

COMPARISON OF THE CARDIOVASCULAR AND RESPIRATORY EFFECTS OF HALOTHANE AND THE HALOTHANE-DIETHYL ETHER AZEOTROPE IN DOGS

ALLEN B. DOBKIN, M.D., JOHN H. HARLAND, M.B., SYLVIA FEDORUK, M.A.

THE cardiorespiratory depression that tends to occur with halothane (Fluothane) anesthesia has led to experimental and clinical trials with the azeotropic mixture of halothane and diethyl ether.^{1, 2, 3} Since the proportion of these respective components is approximately 2:1 (68.3:31.7 v./v.) in halothane-ether, this study was designed to compare the effect of anesthesia in dogs with 2 per cent halothane and 3 per cent halothane-ether in order that each anesthetic would contain approximately the same amount of halothane.

METHOD

Studies were performed on 15 medium-sized mongrel dogs weighing 7.3 to 14.5 kg. (mean 10.8 kg.). Three of these animals (group 1) were anesthetized for two hours with one agent, and after a lapse of two weeks, anesthetized for two hours with the other. The other 12 animals (group 2) were each anesthetized for 4 one hour periods. One agent was administered for an hour, and then, after a short recovery period, the other agent was used for a consecutive hour. After one week, the procedure was repeated, but the order of administration was reversed.

The dogs were given premedication of 5 mg. perphenazine (Trilafon) intramuscularly one hour before each experiment. Light anesthesia was induced with a 'sleep' dose of thiopental (75 to 150 mg.) and the animals' tracheas were intubated. Oxygen, flowing at 8 liters per minute, was given through a calibrated Fluotec vaporizer and a nonbreathing valve attached to the cuffed tube. The anesthetic agent under test was not administered

until the monitoring equipment was set up and initial readings were recorded. This permitted sufficient time to elapse so that the thiopental had virtually no effect on the physiological parameters being measured.

Arterial and venous blood pressures were recorded through cannulae inserted through the femoral vessels into the aorta and inferior vena cava and attached to Statham strain gauges. A ventilation meter was attached to the endotracheal tube to measure the minute volume and to calibrate the pneumograph which was applied round the chest.⁴ Blood pressures, electrocardiogram and pneumograph were monitored continuously either on a Grass polygraph ink recorder or on a multichannel oscilloscope with a photographic recorder (fig. 1). The electrocardiogram was recorded also on a Sanborn visocardiette.

Serial cardiac output estimations were made at half hour intervals during 8 experiments employing iodinated (I^{131}) human serum albumin ('risa') injections in a manner similar to that reported.^{5, 6} The positioning of the well-shielded scintillation counter is shown in figure 1. The aperture of the counter collimator (consisting of a cylindrical hole one inch in diameter and 3 inches deep) was so placed that it was directly over the point where the maximum impulse of the heart was felt. The pulses from the detector were channelled to a Berkeley 2001 decimal scaler. For selected levels of 40, 100 or 200 counts, the scaler provided an output pulse which was registered on the chart of a Brush recorder. The chart speed of the recorder was 2.5 cm./second.

The counting rate was determined by measuring the time interval between the pulses as registered on the chart. Serial injections of 'risa' (usually 6) were flushed rapidly into the right atrium of the heart through an 18 gauge plastic cannula in the jugular vein. Activities of the 'risa' injected in series were approximately 10, 25, 50, 100 and 200 microcuries

Received from the Department of Anesthesia, the Saskatchewan Cancer Commission and the Medical Research Laboratory, University of Saskatchewan College of Medicine, Saskatoon, Canada, and accepted for publication September 21, 1959. This paper was presented at the Annual Meeting of the American Society of Anesthesiologists, Inc., Miami Beach, Florida, October 8, 1959.

