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The Electromyogram and the Mechanical Response of Indirectly Stimulated Muscle in Anesthetized Man following Curarization

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The electromyogram (EMG) and tension evoked by single and tetanic stimuli were studied during curarization in anesthetized subjects. *d*-Tubocurarine depressed both evoked twitch tension and EMG, but not identically. Before curarization posttetanic potentiation (PTP) was present on tension recordings but not on EMG recordings. Small amounts of tetanic fade were present on both tension and EMG recordings before curarization. On tension recordings PTP and fade increased significantly only during profound curarization, while on EMG recordings both increased at all levels of curarization. Electromyography is more sensitive than tension recordings in the investigation or monitoring of curarization. (Key words: Electromyogram; Twitch tension; Neuromuscular transmission; *d*-Tubocurarine; Posttetanic potentiation; Tetanic fade.)

EVALUATION of neuromuscular transmission in anesthetized man has been beset by basic problems of method. First, there has been the question of what is the most useful measurement. Is it the evoked muscle tension or the muscle compound action potential (EMG)? Second, how should the data be analyzed? Tetanic fade and posttetanic potentiation (PTP) have been used to determine the amount of paresis. These indices have each been derived in fundamentally different ways by different investigators. The result of both these problems has been conflicting opinion concerning seemingly simple matters. The very existence of curare-induced posttetanic potentiation and tetanic fade has been questioned. To resolve these problems, we have studied partial paralysis by *d*-tubocurarine with the simultaneous measurement of twitch tension and EMG, and in addition have compared the use of several different indices of fade and PTP.

Methods

ANESTHETIC TECHNIQUES

Eight healthy patients were studied during surgical procedures not requiring entry into a body cavity. After premedication with atropine (0.007 mg/kg, im) alone in five subjects or in combination with secobarbital (1.5 mg/kg, im) in three subjects, all were anesthetized with halothane in 60 per cent nitrous oxide in a high-flow circuit. Endotracheal intubation was performed without the use of a muscle relaxant and ventilation was controlled using a volume-limited ventilator. For at least half an hour prior to and during data collection, inspired halothane concentration (1 per cent) and minute ventilation were held constant. After control data had been obtained, 0.1 mg/kg of *d*-tubocurarine was administered intravenously.

TECHNIQUES OF STUDYING NEUROMUSCULAR TRANSMISSION

The methods used have been described.[1-3] In brief, the thumb tension and adductor pollicis EMG evoked by indirect stimuli were simultaneously recorded. The ulnar nerve was stimulated at the wrist using bare subcutaneous needle electrodes. After testing with paired stimuli to exclude the possibility of repetitive firing,[4] the stimulator was set to deliver isolated supramaximal pulses of 0.1-msec duration (Grass S8 and SIU 4678). At

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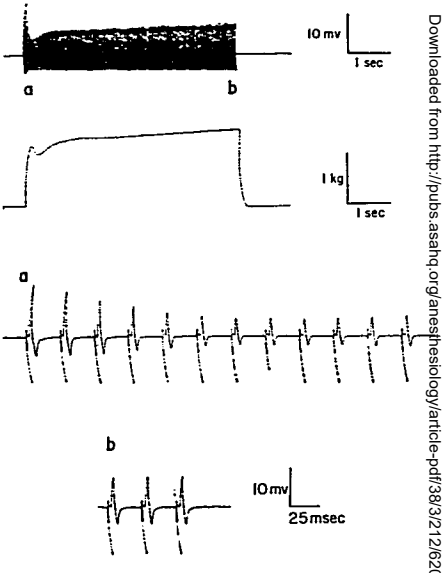

FIG. 1. Tetanic fade in one subject 20 minutes after administration of *d*-tubocurarine. *Top:* EMG and tension during tetanus (EMG bandpass reduced to 800 Hz to decrease stimulus artifact). Initial fade with recovery is evident on both recordings. *Bottom:* EMG at the beginning (*a*) and end (*b*) of tetanus at a faster polygraph speed (EMG bandpass at least 2,400 Hz). The individual compound action potentials can be seen, showing the rapid initial fade and partial recovery.

5-second intervals, a relay driven by a synchronous motor triggered the stimulator. Single stimuli were used, except that at 5-minute intervals a tetanic train at 30 Hz lasting 5 seconds was given. The first posttetanic stimulus always followed the tetanic train by 5 seconds.

Tension was recorded using a force transducer (Grass FT-10) and a chopper-stabilized DC amplifier (Offner 481) with an upper frequency response of 100 Hz. Care was taken to ensure that the force of adduction was applied in the axis of movement of the transducer and that the resting tension (preload) of 300 to 400 g remained constant.

