Neuromuscular Effects of d-Tubocurarine, Edrophonium and Neostigmine in Man

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The neuromuscular effects of *d*-tubocurarine, edrophonium and neostigmine were determined in patients anesthetized with nitrous oxide plus trichlorethylene, meperedine, or thiamylal. The effect of *d*-tubocurarine (0.1 mg./kg.) was variable, ranging from no effect on twitch tension to abolition of the twitch response. Because of this variation in response the routine use of a fixed mg./kg. dose of *d*-tubocurarine was not recommended. Edrophonium (10–100 mg.) was found to be unsatisfactory as an antagonist of *d*-tubocurarine. Neostigmine (2.5–5 mg.), however, was found to be a good antagonist of *d*-tubocurarine. Although there is still some controversy concerning the mechanism of anticurare action of edrophonium and neostigmine, cholinesterase inhibition appears to be a major factor.

Much of the information on the action of drugs affecting neuromuscular transmission is derived from studies in animals. But it has been clearly established that these drugs act differently in the cat, dog, rat, chicken and man. In addition, these drugs are tested differently in the several species. In animals, a common technique is to inject a single dose of a neuromuscular blocking agent and after a variable period of time to inject an antagonist. In clinical practice, however, repeated doses of the neuromuscular blocking agent are given, sometimes over many hours, and the antagonist then is injected. Furthermore, different end points are used in testing the effects of these agents. In animal studies the twitch response is commonly used. In man, onset and adequacy of spontaneous respiration are frequently used. It is clear that many factors other than neuromuscular block may affect respiration.

In man, the actions of neuromuscular blockers have been assessed by determining their effects on grip strength and vital capacity. The value of this work is limited by the use of unanesthetized subjects.[1] In 1961 we began routinely to use a nerve stimulator to monitor, during anesthesia and surgery, the actions of agents affecting neuromuscular transmission. This report concerns our observations on the effects of *d*-tubocurarine, edrophonium and neostigmine.

Methods

Patients undergoing surgery of the upper or lower abdomen or of the head and neck were studied. They weighed 50–90 kg. Most of the patients received atropine or scopolamine (0.4–0.8 mg.), secobarbital or pentobarbital (50–100 mg.) and/or meperidine (50–100 mg.) for preanesthetic medication. Anesthesia was usually induced with thiamylal sodium and maintained with nitrous oxide (7 liters) plus oxygen (3 liters) plus trichlorethylene (approximately 0.3 per cent) or with nitrous oxide (4 liters) plus oxygen (2 liters) plus meperidine or thiamylal. Tracheal intubation, when necessary, was accomplished with the aid of 60–100 mg. of succinylcholine intravenously. A Wright ventilometer, a Collins spirometer or a Wedge spirometer was used when ventilation was measured. Ventilation was spontaneous, or when necessary, controlled manually or with a Frumin respirator. Brachial arterial blood samples were analyzed for *p*H and P_{CO_2} in some patients with an Ingold *p*H electrode and modified Severinghaus P_{CO_2} electrode or by the Astrup technique (AME-1).

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Neuromuscular transmission was studied in 162 patients in a manner previously described.[2] Briefly, the ulnar nerve was stimulated and the adduction of the thumb measured with a force displacement transducer and recorded on a polygraph. In 166 patients the ulnar nerve was stimulated with a Grass stimulator (Model S4) or the Block-Aid Monitor[3] or preliminary models of the Block-Aid Monitor. In these patients, the magnitude of the block was estimated by observing the adduction of the thumb. The response to tetanic stimulation (30 cps) was also determined. The choice of nerve stimulator did not modify the results.

The following drugs were studied: *d*-tubocurarine chloride (Tubarine), edrophonium chloride (Tensilon), neostigmine methylsulfate (Prostigmin). All drugs were injected intravenously. *d*-tubocurarine (dTC) was given in the following manner. To approximate the technique of administration of dTC frequently used in Great Britain, 50 patients received a single dose of 0.6 mg./kg. over 1–3 minutes, or a test dose of 0.1 mg./kg. followed in 3 minutes by 0.5 mg./kg. In the majority of patients, however, a test dose of 0.1 mg./kg. was injected rapidly (1–3 seconds) and the effect on twitch height determined. Five to 10 minutes later, a dose of 0.2–0.4 mg./kg. of dTC was rapidly injected. No additional dTC was given for one hour. Then 0.15–0.2 mg./kg./hour was injected in divided doses. When it became apparent that edrophonium could not adequately antagonize these doses of dTC, edrophonium was then studied in patients in whom the surgical procedure could be carried out with smaller doses of dTC.