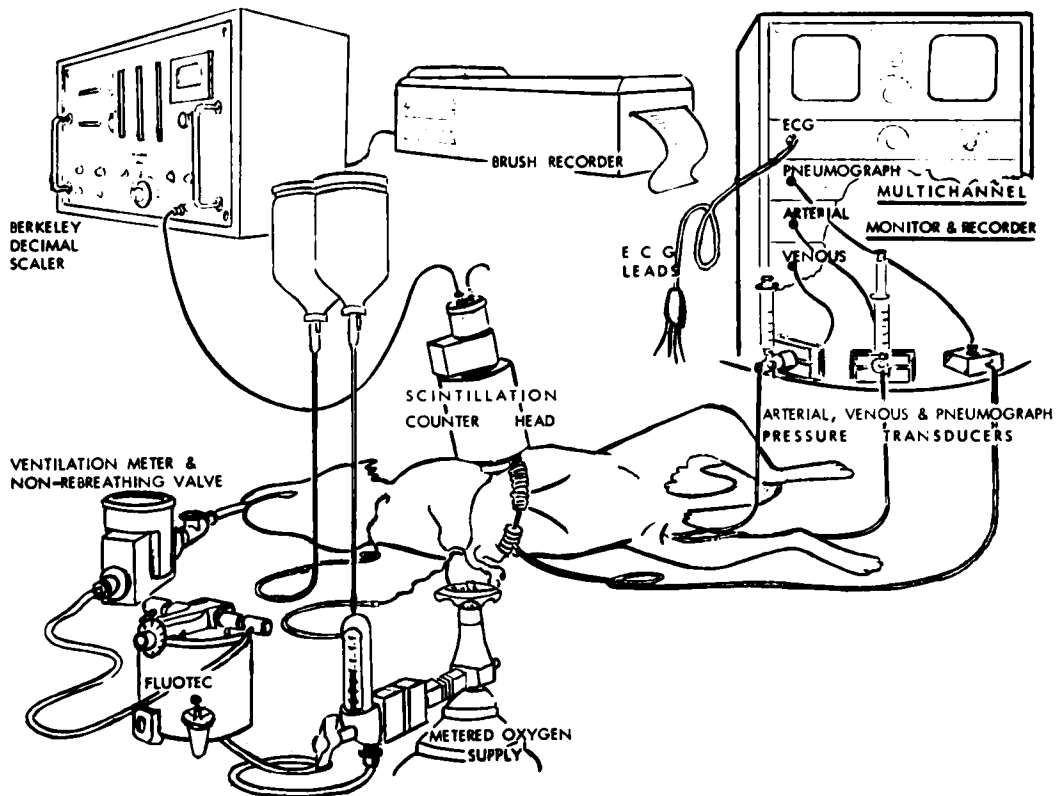


FIG. 1. Arrangement of hemodynamic and respiratory recording equipment to measure the effect of halothane and halothane-ether.

in each dog. The resultant change in count rate with time was plotted on linear graph paper, and the cardiac output in blood volumes per minute was calculated from the formula:

$$\text{C.O.} = \frac{\text{equilibrium value (cm)} \times \text{no. of cm. per minute of linear paper}}{\text{area under curve in cm.}^2}$$

The data derived from the records of each experiment were tabulated and graphed to show the mean values at consecutive 10-minute intervals from the mean value over a representative 10-second strip of recording. The standard deviations were calculated in the 12 cross-over experiments (group 2) and the Fisher *t* test was applied to the measured differences observed between the physiological parameters with the two agents to determine whether they might be due to chance alone. The other 3 cross-over experiments (group 1) were reviewed separately to see whether a longer period of anesthesia would alter any

changes that might be observed in the shorter anesthetic period.

RESULTS

Electrocardiogram. The only irregularity observed on the electrocardiogram was a sinus arrhythmia. This appeared and persisted in the tracings of 6 of the 15 dogs, regardless of whether halothane or halothane-ether was in use. Nodal and ventricular rhythms were absent from all tracings which was probably attributable to the premedication with phenazine.

