THE PHARMACOKINETICS OF HALOTHANE (FLUOTHANE) ANAESTHESIA

BY

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The absorption and elimination of inhalation anaesthetics were studied at the end of the last century and the beginning of this by Bert (1878, 1883a, b, c), Nicloux (1906a, b, 1907a, b) and other research workers, and their findings were confirmed by Haggard (1924a, b, c, d, e), Robbins (1936), McCollum (1930) and other more recent investigators. The findings of the early workers have been collected in monographs by Winterstein (1926) and Kochmann (1923). They showed that the depth of anaesthesia is dependent upon the concentration of anaesthetic in the blood and central nervous system and that these are controlled by the concentration in the inhaled air. From this it follows that the more rapidly can this concentration in the blood be altered, the easier is the control of the depth of anaesthesia by the anaesthetist.

One of us (Raventós, 1956) studied the concentration of Fluothane (halothane)* in the arterial blood of dogs at different depths of anaesthesia. In these preliminary experiments it was found that when halothane is administered in open circuit its concentration in the arterial blood increases rapidly during induction but can be kept constant during the administration of maintenance concentrations of the agent, and that the concentration falls rapidly soon after the administration of the anaesthetic is stopped. These observations explained the rapid onset of anaesthesia with halothane and the facility with which the anaesthesia could be controlled and reversed.

As several reports on the use of halothane using closed-circuit and to-and-fro techniques have been published since then, it was felt that a closer study of the accumulation and distribution of halothane in the body and its exhalation during recovery was necessary (Marrett, 1957, 1959; Brown and Woods, 1958; Johnstone, 1957). This article describes the results of such a study.

METHODS

Chemical estimation of halothane.

Halothane was estimated in blood, tissues and expired air by the method of Duncan (1959).

Spectrophotometric estimation of halothane.

The concentration of halothane was estimated in several samples of expired air by measurement of the optical density at 204 mμ using a Beckmann D. U. Spectrophotometer. A 1 per cent v/v mixture of halothane in air has an optical density of 0.141 in a 1-cm cell at 204 mμ. The ultraviolet absorption spectrum of halothane has been studied by Kalow (1957).

Preparation of vapour mixtures.

The anaesthetic mixtures used in these experiments were prepared by the method of Raventós (1956).

Accumulation of halothane in mice.

The animals were anaesthetized by our standard methods (Raventós, 1956). Batches of twelve mice were put into the exposure chamber and submitted to the action of halothane for different lengths of time, after which they were removed from the chamber and killed at once by breaking the spinal cord high up in the neck. The carcasses were immediately put into beakers containing petroleum ether, homogenized, and their halothane content estimated as described by Duncan (1959). The weight of the mice was measured by difference. By this method the halothane content of the tissues, including the skin, was measured.

*The word “Fluothane” is a registered trade mark of Imperial Chemical Industries Ltd.
In other experiments the mice were submitted to the action of halothane for a period of 2 hours and allowed to recover in the laboratory from the action of halothane. Groups of these mice were killed at regular intervals and treated by the described method.

Absorption of halothane by the blood and tissues of rats.

The animals were anaesthetized with ether and the trachea and one of the carotid arteries cannulated, after which they were placed on an electrically heated dissection table and the tracheal cannula connected by means of a T-piece to the delivery tube of the apparatus used for the preparation of the anaesthetic mixtures. The other arm of the T-piece was fitted with a nonreturn water valve. The anaesthetic mixtures were produced at a rate of 2 l./min, which is several times greater than the average minute volume of the rat. In this way we ensured that the animals were inhaling the anaesthetic in a constant concentration throughout the experiment without the danger of CO₂ accumulation. The carotid cannula was constructed from a thin capillary tube about 10 cm long which was bent at the middle.

The animals were under the action of halothane for different periods of time, with a maximum of 6 hours. Heparin (0.25 mg) was injected intravenously 5 minutes before bleeding the rats. The blood samples were collected by releasing the bulldog clip which had been placed on the carotid artery and allowing the blood to run into petroleum ether, care being taken to keep the tip of the cannula under the surface of the petroleum ether.

Immediately after taking the blood sample, samples of brain, liver, perirenal fat and other tissues were removed and placed immediately into petroleum ether. All the samples were weighed by difference and analyzed for halothane.

