

# Diazepam Prevents Local Anesthetic Seizures

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Diazepam (Valium) proved to be effective in preventing local anesthetic-induced convulsions. In cats with recording electrodes permanently implanted in the brain, the median intravenous convulsant dose of lidocaine ( $CD_{50}$ ) was 8.4 mg/kg. One hour after pretreatment with 0.25 mg/kg of intramuscular diazepam, the lidocaine  $CD_{50}$  doubled to 16.8 mg/kg. This dose of diazepam had no discernible effect on behavior or EEG. However, larger doses of diazepam (0.33 and 0.5 mg/kg) caused ataxia and shifted the EEG to slow high-voltage patterns—without appreciably improving protection against seizures. (Key words: Local anesthetics; Convulsions; Lidocaine; Anti-convulsant; Diazepam.)

CONVULSIONS from cocaine overdose were first described in 1868.<sup>1</sup> While less toxic and more potent local anesthetics have become available since then, all can induce convulsions in animals and man. With the use of intravenous lidocaine by cardiologists increasing, convulsions from local anesthetics are becoming more common.<sup>2</sup>

The current pharmacologic approach to preventing local anesthetic-induced seizures stems from the studies by Tatum and Collins with barbiturates.<sup>3</sup> Based on their work, barbiturates are frequently administered prior to injection of local anesthetics in hopes of preventing or moderating seizures. It is not widely appreciated, however, that about 70 mg/kg of an intravenous barbiturate must be given to abort cocaine-induced seizures in primates.<sup>3</sup>

Several reports pointing to heightening of excitability of limbic brain structures (particu-

larly the amygdala and hippocampus) by local anesthetics have appeared recently.<sup>4-8</sup> Certain benzodiazepine derivatives, conversely, depress hyperexcitability of limbic elements with some specificity, and for this reason are used to treat petit mal and temporal lobe seizures. More to the point, Eidelberg and co-workers<sup>9</sup> reported a lowered incidence of cocaine-induced seizures in rats pretreated with chlor-diazepoxide (Librium).

With this in mind, we reasoned that drugs having a depressant effect on the limbic brain should suppress initiation and subsequent spread of convulsions caused by local anesthetics. To test the hypothesis we investigated the effects of diazepam (Valium) pretreatment on lidocaine-induced seizures in cats with electrodes permanently imbedded in their brains.

## Methods

Ten healthy adult cats were anesthetized with halothane and nitrous oxide. The head of each was mounted firmly in a frame marked with stereotaxic coordinates. Using sterile surgical technique, we drove four to six pin electrodes through the skull with the tips resting extradurally over the frontal, sylvian, and occipital regions of the cerebral cortex. Five more pins were tapped around the circumference of the head and interconnected to provide an isoelectric reference. (Additionally, two to four bipolar electrodes were placed stereotactically in the amygdala and other limbic structures for a related study still in progress.)

Electrode leads were soldered to a 14-lead female plug, which was then bonded to the skull with acrylic dental cement. After the cement hardened, the scalp skin was sutured around the plug. Before discontinuing anesthesia we gave 0.5 mg morphine intravenously for postoperative pain relief. All cats awoke quickly and recovered from surgery within a week.

Two weeks or more after electrode implantation we began recording spontaneous electri-

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cal activity of the brain. A cable terminating in a mate to the skull plug led to a six-channel oscillograph (Grass model 7) and a seven-channel FM tape recorder (Ampex FR-1300). Preamplifier bandpass filter width was 0.3–75 Hz.

When placed in a zippered canvas bag, the cats objected comparatively little to venipuncture with a 21-G needle. (We were unsuccessful in earlier attempts to maintain permanent venous and arterial catheters.) The 1 or 2 per cent lidocaine solution used for injection was prepared from the crystalline hydrochloride salt dissolved in sterile saline solution. The pH of the solution was brought to 7.0, and it contained no preservative. Five to 20 mg/kg lidocaine were injected at a rate of 1 mg/kg/sec. Doses were increased or decreased in 2.5 mg/kg increments at weekly or longer intervals to bracket the doses of lidocaine that just produced and did not produce a seizure. The geometric mean  $\pm$  of these two values yielded the seizure threshold dose.

Bursts of sharp high-voltage spikes appearing synchronously and simultaneously in all recording leads and separated by periods of electrical inactivity were considered evidence of a seizure. Though these seizure paroxysms were always accompanied by generalized tonic-clonic muscle contractions, the direct electrical evidence excluded the possibility that the anesthetic's neuromuscular blocking properties might mask a seizure.

