

Original Articles

Extracorporeal Circulation and Endogenous Epinephrine and Norepinephrine in Plasma, Atrium, and Urine in Man

A Comparison of Ether and Halothane Anesthesia

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In 25 patients epinephrine and norepinephrine concentrations were measured in urine preoperatively and postoperatively, in plasma and atrial tissue during thoracotomy before, during and after cardiopulmonary bypass. Ether or halothane anesthesia was used. Both epinephrine and norepinephrine plasma levels rose during thoracotomy with either anesthetic. During bypass the levels continued to rise under ether but failed to change significantly under halothane anesthesia. Induced hypothermia delayed the rise of plasma catecholamine levels during bypass. Atrial catecholamines did not change. Catecholamine levels were increased in the urine postoperatively with much higher excretion occurring in patients under ether anesthesia than under halothane anesthesia.

None of the patients required sympathomimetic drugs. The changes in catecholamine levels in plasma and urine are believed to reflect a normal response to anesthesia, surgical trauma, and extracorporeal circulation. Ether or halothane anesthesia may modify this normal response significantly.

WHENEVER surgical patients are given sympathomimetic drugs, it is tacitly implied that the liberation of endogenous catecholamines by the body is inadequate to satisfy the needs of the organism. It makes no difference whether the needs are not met because of depression of autonomic centers or ganglionic blockade or because of depletion of stores, or whether the amounts liberated, great as they may be, are inadequate to elicit a response of depressed

cardiac or vascular musculature. Vasopressor substances are relatively frequently required following cardiopulmonary bypass procedures. Assuming that blood volume and pH were normal in the cases requiring sympathomimetic amines, the question arises whether or not the sympathetic activity of these patients was adequate. Before this question can be answered it is necessary to describe a normal or adequate sympathetic response to anesthesia, perfusion, and operation. With this in mind, 25 patients who underwent extracorporeal circulation and who did not require support with sympathomimetic drugs were studied. Changes in catecholamine levels in plasma and urine were measured. These are believed to represent changes in sympathetic activity.

The mobilization of epinephrine and norepinephrine can take place from the adrenal medulla and from tissue which contains sympathetic fibers rich in norepinephrine. It was conceivable that surgical manipulation, extracorporeal circulation and anesthesia might mobilize norepinephrine from the atrium. To test this possibility samples of atrial tissue were obtained during certain phases of the operation for analysis of catecholamines.

Anesthetic agents may affect the responsiveness of the sympathetic nervous system. In recent monographs on ether¹ and halothane,² much of the known effects of these two agents has been summarized. Sympathetic activity in ether anesthesia is apparently stimulated, or at least not inhibited, whereas sympathetic activity in halothane anesthesia appears to be depressed. Significant differences in catecholamine levels in tissue, plasma or urine between patients under ether and those under

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halothane anesthesia would indicate that not only the response to the anesthetic but also the response to the operation is affected differently by the two different inhalation agents.

Methods

Twenty five patients ranging from 7 to 49 years of age who survived operations on the heart for various congenital or acquired defects, and who did not require treatment with sympathomimetic drugs, were studied. Half of these patients received no preanesthetic medication; the rest had, on the average, 100 mg. pentobarbital sodium with 0.4 mg. scopolamine hydrobromide or 0.6 mg. atropine sulfate intramuscularly per 70 kg. body weight one hour before the beginning of anesthesia. The premedication could not be correlated with any changes in catecholamine levels and, therefore, will be ignored. Seventeen of these patients were anesthetized with ether and eight with halothane. Nitrous oxide or cyclopropane was used for induction of patients anesthetized with ether whereas halothane was employed for the halothane cases. After induction of anesthesia the trachea was intubated with the aid of succinylcholine chloride (approximately 60 mg./70 kg. body weight). Anesthesia was maintained with ether and oxygen or halothane and oxygen throughout the operation. Adequate amounts of these vapors were blown through the oxygenator to keep the patient asleep during cardiopulmonary bypass. Ventilation was always assisted or controlled. Arterial blood pH, P_{CO_2} and bicarbonate were determined frequently by the method of Astrup³ and a pH of 7.35 to 7.45 was maintained by the addition of sodium bicarbonate to the oxygenator. The operative procedure required the supine position of the patient and a right thoracotomy with transection of the sternum. The inferior and superior venae cavae were cannulated through the right atrium, and the femoral artery was used for the return of arterial blood. A Kay-Cross disc oxygenator^{*} was used, with venous drainage by gravity. The general blood flow during cardiopulmonary bypass was maintained at 2–2.5 liters/minute/m.² of body surface.

