The Uptake and Release of Norepinephrine:

Effects of Cyclopropane and Halothane

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The uptake and release of norepinephrine (NE) by the peripheral sympathetic nerve endings were studied *in vivo*. A tracer dose of DL-^{3}H-NE was injected intravenously into rats to measure the uptake of ^{3}H-NE by the heart. In comparison with controls, cyclopropane did not change the myocardial NE levels or specific activity. Halothane decreased initial uptake, probably owing to circulatory depression. In dogs myocardial NE stores were labelled by intracoronary ^{3}H-NE infusion. The A-V difference in tritium activity across the heart indicated ^{3}H-NE release. Cyclopropane did not appear to alter the release pattern when arterial pressure was maintained. NE release increased with significant hypotension. Halothane decreased arterial pressure but did not affect NE release. NE stores in the cat iris were labelled by intracarotid ^{3}H-NE injection. Tritium activity in the anterior chamber perfusate during and after cervical sympathetic stimulation reflected indirectly NE uptake by the iris. Again, cyclopropane had no apparent effect.

DIFFERENCES in the circulatory effects of several inhalational anesthetics have been attributed to their actions on the sympathetic nervous system.[1] In man cyclopropane causes minimal changes in the arterial pressure and pulse rate with an increase in plasma norepinephrine (NE) levels. Halothane depresses cardiovascular function; plasma NE levels remain normal. While controversy still exists concerning the action of these anesthetics on neural regulatory mechanisms of circulation,[2-6] plasma NE increases during cyclopropane anesthesia presumably because NE is being released from peripheral sympathetic nerve endings. Alternatively, anesthetics could alter the biochemical processes in synthesis, release, uptake or degradation of NE, reflected in changes of tissue and plasma levels as well as cardiovascular function. In the present study we examined the effects of cyclopropane and halothane on the uptake and release of norepinephrine by peripheral sympathetic nerves in vivo. Tritiated NE was used in tracer doses to follow the movement of endogenous NE. The effects of anesthetics on NE biosynthesis in the heart and the brain will be reported in a subsequent paper.[7]

Methods

Male Sprague-Dawley rats weighing 200 g each were used to study the uptake of norepinephrine by the heart. Animals were placed in individual chambers, each with an inlet for gas mixtures (Medical Instrumentation Laboratory, Columbia University College of Physicians and Surgeons). The chamber has a capacity of about 500 ml (or 300 ml with the rat in place). The anesthetic mixture from an Ohio series 3,000 kinetometer was distributed through a manifold at a flow of 300 ml/min to each chamber. Twenty-five per cent oxygen–75 per cent nitrogen was used as the diluent gas to avoid the possible effect of high concentrations of oxygen on the NE system.[8] Light anesthesia as evidenced by a loss of righting reflexes was produced with 15 per cent cyclopropane or 1 per cent halothane.

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Rats used as controls breathed a mixture of 25 per cent oxygen and 75 per cent nitrogen.

After one hour of anesthesia, DL-^{3}H-norepinephrine,§ 10 μc/kg (equivalent to 0.34 μg/kg base) in one ml of 0.9 per cent saline, was rapidly injected into the tail vein of the rat. Anesthesia was continued. Groups of four or more animals were killed by decapitation at ten, 30 and 60 minutes after isotope injection. The hearts were immediately removed, rinsed in water, blotted, and frozen until assayed for stable and radioactive NE.

Assay for NE was done according to the method of Neff and Costa.[9] Briefly, the hearts were homogenized in 6 volumes of 0.4 N perchloric acid. After centrifugation, 3 ml of the supernatant was brought to a pH of about 8.3 with 6 ml of 0.5 M tris buffer (*p*H 9). About 1 g of alumina (Woelm Neutral, grade 1, prepared according to Crout[10]) was added and the mixture hand-shaken gently for ten minutes for catechol adsorption. The alumina was washed twice with distilled water and the adsorbed catechols eluted with 3 ml of 0.25 N acetic acid. A 0.75-ml aliquot of the eluate was used for fluorometric assay of NE.[10] A separate 1.5-ml portion was transferred to Bray's mixture [11] for counting with a liquid scintillation spectrometer (Packard Instrument Co.). Specific activity was expressed as counts per minute (CPM) per μg of NE. Appropriate standards were carried through the entire procedure. Recovery of NE ranged from 50 to 60 per cent.

