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Clinical Signs of Anesthesia

David J. Cullen, M.D., Edmond I. Eger, II, M.D.,† Wendell C. Stevens, M.D.,‡*
N. Ty Smith, M.D.,§ Thomas H. Cromwell, M.D.,¶ Bruce F. Cullen, M.D.,¶
George A. Gregory, M.D.,‡ Steven H. Bahlman, M.D.,¶
*William M. Dolan, M.D.,¶ Robert K. Stoelting, M.D.,***
Henry E. Fourcade, M.D.‡

The clinical signs of anesthetic depth (heart rate, mean arterial pressure, pupil diameter, pupil reactivity to light, tearing, and eye movement) were correlated with anesthetic dose in healthy young volunteers. During halothane, halothane–nitrous oxide, Forane, or Forane–nitrous oxide anesthesia at normal $Paco_2$ (controlled ventilation), only hypotension in the first hour of anesthesia correlated with anesthetic dose. After five hours of halothane or halothane–nitrous oxide, blood pressure remained constant as anesthetic concentration increased. During cyclopropane, diethyl ether, and fluroxene anesthesia, only pupillary dilatation and reduced pupil reactivity to light correlated with anesthetic dose. When nitrous oxide was added to halothane, ether, or fluroxene, mean arterial pressure rose and pupils dilated. During halothane–oxygen anesthesia with spontaneous ventilation, the rise in $Paco_2$ allowed less hypotension and increased heart rate. Tidal volume decreased and respiratory rate increased as anesthesia deepened. During Forane–oxygen anesthesia with spontaneous respiration, mean arterial pressure, tidal volume, and minute ventilation decreased as anesthesia deepened. In healthy surgical patients anesthetized with halothane or Forane only, incision of the skin modified the clinical signs significantly. While surgery continued, this change in clinical signs persisted during Forane anesthesia, but returned to control during halothane anesthesia. (Key words: Clinical signs of anesthesia; Heart rate; Blood pressure; Eye movement; Tearing; Pupil diameter and reactivity to light; Respiratory rate; Tidal volume; Minute ventilation; $Paco_2$; Halothane; Cyclopropane; Diethyl ether; Fluroxene; Forane; Nitrous oxide; Surgical stimulation.)

DEPTH OF ANESTHESIA is estimated clinically from changes in blood pressure, heart rate, pulse, respiration, muscle relaxation, and eye signs. Though imprecise, these are major guides to the conduct of anesthesia in clinical practice. Based on these signs, reasonable estimates of depth appear possible with some anesthetics (diethyl ether[1]), and difficult to achieve with others (halothane, cyclopropane[2]). Furthermore, many factors may modify the signs of anesthetic depth. These include preanesthetic medications; induction agents; patient's illness, age, and general health; site and extent of surgical stimulation; use of muscle relaxants and/or controlled ventilation; body temperature; $Paco_2$; and duration of anesthesia. Another handicap to the use of clinical signs is the lack of quantitative data relating these signs of the doses of commonly used anesthetics. Our studies of the cardiorespiratory effects of a number of inhaled anesthetics in human volunteers gave us the opportunity to gather such data. We correlated the clinical signs of anesthesia with end-tidal concentrations of halothane, halothane–nitrous oxide, cyclopropane, diethyl ether, fluroxene, Forane,†† and Forane–nitrous oxide in young healthy men. These subjects were not premedicated, received only the inhaled anesthetic, and were not subjected to surgical stimulation. Fixed drugs (induction

* Assistant Professor of Anesthesia, Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts 02114.
† Professor of Anesthesia and Associate of the Cardiovascular Research Institute, University of California, San Francisco, California 94122.
‡ Assistant Professor, Department of Anesthesia, University of California, San Francisco, California 94122.
§ Assistant Professor, Department of Anesthesia, Stanford University, Palo Alto, California.
¶ Resident in Anesthesia, University of California, San Francisco, California 94122.
** Assistant Professor, Department of Anesthesia, Indiana University, Bloomington, Indiana.
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agents and muscle relaxants) were avoided; P_{aCO_2} and body temperature were held at normal levels.

We report these data as guidelines for evaluation of anesthetic depth, realizing that in the clinical situation such data may be modified by the factors we specifically avoided. To illustrate the importance of surgical stimulation we also present data demonstrating the effects of incision of the skin on the signs of halothane and Forane anesthesia in healthy patients.

Methods

Details of the methods have been reported elsewhere, since most of the data were obtained while studying the cardiovascular effects of anesthetics in human volunteers.[3–13]

Volunteer Studies, A Normal P_{aCO_2}

After catheterization of a radial or brachial artery, blood pressure was transduced with a Statham P23 strain gauge, meaned electrically, and recorded on a Grass Model 7 polygraph. Eye signs were evaluated by two of us, noting the position of the eye, movement, and tearing. Pupillary diameter before and after light stimulation was measured with a millimeter rule. Pupillary reactivity to light ranged from 0 (no reaction) to 3+ (brisk response). Awake control measurements were obtained with the subject lying supine, breathing 100 per cent oxygen. Eye signs were not determined in the awake period. Anesthesia was induced with the agent to be studied only (except for diethyl ether, for which anesthesia was induced with cyclopropane). After endotracheal intubation without the aid of muscle relaxants, except in the case of fluroxene, when succinylcholine was used in half the subjects, an esophageal thermistor probe was inserted and esophageal temperature maintained between 36 and 37 C. End-tidal carbon dioxide (P_{ETCO_2}) was monitored with a Beckman LB-1 infrared CO_2 analyzer and maintained at awake levels by controlling ventilation (except for diethyl ether and 5 per cent and 9 per cent fluroxene, when P_{ETCO_2} remained normal during spontaneous respiration). End-tidal anesthetic concentration was measured with a Beckman LB-1 infrared analyzer calibrated for the specific agent being studied. All measurements were obtained at three levels of anesthesia (two with ether) during the first and fifth hours of study.

For comparison at equipotent levels, anesthetic concentrations were converted to multiples of MAC based on the known MAC values for man[14–16]‡‡ and corrected for age[17] (table 1).

Volunteer Studies of Halothane, Diethyl Ether, and Fluroxene in Oxygen, 70 Per Cent Nitrous Oxide Added to Inspired Gas for 15 Minutes

When nitrous oxide was administered with halothane, an ultraviolet halothane analyzer was used instead of an infrared analyzer. After all measurements had been obtained, nitrous oxide was discontinued and the measurements were repeated 15 minutes later. During halothane–nitrous oxide and Forane–nitrous oxide studies, nitrous oxide was discontinued for 15 minutes and measurements were obtained. Fifteen minutes after 70 per cent nitrous oxide was returned to the circuit, the measurements were repeated.

Volunteer Study, P_{aCO_2} Not Controlled

Methods were similar to those described above except that ventilation was spontaneous. Tidal volume and respiratory rate were measured with a recording ventimeter[18] and minute ventilation was calculated. P_{aCO_2} was measured with a Severinghaus electrode and corrected for temperature. Conversion of halothane and Forane concentrations to multiples of MAC is shown in table 1.

Effects of Surgical Stimulation in Patients

Halothane–Oxygen. Eight healthy patients, ages 5 to 66 years, were premedicated with atropine and anesthetized with halothane in oxygen. After endotracheal intubation with the aid of succinylcholine, end-tidal halothane concentration was adjusted to approximately 1.1 MAC, corrected for age. End-tidal halothane was measured with a Beckman LB-1 infrared halothane analyzer. Heart rate and respiratory rate were counted, blood pressure was measured by auscultation, and tidal volume was measured with a Wright venti-

‡‡ Unpublished data for Forane.

