SOME EFFECTS OF SUCCINYLCHOLINE CHLORIDE IN CONSCIOUS HUMAN SUBJECTS*

S. L. VANDEWATER, M.D., F.R.C.P.(C), S. G. LAVERTY, M.B., CH.B., DUGAL CAMPBELL, PH.D., AND R. E. SANDERSON, PH.D.

SUCCINYLCHOLINE has been widely studied as a muscle relaxant in human subjects, usually in conjunction with an anaesthetic agent. The independent effects of the drug have seldom been reported. The present report is concerned with the effects of succinylcholine in conscious unanaesthetized subjects. The reason for using succinylcholine in this manner was to investigate its potentialities as a stimulus in producing avoidance-conditioning towards alcohol. The psychological aspects of this work will be presented separately.[1]

METHOD OF INVESTIGATION

Following preliminary experiments in which the authors and colleagues acted as subjects, patients suffering from alcoholism were given a standard dose of succinylcholine (20 mg.) associated with a conditioning procedure. Four physiological indices (heart rate, respiration, skin resistance, and muscle tension) were recorded between the left palm and left forearm. Respiratory rate and depth was measured using a Manning pneumographic bellows fastened around the chest. A tachographic tracing of the heart rate was obtained from a photosensitive transducer attached to the left ear. Muscle potentials were recorded between two electrodes in the right and left temporalis muscles. These recordings were made synchronously and were examined in relation to signals denoting the time of injection of the succinylcholine and to other clinical data.

The subject lay on a couch and received the succinylcholine through an intravenous drip which had been set up before recording began. At a pre-arranged signal and unknown to the subject 20 mg. of succinylcholine (1 c.c.) was injected into the drip, which was then turned on full to produce a rapid inflow of the drug.

The subjects on whom this report is made were white males between the ages of 26 and 55 suffering from chronic alcoholism but in good physical health. In each case liver function tests (thymol turbidity, indirect Van Den Burgh reaction) and electrocardiogram recording were within normal limits. The nature of the experimental situation was represented to the patients as a possible treatment for alcoholism, and it was indicated that the experience would be highly stressful.

Apparatus failures and difficulty in making reliable readings from the polygraph records resulted in the loss of some data. In all, 14 patients were given succinylcholine. For each category of results discussed in this paper the number of reliable observations is shown; seven patients had complete records and they provide the major part of the data.

*From the Departments of Anaesthesia, Psychiatry, and Psychology, Queen's University, Kingston, Ontario.

Results

The sequence of events following the injection of succinylcholine may be conveniently described under the headings of paralysis of movement and respiration, heart rate, skin resistance, and muscle tension.

Paralysis of Movement and Respiration

The first noticeable disturbance consisted of sudden restless movement, apparently in response to the sensation of twitching in the muscles. In four of the seven cases twitching was easily apparent at this point in the muscles of the face. At the same time recording of respiration showed a disturbed tracing in which one or two small respirations were taken. This was rapidly followed by cessation of normal breathing responses indicated on the recording by an irregular or straight line. The initial disturbance of breathing occurred between 24 and 45 seconds following the injection of succinylcholine (individual figures being 28, 30, 40, 30, 45, 24, and 31 seconds). These variations are probably due more to differences in the rate of the intravenous infusion than to any other single factor. The interval between the first disturbance and paralysis of breathing was short (individual figures being 1, 3, 8, 25, 13, 13, and 9 seconds). During this period there tended to be small, irregular respirations and slight movements, particularly of the hands. Early onset of disturbed breathing was not related to a rapid onset of complete paralysis. The establishment of a respiratory paralysis occurred before total paralysis took place. Several subjects made movements which appeared to be attempts to remove a mask from their mouth. However these actions were made with little strength and, after about 30 seconds, all the patients were still.

After a variable period movement returned, being most evident in movements of the hands, arms, and legs. These movements were weak and ill-sustained and in no case sufficient to dislodge the recording electrodes. Also noted were rotary movements of the trunk which in some instances compressed the pneumographic bellows producing variations of a sharp and irregular type which did not resemble the smoother tracings produced by breathing. Evidence of first recorded muscular movements was noted after 35, 53, 60, 71, 85, 46, and 65 seconds. The first return of respiration was shown by small undulations in the respiration tracing which gradually increased in amplitude until normal breathing, resembling that before the experiment began, was reinstated. The times at which first respirations were noted on the polygraph recording correlated well with the clinical impression that breathing had returned. In two instances return of respiration was assisted by insufflation with a hand respirator. The times for return of first respirations were as follows: 85, 130, 100, 90, 118, 65, and 95 seconds. Return of respiration in each case was later than return of muscular activity, contrary to other reports.[2] Normal breathing was considered to be present at the following intervals of time: 481, 170, 170, 170, 297, 185, and 370 seconds. These times are measured from the first noted disturbance.

