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THE PHARMACOLOGIC PRINCIPLES OF REGIONAL PAIN RELIEF

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Regional pain relief may be obtained by physical means, such as the application of electric currents to peripheral nerves, the spinal cord, and the brain; the cooling of an extremity; total body cooling; the stimulation of the α, β, and γ of the A fibers by needling (acupuncture); sonic waves; or the application of pressure to nerves. It is more often obtained by the use of drugs that interrupt conduction of impulses when applied directly to peripheral nerves. Drugs that block conduction are of two types: the local anesthetics which provide temporary pain relief and the neurolytic agents that cause destruction of nervous tissues and yield long-lasting relief.

The search for the ideal local anesthetic has continued since Karl Koller introduced local anesthesia into medicine. The search for an ideal neurolytic agent that does not cause neuritis likewise continues. New drugs have been adopted and the older ones discarded, but most of the objections of the old are found with the new. The purpose of this review is to present some of the aspects of clinical pharmacology of local anesthetics and a comparison of the effects of newer drugs with the old. In discussing local anesthetics, emphasis is placed upon the relationship of chemical structure to activity; their presumed mode of action; their absorption, distribution, and mode of elimination; and the relationship of these factors to local and systemic toxicity.

LOCAL VERSUS SYSTEMIC EFFECTS

Local anesthetics behave as such only when placed in direct contact with nervous tissues. The plasma levels during regional block, comparatively speaking, are minute. Undesirable systemic effects occur when local anesthetics gain access to the

vascular system in quantities that cause high plasma levels. At certain plasma levels, depression of the inhibitory neurons of the cortex occurs, causing the excitatory neurons to become more active. Convulsions result. As plasma levels increase, the excitatory neurons are affected also, and depression of the central nervous system results. At certain plasma levels there is also a decrease in the electrophysiologic activity of the conductive mechanism of the heart. Increasing the levels further causes a negative inotropic effect on the myocardial tissues and depression of smooth muscle of the vascular tissues. Cardiac output is decreased and hypotension ensues (1–3). Plasma levels attained when these drugs are properly used do not ordinarily exert these effects.

Generally, local anesthetics are applied to somatic nerves, that is, to bundles of axones, and interrupt transmission of stimuli from a nerve cell to a receptor or to another organ. Local anesthetics interfere with this function by causing a temporary, reversible change in the chemical and physical structure of the neuronal membrane. Although they are ordinarily applied to bundles of axones, they are capable of acting anywhere on a neuron. The end result is the same whether they are applied to a cell body, dendrite, axone, or at a synapse.

MOLECULAR CONFIGURATION OF LOCAL ANESTHETICS

Numerous substances are capable of producing the type of blockade referred to as local anesthesia which affords regional pain relief (1–6). Hundreds of compounds that manifest local anesthetic activity have been investigated. Less than several dozen are used clinically. Some were discarded because they were locally destructive to tissue, others because they were too toxic systemically or locally, and others because they were unsatisfactory from the standpoint of potency or effectiveness duration of action. The majority of the clinically suitable injectable local anesthetics are amines (2). The configuration most consistently associated with the amines is one consisting of an aliphatic chain of two or more carbon atoms, one end of which bears a hydrocarbon nucleus or the other end an amino group. The hydrocarbon nucleus, in the majority of cases, is aromatic although it may be aliphatic or alicyclic. The nitrogen atom is, in most cases, a tertiary amine. Primary amines and secondary amines are unimportant. Thus, an aliphatic chain, sometimes referred to as a pivot, separates a hydrophilic nitrogen atom from a lipophilic carbon residue (1–3).

Local anesthetics possess varying degrees of water and lipid solubility. Lipid solubility is essential for penetration of the drug into the neuronal fiber, since the latter is rich in lipids. The water solubility is essential for the transport of the drug to the neurons by the lymph. A balance between these two solubilities is necessary for local anesthetic activity. A compound of high lipid solubility usually has a correspondingly low water solubility. If the lipid-water partition coefficient has a low numerical value, a compound is usually ineffective because the quantity transported to the fiber or the concentration that penetrates into the neuromembrane is inadequate. The nerve fiber is a lipid-rich metalloprotein surrounded by an aqueous

phase. The hydrocarbon residue becomes oriented into the lipid phase and the amino group into the metalloprotein phase of the fiber surrounding the aqueous medium (1–3).

NON-NITROGENOUS LOCAL ANESTHETICS

Presence of the nitrogen atom on a molecule is not mandatory for local anesthetic activity. Certain hydroxy compounds that do not contain nitrogen are used clinically, for surface anesthesia (2). Aliphatic hydroxy compounds possess feeble local anesthetic activity. Derivatives possessing an aromatic nucleus as part of the structure are more effective than aliphatic compounds. The hydroxy compounds are relatively inefficient compared with the nitrogen-containing derivatives. They were used many years ago but have been supplanted by the more effective nitrogenous derivatives. Within the past several years there has been a revival of interest in their efficacy because they are alleged to be the active ingredients in many over-the-counter preparations. The Food and Drug Administration has various advisory panels that are reviewing the efficacy of this type of ingredient in over-the-counter drugs now on sale in order to determine whether or not the claims made in the labeling can be substantiated.

The hydroxyl group probably plays the counterpart of the amino group in the nitrogen-containing compounds and acts as the hydrophilic pole which orients itself into the aqueous phase of the lipid metalloprotein neuronal membrane. The hydrocarbon is lipophilic and orients itself into the lipid phase. Ionization presumably plays no role in pharmacologic activity. The most serviceable compounds of this type which are used clinically are phenol and benzyl alcohol. Benzyl alcohol provides surface anesthesia on the mucous membranes in concentrations ranging from 3–10%. Salicylalcohol (Saligenin®) and monobromosalicyl alcohol (Bromsalizol®) were once used but are no longer in service. Resorcinol and hexylresorcinol are feeble topical local anesthetics.

The hydroxy compounds are locally irritating and may provoke neurolysis when injected perineurally as well as sloughing of soft tissues. Increasing the number of hydroxyl groups in an alcohol causes a decrease in local anesthetic activity (2). Mephenesin, a propane diol, possesses slight local anesthetic activity. Meprobamate, also a diol, possesses some topical anesthetic activity as does glycerol, a triol. The names of the hydroxy compounds usually end with the suffix "ol" in contradistinction to the nitrogen-containing compounds which are designated by appending the suffix "caine" to a descriptive root (4, 7).

ESTERS AND AMIDES

The hydrocarbon nucleus of the amino compounds is usually derived from a carboxylic acid which is joined to the aliphatic pivot by an ester, amide, or ether linkage. The esters are far more numerous than the amides and were once the most widely used drugs. They have now given way to the amides which appear to be

superior. Procaine, cocaine, and tetracaine are the most well-known and widely used esters. The amides in current use are lidocaine (Xylocaine®), mepivacaine (Carbocaine®), prilocaine (Citanest®), bupivacaine (Marcaine®), and dibucaine (Nupercaine®).

