# *The Response of Infants and Children to Muscle Relaxants*

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**The respiratory response of infants and children to *d*-tubocurarine and succinylcholine was examined. Under halothane anesthesia children under one year require about one quarter of the dose of *d*-tubocurarine per kilogram of body weight compared to children over 12 years. The variation in the amount of respiratory depression caused by *d*-tubocurarine at different ages depends upon the general anesthetic agent used. Succinylcholine, with halothane anesthesia, produced greater relaxation in children under one year than in older children. It appeared that children under one year are more sensitive to the drug.**

THE DOSAGE of muscle relaxants for infants and children has, in the past, been calculated from the adult dosage on a body weight basis. In 1955 Stead[1] showed that infants under one month old are more sensitive to *d*-tubocurarine and more resistant to succinylcholine than are adults. Telford and Keats[2] concluded that the younger the child, the greater the amount of succinylcholine required to maintain apnea. Bush and Stead[3] demonstrated a linear relation between the quantity of *d*-tubocurarine initially necessary to allow adequate control of ventilation and age, in the first month of life. They suggested that this relation of dosage to age was dependent upon a change at the motor end-plate and diminution of extracellular volume.

Recently, Churchill-Davidson and Wise[4] investigated neonates and showed that neuromuscular transmission resembled that seen in adults with myasthenia gravis, exhibiting marked tolerance to the paretic effect of decamethonium (Syncurine). They suggested that the motor end-plate becomes adult in type after the first few weeks of life. There is, therefore, excellent evidence in the literature to show that infants and children cannot be looked upon as small adults when muscle relaxants are to be used. Salanitre and Rackow[5] found a higher incidence of postoperative respiratory complications in newborn infants in whom muscle relaxants had been used. This they attributed to overdosage with the relaxants and to hypothermia. The accurate assessment of the dose of a muscle relaxant to be administered to infants and children is therefore demonstrably important.

The methods used to assess relaxant effects[1, 2, 3] have been all or none in nature and it was thought that more valuable information would be obtained if some method could be devised which would reveal effects other than complete apnea. This paper is concerned with an analysis of results so obtained in infants and children.

## Material and Method

One hundred thirty-four normal infants and children, varying from 5 weeks to 16 years in age, were investgiated. Light premedication with combinations of pentobarbital (Nembutal), morphine or promethazine (Phenergan) with scopolamine was used. All the children were intubated and were breathing spontaneously having been subjected to minor surgical procedures before investigation. Anesthesia was maintained postoperatively at plane 1, stage 3 (Guedel), with nitrous oxide and oxygen and either halothane, methoxyflurane or ether during the *d*-tubocurarine investigation. Only halothane with nitrous oxide and oxygen was used during investigation of succinylcholine. A nonrebreathing or Ayre's T piece technique was used. Normal

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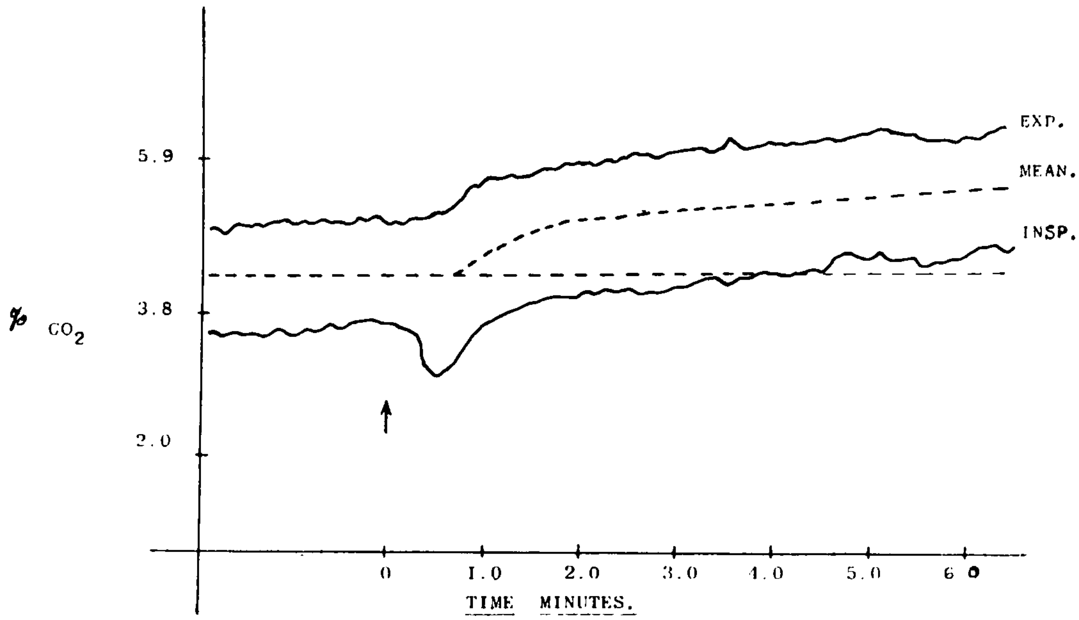


