Br. J. Anaesth. (1982), 54, 209

CLINICAL ASSESSMENT OF NEUROMUSCULAR TRANSMISSION

J. VIBY-MOGENSEN

Traditionally, the degree of neuromuscular blockade during and after anaesthesia is evaluated solely on clinical criteria such as muscle tone, the occurrence of spontaneous muscular movements, the "feel" of the anaesthetic reservoir bag, the inspiratory force, and the ability to open the eyes and to raise the head. In the course of time, however, many anaesthetists have put forward convincing arguments for the use of nerve stimulators to assess objectively the neuromuscular function during anaesthesia (Christie and Churchill-Davidson, 1958; Katz, 1970; Ali and Savarese, 1976). Nevertheless, the use of nerve stimulators is still more the exception than the rule in the majority of anaesthetic departments. A very obvious explanation might be that such a practice is actually unnecessary! In other words—and in the words of others—"One manages quite well without it, so why go to the trouble?". But does one manage quite well? And is it so troublesome?

In this article I shall try to answer the following questions: *Why*, *how* and *when* should the neuromuscular function be monitored during anaesthesia?

WHY MONITOR NEUROMUSCULAR FUNCTION?

As already mentioned, a common argument against the use of nerve stimulators is that they are simply unnecessary. I have no doubt that an experienced anaesthetist can evaluate the degree of neuromuscular blockade in a reassuring way without the use of a nerve stimulator, just as he would be able to anaesthetize a cardiac patient in poor condition without an e.c.g., a CVP-catheter or a Swan–Ganz catheter. However, the question is not how little an experienced anaesthetist can manage with, but rather how we can most easily ensure that *all* patients receive optimal treatment.

In a study of the frequency of residual curarization at three Copenhagen University Hospitals (Viby-Mogensen, Chræmmer-Jørgensen and Ørding, 1979) we found that 24% of the patients were unable to sustain head lift for 5 s on arrival at the recovery room, and 42% had a train-of-four ratio of less than 0.7 (a train-of-four ratio normally taken to reflect adequate recovery; Brand et al., 1977). Of the total of 72 patients examined, none had been monitored with a nerve stimulator before or after operation. Thus in the day-to-day work, the clinical evaluation is apparently not always adequate; but what is the explanation of this? Three factors play a decisive role: the great variation in individual sensitivity to myoneural blocking drugs; the margin of safety of the neuromuscular end-plate; and finally the important relationship between the degree of non-depolarizing neuromuscular block and the effect of an anticholinesterase drug (neostigmine, for example).

The individual difference in sensitivity to myoneural blocking drugs holds for both the depolarizing and the non-depolarizing drugs, but apart from the rare genetic defects in plasma cholinesterase, these differences are of greatest practical significance in the case of the non-depolarizing drugs. Thus, Katz (1967) found that, in a group of patients who received an i.v. injection of tubocurarine 0.1 mg kg^{-1}, the twitch height was unaffected in 6% of the patients, while 7% of the patients experienced total relaxation (100% twitch depression)! Varying degrees of neuromuscular blockade were found in the remaining 87% of the patients. Circumstances are further complicated by the fact that the number of receptors in the neuromuscular end-plate by far exceeds the number required to trigger a muscle action potential under normal conditions; a margin of safety exists. Thus, even with normal inspiratory force and vital capacity, sustained head lift for 5 s, etc., 75–80% of all receptors can still be occupied by the neuromuscular blocker (Waud and Waud, 1971; Ali et al., 1975; Miller, 1976).

If the neuromuscular function is monitored it is possible to antagonize a pancuronium-induced

JØRGEN VIBY-MOGENSEN, M.D., Department of Anaesthesia, Herlev Hospital, University of Copenhagen, DK-2730 Herlev, Denmark

0007-0912/82/020209-15 $01.00

neuromuscular blockade in almost all patients by an i.v. injection of neostigmine 2.5 mg (Katz, 1971). On the other hand, if the patient is evaluated on the basis of clinical criteria alone, it may be necessary to give about 40% of the patients more than 2.5 mg of neostigmine for antagonism—and in some of these patients it will still not be possible to produce sufficient reversal (Viby-Mogensen, Chræmmer-Jørgensen and Ørding, 1979). One reason for this is that the clinical effect of neostigmine depends on the degree of neuromuscular block at the time of the injection (Katz, 1971). At a twitch height which is 20% or more of the control twitch height, it is thus normally possible to antagonize the block in the course of 3–14 min. If the twitch height is less than 20%, restitution takes 8–29 min (Katz, 1971). Furthermore, it can be expected that recovery may take longer when reversal of an even more pronounced neuromuscular block is attempted. When the patient is evaluated without a nerve stimulator the actual degree of neuromuscular block in the individual patient at the time of attempted reversal is often a matter of speculation (Viby-Mogensen, Chræmmer-Jørgensen and Ørding, 1979).

Routine use of a nerve stimulator makes it possible to achieve precise individual dosage of both the myoneural blocking drugs and their antagonists. In addition there are specific clinical situations in which nerve stimulators can provide information which is more difficult to obtain or which can not be obtained at all by means of a clinical evaluation. This is the case in the presence of prolonged apnoea after suxamethonium, in the evaluation of deeper degrees of non-depolarizing neuromuscular blockade by using tetanic stimulation (see later), and in the differential diagnosis of respiratory depression after operation. Finally, our experience shows that the nerve stimulator is a valuable help in training and teaching the rational use of myoneural blocking drugs.

PRINCIPLES OF NERVE STIMULATION

Reaction of muscles to nerve stimulation

With intact neuromuscular transmission, electrical stimulation of a motor nerve will result in contraction of those muscles supplied by the nerve. The reaction of the single muscle fibre to a stimulus follows an all-or-nothing law; that is there is maximum contraction of the muscle fibre if the stimulus intensity exceeds a certain threshold. The augmented force of muscle contraction is graded by and is proportional to the number of muscle fibres activated. If the motor nerve is stimulated with sufficient intensity, all the muscle fibres supplied by the nerve will contract. The maximum force of contraction is thereby triggered. If the intensity of the stimulus is increased further the stimulus is described as being *supramaximal*.

Following administration of a myoneural blocking drug, the force of muscle contraction will be reduced. The measured reduction in contraction force at unchanged supramaximal stimulation is an expression of the degree of neuromuscular block.

Clinical types of neuromuscular blockade

In clinical practice it is traditional to consider three different types of neuromuscular blockade.

Non-depolarizing block (induced, for example, by tubocurarine, gallamine and pancuronium), in which the neuromuscular blocker binds to the receptors of the muscle end-plate region. Reversal of this block is achieved with a cholinesterase-inhibiting drug, for example neostigmine.

Depolarizing block (induced, for example, by suxamethonium), in which the neuromuscular end-plate is depolarized by the myoneural blocking drug.

Phase II block (dual block or desensitizing block). This type of block occurs in normal patients when the muscle end-plate has been under the influence of a depolarizing drug over a prolonged period. The original depolarizing block then alters character in the direction of a non-depolarizing block (Churchill-Davidson, Christie and Wise, 1960; Lee, 1975; Ramsey et al., 1980). In patients with genotypically abnormal plasma cholinesterase, a phase II block may be observed following an otherwise normal dose of suxamethonium (Savarese et al., 1975; Viby-Mogensen, 1981a, b).

As will be seen from the following, these three types of neuromuscular block react differently to different types of nerve stimulation.

Clinical methods of nerve stimulation

There are three commonly used types of stimulation:

Single twitch stimulation (fig. 1). Single supramaximal current impulses (often 10–20%

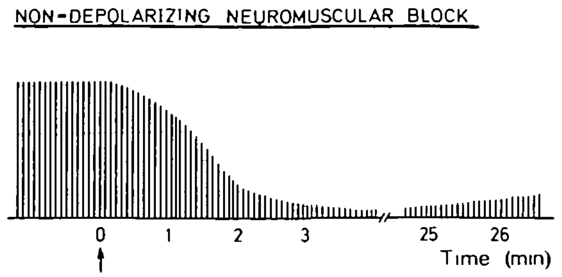

FIG. 1. Diagrammatic illustration of the evoked response to single twitch stimulation following injection of a non-depolarizing (upper panel) and a depolarizing myoneural blocking drug (lower panel). Arrows indicate injection of myoneural blocker.

