STUDIES WITH MUSCLE RELAXANTS IN UNANESTHETIZED SUBJECTS

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Compared to the abundance of clinical observations and experimental studies with muscle relaxants on anesthetized subjects, relatively few reports appear in the medical literature on studies with these agents on unanesthetized man. Furthermore, with the exception of Poulsen and Hougs,[1] who compared the neuromuscular effects of four relaxants on an adequate number of unanesthetized subjects, the various investigators either studied one or two relaxants on the same individuals,[2-8] or if more compounds were studied, only relatively few experimental subjects were utilized.[9 14]

In view of the marked individual variation in the sensitivity to both depolarizing [1, 11, 15-19] and nondepolarizing [11, 20] relaxants, it seemed worthwhile to investigate the neuromuscular effects of five muscle relaxants on the same 10 unanesthetized subjects.

Material and Methods

This investigation was carried out on 10 healthy, young adult volunteers: 5 men and 5 women. The relaxants studied were *d*-tubocurarine chloride, toxiferine chloride, gallamine triethiodide, decamethonium bromide and succinylcholine chloride. In preliminary studies, the dose of each drug which produced a 90 to 95 per cent decrease of grip strength, or a 50 to 55 per cent decrease of vital capacity, whichever was greater, was determined. The enzymatic hydrolysis of succinylcholine was prevented by the intravenous administration of 0.3 mg./kg. hexafluorenium, a selective inhibitor of plasma cholinesterase.[21] The doses of the relaxants studied were: *d*-tubocurarine 100 μg./kg., toxiferine 15 μg./kg., gallamine 700 μg./kg., decamethonium 27 μg./kg., and succinylcholine 80 μg./kg. All relaxants were injected intravenously during a 90-second period. With one exception, two experiments were carried out with each of the five relaxants in all subjects. With toxiferine, however, one of the original 10 subjects became unavailable before the termination of the study, and was replaced by another volunteer. Grip strength, measured by a dynamometer, was determined immediately before and after exercise consisting of the squeezing of the bulb of an ergograph apparatus for one minute with the maximum effort of which the subject was capable, before and at 3, 6, and 10 minutes after the start of the injection of the relaxants and at 5 minute intervals thereafter. With each relaxant, the subject exercised at the rate of 60 per minute on one occasion and at 6 per minute on another. In addition to grip strength, vital capacity was measured at specified intervals with a Bennett ventilation meter. Blood pressure, pulse rate and respiratory rate were also observed at appropriate intervals. With few exceptions, the experiments were continued until grip strength returned to 75 per cent of control. In the *d*-tubocurarine and gallamine experiments, with slow rate of exercise, 5 minutes after the return of grip strength to 75 per cent of control, all subjects exercised at a fast rate for one minute.

Results

There was considerable individual variation in sensitivity to the neuromuscular effects of all 5 compounds tested. Furthermore, in every experimental subject, all compounds affected grip strength more than vital capacity. This is evident from the figures of table 1 which show that while the maximum decrease of the vital capacity varied from 12.3 ± 3.1 per cent of the control value with *d*-tubocurarine to 51.5 ± 5.4 per cent with succinyl-

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TABLE 1

COMPARISON OF THE EFFECT OF RELAXANTS ON GRIP STRENGTH AND VITAL CAPACITY

Agent and Dose (μg./kg.)	Development of Maximal Effect (minutes)	Maximum Decrease of Grip Strength*	Time Required for Return of Grip Strength to 75 Per Cent of Control (minutes)	Maximum Decrease of Vital Capacity	Time Required for Return of Vital Capacity to 75 Per Cent of Control (minutes)	Ratio of Maximum Effect on Grip Strength and Vital Capacity
d-Tubocurarine chloride (100)	5	77.3± 8.1†	14	12.3±3.1†	Never below 75 per cent of control	6.6
Toxiferine chloride (15)	5	92.5± 2.4	38	44.3±5.5	12	2.1
Gallamine triethiodide (700)	5	89.5± 2.9	20	39.8±7.1	7	2.2
Decamethonium bromide (27)	5	53.7±12.2	15	36.9±8.2	8	1.4
Succinylcholine chloride (80)‡	5	68.6± 9.7	20	51.5±5.4	15	1.3

