Evaluation of New Neuromuscular Blocking Agents

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FEW DRUGS introduced in anesthesiology have changed its practice as significantly as the muscle relaxants. Until curare was first used by Griffith in 1942,[1] muscle relaxation during surgical procedures was produced mainly by deep anesthesia. It was frequently associated with undesirable side-effects. It is not surprising, therefore, that 20 years after the introduction of relaxants more than half the general anesthetics given in this country are combined with such agents. The practice of anesthesia without the use of curare and related pharmacologic compounds now seems inconceivable.

Although these drugs are universally used, they still have many drawbacks. Succinylcholine has been associated with increased intraocular pressure,[2] hyperkalemia associated with cardiac arrest,[3] bradycardia,[4] increased intragastric pressure,[5] myoglobinuria,[6] and prolonged muscle weakness and muscle pain.[7] *d*-Tubocurarine has been associated with symptoms of histamine release,[8] hypotension, and prolonged depression of neuromuscular function. Pharmacologists and anesthesiologists have directed their efforts towards the development of neuromuscular blocking drugs free of such side-effects, yet capable of providing adequate surgical relaxation and not causing prolonged respiratory depression following surgery. Logical development of such a compound requires understanding the actions of these drugs on the neuromuscular transmission process as well as the pharmacokinetics of such drugs.

The Neuromuscular Transmission Process

Studies with electron microscopy have shown conclusively that the nerve cell and the muscle cell are not continuous at the neuromuscular junction. In consequence, it is now generally accepted that direct electrical transmission from nerve to muscle across the synaptic cleft does not occur. In 1936, Dale *et al.*[9] showed that acetylcholine (ACh) acts as the chemical transmitter between the excited nerve terminal and the adjacent postjunctional muscle membrane. The surface of the muscle in apposition to the nerve terminal contains many folds, and is markedly chemosensitive. When the nerve is stimulated the cell membrane of the nerve endings at the junction is depolarized, and many of these vesicles (quanta) of ACh are synchronously released. Located on the postjunctional membrane are biologically active sites ("receptors") which on activation by the released ACh give rise to changes in membrane permeability. This, in turn, results in membrane depolarization and an action potential. Under normal circumstances the amount of ACh released is approximately fivefold greater than that necessary for threshold stimulation. It should be emphasized that the effect of a pharmacologic agent on neuromuscular transmission will become apparent only when there has been a marked reduction in released ACh or a corresponding decrease in sensitivity of the postjunctional membrane.

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This is the sequence of steps that follow motor nerve stimulation, in a relatively simplified schema:

Neuron action potential
↓
Depolarization of nerve terminal
↓
Acetylcholine release
↓
Acetylcholine diffusion through synaptic cleft
↓
Acetylcholine activation of receptors at postjunctional membrane
↓
Permeability changes of postjunctional membrane
↓
Sodium flux into and potassium flux out of cell
↓
Depolarization of postjunctional membrane
↓
Muscle fiber action potential
↓
Contraction of muscle fiber

Interference with the events taking place at any of the above levels can cause neuromuscular transmission block. Today, most investigators believe that the major activity of the relaxant drugs used clinically takes place at the postjunctional muscle membrane, although some prejunctional effects may be present in addition. One group of relaxants gives rise to a block called nondepolarizing, competitive, or "curarelike." These drugs (*d*-tubocurarine is typical) "bind the receptors" so that the ACh released from the nerve terminal finds fewer receptors available for activation. It can be shown that after treatment with *d*-tubocurarine the postjunctional muscle membrane fails to depolarize to threshold level upon stimulation by the neurally released ACh, and thus fails to give rise to an action potential.