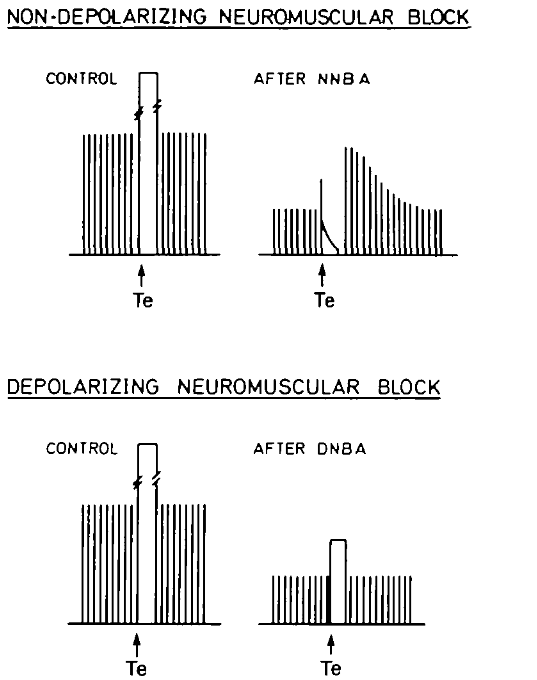

FIG. 2. Diagrammatic illustration of the evoked response to tetanic and post-tetanic twitch stimulation following injection of a non-depolarizing (upper panel) and a depolarizing myoneural blocking drug (lower panel) Te = tetanic stimulation (50 Hz for 5 s); NNBA = non-depolarizing neuromuscular blocking agent, DNBA = depolarizing neuromuscular blocking agent See text for further explanation.

greater than the intensity needed to evoke the maximal response) are applied at greater or smaller intervals (0.1–1.0 Hz). The response to single twitch stimulation depends on the frequency with which the individual stimuli are applied. If the rate of delivery is increased to more than 0.15–0.1 Hz, the evoked response gradually decreases and settles at a lower level (Ali and Savarese, 1977; Lee and Katz, 1980). The impulses should be rectangular or quadratic, with a duration of 0.2 ms or less in order to avoid repetitive nerve firing (Epstein et al., 1969; Epstein and Jackson, 1970).

Tetanic stimulation (fig. 2). The stimuli follow each other at a very rapid rate (e.g. 30, 50 or 100 Hz). In clinical practice today the frequency most commonly used is 50 Hz (for 5 s), because a 50-Hz tetanic stimulation stresses the neuromuscular function to the same extent as does a maximal voluntary effort (Merton, 1954).

At the start of a tetanic stimulation, large amounts of acetylcholine are released from the immediately available stores in the nerve terminal. As these stores become depleted, the rate of acetylcholine release decreases until there is equilibrium between the mobilization and the synthesis of acetylcholine. In spite of this the strength of the mechanical response caused by a tetanic stimulation at for example 50 Hz is maintained in the presence of normal neuromuscular function, because the release of acetylcholine is many times greater than is necessary to evoke a response. There thus exists a wide margin of safety (Paton and Waud, 1967; Gissen and Katz, 1969). When this margin is reduced by a neuromuscular blocker the decrease in the acetylcholine release during tetanic stimulation will result in the development of fade (fig. 2). The degree of fade depends on the extent of the block, on the frequency and duration of the tetanic stimulation, and on how often the latter is applied (Gissen and Katz, 1969; Ali, Utting and Gray, 1970; Stanec et al., 1978).

Tetanic stimulation is often combined with single stimuli, applied both before and after the tetanus. The mobilization and synthesis of acetylcholine remain increased for some time after the tetanic stimulation. This explains the increased post-tetanic twitch response (post-tetanic facilitation (PTF), post-tetanic potentiation) which is observed in non-depolarizing blockade (fig. 2). PTF usually declines in the course of a few minutes, as the release of acetylcholine returns to the pretetanic level.

In mechanical recordings, in contrast to recordings of the summated muscle action potential, it is possible to observe both tetanic fade and PTF in spite of normal neuromuscular function, depending among other factors on the frequency and duration of the tetanic stimulus (Epstein and Epstein, 1973; Stanec et al., 1978). Mechanical measurement of PTF is therefore normally considered to be of little help in detecting slight to moderate neuromuscular blockade.

A disadvantage of tetanic stimulation is the fact that it is painful and therefore not acceptable to an un-anaesthetized patient. Further, under certain conditions tetanic stimulation in itself influences the course of the neuromuscular block in the investigated muscle (decurarizing effect) (Feldman and Tyrrell, 1970).

Train-of-four nerve stimulation (fig. 3). Ali, Utting and Gray (1970, 1971a, b) have suggested that the classic types of stimulation should be replaced by train-of-four (TOF) nerve stimulation. In TOF, stimulation is performed by means of four supramaximal stimuli at intervals of 0.5 s over a period of 2 s (2 Hz). The TOF stimuli are repeated every 10–12 s. The amplitude of the fourth response in relation to the first gives the *train-of-four ratio*.

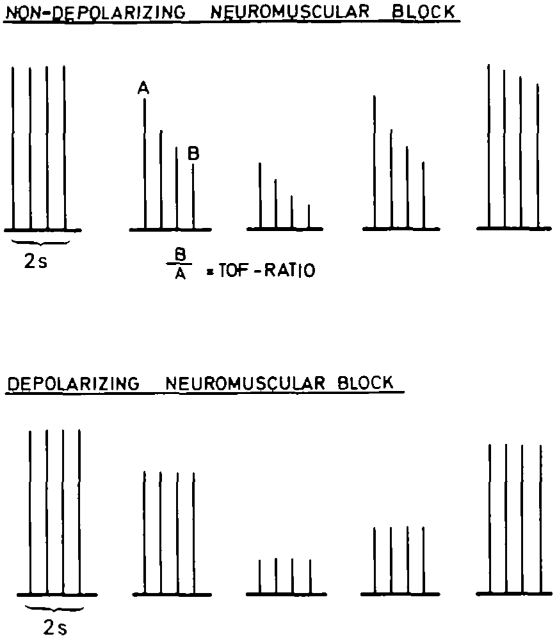

FIG. 3. Diagrammatic illustration of the evoked response to train-of-four (TOF) nerve stimulation following injection of a non-depolarizing (upper curve) and a depolarizing myoneural blocking agent (lower curve). Note "fade" in the TOF response during partial non-depolarizing neuromuscular blockade.

During a non-depolarizing block this ratio is reduced, and within certain limits is inversely proportional to the degree of neuromuscular block (fig. 4). During a depolarizing block, all four

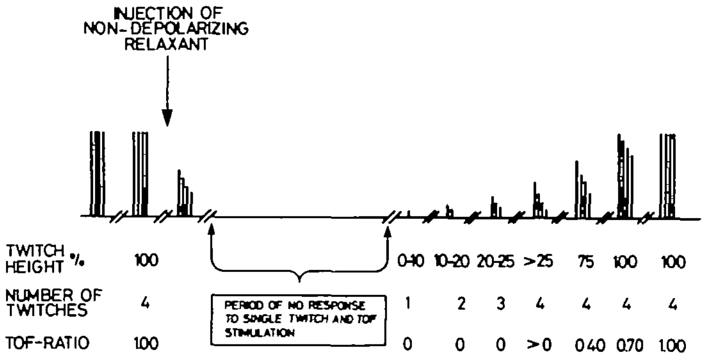

FIG. 4. Diagrammatic illustration of the relationship between the evoked responses to single twitch (0.1 Hz) and train-of-four (TOF) nerve stimulation during a non-depolarizing neuromuscular blockade. This relationship differs during spontaneous and induced recovery (Ali et al., 1981). To mimic the normal clinical situation the relationship during spontaneous recovery is shown until 25% recovery of twitch height (Lee, 1975) In contrast, the relationship given for twitch heights above 25% is valid during induced recovery with a cholinesterase inhibitor (Ali et al., 1981). Note the "period of no response" to either of the two stimulation forms. This period of intense neuromuscular blockade may be evaluated using tetanic and post-tetanic single twitch stimulation (see text for further explanation).

twitch heights will ideally be of equal height (TOF ratio 0.9–1.0). Everything else being equal, a decreasing TOF ratio during a depolarizing block signifies that a phase II block is under development.

