taken to avoid “afterloading” of the muscles. Two pairs of electrodes, connected in series to ensure equality in intensity of stimulation, were attached to the secondary terminals of an ordinary Dubois-Raymond coil. To avoid any risk of polarisation phenomena arising, the primary coil was supplied with alternating current suitably transformed down from the mains.

In the second section rabbits only were employed. A limb muscle, either the tibialis anticus or occasionally the gastrocnemius, and its motor nerve were prepared as before. The normally occurring movements of the diaphragm, in contrast to those artificially produced as in the former section, were recorded.

In the last section the spinal cord of cats, either decerebrate or anaesthetised, was cut at about the 10th dorsal segment. On one side a motor nerve and muscle was prepared as before, either the tibialis anticus or gastrocnemius being employed. On the other side the posterior tibial nerve was cut low down in the thigh and the tibialis anticus tendon prepared for re-
according, as the flexor reflexes are less affected by transection of the cord. Electrodes, in series as before, were applied to the sensory nerve on one side and to the motor nerve on the other so that the effects of stimulation of a muscle by a reflex and by a motor nerve could be compared.

In all cases the blood pressure was recorded from a common carotid artery, and an external jugular vein was cannulated for intravenous injection.

**Experimental Results**

**Section I**

Faradic stimulation of five seconds duration was applied every half minute to the phrenic and anterior tibial nerves. When the height of the contraction of each of the two muscles appeared to be fairly constant, tubocurarine chloride was injected intravenously in small doses, repeated from time to time. Figure 1 shows a typical result. Immediately after the first injection of 0.1 mg., there was a diminution in the height of the contraction of the tibialis anticus with little or no change in that of the diaphragm. As the total amount of tubocurarine administered increased, there was a progressive diminution in the response of each muscle. Of the two, however, the tibialis anticus was much more affected than the diaphragm, as it proved almost unable to maintain any degree of tetanic contraction at a time when the diaphragm, although weakened, was still perfectly capable of giving an air exchange adequate for a motionless animal (see the fifth section of figure 1). With further injections of the drug even the "twitch" response of the tibialis anticus became practically abolished, but at this stage the tetanic response of the diaphragm had also gone.

On the injection of physostigmine in small amounts recovery commenced in both muscles almost at once but was much more complete in the diaphragm than in the tibialis anticus at the close of the experiment. The height of the contraction of the diaphragm had returned to almost one half of
Cat, 2.3 kg., decerebrate and spinal cord cut. Upper tracing, contraction of tibialis anticus on stimulation of motor nerve; second tracing, contraction of tibialis anticus on reflex stimulation. Cutting across the latter is the blood pressure record, 75-80 mm. at the start, rising to 110 mm., then varying from 75-100 mm. Fig. Lowest two lines, as in Fig. 1. Doses of tubocurarine chloride as marked are total doses given. For description see text.

C. & H.
Relative Susceptibility of the Diaphragm

that at the commencement, while that of the tibialis anticus had recovered to less than one third.

Throughout the experiment the blood pressure remained very constant at about 80 mm. Hg, until near the end when it rose to about 100 mm., due to the administration of atropine, used to counteract the circulatory side-actions of physostigmine.

SECTION 2

It was desired to obtain a state of considerable paresis in the limb muscles, but not actual paralysis, and to determine to what extent the normal respiratory excursions of the diaphragm would be diminished as a result. It was thought that the "head-drop" dose would be appropriate for this purpose. This dose was therefore determined in a few animals, and this amount was injected into an anaesthetised rabbit. It was found, however, that when given to an anaesthetised animal the "head-drop" dose was far too large, causing almost instant paralysis of the limb muscles, although the respiration was not arrested immediately. This was repeated with the same result in a second animal.

In later experiments, therefore, repeated small doses were given causing gradual onset of paralysis, as in the first section. Owing to the time taken up by the injections and by the observation of the effects of each, much of the drug was excreted. This fact, together with the known lesser effect of a given amount of curare when given in multiple doses rather than all in one dose, caused a total dosage to be used much greater than the estimated "head-drop" dose.

