FACTORS WHICH ALTER THE EFFECTS OF MUSCLE RELAXANTS

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Muscle relaxants are employed in anesthesiology in combination with a variety of drugs. In recent years, considerable information has become available to indicate that many of these drugs, and others used in the treatment of various pathological conditions encountered in surgical patients, may affect the pharmacological actions of muscle relaxants. Other variables, such as age, sex, body build, pathological changes, alteration of physiological mechanisms by disease or by anesthetic techniques, and physical changes, for example, decrease of body temperature, may significantly alter the effects of muscle relaxants.

Alteration of the pharmacological actions of muscle relaxants by other drugs can be purposely utilized either to potentiate and prolong, or to terminate their neuromuscular effect. From the point of view of the patient's safety, however, the accidental changes produced in the effects of muscle relaxants by drugs and other variables deserve attention. Consequently, it is important that anesthesiologists be aware of changes in intensity and duration of effects of muscle relaxants caused by commonly encountered factors. Not infrequently the lack of such information has led to improper selection, or mode of administration of muscle relaxants and contributed to operative and postoperative complications.1

This review will present the important factors capable of altering the pharmacological actions of muscle relaxants, and will describe the mechanisms responsible for the change. Attention will be focused on: the recognition of circumstances which may lead to alterations in the action of muscle relaxants; the selection of the relaxant of choice; the recognition of the development of unfavorable reactions caused by these agents, and therapeutic measures for the treatment of these complications.

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Factors that may alter the activity of muscle relaxants will be discussed under five headings: I. The Influence of Species and Type of Muscle; II. Physical and Physico-chemical Factors; III. Physiological States; IV. Pathological Changes; and V. Chemical Compounds. For an understanding of the influence of these factors on the effects of muscle relaxants, it will be necessary to review the action of muscle relaxants, and the differences observed in their neuromuscular effects in various species and different muscles of the same species. Without this, it would be difficult to understand how it is possible for the same factor, (e.g., neostigmine) to affect the neuromuscular action of the same agent, (e.g., succinyliholine) differently, not only in various species, but also in different muscles of the same species, and under different circumstances.

I. The Influence of Species and Type of Muscle

As pointed out by Taylor earlier in this symposium it seems reasonable to assume that there is no basic difference in the mode of action of quaternary-ammonium type neuromuscular blocking agents. Under suitable circumstances, both depolarizing and nondepolarizing (also called antidepolarizing or competitive) relaxants can produce either a depolarization or a nondepolarization block. In discussing the effects of variables on the action of muscle relaxants, it will be pointed out whether the block influenced by a particular factor is a typical nondepolarization, a typical depolarization or a biphasic,9 also called “dual”14 block.

The mode of action of nondepolarizing relaxants, e.g., d-tubocurarine, is qualitatively and quantitatively more uniform. There is comparatively little species variation in the mg./kg. dose required to produce a 90 to 100 per cent neuromuscular block. In contrast there is a marked species variation in the mg./kg. potency of depolarizing relaxants, e.g.,
studied most extensively in cats. Paton and Zaimis\textsuperscript{15} reported that in this animal the tibialis, a "white" muscle, is more sensitive to C-10 than the soleus, diaphragm or intercostal muscles, all "red" muscles. Subsequently, Jewel and Zaimis\textsuperscript{16} observed that while C-10 and succinylcholine cause a typical depolarization block in the tibialis of the cat, they produce a biphasic (dual) block in the soleus. Recently Zaimis\textsuperscript{2} demonstrated that after prolonged administration of succinylcholine to the cat, \textit{d}-tubocurarine intensifies the neuromuscular effects of the former on the soleus and the respiration muscles and antagonizes it on the tibialis. Increased sensitivity to the respiratory effects of \textit{d}-tubocurarine and other nondepolarizing relaxants after the prolonged administration of depolarizing agents, \textit{e.g.}, C-10 or succinylcholine, has also been observed in man.\textsuperscript{8} In line with this, chlorpromazine apparently potentiates the effects of succinylcholine on the respiratory muscles, but antagonizes it on the gastrocnemius muscle of cat.\textsuperscript{17}

II. Physical and Physico-Chemical Factors

1. Mode of Administration

Although the mode of administration has no qualitative influence on the mechanism of action of muscle relaxants, it may influence the intensity and duration of their effect.

The intensity of action of muscle relaxants depends on their concentration at the neuromuscular junction. This, in turn, depends on the plasma level of the agent. Following the intravenous administration of moderate doses, the concentration of relaxants falls rapidly, to about 60 per cent of the maximum obtained, in 10 minutes, and then more slowly, to about 25 per cent by the end of an hour.\textsuperscript{18} As mentioned by Taylor in this symposium there is a rapid preferential uptake of quaternary-ammonium type relaxants by the end-plate region. Muscle relaxants also penetrate more slowly into other parts of the extracellular compartment, and after 2 to 3 hours are distributed evenly in it.\textsuperscript{19, 22} The more rapid the intravenous administration of a given dose of relaxant, the higher the plasma level reached, the greater the concentration attained at the end-plate, and the greater the intensity of its neuromuscular effect.\textsuperscript{23} Slow injection will result in lower
Fig. 2. Sensitization to the respiratory effects of d-tubocurarine produced by 830 mg. succinylcholine chloride administered in continuous drip in 126 minutes. Note: The moderate and transient effect of the first dose of d-tubocurarine on tidal volume; the protective effect of d-tubocurarine against the respiratory effects of succinylcholine; apnea for 21 minutes and 30 seconds following a second identical dose of d-tubocurarine; and the antagonistic effect of neostigmine. [Foldes et al.23]

initial plasma level, lower concentration at the end-plate and decreased neuromuscular activity.

When muscle relaxants are administered subcutaneously or intramuscularly, maximal plasma levels will be reached relatively rapidly,22 but these will be lower than those obtained by the rapid intravenous administration of identical doses. Consequently, the intensity of effect at the neuromuscular junction will also be lower. Provided that the subcutaneous or intramuscular dose of a relaxant is large enough to produce discernable neuromuscular effects, the duration of action will usually be longer than after the intravenous injection of identical doses.

The speed of intravenous injection of depolarizing relaxants will also influence the intensity of muscular fasciculation and the twitching seen after these agents. In general, the slower the injection the less marked the intensity of the twitch and presumably also the incidence and severity of postoperative muscle pain encountered.24

2. Duration of Administration

Thesleff has shown that prolonged exposure of the end-plates to acetylcholine25 and other depolarizing substances like C-10, succinylcholine or nicotine26,27 decreases their sensitivity to the effects of acetylcholine. It was also demonstrated in the rabbit,6 guinea pig,28 dog29 and man8,30 that on prolonged exposure to C-10 or succinylcholine the characteristics of the initial depolarization block undergo changes and in time the block assumes many or all of the properties of a nondepolarization block. These changes include an increasing sensitivity to nondepolarizing relaxants,8,30 e.g., d-tubocurarine or gallamine (fig. 2), a decreasing sensitivity to depolarizing agents21,32 (fig. 3), and in most species, but not always in man, reversibility by anticholinesterases3,5,6,8 potassium (K+) or cold (fig. 4).

The changes that occur in the characteristics of the block caused by the prolonged administration of succinylcholine and C-10 in
Fig. 3. Decrease in sensitivity of the sciatic-gastrocnemius preparation of a dog to the neuromuscular effects of succinylcholine, after its prolonged administration. Note the absence of neuromuscular effect following a second identical dose.

Fig. 4. Reversibility of succinylcholine induced neuromuscular block by edrophonium on sciatic-gastrocnemius preparation of a dog.
man may have clinical significance. Decreasing sensitivity to its effects in the course of anesthesia frequently necessitates the administration of large doses of succinylcholine. This may lead to the accumulation of its primary breakdown product, succinylmonocholine, and prolonged postoperative respiratory depression. When faced with a decreasing sensitivity to succinylcholine, it is advisable to discontinue its administration and to maintain muscular relaxation during the remainder of anesthesia by the administration of small doses of d-tubocurarine (6 to 12 mg.) or gallamine (20 to 40 mg.).

Occasionally prolonged respiratory depression or apnea encountered after succinylcholine or C-10 is caused by a nondepolarization block produced by these agents. If this is confirmed by the trial administration of 10 to 20 mg. of edrophonium, recovery of adequate spontaneous respiration may be facilitated by the intravenous injection of neostigmine in small increments.

3. Rate of Stimulation, Tetanus

A. Rate of Stimulation. The frequency of stimulation increases the intensity of both the depolarization and the nondepolarization block. Preston and Van Maanen found that increasing the frequency from 0.05 to 5.0 per second caused a 3 to 5 fold decrease in the effective dose of d-tubocurarine, gallamine and C-10, and also shortened the interval between the time of intravenous injection and the time of the peak neuromuscular effect of these agents.

B. Tetanus. The intensity of the depolarization and nondepolarization block is influenced differently by tetanic stimulation of the nerve. During incomplete, nondepolarization block produced by d-tubocurarine, tetanic stimulation causes a transient increase in the height of the muscle twitch, followed almost immediately by complete neuromuscular block maintained throughout the duration of the tetanus. On returning to slower rates of stimulation, the twitch height will be restored, for a considerable period, above the level maintained before tetanization (fig. 5). This phenomenon is called posttetanic facilitation of neuromuscular transmission or posttetanic decurarization. In contrast to this, the increase of the twitch height produced by tetanic stimulation during incomplete depolarization block, produced by C-10 in cats, is well-maintained for the duration of the tetanus, but on returning to slower rates of stimulation, no posttetanic increase of twitch height occurs.

When C-10 or succinylcholine produces a biphasic block in the dog this is influenced by tetanus, in the second, or nondepolarization phase, similarly to the block produced by d-tubocurarine. According to Hutter the increase in the intensity of the nondepolarization block during tetanic stimulation is caused by progressive decrease in the amount of acetylcholine released at the neuromuscular junction during tetanus. In contrast, the posttetanic improvement of neuromuscular transmission in the partially curarized muscle can be explained by an increased amount of acetylcholine released with each stimulus.

![Fig. 5](image-url)
4. Electric Currents

Anodal and cathodal currents have diametrically opposed effects on depolarization and nondepolarization block.\(^1\) The application of anodal current which hyperpolarizes membranes will increase the intensity of the nondepolarization block produced by d-tubocurarine and will antagonize the depolarization block produced by C-10 in the cat. Cathodal current, which has a depolarizing effect on membranes, will antagonize nondepolarization block and potentiate depolarization block.

5. Temperature

The effect of temperature on the nondepolarization block produced by d-tubocurarine was first studied\(^{42,43}\) on the isolated rat diaphragm preparation of Bülbring.\(^{48a}\) The speed of onset and the intensity of d-tubocurarine block decreased when the temperature of the bath was reduced from 38 to 26°C. Further reduction of the temperature to 15°C increased both the speed of onset and the intensity of the neuromuscular block. Rewarming reversed these changes. Recent investigation of the effect of lowered muscle temperature in vivo in cats and dogs,\(^{44}\) confirmed the finding\(^{43}\) that reduction of the temperature of the whole animal or of a limb alone reduces the intensity of the nondepolarization block produced by d-tubocurarine (fig. 6). These effects were reversed by rewarming. They also found that, in contrast to the effects of cold on the nondepolarization block produced by d-tubocurarine, the depolarization block caused by succinylcholine or C-10 was prolonged and intensified by cooling (fig. 7). These effects were reversed by rewarming. Similar observa-
tions have been made in man.\textsuperscript{44a} When C-10 produced a biphasic block in the isolated rabbit lumbrical muscle\textsuperscript{6} or in the isolated guinea pig diaphragm preparation,\textsuperscript{28} cooling antagonized the second phase, nondepolarization block, the same way it affected the nondepolarization block produced by \textit{d}-tubocurarine.