TABLE 1. Conversion into Multiples of MAC of the Alveolar Concentrations of Anesthetics Used in This Study*

Anesthetic	Alveolar Concentrations Studied (per cent)	MAC (Per Cent Alveolar Concentration)	MAC Multiple
Halothane	1.0	0.84	1.2
	1.5		1.8
	1.6		1.9
	1.8		2.1
	2.0		2.4
Halothane–nitrous oxide	0.5–70 per cent N_2O	0.26 + 70 percent N_2O†	1.3
	1.0–70 per cent N_2O		1.9
	1.5–70 per cent N_2O		2.5
	2.0–70 per cent N_2O		3.1
Forane	1.25	1.3‡	0.96
	1.85		1.4
	2.5		1.92
Forane–nitrous oxide	0.7–70 per cent N_2O	0.39 + 70 percent N_2O§	1.24
	1.3–70 per cent N_2O		1.7
	1.9–70 per cent N_2O		2.2
Cyclopropane	17.5	10.2	1.7
	27.5		2.7
	37.5		3.7
Ether	3.0	2.1	1.4
	4.5		2.1
	6.0		2.85
Fluroxene	5.0	3.8	1.3
	9.0		2.4
	12.0		3.15

* The MAC values have been determined in man [14–16] and adjusted for age.[17]

† 70 per cent nitrous oxide provides 70 per cent of MAC.[16] Therefore, MAC for halothane–nitrous oxide is 0.3 × 0.84 percent = 0.26 percent halothane with 70 percent nitrous oxide.

‡ Unpublished data.

§ MAC for Forane–nitrous oxide is 0.3 × 1.3 per cent = 0.39 per cent Forane with 70 per cent nitrous oxide.

lometer attached to the expiratory limb of the circle system. Pupillary diameter and reaction to light were measured with a millimeter rule. Control measurements were obtained prior to incision of the skin. Immediately after incision, and for the duration of the operation, measurements were made repeatedly. In two patients, clinical signs following second incisions later in the operation were obtained.

Forane–Oxygen. Tenty-one healthy unmedicated patients were anesthetized with Forane and oxygen. After endotracheal intubation without muscle relaxants, end-tidal Forane concentrations averaged 1.24 per cent. Ventilation was controlled to maintain normal P_{ACO_2}. Heart rate was counted from the electrocardiogram, and blood pressure was measured by auscultation. Pupillary responses of 11 patients were recorded. All values were obtained 3 minutes prior to incision and 2 minutes after incision. Then Forane concentration was increased to approximately 1.5 per cent and measurements were made 5, 15, 30, and 60 minutes after incision.

Results

VOLUNTEER STUDIES, NORMAL P_{ACO_2}

Halothane (tables 2 and 3, figs. 1–3). In the first hour of anesthesia, heart rate (HR) remained constant and hypotension was the only clinical sign of deep anesthesia. Pupils

TABLE 2. Clinical Signs

Alveolar concentration (per cent)	Halothane				Cyclopropane			
	Awake Control (Mean ±SE)	1	1.5	2	Awake Control (Mean ±SE)	17.5	27.5	37.5
MAC Multiple		1.2	1.8	2.4		1.7	2.7	3.7
AP*	95 ±2 torr	76† ±2	67† ±4	49†‡ ±5	90 ±3 torr	131† ±5.3	132† ±5.4	131† ±8.4
HR*	77 ±3 beats/min	102 ±3	101 ±4	102 ±5	64 ±2.4 beats/min	99 ±5.4	92 ±5.7	91 ±5.3
Pupil diameter (mm)		1.9 ±0.3	1.9	2 ±0.1		4.3 ±1.6	6.7‡ ±1.1	7‡ ±1.1
Pupil diameter with light (mm)		1.6 ±0.4	1.9	2 ±0.1		3.3 ±0.8	4.9‡ ±1.5	5.6‡ ±1.6
Pupil reactivity to light 0 None + Sluggish ++ Moderate +++ Brisk		+	0	0		+++	+	+
Tearing (number of subjects)		0	0	0		1/7	1/9	5/6
Eyeball movement (number of subjects)		0	0	0		2/7	2/9	0

* During anesthesia, mean arterial pressure ($\overline{AP}$) and heart rate (HR) are *per cent of awake control value* ±SE. † $P < 0.05$ ether, 5 per cent fluroxene, 1.25 per cent Forane). § $P < 0.05$ from 9 per cent fluroxene. ‡ $P < 0.05$ from 1.85 per cent Forane.

TABLE 3. Clinical Signs

Alveolar concentration (per cent)	Halothane			Cyclopropane		
	1	1.5	2	17.5	27.5	37.5
MAC multiple	1.2	1.8	2.4	1.7	2.7	3.7
$\overline{AP}$ (mean per cent of awake control value ± SE)	73 ±3	63 ±3	60 ±5	111§ ±3.8	124† ±5.7	132† ±7
HR (mean per cent of awake control value ± SE)	109 ±3	115 ±3	115 ±5	95 ±3.7	94 ±3.4	97 ±7.1
Pupil diameter (mm)	2.2§ ±0.2	2.2 ±0.1	2.7§ ±0.3	5.4 ±2	7.2†§ ±1	7.8†§ ±0.6
Pupil diameter with light (mm)	2.2§ ±0.3	2.2 ±0.5	2.7§ ±0.3	3.7 ±1.2	5.8†§ ±1.5	6.7†§ ±1.3
Pupil reactivity to light 0 None + sluggish ++ Moderate +++ Brisk	0	0	0	+++	+	+
Tearing (number of subjects)	0	0	0	2/9	0	3/6
Eyeball movement (number of subjects)	0	0	0	4/9	0	0

†$P < 0.05$ from "light" anesthetic concentration (1 per cent halothane, 17.5 per cent cyclopropane, 3 per cent ether, 5 per value at the same anesthetic concentration (table 2).

of Anesthesia, Hour 1

Ether			Fluroxene				Forane			
Awake Control (Mean ±SE)	3	6	Awake Control (Mean ±SE)	5	9	12	Awake Control (Mean ±SE)	1.25	1.85	2.5
	1.4	2.85		1.3	2.4	3.15		0.96	1.4	1.92
88 ±3.1 torr	99 ±5	101 ±6	85 ±2.3 torr	92† ±4.3	94 ±6.5	125†‡§ ±5.3	95 ±2.7 torr	73† ±2.5	64† ±4	46‡¶ ±1.5
64.5 ±2.8 beats/min	124† ±5	132† ±8.5	63 ±2.2 beats/min	91† ±2.8	110‡ ±6.7	163†‡§ ±12	67 ±4 beats/min	120† ±8	118 ±6	125 ±10
	4.1 ±0.05	7.5‡ ±0.3		3.9 ±0.07	7‡ ±0.4	7.1‡ ±0.3		1.9 ±0.1	2 ±0.1	2.3 ±0.2
	2.2 ±0.3	5.8‡ ±0.6		2.6 ±0.2	4.5‡ ±0.4	6.3‡§ ±0.2		1.4 ±0.1	1.6 ±0.1	2 ±0.3
	+++	+		+++	+	+		+++	+++	+++5/7 0 2/7
	5/10	1/9		2/6	6/9	1/5		0	0	0
	0	0		1/6	0	0		0	0	0

