ABSORPTION, DISTRIBUTION AND ELIMINATION OF DI-ETHYL ETHER IN MAN

BY

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In 1924 Haggard published a paper on this subject having carried out his study on dogs. The mode of transfer of di-ethyl ether to and from the human subject in clinical anaesthesia has been deduced from the facts derived from his animal experiments. Since there is no assurance that this deduction is right, a human study of this kind has been awaited. The present study is intended to fill this gap between experimental animals and human subjects.

METHOD

A known concentration of ether was given to healthy volunteers from a large rubber bag through a non-rebreathing valve. Expired air was collected for 1 minute at certain intervals. Samples were drawn from the bag for the determination of ether by a gas-chromatograph. The differences in the amount of ether inhaled and exhaled were used for the calculation of absorption. After the administration of ether in patients and volunteers its elimination was studied by collecting the expired air by the same method as above. Measured volumes of ether vapour were converted to S.T.P. For quantitative analysis of ether vapour in respiratory gas a gas-chromatograph was used. Helium was used as a carrier gas, a katharometer was used for detection and polyethylene glycol was used for the stationary phase. A calibration line was constructed by introducing a known amount of ether vapour, so that the amount of ether vapour in a sample could be found by the measurement of peak area on the recording paper of the gas-chromatograph. The measurement was accurate to 0.005 ml of ether vapour in a 10 ml gas sample.

RESULTS

Absorption of ether.

Liquid ether was mixed with air in a large rubber bag so as to make a 1 per cent vapour concentration. The concentration was measured by the gas-chromatograph. This concentration of ether did not produce mental clouding and did not affect the respiratory minute volume. The ether-air mixture was given by a non-rebreathing valve to two healthy volunteers for 60 minutes. The results obtained in the two volunteers are shown in figure 1. As shown in the figure a phase of steep decrease in ether uptake is completed somewhere between the 15th and 20th minutes from the beginning of inhalation, and a steady slow decrease in ether uptake continues until the 60th minute.

Fig. 1
Ether absorption by two volunteers who were given 1 per cent ether-air mixture by non-rebreathing valve.
The relationship between the amount absorbed and eliminated in the same individual.

A 0.5 per cent mixture of ether in air was administered to three healthy volunteers by a non-rebreathing valve for 20 minutes and the amount of ether absorbed by the subjects was estimated as described in the previous section. After this 20-minute period of inhalation, expired air was collected for three consecutive 40-minute periods. The results are shown in table I. As indicated in the table, in the first subject, 779.7 ml of ether vapour were absorbed during 20 minutes and of this 34 per cent was eliminated in the first 40-minute period; a further 25 per cent (59.5 per cent - 34.3 per cent) in the second 40-minute period, and 24 per cent more in the third 40-minute period. Altogether the amount eliminated in 120 minutes was 83.9 per cent of the amount absorbed in 20 minutes inhalation. In the second and third subjects the amounts recovered in 120 minutes were lower, being 49.9 per cent and 37 per cent respectively.

Concentration of ether in air depots.

During clinical anaesthesia air depots were made in the pleural cavity, the peritoneal cavity and the abdominal fat in different individuals. The concentration of ether in the inspired air during anaesthesia fluctuated between 4 per cent and 8 per cent. The results obtained are shown in figure 2. If it be true that the concentration of ether vapour in the air depots reflects the equilibrium established between the air and the surrounding tissue, then the saturation of the tissue around these air depots to the inspired ether concentration does not seem to be completed.

### Table I

Absorption and elimination balance study

<table>
<thead>
<tr>
<th>Absorption in ml</th>
<th>Subject 1</th>
<th>Subject 2</th>
<th>Subject 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>779.7</td>
<td>943.6</td>
<td>785.6</td>
<td></td>
</tr>
<tr>
<td>Amount eliminated as percentage of the amount absorbed</td>
<td>in 40 min</td>
<td>34.3</td>
<td>23.3</td>
</tr>
<tr>
<td></td>
<td>in 80 min</td>
<td>59.5</td>
<td>38.3</td>
</tr>
<tr>
<td></td>
<td>in 120 min</td>
<td>83.9</td>
<td>49.9</td>
</tr>
</tbody>
</table>

**Fig. 2**

Concentration of ether in the air depots made in the pleural cavity, peritoneal cavity and fat tissue during clinical anaesthesia with ether.
This is especially true in fatty tissue and the ether concentration in fat shows a steady rise for 200 minutes. According to the figure the transfer of ether from blood to fatty tissue seems to be a very slow process.

Elimination of ether.

