Monitoring of Neuromuscular Function

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I. Introduction

It is universally acknowledged that monitoring of neuromuscular transmission provides valuable information to the anesthetist. The acquisition of such data often contributes to, or is mandatory for, improved patient care. In this review the many factors affecting normal neuromuscular transmission are analyzed. The practical value of clinical and laboratory data in anticipating the response of the individual patient to neuromuscular blocking drugs is emphasized. The clinical relevance of twitch height, tetanic fade, train-of-four value, etc., is discussed. We hope that presentation of the data in numerical fashion wherever possible will foster a better appreciation of the graded process of neuromuscular blockade, so that improved anesthetic management may result.

II. Clinical Types of Neuromuscular Blockade

Three types of neuromuscular blockade can be differentiated clinically according to the pattern of the evoked muscle response to changes in stimulus frequency. They are: nondepolarizing neuromuscular block,12,22 depolarizing block12; dual block, desensitizing, or Phase II block.2,10–12 This classification has been questioned by some.13–14

A. Nondepolarizing Block

This type of block is induced by: d-tubocurarine (curare), metocurine (Mebetine), gallamine triethiodide (Flaxedil), pancuronium (Pavulon), and alcuronium (Alloferine).

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It is characterized by:

1. Absence of fasciculation (no muscle fiber activity prior to the onset of paralysis).
2. Non sustained response to twitch (slow) or tetanic (fast) rates of stimulation (i.e., there is fade).
3. Posttetanic potentiation.
4. Antagonism of the block by anticholinesterase drugs.

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B. Depolarizing Block

This type of neuromuscular block follows the administration of succinylcholine, deca-methonium, and similar substances.

It is characterized by:

1. Muscle fasciculation (asynchronous contraction of multiple motor units, manifested usually by fine fibrillar movements and occasionally by full skeletal muscle movements) preceding the onset of block.
2. Initial absence of fade at slow and fast rates of stimulation.
3. Absence of posttetanic potentiation.
4. Potentiation of the block by anticholinesterases.
5. Antagonism of the block by d-tubocurarine.
6. Potentiation of the block by other depolarizing substances.

C. Dual Block (Phase II or Desensitization Block)

Repeated administration of a depolarizing neuromuscular blocking drug over a prolonged period ultimately leads to development of dual block, the onset of which has been said to be a gradual process. Churchill-Davidson et al. found that a dose of at least 0.5 g of succinylcholine was needed in patients anesthetized with thiopental-nitrous oxide to establish a full dual block, which could be reversed by neostigmine. Katz et al., using a variety of anesthetics, found that the earliest signs of phase II block were reached after a succinylcholine dose of only 2.2–3.0 mg/kg (154–210 mg for a 70-kg adult). Crul and associates confirmed that the onset of dual block after succinylcholine is both dose- and time-dependent. Classic dual block has been described to occur following the clinical inhaling dose (1 mg/kg) of succinylcholine in patients who have atypical plasma cholinesterase. De Jong and Freund went further and claimed that depolarization or phase I block never occurred in man. Their patients, however, were studied during deep halothane anesthesia.

Five stages in the development of dual block have been described:

1. A typical depolarization block occurs first.
2. Stage of tachyphylaxis: a diminished response occurs following repeated doses.
3. Stage of Wedensky inhibition: fade of successive EMG potentials develops in response to high-frequency (tetanic) stimulation. Slow (twist) rates are sustained.
4. Stage of “fade and potentiation”: anticholinesterases improve neuromuscular transmission in this stage.
5. Nondepolarization stage: all the classic signs of a nondepolarizing block are present.

Contrary to previous reports that maintain that the change from depolarizing to dual block is a gradual process, Lee has found that if the response to succinylcholine is monitored by the train-of-four stimulus, the ratio of the fourth to the first evoked muscle response shows a relatively sudden shift from phase I to phase II characteristics. Phase I is characterized by a high train-of-four ratio or minimal fade (ratio 0.7–0.9). Phase II is characterized by a low train-of-four ratio (0.3 or less). The phase II block was antagonized by anticholinesterases. Transition from phase I to phase II occurred after administration of 2–4 mg/kg succinylcholine during halothane anesthesia. After 3–5 mg/kg, phase II block is well established. In our experience, 7–8 mg/kg succinylcholine are needed to establish phase II block during nitrous oxide-narcotic anesthesia (unpublished data).

The simultaneous onset of tachyphylaxis and phase II block suggests that the two are causally related. Since succinylcholine antagonizes the effect of tubocurarine, it is possible that in phase II succinylcholine antagonizes its own tubocurarine-like effect. According to Lee, if tetanic stimulation is avoided, dual block can be assessed as often as every 12 seconds. Therefore, it is possible to detect phase II block at its very onset.
III. Clinical Monitoring of Neuroromuscular Function

Early attempts to study the effects of neuromuscular blocking drugs in man were based on clinical observations of signs of muscle weakness such as inability to open the mouth or eyes, protrude the tongue, swallow, or maintain grip strength. Investigators advocated the use of devices that measure maximal voluntary efforts of the abdominal recti. Additional methods included measurement of respiratory variables such as minute volume and vital capacity or maximum inspiration. Others recorded diaphragmatic activity on a fluoroscope screen. Bendixen et al. have measured inspiratory force (the negative pressure developed against an occluded airway) to demonstrate the presence of residual weakness due to neuromuscular blockade. Some clinical investigators have relied upon testing for head-lift, based on the observation that the muscles of the neck are among the first to be influenced by the paralyzing action of muscle relaxants before any significant effect on respiratory muscles can be detected.

Measurement of voluntary muscular contraction cannot be carried out during anesthesia. Even in conscious volunteers, the accuracy of the above-mentioned clinical tests is limited by the ability of an individual to reproduce a given effort. Volitional measurements have, however, proven useful as a guide to laboratory investigation, particularly when repeated measurements are made in the same individual. Tidal volume and inspiratory force measurements in anesthetized patients cannot be considered satisfactory methods for monitoring neuromuscular function because drugs such as narcotics, hypnotics, and inhalation anesthetics all depress respiratory function. It is often assumed wrongly that muscle relaxants are responsible for respiratory depression at the end of an operation. Such an assumption can be documented only when impairment of neuromuscular transmission can be demonstrated.

The only satisfactory method of monitoring neuromuscular function is stimulation of an accessible peripheral motor nerve and observation or measurement of the response of the skeletal muscle supplied by this nerve. The earliest attempts to employ motor nerve stimulation for monitoring neuromuscular function in man date back to 1941. Harvey and Masland realized the importance of delivering to the peripheral motor nerve an electrical stimulus of sufficient intensity to cause all nerve fibers to respond but not strong enough to cause repetitive firing of the nerve. They applied an electrical stimulus to the ulnar nerve at the elbow. The intensity of the pulse was gradually increased until the muscle action potential recorded from the abductor digiti minimi (the hypothenar eminence) reached a maximum amplitude. The stimulus was then increased by 10–15% to ensure supramaximal stimulation. A single supramaximal stimulus applied to a motor nerve evokes a single muscle twitch in the muscles supplied by this nerve. The recorded response is the mechanical or electrical manifestation of the activated contractile apparatus.

The extent of shortening or the tension developed by a single muscle fiber is independent of the nature of the stimulus. It is an “all-or-none” phenomenon. Augmented force of muscle contraction is produced by a graded increase in the number of muscle fibers contracting and depends on the previous state of that muscle. Measurement of the force of muscle contraction or the compound action potential resulting from indirect stimulation is primarily an index of the number of fibers that have been caused to contract. Based on the “all-or-none” law and assuming that conduction along the motor nerve is intact, propagation of an electrical stimulus must result in contraction of all muscle fibers supplied by the activated nerve fibers if neuromuscular transmission is not impaired.

Tension measurements in response to motor nerve stimulation have been used by several investigators. Some stimulated the ulnar nerve and recorded the twitch produced in either the fifth finger or the fourth and fifth fingers. The response in either of these cases, however, cannot be considered isometric. Others have measured the evoked twitch response resulting from adduction of the thumb. Mapleson and Mashin stimulated the median nerve and recorded the force of contraction of the muscles of the thumb.
Evoked electromyography (EMG) in man has been used to measure neuromuscular function and has been much preferred over tension measurements by some investigators.\(^1\)\(^2\)

**IV. Methods of Measurement of Neuromuscular Function (Evoked Responses)**

In contrast to voluntary movements, evoked responses do not require the cooperation of the individual and thus are suitable for use in the unconscious patient. Furthermore, supramaximal electrical nerve stimuli can be used, and hence the muscular responses are reproducible. The resulting activation of the muscle fibers can be measured either mechanically (tension response) or electrically (evoked EMG).