Depolarizing relaxants, on the other hand, first stimulate and then block junctional response. The receptors on the postjunctional membrane are activated to a state similar to that following application of ACh, the normal neurotransmitter. Depolarization of the postjunctional membrane beyond threshold levels is followed by neuromuscular transmission block. Since ACh is rapidly hydrolyzed by acetylcholinesterases, transmission is rapidly restored. Succinylcholine is hydrolyzed much more slowly, while decamethonium, carbamylcholine, and imbretil are even more resistant to hydrolysis. Thus, these drugs cause more enduring depolarization and persistent blocks of neuromuscular transmission. Repolarization does occur slowly even with prolonged drug applications, but despite this, neuromuscular transmission is not re-established and muscle contraction will not follow nerve stimulation. The early block is a "phase I," or "depolarizing," block. The later block (that which develops during membrane repolarization) is a "phase II," or "desensitizing," block. Although the later block superficially resembles neuromuscular block by *d*-tubocurarine, there are many differences. For instance, a desensitizing block cannot be as readily reversed by an anticholinesterase as a block produced by a nondepolarizing agent. This is not surprising, since the anticholinesterase drugs prevent hydrolysis of the neurally released ACh and so render more of the transmitter available for receptor activation. In the case of a desensitizing block the receptors are already freely activated, and an increase of the ACh at the postjunctional membrane will hamper rather than help transmission. In addition, succinylcholine hydrolysis by plasma cholinesterase will be inhibited by anticholinesterases, and in this manner blocks by succinylcholine could be further prolonged. In the case of a nondepolarizing block, an increase of the available transmitter will lead to more receptor activation and more depolarization of the postjunctional membrane. It should be realized, however, that in this situation also the antagonism by anticholinesterases is not unlimited. The ACh concentration at the postjunctional membrane depends not only on the amount released and the speed of hydrolysis but also on diffusion away from the chemosensitive area.

Of interest also is the fact that a depolarizing drug like decamethonium penetrates into the interior of the fiber, while a nondepolarizing drug like *d*-tubocurarine remains on the external membrane surface.

Thus, from the viewpoint that relaxant drugs affect mainly the postjunctional membrane, there are three types of transmission block: competitive, depolarizing, and desensitizing. Competitive block (*e.g.*, by *d*-tubo-

curarine) seems to cause the least physiologic alterations and can be readily antagonized. Depolarizing and desensitizing blocks (*e.g.*, by succinylcholine) cannot be antagonized easily and do cause ionic changes both inside and outside excited cells. Desensitization block may occur without depolarization; the reverse is not known to occur.

The above factors have caused most searches for new relaxant drugs to emphasize as desirable the characteristics of competitive block.

As an added note, it is obvious that blocking agents could act at other sites in the transmission process, *e.g.*, ACh synthesis (hemicholinium-3) or ACh quantum release (magnesium ion or botulinus toxin). However, no agents that produce blocks in this manner have been seriously considered for use in clinical practice.

The Receptors

The concept of biological receptors is an undemonstrable abstraction: no compound has yet been proven to be a "receptor." Yet the concept enables the pharmacologist to examine more critically the behavior of many drugs in the living organism. A receptor is involved in a drug response when 1) only a very minute amount of drug is necessary to produce a response; 2) the drug response can be ascribed to a very specific chemical configuration of the drug molecule; 3) the drug response can be blocked by compounds affecting this specific chemical configuration. The specific chemical interaction enables the pharmacologist to speculate about the structural aspect of the receptor compound. Probably the living interface of the excitable membrane is essential to the function of the receptor, and homogenization of living structures prior to performing chemical analysis destroys this function. Chemical structure was recognized as vital to the function of the relaxant drugs in the investigations of structure–activity relationships by Bovet.[10] He proposed describing the stimulating blocking drugs as "leptocurares" (slender) and the nonstimulating blocking drugs as "pachycurares" (bulky). Present work has become much more sophisticated. Various thermodynamic and physical chemistry techniques have been used in an effort to comprehend and predict the behavior of neuromuscular blockers.[11, 12] In addition, workers in membrane and colloid chemistry have attempted to evaluate the effects of these drugs on living structures by nondestructive techniques (crystallography, nuclear magnetic resonance, optical techniques, etc.). While it is obvious that profound changes in ionic permeability and electrical characteristics of cell membranes are produced by these compounds in reacting with the receptor sites, the molecular change in the structure of the membrane has not been identified.

The past decade has seen great activity by molecular pharmacologists in the field of receptor theory. Discussion centers upon two opposing explanations for drug responses, a "receptor occupation theory" and a "rate theory." The receptor occupation theory makes the assumption that a drug must combine chemically with or occupy a physical site related to a biological system for a finite period of time to cause a change in the state of this system. According to this theory, the potency of a drug in affecting a biological system is determined by two factors: the strength of the chemical combination (*affinity*) and the potency of the resulting chemical combination in causing biological changes (*efficacy*). Thus, responses following application of a drug are not necessarily linearly related to the number of receptors occupied. A strongly-combining drug may still produce little response because of low efficacy of the resulting receptor–drug complex.[13, 14] The rate theory approaches the problem of receptor activation and response as related to the *rate* of drug–receptor combinations. Response occurs at the moment of combining and does not continue during the actual static combination. Strong-acting drugs will make and break many drug receptor combinations per unit period of time, while weak-acting drugs form stable receptor combinations which do not break up readily.[15] The reader interested in these basic studies is advised to consult articles by Ariens,[16] Belleau,[17] Ehrenpreis,[18] Furchgott,[19] and Waud.[20]

A most important step forward in our knowledge of the transmission process would be actual chemical isolation of the receptor substance. This has not yet been accomplished.

