

## Original Articles

# Neuromuscular Block in Man During Prolonged Arterial Infusion with Succinylcholine

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Neuromuscular transmission was studied in anesthetized patients during intra-arterial infusion of succinylcholine. Phase I and Phase II block were demonstrated in man during continuous succinylcholine infusion at various concentrations. During Phase II block, as identified by non-sustained tetanus and post-tetanic facilitation, anticholinesterases (e.g., edrophonium and neostigmine injected intravenously) produced either a slight transient reversal of block or no effect at all during the period of infusion. Recovery of neuromuscular transmission after succinylcholine infusion was rapid and complete unless neostigmine had been used in large doses. Recovery after large doses of neostigmine was markedly prolonged.

It is proposed that the terms "Phase I" and "Phase II" or alternately "Dual Block" be discontinued. Instead it is proposed to label the early period of decreased tension output as "Depolarization Block"; the later period of decreased neuromuscular transmission as "Desensitization Block." Both types of block begin at the moment of application of depolarizing drugs but they are due to different mechanisms which become apparent with time. These suggested descriptions are more consistent with the observed experimental data than are the customary terms.

SINCE its introduction to clinical anesthesia in 1951 (Brücke *et al.*,<sup>1</sup> Mayrhofer,<sup>2</sup> Thesleff<sup>3</sup>), succinylcholine has become an indispensable drug for the production of brief periods of muscular relaxation. Succinylcholine would be considered an ideal relaxant except for the occasional and unpredictable complication of

prolonged neuromuscular block. In spite of many extensive studies, the basic physiological mechanism of this complication is still poorly understood.

This report presents studies in man during general inhalational anesthesia where neuromuscular transmission was evaluated during continuous intra-arterial infusion of succinylcholine. Intra-arterial infusion of the drug accomplished three important purposes: (1) the volume of blood diluting the administered dose before it reached its site of action was reduced, and thus the total drug dosage was markedly reduced; (2) the duration of contact of drug with plasma cholinesterase was reduced, and presumably the total amount of drug hydrolyzed was also reduced; (3) finally, intra-arterially infused succinylcholine affected the local group of muscles under study but had no detectable systemic effect in the dosage used.

Studies based upon the intravenous injection of hydrolyzable depolarizing muscle relaxants are difficult to interpret since only a small fraction of the injected dose reaches the site of action in the muscle. Such studies of drug dosage—muscle response must be in the main a reflection of the activity in the blood cholinesterase system. Twitch tension output studies of frog sartorius muscle preparations (Nastuk and Gissen<sup>4</sup>) have shown that to produce a standard response, the administered acetylcholine concentration could be reduced one hundredfold if the muscle was first treated by the anticholinesterase neostigmine to inactivate the cholinesterase enzymes. Therefore, the method of intra-arterial infusion should provide more precise information as to the behavior of the neuromuscular junction in experiments in man during prolonged exposure to the depolarizing compound succinylcholine than is possible in experiments using intravenous succinylcholine.

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Accepted for publication November 18, 1965. Presented in part before the Section on Anesthesiology at the American Medical Association Meeting, New York City, June 1965. Supported in part by Grant GM-09069-02 from the National Institutes of Health.

Neuromuscular block produced by the depolarizing compounds is particularly interesting because the block changes in time from a depolarizing block to one with the characteristics of a non-depolarizing or curare-like block even though there is no apparent change in experimental conditions. Investigators in this field have used many terms to describe the varying state of neuromuscular transmission during prolonged exposure to depolarizing compounds such as acetylcholine, succinylcholine, decamethonium and hexabiscarbocholine. Those workers primarily concerned with muscle tension output used terms "Phase I" and "Phase II" (Jenden<sup>5</sup>). Neurophysiologists studying the electrical properties of the cell membrane at junctional tissue used the terms "depolarization" and "desensitization" (Thesleff<sup>6</sup>). Anesthesiologists have come to use the term "Dual block" or "Phase II" to describe the later stages of depressed neuromuscular transmission following the use of depolarizing drugs.