Fig. 1

Apparatus for measuring the amounts of halothane eliminated in the expired air of mice during recovery. (Not to scale).
This procedure was slightly modified in the experiments where the concentration of the anaesthetic was measured during recovery. In these experiments batches of twelve rats were anaesthetized for 2 hours in an exposure chamber larger than the one used in the experiments on mice. At the end of the anaesthesia the rats were taken from the chamber and left to recover in the laboratory. One carotid artery was cannulated while the rat was still under the influence of halothane (or under ether anaesthesia if it had recovered) and at intervals samples of blood and tissues were taken as before.

In some experiments, samples of mixed venous blood were taken into a heparinized syringe by direct puncture of the right ventricle, or by puncture of one of the hepatic veins, the tip of the needle being at the juncture of both cavae. These rats were also anaesthetized with ether if necessary.

**Estimation of halothane in the expired air.**

Batches of twelve mice were anaesthetized with halothane in the exposure chamber of our apparatus. Six of these mice were killed at the end of the period of anaesthesia and used for the estimation of the total halothane content of their bodies. The other six mice were transferred to the recovery chamber of the apparatus shown in figure 1, which was flushed continuously with oxygen at a rate of 100 ml/min. This chamber was a round-bottomed flask (Quickfit FR700F).

**Fig. 2**

Apparatus for measuring the elimination of halothane and its concentration in the expired air of rats during recovery. (Not to scale.)
fitted with a multiple adaptor (Quickfit MAF 2/2) and was half submerged in a thermostatically controlled water bath at 25°C. The outlet gases, dried by passing over anhydrous calcium chloride, were bubbled through petroleum ether in test tubes submerged in crushed ice. The petroleum ether tubes were changed every 10 minutes and the halothane in the solvent estimated by the standard method. The mice were kept in the recovery chamber for 2 hours and then killed and their halothane content measured as already described.

In other experiments rats, anaesthetized with allobarbitone (Dial) solution (0.6 mg/kg i.p.), were placed on an electrically warmed operating table and allowed to inhale halothane (1.5 per cent v/v) through a tracheal cannula for 2 hours by the technique described. At the end of this time the tracheal cannula was connected to the apparatus shown in figure 2. The animal inspired oxygen from a spirometer of about 500 ml capacity (S) through a unidirectional valve (V₁) and the expired air passed through the unidirectional valve (V₂) to the side arm of a collection tube (T) and then by a glass coil (C) to the open air.

The halothane in the expired air was extracted by petroleum ether running as a thin layer down the glass coil at a rate of 2 ml/min from a Mariotte bottle reservoir (P). The total amount of oxygen absorbed by the animal from the spirometer was recorded on a smoked drum during the experiment. The collection tube was changed at regular intervals and the halothane content of the petroleum ether samples estimated. In these experiments the total halothane expired by the animal was measured and its concentration in the exhaled air calculated from the spirometer tracings.

The efficiency of the apparatus was tested by passing a stream of 1.5 per cent halothane at 1.1 l/min through the spiral and then passing the air from the outlet tube through petroleum ether. No halothane was found in the latter indicating that extraction by the solvent in the spiral was complete.

In some experiments the expired air of rats during recovery was collected in silica cells and the concentration of halothane estimated spectrophotometrically.

**RESULTS**

Absorption and elimination of halothane in mice.

The rate of accumulation of halothane in the body of the mouse was estimated by anaesthetizing batches of animals with 1.5 per cent v/v halothane in oxygen and killing the mice after different periods of anaesthesia.

It was found that there was an initial rapid uptake of the agent so that after 10 minutes of inhalation the mice contained approximately 32 mg of halothane/100 g. body weight. Following this rapid uptake the amount of halothane in the body increased more slowly, but progressively, with continued anaesthesia, so that after 3 hours it had reached about 170 mg/100 g.

This concentration of anaesthetic does not represent saturation of the tissues with halothane since, as is shown in figure 3, there was no significant decrease in the rate of uptake of the agent, even after 3 hours of anaesthesia.

![Absorption of halothane in mice anaesthetized with 1.5 per cent v/v halothane in oxygen. Each point represents one mouse.](https://example.com/image.png)
to 150 mg/100 g. in 20 minutes and then to about 15 mg/100 g. in 2 hours. The rate of decrease during recovery was logarithmic, there being a 50 per cent decrease in 30 minutes (fig 4).

The distribution of halothane during anaesthesia.

The experiments on mice give an overall picture of the rates of uptake and elimination of halothane from the tissues, without giving any information on its distribution during anaesthesia and recovery. This problem was studied in more detail in experiments on rats where the concentrations of halothane in different tissues were estimated at different times during anaesthesia.

