# HALOTHANE—A CLINICAL STUDY OF 500 CASES

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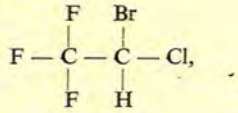
While recent developments have tended to restrict the scope of the inhalation anaesthetic to that of an analgesic component of the respiratory medium, there is a basic physiological simplicity about this method which makes for greater safety and ease of control and it would doubtless attract more attention if some of the shortcomings which limit the value of existing inhalation anaesthetics could be overcome.

Halothane (brom-chlor-trifluoro-ethane), a halogenated ethane having the formula



has recently been the object of considerable interest on account of its potency, non-inflammability, and a number of other properties highly desirable in an anaesthetic. The drug has been developed by Imperial Chemical Industries Ltd.[1,2] under the trade name of Fluothane. Early clinical investigation was carried out in Manchester[3] and in Oxford[4] while, more recently, clinical studies have been undertaken in Canada, the United States and later in South Africa.[14,15] The total number of halothane administrations now available for review already runs into hundreds of thousands, the largest series so far reported being from Manchester.

Halothane is a colourless liquid with a specific gravity of 1·86 and a boiling point of 50°C. It has a pleasant odour

and is non-irritating to inhale. It is a potent agent, the concentrations required for the induction and maintenance of surgical anaesthesia being about the same as for chloroform. Halothane appears to be reasonably stable but, in view of the dangerous nature of its break-down products, strict precautions should be observed with its use and storage. It shows a tendency to oxidize in the presence of heat, light and moisture and should therefore be stored in a cool place in tightly stoppered amber-tinted bottles. The stability of the commercial product is further enhanced by the addition of 0·01% of thymol.

## GENERAL SCOPE OF STUDY

In this clinical trial, in which halothane was administered to 540 cases, the main object was to determine its scope and behaviour when used as a main agent, a necessary prerequisite to the assessment of its place in modern anaesthesia. With this end in view, 459 patients were anaesthetized for a wide variety of operations without the use of any muscle relaxant apart from a normal dose of suxamethonium (50-75 mg.) to facilitate intubation. The only other anaesthetic used was a small induction dose of Na-thiopentone (averaging 300 mg.), which was administered to 407 patients; the remaining 53 had an inhalation induction. Table I shows the operations performed on these 459 patients.

TABLE I. OPERATIONS WITHOUT MUSCLE RELAXANTS EXCEPT FOR INTUBATION

| | |
|---|---|
| *Laparotomy* (8) | |
| Resection of bowel | 2 |
| Biopsy | 1 |
| Colostomy | 2 |
| Drainage | 1 |
| Diverticulectomy | 1 |
| Excision of abdominal sinus | 1 |
| *Gynaecological* (43) | |
| Hysterectomy (abdominal) | 6 |
| Hysterectomy (vaginal) | 4 |
| Vaginal repair | 12 |
| Dilatation and curettage | 21 |
| *ENT* (62) | |
| Tonsillectomy (adult) | 15 |
| Tonsillectomy and adenoidectomy (children) | 15 |
| S.M.R. | 11 |
| Mastoidectomy | 9 |
| Tympanoplasty | 3 |
| Operations on sinuses | 3 |
| Total laryngectomy | 1 |
| Other minor procedures | 5 |
| *Operations on Blood Vessels* (18) | |
| Varicose veins | 14 |
| Femoral embolectomy | 1 |
| Excision of popliteal aneurysm | 1 |
| Aortic/femoral graft | 1 |
| Ligature of common carotid | 1 |
| *Tongue and Jaw* (7) | |
| Mandibulectomy | 2 |
| Hemiglossectomy | 1 |
| Exploration of submaxillary duct | 1 |
| Biopsy | 3 |
| Orthopaedic procedures | 79 |
| Plastic procedures | 40 |
| Inguinal hernia | 38 |
| Ventral hernia | 7 |
| Appendicectomy | 17 |
| Mastectomy (radical) | 11 |
| Mastectomy (local) | 18 |
| Excision of breast tumours | 14 |
| Thyroidectomy | 22 |
| Dissection of cervical glands | 10 |
| Excision of parietal tumours (or F.Bs.) | 16 |
| Sympathectomy (lumbar) | 4 |
| Sympathectomy (Smithwick) | 2 |
| Ophthalmic operations | 6 |
| Urological operations | 8 |
| Haemorrhoids (and other anal procedures) | 21 |
| Other operations | 8 |
| *Total* | 459 |

In a further group, in which major abdominal procedures were carried out, halothane was used with muscle relaxants in the normal manner. Different proportions of relaxant to depth of anaesthesia were tried in an attempt to ascertain whether satisfactory relaxation could be obtained in the presence of adequate natural breathing or whether fully controlled respiration was more satisfactory. Table II shows the operations performed on the 67 patients in this group.

TABLE II. ABDOMINAL OPERATIONS IN WHICH HALOTHANE WAS USED WITH MUSCLE RELAXANTS

| | |
|---|---|
| Gall bladder and bile ducts | 23 |
| Gastrectomy | 19 |
| Bowel resections | 4 |
| Ventral hernia | 5 |
| Pancreatectomy | 1 |
| Hysterectomy | 2 |
| Exploration of aortic graft | 1 |
| Excision of hepatic cyst | 1 |
| Laparotomy and colostomy | 4 |
| Laparotomy with other procedures | 7 |
| *Total* | 67 |

In 14 other cases, muscle relaxants were given as a matter of expediency to afford better operating conditions or to assist control of respiration.