In some clinical cases of Phase II neuromuscular block, the block can be partially antagonized by the use of anticholinesterase agents. However, there are many failures in reversal of block and in some instances the block appears to be markedly prolonged. Vickers<sup>7</sup> incriminated anticholinesterases used in treatment of Phase II block as the agents causing prolonged apnea following succinylcholine administration. In such a clinical situation they were not only ineffective but dangerous.

Two further facts should be emphasized: (1) Although Phase II neuromuscular block is described as curare-like, there are many aspects in which this block differs from the neuromuscular block seen following the use of *d*-tubocurarine (Creese, *et al.*<sup>8</sup>). (2) The hydrolysis of succinylcholine by plasma cholinesterase to relatively inactive succinylmonocholine usually takes place very rapidly in the normal organism (Kvisseigard and Moya<sup>9</sup>). Even if cholinesterase activity is low or absent, hydrolysis and inactivation of succinylcholine still occur, although far more slowly.

### Methods

The action of succinylcholine on neuromuscular transmission during prolonged infusion was examined in 15 patients under-

going neurosurgical procedures. There was no abnormal neuromuscular function. Anesthesia was begun with an intravenous induction dose of 100 to 300 mg. of 2½ per cent thiopental. Endotracheal intubation was performed in all patients during relaxation produced by 80 to 100 mg. of succinylcholine intravenously. No experiment was begun until 1½ to 2 hours had elapsed after the initial dose of succinylcholine. When an experiment began, there were no detectable effects of succinylcholine on neuromuscular transmission. Anesthesia was maintained with halothane, 0.5 to 1.0 per cent, vaporized by means of a Copper Kettle with a 6-liter flow of 33 per cent oxygen and 66 per cent nitrous oxide. Respiration was spontaneous, assisted or controlled as suggested by the use of the Radford nomogram for adequate ventilation. Arterial blood gases and pH were not measured. A brachial artery cannula was placed for monitoring of blood pressure. The relaxant was added to 0.9 per cent saline and perfused intra-arterially at the rate of 1 ml./minute by means of a constant infusion pump (Harvard Apparatus Co.). The concentration varied from 0.2 to 20 mg./ml. in various experiments. In the limb with the arterial infusion, the ulnar nerve was stimulated supramaximally through subcutaneous needles at the wrist by square wave stimuli at 0.5/second frequency, 40 volts intensity and 3 milliseconds duration (American Electronics Laboratory Stimulator). Tetanus was produced with the same characteristics of electrical stimulation but frequency was increased to 50/second. Twitch tension output was recorded from the adductor muscles of the thumb by a Satham Linear Force Transducer mounted in a forearm yoke of our own design. The transducer output was recorded on an Offner Dynograph Direct Ink Recorder modified by Invengineering, Inc. Edrophonium (Tensilon), neostigmine (Prostigmine) and atropine were administered intravenously to avoid disturbing the constant infusion of relaxant during the course of the tension output studies.

Tension output was recorded for at least 30 minutes during the control period before the beginning of the succinylcholine arterial infusion. The height of this recorded twitch was regarded as 100 per cent. All subsequent

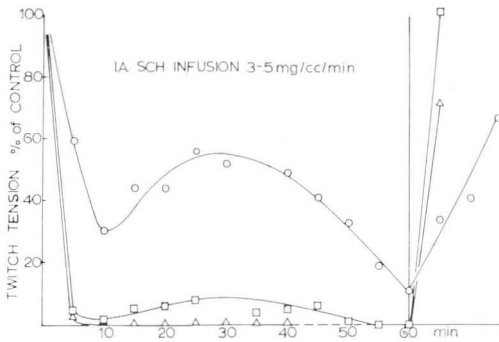


FIG. 1. Tension output versus time during intra-arterial infusion of succinylcholine at indicated concentration. O-O, 0.3 mg./minute; □-□, 0.4 mg./minute; △-△, 0.5 mg./minute. Twitch tension output recorded as percentage with control level equal to 100 per cent. Infusion stopped at 60 minutes.

twitch recordings were read as percentage of the control level.

Results, as presented in this section, represent selections from individual records. While there was inevitable biological variation among patients, the results shown are characteristic of the general changes observed. The data do not permit statistical presentation or analysis. Rather, we are presenting the change in the effects produced by potent pharmacological agents over a period of time. This is a study of pharmacokinetics in man.

