Neurotoxicity of Anesthetics

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Injury and death secondary to anesthesia most commonly occur as the result of technical errors, errors in judgment, or equipment failure. In recent years anesthetic toxicity has received increasing attention as a possible cause of morbidity and mortality. Hepatic and renal toxicity are now generally recognized to occur occasionally following administration of certain anesthetics. Neurotoxicity is less commonly recognized, and is usually viewed as being manifested by seizures following administration of local anesthetics or certain volatile agents. Lay persons and uninformed medical colleagues often refer to an anesthetic “overdose,” which implies some central nervous system (CNS) toxicity. Yet, for the most part, an “overdose” simply magnifies the usual pharmacologic effects in accordance with predictable dose–response curves. Such effects are totally reversible by simply decreasing the dose and therefore cannot be considered true toxic effects. As an example, it is the purpose of general anesthetics to depress CNS function, and they do so in a dose-related fashion. Unless this effect is itself considered toxic, then production of respiratory or circulatory arrest with high anesthetic concentrations should not be considered toxicity. Also some of the “pharmacologic” effects of general anesthetics might be “toxic” in certain circumstances. Thus, the capacity of drugs such as ketamine and halothane to increase cerebral blood flow, although usually of no clinical significance, may in patients with intracerebral mass lesions produce dangerous increases in intracranial pressure. In this review we ignore such effects, as well as exaggerated pharmacologic effects of anesthetics, and attempt instead to examine effects that more clearly fall under the category of toxicity. We define the latter as a potentially harmful action or effect that is not part of the expected anesthetic or pharmacologic action.

Intravenous Anesthetics

Many agents used intravenously to induce or to supplement general anesthesia are not generally classified as anesthetics. These include hypnotics (barbiturates primarily) and narcotics. Barbiturates are still considered in this review for the purpose of comparison with true general anesthetics. Narcotics are not discussed.

Ketamine

Of the various intravenous agents, ketamine is perhaps the most interesting when considering CNS toxicity. Ketamine is said to produce a “dissociative state,” a catatonic-like state accompanied by excellent somatic but minimal visceral analgetic effects. Phencyclidine, the precursor of ketamine, was introduced in 1957 as a general anesthetic, but was never approved for clinical use (it is, however, commonly used in animals). Approval of phencyclidine for human usage was withheld because of a convulsant tendency, coupled with a high incidence of psychotic reactions during emergence from its anesthetic effects. Because of these hallucinogenic effects, it has proven desirable in the illicit drug market. Ketamine is a less potent hallucinogen and convulsant, while retaining significant anesthetic properties. There is, nonetheless, a disturbing incidence of vivid dreams, hypereexcitability, and psychomotor activity following the administration of ketamine. The incidences of delirium and unpleasant dreams in adult patients have been reported by Coppel et al.27 to be 21 and 17 per cent, respectively, after ketamine, 2 mg/kg, iv. In the same study, the incidences were decreased to 3 and 0 per cent, respectively, when diazepam 0.17 mg/kg, was given intravenously at the end of the procedure. A postanesthetic psychotic reaction has also been reported to occur in an adult patient after 300 mg, iv.26 These undesirable effects seem less common in children but recently, prolonged adverse reactions to ketamine, 3 mg/kg, im, were seen in two 3-year-old children undergoing eye examinations.26 (One patient received, in addition, pentobarbitol, 3 mg/kg, im, and N₂O, 66 per cent–O₂, 33 per cent.) One child experienced frightening flashbacks for months after anesthesia. The other child, who previously had been anesthetized 28 times.
with halothane–N₂O–O₂ without problem, experienced a severe mental setback, had a tendency to bite family members, and had not returned to normal behavior ten months later.

The convulsant properties of ketamine have been clearly revealed in two studies of its effects in epileptic patients. Six of nine such patients (with depth electrode recordings) had seizures following 2–4 mg/kg, iv. The seizures developed in the limbic and thalamic areas, were sometimes accompanied by tonic and clonic motor activity, and were not always manifested on surface EEG recordings. For another six of eight such patients, given 4–10 mg/kg, im, plus 0.04–0.6 mg/kg/min, iv, surface EEG changes consisting of intermittent paroxysmal epileptiform discharges were recorded. Immediately postoperatively, two of these patients had focal seizures, one had a grand mal seizure, and three patients had increases in seizure activity for as long as three months postoperatively. In non-epileptic patients, convulsions have also occurred following ketamine. Three children in a combined series of 215 pediatric patients given ketamine experienced generalized transient convulsions after 10–12.5 mg/kg, im, or 2 mg/kg, iv, plus 1 mg/kg increments when necessary. \textsuperscript{48,124} There are also reports of individual cases of post-ketamine seizures with the same doses.\textsuperscript{102,108}

Laboratory animal studies have further elucidated the CNS effects of ketamine. In cats, Mori \textit{et al.}\textsuperscript{111} found that subanesthetic doses (10–20 mg/kg, ip) produced apparent CNS excitation, coupled with severe ataxia and catatonic behavior. Larger doses (20–50 mg/kg, ip) produced intermittent hypersynchrony in limbic and cortical regions, with behavior consistent with excitation, profound catatonia and anesthesia. At doses sufficient to produce near-apnea (40–50 mg/kg, iv) bursts of polyspike–wave complex activity interrupted by postictal depression (0.5–2 sec duration) were recorded, but clinical signs of seizures were not observed. In another study in cats,\textsuperscript{79} ketamine, 5 mg/kg/hr, produced stimulation of the neocortex, hippocampus, and other subcortical nuclei concurrently with eventual seizure activity. Muscle twitching occasionally accompanied the EEG seizure activity. Also in cats,\textsuperscript{100} ketamine, 25–40 mg/kg, resulted in seizure activity only in the hippocampus, without spread or behavioral manifestations. In rats,\textsuperscript{42} daily administration of ketamine, 30–80 mg/kg, for one to three months caused spikes and hypersynchronous burst activity in the amygdala and hippocampus. EEG seizure activity was observed in about half the animals at both dosage levels. Upon withdrawal of ketamine, a progressive increase in epileptiform activity was observed for five days without behavioral manifestations.

In man and animals, ketamine has little effect on brain O₂ consumption rate, but causes a large increase in cerebral blood flow (CBF). The mechanism(s) for this effect is unknown.