FIG. 1. Response of child to the administration of 0.066 mg./kg. *d*-tubocurarine at the arrow. The mean carbon dioxide concentration returned to the base line in about 20 minutes (not shown). The area enclosed by the mean and the base line during the first five minutes was used to assess the relaxant effect.

body temperature was maintained with a warming mattress during the procedure.

A fine plastic catheter, French 5, was introduced into the endotracheal tube so that it reached the tip, and was connected to a Beckman L-B 1 microcell $CO_2$ analyzer to record carbon dioxide changes. Continuous suction was maintained at about 100 ml. per minute so that mean inspiratory/expiratory carbon dioxide concentration was easily obtained. Calibration of the analyzer was carried out with known carbon dioxide and oxygen mixtures. A dose of *d*-tubocurarine in a concentration of 0.3 mg./ml. was given intravenously to produce respiratory depression without apnea. This dose was found by experiment to be 0.066 mg./kg. for all ages under ether anesthesia, 0.10 mg./kg. for all ages with methoxyflurane and 0.16 mg./kg. for all ages with halothane. Sufficient respiratory impairment occurred to cause a rise in the mean expired carbon dioxide concentration which reached a plateau within about three minutes and in most children declined to the base line in about twenty minutes. The mean carbon dioxide concentration was drawn on the tracing and the effect of the relaxant was assessed by measuring, with a planimeter, the area enclosed by this line and the base line in the first five minutes (fig. 1). The gain setting of the analyzer was constant throughout the investigation. The dosage in mg./kg. was divided by this area to give mg./kg./cm.$^2$ as an estimate of relaxant effect. This method appeared to give an accurate expression of respiratory impairment due to the relaxant. Administration of a standard dose allowed direct comparison between children of different ages.

Succinylcholine was given intravenously in a concentration of 5.0 mg./ml. In children over one year old, 0.33 mg./kg. was found to produce respiratory depression without apnea, so that measurements similar to those made with *d*-tubocurarine were possible (fig. 2a). This dosage produced apnea in all infants under one year of age; and in half of them, to avoid this, 0.25 mg./kg. was used. Nevertheless it was found possible to estimate the "area of $CO_2$ rise" as shown in figure 2b for those infants in whom brief apnea occurred. It was assumed that the carbon dioxide concentration