Following inhalation of halothane (1.5 per cent v/v) it was found that the concentration of halothane in the arterial blood increased rapidly and reached an equilibrium with the inhaled vapour mixture in about 1 hour. After this period there was no further increase in the amount of halothane present in the arterial blood; it remained constant at about 20 mg/100 ml for as long as 6 hours anaesthesia.

The concentrations of halothane in the brain and liver were higher than that in the arterial blood and increased steadily during continued anaesthesia. These two organs, which after 30 minutes inhalation of halothane contained about 20 mg of the agent/100 g., accumulated it slowly so that after 6 hours they contained 45–50 mg/100 g.

The accumulation of halothane in the perirenal fat was more rapid than in any other tissue, the concentration of halothane increasing from about

<table>
<thead>
<tr>
<th>Duration of anaesthesia (hr.)</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2.0</th>
<th>2.5</th>
<th>3.0</th>
<th>4.5</th>
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</tr>
</thead>
<tbody>
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<td>16.8</td>
<td>21.0</td>
<td>22.0</td>
<td>18.5</td>
<td>21.5</td>
</tr>
<tr>
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<td>(3)</td>
<td>(3)</td>
<td>(3)</td>
<td>(3)</td>
<td>(3)</td>
<td>(3)</td>
<td>(3)</td>
</tr>
<tr>
<td>Fat</td>
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<td>100</td>
<td>130</td>
<td>250</td>
<td>300</td>
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<td>33</td>
<td>38</td>
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<td>(3)</td>
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<td>(3)</td>
<td>(3)</td>
<td>(3)</td>
<td>(4)</td>
<td>(4)</td>
</tr>
<tr>
<td>Liver</td>
<td>17</td>
<td>22</td>
<td>18</td>
<td>23</td>
<td>26</td>
<td>35</td>
<td>43</td>
<td>48</td>
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<td>(3)</td>
<td>(3)</td>
<td>(3)</td>
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<td>(3)</td>
<td>(4)</td>
<td>(4)</td>
</tr>
</tbody>
</table>
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55 mg/100 g. after 30 minutes to 950 mg/100 g. after 6 hours anaesthesia. The results (figure 5) show that there was no decrease in the rate of uptake of halothane by the perirenal fat and therefore that a considerably longer period of anaesthesia than 6 hours would be required to saturate the fat at this inhaled concentration of halothane.

The results of these experiments are summarized in table I and figure 5.

Elimination of halothane from tissues.

The concentrations of halothane in the arterial and venous blood of rats which had been anaesthetized for 2 hours with 1.5 per cent \( \text{v/v} \) halothane in oxygen were estimated during recovery. The results (figure 6) show that there is a marked difference in the rate of decrease of the concentration of halothane in the arterial and venous blood after cessation of the inhalation of the agent.

In the arterial blood the concentration decreased logarithmically from about 20 mg to 1.4 mg/100 ml in 1 hour. This decrease in concentration represents a rate of clearance of approximately 50 per cent in 14 minutes. Twenty minutes after stopping inhalation, at which time the animals displayed voluntary movement, the concentration of halothane in the arterial blood was about 7.5 mg/100 ml.

In the venous blood after an initial rapid fall in the concentration of halothane the decrease was logarithmic. At the end of the first 10 minutes of the recovery period the concentration of halothane was about 12 mg/100 ml venous blood and after 1 hour it was about 6 mg/100 ml. During this part of the recovery period the rate of clearance was 50 per cent in about 45 minutes.

In the same series of experiments the concentration of halothane in the perirenal fat was estimated with results similar to those found for the venous blood. In the first 20 minutes of the re-

![Graph](https://example.com/graph.png)

**Fig. 5**

Mean concentrations of halothane in the tissues of rats anaesthetized with 1.5 per cent \( \text{v/v} \) halothane.

**Fig. 6**

Concentrations of halothane in the arterial and venous blood and perirenal fat of rats during recovery after 3 hours of anaesthesia with 1.5 per cent \( \text{v/v} \) halothane. Each point represents one animal.
covery period the concentration in the perirenal fat decreased from 310 to 230 mg/100 g. At the end of 1 hour the concentration was 180 mg/100 g; these results represent a 50 per cent clearance from the fat in about 45 minutes, a rate of clearance similar to that found for the venous blood.

**Elimination of halothane in the expired air of mice and rats.**

Estimations of the halothane present in the expired air were carried out in mice and rats during recovery from anaesthesia, using the techniques described.