Stovner has shown that cooling also antagonizes the neuromuscular block produced by lack of calcium\textsuperscript{45} or excess of magnesium\textsuperscript{46} at the end-plate. Since both Ca\textsuperscript{2+} lack and excess of Mg\textsuperscript{2+} inhibit the release of acetylcholine at the presynaptic nerve endings and thereby diminish the acetylcholine concentration at the neuromuscular junction, it is reasonable to assume that cooling influences the intensity of both the depolarization and nondepolarization block by affecting the acetylcholinesterase equilibrium at the neuromuscular junction.

According to Arrhenius,\textsuperscript{47} the rate of chemical reactions slows with decreasing temperatures. This also applies to enzymatic reactions.\textsuperscript{48} In fact, the hydrolysis rate of acetylcholine by red cell cholinesterase\textsuperscript{49} and that of benzoylcholine by plasma cholinesterase\textsuperscript{50} decreases by 16 and 58 per cent, respectively, when the temperature is reduced by 10 C. Consequently, it is probable that lowering muscle temperature will lead to an increased acetylcholine concentration at the neuromuscular junction. Since acetylcholine antagonizes nondepolarization block\textsuperscript{41} and potentiates depolarization block,\textsuperscript{51} it is understandable that cooling will antagonize nondepolarization block. Similarly it is logical to assume that the antagonistic effect of cooling on the neuromuscular block produced by the interference of acetylcholine release by Ca\textsuperscript{2+} lack or excess of Mg\textsuperscript{2+} is also brought about by inhibition of cholinesterase activity at the end-plate. The validity of this hypothesis on the interrelationship between the effects of cold on the action of neuromuscular blocking agents on one hand, and on that of cholinesterase activity on the other, is further substantiated by the finding that botulinus toxin induced paralysis, which is also caused by decreased acetylcholine release at the nerve terminals,\textsuperscript{52, 53} is antagonized by cold.\textsuperscript{53, 54}

6. \textit{pH, Carbon Dioxide Tension, Hypo- and Hyperventilation}

\textbf{A. pH and Carbon Dioxide Tension.} The effects of \textit{pH} on the neuromuscular activity of \textit{d}-tubocurarine and dimethyl-\textit{d}-tubocurarine were investigated on the isolated frog rectus abdominis muscle.\textsuperscript{55} At \textit{pH} 6.7, \textit{d}-tubocurarine was at least as active as dimethyl-\textit{d}-tubocurarine. When the \textit{pH} of the bath was increased to 8.7, the activity of \textit{d}-tubocurarine decreased while that of dimethyl \textit{d}-tubocurarine remained the same. Kalow explained the difference in the neuromuscular activity of \textit{d}-tubocurarine at \textit{pH} 6.7 and 8.7 by differences observed in the degree of ionization of its two OH groups. At \textit{pH} 6.7, neither of these groups is ionized appreciably and the \textit{d}-tubocurarine molecule carries no anionic, but only cationic charges. At \textit{pH} 8.7, one OH group with a pK\textsubscript{a} of 8.1 is ionized more than 50 per cent and there is appreciable dissociation of the second OH group which has a pK\textsubscript{a} of 9.1. It seems that the affinity of the unionized (non-dissociated) \textit{d}-tubocurarine to the end-plate receptors is greater than that of the partially dissociated molecule. This results in a decreased neuromuscular activity of \textit{d}-tubocurarine at higher \textit{pH}. Since dimethyl-\textit{d}-tubocurarine does not contain OH groups, its activity is not influenced by \textit{pH} changes.

Payne\textsuperscript{56} found that 0.1 to 0.2 unit depression of the \textit{pH} produced by the inhalation of 5 to 20 per cent of CO\textsubscript{2} in cats potentiated the neuromuscular effect of \textit{d}-tubocurarine (fig. 8). In contrast to this, the inhalation of CO\textsubscript{2} antagonized the neuromuscular effects of gallopamil (fig. 9), dimethyl-\textit{d}-tubocurarine, C-10, and succinylcholine (fig. 10). None of the relaxants antagonized by CO\textsubscript{2} possesses OH groups.

\textbf{B. Hypo- and Hyperventilation.} Elevation of pCO\textsubscript{2} in the intact animal leads to a depression of the twitch of the indirectly stimulated tibialis anticus muscle in cats.\textsuperscript{56} This effect is probably due to the influence of CO\textsubscript{2} on nerve conduction.\textsuperscript{57} Respiratory depression, simulating persistent neuromuscular block, was also observed after the use of both C-10\textsuperscript{58} and \textit{d}-tubocurarine\textsuperscript{59} accompanied by CO\textsubscript{2} retention. The observations of Kalow\textsuperscript{55} and Payne\textsuperscript{56} might explain the prolonged action of
d-tubocurarine in the presence of CO₂ accumulation but these cannot be reconciled with the increased action of C-10. It is probable that the prolonged respiratory depression observed after C-10 was caused by CO₂ effect on neuronal conduction⁵⁷ and not on neuromuscular transmission.

The effects of hyperventilation on the d-tubocurarine requirements of anesthetized patients were studied by Dundee.⁶⁰ In the first hour of anesthesia more d-tubocurarine was needed in manually-controlled, hyperventilated patients with an elevated blood pH than in those in whom unaided, or inadequately assisted respiration resulted in a decreased pH.

![Graph](image)

**Fig. 8.** The effect of carbon dioxide inhalation on neuromuscular transmission in the tibialis anterior muscle of a cat. At the sign, 0.1 mg. per kg. d-tubocurarine was injected intravenously. Note the potentiation of the d-tubocurarine effect during carbon dioxide inhalation. [Payne ⁵⁶]

**Fig. 9.** The influence of carbon dioxide inhalation on the effect of gallamine in the tibialis anterior muscle of a cat. At the sign, 0.5 mg./kg. gallamine was injected intravenously. Note the antagonistic effect of carbon dioxide inhalations on gallamine. [Payne ⁵⁶]

The fact that after 2 hours of anesthesia, less d-tubocurarine was needed in the hyperventilated than in the hypoventilated group may be due to factors such as decreased urinary excretion, the discussion of which is beyond the scope of this review.

III. Physiological States

1. Age, Sex and Body Build

Little information is available on the influence of age on sensitivity to neuromuscular blocking agents. Stead reported that newborn infants have a decreased sensitivity toward succinylcholine and an increased sensitivity to d-tubocurarine. Unfortunately his observations were made on newborns with intestinal obstruction. The possibility of fluid and electrolyte disturbances with a resulting alteration in the potency of muscle relaxants...
Fig. 10. The effect of carbon dioxide inhalation on the neuromuscular effects of succinylcholine in the tibialis anterior muscle of a cat. At the signs, 10 μg. of succinylcholine was injected intravenously. Note the antagonistic effect of carbon dioxide inhalation on the succinylcholine induced neuromuscular block. [Payne 56] (see later) makes it difficult to accept his conclusions.

Reports on the influence of old age on the potency of muscle relaxants are also few and inconclusive. Dundee 62 in analyzing the d-tubocurarine requirements of 15 patients over the age of 66 years, found no differences from those of younger age groups. Gray 63 found that aged patients need less, while Durrans 64 reported they require more d-tubocurarine for adequate muscular relaxation.

Until more information becomes available, obtained under controlled circumstances in larger series, it may be assumed, 64 that infants, in whom the ratio of body surface area to body weight is greater than in adults, have mg./kg. relaxant requirements which are about the same or somewhat greater than adults. Clinical experience indicates that in the aged the relaxant requirements are decreased; the increased sensitivity is possibly due to the decreased tone and contractile strength of skeletal muscles. The greater potency of succinylcholine in aged, as compared to younger, males may be caused by their lower plasma cholinesterase activity.

Data on the influence of sex on the activity of muscle relaxants are also scant. Dundee 67 found no difference between the mg./kg. d-tubocurarine or laudexium requirements of the sexes. Since females have a lower plasma cholinesterase activity than males, theoretically they should be more sensitive to succinylcholine than males. Although it is the clinical impression of some that females need less muscle relaxants than males, this problem needs clarification.

No accurate information is available on the relationship of body build and muscle relaxant requirements. Empirically, it is generally accepted that patients in whom the ratio of the muscle bulk to body fat is greater require more relaxants on a mg./kg. basis than those in whom body fat is preponderant. Comparative studies on the relationship of the body surface and body mass, as well as the ratio of body weight and body fat on one hand and mg./kg. relaxant requirements on the other are needed to obtain reliable information.

2. Exercise and Changes in Blood Supply

Schmidt and co-workers, 67, 68, 69 reported that exercise increases the sensitivity of muscles to d-tubocurarine. In rabbits, 5 minutes of slow running, or 2 minutes of violent exercise decreased the head-drop dose of d-tubocurarine by more than 50 per cent. Forty minutes were needed for the restoration of d-tubocurarine sensitivity to control values after 2 minutes of violent exercise. The intensity and duration of the potentiating effect of exercise paralleled the elevation of the plasma lactic acid level. When the plasma lactic acid level was elevated after the subcutaneous injection of epinephrine, the d-tubocurarine sensitivity of rabbits was also increased. 69 From this, Schmidt 69 concluded that increased glycolysis and lactic acid production caused by exercise or epinephrine...
are important in the increase of d-tubocurarine sensitivity.

Torda and Wolff \(^{70}\) suggested that the synergistic effect of exercise and d-tubocurarine are caused by a metabolite produced in active muscle. They reported that serum obtained from the ligated hind limbs of cats after exercise inhibited neuromuscular transmission in the frog nerve-muscle preparation. Similar studies in rabbits were negative.\(^{69}\) It is also possible, that like rapid, indirect stimulation, vigorous exercises will diminish acetylcholine release at nerve terminals.

McNamara and Wills \(^{71}\) observed that exercise increased sensitivity to the neuromuscular blocking action of d-tubocurarine, di-isopropylfluorophosphate and sodium arsenite in cats. Recovery was also slower in the exercised limb. In contrast to d-tubocurarine, exercise decreased sensitivity to C-10. Wislicki,\(^{72}\) however, found in cats that exercise sensitized the effects of d-tubocurarine and succinylcholine.

Churchill-Davidson and Richardson \(^{73}\) found that in man exercise facilitated recovery of neuromuscular transmission after C-10 induced depolarization block. They attributed the more rapid recovery to increased blood flow produced by exercise. They showed that factors such as heat or paralysis of the sympathetic vasoconstrictors which increased blood flow, also antagonized, and factors such as cooling or tourniquet, which decreased blood flow, prolonged C-10 induced block.

IV. Pathological Changes

1. Myasthenia Gravis

It was shown by Bennett and Cash \(^{74}\) for d-tubocurarine, and by Dundee \(^{75}\) for gallamine that, in general, the sensitivity of the myasthenic muscle to nondepolarizing relaxants is increased. In contrast, Sellick \(^{76}\) and Churchill-Davidson and Richardson \(^{77}\) demonstrated that myasthenic muscles \(^{78}\) may exhibit variable resistance to depolarizing relaxants. Pelikan et al.\(^{19}\) confirmed the increased sensitivity of myasthenics to d-tubocurarine. They found that these patients were not more affected by C-10 than normal subjects, and that in 13 of 25 patients C-10 induced paralysis was preceded by a transient improvement of muscular activity. While, in general, myasthenics are not more sensitive, and may even be resistant to C-10, involved muscle groups may show an increased sensitivity to it.\(^{78},\,80\) Neither increased nor decreased sensitivity to small doses of succinylcholine was found by Bergh \(^{80}\) in five myasthenic subjects.

It seems probable that the increased sensitivity of the neuromuscular junction of myasthenic subjects to nondepolarizing agents, and its decreased sensitivity to C-10 is due to an increased resistance of the end-plate towards depolarizing influences. Acheson \(^{81}\) and Buchthal \(^{82},\,83\) have shown by intra-arterial injection of acetylcholine that the myasthenic end-plates are less sensitive to acetylcholine than those of normal subjects. The mechanism of this increased resistance has not been clarified. The suggestion that it might be caused by a curare-like substance present in the blood \(^{84}\) or the thymus \(^{85}\) was not confirmed.\(^{86},\,87,\,88\) The prolonged administration of depolarizing blocking agents is reported to cause changes in the sensitivity of respiratory and abdominal muscles of normal human subjects to depolarizing and nondepolarizing relaxants, similar to those observed in myasthenics.\(^{3}\) Consequently, the possibility cannot be excluded that the decreased sensitivity of the myasthenic end-plate to the physiological transmitter is caused by the presence of a circulating depolarizing, instead of a nondepolarizing, substance.\(^{8,\,89}\) A compound, δ-butyrobetaine, capable of producing neuromuscular block in the cat, was recently extracted from the thymus of a myasthenic subject.\(^{90}\) The possibility that the increased resistance of the myasthenic end-plate to depolarization may be due to structural changes of the receptor, caused perhaps by some defect of protein synthesis,\(^{80}\) should be investigated.