Proper stimulus characteristics are necessary,\(^3\) since an excessive stimulus duration or inappropriate waveform can cause repetitive nerve firing,\(^4\) resulting in faulty interpretation. Ideally, it should be a rectangular or square pulse of a duration not exceeding 0.2 msec. In addition, supramaximal stimuli are necessary to ensure full activation of all the nerve (and hence muscle) fibers.

**A. Tension Measurements**

The hand muscles are used most commonly for mechanical twitch measurement, especially the adductor of the thumb. The great advantage in the use of the adductor pollicis is that under appropriate conditions, it is the only muscle acting on the thumb\(^5\) supplied by the ulnar nerve, and hence it approaches the single-muscle precision of the experimental nerve–muscle preparation. Stimulating electrodes are placed on the surface of the skin or percutaneously along the ulnar nerve at either the wrist or the elbow. The evoked tension of the adductor pollicis in response to ulnar nerve stimulation is recorded using a force-displacement transducer. Epstein and Epstein\(^6\) have emphasized the importance of transducer mounting and some specific mechanical characteristics for the interpretation of results. The transducers commonly used (Grass FT-03 and FT-10) are extremely sensitive to the direction of the applied force. Few investigators have consistently positioned these transducers with this consideration in mind. Small shifts in the angle of applied force can produce significant changes in the output of these transducers. The correct positioning of thumb, transducer, and arm, in our practice, is shown in figure 1.

During both tetanic electrical stimulation of the ulnar nerve and voluntary effort, the maximum force of adduction of the thumb of the normal adult volunteer is about 8 kg.\(^7\) In patients anesthetized with nitrous oxide, oxygen and halothane or methoxyflurane, Freund and Merati\(^8\) found the mean measured force of adduction of the thumb in response to tetanic electrical stimulation to be 5.6 ± 1.4 kg (mean ± SE). Both are well above the capacity (2.2 kg) of the Grass FT-03 transducer. Epstein and Epstein\(^9\) and the above-mentioned authors\(^10\) have pointed out that if the FT-03 transducer is used, the true control tetanic tension cannot be recorded since the transducer is overloaded. Therefore, during recovery from neuromuscular blockade tetanic tension may appear to have recovered fully and the tetanic response may appear well sustained when fatigue is still present, simply because of transducer overload. This does not occur when the Grass FT-10, with a capacity of 10 kg, is used. Another consideration is the initial resting tension of the muscle. With the use of certain transducer holders, it is possible that there is little or no resting tension placed on the thumb. In such cases, the experimental conditions do not approach isometric recording and such data may produce erroneous results. On the other hand, Donlon \textit{et al}.\(^1\) have found that the resting tension of the adductor pollicis brevis should be at least 200 g for maximum evoked twitch tension to develop. However, varying the resting tension from 50 to 300 g did not result in any difference in the cumulative dose–response curve for gallamine. Furthermore, use of the biphasic stimulus from a Block-Aid\(^\text{®}\) monitor did not alter the dose–response relationship, although the absolute twitch height was higher in the former

ease than that which resulted from square-wave stimulation by a Grass S-88 stimulator. Therefore, there is little reason to doubt the reliability of prior clinical studies that have not standardized resting tension or have employed biphasic stimulation.

B. Electromyographic Measurements

Evoked EMG measurements can be accomplished by supramaximal stimulation of the ulnar nerve at the elbow and recording of the compound muscle action potential via two surface or needle electrodes applied to the adductor pollicis brevis (thenar EMG),29 the abductor digitii minimi (hypothenar EMG),18,26 or the first dorsal interosseous muscle of the hand.26 The active or negative electrode is placed over the motor point of the muscle to be studied and the indifferent electrode at the tendon of insertion of the respective muscle. A third and larger plate (ground electrode) should be interposed between the stimulating and recording electrodes37,38 to reduce the 60-Hz interference. Movement artefact is reduced by securing the hand and forearm in a suitable splint.

On stimulation of the motor nerve, a full motor unit action potential is recorded. If the surface electrodes are correctly placed on the motor point, a number of biphasic motor unit action potentials are recorded as a single large summated compound action potential. The stimulus artefact detected before the beginning of the action potential represents the arrival of the electrical pulse. The time interval between the stimulus artefact and the beginning of the action potential represents the time taken for the stimulus to travel down the nerve from the point of stimulation to the motor end-plate. If the nerve is stimulated at two different points (e.g., the ulnar nerve at the elbow and wrist) the difference in the time intervals is a measure of conduction rate along that nerve. By using electromyography, problems with transducer fixation, orientation and overload may be avoided. The latter are important factors to be considered when measuring the tension response.39 On the other hand, the EMG is not
without technical difficulties. Despite the availability of modern preamplifiers and storage oscilloscopes, measuring the evoked EMG is difficult and expensive, especially for everyday clinical monitoring of neuromuscular function. Epstein et al. have recommended that the EMG be transcribed after amplification on a high-quality FM instrumentation tape recorder. Playback and writeout on a polygraph can be obtained later, thus cutting down tremendously on the cost of recording high-speed events. Their system includes laboratory instrumentation generally available which need not be dedicated solely to survey of neuromuscular function. We believe that this system is more suited for use as a research tool than for use as a clinical monitoring system.

Recently, Epstein and Epstein have described a more compact, less expensive, and fully automatic system which has been devised using solid-state electronic storage technique. This method allows the direct writing of individual EMG twitch responses. The recording is thus available during the course of anesthetics administration. These authors believe that this technique may prove to be a clinically useful tool in the evaluation of muscle relaxation.

V. Clinical Utility of Various Evoked Responses

The pattern of evoked muscle responses to changes in the frequency of stimulation identifies and quantifies neuromuscular block. This method measures the evoked muscle response to:

A. Single repeated supramaximal nerve stimuli at slow rates (0.1–0.2 Hz, the single twitch).
B. Tetanic or high-frequency rates of stimulation at 50 or more Hz (tetanus).
C. Posttetanic single repeated stimuli (posttetanic potentiation).
D. Train-of-four stimulation at a low frequency (2 Hz for 2 seconds).

The resultant pattern depends upon the factors that control the synthesis, mobilization and release of the chemical transmitter acetylcholine, as outlined in a subsequent section.

A. The Responses to Single Repeated Supramaximal Motor Nerve Stimuli (Single Twitch)

Various investigators have used stimulus frequencies ranging from 0.1 to 1.0 Hz. Since the extent of nondepolarizing neuromuscular blockade is frequency-dependent, the reported results will vary accordingly, and a standard stimulus frequency should be advocated for this purpose. The single twitch is useful as an approach to the comparative study of neuromuscular blocking drugs. A control response is obtained (fig. 2) and the percentage change from control establishes the onset of action and potency of the drug. Duration of action is indicated by the time required for recovery of the evoked twitch response to control level. Single stimuli detect relatively high degrees of enervation, and may be helpful in deciding whether postoperative apnea is peripheral or central in origin.

In clinical situations, unless monitoring is performed routinely, the control level of the twitch response will not be available when postoperative muscle weakness is suspected. Moreover, complete stability of recording over a period of hours cannot be guaranteed. It is questionable whether the measured tension response is the same as the evoked electrical response. It was shown that the muscle action potential amplitude could not be quantitatively related to the tension developed in the muscle, while the integrated EMG was found to correlate linearly with the tension developed during voluntary isometric contraction. Epstein and Epstein noticed that despite a roughly linear relation between depressions of the evoked mechanical twitch and the EMG, the two were not depressed equally. There is dissociation of the electrical and mechanical events in terms of the extents of blocks produced by succinylcholine and d-tubocurarine. Accordingly, the mechanical twitch response is less sensitive to succinylcholine than the thenar or hypothenar EMG. On the other hand, with d-tubocurarine the mechanical twitch response is more sensitive than the thenar or hypothenar EMG. Thus, assessment of recovery from tubocurarine by EMG monitoring may indicate complete neuromuscular recovery upon the return of the response to control levels. On the contrary,
the information obtained from the mechanical twitch response may indicate substantial muscle weakness; the converse is true of succinylcholine. Botelho, who studied simultaneously the evoked mechanical and electrical activities of partially curarized human muscle, found that measurement of isometric muscle contraction evoked by motor nerve stimulation provided a more accurate index of neuromuscular block than measurement of the muscle action potential associated with contraction.

