

THE INTERRELATIONSHIP OF SUCCINYLCHOLINE AND THE BLOOD CHOLINESTERASES DURING ANESTHESIA *†‡

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SINCE the introduction of succinylcholine as a muscle relaxant for use in anesthesia and electroshock therapy (1, 2, 3), clinical reports have emphasized the advantage of its short duration of action, and therefore its degree of controllability (4-7). This brevity of action has been thought to be the result of rapid hydrolysis and inactivation of the drug by the pseudocholinesterase of the plasma (1, 8). The consistency of this rapid chemical reaction would tend to eliminate the possibility of patients showing the prolonged respiratory depression which has been noted with other muscle relaxant drugs.

As experience has accumulated with succinylcholine, the hope that prolonged apnea would not occur has been dampened by numerous reports to the contrary (4, 9-14). Several reasons have been advanced to explain this complication. Some authors have indicated that a central depression of the respiratory center may occur, either due to the drug itself or associated with prolonged "controlled" respirations (15, 16). Others have conjectured that increased acidity of the blood stream may stabilize to some extent the succinylcholine present (14).

Perhaps the most plausible explanation is that inactivation of the relaxant may be delayed if the quantity of cholinesterase in the serum is below the normal range of values. Evans *et al.* (8) have shown a definite relationship in 2 cases between low cholinesterase values and extended periods of apnea. These authors have also reported (17) that injections of cholinesterase in 4 patients shortened the period of apnea observed with 50 mg. doses of succinylcholine given intravenously.

Within the last year, another explanation has been advanced to explain the occasional delayed recovery from succinylcholine relaxation. The first step in the hydrolysis is believed to involve the forma-

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tion of monosuccinylcholine from the diacetylcholine (18). This compound is broken down more slowly in the blood stream and itself possesses relaxant properties, although weaker than those of the parent drug. It is thought that persisting concentrations of monosuccinylcholine might account for prolonged degrees of inadequate respiration (19).

The apparent confusion existing in the relationship between succinylcholine metabolism, cholinesterase, and prolonged apnea led us to investigate this problem further. In 1943, Mendel *et al.* (20) separated the cholinesterase enzymes as they occur in the body into two groups. One commonly thinks of these enzymes as occurring principally in the blood stream, although both types can be extracted from various tissues of the body (21). The "whole blood" cholinesterases are composed of the "true" or red cell cholinesterase and the "pseudo," or plasma, or serum cholinesterase. The "true" enzyme rapidly inactivates acetylcholine, but also is believed to hydrolyze in a slower manner other "choline" compounds, such as succinylcholine. The "pseudo" cholinesterase was so named originally because of its ability to hydrolyze rapidly numerous dicarboxylic esters, including acetylcholine. It is this plasma enzyme which has been linked principally with succinylcholine metabolism.

PROBLEMS INVESTIGATED

Much of the information regarding cholinesterase activity has been gleaned from *in vitro* studies. In an attempt to establish more definitely the pertinent relationship between succinylcholine and the blood cholinesterases in the human being, six different aspects of the problem have been studied:

(1) What are the whole blood and plasma cholinesterase levels in hospital patients being prepared for operation? Is the cholinesterase number within a similar range in health and disease?

(2) Does the administration of anesthetic drugs have any deleterious effect on whole blood cholinesterase values? It is conceivable that such drugs might act as anticholinesterase agents, particularly in the plasma, as do certain insecticides and the so-called nerve gases. These latter compounds may lower the blood enzyme content considerably (22).

(3) Does the addition of succinylcholine in moderate doses during the course of anesthesia alter the cholinesterase values of the blood?

(4) What is the effect of large doses of succinylcholine rapidly administered on the vital functions of respiration and circulation, as well as on blood cholinesterase activity? By such injections, an estimate of the clinical "toxicity" of the drug may be ascertained.

(5) What effect will a known dose of concentrated pseudocholinesterase have upon the duration of apnea and the cholinesterase levels

following intravenous administration of large amounts of succinylcholine? In other words, will the parenteral administration of pseudo-cholinesterase serve as an antidote to the apnea produced by succinylcholine?

(6) In patients who exhibit prolonged respiratory depression following succinylcholine administration, are any factors present which are common to all cases? Will the injection of pseudo-cholinesterase aid in restoring respiratory activity in such patients? Several case histories will be presented to illustrate our findings.

BLOOD CHOLINESTERASE LEVELS IN HOSPITALIZED PATIENTS

In reviewing a number of methods for the determination of the blood cholinesterase, it was thought that the electrometric method of Michel (23) would be the most satisfactory. This technique correlates with the standard Warburg method and, as previously pointed out (22), permits determinations on large numbers of samples with relative ease. Cholinesterase activity is measured by the fall in the hydrogen ion concentration of a barbitone-phosphate buffered system, with acetylcholine being used as a substrate. The cholinesterase number or value obtained is simply the number of units of decrease of hydrogen ion concentration in one hour. Determinations in this investigation were limited to the whole blood and plasma cholinesterase values. True cholinesterase was not measured in view of previous studies

DISTRIBUTION OF WHOLE BLOOD CHOLINESTERASE LEVELS IN 102 MALES

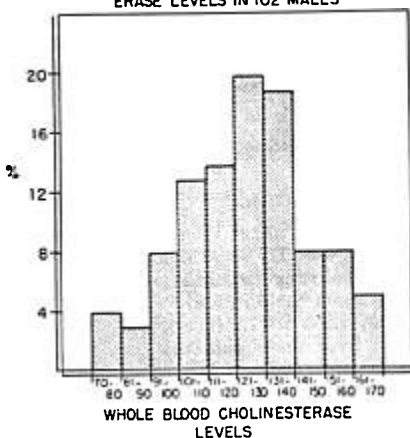


CHART 1.

which indicated it had a minimal hydrolyzing effect on succinylcholine in the blood stream (1).