The altered sensitivity of the myasthenic to neuromuscular blocking agents necessitates great care in their administration to such patients.\(^{91}\) Either small doses of nondepolarizing relaxants, such as, 0.5 to 0.75 mg. d-tubocurarine, or 2.5 to 5.0 mg. gallamine \(^{74}\) or normal doses of succinylcholine \(^{80}\) should be employed. Because of the possibility of an increased and prolonged effect of C-10 in the involved muscles,\(^{80}\) its use in myasthenics should be avoided.
2. Carcinomatous Neuropathy

It has been known for more than two decades that carcinomatous lesions may be associated with neurological and neuromuscular disorders without the presence of metastases in the nervous system. Henson et al. reported that several patients with bronchial carcinoma exhibited symptoms similar to those observed in myasthenia gravis. Anderson et al. encountered 60-minute apnea and 90-minute respiratory depression after the intravenous administration of 50 mg. succinylcholine to a patient suffering from bronchogenic carcinoma and complaining of easy fatiguability. The patient had normal plasma and red cell cholinesterase levels. Further investigation revealed that he was unusually sensitive to d-tubocurarine, C-10 and succinylcholine, but that as in myasthenics the C-10 or succinylcholine induced neuromuscular block could be reversed by edrophonium. Neostigmine therapy improved the patient's muscle power.

Recently, 5 patients with carcinoma and abnormal responses to muscle relaxants were reported by Croft. Three of the 5 had bronchogenic, 1 prostatic and 1 sigmoid carcinoma. Of the 5 had signs of carcinomatous neuropathy preoperatively. Two received d-tubocurarine or gallamine and one succinylcholine. Although the evidence of increased sensitivity to muscle relaxants presented by Croft is not convincing in all 5 cases, his report focused attention on the possibility of this complication in patients with bronchogenic and other forms of carcinomatosis.

Lambert et al. and Eaton and Lambert studied electromyographically a group of patients who had evidence of bronchial carcinoma, and who exhibited weakness in the muscles of the extremities, decreased or absent tendon reflexes, and easy fatiguability. All were sensitive to d-tubocurarine, but neostigmine caused little or no improvement in their muscle strength.

Although the mechanism involved is not clarified, an increased sensitivity to both depolarizing and nondepolarizing relaxants may be present in patients with carcinoma. Consequently, a test dose of the relaxant to be employed should be given to these patients at the start of anesthesia to detect undue sensitivity.

3. Chronic Denervation

Chronic denervation, in line with the general behavior of denervated organs, increases the lability of the end-plate and makes it more sensitive to the depolarizers. The increase in the lability is so great that even nondepolarizing relaxants like d-tubocurarine and gallamine can produce depolarization of the end-plate and cause an initial increase of spontaneous fibrillations of denervated muscle fibers. The cholinesterase content of end-plates of chronically denervated muscles diminished. Waser recently demonstrated that parallel with the disappearance of cholinesterase, the cholinergic receptors also disappear or lose their ability to combine with radioactive C-curarin.

Because of the increased lability of the muscle membrane, the spreading depolarization caused in the normal cat muscle by C-10 is intensified to such an extent that it decreases the sensitivity of the muscle not only to indirect but also to direct stimulation. d-Tubocurarine does not affect the sensitivity of the denervated muscle to direct stimulation, but it prevents the inhibitory effects of C-10 on this structure.

In summary, changes in the sensitivity of the end-plate caused by chronic denervation increase its sensitivity to both the stimulating and blocking action of depolarizing agents. Consequently, the spontaneous fibrillation that frequently follows the intravenous injection of succinylcholine in man is increased when the peripheral motor neuron of a muscle is destroyed either in the spinal cord or distal to it.

Lesions of the cortico-spinal motor neuron cause increased muscle tone and spasticity both in laboratory animals and man. Waser has shown that C-toxinferin and other calabash curares effect the tone of the frog gastrocnemius muscle in lower concentration than is necessary to abolish neuromuscular transmission to indirect stimuli. This phenomenon has not been demonstrated in mammals. A neuromuscular blocking agent with a preferential action on muscle tone and spasticity would be of great therapeutic importance for spastic patients.

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4. Liver Disease

The metabolic detoxification of many compounds, among them d-tubocurarine and dimethyl d-tubocurarine, occurs at least in part, in the liver. This organ is the main site of protein synthesis and, therefore, probably also that of true- (red cell, brain, muscle) and pseudo- (plasma) cholinesterase production. In liver disease, the plasma cholinesterase level is decreased early, but the red cell cholinesterase activity was found to be unchanged even in the terminal stages of cirrhosis. For these reasons it is not surprising that the sensitivity to both depolarizing and nondepolarizing relaxants may be influenced by liver disease.

The duration of apnea and respiratory depression following the intravenous administration of 0.6 mg./kg. succinylcholine C1 was found to be prolonged (2 to 3 fold) in liver disease. The increase in the duration of apnea paralleled the severity of the disease and the decrease in the hydrolysis rate of succinylcholine in the patient's plasma (table 1). It is of interest, however, that excessively long apnea was not encountered in these patients. The significance of this will be discussed later.

In contrast to the increased sensitivity to succinylcholine, a decreased sensitivity to d-tubocurarine in liver disease was observed by Dundee and Gray. They entertained the possibility that the decreased sensitivity to d-tubocurarine might be due to the lower plasma cholinesterase level. Despite this convincing report patients with severe liver damage often show an increased, instead of a decreased sensitivity to d-tubocurarine and other nondepolarizing relaxants. The increased sensitivity is probably due to the patient's poor physical condition caused by electrolyte imbalance or hypoproteinemia. Consequently, muscle relaxants should be administered to patients with liver damage with caution.

5. Qualitative and Quantitative Changes in Plasma Cholinesterase

Altered sensitivity to succinylcholine has been encountered in patients with plasma cholinesterase activity in the absence of liver disease and also in individuals in whom the concentration of this enzyme was normal or moderately reduced. Kalow and co-workers found that besides quantitative changes, qualitative differences may exist between the plasma cholinesterases encountered in different individuals. Based on the inhibitory effect of dibucaine (Nuper-caine), three genetically distinct types of plasma cholinesterase were described. In most subjects the plasma cholinesterase activity was normal and was inhibited by 10-5M dibucaine by more than 74 per cent. The duration of apnea after the intravenous administration of 100 mg. succinylcholine in this group ranged from 2 minutes, 54 seconds to 5 minutes, 52 seconds. In a second group comprising about 3 per cent of the population, both the mean plasma cholinesterase activity and the dibucaine number was moderately decreased and the duration of apnea increased. Infrequently, subjects were encountered whose mean plasma cholinesterase activity and dibucaine number was markedly decreased and in whom the succinylcholine induced apnea was excessively prolonged. Plasma obtained from patients with low dibucaine numbers did not hydrolyze succinylcholine in the Warburg apparatus. Kalow and Ganet also found that the dibucaine number was not changed in patients in whom plasma cholinesterase was reduced by liver disease. Patients with atypical plasma cholinesterase, who were hypersensitive to succinylcholine showed normal sensitivity to C-10.

As already mentioned, the duration of succinylcholine induced apnea was not excessively prolonged in patients in whom plasma cholinesterase activity was reduced by severe cirrhosis of the liver to lower levels than those

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<th>Hydrolysis Rate*</th>
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<tr>
<td>Normal</td>
<td>3.0 ± 0.1†</td>
<td>180 ± 9</td>
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<tr>
<td>Moderate liver disease</td>
<td>1.4 ± 0.2</td>
<td>348 ± 34</td>
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<td>Severe liver disease</td>
<td>0.8 ± 0.1</td>
<td>515 ± 40</td>
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* Micromoles/ml. plasma 30 minutes.
† Standard error.
obtained in Kalow's group. Therefore, the prolonged apnea encountered in patients with low plasma cholinesterase levels cannot be explained by quantitative changes of the enzyme content of the plasma alone. It is possible that subjects who exhibit qualitative changes in the properties of this enzyme may have similar changes in the structurally related cholinergic receptors of the end-plate. These changes might result in the abnormal fixation of succinylcholine to these structures and cause excessively prolonged apnea. It is of interest that atypical plasma cholinesterase is an inherited, familial trait.126

The possibility of encountering individuals who, because of their atypical plasma cholinesterase and/or cholinergic receptors, are extremely sensitive to succinylcholine, cannot be excluded. To avoid one possibility of prolonged apnea after a single dose of succinylcholine, its size should be kept at a minimum, or better, its use should be preceded by the administration of a small test dose. For prolonged muscular relaxation, succinylcholine should be used with assisted, instead of controlled, respiration. When controlled respiration is a necessity, the anesthetist should ascertain at frequent intervals that no overdose is being used, and that on discontinuation of the infusion, the patient will resume spontaneous breathing within a reasonably short period. The tidal volume, however, may be inadequate for variable periods, even after assisted respiration, in such patients.

6. DISTURBANCES OF FLUID AND ELECTROLYTE BALANCE

A. Dehydration. Cailar et al. reported 125 that cellular hyperhydration increases and dehydration decreases the excitability of muscles to indirect stimulation. It has already been mentioned and is discussed in detail elsewhere 23 that dehydration may influence the normal disposition of muscle relaxants. In dehydration both the plasma volume and the volume of extracellular compartments are diminished. Because of this, the intravenous administration of a given dose will result in a higher initial plasma concentration and consequently a relatively higher concentration of the relaxant at the end-plate. The decreased volume of the extracellular compartment will also impede diffusion from plasma and redistribution from the end-plate to this compartment. Dehydration will also interfere with the urinary excretion of the muscle relaxants. It is evident that these factors all tend to intensify and prolong the neuromuscular effect of blocking agents.126, 127 Cohen found in healthy, human, unanesthetized subjects 127 that if d-tubocurarine was administered after 24 hours of fasting, its plasma level was higher (fig. 11) and its urinary excretion slower than when the same dose was injected in a normal state of hydration. It is probable that dehydration similarly affects the action of other neuromuscular blocking agents.

In general, disturbance of fluid metabolism is accompanied by electrolyte imbalance which will also have a profound effect on neuromuscular transmission and on the action of muscle relaxants. To understand the influence of electrolyte disturbances on the action of relaxants the effects of the excess or deficit of a few ions at the endplate should be reviewed. (See also Taylor's review in this symposium.)

