Nerve Impulse Conduction During Intravenous Lidocaine Injection

Rudolph H. de Jong, M.D., and Roger A. Nace, B.S.†*

The purpose of this experiment was to study the effects of an intravenously-given local anesthetic on impulse conduction in myelinated and nonmyelinated axons. In 13 cats, the right femoral nerve was stimulated proximally, and the compound nerve action potential recorded distally from its saphenous branch. From their respective conduction velocities, α-, δ- and C-fiber responses were identified.

Intravenous lidocaine (5.0–17.5 mg./kg.) depressed response amplitude more than conduction time in δ- and C-fibers; C-fibers were more depressed than were δ-fibers. The linear log dose-effect relationship for depression of amplitude and conduction velocity by lidocaine was statistically significant for C-fibers only. Even the largest tolerated intravenous doses of lidocaine depressed the amplitude of the C-fiber potential less than 50 per cent; moreover, such doses barely affected conduction in α-fibers (less than 5 per cent). Recovery of function, slowest in C-fibers, was approximately two times faster in δ-fibers and took less than five minutes in α-fibers.

Arterial hypotension produced by large doses of lidocaine evidently was not responsible for changes in nerve parameters; in contrast to the blocking sequence observed with lidocaine, ischemia profoundly depressed conduction in α-fibers and had little immediate effect on C-fibers.

PROCAINE AND LIDOCAINE injected intravenously in the experimental animal selectively reduce conduction in small- but not in large-diameter myelinated axons,[1, 2, 3] an action similar to the differential block of small-diameter axons when a weak local anesthetic solution is applied directly to a peripheral nerve or a spinal root.[3, 4] In man, "pain impulses" are conducted by small myelinated (delta) and nonmyelinated (C) axons.[5] If intravenous local anesthetics blocked C-fibers in addition to δ-fibers, they might interrupt the transmission of "pain impulses" to produce analgesia.

To evaluate drug action on axons which conduct impulses generated in cutaneous "pain receptors," we studied impulse conduction in the cat's saphenous nerve, which has a high proportion of δ- and C-fibers.[6, 7]

Methods

Thirteen healthy fasting cats, weighing 2.3 to 4.3 kg. were anesthetized intraperitoneally with pentobarbital (30–35 mg./kg.). This was supplemented, when necessary, by one or at most two 10-mg. intravenous injections of pentobarbital. The trachea was intubated after topical anesthesia, and an esophageal thermocouple was placed retrocardiac.

Methods used to stimulate and record neural response have been described.[8] The left saphenous vein and femoral artery were cannulated. The arterial catheter was advanced, according to surface landmarks, to 1 cm. proximal to the bifurcation of the aorta; its position was verified by necropsy in four animals. The left fronto-occipital electroencephalogram (EEG) was recorded continuously, together with the femoral arterial blood pressure, on an oscillograph. Body temperature was maintained between 37° and 38° C. with a heating blanket.

One-cm.-long portions of the right femoral nerve and its saphenous branch were exposed gently through separate incisions in the leg, then placed on platinum electrodes at least 60 mm. apart. Thus much of the nerve was undisturbed with circulation intact. The flaps of skin were elevated to form individual oil

* Associate Professor of Anesthesiology and Pharmacology, University of Washington School of Medicine, Seattle, Washington 98105. Supported by Public Health Service Career Development Award 5-K3-GM-28,168.

† Research Assistant, Department of Anesthesiology, University of Washington School of Medicine, Seattle, Washington.

Accepted for publication July 21, 1967. Supported by University of Washington General Research Support grants 11-9614 and 11-9625, by Washington State Initiative 171 funds, and by a grant from the Astra Pharmaceutical Company.