In order to determine a base line for future observations, 205 hospitalized patients on the surgical service were evaluated. In 102 males, varying in age from 17 to 70 years, the mean whole blood cholinesterase was 123.5, with a standard deviation of 22 (chart 1). The normal range, defined as plus or minus two standard deviations, was 79.5 to 167.5. The mean of the plasma cholinesterase values in 61 males was 75, with a standard deviation of 20.3 (chart 2).

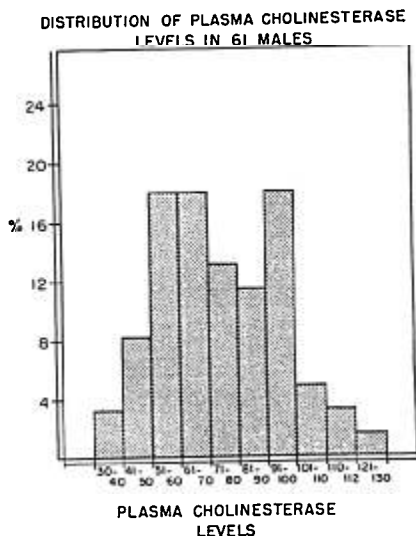


CHART 2.

In 103 females, varying in age from 17 to 78 years, the mean whole blood cholinesterase was 117.6, with a standard deviation of 17.3 (chart 3). The normal range from these figures would be 83 to 152.2. The mean of the plasma cholinesterase values in 41 females was 66.5, with a standard deviation of 17.2 (chart 4).

It can be seen from these data that the range of values in the hospitalized population is wide. Similar variations have been reported in healthy persons (22, 24, 25). In an effort to compare hospitalized and normal patients in this vicinity, cholinesterase determinations were made in 15 healthy males and 16 healthy females. In the males, the mean whole blood cholinesterase value was 124, with a standard

DISTRIBUTION OF WHOLE BLOOD CHOLINESTERASE LEVELS IN 103 FEMALES

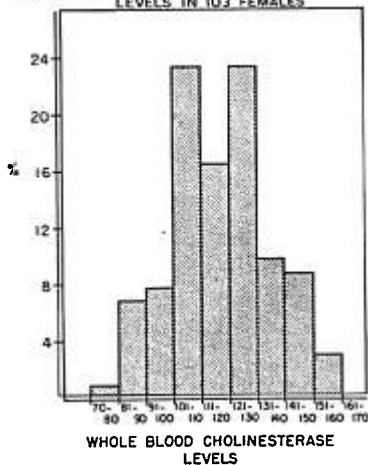


CHART 3.

deviation of 12.2, and the mean plasma value was 84, with a standard deviation of 8.5. In the females, the mean whole blood value was 113, with a standard deviation of 8.1, while the mean plasma cholinesterase was 74, with a standard deviation of 14.2.

The mean values in hospitalized and nonhospitalized patients are not in wide disagreement (table 1), although the plasma cholinesterase tends to be higher in the healthy subjects. The wider range of values found in hospitalized subjects results, perhaps, from the fact that some very ill patients with low cholinesterase values were included in this group.

The relatively wide range of "normal" values, both in hospitalized and healthy persons, makes it difficult at times to determine whether

TABLE 1
MEAN WHOLE BLOOD AND PLASMA CHOLINESTERASE VALUES IN MALE AND FEMALE HOSPITALIZED AND NONHOSPITALIZED SUBJECTS
(Figures in Brackets are Standard Deviations)

	Hospitalized		Nonhospitalized	
	Whole Blood	Plasma	Whole Blood	Plasma
Male	123.5(22)	75(20.3)	124(12.2)	84(8.5)
Female	117.6(17.3)	66.5(17.2)	113(8.1)	74(14.2)

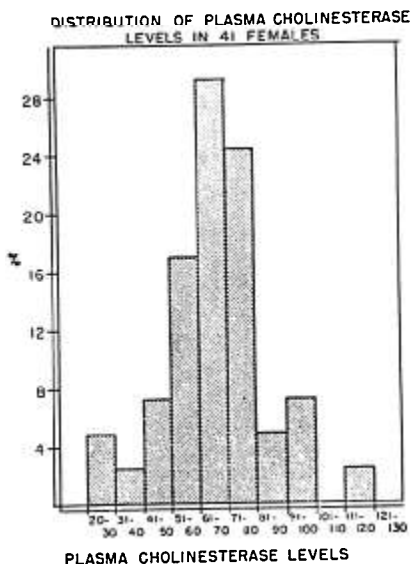


CHART 4.

the activity estimated for any one patient in a single reading is normal for that patient. In clinical practice, the general physical status of the patient must be assessed along with the laboratory findings. As will be noted later, patients exhibiting certain disease patterns usually show unmistakably abnormal cholinesterase levels.

Information gathered in this series tends to indicate that age shows no particular relationship to the cholinesterase values obtained. Females tend to have somewhat lower levels than do males (table 1).

