

THE FUTURE OF MUSCLE RELAXANTS

E. M. PAPPER, M.D.

IN the epilogue of a lucid and comprehensive monograph, Foldes summarized his look into the future of muscle relaxants: "The goal of this search (for other drugs) will be to find a nondepolarizing muscle relaxant which will be as short acting and controllable as succinylcholine, its fate in the organism being little affected by pathological changes, its breakdown products having no neuromuscular blocking effect and which will be easily reversible by a harmless antagonist, in the rare instances, when an atypical response will make this necessary."¹

No one could quarrel, except in small detail, with this ultimate goal. Yet, the specter of imperfection is raised in the concluding phrase of Foldes' hope. Obviously, there is no way of knowing with certainty which steps will be taken toward this or any other "goal," but some guesses can be made as to the nature of the broad path. One way of looking toward the future is to assess the general areas of agreement, at least among clinicians, as a guide toward the directions of search and study in the years to come.

The use of a muscle relaxant of short duration of action like succinylcholine to intubate the trachea is a practice of clear and universal acceptance. To be sure, there are variations in technique, but these are largely matters of detail. There are, for example, differences of opinion as to the proper dose of drugs and differences of opinion as to the best method or methods of inducing anesthesia under these conditions. The important point is the fact that in the majority of instances of intubating the trachea, a muscle relaxant is used and it is almost always succinylcholine.

A second point of reasonable agreement is the use of light planes of general anesthesia or

analgesia, made possible by muscle relaxants, to minimize or prevent the harmful effects of deep anesthesia following large doses of anesthetic agents. This principle is emphasized variously by such terms as "balanced" anesthesia, "ether analgesia," "nonpotent gas" anesthesia, and "nitrous oxide-oxygen-relaxant" anesthesia. It has been both praised and condemned by the word polypharmacy. All these concepts of anesthetic management have in common the preservation of compensatory responses to surgical trauma, hemorrhage and other forms of injury by establishing automatic floors to the depth of anesthesia. This state of affairs during operation with general anesthesia is possible only with the use of muscle relaxants.

The practical application of this method has many variations in the basic theme. All imaginable ways of using muscle relaxants have their advocates. There are those who argue that curare in substantial dosage is the agent of choice for these purposes because it provides ideal working conditions for the surgeon and can be reversed by a specific antidote, neostigmine. The side effects of the antidote can be prevented by atropine.² This group of clinicians see no useful purpose in employing agents other than nitrous oxide and oxygen once intubation of the trachea is successfully accomplished with the aid of a barbiturate and a relaxant. There are those who modify this procedure by adding narcotic drugs, more barbiturates, or more potent general anesthetics permitting a reduction in the dose of muscle relaxant.

Another generalization accepted among clinicians is the fact that muscle relaxants produce relatively few side effects of importance except for the complications resulting from neuromuscular blockade. The chief of these is depression of breathing. This position is held by many despite the imposing factual array presented by Beecher and Todd³ and the con-

Dr. Papper is Professor of Anesthesiology, Columbia University College of Physicians and Surgeons, and Director, Anesthesiology Service, Presbyterian Hospital, New York, N. Y.

siderably modified view of this problem taken by Dripps.⁴ This peculiar conflict of "belief" and "fact" remains one of the curiosities of anesthesiology.

This area of conflict brings into range one view toward the future. Drugs even so widely used as relaxants, cannot at the same time, be an important cause of death during anesthesia and a boon to safer anesthetic care. One way of help in this quandary lies in those studies which will provide clarity in understanding the basic mechanisms of action of relaxants beyond that of convenient (and argumentative) classification labels. Equally important, theoretically and practically, would be improved understanding of what takes place when relaxant "antagonists" are used. Until some of these questions are answered more precisely it will not be possible to proceed with vigor and certitude toward better clinical use of relaxants in the future.

Many of the significant problems under investigation have been described in considerable detail in the articles in this issue. However, some points can stand emphasis at the risk of repetition and a few points have not been touched upon in appropriate framework for the clinician. A clinician would like to ask the pharmacologist whether drugs which paralyze by depolarization, but change the excitability of adjacent muscle to a limited and controllable degree even after prolonged usage could be found. This question arises from the evidence that the persistence of action of depolarizing agents is due to progressive depression of excitability of this area.⁵ If there can be an affirmative answer, we might have safer and more flexible drugs.

A second question a clinician might ask is the possibility of development of specific "pairs" of agonists and antagonists in the relaxant field. An elegant contribution to the clinician would be a desirable relaxant with a totally inactive antagonist so close in molecular configuration that a "receptor" would be occupied with greater ease by the inactive member of the pair. Should the chemist accomplish this task with relaxants of different properties, a group of specialist-pairs for different clinical purposes could be made available.

Another problem of interest relates to the

fact that all relaxants in current use do not affect the normal release of acetylcholine. With competitive relaxants, nervous transmission is normal, muscular excitability is normal, and there is a normal release of acetylcholine. Curare and similar drugs act by the prevention of muscle response to normal stimulation presumably because of the occupation of receptors on the external aspects of the muscle. The depolarizing agents also act in the presence of normal elaboration of acetylcholine, but differ from the curare type of block in that electrical inexcitability at the end-plate region and its immediate surroundings develops. This latter property, according to Paton, is a most important characteristic of the action of depolarizing drugs.⁶

It is possible, in view of these facts, to consider the development of a drug which interferes in a predictable, controllable way with the liberation of acetylcholine or perhaps a drug which hastens its destruction in an equally controllable fashion. However, this type of drug may also have undesirable actions on the central nervous system and perhaps other systems as well. A clinician would like to see interested pharmacologists explore the possibility of finding drugs or methods which may impair the synthesis or hasten the hydrolysis of acetylcholine specifically at the neuromuscular junction of skeletal muscle.

