THE PHARMACOLOGY OF HALOTHANE IN MAN: A REVIEW

BY

E. J. D'Arcy
Windsor Group of Hospitals, England

Martin H:son Holmdahl,
Akademiska Sjukhuset, Uppsala, Sweden

And

J. P. Payne
From the Department of Anaesthesia, Postgraduate Medical School,
Ducane Road, London, W. 12

The pharmacological activity of halothane (chlorobromo-tri-fluoro-ethane) was first investigated by Raventós (1956) in animals and this work was later extended by Burn, Epstein, Feigan and Paton (1957). These reports and the first clinical study of Johnstone (1956) have provoked much controversy and stimulated further clinical research in man. It is inevitable that by their nature such studies must be limited in extent and it is the purpose of this paper to consider some of the accumulating data in the light of our own experience of halothane anaesthesia in more than 1,000 patients, under a wide variety of conditions.

As no particular group of patients was excluded from our assessment, experience was gained in both elective and emergency procedures in all branches of surgery, obstetrics and gynaecology. Patients were of both sexes and their ages ranged from 3 weeks to 92 years. Most were admitted for elective surgery and could therefore be regarded as relatively good operative risks, but a considerable minority by reason of age, general condition, or specific pathology, required very careful management, and a few had such a precarious hold on life that the administration of any anaesthetic was fraught with danger. In some of the patients admitted for elective surgery studies of respiratory, cardiovascular and electro-encephalographic responses were undertaken, but it is not intended to give a detailed analysis of our own cases, but to refer only to observations which emphasize some of the pharmacological aspects of halothane.

Clinical experience has confirmed the claim by Raventós (1956) that halothane is capable of rapid, effective, and flexible anaesthesia. Because it is neither explosive nor inflammable it offers advantages in a wide field of anaesthetic practice. The potency of the drug makes low concentrations effective and also necessitates an accurate control of the vapour strength. The use of the drug without such accuracy of control is potentially dangerous and the interpretation of changes observed may be difficult. It is necessary, therefore, to give some consideration to the various methods of administration employed in the studies to be discussed.

TECHNIQUES OF ADMINISTRATION

In the first clinical trials (Johnstone, 1956), halothane was vaporized from a specially calibrated Trilene bottle by a high flow of gases and administered through a Magill attachment. This system was a fortunate choice for within limits it provided a relatively constant concentration under the direct control of the anaesthetist. Later, largely on account of expense, this technique was modified to reduce the consumption of halothane, and for this purpose a semiclosed technique using a Waters canister and a gas flow of 2-4 litres per minute was employed (Brennan, Hunter and Johnstone, 1957). In addition to reducing the consumption of halothane this to-and-fro method also might be expected to provide a constant concentration of vapour.
THE PHARMACOLOGY OF HALOTHANE IN MAN

For a proper assessment of the changes during clinical anaesthesia in man there is no doubt that the most satisfactory method of administering halothane is by means of a nonrebreathing system incorporating a calibrated vaporizer (Falkner Hill, 1957; Brennan, 1957), whereby the concentration of vapour inhaled can be maintained at a constant level. This is not to deny that in the hands of an experienced anaesthetist the circle system can provide satisfactory clinical anaesthesia (Marrett, 1957), but it must be emphasized that no closed or semiclosed circle system with the vaporizer included in the circle can provide a constant concentration indefinitely under all conditions. Any alteration in the respiratory rate, in the tidal volume, or in the rate of leakage from the system will alter the concentration of halothane in the inspired mixture. In normal circumstances this is of little consequence, as when the patient is breathing spontaneously, the changes tend to be self-limiting (Marrett, 1959), and both Burton (1958) and Marrett have shown that when a concentration of 2.5 per cent or less is employed continuously for less than 90 minutes there is no accumulation of halothane within the circle during spontaneous respiration. This is presumably because the body tissues can absorb halothane from the blood faster than it is supplied through the lungs; but it is obvious that such absorption cannot continue indefinitely, and that the higher the concentration and the more prolonged the procedure the more readily will tissue saturation be reached. Ultimately then, dangerous concentrations of vapour may accumulate if the necessary adjustments in vapour strength are not made. The factors involved have been adequately discussed by Newman (1958). When controlled respiration is employed, this self-limiting safety mechanism is eliminated and it has been shown that, in these circumstances, halothane concentrations in the inspired gases may rise rapidly (Burton, 1958; Marrett, 1957). This is particularly true if the vaporizer setting is unaltered and the flow of fresh gases remains unchanged.

