Brit. J. Anaesth. (1964), 36, 193

PHARMACOKINETICS OF HALOTHANE AND ETHER

BY

R. A. BUTLER

Department of Anesthesia, University of Pennsylvania School of Medicine, 3400 Spruce Street, Philadelphia 4, Pennsylvania, U.S.A.

In 1847 John Snow wrote: "It will be at once admitted that the medical practitioner ought to be acquainted with the strength of the various compounds which he applies as remedial agents, and that he ought, if possible, to be able to regulate their potency. The compound of ether vapour and air is no exception to this rule, although it might be supposed to form one, as the practitioner stands by to watch its effects." It is true today that many practitioners are content to administer drugs without much thought about how or why the drugs produce their effects.

Snow and others since his time were concerned that the description of the effects of an inhalational anaesthetic should be accompanied by an account of the distribution of the drug in the body tissues at the time of the observed effects.

Buchanan (1847), describing the physiology of ether anaesthesia, clearly understood that the brain content of anaesthetic determined the depth of narcosis and that the brain content depended on the arterial level, which in turn was related to the strength of the inhaled mixture. Moreover, he pointed out that for short ether inhalations (amputations were often completed in 1–2 minutes) the major factor in the speed of recovery was redistribution of the anaesthetic in the body. The redistribution was accomplished before any large amount of ether had been exhaled in the breath. He calculated the amounts of ether inhaled, exhaled and retained during the induction of these short anaesthetics.

Since his time there have been many other calculations of the uptake and elimination of volatile anaesthetics; rather fewer calculations of the distribution of the agent within the body and little experimental observation in support.

This review will be concerned mainly with the experimental observations, and will refer only briefly to the theoretical calculations which have been described in other papers in this issue.

DIETHYL ETHER

The fundamental applications of the understanding of the uptake of ether were laid down by Snow (1847b, c). He pointed out that to keep the stage or degree of narcosis at a steady level it was necessary to start with a high concentration of ether and then progressively to reduce the inspired concentration during the conduct of the case. He defined five stages or degrees of ether narcosis, giving figures for the average amounts of ether required for their production and making an allowance for the expired amount. Later (Snow, 1848, 1850) he calculated the degree of blood saturation for various anaesthetics, relating calculated blood concentrations to defined stages of narcosis produced by known amounts of anaesthetic vapour and he also worked out the partition of anaesthetic between the alveolar air and the pulmonary blood. Snow then derived a half-clearance time for chloroform of 2½ minutes with an exponential fall-off.* A more soluble anaesthetic such as ether would take longer to eliminate than a less soluble anaesthetic. For recovery from short periods of anaesthesia he confirmed Buchanan's deduction that redistribution was more important than elimination in the expired breath.

Animal studies.

These simple relationships were obscured during the next seventy-five years and Snow's

*A "half-time" for the uptake or clearance of an anaesthetic is used here in a limited sense: it is the time taken to reach half of the final level in the case of uptake; or to reduce to half of the initial level in the case of clearance.

emphasis on constant *alveolar* or arterial tension became changed by later workers into a constant *inspired* tension. Shaffer and Ronzoni (1923) performed a most careful study of the gas/water and gas/blood distribution ratios and were able to confirm the values obtained by Snow. Ronzoni (1923) collected the data of previous investigators and demonstrated marked discrepancies between the inspired, alveolar and blood concentrations. Using twelve dogs as experimental animals she attempted to use the depression of the homolateral flexion reflex as a fixed "end-point" for depth of anaesthesia and to relate this to a range of arterial concentrations. In three cases she followed the elimination of ether and the half-time of the clearance was 15 minutes, which compared well with the findings of Snow (1848) and Nicloux (1908).

Haggard was also working on the problem of the uptake, distribution and elimination of ether and he published his classical papers in 1924 (Haggard, 1924a–e). He used a total of five dogs and most of his data were obtained from three animals. He demonstrated that, for a soluble agent such as ether, the rate of uptake or elimination was almost entirely dependent on the ventilation and scarcely affected by the pulmonary blood flow. In two morphinized animals the clearance half-time was about 35 minutes; one animal without morphine and breathing 7.5 per cent carbon dioxide for 25 minutes produced a clearance half-time of approximately 3 minutes.