* Expressed as percentage of control.
† Standard error.
‡ Given 5 minutes after the intravenous injection of 0.3 mg./kg. hexafluorenium.

choline, the maximum decrease of the grip strength varied from 53.7 ± 12.2 per cent of the control value with decamethonium to 92.5 ± 2.4 per cent for toxiferine. The relative sparing effect on vital capacity as compared to grip strength was greater for the nondepolarizing (fig. 1) than for the depolarizing (fig. 2) relaxants. The relative effects of toxiferine and gallamine on grip strength and vital capacity were similar to those observed with *d*-tubocurarine and the effects of decamethonium resembled those of succinylcholine.

There was no significant variation in the time necessary for the development of maximum effect. This was about 5 minutes from the start of the injection for all five compounds tested. The time of the maximum decrease of grip strength and vital capacity coincided. There was a marked difference, however, in the average time required for the return of grip strength and vital capacity to 75 per cent of control value. With *d*-tubocurarine, the average vital capacity did not fall below 75 per cent of control and with the other 4 compounds tested, it returned to this value in 7 to 15 minutes from the start of injection. In contrast to this, the time required for the return of the average grip

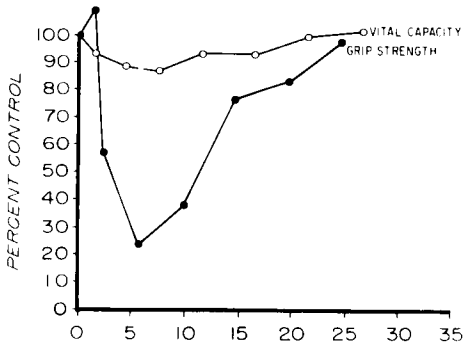

FIG. 1. The effect of 100 mg./kg. *d*-tubocurarine chloride on grip strength and vital capacity. Note the marked difference in the effect of *d*-tubocurarine on these two parameters.

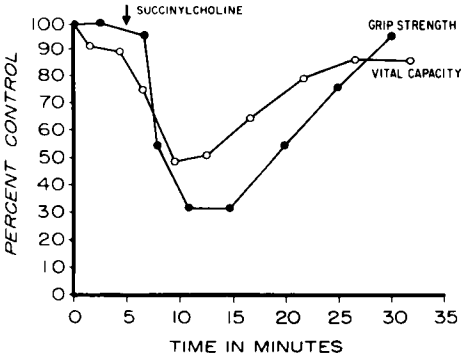

FIG. 2. The effect of 80 mg./kg. succinylcholine chloride (administered after 0.3 mg./kg. hexafluorenium bromide) on grip strength and vital capacity. Note the relatively little difference in the effect of succinylcholine on these two parameters.

TABLE 2

TIME REQUIRED FOR RETURN OF GRIP STRENGTH TO 75 PER CENT OF CONTROL BEFORE AND AFTER EXERCISE AT SLOW OR FAST RATE

Agent	Exercise 6/Minute		Exercise 60/Minute	
	Before	After	Before	After
d-Tubocurarine	14	15	20	37
Toxiferine	38	45*	47*	>60*
Gallamine	20	22	18	26
Decamethonium	15	18	13	16
Succinylcholine	20	21	17	18

* Extrapolated from the curves.

strength measured before exercise at slow rate to 75 per cent of control value, varied from 14 minutes for *d*-tubocurarine to 38 minutes for toxiferine.