The adductor pollicis electromyogram was recorded by means of bare needle electrodes, using a Grass P-15 preamplifier. The electromyogram and tension, along with a code signal from the motor-driven relay, were recorded on frequency-modulated analog tape running at 30 inches per second (Hewlett-Packard 3917B). At a later time, using 16-to-1 speed reduction, the analog signals were played back onto a direct-writing polygraph (Offner-Dynograph Model R). Details of the method can be found on page 287 of this issue.[1] The tetanic stimulus frequency of 30 Hz permitted clean separation and measurement of individual EMG's recorded following each stimulus during the tetanus. The system frequency responses were 0 to 100 Hz for tension recording and 0.1 to at least 2,400 Hz for EMG recording.[2] Data from studies in which resting tension was not maintained or single indirect stimuli caused repetitive muscle firing were rejected.[4]

ADMINISTRATION OF DRUG

After a constant inspired anesthetic concentration had been established for at least 30 minutes, a control tetanus was administered. One minute later, 0.1 mg/kg *d*-tubocurarine was given intravenously, and the evoked tension and EMG were recorded during the onset of block. Stimulation was continuous, with tetanic trains interspersed at 5-minute intervals, usually for at least 50 minutes.

TABLE I. Maximal Twitch Depression after *d*-Tubocurarine

	Maximal Twitch Depression (Per Cent Control)	
	EMG	Tension
Subject 1	36	74
Subject 2	79	86
Subject 3	71	90
Subject 4	90	84
Subject 5	72	85
Subject 6	48	82
Subject 7	57	64
Subject 8	79	82
MEAN	66.5	80.9
SE	±6.4	±2.9

ANALYSIS OF DATA

The data employed in the evaluation of mechanical and electrical events in this study are in each case the amplitudes of the responses. No attempt has been made to quantitate rates of rise, durations, etc., of the waveforms measured. From comparison of the changes in amplitude after *d*-tubocurarine with control values, per cent twitch depression was calculated both for tension and for the primary EMG peak.

To quantitate the effect of tetanus on the twitch response, indices of posttetanic potentiation (PTP) were calculated in two ways. First, the ratio of the amplitude of the first posttetanic twitch to that of the last pretetanic twitch was determined for tension (PTR_T) and for EMG (PTR_E).

Because of recent work of Heisterkamp *et al.*,[5] "incremental" PTP was calculated as well. These workers regarded the absolute enhancement of twitch tension after tetanus as the measure of PTP, as opposed to calculations which relate the change to the existing level of response. For uniformity among different subjects, this increment can be related (at all levels of curarization) to the constant baseline of the pre-curare twitch height. To that end, and to permit numerical comparison of this technique with that of the PTR, we define PTR-I_T as the posttetanic enhancement in the amplitude of twitch divided by the *control* (pre-curare) amplitude. PTR-I_E is defined for EMG amplitudes in the same way. See Appendix 1 for the numerical derivation.

Tetanus was analyzed by noting the maxima and minima of the tension or EMG amplitude during tetanus. In general, during tetanus each shows a local maximum shortly after the onset of tetanus, falls to a local minimum, and recovers at the end of tetanus to an amplitude that may be greater or less than the initial maximum. See figure 1 for a typical tracing. A schematic representation of these waveforms is shown in figure 4 and described in Appendix 2.

We define true fade of tension (F_T) or of EMG (F_E) as the difference between the first maximum and the first minimum. Pseudofade of tension (PF_T) or of EMG (PF_E) (the usual "fade" of other investigators) is defined as the difference between the first maximum and the amplitude existing at the end of tetanus. Each is expressed as a per cent of the first maximum of that tetanus.

Student's *t* tests for paired and unpaired data were used. Changes were considered significant when $P < 0.05$.

Results

EFFECTS OF *d*-TUBOCURARINE ON EVOKED TWITCH TENSION AND EMG

As expected, 0.1 mg/kg *d*-tubocurarine administered intravenously depressed the evoked twitch tension and EMG in every subject. The maximum twitch depressions varied widely, ranging from 64 to 90 per cent for tension (mean 81 per cent) and from 36 to 90 per cent for EMG (mean 67 per cent), and generally occurred 2–4 minutes after administration of the drug (table 1). The mechanical depression and the electrical depression corresponded roughly to each other, although the mean tension depression was significantly greater than the mean EMG depression (*t* test for paired data).

