

tassium depletion, and, with large doses, possibly red cell hemolysis.

**Effects of Local Anesthetic Agents on Heart Force.** W. P. ROGERS, M.D., D. M. STEWART, M.D., J. E. MAHAFFEY, M.D., E. F. WOODS, PH.D., and S. M. WITHERSPOON, M.D., *Departments of Anesthesiology and Pharmacology, Medical College of South Carolina, Charleston, South Carolina.* Six local anesthetic agents: Procaine, cocaine, lidocaine, chlorprocaine, tetracaine, and hexylcaine were assessed for their relative potency in depressing myocardial contractile force (MCF) in dogs. For each animal the cardiovascular response to procaine, 60 mg./kg. intravenously, as well as the response to one or more of the other agents, was determined. This permits calculation of potency of the other agents relative to procaine. *Method:* The HCl salts of the drugs were administered intravenously over a 2-minute period to "open chest" dogs anesthetized with 25 mg./kg. of pentobarbital and ventilated artificially with room air. A Walton-Brodie strain gauge arch was sutured to the right ventricle for direct recording of MCF. Aortic BP, heart rate, and ECG lead 2 are also recorded. In some experiments aortic blood flow, as an index of cardiac output, was recorded using a square-wave electromagnetic flowmeter. *Results:* Sixty-four experiments on 30 animals have been completed. Two animals died following injection, one of ventricular fibrillation after procaine, and a second of asystole following tetracaine. Responses to injection of different agents have been qualitatively similar in the several parameters. Each injection of drug is followed by coincident decrease of MCF, systolic and diastolic blood pressure, heart rate and aortic blood flow and by the development of ECG changes suggesting intraventricular conduction block. Typical tracings showed the following sequence with general parallelism in all parameters: (1) Initial depression appearing at 20 to 90 seconds and reaching a nadir at 3 to 8 minutes after beginning injection. (2) Either temporary stabilization at the low level or a temporary rise to or above control level. This occupies 2 to 5 minutes. (3) A slow decline to or slightly below the immediate postinjection level

over 20 to 30 minutes. (4) A gradual return to control over 20 to 70 minutes. By preliminary experiments, doses of the different drugs to provide roughly similar levels of depression were established so that any compensatory neurohumoral effects would be similar for the different drugs. Mean blood pressure depression ranged from 36 per cent with chlorprocaine to 42 per cent with procaine. The blood pressure response to cocaine has been unpredictable, 2 of 5 animals exhibiting elevation during the period of maximal heart force depression. This has not occurred with any other drug. Depression of aortic blood flow measured in 25 experiments ranged from 32 per cent for lidocaine and procaine to 44 per cent for chlorprocaine. Depressions of MCF were computed as percentage decrease per mg./kg. of drug injected. For each animal the potency of the drug or drugs injected was determined relative to procaine, which was assigned a potency of 1.0 as a depression of MCF. The means of these individual determinations expressed as relative potency are: procaine—1.0, chlorprocaine—2.2, hexylcaine—4.6, lidocaine—5.25, cocaine—6.6, tetracaine—8.3. [Supported by grants from the National Heart Institute and the Rock Hill, South Carolina, United Fund.]

**Effects of Neostigmine on Isolated Human Muscle.** PHIROZE B. SABAWALA, M.D., and JOHN B. DILLON, M.D., *Department of Surgery/Anesthesiology, University of California Medical Center, Los Angeles, California.* Most, if not all, effects produced by a potent anticholinesterase such as neostigmine can be explained on the basis of cholinesterase inhibition at the neuromuscular junction. However, there is equally good evidence that, aside from its powerful anticholinesterase activity, neostigmine also acts directly on the muscle membrane in some unknown manner (Riker, W. F., and Wescoe, W. C.: *J. Pharmacol. Exp. Ther.* 88: 58, 1946). By adding increasing amounts of neostigmine to the physiologic saline bathing an isolated nerve-muscle preparation, the various effects of this drug can easily be demonstrated. These effects can conveniently be described as: (1) anticholinesterase effect, (2) positive inotropic effect, (3) spontaneous twitching and (4) two phase