Twenty-four mongrel dogs weighing 15 to 25 kg were used to study NE release from the heart. Basal anesthesia consisted of 100 mg /kg of α-chloralose, given intravenously. The trachea was intubated with a cuffed tube. A modified Frumin respirator provided constant-volume ventilation through a nonrebreathing system. The chest was opened through a midline sternotomy and the heart suspended in its pericardial cradle. A small catheter (PE 50) was introduced retrograde through a small branch of the anterior descending coronary artery, with the tip placed at or near the left main coronary artery. After heparinization, coronary sinus outflow was diverted with a modified Morawitz cannula, measured with an electromagnetic flowmeter (Biotronex Laboratory, Silver Springs, Md.), and returned to the right atrium. Arterial pressure was transduced with a Statham gauge (P 23d). Both pressure and coronary sinus outflow were recorded on a Grass polygraph.

DL-^{3}H-norepinephrine, 100 μc (3.4 μg base) in 20 ml 0.9 per cent saline solution was infused through the intraarterial catheter over a period of 20 minutes. Upon completion of infusion, samples of arterial and coronary sinus blood were obtained at 15-minute intervals. After centrifugation, two volumes of 0.4 N perchloric acid were added to the plasma to precipitate the proteins. The mixture was centrifuged again and 0.5 ml of the supernatant (plasma water) was put into Bray's mixture, then placed in the liquid scintillation spectrometer. Activity in the plasma is expressed as CPM/ml.

In control experiments the animals were ventilated with oxygen only. Cyclopropane (15 per cent, inspired) or halothane (0.75–1 per cent, inspired) in oxygen was administered for 60 minutes preceded and followed by appropriate control and recovery periods. Dextran and Ringer's solution were given intravenously to replace blood loss. Body temperature was maintained at 38–39 C with heating blankets.

In a third series of experiments NE release from the iris was studied in 15 cats. Under diethyl ether anesthesia, tracheotomy and midcollicular decerebration were performed. After these procedures the animals breathed air for at least one hour. DL-^{3}H-NE, 50 μc (1.7 μg base) in 10 ml 0.9 per cent saline, was injected into one of the common carotid arteries. The anterior chamber of the ipsilateral eye was perfused with Ringer's solution through a 26-gauge needle at a rate of 1.6 ml/min. The effluent perfusate, flowing through another needle, was collected at intervals directly into counting vials, each receiving the perfusate for 15 seconds. Radioactivity was measured as above.

The cervical sympathetic trunk was separated from the vagus nerve and cut at the lower cervical level. A bipolar electrode was placed around the cephalic part for periodic electrical stimulation (one minute at 15-minute intervals). Square-wave currents were de-

§ New England Nuclear Corporation, specific activity 5 c/mM.

TABLE 1. Effects of Cyclopropane and Halothane on the Heart Norepinephrine Level and Specific Activity Following iv Injection of ^{3}H-NE in Rats*

Hours of Exposure	Minutes after ^{3}H-NE Injection	Control (25 per cent oxygen)		Cyclopropane (15 per cent)		Halothane (1 per cent)	
		NE Level (μg/g)	Specific Activity (CMP/μg)	NE Level (μg/g)	Specific Activity (CMP/μg)	NE Level (μg/g)	Specific Activity (CMP/μg)
1	10	1.00 ± 0.03 (16)	3,407 ± 88	0.91 ± 0.08 (10)	3,339 ± 187	1.12 ± 0.03 (7)	2,533 ± 65**
1.5	30	1.04 ± 0.04 (17)	2,382 ± 123	1.03 ± 0.08 (10)	2,219 ± 156	1.11 ± 0.05 (8)	2,086 ± 127
2	60	0.97 ± 0.02 (17)	1,694 ± 100	1.04 ± 0.04 (10)	1,566 ± 89	1.09 ± 0.07 (7)	1,799 ± 72