The receptor occupation theory gives no help in the design of new drugs. The rate theory, however, suggests that small molecules would be more potent and effective blocking agents than large molecules.

Receptor Activation and Muscle Contraction

In the physiologic state, activation of the postjunctional membrane receptors results in muscle fiber contractions. Many steps between the initial activation and the final muscle tension output have been identified. Classical neurophysiology has emphasized the importance of sodium ions in many of these processes. It is becoming more apparent that calcium ions probably play a central role in this process of activation. *In vitro* studies have shown that desensitization of excitable membranes produced by depolarizing relaxants is related to the presence and concentration of calcium ions.[21]

The interaction of neuromuscular blocking drugs and receptors does not result in a linear change in muscle responses. Paton and Waud have estimated for *d*-tubocurarine that approximately 75 per cent of receptors must be blocked before tension output begins to decrease.[22] Conversely, only 25 per cent of the available receptors have to be activated to achieve maximum tension output of the neurally stimulated muscle. This normally-present "safety factor" makes the evaluation of neuromuscular blocking drugs in the human or the intact animal inexact. Frequently during such studies, the effects of the drugs are measured by recording the mechanical tension output of muscle or compound action potentials of the indirectly-stimulated muscle. Under those conditions no changes will be measureable where less than 75 per cent of the receptors are blocked. A recent report by Drs. B. E. Waud and D. R. Waud indicates that mechanical responses to repetitive stimulation are more closely related to the degree of receptor blockade than are the responses to single stimuli.[23] Modern electrophysiologic recordings from single fibers could give us more accurate information, but such techniques have been possible only *in vitro*.

While the behavior of new blocking drugs can be carefully studied under various experimental conditions, the ultimate test of usefulness is determined in the clinic.

Pharmacokinetics

In this section we examine the processes of absorption, distribution, metabolism and excretion.

The clinical practice of anesthesia has bypassed the question of absorption, since these drugs are usually administered intravenously. Absorption of these drugs from an intramuscular injection site or across the alimentary epithelium following oral administration has been unpredictable and unreliable, and is not considered here.

Many of the presently used drugs are quaternary ammonium compounds. Their structure–activity relationships were examined in the basic work of Bovet.[10] All quaternary ammonium compounds are highly ionized and relatively lipoid-insoluble, characteristics important in determining the speed of diffusion and the extent of distribution to the different body compartments.[24] The fast onset of action after intravenous injection of these drugs suggests that the fluid space enclosing the receptors is in ready communication with the intravascular fluids. It would appear logical, therefore, that the degree of neuromuscular block appearing after administration of a blocking drug would be proportional to the number of molecules of the drug present in the plasma. This intuitive supposition has not been substantiated so far. Katz[25] was not able to predict the neuromuscular blocking effects of *d*-tubocurarine at any dosage schedule in man. Cohen *et al.*,[26] although able to measure accurately the plasma concentrations of *d*-tubocurarine, failed to establish a relationship between the drugs effect and the plasma concentration.

Measurement of plasma concentrations of these drugs is not simple. For most depolarization agents it is necessary to depend on difficult and insensitive biological assays. *d*-Tubocurarine can be measured accurately using an ultraviolet spectroscopic absorption method which, however, does not discriminate between the protein-bound and the unbound free form. The plasma concentration of a relaxant drug following intravenous administration reaches an initial peak dependent upon

the dose, the total circulating volume, and the cardiac output. Thereafter, the plasma concentration rapidly falls in an exponential manner. The marked similarities of the plasma concentrations of these drugs (vs. time) suggest that the biological processes following their administration are similar.[27] During the first few cycles of circulation following injection, drug concentrations in the plasma and, presumably, at the neuromuscular junction will be extremely high. Recent unpublished experiments in our laboratory indicate that the course of the subsequent block may depend to a certain degree on the value of this initial high concentration ("slug") to which the junctions are exposed.