Oral intubation, following the use of suxamethonium, was carried out in 308 cases, and 225 were anaesthetized without intubation; 7 patients were intubated under halothane anaesthesia without the assistance of muscle relaxants. If the anaesthetist is prepared to spend a little extra time on the induction, halothane provides excellent conditions for intubation.

The age of the patients ranged from 7 months to 88 years. Table III classifies the patients into age-groups.

TABLE III. CLASSIFICATION BY AGE

| *Age-group* | *Number of Operations* |
|---|---|
| 0– 5 | 17 |
| 6–10 | 19 |
| 11–15 | 30 |
| 16–20 | 37 |
| 21–30 | 67 |
| 31–40 | 70 |
| 41–50 | 104 |
| 51–60 | 97 |
| 61–70 | 72 |
| 71–80 | 22 |
| 81–90 | 5 |
| *Total* | 540 |

While the majority of the patients could be regarded as reasonably good subjects for surgery, no attempt was made to avoid bad risks and the more important pre-operative pathological findings are listed in Table IV.

Apart from general observation, attention was mainly directed to the effects of halothane on the circulation and respiration, since these reactions are of particular interest

TABLE IV. PRE-OPERATIVE PATHOLOGICAL CONDITIONS

| | |
|---|---|
| Congestive cardiac failure | 7 |
| History of coronary thrombosis | 6 |
| Severe hypertension | 12 |
| Malignant hypertension | 1 |
| Dyspnoea | 7 |
| Tachycardia | 1 |
| Chronic bronchitis | 23 |
| Irradiation fibrosis of lung | 1 |
| Asthma | 3 |
| Emphysema | 13 |
| Severe toxaemia (acute) | 4 |
| Severe toxaemia (chronic) | 3 |
| Diabetes | 3 |
| Bad alcoholics | 7 |
| Gross obesity | 15 |
| *Total* | 106 |

and importance. Charts showing variations in blood pressure, pulse rate, respiration rate and anaesthetic concentration were kept for most of the longer cases.

## TECHNIQUE

### *Pre-medication*

In 60% of adult patients pethidine, 50 mg., and atropine, 1/100 gr. was given 1 hour before operation, light pre-medication being favoured as producing minimal respiratory depression. The physical condition of the patient was naturally taken into account in assessing the dose and the 25% who received 100 mg. of pethidine did not exhibit any marked respiratory depression as compared with the other group. In a limited number of cases other drugs and combinations were used, with apparently satisfactory results, including omnopon and scopolamine, morphine, chlorpromazine and promethazine.

The need for adequate atropinization has been stressed by other writers[3] but, in the present series, the normal pre-operative dose of 1/100 gr. for adults was seldom exceeded. In a small group of cases the atropine was stepped up to 1/50 gr. either by giving this dose pre-operatively or by giving an extra 1/100 gr. intravenously with the thiopentone. This sometimes seemed to reduce fluctuations in blood pressure, but it was also responsible for marked tachycardia and it was therefore felt to be better not to exceed the normal dose unless specific indications arose.

### *Administration*

The semi-closed method of administration was employed almost exclusively, using nitrous oxide and oxygen in flow rates of 7-10 litres per minute as the respiratory medium. As confidence in the agent increased, these flow rates were slightly reduced, but never to much below normal minute-volume requirements, and care was taken to keep the expiratory valve lightly adjusted to minimize re-breathing. In the interests of safety the oxygen content was maintained at somewhat above atmospheric concentrations (usually 30-50%) but experience showed that less than this was normally sufficient to avoid any trace of cyanosis.

For the administration of such a potent agent as halothane, accuracy of control is essential and the use of a vaporizer which lends itself to these requirements is important. Three types of vaporizer were tried:

(*a*) *The normal Boyle's trilene or chloroform vaporizer*

In the earlier administrations in this series, a Boyle's trilene vaporizer was employed in a manner similar to that described by Johnstone.[3] The control settings at which gases were first admitted to the vaporizer, and at which the flow through the vaporizer was maximal, were determined and marked on an extended scale, the intervening space being divided into 8 equal sectors. The hood of the plunger was fixed in its highest position. One disadvantage of this arrangement was that the strength of halothane vapour tended to remain low until the control approximated to the half-way mark, after which the increase in concentration was rather sudden.

(*b*) *B.O.C. modification of Boyle's trilene vaporizer*

This modification of the standard vaporizer has certain advantages over the improvisation described above. It has no U-tube or plunger, the gases being admitted through a lateral opening in a single tube which ends blindly. This opening is situated a little above the level of the anaesthetic, which should be kept approximately constant for the best results. The inlet and outlet ports of the control drum are much narrower than in the conventional pattern, thus permitting finer variations in the volume of gas admitted. An extended lever is provided with a scale numbered from 0 to 10. This vaporizer gave a more even increase in the vapour strength as the control was advanced.