### Results

*Figure 1.* This figure presents the effect on twitch tension output of one hour of continuous arterial infusion of succinylcholine at

0.3–0.5 mg. per minute in 3 patients. The control period lasted at least 30 minutes. Control tension output was represented as 100 per cent. Tension output during the test period is plotted as percentage of control. At low concentrations of succinylcholine, tension output usually appears as a diphasic curve. The early depression of tension output is the period of block referred to as Phase I. The later period of block is Phase II. This curve of tension output has been demonstrated during *in vitro* experiments in neurally stimulated skeletal muscle in amphibian (Nastuk and Gissen<sup>4</sup>), avian (Zaimis<sup>10</sup>) and mammalian (Jenden,<sup>11</sup> Creese *et al.*<sup>12</sup>) species. The experiment demonstrates the same type of diphasic curve of tension output in human muscle *in vivo*. At higher concentrations of succinylcholine infusion, there is no recovery of tension output and neuromuscular transmission remains blocked during the entire period of observation. Of note is the very rapid recovery of tension output at all concentrations when the infusion is stopped. Even though complete neuromuscular block has continued for almost an hour, recovery towards 100 per cent of control occurs rapidly. Note also that the block is not stable during the infusion and continually increased during the period of observation.

*Figure 2.* This figure is a presentation of part of a myographic record when succinylcholine is infused at the rate of 0.3 mg. per minute. At 42 minutes tension output has been reduced to 40 per cent of control level. There is only

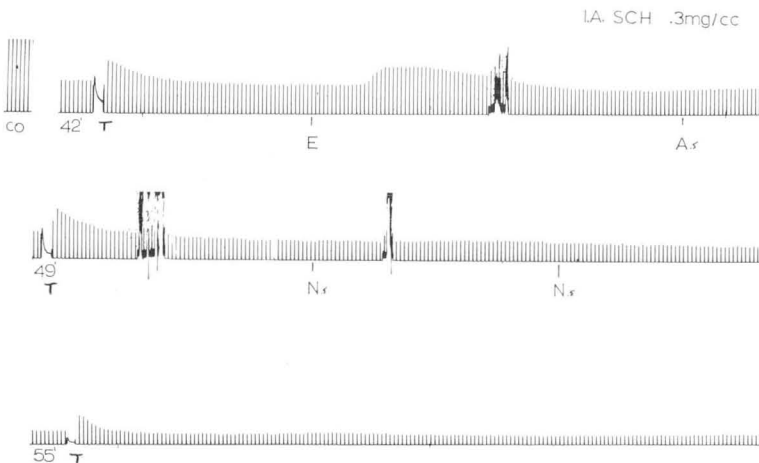
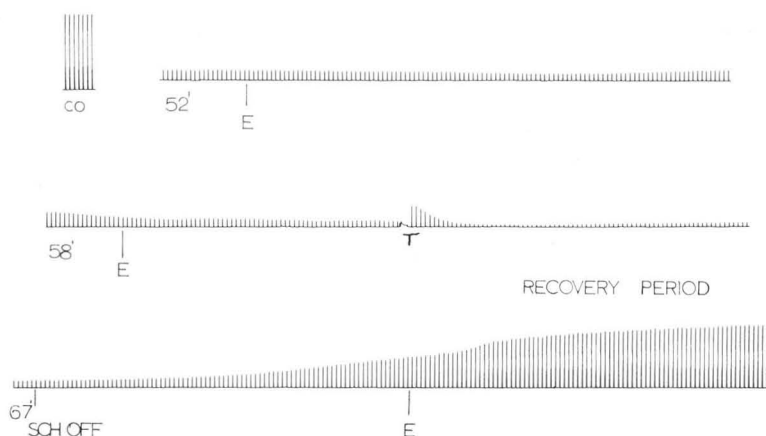


FIG. 2. Part of myograph recording during intra-arterial infusion of succinylcholine 0.3 mg./ml./minute. Twitch frequency 0.5/second. CO = Control Twitch. Numbers below line record minutes since beginning of infusion. E = edrophonium 10 mg. intravenously; A = atropine 0.5 mg. intravenously; N = neostigmine 0.5 mg. intravenously. Artifacts caused by surgical cautery. T = tetanus.