Haggard considered the distribution of ether on theoretical grounds and examined the uptake by the brain in three instances. He demonstrated that the brain [sic] approached equilibrium more rapidly than the body as a whole and that this was due to its high proportional blood flow. He used the internal jugular venous content as a direct measure of the ether content of the brain, contending that the ether content of the cerebrospinal fluid was in close agreement with that of internal jugular venous blood. However, much of the blood in the internal jugular vein of the dog is drained from other tissues and it seems likely that he determined the uptake of ether by the dog's head rather than its brain.

In essence Haggard repeated, using the more sophisticated apparatus of his time, the work of Snow and Nicloux and confirmed their findings on the whole body uptake and elimination of ether together with the rate of uptake by the brain.

Human studies.

It was not until 1961 that these basic studies were applied to humans when Onchi and Asao described their work. Their data would have been more valuable had more details been given. Two volunteers breathing 1 per cent ether vapour at unstated minute volumes showed a biphasic rate of ether uptake over 60 minutes, with a change occurring between the 15th and 20th minutes. A half-time of uptake (within the limited definition used here) was not obtainable over this period. The elimination of ether was studied in two patients following prolonged ether anaesthesia, with varying but not stated respiratory minute volumes. In both cases the half-time for clearance was about 15 minutes. Two volunteers with fixed (unstated) minute volumes inhaled 0.8 and 0.9 per cent ether for 60-minute periods, and the elimination of ether was followed for 120 minutes. For these two the clearance half-time would appear to be of the order of 7 minutes, and an empirical three-term exponential equation for clearance was calculated.

Miscellaneous studies.

An alternative approach was that of Haggard (1924), who injected a solution of ether in saline into the carotid artery of a dog and demonstrated anaesthesia in the isolated head. Eger and his colleagues (1962) used intravenous ether to maintain a constant e.e.g. level. This level was assumed to be due to a constant arterial (equivalent to alveolar) tension of ether, as indicated by the work of Courtin et al. (1950) and Faulconer (1952). The amount of ether required to maintain this level was measured and the average results for thirteen young adult patients over a period of 60 minutes showed an uptake of 900 ml of vapour in the first 5 minutes, with a half-time of about 10 minutes. No arterial samples were taken and there was no measurement of the alveolar concentration.

Using modern analytical techniques, Chenoweth and his co-workers (1962) followed blood levels of various anaesthetics in dogs and determined the distribution within the body after 2½ hours anaesthesia. No attempt was made to control or estimate the inspired or alveolar concentrations of the anaesthetics; nor was the ventilation measured or controlled. The arterial and venous levels pre-

sented only serve as rough comparisons for the four anaesthetics studied—ether, halothane, chloroform, and methoxyflurane. In two dogs the distribution of ether in the tissues after 2½ hours anaesthesia was presented. The methods used for obtaining the samples were not given and it is not clear if the strict anaerobic precautions against loss of anaesthetic (recommended by Tissot, 1906a) had been followed.

HALOTHANE

The introduction of halothane (Raventós, 1956) reawakened interest in the volatile anaesthetic agents and the elegant paper on the pharmacokinetics of halothane anaesthesia by Duncan and Raventós (1959) in particular stimulated many studies on the uptake of halothane and other agents.

Animal studies.

Duncan and Raventós studied the uptake, elimination and distribution of halothane in mice and rats, using a constant inspired concentration and varying spontaneous ventilation. They found an initial rapid rate of uptake which decreased somewhat and then remained virtually constant for several hours. Elimination of the anaesthetic was logarithmic, with a whole-body half-clearance in 30 minutes. The distribution of halothane during uptake of the drug was studied and they found that the arterial blood reached a steady level after about 1 hour of anaesthesia, although the brain, liver and fat continued to take up anaesthetic for many hours. During the elimination of halothane the arterial blood concentration decreased logarithmically with a half-clearance time of 14 minutes. The venous blood concentration decreased rapidly at first and then followed the rate of decrease of the fatty tissues with a half-time of 45 minutes.