Circulatory and Respiratory Effects. The tracings from a typical experiment with halothane and halothane-ether are shown in figure 2. The mean values for the vital signs measured on the 12 dogs (group 2) are shown graphically (fig. 3). Table 1 shows the mean values and standard deviations of the measured vital signs and the mean values for the

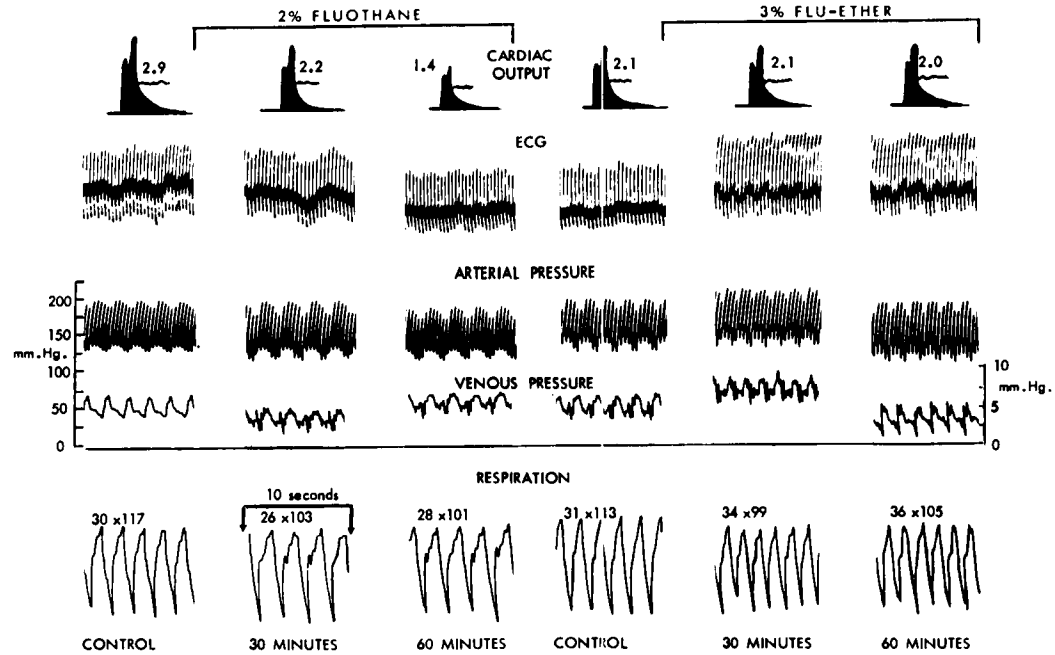


FIG. 2. Tracings from an experiment on a 13.2 kg. mongrel dog that received 2 per cent halothane (Fluothane) for one hour, followed in eight minutes by 3 per cent halothane-ether (flu-ether) for one hour. During the brief recovery period, 100 per cent oxygen was administered. Observe that the arterial blood pressure, pulse pressure and cardiac output were greater after the halothane-ether than after the halothane. The pulse rate slowed slightly with both agents. The venous pressure varied during the experiment, but was less than the control level at the end of one hour of anesthesia with both agents. The rate of breathing was slower and tidal volume was shallower after halothane than after halothane-ether.

Note: Numbers on the cardiac output tracings indicate the output in blood volumes per minute. Numbers on the respiration tracings indicate the rate of breathing and the tidal volume respectively. On the respiration tracings, the down-stroke is inspiration and the upstroke is expiration.

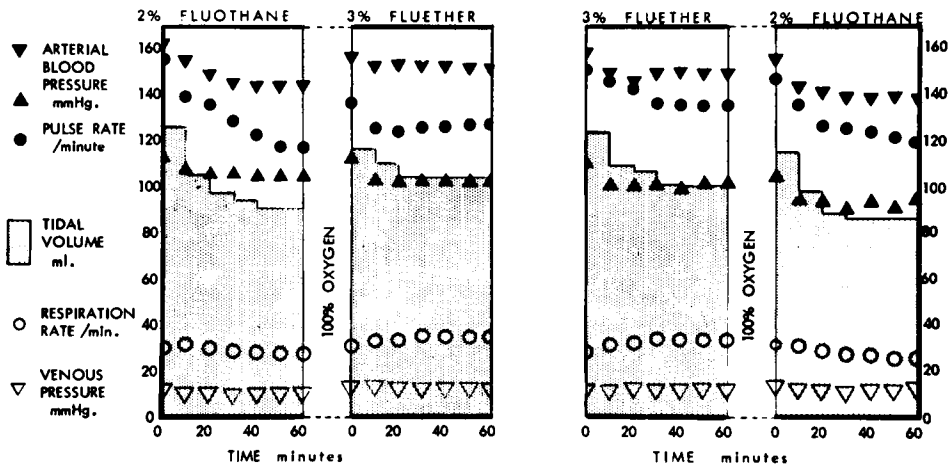


FIG. 3. Graph of the mean values from the twelve cross-over experiments with halothane (Fluothane) and halothane-ether (flu-ether).