POSTTETANIC POTENTIATION BEFORE *d*-TUBOCURARINE

Posttetanic potentiation was always observed on tension recordings prior to administration of *d*-tubocurarine (table 2, control). PTR_T's ranged from 107 to 148 per cent, with a mean of 123 ± 6 per cent, significantly greater than 100 per cent. On the other hand, significant electromyographic PTP did not

TABLE 2. Effects of α-Tubocurarine on PTR and PTR-I

	Level of EMG Twitch Depression									
	None (Control)		Maximum		≦ 65 Per Cent		≦ 40 Per Cent		≦ 20 Per Cent	
Per Cent Mean Twitch Depression for Class:	EMG	Tension	EMG 66	Tension 81	EMG 54	Tension 73	EMG 33	Tension 57	EMG 16	Tension 43
	PTR_E	PTR_T	PTR_E	PTR_T	PTR_E	PTR_T	PTR_E	PTR_T	PTR_E	PTR_T
PTR (per cent)										
Subject 1	95	109	150	124	*	*	150	124	107	115
Subject 2	98	148	273	300	191	168	134	146	112	130
Subject 3	100	120	206	366	165	174	136	180	115	140
Subject 4	110	141	476	256	164	124	140	127	117	132
Subject 5	101	117	218	212	208	183	143	112	117	127
Subject 6	102	132	138	173	138	173	124	134	112	141
Subject 7	107	107	183	160	183	160	130	119	112	114
Subject 8	102	108	352	213	256	181	130	159	118	166
MEAN	102	123	250	226	186	166	136	138	114	133
±SE	2	6	41	30	14	8	3	8	1	6
P†			<.005	<.005	<.001	<.001	<.001	*N.S.*	<.001	*N.S.*
	$PTR\text{-}I_E$	$PTR\text{-}I_T$	$PTR\text{-}I_E$	$PTR\text{-}I_T$	$PTR\text{-}I_E$	$PTR\text{-}I_T$	$PTR\text{-}I_E$	$PTR\text{-}I_T$	$PTR\text{-}I_E$	$PTR\text{-}I_T$
PTR-I (per cent)										
Subject 1	−5	9	34	14	*	*	34	14	7	12
Subject 2	−2	48	39	42	41	43	23	27	10	23
Subject 3	0	20	31	32	32	23	24	32	13	24
Subject 4	10	41	54	50	55	17	28	20	14	23
Subject 5	1	17	32	27	39	26	26	7	14	17
Subject 6	2	32	20	30	20	30	16	20	10	23
Subject 7	7	7	36	30	36	30	21	13	10	10
Subject 8	2	8	53	37	53	37	23	35	16	40
MEAN	2	23	37	33	39	29	24	21	12	22
±SE	2	6	4	4	5	3	2	3	1	3
P†			<.001	*N.S.*	<.001	*N.S.*	<.001	*N.S.*	<.001	*N.S.*

* At no time was the EMG depressed more than 40 per cent.
† Change from mean control (unpaired Student's *t* test). *N.S.* = not significant.

occur before administration of *d*-tubocurarine. The mean PTR_E was 102 ± 2 per cent, with a range of 95 to 107 per cent, not significantly different from 100 per cent.

POSTTETANIC POTENTIATION AFTER *d*-TUBOCURARINE

Table 2 shows the effects of *d*-tubocurarine on posttetanic potentiation at various degrees of EMG twitch depression during recovery from curarization. To permit pooling of data, five points are shown: control, time of maximal EMG twitch depression, and times of the first occurrence of EMG twitch depression of less than or equal to 65, 40, and 20 per cent of control. Because tension recovery was not always complete or was somewhat slower than EMG recovery, mean twitch tension depression was generally greater than mean EMG depression. There was significant PTR_E at every level of curarization, but PTR_T was significantly greater than control only at the times of maximal and 65 per cent depression. When expressed as PTR-I, significant electromyographic $PTR\text{-}I_E$ could still be demonstrated at *any* level of curarization. Tension recordings, however, failed to demonstrate significant $PTR\text{-}I_T$ at *any* level of curarization.

Figure 2 shows pre- and posttetanic twitch tensions from one subject at the various levels

of curarization. The control electromyographic recording shows no PTP, but after curare PTP is obvious. Note particularly that after curare the posttetanic EMG is always equal to or less than the EMG prior to curarization. The tension recordings show PTP both before and after curarization.

Tetanic Fade in Anesthetized Controls

Various patterns of fade were seen on the EMG's. Even before curarization, the initial compound action potential of the tetanic train was generally the largest. In one subject the compound action potential gradually increased in height during the first 500 msec of tetanus but the total increase was only 12 per cent. Fade on the EMG was seen in recordings from three subjects. The greatest F_E was 30 per cent, and the mean F_E was 10.6 ± 4.3 per cent. After this initial fade there was often a small increase in the height of the compound action potentials, causing PF_E to be slightly less than F_E. The mean PF_E was 7.3 ± 5.0 per cent ($P = <0.05$, t test for paired data) (table 3).

The simultaneously recorded mechanical tension was also well sustained. Tension initially increased rapidly and generally reached a maximum after 300 to 400 msec of tetanic stimulation. The greatest fade was 16 per cent, and the mean F_T was 7.8 ± 1.4 per cent, which is not significantly different from the corresponding electromyographic fade. There was little or no increase in tension after this fade, so that mean PF_T was 7.1 ± 1.7 per cent, not different from mean F_T.