Chenoweth et al. (1962) followed the arterial and venous concentrations of halothane in a dog during anaesthesia with varying inspired concentrations of halothane. They also studied the distribution of halothane in various tissues of two dogs following 2½ hours of halothane anaesthesia; their findings were similar to those of Duncan and Raventós.

Human studies.

Studies in human subjects have thus far been confined to whole-body uptake or elimination. Mapleson (1962) studied the rate of uptake of halothane vapour at constant inspired concentration and with measured spontaneous ventilation. He used nine patients during surgery, the duration of anaesthesia varying from 30 to 140 minutes. He expressed the results as the rate of uptake of vapour per unit per cent inspired concentration and recalculated these as per unit per cent alveolar concentration in order to compare them to values computed from theoretical considerations. The half-time for uptake was 15–20 minutes and the mean rate between the 20th and 120th minutes of anaesthesia was about 20 ml vapour per minute for each 1 per cent alveolar concentration.

Uptake of a subanaesthetic concentration of halothane (0.2 per cent) was studied in eight volunteers by Sechzer and his co-workers (1962, 1963; also Sechzer, 1963). They used a constant inspired concentration and spontaneous measured ventilation which was controlled by a chest cuirass. They found a half-time for uptake of about 5 minutes and the elimination appeared to be of the same order.

Variations in the whole-body rate of uptake before and during surgery were examined by Butler (1963a, b). He compared the uptake from a variety of closed, semiclosed and non-return breathing circuits, with spontaneous and controlled ventilation. The rates of uptake were expressed as mg halothane/sq.m/min/1 per cent inspired concentration. The mean half-time for uptake was 17 minutes with controlled ventilation and 32 minutes with spontaneous ventilation, at constant inspired concentrations. When the inspired concentration was allowed to vary with the vaporizer within a circle system, it was found that the arterial concentration (alveolar concentration) tended to remain steady for long periods, with wide variations in alveolar ventilation. The half-time for uptake was then prolonged to an average figure of 68 minutes.

Eger and Guadagni (1963) measured the whole-body uptake of halothane at constant alveolar concentration. The patients' ventilation was controlled at 8.4 l./min and the inspired concentration of halothane was adjusted to maintain a constant end-tidal concentration. The uptake figures were adjusted to a 70-kg weight and to an alveolar concentration of 0.8 per cent in order to compare the uptakes for ten subjects. Their half-time for uptake was approximately 5 minutes.

DISCUSSION

The experimental work which has been outlined above has produced a variety of results, some of which are apparently conflicting. It is worth while to discuss the aims which may have existed for the various investigations.

Snow and the early French workers (Bert, Nicloux and Tissot) were examining the time course of the physiological effects of breathing ether and chloroform at known, constant or varied concentrations. They provided excellent descriptions of the points of anaesthetic interest (e.g., surgical anaesthesia, respiratory arrest, cardiac arrest) and related these to a dosage of anaesthetic (i.e., time × concentration). Tissot (1906a, b) examined the distribution in the arterial blood and brain with time and showed that the brain concentration of anaesthetic was related not simply to the arterial concentration and time, but also to blood flow, thus giving a true measure of the dosage of anaesthetic.

Their efforts were directed to improving the safety of anaesthesia by giving the practitioner the information required for the logical control of the course of anaesthesia. Their conclusions, in brief, were that the attainment of a given plane of anaesthesia required the initial administration of a relatively high concentration of anaesthetic, which should then be progressively reduced to maintain the same arterial level. The rate at which the concentration was reduced depended on the solubility of the agent and on the ventilation of the subject.

At about the same period other workers (including Bert) were interested in the problems of breathing air at increased pressure. Their observations stimulated considerable theoretical work on the uptake of "inert" gases such as nitrogen.

Shaffer, Ronzoni and Haggard all re-established the early anaesthetic work, which had become obscured, and in addition Haggard produced a description of the process of uptake in mathematical terms. He considered the effects of lung mixing and deadspace on the rate of rise of the alveolar concentration of anaesthetic towards the inspired concentration. Anaesthetic removed from the alveoli by the blood was considered to be distributed to a single body mass.