The amide linkage joins the hydrocarbon to the dimethylene chain or pivot. In lidocaine, mepivacaine, prilocaine, bupivacaine, and dibucaine, the pivot replaces a hydrogen atom of the amide of the acid portion of the molecule. The nitrogen atom carries a positive charge which orients itself to a negative charge on the receptor site, while the electrophilic carbon atom bearing the aromatic nucleus carries a negative charge which becomes oriented to the positive charge on the receptor (1, 2, 4). Optimal activity is noted when the distance between the carbon and nitrogen atom averages 7–9 Å. Some compounds have the nitrogen atom incorporated in a heterocyclic nucleus. The nitrogen atoms when arranged in this manner manifest the attributes of secondary or tertiary amines. Such an arrangement is found in cocaine, piperocaine, diperodon (Diothane®), and various other derivatives. Quaternization of the amino group of a potent local anesthetic nullifies its anesthetic activity. This is explained by the fact that quaternary bases penetrate cellular membranes with difficulty (1, 2). Tertiary amines traverse cellular membranes far more readily.

Exceptions to generalizations are always found. Some compounds possessing the aforementioned general structure of a hydrocarbon residue pivot and amino group may be devoid of local anesthetic activity (2). Some compounds which would appear from their structure to be active local anesthetics are not, while others which do not conform to the generalization are active. The molecular structure of atropine, for example, meets the general specifications of a local anesthetic but possesses only a slight degree of local anesthetic activity (2). The chemical structures of certain narcotics, as for example, ethylmorphine (Dionin®), which is a phenanthrene derivative, certain phenothiazines, various antihistamines, and some barbiturates do not conform to this generalization but manifest varying degrees of local anesthetic activity.

In most cases the hydrocarbon residue is aromatic and is derived from the acid that forms the ester or amide. Derivatives of aminobenzoic acid and benzoic acid were, for many years, the most numerous in clinical use. The aromatic nucleus is most often a single benzine ring which is either a simple phenyl radical or possesses side chains at various positions on the ring. However, a double benzine ring or napthoic nucleus may appear in certain local anesthetics (1). The hydrocarbon nucleus may also be derived from quinoline, a double cyclic structure resulting from a fusion of an aromatic nucleus and pyridine. Dibucaine is the most serviceable amide of the quinoline group. Introducing an additional amino group into the aromatic ring usually increases the local anesthetic activity. The aminobenzoates exemplify this.

Substitutions on the amino group on the ring of aminobenzoates increase potency and toxicity. Tetracaine, for example, has a butyl radical replacing one hydrogen atom of the amino group on the aromatic nucleus. The compound, thus, is both a secondary and tertiary amine. In addition, the ethyl radicals on the alcohol portion

of the molecule are shortened to methyl groups. The potency, lipid-water partition coefficient, protein binding capacity, duration of action, and period of latency is increased manyfold over procaine by this alteration in molecular configuration (1, 3).

The amino-acyl amides, of which lidocaine appears to be the most useful, have been studied extensively. Closely allied to these are mepivacaine, prilocaine, bupivacaine, and etidocaine (15). Increasing the molecular weight and substituting into the amino group of the amides likewise increases toxicity, potency, lipid-water partition coefficients, and degree of protein binding. Bupivacaine compared to lidocaine provides longer lasting anesthesia, is more potent and toxic, and manifests a greater degree of protein binding.

Simple esters of aminobenzoic acid series are relatively insoluble (2). Conversion of these esters to amines increases solubility. The conversion of ethyl *p*-aminobenzoate (benzocaine) to the diethyl amino derivative (procaine) confers additional basic properties to the compound and increases its water and lipid solubility and potency. Benzocaine is one of the most widely used topical analgesics and anesthetics in medications sold over the counter. It manifests practically no degree of systemic toxicity due to its low degree of water solubility (0.5g/liter of water).

BASIC NATURE OF LOCAL ANESTHETICS

All local anesthetics in current use are synthetic, except cocaine which is naturally occurring. Local anesthetics, by virtue of the amino nitrogen groups, are bases that form salts with acids. Aqueous solutions of the free base are alkaline (2). The basicity varies with the molecular configuration, which, in turn, influences solubility and degree of ionization. The pH range of aqueous solutions of the bases, in most cases, is between 7.5 and 9. Compounds that have two amino nitrogen atoms, as for example procaine, are more alkaline than those with single amino groups. The bases are less soluble in water than the salts. The base, which is the active form, is liberated in the tissues and penetrates the axonal membrane. Soluble hydroxides, carbonates, and bicarbonates cause the free base to be precipitated from aqueous solutions of salts. The degree of precipitation depends upon the alkalinity of the resultant solution. The bases are viscous liquids or amorphous solids that, though sparingly soluble in water, easily dissolve in lipid substances and various organic solvents (2). The base is necessary for the preparation of most ointments in petrolatum or fatty bases or for the preparation of oil solutions. Salts are sparingly soluble or insoluble in lipids or organic solvents (2). Salts may be used for preparing ointments in water-soluble bases.

Local anesthetics are dispensed as salts because the salts are more stable than the bases and more soluble in water. The interaction of the base and acid is similar to the union of ammonia with an acid to form an ammonium salt. Most salts are crystalline, water-soluble substances. The pH range of aqueous solutions of salts varies between 4 and 7, depending on the base and the acid used to form the salt. Hydrochloric acid is the most commonly used acid although other acids used are lactic, formic, mucic, sulfuric, etc. Selection of the acid is from the standpoint of

solubility, crystal formation, stability, ease in handling the crystals, pH of the resulting aqueous solution, and so on.

The un-ionized base penetrates into the nerve fiber (10, 15). Once it passes into the axone, where the pH is lower than in the membrane, the ionized cation is released and becomes bound to the receptor site. This has been demonstrated by comparing the effect of pH on sheathed and experimentally desheathed nerve fibers. A more effective blockade is obtained in desheathed nerve fibers when solutions of lower pH in which a greater preponderance of ionized base is present than when solutions of higher pH having a more un-ionized base are used (3). Tissue fluids have considerable buffering capacity and, therefore, cause the base to be liberated when solutions of salts and injected into them. The pH of the solution of salts becomes adjusted to that of the tissues (2). Likewise, if an alkaline solution is injected, the pH becomes adjusted to that of the tissues also. The contention that alkalinization of solutions for injection enhances the local anesthetic effect or duration of action is incorrect (2). Enhanced activity does occur when an alkalinized solution is applied topically, because the mucous membranes do not possess the buffering capacity necessary to release the base. Local anesthetics are generally not effective when injected into inflamed areas. Several explanations are offered for this behavior. Absorption from the injection site is increased and the drug is carried away from the tissues because of the hyperemia resulting from the inflammation. Duration of action is thereby shortened (2). The tissues are less alkaline in this area because of the liberation of acid products by the disease process, and the base, which is the effective form of the salt, is not liberated (2).