Having established the animal's threshold to lidocaine-induced seizures, we studied the protective effect of diazepam. As before, spontaneous electrical activity originating from various sites of the brain was recorded with the animal at rest. Diazepam  $\pm$  (0.25 to 0.5 mg/kg) was then injected into the thigh muscles and brain activity followed intermittently. One hour later, lidocaine was injected into a limb vein and electrical activity recorded continu-

ously until the electroencephalogram (EEG) reverted to an approximately normal pattern.

As in the unmedicated cats, the new seizure threshold was determined by increasing or decreasing the dose of lidocaine in 2.5 mg/kg increments. Upon completing the anticonvulsant phase of the study, we retested the animal's threshold to lidocaine alone at weekly intervals. This was to learn whether repeated seizures altered the brain's response to local anesthetics.

Dose-response curves were constructed with the logarithm of the lidocaine dose as the abscissa and the weighted probit of the corresponding percentage incidence of seizures as the ordinate, according to the method of Litchfield and Wilcoxon.<sup>10</sup> The log-probit conversion transforms the sigmoid cumulative normal distribution curve into a straight line, thereby facilitating subsequent calculations such as the median convulsant dose ( $CD_{50}$ ) and its 95 per cent fiducial limits. Goodness of fit was checked with a chi-square test.

## Results

### LIDOCAINE

Every cat convulsed after a sufficient intravenous dose of lidocaine. The representative EEG in figure 1 illustrates the clear-cut signs of a seizure (tracing on lower right) beginning 30 seconds after 7.5 mg/kg lidocaine were injected. Note that the next smaller dose of lidocaine (5 mg/kg; tracing on lower left) hardly altered the electroencephalogram from control (upper tracing).

The dose ranges of lidocaine bracketing a seizure are summarized in table 1. Shown also are the geometric means that estimate the individual seizure thresholds. Most (8/10) cats developed seizures when 10 mg/kg or less of lidocaine were injected.

The best-fitting probit-log dose regression line is shown in figure 2 (leftmost of the two lines), where percentage seizure incidence is plotted against dose of lidocaine. Computations yielded a lidocaine  $CD_{50}$  of 8.4 mg/kg with 95 per cent confidence limits between 7.1 and 10.0 mg/kg. Analogous to the median effective dose ( $ED_{50}$ ), the median convulsant dose ( $CD_{50}$ ) is defined as that dose of drug

<sup>1</sup> Geometric Mean—the  $n$ -th root of the product of  $n$  numbers. The geometric mean is a better estimate of the midpoint than the arithmetic mean because drug-response relationships generally are logarithmic.

<sup>2</sup> Valium, marketed by Hoffman-La Roche as a 0.5 per cent aqueous solution containing 40 per cent propylene glycol, 10 per cent alcohol, and preservatives.