EFFECT OF ANESTHETIC DRUGS ON WHOLE BLOOD CHOLINESTERASE

It has been suggested that barbiturates, morphine and atropine may alter cholinesterase activity (26, 27). In order to find out whether drugs employed clinically for narcosis produced any change in whole blood values, determinations were made in 22 patients. A blood sample was drawn just before induction and a second sample taken upon cessation of anesthesia. The drugs administered were pentothal,[®] nitrous oxide and oxygen; nitrous oxide, oxygen and ether; cyclopropane and oxygen (table 2). The whole blood cholinesterase values for each anesthetic group were averaged to obtain a figure

TABLE 2
EFFECT OF ANESTHETIC DRUGS ON WHOLE BLOOD CHOLINESTERASE LEVELS

Anesthetic Drugs	No. of Patients	Age Group, years	Cholinesterase Levels, average		Variation, per cent
			Preop.	Postop.	
Pentothal Nitrous oxide-Oxygen	10	30-67	123	119	-17 +7
Ether Nitrous oxide-Oxygen	6	5-51	132	131	-6 +5
Cyclopropane-Oxygen	6	21-44	119	114	-14 +2

which might indicate an over-all trend. The percentage variation column indicates the greatest and smallest changes of the individual patients in each series. These alterations were found to be of no statistical significance.

EFFECT OF ANESTHETIC DRUGS AND SUCCINYLCHOLINE ON
WHOLE BLOOD CHOLINESTERASE

Thirty-four patients were investigated to determine whether cholinesterase values altered when moderate doses of succinylcholine were added to the anesthetic drugs utilized (table 3). The addition of succinylcholine did not appear to affect whole blood cholinesterase levels.

EFFECT OF LARGE DOSES OF SUCCINYLCHOLINE ON RESPIRATION,
CIRCULATION AND WHOLE BLOOD CHOLINESTERASE LEVELS

This part of the study was undertaken to determine the clinical "toxicity" of large amounts of succinylcholine injected over a short

TABLE 3
EFFECT OF ANESTHETIC DRUGS PLUS SUCCINYLCHOLINE
ON WHOLE BLOOD CHOLINESTERASE LEVELS

Anesthetic Drugs	No. of Patients	Age Group, years	Succinylcholine, Av., mg.	Cholinesterase Levels, average		Variation, per cent
				Preop.	Postop.	
Pentothal Nitrous oxide-Oxygen Succinylcholine	16	20-52	210	129	123	-16 +8
Ether Nitrous oxide-Oxygen Succinylcholine	6	17-55	258	126	128	-7 +13
Cyclopropane-Oxygen Succinylcholine	12	23-64	198	119	117	-13 +7

period of time. Ten good risk patients were investigated. Eight of these patients had serial determinations of whole blood cholinesterase levels (table 4).

Each patient was given a dose of pentothal sodium sufficient to produce sleep. Then a total of 1000 mg. of succinylcholine was injected in 200 mg. doses every two minutes over a ten minute period. Patients were intubated following the first 200 mg. dose. Respirations were maintained artificially by intermittent manual positive pressure on the reservoir bag of a gas machine, utilizing nitrous oxide and oxygen in a 70 to 30 mixture. Whole blood cholinesterase de-

TABLE 4
BLOOD PRESSURE VARIATIONS, DURATION OF APNEA AND CHOLINESTERASE LEVELS
(WHOLE BLOOD) FOLLOWING ADMINISTRATION OF LARGE DOSES
OF SUCCINYLCOLINE

Case and Race	Age and Sex	Control		Succinylcholine, mg. in 10 min.	After Injection		Apnea, min.	Che. at First Breath	Succinylcholine, Total Dose, mg.	Postop. Che.
		B.P.	Che.*		B.P.	Che.				
1	46	110/80	125	1000	155/106	128	16	128	1900	138
C**	M									
2	35	90/70	100	1000	120/90	102	45	108	1250	110
C	M									
3	51	110/70	128	1000	160/100	148	9	147	2000	145
W†	M									
4	42	120/70	122	1000	130/80	105	23	120	1150	118
W	F									
5	60	110/70	142	1000	130/85	138	25	134	1200	134
C	F									
6	43	100/80	118	1000	110/76	123	8	114	1000	114
C	F									
7	64	100/70	114	1000	150/80	104	15	92	1350	92
W	F									
8	67	120/70	124	1000	170/100	138	15	128	1000	125
W	F									

* Che.—Cholinesterase level.

** C—Colored.

† W—White.

terminations were made just before induction, following the administration of the 1000 mg. of succinylcholine, at the time of the first spontaneous diaphragmatic excursion and at the conclusion of the operative procedure. Continuous electrocardiograms were taken during the first ten minutes and intermittently thereafter. Blood pressure and pulse rate were followed closely. The periods of total apnea were noted carefully for each patient.

All of these patients had surgical procedures and several received additional quantities of succinylcholine for relaxation during the course of the operation. The total amounts injected are noted in table 4. In none of these patients was respiratory apnea or depression evident in the postoperative period.

The duration of apnea following the 1,000 mg. injection varied from eight to forty-five minutes, with the average being in the range of nineteen minutes. The length of apnea did not appear to bear any relationship to cholinesterase activity, to the age of the patient or to the general physical status of the patient. The artificial respiration was performed by several members of the resident staff, and it is thought that individual variations in the rate and depth of ventilation may have contributed to the differences in the length of apnea. It should be remembered also that no 2 patients will react in a similar manner to a given dose of any specific drug. Once spontaneous diaphragmatic excursions began in these patients, normal respiratory exchange with full intercostal action was present within ten minutes.

As reported in a previous communication (28), both systolic and diastolic blood pressures rose consistently after the large dose of succinylcholine (table 4). These increases are seen occasionally after injection of smaller amounts. In this series, blood pressures returned to preoperative levels within ten to twenty minutes after completion of the injection. It is not thought that these rises in pressure were associated with retention of carbon dioxide. No marked variation in pulse rate were seen in this study. Electrocardiograms remained within normal limits in all cases except one, in which premature ventricular contractions appeared. These persisted for approximately fifteen minutes.

Whole blood cholinesterase levels were not affected unduly by these large doses of succinylcholine (table 4). No sharp drops in cholinesterase concentration were seen. This is perhaps to be expected in a reaction which is purely enzymatic and catalytic.