B. Effects of Various Ions on Neuromuscular Transmission. As pointed out by Hunt and Kuffler,128 inorganic ions may influence neuromuscular transmission by affecting the nerve fiber and/or the nerve terminal, the release of the transmitter (acetylcholine) and by changing the sensitivity of the post-junctional membrane and the muscle fiber to de-
polarization. In the following, the effects of the four most important cations (Na⁺, K⁺, Ca²⁺, and Mg²⁺) on the release of acetylcholine, and the electrical properties of the endplate (resting potential of the endplate and endplate potential) will be considered briefly.

a. Sodium. Reducing the Na⁺ concentration in the bathing fluid surrounding a frog nervemuscular junction will cause a reduction in the size of the endplate potential compared to the size obtained in partially curarized muscle. In contrast to curarized muscle, however, the preparation remains sensitive to externally applied acetylcholine, 126 Nastuk 128 working with nerve-muscle fiber preparations of frogs, found that although the magnitude of the resting potential of the endplate was little affected by the complete removal of Na⁺ from the bathing fluid, the magnitude of the endplate potential produced by direct application of acetylcholine was significantly (by a factor of 14) reduced. The changes in neuromuscular transmission produced by Na⁺ deficit are probably due to a post-synaptic blocking action. 131 Nastuk and Hodges 132 working with isolated frog muscle fibers found that decreasing the external Na⁺ concentration produced a slight increase in the resting membrane potential of the muscle fiber, but markedly decreased its action potential. They concluded that the action potential is caused by a specific increase of Na⁺ permeability.

b. Potassium. An excess of externally applied K⁺ causes liberation of acetylcholine from the nerve endings. 133 The permeability for both K⁺ and Na⁺ increases significantly during the action potential. 134 Permeability for Na⁺ increases first, that for K⁺ later. 128 Increasing the extracellular K⁺ concentration causes depolarization not only of the endplate, but also in other parts of the muscle fiber. 128 However, changing the external K⁺ concentration from 2mM to 4mM caused little change in the size of the endplate potential. 129 Further elevation of the K⁺ level, after a transient increase of the endplate potential 133 reduces both the resting potential of the endplate and the endplate potential and causes neuromuscular block. 129

c. Calcium. Ca²⁺ has a dual action at the neuromuscular junction. It can effect both the release of acetylcholine at the endplate and the sensitivity of the endplate to depolarization. These effects of Ca²⁺ may influence neuromuscular transmission in opposite directions. Thus, for example, lowering of the Ca²⁺ concentration diminishes 134 and elevation increases 136 the quantity of acetylcholine released, and this has a similar effect on the size of the endplate potential. 129 Therefore, elevation of the Ca²⁺ concentration would facilitate, and decrease would inhibit transmission. In contrast to this, elevation of the Ca²⁺ concentration, because of its stabilizing effect on the post-junctional membrane, 137 prevents its depolarization by K⁺. Lowering the Ca²⁺ concentration has a labilizing effect 138 and facilitates the depolarization of membranes. 138 The sensitivity of the endplate to externally applied acetylcholine, however, is not affected by changes in Ca²⁺ concentration. 139 Reduction of the Ca²⁺ concentration below a critical level will cause neuromuscular block probably because of the reduction of the acetylcholine release.

d. Magnesium. The effects of Mg²⁺ and Ca²⁺ at the neuromuscular junction are mutually antagonistic 140, 141. An excess of Mg²⁺ decreases the amount of acetylcholine liberated at the nerve ending, diminishes the sensitivity of the endplate to directly applied acetylcholine and depresses the excitability of the muscle membrane. 142 The most important effect of increased Mg²⁺ concentration is the reduction of the acetylcholine release, which results in the reduction of the endplate potential and causes neuromuscular block. Mg²⁺ does not influence the resting potential of the endplate. 140 The effects of excess Mg²⁺ can be antagonized by Ca²⁺ which increases the amount of acetylcholine released and antagonizes the block. It seems that the amount of acetylcholine liberated at the endplate by stimulation of the motor nerve depends on the relative Mg²⁺ and Ca²⁺ concentrations present. 140 While both Mg²⁺ and d-tubocurarine block the effects of acetylcholine at the neuromuscular junction, Mg²⁺ in contrast to d-tubocurarine also blocks the depolarizing effects of K⁺. 142 This indicates that the site of action of Mg²⁺ and d-tubocurarine are probably different. This assumption is further corroborated by the
finding that while increasing the rate of stimulation intensifies the blocking action of d-tubocurarine, it antagonizes that of Mg++.

At low rates of stimulation, the blocking effect of Mg++ is more pronounced.

e. Phosphate. Similarly to lack of Ca++ or excess of Mg++, an excess of phosphate also interferes with the release of acetylcholine at the end-plate and inhibits neuromuscular transmission.

C. Effect of Ions on Action of Muscle Relaxants. As already mentioned, the deficiency of Na+ or Ca++ retards, the depolarization of the end-plate and thereby inhibits neuromuscular transmission. It is therefore, not surprising that Na+ and probably also K+ and Ca++ deficiency increases the blocking effect of d-tubocurarine and other nondepolarizing relaxants. Conversely, there is ample experimental evidence that Na+ and especially K+ antagonizes the effects of d-tubocurarine and similar compounds. In contrast to this, the neuromuscular effects of Mg++ and d-tubocurarine are additive.

Little information is available on the effects of the deficiency or excess of various cations on true depolarization block. In dogs where depolarizing blocking agents produce a biphasic block, the intravenous administration of Ca++ shortened the succinylcholine-induced apnea and in rats, this was prolonged by lowering the Ca++ concentration by the intravenous infusion of disodium ethylenediamine tetraacetic acid.

D. Clinical Implications of Fluid and Electrolyte Imbalance on the Action of Muscle Relaxants. The possible role of K+ deficiency in the abnormally intensified and prolonged reaction to nondepolarizing muscle relaxants has been pointed out by Foldes et al. and subsequently by others. The intravenous infusion of K+ may counteract the prolonged apnea. Since C-10 and succinylcholine on prolonged administration may also produce nondepolarization block in man, the intravenous infusion of potassium chloride may be attempted when other therapeutic measures fail to terminate succinylcholine-induced apnea.

The importance of Na+ and Ca++ in the pathogenesis and treatment of abnormal responses of human subjects to muscle relaxants has received little attention. In view of the role of these cations in physiological neuromuscular transmission, the possibility cannot be excluded that in patients who have severe electrolyte imbalance, or who have received multiple transfusions of citrated blood, Na+ or Ca++ deficiency may contribute to an abnormal response to relaxants. Based on these considerations, sodium chloride or calcium chloride may be administered in prolonged postoperative apnea if the plasma level of these cations is below normal.

Not infrequently, fluid and electrolyte imbalance and low plasma protein levels are present simultaneously. Under normal circumstances, d-tubocurarine and presumably other relaxants are bound to a variable extent to both serum albumen and Y-globulin. Bound d-tubocurarine is inactive. Consequently, excessive binding of relaxants to plasma proteins will diminish, and reduced binding, as in hypoproteninemia, will increase their effect.

Shift of fluid from the extracellular into the intracellular compartment may occur postoperatively in the dehydrated patient. Such a shift may result in increased concentration of relaxants in the extracellular compartment and at the neuromuscular junction and cause recurarization with resulting respiratory embarrassment. Another mechanism whereby neuromuscular transmission may be depressed in the immediate postoperative period is the rapid fall of serum K+ caused by increased urinary excretion, frequently depressed during anesthesia, in dehydrated patients. The rapid decrease of the serum K+ level will change the balance between K+ and muscle relaxants at the end-plate. Since both the depolarizing and nondepolarizing muscle relaxants may cause a nondepolarization block in man, the rapid, postoperative fall of plasma K+ may cause recurarization following the use of both types of agents.

7. Kidney Disease

Kidney disease accompanied by decreased urinary excretion may influence the action of muscle relaxants by at least two mechanisms. The more important of the two is the accumulation of those muscle relaxants which are excreted primarily, e.g., C-10 or gallamine, or partly, e.g., d-tubocurarine, dimethyl d-tubocurarine or succinylmonocholine, unchanged in
the urine. The neuromuscular effects of these agents are terminated following single moderate doses, by redistribution into inactive tissue depots.\textsuperscript{19, 22, 23} After repeated doses these depots become saturated\textsuperscript{19} and urinary excretion becomes the determining factor in the time course of the neuromuscular block.\textsuperscript{23}

If kidney disease causes elevation of the Na\textsuperscript{+} and K\textsuperscript{+} levels in plasma and the extracellular compartment, the theoretical possibility exists that sensitivity to nondepolarizing relaxants will be decreased and that to depolarizing relaxants will be increased. At present, experimental data which may help to clarify this problem are lacking.

V. Chemical Compounds

Chemical compounds may influence the action of muscle relaxants at the end-plate by various mechanisms.\textsuperscript{12a} They can interfere with the production, storage or release of acetylcholine. They can alter the reactivity of the end-plate to acetylcholine either by preventing its access to receptor sites or by exerting a stabilizing influence on the post-junctional membrane, and thereby prevent formation of the end-plate potential. They may also have a stabilizing effect on the whole muscle membrane and prevent the triggering of the action potential by the end-plate potential. They can interfere with the activity of the enzyme (acetylcholine esterase) responsible for the rapid breakdown of acetylcholine at the end-plate. Drugs, themselves, may have an acetylcholine-like depolarizing action. At sites other than the end-plate, drugs may also affect the neuromuscular action of relaxants by altering their rate of metabolic destruction, urinary excretion or redistribution into inactive tissue depots. Finally, they may form chemical or physico-chemical combinations with relaxants which inactivate the latter.

The effects of drugs on the action of muscle relaxants is further complicated by the fact that one agent may influence more than one of the mechanisms discussed and that, not infrequently, the changes influence neuromuscular transmission in opposite directions. Because of this, it will sometimes be necessary to discuss the same drug under more than one heading.

Finally, the effects of drugs on the action of neuromuscular blocking agents is dependent on the type of block produced by the relaxant. As already discussed this depends on the species of the test animal, the choice of muscle in the same species, and on the duration of action of the relaxant. Because of the interaction of so many variables, the analysis of the influence of drugs on the action of muscle relaxants may present problems which cannot be solved on the basis of available evidence. In view of this, it should not be surprising that results published on the effects of drugs on the action of neuromuscular blocking agents are frequently controversial.

1. Acetylcholine

Until recently it was assumed that acetylcholine antagonized nondepolarizing\textsuperscript{41} and had an additive effect with depolarizing\textsuperscript{51} blocking agents. Recent studies\textsuperscript{3, 25-28, 153, 154} have revealed that the interaction of acetylcholine and neuromuscular blocking agents is complicated and that the effect depends on the state of sensitivity of the end-plate. If the end-plate has been desensitized to the effects of acetylcholine by the prolonged administration of depolarizing substances like C-10, succinylcholine or acetylcholine itself, acetylcholine and d-tubocurarine may have an additive effect\textsuperscript{3, 154} on neuromuscular transmission (fig. 12). It seems that acetylcholine antagonizes the block produced by nondepolarizing relaxants, e.g., d-tubocurarine or gallamine, if the end-plate has not been previously desensitized to its effects by the prolonged administration of a depolarizing agent. The effects of acetylcholine on one hand and those of nondepolarizing relaxants on the other may be additive, however, in the previously desensitized end-plate. The interaction of acetylcholine and depolarizing relaxants is still more complicated. When these agents produce a true depolarization block, i.e., when the end-plate remains depolarized during the block, the effects of acetylcholine and the blocking agents may be additive. As resistance of the end-plate to depolarization increases,\textsuperscript{3} there might be an interval during which the depolarizing relaxants produce a nondepolarization block (the end-plate is repolarized during the block), but acetylcholine, the physiological depolarizer, can still depolarize the end-plate. Under these circumstances, acetylcholine, in-
Fig. 12. Synergism between the neuromuscular blocking effect of acetylcholine (ACH), succinylcholine (SCh), and decamethonium (C-10) on one hand and d-tubocurarine (TC) on the other. The records were obtained by intracellular recording from the myoneural junction of a single muscle fiber in the sartorius of a frog. The muscle was allowed to stay in contact with the various agents for 15 minutes before recording. Between B and C the muscle was washed with fresh Ringer’s fluid for 45 minutes. Drug concentrations are expressed in Mols/liter in the bathing fluid. Time in milliseconds. [Foldes et al.3]

Instead of potentiating, may antagonize the block produced by depolarizing relaxants.

Since acetylcholine is not used in anesthesiology to potentiate or antagonize muscle relaxants, the clinical significance of these observations will be discussed when the effects of anticholinesterases are reviewed.

2. Compounds Affecting Acetylcholine Synthesis or Release

Besides the lack of Ca++ and excess of Mg++ or phosphate, other chemical compounds (drugs, hormones, toxins) are capable of interfering with the synthesis or release of acetylcholine at the end-plate. Such compounds potentiate the effects of relaxants, when they produce a nondepolarization block, and antagonize those which cause a classical depolarization block.