Tetanic Fade after *d*-Tubocurarine

The degree of tetanic fade after curarization roughly corresponded to the magnitude of twitch depression. Electromyographic fade invariably exceeded mechanical fade. The initial electromyographic fade was always maximal within 300 msec of the start of tetanus, but the time of maximal mechanical fade varied widely from subject to subject. Generally, after the initial fade there were substantial recoveries of both tension and EMG heights which caused F_E and F_T to exceed PF_E and PF_T. On occasion, after this recovery of tension small secondary decreases occurred. This "secondary fade" was not seen on the electromyogram (fig. 1).

Fade was measured for the tetanus nearest the time of maximal twitch (EMG) depression and during recovery at 65, 40, and 20 per cent twitch depression. F_E was significant at every point. F_T, although less than F_E, was significant when twitch depression was maximal, and at 65 per cent of the control response (table 3). "Pseudofade" was smaller than fade. PF_E was still significant at every level of curarization, whereas PF_T was of only borderline significance when twitch depression was at 65 per cent of control response and was insignificant at other times (table 3).

Recordings from Subjects 5 and 8 showed no mechanical fade at all at *any* level of curarization. The same two subjects also had the smallest amounts of electromyographic fade, which nevertheless reached 64 and 65 per cent at maximal twitch depression.

Discussion

Techniques of Study of Neuromuscular Transmission

The study of neuromuscular transmission in man *in vivo* presents difficulties, because much of the sophisticated apparatus of modern electrophysiology, such as well-localized intracellular electrodes, cannot be used. It is necessary to rely on two far less precise methods involving either mechanical or electrical recording of the indirectly evoked muscle contraction. Both methods have numerous technical pitfalls. These are briefly mentioned below, and specific points are emphasized in the context of the physiologic discussion.

Proper stimulation characteristics are necessary. An excessive stimulus duration or an inappropriate waveform, as used by some earlier investigators, can cause repetitive nerve stimulation.[2] In some subjects repetitive muscle activation occurs in response even to short nerve stimuli.[4] In addition, truly supramaximal stimuli are necessary. The very high-output impedances of older stimulus isolation units such as the Grass SIU 4 make it doubtful that sufficient current density to assure supramaximal conditions has always been attained by investigators.[6]

Mechanical recordings present several technical difficulties. The transducers commonly

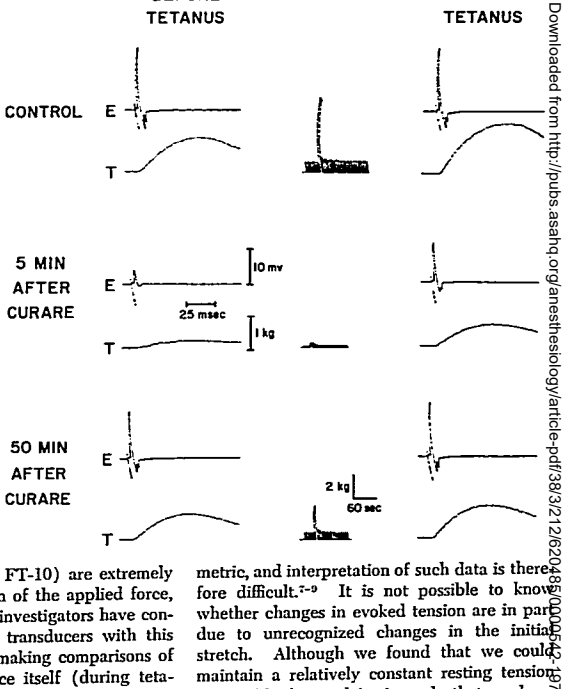

FIG. 2. Posttetanic potentiation before and after administration of *d*-tubocurarine. Individual twitch stimuli immediately before and after tetanus are shown, with EMG (*E*) and tension (*T*) traces. The center panels show a slow-speed recording of tension alone, including the relevant tetanus. Because of the large control PTR_T, the PTP seen on tension recordings at 50 minutes cannot be considered significant. Note the electromyographic PTP appearing only after curarization and persisting at 50 minutes.

used (Grass FT-03 and FT-10) are extremely sensitive to the direction of the applied force, and it appears that few investigators have consistently positioned the transducers with this consideration in mind, making comparisons of data difficult. The force itself (during tetanus) may exceed 8 kg, and it is puzzling that some investigators have used transducers which have a capacity of only 1 or 2 kg (*e.g.*, various models of the Grass FT-03). It is possible that such transducers have been positioned so that the force was applied obliquely to blunt their sensitivity. This cannot be considered stable or reliable, because small shifts in the angle of obliquity can produce significant changes in output.

The lower tension output measured may also have resulted from the initial resting state of the muscle. With the use of certain transducer holders it is possible that there was little or no initial tension. This could easily result in lower levels of evoked tension. In such cases, however, the experimental conditions would not even remotely approach being isometric, and interpretation of such data is therefore difficult.[7–9] It is not possible to know whether changes in evoked tension are in part due to unrecognized changes in the initial stretch. Although we found that we could maintain a relatively constant resting tension (300–400 g), no claim is made that we have studied a perfectly isometric system.

