$Mg(OH)_2$-type structure has been explained on the basis of the high polarizing power of divalent zinc which has ten 3*d* electrons (*10*). Trivalent aluminum exhibits the effect of polarization by directed hydroxyls in $Al(OH)_3$ (*11*). Chromium with three 3*d* electrons is known to form $Cr(OH)_3$, but $Cr(OH)_3$ is unstable even at room temperatures (*2*). It would seem reasonable to assume that $Fe(OH)_3$ would be less stable than $Cr(OH)_3$, since ferric iron has five 3*d* electrons.

The change of $Fe(OH)_3$ to the more stable partially dehydrated form (goethite, reaction *p*) occurs before crystalline $Fe(OH)_3$ forms (reaction *k*). That goethite may be more stable than lepidocrocite is shown by the dehydration temperatures of their respective Al analogs diaspore > boehmite (Fig. 1). The identical temperature recorded for the goethite and lepidocrocite dehydrations (*12*) may be due to smaller particle size of goethite or other difficulties in the method of measurement.

In the presence of silica, a ferrous mineral similar to allophane would be expected from $Fe(OH)_2$ (reaction *u*). Thus far it has not been identified positively, although exchange capacities of amorphous ferruginous soil colloids are at present being postulated at several laboratories. However, there are several crystalline iron 1 : 1 layer silicate minerals that are similar to kaolinite; the minerals cronstedite and greenalite are examples (reaction *v*). The trioctahedral nature of the iron in the mineral cronstedite suggests that cronstedite is formed from ferrous hydroxide. Hendricks (*13*) considers the octahedral iron of cronstedite as being due to the replacement of silicon by large ferric iron in the tetrahedral position, which allows the octahedral layer to be "opened" up. In view of the transformation just considered, it would seem that the ferrous iron in the octahedral position opened up the structure, and this in turn allowed the ferric iron to enter into the tetrahedral position. This would be similar to the kaolin-montmorin transition, except that it would be expected to occur with a deficiency of silica and excess of ferrous iron in the environment. In greenalite there is a mixture of ferrous and ferric ions octahedrally coordinated, and silica presumably in tetrahedral coordination. It is formed in iron-rich environments, from iron silicates in iron ore deposits (*14*).

When great excess of silica is present, the ferric member of the montmorin series can be formed as evidenced by nontronite (reactions *w* and *x*), which typically occurs embedded in a silica matrix.

Franzen and Eyk van Voorthuysen (*15*) have accomplished the synthesis of nickel layer silicates, which further emphasizes the importance of the hydroxyl layer structure such as in $Ni(OH)_2$, to formation of the corresponding layer silicates. Nickel and ferrous ions are similar in their electronic configuration, but both have lower polarizing power than the ferric ion.

Although in the tropics there is an abundance of iron and aluminum oxides and hydroxides, layer silicates with iron are rare. This is due to the rapid oxidation of ferrous iron to ferric, which gives rise to goethite and hematite, owing to the instability of $Fe(OH)_3$ as already discussed. Decomposition of magnetite is generally accompanied by hydrolysis and oxidation. Without hydrolysis, maghemite (γ-Fe_2O_3) is formed. Because silica and the bases are rapidly leached in well-drained soils, the montmorin series in which iron might be substituted is disfavored and the formation of aluminum members of the kaolin family is favored.

In the temperate regions, where decomposition of primary minerals and leaching of silica and bases are relatively slower and less complete than in the tropical weathering referred to, the 2 : 1 layer silicate minerals bearing some iron ions are common, but give way (*8*) to kaolin as weathering progresses.

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Substrate Competition between Procaine and Succinylcholine Diiodide for Plasma Cholinesterase

Francis F. Foldes, Pearl G. McNall, David L. Davis, C. H. Ellis, and A. L. Wnuck

Department of Anesthesia, Mercy Hospital, Pittsburgh, Pennsylvania, Section on Anesthesiology, Department of Surgery, University of Pittsburgh, School of Medicine, and Wellcome Research Laboratories, Tuckahoe, New York

It was shown by Kalow (*1*) that the enzyme responsible for the hydrolysis of procaine in plasma is identical with cholinesterase (nonspecific cholinesterase, pseudo-cholinesterase). It was also demonstrated by Glick (*2*) and more recently by others (*3–7*) that plasma cholinesterase is capable of hydrolyzing succinylcholine, a recently introduced muscle relaxant. In the course of clinical studies with succinylcholine diiodide (*8*), it was observed that, when 100 mg procaine was administered intravenously to patients receiving succinylcholine, the respiratory depth decreased markedly for several minutes, and in