Patients receiving neostigmine were given 1 mg. of atropine sulfate intravenously, usually 1 minute prior to the injection of each 2.5 mg. of neostigmine. Atropine, 1 mg. prior to each 20–30 mg. of edrophonium, was also given to patients receiving more than 10 mg. of edrophonium.

Results

d-Tubocurarine. The effect of 0.1 mg./kg. of dTC on twitch height was determined in 100 patients (fig. 1). In 6 patients there was no demonstrable depression of twitch height (fig. 2A), while in 7 patients the twitch was abolished (fig. 2B). In the remaining patients there was a variable depression of twitch height. It was not possible to predict the response of a given patient to this dose of dTC on the basis of age, sex, body build, or physical status (ASA classification). The intravenous injection of 0.2 mg./kg. of dTC in 10 patients depressed twitch height 70–100 per cent. In 20 patients the intravenous injection of 0.3 mg./kg. of dTC depressed twitch height 90–100 per cent.

The depression of the twitch by dTC was

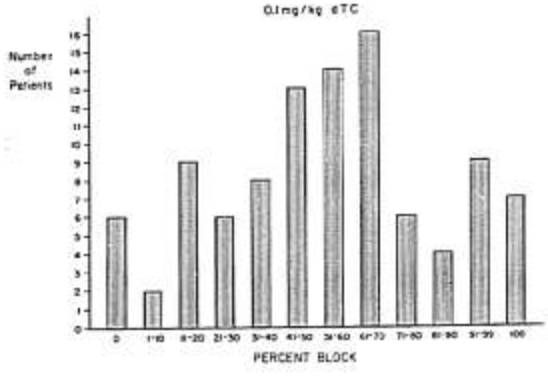

FIG. 1. Effect of 0.1 mg./kg. of *d*-tubocurarine on twitch height in 100 patients. Note the marked variation in percentage block produced by this dose.

quite rapid, usually beginning in less than 1 minute, with the peak or 90 per cent of peak effect occurring within 2 minutes. The maximum effect was attained more rapidly with the larger doses of dTC and in patients who had a profound effect from 0.1 mg./kg. of dTC. When additional doses were given, the maximum effect usually occurred in less than 1 minute.

In the initial experiments, an unsuccessful attempt was made to correlate twitch depression with tidal volume. In some patients, tidal volume was markedly depressed when twitch height was decreased only 50 per cent while in other patients tidal volume remained at the control level although the twitch was abolished. In two of the latter, at the time of absent twitch but adequate tidal volume, the Pa_{CO_2} was 8 and 13 mm. of mercury greater than the pre-dTC levels. Since the variations in respiration were attributable more to preanesthetic medication and the anesthetic agents than to dTC, we abandoned our efforts to correlate twitch depression with respiration and arterial *p*H and P_{CO_2}.

Spontaneous Recovery from d-Tubocurarine. In most of the patients studied, the clinical situation did not permit determination of the time required for spontaneous recovery from dTC. However, some idea of the spontaneous recovery time may be obtained from the following observations: (1) In 8 patients who could be observed for two hours after receiving a single dose of 0.6 mg./kg. of dTC, the degree of recovery varied from 0–60 per cent. (2) Recovery times from single doses of dTC were: 0.1 mg./kg.–40, 57 minutes; 0.2 mg./kg.–62, 78, 94 minutes; 0.3 mg./kg.–73, 96, 115 minutes; 0.4 mg./kg.–108, 130, 153 minutes. (3) Where it was possible to observe the recovery from multiple doses of dTC for 60–90 minutes, full recovery was rarely seen during this time.

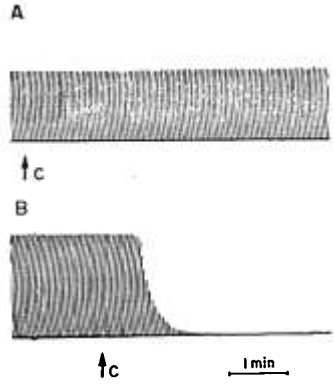

FIG. 2. Effect of *d*-tubocurarine. *Panel A. d*-Tubocurarine (0.1 mg./kg.) at ↑C did not depress twitch height. *Panel B. d*-Tubocurarine (0.1 mg./kg.) at ↑C abolished the twitch response.