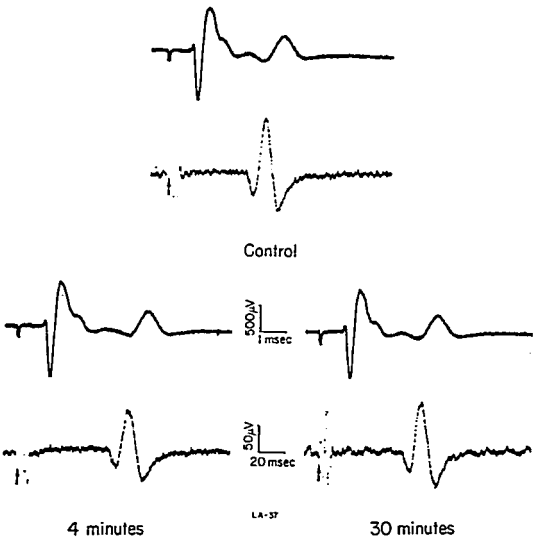

FIG. 1. Representative experiment. Upper tracings in each block, left to right, show the small stimulus artifact, then the large α-potential, followed by the smaller δ-elevation. The lower tracing in each block—compressed in time scale and with a tenfold increase in gain—shows stimulus artifact at arrow, immediately followed by the faintly visible off-screen α- and δ-responses. The triphasic C-wave is clearly seen. Following injection of lidocaine the C-potential fell to 72 per cent and the δ-potential to 84 per cent of control at four minutes. The α-potential was unchanged. Conduction times of C- and δ-waves rose by 11.0 and 0.6 msec., respectively; α conduction time was unchanged.

pools, one for the distal and one for the proximal portion of the nerve. Upon completion of the surgical procedure, gallamine was injected to eliminate muscle artifacts, and the lungs were ventilated mechanically with air.

The compound action potential of components of the saphenous nerve was determined in standard fashion. The nerve was antidromically stimulated at the proximal electrode pair with 0.3 msec. rectangular pulses delivered to an isolation transformer. The stimulus voltage required for maximal amplitude of each response group was recorded, then increased by 30–50 per cent. Biphasic nerve potentials were led from the distal electrode pair to a first preamplifier at wide bandwidth (30 kHz.) to record high-amplitude, fast responses, thence to a second preamplifier with narrower bandwidth (500 Hz.) for the lower-amplitude and slower responses.* Outputs from the first- and second-stage preamplifiers were displayed simultaneously on a dual-beam oscilloscope at sweep speeds of 1 msec./cm. and 20 msec./cm., respectively, and photographed on 35 mm. film.

Seventeen experiments were performed with lidocaine hydrochloride (1 or 2 per cent solution of Xylocaine) given as a single intravenous injection of 5.0–17.5 mg./kg., 1.5–3.5 ml. in volume, in 10 seconds. (In one experiment 30 mg./kg. was given at a rate of 6 mg./kg./min.) Ten experiments were performed by injecting a bolus of lidocaine (5–25 mg./kg.) through the intra-arterial catheter whose tip was close to the origin of the right external iliac artery. Subsequent injections of lidocaine were given no less than 90 minutes apart, and only when nerve responses, EEG and arterial blood pressure had returned to control values.

Peak-to-peak amplitudes of action potentials (in microvolts) and conduction time from stimulus artifact to first rise from baseline (in

* The symbol Hertz (Hz.) supplants cycles/second.

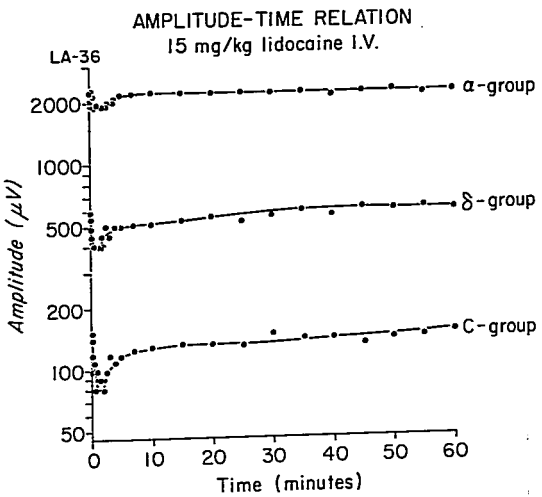

FIG. 2. Amplitude plot of α-, δ- and C-potentials versus time. Absolute magnitude of amplitude shown on log scale. Intravenous dose of lidocaine, 15 mg./kg. Note minimal change and rapid recovery of α-responses, in contrast with marked depression and prolonged recovery of C-amplitude.

milliseconds) were measured on the projection-enlarged film. The conduction velocity (in meters per second) was calculated by dividing conduction time into conduction distance; this ranged from 58 to 102 mm. (mean 82.8 mm.) between stimulating cathode and nearest recording electrode. Control records of the compound nerve action potential were made immediately before lidocaine injection. Nerve responses were then recorded every five seconds in the first half minute, every 20 seconds for the next three minutes, at one-minute intervals for ten minutes, and subsequently every five minutes for one hour following lidocaine injection.