IA. SCH .2mg/cc

FIG. 3. Myograph record during intra-arterial infusion of succinylcholine at 0.2 mg./ml./minute. CO = Control. E = edrophonium 10 mg. intravenously. Numbers record minutes since start of infusion. SCH = cessation of infusion. T = tetanus.



a moderate, transient reversal of block when edrophonium 10 mg. is given intravenously. Subsequent doses of neostigmine intravenously have no effect. When stimulation was increased to 50/second, nonsustained tetanus and post-tetanic facilitation appeared. Nonsustained tetanus and post-tetanic facilitation of twitch tension have been considered typical criteria of a curare-like or competitive block (Wylie and Churchill-Davidson<sup>13</sup>). Yet the anticholinesterases had little effect in reversing the block while the perfusion of succinylcholine continued.

Figure 3. This figure presents a similar segment of the myograph record for succinylcholine infusion at 0.2 mg./minute. A profound block appeared after 52 minutes of infusion. Edrophonium intravenously on two occasions during the infusion had no effect in reversing the block. The response to tetanic stimulation definitely indicates a "curare-like" block. When the infusion is stopped for only a few minutes, the block begins to abate. Edrophonium hastens the recovery from block under these specific circumstances. Thus it is apparent that edrophonium is effective in relieving block only in the absence of succinylcholine in the arterial blood. Similar studies conducted by continuous intravenous infusion of succinylcholine showed the same response to anticholinesterase drugs. Once the criteria of Phase II block on twitch tension had been demonstrated (that is, post-tetanic facilitation and non-sustained tetanus), reversi-

bility by the anticholinesterases depended upon whether the depolarizing drug was still present in the blood. There was no reversal during the infusion while the block was increasing, and there was ready reversibility when the infusion was stopped and the block was decreasing.

Figure 4. This study presents the effect of varying the duration of succinylcholine infusion on the rapidity of recovery. While there is some slight slowing of recovery when the exposure is increased threefold (from 15 minutes to 43 minutes), this slight difference would be imperceptible by clinical evaluation. The fact of importance is that even after complete neuromuscular block of 43 minutes,

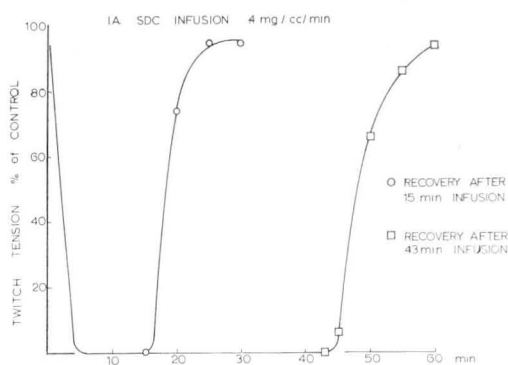


FIG. 4. Twitch tension output versus time during intra-arterial infusion of succinylcholine 0.4 mg./ml./minute. Performed in two separate patients. Tension output recorded as percentage with control equal to 100 per cent.