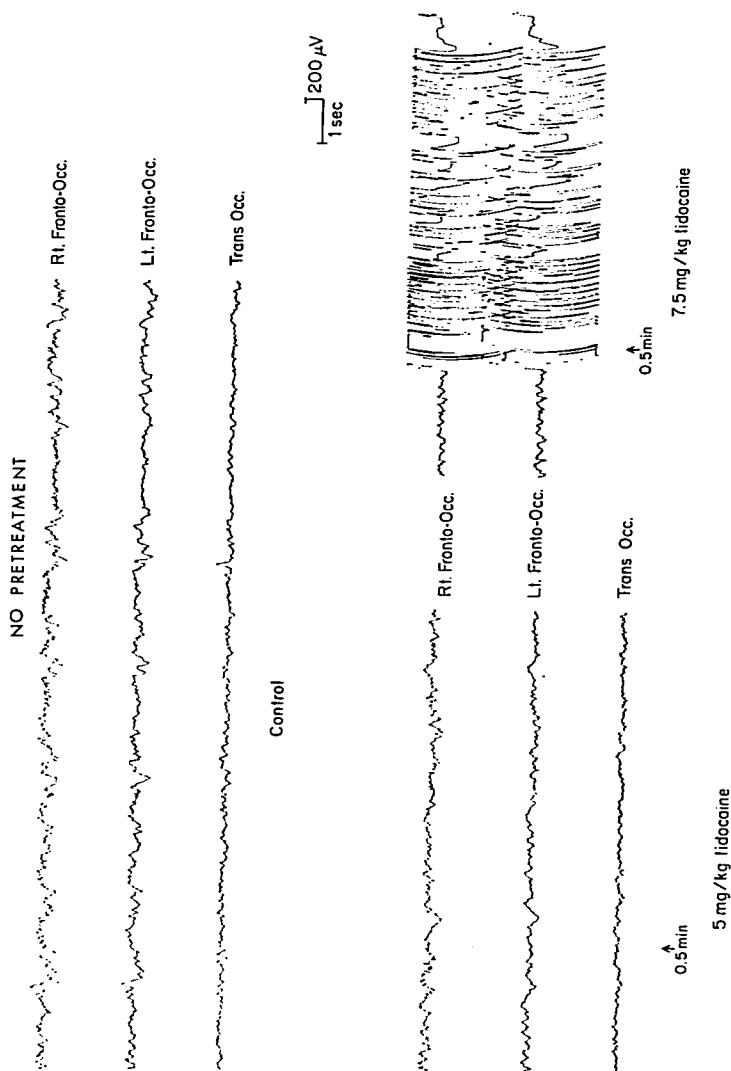


FIG. 1. Effects of increasing doses of lidocaine on the spontaneous electrical activity of the cat's cerebral cortex. Generalized convulsions followed 0.5 minutes after IV injection of 7.5 mg/kg lidocaine.

TABLE 1. Seizure Thresholds to Intravenous Lidocaine (mg/kg)

	Cat 1	Cat 2	Cat 3	Cat 4	Cat 5	Cat 6	Cat 7	Cat 8	Cat 9	Cat 10
Seizure	10.0	10.0	10.0	7.5	7.5	12.5	7.5	7.5	10.0	15.0
No seizure	7.5	7.5	7.5	5.0	5.0	10.0	5.0	5.0	7.5	12.5
Threshold dose (geometric mean)	8.7	8.7	8.7	6.1	6.1	11.2	6.1	6.1	8.7	13.7

that will produce convulsions in 50 per cent of the sample population.

#### DIAZEPAM

Intramuscular injection of 0.25 mg/kg diazepam had little effect on animal behavior and caused no discernible changes in the EEG. Occasionally a cat's gait was somewhat unsteady, but coordinated movements such as jumping remained unaffected.

Belying its minimal behavioral effects, diazepam provided excellent protection against lidocaine-induced seizures. The doses of lidocaine that bracketed seizures one hour after diazepam injection are listed in table 2. Only two of ten diazepam-treated cats convulsed when 15 mg/kg of lidocaine were injected intravenously, as compared with a 100 per cent incidence of seizures in unprotected animals. One cat did not convulse even after 20 mg/kg lidocaine had been given. (We dared not give more lidocaine, as 20 mg/kg produced apnea and flattening of the EEG.)

The seizure protection conveyed by diazepam is shown well in figure 3 (same cat as in fig. 1). Unprotected, this animal convulsed after 7.5 mg/kg of lidocaine, but after pre-

treatment with diazepam, the lidocaine dose had to be doubled before convulsions ensued.

The dose-response relations following diazepam pretreatment are summarized in figure 2 (rightmost line). Computation yields a lidocaine  $CD_{50}$  of 16.8 mg/kg, with 95 per cent fiducial limits of 15.4 to 18.3 mg/kg. Comparison of the  $CD_{50}$  after diazepam with the  $CD_{50}$  without diazepam yielded a potency ratio of 2.0 (95 per cent fiducial limits of 1.7–2.4). Statistically, the pre- and post-diazepam dose-response lines are parallel (slope factors<sup>10</sup> of 1.15 and 1.32, respectively).

Evidence for increasing protection with increasing doses of diazepam could be demonstrated in some animals (fig. 4). But the increase in threshold was slight (table 3), the mean sub-threshold dose of lidocaine rising from 14.7 mg/kg with 0.25 mg/kg diazepam (ten cats), to 15.0 mg/kg with 0.33 mg/kg diazepam (two cats), and to 16.1 mg/kg with 0.5 mg/kg diazepam (eight cats). However, this protection could not be quantitated, as the combination of large doses of diazepam and lidocaine produced severe depression and no seizures in four of eight cats so tested. Side-effects became more pronounced when

TABLE 2. Seizure Thresholds to Intravenous Lidocaine (mg/kg) after 0.25 mg/kg Diazepam

	Cat 1	Cat 2	Cat 3	Cat 4	Cat 5	Cat 6	Cat 7	Cat 8	Cat 9	Cat 10
Seizure	17.5	20.0	17.5	15.0	17.5	20.0*	15.0	17.5	17.5	—
No seizure	15.0	17.5	15.0	12.5	15.0	17.5	12.5	15.0	15.0	20.0*
Threshold dose (geometric mean)	16.2	18.7	16.2	13.7	16.2	18.7	13.7	16.2	16.2	>20.0

\* Apnea.