Studies with isotope-labelled compounds have shown that after injection the drugs will be localized in muscle, especially concentrated in the junctional area.[27] The highest total tissue concentrations are, however, present in the liver, spleen, and kidney.[27, 28]

Of the clinically used relaxants, only succinyldicholine has its pharmacologic activity terminated by metabolic breakdown. Occasional patients are unable to metabolize succinyldicholine because of a genetic absence of plasma cholinesterases. In such patients the usual clinical dose of succinyldicholine represents severe overdosage and may cause prolonged block. The cessation of effects of the other drugs depends on redistribution to many nonreactive sites and on excretion.

Excretion occurs mainly by urinary filtration. It has been shown for *d*-tubocurarine and decamethonium that 75 to 85 per cent is excreted in the urine in the first 24 hours. A secondary avenue of excretion, via the bile, has been demonstrated for *d*-tubocurarine only.[28]

Requirements of New Muscle Relaxants

With the above information, ideal characteristics of new neuromuscular blocking agents can be more sharply defined.[29]

1) The agent should be competitive and nondepolarizing. Cardiac irregularities, electrolyte changes, intraocular pressure increases and muscle pains noted after the administration of succinyldicholine can be attributed directly or indirectly to the strong depolarizing action of this compound. In addition, antagonists for depolarizing blocking agents are not available at this time.

2) The cessation of the block should not depend on excretion by the kidney or liver, since known or unknown disease conditions could markedly prolong the action of such an agent. A gaseous agent which could be administered and eliminated through the lungs would be best, but no such relaxant agent has been found.

3) Chemical decomposition of the drug in the body would be acceptable provided the breakdown products did not possess neuromuscular blocking power or produce other unwanted effects. Succinyldicholine is, in this respect, very acceptable. Unfortunately, its hydrolysis is speeded only by plasma cholinesterase, which is not always present in adequate concentrations. An agent hydrolyzed by tissue cholinesterase would be preferable.

4) The relaxant should have a relatively short duration of action. For prolonged duration of block repeated or continuous administration could be used. In such a mode of usage cumulative effects should not appear.

5) The action should be highly specific, so that no harmful effects on other systems would occur. It would be advantageous to have a compound that is highly ionized, because such a compound does not cross the blood–brain barrier or the placenta easily and thus would be less likely to cause unwanted side-effects.

6) Block by a competitive agent would probably be reversible by an anticholinesterase. This antagonism results indirectly from the inhibition of ACh hydrolysis. Perhaps drug antagonists with more direct actions could be developed, the antagonist displacing the agent from the receptor site or speeding its breakdown directly.

The Evaluation of New Drugs with Neuromuscular Blocking Properties

In spite of the limitations of current knowledge about the mechanism of action of the neuromuscular blocking drugs, anesthesiologists have used these drugs in the operating room regularly, and with apparent safety. If new drugs are to be accepted for clinical use, they should have characteristics superior to those of existing drugs. Careful screening of prom-

ising compounds must be done first in laboratory animals. Unfortunately, there are many pitfalls in this preliminary process. *d*-Tubocurarine, for example, was thought inappropriate for use in man when administration to dogs showed a marked hypotensive effect. Despite this, it was successfully used clinically a few years later, and in millions of administrations since it has proved to be relatively safe. (One might wonder whether *d*-tubocurarine would ever have reached the pharmaceutical market with the present biological standards and restrictive regulations as set by the Federal Drug Administration.) On the other hand, carefully controlled studies in animals may not show desirable effects that will occur in man. Succinyldicholine, synthesized in the early 1900's, was tested in curarized dogs for a ganglionic blocking effect. Its neuromuscular blocking effect was not recognized until 1951, and only then did it enter into general clinical use. In addition, certain side-effects may occur unpredictably, as was the case with thalidomide. No evaluation can be complete; the final testing must be done in man under standard clinical conditions.

Most new drugs today are the result of chemical synthesis rather than botanical extraction. Thus, purity, solubility in various media, and chemical stability can be accurately described and easily tested. Also, with knowledge of the breakdown products and their possible biological activity, side-effects can be anticipated. The earliest evaluations can thus be made in the chemical laboratory.