Following the resumption of normal respiration, subjects lay quietly until the termination of the experiment some twenty minutes later. They were then asked to give an account of their experience. All emphasized that the inability to

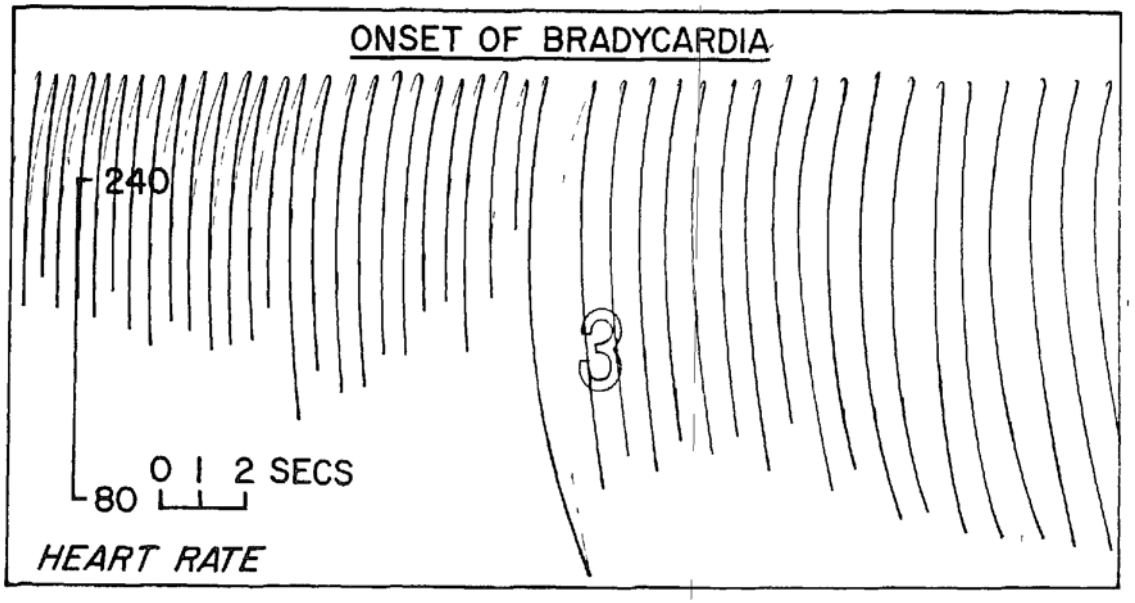

FIGURE 1. An example of a sudden onset of bradycardia occurring during the apnoea (a tachograph recording is shown: the extent of the pen movement shows pulse rate—a longer stroke indicating a slower rate); in this case a change from approximately 165 to 90 beats a minute has taken place within 2 seconds.