In contrast, electromyographic techniques offer far fewer difficulties. A large number of motor units may be sampled with either surface or bare needle electrodes. Maintenance of a constant electrode position as judged by constant EMG waveform has not been a problem. The inconvenience of having to photograph the oscilloscope tracing can be avoided by the system we have developed.[1] For clinical use, observation of the waveform alone may be sufficient.

NEUROMUSCULAR RESPONSES TO SINGLE INDIRECT STIMULI

Of even more concern than these technical problems are several theoretical considera-

tions. If neuromuscular transmission is defined as events occurring between the release of acetylcholine by the nerve terminals and endplate depolarization sufficient to activate the adjacent muscle membrane, then both mechanical and electromyographic techniques fail to study directly the phenomenon of interest. Both methods rely on the preservation of nerve excitability and conduction as well as the excitability of the muscle membrane. Mechanical responses, but not electrical responses, are affected by changes in contractility. It would thus be surprising if the same results were achieved by measuring mechanical and electrical events. While *d*-tubocurarine, of course, depresses both mechanical and electrical responses, we cannot confirm the claim that the two methods are equivalent.[10, 11] Although in our subjects there was a roughly linear relation between depression of the normalized mechanical twitch and the EMG, depression of the two to identical degrees was not seen.

Posttetanic Potentiation

More important, the difference between the utility of mechanical measurements and that of electromyographic measurements is apparent from a consideration of posttetanic potentiation and tetanic fade. It is essential to hold in focus the enormous evidence in favor of the existence of both phenomena during curarization. During rapid stimulation two competing processes act to alter the number of quanta of acetylcholine released per impulse (quantal content). Early in tetanus the supply of readily releasable acetylcholine in the nerve terminal decreases because of its rapid release. This decreases the quantal content.[12] Because maximal muscle responses can be produced by the action of acetylcholine on a small fraction of the endplate receptors, the so-called "margin of safety" of neuromuscular transmission,[13] in the absence of muscle relaxants or deep anesthesia, tetanus should be well sustained despite the decreased quantal content. With a general decrease in the margin of safety, as with curarization, the decreased quantal content does not suffice to depolarize all of the muscle fibers, and fade occurs. While this depletion of the readily releasable acetylcholine fraction is occurring, however, compensatory processes increase the mobilization of acetylcholine from a storage pool and increase its synthesis.[14] This tends to increase the readily releasable fraction, and secondarily the quantal content. These latter processes start only after tetanic stimulation has already decreased the readily releasable fraction, but continue into the posttetanic period. Thus, in the posttetanic period the quantal content exceeds that in the pretetanic control period. In the absence of neuromuscular blocking drugs (and with supramaximal single stimuli), this increased quantal output will fail to cause PTP because the muscle fibers were *maximally* excited by the pretetanic stimulus. However, with curare-induced paresis (or with submaximal stimulation), the pretetanic twitch is submaximal. With the increased posttetanic quantal content a larger number of muscle fibers may be excited by nerve stimulation, thus causing PTP.

The phenomena of fade and PTP are therefore necessary concomitants of curarization, and indeed we have consistently observed them electromyographically in this study. Despite this, previous workers have denied their importance as signs of curarization during clinical anesthesia.[5, 11] We believe that this is because of the widespread use of tension as an index of muscular depolarization, as well as other methodologic problems. Posttetanic potentiation, it seems, has been considered to be a particularly unreliable index of curarization. Various investigators, having observed PTP (tension) before administration of curare, have insisted on 150–200 per cent PTP before they considered it "significant."

The need for resolution of this issue is reflected in our statistical treatment. In table 2 (PTP), and also table 3 (fade), the unpaired *t* test of sample differences rather than the statistically more "efficient" test of paired data was used to examine mean differences. Although the latter is formally "correct," it is not appropriate. Control measurements are not always available in clinical practice. We are not attempting to determine whether the partially curarized muscle behaves differently from its own control—it does—but whether in general PTP and fade can be useful indicators of residual curarization when twitch