from awake control. ‡ $P < 0.05$ from "light" anesthetic concentration (1 per cent halothane, 17.5 per cent cyclopropane, 3 per cent

of Anesthesia, Hour 5

Ether		Fluroxene			Forane		
3	6	5	9	12	1.25	1.85	2.5
1.4	2.85	1.3	2.4	3.15	0.96	1.4	1.92
86§ ±4	92 ±5	85 ±2.7	95† ±3.2	125†‡ ±5.3	71 ±2.9	60† ±2.8	51†‡ ±4
155§ ±9	154 ±9	122§ ±5.1	134§ ±7.4	172†‡ ±7.2	119 ±9	125 ±8	133†‡ ±6
4.9 ±0.6	8.5† ±0.2	5.6§ ±0.5	7.7† ±0.3	7.1†§ ±0.2	2.1 ±0.2	3.3 ±0.6	4.4‡ ±0.7
3.1 ±0.4	7.5† ±0.4	3.2§ ±0.1	6.2†§ ±0.5	7†§ ±0.3	1.6 ±0.1	2.5† ±0.4	3.8†‡ ±0.6
+++	+	+++	+	0	+++	+++4/7 +2/7 01/7	+++3/7 +2/7 02/7
3/9	0	5/5	4/7	4/5	0	0	0
0	0	2/5	0	0	0	0	0

cent fluroxene, 1.25 per cent Forane). ‡ $P < 0.05$ from 9 per cent fluroxene or 1.85 per cent Forane. § $P < 0.05$ from hour 1

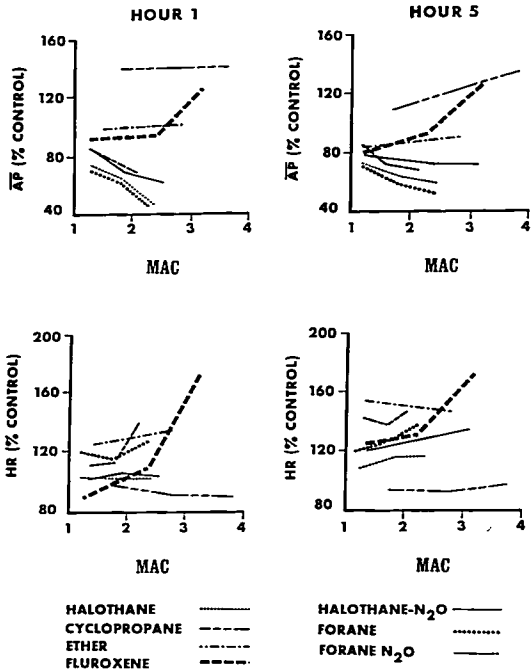

FIG. 1. Mean arterial pressure ($\overline{AP}$) and heart rate (HR) responses to several concentrations of seven anesthetics are shown. To permit comparison of anesthetic agents at equipotent concentrations, the horizontal axis represents multiples of MAC (see table 1). The fine horizontal line is the awake control value. Note that $\overline{AP}$ responses vary widely from one anesthetic to another and that for the same agent $\overline{AP}$ response changes with prolonged anesthesia.

were constricted and nonreactive at all levels of halothane anesthesia after both one and five hours; eye movement and tearing were absent. By the fifth hour of anesthesia, mean arterial pressure ($\overline{AP}$) ceased to fall as anesthesia deepened, thus eliminating the only sign of deep halothane anesthesia.

Halothane–Nitrous Oxide (table 4, figs. 1–3). The clinical signs were as limited during halothane–nitrous oxide as during halothane–oxygen anesthesia. In the first hour, although baseline $\overline{AP}$ was slightly higher than with halothane–oxygen, it decreased significantly as anesthesia deepened. Prolonged anesthesia again eliminated hypothesion as a clinical sign of anesthetic depth because $\overline{AP}$ remained constant even to 3.1 MAC. HR rose slightly with increasing depth. Baseline pupillary diameter was greater after five hours than after one hour of anesthesia, but was unaffected by deeper halothane anesthesia. Reactivity to light was unmeasurable at all concentrations of halothane–nitrous oxide in the first hour, and minimal during the fifth hour of study.

Forane (table 2 and 3, figs. 1–3). $\overline{AP}$ decreased significantly as anesthesia deepened. Although baseline HR was elevated, there was no significant change with anesthetic depth. Pupils were constricted and reactive at all three anesthetic concentrations. After five hours of Forane, hypotension again developed with deep anesthesia. However, HR increased a small but significant degree, and pupils dilated slightly as anesthesia deepened.

Forane–Nitrous Oxide (table 5, figs. 1–3).

Although baseline $\overline{AP}$ was higher, the combination of nitrous oxide and Forane did not prevent the decrease in $\overline{AP}$ and increase in HR seen with Forane–oxygen alone. Pupillary diameter increased slightly, while reactivity to light decreased. Prolonged anesthesia did not greatly change the response to Forane–nitrous oxide, although baseline HR increased. Pupils remained fairly small at all three levels of anesthesia, and reactivity increased. No tearing or eyeball movement was noted.

Cyclopropane (tables 2 and 3, figs. 1–3). Cyclopropane raised baseline $\overline{AP}$ following induction, but deepening anesthesia did not alter $\overline{AP}$ further. HR remained at control levels throughout the study. Pupillary diameter increased and reactivity to light decreased as cyclopropane concentration rose. Tearing was present in five of six subjects at 3.7 MAC. Prolonged anesthesia did not affect the clinical signs, except that $\overline{AP}$ increased slightly with deep cyclopropane by the fifth hour.

Diethyl Ether (tables 2 and 3, figs. 1–3). Although HR and $\overline{AP}$ remained constant, the pupils dilated and became less reactive as ether anesthesia deepened. Tearing was most frequent at 1.4 MAC. After five hours of ether, baseline $\overline{AP}$ decreased and HR increased. Deeper anesthesia did not further change $\overline{AP}$ and HR, but the pupils dilated and became less reactive.

Fluroxene (tables 2 and 3, figs. 1–3). HR and $\overline{AP}$ *increased* significantly as anesthesia deepened. The pupils dilated and became less reactive to light as fluroxene concentration increased. Tearing was most common at 2.4 MAC, an intermediate concentration. Results were similar in the fifth hour of the study, except that tearing was observed at all three levels of anesthesia.

Effect of Nitrous Oxide

Addition of Nitrous Oxide for 15 Minutes (table 6, fig. 4). Fifteen minutes after addition of 70 per cent nitrous oxide to halothane, diethyl ether, or fluroxene, $\overline{AP}$ increased significantly while HR remained constant (except for a decrease in HR at 3 per cent ether). Pupillary diameter increased with all three agents, and reactivity decreased with ether and fluroxene. (There was no reactivity to light during halothane anesthesia prior to adding nitrous oxide.) During ether anesthesia, and especially during 9 per cent fluroxene anesthesia, further pupillary dilatation from nitrous oxide may have been minimal because the pupils were already dilated. For example, at 9 per cent fluroxene, pupillary diameter was 6.5 mm prior to addition of nitrous oxide. Elimination of nitrous oxide lowered $\overline{AP}$ and constricted the pupils with all three agents and increased reactivity to light with ether.

Elimination of Nitrous Oxide for 15 Minutes (Halothane and Forane) (tables 4 and 5). There were no significant changes when nitrous oxide was discontinued for 15 minutes except that $\overline{AP}$ decreased 4 per cent during Forane anesthesia. Adding nitrous oxide back into the system caused a very slight but consistent 0.5-mm increase in pupillary diameter during halothane anesthesia. All other clinical signs remained constant.