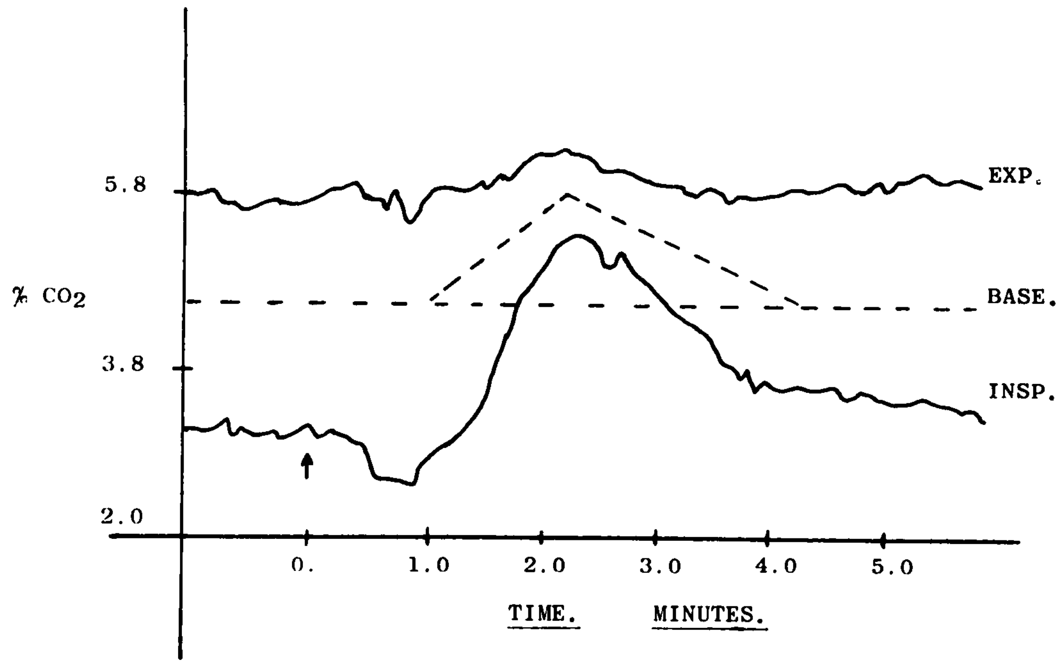


FIG. 2a. Succinylcholine 0.33 mg./kg. at arrow. The area enclosed by the triangle represents the degree of respiratory impairment.

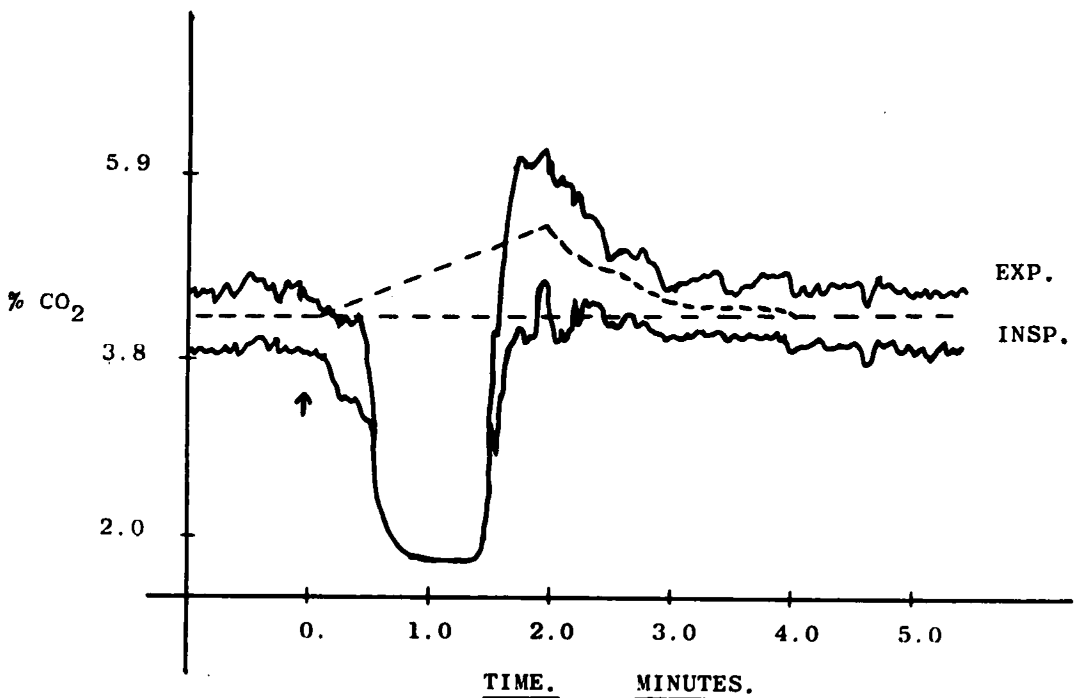


FIG. 2b. Succinylcholine 0.33 mg./kg. given at the arrow to a child under one year of age. Apnea at 30 seconds lasting for one minute. It was assumed that the mean carbon dioxide concentration would follow the dashed triangle and this area above the base line was used to assess relaxant effect.