TABLE 3. Effects of *d*-Tubocurarine on Tetanic Fade

	Level of EMG Twitch Depression									
	None (Control)		Maximum		≤ 65 Per Cent		≤ 40 Per Cent		≤ 20 Per Cent	
Per Cent Mean Twitch Depression for Class:	EMG	Tension	EMG 66	Tension 81	EMG 54	Tension 73	EMG 33	Tension 57	EMG 16	Tension 43
	F_E	F_T	F_E	F_T	F_E	F_T	F_E	F_T	F_E	F_T
Fade (per cent)										
Subject 1	4	10	87	33	*	*	87	33	89	21
Subject 2	24	9	71	33	83	60	83	33	80	20
Subject 3	7	6	87	20	79	36	68	11	55	9
Subject 4	20	6	92	66	94	27	86	8	76	3
Subject 5	0	5	64	0	69	0	73	8	51	0
Subject 6	0	7	88	33	88	33	87	43	68	17
Subject 7	30	16	97	65	97	65	92	22	79	10
Subject 8	0	3	65	0	65	0	32	0	18	0
MEAN	10.6	7.8	81.4	31.3	82.1	31.6	76.0	19.8	64.5	10.0
±SE	4.3	1.4	4.5	8.9	4.6	9.7	6.9	5.4	8.1	3.0
P†			<.001	<.05	<.001	<.05	<.001	=.05	<.001	*N.S.*
	PF_E	PF_T	PT_E	PF_T	PF_E	PF_T	PF_E	PF_T	PF_E	PF_T
Pseudo-fade (per cent)										
Subject 1	−4	10	80	22	*	*	80	22	66	7
Subject 2	22	9	62	16	74	40	70	13	52	−33
Subject 3	3	6	74	20	64	18	60	5	45	−4
Subject 4	20	6	60	66	76	33	71	0	60	0
Subject 5	0	0	55	0	58	0	54	0	19	0
Subject 6	−11	7	83	20	83	20	78	28	57	−25
Subject 7	28	16	88	65	88	65	78	22	73	15
Subject 8	0	3	33	0	30	0	−10	0	−20	0
MEAN	7.3	7.1	66.9	26.1	67.6	25.1	60.1	11.3	44.0	−5.0
±SE	5.0	1.7	6.4	9.1	7.4	8.7	10.5	4.1	10.8	5.7
P†			<.001	*N.S.*	<.001	=.05	<.001	*N.S.*	<.01	*N.S.*

* At no time was the EMG depressed more than 40 per cent.
† Change from mean control (unpaired Student's *t* test). *N.S.* = not significant.

has largely recovered. They are, if the measurement is made on the EMG.

PTP observed in the control period by previous investigators represents a different phenomenon from that observed after curarization. Before curare is given there is no *electromyographic* PTP because neuromuscular transmission is intact and all the muscle fibers depolarize in response to the single supramaximal indirect stimulus before tetanus. Under these conditions, mechanical PTP cannot represent depolarization of additional muscle fibers. PTP detected before curarization, therefore, must represent an increase in contractility following tetanus, and is not indicative of a change in neuromuscular transmission.

With curare-induced paresis the pretetanic EMG is depressed more than the posttetanic EMG, and PTP is invariably observed. The height of the posttetanic EMG never exceeds that of the control EMG observed before curarization. This is predictable, since the latter results from depolarization of all the muscle fibers following a supramaximal stimulus. Thus, the existence of electromyographic PTP establishes the existence of residual depression of neuromuscular transmission, and the PTP dis-

appears only with full return of the EMG twitch height to control.

We believe that electromyographic PTP may be a clinically useful monitor of residual curarization. Tension records are not nearly so useful. The initial "PTP" is fairly large (mean 123 per cent), with a large range. It is impossible on tension records to distinguish this "PTP" originating in contractility changes from true PTP resulting from curarization. It is precisely at the times of least twitch depression, when a clinical guide is needed, that PTP is indistinguishably greater than control PTP. These problems can be obviated by the use of electromyography.

Although these considerations detract from the usefulness of PTP derived from tension measurements, we cannot agree with Heisterkamp *et al.*[5] that curare as used clinically fails to produce PTP. Heisterkamp *et al.* made tension measurements, but compounded the problem by calculating an incremental PTP (which we have called PTR-I_T). We do not disagree with their data, and indeed calculation of our data in a similar fashion shows that PTR-I_T does not increase with curarization (table 2). We do not believe that incremental PTP (PTR-I_T) has any meaning, however. There are two major lines of argument to be considered. First, the great mass of basic physiologic data suggests that curare must cause PTP in man. And indeed, we have demonstrated significant PTR_E at all of our levels of curarization, as well as PTR_T at intense levels of curarization. That PTR-I_T fails to allow detection of PTP at times when one can show that it exists testifies to the inappropriateness of the concept of "incremental" PTP.

Second, a more fundamental consideration is that PTP as measured by tension has both a neuromuscular component and a contractile component. The neuromuscular component is absent prior to curarization and occurs only after administration of curare. The contractile component is present before curarization, and since it is a muscular rather than a neuromuscular event, it may be assumed to be proportional to the number of fibers contracting. Thus, that part of the incremental PTP due to contractile changes may be presumed to *decrease* following curarization. Since after curarization neuromuscular factors tend to increase PTR-I_T while contractile factors produce an offsetting decrease in PTR-I_T, it is not surprising that little change is observed. On the other hand, since PTR_T is the ratio of the post- and pretetanic responses, its contractile component is unaffected by the number of fibers contracting and thus by curarization. PTR_T therefore, may and does increase with the appearance of the neuromuscular component. In passing, it may be noted that PTR-I_E is a valid concept because there is no contractile component to the electromyographic PTP. That is, control PTR-I_E is zero. Indeed, we have demonstrated significant PTR-I_E after curare (table 2). However, because PTR_E and PTR_T are *both* meaningful concepts, we do not find it useful to retain the concept of incremental PTP even when applied to the electromyogram.