Simple vaporizers of this type can be calibrated for a fixed anaesthetic temperature with a fixed rate of flow. During an administration, however, the temperature of the fluid in the vaporizer falls as the result of evaporation and the flow of gas may also require modification. Thus, while the vapour strength tends to fall as the anaesthetic proceeds, it is particularly easy to give a dangerous concentration during induction unless care is exercised. The anaesthetist must be familiar with the idiosyncracies of the particular vaporizer he is using but, with due precautions, the two described gave satisfactory results in 135 cases. It is sometimes helpful to make a rough estimation of the vapour strength by taking a tentative sniff at the breathing tube, although the practice is not without its disadvantages.

(*c*) *Compensated vaporizers*

By far the best type of vaporizer is one which is thermostatically compensated to give a constant vapour strength at any given control setting for any temperature or flow rate likely to prevail during the administration. In this respect, the Fluotec vaporizer (Cyprane Ltd.) proved highly satisfactory and was used almost exclusively (over 400 cases) as soon as it became available. This apparatus delivers known concentrations of halothane from 0 to 3%. It is compensated for variations in total gas flow over a range of 4—15 litres per minute, for cooling of the anaesthetic by evaporation, for variations in theatre temperature between 60°F and 90°F and for changes in the fluid level. It is thus a great advance in accuracy of control and consequently in safety.

## GENERAL IMPRESSIONS

### (*a*) *Induction*

Used without intravenous anaesthesia, halothane affords a smooth and comfortable induction which should not be found unpleasant by any reasonably cooperative patient. Consciousness is rapidly lost and the vapour is completely non-irritant in concentrations up to 3%. Induction is also easy from the anaesthetist's point of view since there is little tendency to coughing or breath-holding even in patients suffering from

chronic respiratory infections. Full surgical anaesthesia can usually be reached in about 5 minutes but, although the vapour is respirable up to and beyond the safety limit, it is probably wise to avoid sudden increases in concentration. The intravenous induction has now become such a universally established practice that no inhalation technique is likely to be so acceptable to the great majority of subjects but, if expedient, an inhalation induction with halothane may be confidently undertaken with minimal waste of time or disturbance to the patient. The concentration required seldom exceeds 2·5%, and 2% will usually suffice. Halothane is an excellent induction medium as a preliminary to ether anaesthesia and greatly shortens the time required to reach surgical narcosis. When given after a sleep dose of Na-thiopentone the induction is rapidly and smoothly completed.

Signs indicating depth of narcosis are of limited value. In full surgical anaesthesia the pupils become fixed in the mid-line and are contracted. Recovery is sometimes heralded by a moving or eccentric pupil which may exhibit some degree of dilatation, but anaesthesia with halothane was never pushed to the extent of showing dilatation at deeper levels. Respiration is often quiet and shallow until the subject is surgically stimulated. Deepening narcosis is indicated by respiratory depression, progressive hypotension and, in many cases, by cardiac arrhythmias.

(*b*) *Maintenance*

Halothane is a potent anaesthetic which, unlike trichlorethylene, has a wide useful range. Light anaesthesia, with concentrations varying between 0·5% and 1·5%, gives sufficient relaxation for almost any type of operation outside the abdomen. In a few cases, however, difficulty was unexpectedly experienced in establishing satisfactory surgical anaesthesia and better results were obtained by changing to other methods.

A regular pulse, tending to be slower than with ether, is normal. The skin is warm and dry and the peripheral veins well filled. There is usually a moderate degree of hypotension but, with the vapour concentrations mentioned above, the fall in blood pressure is seldom excessive although bleeding from the operation site is often conspicuously reduced. Spontaneous pulmonary ventilation appeared to be adequate but in some cases marked tachypnoea with decreased tidal volume was observed in relation to surgical stimulation. This reaction has been commented on by other writers.[3, 4, 7]

Sufficient relaxation for abdominal operations, without the use of neuromuscular block, can sometimes be obtained but deeper anaesthesia is usually needed and in these circumstances the toxic effects of halothane are more in evidence; severe hypotension, respiratory depression and cardiac arrhythmias are frequently observed. For major abdominal surgery, there is no doubt that better operating conditions can be obtained with greater safety by employing the more conventional combined methods.

(*c*) *Recovery*

After short administrations recovery is rapid and, provided the induction dose of Na-thiopentone has been minimal, the patient is often conscious before leaving the operating theatre. Even in longer procedures, consciousness normally returns much sooner than would be expected with ether, especially if care is taken to keep the patient in the lightest level consistent with smooth and uninterrupted anaesthesia. In this respect the non-irritating nature of the vapour favours ease of control.

As regards the post-operative well-being of the patient, the frequency with which claims of relative freedom from nausea and vomiting are made for new anaesthetics, and the many factors which may be concerned in this distressing complication, inevitably invites an attitude of scepticism. It can be said, nevertheless, that halothane made an extremely favourable impression. After short administrations carried out on volunteers, there was not the slightest feeling of malaise on recovery, while the number of patients who spontaneously expressed their appreciation, or favourably compared their experiences with those of previous anaesthetics, was impressive.

*Halothane with Muscle Relaxants*

The use of highly potent inhalation anaesthetics in conjunction with muscle relaxants is somewhat at variance with modern trends. As muscle relaxants completely mask the signs by which the depth of narcosis is normally assessed, a potent anaesthetic must only be used in concentrations which could not *per se* result in overdose. A vaporizer capable of delivering known percentages is thus of great advantage.