The effects of exercise on the time required for the return of grip strength to 75 per cent of control are summarized in table 2. With the 3 nondepolarizing relaxants (*d*-tubocurarine, toxiferine and gallamine), the time required for the return of grip strength to 75 per cent of control was much longer when measured after exercise at a fast rate than when determined before or after exercise at a slow rate, or before exercise at a fast rate. In contrast to this, the rate of exercise did not seem to have any significant effect on the grip strength of subjects in whom partial

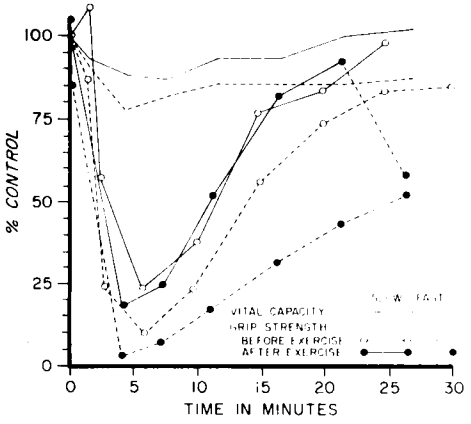

FIG. 3. The relationship between the rate of exercise and the recovery of grip strength after *d*-tubocurarine chloride (dose as in fig. 1). Note the delayed recovery of grip strength measured after exercise at fast rate.

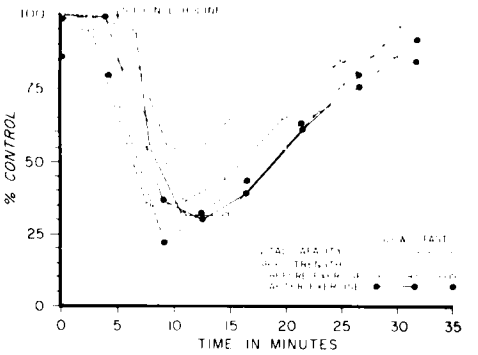

FIG. 4. The relationship between the rate of exercise and the recovery of grip strength after succinylcholine chloride (dose as in fig. 2). Note the absence of any significant influence of the rate of exercise.

neuromuscular block was produced with the two depolarizing relaxants (decamethonium or succinylcholine).

The influence of the rate of exercise on the return of the grip strength to control values is graphically presented in figure 3 for *d*-tubocurarine, a typical nondepolarizing relaxant, and in figure 4 for succinylcholine, a typical depolarizing relaxant. Here again, the results with toxiferine and gallamine or with decamethonium resembled those obtained with *d*-tubocurarine or succinylcholine, respectively. It is also evident, from figure 3, that exercise at a slow rate until the return of grip strength to 75 per cent of control, followed 5 minutes later by exercise at a fast rate, reduced the grip strength to the same extent as did rapid exercise throughout the experiment.

Exercise at a fast rate, after partial neuromuscular block had been induced by a nondepolarizing relaxant, caused rapid fatigue (fig. 5). No such fatigue of the partially curarized muscles developed if the exercise was carried out at a slow rate. In contrast to this, when the partial neuromuscular block was produced by a depolarizing relaxant (fig. 6), no fatigue developed during exercise at either fast or slow rate. The results obtained on the influence of the rate of exercise with the other nondepolarizing and depolarizing relaxants were similar ot those observed with *d*-tubocurarine and succinylcholine, respectively.

With the exception of gallamine which produced moderate tachycardia and hyper-

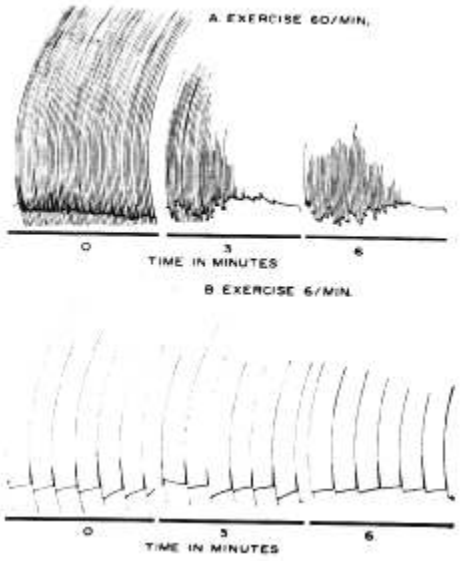

FIG. 5. The effect of the rate of exercise on grip strength after *d*-tubocurarine chloride (dose as in fig. 1). Note the progressive fatigue after exercise at a fast rate.

tension, none of the relaxants tested had a consistent effect on pulse rate, blood pressure or respiratory rate. Similarly, no evidence of histamine release was observed in any subject.

