TABLE 1. Brain Concentrations of 5-HT and 5-HIAA (μg/gm)

Hours	Cyclopropane				Diethyl Ether				Halothane			
	5-HT	P	5-HIAA	P	5-HT	P	5-HIAA	P	5-HT	P	5-HIAA	P
Control	.50±.01		.40±.01		.47±.01		.40±.01		.51±.02		.40±.01	
2	.57±.02	<.02	.42±.01	>.2	.48±.02	>.7	.65±.02	<.001	.46±.01	<.05	.43±.01	>.05
3	.54±.02	>.2	.48±.003	<.001	.49±.02	>.4	.73±.03	<.001	.45±.02	<.05	.46±.01	<.001
4	.56±.02	<.01	.44±.01	>.05	.47±.01	>.9	.81±.03	<.001	.43±.01	<.01	.48±.00	<.001
5	.57±.03	<.05	.45±.009	<.05	.43±.01	>.1	.69±.02	<.001	.42±.02	<.05		

used the righting reflex was abolished. The body temperature was maintained within 2° C. of control.

Brain levels of 5-HT and 5-hydroxyindoleacetic acid (5-HIAA), the main metabolite of 5-HT, were measured after two, three, four and five hours of exposure to each anesthetic; 5-HT by the method of Bogdanski *et al.* (J. Pharmacol. Exp. Therap. *117:* 82, 1956) and 5-HIAA by the method of Udenfriend *et al.* (Methods of Biochemical Analysis, pp. 95–130, 1958). The turnover rate of 5-HT was measured after three to four hours of anesthesia using the method of Neff *et al.* (Pharmacologist *6:* 194, 1964). *Results:* Results are shown in tables 1 and 2.

None of the agents produced a marked change in 5-HT levels. Only halothane caused a slight decrease (17 per cent). This is in contrast with the result of Bonnycastle *et al.* (J. Pharmacol. Exp. Therap. *135:* 17, 1962) who found an increase with diethyl ether. On the other hand, all agents increased the 5-HIAA level: a maximum of 20 per cent with cyclopropane, 20 per cent with halothane and 100 per cent with ether (table 1).

The turnover rate of 5-HT, as measured by the rate of accumulation of 5-HIAA after probenecid, was significantly accelerated by diethyl ether, but not by cyclopropane or halothane.

Over 90 per cent of brain 5-HT is metabolized by monoamine oxidase to 5-HIAA, there being no other major sources of 5-HIAA. When 5-HIAA levels increase, it means either an increased rate of 5-HT oxidation by monoamine oxidase or a decreased rate of 5-HIAA removal from the brain, or both. Diethyl ether belongs in the latter category, but cyclopropane and halothane apparently produce only a transient decrease in the rate of 5-HIAA removal. It is not known whether 5-HIAA leaves the brain by simple diffusion or by an active transport mechanism. The effect of anesthetics on the brain cell membrane and transport mechanisms is presently subject to speculation.

TABLE 2. 5-HT Turnover Rate (μg./Gm/hr.)

Control	Cyclopropane	Diethyl Ether	Halothane
.28±.008	.32±.02	.56±.03	.26±.02

Summary: The effects of cyclopropane, diethyl ether and halothane on the metabolism of brain serotonin (5-HT) were studied in rats. The levels of 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) and the turnover rate of 5-HT during anesthesia were determined. The level of 5-HIAA was increased by all anesthetics studied, but the turnover rate of 5-HT was altered only by diethyl ether. It is concluded that these anesthetics probably block the 5-HIAA transport mechanisms. (Supported by USPHS grants 5T1-GM-00056, GM-09069, NB-05184 and PH 436-454.)

The Cardiovascular Effects of Various Alveolar Halothane Concentrations in Man. E. I. EGER, II, M.D., N. T. SMITH, M.D., R. K. STOELTING, M.D., and C. WHITCHER, M.D., *University of California Medical Center, San Francisco, Calif.* Investigations of cardiovascular effects of halothane in man have not correlated these effects with the alveolar halothane concentrations which produced them. This report supplies such data for both acute and subacute halothane administration. *Methods:* Arterial and central venous (usually right atrial) catheters permitted measurement of pressure, cardiac output (dye dilution) and blood gases (electrodes) in ten healthy 24 ±

TABLE 1.