If the above interpretation is correct it follows that, under the conditions described, substitution of controlled respiration for spontaneous breathing is a dangerous manoeuvre and further that it is likely to be more dangerous towards the end of prolonged procedures than at the beginning, conclusions borne out by reference to the accounts of cardiac arrest under halothane described in the literature (Abajian et al., 1958; Chang et al., 1957; Foster, 1957; Hudon et al., 1957; Kirschner, 1957; Stephen et al., 1957). For this reason it is recommended that if controlled respiration is to be employed with any form of closed circle system the vaporizer should be excluded from the circle, and there is much to be said for Marrett's suggestion that if it can be avoided controlled respiration should not be used during halothane anaesthesia.

The methods of administration employed in our own series have followed the patterns just outlined. The first 150 patients were anaesthetized by the original method described by Johnstone (1956). Then a closed circle system with the vaporizer in the circuit was tried, but this method was soon abandoned because it was found to be impossible to maintain a constant concentration at all times during anaesthesia and a return was made to the use of the semiclosed nonrebreathing system with a calibrated vaporizer. Later, for the sake of economy, the semiclosed technique employing the Waters canister was introduced (Brennan et al., 1957), and this had the added advantage of being suitable for controlled respiration. Most anaesthetics in our series were given by one or other of these two methods, but experience was also gained with the Engstrom respirator and various forms of circle systems. In addition a few patients were anaesthetized by the open-drop method.

EFFECTS ON CENTRAL NERVOUS SYSTEM

The potency of halothane as an anaesthetic agent is now firmly established and most anaesthetists have been impressed by the ease and smoothness of induction whether by open-drop methods or in combination with nitrous oxide and oxygen. Once anaesthesia is begun the abolition of reflexes and the depression of vital activities resemble the pattern described for ether by Guedel (1936) although the time relationships are altered.

Unlike ether, induction of anaesthesia with halothane alone, in our experience, with which Robson and Sheridan (1957) are in agreement, is not usually associated with any degree of excite-
mation, but evidence to the contrary has also been published. Mackay (1957) reported a short stage of excitement in patients induced with halothane, while Stephen et al. (1957) described a brief but intense period of excitement in the majority of their patients similarly induced. It is, however, generally agreed that the stimulating properties of halothane are slight, and that induction is normally accompanied by the absence of tears and salivation. At the same time the suppression of pharyngeal and tracheobronchial secretions reduces the incidence of coughing.

Once induction is begun unconsciousness supervenes rapidly and the stage of surgical anaesthesia is usually reached within 5 minutes. Both pharyngeal and laryngeal reflexes are depressed quickly so that intubation can be undertaken early and is usually easy because the masseter muscles are relaxed. If for any reason the process of intubation is delayed, there is a prompt return of reflexes and further exposure to halothane vapour may be necessary before the manoeuvre can be completed.

The planes of surgical anaesthesia are most readily judged by the advancing paralysis of the intercostal muscles. Once intercostal paralysis is complete respiratory arrest may develop rapidly, particularly in young children, but if oxygenation is adequate normal breathing will return spontaneously, presumably because tissue absorption very quickly lowers the plasma concentration of halothane.