Volunteer Study, $Paco_2$ Not Controlled (Table 7)

Halothane–Oxygen. Deepening anesthesia did not lower blood pressure but did cause significant tachycardia. Pupillary diameter increased while sluggish reactivity to light persisted in five of eight subjects. There was no tearing or eye movement. Respiratory signs of deepening anesthesia were evident because tidal volume (V_t) decreased 9 per cent and respiratory rate increased 71 per cent.

The effects of prolonged anesthesia were minimal. After six hours at 1 per cent halothane, $Paco_2$ had decreased 3 torr, tidal volume increased 10 per cent, and HR increased 14 per cent. Pupils were slightly more dilated but no more reactive than early in the study.

Forane (table 8). In the first hour of anesthesia, $\overline{AP}$ decreased significantly as Forane concentration rose. $Paco_2$ increased and minute ventilation ($\dot{V}_e$) decreased to 57 per cent of control, due to reductions in both respiratory rate and V_t. Prolonged anesthesia raised HR and $\dot{V}_e$ but did not alter $Paco_2$. Wasted ventilation, therefore, increased. Deepening anesthesia in the fifth hour did not change $\overline{AP}$ or HR, but raised $Paco_2$ and

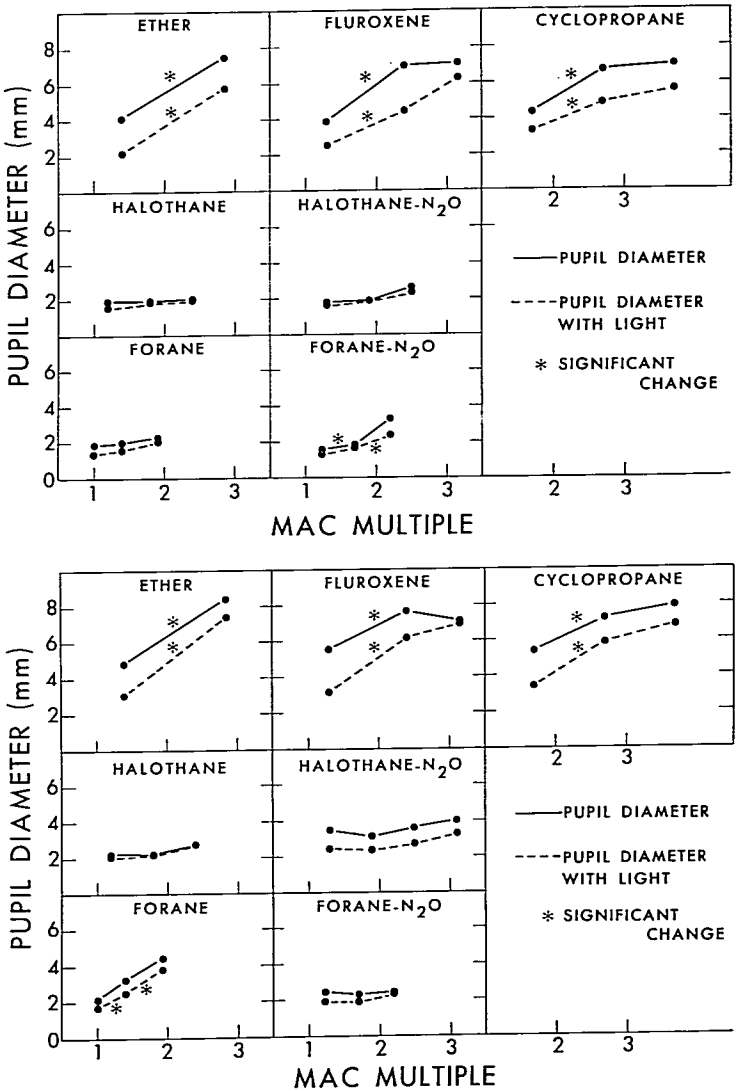

FIG. 2 (*above*). In the first hour of anesthesia, resting pupil diameter in mm (dashed line) is plotted as a function of MAC multiples for each agent studied (see table 1). The dotted line shows the pupil diameter in response to light stimulation. The asterisk (*) denotes significant increase of pupil diameter with increasing anesthetic concentration. Note that pupil diameter and reactivity to light increased with ether, cyclopropane, and fluroxene, compared with minimal changes observed during halothane and Forane anesthesia.

FIG. 3 (*below*). In the fifth hour of anesthesia, resting pupil diameter (dashed line) and response to light (dotted line) are again plotted against MAC multiples. The asterisk (*) denotes significant increase in pupil diameter with increasing anesthetic concentration.

reduced $\dot{V}_e$ as V_t decreased. Pupils were constricted and briskly reactive to light at all concentrations of Forane, both early and late in the study.

PATIENT STUDY, EFFECT OF SURGICAL STIMULATION

Halothane (table 9, fig. 5). A minute after incision of the skin, HR, V_t, $\dot{V}_e$ and pupillary diameter increased significantly. Systolic and diastolic blood pressure and respiratory rate did not change. Twelve minutes after incision, while the operation continued, HR, $\dot{V}_e$, V_t, and pupillary diameter reverted to preincision values. In six patients, the clinical signs were followed throughout operation. No significant alterations occurred unless a second incision of the skin was made (two patients), whereupon HR, $\dot{V}_e$, V_t and pupillary diameter increased as with the first incision, again reverting to pre-incision values within 12 minutes. No patient moved in response to incision.

Forane (table 10). Following incision of the skin, systolic and diastolic blood pressure and heart rate increased. Pupils dilated in all 11 patients in whom pupillary responses were observed. No patient moved in response to incision. Forane concentration was then

TABLE 4. Clinical Signs of Halothane–N_2O Anesthesia

Alveolar halothane concentration (per cent)	Hour 1				Hour 5				Remove N_2O	Add N_2O
	Awake Control	0.5-N_2O	1.0-N_2O	1.5-N_2O	0.5-N_2O	1.0-N_2O	1.5-N_2O	2.0-N_2O	1.0	1.0
MAC multiple		1.3	1.9	2.5	1.3	1.9	2.5	3.1	—	—
$\overline{AP}$*	92.5 ±3.9 torr	86 ±4.2	71† ±5.7	68‡ ±5.2	82 ±3.5	80 ±5.5	76 ±7.3	77 ±7.9	+0.5 ±5	+2 ±4.7
HR*	62 ±3.6 beats/min	102 ±3.1	105 ±5.7	102 ±8	120§ ±6.7	124 ±8	128§ ±10.2	134¶ ±11.5	+3 ±4	+1.7 ±4
Pupil diameter (mm)		1.8 ±0.1	1.9 ±0.1	2.6 ±0.5	3.5§ ±0.45	3.1§ ±0.8	3.6 ±0.6	4 ±0.6	−0.1 ±0.1	+1.1 ±0.45
Pupil diameter with light (mm)		1.7 ±0.1	1.9 ±0.1	2.3 ±0.3	2.5§ ±0.1	2.4§ ±0.1	2.7 ±0.2	3.3 ±0.2	−0.1** ±0.8	+0.5** ±0.15
Pupil reactivity to light 0 None + Sluggish ++ Moderate +++ Brisk		0 6/8 + 1/8 +++ 1/8	0 7/8 + 1/8	0	0 1/7 + 5/7 +++ 1/7	0 4/6 + 2/6	0 4/7 + 3/7	0 5/6 + 1/6	2/6 decrease	2/6 increase 1/6 decrease
Tearing (number of subjects)		1/8	0	0	1/7	1/6	1/6	1/6	0	0
Eyeball movement (number of subjects)		2/8	0	0	1/7	0	0	0	0	0

* Heart rate (HR) and mean arterial pressure ($\overline{AP}$) are per cent of awake control value ±SE. In the last two columns, when nitrous oxide is removed or added, $\overline{AP}$ and HR are per cent changes from previous steady-state determinations.
† P <0.025, 1 per cent halothane–N_2O *vs.* 0.5 per cent halothane–N_2O, hour 1.
‡ P <0.025, 1.5 per cent halothane–N_2O *vs.* 1 per cent halothane–N_2O, hour 1.
§ P <0.01, hour 5 *vs.* hour 1 at identical halothane concentrations.
¶ P <0.05, 2 per cent halothane–N_2O *vs.* 1 per cent halothane–N_2O, hour 5.
** Mean change from previous value. P <0.05. 15 minutes after adding 70 per cent N_2O back into inspired gas, pupils dilated slightly.