**Propranoidid and Althesin**

Two other non-barbiturate intravenous anesthetics in use today are propranoidid and althesin. Both are short-acting drugs and are most frequently used for inducing anesthesia. Propranoidid is known to cause excitatory side effects with either rigidity or uncontrolled movement. The frequency of this complication is a function of dosage; it increases from 10 per cent following 3–4 mg/kg to 70 per cent with 14 mg/kg,\textsuperscript{45} and is not higher than what has been reported for equipotent doses of methohexital (75 per cent with more than 2.6 mg/kg).\textsuperscript{46} When given to epileptic patients (like ketamine), propranoidid (5–7 mg/kg) may precipitate seizures.\textsuperscript{7,45,172} It has also been reported occasionally to produce seizures in non-epileptic patients.\textsuperscript{7,45,172} Althesin, a combination of two steroid nucleus anesthetics, has also been reported\textsuperscript{22,148} to cause similar excitatory side effects in 20 per cent of patients given a normal dosage, 50 µl/kg. The incidence increased with the dose of althesin (50 per cent for 100 µl/kg)\textsuperscript{22} and rapidity of injection.\textsuperscript{148} A few cases of seizures in patients with and without known abnormal EEG tracings given normal doses (50–60 µl/kg) have been reported.\textsuperscript{22,134,172} Neither althesin nor propranoidid has been approved for clinical use in the United States.

**Barbiturates**

Barbiturates may be either hypnotics or convulsants, depending on their chemical structures (fig. 1). Substitution of both H-atoms on C₅ of the barbituric acid molecule produces hypnotics unless substituted with groups having more than five or six carbons, in which case they become convulsants. Alkylation of one of the N-atoms increases anesthetic potency but also increases the possibility of excitatory actions. When both N-atoms are substituted, they again become convulsants. Methohexital, with a methyl group on a N-atom, is more potent than thiopental, but has a higher incidence of excitatory side effects (50 per cent of patients at 1.6 mg/kg,\textsuperscript{25} 75 per cent at >2.6 mg/kg.\textsuperscript{45} When methohexital was first used in clinical trials, convulsions were commonly encountered. By separating the compound into its isomers and identifying and removing the responsible isomers, the convulsant
properties were greatly diminished, although convulsions remain a possibility. The excitatory effects of methohexital have in fact been utilized to activate abnormal EEG tracings in clinical diagnostic investigations of petit mal and temporal lobe epilepsy. Thioental is not generally associated with excitatory side effects, and even when given in doses sufficient to produce an isoelectric EEG, has no apparent direct toxic effect on the CNS. In dogs, thioental was given in massive doses sufficient to produce an isoelectric EEG for 30 min or longer. During this time, cerebral O₂ consumption was stable (about 40 per cent of normal), and at the end of this period, brain energy stores (ATP and phosphocreatine) were normal, as was brain lactate. This is consistent with clinical experience with barbiturate "intoxication," in that when respiratory and circulatory support are initiated early enough and are adequately maintained, cerebral recovery can be expected even when EEG activity is initially absent. In clinical concentrations, barbiturates are the most potent known depressants of cerebral O₂ consumption, producing as much as a 55 per cent decrease in man. Unlike inhalational anesthetics, barbiturates do not uncouple the relationship between cerebral O₂ consumption and blood flow. As cerebral O₂ consumption decreases, so too does blood flow, to approximately the same extent.

Not only is there no evidence in vivo of a direct CNS toxic effect of barbiturates, but instead there is accumulating evidence of a cerebral protective effect in various animal models of ischemia and hypoxia. This subject has been recently reviewed by Smith. The mechanism(s) for such a protective effect remains unknown. Although initially thought to relate primarily to the metabolic depressant effect, there is evidence that this effect alone might not satisfactorily explain the protection provided. It is possible that protection is accounted for by a mechanism unrelated to the anesthetic or metabolic effects.

A potential, although indirect, toxic effect of barbiturates occurs in patients with porphyria variegata and acute intermittent porphyria. Barbiturates are known to precipitate acute increases in plasma levels of delta-aminolevulinic acid in these patients, resulting in peripheral and CNS demyelination with motor neuron chromatolysis. In a series of 22 cases of attacks precipitated by thioental, quadriplegia with bulbar paralysis developed in 11 patients and peripheral neuropathies developed in 19. It is generally accepted not only that barbiturates can precipitate attacks, but also that they may increase the severity of such attacks.

Inhalational Anesthetics

Based upon in-vitro studies, one might conclude that general anesthetics could exert a direct toxic effect on the CNS. Cohen and Marshall found in liver mitochondria that when NAD-linked substrates were used, halothane produced dose-related inhibition of respiration by blocking oxidation of NADH. This inhibition of the so-called state 3 respiration (excess substrate, O₂, P and ADP) was completely reversible at halothane concentrations no higher than 2 per cent. At higher concentrations, there was an increasing failure of recovery. State 4 respiration (no excess ADP) showed an irreversible loss of respiratory control for concentrations greater than 2 per cent. This suggests at least two important effects of halothane on mitochondrial metabolism. It alters the function of electron transfer and diminishes mitochondrial respiratory control (uncoupling). Rosenberg and Haugaard confirmed this for very high concentrations of halothane (8 per cent) in liver, but not in brain, mitochondria. Cohen and McIntyre also found that methoxyflurane, enfurane, and diethyl ether decreased mitochondrial respiration in vitro. With very high concentrations, irreversible diminution of O₂ uptake and loss of respiratory control followed. The significance of such studies and their application to in-vivo circumstances are unknown. As an example, barbiturates can also be shown to uncouple brain mitochondria at high concentrations in vitro, but no such effect is apparent in vivo.

Some data from in-vivo studies do suggest a possible cerebral toxic effect of volatile anesthetics. A puzzling observation over the years has been that all volatile anesthetics dissociate the normally close relationship between cerebral metabolism and cerebral blood flow, and do so in a dose-related fashion (fig. 2). Thus, cerebral O₂ consumption (CMBF) is decreased and CBF tends to increase. Except for its occurrence during anesthetia, such dissociation is seen only in pathologic states. One view might be that this effect is beneficial, since O₂ delivery to the brain is increased relative to O₂ needs. Alternatively, one might conclude that, for reasons unknown, the brain requires a higher
tension of O₂ in the presence of volatile anesthetics. The former view would be considered beneficial, whereas the latter would suggest a possible subclinical toxicity manifested only by an unexplained increase in blood flow.