The next step would be an evaluation of the neuromuscular blocking properties in simple biological *in vitro* preparations. With microelectrophysiologic techniques it is possible to record the actions of drugs on single or multiple fiber preparations by following the electrical and mechanical events subsequent to drug application. The advantage here is that the investigator can more accurately measure the direct action of the drug, where the action occurs (pre- or postjunctional) and how it takes place (depolarizing, nondepolarizing, desensitizing). In addition, the experimental conditions in such a technique can be strictly controlled so that interaction with other drugs can be evaluated.

Traditionally evaluation of these drugs begins with the determination of the lethal dose for small mammals. The investigator will be mainly interested in the most potent compounds. Although the actual dose of a drug is of little importance, it is likely that those drugs that have the greatest potency will have least side-effects. Ability to interrupt neuromuscular transmission at low concentrations indicates a specificity of action, and it would be expected that such a drug would have less influence on other processes.

In the next step neuromuscular blocking capacity is tested in different species by recording the tension outputs of an indirectly stimulated muscle while exposing the animal to increasing concentrations of the drug. Neuromuscular block can, in our opinion, still be evaluated best by measuring the tension outputs of a peripheral muscle following supramaximal nerve stimulation at various frequencies. Although the combined muscle action potential can be elegantly recorded electrically, limitations are also present with this method.

Ventilation and depth of anesthesia must be accurately controlled, since they may influence the neuromuscular transmission process. These tests should be combined with or followed by studies of the actions of the drug on other organs and organ systems, with specific attention to the heart, liver, kidney and lung. All of these can be affected directly or indirectly, as for example by histamine release or the drug's effect on the autonomic nervous system. Histologic studies of the injection site (vein, artery or muscle) should be done immediately and for a period of time after repeated injections.

The duration of action following single and repeated doses can be understood and predicted only when the distribution and excretion of the drug are understood. Studies with radioactive materials have been extremely useful in this phase of investigation.[27, 28]

If the drug still appears promising and safe after completion of these studies, its use in man can be contemplated. Healthy awake volunteers can now be exposed to minimal effective doses. The effects on the central nervous system in the awake individual can be studied. The effects on the respiratory musculature can be more accurately evaluated in man than in animals by the use of such "stress tests" as

maximal breathing capacity and forced expiratory volume. Lately, techniques by which a drug can be administered to a single isolated extremity have been developed. This can be done intravenously distal to a cuff distended above systolic pressure [30] or intra-arterially by slow infusion. Of course, the possibility of vascular intimal reaction should have been excluded by the animal studies. This technique has the advantage that extremely small doses can be given to the awake, normally-breathing individual while potency and duration of action on indirectly stimulated muscle are recorded. Toxic effects should be less common and more easily recognized in awake man.

Next, the drug could be used clinically, first in healthy individuals who need elective surgery, later in the seriously ill patient. It is now well accepted that this should be done by a limited number of well-informed investigators who regularly report to a central office, so that any untoward effects will be immediately known by all members of the group. Measurement of respiratory variables alone, as was common a few years ago, is no longer acceptable. Of course, as in the animal studies, *p*H, P_{CO_2}, blood pressures and electrocardiogram will be constantly monitored.

The entire drug evaluation process should be marked by deliberation and caution. Any unusual drug manifestation should be thoroughly explored and understood before proceeding to the next level of development. The goal should be the safe introduction of a drug offering marked and distinct advantages over those used previously.

Pancuronium

Of the drugs developed during the last decade, none has achieved clinical recognition as a truly superior neuromuscular relaxant. However, the most interesting of the new drugs, in the opinion of the authors, is pancuronium (Pavulon or NA-97; Organon). Lewis and co-workers (1967),[31] using a steroid nucleus as a naturally-occurring organic compound, made various bis-quaternary aminosteroid salts. The acetate esters gave promise as neuromuscular blocking agents and were studied further. Extensive pharmacologic testing [32] of the most promising of this series, 2β,16β-dipiperidine-5α-androstone-3α, 17β-dial diacetate dimethobromide—pancuronium bromide, was done.

Pancuronium is an odorless white crystalline powder with a melting point of 215C. A 2 per cent aqueous solution (w/v) is completely clear, free of impurities, and stable for as long as a year (stored at 4C). Marketed ampules contain 2 ml saline solution with 2 mg pancuronium per ml. One part of pancuronium bromide dissolves (at 20C) in one part of water or 30 parts of chloroform. Breakdown products are the corresponding 3α and 17β monoacetates. There is no indication of halide combinations.