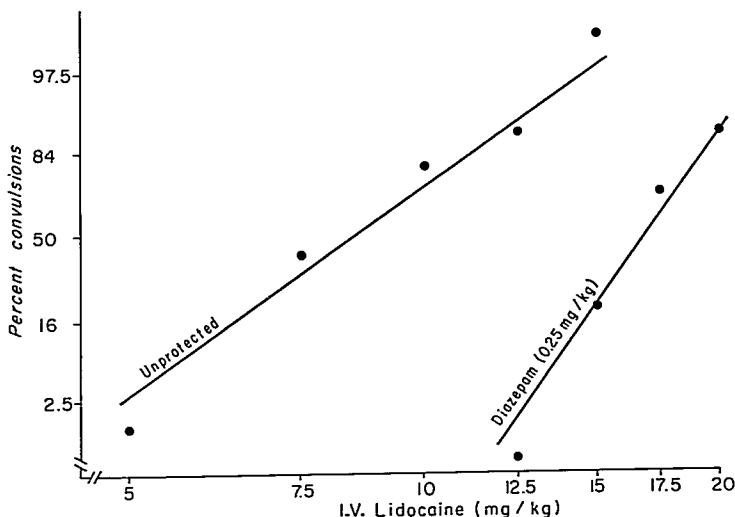


FIG. 2. Dose-response curves of unprotected and diazepam-treated cats. Incidence of seizures in each group of ten cats plotted against intravenous dose of lidocaine on probit-log dose scales. The median convulsant dose ( $CD_{50}$ ) is interpolated from the lines at the 50 per cent response level.

more than 0.25 mg/kg of diazepam was given; 0.33 mg/kg, and particularly 0.5 mg/kg, diazepam noticeably affected the animal's gait and coordination. Moreover, there was a shift to slower and higher-voltage waveforms in the EEG.

#### RESPIRATION AND CIRCULATION

Moderate doses of lidocaine (15 mg/kg or less) produced panting lasting from five to about ten minutes in the controls. The lips, nose and tongue always remained pink and well-perfused, even during seizures. On the other hand, the combination of 0.25 mg/kg diazepam and 20.0 mg/kg lidocaine caused respiratory depression in three cats and brief apnea in two. Oxygen administration by mask, with assisted or controlled ventilation as needed, led to recovery in three to six minutes.

Circulation, too, appeared to be depressed by the combination of drugs. The mucosal surfaces and conjunctivae became pale, heart

rate decreased, cardiac force (palpated through the chest wall) weakened, and venous return through the indwelling needle decreased. We noted too that the greater the dose of diazepam that preceded lidocaine, the more profound was immediate respiratory and circulatory depression—even in the absence of seizures. Three cats given 0.5 mg/kg diazepam followed by 17.5 mg/kg lidocaine required brief external cardiac compression and ventilation with oxygen for resuscitation (table 3). All recovered without apparent brain damage. We have no objective measurements of the cardiorespiratory effects of the diazepam-lidocaine combination, but are pursuing the matter in other experiments.

#### RETESTING THE SEIZURE THRESHOLD

Five convulsions, on the average, were induced in each cat over three to six months, and the animals were exposed repeatedly to large doses of drugs. Because these factors