Attempts have been made to gauge the level of surgical anaesthesia by means of e.e.g. monitoring, and Given, Little and Tovell (1957) claim that there is good correlation between the appearance of the e.e.g. tracings and the depth of anaesthesia. This contention is supported by Robson and Sheridan (1957) who demonstrated characteristic e.e.g. changes and related them to blood concentrations of halothane. It should be noted, however, that in this latter series the e.e.g. changes could also be related to altered blood pressure levels. Gain and Paletz (1957), on the other hand, were unable to correlate the e.e.g. patterns with the clinical signs of anaesthesia, and Burnap, Galla and Vandam (1958) reported that the electroencephalograph was of little help in determining the depth of anaesthesia, as both adequate and inadequate surgical conditions were associated with a similar pattern. This work confirms our own impression, gained from a series of thirty patients monitored throughout anaesthesia, that there is no direct relationship between the e.e.g. and the level of anaesthesia, and that indeed the correlation between the e.e.g. pattern and the blood pressure level was more consistent. This observation requires further investigation, if it is to be substantiated, although again it is worth noting that electroencephalographic changes associated with hypotension have previously been described (Bromage, 1953).

Despite the early onset of surgical anaesthesia the specific analgesic properties of halothane are weak (Bryce-Smith and O'Brien, 1956), particularly when used as the sole anaesthetic agent (Löfström, 1958), and this weak analgesic action may explain the restlessness that has been widely described during recovery from halothane anaesthesia.

The autonomic response to halothane is of considerable importance and the general reduction of secretions is evidence of parasympathetic depression. The vagotonic action of halothane on the other hand, is equally well recognized and many investigators have stressed the need for adequate premedication with atropine as protection against possible circulatory disturbances. Its depressant action on the sympathetic nervous system is also not in doubt, but there is lack of agreement on the means by which this effect is produced. The factors involved will be discussed in detail later in this paper, but one aspect of ganglion block ought to be mentioned at this stage; this is the potentiating effect of halothane on the ganglion blocking properties of tubocurarine. Severe hypotension may follow the intravenous injection of tubocurarine, and for this reason considerable care is required if these two drugs are to be used simultaneously.

Halothane also enhances the neuromuscular blocking action of tubocurarine (Burn et al., 1957; Watland et al., 1957), although there is no evidence that it possesses any specific action of its own at the motor endplate. Another explanation is therefore needed for the adequate muscle relaxation that occurs clinically and this has been attributed to the central effect of the drug (Watland, et al., 1957).
THE PHARMACOLOGY OF HALOTHANE IN MAN

THE CIRCULATORY EFFECTS

The behaviour of the pulse rate during halothane anaesthesia varies considerably and no consistent pattern can be described. In his first series Johnstone (1956) reported that the pulse rate invariably became slower and rates as low as 40 beats per minute were observed by Bryce-Smith and O’Brien (1956) when the blood pressure fell during induction. Similar slow pulse rates were described in the medical Research Council Report (Burns et al., 1957). This bradycardia was regarded by Johnstone as evidence of vagal inhibition and in his later cases he preceded induction with an intravenous injection of 0.5 mg atropine. In this series bradycardia was less evident and an average of 84 beats per minute was reported (Johnstone, 1956). In this respect halothane resembles chloroform in that the bradycardia associated with the induction of anaesthesia can be abolished by intravenous atropine (Payne, 1955). The absence of reports of bradycardia in later papers suggests that premedication with atropine has been generally adopted. One other possibility, however, should be considered. In the initial period of the clinical trials with halothane, the concentration employed for induction and maintenance was generally higher than that commonly used later and it may be that bradycardia was a feature of the unnecessarily deep anaesthesia obtained (Robson and Sheridan, 1957).