TABLE 5. Clinical Signs of Forane–N_2O Anesthesia

Alveolar Forane concentration (per cent)	Hour 1				Hour 5			Remove N_2O	Add N_2O
	Awake Control	0.7–N_2O	1.3–N_2O	1.9–N_2O	0.7–N_2O	1.3–N_2O	1.9–N_2O	1.3	1.3
MAC multiples	0	1.24	1.7	2.2	1.24	1.7	2.2	—	—
$\overline{AP}$*	85 ±2.8 torr	86‡‡ ±4.2	78† ±3.6	72‡ ±5	87 ±4.8	75** ±2.7	74 ±4	+1.2 ±2.6	−0.25 ±3
HR*	60 ±3.1 beats/min	110 ±4.7	114 ±5	133‡§ ±5.6	137¶ ±8.2	132¶ ±6	148†† ±9	−4§§ ±1.3	+0.5 ±1.3
Pupil diameter (mm)		1.6 ±0.04	1.8† ±0.08	3.3 ±0.9	2.5 ±0.5	2.3 ±0.2	2.5 ±0.3	+0.26¶¶ ±0.12	−0.24¶¶ ±0.16
Pupil diameter with light (mm)		1.3 ±0.06	1.6 ±0.09	2.4‡§ ±0.2	1.9¶ ±0.2	1.85 ±0.12	2.3 ±0.24	+0.18	−0.16
Pupil reactivity to light 0 None + Sluggish ++ Moderate +++ Brisk		+1/8 +++7/8	0 1/7 +++6/7	0 5/7 + 2/7	0 2/7 + 1/7 +++ 4/7	0 3/8 + 3/8 +++ 2/8	0 2/5 + 2/5 +++ 1/5	7/8 No change 1/8 ↑reaction	5/6 No change 1/6 ↑reaction
Tearing (number of subjects)		0	0	0	0	0	0	0	0
Eyeball movement (number of subjects)		0	0	0	0	0	0	0	0

* Heart rate (HR) and mean arterial pressure ($\overline{AP}$) are per cent of awake control value ±SE. In the last two columns when nitrous oxide was removed or added, $\overline{AP}$ and HR are per cent change from previous steady-state determinations.
† $P < 0.05$, 1.3 per cent Forane–N_2O *vs.* 0.7 per cent Forane–N_2O, hour 1.
‡ $P < 0.001$, 1.9 per cent Forane–N_2O *vs.* 0.7 per cent Forane–N_2O, hour 1.
§ $P < 0.005$, 1.9 per cent Forane–N_2O *vs.* 1.3 per cent Forane–N_2O, hour 1.
¶ $P < 0.05$, hour 5 *vs.* hour 1 at identical Forane concentrations.
** $P < 0.05$, 1.3 per cent Forane–N_2O *vs.* 0.7 per cent Forane–N_2O, hour 5.
†† $P < 0.025$, 1.9 per cent Forane–N_2O *vs.* 1.3 per cent Forane–N_2O, hour 5.
‡‡ $P < 0.005$, 0.7 per cent Forane–N_2O, hour 1 *vs.* awake control.
§§ $P < 0.025$. 15 minutes after eliminating N_2O, HR decreased.
¶¶ Mean change from previous value.

increased to approximately 1.5 per cent while the operation continued. In general, the increases in blood pressure and heart rate persisted through the first hour of the operation, despite higher Forane concentrations. This contrasts with the results obtained during halothane anesthesia.

Discussion

These data show that anesthetic depth cannot be defined for all anesthetics by a given clinical sign because no clinical sign is affected by all anesthetics in the same way. For example, if blood pressure were to be used as a guide to anesthetic depth in clinical practice, blood pressure should vary predictably with dose of anesthetic. In the first hour of anesthesia, such a relationship exists for halothane, halothane–nitrous oxide, Forane, and Forane–nitrous oxide, whereas no such relationship exists for cyclopropane, diethyl ether or fluroxene. In fact, the hypertension and tachycardia produced at 3.1 MAC fluroxene may deceive the clinician who commonly interprets such changes as signs of light anesthesia. Prolonged anesthesia eliminates the dose–response relationship between halothane and blood pressure, possibly because of increases in sympathetic activity with time.[3,19–21] On the other hand, only during cyclopropane, ether, and fluroxene anesthesia did pupillary dilatation and reduced reactivity to light correlate somewhat with increased anesthetic concentration: halothane or Forane alone or with nitrous oxide failed to give dose-related eye signs.

FIG. 4. During halothane, ether, and fluroxene anesthesia, addition of 70 per cent N_2O for 15 minutes generally increased mean arterial pressure ($\overline{AP}$) and pupil diameter, while not affecting heart rate. Removal of 70 per cent N_2O after 15 minutes reversed these changes. All measurements were obtained following a 15-minute equilibrium period. The asterisk (*) denotes a significant change from the previous steady-state determination.

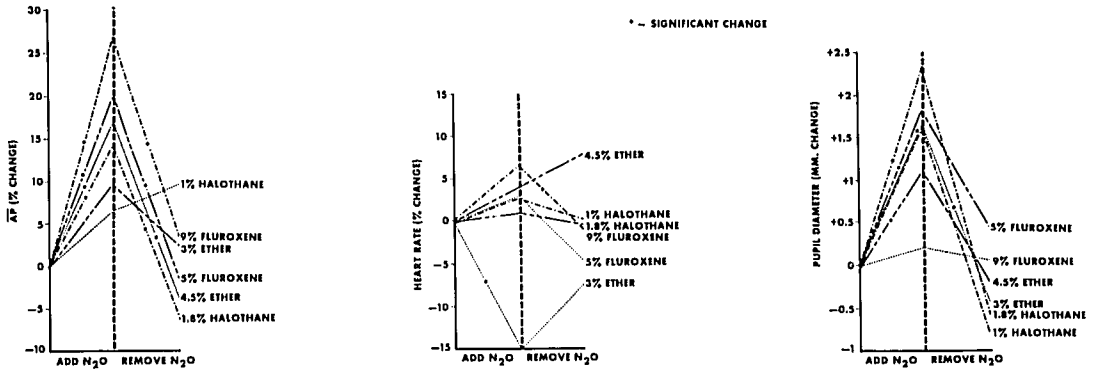

TABLE 6. Modification of the Clinical Signs of Anesthesia by 70 Per Cent Nitrous Oxide during Halothane, Ether, or Fluroxene Anesthesia*