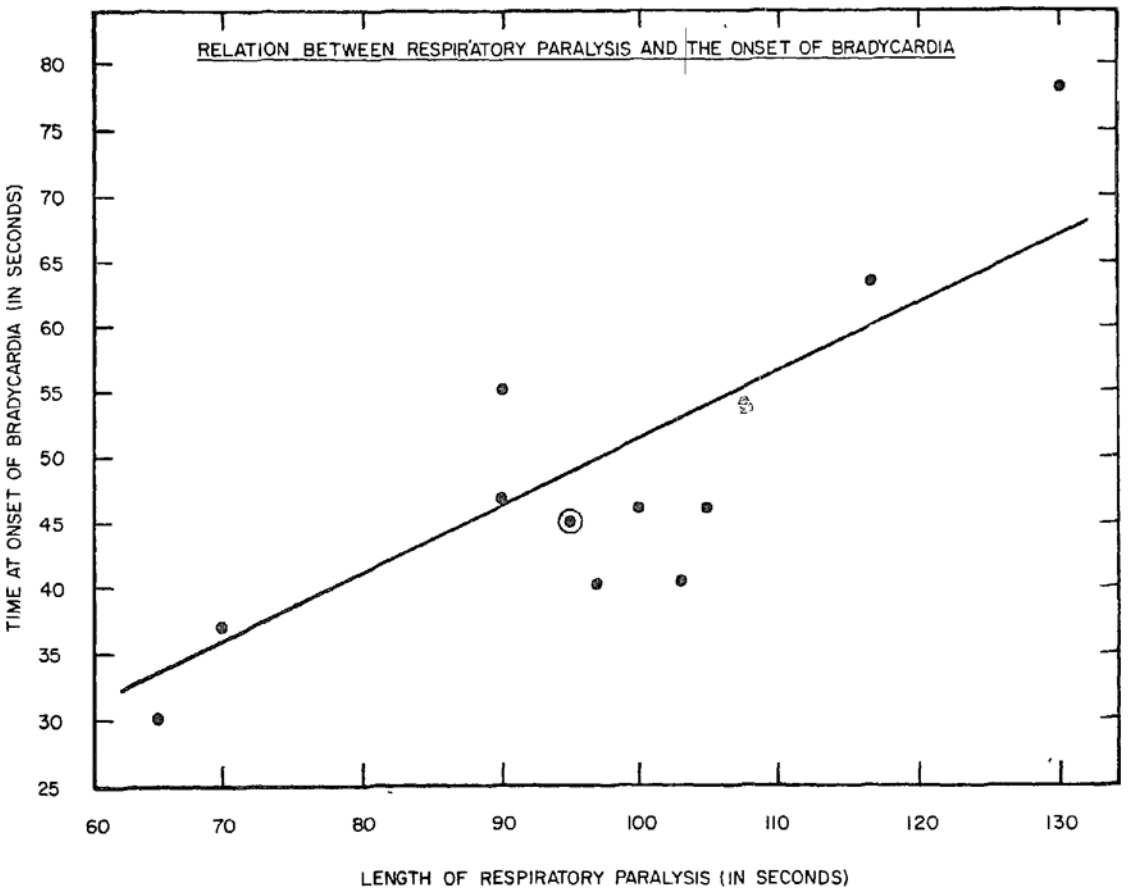

FIGURE 2. The linear relation between onset of bradycardia and duration of respiratory paralysis.

breathe was extremely frightening, and in addition they found that difficulty in moving added to their distress. In addition the subjects described difficulty in seeing and blurring of vision, muscle sensations including pains, dryness of the mouth, difficulty in speaking, and fear of impending dissolution.

During the following 48 hours four patients described some muscle pains, chiefly in the back and legs but these were not considered troublesome.

Heart Rate

Observations on heart rate were made in the seven subjects referred to above, and in an additional five subjects. A moderate or marked tachycardia was present in most cases prior to the experiment and this was attributed to apprehension.

Following the injection of succinylcholine an increase in heart rate was observed in all twelve subjects during the first minute. In the majority of cases this was followed by an abrupt slowing, e.g., a decrease in rate of 40 beats per minute in 5 seconds. However, in some other cases we have examined, the slowing, although observed, was more gradual.

In these 12 cases where slowing was abrupt the moment of the onset of bradycardia bore an interesting linear relation to the duration of apnoea; this is shown in Figure 2. The straight line fitted to the observed data was tested for goodness-of-fit by chi-square; the deviations of the observed data from the line are not significant ($0.50 > p > 0.30$).