A. Epinephrine. The difficulties encountered in assessing the effects of a chemical compound on the action of neuromuscular blocking agents are exemplified by epinephrine. Much of the apparent contradiction arises from the fact that epinephrine has a dual action at the end-plate: it increases the quantity of acetylcholine released by indirect stimulation,155 and it exerts a stabilizing effect and decreases the electrical excitability of the muscle fiber.155 Depending on the circumstances, one or the other effect of epinephrine may be dominant and consequently, it may either antagonize or potentiate the effects of agents producing neuromuscular block.

So far as the effects of epinephrine on the release of acetylcholine are concerned, it has been claimed that epinephrine increases,155 or decreases156 the quantity of acetylcholine released by indirect stimulation at the end-plate. Knejevic and Miledi155 reported that epinephrine increased the amplitude of the end-plate potential both in in vitro experiments with rat...
phrenic nerve-diaphragm preparations and in vivo in the rat's indirectly stimulated gracilis muscle, partially paralyzed by d-tubocurarine. They attributed this effect to an increase in the the amount of acetylcholine released. They also confirmed\textsuperscript{47a} that epinephrine improved neuromuscular transmission in the fatigued phrenic nerve-diaphragm preparation of the rat. Similar observations were made earlier in intact dogs.\textsuperscript{157} Montagu\textsuperscript{158} found that epinephrine in low concentrations potentiated, and in high ones antagonized d-tubocurarine block in the isolated rat diaphragm. In contrast\textsuperscript{156} the increase of partial d-tubocurarine or gallamine block has been attributed to a decrease in amount of acetylcholine released on indirect stimulation.\textsuperscript{156} It has been suggested that the inhibition of the early depolarizing phase, and potentiation of the late nondepolarizing phase of acetylcholine, succinylcholine and C-10 block by epinephrine was also due to diminished acetylcholine release. It is possible to explain this discrepancy with different experimental conditions. The results of Beckett and Ellis\textsuperscript{156} may be explained rather by the stabilizing effect of low epinephrine concentrations on the end-plate than by a decrease of the acetylcholine output. In general, the simultaneous administration of sympatheticic agents, such as ergotoxine, ergotamine, and dibenamine, do not antagonize the neuromuscular effects of epinephrine.\textsuperscript{156a}

The antagonism of epinephrine to the effects of curare\textsuperscript{156, 160, 161} also supports the probability of increased acetylcholine release at the end-plate. The brief anticholinergic action, followed by a prolonged potentiation of d-tubocurarine-induced neuromuscular block\textsuperscript{162} in the rabbit, might be explained by the fact that first, the effects of epinephrine on acetylcholine release, and later its influence on the sensitivity of the end-plate to depolarization is the dominant factor. The possibility that epinephrine may influence neuromuscular transmission by a third mechanism due to its anticholinesterase activity\textsuperscript{163} should also be considered. In Warburg experiments the I\textsubscript{50} value of epinephrine for purified, concentrated human plasma cholinesterase (Cholase) is of the order of 10\textsuperscript{-5}M, and for human red cell cholinesterase 10\textsuperscript{-2}M.\textsuperscript{164} The seemingly high concentration of epinephrine necessary to inhibit red cell cholinesterase might be due to its rapid degradation in the presence of red cells or other tissues.\textsuperscript{165} Undoubtedly, this problem requires further investigation.

Bulbring and Burn\textsuperscript{166} found that ephedrine potentiated the synergistic effect of epinephrine on the neuromuscular action of neostigmine. On this basis, Burn\textsuperscript{167} recently suggested that if neostigmine fails to counteract prolonged apnea encountered after d-tubocurarine, 30 to 60 mg. of ephedrine should be given intramuscularly. He points out that the injection of ephedrine would raise the blood pressure and may increase the K\textsuperscript+ concentration of the muscle fibers.\textsuperscript{167} It seems that the intravenous injection of 20 to 30 mg. as suggested by Zuck\textsuperscript{168} might bring quicker results. A therapeutic trial with ephedrine might be attempted in cases of prolonged apnea after the use of depolarizing relaxants if there is reason to believe that the block has changed to a nondepolarization block.\textsuperscript{3, 9}

B. Procaine. The observations made on the effects of procaine in combination with relaxants on neuromuscular transmission are just as controversial as with epinephrine. This controversy is caused primarily by the multiple effects of procaine at the end-plate. It has been suggested that procaine, besides inhibiting the release of acetylcholine at the end-plate,\textsuperscript{169} may also compete for the cholinergic receptors with acetylcholine,\textsuperscript{170} exert a non-specific stabilizing action on the postjunctional membrane,\textsuperscript{163} and also inhibit the hydrolysis of acetylcholine by both true- and pseudo-cholinesterase.\textsuperscript{171, 172} Besides these effects, procaine inhibits the enzymatic breakdown of succinylcholine by plasma cholinesterase.\textsuperscript{173} Recent work\textsuperscript{174} indicates that of the various actions of procaine competition with acetylcholine is the most important. Therefore, the interaction of procaine and neuromuscular blocking agents will be discussed in the section dealing with agents which exert their effect primarily by this mechanism.

C. Hemicholinium. Macintosh et al.\textsuperscript{175} reported that hemicholinium decreased the amount of acetylcholine released on prolonged preganglionic stimulation of the cat's cervical sympathetic ganglion. Subsequently, it was shown\textsuperscript{176, 177} that hemicholinium inhibits neuromuscular transmission in various laboratory
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Fig. 13. The neuromuscular blocking effect of 0.16 mg./kg. hemicolinium on the sciatic-gastrocnemius preparation of anesthetized rabbits. Upper tracing, tetanic stimulation for 0.2 second every 20 seconds. Bottom tracing, interrupted stimulation once every 10 seconds. Time marking in minutes. Panel A. Intravenous injection of hemicolinium; B. 90 minutes; C. 240 minutes; D. 420 minutes after injection. Note absence of neuromuscular block at low rates of stimulation; the slow onset and prolonged duration of the block after tetanic stimulation. [Reitzel and Long 177]

animals. The properties of the hemicolinium induced block have been suggested to be due to a decreased acetylcholine release at the end-plate. 177 Although it is unlikely that under clinical circumstances an interaction will be encountered between hemicolinium and other neuromuscular blocking agents, the myoneural effects of hemicolinium will be discussed briefly, because of its unique features.

After the intravenous injection of 20 to 160 µg./kg. of hemicolinium in rabbits, maximum effect develops after a latent period of about 60 minutes. With 4.8 mg./kg. the onset of block is instantaneous. After 40 µg./kg. block only develops at high rates of stimulation and there is no effect if the rate of stimulation is 1 per 10 seconds or less (fig. 13). The block is antagonized by removal of the stimulus, the intravenous injection of 10 to 20 mg./kg. of choline chloride, or 50 µg./kg. of neostigmine. The sensitivity of the end-plate to large doses of acetylcholine does not change during hemicolinium block. These findings suggest that hemicolinium exerts its effects by reducing the amount of acetylcholine released on indirect stimulation. It is not clear whether hemicolinium exerts a direct inhibitory action on choline acetylase 177 or if it acts by decreasing the amount of choline available for the synthesis of acetylcholine.

No data are available on the interaction of hemicolinium with other neuromuscular blocking agents. Because of its pharmacological properties, it should intensify nondepolarization block and antagonize a classical depolarization block.

D. Tetraethylammonium. Stovner has suggested 45 that the effects of tetraethylammonium on neuromuscular transmission in the rat diaphragm depressed by Ca++ lack and excess Mg++ are due to an increase in the amount of acetylcholine released by indirect stimulation. He subsequently investigated the antagonistic action of tetraethylammonium on the block induced by relaxants in animals and man 178, 179 and found that it antagonized nondepolarization block more readily than depolarization block. 178 He concluded that tetraethylammonium exerts its effect by increasing the release of acetylcholine at the end-plate. He suggested the therapeutic use of 1.5 to 2.0 mg./kg. tetraethylammonium in conjunction with neostigmine or edrophonium, in the treatment of prolonged apnea encountered after d-tubocurarine. 179 It is possible that tetraethylammonium might also reverse the prolonged apnea encountered after succinylcholine in man. 178

Others have suggested that tetraethylammonium might combine with the receptors at
the neuromuscular junction and might lead to, or support depolarization.180

E. Botulinus Toxin. Botulinus toxin also exerts its neuromuscular action by inhibiting the release of acetylcholine at the end-plate.52, 53 The blocking effect develops slowly, and in vitro preparations can be prevented by immune serum 53 and does not develop in passively immunized animals. Botulinus toxin has no effect either on cholinesterase or on choline acetylase.128 Intra-arterial acetylcholine and nicotine still cause contraction in the presence of a botulinus block.52 Patients with botulinus intoxication would be extremely sensitive to d-tubocurarine and similar relaxants.

F. Streptomycin. Streptomycin has a dual action at the neuromuscular junction.180a These will be discussed in the section on antibiotics.

3. COMPOUNDS AFFECTING ACETYLCHOLINE METABOLISM

A. Cholinesterase Inhibitors. Drugs, such as physostigmine, can antagonize the neuromuscular blocking action of curare.181, 182 Most investigators believe that the neuromuscular action of the quaternary ammonium type anticholinesterases is primarily due to their inhibitory effect on the hydrolysis of acetylcholine and can be interpreted as prolongation and intensification of acetylcholine effects.183-186 This opinion is corroborated by agreement between the relative anticholinergic effects of anticholinesterases and their inhibitory effect on human true cholinesterase.187 Others are of the opinion that neostigmine 188 and edrophonium 180, 190 also have a direct depolarizing action at the neuromuscular junction.180

The clinically used quaternary ammonium-type anticholinergic agents are either urethane derivatives like neostigmine (Prostigmin) and its congeners,191 or are phenyl-trimethylammonium derivatives like edrophonium (Ten-silon).180 Other quaternary ammonium compounds like ambenonium (Mytelase),192 although useful in man by the oral route for treatment of myasthenia gravis,193 are not suitable for intravenous administration. Similarly, the organophosphorus compounds such as diisopropylfluorophosphate,194, 195 tetraethyl phosphosphate,196 dimethylamido-ethoxy-phosphoryl cyanide (Tabun) 197 and others 198 have a marked anticholinergic effect, but are also too toxic for intravenous use.

Hexafluoroenium (Myaxen),199 an anticholinesterase which because of its molecular structure, penetrates cell membranes poorly, and on intravenous injection only affects plasma cholinesterase, will be discussed in the section on drugs which influence the metabolism of muscle relaxants.

Anticholinesterases will antagonize the neuromuscular block caused by nondepolarizing relaxants, such as d-tubocurarine or gallamine, or the nondepolarization block that develops after the use of depolarizing agents because of the changed sensitivity of the end-plate. Clinically, it is not always easy to determine after the use of depolarizing agents, whether the apnea is due to a persistent depolarization or nondepolarization block. When this is the case a short acting anticholinesterase like edrophonium should be tried first.9 Only if this brings transient improvement, should one administer longer lasting agents, such as neostigmine or pyridostigmine (Mestinon).

The need for the cautious administration of anticholinesterases becomes clear when the mechanism of their anticholinergic action is considered. These compounds exert their effect by inhibiting the hydrolysis of acetylcholine by cholinesterase and thereby elevating the acetylcholine concentration at the end-plate. The accumulated acetylcholine, in accordance with the law of mass action, will displace the neuromuscular blocking agents from the cholinergic receptors and re-establish transmission. Anticholinesterases might fail to re-establish transmission if end-plate receptors have lost their sensitivity to acetylcholine.28, 155, 154 if there is pathological fixation of blocking agent to receptor,9, 23 or if excessive concentration of acetylcholine produces an acetylcholine block.200, 201 Under any of these circumstances, persisting with the administration of anticholinesterases will prolong the block. The administration of an anticholinesterase may also prolong the neuromuscular block if it is caused by prolonged depolarization of the end-plate. This has been shown for compounds which are hydrolyzed by cholinesterase, such as succinylcholine,202, 203 and for those which are not metabolized by these enzymes such as C-10 or Prestonal.204, 205
B. Cholinesterases and Agents Which Accelerate Cholinesterase Activity. Cholinesterases, similar to other proteins, do not readily penetrate biological membranes and after intravenous administration, remain in the plasma. Consequently, they will not exert a direct effect at the end-plate. Intravenously injected, concentrated human plasma cholinesterase (Cholase) can accelerate the hydrolysis of succinylcholine and its diethyl derivative, suxethonium. In the dog and man, intravenous Cholase shortens the duration of succinylcholine-induced apnea, the duration of apnea being inversely proportional to the plasma cholinesterase level. In contrast to this, the intravenous injection even of large amounts of Cholase failed to counteract prolonged apnea in patients.