Profound hypotension has been reported after the use of a combination of halothane with d-tubocurarine, but suxamethonium and gallamine appear to be free from this danger and in no instance was any additional fall in blood pressure observed which was attributable to the use of either. Gallamine was found to be the most satisfactory relaxant to employ.

For abdominal surgery, the usual procedure consisted of oral intubation after a sleep dose of Na-thiopentone and 50—75 mg. of suxamethonium. The lungs were then gently inflated with nitrous oxide, oxygen and halothane, which was progressively increased up to 1·5% or 2%; artificial ventilation being continued until normal breathing was re-established. Before the abdomen was opened, gallamine (80—120 mg.) was given and the halothane reduced to 1% or lower. Pulmonary ventilation was then controlled, a soda-lime filter being used, with a total gas flow of 5 litres per minute. In some of the later cases this flow was reduced to 3½ litres per minute, the concentration of halothane being correspondingly reduced in view of the increased re-breathing. Further additions of gallamine (in doses of 20 mg.) were given as required, but often little was needed after the initial dose. Adequate spontaneous breathing was usually present at the end of the operation. By maintaining deeper anaesthesia (with halothane up to 2%) it was sometimes possible to obtain satisfactory relaxation without assisting pulmonary ventilation, but the precipitation of severe tachypnoea was a frequent complication and the technique described above proved more reliable.

The use of light halothane anaesthesia with muscle relaxants in abdominal surgery permits of a better balance between the anaesthetic and the neuromuscular block, without introducing the explosion hazard. The dangers associated with both incomplete anaesthesia and overdose of relaxant can be reduced.

## EFFECT ON RESPIRATION

The two most significant effects of halothane on the respiration are (*a*) depression of pulmonary ventilation in deep

anaesthesia, and (*b*) a tendency for marked tachypnoea to develop in association with surgical stimulation.

(*a*) *Respiratory Depression*

According to Bryce-Smith,[4] respiratory depression is one of the greatest disadvantages of halothane, and it is certainly one of the factors which limit its scope as a main agent. Unlike ether, there is no reflex stimulation of breathing by irritation of the upper respiratory mucosa, and respiration is often quiet and shallow before the commencement of the operation. As a result, the progress of the induction may sometimes be slow and it is not uncommon for the patient to move unexpectedly when the incision is made. The condition resembles the 'chloroform sleep' familiar to anaesthetists of the past and, if light stimulation is permitted, the resulting quicker and deeper breathing rapidly completes the induction.

With the operation in progress, pulmonary ventilation did not appear to be noticeably depressed in light or moderate anaesthesia. In a short series of 10 cases an attempt was made roughly to measure the minute volume by incorporating a non-return valve and adjusting the gas flow so that the breathing bag remained in a steady state of semi-deflation. Leaks were minimized by using a cuffed endotracheal tube or by the careful adjustment of an accurately fitting face-piece. It was found that the minute volume of individual subjects often showed wide fluctuations during the course of the anaesthetic, sometimes varying between 4 and 12 litres per minute.

(*b*) *Tachypnoea*

The respiratory rate during the operation is also widely variable, averaging about 25—35 per minute, but tachypnoea of 50—60 per minute may develop in response to surgical stimulation. This may be attributable to sensitization of the Hering-Breuer reflex, and the exceptional ease with which the respiration can be controlled in halothane anaesthesia seems to support this view. It is not necessary to make any attempt to modify respiratory rates of up to 40 per minute, but at 50 per minute (or over) the tidal volume may be reduced to such an extent that pulmonary ventilation is inadequate while, at the same time, the efficiency of the respiratory effort is reduced by the increased effect of the dead space. Intravenous pethidine is recommended by Johnstone[3] to control excessive tachypnoea and was found to be moderately effective. A better treatment, however, is to control breathing and ventilate the lungs artificially. This is facilitated by muscle relaxants but is often possible without such assistance.

## EFFECT ON THE CIRCULATION

A fall in blood pressure, often accompanied by diminished bleeding from the operation site, is a striking feature with halothane anaesthesia. There is a tendency to slowing of the pulse and, in isolated cases, extreme bradycardia has been observed; other cardiac arrhythmias may also occur. All these reactions are more associated with deep anaesthesia; in the lighter planes the effect of halothane may be more than balanced by the pressor effects of surgical stimulation.

*Hypotension*

As the mechanism of the fall in blood pressure is of considerable importance in the assessment of the intrinsic safety of the agent, it has been the subject of much experimental investigation. Raventos[1] believes that the hypotension is occasioned by pooling of the blood as the result of peripheral