Later workers amplified the theoretical treatment of this process and the model of the body was extended to several compartments containing tissues of similar composition or, more commonly, similar perfusion rates. The mathematical descriptions of these processes could no longer be confined to the single-term exponential expressions used earlier, and multi-term exponential equations had to be used. Reviews of this type of work are to be found in Kety (1951), Robertson (1957) and Papper and Kitz (1963).

In large part, the interest of the theoretical workers has been concerned with the uptake by the body of an *inert* gas. In this context, *inert* gas means one which is not metabolized or chemically combined within the body, but the concept of an inert gas is a difficult one. Evidence is being accumulated to suggest that very few real gases or vapours are truly inert chemically. A considerable volume of theoretical work exists on the problem of inert gas uptake with little experimental data and it was natural that anaesthetists should become interested in this approach to the problems of the uptake and distribution of anaesthetic agents. As a result, experimental work has often been concerned with the inhalation of "sub-anaesthetic" concentrations of anaesthetic agents, and the results have been expressed in terms of fitting some form of exponential equation, usually for a three-compartment model.

In the opinion of this author, such work has limited value due to certain objections. Anaesthetic agents such as ether and halothane may be relatively inert from the chemical point of view, but their chief interest lies in their pharmacological activity and it is the uptake and distribution *during anaesthesia* which is of primary interest.

There are three categories of studies; the first using gases, such as nitrogen, as inert gases; the second using anaesthetic agents at low concentrations as "inert" gases; and the third using anaesthetic agents to produce anaesthesia. An ideal inert gas would have no pharmacological activity, and although nitrogen is not ideal in this respect, its effects are of an entirely different order of magnitude compared to the potent anaesthetic gases or vapours whether they are used in anaesthetic or "sub-anaesthetic" concentrations.

Studies in the second category cannot be expected strictly to confirm theoretical work on inert gas uptake, nor to aid the anaesthetist to follow the distribution during anaesthesia. It is difficult to give a "sub-anaesthetic" concentration

of these agents without some subjective effects; certainly there is abundant clinical evidence that changes in the cardiac output and the distribution of the output, etc., occur with these drugs at many concentrations. The act of using them, even at low concentrations, is likely to produce a change in the values which are used in the computed constants for the equations. These changes will be more marked when anaesthesia is produced as in the third category of study.

Secondly the degree of accuracy of the experimental results is such that no unique three-term exponential equation can be proved or disproved. In fact there is a large number of three-term equations available which could regenerate the data to the degree of accuracy of the results (Lanczos, 1957). Thirdly, most of these equations assume that perfusion, rather than diffusion, is the limiting factor for each compartment. Work by Perl (1963) has demonstrated that diffusion plays a significant part and that for the more soluble anaesthetic agents "the existing perfusion-limited compartment model becomes decidedly fuzzy around the compartment edges".

It is rational to consider the body in terms of a compartmented model and for relatively "inert" gases it may be practicable to confirm, to a limited extent, the mathematical descriptions of the uptake and distribution of such an inert gas, providing that the subjects maintain a very constant physiological status throughout the observations. It may be argued that half-times for uptake or elimination are not valid criteria and this is true if they are to be used throughout a multi-exponential curve. However, since the compartmented model for these experiments is basically the same human body, it is convenient to compare the half-time for the first part of uptake or excretion of these anaesthetics (Butler, 1958). It is apparent that comparing the half-times derived above shows how different the experimental situation of unpremedicated subjects breathing sub-anaesthetic concentrations is from that pertaining during anaesthesia. The former are already half-way to or from their equilibrium value in about 5 minutes (3–7 minutes); during anaesthesia (usually accompanied by a premedication of opiate) this point is usually reached in 15 minutes. Indeed the time required may be even longer, e.g., 30–60 minutes. At first sight one may be tempted to dismiss these differences as being solely due to altered ventilation patterns for the different categories of subjects. However, the interesting work of Yamamura et al. (1963) indicates that variations of tidal volumes, which can markedly affect the uptake of ether, produce very little effect in its elimination. This would support the view that there is a change between the "on" and the "off" patterns due to changes in distribution (e.g., by variations in perfusion) produced by the activity of the anaesthetic agent. It has therefore been suggested that the situation with sub-anaesthetic concentrations probably bears only a limited relationship to the status with either truly inert gas or with anaesthesia.