* DL-^{3}H-NE, 10 μc/kg, was injected after one hour of exposure to anesthesia or 25 per cent oxygen. Values are means ± S.E.
Numbers of animals are indicated in parentheses.
** Different from control, $P < 0.01$.

rived from a laboratory stimulator (American Electronic Laboratories, Model 104) through its stimulus-isolation transformer, having an intensity of 5 volts, a pulse duration of 2 sec, and a frequency of 40 Hz.

Cyclopropane (10–15 per cent, inspired)–oxygen was administered through a nonrebreathing valve connected to the tracheal cannula. These concentrations of cyclopropane had been shown to abolish corneal and masseter reflexes in decerebrate cats.[12] Before and after cyclopropane administration the animal breathed room air. Body temperature was maintained at 38 ± 1 C with a heating blanket.

Student's t test was used to assess the significance of difference between control and experimental values where applicable.

Results

Uptake and Release of Norepinephrine by the Heart in Rats

The heart NE levels and specific activity (S.A.) in rats breathing 25 per cent oxygen (controls) or anesthetic mixtures are summarized in table 1. The mean level for all control animals was 1.00 ± 0.02 μg/g (mean ±SE). The group anesthetized with cyclopropane for one to two hours had a mean level of 0.99 ± 0.04 μg/g, and those anesthetized with halothane, 1.11 ± 0.03 μg/g, slightly higher than the controls ($P < 0.01$).

Following an intravenous injection of ^{3}H-NE, specific activity of the heart NE at earlier times reflects the NE uptake by sympathetic nerve endings in the myocardium. In control animals the mean specific activity declined rapidly from about 3,400 CPM/μg at ten minutes to 1,700 CPM/μg at 60 minutes. As shown in table 1, NE specific activities at ten, 30 and 60 minutes in animals anesthetized with cyclopropane closely approximated the control values.

During halothane anesthesia the heart NE specific activity at ten minutes after ^{3}H-NE injection averaged 2,500 CPM/μg, much lower than that of control at the corresponding time. Subsequently there was no significant difference between control and experimental groups.

Release of Norepinephrine from the Heart in Dogs

After labelling the myocardial NE stores with intraarterial ^{3}H-NE infusion, the radioactivity in the plasma of coronary sinus blood decreased rapidly during the first hour. Thereafter the decline was slow. The pattern in three control experiments with animals breathing oxygen is shown in figure 1. Radioactivity in the coronary sinus plasma 15 minutes after completion of ^{3}H-NE infusion was considered as 100 per cent. At one hour the mean activity fell to 55.4 ± 2.3 (SE) per cent and at two hours, 41.5 ± 4.1 per cent. Further change was negligible. Radioactivity in the arterial plasma paralleled that in the coronary sinus plasma at a lower level. The coronary sinus–arterial difference indicated that NE was being released from the myocardial stores.

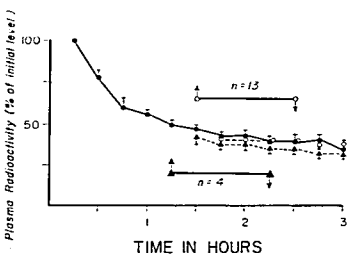

FIG. 1. Radioactivity in the coronary sinus plasma following intraarterial infusion of DL-^{3}H-NE (100 μc, 3.4 μg base) into the left main coronary artery. Infusion was completed at time zero. Initial value at 15 minutes is considered 100 per cent. Values are mean ±S.E. ●——● is the curve of control dogs ventilated with oxygen, ○——○ 15 per cent cyclopropane, and ▲——▲ 0.75–1 per cent halothane. Arrows indicate beginning and end of anesthetic inhalation.