B. The Response to Tetanic Stimulation

Paton and Waal found that in response to single stimuli delivered every 10 seconds, three-fourths of the postsynaptic receptors must be occluded before neuromuscular transmission begins to fail. This can be interpreted as indicating that only one quarter of the receptor pool is necessary for normal transmission at low rates of stimulation, or that the output of transmitter acetylcholine (ACh) is many times greater than necessary to evoke a propagated response in every muscle fiber, or finally, that a high "margin of safety" exists at the neuromuscular synapse. In other words, the end-plate potential is more than adequate to trigger a propagated response over a wide range of frequencies of stimulation, hence the response to tetanic stimulation is sustained at high frequencies during normal neuromuscular transmission despite the decrement in ACh release. When the margin of safety is decreased by disease of the myoneural junction (e.g., myasthenia gravis) or the use of curare-like drugs, then the decrease in ACh output during repetitive nerve stimulation will be manifested by fade or non-sustained response to tetanic stimulation (fig. 3). The extent of tetanic fade depends upon the frequency and duration of stimulation. Gissen and Katz have found that the failure of sustained response to tetanic stimulation at various frequencies is a more sensitive index of neuromuscular blockade than the single twitch or post-tetanic potentiation. During partial neuromuscular blockade with as little as 5 mg d-tubocurarine during administration of nitrous oxide--oxygen with 0.5--2 per cent halothane, tetanus is not sustained at the higher stimuli.
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Fig. 3. Tetanic fade and posttetanic potentiation during partial nondepolarizing neuromuscular blockade produced by pancuronium in a patient during nitrous oxide–narcotic anesthesia. Twitches (0.15 Hz) and tetanus of the thumb were evoked indirectly via the ulnar nerve. At $T_{90}$ tetanic stimulation was applied at 50 Hz for 5 seconds. There are fade of the tetanic response and marked posttetanic potentiation (PTP) of the twitch, which stabilizes after the period of potentiation at approximately twice the height of the pretetanic twitch. At $T_{1}$ train-of-four stimulation was carried out. Only the first response in the train is evoked at this depth of block (90% depression of the single twitch).

frequencies (100–200 Hz) even though twitch may have returned to control levels. In the presence of potent anesthetics (enflurane, halothane, methoxyflurane, isoflurane) fade has been observed during high-frequency tetanus (200–300 Hz) even without the use of muscle relaxant drugs. The response to high-frequency tetanus is difficult to interpret in the presence of these anesthetics. Moreover, extremely high-frequency tetanic stimulation (>50 Hz) is unphysiologic, since during maximal voluntary effort no more than 50 Hz are required to match a comparable evoked response. Rapid tetanus increases the average neuromuscular refractory period, and it is possible that part of the fade seen is secondary to decreased ability of the muscle to respond rapidly during the latter part of the tetanus, rather than to receptor blockade by relaxant drugs.* The report of Waud and Waud correlating the frequency of stimulation to receptor occlusion is less pertinent to the clinical situation. The concept of the margin of safety and receptor occlusion illustrates the extent of interference with the synaptic mechanism that can exist without failure of transmission. The assumption has been made that acetylcholine and blocking drugs such as d-tubocurarine interact with the receptor pool according to the laws of mass action, as do stimulants and antagonists at other receptor sites. The measurement of receptor occupancy applies only to the muscles studied, and by no means can one say that the results obtained in animals apply directly to human muscles. A low-frequency pattern of nerve stimulation (2 Hz) will reveal fade at a time when the mechanical response to high-frequency tetanus (50 Hz) is well sustained in the human adductor pollicis brevis muscle (fig. 2). The authors believe that the train-of-four technique deserves further clinical study to substantiate this concept.

C. Posttetanic Potentiation (PTP)

Mobilization and enhanced synthesis of ACh continue during and after cessation of tetanic stimulation, so that following the end of a tetanus, there is an increase in the readily releasable fraction and subsequently the quantal content. Thus, in the posttetanic period the quantal content exceeds that in the pretetanic control period. In the absence of any decrease in the margin of safety, this increased quantal output will fail to cause PTP because all the muscle fibers are maximally excited by each single stimulus. However, with curare-induced paralysis, 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 (fig. 3). The latter can occur in the control period in the absence of neuromuscular block. This has been observed by several investigators when monitoring the evoked mechanical response. There is no control electromyographic PTP before curarization, because neuromuscular transmission is intact and all the muscle fibers depolarize in response to the single supramaximal indirect stimulus before the tetanus. In this case the phenomenon of control mechanical PTP seems to be explained either by a change in the contractile response of the muscle or by repetitive firing of nerve or muscle and is not indicative of a change in neuromuscular transmission. Epstein and Ep-
stein" consider that the existence of electromyographic PTP establishes the diagnosis of residual depression of neuromuscular transmission, and they believe that it may be a clinically useful monitor of residual curarization. These investigators found that mechanical PTP is not as useful as electromyographic PTP. PTP is markedly influenced by the duration and frequency of the preceding tetanus, as well as by the posttetanic interval.61

**D. Train-of-four stimulation**

From the foregoing discussion, it might appear that there is controversy in the interpretation of results obtained from the responses to single stimuli, tetanic rates of stimulation, and posttetanic single repeated stimuli (posttetanic potentiation). Few will argue that the ability to estimate quantitatively the degree of neuromuscular block without the need for a control response is desirable, particularly if residual curarization is suspected. Ali et al.26-28 have attempted to quantify the degree of residual curare block by describing an additional method for quantitative measurement of the degree of nondepolarizing neuromuscular blockade. This method utilizes a short train of four supramaximal stimuli applied to the ulnar nerve at a frequency of 2 Hz. Each train is repeated not more frequently than once every 10 seconds, either intermittently or continuously. The ratio of the amplitude of the fourth evoked mechanical or electromyographic response to the amplitude of the first response in the same train as shown in figure 4 appeared to provide a convenient method for the assessment of neuromuscular transmission. This method does not require a previous control response and provides a means for quantifying residual curarization after a nondepolarizing relaxant has been given. It can be applied to situations before and after attempted reversal of the neuromuscular block with anticholinesterase. Four stimuli were chosen since it was found that during partial curarization the fourth response was maximally depressed, after which the single twitch response either leveled off or increased slightly in amplitude (fig. 5). In addition, the individual responses can be easily separated. The low frequency (i.e., 2 Hz) is rapid enough to produce significant depletion of the immediately available store of Ach and yet slow enough to prevent transmitter facilitation. There was a highly significant positive linear association (P
< 0.001) between the ratio of the fourth to the first response in the train and the ratio of the first response in the same train to the control response. The train-of-four ratio correlates well with a simple clinical test commonly employed for assessment of clinical recovery from nondepolarizing neuromuscular blocking drugs (i.e., head lift). With a ratio above 60 per cent, patients were able to sustain head lift for a period of 3 seconds or more. A mean (±SD) ratio of 74 ± 5 per cent was found to correlate well with signs of adequate clinical recovery from d-tubocurarine block in anesthetized patients receiving nitrous oxide-oxygen and a narcotic supplement. The clinical signs of muscle function included the ability to open the eyes widely, cough, protrude the tongue, sustain head lift for 5 seconds, develop a vital capacity of at least 15-20 ml/kg, and sustain a tetanus of 30-50 Hz for 5 seconds. Another study in conscious unmedicated volunteers showed that a train-of-four ratio of 60 per cent or higher, the changes in the measured respiratory variables (i.e., the tidal volume, vital capacity, inspiratory force, and peak expiratory flow rate) were negligible, since the lowest values measured were well above the clinically acceptable limits (fig. 6). A train-of-four ratio of 70-75 per cent coincides with the return to the control level of the single twitch response evoked at 0.15 Hz and a sustained mechanical response to tetanic stimulation at 50 Hz for 5 seconds (Ali, Savarese, et al., unpublished data). Figure 2 shows the relation between the single twitch, the train-of-four response, and the tetanic response after reversal of nondepolarizing neuromuscular block. Electromyographically, a train-of-four ratio of 75 per cent correlated well with adequate clinical recovery, including sustained head lift for 5 seconds or more (fig. 7).