To check the adequacy of nerve perfusion and to determine the effects of several variables introduced into the experiments, the following tests were done upon completion of the procedures: (a) saline solution (10 ml.) was injected intravenously or intra-arterially, (b) nerve responses were recorded up to two hours following induced circulatory arrest, (c) large doses of pentobarbital (120 mg.) and gallamine (100 mg.) were injected intravenously, and (d) 95 per cent alcohol (2 ml.) was injected intra-arterially.

Results

Controls. The compound action potential recorded from the saphenous nerve prior to the injection of lidocaine consisted of three distinct groups of elevations identified by their conduction velocities as representing α-fibers (85.9 ± 4.3 m./sec.), δ-fibers (21.2 ± 1.0 m./sec.) and C-fibers (1.15 ± 0.03 m./sec.), in excellent agreement with results obtained by others.[7, 9] In two instances the C-wave consisted of two separate elevations—C_1 and C_2; the latter's conduction velocity was 0.94 m./sec. Because behavior of the two C-wave fractions was identical, calculations were based on the major early (C_1) component only.

Intravenous Injection. Intravenously-administered lidocaine depressed the amplitude of the propagated potentials. The effect was most pronounced in C-fibers. In a representative experiment (fig. 1) lidocaine (10 mg./kg.) reduced the C-potential to 72 per cent, the δ-potential to 84 per cent and the α-potential to 98 per cent of control values. Recovery times also varied with fiber size. Complete recovery of the action potential took five minutes for α-fibers, 30 minutes for δ-fibers, and close

to 60 minutes for C-fibers in another experiment (fig. 2).

In all fiber groups, conduction time (reflecting conduction velocity) was affected considerably less than action potential. Even the more profoundly depressed C-fibers showed relatively small changes in conduction time (figs. 3 and 4). The changes in conduction time of δ- and α-fibers during lidocaine administration were even smaller and were statistically not significant (see below).

The regression of log of lidocaine dose on the lowest observed amplitude of α-, δ- and C-waves, respectively, was computed and plotted (XTAB program B6). A statistically significant linear relationship (fig. 3) between amplitude and log dose was found for C-fibers only ($r = -0.832$; $P < 0.001$).

The relationship was not significant for δ-fibers ($r = -0.647$; $P < 0.1$) and α-fibers ($r = -0.510$; $P > 0.1$). Thus, increasing lidocaine dosage significantly and progressively depressed conduction in the C-fibers only.

The relation between conduction velocity and log of lidocaine dose was examined in similar fashion. A statistically significant linear relation (fig. 4) between these two parameters was found for C-fibers only ($r = -0.679$; $P < 0.01$). Neither δ- nor α-fiber conduction velocity was related significantly to log lidocaine dose ($r_\delta = -0.522$; $r_\alpha = -0.468$; $P > 0.1$).

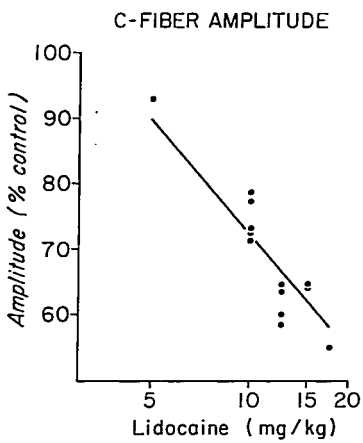

FIG. 3. Scattergram of C-fiber amplitude versus dose of lidocaine. Amplitude expressed as percentage of control value. Calculated regression line (13 experiments) is shown. (Semi-log scale.)

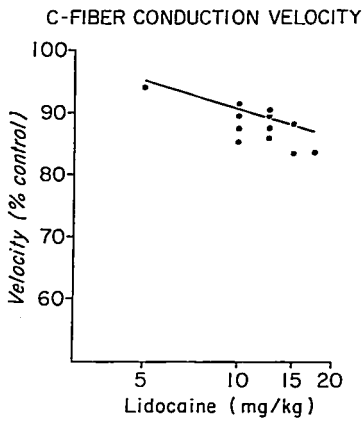

FIG. 4. Scattergram of C-fiber conduction velocity versus dose of lidocaine. Velocity expressed as percentage of control value. Calculated regression line (12 experiments) is shown. (Semi-log scale.)