The postoperative course of these patients was uneventful and showed no evidence of any permanent effect of this relative overdosage with succinylcholine.

EFFECT OF CONCENTRATED PLASMA CHOLINESTERASE UPON DURATION OF APNEA CREATED BY SUCCINYLCHOLINE

Twenty-four women and one man who were good risks were utilized in this aspect of the study. The man underwent thoracotomy for lobectomy. All the women were subjected to gynecological procedures approached through the vaginal route. As a result, the entire chest and abdomen could be observed carefully at all times for minute changes in the character of the respirations. In an effort to eliminate as much as possible human variation in the use of controlled respirations, only one anesthesiologist (R. W. B.) administered the anesthetic agents in these patients.

The patients were divided into five groups, each comprised of 5 patients. One group served as a control, and the remaining groups

received 2, 4, 8, and 12 cc., respectively, of cholase[®].|| Each cubic centimeter of cholase represented the amount of plasma pseudocholinesterase found in 350 cc. of human plasma. It is prepared by ethanol fractionation and is a subfraction of Cohn's globulin fraction IV—6 (29).

In each patient, a preanesthetic blood sample was drawn and then a dose of pentothal sodium large enough to produce sleep was injected. Nitrous oxide and oxygen in a 70 to 30 ratio was administered from a gas machine throughout the operation, with minimal pentothal supplementation as required. When the central respiratory depressant effect, if any, from the original dose of barbiturate was over, 250 mg. of succinylcholine was injected rapidly. The duration of apnea from this initial dose of muscle relaxant was determined. The end point was represented by the first diaphragmatic excursion that could be observed. A second sample of blood was drawn at that time. When normal respiratory excursions had returned, usually five to ten minutes after the first spontaneous diaphragmatic movements, the predetermined amount of cholase was administered intravenously. This was followed immediately by a second dose of 250 mg. of succinylcholine. In the "control" group of 5 patients, no cholase was injected. Again, the duration of apnea was noted in minutes, and a third sample of blood drawn with the first spontaneous movement of the diaphragm. In this way, each patient served as his own control within the limits of clinical experiment.

A fourth sample of blood for cholinesterase determination was taken when full diaphragmatic and intercostal respiratory action had returned. This again was within five to ten minutes of the first movement. A fifth sample was drawn three hours after anesthesia, and a sixth in twenty-four hours. In the group who received 12 cc. of cholase, samples were drawn at twenty-four hour intervals until the patient was discharged from the hospital or the plasma cholinesterase level had returned to near normal. This was done in an effort to determine the duration of a high cholinesterase level following injection of large quantities of cholase.

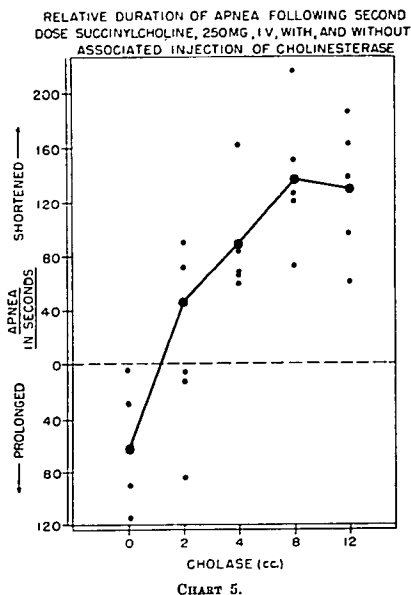
The period of apnea following the first or control dose of succinylcholine averaged nine minutes thirty-six seconds, with a minimum of seven minutes eighteen seconds and a maximum of twelve minutes. It was thought that this variation could be accounted for on the basis of individual difference in susceptibility. All patients had control whole blood and plasma cholinesterases which could be considered within normal limits.

In the "control" group of 5 patients who received no cholase, the period of apnea with the second administration of succinylcholine was consistently of longer duration than with the first dose (chart 5).

|| We are indebted to Dr. E. B. McLean of Cutter Laboratories, Berkeley, California, for generous supplies of cholase[®].

This could be explained on the basis of incomplete metabolism of succinylcholine at the time of the second injection, even though respiratory efforts appeared to have returned to normal at that time.

With the administration of 2 cc. of choline, the comparative period of apnea was equivocal—in 2 patients being shorter, in 2 patients about the same, and in one patient longer. With the larger doses of choline, the periods of apnea were consistently shorter than the equivalent controls (chart 5). This reduction in time of breathing reached its maximum with 8 cc. of the concentrated plasma cholinesterase and was



not shortened significantly by the 12 cc. dosage. With the two greatest quantities administered, recovery time was shortened an average of 36 per cent (chart 6).

In Charts 7 and 8, the alterations which occurred in whole blood and plasma cholinesterase values associated with the injection of the various amounts of choline are revealed. As the parenteral administration of plasma cholinesterase increased in amount, the whole blood and plasma cholinesterase levels in the patients' blood streams increased accordingly. It is notable that, when 12 cc. of choline was

PERCENTAGE VARIATION IN RELATIVE DURATION OF APNEA FOLLOWING SECOND DOSE SUCCINYLCHOLINE, 250 MG, WITH AND WITHOUT ASSOCIATED INJECTION OF CHOLINESTERASE

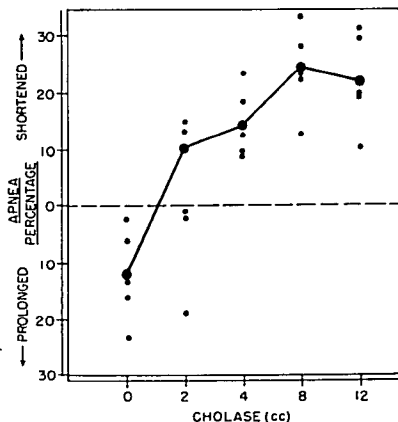


CHART 6.

given, relatively high cholinesterase levels persisted in the blood stream for several days (chart 8).