No.	% H	Time	% of Awake Values			
			CO	MAP	TPR	SV
2	0.8	40	89	78	88	83
4	0.8	106,35	93,4	87,13	91,14	79,13
3	0.8	325	101	80	80	89
5	1.0	31,2	75,8	78,11	95,11	77,5
5	1.0	88,18	83,6	74,21	85,19	81,7
4	1.0	300,18	96,10	69,8	68,5	95,12
3	1.2	28	68	75	101	76
2	1.2	138	83	62	73	78
3	1.6	53	65	72	102	67
8	1.6	123,24	70,16	64,15	88,28	66,17
10	1.6	294,16	94,12	62,11	64,8	82,11
5	2.0	55,12	43,18	51,18	100,11	42,13
5	2.0	128,21	63,17	57,16	84,22	65,20
6	2.0	313,97	87,22	64,16	67,6	76,26
4	2.4	396	81,30	68,13	80,11	64,18

No. is number of subjects; % H is % alveolar halothane; time is in minutes; the number following each comma equals one standard deviation for the preceding value.

6-year-old awake males. Forearm (muscle?) and finger (skin?) blood flow were measured by occlusion plethysmography. A ballistocardiograph measured stroke volume. Other parameters were calculated from these data. Controlled ventilation maintained Pa_{CO_2} at 34.3 ± 2.5 mm. Hg during awake studies. Anesthesia was induced with halothane in oxygen to a depth permitting orotracheal intubation without relaxants. During the studies under anesthesia Pa_{CO_2} was maintained by controlled ventilation near awake values. After 15 minutes of 0.8, 1.0 or 1.2 per cent alveolar halothane (infrared or ultraviolet analysis) the cardiovascular studies were repeated. Alveolar halothane was then raised to 1.6 or 2.0 per cent and measurements were made again after 15 minutes of stabilization. Measurements were repeated at various alveolar concentrations during the ensuing three to seven hours. Serial hematocrits were measured in two subjects. *Results: Acute Effects:* Initially, cardiac output (CO) stroke volume (SV) and mean arterial pressure (MAP) decreased in proportion to increase in anesthetic concentration (see table 1). The ballistocardiogram during induction and periods of acute change of concentration confirmed that CO fell in proportion to alveolar halothane. No early "overshoot" (*i.e.*, acute depression and recovery) of CO was found with the first breaths of halothane. Heart rate (HR) and total peripheral resistance (TPR) remained unchanged. Forearm blood flow (ABF) decreased in proportion to alveolar halothane, whereas finger blood flow (FBF) markedly increased at 1 per cent and 1.6 per cent halothane but decreased at 2 per cent. Central venous pressure (CVP) rose in proportion to halothane increase, rising 5 mm. Hg above awake values at 2 per cent halothane. *Subacute Effects:* In the following three to seven hours the cardiovascular effects of halothane changed (table 1). CO and SV returned to or towards normal. HR was either unchanged or rose slightly. MAP stabilized between 62 and 68 per cent of control pressures for all mean values between 1 and 2.4 per cent halothane. TPR decreased at all levels. ABF rose towards or above awake values while FBF fell to or below awake levels. Central blood volume and hematocrit were unchanged. CVP was either unchanged or fell with time. Hexamethonium 25 to 100 mg. given to four subjects after the above studies produced no significant changes in CO or MAP at a given halothane concentration. *Discussion and Conclusion:* The acute effects (decreased CO, SV and MAP; increased CVP) may result from direct and indirect (sympathetic) depression. Sympathetic depression is also suggested by increased FBF. The subacute effects show recovery of CO and SV, some increase in HR and no change or a decrease in CVP. That these are not the result of increased blood volume is suggested by the constancy of hematocrit, central blood volume and CVP. These subacute results are consistent with development of increased sympathetic (particularly epinephrine) effect with time. Increased sympathetic effect also would explain decrease in FBF and restoration of ABF. The lack of effect of hexamethonium suggests that this increased effect is not mediated centrally but results from either increased release of or sensitivity to catecholamines.