* Pemco, Inc., Cleveland, Ohio.

Catecholamine assays were carried out by the method of Anton and Sayre.⁴ The catecholamine values of the atria are expressed in terms of micrograms of epinephrine or norepinephrine per gram wet weight. The urine values are expressed in micrograms per 25 mg. creatinine in order to correct for variability of urinary output. The catecholamine levels in blood are expressed in micrograms per liter of plasma.

Urine samples were collected on the morning of the operation, the first voiding in the recovery room after the operation, then about a week thereafter. The samples will be called the preoperative, recovery room and post-operative samples, respectively. Arterial blood and atrial samples were taken simultaneously: the first before bypass; the second immediately before cardiopulmonary bypass was discontinued, and the last sample as late as possible after cardiopulmonary bypass. Blood was drawn from a Courmand needle placed in the radial artery for the first and the last blood samples. During cardiopulmonary bypass the blood sample was obtained from the arterial inflow line. Atrial samples, weighing approximately 50–250 mg., were obtained from the right atrium, either from the area in which the venous cannulas were inserted into the right atrium or along the edge of the auriculotomy. The 40 ml. of blood taken for each analysis were replaced with an identical volume of whole blood.

Results

Catecholamines in Blood. Heparinized whole blood † used for priming the heart lung machine contained an average of 0.33 $\mu\text{g./liter}$ norepinephrine and 0.25 $\mu\text{g./liter}$ epinephrine. Venous blood obtained from eight volunteers contained an average of 0.34 $\mu\text{g./liter}$ norepinephrine and 0.11 $\mu\text{g./liter}$ epinephrine. The differences between the levels obtained in volunteers and those of the pump blood were statistically insignificant. It was therefore assumed that subsequent mixing of the pump

† This blood was obtained 18–20 hours prior to bypass, stored at 4° C. until 1 hour prior to bypass, at which time it was warmed to 37° C. and then put into the oxygenator. The sample for catecholamine determination was taken after the oxygenator was primed with the blood.

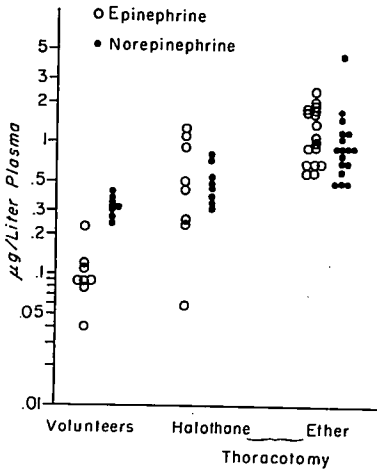


FIG. 1. The concentrations of epinephrine and norepinephrine in plasma are shown. Venous blood was used in the volunteers. Radial arterial blood was used in the patients during thoracotomy. Preoperative control values for the two groups of patients were not available. A logarithmic scale is used in the ordinate.

blood with the patient's blood would not elevate the catecholamine levels of the patient's blood by addition. However, the possibility exists that some factor in the transfused blood might be involved in a release of catecholamines from body stores.

