ever, before McMechan realized that interest in anesthesia was international, not a phenomenon restricted to the United States. Accordingly, 50 years ago, in 1925, the National Anesthesia Research Society was renamed the International Anesthesia Research Society. Today, the International Anesthesia Research Society continues its long and proud tradition as an outstanding contributor to the science and the art of anesthesiology. It is a pleasure to salute the International Anesthesia Research Society on the occasion of its golden anniversary, and to wish it well in the years to come, secure in the knowledge that its second 50 years will be as productive and valuable as the first.—*N.M.G.*

Does Clinical Anesthesia Need New Neuromuscular Blocking Agents?

ASK a population of anesthetists whether new neuromuscular blocking agents are needed in anesthesia and a variety of responses will be elicited, ranging from "absolutely not" to "definitely." After further questioning, however, nearly all might agree that new neuromuscular blockers are *not* needed, unless they are *different* and provide the practitioner with additional clinical options that broaden the scope of services he can safely provide the patient and the surgeon.

AH8165, examined in articles by Post and colleagues and by Hiser, Dretchen, and Kruger in this issue, is a new nondepolarizing neuromuscular blocking agent, especially to the American literature, although its pharmacologic effects in animals and man have been described in the British literature for more than two years.[1-4] In several species the duration of its neuromuscular blocking action is much shorter than those of the standard nondepolarizing agents, *d*-tubocurarine and pancuronium.[1,3] This, unfortunately, is not so in primates, including man.[3,4] The drug has a strong vagolytic action[5] which is manifest at subneuromuscular blocking doses and which far outlasts the duration of neuromuscular blockade. This action produces tachycardia and increased cardiac output in man.[4] What, then, is "different" about AH8165?

At a dose of 1.5 mg/kg in man, AH8165 causes rapid onset of complete neuromuscular blockade such that intubation of the trachea can be accomplished within a similar period (approximately 30–45 seconds), as after succinylcholine,[2,3] thus providing a nondepolarizing alternative to succinylcholine for "crash intubation" of the trachea. AH8165, then, may have a place in clinical anesthesia, but it is certainly not the "ideal" neuromuscular blocking agent.

The perfect relaxant, it is generally acknowledged,[6-9] would have a brief, noncumulative nondepolarizing neuromuscular blocking action, with rapid onset and recovery; it would be reversible by an appropriate antagonist, and it would lack clinically important cardiovascular (autonomic, hemodynamic) side-effects. Such a drug would obviously be new, different, and clinically useful. Experts in the field have been well aware of these requisites for nearly 20 years. Many of us, however, may be unaware of the vast amount of research spent in the quest for such a drug. For example, pancuronium, a drug that has a much shorter duration of action in the dog and cat than in man, is a byproduct of this continuing research.[9] A recent review[9] provides many of the important details, including the demonstration that some agents developed within the past 15 years, including AH8165, do have the desirable characteristics described above in several species of experimental animals, but not in man. Why?

The answer is "species differences." It is now trite to point out that there are marked interspecies differences in the neuro-

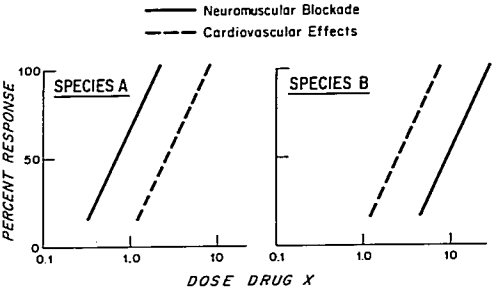

FIG. 1. Example of a species difference in relative sensitivities to the neuromuscular and cardiovascular effects of a hypothetical quaternary ammonium compound, Drug X, which has qualitatively similar cardiovascular effects in species A and species B. In the former, complete neuromuscular blockade is produced by Drug X before any important cardiovascular effect becomes evident. In the latter, the opposite is true. Drug X is therefore safe in species A but disadvantageous and possibly dangerous in species B.

muscular blocking potencies of quaternary ammonium compounds.[10] Recently it has become apparent that the cat, dog, monkey, rat, and chicken, the species most often used for initial evaluation of new quarternary ammonium compounds, differ markedly from man in the rates and routes by which they metabolize and excrete these drugs. Interspecies differences are also seen among certain substances that produce a basic nondepolarizing effect in all species but are antagonized by anticholinesterase agents only in certain species, as shown by Hiser, Dretchen, and Kruger for AH8165 in this issue. Another well-known example of the phenomenon of species differences in antagonism of certain nondepolarizing agents by anticholinesterases is the fact that neuromuscular blockade by benzoquinonium (Mytolon) is reversed by neostigmine in the chicken but not in man or the cat.[11] The underlying reason for the variable success of reversal of some nondepolarizing agents in different species may be interspecies differences in the inherent anticholinesterase properties of quaternary ammonium compounds in general.* On the other hand, the cardiovascular (autonomic, hemodynamic) effects of a particular neuromuscular blocker are usually qualitatively similar from species to species. Thus, for example, the dose–response curve of Drug X for neuromuscular blockade in species A may lie to the left of that for cardiovascular effects, indicating that Drug X is a safe and effective drug in species A (fig. 1). For species B, however, the two curves may occupy opposite positions. For species B, therefore, Drug X is an undesirable or even dangerous drug. An example of this type of species difference is provided by the experimental neuromuscular blocking drug BW403C65.[12] In dogs this agent produces no significant cardiovascular effect, even at fully paralyzing doses, while in cats it has a vagolytic and moderately hypertensive action, the latter effect probably including a beta-adrenergic receptor stimulating component. In man BW403C65 causes clinically unacceptable tachycardia and hypertension.[12] Species differences will undoubtedly continue to confound developers of future neuromuscular blocking drugs. Attempts to predict the clinical effects of these drugs based on results obtained in animals will no doubt continue to prove frustratingly inaccurate, since this appears to be "the nature of the beasts."