It is possible to accelerate hydrolysis of aromatic substrates by plasma cholinesterase and to reactivate neostigmine inhibited plasma cholinesterase by a variety of compounds. However, with the exception of Mg++, and perhaps Ca++, the activity of true cholinesterase cannot be accelerated. The accelerating effect of Mg++ on muscle cholinesterase will reinforce other blocking effects of this ion at the end-plate and will potentiate the nondepolarization block produced by relaxants. This should be considered when a muscle relaxant is given to patients such as eclamptics, who have previously received parentral Mg++.

4. Compounds Which Influence End-plate Stability

Certain chemical compounds exert an acetylcholine-like effect of their own, or facilitate the effect of acetylcholine at the end-plate. These compounds have been classified as "labilizers." Compounds inhibiting the depolarizing effects of acetylcholine and other labilizers are called "stabilizers." Both labilizers and stabilizers may exert their effect by combining with cholinergic receptors at the end-plate, or by changing the permeability of the postjunctional membrane to Na+ and K+.

If labilizers produce neuromuscular block, it is a depolarization block whereas the block caused by stabilizers is a nondepolarization block. The picture, however, is complicated by the fact that a compound, depending on the species, muscle of species, and duration of exposure may either act as a labilizer or a stabilizer.

The compounds capable of influencing end-plate stability will be discussed in two groups: labilizers and stabilizers.

A. Compounds with Acetylcholine-like Effects (Labilizers). a. Choline. The intravenous or close intraarterial injection of choline in cats in small doses produces fibrillation and repetitive firing of muscle after a single nerve stimulation. In larger doses, it produces neuromuscular block (fig. 14). Choline also antagonizes d-tubocurarine induced block in cats. On close intraarterial injection, the decuraring effect of choline was the same as that of an equivalent amount of acetylcholine. Castillo and Katz working with the isolated nerve-muscle fiber preparation of frogs found that the iontophoretic application of choline produced weak depolarization, potentiated the depolarizing effect of acetylcholine in the absence of, and inhibited it in the presence of neostigmine. The depolarizing effect of choline on iontophoretic application was found to be about 1/100 of that of acetylcholine.

Small intraarterial doses of choline in human volunteers, produced a depolarization and larger doses a nondepolarization block. The first was potentiated, the latter antagonized by neostigmine. In myasthenic patients, the intrarterial injection of choline always caused a nondepolarization type block reversible by neostigmine.

Hutter suggested that besides its direct effect on the end-plate choline might also increase the output of acetylcholine at nerve terminals. He claimed that choline did not inhibit cholinesterase at the end-plate. Castillo and Katz, however, entertained the possibility that the effects of the interaction of choline and acetylcholine on one hand, and choline and stable choline esters on the other, at the end-plate, could be explained by the inhibitory effect of choline on cholinesterase.

The neuromuscular effects of choline might have clinical significance. The primary breakdown product of succinylcholine, succinylmonocholine, has neuromuscular blocking activity and might be responsible for the prolonged postoperative apnea caused by succinylcholine.
dence, it is conceivable that choline, the final enzymatic breakdown product of succinylcholine, may also contribute to the block caused by this relaxant.

Large doses of choline will probably antagonize nondepolarization block in man.

b. Nicotine. Nicotine, a tertiary amine, in small concentrations stimulates and in higher concentrations inhibits neuromuscular transmission. The actions of nicotine are so similar to those of acetylcholine at the end-plate and at the autonomic ganglia, that the subsequently discovered autonomic and neuromuscular actions of acetylcholine were termed "nicotinic" in contradistinction to its muscarinic effects at the postganglionic parasympathetic nerve endings. Recently the effects of nicotine on the resting potential and neuromuscular transmission in the isolated nerve-muscle preparation of the frog and rat were studied by Thesleff. He also found that the effects of nicotine were similar to those of acetylcholine.

c. Tetraethylammonium. Tetraethylammonium produces fibrillatory twitching and augments the response of frog muscle to indirect stimulation. Rothberger first observed that tetraethylammonium has an anticholinergic effect.

Kensler studied its antagonistic effect against several relaxants in different species and found that it antagonized d-tubocurarine in the rat phrenic nerve-diaphragm preparation, gallamine and C-10 in the same preparation of rats and kittens, and d-tubocurarine, gallamine and to a lesser extent, C-10 in the cat's sciatic-gastrocnemius preparation. Stovner recently reported that tetrathyamine antagonized succinylcholine and succinylmonocholine in the phrenic nerve-diaphragm preparation of rats and kittens, also in the tibialis and soleus muscles of cats and in the flexor digitorum longus muscles of rabbits. It also had a marked antagonistic effect on d-tubocurarine-induced neuromuscular block.

As already mentioned, Stovner attributed the neuromuscular effects of tetraethylammonium to an increase in the amount of acetylcholine released at the end-plate. However, the possibility of its direct stimulating effect cannot be disregarded.

d. Miscellaneous Compounds with Ill-defined Acetylcholine-like Effects. The following compounds cannot be classified as typical labilizers, but the majority of evidence indicates that they exert their neuromuscular action by this mechanism.

PHENOL DERIVATIVES: The anticholinergic effects of phenol and its derivatives were investigated in the phrenic nerve-diaphragm preparation of the rat and mouse. The phenolic substances were found to antagonize the effect of d-tubocurarine and dimethyl d-tubocurarine. Catechol, the most active compound, was about five times more potent than phenol. Since the anticholinesterase effect of the compounds was negligible, their anticholinergic action could not be explained by this mechanism. Coppée suggested that the effect
of phenol might be due to an increase in the efficacy of the stimulus. It is unlikely that the anticure effect of phenolic substances should have clinical significance.

**Heparin and Related Compounds:** These have no demonstrable anti-cholinesterase effect, but antagonize, in relatively large doses, the neuromuscular activity of d-tubocurarine on the sciatic-tibialis anterior preparation of rabbits.\(^{228}\) Prolamine, the biological antagonist of heparin, potentiates d-tubocurarine and antagonizes C-10 block.\(^{229}\) The antagonistic effect of heparin on block produced by d-tubocurarine, however, is too weak to be of significance in patients.

**Thiamine and Its Congeners:** Thiamine inhibits neuromuscular transmission,\(^{230, 231, 232}\) but the mechanism of the block is subject to controversy. Gjone\(^{233}\) found that the action of thiamine resembled that of d-tubocurarine in the rat phrenic nerve-diaphragm preparation and in the flexor-digitorum-longus preparation of the rabbit. Thiamine antagonized the neuromuscular effects of neostigmine, and was in turn antagonized by it in the rat-diaphragm preparation. It had an additive effect with d-tubocurarine and Mg\(^{++}\), and also with C-10 and succinylcholine in this preparation. It also had a d-tubocurarine-like effect in the rabbit flexor-digitorum-longus preparation on tetanic stimulation. Cheyml and associates\(^{234}\) found an initial stimulation followed by block in the rat phrenic nerve-diaphragm preparation but noted no acetylcholine-like effect in the frog nerve-muscle preparation or in pigeons. They observed that neostigmine antagonized thiamine-induced neuromuscular block in cats; thiamine at first antagonized d-tubocurarine, but the effects of successive doses became progressively less, and there was an additive effect between d-tubocurarine and thiamine. Thiamine also antagonized succinylcholine in the cat. The blocking dose of thiamine was about five times greater than that required to antagonize d-tubocurarine or succinylcholine. Several thiamine derivatives e.g., cocarboxylase, acetylthiamine, and thiochrome, also antagonized d-tubocurarine. Finally, di Palma and Hitchcock\(^{235}\) found that thiamine produced neuromuscular block in 20 mg./kg. doses in cats and 80 mg./kg. doses in dogs and a 50 to 95 per cent ganglionic blockade. They reported that acetylthiamine had the same activity as thiamine; oxathiamine was weaker, but pyrithiamine was ten times more potent than thiamine. They were unable to antagonize the neuromuscular effect of thiamine by edrophonium or neostigmine. Unna and Pick\(^ {211}\) also obtained no effect with neostigmine.

The controversial results can probably be explained by the different preparations and techniques used. It is possible that thiamine and its congeners are depolarizing agents, but under their influence the sensitivity of the end-plate changes and the thiamine induced block assumes the characteristics of a nondepolarization block. Further investigation will be necessary to settle this problem.

**Veratrine and Veratridine:** In contrast to other libilizers which primarily exert their effect at cholinergic receptors of end-plates, veratrine and veratridine affect the stability of the whole muscle membrane.\(^ {183, 131a}\) The muscle reacts to a single stimulus with repeated contractions.\(^ {126, 256}\) The effects of veratrine are antagonized by procaine, cocaine, Ca\(^{++}\) and removal of Na\(^{+}\).\(^ {163}\)

**B. Compounds Which Antagonize the Effects of Acetylcholine (Stabilizers).** Besides bivalent cations, such as Ca\(^{++}\) and Mg\(^{++}\), a variety of substances hinder the effects of acetylcholine on cholinergic receptors, or influence by other mechanisms the sensitivity of end-plates or that of the whole muscle membrane to depolarization.

Here again experimental data are controversial, the conflict again resulting from differences in test preparations and experimental conditions.

a. Procaine. Besides the inhibition of acetylcholine release at the end-plate,\(^ {109}\) procaine also inhibits depolarization by competing with acetylcholine for cholinergic receptors and by exerting a nonspecific, stabilizing action on the post-junctional membrane.\(^ {163}\) These effects may be antagonized by the inhibitory effect of procaine on cholinesterases.\(^ {117, 172}\) Because of this inhibitory effect on plasma cholinesterase, procaine also inhibits the enzymatic breakdown of succinylcholine.\(^ {173}\) Due to the effects of procaine at the neuromuscular junction, some of which facilitate and others antagonize depolarization, the actions of different muscle
relaxants and those of the same relaxant under different conditions, may either be potentiated or antagonized.\textsuperscript{170}

Ellis et al.\textsuperscript{170} found that 4 to 64 mg./kg. doses of procaine had no effect on neuromuscular transmission in the sciatic-gastrocnemius preparation of cats and dogs, although the largest dose caused respiratory arrest, presumably depressing the respiratory center. Procaine always intensified the blocking action of d-tubocurarine; its effect on succinylcholine or C-10 induced block, however, depended on the sequence of administration. When procaine was injected before succinylcholine or C-10, it antagonized, if injected simultaneously with or after, it intensified their neuromuscular effect. It is conceivable that procaine, when injected before succinylcholine or C-10, interferes with the absorption of these relaxants to cholinergic receptors and thereby decreases their efficacy. When injected after succinylcholine or C-10, the effect of procaine on cholinesterase becomes the determining factor and the elevation of acetylcholine concentration at the end-plate has an additive effect with that of the depolarizing relaxant.

In man 100 mg. intravenous procaine augmented respiratory depression or caused apnea in patients receiving succinylcholine by continuous infusion.\textsuperscript{172} In view of these findings, caution should be exercised when procaine, or other local anesthetic agents, which inhibit cholinesterase activity,\textsuperscript{172} are administered with muscle relaxants. This may occur when local anesthetics are administered intravenously to supplement general anesthesia, or when inadequate operating conditions during infiltration or regional analgesia necessitate the use of relaxants.

b. Epinephrine. Similarly to procaine, epinephrine also exerts multiple effects at the neuromuscular junction: it increases the amount of acetylcholine released;\textsuperscript{155} decreases the electrical excitability of the muscle fiber;\textsuperscript{156} and inhibits cholinesterase at the end-plate.\textsuperscript{158} Depending on the predominance of one or the other of these factors, epinephrine will antagonize or intensify the effect of relaxants.