If the brain does require a higher O₂ tension during anesthesia, this is not reflected by any alteration in brain energy stores or brain lactate levels in the presence of a variety of anesthetics at clinical concentrations. However, at concentrations greater than those used clinically, a toxic effect on cerebral metabolism can be demonstrated. When dogs are exposed to halothane concentrations (in the blood) greater than 2.3 per cent (to as high as 9 per cent), a dose-related, striking diminution in brain energy stores and an increase in brain lactate occur. This is observed despite maintenance of adequate O₂ delivery to the brain, and is in direct contradiction to the lack of such detrimental effects when high doses of barbiturates are used (see above). Also, as opposed to the effects of barbiturates, CMR₀₂ does not stabilize with onset of an isoelectric EEG, but instead continues to decrease in a dose-related fashion. Similar effects were observed with two other volatile anesthetics (enflurane and isoflurane). Thus, at concentrations three times the minimal anesthetic concentration, halothane can be shown in vivo to have a dose-related direct toxic effect on cerebral metabolic pathways, resulting in significant interference with oxidative phosphorylation. These metabolic changes were shown to be reversible when the halothane concentration was decreased from 9 per cent after 30–40 min, and two dogs that were allowed to recover showed no gross alteration in function during the subsequent 48-hour period of observation.

In animal models of cerebral ischemia, there is again a striking difference between barbiturate effects and those of halothane. As already discussed, barbiturates have been shown to protect ischemic or hypoxic brain, but not so halothane and other volatile anesthetics. In one study in dogs, a middle cerebral artery and an ipsilateral common carotid artery were ligated and the resulting infarctions in animals receiving barbiturates, halothane, and no anesthesia were compared. Barbiturate-treated animals had the fewest and smallest infarctions, while animals receiving halothane, 1.9 per cent, had the highest frequency and largest infarctions. Similar differences have been found in other studies. It is possible that this effect is only secondary to an overall increase in CBF produced by halothane, which serves to increase intracranial pressure and, thus, aggravate the ischemic lesion. However, in view of the other effects of halothane already described, a direct toxic effect that is more prominent in the presence of ischemia or hypoxia is also possible. It is perhaps more than coincidental that results of both in-vitro and in-vivo studies suggest that at halothane concentrations near 2 per cent, apparent toxic effects can be shown. Even if this is of no clinical significance, it is clear from these studies that volatile anesthetics act in a manner quite different from barbiturates.

**Toxicity of Metabolites**

Many inhalational anesthetics undergo biodegradation in the body, and toxicity of some of the products has been demonstrated. Most interest has accumulated around hepatic and renal histotoxicity, but CNS toxicity has also been suggested. Bromide, a breakdown product of halothane, will, in sufficient amounts, cause headache, ataxia, lethargy and diffuse EEG changes. In a study of 25 patients given halothane anesthesia, peak plasma bromide values were increased postoperatively to 0.65–2.25 mEq/l, levels at which CNS effects can be expected in patients without unusual tolerance for bromide. The plasma bromide levels were proportional to the halothane
neurotoxicity of anesthetics

exposure in MAC hours and remained increased for at least 22 days in some patients.

Prolonged sedation can be seen following the use of trichloroethylene. One of its metabolites, trichloroethanol, is a sedative with very slow elimination. When trichloroethylene comes into contact with soda lime it is converted into dichloracetylene, which may cause paralysis of cranial nerves, and with further metabolism can yield phosgene.57

To date no other metabolic breakdown product of anesthetics has been implicated as neurotoxic in man. Fluroxene is particularly toxic in dogs, causing convulsions, bloody diarrhea, vomiting, and death.57 This is probably caused by breakdown products that are not produced by man, and there is no evidence of fluroxene toxicity in man.

Convulsant Effects

Most inhalational anesthetics have been reported to cause convulsions.40,54,55,82,84,110,116,164 Until the recent introduction of enflurane, convulsions had been most frequently observed with ether anesthesia.40 On the other hand, halothane rarely, if ever, produces convulsions. Two cases in children were reported, but both had received N₂O as well.101 In another child who convulsed with exposure to halothane–N₂O, it was shown that halothane alone would not precipitate a seizure, whereas N₂O alone did.54 Epileptogenic activity has been seen in cats given a gross overdose of halothane (7 per cent) with blood pressure supported by phenylephrine,82 but, as previously described, cerebral metabolism is likely to be greatly disturbed at this concentration.101

Working with a series of halogenated volatile agents, it was observed that the numbers of halogen atoms (especially inorganic fluoride) were important determinants of anesthetic and convulsant properties.164 As the number substituted in the molecule increases, the pharmacologic effects progress from anesthesia through convulsions to lack of anesthetic or convulsant properties with full fluorination. The importance of fluorine atoms for other epileptogenicity has also been pointed out by others.82,105

Perhaps because of the relative ease with which convulsions can be produced by enflurane, it has been the most thoroughly investigated anesthetic in this regard. All investigators agree that by using relatively high concentrations (to 3.5 per cent) and hypocapnia, seizures can be induced either spontaneously or by a sudden auditory stimulus. In volunteers, it was found that enflurane, 3 per cent, decreased MCR₂O₂ about 50 per cent, but with onset of grand mal seizures, MCR₂O₂ returned to control levels.101 There was no evidence of cerebral hypoxia during the seizures. In 25 normal children,119 enflurane consistently produced spike waves on the surface-recorded EEG. In five of these patients, EEG changes were seen at concentrations as low as 1 per cent. The children were breathing spontaneously, and the extent of EEG changes correlated roughly with severity of hypocapnia. The incidence of muscle twiching in patients receiving enflurane has been reported to be 7 per cent,144 and is accompanied by intermittent spiking activity, followed by periods of suppression. In 12 patients with temporal epilepsy and depth electrodes, persistent spike discharge was seen at enflurane concentrations greater than 2.5 per cent. Hyperventilation markedly increased these discharges, whereas the addition of CO₂ completely suppressed spiking activity (Paco₂, 91 torr). In a study in dogs,86 CMR₂O₂ increased to above control levels during enflurane-induced seizures, as did CBF (thus, O₂ delivery was adequate). The metabolic manifestations of enflurane-induced seizures could not be distinguished from those of pentyleneetetrazol-induced seizures. Some investigators,160 in spite of what we believe to be convincing evidence to the contrary, believe that the typical enflurane EEG pattern, a paroxysmal polyspike–wave pattern followed by electrical depression of variable duration, is a manifestation of a particular variety of sleep rather than an authentic epileptic manifestation, even though it eventually is accompanied by myoclonus. They further suggest that the apparent silent period after the spikes represents in fact only a very-low-amplitude rapid activity corresponding to active inhibition.