In 17 dogs cyclopropane (15 per cent) was added to the inspired mixture 90 minutes after completion of ^{3}H-NE infusion. Inhalation of the anesthetic lasted one hour, following which oxygen breathing was continued for another 30–45 minutes. In 13 dogs mean arterial pressure just before cyclopropane inhalation averaged 107 ± 5.8 mm Hg, the coronary sinus blood flow, 42 ± 2.1 ml/min. Corresponding values during cyclopropane inhalation were 100 ± 7.4 mm Hg ($P < 0.05$) and 41 ± 1.7 ml/min, respectively. Cyclopropane did not significantly change the pattern of NE release from the myocardial stores (fig. 1). The time course of plasma radioactivity from one experiment is shown in fig. 2. Expressed in CPM /ml, the smooth decline of activity in the arterial and coronary sinus plasma was not affected by cyclopropane.

However, in four other dogs the plasma radioactivity increased during cyclopropane inhalation. An example is shown in figure 3. The coronary sinus–arterial activity also widened, from 20 CPM/ml immediately before cyclopropane inhalation to 120 CPM/ml. Arterial pressure fell to a greater extent from an average of 98 ± 10.5 to 78 ± 6.3 mm Hg ($P < 0.02$).

Halothane (0.75–1 per cent, inspired) was administered to five dogs 75 minutes after completion of ^{3}H-NE infusion. Arterial pressure decreased in each instance, averaging 116 ± 4.3 mm Hg before and 96 ± 6.2 mm Hg ($P < 0.01$) during halothane inhalation. Changes in coronary sinus outflow were inconsistent. The mean control value was 35 ± 5.4 ml/min, that during halothane inhalation, 34 ± 7.6 ml/min. In spite of the fall in arterial pressure, the pattern of NE release was unaffected (fig. 1).

RELEASE OF NOREPINEPHRINE FROM THE IRIS IN CATS

Arterial pressure in decerebrate cats averaged 118 ± 6.5 (SE) mm Hg before cyclopropane inhalation. Electrical stimulation of the cervical sympathetic nerve elicited retraction of the nictitating membrane and maximal dilatation of the pupil. Radioactivity in the effluent perfusate from the anterior chamber ranged between 20 and 200 CPM/ml at rest, increasing sharply during sympathetic nerve stimulation. Figure 4 shows an example of the total perfusate activity resulting from successive periods of stimulation.

In 12 cats cyclopropane was administered after three to six bouts of cervical sympathetic

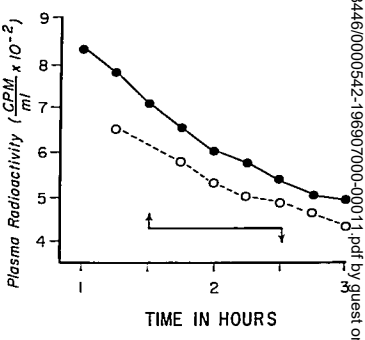

FIG. 2. Radioactivity in the coronary sinus (●——●) and arterial (○——○) plasma in CPM/ml. Dog 13, 21 kg. Cyclopropane (15 per cent) was added to the inspired mixture 1.5 hours after completion of ^{3}H-NE infusion (↑) and discontinued one hour later (↓). Note the smooth decline of activity. A-V differences remained about the same during cyclopropane administration. The mean arterial pressure was 115 before and 105 mm Hg during cyclopropane.

stimulation. During cyclopropane inhalation the arterial pressure averaged 114 ± 6.9 mm Hg. not significantly different from the pre-anesthetic levels. Responses of the nictitating membrane and the pupil to sympathetic nerve stimulation remained the same. Activity in the perfusate did not appear to change either (fig. 5).