The anticholinergic effects of epinephrine, probably caused by increased acetylcholine release, or anticholinesterase activity, have already been considered. In this section, those circumstances will be discussed in which epinephrine intensifies the action of neuromuscular blocking agents.

Paton and Zaimis have shown\textsuperscript{237} that intravenous epinephrine inhibited the neuromuscular effects of C-10 and increased those of d-tubocurarine on the tibialis muscle of the cat. Beckett and Ellis\textsuperscript{154} made similar observations on the interaction of depolarizing agents and nondepolarizing agents and epinephrine on the rat nerve-diaphragm preparation. Naess and Sirnes\textsuperscript{162} attributed the synergistic effect of epinephrine and d-tubocurarine, observed in rabbits, to a decreased sensitivity of the end-plate to depolarization. Dybing observed that norepinephrine and isopropyl norepinephrine also intensified d-tubocurarine block in the rabbit.\textsuperscript{238} It has also been observed that epinephrine antagonized the anticholinergic effect of neostigmine\textsuperscript{239} and intensified the effects of Mg\textsuperscript{2+} which produces a curare-like block.\textsuperscript{240}

The stabilizing effects of epinephrine on the end-plate, which result in intensification of the effects of nondepolarizing, and antagonism to depolarizing relaxants, were obtained with relatively large doses of epinephrine. It is improbable that epinephrine would be used clinically in doses capable of intensifying a nondepolarization block. It therefore seems reasonable in cases of prolonged apnea, encountered with the use of muscle relaxants, to inhibit by the administration of ephedrine\textsuperscript{157, 158} the enzymatic breakdown of endogenous epinephrine and thereby increase the release of acetylcholine at the end-plate.

c. Inhalation Anesthetic Agents. Ether: Auer and Meltzer\textsuperscript{241} reported in 1914, that ether inhibits neuromuscular transmission. It is generally accepted that ether intensifies the neuromuscular effect of curare.\textsuperscript{242-246} The exact mechanism whereby ether exerts these effects is not known. Gross and Cullen\textsuperscript{240} suggested that ether and curare influence neuromuscular transmission by identical mechanisms. They confirmed on dogs the finding of Simonart and Simonart\textsuperscript{250} that ether-inhibited acetylcholine-induced muscle contractions in cats. It was also observed that neostigmine\textsuperscript{242, 244} antagonized the neuromuscular effects of ether. Naess, studying the interaction of ether and d-tubocurarine,\textsuperscript{245} and ether and neostigmine\textsuperscript{251} on neuromuscular transmission, be-
lies that ether and d-tubocurarine decrease the sensitivity of the end-plate to depolarization by different mechanisms. This view was shared by Secher who observed that neostigmine produced neuromuscular block in the rat nerve-diaphragm preparation under the influence of ether in 1/6 the concentration that produced this effect in the absence of ether.

It is possible that ether might change the sensitivity of the end-plate to depolarization by a mechanism similar to that suggested for depolarizing relaxants.

Ether in man intensifies the action of other nondepolarizing relaxants such as dimethyl d-tubocurarine and gallamine. Secher reported that ether potentiated the effects of C-10 in the rat nerve-diaphragm preparation. In man, the neuromuscular effects of C-10 and succinylcholine and in mice those of C-10 do not seem to be influenced by ether.

Whatever the mechanism in man, ether potentiates the neuromuscular effects of d-tubocurarine and to a lesser extent those of gallamine. The dose of d-tubocurarine and gallamine during ether anesthesia should be 1/6 to 1/4 and 3/4, respectively, of that used with thiopental anesthesia.

Chloroform: The effects of chloroform on the neuromuscular transmission are controversial. Githens and Meltzer and Huston et al. found no effect; Watland et al. and Torda observed potentiation of the twitch response to single stimuli and Naess and Secher noted depression of neuromuscular transmission during chloroform anesthesia. Most workers have reported that chloroform intensified the neuromuscular effects of d-tubocurarine, but Lang et al. found no potentiation. In man, deep chloroform anesthesia causes profound muscular relaxation and intensifies the action of d-tubocurarine. The transient increase of the twitch height during chloroform anesthesia suggests an initial depolarizing effect on the end-plate.

Fluothane does not affect neuromuscular transmission but it intensifies the neuromuscular action of d-tubocurarine as does divinyl ether.

Cyclopropane causes an initial increase in height of the muscle twitch on indirect stimulation and potentiates the neuromuscular effects of d-tubocurarine and gallamine. The latter is less marked than that of ether.

Nitrous Oxide and Ethylene in the concentrations used for clinical anesthesia have no effect on neuromuscular transmission and do not potentiate d-tubocurarine.

d. Nonvolatile Anesthetics, Narcotics, Alcohol. Little information is available on the effects of these drugs on neuromuscular transmission. Some controversial data exist but more work will be necessary for clarification. It seems that the doses of these compounds necessary to produce a neuromuscular effect alone are far greater than those used in anesthesiology. This, however, does not exclude the possibility that in usual doses, they might reinforce the activity of muscle relaxants. It is also possible that neuromuscular effects play a role in accidental or intentional intoxication with these agents.

Barbiturates: Pentobarbital has been studied extensively and seems to have the most marked neuromuscular action. It facilitates neuromuscular transmission before exerting its blocking action. These effects are the effects of pentobarbital with intracellular recording and found that it produces a nondepolarization block on the isolated frog nerve-muscle preparation. Pentobarbital intensifies the effects of curare and also potentiates C-10. The effects of secobarbital on the end-plate are similar to those of pentobarbital and phenobarbital also potentiates curare.

It seems that the initial stimulating action of thiopental at the end-plate is more marked than its blocking effect, which Gross and Cullen found to be weak. Intra-arterial thiopental increased the height of the muscle twitch on indirect stimulation while decreasing the voltage and increasing the latency period and duration of the action potential.

More information may be obtained on the neuromuscular effects of barbiturates from the excellent monograph of Sirnes according to whom, barbiturates may antagonize the anticontact effects of neostigmine and thereby contribute to a prolonged postoperative neuromuscular block sometimes seen after the combined use of barbiturates and relaxants in anesthesiology.
OTHER NONVOLATILE ANESTHETICS: Urethane, chloral hydrate, chloralose and para-ethylene have little or no effect on neuromuscular transmission.\textsuperscript{258}

CHLORPROMAZINE: Reports on the neuromuscular effects of chlorpromazine are controversial.\textsuperscript{260} In cats according to Dyberg and Houg\textsuperscript{266} chlorpromazine had no effect on neuromuscular transmission. It intensified, however, the effects of \textit{d}-tubocurarine and gallamine and antagonized those of \textit{C}-10 and succinylcholine. In contrast to this, Aronsen et al.\textsuperscript{267} found that in the isolated nerve-muscle preparation of the golden hamster, large doses of chlorpromazine produced contracture and prolonged the effects of succinylcholine. It is unlikely that chlorpromazine influences the effects of neuromuscular blocking agents clinically.

NARCOTICS: Morphine, codeine, methadone and meperidine have no effect on neuromuscular transmission, but they potentiate \textit{d}-tubocurarine.\textsuperscript{253} Morphine has little effect on C-10.\textsuperscript{253}

ALCOHOLS: Ethyl alcohol in high concentrations inhibits neuromuscular transmission.\textsuperscript{258, 268, 269} Rummel \textsuperscript{260} found that alcohol produces a depolarization block, potentiates the neuromuscular effects of K\textsuperscript{+}, and antagonizes nondepolarizing relaxants, e.g., \textit{d}-tubocurarine. Tribromethyl alcohol (Avertin) also has a weak neuromuscular blocking effect.\textsuperscript{210, 258}

e. Compounds Which Influence the Neuromuscular Effects of Decamethonium and Succinylcholine. A group of quaternary ammonium compounds (B.W. 49–204, B.W. 51–212, B.W. 49–164, and B.W. 50–354) are capable of influencing the duration of the C-10 and succinylcholine-induced neuromuscular block both in laboratory animals\textsuperscript{203, 270, 271} and in man.\textsuperscript{272, 273} The mechanism of action of these compounds has not been clarified as yet.\textsuperscript{276, 277, 278} and they have little or no clinical significance.

f. Ganglionic Blocking Agents. Most ganglionic blocking agents inhibit transmission by competing with acetylcholine for the cholinergic receptors of ganglia.\textsuperscript{41, 279} Ganglionic blocking agents may also affect neuromuscular transmission and neuromuscular blocking agents may have autonomic effects.\textsuperscript{24} Consequently, it is not surprising that ganglionic blocking agents are capable of influencing the activity of neuromuscular blocking agents and that the interaction of ganglionic blocking agents and muscle relaxants may have clinical significance.\textsuperscript{280, 281, 282}

HEXAMETHIONIUM: Paton and Zaimis \textsuperscript{283} first reported that hexamethonium and pentamethonium produce neuromuscular block in the cat, potentiate the effects of \textit{d}-tubocurarine,\textsuperscript{41} and antagonize those of C-10.\textsuperscript{41} Deacock and Davies\textsuperscript{284} using the phrenic nerve-diaphragm preparation of rats found that hexamethonium produced a nondepolarization block which was antagonized by neostigmine. They also found that hexamethonium and \textit{d}-tubocurarine mutually intensified the neuromuscular actions of one another. Payne\textsuperscript{281} observed similar interaction between hexamethonium and mepacrine.

HOMATROPINUM (Trophenium) depresses\textsuperscript{41} neuromuscular transmission in the rat diaphragm preparation\textsuperscript{222} and the block is reversed by neostigmine. The neuromuscular effects of homatropinum and \textit{d}-tubocurarine are additive.

TRIMETHAPHAN has a weak neuromuscular blocking effect\textsuperscript{282, 284} that is intensified by the previous administration of \textit{d}-tubocurarine, and is not reversible by neostigmine.\textsuperscript{282} Payne\textsuperscript{281} noted that the prior injection of mepacrine potentiated the neuromuscular effects of trimethaphan in cats.

MECAMYLAMINE: Stone et al.\textsuperscript{285} reported that mecamylamine in 10 mg./kg. doses had a weak neuromuscular blocking effect in dogs, but Bennett et al.\textsuperscript{280} were unable to confirm these findings in cats. Payne,\textsuperscript{281} also working with cats, found that mecamylamine had a transient stimulant effect on the twitch response elicited by indirect stimulation. Doses of mecamylamine, which have no neuromuscular blocking effect at slow rates of stimulation, produce a block with tetanic stimulation. Bennett et al.\textsuperscript{286} found that mecamylamine intensified the effects of nondepolarizing relaxants. Furthermore, the previous administration of mecamylamine antagonized the effect of small doses of depolarizing relaxants and changed the character of the block produced by large doses to nondepolarization block, reversible by neostigmine. Payne\textsuperscript{281} observed that mecamylamine potentiated the neuromuscular effects of both hexamethonium and trimethaphan. He also
found \(^{286}\) that CO\(_2\) inhalation intensified the neuromuscular action of mecamylamine.