The advantages of using TOF stimulation are greatest in non-depolarizing block, and when phase II block is suspected, as the degree of block can then be read directly from the TOF ratio even though a preoperative control value may be lacking. For this reason, and because TOF is less painful than tetanic stimulation, this type of stimulation can be used at any time during and after anaesthesia. A further advantage of TOF is that the neuromuscular block remains uninfluenced by the stimulation. Also, in revealing residual curarization its sensitivity is greater than single twitch stimulation or tetanic stimulation of 50 Hz (Ali et al., 1981).

Relation between different methods of stimulation

The least sensitive method in demonstrating a partial neuromuscular block is single twitch stimulation. The twitch response is not reduced before more than 75–80% of the cholinergic receptors in the neuromuscular end-plate are blocked. The response disappears completely when 90% of the receptors are blocked (Waud and Waud, 1971).

The same or possibly a slightly greater sensitivity can be obtained with tetanic stimulation at 30 Hz for 5 s. Greater sensitivity is achieved by tetanic stimulation at higher frequencies. At 100 Hz for 5 s, fade develops already when 50% of the receptors are blocked, and at 200 Hz for 5 s, fade is observed when merely 30% of the receptors are blocked (Gissen and Katz, 1969; Waud and Waud, 1971).

With TOF, the TOF ratio begins to decrease when more than 70–75% of the receptors are blocked (Waud and Waud, 1972).

When a non-depolarizing block is developing, the following relation exists between the reaction to TOF and the single twitch response: the response to the fourth stimulus disappears (TOF ratio = 0) when the height of the first response is about 25% of control. The response to the third stimulus disappears when the height of the first response is about 20% of control, while the response to the second stimulus disappears when the height of the first response is about 10% of control. With reversal of the block, the reappearance of the four twitches is in inverse sequence to their disappearance (Lee, 1975) (fig. 4). At a TOF ratio of 0.70–0.75 (induced recovery) the twitch response will have reached control value, and there will be no fade in the response to a tetanic stimulation of 50 Hz for 5 s (Ali and Kitz, 1973; Ali and Savarese, 1976; Ali et al., 1981).

Intense non-depolarizing neuromuscular blockade cannot be evaluated using single twitch stimulation or TOF nerve stimulation. Thus, during halothane anaesthesia, injection of pancuronium 0.1 mg kg^{-1} for tracheal intubation causes disappearance of the response to single twitch stimulation and TOF stimulation for 20–100 min (fig. 4). During this "period of no response" it is impossible to tell clinically whether the response to TOF stimulation—and hence the possibility of sufficient reversal—will return in say 20, 60, or perhaps 100 min. It is, however, possible to quantify at least a part of this period by applying tetanic stimulation (50 Hz for 5 s) and observing post-tetanic responses (fig. 5). During a pancuronium-induced neuromuscular blockade the response to post-tetanic twitch stimulation appears an average of 36 min before the first reaction to TOF nerve stimulation, and there is a correlation between the maximal post-tetanic twitch height in per cent of control twitch height, and the time to first response to TOF stimulation (Viby-Mogensen, Howardy-Hansen et al., 1981). Evaluation of post-tetanic twitch response in relation to a control twitch response presupposes access to monitoring equipment, whereas the number of post-tetanic twitch responses can simply be counted (the post-tetanic count: PTC). It appears from figure 6 that time until return of response to TOF nerve stimulation is related to the number of post-tetanic twitch responses present (PTC) at any given time.

CLINICAL MONITORING OF NEUROMUSCULAR FUNCTION

Nerve stimulators for clinical use

Several nerve stimulators for clinical use are commercially available (Churchill-Davidson, 1965; Katz, 1965a; Zeh and Katz, 1978; Crul et al., 1980; Viby-Mogensen et al., 1980). In my opinion it is not so important which stimulator is used, the important thing is to know its characteristics! For instance, the response to tetanic stimulation and the degree of PTF are

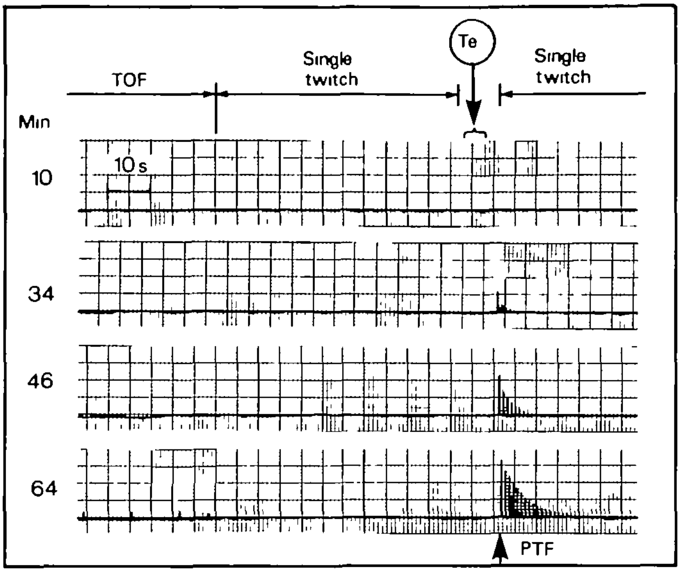

FIG 5 Post-tetanic facilitation (PTF) during intense neuromuscular blockade following pancuronium 0.1 mg kg^{-1} (halothane anaesthesia). Basically train-of-four (TOF) nerve stimulation was used, but 10, 34, 46 and 64 min after the injection of pancuronium the mode of stimulation was changed to 1.0 Hz single-twitch stimulation. After 1 min a tetanic stimulus (50 Hz) was applied for 5 s (Te) Three seconds later single twitch (1 Hz) was again applied for 1 min followed by TOF nerve stimulation. Ten minutes after injection of pancuronium there was no response to any of the stimulation forms Thirty-four minutes after the administration of pancuronium there was still no response to TOF, single twitch or tetanic stimulation, but now post-tetanic facilitation was present. Twelve minutes later there was still no response to TOF, single twitch or tetanic stimulation, but the post-tetanic twitch response had increased considerably. Sixty-four minutes after the injection of pancuronium the first response to TOF stimulation appeared, but still there was no reaction to single twitch (1 Hz) or tetanic stimulation. The post-tetanic twitch response had increased further

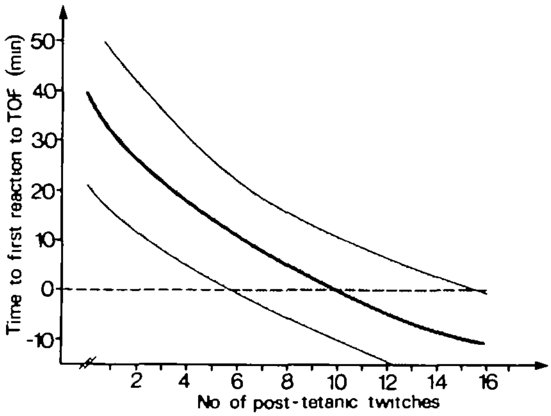

FIG. 6. Relationship between minutes to first reaction to train-of-four (TOF) and number of post-tetanic twitches (the post-tetanic count: PTC) in 17 patients anaesthetized with halothane and given pancuronium 0.1 mg kg^{-1} for tracheal intubation. The mean curve and 95% prediction region are shown (Viby-Mogensen, Howardy-Hansen et al , 1981).

