

The Effects of Nondepolarizing Relaxants and Anticholinesterases on the Neuromuscular Refractory Period of Anesthetized Man

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Neuromuscular refractory period was determined in anesthetized patients by measuring thenar EMG and adductor pollicis tension during single and paired ulnar nerve stimulation. Nondepolarizing muscle relaxants, *d*-tubocurarine and gallamine, decreased the refractory period. The anticholinesterases, neostigmine and edrophonium, increased the refractory period. The effects of *d*-tubocurarine and gallamine occurred at doses lower than those which cause any depression of the evoked twitch tension.

NEUROMUSCULAR TRANSMISSION in anesthetized man has been studied by observing the muscle tension or compound action potential evoked by stimulation of a motor nerve with a single stimulus. This method is relatively insensitive in demonstrating drug-induced neuromuscular blockade because the depression of the indirect twitch response does not occur until there is a considerable occupancy of receptor sites.¹ This communication describes the measurement of the neuromuscular refractory period in anesthetized man and its exquisite sensitivity to the nondepolarizing muscle relaxants, *d*-tubocurarine and gallamine. The effects of the anticholinesterase drugs, edrophonium and neostigmine, are also presented.

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Methods

Twenty-one patients with no clinical evidence of neuromuscular disease, receiving no medications known to affect neuromuscular transmission, were studied during surgical anesthesia. The patients were either unpremedicated or were given atropine sulfate (0.007 mg/kg intramuscularly) 45 minutes prior to induction of anesthesia. Anesthesia was induced and maintained with 60 per cent nitrous oxide in oxygen, supplemented as required with diethyl ether, fluorene, halothane or methoxyflurane. No other drugs, except as described below, were administered.

The tracheas of all patients were intubated without the use of muscle relaxants. Ventilation was controlled and constant minute ventilation maintained with a volume-limited ventilator. During, and for at least one hour prior to, data collection, each subject inspired a constant mixture of anesthetic gases. An anesthetic concentration was selected to produce a light plane of surgical anesthesia, as judged by clinical criteria.

The ulnar nerve was stimulated every five seconds, at the wrist (or in a few early studies, at the elbow) through subcutaneous 25-gauge hypodermic needles with rectangular wave pulses of 0.1-msec duration derived from a Grass S-4 stimulator with a SIU-478 isolation unit. The voltage used was twice that required to evoke a maximal twitch tension. Either a single stimulus or a pair of identical stimuli was used. The second members of a stimulus pair occurred 0.5 to 10 msec after the first stimulus, which time period is referred to as the "pair interval." In a typical study the pair interval was increased progressively by

0.1 msec from 0.5 to 2.5 msec, then in greater increments up to 10 msec.

The evoked thenar electromyogram (EMG) and the evoked adductor pollicis muscle tension were recorded as previously described.² The evoked tension was plotted on linear graph paper as a function of the pair interval (fig. 1). For each such function, the average neuromuscular refractory period (ARP) was calculated. *The ARP is defined as that pair interval which determines that tension which is the average of the tension evoked by a single stimulus and the maximum tension that can be evoked with a paired stimulus.* Preliminary studies had indicated that the ARP was constant (within 0.1 msec) for periods exceeding 90 minutes in patients maintained at constant

levels of anesthesia and minute ventilation. The thenar muscle temperature (determined with a Yellow Springs Instrument Company hypodermic probe, #524) varied by no more than one-half degree C during the study period.

The changes in tension and EMG evoked by single and paired stimuli caused by intravenous administration of *d*-tubocurarine chloride (0.15–1.2 mg), gallamine triethiodide (2–8 mg), neostigmine methylsulfate (0.5–1 mg) and edrophonium bitartrate (1–10 mg) were determined. Preliminary studies indicated that these doses caused no reduction in the tension evoked by the single stimulus, that is, they were subparalytic. For statistical purposes the effects of various subparalytic doses of *d*-tubu-