The first blood sample from the patients was obtained at a time when the atrium was accessible to the surgeon, *i.e.*, usually one hour or more after the beginning of anesthesia and 10 to 20 minutes after the chest had been opened. In the group anesthetized with halothane the plasma epinephrine and norepinephrine levels during thoracotomy (before cardiopulmonary bypass) were significantly higher than the levels observed in the volunteers. The catecholamine response to anesthesia and thoracotomy in the patients under ether anesthesia was significantly higher ($P < .01$) for both norepinephrine and epinephrine than that seen in the patients under halothane anesthesia. Figure 1 shows the distribution of the individual values in the three groups in a semilogarithmic plot. It is assumed that

the resting values of catecholamines in the patients were similar to those in the volunteers.

Eight of the patients under ether anesthesia were cooled to 20° C., their hearts were arrested by the external application of Ringer's solution "ice mush,"⁵ their aorta occluded and coronary perfusion stopped for varying lengths of time. These patients usually had a longer total operative procedure and a more serious cardiac defect which may have interfered more with normal cardiovascular activity than was the case in those patients in whom cooling and cardiac arrest for the surgical repair were not deemed necessary. The "cooled" group, therefore, differed not only in the factor of temperature from the "not-cooled" † group.

† "Not-cooled" rather than "normothermic" is used throughout, since the temperature drifted in some of the not-cooled patients spontaneously to 34° C.

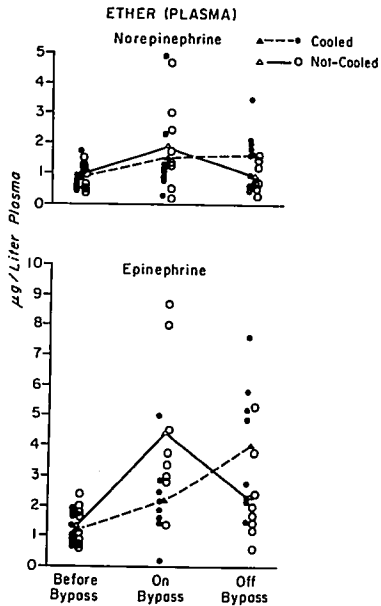


FIG. 2. The norepinephrine and epinephrine concentrations in plasma before, during and after cardiopulmonary bypass in patients anesthetized with ether are plotted on a linear scale. Mean values or represented by triangles and are connected by lines.

Nevertheless, the overall rise in epinephrine and norepinephrine plasma levels was about the same for the cooled and the not-cooled group (fig. 2). However, figure 2 suggests that statistical analyses confirm that epinephrine and norepinephrine levels were rising nearly in the cooled group, *i.e.*, they steadily climbed to the peak value after bypass whereas in the not-cooled group they reached their peak during bypass and then returned toward normal after bypass.

Six of the eight patients under halothane anesthesia were cooled, and the data of their plasma catecholamine levels are shown in figure 3. The values from the two not-cooled patients are indicated by open circles. The scale of this figure is the same as that of figure 2 where the data from the patients under ether anesthesia are shown. The differences in norepinephrine and epinephrine

† Tabulation of these and subsequent analyses are available to the interested reader on request.

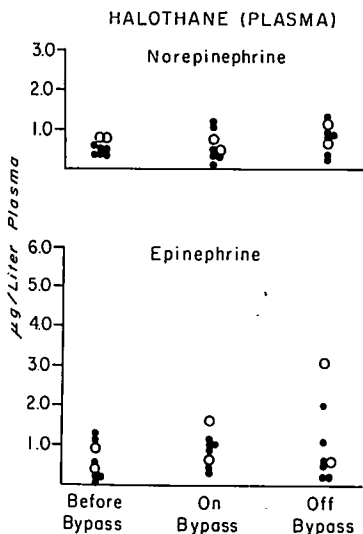


FIG. 3. The norepinephrine and epinephrine concentrations in plasma before, during and after cardiopulmonary bypass in patients anesthetized with halothane are plotted on a linear scale. The values from two patients who were not cooled are represented by open circles.