The train-of-four pattern of stimulation, in addition, causes much less discomfort to the conscious patient recovering from anesthesia than tetanic stimulation at 30 Hz or more. Furthermore, it does not affect the subsequent pattern of recovery from neuromuscular blockade as does tetanic stimulation (fig. 3). The ratio of the train-of-four is also a valuable guide for quantitative assessment of residual nondepolarizing neuromuscular block in infants and children, as demonstrated by correlation with single-twitch depression (r = 0.93, P < 0.001).

Lee has correlated the movement of the fifth finger with recorded thumb adduction in response to train-of-four stimulation and utilized the finger movements as a method of estimating the degree of d-tubocurarine block. He found that during the onset of block, the fourth twitch in the train was eliminated at approximately 75 per cent depression of the first twitch compared with control. The third twitch in the train was abolished at 80 per cent depression of the first twitch, while the second twitch in the train became undetectable at about 90 per cent block of the first response.
When all four twitches in the train were absent, 100 per cent or complete block was present (fig. 8). Thus, for clinical purposes, merely counting the twitches in the train-of-four response quantifies both the extent of neuromuscular blockade and the dose of muscle relaxant required to achieve a certain degree of relaxation. This method affords a means by which the anesthesiologist can predict the prospects of adequate reversal of nondepolarizing blockade by anticholinesterase drugs, since reversal at 75 per cent twitch depression (25 per cent twitch height) is usually complete within 10–15 minutes.67

For practical purposes, the train-of-four technique can provide the following clinical information:

1. An estimate of the dose of nondepolarizing relaxant drugs necessary to achieve 90–95 per cent twitch suppression (satisfactory surgical relaxation during nitrous oxide anesthesia).65-73

2. Prediction of adequate reversal of nonde-

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**Fig. 8.** Correlation of the single twitch height at a frequency of 0.1 Hz (the first response in the train of four responses) and the train-of-four ratio (T4, the calculated ratio of the height of the fourth to the first response in the train). A, control response. B, when the single twitch is 95 per cent of control, the train-of-four ratio is 75 per cent or less. C through E, disappearance of the fourth twitch, the third and fourth twitches, and the second, third, and fourth twitches in the train corresponds to 25, 20 and 10 per cent single twitch height, respectively,62 and the ratio of the train-of-four is zero. F, when all four responses in the train are abolished, the depth of block is the same as indicated by the absence of the single twitch.
polarizing block following administration of anticholinesterases.

3. Assessment of residual curarization and adequacy of recovery from nondepolarizing neuromuscular blockade.

4. A ratio of the fourth/first response of greater than 0.70 correlates well with clinical tests of adequacy of reversal.

5. Diagnosis and follow-up of the course of phase II block following depolarizing relaxants.

Ali et al.\textsuperscript{1} developed a self-contained monitor to measure the response to train-of-four stimulation in clinical situations. It includes a nerve stimulator that delivers the proper impulse pattern (i.e., train of four stimuli at 2 Hz, each repeated either intermittently or continuously once every 10 seconds) and a twitch-response analyzer, consisting of a thumb force transducer assembled in a specially designed armboard and digital readout circuit that calculates and displays the ratio of the fourth to the first response\textsuperscript{25,26} (fig. 9). This monitor is currently used in the operating and acute care suites at the Massachusetts General Hospital. A small portable nerve stimulator that delivers train-of-four stimuli is being used to estimate the dose requirements of nondepolarizing relaxants to provide adequate surgical relaxation.

VI. Integrated Electromyography (IEMG)

A final method for monitoring relaxation of the abdominal wall musculature depends upon integrating the spontaneous electrical activity of the latter muscle group.

Fink\textsuperscript{27} used the spontaneous EMG of the abdominal muscles as a guide to management of muscle relaxation. The EMG activity can be obtained by inserting needle electrodes into the oblique transverse group of abdominal muscles. The EMG can be observed on an oscilloscope or the electrical activity may be filtered, amplified, rectified and integrated, thus providing an integrated electromyogram (IEMG). The latter measures spontaneous activity of the abdominal muscles, which depends upon the afferent input to the CNS, the efferent motor nerve transmission to the muscle, neuromuscular transmission, and normal electrical and mechanical muscular function. The IEMG is thus affected by general anesthetics, local anesthetics, neuromuscular blockers, surgical stimulation, and
hyperventilation. Simultaneous monitoring of both twitch response and IEMG was found to be valuable in research studies, but technical difficulties associated with the latter preclude its routine clinical use.

VII. Correlation of Evoked Responses with Clinical Observations

Although the desired clinical effect of neuromuscular blocking drugs is "relaxation," most clinical studies quantitate this result in terms of twitch suppression, train-of-four value, and per cent tetanic fade. These evoked responses permit precise quantification of depth and duration of neuromuscular blockade and facilitate comparison of various drugs. Certain well-recognized stages of clinical relaxation occur within reasonably well-defined limits of the evoked responses. Figures 2, 8 and 10 attempt to summarize these data, to allow the clinician not accustomed to twitch and train-of-four values to interpret the data within his own frame of reference.

At 95 per cent or more twitch suppression, jaw and laryngeal paralysis is sufficient for reasonably smooth laryngoscopy and endotracheal intubation. Ninety per cent block provides excellent abдомinal relaxation with nitrous oxide-narcotic anesthesia. When potent anesthetic vapors are employed, 75 per cent twitch depression results in similar surgical relaxation. The abdominal musculature generally feels "tight" at 25 per cent or greater twitch height, but the head cannot usually be lifted until the twitch height is at least 90 per cent of control (Kavarese JJ, Ali HH, unpublished observation).

The clinical use of a nerve stimulator can provide confirmation of the adequacy of relaxation without the actual recording of thumb twitch. Observation of finger movements in response to twitch stimulation during graded administration of relaxants permits titration of dosage until the twitch is barely visible. This easily observed end-point corresponds to 95-98 per cent measured twitch depression at 0.1-0.2 Hz. Lee has correlated the disappearance of the fourth, third, and second responses in train-of-four stimulation with single twitch heights of 25, 20 and 10 per cent of control (see train-of-four stimulation, section V), thus allowing visual estimation of deep levels of neuromuscular block.

When recovery from neuromuscular blockade is to be evaluated clinically, adequacy of ventilation and muscular strength are the important criteria. Again, the evoked responses define precisely the level of neuromuscular function necessary to perform the clinical tests satisfactorily in the absence of patient cooperation. The return of the evoked responses to these levels assures normal grip strength, sustained head lift for at least 5 seconds, tongue protrusion, upper eyelid tone, jaw tone, and other clinical criteria.

VIII. Anatomy of the Neuromuscular Junction and Physiology of Neuromuscular Transmission

A. Anatomy

The myoneural junction consists of two structures: the motor nerve terminal and the motor end-plate region of the skeletal muscle membrane (fig. 11). These structures are separated by a gap, the synaptic cleft, which is filled with extracellular fluid. The motor nerve terminal is nonmyelinated, and certain subcellular structures involved in energy production (mitochondria), protein synthesis, and acetylcholine synthesis and storage (endoplasmic reticulum and synaptic vesicles), and calcium binding and storage are prominent in the terminal axoplasm. The motor end-plate is a uniquely cholinergic, highly folded area of muscle membrane located opposite the motor nerve terminal. The surrounding sarcoplasm is also richly invested with mitochondria and calcium-binding and storage sites. A number of reviews may be consulted for further anatomic details.

Several important subsites are located at the motor nerve terminal and the motor end-plate. These include the cholinergic receptor, the enzymes acetylcholinesterase and plasma cholinesterase, and an acetylcholine-
sensitive area at the motor nerve terminal. These specialized sites interact with and modify the action of acetylcholine, the normal neuromuscular transmitter. They are called cholinceptive sites. Their locations are shown in figure 11.

**B. Synthesis, Storage and Release of Acetylcholine**

Acetylcholine (ACh) is synthesized within the motor nerve following acetylation of choline by the enzyme choline acetyltrans-
Fig. 11. Schematic representation of the neuromuscular junction. The locations of important acetylcholine-binding sites (cholinoreceptive sites) are shown in italics.