LIPID SOLUBILITY AND POLAR ASSOCIATION

Both local and general anesthetics are lipid soluble. It was once assumed that local anesthetics followed the Meyer-Overton rule as a result of their lipid solubility and the relative insolubility in water (7, 10, 15). Determining the distribution coefficients of twenty-two local anesthetics of the amino-acyl amide type in oleyl alcohol-water systems indicated that the Meyer-Overton rule, in the true sense, is not valid for local anesthetics (2). Comparisons were made with procaine. No correlation was found between the distribution coefficient and anesthetic potency. Others have since reported similar findings. The Meyer-Overton rule is applicable to inert substances. Inhaled anesthetics are inert when they act to cause anesthesia; local anesthetics are not (2). Local anesthetics have active groups that act by polar association. Isolated nerves are blocked when exposed to ether, chloroform, and other volatile anesthetics. The concentrations of these agents necessary to produce a blockade when applied locally are greater than those that are necessary in the circulating blood to induce general anesthesia. The blockade produced by local anesthetics results from the biochemical changes caused by the drug in the axonal membrane. In the polar association of local anesthetics, the hydrophilic pole becomes oriented into the aqueous phase and the aromatic hydrocarbon residue into the lipid phase as the membrane proper. The indifferent anesthetics, such as ether and chloroform, probably exert their effects by the electronic attraction of forces explained by Van der Waals' concepts (1, 2).

TRANSMISSION OF THE NERVE IMPULSE

Normally a nerve fiber possesses two attributes—the ability to respond to excitation and the ability to conduct. The plasma membrane delineates the cytoplasm of a nerve fiber from the surrounding extracellular fluid. This membrane is composed of a lipid outer and inner phase and a protein layer in between. It is common knowledge that a stimulus applied to a nerve fiber establishes an electrical current, referred to as an action potential, in the plasma membrane in the area of stimulation (3). This action potential is propagated in succession to contiguous areas along the fiber to its point of termination. When the fiber is in the resting state, the plasma membrane is permeable to certain ions, notably potassium and chloride, and impermeable to others, notably ions of sodium, protein, and amino acids (1, 2, 4). The protein ions are, as are those of potassium and sodium, positively charged, since they are derived from the amino group of the amino acids that compose the protein of the nerve. They are unable to diffuse out of the axone into the interstitial fluid. Potassium ions diffuse readily.

As a result of this selective permeability, a difference in ionic concentration develops on either side of the membrane. In a resting fiber, the concentration of potassium ions on the interior of the membrane is greater than on the exterior; the probable ratio is 30 inside to one outside (3). During inactivity, a difference in electrical potential develops between the exterior and the interior of the membrane as a result of this asymmetric ionic distribution. The polarity on the interior of the membrane is negative with reference to the exterior. During the resting phase of a nerve fiber, sodium ions are constantly forced out of the interior, where the concentration is minimal, by a mechanism referred to as the sodium pump.

Energy is necessary to operate the sodium pump, since ions are being extruded outward against a gradient. This energy is provided by the oxidative metabolism of adenosine triphosphate. The potential difference which develops between the two sides of the membrane ranges between 70 to 90 mV. The initiation and transmission of impulses along a nerve fiber are associated with alterations in this membrane potential. Changes in membrane potential are characterized by removal of the polarity, which in turn causes depolarization of the adjacent normal membrane. Thus, a wave of transient depolarization or activity is present along the nerve fiber. When a stimulus is applied, the permeability of the membrane in the area of excitation is altered and the membrane becomes more permeable to sodium. Sodium ions are then able to migrate inward.

Local anesthetics interrupt the propagation of the impulse and prevent its passage at the site of application on the axone. The blockade of a nerve fiber may be accomplished in a number of ways; (*a*) by alteration of the resting potential of the membrane, (*b*) by alteration of the threshold potential or "firing" level, (*c*) by prolonging the rate of depolarization, or (*e*) by prolonging the rate of repolarization. Most data reveal that local anesthetics alter neither the resting potential nor the threshold potential. Measurements of rate of depolarization and rate of repolarization reveal that there is a marked delay in rate of depolarization (2–4). Rate of repolarization is affected to a minimal degree. Thus, the blockade is due to a delay in the rate of depolarization. This phenomenon is often believed to result from some

mechanism which stabilizes the membrane so that changes in permeability to sodium and potassium ions do not occur.

Considerable controversy has existed over the years concerning the mechanism of action of local anesthetics. At one time acetylcholine was believed to be the transmitter substance which caused the membrane to stabilize and inhibit the enlargement of pores that permitted passage of sodium ion inwards. More recent studies implicate the competition of the local anesthetic with calcium ions at the binding site. Calcium ions are believed to play a role in facilitating the migration of sodium ions across the membrane. Thus, development of the action potential is delayed as a result of the decreased concentration of calcium ions and does not attain the "firing" level for complete depolarization. The amplitude of voltage necessary for conduction is not attained and failure of conduction results (3, 6, 7).

IMPORTANCE OF THE MYELIN SHEATH

The myelin sheath which surrounds certain nerve fibers is enclosed by a histologically distinguishable membrane called the neurolemma. The sheath is interrupted at intervals of 1 mm or less into sausage-like segments known to all as the nodes of Ranvier (1–3). At these points myelin is absent and the sheath dips down and makes contact with the nerve fiber. The myelin acts as an insulator for the nerve fiber and increases the efficiency of conduction by conserving energy. Local anesthetics do not penetrate the myelin sheath and can, therefore, pass into the nerve fibers only at the nodes of Ranvier. Seven or eight nodes must be blocked to obtain a complete blockade of a fiber. Local anesthetics penetrate unmyelinated fibers. Anesthesia is established sooner and with less concentrated solutions in such uninsulated fibers.