Edrophonium. Edrophonium (10–100 mg., usually in 10-mg. increments) was injected intravenously in 50 patients who had received an average dose of dTC of 0.19 mg./kg./hour (range of 0.1–0.6 mg./kg./hour). In 23 of 50 patients, the commonly used doses of edrophonium (10–20 mg.) rapidly restored twitch height to the control level (fig. 3A). In 27 patients, a prompt increase in twitch height was seen with the first dose and then it appeared that the slope of recovery returned to that seen prior to edrophonium. Additional

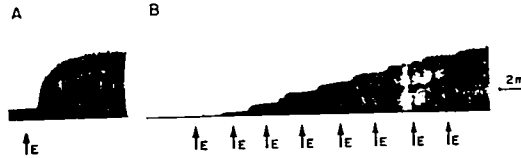

FIG. 3. Antagonism of *d*-tubocurarine by edrophonium. *Panel A.* Patient received 0.2 mg./kg. of *d*-tubocurarine. Thirty minutes later, at ↑E 20 mg. of edrophonium injected. The twitch response was rapidly restored to the control level. *Panel B.* Patient received 0.3 mg./kg. of *d*-tubocurarine. Twenty-five minutes later, edrophonium (10 mg.) was injected at first ↑E. Note prompt but small and brief increase in twitch height. Seven additional injections of 10 mg. of edrophonium (at each ↑E) were required to restore twitch height to the control level.

FIG. 4. Comparison of spontaneous recovery from *d*-tubocurarine with effect of neostigmine. Patient received total dose of 0.4 mg./kg. of *d*-tubocurarine. At ↑N 2.5 mg. of neostigmine was injected (69 minutes after initial dose of *d*-tubocurarine). Note slow and small spontaneous rate of recovery over ten minutes before neostigmine and rapid recovery to control twitch height in ten minutes after neostigmine.

doses of edrophonium produced further increase in twitch height at some times (fig. 3B) but not at others.

The effectiveness of edrophonium depended in large measure upon the extent of spontaneous recovery from dTC. Edrophonium (10–20 mg.) restored twitch height to the control level in 18 of 22 patients whose twitch had spontaneously recovered to 25–75 per cent of control. Where spontaneous recovery was 0–24 per cent, 10–20 mg. of edrophonium was effective in only 5 of 28 patients. Additional injections of edrophonium (to a total dose of 70–100 mg.) restored twitch height to the control level in 6 of 14 patients. Given the same degree of spontaneous recovery, edrophonium was more likely to be effective, the smaller the total dose of dTC and the greater the interval between injections of dTC and edrophonium.

Neostigmine. The effects of neostigmine on twitch height were determined in 216 patients who had received an average dose of dTC of 0.28 mg./kg./hour (range of 0.1–0.6 mg./kg./hour). In 50 patients twitch was recorded while in the remaining patients the movement of the thumb was observed. The results with neostigmine were quite consistent. In every patient except 2 (see below), 1 or 2 intravenous injections of 2.5 mg. of neostigmine restored twitch height to the control level (figs. 4 and 5). This included 30 patients in whom no twitch could be seen or recorded at the time of reversal. The smaller the dose of dTC, the greater the time interval between the doses of dTC and neostigmine and the

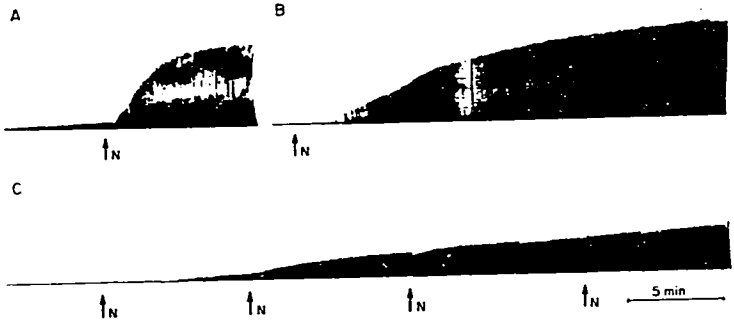

FIG. 5. Variation in speed of antagonism of *d*-tubocurarine by neostigmine. ↑N = neostigmine 2.5 mg. *Panel A.* Patient received 0.3 mg./kg. of *d*-tubocurarine 20 minutes prior to neostigmine. Note rapid return to control twitch height. *Panel B.* Patient received 0.6 mg./kg. of *d*-tubocurarine 31 minutes prior to neostigmine. More than 20 minutes was required for twitch height to return to control level. *Panel C.* Patient received 0.6 mg./kg. of *d*-tubocurarine 53 minutes prior to neostigmine. Spontaneous respiration began two minutes after neostigmine, at a time when the twitch response was absent. Recovery of twitch height to control level required more than 30 minutes; additional doses of neostigmine did not appear to increase the recovery slope of the twitch.