Any consideration of future events in the field of muscle relaxants must come to terms with the problem of interference with respiration. In the first place, one must restate the proven fact that apnea is not necessarily relaxant-inspired. In a given patient, there are aids to establishing the relationship of relaxant action to apnea.⁷ It has become plain that further studies of the action of relaxants on the central driving force of respiration are needed. More information on the action of carbon dioxide on the center during the action of relaxants is required. Since positive pressure respiration in one form or another is used when muscle relaxants are employed, one must understand more about neural reflexes under these conditions and their possible role in the change of the driving force of respiration. It may be that one could block the neural effects generated by positive pressure respiration and its effects on

pulmonary receptors, or that one might discover a drug or drugs that would be useful in keeping the driving force to breathing in the central nervous system normal and intact.

Extensive physiological and pharmacological study is required to develop knowledge beyond the relatively primitive stages of current uses of "antagonists" to the respiratory effects of muscle relaxants. More must be known about the importance of the ionic environment of the nerve and muscle cell on the action of anticholinesterases on a curare type block; the influence of the circulation on all types of block by muscle relaxants requires elucidation; and the effect of local or generalized tissue changes on these phenomena must be studied further.

It is now clear that the actions of some "antagonists" on both neuromuscular blockade and respiration may be quite complex. For example, pyridine-2-aldoxime methiodide (2-PAM), an "antagonist" under special conditions, has been shown to stimulate breathing and yet at the same time potentiate the action of depolarizing relaxants in a peripheral skeletal muscle in both the cat and man.⁸ This apparent conflict in action is not as yet understood. The specific antagonist to decamethonium (BW 49-204) may, and does frequently, depress respiration at the same time that it relieves a depolarizing type of block in a peripheral muscle.⁹ Are these unexpected respiratory responses central in origin? Why may respiration be increased in amplitude in the face of a clearly potentiated peripheral muscle paralysis? Does this mean that the muscles of respiration are, in some as yet poorly understood way, different from other types of skeletal muscle?

In any event, these data show that the measurement of any one function as an index of neuromuscular blockade, even if it be respiration, may be misleading. It cannot be assumed that respiratory activity and peripheral muscle blockade are changed in the same way by depolarizing relaxants in all circumstances or that respiratory depression and neuromuscular blockade can be "antagonized" by the same "antagonist." More knowledge of the central drive to breathing during the action of muscle relaxants must be obtained before one can expect to develop a relaxant which is relatively

or entirely free of this most important undesirable side effect of relaxants.

Recent work suggests that thiamine, which has curare-like action in large doses, may also have the ability to antagonize muscle relaxants.¹⁰ In small doses thiamine and thiamine fragments appear to antagonize relaxants of both the competitive and depolarizing types. It is difficult to explain the antagonism between thiamine and thiamine derivatives against curare on the basis of classical theory. It is easier to understand the antagonism against the depolarizing agents. It could be that thiamine and thiamine derivatives act in some unexplained way, depending on dosage, to displace all muscle relaxants regardless of type from the end-plate area. This may be due to a specific effect on blood flow, on electrolyte concentration, or on the binding properties which thiamine may have to a greater degree than the muscle relaxants. The picture is further confused by the fact that thiamine apparently does not interfere with acetylcholine action under these circumstances.

The future is therefore not so simple a situation as finding a drug which hits, runs, and leaves no memory. More needs to be known about the basic function of the neuromuscular junction before one can build the right sort of drugs. The continued work of the pharmacologist in studying the subtle, important details of physiology at the neuromuscular junction and his assistance to his clinical confrere in the grosser studies of neuromuscular physiology and pharmacology in man under complex clinical conditions should help point the way to better understanding and a more rational use of relaxants, and to the development of better drugs.

REFERENCES

1. Foldes, F. F.: *Muscle Relaxants in Anesthesiology*, Springfield, Illinois, Charles C Thomas, Publisher, 1957, p. 159.
2. Gray, T. C., and Rees, G. J.: Role of apnoea in anesthesia for major surgery, *Brit. M. J.* 2: 891, 1952.
3. Beecher, H. K., and Todd, D. P.: Study of deaths associated with anesthesia and surgery, *Ann. Surg.* 140: 2, 1954.
4. Dripps, R. D.: Role of muscle relaxants in anesthesia deaths, *ANESTHESIOLOGY* 20: 542, 1959.

5. Burns, B. D., and Paton, W. D. M.: Depolarization of motor endplate by decamethonium and acetylcholine, *J. Physiol.* **115**: 41, 1951.
6. Paton, W. D. M.: The Relaxant Drugs. In *Modern Trends in Anesthesia*. Edited by F. T. Evans, & Gray, T. C., New York, Paul B. Hoeber, Inc., 1958, p. 6.
7. Churchill-Davidson, H. C.: Causes and treatment of prolonged apnoea, *ANESTHESIOLOGY* **20**: 535, 1959.
8. Ngai, S. H., Fink, B. R., Hanks, E. C.: Holiday, D. A., and Papper, E. M.: Unpublished data.
9. Vandam, L. D., Safar, P., and Dumke, P. R.: New antagonist to syncurine, *Anesth. & Analg.* **32**: 113, 1953.
10. Di Palma, J. R., and Hitchcock, P.: Neuromuscular and ganglionic blocking action of thiamine and its derivatives, *ANESTHESIOLOGY* **19**: 762, 1958.

ANNUAL MEETING

THE AMERICAN SOCIETY OF ANESTHESIOLOGISTS, INC.

October 5-9, 1959

Bal Harbour (Miami Area), Florida