Ganglionic blocking agents, similarly to muscle relaxants, may have an initially stabilizing (nondepolarizing), or an initially labilizing (depolarizing) and later stabilizing effect on the neuromuscular junction. Hexamethonium and trophenium probably act by the first, and mecamylamine and trimethaphan by the second mechanism. From the influence of tetanic stimulation on the neuromuscular action of mecamylamine,\(^{280}\) it is probable that it also decreases the amount of acetylcholine released at the end-plate.\(^{281}\)

The above evidence indicates the necessity of caution when ganglionic blocking agents and muscle relaxants are used simultaneously. Depending on the agents used and their sequence of administration, either potentiation or antagonism might occur. These interrelationships need clarification in man.

g. Antibiotics. The possibility that antibiotics, can produce neuromuscular block resulting in apnea and death was only recognized recently.\(^{287}\) Following Prigden's publication,\(^{287}\) reports have appeared of complications following the intraperitoneal administration of neomycin.\(^{288-289}\) Subsequently, the neuromuscular effects of neomycin were investigated by Pittinger and associates;\(^{293,295}\) those of streptomycin by Brazil and Corrado.\(^{180a}\)

Neomycin: Pittinger and associates conducted studies on the sciatic-gastrocnemius preparation of rabbits and dogs. They also determined the LD\(_{50}\) in mice and the headdrop dose (HD\(_{50}\)) and LD\(_{50}\) in rabbits. Seven 20 mg./kg. doses of neomycin produced complete neuromuscular block in unanesthetized rabbits while in rabbits and dogs anesthetized with ether, 5 to 10 mg./kg. doses produced an 80 to 90 per cent block which could be antagonized by 75 \(\mu\)g./kg. neostigmine (fig. 15). Neostigmine also counteracted the LD\(_{50}\) dose of neomycin in mice and rabbits and the HD\(_{50}\) dose in rabbits. Their findings indicate that neostigmine causes a typical nondepolarization block which is potentiated by ether.

Streptomycin. Molitor et al.\(^{297}\) reported that in mammals streptomycin caused death by respiratory paralysis. Studies by Brazil and Corrado\(^{180a}\) revealed that streptomycin pro-
duced complete neuromuscular block in 110 and 580 mg./kg. doses in dogs and pigeons, respectively. Both Ca++, 50 mg./kg., and neostigmine, 0.15 mg./kg., antagonized the block. The neuromuscular block was accompanied by ganglionic block which was also antagonized by Ca++. From the effects of Ca++, it was concluded that streptomycin-induced neuromuscular block is similar to that caused by Mg++, and is characterized by a decreased acetylcholine output at the end plate and an increased resistance of this structure to the depolarizing effects of acetylcholine.

The fatalities observed with neomycin have usually occurred in infants and children, who have received the dose of neomycin usually employed for adults. The general anesthetic agent in all cases was ether. While the dose-body weight relationship is usually observed with drugs, it is frequently not considered when antibiotics, vitamins and similar compounds are given to children or underweight adults. The consequences of such illogical practices are evident from the fatalities encountered.291 The work of Pittinger and co-workers emphasizes two more points: one is the increased danger that results from the combined use of ether and neomycin, and the other the therapeutic efficacy of neostigmine. Nondepolarizing relaxants and neomycin mutually intensify the neuromuscular effects of one another. Mutual potentiation can also occur between depolarizing drugs and neomycin292 if the prolonged administration of the former changed the sensitivity of the end plate towards depolarizing influences.3, 295

Miscellaneous Compounds. Histamine and Histamine Liberators: Certain histamine liberating compounds such as protamine, antagonize depolarization block,296-300 potentiate nondepolarization block and themselves produce a nondepolarization block in cats. Schenk and Anderson299 also found that on close intravenous injection, histamine antagonized depolarization, and potentiated nondepolarization block in cats.

5. Compounds Which Influence Permeability, Distribution, Metabolism and Elimination of Relaxants

The intensity and duration of action of muscle relaxants depends on the relative proportion of the relaxant taken up by the end-plate and inactive sites of loss in other parts of the organism. This has been discussed in this symposium by Kalow.

Any agent that will interfere with the permeability of relaxants through the blood tissue barrier, influence its distribution to sites of loss, or affect its metabolism or excretion will alter the intensity and/or duration of their action.

A. Compounds Which Influence Permeability. The anticholinesterase effects of Congo red and other dyes were first described by Petroff204 and later investigated in frogs305 and in mammals.306 Congo red, when given before, prevents, and when given after, accelerates recovery from d-tubocurarine-induced neuromuscular block.305 Kinsler305 concluded that the anticholinesterase effect of Congo red is due to its complex formation with d-tubocurarine. This complex does not penetrate cellophane membranes and presumably interferes with the passage of d-tubocurarine from plasma to end-plates. Congo red had no effect on the end-plates themselves. No relationship was found between the moderate anticholinesterase activity of Congo red and the anticholinester effect. Brucke et al.306 confirmed this on mammals and also showed that similar compounds of large molecular weight, e.g., anilin blue, germanin, and agents with smaller molecules, e.g., naphthylamine sulfonate or sulfanilic acid, also had an anticholinester effect. These compounds, besides d-tubocurarine, also antagonized the neuromuscular effects of C-10 and hexamethylene-bis-carbaminoxycholine (Imbrelit). They showed that precipitate formation between muscle relaxant and Congo red type "antagonists" is not an indispensable condition. The formation of water-soluble complexes between the relaxants and these compounds can probably inhibit the neuromuscular activity of the former.

B. Compounds Which Influence Distribution. Cavallito suggested202 that lipophilic substances such as dibenzylamine, when given in quantities that have no specific effect on neuromuscular transmission, potentiated the effects of hexafluorenium at the end-plates. It was also reported that hexafluorenium was only active in man when given together with lipophilic general anesthetic agents.307 Cavallito308 suggested that the potentiation of the
neuromuscular effect of hexafluorenium by anesthetic agents and other lipophilic compounds is due to the prevention of its distribution to inactive sites of loss. While this explanation might be correct for other species, in man, potentiation of the neuromuscular effect of hexafluorenium by anesthetic agents (with the exception of deep ether anesthesia) could not be confirmed. Study of its in vivo anticholinesterase suggested that the weak neuromuscular activity of hexafluorenium is due to its inability to get to the human end-plate in high enough concentration to produce block.

Bovet et al. are of the opinion that the potentiating effect of diethylamino-ethylidiphenylpropylacetate·HCl (SKF 525-A) on neuromuscular blocking agents might be due to the prevention of their absorption to sites other than the end-plate. The influence of SKF 525-A on the uptake of radioactive C-Curarine by end-plates and on its neuromuscular effect was recently demonstrated by Waser.

C. Compounds Which Influence Metabolism. Little information is available on chemical compounds which influence the metabolism of neuromuscular blocking agents other than succinylcholine and suxethonium.

Inhibitors of plasma cholinesterase such as, neostigmine, inhibit the enzymatic breakdown of succinylcholine and potentiate its neuromuscular effect. This was also demonstrated with eserine, tetraethylpyrophosphate and hexafluorenium.

Hexafluorenium, originally recommended as a neuromuscular blocking agent, proved to be a potent inhibitor of plasma cholinesterase. Presumably because of its molecular structure, it does not penetrate cell membranes and its inhibitory effect is limited on human cells. The intravenous injection of 0.5 mg./kg. inhibits hydrolysis of acetylcholine and succinylcholine, at first almost completely, and even after 60 to 90 minutes by more than 50 per cent. Although it inhibits the cholinesterase activity of hemolyzed red cells, it is not effective in vivo against intact red cells. The administration of hexafluorenium to human subjects in the above dosage is not followed by signs of increased cholinergic activity. This effect of hexafluorenium was utilized clinically to potentiate and prolong the

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**Figure 16.** Influence of hexafluorenium on the respiratory effects of succinylcholine and suxethonium. The data are the averages obtained from 10 patients each, lightly anesthetized by thiopental-nitrous oxide-oxygen. Dosages used were succinylcholine chloride 0.6 mg./kg, suxethonium bromide 1.2 mg./kg, and hexafluorenium bromide 0.5 mg./kg. Duration of respiratory depression was measured from time of injection of succinylcholine or suxethonium to return of tidal volume to control values.
neuromuscular activity of succinylcholine and suxethonium (fig. 16). With its use, the mg./min. dose of succinylcholine necessary for the production of muscular relaxation, could be reduced by 70 to 90 per cent.

Because of their generalized cholinergic effects, other cholinesterase inhibitors are not suitable for the prolongation of action of succinylcholine.

Since succinylcholine is little, or not at all hydrolyzed by true cholinesterase, specific inhibitors of this enzyme do not influence its neuromuscular action.

D. Compounds Which Influence Excretion. Little information is available on the neuromuscular effects of compounds which accelerate or retard urinary excretion of relaxants.

In cases of prolonged postoperative neuromuscular block, recovery may be accelerated by the administration of osmotic diuretics. It is conceivable that with the extensive use of certain diuretics, such as chlorothiazide, in the treatment of hypertension and other conditions, patients will be encountered who will show decreased sensitivity to muscle relaxants, such as C-10 or gallamine, which are primarily excreted unchanged in the urine. This effect of diuretics, and that of chlorothiazide, in particular, may be counteracted by the loss of Na+ and K+ which would tend to increase sensitivity of the neuromuscular junction to relaxants.

6. Interaction of Muscle Relaxants

Results of the interaction of muscle relaxants at the end-plate are variable and are influenced by the species of experimental animal, and the sequence and duration of their administration.

Neuromuscular blocking agents which produce the same type of block, e.g., d-tubocurarine and gallamine, or C-10 and succinylcholine, have additive effects. If a nondepolarizing relaxant, e.g., d-tubocurarine or gallamine, is administered first to a species in which C-10 or succinylcholine produces a depolarization block, e.g., cat or man, nondepolarizing agents will antagonize the effects of depolarizing agents (fig. 2). In man this antagonism is so great that at a time when there is no discernable residual effect of the nondepolarizing relaxant, three to four times more depolarizing relaxant is required for production of neuromuscular block than under ordinary circumstances. In the cat, but not in the dog, d-tubocurarine counteracts the neuromuscular effects of C-10 and other depolarizing relaxants.

When C-10 is injected first, it does not antagonize the neuromuscular action of subsequent doses of d-tubocurarine. If it is administered after d-tubocurarine, however, C-10 antagonizes the neuromuscular blocking action in cats (fig. 17).

When C-10 or succinylcholine are administered for prolonged periods to human subjects or to dogs, they will become increasingly sensitive to nondepolarizing relaxants. To a lesser extent, this was also observed in cats.

The marked intensification and prolongation of the neuromuscular effects of succinylcholine and suxethonium by hexafluoromethane have already been discussed and it was shown that this potentiation is due, not to the neuromuscular, but to the anticholinesterase effect of hexafluoromethane.

In clinical practice different types of muscle relaxants should only be used in a certain sequence and with care. There seems to be no contraindication to the administration of

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**Fig. 17. The antagonistic effect of decamethonium on the neuromuscular blocking action of d-tubocurarine in the tibialis anterior muscle of a cat. (a) Twitch height before curarization (b) 90 per cent neuromuscular block after curare. At arrow intravenous injection of 0.5 mg. decamethonium iodide. [Hutter]"
nondepolarizing relaxants after a single dose of succinylcholine. Under certain circumstances the use of a nondepolarizing relaxant after the prolonged administration of a depolarizing relaxant might be indicated. Usually, however, such combinations offer no advantages. The use of depolarizing relaxants, after nondepolarizing relaxants, is pharmacologically unsound and may lead to prolonged postoperative apnea.

The multiplicity of factors which can potentiate or antagonize the pharmacological effects of relaxants emphasizes the necessity for the anesthesiologist to be cognizant of pathophysiological changes present in the patient. He should be familiar with the properties of drugs the patient might receive immediately before, after, or during anesthesia. Furthermore, the interaction of muscle relaxants, not only with new anesthetic agents, but also with every new compound administered to surgical patients should be carefully investigated. Only in this way will it be possible to predict and avoid tragic consequences like those which have occurred after the intraperitoneal administration of neomycin to anesthetized patients.

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REFERENCES

21. Waser, P. G., and Lüthi, U.: Autoradiography of endplates with carbon-14-cal-


217. Langley, J. N.: On reaction of cells and of nerve-endings to certain poisons, chiefly as regards reaction of striated muscle to nicotine and to curare, J. Physiol. 33: 374, 1905.


220. Loewi, O.: Humoral transmission of nervous impulses, Harvey Lect. 28: 218, 1933.


276. Pharmacology of Compound 49–204. Welcome Research Laboratories, Tuckahoe, N. Y.


287. Prigden, J. E.: Respiratory arrest thought to be due to intraperitoneal neuromycin, Surgery 40: 571, 1956.