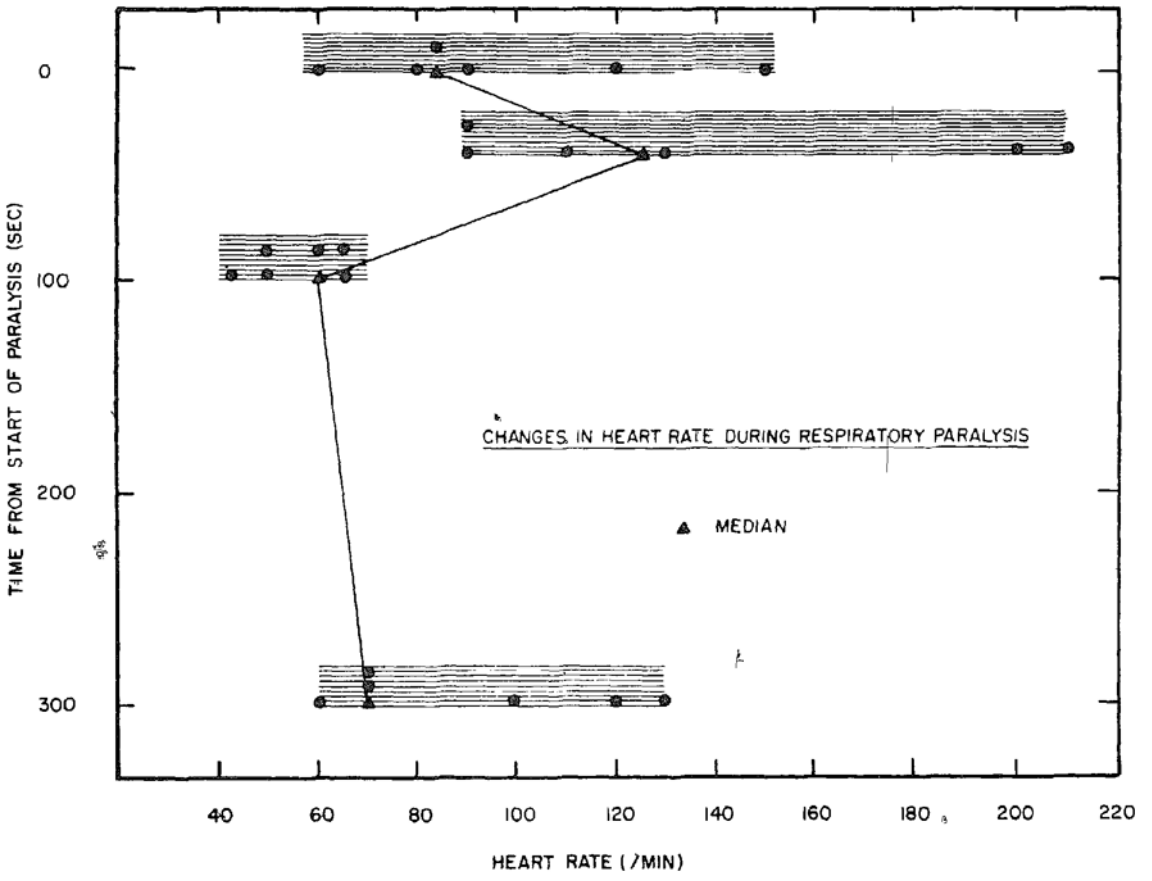

FIGURE 3. The sequence of changes in heart rate during respiratory paralysis.

The bradycardia persisted and increased gradually during the latter part of the experiment and after breathing had begun. Figure 3 shows the sequence of changes in heart rate for the seven subjects for whom reliable records were obtained for each stage. An analysis of variance shows the changes to be significant ($p < 0.001$); all successive shifts in the heart rate are significant at the 0.05 level of confidence, and the shift from tachycardia to bradycardia is significant at the 0.01 level, of confidence.

A more complex association was found between the pretreatment heart rate and the duration of the apnoea. A reliable reading for this relation was made for 14 subjects. The relation is non-linear but apparently quite close as the two measures have a rank order correlation of 0.709. A hyperbolic curve was fitted to the data and is shown in Figure 4. The curve was tested for goodness-of-fit by chi-square and the deviations of the observed data from the line were found to be not significant ($0.30 > p > 0.20$).

Since bradycardia is rarely observed during the normal induction of anaesthesia combined with succinylcholine,[3,4] three subjects were given two injections, the first being thiopentone 0.4 gm. in 8 c.c. of water. In every case the thiopentone was given rapidly and the injection occupied less than a minute. Immediately