TABLE 1
SUMMARY OF THE MEAN HEMODYNAMIC AND RESPIRATORY EFFECTS OF 2 PER CENT HALOTHANE
AND 3 PER CENT HALOTHANE-ETHER IN 12 DOGS

Parameters	Halothane		Halothane-Ether		Halothane-Ether		Halothane	
	Control	One Hour	Control	One Hour	Control	One Hour	Control	One Hour
Systolic B.P., mm. Hg	159	140	155	147	153	145	152	133
S.D. \pm	17	19	17	23	17	21	17	15
Diastolic B.P., mm. Hg	115	107	113	102	112	104	108	97
S.D. \pm	15	16	13	16	17	17	18	14
Mean B.P., mm. Hg	130	118	127	117	126	118	123	109
Pulse pressure, mm. Hg	44	33	42	45	41	41	44	36
Venous pressure, mm. Hg	7	6	7	6	7	6	7	6
Pulse rate/minute	153	146	137	128	150	137	148	118
S.D. \pm	22	26	29	39	21	48	32	43
Cardiac output* (blood volumes/min.)	2.95	1.95	2.43	2.14	2.95	2.95	2.86	2.60
Respiration rate/min.	30	29	32	35	29	33	33	26
S.D. \pm	4	7	5	4	2	2	3	3
Tidal volume, ml.	126	90	114	104	123	100	113	85
S.D. \pm	26	20	24	21	25	18	22	21
Minute volume, liters	3.8	2.6	3.6	3.6	3.6	3.3	3.7	2.2

* 6 experiments.

derived circulatory and respiratory parameters. In table 2 the individual differences between the initial and final readings of the major vital signs after a one hour period of halothane and halothane-ether anesthesia are shown, with the results of the Fisher *t* test.

In the 12 cross-over experiments, the systolic blood pressure, mean blood pressure, pulse pressure, pulse rate, respiration rate, tidal volume and minute volume fell more during anesthesia with 2 per cent halothane than during anesthesia with 3 per cent halothane-ether. Although the differences were not large, they were significant. There was no difference in

the changes in the diastolic blood pressure and in the venous pressure with the two agents, both of which caused a relatively slight decrease in these parameters.

In the other 3 dogs (group 1), the changes in the vital signs observed during halothane and halothane-ether anesthesia were similar to those observed during the shorter period, except that the serial cardiac output estimations were lower after two hours of halothane (36 per cent) and halothane-ether (22 per cent) than after one hour of anesthesia (21 and 6 per cent respectively).

When anesthesia was discontinued at the

TABLE 2
STATISTICAL COMPARISON OF THE EFFECT OF 2 PER CENT HALOTHANE AND 3 PER CENT
HALOTHANE-ETHER ON THE MAJOR VITAL SIGNS (12 DOGS)

Vital Signs	2% Halothane	3% Halothane-Ether	Significance of the Difference in Effect Between the 2 Agents After 1 Hr. of Anesthesia	
	Individual Differences After 1 Hr. Anesthesia (24 Administrations)	Individual Differences After 1 Hr. Anesthesia (24 Administrations)	<i>t</i>	<i>p</i>
Systolic blood pressure	-18.5	- 7.1	3.12	0.005
Diastolic blood pressure	- 9.8	- 9.8	0	
Pulse rate	-29.4	-10.3	2.94	0.008
Respiration rate	- 2.5	+ 4.8	3.75	0.001
Tidal volume	-32	-16	4.30	0.001

end of each experiment, the dogs recovered within a short time, regardless of the order in which the agents were administered in the twelve cross-over experiments. This was true also after the continuous two hour anesthetics. Each animal recovered smoothly from the experiment.