TABLE V. EFFECT OF HALOTHANE ON SYSTOLIC AND PULSE PRESSURES

| *Preop. Syst. B.P.* | *Preop. Diast. B.P.* | *Min. Syst. B.P.* | *Max. Syst. Fall* | *% Syst. Fall* | *Preop. Pulse Press.* | *Min. Pulse Press.* | *Max. Pulse Fall* | *% Pulse Fall* |
|---|---|---|---|---|---|---|---|---|
| (*A*) 51 *patients receiving Na-thiopentone induction* | | | | | | | | |
| 122 | 88 | 100 | 22 | 18·0 | 34 | 25 | 9 | 26·0 |
| 110 | 70 | 85 | 25 | 22·7 | 40 | 25 | 15 | 37·5 |
| 110 | 70 | 90 | 20 | 17·0 | 40 | 30 | 10 | 25·0 |
| 114 | 70 | 52 | 62 | 54·4 | 44 | 8 | 36 | 81·8 |
| 116 | 74 | 66 | 50 | 43·1 | 42 | 10 | 32 | 76·2 |
| 140 | 95 | 75 | 65 | 46·5 | 45 | 10 | 35 | 77·8 |
| 124 | 90 | 50 | 74 | 59·6 | 34 | 10 | 24 | 70·6 |
| 140 | 80 | 145 | −5 | −3·6 | 60 | 40 | 20 | 33·3 |
| 100 | 60 | 100 | 0 | 0·0 | 40 | 15 | 25 | 62·5 |
| 130 | 90 | 120 | 10 | 7·7 | 40 | 20 | 20 | 50·0 |
| 130 | 90 | 84 | 46 | 35·4 | 40 | 12 | 28 | 70·0 |
| 126 | 80 | 70 | 56 | 44·4 | 46 | 20 | 26 | 56·5 |
| 112 | 82 | 83 | 29 | 25·9 | 30 | 15 | 15 | 50·0 |
| 110 | 70 | 80 | 30 | 27·3 | 40 | 15 | 25 | 62·5 |
| 124 | 92 | 70 | 54 | 43·5 | 32 | 12 | 20 | 62·5 |
| 120 | 80 | 95 | 25 | 20·9 | 40 | 15 | 25 | 62·5 |
| 120 | 80 | 115 | 5 | 4·2 | 40 | 25 | 15 | 37·5 |
| 130 | 90 | 90 | 40 | 30·8 | 40 | 20 | 20 | 50·0 |
| 132 | 82 | 100 | 32 | 24·2 | 50 | 30 | 20 | 40·0 |
| 142 | 96 | 120 | 22 | 15·5 | 46 | 36 | 10 | 21·7 |
| 125 | 80 | 78 | 47 | 37·6 | 45 | 10 | 35 | 77·8 |
| 110 | 80 | 100 | 10 | 9·1 | 30 | 20 | 10 | 33·3 |
| 110 | 80 | 90 | 20 | 18·2 | 30 | 22 | 8 | 26·7 |
| 120 | 74 | 75 | 45 | 37·5 | 46 | 25 | 21 | 45·6 |
| 120 | 80 | 110 | 10 | 8·3 | 40 | 20 | 20 | 50·0 |
| 140 | 80 | 100 | 40 | 28·6 | 60 | 16 | 44 | 73·3 |
| 110 | 50 | 90 | 20 | 18·2 | 60 | 30 | 30 | 50·0 |
| 132 | 92 | 108 | 24 | 18·2 | 40 | 22 | 18 | 45·0 |
| 140 | 96 | 114 | 26 | 18·6 | 44 | 20 | 24 | 54·5 |
| 120 | 80 | 105 | 15 | 12·5 | 40 | 25 | 15 | 37·5 |
| 135 | 80 | 100 | 35 | 26·0 | 55 | 20 | 35 | 63·6 |
| 120 | 80 | 90 | 30 | 25·0 | 40 | 30 | 10 | 25·0 |
| 100 | 70 | 85 | 15 | 15·0 | 30 | 20 | 10 | 33·3 |
| 126 | 80 | 80 | 46 | 36·5 | 46 | 20 | 26 | 56·5 |
| 130 | 90 | 100 | 30 | 23·1 | 40 | 18 | 22 | 55·0 |
| 140 | 100 | 104 | 36 | 25·7 | 40 | 22 | 18 | 45·0 |
| 120 | 80 | 105 | 15 | 12·5 | 40 | 20 | 20 | 50·0 |
| 132 | 82 | 96 | 36 | 27·3 | 50 | 28 | 22 | 44·0 |
| 120 | 70 | 80 | 40 | 33·3 | 50 | 20 | 30 | 60·0 |
| 132 | 84 | 118 | 14 | 10·6 | 48 | 28 | 20 | 41·7 |
| 120 | 80 | 100 | 20 | 16·7 | 40 | 30 | 10 | 25·0 |
| 130 | 75 | 80 | 50 | 38·4 | 55 | 20 | 35 | 65·5 |
| 130 | 70 | 90 | 40 | 30·8 | 60 | 20 | 40 | 66·7 |
| 118 | 80 | 100 | 18 | 15·3 | 38 | 20 | 18 | 47·4 |
| 120 | 75 | 100 | 20 | 16·7 | 45 | 40 | 5 | 11·1 |
| 140 | 90 | 120 | 20 | 14·3 | 50 | 20 | 30 | 60·0 |
| 130 | 75 | 90 | 40 | 30·8 | 55 | 20 | 35 | 65·4 |
| 130 | 80 | 95 | 35 | 27·0 | 50 | 25 | 25 | 50·0 |
| 120 | 86 | 90 | 30 | 25·0 | 34 | 20 | 14 | 41·2 |
| 140 | 90 | 76 | 64 | 45·7 | 50 | 18 | 32 | 64·0 |
| 120 | 80 | 80 | 40 | 33·3 | 40 | 15 | 25 | 62·5 |
| (*B*) 11 *patients receiving no Na-thiopentone* | | | | | | | | |
| 140 | 100 | 104 | 36 | 25·8 | 40 | 22 | 18 | 45·0 |
| 140 | 100 | 120 | 20 | 14·3 | 40 | 25 | 15 | 26·7 |
| 130 | 95 | 108 | 22 | 16·9 | 35 | 18 | 17 | 48·6 |
| 120 | 80 | 102 | 18 | 15·0 | 40 | 30 | 10 | 25·0 |
| 110 | 70 | 90 | 20 | 18·2 | 40 | 20 | 20 | 50·0 |
| 120 | 80 | 110 | 10 | 8·3 | 40 | 40 | 0 | 0·0 |
| 130 | 100 | 130 | 0 | 0·0 | 30 | 30 | 0 | 0·0 |
| 140 | 90 | 120 | 20 | 14·3 | 50 | 30 | 20 | 40·0 |
| 120 | 80 | 105 | 15 | 12·5 | 40 | 25 | 15 | 37·5 |
| 110 | 50 | 90 | 20 | 18·2 | 60 | 30 | 30 | 50·0 |
| 110 | 80 | 90 | 20 | 18·2 | 30 | 24 | 6 | 20·0 |

