

# Solubility of Methoxyflurane in Rubber

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A PREVIOUS report on the solubility of halothane in rubber<sup>1</sup> suggested that solubility in rubber may be related to fat solubility. Recent determinations of methoxyflurane solubility in fat<sup>2</sup> gave an extremely high figure (a fat/gas partition coefficient of 825) and suggested a correspondingly high rubber solubility. To test this and to explore the clinical implications, the following experiments were performed.

## Methods and Results

**Solubility in Rubber.** The solubility of methoxyflurane (expressed as the Ostwald partition coefficient) was determined at 25° C. in small pieces of conductive corrugated rubber tubing. The method used has been previously described.<sup>1</sup> Equilibrium was assumed to have taken place after 70 hours. (Final equilibrium concentration was 0.61 per cent.) Triplicate determinations were made with an infrared halothane analyzer that is also sensitive to methoxyflurane.<sup>2</sup> Solubility thus determined was 742, with an experimental range from 731 to 754. As anticipated, the solubility in rubber (742) is close to that in oil (825).

**Influence of Rubber Solubility on Clinical Anesthesia.** To observe the effect of methoxyflurane solubility in rubber on the course of anesthesia, a model circle system was prepared, similar to that previously described.<sup>1</sup> A double-ended 5-liter rubber bag, two corrugated rubber tubes identical to those commonly used in circle systems, and a Revel circulator were connected end-to-end to form a circle. Inflow and outflow tubes were widely separated. Methoxyflurane was vaporized from a Forregger Copper Kettle. Inflow concentration was monitored with the infrared analyzer and was held constant through-

out the experiment. Gas entering the system was rapidly mixed with the gas within the system by the Revel circulator. Mixed gas escaped from the outflow tube at a rate sufficient to balance the inflow rate. Total system volume, therefore, remained constant. Methoxyflurane concentrations sampled from the system or from the outflow tube were identical at the same point of time as determined with the infrared analyzer.

Two types of experiment were performed with this model. The first was designed to ascertain the uptake of methoxyflurane by rubber under conditions resembling induction of anesthesia. Methoxyflurane in oxygen was admitted to the model at a constant flow rate, and the changing concentration within the system monitored at frequent intervals. In successive tests, with new rubber goods for each, inflow rates were 1, 3, and 8 liters per minute. Though similar (about 1.9 per cent), the inflow methoxyflurane concentration was not identical in all tests. The concentration within the model was expressed as a percentage of that in the inflowing gas.

Figure 1 shows the changes in methoxyflurane concentration for the three inflow rates. The log scale is inverted from its usual form so that the graphs rise with rise in percentage. The effect of high rubber solubility is seen in the retarded rate of rise in concentration in the circle. After 10 minutes, at 3 liters per minute inflow, the concentration was only 82 per cent of that entering the system. As expected, the effect was greater at the low flow rate and less marked at the high. But even at 8 liters per minute, 15 minutes elapsed before the circle concentration approached within 10 per cent of that in the inflowing mixture. If there were no absorption of methoxyflurane by rubber, the rate of rise would depend only upon ventilation of the model, and would follow the equation:

$$\text{concentration} = 100 (1 - e^{-t/Vs})$$

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where  $r$  = inflow rate,  $t$  = time,  $V_s$  = volume of the system. This is the washout equation of any space when (1) the inflow concentration is constant; (2) immediate mixing of inflow and gases within  $V_s$  occurs; and (3) no differential solubilities exist (*i.e.*, the substance in the inflow is not more soluble in  $V_s$  than in the inflowing material. This condition is important when tissue uptake is considered but not in the case of gases.) Kety has ex-