In an extensive study in dogs, a number of anesthetics were examined for their potentials to induce seizures in the presence of hypocapnia (Paco₂, 20 torr).75 In high concentrations, both diethyl ether and divinyl ether produced spontaneous seizures. Halogenated ethers (enflurane and fluroxene) produced seizures after loud hand-clapping. Isoflurane caused spontaneous spiking but not seizures, and seizures could not be elicited with halothane, chloroform and cyclopropane. Seizure activity with cyclopropane has been seen by others, however.109

Chronic Toxicity

There has been considerable speculation and concern expressed in the past few years about a possibly toxic effect resulting from chronic exposure of operating room personnel to trace amounts of anesthetics.5,24,179 These studies indicate that there is an increased health hazard in connection with operating room work, but it is difficult to separate the effects of
trace anesthetics from the effects of other inherent factors, such as emotional stress. A causal connection has not been established.14

The concern is mostly related to increased incidences of teratogenicity and spontaneous abortions, hepatic disease, and cancer. In man, the only evidence of CNS effects relates to possible behavioral changes during or immediately after a few hours of exposure. Bruce et al.14,15 reported that subjects exposed to 500 ppm N2O combined with 15 ppm of either halothane or enflurane for four hours scored significantly less on a battery of psychologic tests than controls immediately after exposure. These results could not be reproduced by others, although the experimental approaches employed were somewhat different.12,108,4 Permanent damage has not been reported, and even if such effects should be real, it is most likely that these would be direct pharmacologic effects of subanesthetic concentrations, and not toxic effects.

Most animal studies of chronic exposure have also been concerned with organ systems other than the brain. Stevens et al.166 found no consistent organ injury other than in the liver after 35 days of exposure to subanesthetic doses of halothane (15–300 ppm), isoflurane (150–1,500 ppm) or diethyl ether (0.1–1 per cent) in young rats, mice or guinea pigs.

Chang et al.18 exposed rats to halothane, 10 or 500 ppm, eight hours a day, for eight and four weeks, respectively. The animals exposed to 10 ppm showed only ultrastructural changes, including collapse of the neuronal rough endoplasmic reticulum, dilatation of the Golgi complex, and focal cytoplasmic vacuolation in many neurons. Animals exposed to 500 ppm showed more severe changes, including membrane degeneration of neuronal mitochondria, intracellular edema of the glial cells, and necrosis of the cortical neurons. Chang et al. also reported17 degenerative changes in cortical neurons of neonatal rats exposed to halothane, 10 ppm, throughout gestation. When rats were exposed to the same concentration for 60 days from conception, there was evidence of neuronal degeneration, as well as permanent failure of formation of the synaptic web and postsynaptic membrane density, in 30 per cent of postsynaptic membranes.130 The last animals showed later defects of learning. No such effect was apparent after adult exposure. It should be noted that the scientific validity of the work of Chang et al. has been questioned and criticized.140

Local Anesthetics

Local anesthetics, which act in part by stabilizing membranes, rapidly cross the blood–brain barrier.177 It is not surprising, therefore, that a major toxic side effect arises within the CNS.

Clinical Toxicity

The incidence of CNS reactions following regional block procedures has been reported by Moore and Bridenbaugh165 to be 1.5 per cent. This figure was derived from a survey of 36,113 procedures. In the same survey, only 2 per cent of the untoward reactions were thought to be allergic in origin, whereas the remainder (98 per cent) were consistent with a toxic effect of the local anesthetic.

As blood and brain concentrations of local anesthetic increase, a well-described sequence of signs and symptoms occurs. The concentrations at which the changes occur vary with different drugs (table 1), but the patterns are virtually identical. At low drug concentrations, the initial CNS effects are those of sedation and analgesia, combined with an anticonvulsant property.81 Since these effects are sometimes sought therapeutically, they should probably not be considered signs of toxicity. Progressive sensations experienced by the patient at higher concentrations may include lightheadedness, dizziness, numbness, a metallic taste, visual–auditory disturbances, nausea, sleepiness, disorientation, and a sensation of twitching before the latter can be objectively observed.30,61,106,108 Parallel objective signs may include euphoria, dysarthria, nystagmus, sweating, vomiting, pungnaciousness, loquaciousness, unreasenableness, disorientation, and periodic unconsciousness. At higher concentrations, objective signs progress primarily to those of neuronal irritation, including shivering, fasciculations, choreiform movements, twitching, and ultimately frank convulsions.29,30,61,106,108 Convulsions may be either clonic or tonic–clonic.195 This may progress to generalized depression of the CNS, with coma and ultimately, death due to respiratory arrest.88 Local anesthetics are also cardiotoxic, and cardiovascular depression may be observed prior to respiratory arrest, but this is variable,3,178 and most agree that respiratory arrest precedes severe cardiovascular depression.2,29,56,74,106,179,180

EEG Effects

In man, recording the surface EEG has not been very useful in detection of the onset of toxicity prior to convulsions. A decrease in alpha activity and increased delta–theta activity have been reported.29,51,61

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as well as a progressive blocking of the EEG response to painful stimulation (desynchronization). In two studies of a total of 17 volunteers (65 drug exposures), the administration of a local anesthetic resulted in the production of subjective and objective signs of toxicity, including convulsions in two subjects. In none of these experiments was any alteration detected in the surface EEG before the onset of convulsions. In these studies, a variety of local anesthetics was used (bupivacaine, etidocaine, lidocaine, procaine, chloroprocaine, and tetracaine). In another human study with lidocaine and procaine, abnormal pre-seizure EEG activity was not found, and the onset of a convulsive EEG pattern was simultaneous with tonic-clonic muscle activity. In a study in eight male patients who had long-standing temporal-lobe epilepsy and stereotactically implanted electrodes, de Jong and Walts demonstrated that lidocaine infusion produced psychomotor seizures. Three of these subjects showed an amygdala–hippocampus focus, whereas the remainder showed only generalized slowing with irregular paroxysmal activity in the temporal lobe leads. It has been suggested that the prodromata of local anesthetic-induced seizures in man may be manifestations of psychomotor seizures.

