

The Effects of Muscle Relaxants and Anticholinesterases on the Neuromuscular Refractory Period in Anesthetized Man. R. A. EPSTEIN, M.D., S. R. WYTE, M.D., S. JACKSON, M.D., and S. SITTEB, M.D., *National Institutes of Health, Bethesda, Md., and Walter Reed General Hospital, Washington, D. C.*

The effects of minimal quantities of nondepolarizing muscle relaxants and anticholinesterases on the neuromuscular refractory period were determined in healthy adult humans maintained at a constant anesthetic depth. **Methods:** The ulnar nerve was stimulated at the elbow with single or paired supramaximal stimuli of 0.1-msec duration. The twitch tension on the adductor pollicis was recorded, and the compound muscle action potential (EMG) of the thenar eminence was displayed on an oscilloscope and photographed. The electromechanical response to paired stimulation is dependent upon the interval between the two stimuli. At intervals less than the refractory period, the response is identical to that seen with a single stimulus. The electromechanical response to paired stimulation begins to increase at a pair interval of 1.0 msec (average) and reaches a maximum at 2.0 msec (average). The "average neuromuscular refractory period" (ARP) is defined as the interval between that pair of stimuli which evokes a mechanical response equal to the average of the response to a single stimulus and the maximal response obtainable with a paired stimulus. **Results:** *d*-tubocurarine (0.5–1.0 mg), gallamine (5–10 mg), edrophonium (2–5 mg), and neostigmine (0.5–1.0 mg) administered intravenously had no effect on the mechanical response to a single stimulus or on the maximal obtainable response to paired stimuli. However, *d*-tubocurarine and gallamine decreased the ARP, while edrophonium and neostigmine increased the ARP. The EMG resulting from paired stimuli separated by an interval greater than the refractory period of some or all of the muscle fibers was distinguished from the single response by the presence of a second positive component in its waveform. After the intravenous administration of *d*-tubocurarine or gallamine there was an increase in the second component of the EMG evoked by paired stim-

uli separated by the ARP. Edrophonium and neostigmine caused decreases in this second component. The first component of the EMG was not affected. **Summary:** In man, nondepolarizing muscle relaxants decrease the neuromuscular refractory period, while anticholinesterases increase the neuromuscular refractory period.

The Effects of Germine Diacetate on the Rat Phrenic Nerve-Diaphragm Preparation. F. F. FOLDES, M.D., E. B. BRODMAN, M.D., H. N. KRANZLER, M.A., P. S. UNDERWOOD, M.D., and B. A. HENSWORTH, PH.D., *Departments of Anesthesiology, Montefiore Hospital and Medical Center, and the Albert Einstein College of Medicine, New York, N. Y.*

Germine diacetate (GDA) has been employed on a limited scale in the treatment of myasthenia gravis (New Engl. J. Med. 275: 1207, 1966) and the reversal of residual neuromuscular block (ANESTHESIOLOGY 29: 850, 1968). The purpose of this study was to obtain information, under controlled conditions, about the dose-effect relationship and the time course of action of GDA and on its interaction with *d*-Tc and C10. **Results:** Concentrations of GDA ranging from 2.5 to 100.0 µg/ml caused 240 to 438 per cent mean increases in the twitch tension of the indirectly-stimulated isolated phrenic nerve-diaphragm preparation of the rat. The intensity of action of GDA was proportional, and the time required for the development of its maximal effect was inversely proportional to its concentration. Repeated administrations of GDA had progressively less and less effect. Tetanus was poorly maintained in the presence of GDA. GDA also increased the twitch tension of the directly-stimulated preparation. Muscle performance was improved by GDA during partial (40 to 60 per cent), but not during complete, *d*-Tc or C10-induced neuromuscular block. The improvement probably was due to the increase of the twitch tension of the unblocked fibers. **Summary:** These findings confirm earlier reports (J. Pharmacol. Exp. Ther. 160: 349, 1968) that the site of action of GDA is primarily postjunctional, and indicate that GDA preferably in conjunction with anticholinester-

ases, may be useful for the management of myasthenia gravis and the reversal of residual neuromuscular block.