DISCUSSION

On the basis of these and previous studies,^{3, 7, 8} we find ourselves at variance with some of the conclusions reached by Raventós and Dee.² They observed that halothane-ether causes about the same degree of hypotension, bradycardia and respiratory depression as halothane. In the cross-over experiments reported here, statistical analysis indicates that the fall in systolic blood pressure, pulse rate and minute volume of respiration is significantly less with halothane-ether. Their conclusion that epinephrine hypersensitivity is about the same with both agents is not adequately supported by their own published findings.² On the contrary, experimental comparison indicates that in the dog, epinephrine-induced arrhythmias are of shorter duration and less likely to prove lethal with halothane-ether than with halothane.⁸

Parkhouse and Simpson have objected to the experimental comparison of concentrations of these two agents which are not equipotent, or as they term it, "iso-narcotic."⁹ The present study, like that of Raventós and Dee, is open to this criticism. We believe, however, that this type of comparison eliminates certain difficulties and is valid in the present instance for the following reasons: First, the determination of iso-narcotic concentrations of halothane and halothane-ether is a problem not amenable to a precise answer. Second, the addition of diethyl ether to halothane to form the azeotropic mixture results in lesser rather than greater cardiorespiratory depression. However, it does contribute, at least slightly, to the over-all anesthetic effect. If one could determine precisely what concentrations of each agent were equianalgesic and compared these, any lessening of cardiorespiratory depression found with halothane-ether could be ascribed to the lower concentration of halothane. Since the halothane concentrations were kept the same and we found that the cardiorespiratory

depression was significantly less with halothane-ether, this "protective" action must have been due to the addition of ether and not to a lower concentration of halothane.

In clinical practice, halothane-ether has several of the main advantages of halothane alone. It is nonexplosive in the concentrations required for surgical anesthesia.¹ Induction is smooth because of its high potency associated with little tendency to irritate the respiratory tract. Emergence, although a little slower than with halothane alone, is just as smooth. Metabolic disturbances are minimal provided that pulmonary ventilation is adequate.^{1, 3, 10, 11}

Halothane's ability to cause hypotension is stated to be a useful effect.¹² This opinion has not found universal acceptance.¹³⁻¹⁹ If it does in fact constitute an advantage, it is a feature which is much less apparent with halothane-ether. It is also claimed that halothane prevents surgical shock.²⁰ Clinically this is open to question and it is not supported by experimental studies in dogs and in humans.^{21, 22, 23}

It has been alleged that halothane-ether provides halothane-like anesthesia "at a greatly reduced cost."⁹ Although it costs about 30 per cent less than halothane by volume, our clinical experience indicates that the saving is negligible because, on the average, a greater amount of halothane-ether is required for a corresponding level of anesthesia. In any case, cost alone should not be a major factor in selecting an anesthetic agent.

Apart from these considerations, halothane-ether appears to have some decided clinical advantages over halothane alone. The necessity for precise vapor concentration control is much less apparent with halothane-ether, and unlike halothane, it can be administered safely with the standard ether or trichloroethylene vaporizer in the regular way. Cardiovascular depression is less frequent and less severe even when muscle relaxants, including *d*-tubocurarine, have been used. In contradistinction to halothane, spontaneous ventricular arrhythmias are not provoked, nor does halothane-ether aggravate any existing arrhythmias in the human heart.^{3, 7, 14, 24, 25}

Our clinical and experimental experience indicates that halothane-ether provides smoother anesthesia than does halothane alone. The

difference between the effects of the two agents is not marked when the individual physiological changes which occur are compared. However, when one summates all the small differences that are apparent in the laboratory and in the operating room, it becomes evident that halothane-ether has a decided edge over halothane alone as an anesthetic agent.

SUMMARY AND CONCLUSIONS

Cross-over experiments were performed on 15 medium-sized mongrel dogs with 2 per cent halothane and 3 per cent halothane-ether anesthesia. Three of the dogs were given a two hour anesthetic with each agent on separate occasions. The other 12 dogs were given an anesthetic with one agent for one hour and then, after a short recovery period, were subjected to a further hour of anesthesia with the other agent. One week later this was repeated, but the order of administration of the anesthetics was reversed.