In two patients quantitative analysis of ether in expired air was continued for 540 minutes after the end of anaesthesia. The results are shown in figure 3. The solid line in the figure represents the findings in a 55-year-old male weighing 48 kg who had ether anaesthesia by endotracheal, closed circle, carbon dioxide absorption system for 120 minutes. The ether concentration in the breathing bag at the end of anaesthesia was 5.3 per cent. The broken line in the figure shows the results obtained in a 35-year-old female weighing 52 kg who had ether anaesthesia for 55 minutes by the same method. The ether concentration in the breathing bag at the end of anaesthesia was 3.7 per cent. As shown in the figure the decrease in the amount of ether eliminated is very rapid during the first 15 to 20 minutes, followed by a phase of slow decrease for the next 40 minutes. A slower decrease continues for the rest of the experimental period. It is worth pointing out that it was possible to detect a trace of ether by the gas-chromatograph in the expired air until 20 hours after the anaesthesia.

In two healthy volunteers 0.8 and 0.9 per cent ether-air mixture was administered by a non-rebreathing valve for 60 minute periods. The elimination of ether was measured by the same method as used in the clinical case. While in patients the respiratory minute volume is small in the first part of the recovery period and increases later on, the respiratory minute volume remained constant in the volunteers who were breathing a low concentration of ether. Since the respiratory minute volume had a considerable influence on the amount of ether eliminated, it is desirable to have constant respiration to obtain an ether elimination curve in near-physiological condition. The curve shown in figure 4 is drawn from an empirical equation which seems to fit the values obtained by the measurements. The black solid dots in the figure represent the mean of each measured value in two cases.

![Figure 3](image)  
**Fig. 3**  
Elimination of ether after clinical anaesthesia. Solid line represents 55-year-old male weighing 48 kg. Broken line represents 35-year-old female weighing 52 kg. Ether concentration in the rebreathing bag at the end of anaesthesia was 5.3 per cent in the former and 3.7 per cent in the latter. The duration of anaesthesia was 120 minutes in the former and 55 minutes in the latter.
DISCUSSION

In the second experiment it was shown that 37 to 84 per cent of absorbed ether was collected in the elimination period of 2 hours. The value is smaller than that obtained by Haggard (1924) in dogs. He could recover more than 87 per cent of the amount absorbed. The question arises as to the cause of the difference in these results.

One explanation is the difference in the size of dogs and human subjects. In the dog the elimination of ether may be completed sooner than in human subjects because of the smaller body size and the difference in the proportion of adipose tissue. Another explanation is the difference in the concentration of ether vapour used. Concentrations of ether vapour much lower than those used by Haggard were used in this absorption-elimination balance study. At the concentrations of ether used in this balance study, experiments show that the factor of diffusion through the rubber bag is negligible. The authors are suspicious, however, of the current concept that most of the ether vapour absorbed by the human can be recovered in the expiration especially in diluted concentration. It has been shown that nitrous oxide and cyclopropane can be eliminated through the intact human skin (Orcutt and Waters, 1933); but since the authors have proved that ether in anaesthetic concentrations does not pass through the intact human skin (Asao, 1960), elimination by this route can be excluded from the discussion. At least it is felt that a more detailed balance study is needed to prove the current concept.

Table II was derived from the calculation of each component of the empirical equation for ether elimination in the two volunteers. This table illustrates some interesting points in the mode of elimination of ether from the human body. An empirical equation which fits the ether elimination curve consists of three exponentials. The first exponential comes close to zero at the 20th minute, the second one comes close to zero at the 90th minute and the third one remains at a higher level at the end of experiment. From the previous studies on the elimination and absorption of cyclopropane and nitrous oxide in man (Onchi et al., 1961; Ono, 1960) there can be seen both differences and resemblances between the elimination of ether, nitrous oxide and cyclopropane. They resemble each other in that the elimination curve consists of three phases; the first steep decline, the second slow decline,
and the very flat long tail. Ether elimination is different from the others in that the first and the second phases last much longer. In the absence of direct evidence, it is considered that the first exponential represents ether elimination from the blood, the second exponential represents elimination from a part of body which has a relatively rich blood supply, and the third exponential represents elimination from a part of body which is remote from the circulation. Because ether has a much higher solubility for blood than cyclopropane and nitrous oxide, it takes longer for ether than for cyclopropane and nitrous oxide to be eliminated from the blood.

As a result the first exponential of the empirical equation comes close to zero sooner for cyclopropane and nitrous oxide than for ether. It is most probable that the greater part of the third component consists of fat.

**SUMMARY**

The mode of transfer of ether to and from man has been studied under clinical and experimental conditions. An empirical equation has been constructed from changes in the amount of ether eliminated after experimental administration of ether.

**REFERENCES**