In animals, preseizure abnormal EEG activity, which apparently varies with the type of local anesthetic used, has been found. In cats, lidocaine produces marked increases in amplitude for a considerable period prior to seizures, whereas bupivacaine does so only shortly before seizures. Likewise, in rhesus monkeys, lidocaine routinely produces prolonged abnormal activity, whereas bupivacaine effects are variable and of brief duration. Various animal studies have demonstrated development of a seizure focus in the amygdala following administration of a local anesthetic, usually lidocaine. Ablation of the amygdala has been reported to prevent anesthetic-induced seizures. Amygdaloid hypersynchronous activity at low concentrations appears dependent upon olfactory stimulation. At higher concentrations, olfactory stimulation is probably not necessary, although a seizure focus still appears in the amygdala. In rhesus monkeys, a seizure focus in the amygdala could not be detected; however, amygdaloid spindling is normal background activity for awake monkeys.

### Anticonvulsant Effects

At subtoxic doses, it is established that local anesthetics exert an anticonvulsant effect and will diminish or abolish convulsions produced by either electrical or chemical stimulation. Although still controversial and not consistently supported by results of animal studies, most investigators believe that local anesthetics generally inhibit neuronal activity, but that excitatory pathways are more resistant than inhibitory pathways. Thus, at subtoxic doses, they act as anticonvulsants; at higher concentrations, resistant unopposed excitatory pathways cause convulsions; at still higher concentrations, all pathways are inhibited. It is interesting that local anesthetics do not elicit seizures when applied topically to the cerebral cortex, or injected subcutaneously in rabbits (amylcaine, 5 per cent, hexylcaine, 5 per cent, or lidocaine, 1–5

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**Table 1. Suggested Toxic Arterial Blood Levels and Doses of Local Anesthetics**

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<th>Seizure Activity — Threshold</th>
<th>Pre-seizure Activity</th>
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<tr>
<td></td>
<td>Cat Arterial Blood Level</td>
<td>Dog Arterial Blood Level</td>
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<td></td>
<td>Dose (µg/kg)</td>
<td>Dose (µg/kg)</td>
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<tr>
<td>Mepivacaine</td>
<td>22 (10)</td>
<td>9–20 (8)</td>
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<tr>
<td></td>
<td>20.5 (convulsions)</td>
<td>&gt;55 µg/kg/min (convulsions)</td>
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<tr>
<td>Lidocaine</td>
<td>8–20 (14)</td>
<td>23–26 (14)</td>
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<td></td>
<td>19.6 (convulsions)</td>
<td>&gt;4 (10)</td>
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<tr>
<td>Bupivacaine</td>
<td>3–6 (12)</td>
<td>4–5 (11)</td>
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<tr>
<td>Tetracaine</td>
<td>45 (50)</td>
<td>100 (90)</td>
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<tr>
<td>Procaine</td>
<td>35 (50)</td>
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<tr>
<td>Chloroprocaine</td>
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<td>Prilocaine</td>
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per cent). In man, lidocaine failed to elicit seizures when applied to the cerebral cortex.\textsuperscript{40}

**Toxic Dose**

Precise determination of the toxic dose for individual local anesthetics has not been possible, presumably because of the multiplicity of factors involved. Among these, individual susceptibility appears to be a major and unknown determinant. Factors that determine the availability of the local anesthetic in its active form to the CNS include: mode of administration, site of administration, drug concentration, protein binding, lipid solubility, metabolism, acid–base balance, and interaction with other drugs.

When local anesthetics are administered locally in high concentrations, absorption is generally fast because of a large gradient that favors absorption.\textsuperscript{195} The vascularity of the area is a prime determinant of absorption and toxicity. This may be favorably altered by simultaneous administration of a vasoconstricting drug such as epinephrine,\textsuperscript{13} although systemic administration of epinephrine has been shown to increase toxicity of local anesthetics.\textsuperscript{12,13,185} When local anesthetics are administered in the bronchial tree, absorption and distribution are almost equivalent to absorption and distribution after intravenous administration.\textsuperscript{15,185} After paracervical or pudendal block, uptake is faster with higher peak plasma levels than after epidural block,\textsuperscript{112,128,194} even when the total dose is lower.\textsuperscript{154} In another study, the plasma level of lidocaine after caudal anesthesia (6.6 mg/kg) was found to be only 50 per cent of that obtained after lumbar epidural anesthesia (5.5 mg/kg) or axillary block (6.2 mg/kg).\textsuperscript{95}

Because local anesthetics are bound by plasma proteins, the presence of other drugs that also bind plasma proteins would favor higher concentrations of unbound local anesthetic. In an in-vitro study,\textsuperscript{85} 92 per cent of bupivacaine was found bound by plasma protein at a total plasma concentration of 5 µg/ml, a level probably close to seizure threshold (table 1). The free fraction only doubled to 16 per cent with a fourfold increase in total plasma concentration, but increased as much as 300–500 per cent when instead a drug that binds to plasma protein was added. This effect was demonstrated following addition of diphenhydantoin (20 µg/ml), meperidine (20 µg/ml), quinidine (8 µg/ml), or desipramine (3 µg/ml) to plasmas from healthy volunteers, and was also found in plasmas from patients receiving the same drugs. This might explain why diphenhydantoin enhances seizures caused by local anesthetics,\textsuperscript{85} although this drug has been suggested to act on the amygdala in a manner similar to local anesthetics.\textsuperscript{131} The presence of other drugs that affect CNS function may greatly alter the toxic effects of local anesthetics on the CNS (see below). Thus, measurements of toxic doses in animals anesthetized with barbiturates, frequently described in the early reports, are probably of little value.

Differences in enzymatic hydrolysis might modify toxicity.\textsuperscript{56} The ester group of local anesthetics (procaine, etc.) is rapidly hydrolyzed by plasma cholinesterase, as opposed to the slower metabolism of the amide group (lidocaine, etc.). For both groups, the metabolic breakdown products are less potent than the parent compounds.\textsuperscript{56} When local anesthetics are absorbed systemically from an injection site, the esters might therefore be expected to be less toxic,\textsuperscript{16} and in case of toxicity, the duration should be significantly less.\textsuperscript{56} For the same reason, patients who have congenital atypical plasma cholinesterase might be expected to be less tolerant of the ester type of local anesthetic.\textsuperscript{73,80,196} Cahill et al.\textsuperscript{16} described a critical rate of disposal by continuous intravenous infusion of various local anesthetics in rabbits. Time before onset of convulsions increased as a hyperbolic function of decreasing rate of drug administration until seizures could no longer be elicited. The rate of administration at that point should then be equal to the rate of drug disposal, thus avoiding accumulation and seizures.