In some of these experiments batches of twelve mice were anaesthetized for 2 hours with 1.5 per cent v/v halothane. One half of these animals were sacrificed immediately after the anaesthesia period and their halothane content estimated. The other six mice were placed in the recovery chamber of the apparatus shown in figure 1 which was then flushed for 2 hours with oxygen at a rate of 100 ml/min. The effluent gases from the chamber were passed through petroleum ether which extracted the halothane exhaled by the animals. These mice were killed at the end of the experiment and their halothane content estimated.

The results of these experiments, summarized in Table II, show that the exhalation of halothane was rather slow at the beginning of the recovery period but increased 10 to 20 minutes after the mice had been put in the recovery chamber. This abnormal result could be due to the relatively large deadspace of the apparatus and to the intense respiratory depression of the animals at the end of the anaesthesia, which was not corrected until their body temperature increased. About 50–60 per cent of the halothane absorbed by the mice during anaesthesia was exhaled in 2 hours. The mice in this experiment took longer to recover from anaesthesia than those in the experiments where the halothane content alone was estimated, and the rate of elimination of halothane was lower.

In rats it was found that the concentration of halothane in the expired air was 10–13 mg per cent (1.2–1.5 per cent v/v) at the start of the recovery period and that the concentration decreased progressively to values of 1–2.5 mg per cent (0.12–0.3 per cent v/v) in 3 hours. The amount of halothane eliminated in the expired air per unit time decreased as the recovery from anaesthesia progressed and the elimination was

### Table II

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Time after cessation of halothane inhalation (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10</td>
</tr>
<tr>
<td>1</td>
<td>1.4</td>
</tr>
<tr>
<td>2</td>
<td>1.4</td>
</tr>
</tbody>
</table>

![Figure 7](https://academic.oup.com/bja/article/31/7/302/241668/fig7)
complete in 9 to 10 hours (figure 7), as the expired air collected between 9 and 10 hours, between 12 and 15 hours and between 18 and 21 hours after the end of anaesthesia did not contain any traces of halothane. There was no significant difference between the results of the experiments where the concentration of halothane was measured by the chemical method and those where the spectrophotometric method was used.

The graph (figure 8) shows that at the moment of recovery, as judged by the presence of voluntary movement 20 minutes after the end of anaesthesia, the halothane concentration in the expired air was around 8–10 mg per cent (1 per cent v/v) which is a concentration which can be used for the maintenance of anaesthesia.

The metabolism of halothane.

Four different methods have been used to investigate the fate of halothane in the body.

Three rabbits (2–3 kg) were anaesthetized with 1.5 per cent v/v halothane in oxygen for about 3 hours. The animals were bled to death, whilst still under halothane anaesthesia, by placing a cannula in one of the carotid arteries. The blood (40–50 ml) was heparinized and shaken for 10 minutes with cyclohexane (10 ml). The cyclohexane extract was separated by centrifugation and examined by vapour phase chromatography using a column (184 cm × 4 mm) of a 30 per cent chlorinated diphenyl on graded celite at a temperature of 60°C. The carrier gas, dry nitrogen, at a flow rate of 0.9 l./hr. had an inlet pressure of 642 mm Hg with a pressure drop of 361 mm Hg. The effluent gases were examined using a katharometer at 35°C and the galvanometer readings were recorded on a chart moving at a speed of 15.5 cm/hr. The chromatogram of the extracts showed only the characteristic peaks of halothane and cyclohexane.

The second approach to the problem was to examine the urine of animals for trifluoroacetic acid (CF<sub>3</sub>COOH) which seemed to be a possible metabolic product of halothane. Two dogs, after anaesthesia for 3 hours with halothane, were placed in a metabolism cage to recover and their urine was collected over the following 24 hours. The urine was acidified, extracted with ether and the ether extract chromatographed on Whatman No. 1 paper using butanol saturated with 2N ammonium hydroxide as the irrigant. The chromatograms were run for about 16 hours, dried in the open air and then sprayed with a bromophenol indicator solution. No trifluoroacetic acid was detected in the ether extracts by this method which gave good results using synthetic mixtures of urine and trifluoroacetic acid.

The third method involved measurement of the total recovery of halothane from anaesthetized animals. These experiments were combined with those in which exhalation of halothane by mice was measured. The results (table III) show that the total halothane detected in the expired air over a 2-hour period plus the halothane remaining in the mice at the end of this period accounts for 87 and 94 per cent of the halothane found in the control groups of mice killed at the end of the period of anaesthesia.

