Oliver Wendell Holmes and Anesthesia

To the Editor:—A number of years ago Dr. John Gillies of Edinburgh came into my office bearing an old book. He said, "I want you to have this." It was Bailey's *English Dictionary*, in which anaesthesia is defined as "a Defect of Sensation." The point of interest is that this dictionary was published in 1724. I pressed him to publish a note about this. He said, "Oh, no, this is just a sample of my warped sense of humor—what price O. W. Holmes now?" A number of years have gone by and he has done nothing about publishing it, so I would like to see that *his* find is recorded.

HENRY K. BEECHER, M.D.
Harvard Medical School
Massachusetts General Hospital
Boston, Massachusetts

Potentiation of Muscle Relaxants by Quinidine

To the Editor:—In a recent paper, Dr. Miller and his associates (ANESTHESIOLOGY 28: 1036, 1967) report that quinidine potentiates both depolarizing and nondepolarizing muscle relaxants. Their results confirm the observations by Schmid *et al.*[1] The paper cannot elucidate the nature of the interaction of these drugs, however, for two reasons: first, attempts to separate sites of drug action by measuring changes of height of the muscle twitch are inconclusive. Muscle twitch is the final result of a chain of events which starts at the nerve terminal, traverses synapses, depolarizes the endplate, initiates a propagated potential in the muscle cell and, finally, triggers the contracting mechanism. Since neuromuscular blocking drugs, such as quinidine, can affect one or more steps of this chain, each element must be studied separately. The second problem is that it is difficult to evaluate sensitivity to drugs without a defined dose–response relationship. Wislicki[2] and Dutta[3] have characterized three dose-related effects of quinidine: 1) twitch potentiation, 2) neuromuscular blockade, and 3) depression of the directly-stimulated muscle. In this context, the finding by the authors that quinidine increased the twitch tension *in vivo* but failed to do so in the *in vitro* experiments could be a reflection of this dose–effect relationship.

Dr. Miller and his colleagues discuss the potentiation of muscle relaxant effects by quinidine at the myoneural junction. This may apply in an organ bath. *In vivo*, however, significant drug interaction can occur at extrajunctional sites, for instance, on plasma proteins[4] to which quinidine and muscle relaxants bind.

The authors entertain the possibility that intensification of neuromuscular blockade by quinidine may result from depression of "intermediate" postsynaptic receptors or, alternately, from interference with the presynaptic release of acetylcholine, similar to the action of local anesthetics. The first hypothesis should be questioned for the following reasons: a) the authors' work does not present evidence to support this theory; it only excludes curare-like and cholinesterase inhibition mechanisms; b) "intermediate" receptors have not yet been structurally or pharmacologically defined; c) the effect of quinidine on the electrical potentials of the postsynaptic membrane (miniature, endplate and action potentials) is unknown; and last, d) previous work by others[2,5] points to an effect of quinidine on the muscle fiber.

Regarding the hypothesis of blockade due to curtailment of acetylcholine liberation, it should be recalled that there is no proof that local anesthetics depress synaptic transmission by inhibiting the release of acetylcholine. Indeed, acetylcholine release can be reduced by half by procaine, with no impairment in neuromuscular transmission.[6] The blocking effect of local anesthetics depends upon stabilization of cell membranes, to which the fine prejunctional nerve endings are particularly sensitive. There is ample evidence demonstrating that local anesthetic drugs, including procaine, lidocaine, prilocaine, mepivacaine, tetracaine and dibucaine, can impair the propa-

gation of action potentials at the nerve terminal initiated by electrical means[7,8] or depolarizing drugs.[9] By comparison, our knowledge of the relationship among the membrane effects of local anesthetics and acetylcholine synthesis, storage, mobilization and release is rudimentary.

In summary, although their evidence for drug potentiation appears sound, Drs. Miller, Way and Katzung have not established that this occurs only at the myoneural junction, nor have they advanced plausible arguments to support the two mechanisms postulated for interaction.