## DIAZEPAM (0.25 mg/kg)

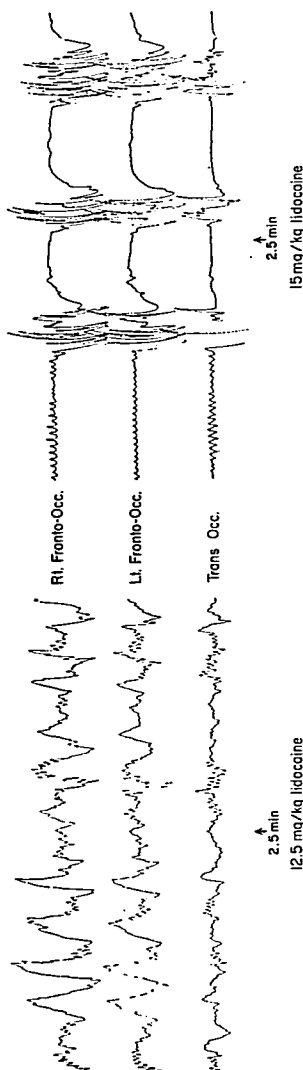
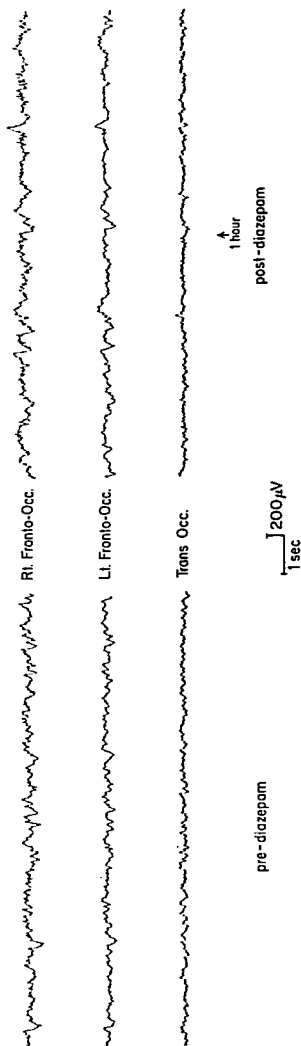


FIG. 3. The same cat as in figure 1 after pretreatment with 0.25 mg/kg of diazepam. Not until 15 mg/kg of lidocaine had been given did convulsions ensue. Bottom tracings represent comparable time spans after lidocaine injection.

2 1/2 MIN POST-LIDOCAINE

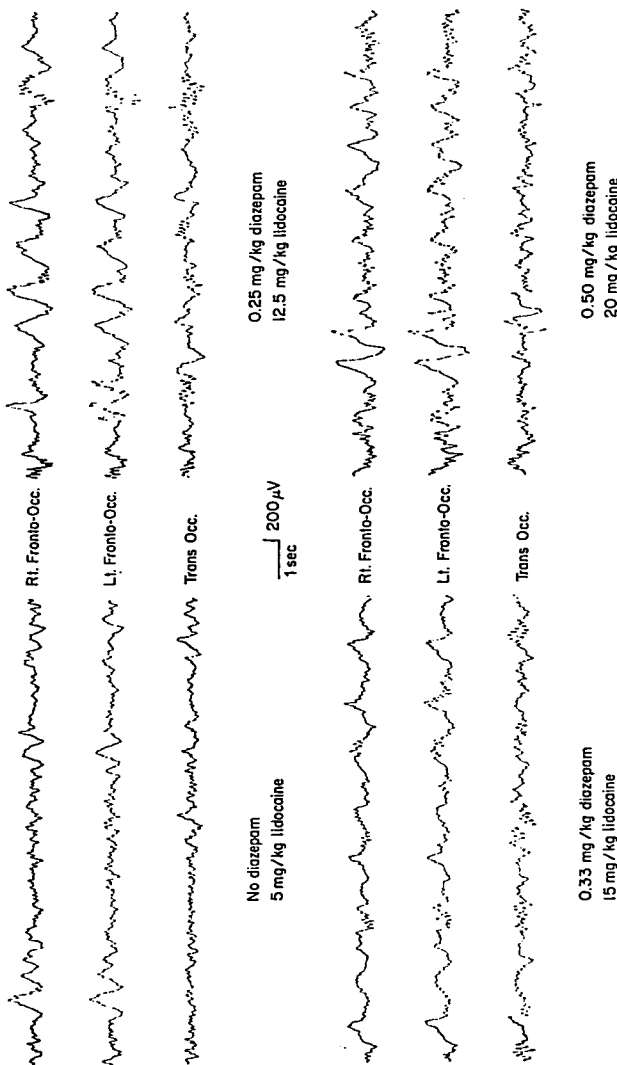


FIG. 4. The same cat as in figures 1 and 3. Increasing the dose of diazepam increased tolerance to intravenously-given lidocaine. Even 20 mg/kg lidocaine failed to induce a seizure one hour after 0.5 mg/kg diazepam. While seizures did not ensue, the larger drug doses did give rise to increasingly erratic ECG patterns.

