x-irradiation and returns in surviving animals by the twentieth post-irradiation day. 3. Following a second dose of 650r, serum bactericidal activity is depressed earlier and remains depressed for a longer time than after the first 650r x-irradiation exposure.

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Succinylmonocholine Iodide: Its Enzymatic Hydrolysis and Neuromuscular Activity.* (20304)

FRANCIS F. FOLDES.

From the Mercy Hospital and Department of Surgery, University of Pittsburgh School of Medicine.

In the past two years, succinylcholine has been used with increasing frequency for the production of muscular relaxation in the anesthetized patient. It was shown by Glick(1), Bovet-Nitti(2), and Castillo and de Beer(3), that succinylcholine is hydrolyzed by the plasma cholinesterase of various mammals. It was suggested by Ginzel *et al.*(4), by Whittaker and Wijesundera(5), and recently demonstrated by the latter(6) that the hydrolysis of succinylcholine by concentrated horse serum cholinesterase occurs in two steps. First, succinylcholine is hydrolyzed to succinylmonocholine and choline; succinylmonocholine is then very slowly hydrolyzed to succinic acid and choline. Because of its more rapid enzymatic hydrolysis in the human plasma(7), the mg/kg dose of succinylcholine necessary for the production of neuromuscular blockade, and the mg/kg/min dose used for the maintenance of muscular relaxation in anesthetized man is considerably greater than in other mammals(8).

Since under these circumstances the possibility of the accumulation of succinylmonocholine in anesthetized patients cannot be excluded, it seemed worthwhile to investigate the hydrolysis of succinylmonocholine in human plasma and to reinvestigate its neuromuscular effect in laboratory animals.

Methods. The hydrolysis of succinylmonocholine iodide† and succinyldicholine dichloride by normal heparinized and heat-inactivated heparinized human plasma was measured with Warburg's manometric technic at 37°C and pH 7.4 using a bicarbonate-carbonate buffer system. 0.4 ml of plasma or heat-inactivated plasma diluted to 1.6 ml with 0.025 M $NaHCO_3$ was placed in the main chamber of the Warburg vessels and 2 mg of succinyldicholine dichloride or succinylmonocholine iodide dissolved in 0.2 ml and titrated to pH 7.4 with NaOH was placed in the sidearms of the vessels. After the systems were brought into equilibrium with a 5% CO_2-95% O_2 gas mixture, the substrates were added to

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† The succinylmonocholine iodide used was supplied through the courtesy of Dr. E. J. de Beer of the Wellcome Research Laboratories, Tuckahoe, N. Y.

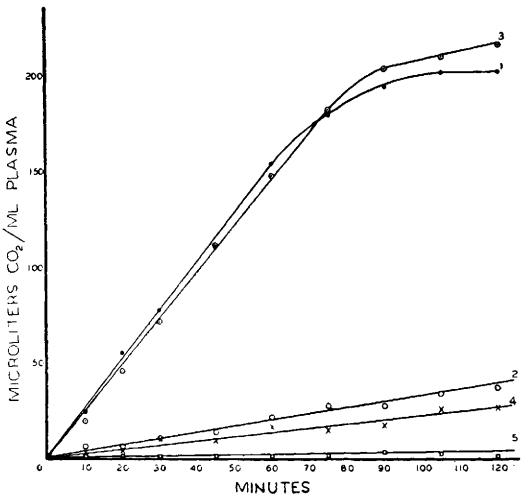

FIG. 1. Curve 1: Enzymatic hydrolysis of succinyldicholine dichloride. Curve 2: Enzymatic hydrolysis of succinylmonocholine iodide. Curve 3: Enzymatic hydrolysis of succinyldicholine dichloride and succinylmonocholine iodide. Curve 4: Non-enzymatic hydrolysis of succinyldicholine dichloride. Curve 5: Non-enzymatic hydrolysis of succinylmonocholine iodide. Substrate concentration 5.0 mg of succinyldicholine dichloride or succinylmonocholine iodide, or both (Curve 3), per ml of plasma.

the diluted plasma and the evolved CO_2 was measured at 10 minute intervals for 30 minutes and at 15 minute intervals thereafter for another 90 minutes. The results of the hydrolysis studies are presented in Fig. 1. The curves represent the average values obtained in duplicate observations with three different human plasmas. The curves of Fig. 1 indicate that the enzymatic hydrolysis rate of succinyldicholine dichloride (Curve 1) is about 8 times greater than that of succinylmonocholine iodide (Curve 2). The carbon dioxide produced by the enzymatic hydrolysis of mixtures of succinyldicholine dichloride and succinylmonocholine iodide (Curve 3), in the first 75 minutes was the same as that of the succinyldicholine component alone. Only after the hydrolysis of the dicholine component slowed down, did the quantity of carbon dioxide produced by the mixture surpass that produced by the dicholine component. The hydrolysis rate of succinyldicholine dichloride in heat-inactivated plasma (Curve 4) was considerable, but that of the succinylmonocholine iodide (Curve 5) was negligible.