greater the degree of spontaneous recovery, the more rapid the reversal. In figure 6 it can be seen that with spontaneous recovery from dTC of 25 per cent or less, neostigmine restored twitch height to the control level in 6 to 40 minutes. Where spontaneous recovery was greater than 25 per cent, recovery occurred in 3–14 minutes.

In 2 patients, the dTC-induced twitch depression (recorded on the polygraph) could not be completely antagonized by neostigmine. There was no obvious cause (such as myasthenia gravis, circulatory impairment, electrolyte abnormalities, acid-base imbalance or use of intraperitoneal antibiotics), for the failure of reversal. One patient was a 62-year-old man (physical status 2) whose twitch was abolished following the injection of 0.6 mg./kg. of dTC (over 3 minutes). Fifty minutes later, when no twitch was present (although following tetanus, the twitch was restored temporarily), the patient received 2.5 mg. of neostigmine. This brought the twitch back to 60 per cent of the control level over the next 28 minutes. The slope of recovery then decreased, and another 42 minutes was required before the twitch height returned to the control level. An additional 2.5 mg. of neostigmine did not modify the recovery time. Spontaneous respiration which appeared adequate (as measured with a Wright ventilometer) was present 20 minutes after the initial dose of neostigmine. The Pa_{CO_2} 15 minutes later (35 minutes after the initial dose of neostigmine) was 42 mm. of mercury.

The second patient was a 38 year old woman (physical status 1) who received 0.5 mg./kg. of dTC over 178 minutes. Fifty minutes later, with the twitch height at 15 per cent of the control level, neostigmine 2.5 mg. was injected intravenously. There was no increase in the slope of recovery. The injection of 2.5 mg. 8 and 19 minutes later did not increase the recovery slope. The twitch height returned to the control level 92 minutes after the last dose of dTC.

A dose of 2.5 mg. of neostigmine was used to reverse dTC in 159 patients. A second dose of 2.5 mg. was used in 34 patients while in 23 patients where reversal of the effects of dTC appeared slow, additional doses of 2.5 mg. were given to a maximum total dose of 15 mg. of neostigmine. Although a second dose of 2.5 mg. of neostigmine did sometimes increase recovery, in no case was there a demonstrable improvement in recovery produced by doses of neostigmine in excess of 5 mg. (fig. 5C). There were no harmful effects from these large doses of neostigmine.

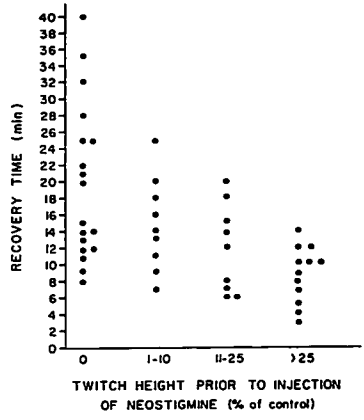

FIG. 6. Time required for antagonism of d-tubocurarine by neostigmine. The greater the twitch height (*i.e.*, degree of spontaneous recovery) prior to the injection of neostigmine, the more rapid the return of twitch height to the control level. These results were observed in 48 patients in whom the twitch was recorded.

Failure to Observe Recurarization. In none of the patients who received edrophonium or neostigmine did the twitch initially increase and subsequently decrease. Because recurarization has been reported following the use of edrophonium to antagonize dTC, an attempt was made to demonstrate recurarization in 10 patients. A test dose of 0.1 mg./kg. of dTC followed by an additional 0.5 mg./kg. abolished the twitch. When the twitch returned, the spontaneous recovery slope was observed for 10 minutes. Then 10 mg. of edrophonium was injected. An abrupt increase in twitch height (of variable magnitude) was observed in every patient. This was followed either by a return to the spontaneous rate of recovery

or a slightly greater rate of recovery. In none of these patients did the twitch, which was recorded for another 45–70 minutes, decrease following the increase produced by edrophonium.