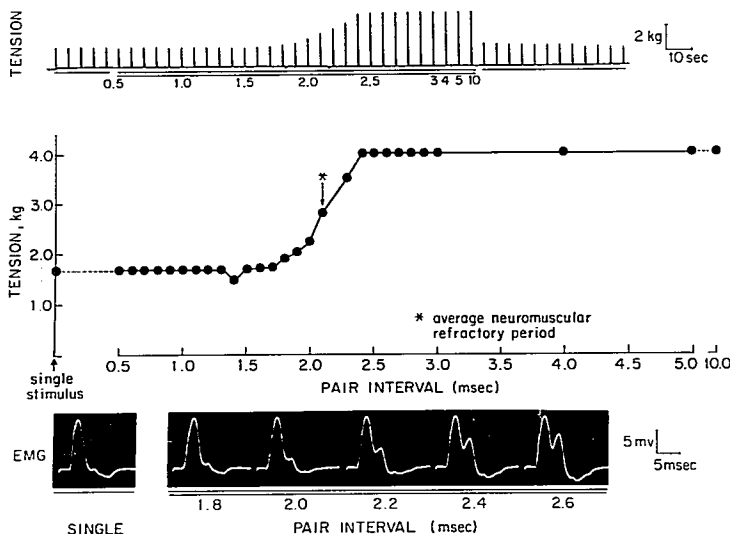


FIG. 1. The neuromuscular refractory period. *Top:* Polygraph record showing the tension developed by the adductor pollicis muscle upon stimulation of the ulnar nerve with single stimuli (designated by the single horizontal bar) and paired stimuli (designated by the double horizontal bar). The pair interval was increased in 0.1-msec increments from 0.5 to 3.0 msec, then in larger increments to 10 msec. *Middle:* A graph of tension as a function of pair interval derived from the polygraph record (top). *Bottom:* Simultaneously-evoked EMG's. Paired stimuli which evoked the same tension as single stimuli also evoked identical EMG's. The EMG's of paired stimuli with greater pair intervals show progressively larger second upright deflections which increased *pari passu* with the increase in evoked tension.

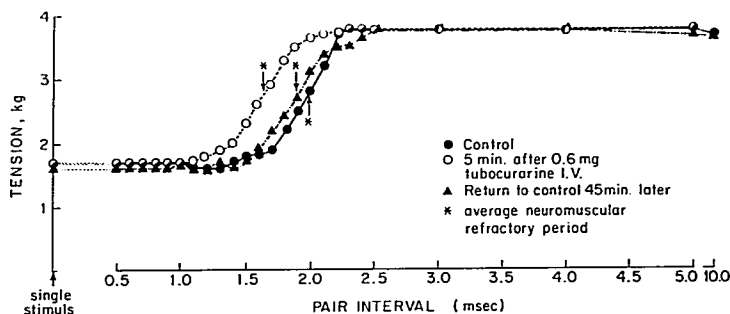


FIG. 2. Typical effect of *d*-tubocurarine on the average neuromuscular refractory period. Tension is plotted as a function of the pair interval. *d*-Tubocurarine caused the curve to shift to the left, and thus, the ARP to decrease. Forty-five minutes later there was a return to control values.

curarine and gallamine were pooled, as were those of neostigmine and edrophonium. Also, studies done in the presence of the various anesthetics were pooled. The significance of changes in the ARP was tested by Student's *t* test for differences in paired samples.

Results

THE NEUROMUSCULAR REFRACTORY PERIOD IN ANESTHETIZED MAN

Evoked muscle tension. In each of 21 subjects the tensions evoked by a single stimulus and by pairs of stimuli separated by increasing intervals were recorded and graphed. The tension in kilograms evoked by paired stimuli was recorded on the ordinate, and the pair interval on the abscissa. Figure 1 shows the sigmoid curve typically seen. The tension evoked by the shortest pair interval is equal to that evoked by a single stimulus.† In the

21 subjects tension began to increase at a mean pair interval of 1.15 msec (range 0.9 to 1.8 msec) and reached a maximum at a mean of 2.40 msec (range 1.6 to 3.0 msec). The mean ARP was 1.64 msec (range 0.95 to 2.30 msec). At the 10-msec pair interval there was sometimes a slight decrease from the maximal evoked tension.

Evoked electromyogram. In 14 subjects the compound action potential (EMG) was recorded simultaneously. The recording needle electrode was positioned so that the EMG evoked by a single stimulus had a single major positive deflection. Paired stimuli which evoked the same tension as a single stimulus evoked the identical EMC. However, at increasing pair intervals, the EMG showed a second positive deflection which increased *pari passu* with the increase in the evoked tension (fig. 1).