Acid–base balance may significantly affect toxicity (fig. 3). Decreasing blood and brain pH (most readily accomplished by increasing arterial blood CO\textsubscript{2}) will increase the ratio of the ionized to the unionized form of the local anesthetic. This will decrease the amount of local anesthetic crossing the blood–brain barrier at any given moment (primarily the unionized form), but will increase the activity of the local anesthetic that has already entered the brain (the ionized form is considered to be the active form). Change in concentration of the unionized form in the blood with change in pH is probably considerably dampened by a parallel shift in the binding of the local anesthetic to plasma lipids and proteins.\textsuperscript{131} The important factor is therefore the ratio of the unionized to the ionized form in the brain, and an acute decrease in brain pH has been shown to increase toxicity,\textsuperscript{30,56,68} whether of respiratory or metabolic origin.\textsuperscript{56} An increase in CO\textsubscript{2} level, in addition to lowering pH, will also favor toxicity, because of an increase in CBF that will increase drug delivery. Others have speculated that there might be a possible direct excitatory effect of CO\textsubscript{2} on the amygdala.\textsuperscript{131}

Despite these variables, efforts have been made to define toxic doses. In general, there is a relationship be-
between anesthetic potency and toxicity, as has been demonstrated both by animal convulsion studies,38,96,115,116 and by human preconvulsion studies.33,61,78,151,174 Arterial blood levels appear to correlate best with toxicity.30,23 Brain levels have not been reported, and venous blood levels do not correlate well,151 probably because of significant peripheral uptake and redistribution.174 Data derived from intravenous infusions of various local anesthetics have been used to correlate toxicity with arterial blood levels. Representative results of these studies are summarized in Table 1. It should be noted that, in addition to the multiplicity of variables already discussed, these studies were done at different infusion rates (from 5–25 min), which will in itself alter the toxic threshold.12,16,131 Thus, at best, the values reported in Table 1 can be used only as rough guidelines.

**Protection Against CNS Toxicity**

Until recently, the standard treatment of CNS toxicity produced by local anesthetics has been intravenous administration of barbiturates. This dates back to 1925, when Tatum et al.166 reported that the LD50 for cocaine was increased fourfold by sodium barbital and paraldehyde. Later reports178,186 also described an increase in the toxic threshold produced by prophylactic barbiturate therapy, although not of the magnitude initially described. More recently, barbiturates were found to be ineffective prophylactically,4 and their use for this purpose has been largely abandoned.2 Although still considered effective in the treatment of convulsions, some believe that barbiturates may be hazardous because of obscured symptomatology and depression of vital centers.165

Most recently, diazepam has gained favor,35,118,187 as both a prophylactic and a therapeutic agent. Possibly diazepam acts by suppression of the limbic system,56 although this was not supported in a study using implanted chemiodes in the cat.185 Using the latter approach, diazepam blocked seizures only when placed in brain-stem reticular-formation sites, and had no effect when placed in the amygdala. Further, since diazepam can abolish existing convulsions, its effects must be more generalized than simple effects on the limbic system. Studies in cats, mice, and monkeys have consistently demonstrated an increase in seizure threshold with diazepam to as much as a doubling of the dose of local anesthetic.34,35,118,137,187 Thus, the prophylactic merits of diazepam seem unquestioned. For the treatment of seizures, diazepam appears to be as effective as small doses of thiopental, with the advantage of not severely depressing the cardiovascular system.35,118

![Fig. 3. The convulsive thresholds for five local anesthetics of various potencies. When PaCO2 is increased to above 65 mm Hg, the thresholds are decreased for all five. From Covino and Vassalo.94 by permission of authors and publisher (Grune and Stratton).](image)

Various other drugs have been tested and have been found unsatisfactory. These include ketamine, α-OH-butyrate, diphenylhydantoin (see above), halothane, methoxyflurane, fluoxetine, succinylcholine, and oxygen.5,4,114,131,139,162,178,186 Although not anticonvulsant, succinylcholine will abolish muscular activity and permit control of ventilation and CO2, while O2 administration is generally advisable as a means of minimizing brain hypoxia.

**Fetal Toxicity**

The determinants of drug passage across the placental barrier are similar to those for the blood–brain barrier, and it should be expected that local anesthetics administered to the mother well may affect the neonate. The pharmacodynamics of this passage and the fetal handling of the drugs has been excellently reviewed recently by Ralston and Shnider,193 and we only briefly list the important determinants.

The amount presented to the placenta is a function of maternal plasma level of free drug (as described above under Toxic Dose). The transplacental passage of local anesthetics32,107,112,129,149,150,153,154,176 is probably a process of simple diffusion,30,112 and the drug can generally be detected in the fetus within a few minutes after appearing in the maternal circulation.112,129,153,154 The capacity for fetal plasma protein binding of local anesthetics has been estimated to be half that in the mother,94 and therefore the fetal–maternal plasma concentration ratio seems inversely correlated to plasma protein binding.30,128 Local anesthetics with greater protein binding are, on the
other hand, generally more lipid-soluble. This might increase fetal CNS uptake. Thus, while prilocaine quickly attains equilibrium across the placenta, the concentration of bupivacaine in the umbilical vein seldom reaches 50 per cent of the maternal level, and that of etidocaine, only 14–35 per cent. Since CNS toxicity is ultimately a function of cerebral tissue uptake (and removal), plasma drug concentration differences per se, without consideration given to such factors as pH and protein binding, do not necessarily reflect relative drug safety. The relative safety of procaine and 2-chloroprocaine is, for instance, probably due to the rapid breakdown by plasma cholinesterase, not placental metabolism as has been claimed recently. Cholinesterase activity as measured in placental homogenates is probably the result of contamination by blood.

Signs of neonatal toxicity include seizures, mydriasis, loss of oculocephalic reflexes, and apnea. Apnea may be either posical or due to pharmacologic brain-stem depression. Seizures have been reported to be tonic, clonic, and tonic–clonic. According to Poppers, the most common adverse effect of obstetric anesthesia is drug-induced fetal depression, and many studies use low Apgar scoring as an indicator of toxicity induced by local anesthetics. The same symptoms can result from other factors leading to hypoxic episodes, making interpretation of the results more difficult.

Susceptibility of the fetus to the toxic effects of local anesthetics has been reported to increase with gestational age. When lidocaine was infused intravenously into fetal lambs, threshold arterial concentrations causing seizures decreased gradually from 40 µg/ml to 7–13 µg/ml as fetal age increased from 0.77 to 0.92 gestation. The threshold in pregnant ewes has been reported to be 6.4 µg/ml, indicating little difference in the susceptibilities of the term fetus and the mother.