dependent on the frequency of the tetanic stimulus, the duration of that stimulus and the time lapse between the conclusion of the tetanic stimulus and the first post-tetanic single stimulus. It is therefore of importance that these variables be held constant, if a valid comparison is to be made between the neuromuscular responses to tetanic stimulation at different times during anaesthesia. We use the Myotest nerve stimulator (Viby-Mogensen et al., 1980) (fig. 7). This stimulator gives a unipolar constant-current impulse, with an adjustable amplitude from 0 to 40 mA (the latest version gives up to 60 mA) and with a constant impulse duration of 0.2 ms. The constant-current impulse means that, irrespective of changes in impedance between the electrodes, the current to the stimulated nerve will be unchanged. The stimulator offers the following stimulation forms: 1.0- and 0.1-Hz single twitch stimulation, TOF nerve stimulation, and 50-Hz tetanic stimulation for 5 s followed by a 3-s pause before returning to single twitch stimulation. A stimulation frequency of 0.1 Hz allows the greatest possible response to a single stimulus. The 1.0 Hz frequency makes it easier to elicit the

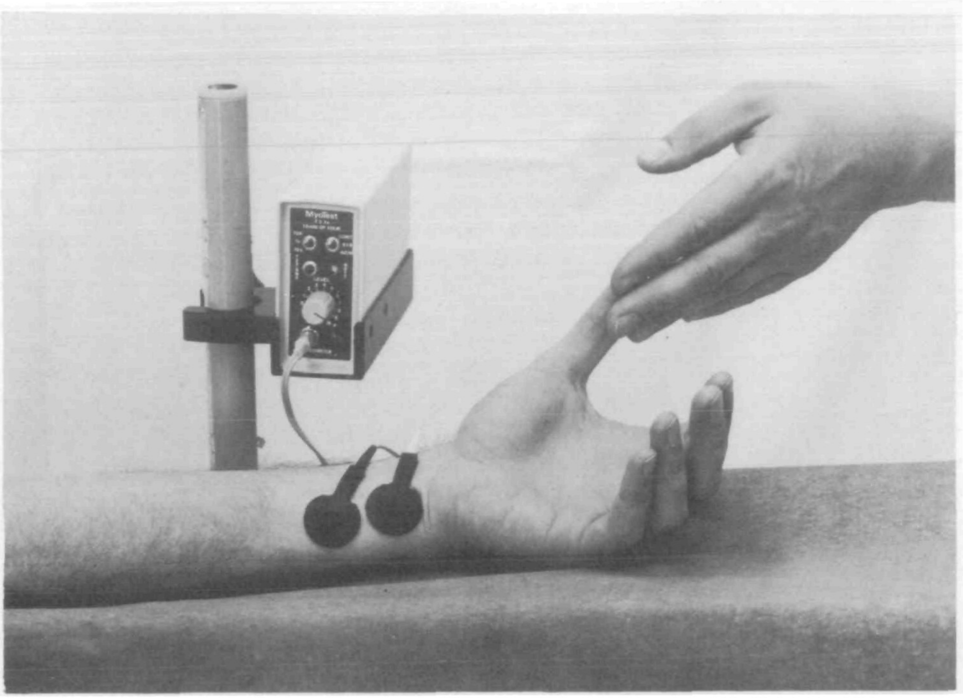

FIG. 7. Monitoring of neuromuscular blockade without recording equipment. A Myotest nerve stimulator and surface electrodes are used The evoked response is determined by tactile evaluation.

necessary supramaximal intensity in a shorter time and may be used (in combination with a 50-Hz tetanic stimulus for 5 s) in the evaluation of an intense non-depolarizing neuromuscular blockade (Viby-Mogensen, Howardy-Hansen et al., 1981).

Transmission of impulses from stimulator to nerve

Both surface and needle electrodes can be used.

Surface electrodes. A set of non-disposable surface electrodes (conducting rubber) may be delivered with the nerve stimulator, but disposable electrodes, as e.c.g. electrodes, can also be used. After careful cleansing of the skin, the electrodes are placed, for example, over the ulnar nerve at the volar side of the wrist (fig. 7). The distal electrode is placed about 1 cm proximal to the point where the proximal flexion crease of the wrist crosses the radial side of the tendon to the ulnar flexor carpi muscle. The proximal electrode can be placed either 2–3 cm proximal to the distal electrode (preferably on the other side of the nerve) or over the ulnar nerve at the elbow. The placing of the electrodes is very important. Small displacements may result in considerable changes in stimulation current requirements. Furthermore, the electrodes must be so placed that nerve and not muscle is stimulated.

As the stimulation pulses are monophasic, interchanging the electrode connections (exchange + with −) may sometimes increase the stimulation considerably.

Needle electrodes. In some cases—particularly in obese patients and in patients with very cold extremities—surface stimulation at the supramaximal level is not possible. In these cases needle electrodes should be used. The needles should be placed subcutaneously and not in the nerve. If the patient is awake this is best done with local analgesia. The needle electrodes must be held in place with tape, as movements of the needle tips may influence monitoring.

Special needle electrodes for nerve stimulation are commercially available, but ordinary steel injection needles may also be used.

Evaluation of the evoked response

In principle, it is possible to stimulate any superficially placed, peripheral motor nerve and evaluate the response to this stimulation. In the clinic, however, it is most often convenient to stimulate the ulnar nerve, and the evoked response can then be evaluated visually, by touch, mechanically or electrically (by electromyography).

Visual evaluation. The arm is placed in 90° abduction with the hand in supination (fig. 7).

Using single stimuli, the movements of the thumb are evaluated and compared, if possible, with the control value.

In TOF stimulation, the primary observation is the count of the number of responses to the TOF stimulation, since as already mentioned there is a relationship between the number of visible finger movements and the degree of the neuromuscular block (Lee, 1975) (fig. 4). If there is a reaction to all four stimuli, an estimation of the magnitude of the fourth deflection in relation to that of the first can be attempted (TOF ratio). This, however, is difficult, especially for an untrained person. On a visual basis it is often impossible to decide whether the TOF ratio is 0.4, 0.7, or perhaps 1.0 (Savarese and Ali, 1977). On the other hand, there is no fade in a tetanic response (50 Hz for 5 s) when TOF ratio is greater than 0.7 (Ali et al., 1981) and it is normally easy visually to decide whether there is fade in a tetanic response.

Tactile evaluation. With one's hand resting loosely in the patient's hand, or better still with the finger tips resting lightly on the patient's thumb in slight abduction (fig. 7), it is often possible to get a better impression of the force of contraction than can be obtained visually. In addition, there is no risk of direct nerve stimulation of the muscles of the thumb, which could be the case with the 4th and 5th finger. It is easy to decide by touch if there is any reaction to TOF stimulation and how many responses are present. Even by touch, however, it is difficult to estimate the TOF ratio when all four responses are present. The only way in which one can be sure by touch that the patient has reached sufficient reversal at the end of surgery, is by evaluating the patient's reaction to a tetanic stimulation (50 Hz for 5 s).

Deeper degrees of neuromuscular blockade—that is when there is no reaction to single twitch (0.1 Hz) or TOF stimulation—can also be evaluated by touch, as there is a relationship between the number of post-tetanic reactions recognizable by touch and the time to first reaction to TOF stimulation. However, studies still in progress suggest that the curve expressing the relationship between the number of post-tetanic twitches and the time to the first reaction to TOF has a somewhat steeper course when the number of post-tetanic twitches is evaluated by touch, than when the number is counted from a recorder (fig. 6).