Table 1. *d*-Tubocurarine

| Ether | | Methoxyflurane | | Halothane | |
|---|---|---|---|---|---|
| Age W = Week M = Month Y = Year | mg. × $10^{-3}$/kg./cm.$^2$ | Age | mg. × $10^{-3}$/kg./cm.$^2$ | Age | mg. × $10^{-3}$/kg./cm.$^2$ |
| 6 W | 3.15 | 6 W | 11.62 | 6 W | 12.48 |
| 8 W | 2.64 | 8 W | 8.34 | 8 W | 13.02 |
| | | | | 10 W | 14.19 |
| 3 M | 2.94 | 3 M | 9.11 | 3 M | 10.26 |
| 6 M | 3.57 | 6 M | 9.39 | 5 M | 15.97 |
| 9 M | 4.03 | 9 M | 9.03 | 9 M | 13.25 |
| 1 Y | 3.76 | 1 Y | 10.07 | 1 Y | 14.37 |
| 1½ Y | 3.07 | 1½ Y | 9.17 | 1½ Y | 16.65 |
| | | 1½ Y | 9.47 | | |
| | | 2 Y | 9.37 | | |
| 2 Y | 4.36 | 2 Y | 8.13 | 2 Y | 15.63 |
| 2½ Y | 5.93 | 3 Y | 11.09 | 2 Y | 21.44 |
| 3 Y | 6.77 | 3 Y | 11.36 | 3 Y | 18.02 |
| | | 3 Y | 11.04 | | |
| 4 Y | 4.91 | 4 Y | 9.57 | 4 Y | 17.98 |
| 4½ Y | 4.51 | 4 Y | 9.20 | 4½ Y | 16.28 |
| | | 4 Y | 10.88 | | |
| 5 Y | 7.41 | 5 Y | 13.45 | 5 Y | 24.80 |
| | | 5 Y | 11.07 | | |
| 6 Y | 6.08 | 6 Y | 11.47 | 6 Y | 24.11 |
| 7 Y | 8.21 | 7 Y | 14.87 | 7 Y | 26.78 |
| 8 Y | 9.29 | 8 Y | 14.41 | 8 Y | 27.08 |
| 9 Y | 9.07 | 9 Y | 12.82 | 9 Y | 33.42 |
| 10 Y | 9.34 | 10 Y | 13.17 | 10 Y | 40.05 |
| | | | | 10 Y | 43.37 |
| 11 Y | 8.29 | 11 Y | 14.13 | 11 Y | 41.07 |
| 13 Y | 9.57 | 13 Y | 15.27 | 13 Y | 42.44 |
| | | 14 Y | 17.32 | 14 Y | 43.48 |
| 15 Y | 10.65 | 16 Y | 16.05 | | |

would rise smoothly and that the effect measured in this way would be fairly representative of the truth.

## Results

The results with *d*-tubocurarine are presented in table 1 and figure 3. It is notable that a linear relation exists between age and effect of *d*-tubocurarine and that this effect is dependent upon which anesthetic drug is being used. No abrupt change in the dose required to produce one square centimeter of area occurs at any age group.

The results obtained with succinylcholine are presented in table 2 and figure 4. The figures of table 2 show a statistically significant increase in the dose of succinylcholine required to produce one square centimeter of area of respiratory depression under the age of one year. The probability that the difference between the means of the results over and under one year could have been due to chance is between one in fifty and one in a hundred cases. It is interesting to note in figure 4 that the dosage required to produce one square centimeter in those over one year is not age dependent. The standard deviation of these grouped results is 1.388 mg. × $10^{-2}$/kg./cm.$^2$

## Discussion

No infants under one month old were investigated but marked age dependent differences in the respiratory depressant effects of muscle relaxants are demonstrable. It is apparent that under anesthesia, the younger the children the more sensitive they are to the effects of *d*-tubocurarine when the dose is assessed on a body weight basis. Straight lines could be drawn through the points of figure 3 so that no abrupt change in motor end-plate properties could be postulated in those patients between the ages of 6 weeks and 16 years. It is possible that if the dose of *d*-tubocurarine had been calculated on the basis of muscle mass the lines would have been horizontal. However, with the assumption that newborn children have only ⅕ of their body weight as muscle and that by maturity this becomes ⅖[6] we have recalculated the results shown in table 1. A relation was apparent between the dose of the drug and age, similar to that shown in figure 3. Infants have their full complement of muscle fibers at birth,[7] although the motor innervation is not complete until the age of two. It would appear that under anesthesia there is a declining response of the motor end-plates to *d*-tubocurarine with increasing age unrelated to muscle mass and this has to be taken into account in calculating the dosage.