None of the patients to whom the various amounts of cholase were administered showed any deleterious clinical manifestations during anesthesia or in the postoperative period (30). No significant alterations in blood pressure, pulse or respirations were noted.

CLINICAL APPLICATIONS OF CHOLASE THERAPY

The clinical demonstration under controlled conditions that relatively large quantities of injected plasma cholinesterase appeared to reduce the period of apnea resulting from succinylcholine led to a consideration of whether this enzyme might be useful in the therapy of prolonged respiratory depression seen occasionally in the operating room. The following case histories illustrate the type of patients in whom recovery of normal respirations has been delayed in our experience. An attempt is made to analyze the possible factors contributing to the prolonged depression.

Case 1. A 24 year old, white, single woman had been suffering from severe idiopathic ulcerative colitis for six weeks. She came to the operating room as an emergency with intestinal obstruction. Despite previous vigorous therapy, she was emaciated, dehydrated, semicomatose, and had involuntary muscle

fibrillations. Hemoglobin was 9.1 Gm., hematocrit 30, albumin and globulin 2.4 and 3.3 Gm. per 100 cc., respectively. Carbon dioxide combining power 84 volumes per cent, chlorides 94 mEq. per liter, sodium 141 mEq. per liter, and potassium 3.59 mEq. per liter. Induction of anesthesia and intubation were accomplished with pentothal sodium, 200 mg., and anectine[®], 75 mg. by intravenous drip. With these drugs, the patient remained apneic for twenty-five minutes. Anesthesia was maintained for one and a quarter hours with nitrous oxide and cyclopropane, employing assisted respirations. Relaxation was adequate for laparotomy without further muscle relaxant. Spontaneous respirations were satisfactory at the conclusion of operation. The patient died thirty-two days later.

Preoperative cholinesterase values were 89 for whole blood and 29 for

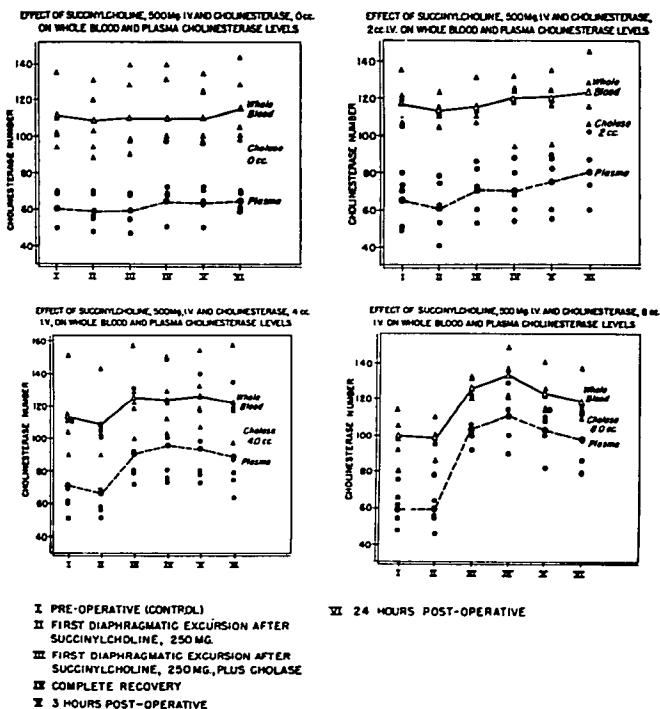
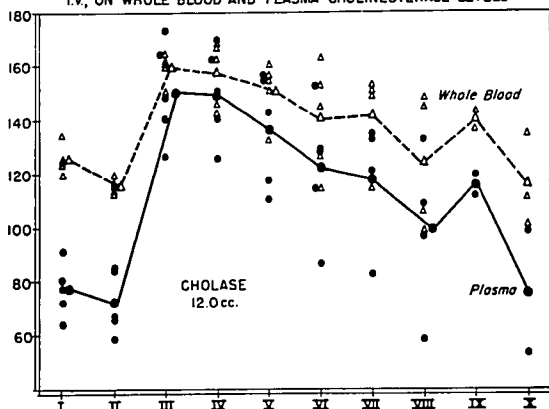


CHART 7.

¶ We are indebted to Burroughs Wellcome & Co. for generous supplies of anectine[®] used in this study.

EFFECT OF SUCCINYLCHOLINE, 500 MG. I.V. AND CHOLINESTERASE, 12 cc. I.V., ON WHOLE BLOOD AND PLASMA CHOLINESTERASE LEVELS



I PREOPERATIVE (CONTROL)	V 3 HOURS POST-OPERATIVE
II FIRST DIAPHRAGMATIC EXCURSION AFTER SUCCINYLCHOLINE, 250 MG	VI 24 " " "
III FIRST DIAPHRAGMATIC EXCURSION AFTER SUCCINYLCHOLINE, 250 MG. PLUS CHOLASE	VII 2 DAYS POST-OPERATIVE
IV COMPLETE RECOVERY	VIII 3 " " "
	IX 4 " " "
	X 5 " " "

CHART 8.

plasma. Postoperative values were 67 and 23, respectively. Twenty minutes after the administration of choline, 1 cc. whole blood cholinesterase was 86 and plasma cholinesterase 35.

This acutely ill patient with marked electrolyte imbalance is representative of one group who show low cholinesterase levels. The length of apnea and muscular relaxation observed after succinylcholine, 75 mg., was much longer than is anticipated in "normal" patients. The prolongation of effect probably was related directly to the low cholinesterase values. The postoperative administration of choline, 1 cc.—a relatively small amount—served to increase cholinesterase levels to some extent.