Mechanical measurements. In order to obtain a more exact measurement of muscular reaction to the nerve stimulation, the tension developed in the muscle can be measured. A condition for correct and reproducible measurements is that the contractions are isometric. This presupposes that it is possible to apply (and maintain) a preload. In clinical practice this is most easily achieved by making measurements on the thumb using a preload of 100–300 g. In addition, as the adductor pollicis muscle is the only muscle in the thumb innervated by the ulnar nerve, measurements on this digit are about the nearest one can come to *in vitro* investigation in the clinic. The principle is that the thumb acts on a force–displacement transducer, whereby the force of contraction is converted into an electrical signal, which via an amplifier can be presented on a screen or in a write-out on a paper strip, or both.

For several years we have used a specially constructed armboard, on which the arm is placed in abduction and pronation, so that the four ulnar fingers grasp the armboard and the thumb acts on the rigidly fixed transducer (Statham UC 3, gold cell) (fig. 8). The armboard is mounted on a ball-head attached to the operating table. The advantages of this system are primarily that it can be assembled in a few minutes, that it is stable in every-day use, and that it can be manufactured in any department of anaesthesia without great expense. A disadvantage of the system is that the hand lies in pronation. This may cause trouble in placing the electrodes to achieve a supramaximal response, because the electrodes may be displaced when the hand is turned. In collaboration with a Danish firm (Biometer), therefore, we have developed a new armboard ("The Herlev armboard"), and a new transducer (fig. 9). With this the arm is placed in supination on a vacuum cushion filled with plastic balls. When the cushion has been modelled in accordance with the patient's arm, the arm is fixed firmly and the cushion evacuated for air. The thumb is then placed in a ring fastened to the transducer. This is placed in a special holder which allows the

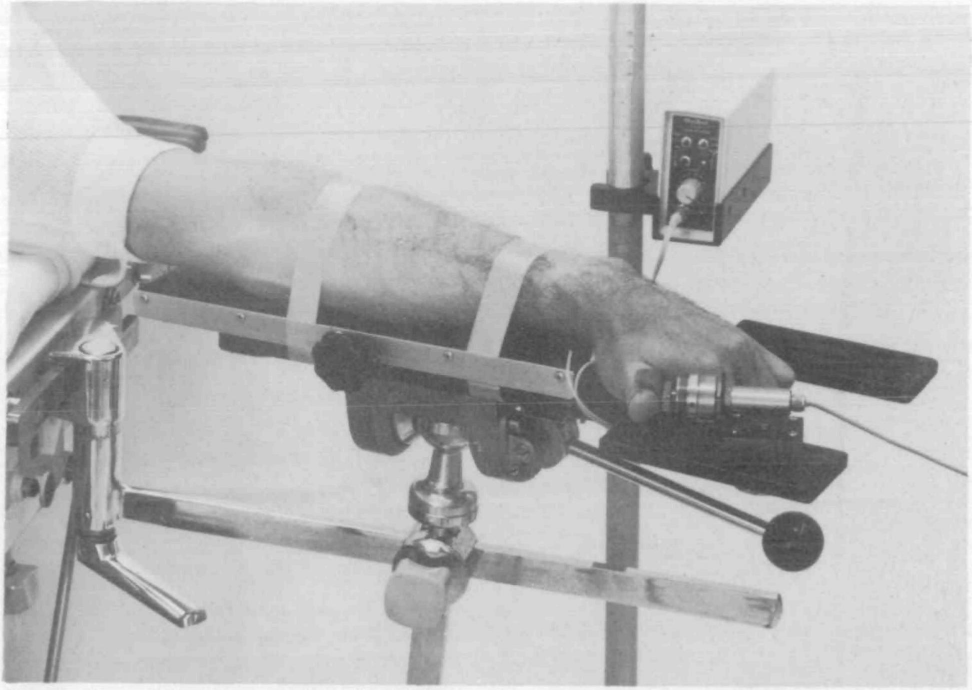

FIG. 8. A specially constructed armboard for mechanical measurements of evoked responses. The force–displacement transducer (Statham UC 3, Gold cell) is mounted on the armboard by a screw (not shown in the picture) allowing a preload to be set and the transducer to be moved in any direction in the horizontal plane. The armboard itself, which is attached to the operating table, can be moved in any desired direction.

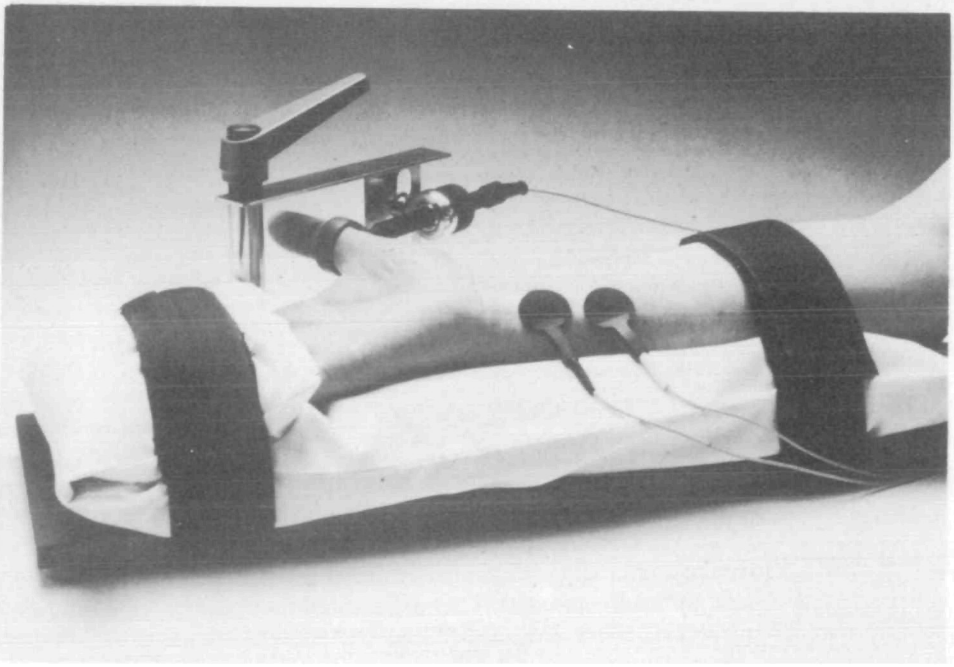

FIG 9. The "Herlev armboard" for mechanical measurements of evoked responses. See text for further explanation.

transducer to be so suspended that the thumb always applies tension exactly along the length of the transducer. A screw placed behind the transducer makes it possible to adjust and record preload at any time. The transducer is made of plastic and has a capacity of up to 15 kg. This avoids problems of overloaded transducers which have been described (Freund and Merati, 1973). The armboard, with an accompanying neuromuscular transmission analyser and recorder (see later) is now commercially available in most European countries.

Besides the methods described here for mechanical recording of the evoked response, numerous others have been published (Katz, 1965b; Tyrrell, 1969; Baraka, 1973; Walts, 1973; Ali and Savarese, 1976; Armstrong, Goat and Loach, 1977; Crul, 1980; Stanec et al., 1980). No matter which method is used, however, it is important, first that the transducer is placed correctly in relation to the muscle in which the measurements are being made (Epstein and Epstein, 1975), second that a preload is used and maintained (Donlon, Savarese and Ali, 1979), and finally that the transducer used is not overloaded (Freund and Merati, 1973).

Electromyographic measurements. It is also possible to monitor the neuromuscular function by electromyography (e.m.g.). In this method the evoked compound action potential is registered from the muscle via two surface or needle electrodes (in most cases the adductor pollicis brevis or the abductor digiti minimi). The active electrode is usually placed over the motor point of the muscle and the indifferent electrode over the tendon of insertion of the muscle. The ground electrode, which it is advantageous to have larger than the lead-off electrodes, can then be interposed between the stimulating and recording electrodes. The compound e.m.g. evoked by the nerve stimulation is collected by the recording electrodes and transmitted via an amplifier to an oscilloscope, for example.