TABLE 1

THE EFFECT OF THE INTRAVENOUS INJECTION OF PROCAINE ON RESPIRATION IN PATIENTS RECEIVING SUCCINYLCHOLINE DIIODIDE IN CONTINUOUS INTRAVENOUS DRIP

Patient	Procaine (mg)	Onset of respiratory depression* (sec)	Duration of respiratory depression (min)	Remarks
B. M.	30	60	12	Apnea 8 min
A. G.	100	30	2	Moderate effect
H. C.	100	55	6	
J. W.	100	30	2	
S. E.	100	—	—	No appreciable respiratory depression
M. K.	100	70	6	
M. B.	100	45	5	Respiratory arrest; succinylcholine discontinued at 2½ min
J. F.	100	30	6	
E. P.	100	60	4	Moderate effect
G. M.	50	60	2	
J. J.	100	60	6	

* After the injection of procaine.

a few instances respiratory arrest developed (Table 1). These patients were anesthetized with a combination of nitrous oxide-oxygen and thiopental sodium, and received succinylcholine by continuous intravenous drip at a rate of 2–8 mg/min.

It was conceivable that since both procaine and succinylcholine are hydrolyzed by the same enzyme, the additive effect of the simultaneous administration of procaine and succinylcholine diiodide on respiratory depth might be due to substrate competition between the two agents for the plasma cholinesterase. Under clinical conditions, the measurement of this effect could not be carried out easily; therefore experiments were designed for the quantitative determination of this substrate competition by *in vitro* hydrolysis studies and to observe the action of procaine on the succinylcholine-induced neuromuscular blockade in animal experiments.

To four 1.6-ml aliquots of heparinized human plasma, procaine was added in sufficient quantities to obtain procaine concentrations of 50, 100, 200, and 400 μg/ml, respectively. To another four plasma samples, in addition to the same procaine concentrations, 100 μg/ml succinylcholine diiodide was added. In yet another four plasma samples, the procaine concentration was kept constant, and the succinylcholine diiodide concentrations were made to be 50, 100, 200, and 400 μg/ml, respectively. All plasma samples were incubated at 37° C for 10 min. The procaine and *p*-aminobenzoic acid concentrations at the end of the hydrolysis were determined in duplicate by Ting's method (*9*). The findings are summarized in Table 2.

TABLE 2

THE EFFECT OF SUCCINYLCHOLINE ON THE ENZYMATIC HYDROLYSIS OF PROCAINE IN PLASMA

Procaine concentration (μg/ml)	Succinylcholine concentration (μg/ml)	Procaine hydrolyzed (μg/ml)	
		Plasma 1	Plasma 2
50	0	48	48
100	0	50	44
200	0	54	53
400	0	56	47
50	100	28	26
100	100	38	32
200	100	47	38
400	100	57	46
100	50	42	37
100	100	35	31
100	200	31	25
100	400	24	19

It can be seen from Table 2 that, in agreement with previous findings (*10*), increasing the procaine concentration from 50 to 400 μg/ml had very little effect on the quantity of procaine hydrolyzed (zero order reaction). In contrast to this, when 100 μg/ml succinylcholine diiodide was added to the systems before incubation, the quantities of procaine hydrolyzed increased with increasing procaine concentrations. Similarly, when the procaine concentration was kept constant at 100 μg/ml and the succinylcholine diiodide concentration was increased, the quantity of procaine hydrolyzed decreased with increasing succinylcholine diiodide concentrations.

The inhibitory effect of procaine-HCl and succinylcholine dichloride on the enzymatic hydrolysis of one another was further investigated by Warburg's micromanometric technique and Ting's method for the determination of procaine-HCl. The findings of these experiments (to be presented in detail elsewhere) are summarized in Table 3. The figures of Table 3 indicate that procaine-HCl inhibits the enzymatic hydrolysis of succinylcholine dichloride and, in agreement with the experiment summarized in Table 2, succinylcholine inhibits the enzymatic hydrolysis of procaine-HCl. It is also evident that the inhibitory effect of procaine-HCl on the enzymatic hydrolysis of succinylcholine dichloride depends on the relative concentration of the two substrates. The greater the procaine-HCl/succinylcholine dichloride ratio, the greater the inhibitory effect. The figures of Table 3 also show