INFLUENCE OF FIBER SIZE ON THE BLOCKADE

A difference in susceptibility of various types of fibers has been noted both clinically and experimentally. Autonomic and sensory fibers are affected before motor fibers. It is well known now that this behavior is due to fiber size rather than inherent chemical differences of the protoplasm of the axone. The time required for induction of a blockade by a particular drug varies inversely with the concentration of a drug and directly with the square of the radius of the nerve (1–3). Smaller fibers have a greater surface per unit volume than the larger and, therefore, are blocked first. The small, thinly myelinated or the nonmyelinated autonomic fibers are most easily blocked by local anesthetics. Sensory fibers as a rule vary from 1 to 5 μm in diameter. Such fibers conduct temperature and pain impulses and appear to be more resistant to local anesthetics than autonomic fibers. They are more sensitive, however, to local anesthetics than the larger sensory fibers whose diameters vary from 5 to 15 μm. These larger fibers transmit tactile and pressure sensations and vibratory sense. The large myelinated somatic motor fibers are more resistant than the sensory, which are as a rule smaller. A local anesthetic applied in a concentration sufficient to block all fibers in a mixed nerve produces a blockade in this sequence:

the sympathetic and parasympathetic fibers are inactivated first, next the fibers that transmit temperature. The sensation of cold is obtunded before the sensation of warmth. Next to be blocked are somatic motor fibers carrying pin-prick, pain, touch, pressure sense, vibratory sense, and proprioceptive impulses. The recovery of function appears to occur in the reverse order.

EFFECT ON METABOLISM

Normally, there is an increased oxygen uptake by a nerve during transmission of an impulse. This increased uptake appears to be prevented by local anesthetics. The findings concerning the relationship between the local anesthetic effect and the metabolic rate of a nerve fiber are not consistent (1, 2). Depolarization of a nerve with potassium ions, for instance, blocks conduction but causes an increase in oxygen uptake. Decreased oxygen consumption without impairment of conduction has been observed when nonanesthetic substances are applied to a nerve. Cocaine reduces the oxygen consumption when applied in concentrations that block conduction. Chlorobutanol (Chloretone®), on the other hand, has the opposite effect (1, 2).

PENETRATION INTO THE NERVE

The drug requires time for diffusion into the nerve fiber. Relatively speaking, passage into a membrane is quite rapid because of the high external gradient. The rate of entry varies with the chemical nature of the drug, the concentration, and the type and size of the fiber. Thus, a latent period is noted from the moment the drug is applied until a blockade is fully established. After perineural application, as the drug is carried away by the lymph, the concentration gradually falls. When the perineural concentration falls below the intraneural level, the drug begins to pass from the fiber into the lymph. Conduction is reestablished as soon as the concentration falls below the threshold value often referred to as the Cm or minimum effective concentration. The threshold value differs for each drug under a uniform set of experimental conditions. In other words, the blockade is as complete in fibers exposed to a greater than threshold concentration as it is in those exposed to the minimal effective concentration. The blockade continues until the concentration falls below the threshold level and the membrane is restored to its active state. Exceeding the threshold concentration does not increase the intensity of the block, since it is all or none. It may, however, prolong the block somewhat because more time is required to carry the additional quantity from the perineural area. Increase in duration is not proportional to the increase in total quantity applied. For example, doubling the quantity applied does not double the duration of the blockade (2, 3).

BINDING

The passage of the drug into the fiber and its union with receptors in the axonal membrane are often referred to as "fixing" by clinicians. The term is unscientific and

should be discarded because it implies that some irreversible chemical union or binding occurs. This term most likely arose because longer-lasting drugs have a slow onset of action or latent period. The interaction, which occurs at the molecular level between protoplasm and local anesthetics, is not clearly understood. The attachment to receptors is reversible. However, the effects of binding to proteins cannot be excluded (8). It has been proposed that certain agents possess chemical affinity for the nerve tissue components which tends to hold the long-acting drugs within the nerve fiber. Correlation between rate of penetration and anesthetic activity is not uniform. Procaine, lidocaine, and propoxycaine have equal rates of penetration but manifest different activity, potency, and duration when compared on the basis of molar concentration (1, 2). Likewise, there is no strict correlation between speed of penetration and duration of action.

The outward diffusion of a local anesthetic from the fiber occurs gradually, the speed, therefore, depending upon the drug, binding power, diffusibility, electric changes in the pores, and so on. Recovery occurs when the intraneural concentration of a drug falls below the threshold level or Cm. Some drug still remains in the fiber even though conduction has been fully restored. The blockade may be reestablished by adding the difference between the amount present and the threshold concentration. If the reapplication is made several hours after recovery, the original threshold concentration is necessary. This is presumptive evidence that none of the drug is present in the fiber at this time (1, 2).

LATENT PERIOD

It has been mentioned that a latent period of several minutes or more elapses from the moment the drug is applied until a blockade is established. Periods of latency increase progressively as the duration of action of a particular drug increases. Thus, dibucaine has a longer latent period than tetracaine, which in turn has a longer latent period than procaine. Lidocaine has a shorter latent period than procaine yet their duration of actions is similar (1, 2). Data concerning time of onset obtained in vitro using isolated nerve preparations differ from those obtained in vivo. In vivo, a number of variable factors are introduced which explain this discrepancy. Clinically the drug is injected into the tissues surrounding the nerve, while experimentally the drug is applied directly to the fibers. Time, concentration, and dosage are fixed in vitro. In vivo, the drug becomes diluted with the perineural tissue fluid. The greater the distance between the point of injection and the nerve, the greater the dilution (7). Then, in addition, some of the drug is carried away by the blood and lymph and does not reach the nerve; therefore, variable results are to be expected in studies in the intact animal or in man, since all conditions are not fixed. In vivo, the concentration of the injected solution must be greater than the threshold concentration necessary to establish an effective block. When isolated nerve preparations are used, data are more precise and present a more realistic picture in regard to the time-dose relationship. The latent period is quite apparent when inducing spinal block (2). When procaine is used, the blockade is established within 1–2 min. When tetracaine is used, sensory changes are apparent within 2–3 min. Hypalgesia appears

first, then diminished ability to perceive light touch, pain, and temperature. Ability to perceive pressure and vibratory sense lingers for 5 min or more. Loss of motor function is, in many cases, complete between 5–10 min after application.

The clinical importance of the latent period cannot be emphasized too strongly. Failure to allow sufficient time for establishment of a block conveys the erroneous impression that the dose employed was inadequate and leads to application of unnecessary subsequent doses and uses of quantities that may be lethal. Disastrous results have occurred after the use of excessive quantities of tetracaine and cocaine topically as a result of this misunderstanding (2).