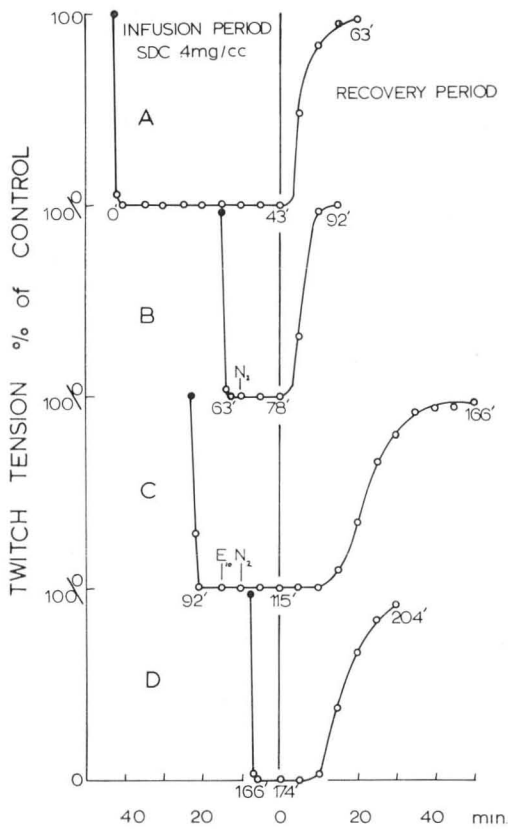


FIG. 5. Twitch tension output versus time during intra-arterial infusion of succinylcholine 0.4 mg./ml./minute in a patient. Panels A, B, C, D represent successive periods of neuromuscular block during succinylcholine infusion. The vertical line represents the point of stopping the infusion in each panel. Numbers represent minutes since the beginning of the experiment. N = 2 mg. of neostigmine intravenously. E = 10 mg. edrophonium intravenously.

recovery to control levels of tension output is complete in 15 to 20 minutes. This is approximately the same time for recovery as following the infusion of succinylcholine for 15 minutes.

Periods of repeated neuromuscular block by succinylcholine infusion followed by recovery showed in almost all cases similar recovery times. It is realized that the experimental design using small total dosage of relaxant avoids exposing the organism to the metabolic breakdown products of succinylcholine; choline and succinylmonocholine do have a demonstrable although mild blocking effect. However, similar results have been obtained

during the intravenous administration of depolarizing drugs by continuous infusion.

Figure 5. This study presents a continuous record of the effects of anticholinesterase drugs on the rapidity of recovery from neuromuscular block produced by intra-arterial infusion of succinylcholine. The four panels A, B, C and D represent four successive periods of neuromuscular block produced by succinylcholine infusion, 0.4 mg./ml. The vertical line represents cessation of the infusion and the beginning of recovery. Panel A shows complete neuromuscular block for 43 minutes. Recovery to control levels of twitch tension took 20 minutes. In Panel B the infusion was started again and continued for 15 minutes. Neostigmine 2 mg. was given intravenously ten minutes prior to stopping the infusion. Although there was no evidence of reversal of the block during the infusion, recovery of tension output apparently was hastened, now taking 14 minutes as against the control 20 minutes shown in Panel A. In Panel C the infusion was given for 23 minutes. Edrophonium and neostigmine were given intravenously during the infusion but again had no apparent effect. When the infusion was stopped, recovery to control levels was markedly delayed and required 50 minutes. In Panel D block was again instituted by infusion for 8 minutes. Recovery to control levels took 30 minutes. While this period was shorter than in Panel C, it is markedly longer than prior to injection of the anticholinesterase drugs (Panel A). The last dose of neostigmine was given over one hour prior to this final recovery period; and while the effect is decreasing as shown by the recovery period in D, it still has an effect on neuromuscular transmission.

Figure 6. This experiment was done to elucidate the mechanism involved in the prolongation of twitch tension recovery in Panel C in the previous figure. Neuromuscular block was instituted by succinylcholine infusion at a concentration of 0.4 mg./minute for 44 minutes. At the end of this period the succinylcholine concentration was increased to 20 mg./minute for a total of 10 minutes. Then the succinylcholine infusion was stopped altogether and recovery allowed to proceed.

In this situation, recovery was markedly prolonged; at the end of 60 minutes, only 25 per cent recovery had occurred, at 90 minutes only 45 per cent recovery. No anticholinesterases were used during the experiment.

### Discussion

We believe this approach to the clinical problems of neuromuscular transmission is of value because by minimizing the factors of dilution and hydrolysis of succinylcholine one can see more clearly the factors operating at the neuromuscular junction. While we have not achieved the simplicity of muscle-bath experiments *in vitro*, the curves of tension output versus time demonstrated in figure 1 so clearly resemble *in vitro* results that we must suppose the same factors are in operation. We believe figure 1 demonstrates "Phase I Block" and Phase II Block" clearly in spite of the suggestion by Zaimis<sup>14</sup> and MacLagen<sup>15</sup> that "Phase I" and "Phase II" are experimental artifacts, only demonstrable in *in-vitro* preparations.