The effect of succinylmonocholine iodide on neuromuscular transmission was observed on sciatic-gastrocnemius preparations of cats anesthetized with pentobarbital.‡ The result of a representative experiment is shown in Fig. 2. One mg per kg of succinylmonocholine iodide produced a definite neuromuscular block. The same dose repeated at 20-minute intervals showed a marked cumulative effect. On another animal, a 2.5 mg per kg dose produced complete neuromuscular block of 16 minutes duration and a partial block of about 40 minutes duration. In yet another cat, a 1 mg per kg dose of succinylmonocholine iodide administered 30 minutes after an 0.1 mg per kg dose of succinyldicholine dichloride caused a more profound neuromuscular block.

Comment. Our findings indicate that succinylmonocholine iodide is hydrolyzed by human plasma cholinesterase. The hydrolysis rate of succinylmonocholine iodide is about 8 times slower than that of succinyldicholine dichloride. The alkaline hydrolysis of succinylmonocholine iodide in the two-hour observation period was negligible.

In contrast to the observations of Bovet on rabbits(9) and to the statements made by Whittaker and Wijesundera(6), and Mayrhofer(10), succinylmonocholine iodide proved to be an effective inhibitor of neuromuscular transmission in cats. The onset of the neuromuscular blockade is somewhat slower and its duration is considerably longer than that of succinyldicholine dichloride and given at 20-minute intervals it showed marked cumulative effect. This fact together with the finding that a previous dose of succinyldicholine dichloride seems to have an additive effect on the action of succinylmonocholine iodide suggests that this compound might have a decamethionium-like effect on neuromuscular conduction.

Summary. The hydrolysis of succinylmonocholine iodide in normal and heat inactivated human plasmas was compared to the hydrolysis of succinyldicholine dichloride. In normal plasma, the hydrolysis rate of succinylmono-

‡ The animal experiments were carried out in conjunction with Dr. C. H. Ellis and Mr. A. L. Wnuck of the Wellcome Research Laboratories, Tuckahoe, N. Y.

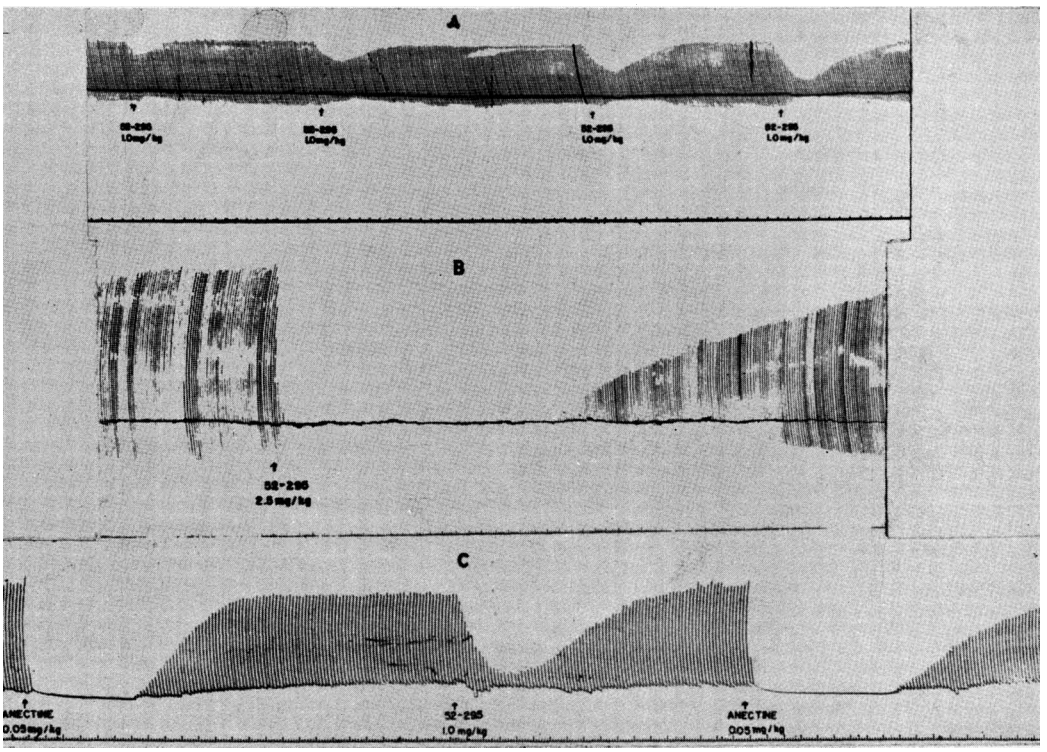

FIG. 2. A. The cumulative neuromuscular blocking action of 1 mg/kg succinylmonocholine iodide given at 20 min. intervals. B. The effect of a single 2.5 mg/kg dose. C. The mutually additive effects of succinyldicholine dichloride and succinylmonocholine iodide. Supramaximal stimuli with square wave pulses of 3 milliseconds duration at 6 sec. intervals. Time signal: 1 min.

choline iodide was found to be about 8 times slower than that of succinyldicholine dichloride. In heat inactivated plasma, the hydrolysis rate of succinylmonocholine iodide was negligible in the 2-hour observation period. Succinylmonocholine iodide in 1.0 to 2.5 mg/kg doses inhibited neuromuscular transmission in the sciatic-gastrocnemius preparation of cats.

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