OVERLAPPING OF ACTIONS

Overlapping of actions among drugs is a common finding in pharmacology. Local anesthetics may possess varying degrees of antihistaminic, anticholinergic, myoneural-blocking, narcotic, and vasopressor activity (2). On the other hand, many antihistamines possess varying degrees of local anesthetic, anticholinergic, and central nervous system depressant activity. The local anesthetic activity of antihistaminic drugs has been demonstrated in animals and utilized to a limited extent in man. Tripelennamine (Pyribenzamine®), for example, has been used for topical anesthesia of the mucous membranes of the pharynx, larynx, trachea, and urethra with some degree of success. Considerable local irritation has been reported by some workers. Its virtue as a local anesthetic is in no way comparable to its value as an antihistamine. Anticholinergic drugs also exhibit some local anesthetic as well as antihistaminic activity. Atropine, for example, possesses a feeble local anesthetic action and some antihistaminic activity. The antihistaminic activity, however, is of a low degree and is of little usefulness clinically. It has been estimated to be in the order of one hundredth that of the common antihistamines, such as diphenhydramine (Benadryl®). Procaine manifests some degree of antihistaminic and anticholinergic activity. The anticholinergic activity is less pronounced than the antihistaminic. Usually, when a drug possesses a multitude of actions, one action predominates over all others. This predominant action determines for what purpose a drug will be used. Local anesthetic activity has been ascribed to epinephrine, ephedrine, meperidine, and a host of other substances. Their potency and clinical usefulness in this regard are limited (2).

RATE OF ABSORPTION

Regardless of the site of application of a local anesthetic, ultimately all of it passes into the bloodstream and establishes a plasma level (1, 2, 9–11). The rate of absorption depends to a large extent upon the blood supply to the tissue. Therefore, the absorption, distribution, and elimination of local anesthetics are quite important. Adriani & Campbell (12) studied plasma levels after infiltration and topical application to mucous and cutaneous surfaces and compared them with those after intravenous injection. Their studies were centered about procaine, tetracaine, cocaine, and benzocaine.

Striking differences
intravenous injection of a particular dose over a period of 1 min and those after the infusion of the same quantity slowly over a 20-min period. Rapid injection results in a marked upsweep of a curve of drug concentration in the blood and a peak level within 2 min. The same quantity infused slowly gives barely detectable blood levels. The basic contours of the drug level curves are the same with use of procaine, tetracaine, and cocaine. The rapid intravenous injection of 6 mg of tetracaine per kilogram of body weight in dogs produced respiratory paralysis. The slow infusion of the same amount causes no significant response. The slow infusion allows time for dilution and storage in various tissues and perhaps hydrolysis or elimination of a portion of the drug. The susceptible cells, therefore, are not suddenly perfused with the high concentration which confronts them after rapid infusion.

Studies on the tissue distribution of local anesthetics in animals indicate that a rapid uptake by all tissues of the body occurs (1, 2, 13, 14). Differences of relative distribution in various tissues do exist between different agents, however. Lidocaine has a greater affinity for fat than procaine. More lidocaine is found in the liver than procaine. A greater amount of prilocaine is found in the lung of rats than lidocaine. Mepivacaine shows a similar distribution pattern to that of lidocaine. A rapid accumulation occurs in liver, kidney, salivary glands, and brain (3, 13).

Curves of drug levels in the blood after topical application simulate those of rapid intravenous injection. Peaks are lower, take longer time to develop, and do not rise as abruptly. However, within 4–6 min the peak is one third to one half that obtained after rapid intravenous injection when an equivalent dose is applied to the pyriform fossae (12).

Plasma erythrocyte distribution (PE) in man reveals higher PE ratios for lidocaine than prilocaine. Values for mepivacaine and lidocaine are similar. There is evidence that there is a correlation between protein binding capacity of the agents and the PE ratio. Bupivacaine shows the highest PE ratio as well as highest protein binding capacity of the amides studied. The muscle mass takes up the greater portion of a local anesthetic, but this is due to redistribution and the fact that the weight of the muscle mass is greater than that of other tissues and not to an affinity of muscle for local anesthetics (3, 13, 15). Thus, a slow infusion continued indefinitely may ultimately cause the plasma level to rise to deleterious levels, with subsequent appearance of symptoms of systemic toxicity.

CAUSE OF SYSTEMIC REACTIONS

Many reactions that occur after the topical use of local anesthetics are caused by the use of excessive quantities at one time (2, 12). Tetracaine levels in the blood are lower when a given dose of the drug is applied to the pyriform fossae in three fractions at 3-min intervals instead of a single dose at one time. Peak levels are approximately one third those obtained after single application. They rise and fall with each application. The contours of the drug level curves are alike for both cocaine and tetracaine when divided doses are used. The levels, even though lower than those resulting with intravenous administration, are measurable and greater

than those obtained after infiltration or slow infusion. Thus, it is obvious that blood levels are a function of the total dose and not the concentration of the solution. Plasma levels are similar when a particular total milligram dose of tetracaine is applied over identical areas as a 2 or 4% solution. The same is found to be the case when cocaine was applied as a 4 and 10% solution. The blood levels after infiltration reach a peak of 5–10 min after completion of the injection. With use of comparable doses, the peak level of tetracaine after topical application to the pyriform fossae was 35 μg, while after infiltration the peak was 2 μg. The peak level when slow infusion is used is 3 μg; with rapid infusion 80 μg (12). Thus, it is apparent that application of a local anesthetic to a mucous membrane causes blood levels that simulate those obtained after rapid intravenous injection. Untoward reactions occur far more frequently after topical use than after injection. The pattern of absorption presented by these data strongly suggests that the high plasma levels after topical use are directly responsible for reactions (19).

The rate of absorption varies with the mucous surface. Absorption is more rapid from the trachea than from the pharynx. Instillation of either cocaine or tetracaine into the trachea results in higher peak levels, a steeper slope, and a more rapid buildup than application to the pharynx. Higher levels and steeper curves are obtained when animals were placed in the upright position than prone (2). The solution obviously gravitates into the alveoli, from which it is more rapidly absorbed. Cocaine solutions nebulized into particles of 3 μg or less diameter pass into the alveoli and are rapidly absorbed when inhaled (12).

The absorption from the epithelium of the respiratory tract seems to differ from that of the mucous membranes elsewhere. No significant blood drug levels are noted after instilling cocaine into the stomach of dogs. Adriani & Campbell (12) likewise obtained no detectable drug levels after instilling tetracaine and cocaine into the stomach or esophagus. The most plausible explanation for this type of behavior is the fact that the acid in the stomach forms the salt of the local anesthetic which is highly ionized and poorly absorbed from the gastric mucosa. Massive doses of local anesthetics given orally have been absorbed and have caused death (14).

No blood drug levels can be demonstrated after instillation of either tetracaine or cocaine into the bladder (3). This is a reasonable finding since few drugs pass through the mucous surface of the bladder. Besides, the contents of the bladder are acid. If alkalinized, some absorption of some drugs occurs. Data obtained after urethral instillation are inconclusive. However, reactions are common after urethral instillation in human beings. How many of these reactions are due to absorption from mucosa traumatized by instruments is difficult to say, since this appears as a frequent complicating factor (2, 12).