Preop.= pre-operative. Syst.= systolic. Diast.= diastolic. B.P.= blood pressure. Min.= minimum. Max.= maximum. Press.= pressure. Syst. Fall= fall in systolic blood pressure. Pulse Fall= fall in pulse pressure.

ganglion block. On the other hand, a report from the Medical Research Council[5] suggests that halothane reduces the cardiac output and is, in this respect, 70% as potent as chloroform. In this report the opinion is expressed that direct myocardial depression plays an important part and that ganglion block is a minor factor.

Observation of blood-pressure variations in a group of 62 cases, which were selective only in so far as their pre-operative blood-pressure figures fell within reasonably normal limits, appeared to suggest a diminished cardiac output. In these cases the following factors were noted: (*a*) The pre-operative systolic, diastolic and pulse pressures, and (*b*) the lowest systolic and the lowest pulse pressure recorded during the administration. From these data, the *maximum fall in systolic pressure* and the *maximum fall in pulse pressure* were calculated *as percentages of their pre-operative values*. In 51 cases anaesthesia was induced with a small dose of Na-thiopentone while in the remaining 11 an inhalation induction was employed. The figures are set out in Table V; they show that:

(*a*) In a group of 51 cases which were induced with Na-thiopentone the percentage fall in pulse pressure was substantially greater than that in systolic blood pressure in every case except one. The average fall in systolic blood pressure was 26·4% and that in pulse pressure 49·8%.

(*b*) In 11 cases where the intravenous induction was omitted the same tendency was shown and the percentage fall in pulse pressure was greater than that in systolic blood pressure in all but 2 cases. The average fall in systolic blood pressure was 14·7% and that in pulse pressure 31·2%.

Maximum falls in both systolic blood pressure and pulse pressure often followed an attempt to 'push' the anaesthetic, and were frequently noticed in the post-induction period, before the vapour strength had been reduced. In the latter case, Na-thiopentone may have been a factor, but the figures for Group B in Table V do not suggest that it was an important one. Most of the records showed that the diastolic pressure was relatively well maintained and, in a considerable number of cases, it actually rose. Taken collectively, all these observations seem to point to a diminished ventricular stroke volume.

There would thus appear to be 3 possible factors which may be concerned in the hypotension associated with halothane narcosis, viz. (*a*) peripheral ganglion block, (*b*) central vasomotor depression, and (*c*) direct action on the myocardium. Up to the present, there is no unanimity of opinion on which is the most important.

*Arrhythmias*

The effect of halothane on cardiac neuromuscular transmission has been studied electrocardiographically by Johnstone,[3] who found that normal sinus rhythm usually persisted throughout the administration. In some cases, especially where higher concentrations were used, arrhythmias of the vagal type were noted, including sinus bradycardia, A.V. nodal rhythm and coupled sinus beats; all these irregularities could be controlled by the administration of atropine. On a few occasions ventricular extrasystoles were observed in association with under-ventilation but disappeared when this was rectified.

In the present series cardiac arrhythmias were seldom noted with concentrations below 1·5% (except where irregular heart action was present pre-operatively), but occurred more frequently with higher concentrations. Irregular pulses were observed in about 5% of all subjects and included extrasystoles (11), bradycardia (2), tachycardia (6), pulsus alternans (4) and pulsus bigeminus (1). The irregularities were for the most part similar in type to those associated with cyclopropane anaesthesia. When conditions permitted, the anaesthesia was lightened and this often resulted in the restoration of normal rhythm. If not, provided the peripheral circulation and blood pressure remained satisfactory, no further action was deemed necessary. Halothane was administered with perfectly satisfactory results to patients suffering from gross cardiac disease.