neuromuscular block. **Anticuraré Effect:** A significant correlation between the inhibition of acetylcholinesterase and the anticuraré activity of neostigmine has been described (Blaschko, H., Bulbring, E., and Chou, T. C.: Brit. J. Pharmacol. 4: 29, 1949). However, it has also been shown that nikethamide, which has no anticholinesterase activity, does possess an anticuraré effect (Huidobro, F., and Jordan, J. J.: J. Pharmacol. Exper. Ther. 86: 49, 1946). Our experiments with isolated human intercostal muscle show that very small doses of neostigmine possess an anticuraré activity which can be correlated to its anticholinesterase activity. This part of its action reaches a maximum at a concentration of neostigmine of less than 0.1  $\mu\text{g}$ . neostigmine/ml. Small increments of neostigmine at this stage, do not significantly increase its anticuraré activity. We assume, therefore, that at this concentration of neostigmine, acetylcholinesterase is completely inhibited. But this constitutes only about 50 per cent of the total anticuraré activity of neostigmine, since large increments of neostigmine (ten times the previous dose) will antagonize *d*-tubocurarine completely. **Positive Inotropic Action and Spontaneous Twitching:** If neostigmine is administered alone in large doses (1  $\mu\text{g}$ ./ml. and above) its positive inotropic action becomes quite obvious. Increasing the dose of neostigmine still further gives rise to twitching independent of any electrical stimulation. The positive inotropic action of neostigmine can be suppressed (1) by the addition of *d*-tubocurarine and (2) by the addition of more neostigmine. Except in those specimens rendered hyperirritable by prolonged periods of anoxia, it is difficult to produce spontaneous twitching in isolated human intercostal muscle. However, it is quite easy to produce spontaneous twitching in isolated guinea pig and mouse muscles which appear to be more sensitive to neostigmine than isolated human muscle. **Two Phase Neuromuscular Block:** As the concentration of neostigmine is increased further, its positive inotropic action disappears and a neuromuscular block becomes more evident. By introducing suitable doses of neostigmine (between 20 and 40  $\mu\text{g}$ ./ml.) it can be shown that this paralysis is of the two phase type described for any "depolarizing"

agent (Sabawala, P. B., and Dillon, J. B. Acta Anaesth. Scand. 3: 83, 1959). [Supported by a grant from the United States Public Health Service.]

#### Uptake of Halothane by the Human Body

PHILIP H. SECHZER, M.D., HARRY W. LINDE, PH.D., AND ROBERT D. DRIPPS, M.D., *Department of Anesthesiology, Schools of Medicine of the University of Pennsylvania, Philadelphia, Pennsylvania.* A rational approach to halothane as an inhalational anesthetic agent requires that its uptake by the human body be understood. This would extend basic knowledge regarding the exchange of inert gas at the lungs and tissues and might clarify the mechanism of the relatively slow onset of halothane analgesia. Given certain physical and physiological information, the uptake can be predicted from theory (Kety, S. S.: Pharmacol. Rev. 3: 1, 1951). However, because of basic assumptions involved and incompleteness of some of the physical data used in the calculations, previous attempts to plot the uptake have not been entirely satisfactory. Using a method similar to that described for cyclopropane (Sechzer, P. H., Dripps, R. D., and Price, H. L.: J. Appl. Physiol. 14: 887, 1959) the uptake of halothane was determined by continuously measuring the expired concentration of the gas in subjects who breathed a known gas mixture. **Method:** Eight, white, normal subjects (5 males; ages, 19-28; weight, 52-89 kg.; height, 162-187 cm.; surface area, 1.52-2.14 m.<sup>2</sup>) who received no drugs other than halothane were studied in the supine position. The nostrils were occluded and breathing took place through a rubber mouthpiece and competent unidirectional valve. A portion of the respired gas mixture was drawn continuously from the lumen of the mouthpiece through a needle and a lead tube to a halothane and to a CO<sub>2</sub> analyzer standardized using known mixtures. The temperature of the respired gases was measured continuously with a calibrated (copper-constantan) thermocouple inserted through a needle into the lumen of the mouthpiece. The respiratory minute volume was measured by passing the exhaled gases through a dry gas volume meter. The meter's pointer activated a loudspeaker producing an electrical signal with each revolution. Lead 2 of the