The changes in amplitude and conduction velocity were seen only when arterial circulation was sufficient to perfuse the nerve. In several instances where large intravenous doses of lidocaine (15 to 25 mg./kg.) produced instantaneous circulatory arrest, significant immediate changes in nerve function were not seen. Similarly, in one experiment where a 30 mg./kg. dose of lidocaine was given at a rate of 6 mg./kg./min., blood pressure rapidly fell to 35 mm. Hg and nerve changes resembled those seen during rapid injection of a 7.5 mg./kg. dose of lidocaine.

Circulatory Arrest. Instantaneous circulatory arrest was produced by large intravenous doses of pentobarbital (240 mg.) or lidocaine (20–30 mg./kg.). Nerve responses were recorded up to two hours following death. The α-potentials started to fall at 30 minutes and disappeared at 75 minutes. The δ-potential was 50 per cent of control at 30 minutes and

disappeared at 40 minutes. The C-fibers were very resistant to anoxia. Their potential increased slightly at first (110 per cent of control at 60 minutes) and then fell gradually, so that at 120 minutes it was still 40 per cent of control. Thus, the changes produced by lidocaine in C-fibers appear not to have been due to arterial hypotension.

Ancillary Drugs. Neither pentobarbital nor gallamine, in large intravenous doses, affected the amplitude or conduction time of any fiber group. Similarly, rapid injection of 10 ml. saline solution intravenously or intra-arterially had no effect on nerve response.

Intra-arterial Injection. Since the intravenous injection of lidocaine had less effect on nerve properties than anticipated, we wanted to be certain that circulation to the nerve had not been altered by the dissection. Fast intra-arterial injection of lidocaine into the right external iliac artery close to its origin produced profound and rapid though short-lasting changes in the nerve; these corresponded to the changes seen during intravenous injection. The dose-effect response to lidocaine given intra-arterially was not greatly different from that to lidocaine given intravenously, except that considerably larger doses could be given by the intra-arterial route without producing severe hypotension.

The arterial blood supply to the nerve was further tested by rapid intra-arterial injection of 2 ml. 95 per cent alcohol. Within five seconds effects of the alcohol became apparent. The C_2-wave disappeared at ten seconds, the C_1-wave at 15 seconds, and the δ-wave at 40 seconds. The α-wave was one-half control size at 80 seconds, completely disappearing at six minutes. Thus there can be little doubt that the arterial circulation to the nerve was intact.

Electroencephalogram. Even large intravenous doses (10–15 mg./kg.) of lidocaine had relatively little effect on the EEG in cats lightly anesthetized with pentobarbital. The general appearance of the EEG during lidocaine administration was a slow (0.2–0.5 Hz.) rhythm of moderate amplitude (50–75 μV.). When blood pressure fell to 50 mm. Hg or lower the EEG became flat. When the blood pressure returned to 50 or 60 mm. Hg, slow moderate-amplitude spontaneous activity resumed. At no time was there evidence of synchronous electrical seizure activity previously observed in unanesthetized mechanically-ventilated cats.[10]

Discussion

We have shown that an intravenously-injected local anesthetic produces demonstrable effects on conduction in small-diameter myelinated (delta) and in nonmyelinated (C) fibers, and has a negligible effect on conduction in large-diameter myelinated (alpha) fibers. Although conduction block became more profound when a greater dose was injected, the effect was not statistically significant for myelinated axons. These findings correspond to the observations by Wagers and Smith that intravenous procaine and lidocaine produce dose-dependent, rapid depression of small-diameter myelinated fibers (γ- and δ-group) in the dog's tooth pulp.[2]

The amplitude of the action potential in nonmyelinated C-fibers, on the other hand, was inversely and significantly related to the logarithm of the local anesthetic dose. Nevertheless, near-lethal doses of intravenous lidocaine (12.5 mg./kg. or greater) were required to reduce the control amplitude by more than 25 per cent. Thus, for practical purposes, the intravenous injection of a local anesthetic does not have a clinically important effect on the conduction of impulses in nerve fibers. The small effect seen is dissipated in less than five minutes.