No muscular twitching or muscle pain developed in any of the volunteers who received succinylcholine following the intravenous

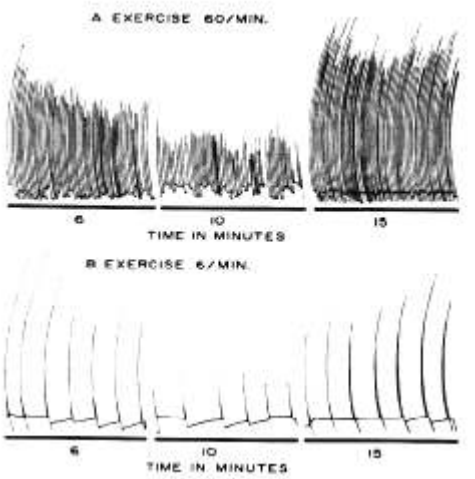

FIG. 6. The effect of the rate of exercise on grip strength after succinylcholine chloride (dose as in fig. 2). Note the absence of fatigue after fast rate of exercise.

administration of hexafluorenium. Two subjects, however, who received decamethonium complained of muscle pain which developed after the termination of the experiment. In one of these, muscular fasciculations could be observed after the intravenous administration of decamethonium. Several other subjects commented that they had a subjective feeling of muscle fasciculation immediately after the the injection of decamethonium.

Several volunteers experienced mild abdominal cramps following the administration of hexafluorenium even though it was preceded by the intravenous administration of 0.4 mg. atropine sulfate.

DISCUSSION

The relatively greater sparing effect of the nondepolarizing relaxants on respiratory muscles (table 1) observed in this study is in agreement with the findings of Unna and his associates.[12] The outstanding sparing effect of *d*-tubocurarine on respiration found in the present study, however, might be due partly to the fact that, in comparison to toxiferine and gallamine, relatively smaller doses (μg./kg.) of *d*-tubocurarine were used. While the average decrease of grip strength after toxiferine and gallamine was 92.5 and 89.5 per cent respectively, the average decrease after *d*-tubocurarine was only 77.3 per cent. The vital capacity was also more affected by these relatively large doses of toxiferine and gallamine. It was also observed in experiments, not here reported, that doses of nondepolarizing relaxants which produced a 50 to 70 per cent decrease of grip strength had practically no effect on vital capacity. In contrast, the doses of decamethonium and succinylcholine, which produced similar decreases of grip strength in the present study, decreased vital capacity by 37 and 51 per cent respectively (table 1).

When its enzymatic hydrolysis was prevented by the selective inhibition of plasma cholinesterase by hexafluorenium, the potency, onset and duration of action of succinylcholine was found to be similar to that of *d*-tubocurarine. The rapid onset of action of succinylcholine and the excellent conditions produced by it for endotracheal intubation are due to the fact that it is administered in

comparatively much higher initial doses than other relaxants in clinical use. These large doses may be used with impunity in most instances because the profound block is rapidly terminated by the enzymatic hydrolysis of succinylcholine.