THE EFFECTS OF NONDEPOLARIZING MUSCLE RELAXANTS ON THE NEUROMUSCULAR REFRACTORY PERIOD

Evoked muscle tension. After control data were obtained in each of 14 subjects a subparalytic dose of *d*-tubocurarine (0.15–1.2 mg) or gallamine (2–6 mg) was administered intravenously. The tension functions from a typical study are depicted in figure 2. *d*-Tubocurarine (0.6 mg) caused the tension curve to

† An occasional patient had a slightly different tension curve. The tension at pair intervals of approximately 0.8 to 1.0 msec was decreased (usually about 10 per cent) from the tension evoked by the single stimulus. In these patients the associated EMG's showed that the single stimulus evoked some repetitive muscle firing. This was abolished by paired stimuli which presumably lengthened the nerve refractory period and thereby blocked the repetitive firing. The magnitude of this phenomenon was too small to interfere with the calculation of the ARP. Nevertheless, patients exhibiting this phenomenon have not been included in the study.

TUBOCURARINE
0.6 mg I.V.

↓

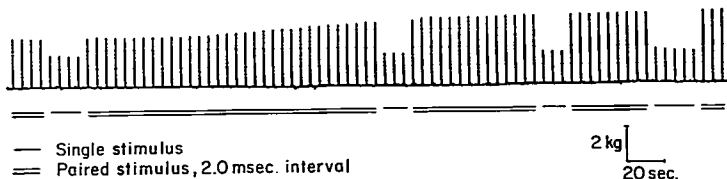


FIG. 3. Polygraph record showing the immediate effect of *d*-tubocurarine on the tension evoked by a single stimulus and a paired stimulus with a 2.0-msec pair interval. Since *d*-tubocurarine caused the curve of figure 2 to shift to the left, there was a range of pair intervals at which the tension was increased by this subparalytic dose of *d*-tubocurarine.

shift to the left, and the ARP decreased by 0.40 msec. There was no effect on the maximal tension that could be evoked by a paired stimulus. Because of the shift of the curve to the left, there was a range of pair intervals in which the tension evoked by the paired stimulus was increased by the nondepolarizing muscle relaxant. Figure 3 shows the increase in

tension evoked by such a paired stimulus upon administration of 0.6 mg of *d*-tubocurarine. In all subjects, subparalytic doses of *d*-tubocurarine or gallamine caused the tension curve to shift to the left. The mean decrease in the ARP was 0.35 ± 0.03 msec ($P < 0.001$) (table 1).

In five subjects observations were continued

TABLE 1. Neuromuscular Refractory Period: Effect of Nondepolarizing Relaxants

Patient No.	Anesthetic	Sex	Age (years)	Wt. (kg)	Drug	Dose (mg)	ARP (msec)			
							Control	Experimental	Δ	Recovery
1*	H	♂	28	70	C	0.6	1.30	1.05	-0.25	
2*	H	♂	30	114	C	0.6	2.00	1.60	-0.40	1.90
3†	H	♂	37	70	C	0.6	1.50	1.10	-0.40	
4†	H	♀	43	55	C	0.3	1.60	1.20	-0.40	
5†	H	♂	22	70	C	0.9	1.65	1.25	-0.40	
6†	M	♀	46	77	C	1.2	1.95	1.55	-0.40	1.85
7†	H	♀	35	65	C	0.6	1.45	1.15	-0.30	
8*	Et	♂	37	65	C	0.3	1.90	1.75	-0.15	
9*	Et	♀	54	78	C	0.6	2.30	2.00	-0.30	
10*	F	♂	28	58	C	0.6	1.65	1.20	-0.45	
11*	H	♀	42	80	C	0.15	1.50	1.20	-0.30	1.50
12	H	♂	50	70	G	6.0	1.50	1.25	-0.25	
13*	M	♀	53	57	G	4.0	1.70	1.10	-0.60	1.65
14*	H	♂	23	63	G	2.0	1.95	1.70	-0.25	1.90
Mean \pm SE							1.71	1.36	-0.35 ± 0.03 †	

Et = ether; F = fluorene; H = halothane; M = methoxyflurane; C = tubocurarine; G = gallamine.
ARP = average neuromuscular refractory period.

* EMG recorded. † $P < 0.001$.

Recovery is recorded in studies where observations were continued for at least 45 minutes after the drug was given.

for at least 45 minutes after drug administration. In each of these patients the tension curve returned to control.