TABLE 3. Seizure Thresholds to Intravenous Lidocaine (mg/kg) after 0.5 mg/kg Diazepam

	Cat 1	Cat 3	Cat 4	Cat 5	Cat 6	Cat 7	Cat 8	Cat 9
Seizure	—	17.5†	15.0	—	—	—	17.5	17.5†
No seizure	15.0*	15.0	12.5	17.5†	20.0*	20.0	15.0	15.0
Threshold $\frac{1}{2}$ dose (geometric mean)	>15.0	16.2	13.7	>17.5	>20.0	>20.0	16.2	16.2

\* Apnea.

† Apnea and flat EEG.

could alter the seizure threshold, we always retested the latter prior to sacrifice. There were some changes, but they were inconsistent in direction and the  $CD_{50}$  in the final experiments was exactly the same as that obtained in the initial experiments.

### Discussion

We have shown in cats that pretreatment with 0.25 mg/kg of intramuscularly injected diazepam doubles the median convulsant dose of lidocaine. Diazepam is one of a series of benzodiazepine compounds that suppress seizures or after-discharges arising from subcortical loci—notably the amygdala and hippocampus—with a considerable degree of specificity.<sup>11-14</sup> The benzodiazepines appear to be especially effective in arresting drug-induced seizures.<sup>15</sup> Chlordiazepoxide, for instance, prevents or reduces the severity and duration of cocaine-induced convulsions in rodents.<sup>9</sup>

A recent report<sup>16</sup> that procaine-induced convulsions also are prevented by prior administration of diazepam extends the usefulness of this anticonvulsant to the ester as well as the amide type of local anesthetic. Feinstein and co-workers further noted that intravenous injection of 0.3 mg/kg diazepam aborted procaine-induced (about 100 to 150 mg/kg procaine IP) convulsions in 22 of 26 cats, and shortened their durations in the remaining four.

These studies leave little doubt that diazepam and related compounds lessen the severity of, and often prevent, convulsions induced in experimental animals by local anesthetics such as lidocaine, cocaine, and procaine. The moot

point is whether these laboratory findings can be extrapolated to man. Rhesus monkeys, for one, do not exhibit the typical spindle discharges so readily elicited by local anesthetics in the cat's amygdala,<sup>17</sup> perhaps because spindling is a normal background response in awake monkeys.<sup>18</sup> Against this should be set the fact that local anesthetics induce focal discharges in deep temporal-lobe structures of man<sup>19</sup> and that diazepam most effectively arrests temporal-lobe (limbic) seizures in man.<sup>20</sup>

Considerable clinical experience with acute as well as chronic administration attests to diazepam's safety. Even large doses (1 mg/kg IV) are well tolerated by patients and attended by little cardiorespiratory depression.<sup>21</sup> Based on its efficacy as an anticonvulsant and its wide margin of safety, we recommend judicious clinical trial of diazepam as a local anesthetic premedicant.

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## Drugs

**RECOVERY FROM CURARE** The major hazard to the use of curare-like drugs in anesthesia is the failure to antagonize residual muscle weakness. The head-raising test is not always a reliable index of recovery from neuromuscular blockade. On the other hand, a sustained contraction in response to tetanic nerve stimulation could always be correlated with greater than 90 per cent recovery in vital capacity and maximum voluntary ventilation. In the event a patient cannot maintain a tetanic contraction of muscle during nerve stimulation, the residual effects from the administration of curare should be treated with an anticholinesterase drug. (Waltz, L. F., and others: *Assessment of Recovery from Curare*, J.A.M.A. 213: 1894 (Sept.) 1970.)

**SUCCINYLCHOLINE** The dangerously high levels of plasma potassium known to follow administration of succinylcholine chloride in patients with burns or trauma have also been noted in patients with paraplegia or hemiplegia, muscular dystrophy, and multiple sclerosis. Of 40 patients with these neuromuscular diseases, 15 had increases in potassium levels of between 1 and 6 mEq/l after receiving succinylcholine chloride, 1 mg/kg body weight. Most increases greater than 1 mEq/l occurred in patients who had been ill for less than six months or, if longer, who had progressive diseases. The degree and extent of muscle paralysis seemed to correlate directly with the relaxant-induced hyperkalemia. (Cooperman, L. H.: *Succinylcholine-induced Hyperkalemia in Neuromuscular Disease*, J.A.M.A. 213: 1867 (Sept.) 1970.)