The latter may result as a denervation hypersensitivity since halothane produces partial sympathetic blockade. (Supported in part by USPHS Grant 5 R01 HE07946, USPHS Grant GM 12527 and USPHS Career Development Award 1-K3-GM-31757.)

The Effect of the Concentration of Local Anesthetic during Epidural Anesthesia on the Forces of Labor. BURTON S. EPSTEIN, M.D., SREELA BANERJEE, M.D., GEOFFREY CHAMBERLAIN, F.R.C.S., M.R.C.G., and CHARLES S. COAKLEY, M.D., *Departments of Anesthesiology and Obstetrics Gynecology, George Washington University School of Medicine, Washington, D. C.* It has been stated that during epidural anesthesia for obstetrics large doses of local anesthetics may depress the myometrium (Bonica, J. J., and Hunter, C. A.: Clinical Anesthesia *3:* 116, 1965) and that high blood concentrations of local anesthetics depress uterine activity, probably by direct action on the myometrium (Bromage, P. R.: ANESTHESIOLOGY *28:* 610, 1967). A study was undertaken to determine if a change in dose and concentration of a local anesthetic would alter the force of uterine contractions and prolong the first stage of labor. *Method:* As the active phase of the first stage of labor was entered, a volume of 1.0, 1.5, or 2.0 per cent prilocaine (Citanest) was injected through a peridural catheter in a blind, random sequence until sensory anesthesia was obtained at T10-T11. Blood samples drawn 10, 20, and 30 minutes following the injection were analyzed for concentration with gas chromatography. The frequency and intensity of uterine contractions with time was measured by external tocography (Stanley Cox Twin Channel Guard Ring Tocograph, Rank Murphy Electronics, Hertfordshire, England) with a surface transducer placed on the abdomen. The intensity of the contraction with time (area under the curve) was determined by planimetry. The relationships between the injected concentration of the local anesthetic, its blood concentration, the change in uterine force and progress of labor were measured for a 30-minute period following the first injection. These were compared to values during an initial control period prior to anesthesia. The effect of the local anesthetic on the rate of cervical dilatation was also compared to Friedman's curves for multigravidas and primigravidas (Friedman, E. A.: Obstet. Gynec. *8:* 691, 1956; Friedman, E. A.: Obstet. Gynec. *6:* 567, 1955). *Results:* Of the 18 patients studied, 13 were primigravidas; the remainder multigravidas. Labor was induced with an oxytoxic in 13 patients. A volume of 8–13 cc. (mean, 10 cc.) of local anesthetic was injected. No hypotension was observed. There was a tendency for contractions to diminish slightly in frequency in all groups except those receiving 1.0 per cent prilocaine (no stat. sig.). In the first 15 minutes following anesthesia, tocographic measurements showed a decrease in uterine force in 12 patients and an increase or no change in six. In the second 15 minutes, nine patients showed a decrease, two were unchanged and seven showed increases. No difference was noted as the concentration of the local anesthetic was increased. Dilatation of the cervix occurred in 13 of the 16 patients even though the force of contraction was decreased; or no dilatation was noted as the force was increased. Of 16 patients for whom complete data were available, the tocographic measurement showed a positive correlation with the slope of the Friedman Curve in only four. Eight labors were hastened, seven unchanged, and one depressed from the normal slope. No difference was noted between concentrations of local anesthetics employed and blood concentrations measured (0.5–2.2 μg./ml.; mean 1.0 μg./ml.). *Discussion and Conclusion:* When one of three concentrations of prilocaine was used for epidural anesthesia in obstetrics, no correlation was observed between concentration of local anesthetic or its blood level on the force of uterine contractions or rate of dilatation of the cervix. No correlation was noted between the strength of uterine contractions measured by external tocography and rate of change of cervical dilatation. (Supported by Astra Pharmaceutical Products, Inc., Worcester, Mass.)

Theoretical Analysis of the Effect of Concentration-dependent Solubility Upon the Uptake of Anesthetic Agents. ROBERT M. EPSTEIN, M.D., *Columbia University, College*