Alveolar concentration (per cent)	Add 70 per cent N_2O						Remove 70 per cent N_2O					
	Halothane		Ether		Fluroxene		Halothane		Ether		Fluroxene	
	0.8–1.2	1.6–2.0	3	4.5	5	9	0.8–1.2	1.6–2.0	3	4.5	5	9
$\overline{AP}$ (per cent change)	+5.7 ±3.8	+14† ±4	+9 ±4.5	+10† ±4.6	+10† ±4.7	+20† ±4.1	+3.8 ±2	−20‡ ±5	−7 ±3.2	−20‡ ±4.2	−21‡ ±4.3	−23‡ ±3.6
HR (per cent change)	+2.6 ±1.4	+0.8 ±1.7	−15.3† ±4.2	+4 ±4.2	+2.6 ±2	+5.7 ±3.5	−1.2 ±4	−1.2 ±1.6	+8.3 ±4.3	+3.3 ±5.5	−7 ±2.1	−7‡ ±1.8
Pupil diameter (mm change)	+1.8	+2.3†	+1.7† ±0.4	+1.1† ±0.3	+1.8† ±0.5	+0.2 ±0.1	−2.7	−2.9	−2.3‡ ±0.6	−1.3‡ ±0.8	−1.4	−0.1 ±0.2
Reactivity of pupil to light	None	None	Decrease	Decrease	Decrease	Decrease	None	None	Increase	Increase	No change	Decrease 1/6 Increase 2/6 No change 3/6

* The effects of adding 70 per cent nitrous oxide to inspired gas for 15 minutes on mean arterial pressure ($\overline{AP}$) and heart rate (HR) are expressed as mean per cent changes from pre-N_2O value ±SE. For pupil diameter, millimeter change ±SE is shown. Similarly, the effects of eliminating 70 per cent N_2O from inspired gas are shown as mean per cent changes ±SE from values prior to N_2O elimination.

† $P < 0.05$ compared with pre-N_2O value.

‡ $P < 0.025$ compared with values just prior to elimination of N_2O.

TABLE 7. Clinical Signs of Anesthesia during Halothane-Oxygen Anesthesia (Spontaneous Respiration)*

	Awake Control	Hour 2, 1 Per Cent Alveolar Halothane	Hour 4, 1.6 Per Cent Alveolar Halothane	Hour 6, 1 Per Cent Alveolar Halothane
MAC multiple		1.2	1.9	1.2
$\overline{AP}$	89	75†	75	78
	±3.3 torr	±4.9	±3.8	±3.2
HR	59	126†	146‡	140§
	±1.3 beats/min	±3.6	±6	±6
Pupil diameter (mm)		2.0	3.6‡¶	2.4§
		±0.1	±0.5	±0.2
Pupil diameter with light (mm)		2.0	2.6‡¶	2.2
		±0.1	±0.1‡	±0.1
Reactivity to light		+++ 1/8	+++ 2/8	+ 5/8
		+ 1/8	+ 1/8	0 3/8
		0 6/8	0 5/8	
Eyeball movement		0	0	0
Tearing		0	1/8	0
P_{aCO_2} (torr)	36.3	51.4†	59.9‡¶	48.6§
	±1.2	±1.4	±1.0	±2.3
V_t	489	47†	38‡¶	57§
	±31 ml	±11	±4	±7.9
$\dot{V}_E$	7.4	96	104	123
	±0.5 l/min	±10	±27	±31
f	15.5	200†	271‡¶	206
	±1.2/min	±7	±8	±6

* During anesthesia, spontaneous respiration allowed P_{aCO_2} to rise as respiratory depression ensued. Mean values ±SE during anesthesia are per cent of awake control for mean arterial pressure ($\overline{AP}$), heart rate (HR), tidal volume (V_t), minute ventilation ($\dot{V}_E$) and respiratory rate (f). Reactivity to light is described in table 2.

† $P < 0.01$, 1 per cent halothane, hour 2, *vs.* awake control value.

‡ $P < 0.01$, 1.6 per cent halothane, hour 4, *vs.* 1 per cent halothane, hour 2.

§ $P < 0.025$, 1 per cent halothane, hour 6, *vs.* 1 per cent halothane, hour 2.

¶ $P < 0.05$, 1.6 per cent halothane, hour 4, *vs.* 1 per cent halothane, hour 6.

Addition of nitrous oxide to halothane, ether, or fluroxene generally raised $\overline{AP}$ and dilated pupils, a result of sympathetic stimulation.[4,22] However, this effect was not observed when nitrous oxide was adminstered with halothane from the beginning of the study. The reason for the difference between the two nitrous oxide studies is not apparent.

The eye signs of anesthesia appear to be an expression of sympathetic activity. A dilated pupil may signify parasympathetic inhibition or sympathetic stimulation.[23] During normal sleep,[24,25] or halothane anesthesia, pupils are constricted, presumably because sympathetic tone is reduced.[26] In contrast, nitrous oxide, cyclopropane, ether and fluroxene increase sympathetic tone, and/or elevate circulating norepinephrine, and thereby dilate the pupils.[4,22,27–30]

Pupillary reactivity to light is a reflex controlled by the parasympathetic nervous system.[22] Although deep anesthesia reduced or abolished the light reflex, the mechanism and site of action are unknown. Lacrimation, a parasympathetic function,[24] was observed with cyclopropane, ether, and fluroxene at various depths of anesthesia. Eye movement almost invariably was absent at all anesthetic doses. This finding suggests that eye movement is a sign of extremely light anesthesia or that it is activity (?) which fatigues early in anesthesia.

The cardiovascular signs of anesthesia appear to be an expression of a balance between sympathetic stimulation and the direct depressant effects of anesthesia. During halothane anesthesia, which initially does not stimulate sympathetic activity,[3,26] HR remained constant. $\overline{AP}$ however, fell as stroke

TABLE 8. Clinical Signs of Anesthesia during Forane Anesthesia (Spontaneous Respiration)*

	Awake Control	Hour 1		Hour 5	
		1.25 Per Cent Alveolar Forane	1.9 Per Cent Alveolar Forane	1.25 Per Cent Alveolar Forane	1.9 Per Cent Alveolar Forane
MAC multiple		0.96	1.4	0.96	1.4
$\overline{AP}$	89	74†	63‡	70	68
	±2.5 torr	±3.6	±5	±2	±3
HR	62	127†	126	146§	150¶
	±3.6 beats/min	±6	±6	±8	±9
Pupil diameter (mm)		1.7	2†	2.3	2.5
		±0.1	±0.1	±0.2	±0.1
Pupil diameter with light (mm)		1.5	1.8‡	1.9	2.1
		±0.1	±0.1	±0.2	±0.1
Reactivity to light		+++	+++	+++	+++
Eyeball movement		0	0	0	0
Tearing		0	0	0	0
$Paco_2$ (torr)	38.9	48.5†	61†	48.6	58.5**
	±0.8	±1.7	±4.6	±1.9	±1.4
V_T	534	47†	35	58§	45¶**
	±40 ml	±5.2	±8	±8	±5
$\dot{V}_E$	7	84†	57‡	107§	83¶**
	±0.3 l/min	±7	±7.5	±8	±8.6
f	14	172†	156	172	178¶
	±1/min	±4	±5	±4	±4

* During anesthesia, spontaneous respiration allowed $Paco_2$ to rise as respiratory depression ensued. Mean arterial pressure ($\overline{AP}$), heart rate (HR), respiratory rate (f), tidal volume (V_T), and minute ventilation ($\dot{V}_E$) are per cent of awake control value ±SE.