TABLE 3

THE EFFECT OF PROCAINE AND SUCCINYLCHOLINE ON THE ENZYMATIC HYDROLYSIS OF EACH OTHER*

Substrate concentration/ml plasma	Succinylcholine dichloride hydrolyzed (μg/ml)		Procaine HCl hydrolyzed (μg/ml)	
	Plasma 1	Plasma 2	Plasma 1	Plasma 2
Succinylcholine dichloride 5000 μg	3490	3120	—	—
Procaine HCl† > 100 μg	—	—	1650	1650
Succinylcholine dichloride 5000 μg Procaine HCl 500 μg	1375	1920	219	297
Succinylcholine dichloride 5000 μg Procaine HCl 2500 μg	484	790	562	734

* Hydrolysis carried out at 37° C in 0.025 *M* bicarbonate–5% CO_2 buffer system in Warburg vessels for 120 min.
† Calculated from the data of Table 2.

that the inhibitory effect of procaine-HCl on the enzymatic hydrolysis of succinylcholine dichloride is greater than that of succinylcholine dichloride on the enzymatic hydrolysis of procaine-HCl. This indicates that although the hydrolysis rate of succinylcholine dichloride is greater than that of procaine-HCl, the affinity of procaine-HCl to the enzyme is considerably greater than that of the succinylcholine dichloride. This finding is in agreement with the observation of Kalow (*11*) who found that the affinity of the plasma cholinesterase for procaine is about 220 times greater than that of acetylcholine.

The additive effects of succinylcholine and procaine could also be demonstrated with mammalian sciatic-gastrocnemius preparations. Dogs and cats were anesthetized by the intraperitoneal injection of sodium pentobarbital in a dosage of about 35 mg/kg. The isometric twitches of the gastrocnemius in response to single submaximal stimuli applied to the sciatic nerve were recorded, and arterial blood pressure was recorded from a carotid cannula. In the experiment presented in Fig. 1, the gastrocnemius twitch was depressed to about 10% of the control value by the continuous intravenous administration of 0.02 mg/kg/min of succinylcholine diiodide. At the point indicated by the arrow, 2.0 mg/kg of procaine was administered intravenously. Within a minute the gastrocnemius twitch was completely abolished. On discontinuing the infusion of succinylcholine, the gastrocnemius twitch began to return. Infusion of succinylcholine diiodide at the rate of 0.04 mg/kg/min again rapidly abolished the twitch. Subsequently, 90% depression of the twitch response could be maintained by the continuous intravenous infusion of only 0.01 mg/kg/min.

TABLE 4

THE HYDROLYSIS RATE OF PROCAINE* IN PLASMA AT 37° C

Species	Percentage hydrolyzed in 20 min	Percentage hydrolyzed in 180 min
Man	100	—
Cat	7	74
Dog	3	16

* The procaine concentration was 100 μg/ml.

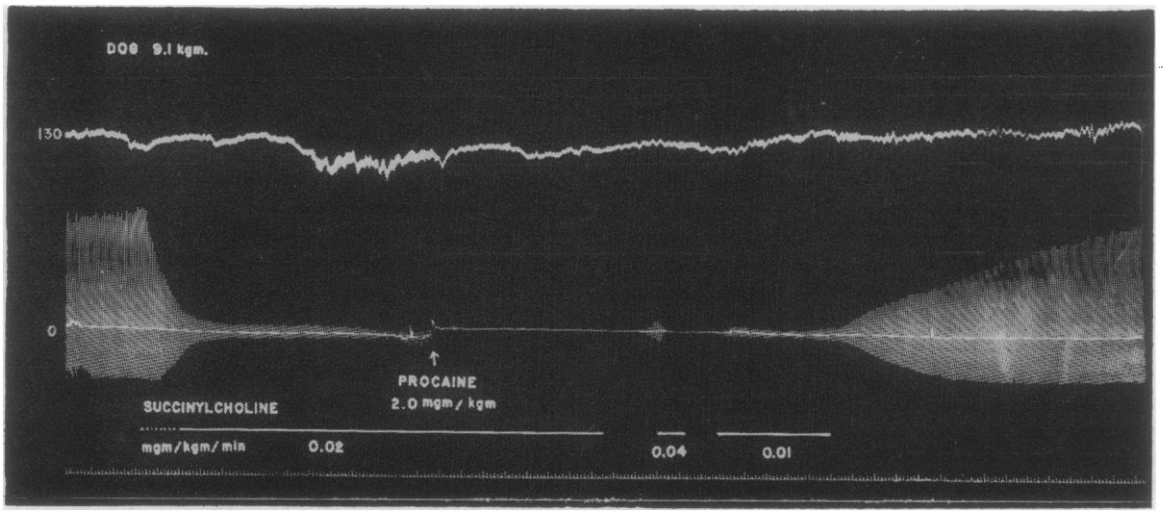

FIG. 1. The effect of procaine on neuromuscular block produced by succinylcholine in dog.