The major cardiorespiratory parameters were continuously monitored throughout these experiments and were recorded at least every ten minutes for future review and analysis.

Halothane-ether caused less fall in systolic blood pressure, pulse rate, cardiac output, respiratory rate and tidal volume than did halothane. The difference in effect with individual parameters was not large, but statistically significant. In our opinion, the combination of these differences confirm our clinical findings and indicate that halothane-ether is easier to use than halothane alone and will undoubtedly prove to be the safer of the two agents.

We wish to thank Dr. Leighton Smith of Ayerst, McKenna and Harrison of Montreal, Canada, who supported this work with a grant-in-aid, and Stan Meakin, Morris Wice, Ronald Welgren, Kenneth Varley and James Yourk for their able technical assistance.

REFERENCES

- Hudon, F., Jacques, A., and Boivin, P. A.: Fluothane-ether: azeotropic mixture, *Canad. Anaesth. Soc. J.* 5: 403, 1958.
- Raventós, J., and Dec, J.: Action of halothane-diethyl ether azeotrope mixture on experimental animals, *Brit. J. Anaesth.* 31: 46, 1959.
- Dobkin, A. B., Drummond, K., and Purkin, N.: Anaesthesia with azeotropic mixture of halothane and diethyl ether: effect on acid-base balance, electrolyte balance, cardiac rhythm and circulatory dynamics, *Brit. J. Anaesth.* 31: 53, 1959.
- Safar, P.: Calibrated pneumograph (Current Comment), *ANESTHESIOLOGY* 20: 216, 1959.
- Huff, R. L., Feller, D. D., Judd, O. J., and Bogardus, G. M.: Cardiac output of men and dogs measured by *in vivo* analysis of iodinated (I^{131}) human serum albumin, *Circulation Res.* 3: 564, 1955.
- Dobkin, A. B., and Wyant, G. M.: Physiological effects of intravenous anaesthesia, *Canad. Anaesth. Soc. J.* 4: 295, 1957.
- Dobkin, A. B.: Anaesthesia with Fluothane and Fluothane-diethyl ether azeotrope: clinical comparison, *Rev. brasil. anesth.* 9: 1959.
- Dobkin, A. B., and Purkin, N.: Effect of perphenazine on epinephrine-induced cardiac arrhythmias in dogs; anaesthesia with Fluothane and Fluothane-ether azeotrope, *Canad. Anaesth. Soc. J.* 6: 243, 1959.
- Parkhouse, J., and Simpson, B. R.: Action of azeotropic mixture (Correspondence), *Brit. J. Anaesth.* 31: 186, 1959.
- Dobkin, A. B.: Effect of Fluothane on acid-base balance, *ANESTHESIOLOGY* 20: 10, 1959.
- Virtue, R. W., Payne, K. W., Caranna, L. J., Gordon, G. S., and Rember, R. R.: Observations during experimental and clinical use of Fluothane, *ANESTHESIOLOGY* 19: 478, 1958.
- Chang, J., Macartney, H. H., and Graves, H. B.: Clinical experiences with Fluothane: new non-explosive anaesthetic agent, *Canad. Anaesth. Soc. J.* 4: 187, 1957.
- Stephen, C. R., Grosskreutz, D. C., Lawrence, J. H. A., Fabian, L. W., Bourgeois-Garvardin, M., and Coughlin, J.: Evaluation of Fluothane for clinical anaesthesia, *Canad. Anaesth. Soc. J.* 4: 246, 1957.
- Brindle, F. G., Gilbert, R. G. B., and Miller, R. A.: Use of Fluothane in anaesthesia for neurosurgery: preliminary report, *Canad. Anaesth. Soc. J.* 4: 265, 1957.
- McGregor, M., Davenport, H. T., Jegier, W., Sekelj, P., Gibbons, J. E., and Demers, P. P.: Cardiovascular effects of halothane in normal children, *Brit. J. Anaesth.* 30: 398, 1958.
- Dixon, G. D., and Matheson, D. I.: Fluothane and other nonexplosive halogenated hydrocarbons in clinical anaesthesia, *Canad. M. A. J.* 79: 365, 1958.
- Pederson, D., and Secher, O.: Halothane anaesthesia in cardiac surgery, *Acta anaesth. scandinav.* 2: 169, 1958.
- Dobkin, A. B.: Circulatory dynamics during light halothane anaesthesia, *Brit. J. Anaesth.* 30: 568, 1958.
- Wyant, G. M., Merriman, J. E., Kilduff, C. J., and Thomas, E. T.: Cardiovascular effects