In principle, recording the electromyographic response to nerve stimulation is preferable to the mechanical twitch measurement. In particular, only changes in the neuromuscular end-plate are measured on the e.m.g. In mechanical recording the tension measured depends both on those changes that may have occurred in the neuromuscular end-plate region, and on possible changes in the contractility of the muscle. Further, with e.m.g. recording, in contrast to mechanical recordings, it is possible to measure very rapid changes in the neuromuscular function. Tetanic fade will thus often be more pronounced in e.m.g. recording than in mechanical recording, because it takes some time for the muscle to reach maximal contractility (Epstein and Epstein, 1975). Finally, by using electromyography it may be possible to reduce the problem of transducer fixation already mentioned.

Despite the above, the clinical use of electromyography is still uncommon, although used for research in a number of laboratories. One reason for this is that there are still a number of unsolved technical problems associated with its use. Epstein and Epstein (1975) and Lee and coworkers (1977) are among those who have now described methods allowing a direct transcription of the evoked e.m.g., and quite recently the first apparatus for monitoring based on e.m.g. measurements has become commercially available (Crul et al., 1980). However, it is important to be aware that there may be differences between the electromyographic and the mechanical response (Epstein and Epstein, 1973; Katz, 1973).

For additional information on electromyographic monitoring of neuromuscular transmission see Epstein and Epstein (1975).

Neuromuscular transmission analysers. The different neuromuscular variables such as TOF ratio and twitch height depression are most often calculated manually from the recorded curves. In a number of centres work has been going on for some years developing so-called neuromuscular transmission analysers (Ali and Kitz, 1973; Perry et al., 1975; Lee et al., 1977; Viby-Mogensen, Kann et al., 1981), which automatically calculate these variables, facilitating both the clinical work and the work in research projects. Recently, two such types of apparatus have become commercially available. The one apparatus is based on measurements of the evoked electromyographic response (Crul et al., 1980) and the other (Myograph 2000) on measurements and recordings of the mechanical response (figs 9, 10). We have not had the opportunity to test the first-mentioned instrument, but have been involved in the development and testing of the Myograph. This instrument constitutes the first series-produced apparatus containing all the elements necessary for the mechanical monitoring and

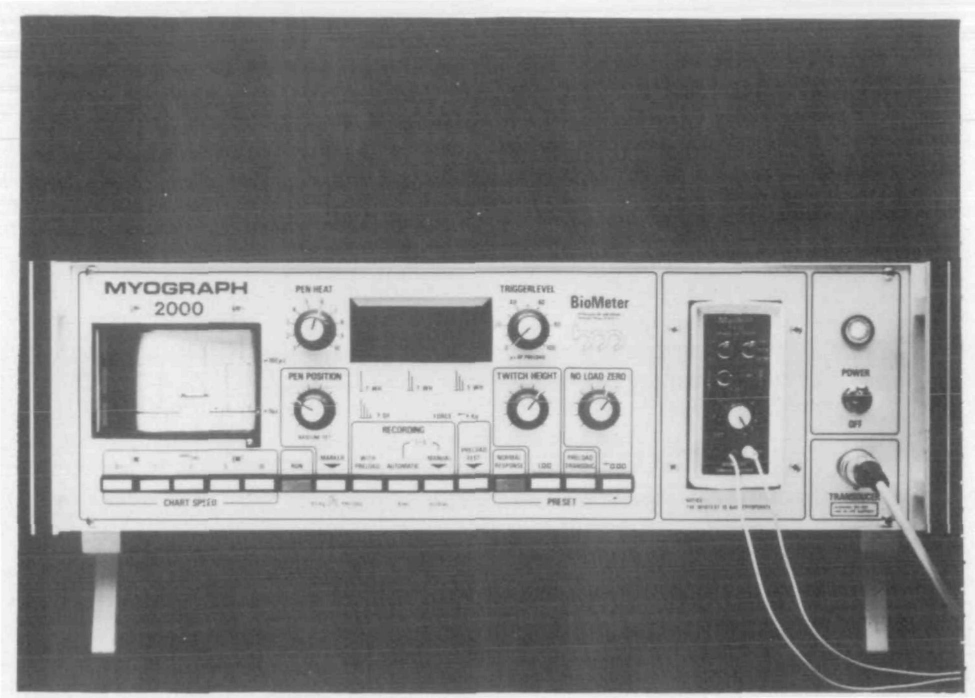

FIG 10. Myograph 2000, a neuromuscular transmission analyser for mechanical measurements See text for further explanation.

recording of neuromuscular function: a nerve stimulator, an armboard with transducer, a measuring and calculating unit with digital display and a write-out. Among other things the Myograph allows measurements of the absolute force developed in the thumb in reaction to a nerve stimulation, the control and adjustment of preload at any time during the measurements, and automatic or manual reduction of the amplification when using tetanic stimulation. The display shows the twitch height in per cent of control, the number of responses to TOF or, if all four responses are present, the TOF ratio. Simultaneously, the response is recorded in the write-out permitting continuous control of the calculating unit and documenting material for research work.

CORRELATION BETWEEN EVOKED RESPONSES AND CLINICAL OBSERVATIONS

Single stimulation. A twitch height of 5% or less secures sufficient relaxation of the musculature of the jaw and larynx for laryngoscopy and endotracheal intubation and of the abdominal wall for surgery (Katz, 1971; Ali and Savarese, 1976). The abdominal musculature usually feels tight at twitch heights greater than 25%. The head cannot be lifted from the table before the twitch height is about 90% of the control value (corresponding to a TOF ratio of 0.5–0.6), but even 100% recovery of twitch height does not always indicate normal clinical neuromuscular function (Ali and Savarese, 1976; Ali et al., 1981).

TOF stimulation. The relationship between the reaction to single twitch stimulation and TOF stimulation has already been discussed (fig. 4).

There is a good correlation between TOF ratio and head-lift. At a ratio of 0.4 or less, no patient is able to lift the head from the table. At a ratio of 0.6 the patient is able to sustain head-lift for 3 s (Ali, Utting and Gray, 1971a, b), but vital capacity and inspiratory force will often be reduced (Ali et al., 1975; Brand et al., 1977). A TOF ratio of 0.75 enables the patient to open the eyes widely, protrude the tongue, exhibit cough-sufficiency and sustain head-lift for at least 5 s (Ali and Kitz, 1973; Brand et al., 1977). At a TOF ratio of 0.8 and more, the vital capacity and inspiratory force are normal (Ali et al., 1975).

Tetanic stimulation. Tetanus of 50 Hz for 5 s without fade indicates that the patient is able to maintain a head-lift for 5 s, protrude the tongue, open the eyes, and that vital capacity and maximum voluntary ventilation are at least 90% of control (Walts, Levin and Dillon, 1970; Ali and Kitz, 1973).

PRACTICAL CLINICAL USE OF A NERVE STIMULATOR

During induction of anaesthesia

It is convenient to attach the nerve stimulator before induction of anaesthesia (fig. 7), but normally it should not be switched on until *after* the patient is asleep. When the supramaximal stimulus is reached—and the reaction of the finger to this is known—the myoneural blocking drug is injected.

There are large individual variations in sensitivity to the non-depolarizing neuromuscular blocking drugs (Katz, 1967). By means of the nerve stimulator it is possible, in the individual patient, to determine the dose sufficient to achieve the desired degree of neuromuscular block. If a non-depolarizing neuromuscular blocking drug is administered in small doses until the response to TOF stimulation, evaluated visually, just shows fade (TOF ratio about 0.4), then a doubling of this dose will result in about 80% depression of the twitch height, and tripling the dose will result in about 95% depression (Savarese and Ali, 1977).

During operation

In most situations, a twitch depression of 90–95% will be enough to ensure sufficient muscle relaxation. If the patient is relaxed with a non-depolarizing drug, this means that the reaction to single twitch stimuli (0.1 Hz) can just be seen or felt, and only the response to the first of the four stimulations of TOF can be seen or felt. The advantage of keeping the patient relaxed at this level is above all that antagonism of the postoperative block is facilitated (see later).