Case 2. A 42 year old white woman, who weighed 100 pounds, was admitted to hospital with acute fulminating ulcerative colitis. Medical therapy did not control the condition, and she was brought to the operating room for a subtotal colectomy and ileostomy. At that time, the electrolyte balance was abnormal. Hemoglobin was 11.7 Gm., total proteins 4.9 Gm. per 100 cc., albumin

and globulin 2.5 and 2.4 Gm. per 100 cc., respectively, and carbon dioxide combining power 77 volumes per cent. Over a period of five hours, she was anesthetized with pentothal sodium, 250 mg., cyclopropane and succinylcholine drip, 200 mg. Respirations were assisted throughout, and were adequate at the conclusion of operation. The postoperative course was satisfactory. The plasma cholinesterase level after operation was 44.

This patient is included to demonstrate that succinylcholine can be employed for muscular relaxation in poor risk cases when it is utilized judiciously and in relatively small total quantities. From time to time, it is worth while to discontinue the slow drip and determine how long it takes for muscle tone to assert itself. In this way, an approximate idea of the rate of metabolism for each patient may be gained.

Case 3. A 52 year old white, obese, hypertensive woman had been suffering from intermittent intestinal obstruction for seven days caused by an annular carcinoma of the sigmoid colon. The hemoglobin was 13.5 Gm., carbon dioxide combining power 84 volumes per cent, chlorides 97.8 mEq. per liter, and potassium 2.82 mEq. per liter. After being hydrated parenterally for forty-eight hours, she was operated on for two hours, at which time a transverse colostomy was done. Induction of anesthesia and intubation were carried out with pentothal sodium, 300 mg., and succinylcholine, 100 mg. Anesthesia was maintained with cyclopropane, nitrous oxide, oxygen and intermittent doses of pentothal. A total of 1,300 mg. of succinylcholine was given by intravenous drip during operation to obtain relaxation. Controlled respirations were maintained throughout. Adequate spontaneous respirations did not return for twenty-five minutes after completion of the operation.

Cholinesterase levels are shown in table 5.

TABLE 5
CHOLINESTERASE LEVELS, CASE 3

	Whole Blood	Plasma
9/3 (immediately after operation)	89	47
9/4	92	48
9/5	85	39
9/15	90	42

This case exemplifies a prolonged succinylcholine effect in the presence of some degree of electrolytic imbalance and associated with low cholinesterase levels. Complicating the picture in this instance was a relative overdosage of the muscle relaxant. The return of spontaneous respirations in this patient represented a typical chain of events. First, jerking movements of the diaphragm were noted. Within five minutes, intercostal movements began and these gradually increased in depth over a period of ten minutes. A tracheal tug persisted for another ten minutes after full intercostal movements appeared to be present. Respiratory action was considered inadequate until the tracheal tug disappeared completely. Two subsequent operations performed ten days and thirty days later were uneventful and not associated with prolonged apnea. Cholinesterase levels were still low at that time, but the succinylcholine used in each instance was

titrated carefully and limited to 200 mg. A low cholinesterase level does not contraindicate the employment of succinylcholine, but it does indicate caution in its use.

Case 4. A 64 year old colored woman was admitted to hospital with a diagnosis of carcinoma of the rectum. Blood pressure was 170 mm. systolic and 100 mm. diastolic, the hemoglobin was adequate, the electrocardiogram within normal limits, and electrolytes were in balance. On May 12, she underwent an abdominoperineal resection which lasted four hours and ten minutes. For anesthesia, pentothal sodium, 300 mg., cyclopropane and succinylcholine drip, 200 mg. were given. Respirations were assisted or controlled during the procedure. The postoperative recovery was uneventful. On May 22, wound separation with partial evisceration occurred. The electrolyte balance was again adequate according to laboratory tests. A secondary closure was performed and anesthesia was maintained for one and three-fourths hours with pentothal sodium, 325 mg., cyclopropane and succinylcholine drip, 250 mg. Assisted or controlled respirations were carried out during operation. Respiratory excursions were poor at the conclusion of this procedure and did not return adequately for fifteen minutes. Otherwise, the postoperative course was uneventful.

Cholinesterase levels following the second operation are shown in table 6.

TABLE 6
CHOLINESTERASE LEVELS, CASE 4

	Whole Blood	Plasma
5/22 (immediately after operation)	88	23
5/26	85	22
5/26 (after 3 cc. of cholase)	91	51
5/27	90	41
5/28	88	45

This case represents again a prolonged respiratory depression in the presence of low cholinesterase levels. At the time of the first operation, there was no obvious clinical indication of such a condition, although in retrospect it might be suspected because of the relatively small amount of succinylcholine required for relaxation over a period of four hours. At the time of the evisceration ten days later, the electrolyte balance apparently was not disturbed grossly, but it is quite possible, as has been noted by Nicholson (31), that the blood volume was depleted. Low blood volumes often are associated with diminished cholinesterase values. It is interesting that, when cholase was given parenterally in the postoperative period, the plasma cholinesterase value doubled and remained elevated for at least forty-eight hours.

Case 5. A 56 year old colored man, a known hypertensive, was admitted to hospital with a history of massive gastrointestinal bleeding. The blood pressure on admission was 120 mm. systolic and 80 mm. diastolic, and the hemoglobin was 11.0 Gm. A transfusion of 4,000 cc. of blood did not produce improvement because of continued hemorrhage. Forty-eight hours after admission, because of deterioration in his condition, subtotal gastric resection was

done. During the operation, which lasted three and a half hours, anesthesia was maintained with nitrous oxide, oxygen and ether by a partial rebreathing system, and succinylcholine, 850 mg., was given by continuous drip. The patient received 1,000 cc. blood. Respirations were assisted throughout the procedure. Adequate spontaneous respirations did not return for twenty minutes after completion of the operation. Otherwise, the postoperative course was uneventful.