ABSORPTION FROM THE SKIN

Salts of local anesthetics are not absorbed from the unbroken skin (16–18). They do pass into the blood if the skin is abraded or damaged in other ways. Blood levels are measurable when aqueous solutions of the salts of tetracaine, cocaine, procaine, and ointments of cocaine, tetracaine, and benzocaine in a water-soluble base are

applied to the skin over the abdomen, which has been freshly abraded. Peak concentrations of a magnitude obtained after infiltration resulted in 6–10 min (12). Percutaneous absorption of local anesthetics does not occur when the salts are applied but does occur if the base is used. The epithelial barriers permit the passage of unionized, lipid-soluble substances but not those that are ionized. The degree of absorption is related to the lipid-water distribution coefficient. The concentration required for effectiveness is greater than would ordinarily be required on the mucous membranes (16–18).

RETARDING ABSORPTION BY USE OF VASOCONSTRICTORS

Vasoconstrictors are added to solutions of local anesthetics to retard absorption in order to prolong the blockade, decrease the rate of absorption, and reduce systemic toxicity. Their use in highly vascular areas, as for example the scalp, gums, and face is mandatory. The vasoconstrictor also keeps plasma levels minimal and thereby reduces systemic toxicity (1–3).

A host of vasoconstrictor substances has been suggested for the purpose, the majority of which are aromatic amines closely allied to epinephrine (2). It is surprising that, among all these, epinephrine is the most effective. Ephedrine, phenylephrine, nordefrin (Cobefrin®), and other drugs are comparatively less potent and must be used in far greater concentrations than epinephrine. Even then, they are not as effective. Norepinephrine, although as effective as epinephrine, has caused sloughs and for this reason is not used. Anesthesia in intracutaneous wheals using 0.5% procaine with 1:10,000 epinephrine persists for 2 hr compared with the control. Ephedrine (1:100) in 0.5% procaine produced anesthesia for approximately 20 min. This is slightly better than a control using procaine alone. Vasoconstrictors are less effective subcutaneously than intracutaneously because the blood supply is less abundant in intracutaneous structures. The ischemia is, therefore, more transient. Intrathecally, the duration of anesthesia using procaine or lidocaine is increased 60% or more when epinephrine (1.0 mg) (2) is combined with the spinal anesthetic drug. Blood levels of local anesthetics are difficult to measure after intrathecal instillation for spinal anesthesia since only traces appear (2). The circulating blood level is less after epinephrine is combined with the drug, indicating that vasoconstriction retards its passage from the intrathecal space into the blood. The concentration in cerebrospinal fluid persists for a longer period of time when epinephrine is combined with the drug than it does in the control. Interestingly, the systemic effects of the vasopressor are insignificant. Presumably, the quantity of epinephrine absorbed per unit of time is relatively small and undergoes rapid destruction or elimination.

Blood levels after infiltration or perineural injection are less when epinephrine is combined with the agent than they are in the control. On the mucous membranes, however, the situation is different. Neither epinephrine nor norepinephrine remarkably retards absorption of topical anesthetics when mixed with the agent or when sprayed on the surface prior to application of the anesthetic (19, 20). Blood levels do not differ significantly from the control. Clinicians use far more epinephrine for

infiltration than is necessary. Effective vasoconstriction is obtained using a dilution of 1:100,000–1:200,000. Absorption of the vasoconstrictor causes pallor, tachycardia, hypertension, and other systemic disturbances. These are mistaken for a "reaction" but such reactions are not difficult to distinguish from the symptoms of overdosage or intolerance to local anesthetics. However, vasoconstrictors never cause convulsions, coma, or respiratory or cardiac failure.

All local anesthetics with the exception of cocaine cause vasodilatation when injected subcutaneously or perineurally. This comes about by a direct action on smooth muscle and by denervation of the blood vessels that supply the area. Cocaine possesses a sympathomimetic action and causes vasoconstriction. The sympathomimetic effects are due to inhibition of binding of norepinephrine at receptor sites and reuptake by monamine oxidase (1). Butethamine (Monocaine®) was alleged to possess some degree of vasoconstrictor activity but not to the degree necessary for clinical effectiveness. Mepivacaine is alleged to possess some vasoconstrictor activity but clear-cut evidence that this is so is lacking (2).

The behavior of cocaine topically on the mucous membranes is interesting. Otolaryngologists use the drug to "shrink" the mucous membranes. The vasoconstrictor effect apparently does not act to retard absorption and reduce blood levels. Ten and 4% cocaine in quantities containing equivalent weights applied over the same surface areas result in similar blood levels. Many clinicians erroneously believe that a 10% solution causes more intense vasoconstriction and retards the absorption to a greater extent, thereby decreasing toxicity (12, 19).

BIOTRANSFORMATION

The importance of the metabolic fate of local anesthetics is obvious. The more slowly and incompletely a drug is detoxified or eliminated, the greater its systemic toxicity. The metabolism of local anesthetics is related to their chemical configuration. Most of the information on detoxification of local anesthetics is from animal studies. Some data are available from studies on man.

The ester type is hydrolyzed by plasma esterases and to a certain extent by the liver. Unmetabolized portions are eliminated unchanged into the urine by the kidney. Detoxification of the amide type is accomplished almost entirely by the liver. Not all esters are metabolized, however. Cocaine is an ester; yet it is eliminated almost unchanged into the urine. Breakdown of some drugs occurs in the kidney. Prilocaine is partially detoxified by kidney slices in vitro (2, 3).

The ester type of compounds is hydrolyzed to its respective acid and amino alcohol (2, 3). Hydrolysis may also be accelerated by enzymes in the liver, in other tissues, and in plasma. The hydrolysis of procaine, for example, is catalyzed by a group of several enzymes, which was once referred to as procaine esterase, into *p*-aminobenzoic acid with diethylaminoethanol. Procaine esterase was shown to be identical with the pseudocholinesterases. Serum pseudocholinesterases are not specific for procaine, since they aid in the hydrolysis of acetylcholine, tetracaine, chlorprocaine, methylcholine, succinylcholine, and so on. Physostigmine retards the hydrolysis of procaine in vitro. In the intact animal, however, anticholinesterases

appear to exert little or no effect on the rate of hydrolysis of local anesthetics (2). The rate of detoxification of a drug depends upon the metabolic state of the individual who receives the drug. Whether or not variations in activity of the enzyme play a role has not been established with certainty. Plasma pseudocholinesterase levels are decreased in certain disease states. Low levels are found in hepatic dysfunction, in toxic goiters, severe anemias, and diseases caused by inadequate nutrition. Detoxification of local anesthetics may be retarded, and symptoms of systemic toxicity may appear in this type of patient (2, 3).