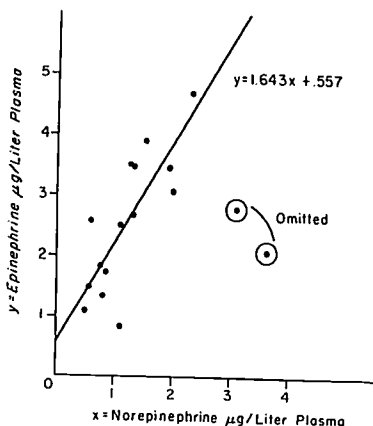


FIG. 4. For every patient under ether anesthesia a mean value for norepinephrine and epinephrine was obtained by averaging the "before," "on," and "off" bypass concentrations. The mean epinephrine concentration was then plotted against the mean norepinephrine for each patient. For the calculation of the line $y = 1.6x + 0.6$ the indicated values were omitted.

levels in plasma in the patients under halothane anesthesia demonstrate the same trend as seen in the ether group but they are statistically insignificant. Inspection of figures 2 and 3 suggests that the catecholamine response in the ether group was much stronger than in the halothane group. By means of an analysis of variance, subject and time variability were removed and the mean response in the halothane group was compared to that in the ether group. Norepinephrine and epinephrine rose significantly higher in the ether group ($P < .001$) than in the halothane group.

Since norepinephrine and epinephrine levels increased together in the ether group, we hypothesized that the appearance of norepinephrine was linked with that of epinephrine. To test this hypothesis the means of all norepinephrine determinations were plotted against the means of the epinephrine values (fig. 4). On the assumption that high norepinephrine values are likely to occur together with high epinephrine values, the two extreme values on the x axis in figure 4 (high norepinephrine with relatively low epinephrine) were arbitrarily omitted for the calculation of

TABLE 1. Catecholamine Levels in Atrial Tissue

Anesthesia	Number of Patients		Before Bypass		On Bypass		Off Bypass	
			NE†	E‡	NE	E	NE	E
Ether	8	Not cooled	1.20 ± 0.10	0.26 ± 0.07	1.24 ± 0.13	0.23 ± 0.07	1.08 ± 0.12	0.18 ± 0.03
	8	Cooled*	1.04 ± 0.13	0.16 ± 0.04	1.26 ± 0.14	0.16 ± 0.05	1.09 ± 0.10	0.16 ± 0.05
Halothane	2	Not cooled	0.53	0.08	0.75	0.11	0.60	0.06
	6	Cooled*	1.32 ± 0.30	0.07 ± 0.03	1.19 ± 0.29	0.10 ± 0.03	1.12 ± 0.26	0.11 ± 0.03

Values expressed in $\mu\text{g}/\text{gram}$ wet weight ± 1 standard error of the mean.

* Cooling was started during cardiopulmonary bypass and did not affect the "before bypass" group.

† NE = Norepinephrine.

‡ E = Epinephrine.

the best fitting line. The distribution of the remaining values can be described by the expression $y = 1.6x + 0.6$.

Catecholamines in Atrial Tissue. The norepinephrine and epinephrine levels in atrial tissue did not change with time or as a func-

tion of the different operative procedures or anesthetics. The data are summarized in table 1. We assume that chance was responsible for the unusually low norepinephrine values in the two atria from the patients in the "not-cooled halothane" group.