The toxic blood levels in the human fetus are unknown. In a study of 156 epidual blocks with mepivacaine for vaginal delivery, 12 infants were depressed at birth (Apgar < 7). In six instances the depression could be explained by obstetric causes, and five other infants had significantly higher concentrations of mepivacaine in plasma than the mean for all babies (4.0 ± 0.3 vs. 2.5 ± 0.2 µg/ml). The mothers of five of the latter experienced various untoward effects of the anesthetic. In a series of 57 lidocaine obstetrical blocks of different kinds, five infants had Apgar scores < 7. The three infants who had plasma lidocaine levels greater than 3 µg/ml were all depressed.

Even if these blood levels are lower than toxic levels in adults (table 1), they do not necessarily indicate greater susceptibility. The relative amount of free drug is larger in the fetus, and other investigators have, in addition, failed to confirm the findings described above, possibly indicating the inadequacy of Apgar scores as a tool in these studies. In 180 patients, 11 of 12 low Apgar scores could be explained by obstetric difficulties, and there was no correlation with lidocaine concentrations of more than 3 µg/ml. The same conclusions were drawn for mepivacaine in another study.

There are single case reports of more serious toxic effects, seizures, coma, or death, often following inadvertent direct injection into the fetal scalp during attempted paracervical or caudal blocks. Exchange transfusions and gastric lavage (the concentration of local anesthetic is high in the low-pH gastric content) have both proven of value in combination with standard treatment for local anesthetic toxicity.

In another study, four of five severely intoxicated neonates ultimately developed normally. More subtle neurobehavioral effects of local anesthetics have been reported. The significance of such effects remains controversial, and no data exist concerning growth and developmental effects.

**Metabolic Effects**

Local anesthetics have been reported to decrease brain and peripheral nerve oxidative metabolism, both in vivo and in vitro. In porcine brain mitochondria, lidocaine produced a dose-dependent inhibition of oxygen consumption with glutamate as substrate (50 per cent inhibition for lidocaine 0.23 per cent), but not with succinate, indicating inhibition at the NADH dehydrogenase level. A reversible uncoupling of oxidative phosphorylation was observed with both substrates for the same concentration of lidocaine. Inhibition of ATPase activity and uncoupling of oxidative phosphorylation have also been found for other local anesthetics in rat brain mitochondria. At lower concentrations there is no effect on rat liver mitochondria. Results of other in-vitro studies have suggested interference with citrate production or with the electron-transport chain at the cytochrome C–cytochrome oxidase level. Interpretation of such studies is impossible, since normal local anesthetic concentrations in mitochondria in vivo are unknown.
Peripheral Nerves

In isolated nerve trunks, irreversible block of bioelectric events can be produced by local anesthetics; this is a function of drug concentration, duration of exposure, and pH.171,172 Skou156 found that the concentrations needed in vitro to produce irreversible block of the nerve impulse in the motor fibers of the sciatic nerve of the frog (dibucaine 0.03 per cent, tetracaine 0.08 per cent, cocaine 1.6 per cent and procaine 4.4 per cent) were significantly higher (20 to 270 times) than the minimum reversible blocking concentrations (0.0002, 0.0003, 0.08 and 0.12 per cent, respectively) and would also hemolyze erythrocytes, suggesting a generalized effect on membranes. Skou also found that toxicity increased with increasing pH.

An inhibitory effect of local anesthetics on rapid axonal transport has recently been reported. Fink et al.57 showed this inhibition in rabbit vagus nerve (in vitro) to be reversible for lidocaine 0.1–0.5 per cent; for 0.6 per cent there was no significant recovery of rapid axonal transport or conduction of the action potential when exposure lasted longer than an hour. After 90 min of exposure there was an almost complete loss of axonal and Schwann-cell microtubuli. With procaine, reversible arrest of transport occurred at 0.4 per cent and irreversible arrest (in two of five nerves) at 0.5 per cent, but recovery of impulse conduction did occur.1 Ngai et al.120 failed to confirm an inhibitory effect on rapid transport of enzymes when lidocaine, 0.5–1 per cent, or etidocaine, 2 per cent, was applied to guinea pig sciatic nerve (in vivo), although the results were somewhat difficult to interpret due to a stimulatory effect of the local anesthetic on enzymatic activity. Likewise, Ochs et al.122 found no effect of procaine, 1 per cent, on cat sciatic nerve in vitro. If there is a blocking effect it is probably determined by the intraneuronal concentration of the anesthetic, and equilibration of intra- and extraneuronal concentrations takes hours.1 A reason for the discrepancy between the above-mentioned studies might therefore be the difference in methods of administration (in-vitro bath vs. in-vivo instillation via a catheter) or types of nerves (vagus nerve vs. the thicker sciatic nerve). In-vivo studies by Fink et al.58 on the rat trigeminal nerve support such a conclusion. Lidocaine, 1–4 per cent, resulted in inhibition that was related to concentration and duration of exposure and was doubled by the addition of epinephrine 1:200,000. However, this effect was reversible, although with 4 per cent, recovery was not complete even after 4.5 hours. Inhibition of rapid axonal transport has been suggested as an indicator of neurotoxicity,120 possibly due to interference with energy metabolism (see metabolic effects). While Fink et al.58 reported the minimal intraneuronal blocking concentration of lidocaine to be 1 μmol/g nerve, the concentration needed for block of rapid axonal transport was 4–10 μmol/g (found an hour after injection of a 2–4 per cent solution). If block of rapid axonal transport is a toxic effect, the margin of safety is much narrower than indicated by Skou’s studies.

There have been reports of local nerve damage following injection of local anesthetics,80,87,104,109 but these complications appear rarely, and their causes are largely unknown. They need not imply toxicity of the local anesthetic because of the multiplicity of other possible causes. These include contamination with antiseptic solutions, traumatic technique, bacteriologic contamination, drug-induced vasocircstriction, bleeding tendencies, and trauma from the needle, an indwelling catheter, or the surgical procedure. In one study,57 healthy volunteers were subjected to intraneural or perineural ulnar injections of 1–2 per cent mepivacaine, with deliberate variations in severity of mechanical trauma. Three subjects who received intraneural injections (two with 1 per cent, one with 2 per cent mepivacaine) with relatively severe mechanical trauma developed nerve damage. In one of these the damage persisted after three months. In rats,177 intraneural injection of tetracaine, 1 per cent, dibucaine, 0.5 per cent, hxyclaine, 1 or 2 per cent, or duracaine produced swollen nerve fibers with vacuoles and axonal fragmentation. Within 60 days regeneration was complete histologically. After perineural injection of the same substances or intraneural injection of procaine, 5 per cent, or piperocaine, 1.5 per cent, the changes were less severe, with complete regeneration in 90 days. Lidocaine, 1–2 per cent, dibucaine, 0.07 per cent, or procaine, 1–2 per cent, did not cause similar changes.