The general anesthetic drug used exerts a profound effect upon the quantity of *d*-tubocurarine required to produce this standard amount of respiratory depression. It is realized that the depth of anesthesia might affect the results and that the more respiratory depressant drugs could markedly influence the method of assessment. The anesthetics were administered by 5 anesthesiologists who judged anesthesia to be in light surgical planes. If the depth of anesthesia had had any profound effect this would have become apparent by scatter in the results. The three groups of results illustrated in figure 3, there-

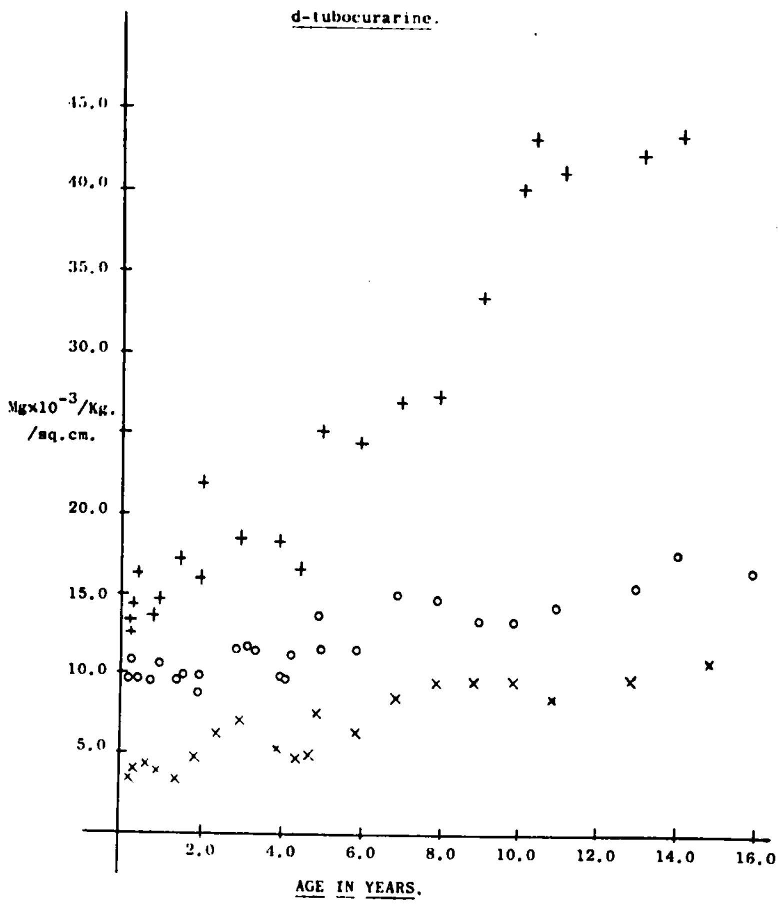


FIG. 3. Effect of *d*-tubocurarine with halothane (+), methoxyflurane (o), and diethyl ether (x). The ordinate represents the quantity of *d*-tubocurarine which was required to produce a standard impairment of respiration.