The early fatigue caused by rapid rate of exercise in the grip strength of subjects in whom partial neuromuscular block was produced by nondepolarizing agents has at least two possible explanations. One is the progressive exhaustion of the acetylcholine reserves by exercise, resulting in the decrease of the quantity of acetylcholine available, to a level lower than that required for the transmission of the nerve impulse in the presence of a nondepolarizing blocking agent. The other is an interference by the nondepolarizing relaxant with the synthesis or release of acetylcholine at the neuromuscular junction. Such a mechanism has been postulated as the cause of a neuromuscular block by hemicholinium.[22] It is of interest that the intensity of the hemicholinium block is markedly influenced by the rate of stimulation.[22] Both the exhaustion of the acetylcholine reserves or interference with the synthesis or release of acetylcholine would lead to a decrease of the quantity of acetylcholine available at the end-plate. Since acetylcholine and *d*-tubocurarine are in competiton for the cholinergic receptors of the end-plate, the decrease of the acetylcholine concentration will increase the blocking effect of *d*-tubocurarine. In contrast, the depolarizing relaxants, similarly to acetylcholine, increase the "lability" of the end-plate to depolarizing influences.[23, 24] Because of this, during the partial block produced by these compounds, the end-plate region may be reversibly depolarized by smaller quantities of acetylcholine. Consequently, partial exhaustion of the acetylcholine reserves during exercise would not have the same effect on neuromuscular transmission as under the influence of nondepolarizing relaxants. It is also possible that, whereas nondepolarizing relaxants interfere with the synthesis or release of acetylcholine at the neuromuscular junction, the depolarizing relaxants have no such effect.

Our observations on the relationship between the rate of exercise and the development of fatigue are in agreement with the recent findings of Churchill-Davidson and Christy.[25] They observed, in human subjects, a gradual decrease in the amplitude of the electromyogram induced by repeated indirect stimulation during partial neuromuscular block caused by *d*-tubocurarine. No such decrease in the amplitude of the electromyographic tracing was observed by them if partial neuromuscular block was produced by decamethonium.

The results of the present study also indicate that if the rate of exercise is 6 per minute or less, there is no apparent exhaustion of the acetylcholine reserves and enough acetylcholine is released by the nerve impulse to maintain neuromuscular transmission at a constant level in the partially curarized muscle. Furthermore, it appears that the acetylcholine reserves, exhausted by rapid rate of exercise, are replenished within 3 to 5 minutes. This is indicated by the finding that there is little or no difference in pre-exercise grip strength of partially curarized subjects who exercised at fast or slow rate for one minute at 5-minute intervals (figs. 5 and 6).

Besides its theoretical interest, the effect of the rate of exercise on the course of partial neuromuscular block induced by nondepolarizing relaxants may also have clinical significance. Following the use of relaxant drugs, partial neuromuscular block is frequently present at the termination of operation. Immediately after discontinuing assisted or controlled respiration, as used during anesthesia, spontaneous respiratory activity may seem adequate. Later, however, the partially curarized respiratory muscles may become exhausted and if, under such circumstances, the patient is unattended, hypoxia and hypercarbia may develop. In extreme cases, exhaustion of the respiratory muscles may result in the patient's death. Since in man the properties of the neuromuscular block induced by depolarizing relaxants on prolonged administration may become similar to those caused by nondepolarizing agents,[26] the danger of postanesthetic recurarization due to fatigue may also be present after the use of depolarizing agents. On the basis of the present findings, it should be re-emphasized that patients to whom neuromuscular block-

ing agents have been administered, even if their respiratory activity appears adequate at the termination of anesthesia, should be kept under competent supervision until all possibility of "recurarization" is eliminated.

Summary

The neuromuscular activity of three nondepolarizing (*d*-tubocurarine chloride, toxiferine chloride, gallamine triethiodide) and two depolarizing relaxants (decamethonium bromide, succinylcholine chloride) was investigated in 10 unanesthetized, healthy, young adult volunteers. Two experiments were carried out with each relaxant on every subject.

Grip strength and vital capacity were measured at specified intervals, before and after exercise of the hand, on one occasion at the rate of 6 times, and on another occasion at the rate of 60 times per minute. The time necessary for the return of grip strength to 75 per cent of control was also observed.

All compounds affected grip strength more than vital capacity. This relative respiration sparing effect was greater with the nondepolarizing than with the depolarizing relaxants.