Finally, a group of six rats was anaesthetized with halothane for two periods of 3 hours in the one day and their urine collected over the following 48 hours. The urine was analyzed for total halide by potentiometric titration and for bromine using the method of Kaplan and Schnerb (1958). No significant differences were observed between the amounts found in the urine from these animals and from untreated rats.
TABLE III
Recovery of halothane in the expired air of mice compared with the amount of halothane in the body at the end of anaesthesia and 2 hours after recovery.

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Halothane (mg) in mice after 2-hrs. anaesthesia</th>
<th>Halothane (mg) exhaled in 2-hr. recovery period</th>
<th>Halothane (mg) in mice after 2-hr. recovery period</th>
<th>Per cent halothane accounted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>120</td>
<td>62</td>
<td>42</td>
<td>87.0</td>
</tr>
<tr>
<td>2</td>
<td>87</td>
<td>63</td>
<td>19</td>
<td>94.0</td>
</tr>
</tbody>
</table>

These four experiments, although not conclusive, would seem to indicate that there is little, if any, metabolism of halothane in the body and that it is mainly excreted in the expired air.

Halothane concentrations in the venous blood of patients during anaesthesia and recovery.

Samples of blood from patients undergoing surgical operations of varying complexity and duration were taken from the cubital vein and analyzed for halothane. All the patients were anaesthetized by Dr. M. W. Johnstone with 1.5 to 2.5 per cent v/v halothane in oxygen or in 50 per cent nitrous oxide in open circuit using the trichlorethylene vaporizer of the Boyle's apparatus or with the Fluotec vaporizer. The authors wish to express their gratitude to Dr. Johnstone for allowing them to carry out these estimations.

From thirteen patients, slim to obese and from 25 to 81 years of age, a total of thirty blood samples were taken during the maintenance of anaesthesia. One sample was always taken from each patient no more than 5 minutes before stopping the inhalation of halothane. One or more blood samples were taken from each patient during the recovery from anaesthesia. The data of these estimations are collected in table IV. All

TABLE IV
The concentrations of halothane in the venous blood of patients anaesthetized for varying lengths of time with halothane.

<table>
<thead>
<tr>
<th>Duration of anaesthesia</th>
<th>Time (min) after cessation of inhalation of halothane</th>
<th>Mg halothane per 100 ml venous blood</th>
<th>Half clearance time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0  4  6  8  10  12  20  23  30  40  45  60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 min</td>
<td></td>
<td>5.5  3.2</td>
<td>10  6</td>
</tr>
<tr>
<td>15 &quot;</td>
<td></td>
<td>7.9  4.6</td>
<td></td>
</tr>
<tr>
<td>16 &quot;</td>
<td></td>
<td>9.9  5.9</td>
<td>8</td>
</tr>
<tr>
<td>19 &quot;</td>
<td></td>
<td>17.3  4.7</td>
<td>3</td>
</tr>
<tr>
<td>30 &quot;</td>
<td></td>
<td>12.0  4.3</td>
<td>14  27</td>
</tr>
<tr>
<td>35 &quot;</td>
<td></td>
<td>7.0  6.7</td>
<td></td>
</tr>
<tr>
<td>40 &quot;</td>
<td></td>
<td>5.9  3.7</td>
<td>22  29</td>
</tr>
<tr>
<td>47 &quot;</td>
<td></td>
<td>6.0  3.3</td>
<td></td>
</tr>
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<td>50 &quot;</td>
<td></td>
<td>7.0  5.5</td>
<td>26  45</td>
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<td>55 &quot;</td>
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<td>4.9  3.4</td>
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<td>120 &quot;</td>
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<td>160 &quot;</td>
<td></td>
<td>7.4  4.7</td>
<td>2.5  25</td>
</tr>
</tbody>
</table>
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patients, irrespective of the length of anaesthesia, showed vigorous corneal reflexes and responded to commands within 10–15 minutes of the cessation of halothane administration; at this time the concentrations of halothane in the venous blood was 2–4.5 mg/100 ml. The patients can be divided into two groups: those who were anaesthetized for about 30 minutes or less and those who were anaesthetized for more than 30 minutes. In the first group the halothane concentration in the venous blood varied from 5.5 to 17.3 mg/100 ml, with half-clearance times of less than 20 minutes, whilst in the eight patients in the latter group the concentrations varied between 4.9 and 7.4 mg/100 ml and the half-clearance times showed a mean value of about 26 minutes.

