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.

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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-