*Dangerous Circulatory Complications*

Up to the present, at least 7 cases of cardiac arrest under halothane have been reported,[6–9] one of which terminated fatally. In some of these records the clinical details are not sufficiently complete for accurate assessment, but in each case the anaesthetic technique seems to have involved re-breathing or the use of vaporizers capable of giving dangerously high concentrations. From the available data, therefore, overdose cannot be ruled out as a possible (or even probable) causal factor. It also appears significant that these grave complications were invariably associated with the early phases of a trial and that they were eliminated as increased experience and respect for the potency of the drug were acquired. Up to the present there is nothing in the available literature to suggest that halothane in moderate concentrations is liable to cause sudden cardiac arrest, although it may be a contributory factor if adrenalin is injected in a subject under halothane anaesthesia. Brennan,[10] on the backing of impressive clinical experience, believes that concentrations up to 2% are safe, but, with such a potent agent it would be dangerous to assume that there is a wide margin between normal and potentially dangerous dosage. The following case is worth quoting:

> A somewhat obese but otherwise healthy girl of 16 was being operated on for the removal of an interval appendix. She was big for her age, and highly nervous, and was premedicated with 100 mg. of pethidine and 1/100 gr. of atropine 1 hour before operation. For induction, 500 mg. of Na-hexobarbitone was administered intravenously, followed by the inhalation of nitrous oxide and oxygen (5/3) with halothane, which was raised to 2·5% and, when adequate surgical anaesthesia was thought to be present, reduced to 2%. When the skin incision was made the patient moved slightly and the halothane was again raised to 2·5%, with the desired result. While the muscles were being separated the surgeon complained of inadequate relaxation, whereupon the control was advanced to 3%, the pulse being kept under continuous observation. At this stage the pulse was 120, full and regular, but within a minute or so it became suddenly irregular and almost imperceptible. The halothane was immediately turned off and pure oxygen administered, which brought about an equally dramatic return of the pulse to its previous rhythm and volume. The operation was completed with 1·5% to 2% of halothane without further incident.

While no electrocardiograph records are available in the above case, a strong impression was left that a cardiac arrest was imminent if prompt action had not been taken, and any sudden slowing or weakening of the pulse, or precipitant fall in blood pressure, must be regarded as urgent danger signals. Such sudden hypotension and reduction in pulse volume, following an injudicious attempt to improve abdominal relaxation, were observed on several occasions in the earlier stages of this investigation, and the necessity for close

observation of the circulation if higher than normal concentrations of halothane are being administered cannot be overstressed. If, however, temptation to 'push' the anaesthetic is resisted and attention is focussed on using the minimum amount required for satisfactory anaesthesia, such complications need not occur.

### EFFECT ON LIVER AND METABOLISM

Observations in this field were confined to general clinical assessment with the exception of one case where liver function tests were carried out before operation, 48 hours after operation, and 6 weeks later. This operation was a total laryngectomy lasting 10½ hours, for which halothane was used throughout as the main agent and which, therefore, provided a particularly severe test. In this case there was some residual depression of liver function but no evidence of serious impairment although the patient was in poor general condition and liver function was not normal before operation.

In the whole series, which included 203 operations lasting between 1 and 2 hours, 43 between 2 and 3 hours, 10 between 3 and 4 hours, 1 between 4 and 5 hours, and 1 over 5 hours, clinical evidence of liver damage was entirely absent. Nausea and vomiting during the recovery period occurred in a few cases but were usually minimal; in no instance was post-operative jaundice observed. The effect of halothane on liver function has been studied by Brindle *et al.*[11] in neurosurgical cases and their findings are in agreement with the above observations. It would, therefore, appear that while protracted halothane anaesthesia does cause some depression of liver function it compares favourably with most other anaesthetic agents in this respect.

### MORTALITY

There were no deaths in this series that could be attributed to the anaesthetic. One patient died in the immediate post-operative period. This was a man of 49 suffering from a large carotid-body tumour for which ligation of the common carotid artery was performed. The anaesthesia was uneventful but on return to the ward the patient developed a hemiplegia, became unconscious, and died about 24 hours later.

### COMPARISON OF HALOTHANE AND CHLOROFORM

As a halogenated hydrocarbon of high potency, halothane invites comparison with chloroform, especially in its efficiency as an anaesthetic and its effect on the heart and circulation. Such a comparison is not so easy as it might appear, for in specialist practice chloroform has been little used as a main agent for the past 30 years and the post-war generation of anaesthetists has little or no experience with it. Recent work carried out in the department of anaesthesiology of the University of Wisconsin under the direction of Dr. Ralph Waters,[12] and aimed at the reassessment of chloroform in the light of modern experience, is of great assistance.

As a result of extensive experimental and clinical observation, Waters and his co-workers conclude that chloroform affects reflex cardiac automaticity and has a direct depressant action on the myocardium. Out of 52 cases where chloroform was administered to human subjects, and which were monitored electrocardiographically throughout, only 5 failed to show cardiac irregularities. No less than 36 patients exhibited ventricular extrasystoles and 20 ventricular tachycardia, signs indicative of increased myocardial irritability. Johnstone,[3] on the other hand, reporting on 500 halothane cases where electrocardiograms were taken, found that sinus rhythm normally persisted at a steady rate. Ventricular extrasystoles were only observed on 12 occasions and in all cases could be attributed to inadequate pulmonary ventilation, for the irregularity disappeared as soon as steps were taken to improve it.