CONCLUSIONS

The question which remains is this: how does the foregoing work help the clinical anaesthetist? A certain amount of this knowledge is inherent in his personal clinical experience; if he is aware of this, the basic outlines of whole-body uptake of agents such as ether may be found in the simple work performed between 1848 and 1910. Certainly the work with inert gases or with sub-anaesthetic amounts of anaesthetic gases can help towards an understanding of the problems involved, but there appears to be a very real danger that concern with an imperfect model may blind an investigator and his readers to its real purpose.

What the anaesthetist requires is a description of the temporal changes of *distribution* of the anaesthetic within the body, during anaesthesia. It is known that alterations in cardiac output, peripheral resistance and perfusion occur. It is not known what alterations in diffusion may occur.

The main areas of interest to the anaesthetist are local ones such as the brain, liver, kidney and the large muscle masses. The changes in cerebral function described as anaesthesia would be greatly heightened by a knowledge of the tension of anaesthetic in the affected cells. For example, there appears to be a poor correlation of e.e.g. pattern, clinical depth of anaesthesia, and arterial concentration of anaesthetic for halothane (Gain and Paletz, 1957, 1962; Robson and Sheridan, 1957; Galla et al., 1962) as opposed to ether (Faulconer, 1952). It may be that the "evoked response" approach of Abrahamian et al. (1963) would reveal changes in the conducting pathways at different tensions of anaesthetic. There is a suggestion that

the isolated superior cervical ganglion of the cat may show a change in the form of blockade when its equilibrium halothane tension is changed from about 4 mm Hg to 13 mm Hg (Purchase, 1962, personal communication). Changes in liver perfusion and secretion are probably related to the tension of anaesthetic within the organ and studies of these activities at known drug tension would shed much light on the metabolic effects of anaesthesia. Alterations of the pattern of renal blood flow and glomerular filtration probably occur and may in part be due to a local effect of the anaesthetic at the organ. Both from the theoretical and practical points of view, changes in perfusion of the large muscle masses are important and deserve attention.

Useful information on these points will come only from experimental measurement rather than from theoretical estimates of both perfusions and anaesthetic tensions. Until these are performed there will have been no real progress in the knowledge of the pharmacokinetics of agents such as ether and halothane since the turn of the century.

REFERENCES

Abrahamian, H. A., Allison, T., Goff, W. R., and Rosner, B. S. (1963). Effect of thiopental on human cerebral evoked responses. *Anesthesiology*, **24**, 650.

Buchanan (1847). The physiology of ether inhalation. *London med. Gaz.*, **39**, 715.

Butler, R. A. (1963a). The uptake of halothane. *Proc. roy. Soc. Med.*, **56**, 89, 95.

—— (1963b), in *Uptake and Distribution of Anesthetic Agents* (eds. Papper, E. M., and Kitz, R. J.), Ch. 22, p. 274. New York: McGraw-Hill.

Butler, T. C. (1958). Termination of drug action by elimination of unchanged drug. *Fed. Proc.*, **17**, 1158.

Chenoweth, M. B., Robertson, D. N., Erley, D. S., and Golhke, R. (1962). Blood and tissue levels of ether, chloroform, halothane and methoxyflurane in dogs. *Anesthesiology*, **23**, 101.

Courtin, R. F., Bickford, R. G., and Faulconer, A. jr. (1950). Classification and significance of electroencephalographic patterns produced by nitrous oxide-ether anaesthesia during surgical operations. *Proc. Mayo Clin.*, **25**, 197.

Duncan, W. A. M., and Raventós, J. (1959). The pharmacokinetics of halothane anaesthesia. *Brit. J. Anaesth.*, **31**, 302.