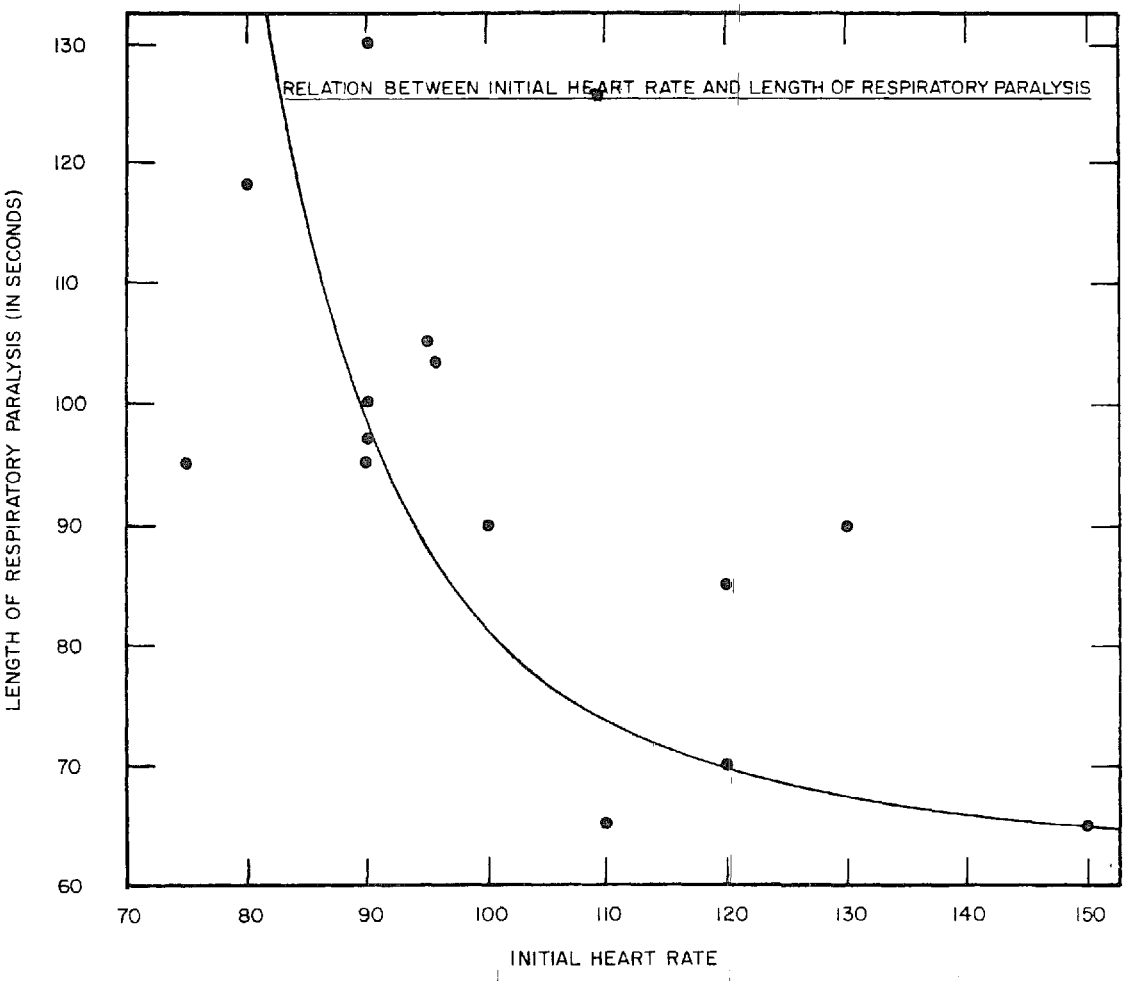

FIGURE 4. The hyperbolic relation between initial heart rate and duration of respiratory paralysis.

following the thiopentone injection a 20 mg. injection of succinylcholine was given. This sequence parallels the usual form of administration of the two drugs before electroconvulsive therapy. This experiment was carried out approximately three weeks after the initial one using succinylcholine alone. In none of these three cases did a bradycardia appear. It was noted also that the duration of apnoea was definitely shorter after the combined injection: the respective times in seconds (succinylcholine/combined injection) being 118/15, 105/40, 103/20. An examination of the polygraph tracings in relation to the signals indicating the time at which the two injections were made showed that no apnoea occurred until some seconds after the injection of succinylcholine. No evidence of hypoxia, such as sweating or cyanosis, was observed in these subjects during the period in which the two drugs were active.

It is unlikely that any tolerance for succinylcholine could have been developed by the single dose given three weeks before. Therefore one may argue that the use of succinylcholine in normal anaesthetic practice with other drugs disguises the equilibration of succinylcholine given alone. Similarly one might argue that succinylcholine may have an effect on the normal sequence of events due to an anaesthetic drug.

Skin Resistance

A sudden change in skin resistance was frequently the first sign of the drug effect and coincided with the first slight changes in respiration. A second change in skin resistance occurred at about the same time as the bradycardia. At this point the initial change in skin resistance was reversed and slowly returned to a resting level. Once returned to a resting level frequent moment-to-moment fluctuations were observed. This variation of level is regarded as an association of anxiety.[5]

Muscle Tension

At the onset of the succinylcholine effect an electromyographic discharge was observed associated with the clinically apparent muscle twitches and movement. Following this a reduction in recorded muscle tension occurred, but a return to pretreatment levels (or greater) was observed considerably before apnoea was concluded.