As regards potency, the vapour concentrations of halothane and chloroform which are required to induce and maintain surgical anaesthesia, and the time necessary for induction in each case, are about the same but, if the capacity to provide adequate relaxation for abdominal surgery with a workable margin of safety is accepted as the criterion of potency, chloroform is by far the more powerful agent. In the Wisconsin trials it was used as the sole agent for upper abdominal surgery, and without the assistance of any muscle relaxant just as it has been employed for the best part of a century. Experience has shown this type of surgery to be beyond the useful scope of halothane anaesthesia and also that halothane may, in overdose, be extremely dangerous. If, therefore, the comparison is made on the above terms, halothane must be accepted as having a lower safety margin. The same criticism could, of course, be levelled at many drugs which have a valuable place in modern anaesthesia, and it only implies that halothane could not have fulfilled the role of universal anaesthetic in the manner in which ether and chloroform have done in the past. There is, however, no longer any need for such a role and the available evidence seems to indicate that if the use of halothane is confined to cases where satisfactory anaesthesia can be maintained with 1·5% or less it can be employed with safety and confidence without fear of precipitating serious cardiac complications.

### DISCUSSIONS AND CONCLUSIONS

Probably most anaesthetists would agree that the most valuable single property of halothane is its non-inflammability; but its considerable potency and wide range of usefulness give it a great advantage over trichlorethylene, while its rapid action, ease of administration and relatively short recovery period are all attractive attributes. Elimination of the necessity for repeated intravenous injections during the course of the operation is often a welcome convenience.

Halothane is an excellent induction medium and is not unpleasant to the patient even if, for any reason, it is thought advisable to omit the intravenous administration of Na-thiopentone. The infrequency of disagreeable post-operative sequelae is a further advantage.

There is a tendency for bleeding from the operation site to be reduced which, from the surgeon's point of view, makes halothane a popular choice in plastic surgery, otolaryngology, thyroidectomy and other procedures where bleeding is likely to be troublesome. Reduced bleeding, however, is not invariable and it is inadvisable to use deep anaesthesia merely to provide a bloodless operation field. Halothane should be regarded as an agent which may ordinarily be expected to give relatively satisfactory conditions in this respect but it should never be used *specifically* for its hypotensive effects.

Most of the characteristics of halothane appear to commend it as an almost ideal answer to the problems of anaesthesia in neurosurgery. Unfortunately, natural conservatism prevented an adequate trial in this field, but reports have been most

encouraging and its use has been favourably commented on by other writers.[11]

In spite of its high cost, there is a growing demand for halothane and its scope is potentially wide; time alone will determine its exact place in anaesthesia. When used with muscle relaxants, halothane anaesthesia would obviously be applicable to practically any type of surgical procedure, but in these circumstances minimal demands are made on the anaesthetic, so that its comparative value is largely a matter of individual opinion.

Perhaps the most important point to be born in mind is the fact that halothane is a powerful and rapidly acting anaesthetic which, in overdose, may easily produce cardiac arrest. The safety margin between normal and dangerous concentrations is not known with certainty, but may be assumed to be a factor showing considerable variation in different individuals and it is probably influenced by other circumstances connected with the administration. Brennan[10] mentions 2% as an arbitrary safe limit for maintenance, while in the series of cases under discussion a case is recorded where 3% produced alarming symptoms in a healthy subject. While acceptable relaxation of the abdominal muscles cannot be uniformly produced without having recourse to potentially dangerous concentrations, it is safe to say that the possibility of cardiac arrest in the absence of overdose is extremely remote provided that gross anoxia, or the introduction of adrenalin into the circulation of a subject under halothane anaesthesia, are avoided.

The method of administration of halothane is worthy of special consideration. In his original investigation, Johnstone[3] used a semi-closed method with a total gas flow of 10 litres per minute, but the high cost of the agent has led to the increasing popularity of re-breathing techniques.[10, 13] Doubtless these methods can be reasonably safe with expert individual supervision but there are strong arguments against their general use. Accurate control of the vapour strength is more difficult and great care is needed to avoid dangerous concentrations in the breathing system. Further, an adequate gas flow, especially if delivered through an endotracheal tube, is a valuable safeguard against under-ventilation because it eliminates dead space and helps to flush out the lungs by convection; these advantages are lost when the flow of gas is restricted. The significance of these points is enhanced by the fact that halothane anaesthesia may sometimes be associated with a tendency to under-ventilation and Johnstone[3] has attributed the occurrence of ventricular extrasystoles to this factor. It is felt, therefore, that the only advantage of closed-circuit techniques is on the grounds of economy and that they have nothing to contribute in the interests of safety.

To sum up, it is suggested that the following principles should be observed when halothane is administered:

1. Its scope, as a main agent, should be limited to the type of operative procedure which can be handled satisfactorily with moderate concentrations (say 2—2·5% for induction and 1—1·5% for maintenance). Where any difficulty is experienced in maintaining satisfactory anaesthesia, it is better to employ muscle relaxants or to change to some other method.

2. The vapour strength should be carefully controlled; the use of a vaporizer capable of delivering known percentages being the ideal way of achieving this.

3. The pulse and blood pressure should be kept under close observation when approaching the arbitrary safe limits.

4. It is necessary to be on the look-out for tachypnoea and under-ventilation. If there is any doubt about the adequacy of natural breathing, the anaesthetist should assume control and ventilate the lungs artificially.

5. It is advisable to observe the same precautions with regard to injections of adrenalin as would be applicable to chloroform or cyclopropane.

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