TABLE 2. Succinylcholine

| Under One Year | | | | Over One Year | |
|---|---|---|---|---|---|
| Nonapneic Group (0.25 mg./kg.) | | Apneic Group (0.33 mg./kg.) | | No Apnea 0.33 mg./kg. | |
| Age Months | mg. $\times 10^{-2}$/kg./cm.$^2$ | Age Months | mg. $\times 10^{-2}$/kg./cm.$^2$ | Age Years | *Mean* (mg. $\times 10^{-2}$/kg./cm.$^2$) ( ) Number of Cases |
| 1¼ | 7.212 | 1½ | 2.148 | 1½ | 4.016 (1) |
| 1¼ | 14.647 | 1¾ | 9.523 | 2 | 5.494 (3) |
| 2½ | 5.149 | 2½ | 2.435 | 3 | 5.284 (4) |
| 3½ | 11.140 | 3 | 12.333 | 4 | 4.811 (6) |
| 5½ | 2.642 | 3 | 6.778 | 5 | 4.775 (6) |
| 7 | 10.338 | 3½ | 7.110 | 6 | 5.705 (6) |
| 7½ | 8.333 | 3½ | 8.048 | 7 | 4.869 (5) |
| 8 | 14.287 | 6 | 2.076 | 8 | 4.095 (3) |
| 12 | 5.115 | 7½ | 7.322 | 9 | 4.474 (3) |
| | | 9 | 3.668 | 10 | 5.721 (2) |
| | | | | 12 | 6.329 (1) |
| | | | | 14 | 5.916 (3) |
| Mean | 9.873 | Mean | 6.144 | 15 | 7.935 (1) |
| Mean | | | 7.437 | Mean | 5.156 |
| Standard deviation | | | ±3.944 | Standard deviation | ±1.388 |
| Stand. error of mean | | | ±0.9048 | Stand. error of mean | ±0.2118 |
| $P$ = 0.02–0.01 | | | | | |

fore, can be interpreted to mean that the effects of *d*-tubocurarine are enhanced in ascending order by halothane, methoxyflurane and ether.

It is notable that the slope of the points is approximately the same for methoxyflurane and ether but that for halothane is much steeper. The explanation for this escapes us, although we might speculate that the anesthetic drugs themselves have an age dependent effect upon the muscle, neuro-neural or myoneural transmission and that this is particularly marked with halothane. Figure 3 can then only illustrate what is clinically apparent when these three inhalational anesthetics are used in conjunction with *d*-tubocurarine but it does not illustrate orders of sensitivity with age to *d*-tubocurarine alone.

A consideration of table 2 reveals that considerable over-estimation of the effects of succinylcholine occurred when apnea was produced in children under one year with a dosage of 0.33 mg./kg. If the results obtained with this dosage were to be excluded on the basis that apnea had occurred, the observed difference in the dose required to give a standard amount of respiratory depression between children over and under one year, would have been very much more significant. The probability that the observed differences between the means could have arisen by chance alone would then increase to less than one in one thousand trials.

Judged on the basis that 0.33 mg./kg. produced apnea in children under one year of age yet did not do so in children over one year, one might conclude that children under one year are more sensitive to succinylcholine, yet when assessed by the method described it is apparent that they are more resistant. Resistence to succinylcholine could have at least two components. Firstly, the concentration in which the drug arrives at the motor endplates must be considered. If we assume that the dose given intravenously is distributed throughout the blood volume, then children under one year must dilute the drug more than those over one year. The blood volume

