rameters of "NE status" measured by these authors. This may well offer some support, admittedly obtuse, for the contention that altered biochemistry of peripheral adrenergic neurons is unlikely to be involved in the much-less-pronounced cardiovascular alterations produced by cyclopropane.

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Clinical Pharmacology of the Neuromuscular Junction

PRESENT KNOWLEDGE of the physiology and pharmacology of the neuromuscular junction shows that transmission between motor neuron and muscle fiber is carried out in a series of complicated steps. Operation of the prejunctional elements includes the synthesis, storage and release of acetylcholine. The initiation of the chain of postjunctional events begins with the arrival of neurally-released acetylcholine, which reacts with postjunctional membrane receptive sites. At the postjunctional membrane, permeability-controlling elements are thereby activated, causing impedance to fall. This change allows an increase in transmembrane ionic flux to occur, producing a depolarization of the postsynaptic membrane (the endplate potential). If these local changes in membrane potential are sufficiently great, a muscle-fiber action potential is initiated and is propagated along the length of the muscle fiber. In the wake of the propagated action potential, excitation–contraction coupling occurs, and thereafter the muscle tension rises.

The complex train of events involved in neuromuscular transmission can be facilitated or depressed in many ways and by many factors. Among the various modifying influences are the ionic composition of the extracellular fluid, the rate at which the neuromuscular junction is activated, and the presence of pharmacologically-active substances, such as anesthetic agents, quaternary ammonium compounds, anticholinesterase drugs, etc. In setting up various procedures designed to produce alterations in the neuromuscular transmission of a patient, and also in interpreting clinical data, the anesthesiologist relies both on basic principles and on empirical observations. The former are derived from laboratory experimentation carried out on whole animals or tissue preparations, the latter obtained from clinical practice. When he makes plans and sets procedures for practical application and when he interprets clinical data obtained from the patient, the anesthesiologist often wonders to what extent the results of laboratory experiments are applicable to patients. His questions and doubts generally do not represent a complete scepticism of the value of basic research in clinical practice; rather, they stem from the realization that it is difficult to assess neuromuscular block in a patient where one must contend with a large number of uncontrollable factors. Frequently, the action of a drug at the human neuromuscular junction must be surmised from indirect clinical ob-

servations whose interpretation is extrapolated from more direct data obtained from other species. An even more important consideration is that at the neuromuscular junctions of the patient, the concentration of an administered drug both is unknown and changes with time. Additional complications arise from the multiplicity of agents administered to the surgical patient. For example, general anesthetic agents, such as diethyl ether and halothane, have a depressant effect on neuromuscular transmission which cannot simply be described as "curare-like." To a variable degree such general anesthetics contribute to the neuromuscular-blocking actions of the more powerful specific blocking agents which are administered. Thus, it becomes difficult, if not impossible, to predict, characterize, or evaluate neuromuscular block in the human on logical grounds alone. Therefore, evidence obtained from the patient is essential in making reasonable judgments as to courses of action to be followed during surgery and in the recovery period.

The paper by Epstein, Jackson and Wyte in the present issue of the Journal describes a testing procedure designed to provide clinical data which can help the anthesiologist in evaluating nuromuscular block in surgical patients. The authors have used tension output measurements and electromyography to show that the "average refractory period" of indirectly-stimulated muscle is diminished by *d*-tubocurarine and that it is increased by anticholinesterase agents, such as neostigmine and edrophonium. The technique of Epstein *et al.* can be useful under conditions where neuromuscular transmission is lightly potentiated, or inhibited but not blocked. It depends on the fact that variations in the rate of repolarization of junctionally-initiated action potentials are produced by alterations in the amplitude and duration of the endplate potential. Such changes in rate of repolarization at the neuromuscular junction modify the refractory period of neuromuscular transmission. On this basis, results described by Epstein *et al.* might have been anticipated from examination of the repolarization rates of junctionally-initiated action potentials. In our laboratory we have obtained such data from single-muscle-fiber membrane-potential recordings made from amphibian neuromuscular preparations under normal conditions and after application of *d*-tubocurarine or anticholinesterases such as edrophonium or neostigmine. It would have been helpful if we had made direct determinations of the refractory periods associated with such action potentials, but unfortunately technical problems as yet unsolved prevented us from doing so in a satisfactory manner.

Although the double-stimulus technique may be helpful in making a clinical assessment of neuromuscular transmission, one should be cautious in attempting to use this procedure to determine the intimate nature of neuromuscular block produced by various pharmacologic agents. This restriction is particularly true in the case of neuromuscular block produced by depolarizing quaternary ammonium compounds, whose desensitizing action has been erroneously reported to be curariform. Callamine, tetraethylammonium, hexafluorenium and certain other quaternary ammonium compounds are not simple competitive curare-like agents, contrary to common belief. Detailed information about molecular mechanisms and sites of action of these and other blocking agents is best obtained from single-fiber laboratory-based experimental approaches which allow direct measurements of the critical processes involved. These fundamental matters have been and will continue to be of practical interest to the anesthesiologist, who must control the production, duration and recovery of neuromuscular block in the surgical patient.

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