Acetylcholinesterase and Ach receptors

Acetylcholinesterase

Motor nerve terminal membrane

Endoplasmic Reticulum

Motor end plate membrane

Transverse tubules and calcium binding sites

Mitochondria

Choline acetylase

Acetylcholine-bearing vesicles

Myotubules

Myofibrils

Muscle membrane

Nerve Axon

Myelin Sheath

= Plasma Cholinesterase (in Synaptic Cleft)

fenase (choline acetylase) and acetylcholinesterase A. The synthesized acetylcholine is transferred to and stored in synaptic vesicles to be released from the latter into the synaptic cleft in uniform amounts called “quanta.” In the absence of stimulation, the end-plate region of the muscle fiber displays spontaneous electrical activity in the form of discrete, randomly occurring “miniature” end-plate potentials (mepps). Each mepp is of the order of 0.5–1.5 mV in amplitude, but in other respects resembles the much larger end-plate potential evoked by the nerve impulse. Each mepp probably arises from the impact upon the motor end-plate of a single quantum of ACh spontaneously discharged by the adjacent nerve terminal. At least one thousand molecules of ACh are contained within an elementary packet or quantum, possibly more \([4–5 \times 10^4] \text{ or } (10^5)\). The normal end-plate potential is made up of a statistical fusion of quantal components, identical to the spontaneously occurring units (mepps). The nerve impulse in effect facilitates or, in statistical terms, raises the probability of events that occur all the time at a low rate, and instead of an average of one packet per second, a few hundred packets, or quanta of acetylcholine, are released within a millisecond. Calcium ions must be present in the extracellular medium for effective depolarization. Katz and Miledi have concluded that calcium is the only immediate ionic requirement for depolarization to evoke acetylcholine release.
Depolarization opens specific calcium gates in the terminal axon membrane and leads to an influx of calcium ions.\textsuperscript{8} Having reached the internal surface of the axon membrane, calcium ions then initiate the quantal release reaction. Katz\textsuperscript{94} has postulated that the quanta of ACh molecules are enclosed within synaptic vesicles that undergo frequent transient collisions with the axon membrane. Calcium ions bring about attachment and local fusion between vesicular and axonal membranes, followed by an all-or-none discharge of the vesicular content into the synaptic cleft.

The changes in end-plate potential amplitude that occur when stimulus frequency is altered can best be understood by reference to a simple model of ACh release. Birks and McIntosh\textsuperscript{85} have characterized their findings from ganglion perfusion experiments in terms of a model of presynaptic storage and release of ACh. Eliqvi\textsuperscript{96} and Quastel\textsuperscript{97} have adapted this model to interpret their results obtained from human intercostal muscles. This model is described below in simplified fashion to illustrate the results obtained from twitch tension or electromyographic measurements.

The presynaptic store of ACh consists of two fractions:

1. A small part of the total ACh store that is immediately available for release (i.e., the immediately available store, or IAS).
2. A very large store from which ACh cannot be directly released. Part of this fraction is more readily mobilizable than the rest in order to replenish the IAS. The fractional rate of mobilization from this was found to be 1.4 per cent/sec.\textsuperscript{94} The rest is the non-readily-releasable fraction, which consists of ACh not already in the form of quanta. This part of the presynaptic store represents a reservoir of transmitter from which quanta can be formed.

The immediately available store (IAS) consists normally of about 300–1,000 quanta,\textsuperscript{94} presumably packeted as such. If the immediately available store consists of N quanta (fig. 12), each with a probability of release (p), then the acetylcholine released in response to a nerve action potential will be

\[ M = N \times p \]

where M is the mean quantal content of the end-plate potential (epp) or the number of ACh quanta released by a single nerve impulse. M can be calculated from the amplitude of the epp and the quantum size (mqpp). The probability factor (p) can be considered to be the proportion of the IAS actually released by a nerve action potential. Thus, the number of quanta released by an impulse is governed by the amount of ACh in the store and the probability of release of each quantum from this store. The effects of calcium, magnesium, and posttetanic potentiation appear to influence mainly the probability of quantal liberation. The amplitude of the epp is approximately proportional to the mean quantal content. The amount of ACh released by a subsequent nerve impulse is dependent on three factors:

a. transmitter depletion
b. transmitter mobilization
c. transmitter facilitation

a. Transmitter Depletion

In response to the first nerve action potential (NAP), the release of the mean quantal content (M) will reduce the IAS by this amount of ACh released into the synaptic cleft. In the absence of changes in p or mobilization of ACh from the readily releasable store into the IAS, a second NAP would release a smaller amount of ACh with a subsequent progressive rundown of ACh released by the succeeding NAP's. Figure 13\textsuperscript{a} illustrates this with typical figures.
obtained from the rat phrenic nerve-diaphragm preparation (Redfern and Roberts, personal communication). This depletion is immediate and cumulative.

b. Transmitter Mobilization

Depletion of the IAS results in the transfer of Ach quanta from the mobilization store to the IAS. This process is time-dependent, and during stimulation at 10 Hz or less, Ach mobilization does not balance Ach release until the fourth or fifth NAP (fig. 13b).

c. Transmitter Facilitation

Following a single nerve impulse, there is a transient increase in p. Facilitation of the second response occurs at short intervals, but simple facilitation disappears after 300–400 msec. At this time transmitter depletion by the first stimulus is revealed. However, during tetanic stimulation, two opposing processes influence the fractional release of Ach by a single nerve impulse. One is the increased synthesis and mobilization and hence the increase in fractional release of Ach. The extent and duration of this increase are limited by the second process, namely, the progressive depletion of the IAS. The net result is a progressive decline in the mean quantal content (M) or the amplitude of the epp (i.e., the early tetanic rundown of the epp's). The increased fractional release of Ach is maintained for a time after discontinuation of tetanus and is responsible for the phenomenon of posttetanic facilitation. Thus, the amount of Ach released from the nerve ending in response to a NAP is conditioned by the previous NAP and is determined by the above-mentioned three factors (i.e., transmitter depletion, mobilization, and facilitation).

In practice, the epp amplitudes of a train of stimuli at rates between 0.1 Hz and 10 Hz decrease only during the first four or five epp's and change little thereafter. By stimulation of a nerve four times at 2 Hz and repetition of this pattern not more than once every 10 seconds, depletion uncomplicated by facilitation can be revealed (train-of-four stimulation).

The relationship between epp amplitude and the mechanical or electrical twitch response is indirect. Since the response of an individual muscle fiber is all-or-none, epp's greater than threshold will result in normal fiber contraction, whereas a subthreshold epp will cause no contraction.

Attempts to relate the changes in epp amplitude to the resultant changes in the evoked twitch or EMG measurements indicate that the fourth or fifth epp in a short train (or the late epp's in a tetanus) are always smaller.
than the first. This is illustrated diagrammatically in figure 14. In the absence of post-junctional block all epp's are above threshold and there is no rundown or fade in the evoked response. Following progressive reduction in post-junctional sensitivity to ACh by a non-polarizing neuromuscular blocker, the epp amplitudes are reduced but maintain the same relationship, namely, the fourth epp will be smaller than the first in a short train; similarly, the late epp's in a tetanus will be decreased in amplitude with respect to the first. This results in the selective reduction in the fourth twitch response in a train-of-four stimuli and in the late responses in a tetanus. As post-junctional block increases, there is a progressive reduction of all responses, until the epp response to the fourth stimulus becomes sub-threshold, whereupon the fourth evoked twitch disappears. Finally, all epp's become subthreshold, and there is no detectable response to nerve stimulation, whether it be train-of-four stimulation or tetanic stimulation at various frequencies.