This finding is germane to the interpretation of the actions of systemically-administered local anesthetics on the nervous system, since exclusion of an important effect on conducted impulses in fiber tracts implies a predominant effect on central synaptic transmission. This has been borne out by several studies. For instance, Blom has shown that the linguomandibular reflex (a polysynaptic cranial nerve reflex) is depressed profoundly, though briefly, by doses of lidocaine greater than 5 mg./kg.[11] Taverner showed that lidocaine and tetracaine injected intravenously profoundly depress polysynaptic ventral root reflexes, in the absence of major changes in perfusion of the spinal cord.[12] Whether the intravenous injection of a local anesthetic produces analgesia in sub-

jects with chronic pain or as an adjunct to general anesthetics is a moot question. Whatever the benefits, they almost certainly may be ascribed to central synaptic mechanisms, as suggested by, for example, Steinhaus and Gaskin.[13]

The rapid onset of partial conduction block in small-diameter fibers is evidence that the local anesthetic passes readily from the vascular to the perineural space. Dilution and removal by the bloodstream in these experiments presumably prevented attainment of a sufficient concentration of local anesthetic to cause complete conduction block in the peripheral nerve. Vascular isolation of a limb by means of a tourniquet might favor exposure of extremity nerves to a local anesthetic for a period of time sufficient to produce impulse-conduction block in the small-diameter axons (δ- and C-fibers) which conduct impulses originating in "pain receptors."[5] The large myelinated fibers evidently are little affected by local anesthetics during intravenous regional anesthesia.[14, 15] Nevertheless additional studies of conduction in smaller-diameter axons during the intravenous injection of local anesthetics in the vascularly isolated limb should be done before ascribing the analgesia to local anesthetic action on nerve terminals alone.[14] Rigid experimental verification of this hypothesis may be difficult, since ischemia itself depresses impulse conduction.[16, 17]

It remains to be shown that the pentobarbital given to provide surgical anesthesia did not affect impulse conduction, and that the local anesthetic actually reached nerve fibers. Pentobarbital in customary anesthetic concentrations does not affect nerve conduction.[18] Since the EEG indicated only light barbiturate depression during our studies, and since large intravenous doses of pentobarbital (60–90 mg.) did not have any measurable effect on nerve potentials, we are reasonably certain that pentobarbital did not modify our findings. The intra-arterial injection of lidocaine near the origin of the main arterial trunk supplying the nerve had an almost instantaneous effect on nerve conduction, which confirmed that lidocaine passed rapidly from the vascular space to the neural membrane. The possibility that hypotension, seen with large intravenous doses of lidocaine, might contribute to the increasing block of impulse conduction was eliminated by showing that a larger drug dose, injected intra-arterially, caused only a slight, brief fall in blood pressure, but produced an identical effect on the action potential.

Summary and Conclusions

We investigated the effect of intravenously-injected lidocaine on impulse conduction in cat's saphenous nerve. Even the largest doses of lidocaine had no significant effect on α-fiber conduction. Amplitude of the δ- and C-fibers was clearly depressed by lidocaine, but even near-lethal (15 mg./kg. or more) doses of lidocaine reduced the amplitude of the C-fiber potential no more than 50 per cent. A significant relationship between dose and decrement in amplitude existed for C-fibers only.

We conclude that an intravenously-injected local anesthetic slows and reduces impulse conduction in small-caliber fibers for a few minutes; conduction in large fibers is not importantly affected.

The authors thank Dr. Wagman for his helpful suggestions.

References

1. Peterson, C. G.: Neuropharmacology of procaine. I. Peripheral nervous actions, ANESTHESIOLOGY 16: 678, 1955.
2. Wagers, P. W., and Smith, C. M.: Responses in dental nerves of dogs to tooth stimulation and the effects of systemically administered procaine, lidocaine and morphine, J. Pharmacol. Exp. Ther. 130: 89, 1960.
3. de Jong, R. H., and Wagman, I. H.: Physiological mechanisms of peripheral nerve block by local anesthetics, ANESTHESIOLOGY 24: 684, 1963.
4. Nathan, P. W., and Sears, T. A.: Some factors concerned in differential nerve block by local anaesthetics, J. Physiol. 157: 565, 1961.
5. Collins, W. F., Nulsen, F. E., and Randt, C. T.: Relation of peripheral nerve fiber size and sensation in man, Arch. Neurol., 3: 381, 1960.
6. Hunt, C. C., and McIntyre, A. K.: An analysis of fibre diameter and receptor characteristics of myelinated cutaneous afferent fibres in cat, J. Physiol. 153: 99, 1960.
7. Douglas, W. W., and Ritchie, J. M.: Non-medullated fibres in the saphenous nerve