Evoked electromyogram. In each of eight subjects the evoked EMG was recorded along with the muscle tension. Figure 4 shows the EMG's obtained during the tension recording depicted in figure 2. The EMG evoked by the single stimulus was unchanged by this subparalytic dose of *d*-tubocurarine. Before *d*-tubocurarine was administered the second upright component of the EMG was apparent only at a pair interval of 2.0 msec or greater, but after *d*-tubocurarine it occurred at intervals as short as 1.6 msec. At pair intervals from 2.0 to 2.6 msec *d*-tubocurarine increased the second upright component. In each of the eight subjects the EMG reflected a decrease in the ARP in this manner.

THE EFFECTS OF ANTICHLINESTERASE
DRUGS ON THE NEUROMUSCULAR
REFRACTORY PERIOD

Evoked muscle tension. After control data had been obtained in each of seven subjects, neostigmine (0.5–1.0 mg) or edrophonium (1–10 mg) was administered intravenously. Figure 5 shows the typical effect of these drugs. Neostigmine (0.5 mg intravenously) caused the tension curve to shift to the right without affecting the tension evoked by a single stimulus or the maximal tension that could be evoked by a paired stimulus. In all seven subjects, the ARP increased. The mean increase was 0.50 ± 0.08 msec ($P < 0.001$) (table 2).

Evoked electromyogram. In six subjects the evoked EMG was recorded along with the muscle tension. The EMG's in figure 6 correspond to the tension curves of figure 5. The EMG's evoked by the single stimulus and by the paired stimulus with a 4-msec interval were unchanged by 0.5 mg of neostigmine. However, neostigmine increased the minimum pair interval at which the EMG showed a second positive deflection from 1.0 msec to 1.6 msec. At pair intervals from 1.0 to 3.0 msec neostigmine decreased the second positive deflection. The increase in the ARP was reflected in this manner in all six subjects.

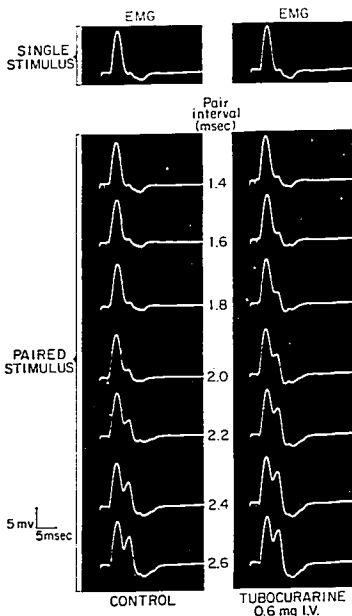


FIG. 4. The effects of *d*-tubocurarine on the EMG's evoked by single and paired stimuli. The subparalytic dose of *d*-tubocurarine had no effect on the EMG evoked by the single stimulus, but decreased from 2.0 to 1.6 msec the minimal pair interval at which the second upright deflection was apparent. At pair intervals of 2.0 to 2.6 msec *d*-tubocurarine increased the height of the second positive deflection, thereby reflecting the decrease in the ARP. (Figures 1, 2, 3, and 4 are from the same study.)

Discussion

There have been few attempts to quantify neuromuscular refractoriness in man. Hoefel Glaser *et al.*³ stimulated muscle indirectly with paired stimuli and considered the refractory period to be the least pair interval which produced a detectable second action potential. The data obtained by this method relate only to those neuromuscular units with the shortest refractory period and are not characteristic of the muscle as a whole. In order to obtain an

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TABLE 2. Neuromuscular Refractory Period: Effect of Anticholinesterases

Patient No.	Anesthetic	Sex	Age (years)	Wt. (kg)	Drug	Dose (mg)	ARP (msec)		
							Control	Experimental	Δ
15*	H	♂	50	70	N	0.5	1.10	1.80	+0.70
16*	M	♂	33	65	N	1.0	1.40	1.55	+0.15
17*	H	♀	24	50	N	1.0	1.70	2.40	+0.70
18	H	♂	64	64	E	1.0	2.30	2.60	+0.30
19*	H	♀	46	82	E	5.0	0.95	1.50	+0.55
20*	M	♀	58	60	E	4.0	1.10	1.75	+0.65
21*	H	♀	65	49	E	10.0	1.85	2.30	+0.45
Mean \pm SE							1.49	1.99	+0.50 \pm 0.08†

H = halothane; M = methoxyflurane; N = neostigmine; E = edrophonium.

ARP = average neuromuscular refractory period.

* EMG recorded.

† $P < 0.001$.