Discussion

Cyclopropane and halothane were used in these studies because of their diverse circulatory effects. Controversial results concerning their action on the central vasomotor mechanisms have been reported.[2-6] Anesthetic effects on the peripheral adrenergic mechanisms could perhaps offer some bases to explain the diversity of circulatory actions. For instance, the rise in plasma NE level during cyclopropane anesthesia could result from NE release from increased sympathetic activity, as has been assumed. Or, cyclopropane could interfere with the reuptake of NE, allowing a greater portion of released NE to enter the circulation, without a change in efferent sympathetic activity. Anesthetics could also inhibit the enzymes, monoamine oxidase and catechol-O-methyltransferase, which degradate NE. (See reviews by Kopin,[12] Crout,[14] and Wurtzman and Zigmond[15] on the synthesis and fate of catecholamines.)

The present study examined the effects of cyclopropane and halothane on the uptake and release of NE by peripheral sympathetic nerve endings *in vivo*. The target organ, the heart, had intact innervation. Presumably any significant change in the sympathetic activity would have been reflected in NE release. NE uptake may be estimated whether the target organ is innervatd (rat heart) or decentralized (cat iris). The specific activity of tissue NE in the rat heart shortly after ^{3}H-NE injection indicated NE uptake. In the cat iris, assay of activity in the anterior chamber perfusate gives a measure of NE released upon sympathetic stimulation, the NE store being previously labelled with ^{3}H-NE. With a stimulus frequency of 40 Hz, much of the released NE escaped recapture, and presumably part of it diffused into the anterior chamber. Activity in the perfusate may also indirectly indicate NE uptake by the iris. A decreased NE uptake could be reflected as an increase in activity, as more NE would be available for diffusion immediately after stimulation.

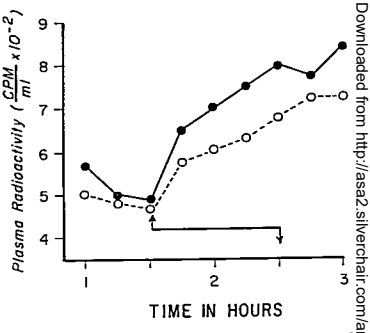

FIG. 3. Radioactivity in the coronary sinus and arterial plasma in CPM/ml. Symbols are the same as in figure 2. Dog 8, 20 kg. The mean arterial pressure fell from 110 to 85 mm Hg ten minutes after cyclopropane (15 per cent) was added to the inspired mixture. Note the increased activity and widened A-V difference.

Tracer doses of ^{3}H-NE were injected into each of three experimental preparations to label tissue NE stores. This is an important consideration, because larger amounts of NE may change the steady level of tissue NE. Increased tissue stores of NE may alter the subsequent release pattern.

Data on NE uptake by the rat heart show that cyclopropane has no apparent effect on this mechanism. The early rapid decline of NE specific activity (from ten to 60 minutes) in animals anesthetized with cyclopropane paralleled that in control animals. The rapid decrease of specific activity probably reflects the loss of the dextroisomer. D-NE can penetrate (or be adsorbed to) nerve endings but is not capable of being stored.

In animals anesthetized with halothane, the NE specific activity in the heart at ten minutes was lower than that of controls. This finding could be interpreted as an anesthetic action on NE uptake. But, at 30 and 60 minutes after ^{3}H-NE injection, specific activity in the experimental group approximated that in control animals. Therefore, a more likely explanation for the lower value at ten minutes

