The introduction of succinylcholine into clinical anesthesia some fourteen years ago was hailed as a major advance. Here, at last, was a muscle relaxant capable of producing total paralysis yet lasting in effect only a few minutes. Another remarkable feature of this drug was the relative absence of side effects, so that large doses could be administered without any apparent harm. So great became the enthusiasm for this new drug that many anesthesiologists adopted a technique whereby the relaxant was infused intravenously to produce the requisite length of paralysis.

Normally, recovery of respiration from a succinylcholine paralysis is rapid. Once movements are observed it is seldom more than two minutes before full ventilation has returned. Occasionally, however, a different clinical picture is observed after a prolonged infusion of succinylcholine: the patient only slowly recovers respiratory activity and the movements are similar to those seen in a patient recovering from paralysis due to d-tubocurarine. Typically, the patient makes jerky or gasping attempts at respiration and a "tracheal tug" is an obvious feature as the accessory muscles of respiration are mobilized. Gradually, over the next half-hour or so, the ventilation improves, but in the meantime it is grossly inadequate. In some cases this state of affairs persisted for an hour or more, and it was not long before impatience or curiosity tempted someone to try the effects of an anti-cholinesterase drug. The result was a dramatic improvement in ventilation. This observation introduced considerable confusion of thought into our understanding of the mode of action of depolarizing drugs, because there was ample pharmacological evidence (based, it is true, mainly on work done on the cat) that persistent doses of a depolarizing drug produced only a depolarizing type of block, and in these circumstances the administration of an anti-cholinesterase drug only increases the degree of paralysis.

In course of time, however, the concept has grown that in man these depolarizing drugs do not behave in such a straightforward manner. It is mainly to electromyographic studies that anesthesiologists owe their present knowledge of muscle relaxant drugs, and on them that they must rely when assessing new agents which come up for trial. With depolarizing drugs, the block at first shows all the signs of depolarization, but gradually these give way to the signs of non-depolarization. When this happens the block has been termed "dual" or "biphasic." Electromyography has revealed a constant pattern of events which can be traced from beginning to end.1

Unfortunately this concept did not at first receive widespread recognition, and a period of confusion developed in clinical practice. A new drug—hexamethylene bischrominoylcholine (Imbrel)—was introduced as a relaxant that could be reversed by an anti-cholinesterase drug. Electromyographic studies proved that Imbrel was a long-acting depolarizing drug, and as with all other drugs
in this group the block gradually underwent a change so that ultimately it could be reversed by neostigmine or edrophonium (Tensilon).

Now it is widely recognized that all depolarizing drugs are capable of producing a dual block. The non-depolarizing aspect of this block is interesting in that it is often referred to as being similar to d-tubocurarine. In fact they do have many features in common, but only in very rare instances does the block appear to be so readily reversible with anti-cholinesterase drugs. The findings of Taylor and Waser suggest that depolarizing drugs may well diffuse into the interior of the muscle cell, and even though muscle activity is resumed it seems unlikely that the train of events is exactly the same as that found after paralysis with d-tubocurarine.

In this issue of the Journal, Drs. Katz, Wolf and Papper have meticulously studied the depolarization block of succinylcholine in man and have clearly shown that a dual or biphasic block occurs every time a depolarizing drug is administered. One of the most surprising findings is that some change in the block occurred after only very small doses had been administered. From a purely clinical view, however, it would be completely wrong to assume that the administration of an anti-cholinesterase to a patient recovering from a small dose of succinylcholine will automatically speed up the onset of full muscular activity. Such a policy is fraught with danger, because in most instances it will merely prolong the period of paralysis.

What is the present position? The knowledge that the type of neuromuscular block after succinylcholine gradually changes is disturbing, and, although difficulty is only rarely encountered, many anesthesiologists have preferred to restrict the use of this drug to short procedures. In a recent survey in Great Britain it was estimated that 96 per cent of anesthesiologists preferred a non-depolarizing relaxant for prolonged paralysis and the occurrence of dual block with succinylcholine is the most likely explanation for this preference. Succinylcholine is still the agent of choice for intubation, bronchoscopy, electro-convulsive therapy, reduction of fractures, etc., whereas d-tubocurarine and gallamine have become firmly established for long procedures—after full recovery from the pre-intubation dose of succinylcholine—because their effects can be reversed at any time provided a gross overdosage has not been administered.