"average" refractory period for the muscle, Glaser and Stark⁴ extended this method in animal preparations and measured the relative heights of the two upright deflections of the action potentials evoked by paired stimuli. Their derived "time constant" of the curve which resulted when this relative height was plotted as a function of the pair interval is analogous to our ARP. However, the relatively long time course of the human compound action potential causes the potentials evoked by the two members of the stimulus pair to overlap, and the quantification of such

EMG data is both complex and uncertain. Farmer, Buchthal and Rosenfalck⁵ avoided this problem by directly stimulating very small bundles of muscle fibers, thereby evoking very short potentials. This enabled them to measure the refractory period of human muscle fibers. However, in order to characterize the refractory period of an entire muscle, one must examine separately a very large number of such groups of muscle fibers. Although this method has yielded important data concerning the pathophysiology of myopathies,⁶ it is impractical for pharmacologic studies. Also, such

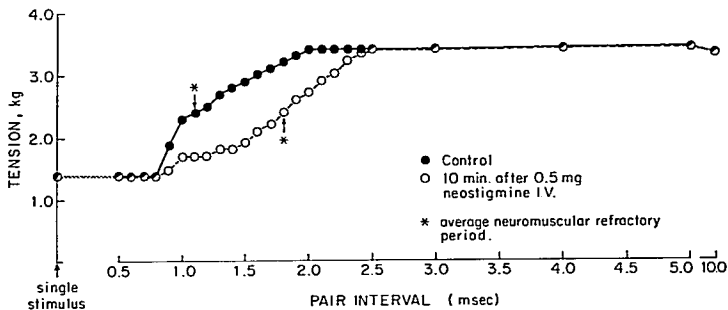


FIG. 5. The typical effect of neostigmine on the average neuromuscular refractory period. Neostigmine caused the curve to shift to the right, and thus, the ARP to increase.

direct muscle stimulation does not provide information concerning the neuromuscular junction.

The tension evoked by indirect paired muscle stimulation has proved useful as an index of the proportion of muscle fibers which have recovered excitability after responding to the first stimulus of the stimulus pair. Because of the heterogeneous nature of the population of neuromuscular units, refractoriness is defined most accurately by the complete tension curve. Nevertheless, the derived ARP is useful and valid as a simple method of quantifying the position of the tension curve for comparative purposes.

The ARP remains constant long enough to complete pharmacologic investigations. However, our mean "control" ARP should not be construed as being the "normal" for anesthetized man. Numerous factors affect refractoriness, including depth of anesthesia (unpublished observations) and temperature.^{6,7} Our patients were maintained at a constant level of anesthesia and the muscle temperature varied by no more than one-half degree C during the study period. In order to use our methodology to investigate neuromuscular disease, it would be necessary to obtain control measurements in normal conscious subjects.

Our methodology does not reveal the site or sites that are critical for determining the neuromuscular refractory period. It is not the nerve trunk itself, because the nerve refractory period is shorter than that of the total neuromuscular system.⁸ The critical locus may be pre- or postsynaptic, or at the muscle membrane distal to the endplate. It is for this reason that we use the term "neuromuscular refractory period."²

The pharmacology of the refractory period has been studied previously only *in vitro* in lower-animal preparations. Eccles and Kuffler⁹ found that curare decreased the refractory period and that eserine increased it. More recent studies by McIntyre *et al.*¹⁰ reported opposite results with *d*-tubocurarine. We cannot propose an adequate electrophysiologic hypothesis to explain the drug effects that we have observed *in vivo*. *In vitro* intracellular recordings have shown that edrophonium and neostigmine markedly slow the rate of repolarization, thus prolonging the po-

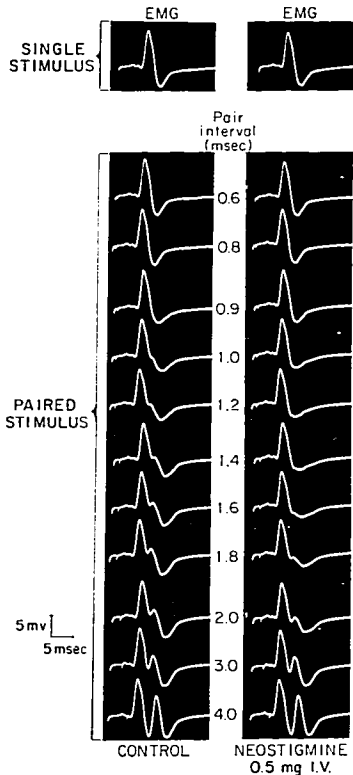


FIG. 6. The typical effects of neostigmine on the EMG's evoked by single and paired stimuli. Neostigmine had no effect on the EMG's evoked by the single stimulus or the paired stimulus with a 4-msec pair interval, but increased from 1.0 to 1.6 msec the minimal pair interval at which the second upright deflection was first apparent. At pair intervals from 1.0 to 3.0 msec neostigmine decreased the height of the second positive deflection, thus reflecting the increase in the ARP. (Figures 5 and 6 are from the same study.)