The *p*-aminobenzoic acid resulting from the breakdown of procaine may be conjugated in the liver with glycine to aminohippuric acid, methylated to *p*-ethyl aminobenzoic acid, or eliminated unchanged into the urine. The three reactions may occur simultaneously. The conjugated products are also eliminated into the urine (2, 3). Approximately 25% of the alcohol (diethylaminoethanol) is excreted unchanged into the urine. Presumably, the remainder is metabolized in the body. The hydrolysis of procaine occurs rapidly. In the cat, a fatal intravenous dose is hydrolyzed within 20 min. The toxic dose in man is not known. Human plasma hydrolyzes the ester type of compound twenty to forty times faster than plasma of laboratory animals. Halogenation of procaine increases the facility for hydrolysis. Procaine is hydrolyzed at one third the rate of 2-chloroprocaine. This increased facility for hydrolysis is also seen with 2-bromoprocaine, 3,5-dichloroprocaine, and 2-chlorthiocaine. Rapid hydrolysis confers upon a drug the clinical advantage of low systemic toxicity. The majority of benzoic and aminobenzoic acid esters are hydrolyzed partially or completely in the body. Tetracaine is hydrolyzed at one fifth the rate of procaine (2, 3).

The amides are detoxified by amidases and oxidases. Lidocaine is very stable and resists hydrolysis in vitro. In vivo, however, it undergoes rapid metabolic change. The first step appears to be oxidative deethylation to monoethylglycinexylidide and acetaldehyde (22, 26). This is hydrolyzed to xylidine and monoethyl glycine. Less than 10% appears in the urine unchanged. Mepivacaine appears to undergo N-demethylation and some hydroxylation (3, 13). Prilocaine appears to be converted to *o*-toluidine and L-N-*n*-propylamine. This occurs in the liver, although the kidney plays a role. Bupivacaine is N-dealkylated to form pipecoloxylidide (11, 22, 26). The metabolites of lidocaine appear to have some convulsive activity and may cause systemic reactions should cumulative effects occur (22, 26). The metabolites of prilocaine, particularly the *o*-toluidine causes methemoglobinemia (3). Undetoxified portions of local anesthetics are excreted into the urine as are most of the metabolites.

Wide species differences are often noted. In dogs and in man, for example, cocaine is excreted unchanged into the urine, while rabbits detoxify the drug completely by hydrolysis to ecgonine and benzoic acid (2).

DESTRUCTION IN SITU

Little is known about the destruction of the drugs in the nerve and perineural tissues. The general behavior of the drug in the nerve fiber strongly suggests that little or no destruction occurs. Chloroprocaine, for example, is more potent than procaine

in regard to its local blocking effect but is hydrolyzed in one third the time in the plasma; yet the block it produces lasts more than 1 hr. The hydrolysis in plasma is complete within 5 min (11).

Drugs that are destroyed or eliminated slowly are, as a rule, more toxic systemically than those that are easily eliminated or detoxified (2, 3). Practically speaking, the safety of most local anesthetics depends upon the balance between the absorption of the drug into the bloodstream and its removal from the blood by destruction, storage, or excretion, into the urine (2).

TOXICITY

Although potency and duration of action are important characteristics, the worthiness of a local anesthetic drug is decided by its toxicity. Toxicity may be either local to the tissues or systemic. Irrespective of the manner by which a drug is administered, whether it be topically, perineurally, or intrathecally, it ultimately passes into the vascular system and then is eliminated. The attainment of a certain blood level, the value of which varies with the drug and the susceptibility of the individual, causes a train of symptoms referred to as a reaction. The type of symptoms that develop, their severity, and their duration depend upon the blood level, the rapidity by which it is attained, and the amount of drug that perfuses the susceptible organs. The organ systems that manifest the most obvious susceptibility are the central nervous system and the cardiovascular system (2, 3, 21, 25).

The more toxic the drug the lower the blood level necessary to precipitate an untoward response. It has been emphasized that blood level depends largely upon the rate of absorption of a drug from the injection site and the rate of clearance from the bloodstream. These two factors are of utmost importance in establishing precautionary measures and in selecting proper drugs for clinical use. The maintenance of a low plasma level depends upon the ease with which destruction of the drug occurs, the rate of clearance by the kidney or detoxification by the liver, and the capability of storage in the tissues (2, 23). After infiltration or nerve-blocking techniques, minute amounts of a local anesthetic drug may be detected in the blood for some time after the injection is completed. A perceptible degree of systemic general analgesia may be detected (2).

Potency and toxicity of local anesthetic drugs do not necessarily parallel each other. A drug may, for example, be ten times more potent than the standard of comparison and fifteen times more toxic on a weight-for-weight basis. On the other hand, the drug could be ten times more potent but only half as toxic. Such a drug, if one could be found, would have a definite clinical advantage over the standard. The potency and toxicity of a drug under study are compared with a standard. Procaine is now used as the standard of comparison for anesthetics intended for infiltration, perineural, and other types of blocking. The effectiveness of drugs intended for surface anesthesia is compared with cocaine, since procaine possesses a feeble topical effect. The principal factors in determining the toxicity of local anesthetic drugs are (*a*) the rate of inactivation, (*b*) the rate of diffusion into the tissues, (*c*) the rate of absorption from the site of injection, (*d*) the inherent toxicity of the drug, and (*e*) the susceptibility of the individual to the drug (1, 3).

METHODS OF TESTING

It is virtually impossible to correlate the vast accumulation of data from various laboratories concerning potency and toxicity because of the diversity of the experimental methods employed to obtain the data. Standardized, uniform methods of testing are still nonexistent. Each investigator has his own method or routine for evaluating a new drug. Some authors emphasize the minimal effective concentrations when investigating a drug; others determine the duration of action; others the period of latency. The anesthetic index is used by some in evaluation of a new drug in the laboratory. The anesthetic index takes into consideration toxicity and potency in relationship to a standard of comparison. The index for a particular drug is meaningless unless the method employed and conditions used to determine the index, such as species of animals, status of the animal, environmental room temperature, concentration time, and so on, are stated. Comparisons of indices are valid only when data concerning each drug are obtained under identical experimental conditions. Expressions of potency and anesthetic indices disregard duration of action and period of latency, both of which are important considerations. The more potent drugs not only are longer lasting but also are characterized by slower onset and slower recovery.

The inherent toxicity of a drug is determined by the rapid intravenous administration into several species of animals. The rate of inactivation and diffusion from the site of injection have little influence on the results and, therefore, do not enter to any degree into intravenous studies. Comparisons must be made under identical circumstances to be valid. The rate of injection, concentration of the solution, age, size, and state of nutrition of the animal, body temperature, environmental temperature, temperature of the solution, and so on, must be identical (1–3). Data on toxicity obtained from intravenous administration studies differ from those obtained from subcutaneous or intraperitoneal injection because the rate of absorption and diffusion then enters into the picture. Subcutaneous and intraperitoneal injections are used to study the influence of diffusion and the rate of inactivation. Cumulative effects are studied by observing the responses after intermittent, subcutaneous, or intravenous injection. Delayed and chronic toxicity are studied by repeatedly injecting the drug into animals over a period of weeks or even months. Obviously, information on toxicity of a new local anesthetic can be obtained only from studies in the laboratory of several species of animals. Then cautious clinical use must be resorted to before the drug can be released. Confirmation of the safety and usefulness is obtained only after extensive clinical experience. It is not uncommon for a drug that appears to be ideal in the laboratory to be disappointingly unsuitable clinically.