Concentration of halothane in the vapour mixture during closed-circuit anaesthesia.

The concentrations of halothane in the rebreathing bag of a Boyle’s apparatus was measured during anaesthesia of dogs using a completely closed-circuit technique. Anaesthesia was induced with halothane, without premedication, and the dogs were intubated and put on to a closed circuit for the rest of the experiment. Oxygen was introduced into the circuit at a rate of 200 ml/min and the control of the vaporizer adjusted so that a steady level of anaesthesia was maintained. The concentration of halothane in samples of the gases obtained from the rebreathing bag was measured spectrophotometrically using 5-cm silica gas cells.

In these experiments it was possible to maintain the same depth of anaesthesia, once the control of the vaporizer had been correctly set, for as long as 3 hours, the maximum duration studied. There was no progressive increase in the concentration of halothane in the rebreathing bag, the concentration varying between 2.1 and 2.4 per cent v/v.

DISCUSSION

The results of our experiments offer an explanation of some of the characteristics of the action of halothane. For instance, the short induction period is due to the rapid absorption of halothane by the arterial blood which quickly reaches an equilibrium with the concentration of the inhaled gas, and the rapidity of the transfer across the alveolar membrane is also partly responsible for the short recovery times after anaesthesia. In spite of the large quantities of halothane absorbed by the body during anaesthesia, there is a relatively small amount of agent in the c.n.s. and in the arterial blood, from which it is quickly eliminated after the cessation of the inhalation of the anaesthetic.

The accumulation in the body of inhalation anaesthetics has been studied in the past by determining the amount of agent eliminated in the expired air during recovery. Using this technique Haggard (1924a) deduced that the amount of ether fixed in the tissues at any moment during anaesthesia could be calculated from the concentration in the mixed venous blood. This rule cannot be applied to halothane because the amount absorbed by the body increases progressively during anaesthesia so that calculations based on the concentration in the venous blood give values which are lower than those determined experimentally.

In experiments in which the halothane absorbed by the mouse was measured directly it was observed that the uptake was rapid during the first 20 minutes of anaesthesia, but after this the absorption of the agent continued at a slow but steady rate for the duration of the anaesthesia. In none of the experiments was an equilibrium attained between the concentration of halothane in the inspired air (1.5 per cent v/v) and in the tissues; it is probable that to reach this equilibrium some 20 hours of anaesthesia would be required. This observation is in agreement with those reported for chloroform (Tissot, 1906a) and ether (Haggard, 1924b, c), where the theoretical equilibrium between the inhaled gas mixture and the tissues was not reached.

The uptake of halothane by the different tissues is not uniform as it is influenced by their chemical constitution. The blood, which has a low lipid content, attains equilibrium with the inspired gas rapidly, whilst the tissues with a higher lipid content absorb halothane at a constant rate for longer than 6 hours. The high concentrations of halothane in the adipose tissue are not surprising, as halothane has a high oil/water partition coefficient (halothane 330; ether 3.2; chloroform 110). This ratio, which is an indication of how much anaesthetic the fat can absorb when in equilibrium with a known concentration in the blood, does not define the rate of uptake...
by the tissues. This is influenced by other factors, such as the blood flow through the organ and the concentrations of the different lipid fractions present in each tissue. Thus the brain has a higher lipid concentration than the liver, yet the results obtained for these tissues show that halothane is absorbed at the same rate and in similar concentrations. We presume that this is due to the fact that the brain has a lower blood flow per unit weight than the liver. As these two organs contain less neutral fat than adipose tissue it would appear that halothane is less readily absorbed by phospholipids than by neutral fats.

The perirenal fat absorbs halothane continuously and concentrations between 900 and 1000 mg/100 g were found at the end of 6 hours anaesthesia with 1.5 per cent v/v; this is about fifty times greater than the concentration in the arterial blood. The fat/blood concentration ratio is only 2–3 (Tissot, 1906a, b) for the more water soluble volatile anaesthetics, such as ether and chloroform, and about 1 for barbiturates such as pentobarbitone (Brodie et al., 1953). With the less water soluble barbiturates the fat/blood concentration ratio is greater—12 for thiopentone (Brodie, Bernstein and Mark, 1952) whilst a value of 100 has been reported for n-methyl thiopentone (Peterson et al., 1953). Brodie and his co-workers suggested that the fixation of short acting barbiturates by the fat is the limiting factor of the duration of single i.v. doses of these compounds. This same property also contributes to the quick recovery of animals after halothane anaesthesia.