Eger, E. I. (II), and Guadagni, N. P. (1963). Halothane uptake in man at constant alveolar concentration. *Anesthesiology*, **24**, 299.

—— Johnson, E. A., Larson, C. P. jr., and Severinghaus, J. W. (1962). The uptake and distribution of intravenous ether. *Anesthesiology*, **23**, 647.

Faulconer, A. jr. (1952). Correlation of concentrations of ether in arterial blood and electroencephalographic patterns occurring during ether-oxygen and during nitrous oxide, oxygen and ether anesthesia of human surgical patients. *Anesthesiology*, **13**, 361.

Gain, E. A. (1962). EEG patterns during halothane anesthesia. *Anesthesiology*, **23**, 590.

—— Paletz, S. G. (1957). An attempt to correlate the clinical signs of Fluothane anaesthesia with the electro-encephalographic levels. *Canad. Anaesth. Soc. J.*, **4**, 289.

Galla, S. J., Olmedo, A. K., Kretchmer, H. E., and Simeone, F. A. (1962). Correlation of EEG patterns with arterial concentrations and clinical signs during halothane anesthesia. *Anesthesiology*, **23**, 147.

Haggard, H. W. (1924a). The absorption, distribution and elimination of ethyl ether. I: The amount of ether absorbed in relation to the concentration inhaled and its fate in the body. *J. biol. Chem.*, **59**, 737.

—— (1924b). The absorption, distribution and elimination of ethyl ether. II: Analysis of the mechanism of absorption and elimination of such a gas or vapour as ethyl ether. *J. biol. Chem.*, **59**, 753.

—— (1924c). The absorption, distribution and elimination of ethyl ether. III: The relation of the concentration of ether, or any similar volatile substance, in the central nervous system to the concentration in the arterial blood, and the buffer action of the body. *J. biol. Chem.*, **59**, 771.

—— (1924d). The absorption, distribution and elimination of ethyl ether. IV: Anaesthetic tension of ether and the physiological response to various concentrations. *J. biol. Chem.*, **59**, 783.

—— (1924e). The absorption, distribution and elimination of ethyl ether. V: Importance of the volume of breathing during the induction and termination of ether anaesthesia. *J. biol. Chem.*, **59**, 795.

Kety, S. S. (1951). The theory of applications of the exchange of inert gas at the lungs and tissues. *Pharmacol. Rev.*, **3**, 1.

Lanczos, C. (1957). *Applied Analysis*. London: Pitman.

Mapleson, W. W. (1962). The rate of uptake of halothane vapour in man. *Brit. J. Anaesth.*, **34**, 11.

Nicloux, M. (1908). *Les Anesthésiques généraux au point de vue chemicophysiologique*. Paris: O. Doin.

Onchi, Y., and Asao, Y. (1961). Absorption, distribution and elimination of di-ethyl ether in man. *Brit. J. Anaesth.*, **33**, 544.

Papper, E. M., and Kitz, R. J. (1963). *Uptake and Distribution of Anesthetic Agents* (eds. Papper, E. M., and Kitz, R. J.). New York: McGraw-Hill.

Perl, W. (1963), in *Uptake and Distribution of Anesthetic Agents* (eds. Papper, E. M., and Kitz, R. J.), Ch. 18, p. 224. New York: McGraw-Hill.

Raventós, J. (1956). The action of Fluothane—a new volatile anaesthetic. *Brit. J. Pharmacol.*, **11**, 394.