There is one final question to be answered. In clinical practice, can anyone detect the precise stage of development of a dual block without complex apparatus? Fortunately there are fundamental differences between a depolarizing and a non-depolarizing type of block. These can be demonstrated by stimulating any motor nerve with the appropriate electric current. Such an apparatus is simple and is present in most physiotherapy departments.

In anesthesia the hand muscles have been found the most convenient for study. In the unconscious patient the stimulus is best administered by needle electrodes placed under the skin in the region of the ulnar nerve at the elbow. Surface electrodes can be used, but a far greater current is required to overcome the resistance of the skin. The principal advantage of the hand muscles for study is that not only are they usually readily accessible, but also they are among the last muscles to recover activity. Thus, if the hand muscles contract vigorously upon stimulation one can confidently deduce that the respiratory muscles are not under the influence of the muscle relaxant, and in the case of an apneic patient a search for the cause of apnea must be made elsewhere. Furthermore, the pattern of movement of the fingers upon stimulation of the ulnar nerve reveals the exact type of block that is present. After a little practice with the nerve-stimulator it is possible to recognize the sustained contractions and absence of post-tetanic facilitation so characteristic of a depolarization block. Alternatively, a "fade" of successive stimuli and post-tetanic facilitation denotes a non-depolarizing type of block.

In conclusion, it is necessary to repeat that the use of neostigmine to reverse the paralysis produced by succinylcholine is fraught with danger. If the dual block is not completely established, then this drug will merely prolong the paralysis. But in experienced hands the nerve stimulator will reveal the point at which a reversal of the paralysis can confi-
dently be predicted. Nevertheless, although recovery from a dual block is slow it is always steady, and in the vast majority of patients it is far better to go on ventilating the patient adequately and to rely on patience!

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References

Connecting Links to Solve Discrepancies of Actions of Pressor Drugs

About five years ago, the cardiovascular effects of some commonly used pressor amines were reviewed in the Journal.¹ The review article ended as follows: “It is important to emphasize the fact that the available information on the mechanism of cardiovascular effects of pressor agents has been derived from two types of preparations: anesthetized animals and unanesthetized human subjects. The connecting link of studies on anesthetized subjects would be a welcome addition that might help resolve some of the existing discrepancies.”

It is pleasant to note that elsewhere in this issue, one “connecting link” is offered to resolve the discrepancies regarding the cardiovascular effects of one pressor drug, mephenetermine. Li, Shimosato and Etsten² report the hemodynamic effects of mephenetermine in human subjects under spinal anesthesia. The three conclusions and the significance of each are as follows:

(1) The hemodynamic responses following the administration of mephenetermine to hypertensive subjects under spinal anesthesia consist largely of a combined increase in cardiac output and total peripheral vascular resistance. The increase in cardiac output is to be expected because of the known positive chronotropic and inotropic actions of mephenetermine. The simultaneous increase in total peripheral vascular resistance is surprising because, heretofore, mephenetermine has been shown to be free of any local vasoconstrictor action when tested in various preparations, with the exception of two abstracts describing a local vasoconstrictor action.³⁻⁴ Two possibilities remain to explain the increase in peripheral vascular resistance, other than a local vasoconstrictor action. First, is the release of circulating catecholamines when mephenetermine is administered intravenously, a possibility demonstrated in the isolated heart perhaps readily tested in the patient by measurements of blood levels. Secondly, is a stimulation of the medullary vasoconstrictor centers by mephenetermine, a likely explanation requiring direct proof.

(2) The simultaneous occurrence of increase in blood pressure, cardiac output and peripheral resistance reported to occur following the administration of mephenetermine in subjects under spinal anesthesia³ has been previously described for norepinephrine in human subjects with either atropine or ganglionic blocking drugs.⁵ A hemodynamic change in which all three measurements simultaneously increase cannot be elicited by any pressor drug if the autonomic nervous system is not blocked. For example, mephenetermine in normotensive individuals, initially increases output and later increases peripheral vascular