The general picture is shown in Figure 2. Small amounts, totalling 0.175 mg., had been given at a stage earlier than that shown in the beginning of the tracing. As a sharp fall of blood pressure had followed each injection of tubocurarine, atropine had also been given. It will be seen that, at the beginning, the tetanic response of the gastrocnemius was well maintained throughout the five second period of stimulation. At this time,
the respiratory rate was 47 per minute, and the excursion of the lever attached to the diaphragm measured about 19 mm. With further doses the height of the record from the gastrocnemius gradually became less, and the maintenance of tetanus steadily more impaired. When the total dosage had reached 0.525 mg., the height of the "twitch" part had been reduced to one half, but that of the tetanic part of the gastrocnemius record to only one tenth of the original. At the same time the respiration was still perfectly adequate, the rate being 57 per minute and the lever excursion measuring 18 mm. Another dose of 0.1 mg. reduced still further the tetanic response, although having little effect on the height of the "twitch". In an attempt to abolish the latter a further 0.2 mg. was administered with the result that the last traces of tetanus were annulled, and the twitch reduced to about one eighth of the original height. At the same time, however, the diaphragm was greatly affected, the respiratory excursions becoming slower and weaker until they finally stopped.

SECTION 3

The object of this section was to determine whether tubocurarine chloride affects in a different manner the response of a muscle when stimulated through its motor nerve on the one hand and on the other reflexly by stimulation of a sensory nerve. A typical tracing is shown in Figure 3, although the blood pressure was less constant than might have been desired. It will be seen that the contraction in response to a sensory nerve stimulus was more quickly and more markedly affected than that caused by stimulation of the motor nerve. The "twitch" part of the contraction was reduced by the action of the drug in the two muscles in almost equal measure. The tetanic part of the reflexly induced contraction failed more quickly, however, so much so that it was practically abolished at a time when that caused by motor nerve stimulation was still one third as great as in the normal. This effect was observed in both the decerebrate and the anaesthetised cat,
Discussion

The results obtained in the first two sections of this work speak for themselves and little discussion is needed. They show clearly that when the diaphragm and a limb muscle, under exactly similar conditions, are exposed to the action of tubocurarine chloride, the former muscle is more resistant to the drug. This is true whether both muscles receive their stimulus in the form of faradic currents applied to the motor nerve, or the limb muscle alone receives such stimulation while the diaphragm is responding to the normal form of stimulation. The difference in susceptibility was not found to be very great, of the order of 4:5. An analogy may perhaps be sought in the reactions of unstriated muscle to drugs. There is little apparent histological difference in the smooth muscle fibres of the various organs of the body. None the less, great differences exist in their reactions to drugs. Thus the blood vessels are readily affected by the nitrites at a concentration which is without action on the bronchial musculature. Again, the blood vessels are more sensitive than any other organ to the action of adrenaline.

The chief justification for the use of tubocurarine in anaesthesia is that it allows complete abolition of tone in the voluntary muscles at a relatively light level of anaesthesia. Tone in voluntary muscle being a reflex phenomenon, the third section of this work was undertaken to determine what effect tubocurarine might exert on the responses of muscles stimulated (a) through the motor nerve, and (b) by a reflex, and whether any difference might exist between the responses. It has been found that both responses are reduced by tubocurarine, but that the reflex is the more rapidly affected of the two. Now, it has been shown in the second section of this work that the diaphragm responding to its natural stimulus is less
affected by the drug than is the limb muscle, stimulated through its motor nerve. A fortiori, therefore, it should be relatively more capable of carrying on its necessary movements at a time when the reflex phenomenon of tone has been abolished.

An important aspect of the use of any potent drug is its therapeutic index, which in the case of tubocurarine would be the ratio of the dose required to arrest respiration to that needed to abolish muscular tone. From the first and second sections of this work we should estimate that the dose required to arrest respiration is about one fourth higher than that required to abolish the tetanic response to nerve stimulation in a voluntary muscle. From our experiments on anaesthetised animals in the third section of this work, we conclude that there is little difference, about 10–20 per cent, in the dose required to abolish tetanic responses in muscles stimulated through the motor nerve and by a reflex. This would bring the therapeutic index of tubocurarine, as defined above, to about 1.4, a figure in sufficiently close agreement with that obtained by Mushin et al. (1949).

**Summary**

1. Direct recording of the effects of tubocurarine chloride on the contractions of the diaphragm and of a voluntary muscle has shown that the former, whether stimulated naturally or artificially through the phrenic nerve, is less susceptible to the drug than is the latter.

2. Similarly, it has been shown that the response of voluntary muscle to a reflex stimulation is more readily affected by tubocurarine chloride than is its response to stimulation of its motor nerve.

3. The therapeutic index of the drug is estimated as being about 1.4.

**References**