On occasion, respiratory movements, cough or hiccup, may occur, even though the twitch height is less than 5–10% of the control twitch height. There are several explanations for this. The respiratory muscles are less sensitive to myoneural blocking drugs than the peripheral muscles (Johansen, Jørgensen and Molbech, 1964; Wymore and Eisele, 1978), and a 95% depression of the twitch height corresponds to only an 80% depression of the tetanic response (Lee and Katz, 1980). Powerful nerve stimulation triggered off by the surgical intervention during a superficial anaesthesia can therefore elicit respiratory movements. Finally, peripheral cooling may reduce the blood flow to the muscle on which measurements are being made. This may result in inhibition of the diffusion of the myoneural blockers away from the neuromuscular end-plates, so that the reversal of the peripheral muscles may "drag after" the reversal of the respiratory muscles.

In continuous infusion of suxamethonium, it may be difficult to adjust the patient to a constant twitch height, because of the rapid breakdown of the drug. In order to achieve a sufficient degree of muscle relaxation it is often necessary that there just is *no* reaction to nerve stimulation. To avoid overdosage it is necessary to stop the infusion at regular intervals or to reduce the rate of infusion of suxamethonium and evaluate the response to nerve stimulation.

During reversal of neuromuscular block

Reversal of the non-depolarizing block by means of a cholinesterase inhibitor should not be started before there is a reaction to single stimuli (0.1 Hz) or TOF. If the reversal is started when only the first response in the TOF is present (corresponding to a twitch height < 10%), it will take 10–30 min to reach a TOF ratio of 0.7 (corresponding to 100% recovery of twitch height. If, on the other hand, all four responses to TOF stimulation can be seen or felt (corresponding to a twitch height of at least 25%), reversal of the block should be possible in less than 10 min (Katz, 1971).

Reversal of the depolarizing block normally occurs spontaneously in 5–10 min after the termination of the suxamethonium infusion.

After operation

Even if a nerve stimulator may not have been used during operation, it can be of great diagnostic and therapeutic value after the operation. A TOF ratio greater than 0.7 and absence of fade in the tetanic response (e.g. 50 Hz for 5 s) in a patient with cough- and respiratory-insufficiency, excludes the presence of residual curarization. On the other hand, a low TOF ratio or fade in the tetanic response suggests that the patient still experiences partial relaxation. Treatment of this residual curarization can then be controlled by a nerve stimulator.

WHICH PATIENTS SHOULD BE MONITORED WITH A NERVE STIMULATOR?

A nerve stimulator makes it possible to provide precise, individual dosage of the neuromuscular blocking drugs. This speaks in favour of monitoring all patients during operation. As already mentioned, careful clinical evaluation of the patient during and after operation will often be sufficient to ensure optimal treatment. There is no doubt, however, that patient safety can be considerably increased, if neuromuscular function is monitored during operation in the following patient categories:

(1) Patients with severely reduced kidney or liver function, or both.
(2) Patients in poor general condition.
(3) Patients with severe pulmonary disease.
(4) Patients with severe heart disease or bronchial asthma, in whom achievement of reversal by means of a cholinesterase inhibitor might be problematic.
(5) Patients with neuromuscular disease (monitoring may, however, be unreliable in patients with upper motor neurone lesions (Graham, 1980; Moorthy and Hilgenberg, 1980)).
(6) Severely obese patients.
(7) Patients who have to undergo prolonged surgery (>3–4 h).
(8) Patients in whom relaxation is produced with continuous infusion of suxamethonium.

SUMMARY OF SOME IMPORTANT RULES FOR MONITORING OF NEUROMUSCULAR FUNCTION

Experience shows that, the first time an anaesthetist has to use a nerve stimulator, it is always the same problems that are encountered. Some important rules are summarized below.

Stimulation should be definitely supramaximal (if necessary move the electrodes), and the various forms of stimuli should not be applied too often. The reaction to single-twitch stimulation decreases if stimulation is more frequent than every 6–10 s; TOF must not be applied more frequently than every 10 s; tetanic stimulation not more frequently than every 6–10 min. The reaction to a tetanic stimulus and to post-tetanic twitch stimulation depends both on the duration of the tetanic impulse (1–10 s) and on the frequency (30–200 Hz). Direct muscle stimulation (the response does not appear in spite of total neuromuscular block) can usually be avoided by correct placing of the electrodes and by avoiding too high stimulation intensity.

In mechanical recordings it is important to apply and maintain a preload of 100–300 g, to site and fasten the transducer in the correct position in relation to the muscle on which measurements are to be made, and finally to avoid overloading the transducer. In clinical studies in particular, it is of importance to bear in mind that the reaction to supramaximal single-twitch stimulation increases during the first 8–12 min after commencement of the stimulation.

Without e.m.g. or mechanical recording, *tactile evaluation* of the thumb reaction is normally the best way to evaluate muscle force. No matter how the evaluation is made it is, however, decisive to compare the reaction to nerve stimulation with the clinical condition of the patient. Particularly if the extremities are very cold, there may be a disproportion between the degree of relaxation of the peripheral muscles and that of the respiratory muscles.

REFERENCES

Ali, H. H., and Kitz, R. J. (1973). Evaluation of recovery from non-depolarizing neuromuscular block, using a digital neuromuscular transmission analyzer: Preliminary report. *Anesth Analg. (Cleve.)*, **52**, 740.

—— Savarese, J. J. (1976). Monitoring of neuromuscular function. *Anesthesiology*, **45**, 216.

—— —— (1977). Stimulus frequency and the dose-response to D-tubocurarine in man. Abstract from 1977 Annual Meeting of the American Society of Anesthesiologists, New Orleans, 1977.

—— —— Lebowitz, P. W., and Ramsey, F. M. (1981). Twitch, tetanus and train-of-four as indices of recovery from non-depolarizing neuromuscular blockade. *Anesthesiology*, **54**, 294.

—— Utting, J. E., and Gray, C. (1970). Stimulus frequency in the detection of neuromuscular block in humans. *Br. J. Anaesth.*, **42**, 967.

—— —— —— (1971a). Quantitative assessment of residual antidepolarizing block (part I). *Br. J Anaesth.*, **43**, 473.

—— —— —— (1971b). Quantitative assessment of residual antidepolarizing block (part II). *Br. J. Anaesth.*, **43**, 478

—— Wilson, R. S., Savarese, J. J., and Kitz, R. J. (1975). The effect of tubocurarine on indirectly elicited train-of-four muscle response and respiratory measurements in humans. *Br. J Anaesth.*, **47**, 570.

Armstrong, J. E., Goat, V. A., and Loach, A. B. (1977). Measurement of neuromuscular blockade in man. A simple modification of a clinical pressure transducer. *Anaesthesia*, **32**, 480.

Baraka, A. (1973). Monitoring of neuromuscular transmission in anesthetized man by a bulb-transducer assembly. *Anesth. Analg. (Cleve.)*, **52**, 36.

Brand, J. B., Cullen, D. J., Wilson, N. E., and Ali, H. H. (1977). Spontaneous recovery from nondepolarizing neuromuscular blockade Correlation between clinical and evoked responses. *Anesth. Analg. (Cleve.)*, **56**, 55.

Christie, T. H., and Churchill-Davidson, H. C. (1958). The St Thomas's Hospital nerve stimulator in the diagnosis of prolonged apnoea. *Lancet*, **1**, 776.

Churchill-Davidson, H. C. (1965). A portable peripheral nerve-stimulator. *Anesthesiology*, **26**, 224.

—— Christie, T. H., and Wise, R. P. (1960). Dual neuromuscular block in man. *Anesthesiology*, **21**, 144.

Crul, J. F. (1980). Erfassung und Registrierung der Impulsübertragung und ihrer Beeinflussung; in *Muskelrelaxanzien* (eds F. W. Ahnefeld, H. Bergmann, C. Burri, W. Dick, M. Halmágyi, G. Hossli and E. Rügheimer), p. 51. Berlin, Heidelberg, New York: Springer Verlag.

—— Severinghaus, J. W., Booij, L., Kleinhans, W., and Krieg, N. (1980). New neuromuscular transmission monitor. Abstract from 7th World Congress of Anaesthesiologists, Hamburg, 1980.