Recovery of grip strength after exercise at a fast rate was markedly delayed with the nondepolarizing relaxants. No such difference in the recovery of grip strength was observed after the use of depolarizing agents.

Toxiferine was supplied by Hoffman-La Roche, Inc., Nutley, New Jersey, and hexafluorenium bromide (Mylaxen), by Irwin, Neisler Co., Decatur, Illinois. Ergograph apparatus was made by Physiological Apparatus, Watertown, Massachusetts.

REFERENCES

1. Poulsen, H., and Hougs, W.: Effect of some curarizing drugs in unanesthetized man, Acta anaesth. scand. **1**: 15, 1957.
2. Bodman, R. I.: Evaluation of two synthetic curarizing agents in conscious volunteers, Brit. J. Pharmacol. **7**: 409, 1952.
3. Churchill-Davidson, H. C., and Richardson, A. T.: Action of decamethonium iodide (C10) in myasthenia gravis, J. Neurol. Neurosurg. Psychiat. **15**: 129, 1952.
4. Mushin, W. W., Wien, R., Mason, D. F. J., and Langston, G. T.: Curare-like actions of tri(diethylamino-ethoxy)benzene triethyliodide, Lancet **1**: 726, 1949.
5. Mayrhofer, O. K.: Self-experiments with succinylcholine chloride, Brit. Med. J. **1**: 1332, 1952.
6. Irmer, W., Rotthoff, F., and Schneider, H.: Vergleichende spirometrische Untersuchungen nach Anwendung verschiedener Muskelrelasantien an nicht narkotisierten Menschen, Anaesthesist **2**: 103, 1953.
7. Harvey, A. M., Grob, D., and Holaday, D. A.: Some preliminary observations on neuromuscular and ganglionic blocking action in man of bis-trimethyl-ammonium decane and pentane diiodide, Trans. Amer. Clin. Climat. Ass. **60**: 133, 1949.
8. Grob, Johns, R. J., and Harvey, A. M.: Studies in neuromuscular function; effects of anticholinesterase compounds, *d*-tubocurarine and decamethonium in normal subjects, Bull. Johns Hopkins Hosp. **99**: 195, 1956.
9. Macfarlane, D. W., Pelikan, E. W., and Unna, K. R.: Evaluation of curarizing drugs in man; antagonism to curarizing effects of *d*-tubocurarine by neostigmine m-hydroxyphenyltrimethylammonium and m-hydroxyphenylethyldimethylammonium, J. Pharmacol. Exp. Ther. **100**: 382, 1950.
10. Macfarlane, D. W., Unna, K. R., Pelikan, E. W., Cazort, R. J., Sadove, M. S., and Nelson, J. T.: Evaluation of curarizing drugs in man; antagonism to curarizing effects of *d*-tubocurarine and decamethylene-bis (trimethylammonium bromide), J. Pharmacol. Exp. Ther. **99**: 226, 1950.
11. Pelikan, E. W., Unna, K. R., Macfarlane, D. W., Cazort, R. J., Sadove, M. S., and Nelson, J. T.: Evaluation of curarizing drugs in man; analysis of response curves and effects of repeated administration of *d*-tubocurarine, dimethyl-*d*-tubocurarine and decamethylene-bis-(trimethylammonium bromide), J. Pharmacol. Exp. Ther. **99**: 215, 1950.
12. Unna, K. R., and Pelikan, E. W.: Evaluation of curarizing drugs in man; critique of experiments on unanesthetized subjects, Ann. New York Acad. Sci. **54**: 480, 1951.
13. Unna, K. R., Pelikan, E. W., Macfarlane, D. W., Cazort, R. J., Sadove, M. S., Nelson, J. T., and Drucker, A. P.: Evaluation of curarizing drugs in man; potency, duration of action, and effects on vital capacity of *d*-tubocurarine, dimethyl-*d*-tubocurarine and decamethylene-bis-(trimethylammonium bromide), J. Pharmacol. Exp. Ther. **98**: 318, 1950.
14. Unna, K. R., Pelikan, E. W., Macfarlane, D. W., Cazort, R. J., Sadove, M. S., and Nelson, J. T.: Evaluation of curarizing agents in man, J. A. M. A. **144**: 448, 1950.
15. Churchill-Davidson, H. C., and Richardson, A. T.: Decamethonium iodide (C10): some observations on its action using electro-