Discussion

One of the most striking observations in this study was the marked variability in the response of patients to a dose of 0.1 mg./kg. of dTC. The results obtained with this dose ranged from no demonstrable effect to abolition of the twitch. Other studies of dTC, using different end points to determine the magnitude and duration of action, have also demonstrated a great variation in response. Artusio *et al.*,[4] studying the respiratory effects of muscle relaxants, felt that a dose response curve for dTC was not predictable on a mg./kg. basis. Pelikan *et al.*,[5] measuring the grip strength and the near point of binocular conversion, found that the threshold dose of dTC varied from 7.1 to 46.2 μg./kg. Poulsen and Hougs[6] determined the dose of dTC which produced at least a 75 per cent decrease in voluntary and stimulated (nerve stimulator) contractions of muscles of the extremities. The range of dosage in 16 patients was 0.14 to 0.29 mg./kg. with the average 0.23 mg./kg. This average dose of 0.23 mg./kg. (determined with the aid of a nerve stimulator) is similar to the results observed in this study in which a fixed dose of 0.2 mg./kg. produced a 70 per cent or greater depression of twitch response in 10 patients. The variation in response to dTC cannot be attributed solely to differences in blood flow, diffusion to the neuromuscular junction, rates of destruction, storage and elimination; for even in the *in vitro* preparation,[7] marked differences in the magnitude of response to dTC have been demonstrated. Nastuk and Alving[7] determined the effect of a dTC concentration of 1 mg./liter on the isolated frog sartorius muscle. In the figures shown in that paper, the magnitude of block produced in 5 muscles varied from 30 to 95 per cent.

The abolition of the twitch in 7 patients recalls the study of Pelikan *et al.*[5] in which it was stated, "About 3 to 4 per cent of normal subjects are as sensitive to tubocurarine as an average patient with myasthenia gravis." They felt that this emphasized the necessity of testing patients with small doses of dTC. Because of the marked patient variation in response to dTC, the author is opposed to techniques utilizing fixed mg./kg. doses or injections at fixed intervals, particularly since the effects of a test dose can easily be determined with the aid of a nerve stimulator. It seems more reasonable to take into account the response of the patient, along with other pertinent clinical factors.

Edrophonium is still used as an antagonist of dTC. It has been reported that the greater the dose of dTC the larger the dose of edrophonium required for reversal, but regardless of the depth of block, the curarization is immediately reversible by edrophonium.[4] On the contrary, the results of the present study suggest that edrophonium is a poor choice as an antagonist to dTC, although in some patients the block could be adequately reversed by edrophonium. In more than half the patients, the twitch could not be restored to the control level by the commonly used doses of edrophonium. The inadequacy of edrophonium as an antagonist of dTC has been observed by others. Artusio *et al.*[8] reported that where respiratory minute volume was decreased to 20–40 per cent of control or 40–60 per cent of control, complete reversal (as measured by restoration of resting minute volume) could be achieved. However, if the resting minute volume was 0–20 per cent of control, then edrophonium could not fully reverse the dTC. Doughty and Wylie,[9] studying patients who had received 140 or 160 mg. of gallamine, found that in no case was respiratory adequacy restored by 20–45 mg. of edrophonium. They found that edrophonium was adequate if only one dose of the muscle relaxant had been given, but if additional doses had been given, edrophonium was not reliable.

The action of neostigmine is believed to be rapid, and in an excellent review of the pharmacology of neuromuscular blocking agents in man it was stated that the full effect of neostigmine was reached in 2–4 minutes.[10] In the present study the restoration of twitch height to the control level by neostigmine re-

quired 3–10 minutes, depending upon the patient and the clinical circumstances. These results are similar to those of Macfarlane *et al.*[11] who found that 0.75 mg. of neostigmine following a dose of 9–10 mg. of dTC restored grip strength to 75 per cent of the control level in 10–12 minutes. The antagonism of dTC by neostigmine *appears* to be rapid if the return of adequate spontaneous respiration is used as the end point of reversal. However, it is possible to have apparently adequate spontaneous respiration in the absence of a recordable twitch.