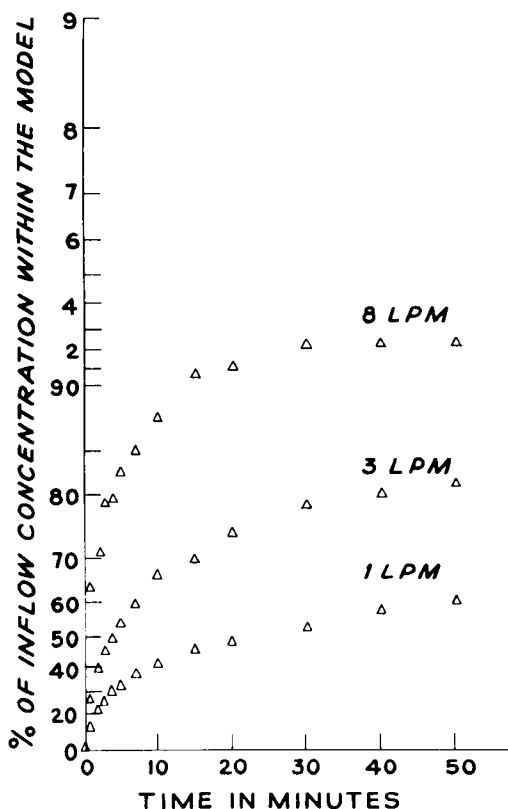


FIG. 1. Illustrates uptake of methoxyflurane by rubber in an anesthetic circle. The concentration, expressed as percentage of inflow concentration, is plotted at three different inflow rates. If no uptake occurred, each graph would follow the equation: concentration =  $100(1 - e^{-rt/V_s})$ , and would appear as a straight line. The 1-liter/minute graph reaches 95 per cent in 19 minutes, the 3-liters/minute graph would reach it in 6 minutes, and the 8-liters/minute graph in  $2\frac{1}{2}$  minutes. The results are plotted on semilogarithmic paper to allow a visual separation of the effect of ventilation (the initial upsweep) and the slowly diminishing effect of uptake by the rubber (the slower, continuing rise after the initial upsweep). This form of presentation also increases the separation of graphs at the part of the scale where most of the plateaus are found.

amined this equation in some detail in his review of uptake of anesthetic gases.<sup>3</sup> The straight line in figure 2 is a graphic expression of this equation when  $r = 3$  liters/minute and  $V_s = 6.25$  liters. Since nitrous oxide has a low solubility in rubber the graph for this gas (filled circles) falls upon this line.<sup>1</sup> Against this are contrasted the curves for methoxyflurane and halothane entering the system at the same flow rate. The effect of differing rubber solubilities is clearly seen. After 50 minutes, the concentration of methoxyflurane in the circle arrived within 18.5 per cent of full equilibration. Halothane concentration in

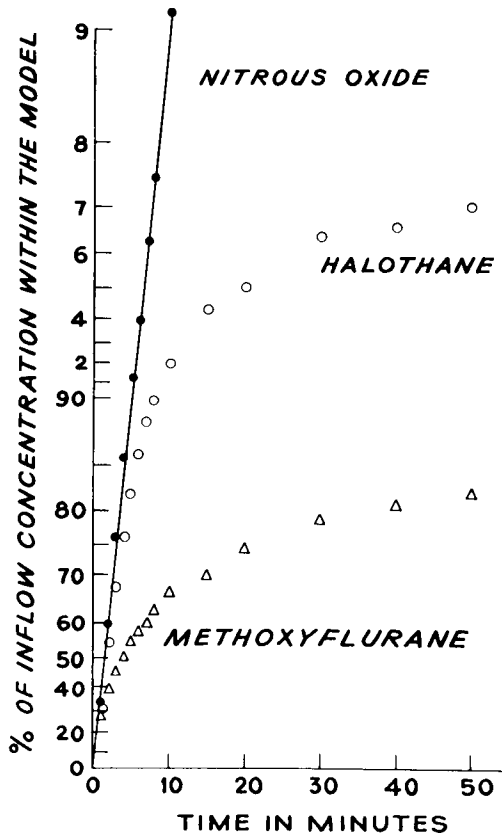


FIG. 2. The effects of differing solubilities in rubber of nitrous oxide, halothane and methoxyflurane are shown in this figure. The straight line is a plot of the equation: concentration =  $100(1 - e^{-rt/V_s})$  where inflow ( $r$ ) is 3 liters/minute and  $V_s$  is 6.25 liters. The graph for nitrous oxide (filled circles) overlies this line, while the graphs for halothane (open circles) and for methoxyflurane (open triangles) deviate from it according to their solubility in rubber.

the same period was 3 per cent short of full equilibration. The ratio of the methoxyflurane to the halothane lag (18.5/3.0) was 6.2. At this point in time the difference between the two curves is essentially due to uptake, rather than to ventilation or "washout" effects. Since uptake in rubber is proportional to solubility, the 6.2 ratio should show close correlation with the rubber solubility ratio for the two gases. The Ostwald solubility coefficient for methoxyflurane is 724, and for halothane is 121.<sup>1</sup> The ratio of these is 6.1.