Fade during Tetanus

Tetanic fade can be quantitated both by tension measurements and by electromyographic measurements. Fade is a complicated phenomenon depending upon depletion of readily releasable acetylcholine, which competes with a delayed increased mobilization and synthesis of acetylcholine. Furthermore, its demonstration is dependent upon a requirement for a high concentration of acetylcholine at the endplate, and thus it is seen following curarization, when most receptors are unavailable. Our data show that electromyography is more useful in demonstrating fade than are tension measurements. F_E was seen at every level of curarization, while F_T was always less than F_E and insignificantly different from control when the single twitch amplitude had recovered to within 20 per cent of control. The reasons EMG measurements of fade give more information than tension measurements are not obscure. They can be understood in termset of the opposing processes which control the quantal content during tetanus, along with the "averaging" aspects of tension measurements. During a 5-second tetanus at 30 Hz, the muscle fiber depolarizes 150 times. Each depolarization causes a compound action potential whose amplitude reflects the state of the neuromuscular junction *at that time*. The development of tension, however, is a slower

process. It takes approximately 350 msec to develop maximal tension at the start of tetanus and 150 msec for tension to disappear at the end of tetanus. Thus, the tension at any point in time reflects a sort of moving average of the neuromuscular events of the last few hundred milliseconds. Since the actual neuromuscular events causing fade occur in a few hundred milliseconds (electromyographic fade was generally complete within ten stimuli) the frequency bandpass inherent in tension recording substantially degrades the registration of this event and blunts its magnitude. Thus, in tension recordings from Subject 5, whose EMG showed relatively little fade, and in those from Subject 8, whose EMG showed considerable recovery during tetanus after the initial fade, no mechanical fade was seen at all. Whether there are contractility changes *during* tetanus as well, which would further confuse the interpretation of tension records, is unknown.

Technical problems may contribute to difficulties in demonstrating significant fade on tension recordings. A constant preload in the tension-measuring system is essential to define the initial condition of the muscle and set it at a given point on the curve defining maximum tension output as a function of length. In addition, the absence of a preload implies slack and therefore backlash (mechanical hysteresis) in the system. Not only does this make the system non-isometric, but it can prevent registration of the true peak tension and thus further decrease the incidence of detected fade. It has been uncommon for clinical investigators to state under what resting tension, if any, they have placed the muscle (thumb).

Because of the widespread use in previous human studies of the Grass FT-03 transducer, which overloads with constant output on forces greater than 1 kg,‡ we suspect that peak tetanic force has not been registered and that tetanic fade may have been undetected. Transducer overload must always be suspected when the maximal tetanic force is less than two to three times twitch tension. Apparently this transducer may have been carried uncritically from the tissue bath into the operating room. We have often found the FT-03 to be overloaded by tetanus even in a cat tibialis preparation.

The difficulties in interpretation of fade can be compounded by errors in definition of fade. "Fade" properly refers to the initial rapid decrease in muscle electrical or mechanical activity, and we have defined F_E and F_T as per cent decrease between the first maximum and the first minimum recording. Fade, however, is often defined as the per cent decrease from the initial maximum to the tension or EMG height at the *end* of tetanus.[15] Because of the frequent occurrence of recovery *during* tetanus, presumably from increased mobilization or synthesis of acetylcholine, this is a smaller value. We have called this "pseudofade" (PF_E and PF_T). Although PF_E is smaller than F_E it was significant at every point measured in this study after administration of curare. However, PF_T was so decreased as to be of borderline significance at 65 per cent depression and was insignificant at all other levels of curarization.

To improve the sensitivity of F_T measurements, clinical investigators have proposed the use of high-frequency tetanus at 200 Hz. This indeed will increase depletion of transmitter and therefore increase fade, but extremely high-frequency stimulation is unphysiologic, since muscle cannot respond this rapidly. Even during maximal voluntary efforts there are seldom more than 30 to 50 depolarizations per second. Moreover, tetanus, especially rapid tetanus, increases the average neuromuscular refractory period (unpublished data). It is possible, therefore, that part of the "fade" seen is due to a decreased ability of muscle to respond rapidly during the latter part of tetanus rather than to receptor blockade or inactivation by relaxant drugs. Observation of the electromyogram during high-frequency tetanus shows a widening and a prolongation, as well as a diminution of the height, of the compound action potential (unpublished data). This probably implies an increase in the asynchrony of excitation, which would be expected to decrease the force of contraction.[16] While these changes may be