† $P < 0.05$, 1.25 per cent, hour 1, *vs.* awake.

‡ $P < 0.05$, 1.9 per cent *vs.* 1.25 per cent, hour 1.

§ $P < 0.05$, 1.25 per cent, hour 5, *vs.* 1.25 per cent, hour 1.

¶ $P < 0.05$ 1.9 per cent, hour 5, *vs.* 1.9 per cent, hour 1.

** $P < 0.05$ 1.9 per cent, hour 5, *vs.* 1.25 per cent, hour 1.

TABLE 9. Effects of Surgical Stimulation on the Clinical Signs of Halothane Anesthesia*

	Prior to Incision of the skin	Immediately after Incision	12 Minutes after Incision
End-tidal halothane concentration (per cent alveolar)	1.02 ±0.04	1.06 ±0.04	1.08 ±0.05
Blood pressure			
Systolic (torr)	108 ±7	113 ±8	110 ±9
Diastolic (torr)	62 ±7	70 ±7	72 ±11
Heart rate (beats/min)	91 ±6	113† ±8	103 ±7
Respiratory rate (/min)	36 ±4	43 ±4.5	41 ±4
Tidal volume (ml)	151 ±24	204† ±34	158‡ ±38
Minute ventilation (l)	5.23 ±0.7	8.14† ±1.19	5.91 ±1.29
Pupil diameter (mm)	2 ±0.2	5.5† ±0.6	3.2‡ ±0.8

* The clinical signs of anesthesia were evaluated immediately after incision and following 12 minutes of ongoing surgery. All values are mean ±SE. There were no significant differences between values obtained 12 minutes after incision and prior to incision.

† $P < 0.005$ immediately after incision *vs.* pre-incision.

‡ $P < 0.05$ 12 minutes after incision *vs.* immediately after incision.

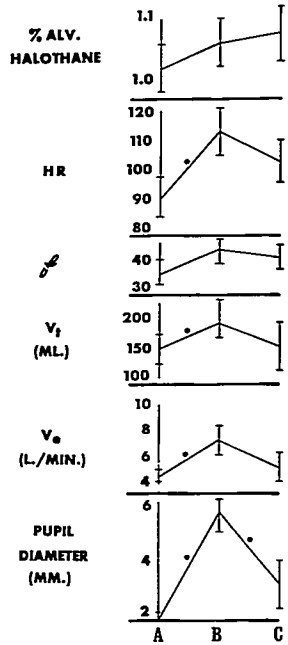

FIG. 5. The effects of incision of the skin on clinical signs of anesthesia in eight healthy patients. Values at *A* were obtained immediately prior to incision, at *B* immediately after incision, and at *C* 12 minutes after incision while the operations continued. The asterisk (*) denotes significant change from previous values. Note that immediately after incision, heart rate (HR), tidal volume (V_T), minute ventilation (V_E) and pupil diameter increased significantly, while respiratory rate (f) failed to change significantly. These values had returned towards control levels 12 minutes after incision although the operations continued.

volume and ejection rate decreased, both the result of direct myocardial depression.[3]

Anesthetics with known alpha- and/or beta-sympathetic-stimulating properties, such as nitrous oxide,[4,22] cyclopropane,[5,27] ether,[7,28,30] and fluroxene,[6,29] increased HR and/or $\overline{AP}$. Forane has not been fully evaluated but appears to produce beta stimulation, thus explaining the increase in heart rate and decrease in arterial pressure by decreased total peripheral resistance.[8]

Two major factors which change the level of sympathetic tone also affect clinical signs. First, prolonged anesthesia increases beta-sympathetic activity with halothane,[3,21] and probably with ether and fluroxene, and is manifested by increased HR and a slight increase in pupillary diameter. During halothane–oxygen anesthesia, $\overline{AP}$ rose due to increased stroke volume, although total peripheral resistance fell. Second, the rise in P_{aCO_2} during halothane–oxygen and spontaneous respiration stimulated sympathetic activity.[22,31,32] Thus, there was less reduction of $\overline{AP}$, during hypercarbia HR increased, and the pupils slightly dilated and increased in reactivity.

It is difficult to assess depth of anesthesia adequately by the effect of the anesthetic on autonomic activity, since many variables interact with the anesthetic to alter such activity. Respiratory signs are less affected by autonomic activity and may be a better guide to anesthetic depth. The predictable decrease in tidal volume and increase in respiratory rate during halothane anesthesia make these changes reasonable signs of halothane anesthetic depth.[33,34] During halothane anesthesia, when ventilation was controlled to keep P_{aCO_2} normal, only the blood pressure indicated the depth of anesthesia. When ventilation was spontaneous, only the respiratory signs indicated anesthetic depth, since the sympathetic stimulation attendant on the rise in P_{aCO_2} altered the nonrespiratory signs.

Our patient studies with halothane emphasize the importance of the skin-incision stimulus. Although HR, pupillary diameter, tidal volume, and minute ventilation increased significantly with incision of the skin, these all returned to pre-incision values 12 minutes later despite continued surgery. This suggests that once the incision is completed, clinical signs will not indicate anesthetic depth. This contrasts with data obtained during Forane anesthesia in surgical patients. Even though the end-tidal Forane concentration was raised to 1.5 per cent after incision, blood pressure and HR remained elevated, similar to values at 1.24 per cent Forane immediately after incision. Thus, during surgery, the clinical signs are better maintained with Forane than with halothane anesthesia.

Our studies in young, healthy unmedicated men give a quantitative set of "normal" values

TABLE 10. Effects of Surgical Stimulation on the Clinical Signs of Forane Anesthesia*

	3 Minutes Prior to Incision of the skin	2 Minutes after Incision	5 Minutes after Incision	15 Minutes after Incision	30 Minutes after Incision	60 Minutes after Incision
Number of patients	21	21	20	20	19	17
End-tidal Forane concentration (per cent alveolar)	1.24 ±0.2	1.24 ±0.2	1.44† ±0.03	1.52† ±0.02	1.46† ±0.04	1.55† ±0.02
Blood pressure						
Systolic (torr)	100.6 ±6.4	121† ±6	121† ±5.8	114 ±6.6	114 ±7.7	113 ±5
Diastolic (torr)	62 ±6.1	72 ±5	72 ±4.2	73 ±4.7	67 ±4.9	67 ±4.5
Heart rate (beats/min)	85 ±5	96† ±3	93 ±4.2	91 ±4.2	94 ±4.6	95 ±3.9

* Some of the clinical signs of Forane anesthesia were evaluated immediately after incision. Forane concentration was then raised and the clinical signs were followed for an hour. All values are mean ±SE. Pupils dilated following incision in all 11 patients in whom pupillary responses were noted.

† $P < 0.005$ compared with pre-incision value.

for clinical signs. Even within a reasonably homogeneous group, we found an occasional response differing markedly from the mean. Further studies of the effects of premedication and other drugs, age,[35] debility,[36] and surgical stimulation are needed before we can apply these signs with confidence to all patients. Regardless of the results of such future studies, we can say now that it is difficult to categorize the clinical signs of anesthesia for one anesthetic, let alone for inhalation agents in general.

Halothane (Fluothane) for these studies was donated by Ayerst Laboratories; Fluroxene (Fluoromar) by Ohio Medical Products, Division of Air Reduction Corp. D. R. Eger contributed to the body of this work.