During recovery the total halothane in the mouse decreases exponentially with a half-clearance rate of about 30 minutes. When the mice have recovered sufficiently to be able to walk, the brain will contain subanaesthetic concentrations of halothane, although the other tissues still contain relatively large amounts in what must be considered as nonactive depots. The factors which regulate the absorption of halothane during anaesthesia also influence its elimination from the body during recovery. The concentration of halothane in the arterial blood decreases rapidly, with a half-clearance rate of 14 minutes, so that subanaesthetic concentrations are found some 10 to 15 minutes after stopping the inhalation of the agent.

On the other hand, the concentrations of halothane in the venous blood during recovery are always higher than those found in the arterial blood. At the start of the recovery period the concentration decreases at about the same rate as in the arterial blood, but after 10 minutes the rate of clearance falls so that relatively high concentrations are found in the venous blood 2 hours after cessation of inhalation of the agent. Nicloux (1906a, 1907a) and Haggard (1924b) made similar observations with chloroform and ether, but because of the higher blood/gas partition coefficients of these two anaesthetics (halothane 3.6; chloroform 7.3; ether 15) the differences between the concentrations in the venous and arterial bloods were not so great as with halothane.

The rate of clearance of halothane from the few samples of perirenal fat examined during recovery was practically the same as that found in the venous blood (45 minutes). During recovery halothane is released from the fat and other tissues into the venous blood from which the anaesthetic is cleared almost completely during its passage through the lungs. Only small amounts of halothane are carried over into the arterial blood so that no "re-anaesthetization" of the animals can occur.

The elimination of halothane in the expired air during recovery is completed in about 9 hours, which is less than the time necessary for the complete elimination of ether or chloroform. The concentration of halothane in the expired air immediately after anaesthesia is approximately the same as the concentration used during the anaesthesia and it decreases during recovery. Concentrations of 1 per cent v/v, which will maintain anaesthesia in rats, were found in the exhaled air of animals previously anaesthetized with 1.5 per cent v/v when they had recovered sufficiently to be able to walk.

Significant differences in the rate of elimination of halothane during recovery were found in experiments on mice. If the mice were left to recover on a warm plate in the laboratory, the half-clearance rate was about 30 minutes, whilst in other experiments only 52 per cent and 72 per cent (table III) of the total halothane originally present in the body were exhaled in 2 hours. This anomaly is apparently due to the fact that mice show an intense respiratory depression and hypo-
thermia after an anaesthesia of 2 or 3 hours. These effects are longer-lasting if the animals are left to recover in the chamber of our apparatus (figure 1), which is flushed continuously with a stream of oxygen, so that the recovery times of these mice were considerably longer than those used in the other experiments. These results show that, as in the case of ether (Haggard, 1924), the elimination of halothane is influenced by changes in the respiratory minute volume of the animals.

The concentrations of halothane found in the venous blood of human patients (table IV) were lower than those found in experimental animals; a similar observation was made by Morris, Frederickson and Orth (1951) for chloroform. It is difficult to discuss the significance of these results because the concentration found in the venous blood depends on the depth and duration of anaesthesia and on the site of sampling. In spite of these limitations it was observed that the half-clearance times of halothane from the venous blood of patients who had been anaesthetized for 35 minutes or longer were fairly consistent, varying from 10 to 45 minutes with a mean of 26 minutes; this value is very similar to that found in mice and rats after long anaesthesias. In anaesthesias shorter than 30 minutes the half-clearance times were more irregular but were all less than those observed for the longer anaesthesias.

During the first 30 to 60 minutes of anaesthesia halothane is being distributed throughout the body fluids and only a small fraction of the quantity inhaled is being absorbed by the tissue fats. Therefore the half-clearance time of halothane from the venous blood is proportional to the amount distributed throughout the body, being shorter in brief anaesthesias and greater in longer anaesthesias, since the anaesthetic has been accumulated in certain tissue depots, from which it is cleared during recovery.

Butler (1958) derived a formula from which the half-clearance time of an anaesthetic from the whole body can be calculated approximately.

\[
\text{Half life in minutes} = \ln(2) \times \frac{Vd(Vp + \lambda Cp)}{Vp \times Cp}
\]

where \(Vd\) = apparent volume of distribution of the drug in litres.