Spinal Cord

Prior to 1955 it was commonly believed that a relatively high incidence of neurologic sequelae resulted from spinal and epidural administration of local anesthetics. Because the same concern was not associated with diagnostic lumbar subarachnoid punctures, it was assumed that the local anesthetic per se introduced the risk of neural toxicity. It should be noted that this view still prevails in some recent textbooks.85,112 Much of this concern, however, was based on early studies which were less than ideally controlled and analyzed. One such study reported by Thorsen,105 was based on 2,493 spinal anesthesias, as well as a survey of the
medical literature from 1906 to 1947. Complications were variously explained by perineural toxicity, intramedullary injections, endoneural injections, and arachnoiditis. More than 300 complications were found reported in the medical literature. In the series of 2,493 cases, 7 per cent of patients complained immediately postanesthesia of leg weakness, and 13 per cent, of leg numbness. Of this total (506 patients), only 11 demonstrated neurologic sequelae on follow-up examination. Two studies\textsuperscript{121,148} that showed virtually no serious complications of spinal anesthesia can be criticized for inadequacy of follow-up data. Beginning in 1954, a series of studies was carried out utilizing careful controls and extensive analysis, usually with long-term follow-up. Of these, the studies of Dripps and Vandam\textsuperscript{144,146,148} had perhaps the greatest impact on the medical community. They reported results following 10,098 spinal anesthetics with follow-up of periods of six months to five years. A parallel control series consisted of 1,000 patients who received general anesthesia only. Of the 10,098 patients who received spinal anesthesia only, one experienced incapacitating neurologic disease, and that secondary to a meningioma. There were minor neurologic sequelae that were not seen in the control group. These totaled 71 cases (0.8 per cent) in which there was either subjective or objective findings of neurologic dysfunction. Symptoms were largely confined to the lumbosacral nerves, consisting of numbness and/or paresthesias. Onset was usually immediately postoperatively, and durations of symptoms in a few cases exceeded six months. Of interest were 11 patients with known pre-existing neurologic diseases that were apparently exacerbated following the spinal anesthesia; a cause–effect relationship could not be established.

In another series of 11,574 spinal anesthetics, reported by Moore and Bridenbaugh,\textsuperscript{106} two patients had prolonged blocks (36 and 48 hours); one of these complained of leg weakness for eight months. No other prolonged or serious complication secondary to the spinal anesthesia was encountered. In a study of 10,440 patients given spinal anesthesia, Phillips et al.\textsuperscript{129} found that only eight were discharged from the hospital with persistent neurologic symptoms of weakness, hypesthesia, or paresthesia. Prior to discharge, 30 patients had transient symptoms or signs of neurologic dysfunction.

Epidual anesthesia has also been shown to be associated with a very low incidence of neurologic complications. In a series of 10,000 cases, Luedtke\textsuperscript{89} that one patient inadvertently given a subarachnoid injection had residual leg weakness. The major complication in this series resulted from systemic toxicity, with 45 patients manifesting various signs of cerebral depression or irritation. In another study, by Moore et al.,\textsuperscript{108} six of 7,286 patients experienced generalized CNS toxicity after epidural block. One other patient had postoperative bilateral quadriiceps weakness. A survey of 66,366 cases taken from the world medical literature showed the frequency of systemic CNS toxic reactions following epidural anesthesia to be 0.2 per cent.\textsuperscript{31} Transient leg weakness was reported in 0.1 per cent of the cases and permanent weakness in 0.02 per cent.

Based upon these large series of cases (see table 2), and recognizing that many of the reported complications could have been secondary to the technique per se (as pointed out in the section dealing with peripheral nerves), it seems justified to conclude that when local anesthetics are used in clinically appropriate concentrations, a true toxic effect on the spinal cord or cauda equina following subarachnoidal or epidural injection is very rare indeed.\textsuperscript{66} When they are used in inappropriate concentrations, cord damage can be produced in animals. Procaine, 20 per cent, will produce permanent paralysis in dogs,\textsuperscript{80} as will procaine, 10 per cent, in cats.\textsuperscript{91} The effect of high concentrations may relate at least in part to hyperosmolarity rather than a specific toxicity.

In general, it appears that when local anesthetics are used in appropriate clinical concentrations, they have little, if any, irritating or toxic effect on neural tissue, as judged by complete recovery of function after regional nerve block and results of histologic studies after intraneural injections.\textsuperscript{37,80,104}

**Summary**

It is clear that the major and most obvious manifestation of a toxic effect of either a local or a general anesthetic is CNS irritability. When this progresses to
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frank seizures, a marked increase in the rate of cerebral metabolism is known to occur. Thus, delivery of adequate oxygen to the brain by an increase in blood flow becomes critical, and is the usual compensatory response. Assuming such a response is possible and ventilation is adequate, there is, to our knowledge, no evidence of neurologic damage resulting from seizures. With repeated seizures and inadequate ventilation, brain damage will occur. Seizures produced by local anesthetics are perhaps more life-threatening, in part because the patient may not be as closely monitored and loss of airway is more likely. In addition, when seizures are produced by general anesthetics, treatment usually consists of simply decreasing the inspired concentration and correcting any hypoxia. With local anesthetics, an abrupt decrease in brain concentration is not possible, and some kind of pharmacologic CNS depression is necessary. In this regard, prevention and treatment have been improved by the use of diazepam. Other toxic effects of local anesthetics on neural tissue are difficult to demonstrate and, assuming use of proper concentrations, must be very rare. CNS toxicity of general anesthetics other than seizures is also difficult to demonstrate, and is largely speculative. Clearly, general anesthesia produced by inhalational agents cannot be equated with that produced by intravenous administration of barbiturates. Despite the clinical syndrome of "barbiturate intoxication," it seems clear that CNS "toxicity" secondary to an overdose of barbiturates consists of only an exaggerated pharmacologic depression, which is totally reversible by adequate supportive measures. By contrast, there is evidence that gross overdoses of volatile anesthetics can produce, in addition to pharmacologic CNS depression, a direct toxic effect on cerebral metabolic pathways.

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