- of halothane, *Canad. Anaesth. Soc. J.* 5: 384, 1958.
20. Johnstone, M.: Role of halothane in prevention of surgical shock, *Brit. J. Anaesth.* 30: 435, 1958.
 21. Burn, J. H., Epstein, H. G., Feigan, G. A., and Paton, W. D. M.: Some pharmacological actions of Fluothane, *Brit. M. J.* 2: 479, 1957.
 22. Burns, T. H. S., Mushin, W. W., Organe, G. S. W., and Robertson, J. D.: Clinical investigations of Fluothane, *Brit. M. J.* 2: 483, 1957.
 23. Severinghaus, J. W., and Cullen, S. C.: Depression of myocardium and body oxygen consumption with Fluothane, *ANESTHESIOLOGY* 19: 165, 1958.
 24. Heimpel, H.: Elektrokardiographische Untersuchungen zur Wirkung von Halothan auf das Herz, *Anaesthesist* 8: 171, 1959.
 25. Delaney, E. J.: Cardiac irregularities during induction with halothane, *Brit. J. Anaesth.* 30: 188, 1958.

ENDOBRONCHIAL MUCUS A special stethoscope is attached to the endotracheal tube. It allows of early detection of even small amounts of endobronchial secretions. Phonography demonstrates visibly what can be heard. (*Kronschwitz, H., and Kaufmann, G.: Aid for Early Detection of Bronchial Secretions During Anesthesia, Der Anaesthesist* 8: 200 (July) 1959.)

LARYNGOSCOPE BLADE By cutting away the proximal inferior surface of a regular Wis-Foregger laryngoscope blade for a distance of 7 cm. the incorrect use of the blade as a lever is reduced. Trauma to the patient's teeth, dental prosthesis and epiglottis is thereby avoided. (*Portzer, M., and Wasmuth, C. E.: Endotracheal Anesthesia Using Modified Wis-Foregger Laryngoscope Blade, Cleveland Clinic Quart.* 26: 140 (July) 1959.)

INTRAOSSEOUS ANESTHESIA Intraosseal anaesthesia was employed in operations on extremities on 350 patients, 17-45 years of age. The point of introduction of the needle in the upper extremity depended on the site of the operation. For this purpose the distal part of the metaphysis of the radius, the olecranon process, the epicondyles of the humerus, or the heads of the first and second metacarpal bones may be used. On the lower

extremity the malleoli, the condyles of femur and tibia, calcaneus, or the heads of the first and fifth metatarsal bones can be used. 80-150 ml. of a 0.5% solution of procaine per lower extremity was used; the anaesthesia lasted for 20 minutes to 2 hours. (*Okhotskii, V. P.: Intraosseal Anaesthesia for Operations on Extremities, Khirurgiya* 6: 84, 1958.)

LOCAL ANESTHESIA Three thousand operations performed on the thoracic organs under local anesthesia during 1941-1958 are reported. There was 12.8 per cent mortality noted among the operated patients during the whole period; during the last year mortality dropped to 4.5 per cent. Anesthesia was carried out in all patients after Vishnevskii's creeping pressure infiltration method. In operations on lungs and posterior mediastinum local anesthesia was effected through a posterolateral incision; a unilateral vagosympathetic block was done first. Intercostal nerves (T2-T9) were anesthetized by injecting procaine solution into the intercostal spaces close to the vertebrae. The pleural cavity was opened at the site of the resected sixth or seventh rib. Then the whole thoracic portion of the sympathetic and vagus nerves were anaesthetized. (*Osipov, B. K.: 3,000 Operations on Organs of Thora.: Under Local Anaesthesia, Khirurgiya* 6: 33, 1958.)