tential at the endplate.^{11,12} This would be expected to cause an increase in the refractory period. Less is known about the effect of *d*-tubocurarine, but it is doubtful that it mark-

edly alters the time course of the endplate potential.¹¹ In fact, by decreasing the magnitude of the endplate potential it increases the critical depolarization time, which should increase the refractory period. A basic understanding of the phenomena that we have observed must await a more detailed investigation of the effects of these drugs on the action potential as well as a better understanding of the electrophysiologic determinants of refractoriness. It would seem reasonable, however, to postulate that the amount of depolarizing agent active at the endplate might be a factor influencing the duration of the refractory period. This, in turn, might be related to accommodation or desensitization occurring during the first few milliseconds following each depolarization. Thus, by blocking the action of released acetylcholine, *d*-tubocurarine and gallamine might decrease the refractory period, although there is no overt blockade at the doses employed because of the large margin of safety of neuromuscular transmission. Neostigmine and edrophonium might increase the refractory period by slowing the destruction of acetylcholine. Our findings in more recent studies that tetanic stimulation and the administration of subparalytic doses of succinylcholine and decamethonium markedly increase the ARP are consistent with this hypothesis (unpublished observations).

The nature of neuromuscular refractoriness restricts the type of stimulus pulse that can be used to study twitch tension. If a paired stimulus is used, it is possible that the evoked tension may be a function of changes in both neuromuscular blockade and refractoriness. With the nondepolarizing muscle relaxants the apparent degree of neuromuscular blockade may be reduced secondary to the decreased refractoriness (fig. 3). On the other hand, an increase in the apparent degree of neuromuscular blockade may be seen with drugs that increase the refractory period. Recently, we indicated that the Block-Aid Monitor (Burrhead Wellcome Company), a clinical nerve stimulator, cannot be used to study twitch tension because it generates a biphasic stimulus pulse which causes paired stimulation.² In addition, because a single stimulus of long duration may cause nerve fibers to respond repetitively, a single stimulus of short dura-

tion should be used. We have observed double nerve (and muscle) response from stimulus as short as one msec. Since the nerve refractory period may be as short as 0.5 msec it is possible that single pulses even less than one msec in duration may effect double firing (unpublished observations). The use of stimulus of long duration may cause confusing results. For example, in a recent study it was observed that small doses of curare *in vitro* paradoxically caused an increase in the indirectly-evoked tension.¹² However, since the stimulus used was 0.7 msec in duration, the tension increase was probably due to drug-induced changes in the refractory period. It also has been common practice for clinical investigators to use a long stimulus duration in order to attain supramaximal stimulation. We recommend a stimulus duration no longer than 0.3 msec.

The ARP is an exquisitely sensitive indicator of the presence of nondepolarizing relaxants. In any individual subject there is a progressive decrease in the ARP with increasing subparalytic doses of *d*-tubocurarine and gallamine. Fade during high frequency tetanic stimulation also has been used as a sensitive index of curarization.¹⁴ Tetanic fade, however, is an extremely complex phenomenon, and indeed, one of the numerous factors which may determine the characteristics of the response to high-frequency tetanic stimulation is the increase in the ARP that occurs during tetanus (unpublished observations).

Our demonstration of an effect of subparalytic doses of *d*-tubocurarine at the neuromuscular junction in man is direct evidence for the presence of a "margin of safety" of neuromuscular transmission.¹ Yet this "margin" may not correspond to a clinical one. For example, two of the authors (R. A. E. and S. R. W.), while awake, have received subparalytic doses of *d*-tubocurarine. Although there was no depression of the response to a single stimulus, there were symptoms of curarization (diplopia, difficulty in handling secretions) along with the decrease in the ARP (unpublished observations). We therefore must emphasize that the complete restoration of the indirect twitch response does not preclude the presence of a significant degree of residual curarization.

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