As with many other anaesthetic agents halothane anaesthesia is sometimes associated with cardiac irregularities which vary greatly in their type and frequency. Absent or inverted P waves associated with the bradycardia just described emphasize the influence of vagal inhibition, and the restitution of normal sinus rhythm by intravenous atropine reinforces that view. Ventricular extrasystoles provide another group of arrhythmias; sometimes only occasional extrasystoles are noted, but more commonly bursts of unifocal ventricular extrasystoles coupled with sinus beats are seen. Rarely the multifocal variety has been described. These latter cases followed the subcutaneous injection of adrenaline and were reported by Brindle and his colleagues (Brindle et al., 1957; Millar et al., 1958), who concluded that the combination of halothane and adrenaline was potentially dangerous in man. Considerably more clinical experience will be required before this conclusion can be refuted, but it is worth noting that many groups (Bryce-Smith and O’Brien, 1956; Hudon et al., 1957; Marrett, 1957; Mackay, 1957) including ourselves have used the combination freely without incident.

On the whole disturbances in cardiac rhythm during halothane anaesthesia are not considered to be intrinsically dangerous (Brennan et al., 1957) but they may well draw attention to some irregularity in the administration of the drug as shown by the following example from our case records.

Case Record.

A healthy young woman was undergoing a radical mastoidectomy under general anaesthesia (nitrous oxide and oxygen 5:3 litres/min and halothane). Multifocal ventricular extrasystoles suddenly developed associated with a noticeable increase in the respiratory rate and tidal volume. Examination of the machine revealed that the carbon dioxide control had inadvertently been opened to give a 20 per cent concentration of carbon dioxide in the inhaled mixture. As soon as this was corrected the ventricular extrasystoles disappeared without any alteration in the halothane vaporizer setting.

In only one of our patients was it thought safer to abandon the use of halothane. This patient was a 20-year-old girl with a congenital heart anomaly consisting of transposition of the pulmonary veins, an atrioseptal defect and pulmonary stenosis, in whom extrasystoles appeared within 10 minutes of introducing halothane vapour. During the course of the anaesthetic these extrasystoles, which were multifocal in origin, became more frequent and ultimately completely dominated the monitoring screen. For this reason halothane administration was discontinued and almost immediately the multifocal extrasystoles disappeared.

A feature of halothane anaesthesia is the almost inevitable hypotension that accompanies induction. Originally observed by Johnstone (1956) it has been reported widely since and there is considerable evidence accumulating to indicate that the degree of hypotension obtained is directly related to the concentration of drug employed (Severinghaus and Cullen, 1958; Hudon et al., 1957; Stephen et al., 1957). This suggests that hypotension is a function of the depth of anaesthesia and ought to be reduced or indeed eliminated by careful administration. In our own series a slight degree of hypotension was observed in nearly every case. After the initial hypotension
following the inhalation of halothane there was a gradual recovery which tended to coincide with the application of surgical stimuli and which stabilized usually slightly below the conscious level (see also Dobkin, 1958). Further hypotension, except in a few cases to be described, was only seen when uncompensated bleeding occurred.

The mechanism by which hypotension occurs is not clear. Raventós (1956b), on the basis of experiments involving plethysmography of abdominal viscera and contractions of the nictitating membrane in the cat, concluded that it was due to a selective ganglion blocking action of the drug, the mesenteric ganglia being the most sensitive. Burn et al. (1957) disagreed with this conclusion not only because they were unable to demonstrate any strong ganglion blocking action when the nictitating membrane preparation was used, but also because they found that hypotension still occurred in cats that had been eviscerated. Further, they observed a fall in cardiac output in the dog's heart-lung preparation, and concluded that two additional factors ought to be considered; namely a distinct depressant action on heart muscle and a central depression of the vasomotor mechanism.

Evidence of myocardial depression during halothane anaesthesia in man has been presented by Severinghaus and Cullen (1958). These authors showed that during sympathetic blockade with both spinal anaesthesia and trimetaphan, artificial ventilation with 1.5 per cent halothane produced a greater reduction in cardiac output, arterial pressure, and stroke volume than when sympathetic blockade was not employed. They further showed that the fall in cardiac output was proportional to the degree of hypotension, and that it was associated with an increased peripheral resistance. From these results it was concluded that halothane has a direct depressant effect on the myocardium and no significant ganglion blocking action.