IX. Pharmacology of Neuromuscular Blockade

The depolarization process at the motor end-plate is presumably initiated by the binding of ACh to the cholinergic receptor at a specialized locus on the end-plate membrane. Details about the cholinergic receptor and its relationship to acetylcholinesterase may be found elsewhere.125–129

Neuromuscular blocking drugs also bind to

![Diagram showing the relation between end-plate potential (epp) amplitude and the size of the evoked twitch response to train-of-four stimulation (2 Hz for 2 seconds). A, in the non-narcotized situation, the population of epp amplitudes probably varies in a normal distribution. The two curves represent the normal distribution of epp's of the first and fourth responses. The fourth epp's are shifted to the left or smaller in amplitude than the first epp's. The evoked muscle twitches are equal and maximal in height (right), representing 100% transmission since all epp's are above threshold. B through E, epp amplitudes are reduced progressively by decreased sensitivity to acetylcholine, as in the presence of increasing dosage of a non-depolarizing neuromuscular blocking drug. An increasing number of epp's therefore becomes sub-threshold (shaded areas), reducing the number of fibers responding and consequently the evoked twitch height (right). F, all epp's are below threshold, and no twitch is detected.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931517/)
the cholinergic receptor and in so doing interfere with the physiologic function of ACh. Whether neuromuscular blockers depolarize the end-plate or inhibit its depolarization depends on a variety of factors\textsuperscript{7,29,106,111} that relate the structure of the drugs to ACh (fig. 15). Neuromuscular blocking drugs therefore mimic or inhibit the effect of ACh at the motor end-plate. The nondepolarizing drugs prevent depolarization, whereas the depolarizing drugs prevent repolarization, i.e., maintain the end-plate in a depolarized state, refractory to the action of ACh.\textsuperscript{112}

Normal function of the neuromuscular synapse depends ultimately upon the availability and release of adequate quantities of ACh from the motor nerve terminal and on appropriate sensitivity of the motor end-plate to ACh. Although evidence suggests that some neuromuscular blockers inhibit ACh synthesis\textsuperscript{112} and release,\textsuperscript{113,115} the majority would agree that any such component is not very important in defining their action.\textsuperscript{103,104,105} In fact, the quantity of ACh released in the normal situation is far greater than necessary for normal muscular contraction,\textsuperscript{12} thereby providing a wide "margin of safety."\textsuperscript{2,117-119} of neuromuscular transmission.

X. Physiologic and Pharmacologic Factors that May Alter Neuromuscular Function or the Normal Response to Neuromuscular Blocking Drugs

Knowledge of the interaction between muscle relaxants, drugs, and disease permits dosage adjustment. Anticipation of abnormal circumstances surrounding the use of neuromuscular blockers is an important aspect of the monitoring of neuromuscular function. In some cases, such as in the interaction of relaxants with general anesthetic agents, precise quantification of modifying factors is possible because the subject can be and has been carefully studied. More often, however, clinical information is relatively scant, and is based on isolated case reports or extrapolated from basic scientific studies. In these cases precise evaluation of the effects of neuromuscular blockers in the individual patient requires the use of a nerve stimulator.

A. General Anesthetic Agents

The augmentation of the action of nondepolarizing neuromuscular blockers by potent inhalation anesthetics has been recognized for many years, but only recently have the studies of Miller and associates\textsuperscript{26,129} quantified the relationship. Such information is particularly valuable in estimating relaxant dosage.

Not only does the potentiation of relaxants vary with equipotent doses of different inhalation agents, but the degree of potentiation
also depends on anesthetic depth (MAC value). The management of relaxation for a given surgical procedure may therefore be satisfactorily achieved with a minimum of inhalation anesthetic and large doses of relaxant or with deep inhalation anesthesia and small doses of neuromuscular blockers, or any technique between these extremes.

General anesthetic vapors produce a parallel shift of the relaxant dose-response curve to the left. The relationship is summarized in figure 16, which shows the action of d-tubocurarine during administration of nitrous oxide (balanced anesthesia), halothane, isoflurane, and enflurane. The volatile anesthetics were given at equipotent dosages (1.25 MAC). Such curves are useful as a guideline to relaxant dosage in the “typical” patient under given anesthetic conditions. Most patients will fall within a relatively narrow range of relaxant requirements, but the number of exceptions is large enough to make a fixed dosage schedule imprudent. It is best to use the guidelines given in figure 16 as the background for an approximate scheme, using the techniques of clinical monitoring suggested elsewhere in this review for “fine tuning.”

According to figure 16, approximately 0.3 mg/kg d-tubocurarine will produce 95 percent twitch inhibition during nitrous oxide anesthesia. This degree of block is consistent with good surgical relaxation (fig. 10). Twice this dose (0.6 mg/kg) results in the profound relaxation required for smooth intubation of the trachea under similar anesthetic conditions. Halothane (fig. 16) shifts the d-tubocurarine dose-response curve leftward from the nitrous oxide curve by a factor of approximately 0.5. In other words, the average patient requires only half as much d-tubocurarine with 1.25 MAC halothane as he might with a nitrous oxide-narcotic technique. Isoflurane and enflurane at 1.25 MAC further shift the curve to the left, such that the same patient requires only approximately 30 percent as much d-tubocurarine as he might with nitrous oxide, or about half the requirement with halothane. A similar relationship exists for pancuronium, and probably for other nondepolarizing drugs.

Desensitization of the motor end-plate at a site beyond the cholinergic receptor is generally accepted as the mechanism of anesthetic potentiation of the effects of nondepolarizing relaxants. Other factors such as alteration of muscle blood flow are also important. This is especially true with enflurane and isoflurane, and probably explains the potentiation of succinylcholine during enflurane anesthesia, found in the only study in which augmentation of depolarizing block by general anesthetics in the human subject has been documented.

The effect of inhalation anesthetics on the duration of nondepolarizing block has not been quantitated. For example, does a given degree of neuromuscular block achieved during administration of halothane dissipate within the same time span as the same degree of block (achieved at twice the relaxant dose)

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during nitrous oxide anesthesia? We suggest that this may be so, i.e., the general patterns of neuromuscular blockade are the same with different anesthetics, when the relaxant dosages are properly adjusted to produce similar degrees of block in all cases. This concept is suggested in the work of Katz with pancuronium. Further documentation is required, however, before this concept may be entirely accepted.

B. Electrolyte Imbalance

Abnormal electrolyte concentrations may interfere with neuromuscular transmission and alter the typical response to neuromuscular blocking drugs. Although there is ample laboratory confirmation of this effect,\cite{127-131} controlled clinical studies are lacking, and there are few instances where clinically significant changes in neuromuscular function have been documented.\cite{131,132}

The membranes of conducting tissues maintain a negative electrical potential within the cell. The generation of action potentials within nerve and muscle follows the development of increased membrane permeability to sodium and potassium.\cite{127,132} Neuromuscular function thus depends directly on the maintenance of the proper intracellular-to-extracellular ratios of these and other ions.\cite{126,129-132}

Reductions in normal extracellular fluid concentrations of sodium and potassium may prevent the development of adequate current (ionic) flow across nerve and muscle membranes, thus weakening normal neuromuscular function. In such a clinical situation, increased sensitivity to nondepolarizing relaxants theoretically may be anticipated.\cite{127,129,132}

An increased extracellular potassium level, on the other hand, partially depolarizes the cell membrane, i.e., reduces the resting membrane potential, and therefore theoretically sensitizes the individual to depolarizing agents, while the actions of nondepolarizing agents are opposed.\cite{129,132}

The size of the motor end-plate potential is governed by the quantity of acetylcholine released from the motor nerve terminal by the action potential.\cite{111} Calcium and magnesium ion concentrations directly affect acetylcholine release, increases in the former promoting, and in the latter inhibiting, transmitter output by the motor nerve terminal.\cite{128,129} Decreases in the extracellular contents of these ions have the opposite effects. The proper calcium ion content within skeletal muscle assures normal excitation-contraction coupling.\cite{133}

Since end-plate potential size must reach threshold before the propagation of depolarization to the muscle fiber may occur, it follows that clinical conditions producing hypocalemia or hypermagnesemia may reduce acetylcholine output, inhibit neuromuscular transmission (table 2) and accentuate the action of neuromuscular blocking drugs.\cite{125,129,130,134}

C. pH Changes

Although considerable disagreement exists, much has been written concerning the effects of respiratory and metabolic acidosis or alkalosis upon the actions of various relaxants, especially d-tubocurarine.\cite{122,130,140,146-152}

Everett et al.\cite{127} have shown that the curare molecule is a monoquaternary substance, the second nitrogen atom being a tertiary amine. Kalow,\cite{126} has shown that the $pK_a$ of $d$-tubocurarine is 8.6. This was attributed to the dissociation of the two phenolic hydroxyl groups in the molecule, but in fact the tertiary amine may have been the principal structural titrated. Acidification would favor protonation of the tertiary amine, and shift the equilibrium in favor of the diquaternary form, which has greater potency than the monoquaternary. Reports of antagonism of $d$-tubocurarine block by alkalosis,\cite{125,140,126,152} and of "neostigmine-resistant" curarization in acidic states\cite{141,146} therefore become chemically understandable.