Although the twitch height could not be restored to the control level in 2 patients who received dTC, we hesitate to classify these cases as neostigmine-resistant curarization. This term, proposed by Hunter,[12] referred to elderly patients in poor condition, in whom neostigmine did not antagonize the effects of dTC. In one of our patients in whom the dTC block could not be reversed with neostigmine, it is believed that the use of a nerve stimulator was of value in minimizing the difficulty. In this patient, the use of fractional doses guided by the response to nerve stimulation resulted in the use of relatively small doses of dTC over a prolonged period, and therefore even with the failure of neostigmine to reverse the block, it was possible for the patient to recover spontaneously over 92 minutes. In the other patient, it is believed that difficulty would have been avoided if the nerve stimulator had been used properly and a test dose of dTC (0.1 mg./kg.) given rather than an initial dose of 0.6 mg./kg. of curare. It was subsequently shown that the twitch was abolished in this patient by 0.1 mg./kg. of dTC. Had this been known, an initial dose of 0.6 mg./kg. would not have been used.

Although recurarization following the use of anticholinesterases, particularly edrophonium, has been reported in experimental animals [13, 14, 15] and in man,[8, 9, 16, 17, 18] we were unable to demonstrate this phenomenon in our patients, even when large doses of dTC were given and edrophonium used to antagonize the block. Following the injection of edrophonium, a variable degree of antagonism of the block was produced. Regardless of the degree of antagonism, the effect produced by edrophonium persisted and in no case was there an initial increase in twitch height followed by a decrease. It was noted that in some of the reports of recurarization the responses to the curarizing agents and edrophonium were measured in terms of the effects upon respiration.[8, 9] A possible explanation for apparent recurarization was seen in several patients in whom the resident giving the anesthetic was not permitted to observe the twitch response or the recording of twitch height. In these patients, following the injection of edrophonium or neostigmine, spontaneous respiration began in a previously apneic patient or there was a marked increase in ventilation. The patients also opened their eyes, and began to move about and were thought to have recovered from the effects of dTC. This frequently occurred at a time when the surgeon was placing the skin sutures. Following the completion of operation the patients then appeared to become drowsy. Their spontaneous movements ceased and ventilation decreased markedly. In some cases, the resident felt that he had demonstrated recurarization. However, upon looking at the twitch response at the time of apparent recovery, it was noted that the twitch was markedly depressed, and in 2 cases no twitch was recorded at the time the patient appeared to have recovered. By rousing the patient, it was possible to increase his ventilation and his movements. If nothing further was done to the patient, the twitch height continued to recover to the control response, at which time ventilation was adequate and the patient was more alert. In patients in whom an additional dose of 2.5 mg. neostigmine was injected at the time of apparent recurarization, an alerting or analeptic effect of the neostigmine was observed, although the rate of recovery of the twitch was not increased. It has been possible to demonstrate an alerting effect, sometimes associated with an increase in ventilation, in patients receiving edrophonium or neostigmine who have not received any prior dTC (unpublished data). Central nervous system stimulation and respiratory stimulation (directly on the brain stem and reflexly via chemoreceptors) have previously been reported.[19, 20, 21, 22] While an analeptic effect may account for some of the

cases of apparent recurarization, it cannot account for all the cases of recurarization reported. It is quite clear that patients with poor renal function who have received gallamine, which is excreted to a large degree by the kidneys, may exhibit persistent curarization or recurarization because of the failure of excretion of the gallamine.[17, 18]

Despite the widespread use of anticholinesterases as antagonists of neuromuscular blocking agents, the mode of action is still a subject of controversy. There are at least 4 possible explanations for the anticurare action of anticholinesterases. These include: (1) cholinesterase inhibition; (2) a direct acetylcholine-like stimulant action on the motor endplate; (3) a direct action on the motor nerve terminal causing acetylcholine release; (4) displacement of dTC by the anticholinesterase with subsequent redistribution and breakdown of the dTC.