In order to study washout of methoxyflurane from the rubber of an anesthetic system, a second experiment was performed utilizing the model. The system was first equilibrated with 1.7 per cent mixture of methoxyflurane in oxygen, entering the system at a rate of 1 liter per minute for a period of 17 hours. After flushing the system with 8 liters of oxygen per minute for three minutes, oxygen inflow was reduced to 3 liters per minute and kept at this level for 60 minutes. The system was flushed again with oxygen, 8 liters per minute for five minutes. Oxygen flow was maintained thereafter at 1 liter per minute. Methoxyflurane

concentration within the circle was monitored throughout.

The results obtained in this experiment are shown in figure 3, and demonstrate significant concentrations of methoxyflurane maintained in the system through release of drug from rubber. Concentration in the circle is expressed as a percentage of the initial saturating concentration. From a peak of 37 per cent at three minutes, the concentration slowly fell so that at ten minutes it was 31 per cent, at 30 minutes it was 22.5 per cent, and at 60 minutes it was 15 per cent. At this time, increase in the washout flow to 8 liters per minute resulted in a fall in five minutes to less than 5 per cent. Subsequent reduction of washout flow to 1 liter per minute resulted in a return to 25 per cent of the initial saturating concentration. After 500 minutes the residual concentration was 10 per cent. After an additional washout of 15 hours there was still a measurable amount of methoxyflurane in the circle.

*Diffusion of Methoxyflurane through Rubber.* It was found in the previous experiments that even after 17 hours of equilibration a significant concentration gradient remained between

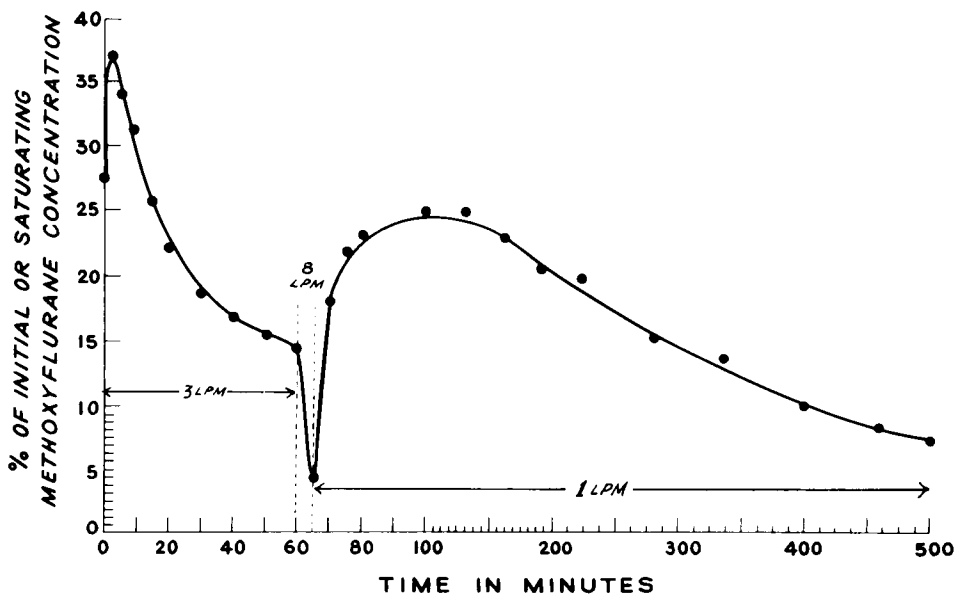


FIG. 3. Illustrates washout of methoxyflurane from a saturated anesthetic circle. The flow of oxygen for washout was 3 liters/minute for the first hour, 8 liters/minute for the next 5 minutes and 1 liter/minute thereafter. The concentration within the circle is expressed as a percentage of the concentration (1.7 per cent) with which the system had been initially equilibrated after 17 hours.