Further studies on the cardiovascular effects of halothane have been carried out in normal children by McGregor et al. (1958) and in adult volunteers by Wyant et al. (1958). Using the Evans blue dye dilution technique McGregor and his colleagues demonstrated a reduction in cardiac output during moderate and deep anaesthesia, but were reluctant to ascribe it to myocardial depression. Unlike Severinghaus and Cullen they were unable to show any significant change in peripheral resistance. Also using the dye dilution technique Wyant and his group carried out their investigations by means of serial cardiac outputs and concluded that the fall in peripheral resistance was the main cause of the hypotension observed, and that there was no serious impairment of cardiovascular efficiency until overdosage with halothane had been achieved. When this occurred there was a compensatory increase in peripheral resistance which tended to maintain the circulation despite the low output.

There seems little doubt that halothane in heavy dosage in common with other anaesthetics, does have a depressant effect on the heart, but in contrast to the findings of Severinghaus and Cullen and McGregor et al., Payne, Gardiner and Ver- ner (1959) have shown that when patients premedicated with atropine and allowed to breathe spontaneously are anaesthetized with halothane alone, the fall in blood pressure is often associated with increased cardiac output. This suggests that there is a lowered peripheral resistance partially compensated for by an increase in cardiac output. The rise in skin temperature and the increased finger volume observed in man during halothane anaesthesia (Payne, unpublished data) together with the experimental study of Hall and Norris (1958), which showed a net increase in pulse pressure, provide further evidence of peripheral vasodilatation. The extreme sensitivity of patients under halothane anaesthesia to sudden changes in posture also points to a depression of the vasomotor system (Burnap, Galla and Vandam, 1958). Finally, the fall in body temperature which has been reported by Löfström (1958) and which probably gives rise to the frequent occurrence of postanaesthetic shivering can be explained on the same basis.

It seems probable from the above data that when the atropinized patient is exposed to halothane concentrations of not more than 2 per cent the heart is able to compensate for a decrease in peripheral resistance, thus minimizing the blood pressure fall. In higher concentrations, especially when controlled respiration is used, this mechanism may fail, leading to profound hypotension and even cardiac arrest.

Clinically the relationship between high concen-
trations of halothane, controlled respiration, and circulatory failure has been repeatedly observed since Foster reported the first death during halothane anaesthesia in 1957. Reports of cardiac arrest continue to be published and it is remarkable how consistent these are. Typically, immediately before a sudden severe fall in blood pressure the anaesthetist has begun controlled respiration on a circle system with the vaporizer included in the circle. From what has been said previously a rapid increase in vapour concentration can be postulated and this together with the known deleterious effect of positive pressure respiration on the haemodynamics (Cathcart et al., 1958) may very well explain the sudden catastrophe.

In our own series four patients developed profound hypotension. In two of these anaesthesia was maintained by a closed circle system using a Marrett machine. A sudden, severe fall in blood pressure occurred when controlled respiration was started after the intravenous injection of 40 mg of suxamethonium to facilitate cholangiography. In both cases the exclusion of halothane from the circuit and ventilation with pure oxygen followed by the return of spontaneous breathing restored the blood pressure to normal levels. We have since abandoned the use of controlled respiration at any time when halothane is vaporized in a closed circle system.

In the remaining two patients chlorpromazine had been given pre-operatively; in one instance the drug was given for 6 weeks previously but was withdrawn 5 days before operation; in the other patient chlorpromazine was used as premedication. In both cases the exclusion of halothane from the circuit and ventilation with pure oxygen followed by the return of spontaneous breathing restored the blood pressure to normal levels. We have since abandoned the use of controlled respiration at any time when halothane is vaporized in a closed circle system.