Extensive pharmacologic testing showed pancuronium to be an effective neuromuscular blocking drug in mice, rats, rabbits, cats, and dogs. Effective doses varied from 0.02 to 0.05 mg/kg. Pancuronium was shown to be a nondepolarizing drug like *d*-tubocurarine, but with fivefold to tenfold greater potency. It is free of histamine-releasing properties and ganglionic blocking activity and does not cause hypotension. It showed no atropine activity. The block was readily reversed by neostigmine, antagonized by succinylcholine, and potentiated by *d*-tubocurarine. Hypothermia reduced the intensity of block. Tetanus was poorly sustained during pancuronium block, and post-tetanic potentiation occurred. There was no evidence of toxicity (when respiration was mantained at adequate levels) in doses 25,000 times the blocking dose in cats. In spite of its steroid structure, there was no evidence that the drug had any endocrine activity. Radioactive isotope studies in rats showed the highest organ content to be in the liver and kidneys. In three hours as much as 25–35 percent of the drug appeared to be excreted unchanged in the urine. Thus, all studies show that pancuronium has many actions similar to those of *d*-tubocurarine.

Experimental studies of amphibian single-fiber nerve–muscle preparations in our laboratory (unpublished) have shown behavior like that of *d*-tubocurarine. The action potential of the nerve terminal was unchanged during endplate perfusion with pancuronium. Transmembrane resting potential of the postjunctional membrane was unchanged. During this time the postjunctional membrane response to

neurotransmitter was rapidly reduced. Pharmacologic studies by Buckett *et al.*[32] showed that pancuronium blocked the muscle response to close arterial injection of acetylcholine: this also indicates a postjunctional effect.

Studies were next done in conscious volunteers, to evaluate onset and duration of action, effect on vital capacity, dose–response relationship, and potency.[33] These studies showed than pancuronium has a rapid onset of action and no adverse cardiovascular effects. Intracutaneous testing in man showed no evidence of histamine release.

Since 1967, pilot studies of the use of pancuronium during clinical surgery and anesthesia have been reported.[34–38] Patients for such studies are carefully selected and intensively monitored during surgery. It has been found that 2 mg of pancuronium are equivalent in neuromuscular blocking power to 10–15 mg of *d*-tubocurarine. Pancuronium seems to have little effect on pulse rate or systolic blood pressure. The block is of the nondepolarizing type. Onset and duration are directly comparable to those resulting from the use of *d*-tubocurarine. Of special note is that pancuronium causes no hypotension even when used during halothane anesthesia. There has been no evidence of bronchospasm even in patients with respiratory disease. Used as a relaxant, pancuronium has been compatible with all anesthetic agents and techniques.[39]

This careful progression of evaluation of pancuronium has resulted in the safe clinical introduction of a useful new drug. Pancuronium is similar to *d*-tubocurarine in clinical safety and effect, but free of histamine release and hypotension. This method of introduction, progressing from careful chemical studies through pharmacologic evaluation of isolated tissues and whole animals to pilot studies in clinical situations, has avoided any serious mishap in the use of this drug. We hope that introduction of new drugs in the future will follow such a controlled and benign course.

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Drugs

METHOXYFLURANE TOXICITY Two patients who received methoxyflurane anesthesia during abdominal operations developed polyuric renal failure within 24 hours after their operations. Both patients died after complicated clinical courses characterized by polyuria, progressive azotemia, and renal failure. Postmortem examination in each case revealed crystals resembling calcium oxalate in the renal tubules. The probable cause of death in these two cases was methoxyflurane nephrotoxicity. The possibility of concurrent toxic effects to the liver was also considered. (*Panner, B. J., and others: Toxicity Following Methoxyflurane Anesthesia. I. Clinical and Pathological Observations in Two Fatal Cases, J.A.M.A. 214: 86 (Oct.) 1970.*)

PANCURONIUM Preliminary clinical trials using pancuronium bromide, a new nondepolarizing muscle relaxant, showed the following advantages: rapid onset of action; no histamine release; little disturbance of blood pressure. Actions of pancuronium were easily reversed by use of a neostigmine–atropine combination. (*Chaouki, K., Viljoen, J. F., and Kellner, G. A.: Pancuronium Bromide—a New Nondepolarizing Muscle Relaxant, Cleveland Clin. Quart. 37: 133 (July) 1970.*)