\(Vp\) = effective pulmonary ventilation in l./min.

\(Cp\) = pulmonary circulation in l./min.

\(\lambda\) = the blood/air distribution coefficient of the anaesthetic.

\(\ln(2)\) = natural logarithm 2.

For comparison we can assume that for man the \(Vd\) for halothane, chloroform and ether is approximately the same, and is 70 l.; \(Vp\) is 8 l./min; \(Cp\) is 5 l./min and \(\lambda\) halothane is 3.6; \(\lambda\) chloroform is 7.3 and \(\lambda\) ether is 15. Therefore, using these values, the calculated half-clearance time of halothane is 31 minutes, chloroform is 54 minutes, and ether is 100 minutes.

It is interesting to note that the half-clearance time of halothane from the whole mouse was approximately 30 minutes; from the perirenal fat and venous blood of the rat around 45 minutes and from the venous blood of man around 26 minutes, values that are in close agreement with that calculated from the above formula. This relatively small clearance time for halothane is the reason for the shorter recovery time after halothane anaesthesia compared to that found after ether and chloroform anaesthesias.

The importance of the uptake of halothane by the tissues is more evident during closed-circuit anaesthesia. Marrett (1957, 1959) and Brown and Woods (1958) using the closed-circuit circle and Johnstone (1957) with the to-and-fro methods of anaesthesia have reported that during anaesthesia there is no build-up in the concentration of halothane in the circuit. This has been confirmed by experiments on dogs anaesthetized in closed circuit with halothane for over 3 hours, where it was found that the concentration of agent in the rebreathing bag remained constant within the limits of 2.1 and 2.4 per cent v/v without any alteration in the setting of the vaporizer. The vaporizer, at the setting used in these experiments, delivered around 0.2 per cent v/v at a flow rate approximately the same as the minute volume of the dogs. Therefore these animals, of an average weight of 12 kg, absorbed 15 to 20 mg of halothane per minute, which is equivalent to 90 to 120 mg for a 70-kg man. This last figure is in agreement with the results of Robson et al. (1958) who found that their patients absorbed 3 to 5 ml of halothane per hour, equivalent to 95–155 mg/min. If the vaporizer of an
anaesthesia apparatus delivers halothane more rapidly than the subject can absorb it there will be an increase in the concentration in the circuit. However, experience has shown that during closed-circuit anaesthesia it is possible to maintain this equilibrium between the amount absorbed by the body and the halothane volatilized in the circuit. If the vaporizer is included in the circuit, the rate of volatilization of the agent depends to a great extent on the respiratory minute volume of the subject and, if this changes because of variations in the depth of anaesthesia, the rate of volatilization of the agent will vary accordingly. Therefore, with spontaneous respiration, these changes will tend to keep constant the concentration of halothane in the circuit and to achieve a steady level of anaesthesia.

Predictions are usually made about the possible metabolism of any new drug and it was considered possible that halothane could be metabolized. However, four different analytical procedures have given negative results, so that we feel justified in stating that halothane is not metabolized but is eliminated unchanged in the expired air during recovery.

SUMMARY

The absorption, distribution and elimination of halothane has been studied using rats and mice. The results of these experiments show that:

1. The anaesthetic is rapidly absorbed during induction.
2. The concentration of halothane in the arterial blood reaches an equilibrium with the inhaled concentration in a relatively short time, after which it remains constant.
3. The concentration of halothane in the brain and liver increases slowly during anaesthesia, whereas there is a more rapid accumulation of the anaesthetic by the adipose tissue. It is estimated that some 20 to 30 hours of anaesthesia with 1.5 per cent v/v halothane would be required to saturate the adipose tissue with the agent.
4. As the brain does not absorb large amounts of halothane and because of the low blood/gas partition coefficient of this anaesthetic, the recovery from anaesthesia is more rapid than with ether or chloroform.
5. The halothane fixed in the body during anaesthetics of 3 hours duration is completely eliminated in 9 to 10 hours.

6. Because of the fixation of halothane by the tissues there is no build-up in the concentration of halothane in the circuit during closed-circuit anaesthesia.

7. Attempts to demonstrate metabolic products of halothane were unsuccessful and it is assumed that it is not metabolized.

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REFERENCES


— (1906b). Etude experimentale de rapports entre les proportions de chloroforme contenues dans le sang et dans les tissus pendant l'anesthesie et les effets qu'elles produisent (2e memoire). *J. Physiol. Path. gén.*, 8, 442.