In Respiratory Effects

The effects of halothane on respiration are complex. The vapour is nonirritant and relatively high concentrations are tolerated during induction even in highly premedicated patients. These advantages have been particularly appreciated by those workers engaged in the investigation of the respiratory effects of halothane as the absence of coughing and straining has greatly facilitated their clinical measurements.

Although Raventós (1956) showed that in dogs exposed to halothane the respiratory rate was decreased, an observation confirmed by Hall and Norris (1958), it is now well established that in man the respiratory rate is increased during halothane anaesthesia and a frequency of 50 breaths per minute has been reported (Chang et al., 1957). An outstanding feature of our own experience with the drug was the almost immediate return to normal rates when halothane was withdrawn. This observation suggested that the tachypnoea may be due to an irritant effect of the vapour on the stretch receptors of the lung but attempts to substantiate this hypothesis have so far proved unsuccessful.

Synchronous with the increased rate there is a reduction in the tidal air with the result that the minute volume is either unchanged or even slightly decreased during surgical anaesthesia. It is obvious, therefore, that the alveolar ventilation must be reduced. When tachypnoea becomes excessive the tidal air is lowered still further and the alveolar ventilation becomes inadequate, with a rise in arterial carbon dioxide tension (Holm-dahl and Payne, 1959). Because of the high oxygen concentrations commonly used in the inhaled mixtures, such inadequacy is usually masked in anaesthetic practice, but Bryce-Smith and O'Brien (1956) effectively verified this assumption by...
demonstrating the development of cyanosis in a group of patients breathing a halothane-air mixture.

The degree of carbon dioxide retention due to insufficient ventilation has been studied by end-tidal air analysis (Devine et al., 1958; Long and Pittinger, 1958) and by the measurement of the carbon dioxide tension of arterial blood (Holmdahl and Payne, 1959). In the latter investigation the rise in arterial carbon dioxide tension was less than that expected from the observed decrease in alveolar ventilation, and it was concluded that the production of carbon dioxide must be depressed during halothane anaesthesia. Although the possibility of an altered production of carbon dioxide was mentioned by Devine et al. (1958) it was not specifically investigated by them; but it seems likely from their data that such a depression did occur if it is assumed that the end-tidal air samples were truly alveolar and that a steady state of anaesthesia had been established when the measurements were made.

METABOLIC EFFECTS

The diminished carbon dioxide production described above might have been anticipated from the work of Severinghaus and Cullen (1958) who showed that the oxygen uptake fell in proportion to the increase in concentration of halothane breathed in a group of six patients. They postulated that this fall was due to the muscle relaxation and to the reduced respiratory and cardiac work associated with exposure to the drug. In one of their patients who showed a marked depression of cardiac output, stroke volume, blood pressure and oxygen consumption, and whose mixed venous blood oxygen saturation fell from 79 per cent to 51 per cent, it was observed that, despite the severe cardiovascular depression and increased oxygen utilization, there was no evidence of shock nor of metabolic acidosis. The absence of metabolic acidosis during halothane anaesthesia was confirmed by Holmdahl and Payne (1959), who in addition to studying the effects of the drug on ventilation also investigated the acid-base state of their patients.

Other metabolic aspects of halothane that have been investigated are those concerned with the activity of the liver and the kidney. Raventós (1956) carried out hepatic and renal function tests in rats and dogs exposed to repeated anaesthesia with halothane and found no significant changes in the results before and after exposure; but histological examination of the liver and kidneys in animals sacrificed when the experiments were completed showed unspecified minor changes in the liver, and in the kidney dilatation of the proximal convoluted tubules associated with slight cytological changes in the cells of those tubules. Chronic toxicity tests were repeated by Krantz et al. (1958), but they were unable to find evidence of histological damage either in the kidney, liver or brain of rats exposed to halothane.