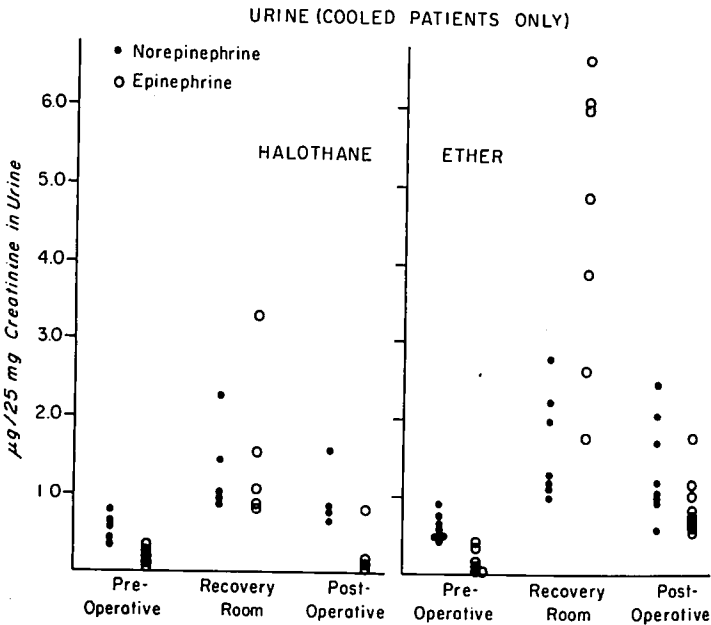


FIG. 5. In order to allow a comparison of the catecholamine excretion in urine between patients under ether and halothane anesthesia, only the values from "cooled" patients were plotted. Following cardiopulmonary bypass both groups excreted significantly more epinephrine than preoperatively. The excretion of epinephrine and norepinephrine following ether anesthesia was greater than after halothane anesthesia.

Urine Catecholamines. When the catecholamine levels rise in the circulating blood, proportional increases in catecholamine excretion in the urine may be anticipated. Particularly in the patients anesthetized with ether the excretion of both epinephrine and norepinephrine was significantly increased over the preoperative values. The group of patients cooled during cardiopulmonary bypass excreted significantly more epinephrine (but not more norepinephrine) than the not-cooled group. Since the excretion levels reached their peak values in the recovery room and decreased in the postoperative sample, quadratic rather than linear expressions best describe the changes in urinary norepinephrine and epinephrine. The excretion of epinephrine and norepinephrine in the patients anesthetized with halothane was much lower than in those who had ether. Figure 5 presents data of the patients who had been cooled under the two different anesthetics. The changes in norepinephrine levels in urine in the halothane group suggest a rise of concentration in the recovery room over that pre- and postoperatively, but the differences are not statistically significant. The excretion of epinephrine on the other hand was significantly higher in the recovery room than preoperatively or postoperatively. The concentration of urinary catecholamines in the halothane group dropped off quicker from the recovery room to the postoperative samples than was the case in the ether group. This was presumably due to biased sampling since by chance the urines were collected 2 days earlier postoperatively in the ether group than in the halothane group.

The age of the patient had no effect on the concentrations of catecholamines in urine preoperatively, but in the ether group there was a striking inverse correlation between age and the epinephrine concentration in urine in the recovery room samples ($t_b = 3.74$; $P < .01$) (fig. 6). Cooling did not affect this correlation. No clear interrelationship between urinary norepinephrine and age was apparent.

Discussion

Replogle and his associates⁶ have reported on increased catecholamine levels in the blood of patients on cardiopulmonary bypass. A

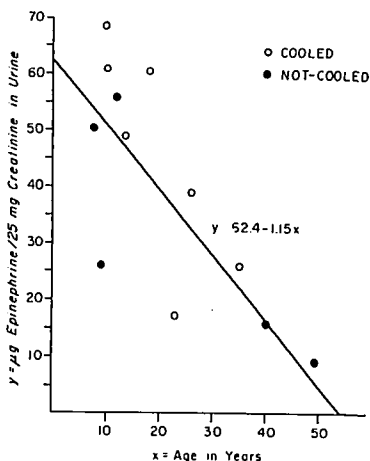


FIG. 6. The concentration of epinephrine in urine is plotted against the age of the patient. Only data from patients who had ether anesthesia were used. Younger patients excreted more epinephrine than older ones. Hypothermia during the operation is indicated by open circles.

sympathetic response to shock and anesthesia or severe surgical stress has frequently been documented by the measurements of catecholamines in plasma.⁷⁻¹¹ Our data confirm these findings. In addition to this a number of interesting points emerge, which deserve attention.