It is quite apparent that the response of muscle to anticholinesterases depends on the presence or absence of succinylcholine in the perfusing arterial blood. The continued presence of succinylcholine during the arterial perfusion results in a gradual increase in the degree of neuromuscular block. Acetylcholine, which is believed to be the normal chemical transmitter at the neuromuscular junction, is a depolarizing compound similar to succinylcholine. The anticholinesterases effectively increase the concentration and duration of action of acetylcholine by inactivating the enzymes. This effect is additive to that of the perfusant succinylcholine and thus the block is increased. In addition, the anticholinesterase drugs in high concentrations in themselves act like neuromuscular blocking agents. These are the reasons for lack of reversal of Phase II block by anticholinesterases during succinylcholine infusion. Such a clinical situation might be expected to follow the use of repeated large doses of succinylcholine, or continuous infusion, or perhaps in a case of defective or absent cholinesterase enzymes.

The usual clinical practice during anesthesia is to administer a large dose of succinylcholine

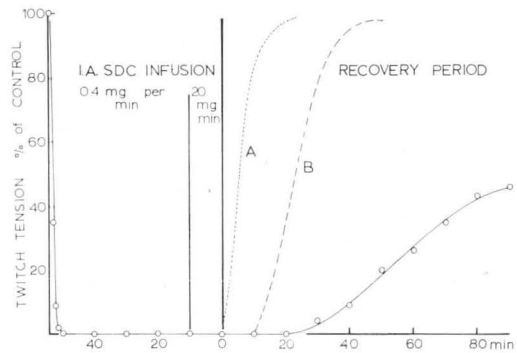


FIG. 6. Twitch tension output versus time during intra-arterial infusion of succinylcholine at 0.4 mg./minute and then at 20 mg./minute. Tension recorded as percentage with control level equal to 100 per cent. Infusion stopped at time marked 0. Curve A represents recovery of tension output following succinylcholine infusion of 0.4 mg./minute as in Panel A in figure 5. Curve B represents recovery of tension output following succinylcholine infusion of 0.4 mg./minute plus neostigmine as in Panel C in figure 5.

in a short period of time. This high plasma concentration causes neuromuscular block; within minutes, however, the concentration rapidly falls to very low levels (Kvisselgard and Moya<sup>9</sup>). In a short period of time, the blood perfusing the neuromuscular junction is free of depolarizing drug and the drug bound to end-plate receptors diffuses away, ending the block and re-establishing neuromuscular transmission. However, there are many fibers that still do not respond in the recovering muscle. The anticholinesterases decrease the hydrolysis of acetylcholine (the natural neurotransmitter) and act as though a larger concentration of acetylcholine were present. This increase in transmitter recruits active contraction by a greater number of fibers and thus the anticholinesterases now produce an increase in tension output.

While there are many possible causes for prolonged block of neuromuscular transmission following succinylcholine administration in man, we believe these experiments point out that one possible cause resides in the misuse of anticholinesterases in the treatment of succinylcholine block. Figure 4 demonstrates the rapid recovery from neuromuscular block that usually follows the continuous infusion of succinylcholine. This study emphasizes the factors involved in a prolonged block produced



by relatively low concentrations of succinylcholine. Recovery from even a prolonged exposure to succinylcholine is rapid if the concentration used is just sufficient to produce neuromuscular block. This finding clearly substantiates the clinical practice of using continuous intravenous succinylcholine in such a manner that spontaneous respiration resumes within minutes of stopping the infusion (Foldes<sup>19</sup>). However, figure 5 demonstrates the danger of persistent use of anticholinesterases in the face of depressed neuromuscular function caused by the continued presence of the depolarizing drugs. Even though moderate dosage of neostigmine was used, neuromuscular transmission was depressed for a long period after the cessation of the infusion. The last experiments demonstrated that this prolonged block was probably the result of a marked increase in the concentration of succinylcholine at the myoneural junction. The effect of the neostigmine in the concentration used was to inactivate the plasma cholinesterase enzymes permitting the succinylcholine to persist for a longer period and at a higher concentration. As suggested in the introduction (Nastuk and Gissen<sup>4</sup>), in *in-vitro* experiments with frog muscle, use of anticholinesterase drugs permitted a 100-fold reduction in depolarizer drug concentration required to produce a given effect. Since we have no simple method of determining the presence or absence of depolarizer drug in the blood stream, the anticholinesterase drugs should be avoided in the clinical situation of impaired neuromuscular transmission following the use of the depolarizing compounds.