Robertson, J. S. (1957). Theory and use of tracers in determining transfer rates in biological systems. *Physiol. Rev.*, **37**, 133.
Robson, J. G., and Sheridan, C. A. (1957). Preliminary investigation with Fluothane. *Curr. Res. Anesth.*, **36**, 62.
Ronzoni, E. (1923). Anaesthetic concentration of ether for dogs. *J. biol. Chem.*, **57**, 761.
Sechzer, P. H. (1963), in *Uptake and Distribution of Anesthetic Agents* (eds. Papper, E. M., and Kitz, R. J.), p. 285. New York: McGraw-Hill.
—— Linde, H. W., and Dripps, R. D. (1962). Uptake of halothane by the human body. *Anesthesiology*, **23**, 161.
—— —— —— Price, H. L. (1963). Uptake of halothane by the human body. *Anesthesiology*, **24**, 779.
Shaffer, P. A., and Ronzoni, E. (1923). The determination of ethyl ether in air and blood, and its distribution ratio between blood and air. *J. biol. Chem.*, **57**, 741.
Snow, J. (1847a). On the inhalation of the vapour of ether. *London med. Gaz.*, **39**, 498.
—— (1847b). On the inhalation of the vapour of ether. *London med. Gaz.*, **39**, 539.
—— (1847c). *On the Inhalation of the Vapour of Ether in Surgical Operations.* London: Churchill.
—— (1848). On narcotism by the inhalation of vapours. *London med. Gaz.*, **41**, 893; **42**, 330.
—— (1850). On narcotism by the inhalation of vapours. *London med. Gaz.*, **46**, 749.
Tissot, J. (1906a). Determination des proportions de chloroforme que l'on constate dans le cerveau et dans le sang, dans la mort par le chloroforme. *C.R. Soc. Biol. (Paris)*, **60**, 195.
—— (1906b). Proportions de chloroforme que peut contenir le sang au debut de l'anesthésie chloroformique. *C.R. Soc. Biol. (Paris)*, **60**, 198.
Yamamura, H., Wakasugi, B., Okuma, Y., and Maki, K. (1963). The effect of ventilation on the absorption and elimination of inhalational anaesthetics. *Anaesthesia*, **18**, 427.

CORRESPONDENCE

NEONATAL DEFORMITIES ASSOCIATED WITH THE USE OF A PHENOXYACETAMIDE DERIVATIVE

Sir,—Being involved in the initial clinical trials of the phenoxyacetamide derivative, FBA.1420, we are interested in Dr. Lear's report of neonatal deformities following its administration to pregnant bitches. We wonder if he has any data on the effects of comparable doses of thiopentone, administered under similar circumstances. It is also desirable to be reassured that the dosage employed was not grossly above the clinical range.

It is not beyond the realms of possibility that anaesthetics may be potentially teratogenic, but before limiting our clinical use of this promising new drug because of this report, it is important to know whether this would not have happened with any anaesthetic.

JOHN W. DUNDEE
R. S. J. CLARKE
Belfast

CEREBRAL BLOOD FLOW DURING HYPOTHERMIA

Sir,—In the study on the effect of hypothermia on the cerebral blood flow (*Brit. J. Anaesth.*, 1963, **35**, 765) no attempt was made to investigate the factors causing the decrease in flow. The work was undertaken as an attempt to compare the two methods of induction of hypothermia. The many variables influencing the cerebral blood flow were thought to be comparable during the hypothermia periods with the exception of muscle relaxant which was given to the surface cooling group.

It is hardly necessary to do further experiments to confirm the decrease in cerebral blood flow during hypothermia. The purpose of this study was to show that the decrease found following surface cooling is comparable to that following blood stream cooling. Thus in future experiments we shall be able to use the latter method which allows a better control of the body temperature of the experimental animal. These experiments will be undertaken in order to study the regulatory mechanisms of the cerebral blood flow under hypothermia. It is generally recognized that at normal temperature the Pco_2 is the most important variable influencing the cerebral blood flow. We believe, however, that Dr. Nunn's assumption (*Brit. J. Anaesth.*, **36**, 121), that this is also true during hypothermia, still remains to be proved.

WALTER ZINGG
Winnipeg

CORRECTION

Sir,—I would like to draw your attention to a mistake in the article "Pulmonary Gas Exchange during Deliberate Hypotension" (*Brit. J. Anaesth.*, **35**, 750), which occurs on line 29, righthand column, page 756.

The sentence states: "In all three instances, increased airway pressure resulted in a widening of the A-aPco_2 difference and in two of the A-aPco_2 difference as well." The sentence should read: "In all three instances, increased airway pressure resulted in a widening of the A-aPco_2 difference and in two of the A-aPO_2 difference as well."

G. E. HALE ENDERBY
London