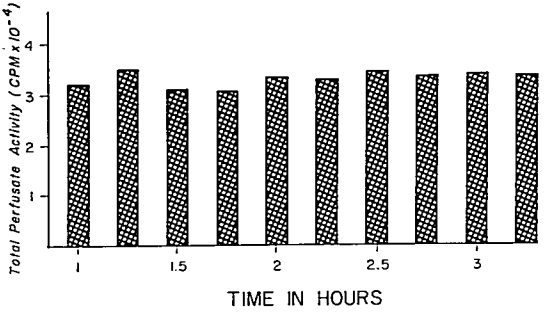

FIG. 4. Radioactivity of effluent perfusate from the anterior chamber of the eye. Cat 19, 4 kg. ^{3}H-NE (50 μc, 1.7 μg base) was injected into the carotid artery one hour before the first stimulation of the cervical sympathetic nerve. Stimulus currents were square waves with an intensity of 5 volts; pulse duration, 2 msec; frequency, 40 Hz. Each bar represents the total activity of 15 minutes following one minute of stimulation. The cat breathed air.

would be the depressed circulatory function observed during halothane anesthesia, leading to some delay in NE uptake.

The lack of effect of cyclopropane and halothane on NE uptake confirms the *in vitro* results of Naito and Gillies [16] and Brown *et al.*[17] Naito and Gillies incubated cat ventricular slices with ^{3}H-NE added to the medium. Of four anesthetics studied (including cyclopropane and halothane), only methoxyflurane appeared to decrease tissue retention (or uptake) of ^{3}H-NE. From these and other data on the atrial response to electrical stimulation, they concluded that anesthetics have little, if any, effect on the disposition of NE after its release. Brown *et al.*[17] using guinea pig atria and L-^{3}H-NE, also observed that cyclopropane, halothane, diethyl ether and compound 347 (Ethrane, CHF_2OCF_2CHFCl) do not alter the initial rate of ^{3}H-NE uptake.

Studies in dogs show that, under the experimental conditions, cyclopropane did not appear to change the pattern of NE release. When the arterial pressure remained close to the control level plasma activity declined smoothly during one hour of cyclopropane inhalation. The coronary sinus–arterial difference in plasma activity stayed steady (fig. 2). Evidence of NE release from the myocardial stores was seen *only* when the arterial pressure fell significantly during cyclopropane inhalation (fig. 3). Presumably, compensatory increase in sympathetic outflow accounts for the release.

These findings do not support the generally accepted thesis that cyclopropane causes NE release. The use of basal anesthesia does not appear to be a factor since the vasomotor compensatory mechanisms are functioning. Furthermore, in a few experiments not included

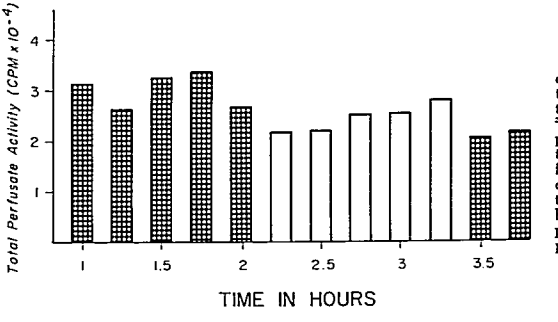

FIG. 5. Radioactivity of effluent perfusate from the anterior chamber of the eye. Cat 20, 3 kg. ^{3}H-NE injection and sympathetic nerve stimulation were the same as in figure 4. Crossed bars, control and recovery with the cat breathing air; blank bars, during cyclopropane anesthesia (15 per cent, inspired).

here, electrical stimulation of the left stellate ganglion (supramaximal intensity, 3–7 Hz) promptly and markedly increased NE activity in coronary sinus plasma, accompanied by increases in myocardial contractility and coronary sinus outflow. These responses were the same before and during cyclopropane administration. Therefore, any increase in sympathetic activity can be (and is) reflected in NE release. This was not observed when cyclopropane did not alter the arterial pressure, indicating (indirectly) that sympathetic activity likewise was not changed.

An alternative explanation for these negative results is that the concentration of cyclopropane used (15 per cent) may not be high enough to cause NE release, if indeed it has such an action. This question must remain unanswered. In the presence of basal anesthesia and a rather extensive surgical dissection, higher concentrations of cyclopropane decreased the arterial pressure. An increase in NE release could result from the hypotension as seen in four of the 17 dogs studied.