Whole blood and plasma cholinesterase determinations are shown in table 7.

TABLE 7
CHOLINESTERASE LEVELS, CASE 5

	Whole Blood	Plasma
5/25 (day after operation)	76	63
5/26	97	42
5/26 (one hour after 3 cc. of choline)	107	59
5/27	109	61
5/28	110	68

As in case 4, this case is believed to represent a prolonged succinylcholine effect because of low cholinesterase values which are associated with diminished blood volumes. Actually, this alteration may be a factor in all the cases enumerated thus far. The abnormal enzyme values in the postoperative period were corrected to some extent by the administration of choline.

Case 6. A 57 year old white farmer had suffered for many years with recurrent gastrointestinal upsets. On admission to hospital, he was thin and undernourished, weighing only 108 pounds. Partial intestinal obstruction had been present for three weeks. Although hemoglobin and blood chemical studies were normal, his condition resembled that of patients with low blood volumes. Repeated blood pressures showed a small pulse pressure, the average reading being 100 mm. systolic and 80 mm. diastolic. Partial gastric resection was performed for chronic duodenal ulcer with posterior perforation. A total of 500 cc. of blood was given during anesthesia. For induction of anesthesia and intubation the patient received pentothal sodium, 250 mg., and succinylcholine, 200 mg., by intravenous drip. Anesthesia was maintained with nitrous oxide, oxygen and ether in a partial rebreathing system, employing controlled respirations throughout the procedure. A total of 350 mg. succinylcholine was given by intravenous drip over the anesthetic period of two hours and forty minutes. Operation was completed at 10:55 a.m., but no spontaneous respirations were present. At 11:05 a.m., 5 cc. of choline was given intravenously. At 11:06, the first diaphragmatic respiratory excursion occurred. Spontaneous respirations continued, but adequate diaphragmatic and intercostal activity were not present until 11:30. Otherwise, the postoperative period was uneventful.

Cholinesterase levels were obtained and are shown in table 8.

It is thought that this case represents an example of prolonged apnea associated with malnourishment, low blood volume, and controlled respirations. Of several patients who exhibited this delay in spontaneous respirations, and to whom choline was given as a therapeutic measure, this was the only one who showed a direct improvement

TABLE 8
CHOLINESTERASE LEVELS, CASE 6

	Whole Blood	Plasma
Apneic (immediately after operation)	106	74
First spontaneous respiration after choline	111	85
Adequate spontaneous ventilation	120	100
3 hours after operation	128	98
24 hours after operation	126	87

in respiratory activity following its administration. The instigation of spontaneous respirations in this instance may have been pure coincidence. Before the injection of choline[®], cholinesterase values could be considered a low normal. These levels showed the typical increase to a definite normal range in the hours after the administration of choline.

Case 7. A 64 year old, normotensive, white woman came to operation for removal of a diverticulum of the hypopharynx. She was thin, weighing only 97 pounds, and emphysematous changes were apparent in a roentgenogram of the chest. The hemoglobin was 12.7 Gm. Pentothal sodium, 750 mg., nitrous oxide and oxygen, and succinylcholine drip, 300 mg., were used for induction, intubation and maintenance of anesthesia. Operation lasted one and three-fourths hours, and during this period she was purposely carried on controlled respirations. Following operation, adequate spontaneous ventilation was not evident for forty minutes. Whole blood and plasma cholinesterase levels were 100 and 73, respectively, and were considered to be within normal limits.

The prolonged respiratory depression in this instance was believed to be the result primarily of hyperventilation associated with controlled respirations in a small, thin patient who showed emphysematous changes in the lungs. Similar complications have been observed when no muscle relaxant drug was used. The problem in such patients as this is one of anesthetic technique.

Case 8. A 52 year old white man who weighed 158 pounds was admitted to hospital with the complaint of a mass in the left upper abdominal quadrant. Roentgenograms of the gastrointestinal tract were normal, but those of the chest showed a density in the right upper lobe. Preoperative blood chemistry studies were essentially normal. On January 28, an exploratory laparotomy and biopsy of a large retroperitoneal mass were performed. Induction of anesthesia and intubation were accomplished with pentothal sodium, 400 mg., and succinylcholine, 250 mg., administered by continuous intravenous drip of 0.1 per cent solution. Anesthesia was maintained with cyclopropane, an additional 100 mg. of succinylcholine being required for relaxation. Controlled respirations were employed throughout the procedure which lasted two and a half hours. After termination of the operation, spontaneous respirations failed to return for twenty minutes, at which time diaphragmatic excursions began. Adequate spontaneous respirations were not present for another fifteen minutes. Whole blood cholinesterase levels were within normal limits preoperatively [139] and were unchanged after operation [147]. Recovery from operation was uneventful.

On February 4, seven days after the first operation, a thoracotomy was performed and the upper lobe of the right lung removed because of carcinoma. Induction of anesthesia and intubation were completed as before with pentothal sodium and succinylcholine by continuous intravenous drip. Anesthesia was maintained with nitrous oxide and oxygen, supplemented by pentothal sodium and succinylcholine drip as required. The patient's respirations were assisted continually throughout this five and a half hour procedure. A total of 500 mg. of succinylcholine was administered. Adequate spontaneous respirations were present at the conclusion of the procedure. Whole blood cholinesterase levels were within normal limits before and after operation, being 125 and 126, respectively.