Miller et al.\cite{119} have shown that antagonism of $d$-tubocurarine by neostigmine is less effective during metabolic alkalosis and respiratory acidosis. They suggest that these acid-base states may result in hypokalemia and intracellular acidosis, respectively. Both conditions are compatible with potentiation of $d$-tubocurarine and hence decreased effectiveness of its antagonism by neostigmine. Hypokalemia, as indicated in the previous discussion of electrolyte imbalance, may increase the apparent effectiveness of any nondepolarizing neuromuscular blocking drug.\cite{127,129,130,134,140}

The effects of pH changes on the actions
of relaxants other than d-tubocurarine are scantily documented. As suggested by several investigators, \textsuperscript{105,106,121,122} pH II probably plays a less significant and less consistent role in modifying the actions of other nondepolarizing relaxants, unless severe metabolic alkalosis produces hypokalemia.\textsuperscript{110}

The determination of serum electrolyte and pH II values should be considered in the diagnostic work-up of any neuromuscular disorder or atypical response to neuromuscular blocking drugs.

D. Hypothermia

There are conflicting reports regarding the effect of hypothermia on the response to neuromuscular blocking drugs. One opinion\textsuperscript{103-104} maintains that hypothermia (27°C) decreases the response to d-tubocurarine. At 26°C and lower temperatures \textit{(in vitro)} the action of d-tubocurarine is potentiated.\textsuperscript{126} Recently, Foldes et al.\textsuperscript{5} have found that decreasing ambient temperature from 37 to 27°C causes statistically significant increases in the intensities of neuromuscular blockades by d-tubocurarine, pancuronium, succinylcholine, and decamethonium. Similarly, the intensities of the blocks decreased as the temperature was increased from 27 to 37°C (isolated phrenic nerve-diaphragm preparation). This was confirmed in the intact cat by Miller et al.,\textsuperscript{105} who attributed the greater intensity of block at low temperatures to the possible retardation of metabolism and renal excretion of the drugs. McKieen et al.\textsuperscript{105} were unable to confirm the belief that the antagonism of d-tubocurarine-induced neuromuscular blockade with neostigmine during hypothermia may dissipate upon rewarming.

It is evident that the response to relaxants may be altered by changes in temperature. Furthermore, erroneous conclusions may be reached if the evoked responses obtained in a hypothermic peripheral muscle are used to indicate the state of neuromuscular function of the rest of the body.


E. Hepatic and Renal Disease

With the exception of succinylcholine, all relaxants are excreted almost entirely by the kidney.\textsuperscript{109} The hydrophilic nature of the relaxant molecule promotes excretion by glomerular filtration. There is no tubular reabsorption. Consequently, excretion is proportional to the glomerular filtration rate, and will be diminished according to the severity of renal parenchymal dysfunction. This is qualitatively easy to understand, but the only controlled clinical study that provides some quantification of this principle is that of Miller et al.,\textsuperscript{105} with pancuronium. These investigators showed that the duration of pancuronium block in anephric patients was prolonged about 50 per cent. In a similar but not as well-controlled study, Churchill-Davidson, Way and de Jong\textsuperscript{106} administered d-tubocurarine, 0.4–1.0 mg/kg to six anephric patients. No unusually prolonged response to d-tubocurarine was seen, reversal was easily accomplished with neostigmine, and no "recantrization" occurred. The same investigators, on the other hand, found unsatisfactory reversal and prolonged paralysis in three of five anephric patients who had received gallamine, 2–6 mg/kg. There have been numerous reports of the prolonged effect of gallamine in patients with renal failure.\textsuperscript{109–111}

The only neuromuscular blocker other than succinylcholine that is metabolized in the liver is pancuronium; about 15 per cent of an injected dose of this drug undergoes deacetylation and biliary excretion in the human liver.\textsuperscript{112} Two other nondepolarizers, d-tubocurarine\textsuperscript{113} and aconitum,\textsuperscript{114} may be excreted unchanged in the bile. This alternative hepatic route for the handling of d-tubocurarine and pancuronium is the probable reason why these drugs may be safely employed in anephric patients.\textsuperscript{107,108} Ordinary doses, however, may lead to relative overdosage, persistent curarization,\textsuperscript{112} and inadequate reversal. In consideration of the above evidence, the dosages of pancuronium and d-tubocurarine should be reduced approximately 50 per cent for anephric individuals. Gallamine and dimethyl tubocurarine should not be given to the anephric patient.

The minor role of the liver in the handling of relaxants indicates that severe hepatic dys-
<table>
<thead>
<tr>
<th>Disease</th>
<th>Type of Relaxant Interaction and Clinical Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myasthenia gravis</td>
<td>1) Resistance to depolarizing drugs. Rapid development of phase II block. (This is the basis for using decamethonium as a test for myasthenia.</td>
</tr>
<tr>
<td>Myasthenic syndrome (Eaton-Lambert syndrome)</td>
<td>1) Marked sensitivity to nondepolarizing relaxants. The block is not readily reversed with neostigmine. In contrast to myasthenia gravis, the response to fast rates of stimulation is a progressive increase in twitch amplitude to as much as six times the initial height.</td>
</tr>
<tr>
<td>Thyrtoxic myopathy</td>
<td>1) Decreased response to succinylcholine (pseudocholinesterase levels are at the upper limit of normal). There is an increase in the level of pseudocholinesterase in hyperthyroidism.</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis and other</td>
<td>1) Defective neuromuscular transmission and nerve conduction.</td>
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<td>diseases in which the lower motor neuron is</td>
<td></td>
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<tr>
<td>involved, such as syringomyelia and poliomyelitis</td>
<td></td>
</tr>
<tr>
<td>Von Recklinghausen’s disease (multiple</td>
<td>The response is variable. Some subjects show prolonged responses to both nondepolarizing and depolarizing relaxants.</td>
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<tr>
<td>muscular dystrophy)</td>
<td></td>
</tr>
<tr>
<td>Myotonic syndrome</td>
<td>Generalized muscle spasm (myotonic response) occurs after depolarizing agents. d-Tubocurarine does not terminate the myotonic state.</td>
</tr>
<tr>
<td>a) Myotonia dystrophica</td>
<td></td>
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<tr>
<td>b) Myotonia congenita</td>
<td></td>
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<tr>
<td>c) Paranytonia</td>
<td></td>
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<tr>
<td>Other genetically determined myopathies:</td>
<td>The response to relaxants is unpredictable, and their use is better avoided.</td>
</tr>
<tr>
<td>Muscular dystrophy</td>
<td></td>
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<tr>
<td>Obstructive congenital myopathies</td>
<td></td>
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<tr>
<td>Familial periodic paralysis</td>
<td></td>
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<tr>
<td>Other types of myopathy:</td>
<td>Unpredictable response to relaxants.</td>
</tr>
<tr>
<td>Steroid</td>
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<td>Myxedema</td>
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<td>Alcoholic</td>
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<td>Diabetic</td>
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<tr>
<td>Polymyositis</td>
<td>The muscle weakness and fatigability respond to neostigmine, hence the term &quot;myasthenic state.&quot;</td>
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<tr>
<td>Dermatomyositis</td>
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<td>Systemic lupus erythematosus</td>
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<tr>
<td>Polymyositis nodosa</td>
<td></td>
</tr>
<tr>
<td>Hypokalemia, e.g., from excessive loss</td>
<td>Theoretically increased sensitivity to nondepolarizing relaxants.</td>
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<tr>
<td>of potassium from bowel or kidney</td>
<td></td>
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### Table 1 (Continued)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Type of Relevant Interaction and Clinical Implication</th>
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<tbody>
<tr>
<td>Hyperkalemia, e.g., from an efflux of intracellular potassium with rapid increase in serum potassium in disorders of muscles that are subjected to depolarizing drugs. This can occur in the following disease states: 1) Traumatized patients; 2) Burned patients; 3) Muscle-wasting disease: Lower motor-neuron lesions with hemiplegia; Muscular dystrophy; Denervation and spinal-cord transection; Multiple sclerosis; Tetanus; Denervation.</td>
<td>The dangerous effect of hyperkalemia on the heart is well recognized. Ventricular arrhythmias, ventricular fibrillation and cardiac arrest have been reported. Theoretically increased sensitivity to depolarizing relaxants and decreased sensitivity to nondepolarizing relaxants. No significant rise of serum potassium within a few hours of gross trauma.</td>
</tr>
<tr>
<td>Primary muscle disease or myopathy</td>
<td>High incidence of malignant hyperpyrexia in these patients and susceptible relatives. Usually the myopathy is mild or subclinical. Spiirost, hernias and minor orthopedic problems are often found in affected families. It has been shown that malignant hyperpyrexia muscle is more sensitive to caffeine-induced rigor than normal muscle.</td>
</tr>
</tbody>
</table>

Function alone does not necessitate any important modification of their use, except in the case of succinylcholine (see section on plasma cholinesterase). Dundee and Gray, however, have reported resistance to d-tubocurarine in the presence of hepatic disease. Reversed albumin/globulin ratios in these patients, causing increased binding of d-tubocurarine to plasma globulin, may be the reason for this finding.