Halothane reduced the arterial pressure, but the pattern of NE release from the heart was not affected. Apparently, with the concentration used (0.75–1 per cent), circulatory compensation through barostatic mechanisms was not operative. General agreement from studies on dogs exists in this respect.[5, 6] However, it should be mentioned that Price *et al.*[5] believe that the depressant action of halothane on the circulation is mediated both centrally and peripherally; while Wang *et al.*[6] held that halothane may exert its effect mostly in the periphery.

The results of experiments on the cat iris corroborate the view that cyclopropane does not interfere with NE uptake, but the evidence is indirect. During and immediately after stimulation of the sympathetic nerve supplying the iris, the released NE can follow three paths. With a stimulus frequency of 40 Hz, the major portion of released NE probably leaves the vicinity through the capillaries. Some of it (an unknown portion) diffuses into the anterior chamber, as indicated by the increase in radioactivity in the effluent perfusate. The third important pathway is the reuptake of free NE by sympathetic nerve endings upon terminating the stimulation. If the proportion of NE diffusing into the anterior chamber is assumed to be the same before and during cyclopropane anesthesia, then the relative constancy of activity in the perfusate can be taken as presumptive evidence for an unchanged uptake of NE.

From the results obtained in three experimental models it may be concluded that cyclopropane and halothane do not affect the release and uptake of NE by the peripheral sympathetic nerve endings. We infer from these results that cyclopropane does not change sympathetic activity either.

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Drugs

CORTICOTROPIN RELEASE After daily injections of ACTH, the administration of ether, histamine, 1 per cent formalin, or lysine-8-vasopressin produced no increases in plasma corticosterone levels in rats but increased them significantly in saline-treated control animals. Endotoxin induced nearly equal statistically-significant elevations in ACTH-treated and saline-treated animals. Apparently the high corticosterone levels produced by ACTH injection suppresses the corticotropin-releasing factor liberated by some stressors but not those liberated by other stressors. (*Stark, E. Makara, G. B., and Mihaly, K.: Hypophyseal-Adrenocortical Response to Various Different Stressing Procedures in ACTH-treated Rats, Canad. J. Physiol. Pharmacol. 46: 567 (July) 1968.*)

LOCAL ANESTHETICS AND pH Lidocaine and dibucaine are more effective in neutral than in alkaline solution when tested on the nonmyelinated fibers of the desheathed vagus nerve of the rabbit. Procaine, however, is more effective in alkaline solution. The activity of benzocaine is unaffected by *p*H. Both the charged and the uncharged forms of local anesthetics thus seem capable of blocking conduction. (*Ritchie, J. M., and Ritchie, B. R.: Local Anesthetics: Effect of pH on Activity, Science 162: 1394 (Dec.) 1968.*)

VENOUS CATHETERS Indwelling venous catheters were responsible for 19 of 44 hospital-acquired septicemias. The catheter was in place an average of 5.2 days and was associated with phlebitis or infected wounds or both in 18 cases (95 per cent). Etiologic agents were *Staphylococcus aureus*, 13, gram-negative bacilli, 5, and a nonpathogenic yeast. Neither associated diseases (12) nor inappropriate diagnosis (12) or treatment (9) affected survival (17, or 89 per cent), provided the catheter was removed. Both related deaths were due to *S. aureus;* endocarditis was a complication in one. The septicemia rate for the 756 patients with catheters in place more than 48 hours was 2.5 per cent. House physicians maintained 10 per cent of the total catheters but were responsible for 17 (89 per cent) of the related septicemias. Daily observation of the catheter and immediate removal from phlebitis sites is recommended. (*Bentley, D. W., and Lepper, M. H.: Septicemia Related to Indwelling Venous Catheters, J.A.M.A. 206: 1749 (Nov.) 1968.*)