JOSE E. USUBIAGA, M.D.
Department of Anesthesiology
School of Medicine
University of Miami
Miami, Florida

REFERENCES

1. Schmidt, J. L., Vick, N. A., and Sadove, J. S.: The effect of quinidine on the action of muscle relaxants, J.A.M.A. 183: 669, 1963.
2. Wislicki, L.: Effect of quinidine on contraction of skeletal muscle, Arch. Int. Pharmacol. 124: 76, 1960.
3. Dutta, N. D.: Some pharmacological properties common to atropine, pethidine, procaine and quinidine, Brit. J. Pharmacol. 4: 197, 1949.
4. Usubiaga, J. E.: *In* Bromage, P. R., ed.: The Mechanism of Action of Local Anesthetics. Berlin, Springer-Verlag, 1966, pp. 120–129.
5. Lammers, E., and Ritchie, J. M.: The actions of quinine and quinidine on the contractions of striated muscle, J. Physiol. 129: 412, 1955.
6. Straughan, D. W.: The action of procaine at the neuromuscular junction, J. Pharm. Pharmacol. 13: 49, 1961.
7. Usubiaga, J. E., and Standaert, F.: The effects of local anesthetics on motor nerve terminals, J. Pharmacol. Exp. Therap. 159: 353, 1968.
8. Usubiaga, J. E., and Moya, F.: Neuromuscular effects of six local anesthetics on anaesthetized subjects, Can. Anaesth. Soc. J. 15: 56, 1968.
9. Usubiaga, J. E., Wikinski, J. A., Wikinski, R., and Usubiaga, L.: Prevention of succinylcholine fasciculations with local anesthetics, ANESTHESIOLOGY 26: 3, 1955.

To the Editor:—We appreciate the opportunity to reply to Dr. Usubiaga. Judging from his comments, a brief review of our paper is indicated. Because of apparent disagreement among previous investigators,[1,2] our *stated* purpose was "to define more precisely the characteristics of the interaction between quinidine and the clinically used muscle relaxants." We were able to establish that quinidine potentiates both nondepolarizing and depolarizing muscle relaxants *in vivo* and *in vitro*. Edrophonium was not effective in antagonizing a nondepolarizing blockade after quinidine.

The summary of our paper clearly states "No single classical mechanism can explain all of these interactions." The results *do not* establish that this action occurs at the neuromuscular junction, and at no point in the paper is this statement made. We are pleased that Dr. Usubiaga concurs with our opinion that quinidine's curare-like and anticholinesterase actions do not satisfactorily explain our results. Since these classical mechanisms could not explain our results it seems reasonable to consider other mechanisms of drug action.

There is no question that drug effect will vary with dose and as Dr. Usubiaga points out the effects of quinidine on the neuromuscular junction are dose-dependent. The doses of quinidine used in our study resulted in either no change or increased twitch tension when given alone. Larger intra-arterial doses of quinidine may produce depression of indirectly-stimulated muscle (neuromuscular blockade), but the evidence for depression of directly-stimulated muscle is not convincing. Although inferred, a depression of directly-stimulated rat diaphragm is not specified or illustrated in Dutta's work.[3]

We have two objections to Wislicki's work:

1. The cats were anesthetized with ether and pentobarbital, each of which has significant neuromuscular blocking effects;

2. Direct stimulation which elicited twitch tension in Wislicki's experiments represents not only muscle membrane stimulation but also stimulation of intramuscular nerve branches.[5] It is imperative that muscle membrane depression of any drug be evaluated by direct stimulation of a curarized muscle in which intramuscular nerve branches are blocked. At the dose levels employed by Wislicki we were unable to demonstrate direct muscle membrane depression in the peroneal nerve-anterior tibialis preparation of the curarized cat.[7]

That a dose of procaine which reduces acetylcholine by half has no effect on twitch tension does not mean that procaine cannot produce neuromuscular blockade by this mecha-