Discussion

The effects of succinylcholine as administered in these reported experiments are essentially those reported in conjunction with anaesthesia, namely paralysis of movement and respiration. However the form and duration of the effects were different. In the present instance the duration, sequence of paralysis, and the presence of bradycardia are points of difference.

Duration of Paralysis

It has been reported that thiopentone conjoined with succinylcholine will produce a longer period of apnoea than one of these agents alone.[6] The contrary finding was made in three subjects observed here. In these the duration of apnoea was definitely shorter in each case when thiopentone was used.

Sequence of Paralysis Recovery

Respiration appeared to be the first muscular function to be paralysed and the last to return. Peripheral limb movements were seen after breathing had stopped, and also well before respiratory movement returned. This is the reverse of the commonly reported sequence.[2] A hyperbolic relation was discovered between the initial (resting) heart rate and the duration of apnoea. The longest periods of apnoea were associated with the lowest heart rates.

The relation found between initial heart rate and length of apnoea has no obvious explanation. If one assumes that a slow heart rate leads to a slow distribution of the drug it is possible to suppose that a long apnoea may result. However the succinylcholine is broken down by the enzyme pseudo-cholinesterase in the blood acting as a catalyst so it is also possible to argue that a slower distribution of the drug should lead to a greater destruction of succinylcholine and consequently to a shorter action. Another possible complicating factor in the argument is the concentration gradients at the motor end-plate which may control the rate of exchange between the end-plates and the blood stream.[7]

Bradycardia

The appearance of bradycardia after the administration of succinylcholine has been reported after intermittent repeated doses, and/or in children,[4,6] but is not normally seen in anaesthetic practice after a single dose. The onset of bradycardia in the present series was a regular event. When it occurred early and rapidly, it showed a relation to the duration of apnoea. It is probable that its occurrence in this form is a direct effect of breakdown of succinylcholine with the production of acetylcholine. This effect was not observed after thiopentone in accordance with former observations. The relation between changes in heart rate and biochemical and physiological factors requires further investigation.

Summary

Succinylcholine (20 mg.) was administered to alcoholic patients as part of a conditioned aversion therapy against alcohol. No anaesthesia was used. The effects of succinylcholine on respiration, heart rate, skin resistance, and muscle tension were recorded. A marked bradycardia was consistently observed during the period of apnoea.

In three subjects these observations were repeated combining the injection of thiopentone (0.4 gm.) with succinylcholine (20 mg.). No bradycardia appeared and the period of apnoea was shorter than when the succinylcholine was given alone.

Résumé

Nous avons donné de la succinylcholine (20 mg.) à des alcooliques comme partie d'un traitement destiné à provoquer de l'aversion pour l'alcool. Nous n'avons pas employé d'anesthésie. Nous avons enrégistré les effets de la succinylcholine sur la respiration, le rythme cardiaque, la résistance de la peau et le tonus musculaire. De façon constante, durant la période d'apnée, nous avons noté une bradycardie marquée.

Chez trois malades, nous avons repris notre étude en associant du thiopentone (0.4 gm.) à la succinylcholine (20 mg.). Nous n'avons plus observé de bradycardie et la période d'apnée a été plus courte que lorsque la succinylcholine était donnée seule.

REFERENCES

1. SANDERSON, R. E.; CAMPBELL, D.; & LAVERTY, S. G. An Investigation of a New Aversive Conditioning Treatment for Alcoholism (in preparation).
2. HOLMBERG, G., & THESLEFF, S. Succinylcholine as Muscle Relaxant in Electroshock Therapy. Nordisk. Med. *46*: 1567–1569 (1951).
3. BARRETO, R. S. Effect of Intravenously Administered Succinylcholine upon Cardiac Rate and Rhythm. Anesthesiology *21*: 401–404 (1960).
4. BULLOUGH, J. Intermittent Suxamethonium Injections. Brit. Med. J. *1*: 786–787 (1959).
5. BECKER, W. C. & MATTESON, H. H. GSR Conditioning, Anxiety, and Extraversion. J. Abnorm. Soc. Psychol. *62*: 427–430 (1961).
6. LEIGH, M.; DIGBY, G.; MCCOY, P. D.; BELTON, K. M.; & LEWIS, G. B. JR. Bradycardia Following Intravenous Administration of Succinylcholine Chloride to Infants and Children. Anesthesiology *18*: 698–702 (1959).
7. KALOW, W. *In* Relaxants, in Uptake and Distribution of Anesthetic Agents, *edited by* E. M. Papper and R. J. Kitz, pp. 302–313. New York: McGraw Hill Publishing Company (1963).