Both epinephrine and norepinephrine values in plasma were increased before cardiopulmonary bypass had started, but at a time when manipulation of the heart was taking place. At this time a large elevation of epinephrine as well as norepinephrine concentration in plasma was not expected since ether anesthesia has been reported to cause only an increase in norepinephrine and not in epinephrine levels, although this point needs further clarification.^{12, 13, 14} Once cardiopulmonary bypass had started a great increase in circulating epinephrine levels occurred in both the cooled and the not-cooled groups. It must be remembered that when the sample was taken, the patient's blood had been thoroughly mixed with a blood volume which in many instances was equal to the patient's blood volume and which contained only small amounts of cate-

cholamines. The values reported, therefore, probably understate the true liberation of epinephrine into the bloodstream by a large factor. The sample taken during cardiopulmonary bypass was, as mentioned, obtained shortly before the patient was disconnected from the heart-lung machine. In the patients operated upon under hypothermia this meant that the body temperature had been returned to close to normal. It is quite conceivable that larger differences in plasma catecholamines between the cooled and the not-cooled group could have been obtained if blood samples had been taken at the depth of hypothermia and compared to those taken at a similar interval after the start of extracorporeal circulation in the not-cooled group. That cooling did not prevent but merely delayed the liberation of epinephrine is apparent from the large concentration of epinephrine in the urine which occurred in the recovery room and which was larger in the cooled than in the not-cooled group of patients.

The significant difference in the catecholamine response to operation and perfusion between the patients anesthetized with halothane and with ether is quite remarkable. The clinical importance of this observation is obscure. It is our experience that patients anesthetized with halothane do not require support of their cardiovascular system with sympathomimetic amines more frequently than do patients anesthetized with ether. This is particularly surprising since halothane is presumably more depressant to the cardiovascular responsiveness to sympathomimetic amines than is ether.¹⁵

There was no correlation between the clinical status of the patient, the duration of the operation, blood pressure, or pulse rate with the measured catecholamine levels. Some patients who had short procedures in which no cardiovascular disturbances occurred had very high epinephrine and norepinephrine levels whereas others doing equally well had very low levels. This may merely indicate that all patients studied had a physiologically sufficient catecholamine response.

The observation that young people responded with a stronger epinephrine secretion than the older patients is interesting. We are tempted to argue that young people usually

tolerate cardiac operations better than do older people and that perhaps a vigorous adrenal response is part of such physiological adjustment to cardiac operations and extracorporeal circulation. This would indicate that ether anesthesia has something to recommend it since it allows a vigorous adrenal and sympathetic reaction to the challenges of this type of operation. Many cases would be needed to establish whether one anesthetic was better than the other. The numerable variables in cardiac defect, surgical approach and status of the patient make it impossible to reach a conclusion in such a small series as ours.

We believe that the levels of catecholamines in the atria did not reflect the levels of circulating norepinephrine because the concentration of norepinephrine in the atrium is almost a thousandfold of that in plasma. A relatively small discharge from organs as richly stocked with norepinephrine as the atria could easily bring about substantial increases in catecholamine levels in blood without showing any measurable depletion of the donor organ.

An increase of epinephrine or norepinephrine levels in blood can be brought about by different mechanisms. Either increased liberation, or decreased tissue uptake, utilization, excretion or destruction can lead to higher blood levels. We assume that increased liberation was responsible for most of the changes, since it appears at the present time to be the most reasonable explanation for such changes.

Summary

Epinephrine and norepinephrine concentrations were measured in urine preoperatively, immediately postoperatively, and again five to ten days following cardiopulmonary bypass for surgical repair of cardiac defects. Catecholamine levels in arterial blood and atrial tissue were measured during thoracotomy prior to bypass, immediately before discontinuing cardiopulmonary bypass, and again following cardiopulmonary bypass. Some patients were anesthetized with ether, others with halothane; some were cooled during cardiopulmonary bypass, others were maintained at a normal body temperature. No changes in norepinephrine or epinephrine levels in the atrial tissue were detected. Significant rises in both epi-

nephrine and norepinephrine levels occurred in the blood during thoracotomy and prior to cardiopulmonary bypass. With bypass the levels rose considerably higher under ether anesthesia but failed to change significantly under halothane anesthesia. Induced hypothermia tended to delay the rise of epinephrine and norepinephrine levels during cardiopulmonary bypass. Great increases in epinephrine and norepinephrine levels were found in the urine in the recovery room samples. Much higher excretions occurred in the patients who had had ether anesthesia than in those under halothane anesthesia. Five to ten days later the levels in the urine had returned toward normal. The younger the patients, the more epinephrine they excreted in the urine.