The safe use of relaxants in management of patients who have hepatic and renal disease therefore depends, first, upon a knowledge of the modification of the actions of these drugs by these disorders, and second, more importantly, upon the proper evaluation of their effects in the individual patient by the use of a nerve stimulator. This type of monitoring is mandatory when relaxants are to be used in anephric patients.

**F. Enzymatic Abnormalities**

**A. Plasma Cholinesterase**

The short duration of action of succinylcholine is due to the hydrolysis of the drug by this enzyme, which is synthesized in the liver. There is wide variation in the time-responses to succinylcholine in normal patients due to considerable differences in plasma cholinesterase activity.

A prolonged response to succinylcholine may be expected in individuals whose plasma cholinesterase activity is abnormally low due to congenital factors, e.g., atypical enzyme, or acquired factors, e.g., hepatic disease and drugs that inhibit the enzyme. For reviews, see Pantuck and Pantuck, Pantuck, Whitaker and Vickers, and Kalow. A list of compounds that inhibit plasma cholinesterase is included in table 2.

Unfortunately, a prolonged response to succinylcholine usually occurs unexpectedly. The extended period of paralysis requiring mechanical ventilation for one to several hours places the patient in an uncomfortable and dangerous position. This may be an embarrassing and inconvenient task for the anesthesiologist. Although determination of the dibucaine number and plasma cholinesterase activity of every patient who is to receive
<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Interaction</th>
<th>Clinical Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnesium</td>
<td>Blocks the release of acetylcholine at the neuromuscular junction as well as accelerates the action of true cholinesterase.</td>
<td>Potentiates the action of all relaxants when used in large amounts (e.g., eclampsia). This effect is reversed by calcium ions.</td>
</tr>
<tr>
<td>Procaine and other local anesthetics</td>
<td>Inhibit the release of acetylcholine.</td>
<td>Potentiates nondepolarizing drugs and prolong the action of succinylcholine.</td>
</tr>
<tr>
<td>Pitocin (Syntocinon)</td>
<td>Prolonged infusion alters the sensitivity of the endplate to depolarization by succinylcholine.</td>
<td>The duration of action of succinylcholine is prolonged and increased dosage may be needed. This has not been confirmed.</td>
</tr>
<tr>
<td>Ganglion-blocking drugs</td>
<td>Compete with acetylcholine at the neuromuscular junction.</td>
<td>Potentiates nondepolarizers and antagonize depolarizers. Triethylmethaphan may potentiate succinylcholine.</td>
</tr>
<tr>
<td>Pentamethonium</td>
<td></td>
<td></td>
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<tr>
<td>Hexamethonium</td>
<td></td>
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</tr>
<tr>
<td>Trimethaphan (Arfonad)</td>
<td></td>
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<tr>
<td>Cytotoxic drugs (alkylating agents)</td>
<td>Inhibition of plasma cholinesterase by alkylating the enzyme.</td>
<td>Prolong succinylcholine action.</td>
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<tr>
<td>Nitrogen mustard and related drugs, e.g., mechlorothamine</td>
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<tr>
<td>Cyclophosphamide</td>
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<tr>
<td>Triethylmelamine</td>
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<td></td>
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<tr>
<td>Chlorambucil AB132</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetrahydroaminicaine (Tailer)</td>
<td>Inhibition of plasma cholinesterase.</td>
<td></td>
</tr>
<tr>
<td>Hexafluoridene (Mylanen)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics (streptomycin, Neomycin, polymyxin, Colimycin, kanamyacin)</td>
<td>Reduce acetylcholine output by competing with calcium at presynaptic membrane binding sites (a &quot;magnesium-like effect&quot;).</td>
<td>Increased sensitivity to curare-like drugs.</td>
</tr>
<tr>
<td>Diuretics (acetazolamide, chlorthalidone, frusemide, ethacrynic acid)</td>
<td>Potassium loss.</td>
<td>Hypokalemia may theoretically potentiate nondepolarizing block.</td>
</tr>
</tbody>
</table>

sucinylcholine has been advocated, this task is too expensive for practical purposes. The anesthesiologist is nevertheless faced with the problem of anticipating which individual may develop an inappropriately prolonged response to an ordinary (0.5-1.0 mg/kg) dose of succinylcholine. History and physical examination provide the first indication (hepatitis disease preventing synthesis of plasma cholinesterase, concomitant reaction of drugs [see table 2] that may inhibit the enzyme, or family or personal history of prolonged mechanical ventilation after surgery).

The second clue may be found in a simple clinical test. A dose of 0.05-0.1 mg/kg succinylcholine may be given to the already-anesthetized spontaneously breathing patient in whom a prolonged response to succinylcholine is suspected on the basis of history, or for that matter, to any patient in whom such a problem is to be avoided, such as the out-patient undergoing minor surgery. Apnea does not occur in normal patients after such doses, and respiratory depression, if any, dissipates within 2-3 minutes. The occurrence of profound paralysis or apnea lasting more than 5 minutes in this situation suggests the presence of one of the above-mentioned congenital or acquired disorders of plasma cholinesterase. Further immediate diagnostic aid is achieved by the use of a nerve stimulator. The above-described test should virtually abolish the evoked twitch in a patient who has a plasma cholinesterase abnormality, but not in a normal individual. The diagnosis may later be confirmed by the dibucaine test or another measurement of plasma cholinesterase activity and genotype.

B. Creatine Phosphokinase (CPK), Aldolase, Lactic Dehydrogenase (LDH)

Predisposition to the development of malignant hyperthermia is familial, the abnormality being inherited as a mendelian autosomal dominant trait. A priori identification of individuals potentially susceptible to this disastrous complication is mandatory, since this syndrome is fatal in an estimated 66 per cent of affected patients. Elevated serum concentrations of several skeletal-muscle enzymes have been found in families and individuals carrying the malignant hyperthermic trait. These include creatine phosphokinase (CPK), aldolase, serum glutamic-oxaloacetic transaminase (SGOT), hydroxybutyric dehydrogenase (HBDH), and lactic dehydrogenase (LDH).

The most important for identification of individuals potentially susceptible to the hyperthermic syndrome is CPK, since nearly all of this enzyme is found in skeletal muscle, whereas the others listed above may be obtained from other organs, such as liver, lungs, kidney, and brain.

CPK determination is therefore an important aspect in the total evaluation of neuromuscular function relative to anesthesia. The discovery of a high serum CPK in a patient showing a positive family history of malignant hyperthermia, muscle or musculoskeletal disease, or unexplained death under anesthesia should prompt the adoption of a variety of potentially life-saving precautions if the patient is to undergo anesthesia.

C. Neuromuscular Diseases

Diseases affecting the neuromuscular system are not uncommon. In addition, muscle weakness is a feature of many illnesses. Possible interactions of some of these disease states with neuromuscular blocking drugs are summarized in table 1. The necessity of monitoring neuromuscular function under these circumstances, where the customary use of and response to relaxants cannot be anticipated, is obvious.

II. Drug Interactions

Many drugs modify the action of muscle relaxants. Such substances may interfere directly with neuromuscular transmission or they may influence the action of relaxants by extrajunctional mechanisms. A brief description of these drugs is presented in table 2. Knowledge of these interactions and the monitoring of neuromuscular function during anesthesia may prevent the occurrence of clinical complications.
XI. Conclusion

Detailed assessment of neuromuscular function must begin preoperatively, extend throughout the conduct of anesthesia, and end postoperatively when the anesthesiologist achieves a satisfactory demonstration of adequate muscular strength from the patient. The anesthesiologist must consider the prior medical history of the patient, including family history and genetic background, the dosage and duration of action of any drugs he may be taking, and their possible interaction with neuromuscular blocking drugs; the presence of neurologic deficits on physical examination; the fluid and electrolyte status; serum enzyme values; and both hepatic and renal function. These considerations only serve to modify the choice and dosage of neuromuscular blocker. The anesthesiologist must, in addition, be familiar with the use of clinical techniques of monitoring of neuromuscular function, as a guide to relaxant dosage and to confirm the adequacy of postoperative recovery.

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