References

1. Guedel AE: Inhalation Anesthesia. New York, MacMillan, 1954
2. Guedel AE: Cyclopropane anesthesia. ANESTHESIOLOGY 1:13–25, 1940
3. Eger EI II, Smith NT, Stoelting RK, *et al*: The cardiovascular effects of halothane in man. ANESTHESIOLOGY 32:396–409, 1970
4. Smith NT, Eger EI II, Stoelting RK, *et al*: The cardiovascular and sympathomimetic responses to the addition of nitrous oxide to halothane in man. ANESTHESIOLOGY 32:410–421, 1970
5. Cullen DJ, Eger EI II, Gregory GA: The cardiovascular effects of cyclopropane in man. ANESTHESIOLOGY 31:398–406, 1969
6. Cullen BF, Eger EI II, Smith NT, *et al*: The cardiovascular effects of fluoxene in man. ANESTHESIOLOGY 32:218–230, 1970
7. Gregory GA, Eger EI II, Smith NT, *et al*: The cardiovascular effects of diethyl ether in man. ANESTHESIOLOGY 34:19–24, 1971
8. Stevens WC, Cromwell TH, Halsey MJ, *et al*: The cardiovascular effects of a new inhalation anesthestic, Forane, in human volunteers at constant arterial carbon dioxide tension. ANESTHESIOLOGY 35:8–16, 1971
9. Cromwell TH, Stevens WC, EI II, *et al.*: The cardiovascular effects of Compound 469 (Forane) during spontaneous ventilation and CO_2 challenge in man. ANESTHESIOLOGY 35:17–25, 1971
10. Fourcade HE, Stevens WC, Larson CP Jr: The ventilatory effects of Forane, a new inhaled anesthetic. ANESTHESIOLOGY 35:26–31, 1971
11. Bahlman SH, Eger EI II, Smith NT, *et al*: The cardiovascular effects of nitrous oxide–halothane anesthesia in man. ANESTHESIOLOGY 35:274–285, 1971
12. Fourcade H, Larson CP Jr, Eger EI II, *et al*: The effect of duration of halothane or cyclopropane anesthesia on ventilatory response to carbon dioxide in man (in preparation)
13. Eger EI II, Smith NT, Cullen DC, *et al*: A comparison of the cardiovascular effects of halothane, fluroxene, ether and cyclopropane in man: A resumé. ANESTHESIOLOGY 34:25–41, 1971
14. Saidman LJ, Eger EI II, Munson ES, *et al*: Minimum alveolar concentrations of methoxyflurane, halothane, ether, and cyclopropane in man: Correlation with theories of anesthesia. ANESTHESIOLOGY 28:994–1002, 1967
15. Munson ES, Saidman LJ, Eger EI II: Effect of nitrous oxide and morphine on the minimum anesthetic concentration of fluroxene. ANESTHESIOLOGY 26:134–139, 1965
16. Saidman LJ, Eger EI II: Effect of nitrous oxide and of narcotic premedication on the alveolar

concentration of halothane required for anesthesia. ANESTHESIOLOGY 25:302–306, 1964
17. Gregory GA, Eger EI II, Munson ES: The relationship between age and halothane requirement in man. ANESTHESIOLOGY 30:488–491, 1969
18. Severinghaus JW: Continuously recording ventimeter. ANESTHESIOLOGY 23:482–483, 1962
19. Deutsch, S, Linde HW, Dripps RD, *et al*: Circulatory and respiratory actions of halothane in normal man. ANESTHESIOLOGY 23:631–638, 1962
20. MacGregor M, Davenport HT, Jegier W, *et al*: The cardiovascular effects of halothane in normal children. Brit J. Anaesth 30:398–408, 1958
21. Price HL, Skovsted P, Pauca AC, *et al*: Evidence for β-receptor activation by halothane in normal man. ANESTHESIOLOGY 32:389–395, 1970
22. Hornbein TF, Martin WE, Bonica JJ, *et al*: Nitrous oxide effects on the circulatory responses to halothane. ANESTHESIOLOGY 31: 250–260, 1969
23. Crosby EC, Humphrey TH, Lauer EW: Correlative Anatomy of the Nervous System. New York, MacMillan, 1962, p 525
24. Crosby EC, Humphrey TH, Lauer EW: *ibid*, p. 526
25. Yoss RE, Mayer NJ, Hallenhorst RW: Pupil size and spontaneous pupillary waves associated with alertness, drowsiness and sleep. Neurology 20:545–554, 1970
26. Skovsted, P, Price ML, Price HL: The effects of halothane on arterial pressure, preganglionic sympathetic activity, and barostatic reflexes. ANESTHESIOLOGY 31:507–514, 1969
27. Price HL, Warden JC, Cooperman LH, *et al*: Central sympathetic excitation caused by cyclopropane. ANESTHESIOLOGY 30:426–438, 1969
28. Skovsted P, Price HL: Central sympathetic excitation caused by diethyl ether. ANESTHESIOLOGY 32:202–209, 1970
29. Skovsted P, Price HL: Central sympathetic excitation caused by fluroxene. ANESTHESIOLOGY 32:210–217, 1970
30. Black GW, McArdle L, McCullough H: Circulating catecholamines and some cardiovascular, respiratory, metabolic and pupillary responses during diethyl ether anesthesia. Anaesthesia 24:168–179, 1969
31. Cross BA, Silver IA: Central sympathetic activation of sympathoadrenal system by hypoxia and hypercapnia. J Endocrin 24: 91–103, 1962
32. Price HL: Effect of carbon dioxide on the cardiovascular system. ANESTHESIOLOGY 21:652–663, 1960
33. Munson ES, Larson CP Jr, Babad AA, *et al*: The effects of halothane, fluroxene, and cyclopropane on ventilation. A comparative study in man. ANESTHESIOLOGY 27:716–728, 1966
34. Larson CP Jr, Eger EI II, Muallem M, *et al*: The effects of diethyl ether and methoxyflurane on ventilation. A comparative study in man. ANESTHESIOLOGY 30:174–184, 1969
35. Duke P, Wade JG, Hickey R, *et al*: The effect of age on baroreceptor function in man. In Abstracts of Scientific Papers, p 58. Presented at the American Society of Anesthesiologists Scientific Session, San Francisco, 1969
36. Thompson PD, Melmon KL: Clinical assessment of autonomic function. ANESTHESIOLOGY 29:724–731, 1968

Errata

Several errors appeared in the article, "Correlation of the Ethrane Electroencephalogram with Motor Activity in Cats," by Rudolph H. de Jong and James E. Heavner, in the November issue (ANESTHESIOLOGY 35:474–481, 1971). The legends to figures 1, 3 and 4 (pages 476, 478, 479) should be:

FIG. 1. All figures are records from the same animal. *Left*, control EEG of alert resting cat prior to induction. Very low-voltage fast activity predominates. *Right*, EEG level I tracing of low-voltage moderately fast activity seen during induction and emergence. Rt. = right; Lt. = left; Bas. = basal; Occip. = occipital (posterior suprasylvian gyrus); Fronto = cruciate sulcus; Sylvian = mid-sylvian gyrus.

FIG. 3. Level V EEG (burst suppression of 3 to 10 seconds) is divided into early (left) and late (right) phases according to duration of bursts (see text). Cortical and limbic spiking now clearly synchronous.

FIG. 4. EEG level VI tracing. Burst suppression of about 20 seconds, interrupted only rarely by tall single or grouped spikes in all leads.