Clinicians continually seek tables of limits of dosage. It is virtually impossible to provide such information, since so many variable factors are involved in clinical usage of a drug. Qualitatively, species responses are quite similar; quantitatively, they may be quite different. Then, too, variations occur within a species. One variable that cannot be assessed in the clinical use of a local anesthetic is the degree to which tolerance is altered by the pathophysiologic effects of the patient's disease.

PRECAUTIONARY MEASURES

Ordinarily, during various forms of regional anesthesia, blood levels are less than the toxic level for a particular drug and no systemic manifestations develop. Precautionary measures followed to avoid systemic intoxication are (*a*) limitation of the total quantity of the drug used, (*b*) use of the minimum quantity of the most dilute effective solution, (*c*) retardation of absorption by adding vasoconstrictors, and (*d*) avoidance of inadvertent intravenous injection. When the plasma concentration exceeds the tolerable level, symptoms of overdosage appear. These appear to be directed to either the nervous system or the vascular system (24). Both may be involved simultaneously. Other organ systems may be involved, but the symptoms in these two systems mask effects in other organs. Clinicians refer to reactions as the *vascular type* or the *central nervous system type.* If the drug is one of great potency or if the overdosage is massive, however, both systems may be involved simultaneously. As a rule, when systemic intoxication occurs clinically, the central nervous system is involved more frequently than the vascular system. Central excitation develops when the blood level rises abruptly, as might occur after an inadvertent intravenous administration. The more gradual buildup to the intolerable level usually involves absorption of greater quantities of drug and is characterized by the vascular type of response.

Literature Cited

1. deJong, R. H. 1970. *Physiology and Pharmacology of Local Anesthesia.* Springfield, Ill.: Thomas
2. Adriani, J. 1960. The clinical pharmacology of local anesthetics. *Clin. Pharmacol. Ther.* 1:645–37
3. Corvino, B. G. 1973. Local anesthesia. *N. Engl. J. Med.* 286(18):975–83, 1035–42
4. Corvino, B. G. 1971. Comparative clinical pharmacology of local anesthetic agents. *Anesthesiology* 35:158–167
5. Ritchie, J. M., Ritchie, B., Greengard, P. 1965. The active structure of local anesthetics. *J. Pharmacol. Exp. Ther.* 150:152–59
6. Aceves, J., Machne, X. 1963. The action of calcium and of local anesthetics on nerve cells and their interaction during excitation. *J. Pharmacol. Exp. Ther.* 140:138–48
7. Blaustein, N. P., Goldman, D. E. 1966. Comparative action of calcium and procaine on lobster axone: A study of the mechanism of certain local anesthetics. *J. Gen. Physiol.* 49:1043–63
8. Reynolds, F., Taylor, G. 1970. Maternal and neonatal blood concentrations of bupivacaine: A comparison with lignocaine during continuous extradural analgesia. *Anaethesia* 25:14–23
9. Mazze, R. I., Dunbar, R. W. 1966. Plasma lidocaine concentrations after caudal, lumbar epidural, axillary block, and intravenous regional anesthesia. *Anesthesiology* 27:574–79
10. Moore, D. C., Bridenbaugh, L. D. 1970. Bupivacaine: A review of 2077 cases. *J. Am. Med. Assoc.* 214:713–18
11. Foldes, F. F., Davidson, G. M., Duncalf, D. 1965. The intravenous toxicity of local anesthetic agents in man. *Clin. Pharmacol. Ther.* 6:328–35
12. Adriani, J., Campbell, D. 1956. Fatalities following topical application of local anesthetics to mucous membranes. *J. Am. Med. Assoc.* 162:1527–38
13. Katz, J. 1968. The distribution of C-labelled lidocaine injected intravenously in the rat. *Anesthesiology* 29:249–53
14. Boyes, R. N., Adams, H. J., Duce, B. R. 1970. Oral absorption and dispostion kinetic of lidocaine hydrochloride in dogs. *J. Pharmacol. Exp. Ther.* 174:1–8
15. Reynolds, F. 1971. Metabolism and excretion of bupivacaine in man: a comparison with mepivacaine. *Br. J. Anaesth.* 43:33–37
16. Dalili, H., Adriani, J. 1971. Efficacy of local anesthetics in blocking the sensations of itch and pain in normal and

sunburned skin. *Clin. Pharmacol. Ther.* 12:913–19
17. Adriani, J., Dalili, H. 1971. Penetration of local anesthetics through epithelial barriers. *Anesth. Analg. Cleveland* 50: 834–41
18. Monash, S. 1957. Topical anesthesia of the unbroken skin. *Arch. Dermatol.* 76:752–56
19. Adriani, J., Zepernick, R., Arens, J. 1964. The comparative potency and effectiveness of topical anesthetics in man. *Clin. Pharmacol. Ther.* 5:49–62
20. Adriani, J., Zepernick, R. 1964. Clinical effectiveness of drugs used for topical anesthesia. *J. Am. Med. Assoc.* 188: 711–16
21. Strong, J. M., Mayfield, D. E., Atkinson, A. J., Burris, B. C., Raymon, F., Webster, L. T. 1975. Pharmacological activity, metabolism and pharmacokinetics of glycinexylidide. *Clin. Pharmacol. Ther.* 17:184–95
22. Collinsworth, K. A., Strong, J. M., Atkinson, A. J., Winkle, R. A. 1975. Pharmacokinetics and metabolism of lidocaine in patients with renal failure. *Clin. Pharmacol. Ther.* 18:59–64
23. Bonica, J. J., Akamatsu, T. J., Berges, P. U. 1971. Circulatory effects of peridural block: Effects of epinephrine. *Anesthesiology* 34:514–22
24. Bigger, J. T., Mandel, W. J. 1970. Effect of lidocaine on the electrophysiological properties of ventricular muscle and Purkinje fibers. *J. Clin. Invest.* 49:63–77
25. Engel, T. R., Soly, K., Meister, S. G., Frankl, W. S. 1976. Effect of lidocaine on right ventricular muscle refractoriness. *Clin. Pharmacol. Ther.* 19:515–22
26. Halkin, H., Meffin, P., Melmon, K., Rowland, M. 1975. Influence of congestive heart failure on blood levels of lidocaine and its active monodeethylated metabolite. *Clin. Pharmacol. Exp.* 17: 669–76