In view of the fact that procaine is hydrolyzed very rapidly both *in vivo* (*12*) and *in vitro* (*10*) by human plasma, the long-lasting additive effect of procaine on succinylcholine activity in dogs (and also in cats) was surprising. However, *in vitro* hydrolysis experiments with dog and cat plasma (Table 4) indicated that compared to man, the plasma cholinesterase activity in these animals was very low.

This circumstance might account for the finding

that the mg/kg dose of succinylcholine diiodide on single intravenous administration was much lower (0.05 mg) in dog and cat (*4, 13*) than in man (0.5 mg) (*8*), and that the inhibition of neuromuscular transmission following a single dose also lasted longer in dog and cat than in man. Similarly, the mg/kg/min dose of succinylcholine diiodide (0.04–0.12) was also considerably greater in man (*8*) than in dog and cat.

According to Harvey, procaine prevents acetylcholine from acting, by interfering with the acetylcholine receptor mechanism (*14*). It has also been shown that procaine inhibits acetylcholine release at the neuromuscular junction (*15*). According to the present accepted theory of the mechanism of action of the different types of muscle relaxants (*16*), the suppression of acetylcholine release or prevention of its action should increase the effectiveness of the antidepolarizing muscle relaxants (curare, Flaxedil, etc.), but decrease the effect of the depolarizing agents (decamethonium). Inasmuch as succinylcholine has been classified as one of the depolarizing relaxants (*17, 18*), procaine would be expected to decrease its effectiveness. In contrast to this, it was found (Fig. 1) that in the dosage and manner used (2 mg/kg in dogs) procaine increased the intensity of neuromuscular blockade produced by succinylcholine. It is conceivable that under the experimental conditions reported, the effect of procaine on plasma cholinesterase activity was dominant over its antidepolarizing action (*14, 15*). Under other experimental conditions, it was possible to demonstrate that procaine is also capable of antagonizing the succinylcholine-induced neuromuscular blockade (*19*).

It was observed in patients and demonstrated in animal experiments that the intravenous injection of procaine during succinylcholine administration increased the inhibitory effect of succinylcholine on neuromuscular transmission. This resulted in an increased respiratory depression in patients, and a decreased response of the sciatic-gastrocnemius preparation to repeated single electrical stimuli in animals. *In vitro* hydrolysis studies demonstrated that substrate competition exists between procaine and succinylcholine for the plasma cholinesterase. The practical importance of this observation lies in the fact that procaine and succinylcholine might be employed simultaneously in anesthetized patients, and therefore the anesthesiologist has to be aware of possible additive effects of these two agents.

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Effects of Ferric Chloride and Bile on Plasma Cholesterol and Atherosclerosis in the Cholesterol-fed Bird[1]

M. D. Siperstein, C. W. Nichols, Jr., and I. L. Chaikoff[2]

Department of Physiology, University of California School of Medicine, Berkeley

Because of its possible importance in atherogenesis, the level of plasma cholesterol has received considerable attention in recent years. Severe restriction of foodstuffs rich in lipides has been the most practical method so far proposed for lowering the concentration of circulating cholesterol. In this laboratory, however, we have been interested in procedures other than those involving dietary restrictions for the control of plasma cholesterol. We have recently shown that absorption of cholesterol from the intestinal tract stops completely in the absence of bile (*1*), and this observation suggested to us the feeding of ferric chloride, which is known to precipitate bile salts *in vitro*. It is shown here that the rise in plasma cholesterol, as well as the associated atheromata resulting from cholesterol feeding, can to a large degree be prevented by the feeding of ferric chloride.

Experiment I. Four-month-old White Leghorn cockerels, obtained through the courtesy of the Depart-

TABLE 1

COMPOSITION OF DIETS*

Expt.	Group	Diet	Wesson oil	Cholesterol	Ferric chloride	Bile concentrate
I	1	A	5	None	None	None
	2	B	5	1	"	"
	3	C	5	1	3	"
II	4	D	5	None	None	10
	5	E	5	1	"	10
	6	F	5	1	3	10
III	7	E as above				
	8	F " "				

* Percentage of Purina broiler chow (starter ration), with added constituents.

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