which signal touch, J. Physiol. 139: 385, 1957.
8. de Jong, R. H., and Nace, R. A.: Nerve impulses conduction and cutaneous receptor responses during general anesthesia, ANESTHESIOLOGY 28: 851, 1967.
9. Paintal, S. A.: Effects of temperature on conduction in single vagal and saphenous, myelinated nerve fibres of the cat, J. Physiol. 180: 20, 1964.
10. Wagman, I. H., de Jong, R. H., and Prince, D. A.: Effects of lidocaine on the central nervous system, ANESTHESIOLOGY 28: 155, 1967.
11. Blom, S.: Diphenylhydantoin and lidocaine in decerebrate cats, Arch. Neurol. 8: 506, 1963.
12. Taverner, D.: The action of local anaesthetics on the spinal cord of the cat, Brit. J. Pharmacol. 15: 201, 1960.
13. Steinhaus, J. E., and Gaskin, L.: A study of intravenous lidocaine as a suppressant of cough reflex, ANESTHESIOLOGY 24: 285, 1963.
14. Miles, D. W., James, J. L., Clark, D. E., and Whitwam, J. G.: Site of action of "intravenous regional anaesthesia," J. Neurol. Neurosurg. Psychiat. 27: 574, 1964.
15. Adams, J. P., Dealy, E. J., and Kenmore, P. L.: Intravenous regional anesthesia in hand surgery, J. Bone Jt. Surg. 46: 811, 1964.
16. Wagman, I. H.: Effects of ischemia on properties of the neuromuscular system of man, XXIInd Int. Congr. Physiol. Sci., Abstract #956, 1962.
17. Bentley, F. H., and Schlapp, W.: The effects of pressure on conduction in peripheral nerve, J. Physiol. 102: 72, 1943.
18. Larrabee, M. G., and Posternak, J. M.: Selective action of anesthetics on synapses and axons in mammalian sympathetic ganglia, J. Neurophysiol. 15: 91, 1952.

Anesthesia

MATERNAL HYPOCAPNIA In 18 patients undergoing cesarean section with an anesthetic technique which included hyperventilation, mean maternal arterial P_{CO_2} was 16.5 mm. Hg, mean *p*H 7.618, and mean P_{O_2} 147 mm. Hg. The mean blood gas values of cord blood at delivery were: umbilical artery *p*H 7.248, P_{O_2} 16.2 mm. Hg, P_{CO_2} 41 mm. Hg; umbilical vein *p*H 7.313, P_{O_2} 27.5 mm. Hg, P_{CO_2} 36.3 mm. Hg. The findings indicate that babies of hypocapnic mothers have normal blood gas values at delivery. (*Coleman, A. J., and Lond, M. B.: Absence of Harmful Effects of Maternal Hypocapnia in Babies Delivered at Caesarean Section, Lancet 1: 813 (April) 1967.*)

UMBILICAL CORD BLOOD PRESSURE Blood pressure in umbilical artery and vein was measured in eleven patients during term cesarean section. Anesthesia consisted of methohexital induction and maintainence with nitrous oxide-oxygen and a muscle relaxant. No maternal hypotension occurred. Average systolic arterial pressure was 88 mm. Hg and average diastolic pressure 77 mm. Hg. The average umbilical venous pressure was 41 mm. Hg, with no pulse pressure. These figures are higher than those reported by others for patients in whom spinal anesthesia was used. (*Malpar, P., and Symonds, E. M.: Arterial and Venous Pressures in the Human Umbilical Cord, Amer. J. Obstet. Gynec. 98: 261 (May) 1967.*)

EPIDURAL ANALGESIA It was found that upper thoracic epidural analgesia reduces cardiac performance in two ways: by slowing the heart rate and by reducing the myocardial response to its filling pressure. Even with lumbar technique, there may be a cardiac component by adding peripheral pooling and a failure to venous return. Isoproterenol corrects the central effects by increasing force and rate of cardiac contraction and produces a higher cardiac output than norepinephrine for a similar energy expenditure. The latter drug increases blood pressure without significant increase in cardiac output and with a further slowing of pulse rate. (*McLean, A. P. H., and others: Hemodynamic Alterations Associated with Epidural Anesthesia, Surgery 62: 79 (July) 1967.*)