The most important information gleaned from the development and study of new neuromuscular blocking agents in the past ten years has been the establishment of new structure–activity relationships. It is now known, for example, that *d*-tubocurarine is a monoquaternary compound,[13] thus explaining its ganglion-blocking effect. Neuromuscular blocking potency is no longer linked to the classic 14-Å interquaternary distance; active agents having internitrogen distances of approximately 7 Å (AH8165), 10 Å (Toxiferine and pancuronium) and even 21 Å (car-

* Savarese JJ, Kitz RJ, Braswell L, et al: Unpublished data.

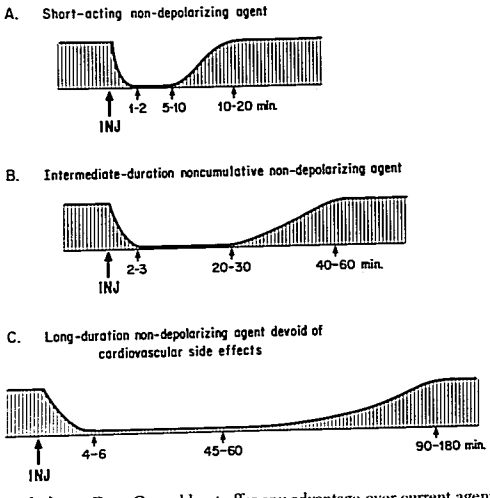

FIG. 2. In the authors' opinion, three new nondepolarizing neuromuscular blocking agents are needed for use in clinical anesthesia. A, B, and C represent hypothetical adductor thumb-twitch tracings of the "typical" effect of each of these drugs in an average anesthetized patient. Numbers beneath tracings represent cumulative times from injection. For example, Drug A, a short-acting agent, would within 1–2 minutes produce complete paralysis lasting 5–10 minutes, complete recovery occurring within 10–20 minutes. Drug B, an intermediate-duration agent, would have a total duration of action approximately twice that of Drug A. Drugs A and B would ideally lack significant autonomic side-effects. Some clinically acceptable autonomic effect such as a mild vagolytic or ganglion-blocking effect, resulting in slight tachycardia or hypotension, would not detract from the clinical usefulness of such drugs. Drug C would not offer any advantage over current agents in duration of action. A total lack of cardiovascular effect, even at fully paralyzing doses, would make Drug C the agent of choice for patients who have a variety of cardiovascular disorders (see text).

bolonium) exist. This means that the medicinal chemists and chemical pharmacologists of today are free to work with a wide variety of structures in designing potent new neuromuscular blocking agents. Further structure–activity work should also permit the correlation of chemical structure of neuromuscular blockers with cardiovascular effects, thus producing new and clinically safer drugs. Hopefully, molecular biologists may eventually be able to characterize the chemical structure of the cholinergic receptor, and thereby allow the rational design of inhibitor molecules. This, however, appears to be a remote possibility at present.

What new neuromuscular blockers does the anesthesiologist need? In our opinion, three are needed. These hypothetical agents are described in figure 2. The need for Drug A, a short-acting nondepolarizing drug, has been discussed. It would replace succinylcholine in clinical situations in which the latter is now useful, as well as in most situations where succinylcholine is contraindicated.[6–9] Drug B, an intermediate-duration nondepolarizing agent without cumulative effect, would provide an action span not available in nondepolarizing agents at present, a duration suitable for operative procedures lasting approximately an hour. Lack of cumulation in such a drug would allow repetitive administration of the same dose-increment at constant intervals. A rapid recovery pattern (15–20 minutes) associated with such a drug would decrease the need for reversal of neuromuscular blockade at the termination of anesthesia, thereby decreasing the possibility or danger of postoperative residual curarization. A drug metabolized by the body, whose action was terminated by its own destruction, would also be very appealing. Drug C, a long-acting nondepolarizing agent devoid of cardiovascular side-effects, is also needed. Admittedly, the advent of pancuronium has eliminated the problem of hypotension secondary to histamine release or autonomic ganglionic blockade. On the other hand, pancuronium's vagolytic effect,

most evident at fully paralyzing doses, causes tachycardia, which often has deleterious hemodynamic results in patients who have coronary-artery disease, stenotic coronary valvular lesions, and hypertension. Drug C is therefore most needed in cardiac surgical procedures.

The imaginative anesthetist could easily incorporate such agents into a variety of new clinical techniques, thereby broadening the scope and quality of his care of his patients and his services to his surgical colleagues. We feel that this era lies not more than five or ten years ahead.

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