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References

- Dodd, R. B.: Diethyl Ether. Springfield, Ill., Charles C Thomas, 1962.
- Stephen, R. C., and Little, D. M.: Halothane (Fluothane). Baltimore, The Williams & Wilkins Co., 1961.
- Astrup, P.: A simple electrometric technique for the determination of carbon dioxide tension in blood and plasma, total content of carbon dioxide in plasma, and bicarbonate content in "separated" plasma at a fixed carbon dioxide tension, *Scand. J. Clin. Lab. Invest.* 8: 33, 1957.
- Anton, A. H., and Sayre, D. F.: A study of the factors affecting the aluminum oxide—trihydroxyindole procedure for the analysis of catecholamines, *J. Pharmacol. Exp. Ther.* 138: 360, 1962.
- Hufnagel, C. A., and Conrad, P. W.: The direct approach for the correction of aortic insufficiency, *J.A.M.A.* 178: 275, 1961.
- Replogle, R., Levey, M., DeWall, R. A., and Lillehei, R. C.: Catecholamine and serotonin response to cardiopulmonary bypass, *J. Thorac. Cardio. Surg.* 44: 638, 1962.
- Hammond, W. G., Aronow, L., and Moore, F. D.: Studies in surgical endocrinology; plasma concentrations of epinephrine and norepinephrine in anesthesia, trauma and surgery, as measured by a modification of the method of Weil-Malherbe and Bone. *Ann. Surg.* 144: 715, 1956.
- Hume, D. M., and Bell, C. C., Jr.: The secretion of epinephrine, norepinephrine, and corticosteroid in the adrenal venous blood of the human, *Surg. Forum* 9: 6, 1958.
- Carter, T. E., and Hardy, J. D.: Source of epinephrine vs. norepinephrine: further studies, *Surg. Forum* 10: 108, 1959.
- Franksson, C., Gemzell, C. A., and Von Euler, U. S.: Cortical and medullary adrenal activity in surgical and allied conditions, *J. Clin. Endocr.* 14: 608, 1954.
- Von Euler, U. S.: Epinephrine and norepinephrine actions and use in man, *Clin. Pharmacol. Ther.* 1: 65, 1960.
- Hardy, J. D., Carter, T., and Turner, M. D.: Catechol amine metabolism, *Ann. Surg.* 150: 666, 1959.
- Price, H. L., Linde, H. W., Jones, R. E., Black, G. W., and Price, M. L.: Sympathoadrenal responses to general anesthesia in man and their relation to hemodynamics, *ANESTHESIOLOGY* 20: 563, 1959.
- Price, H. L., Linde, H. W., and Price, M. L.: Failure of ethylenediamine condensation method to detect increased plasma norepinephrine concentrations during general anesthesia in man, *Clin. Pharmacol. Ther.* 1: 298, 1960.
- Andersen, T. W., Perkins, H. M., and Gravenstein, J. S.: Cardiovascular effects of mephentermine sulfate in man and their modification by anesthetic agents, *Anesth. Analg.* 42: 87, 1963.

ECLAMPSIA Muscle-relaxant drugs and artificial ventilation of the lungs by intermittent positive-pressure respiration have become an established method of treatment of tetanus and status epilepticus. Sedation, narcotics, relaxants and mechanical ventilation have been used in the treatment of three patients admitted with severe eclampsia and convulsions. (Hegarty, W. J.: *Total Paralysis as Treatment of Severe Eclampsia*, *Lancet* 2: 540 (Sept. 4) 1963.)