myography, Proc. Roy. Soc. Med. **45**: 179, 1952.
16. Foldes, F. F., Swerdlow, M., Lipschitz, E., van Hees, G. R., and Shanor, S. P.: Comparison of respiratory effects of suxamethonium and suxethonium in man, ANESTHESIOLOGY **17**: 559, 1956.
17. Guerrier, S. M., and Mason, J. C.: Undesirable side effects from decamethonium iodide, Brit. Med. J. **1**: 1329, 1952.
18. Organe, G.: Decamethonium iodide (bistrimethyl ammonium decane diiodide) in anaesthesia, Lancet **1**: 773, 1949.
19. Thesleff, S.: Investigation of muscle relaxing action of succinylcholine iodide in man, Acta physiol. scand. **25**: 348, 1952.
20. Pelikan, E. W., Tether, J. E., and Unna, K. R.: Sensitivity of myasthenia gravis patients to *d*-tubocurarine and decamethonium, Neurology **3**: 284, 1953.
21. Foldes, F. F., Hillmer, N. R., Molloy, R. E., and Monte, A. P.: Potentiation of neuromuscular effect of succinylcholine by hexafluorenium, ANESTHESIOLOGY **21**: 50, 1960.
22. Reitzel, N. L., and Long, J. P.: Neuromuscular blocking properties of α, α′-dimethylethamolamino - 4, 4′ - biacetophenone (hemicholinium), Arch. internat. pharmacodyn. **119**: 20, 1959.
23. Shanes, A. M.: Drug and ion effects in frog muscle, J. Gen. Physiol. **33**: 729, 1950.
24. Shanes, A. M.: Electrochemical aspects of physiological and pharmacological action in excitable cells: Action potential and excitation, Pharmacol. Rev. **10**: 165, 1958.
25. Churchill-Davidson, H. C., and Christie, T. H.: Diagnosis of neuromuscular block in man, Brit. J. Anaesth. **31**: 290, 1959.
26. Foldes, F. F., Wnuck, A. L., Hodges, R. J. H., Thesleff, S., and deBeer, E. J.: Mode of action of depolarizing relaxants, Anesth. Analg. **36**: 23, 1957.

AZEOTROPIC MIXTURE An exact azeotropic mixture is obtained when 68.3 ml. of halothane is added to 31.7 ml. of diethyl ether. Physically, the mixture behaves like a pure compound. It evaporates at a constant boiling point of 51.5 C. The lower limit of inflammability with oxygen is from 8 to 10 per cent. In the azeotropic mixture, the actions of the two components are additive. In clinical experience, the mixture has been found to enhance the advantages of these two agents and minimize their unwanted side effects. Thus mixed with halothane, diethyl ether can augment analgesia, increase ventilation, and diminish pain reflexes and reflex arrhythmias. (*Jacques, A.: Halothane-Ether Azeotropic Mixture, Canad. M. A. J. 83: 539 (Sept. 3) 1960.*)

MASS CASUALTIES A simple, portable, anesthetic apparatus for use in the anesthetization of mass casualties is described. The apparatus consists of a face mask, a 6-liter breathing bag, a small soda-lime canister for absorbing carbon dioxide, and a small device for charging the bag with a preset mixture of cyclopropane, oxygen and nitrogen. The bag is filled with the preset mixture and the patient allowed to breathe from the bag. The bag is recharged as indicated for continuation of anesthesia. With a single charging, the surgeon has about five minutes' operating time in adults and up to nine or ten minutes in small children. (*Stephens, K. F.: Anaesthesia for Mass Casualties, Lancet 2: 481 (Aug. 27) 1960.*)