In man blood sugar determinations made in twenty patients by Stephen et al. (1957), in an attempt to assess the effects of halothane on the liver were within normal limits. Burnap et al. (1958), however claimed that halothane raised the blood sugar level by interfering with the glucose phosphorylating mechanisms, but pointed out that in this respect its effect was no greater than cyclopropane or ether. This comparison between halothane and cyclopropane and ether was extended by Little and Barbour (1958) who applied a series of five liver function tests without demonstrating any difference in response.

Evidence of definitely abnormal results in liver function tests after prolonged anaesthesia with halothane has been provided by Brindle et al. (1957), but they were careful to state that the disturbance observed was probably no greater than that produced by other agents in the same circumstances. A similar conclusion was reached by Burns et al. (1957), who reported that despite a high incidence of deterioration in both liver and kidney function tests, after halothane there was no substantial difference between the control group and the halothane series.

Although one death has been reported that could possibly be attributed to delayed halothane poisoning (Virtue and Payne, 1958) other factors were also involved and the general failure to demonstrate a standard pattern of hepatic damage suggests that the drug has no specific toxic action on the liver and that any damage that does occur results from the combination of halothane anaesthesia with such potentially dangerous hazards as hypoxia, prolonged hypotension and pre-existing liver disease.
EFFECTS ON THE UTERUS

In the early experimental studies carried out to assess the value of halothane its effects on the uterus were comparatively neglected. The first clinical report of its use in obstetric practice suggested that halothane would find a place in most obstetric units as a substitute for chloroform, but the authors reported that of 233 patients studied 27 mothers had a period of reduced uterine tone following halothane anaesthesia and a further 4 had postpartum haemorrhages (Robson and Sheridan, 1957). These findings are in agreement with those of Russell (1958) who observed that after Caesarean section the uterus occasionally failed to contract in patients given halothane, and Dixon and Matheson (1958) who described the occurrence of retained placenta and postpartum haemorrhage after halothane.

The inhibition of contractility by halothane in the human pregnant uterus was demonstrated by Embrey, Garrett and Pryer (1958). By means of tocographic recordings these investigators showed that halothane depressed both spontaneous contractility and contractions artificially induced with intravenous oxytocin. Embrey and his colleagues were impressed by the rapidity with which the inhibitory effect developed on exposure to halothane and by the speed with which activity returned when consciousness was restored, and they pointed out, notwithstanding the potential dangers of uterine relaxation in certain circumstances, this property of halothane might be of considerable value in the management of such conditions as constriction ring and threatened uterine rupture.

CONCLUSION

Since halothane was first introduced in 1956 it has been the subject of a large number of clinical and experimental studies. Indeed it is unlikely that any other new drug has had so much attention in so short a time from chemists, physiologists, pharmacologists and clinicians with the result that not only has a great deal been learned about halothane but its introduction has also provoked the re-assessment of other anaesthetic drugs.

On the whole the claim by Raventós that halothane is capable of rapid, effective and flexible anaesthesia has been substantiated. Because it is neither explosive nor inflammable, it is of particular value in a wide field of surgery and its tendency to produce hypotension can be utilized to advantage in many specialties, especially as some understanding of the hypotensive mechanism has now been reached.

The safety of halothane has been virtually proved by its use in many hundreds of thousands of anaesthetics without incident and, though several cases of cardiac arrest have been reported, the recognition that the use of controlled respiration combined with a closed circle system incorporating a halothane vaporizer can lead to dangerously high concentrations of inspired vapour ought to eliminate this hazard in the future.

The nonirritant nature of halothane vapour produces a peaceful induction with quiet breathing once anaesthesia is established. There is some evidence that carbon dioxide may accumulate but this has not proved troublesome in practice and the absence of any marked metabolic disturbance emphasizes its safety.

The ability of halothane to inhibit the contractility of the human pregnant uterus explains the occasional occurrence of retained placenta and postpartum haemorrhage and defines its limitations in obstetric practice.

REFERENCES