Although it was originally thought that the antagonism of dTC by anticholinesterases could be attributed to cholinesterase inhibition, the development of the phenyltrialkylammonium compounds (of which edrophonium is an example) cast some doubt on this explanation. Randall and Lehmann [23] felt that the cholinesterase inhibiting activity of the phenyltrialkylammonium compounds (less than 1/100 that of neostigmine, using electric eel cholinesterase) was too small to account for their anticurare action. It was further suggested that there was a poor correlation between anticholinesterase and anticurare activity, and that the anticurare action of the phenyltrialkylammonium compounds could not be attributed to cholinesterase inhibition.[15, 16, 23-25] It was also noted that many of the anticholinesterases had a direct acetylcholine-like stimulating action on the motor endplate.[13, 15, 26, 27] This effect could not be attributed to anticholinesterase activity since it was demonstrated in the chronically denervated cat muscle (where acetylcholine is not present) that neostigmine and the phenyltrialkylammonium compounds were still capable of producing a muscle contraction.[13, 23, 26, 28] It was further shown that despite the prior inactivation of acetylcholine by diisopropylfluorophosphate, the subsequent injection of neostigmine still produced a muscle contraction.[28] It was therefore suggested that a direct acetylcholine-like stimulant action of the anticholinesterases might account for their anti-curare activity.[13, 15, 26, 27] However, other studies demonstrated that there was a poor correlation between the direct stimulant and the anticurare action of the anticholinesterases and that the direct stimulant action could not account for the anticurare action.[14, 21, 29] Nastuk and Alexander,[30] in careful *in vitro* studies, demonstrated that it was possible to antagonize dTC with small doses of edrophonium which did not have a direct stimulant effect. Smith *et al.*[29] answered the question of the weak anticholinesterase activity of edrophonium by pointing out that although there was a poor correlation between anticurare action and anticholinesterase activity of edrophonium determined with electric eel cholinesterase, there was a good correlation between anticurare action and anticholinesterase activity determined with frog rectus muscle cholinesterase. In the present study, it was clear from the effects on heart rate and salivation that edrophonium had a significant anticholinesterase action. Further evidence that cholinesterase inhibition is an important factor in anticurare action is the demonstration that prior inactivation of cholinesterase by tetraethylpyrophosphate abolishes the anticurare action of edrophonium and neostigmine but not that of acetylcholine.[14, 21] It is fair to point out that many of the above studies and interpretations demonstrating the importance of cholinesterase inhibition in the anticurare action of anticholinesterase have been challenged by Riker.[31]

It has also been suggested that the anticurare action of the anticholinesterases may be in part attributable to direct stimulation of the motor nerve terminal causing an increased release of transmitter substance.[32, 33, 34] Whether or not this mechanism of action contributes to the anticurare action of the anticholinesterases remains to be proven.

Finally, it has been suggested that the anticholinesterases displace dTC from the receptor site, thus permitting the redistribution, elimination and destruction of dTC.[8, 13, 15, 31] However, Nastuk and Alexander [30] and Peli-

kan [35] reported that the action of edrophonium could not be explained on the basis of dTC displacement. Furthermore, the studies of Waser [36] do not support the displacement concept. Waser, using autoradiographic techniques, showed that following anticholinesterase injection, it was still possible to demonstrate the presence of dTC at the endplate. From the present evidence, it appears that the anticholinesterases antagonized dTC mainly by means of cholinesterase inhibition.

Summary

The intravenous injection of 0.1 mg./kg. of dTC in 100 patients produced a markedly variable response, ranging from no effect on twitch height to abolition of the twitch response. In over half the curarized patients studied, edrophonium (10–20 mg.) failed to fully restore twitch height to the control level. Neostigmine (2.5–5 mg.) was found to be a good antagonist of the neuromuscular blocking action of dTC. The possible mechanisms of action of edrophonium and neostigmine were discussed. It was concluded that cholinesterase inhibition is a major factor.

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Anesthesia

SPINAL ANESTHESIA There is a small but definite increase in femoral vein oxygen tension and a small but definite decrease in arteriovenous oxygen difference after spinal block in patients with peripheral vascular disease. This is presumably due to an increase in flow to the extremity, primarily to muscle. The mechanism is presumably that of a preganglionic block causing an arterial and arteriolar dilatation. (*Cerilli, G. J., and Engell, H. C.: The Effect of Spinal Anesthesia on Femoral Vein Oxygen Tension, Surgery 60: 668 (Sept.) 1966.*)

OPIATES IN OBSTETRICS In a double blind study of 471 patients using four treatment groups nearly similar in all respects to insure random sampling, it was found that anileridine and meperidine produced exactly comparable effects, with 30 mg. anileridine being equivalent to 75 mg. meperidine. Apgar ratings were essentially the same in all four treatment groups. No significant side effects were noted with either drug and no real advantage was obtained when either were combined with a phenothiazine. (*Cavanagh, D., and others: Comparison of Anileridine and Meperidine as Obstetric Analgesia, Amer. J. Obstet. Gynec. 96: 213 (Sept.) 1966.*)