The Effects of Halothane and Paired Electrical Stimulation on Isotonic Contractions of Isolated Heart Muscle. A. H. GOLDBERG, M.D., Ph.D., and W. P. C. PHEAR, B.Sc., *Department of Anesthesiology, Boston University School of Medicine, Boston, Mass.* These experiments were designed to determine the effects of halothane (H) and paired electrical stimulation (PS) on resting compliance (C) of heart muscle, and to evaluate the ability of PS to improve myocardial performance in the presence of H. *Methods:* Heart muscle preparations (37°C, pH 7.4) from 28 rats were studied in the presence and absence of H (0.6 per cent). The contractions were isotonic and free-loaded. Changes in muscle length could be accurately detected to 10 μ . C was assessed during stretch of the muscle by a 0.75-gm load by measuring the rate of change of resting muscle length ($d(l-r)/dt$; direct correlation with C, with the excitation consisting of alternating 45-second periods of single stimulation (SS) and PS; or, with the mode of stimulation held constant (SS, PS, or no stimulation), by calculating Young's Modulus (force per muscle cross-sectional area per relative length change; inverse correlation with C) at $\frac{1}{2}$ (Y_1) and five (Y_5) minutes following the onset of muscle stretch. *Results:* With SS, H depressed the maximum rate and extent of isotonic shortening 55 per cent and 54 per cent. PS in the presence of H restored the contractility to the level found with SS in the absence of H, but not to the higher values found with PS in the absence of H. C was increased by PS alone ($d(l-r)/dt$: +36 per cent; Y_1 : -6 per cent; Y_5 : -11 per cent), and was decreased by H with SS ($d(l-r)/dt$: -35 per cent; Y_1 : +10 per cent; Y_5 : +14 per cent). PS in the presence of H reduced C ($d(l-r)/dt$) 9 per cent below the value obtained with SS and H. C was reduced by H even in the absence of all muscle contractions (Y_1 : +11 per cent; Y_5 : +17 per cent). *Summary:* Therefore, C is increased by PS and decreased by H. Since this effect of H occurs whether the muscle is being driven

by SS, whether the contractility is restored to control conditions by PS, or even if the muscle is not contracting at all, it appears that H stiffens heart muscle by a direct action on the mechanism responsible for maintenance of C.

Why Do Chronic Alcoholics Require More Anesthesia? Y. H. HAN, M.D., *Department of Anesthesiology, St. Vincent's Hospital and Medical Center of New York, New York, N. Y.* It is well known that some chronic alcoholics require greater than usual amounts of both inhalational and intravenous anesthetics. In the present study, the minimum alveolar concentration (MAC) of halothane in chronic alcoholics was determined and compared with the normal MAC. The Ostwald solubility coefficients (λ) of halothane in homogenized human adult brain tissues from normal individuals and chronic alcoholics were compared. *Methods:* Six normal healthy adult subjects and six chronic alcoholics who had been heavy drinkers for more than ten years were studied and mean MAC values of halothane of the two groups were compared. The MAC value of halothane was determined by the technique of Eger. The λ of halothane was determined *in vitro* in brain tissue from six normal adults and twelve chronic alcoholics and mean values for the two groups were compared. All alcoholic subjects had died from causes other than brain diseases. Histopathologic changes of the same brain tissue specimens were also observed by a neuropathologist. *Results:* The mean MAC values of halothane in chronic alcoholics were increased significantly above normal. Significant increases in the mean λ of halothane in chronic alcoholic brain white matter to air were also observed. These increases appeared to be mainly due to decreases in CNS excitability threshold, phospholipid demyelination, and increase in phospholipid content in the white matter of the alcoholic subjects. *Summary:* Chronic alcoholism is associated with demyelination and increase in phospholipid content in the central nervous system. These patients require higher concentrations of inhalational anesthetic agents with lower lipid

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