The descriptive terms "Phase I" and "Phase II" or "Dual Block" have outlived their usefulness and now confuse rather than illuminate the nature of the neuromuscular block caused by prolonged exposure to depolarizing compounds. Studies have indicated that the action of these compounds are twofold, depolarizing and desensitizing (Thesleff,<sup>6</sup> Nastuk and Gissen<sup>4</sup>). The early period of neuromuscular block following prolonged exposure to the depolarizing compounds is usually due to "depolarization" and electrical inexcitability of the fiber membrane. The later period of neuromuscular transmission failure is due to "desensitization" and decreasing chemical response

of the neuromuscular junction. Both processes begin simultaneously with the application of the depolarizing drug. We propose that the early period be termed "Depolarization Block" and the later period "Desensitization Block."

### Summary

Phase I and Phase II type of block following intra-arterial injection of the depolarizing drug succinylcholine are demonstrable in man *in vivo*. The response of muscle blocked by succinylcholine depends upon whether the muscle is still exposed to effective pharmacological levels of the drug in the plasma. If a profound block is present and drug is still present in the arterial blood, there will be no response to anticholinesterase drugs. The presence of nonsustained tetanus and post-tetanic facilitation are not necessarily reliable guides as to the ability of the anticholinesterase drugs to relieve the block. The block, therefore, cannot be classified as truly "curare-like." The use of anticholinesterases may result in further neuromuscular depression for prolonged periods, probably due to the reduction in the hydrolysis of succinylcholine. The use of long-acting anticholinesterases is contraindicated at any time during or after the use of depolarizing compounds. The duration of muscular blockade following the use of succinylcholine is not as much dependent on total dosage used as on concentration and rate of administration. This consideration applies only with regard to the drug concentration presented at the myoneural junction. If the amount of succinylcholine administered is just sufficient to cause complete blockade and no excess of relaxant is administered, recovery will be prompt even after prolonged administration. We suggest the substitution of the terms "Depolarization Block" and "Desensitization Block" for the usual ones of "Phase I" and "Phase II" or "Dual Block."

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**POSTANESTHESIA MORTALITY** For 114,866 anesthetics administered over a ten-year period by a group of anesthesiologists in private practice, the incidence of primary anesthetic death in surgery was 1:3,145. Spinal anesthesia was employed in 28,529 patients with six primary anesthetic deaths, an incidence of 1:4,754. In this mortality group, the anesthetic was supplemented in four cases with sodium thiopental and in each case the thiopental contributed to the death of the patient. General anesthesia was employed in 40,003 patients with 15 primary anesthetic deaths, an incidence of 1:2,666. Eight of the contributory deaths involved inadequate respiratory exchange which went unrecognized or was improperly treated. A high mortality rate in therapeutic nerve block procedures (1:36) was attributed in part to administration under adverse conditions, *i.e.*, in the patient's room, and subsequently all blocks have been performed in the operating suite where proper equipment, drugs and personnel are available for resuscitation. The common denominator in faulty management of both general and regional anesthesia was inadequate monitoring of the patient and this was especially true in those deaths which occurred in good-risk patients. No primary or contributory anesthetic deaths occurred in 43,045 consecutive deliveries, a reflection of the age and physical state of the recipients. Moreover, low dosage-small volume spinal anesthesia, which was used almost to the exclusion of any other method, obviated the disaster of aspiration of gastric content. Over the entire series, the incidence of primary cardiac arrest was 1:4,994 and the recovery rate was 44.4 per cent. Although both closed-chest and open cardiac massage appeared equally effective, closed-chest compression saved precious moments in starting effective circulation. (*Memery, H. N.: Anesthesia Mortality in Private Practice, J.A.M.A. 194: 1185 (Dec. 13) 1965.*)