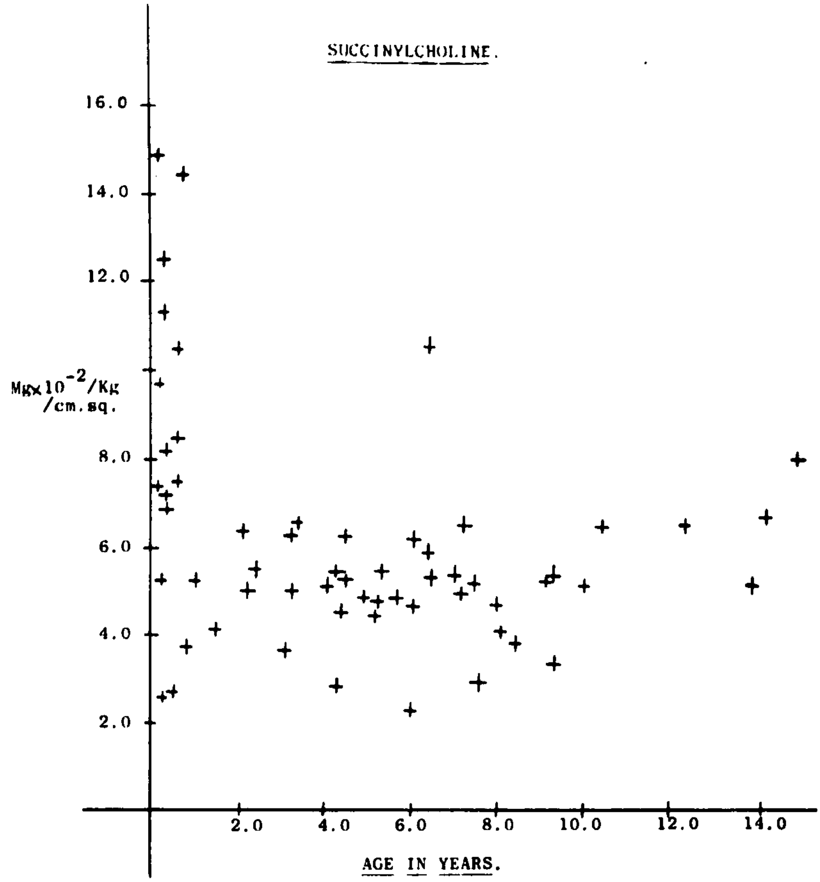


FIG. 4. Effect of succinylcholine with halothane. The ordinate represents the quantity of succinylcholine which will produce a standard impairment of respiration.

under one year ranges from 80–110 ml./kg., while over one year it ranges from 70–80 ml./kg.[8, 9] On the average the child in the apneic group of table 2 must therefore dilute his succinylcholine to a greater extent than the average in the over-one-year group and, since apnea is produced, the motor end-plates must be more sensitive to the action of the drug. In fact a reduction of dosage by roughly 25 per cent is required to avoid apnea which indicates greater sensitivity. Secondly, the rate of destruction must play a part. The differences between the means in table 2 show that the rate of destruction is higher in those under one year since the "area of apnea" is assessed for the total duration of respiratory inadequacy. We might therefore say that neuromuscular conduction is more susceptible to the effects of succinylcholine in infants under one year but that the rate of destruction of the drug is faster than in older children. In children over one year of age the blood volume bears a linear relationship to body weight and one can conclude from figure 4 that the sensitivity of the motor end-plate to succinylcholine and the rate of destrutcion of the drug do not vary widely after one year. These findings would not hold true for repeated doses of succinylcholine or for continuous administration since end-plate changes must alter the results.

## Summary and Conclusions

(1) The respiratory response of infants and children to *d*-tubocurarine and succinylcholine has been examined.

(2) Under halothane anesthesia children under one year require about one quarter of the dose of the *d*-tubocurarine per kilogram when compared to children over 12 years of

age. This relation varies linearly with age. The complementary relaxation provided by some anesthetic agents is variable and important. Figure 3 could be used as an approximate clinical guide to the dosage of *d*-tubocurarine with three commonly used anesthetic agents.

(3) Succinylcholine, with halothane anesthesia, produces greater relaxation in children under one year than in older children. Since the blood volume under one year is greater in relation to body weight than in older children the drug must be relatively more diluted on administration. It would appear that children under one year are more sensitive to the drug. The duration of action in this group is shorter so that the rate of destruction is higher. If succinylcholine were to be administered continuously this high rate of destruction would be interpreted as greater resistance, although this work indicates that sensitivity is higher.

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**SITTING POSITION** Reduced blood loss, drier field, sharper anatomic delineation, decreased operating time, and a more physiologic position for "poor operative risks from cardiopulmonary causes" are listed as advantages of the sitting position. Disadvantages are the possibility of tracheal aspiration, venous air embolism and postoperative airway obstruction in certain patients so that the anesthesiologist must be prepared to reintubate the patient under adverse conditions. (*Pigott, J. D., Shapiro, N. D., and McCarthy, D.: Semi-Sitting Position for Blood Conservation in Head and Neck Surgery, Amer. J. Surg. 106: 872 (Nov.) 1693.*) (ABSTRACTOR'S NOTE: This discussion fails to appreciate the very real hazards of arterial hypotension and aspiration in the semi-sitting position, hazards well known to the experienced anesthesiologist.)