‡ The Grass FT-03a and FT-03b overload at 1 kg. The newer FT-03c overloads at 2 kg. R. de Jong[11] correctly notes that a transducer with linear responses to 10 kg is essential. In the present study the greatest twitch tension we observed was 2.4 kg. while the greatest tetanic tension was 8.8 kg.

real enough, they are distinct from the phenomena we have been discussing, which are generally understood to represent decreased neuromuscular transmission. Indeed, in the presence of potent anesthetics, fade has been observed during high-frequency tetanus even without relaxant drugs, and thus it appears that interpretation of high-frequency tetanus is difficult at best.[17] With the use of electromyography, tetanus at reasonable frequencies (30–50 Hz) lasting a few hundred milliseconds appears adequate to study or monitor curarization.

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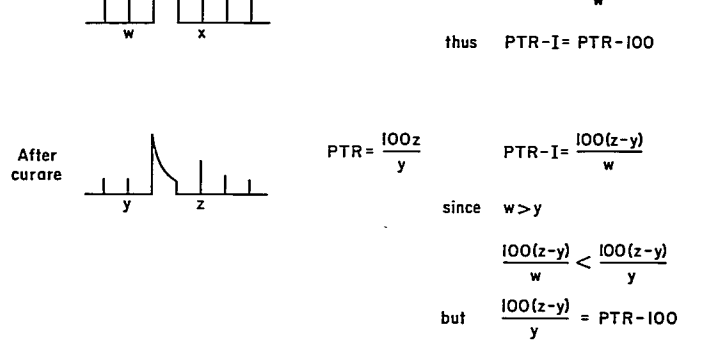

FIG. 3. Calculation of posttetanic potentiation. *Top:* before curarization. *Bottom:* after curarization. *w*, *x*, *y*, and *z* are twitch EMG or tension amplitudes. The greater the twitch depression, the more incremental PTP underestimates true PTP. See Appendix 1 for details.

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APPENDIX 1

Calculation of PTP

Two fundamentally different indices have been used to quantitate PTP (fig. 3). The first, which we call "PTR," is the ratio between the amplitudes of the post- and pretetanic responses. Expressed as a per cent, PTR = 100 x/w or 100 z/y. Alternatively, this concept can be expressed as 100 (x − w)/w or 100 (z − y)/y, as the value of these expressions differs from the original only by a constant (100). Thus, PTR may be considered to be the difference between the post- and pretetanic responses normalized to the *current* pretetanic response.

On the other hand, the incremental PTP of Heisterkamp, for which we use the term "PTR-I," is the difference between the post- and pretetanic responses normalized to the pretetanic response *that was obtained before curare.* Thus, PTR-I = 100 (x − w)/w before curare and 100 (z − y)/w after curare. Before curare, PTR and PTR-I are equivalent (except that they differ by a constant 100). *I.e.,* PTR-I = PTR − 100 (see derivation in fig. 3). After curare the two indices diverge, since with twitch depression w > y. Thus, when twitch depression exists, PTR-I < PTR − 100 (see derivation in fig. 3). This underestimation of PTP by PTR-I becomes greater as curarization becomes more profound (see diagrammatic fig. 3 and original data in fig. 2).

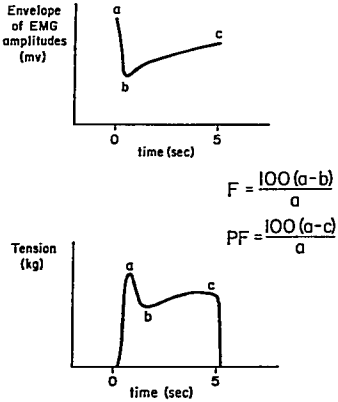

FIG. 4. Calculation of fade. *Top:* envelope of EMG amplitude during tetanus. *Bottom:* tension amplitudes during tetanus. *a, b,* and *c* are EMG or tension amplitudes and are the initial maximum, the succeeding minimum, and the final amplitudes, respectively. Recovery of the initial fade usually occurred during tetanus on both EMG and tension records. Thus, PF < F. See Appendix 2 for details.

APPENDIX 2

Calculation of Fade

Fade induced by curare develops rapidly during tetanus and is maximal at about 300 msec with a 30-Hz stimulus. If tetanic stimulation is continued for the 5 seconds traditionally used in clinical studies there may be recovery of the amplitude of the response. Fade (F) is calculated as the difference between the first maximal response and the following minimum, normalized to the value of the maximum. Expressed as a percentage, F = 100 (a − b)/a.

Pseudofade (PF), on the other hand, is defined as the difference between the first maximum and the response at the end of tetanus, again normalized to the original response. As a percentage, PF = 100 (a − c)/a. Since, in general, c > b, PF < F. (See diagrammatic fig. 4 and original data in fig. 1.)