This patient tended to serve as his own control. Whole blood cholinesterase levels were within normal limits at both operations, and yet prolonged apnea was present during the first procedure. Two factors are worthy of consideration as possible explanations of the respiratory depression. The first is the employment of cyclopropane. The use of this narcotic, itself a potent respiratory depressant, in combination with succinylcholine, may increase the possibility of apnea. Difficulty in re-establishing spontaneous respirations toward the end of operations has been noted repeatedly with this association of drugs. The second significant difference in the two anesthetics is the employment of controlled respirations in the first, and assisted respirations in the second. Controlled respirations in and of themselves, through some factor as yet unknown, may serve to delay the onset of adequate spontaneous respirations.

DISCUSSION

The crux of this investigation has been to determine the influence of the blood cholinesterases on the duration of apnea produced by succinylcholine in human beings. It has been shown that the injection of plasma cholinesterase in sufficient quantity will hasten the recovery of spontaneous respirations in normal "experimental" subjects.

On the other hand, it has been impossible to illustrate in patients in whom respiratory arrest is prolonged beyond the normal period of expectation, that the parenteral injection of plasma cholinesterase at the time of apnea has any significant therapeutic or antidotal value. This discrepancy may be attributable in large part to the few patients in whom there has been an opportunity to attempt therapy of this nature. In only one patient did there appear to be a cause and effect relationship, and in this instance, the long arm of coincidence could not be overlooked.

At the same time, the discrepancy may result from the fact that the indications of success in the "experimental" subjects were of too little significance in the over-all picture. The case histories have been presented in an effort to demonstrate that a number of factors may play a part in the production of inadequate ventilation post-

operatively. The first of these is the presence of low cholinesterase levels. An inadequate amount of enzyme in the blood stream probably delays metabolism of succinylcholine and prolongs its action. It has been shown, both experimentally and in the case histories, that concentrated plasma cholinesterase given parenterally increases the whole blood and plasma cholinesterase in the blood stream over a period of several days (chart 8). This finding fits in with the observation that the life span of the cholinesterase molecule is approximately twenty-eight days (25). Theoretically, this increase in cholinesterase should aid in succinylcholine metabolism. In order for such therapy to be effective in surgical patients known or believed to have low plasma cholinesterase activity, probably the enzyme should be given two or three days before operation. The protective action of such administration would be difficult to prove. A shortage of cholinesterase prevented us from attempting it. On the basis of our experience, however, assurance can be given that the injection of the enzyme is not harmful to the patient.

A second element of importance in inadequate return of ventilation is the employment of controlled respirations during anesthesia. In at least 2 of the case histories presented, it is thought that a relative hyperventilation contributed to the prolonged apnea. As necessary as this technique may be when muscle relaxants are employed, it may delay the return of adequate spontaneous respirations. If adequate ventilation and relaxation can be attained with assisted respirations, there is perhaps less likelihood of prolonged apnea after operation.

There is some clinical evidence to suggest that a third element contributing to depressed respirations is the employment of cyclopropane along with succinylcholine. The depression of the respiratory center by cyclopropane, to which some patients seem particularly sensitive, may delay what otherwise would be a normal return of ventilation.

Finally, it must be admitted that some anesthetists will rely too heavily on muscle relaxant drugs to achieve their aims in anesthesia. A fourth factor contributing to depressed respirations is too much relaxant and not enough anesthetic. A relative overdosage of succinylcholine, even though cholinesterase levels are presumed to be normal, may delay the onset of spontaneous respirations. It is interesting to note that, as anesthetists in training become more cognizant of the capacities of their tools, the amount of muscle relaxant used in any given case becomes less.

It can be seen from the above paragraphs that the etiological factors involved in inadequate respiratory activity after operation may be complex. In the present state of knowledge, administration of succinylcholine to patients presumed to have low plasma cholinesterase activity should be undertaken with restraint. It seems apparent that the drug can be used safely in such patients, but it must be remembered that a "little bit may go a long way." Individuals falling into this

category include those with chronic debilitation associated with a low blood volume, those who are acutely ill with a disturbed electrolyte balance, and those with severe anemia, particularly associated with recent hemorrhage. Plasma cholinesterase by parenteral injection has not yet proved to be a satisfactory therapeutic measure when given at the time prolonged respiratory depression occurs in these patients.

Other factors of clinical interest have been established in this study. It appears that narcotic drugs as administered to produce general anesthesia do not interfere with cholinesterase activity in the blood stream. It is also evident from a small series of "normal" patients that succinylcholine administered in large doses over a short period of time can be hydrolyzed in a relatively rapid manner by the patient without clinical deleterious effect to the vital organ systems. Moreover, such metabolism does not alter significantly the cholinesterase level in the blood stream. One could infer from this that increased enzyme activity of plasma cholinesterase does not hasten its disappearance from the blood stream.

SUMMARY

Whole blood and plasma cholinesterase values in hospitalized surgical patients tend to be similar to those found in nonhospitalized persons.

The administration of anesthetic drugs produces no apparent change in cholinesterase activity, as judged by levels found in the blood stream.

Relative overdoses of succinylcholine are hydrolyzed rapidly by "normal" surgical patients. Such metabolic activity has no deleterious effects clinically on the vital organ systems of the patient, nor does it alter the cholinesterase levels of the blood.

Concentrated plasma cholinesterase administered parenterally in sufficient quantity to the "normal" surgical patient shortens the period of apnea produced by a given amount of succinylcholine.

Concentrated plasma cholinesterase injected intravenously in adequate amounts increases the plasma and whole blood cholinesterase values for several days.

Case histories are presented to illustrate the factors associated with postoperative respiratory inefficiency and succinylcholine administration.

No conclusive evidence has been found to indicate a therapeutic value for concentrated plasma cholinesterase when given to patients at the time they are exhibiting a prolonged respiratory depression following succinylcholine administration.

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