Donlon, J. V., Savarese, J. J., and Ali, H. H. (1979). Cumulative dose–response curves for gallamine. Effect of altered resting thumb tension and mode of stimulation. *Anesth. Analg. (Cleve.)*, **58**, 377.

Epstein, R. A., and Epstein, R. M. (1973). The electromyogram and the mechanical response of indirectly stimulated muscle in anesthetized man following curarization. *Anesthesiology*, **38**, 212.

—— —— (1975). Electromyography in evaluation of the response to muscle relaxants; in *Muscle Relaxants* (ed. R. L. Katz), p. 299. New York: Excerpta Medica.

—— Jackson, S. H. (1970). Repetitive muscle depolarization from single indirect stimulation in anaesthetized man. *J. Appl. Physiol.*, **28**, 407.

—— Wyte, S. R., Jackson, S. H., and Sitter, S. (1969). The electromechanical response to stimulation by the block-aid monitor. *Anesthesiology*, **30**, 43.

Feldman, S. A., and Tyrrell, M. F. (1970). A new theory of the termination of action of the muscle relaxants. *Proc. R. Soc. Med.*, **63**, 692.

Freund, F. G., and Merati, J. K. (1973). A source of errors in assessing neuromuscular blockade. *Anesthesiology*, **39**, 540.

Gissen, A. J., and Katz, R. L. (1969). Twitch, tetanus and post-tetanic potentiation as indices of nerve–muscle block in man. *Anesthesiology*, **30**, 481.

Graham, D. H. (1980). Monitoring neuromuscular block may be unreliable in patients with upper-motor-neuron lesions. *Anesthesiology*, **52**, 74.

Johansen, S. H., Jørgensen, M., and Molbech, S. (1964). Effect of tubocurarine on respiratory and non-respiratory muscle power in man. *J. Appl. Physiol.*, **19**, 990.

Katz, R. L. (1965a). A nerve stimulator for the continuous monitoring of muscle relaxant action. *Anesthesiology*, **26**, 832.

—— (1965b). Comparison of electrical and mechanical recording of spontaneous and evoked muscle activity. *Anesthesiology*, **26**, 204.

—— (1967). Neuromuscular effects of d-tubocurarine, edrophonium and neostigmine in man. *Anesthesiology*, **28**, 327.

—— (1970). Monitoring of muscle relaxation and neuromuscular transmission; in *Patient Monitoring* (eds J. F. Crul and J. P. Payne), p. 125. Amsterdam: Excerpta Medica.

—— (1971). Clinical neuromuscular pharmacology of pancuronium. *Anesthesiology*, **34**, 550.

—— (1973). Electromyographic and mechanical effects of suxamethonium and tubocurarine on twitch, tetanic and post-tetanic responses. *Br. J. Anaesth.*, **45**, 849.

Lee, C. (1975). Train-of-4 quantitation of competitive neuromuscular block. *Anesth. Analg. (Cleve.)*, **54**, 649.

—— Katz, R. L. (1980). Neuromuscular pharmacology. A clinical update and commentary. *Br. J. Anaesth.*, **52**, 173.

—— —— Lee, A. S. J., and Glaser, B. (1977). A new instrument for continuous recording of the evoked compound electromyogram in the clinical setting. *Anesth. Analg. (Cleve.)*, **56**, 260.

Merton, P. A. (1954). Voluntary strength and fatigue. *J. Physiol. (Lond.)*, **123**, 553.

Miller, R. D. (1976). Antagonism of neuromuscular blockade. *Anesthesiology*, **44**, 318.

Moorthy, S. S., and Hilgenberg, J. C. (1980). Resistance to non-depolarizing muscle relaxants in paretic upper extremities of patients with residual hemiplegia. *Anesth. Analg. (Cleve.)*, **59**, 624.

Paton, W. D. M., and Waud, D. R. (1967). The margin of safety of neuromuscular transmission. *J. Physiol. (Lond.)*, **191**, 59.

Perry, I. R., Worsley, R., Sugai, N., and Payne, J. P. (1975). The use of digital computer for the on-line real-time assessment of neuromuscular blockade in anaesthetized man. *Br. J. Anaesth.*, **47**, 1097.

Ramsey, F. M., Lebowitz, P. W., Savarese, J. J., and Ali, H. H. (1980). Clinical characteristics of long-term succinylcholine neuromuscular blockade during balanced anesthesia. *Anesth. Analg. (Cleve.)*, **59**, 110.

Savarese, J. J., and Ali, H. H. (1977). Accurate prediction of individual metocurine dosage by clinical observation of "threshold fade" on train-of-four stimulation. Abstract from Meeting of the American Society of Anesthesiologists, New Orleans, 1977.

—— —— Murphy, J. D., Padget, C., Lee, C., and Ponitz, J. (1975). *Train-of-four nerve stimulation in the management* of prolonged neuromuscular blockade following succinylcholine. *Anesthesiology*, **42**, 106.

Stanec, A., Heyduk, J., Stanec, G., and Orkin, L. R. (1978). Tetanic fade and post-tetanic tension in the absence of neuromuscular blocking agents in anesthetized man. *Anesth. Analg. (Cleve.)*, **57**, 102.

—— Stanec, G., Baker, T., Stanec, D., and Hupert, C. (1980). Apparatus for quantitative measurement of the isometric contraction of the adductor pollicis muscle. Abstract from 7th World Congress of Anaesthesiologists, Hamburg, 1980.

Tyrrell, H. F. (1969). The measurement of the force of thumb adduction. *Anaesthesia*, **24**, 626.

Viby-Mogensen, J. (1981a). Succinylcholine neuromuscular blockade in subjects homozygous for atypical plasma cholinesterase. *Anesthesiology*, **55**, 429.

—— (1981b). Succinylcholine neuromuscular blockade in subjects heterozygous for abnormal plasma cholinesterase. *Anesthesiology*, **55**, 231.

—— Chræmmer-Jørgensen, B., and Ørding, H. (1979). Residual curarization in the recovery room. *Anesthesiology*, **50**, 539.

—— Hansen, P. H., Jørgensen, B. C., Ørding, H., Kann, T., and Fries, B. (1980). A new nerve stimulator (Myotest). *Br. J. Anaesth.*, **52**, 547.

—— Howardy-Hansen, P., Chræmmer-Jørgensen, B., Ørding, H., Engbæk, J., and Nielsen, A. (1981). Post-tetanic count (PTC). A new method of evaluating an intense non-depolarizing neuromuscular blockade. *Anesthesiology*, **55**, 458.

Viby-Mogensen, J., Kann, T., Fries, B., Nielsen, E. V., and Chræmmer-Jørgensen, B. (1981) Micro-train-of-four (μ-TOF): A new neuromuscular transmission analyser, in *Anaesthesiology* (eds E Rügheimer and M. Zindler) Amsterdam: Excerpta Medica.

Walts, L F. (1973). The "boomerang"—A method of recording adductor pollicis tension. *Can. Anaesth Soc. J*, **20**, 706.

—— Levin, N., and Dillon, J. B. (1970) Assessment of recovery from curare. *J.A.M.A.*, **213**, 1894.

Waud, B. E , and Waud, D R. (1971). The relation between tetanic fade and receptor occlusion in the presence of competitive neuromuscular block. *Anesthesiology*, **35**, 456

Waud, B. E., and Waud, D. R. (1972). The relation between the response to "train-of-four" stimulation and receptor occlusion during competitive neuromuscular block. *Anesthesiology*, **37**, 413.

Wymore, M. L., and Eisele, J. H (1978) Differential effects of d-tubocurarine on inspiratory muscles and two peripheral muscle groups in anesthetized man. *Anesthesiology*, **48**, 360.

Zeh, D. W., and Katz, R L. (1978). A new nerve stimulator for monitoring neuromuscular blockade and performing nerve blocks. *Anesth. Analg.* (*Cleve.*), **57**, 13