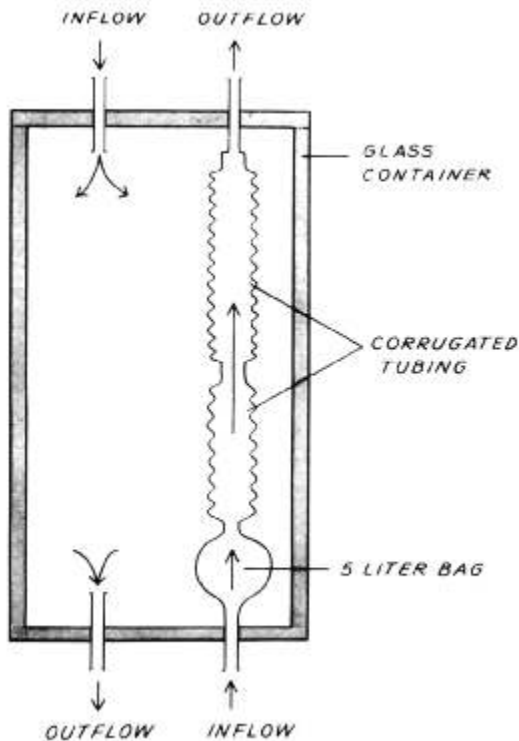


FIG. 4. The model used to determine diffusion of methoxyflurane through rubber. A 1 liter/minute flow containing methoxyflurane was directed through the rubber components. A counter-current 1 liter/minute flow of pure oxygen was directed through the space about the rubber goods. The concentration surrounding the rubber, divided by the mean concentration within the rubber, gave the fraction of methoxyflurane lost by diffusion.

the inflowing gas and the mixture within the circle. To determine how much of this was affected by diffusion through the rubber, the following experiment was performed. A 5-liter rubber bag and two lengths of corrugated rubber tubing were connected in series and tested for leaks. This system was then enclosed within a glass container as shown in figure 4. One liter per minute of oxygen containing a constant concentration of methoxyflurane was passed through it; inflow and outflow concentrations were monitored. At the same time, the space surrounding the rubber goods within the container was ventilated with a 1-liter per minute flow of pure oxygen. As

it escaped, this gas was analyzed for methoxyflurane.

After six hours, 11.2 per cent of insufflated methoxyflurane remained in the rubber, while 5.6 per cent had passed through by diffusion. After 22 hours, 6.3 per cent remained in the rubber, and a further 6.3 per cent was lost by diffusion.

### Discussion

The clinical implications of the enormous solubility of methoxyflurane in rubber are as follows:

(1) When methoxyflurane is first introduced into an anesthetic system, rapid loss to rubber retards the rise in its concentration. Though this drug has a high potency, this retarding effect, combined with its low vapor pressure and its high blood and tissue solubility,<sup>2</sup> prolong the induction of anesthesia. Induction may be speeded by using a high-output vaporizer or by placing a vaporizer within the circle on the inspiratory side.

(2) Desaturation of tissues in a patient at the end of anesthesia is slowed by re-entry of anesthetic from rubber parts of the system. During washout flows of 3 liters per minute, this re-entry maintains concentrations above 25 per cent of the initial equilibration concentration, for 20 minutes. At lower washout flows, inspired concentrations are greater. Effective reduction of concentration within a saturated rubber system can only be achieved with high flow rates (greater than 8 liters per minute). Re-entry of methoxyflurane from rubber may explain in part the prolonged recovery times seen with this agent. Even though no anesthetic is administered from a vaporizer for the last 30-60 minutes of an operation, the patient may not begin to eliminate methoxyflurane until disconnected from the system.

(3) The use of equipment saturated with methoxyflurane may add to an anesthetic administered subsequently. If, for example, closed cyclopropane were used, there would be significant additive effects from released methoxyflurane. Unexpectedly profound levels of anesthetic might result.

### Summary

The Ostwald partition coefficient for methoxyflurane in rubber was found to be 742 at 25° C. Uptake by the rubber components of an anesthetic system was shown to significantly retard the rise of methoxyflurane concentration within it. The release of methoxyflurane from saturated rubber components was shown to retard the fall of methoxyflurane concentration in the circle during washout. (These effects were greatest at low flow rates.) In clinical use, these factors contribute to slow induction and emergence. Release of methoxyflurane may significantly affect a subsequent anesthetic for which the same rubber goods are used.

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### References

1. Eger, E. I., II, Larson, C. P., Jr., and Severinghaus, J. W.: Solubility of halothane in rubber, soda lime, and various plastics, *ANESTHESIOLOGY* 23: 356, 1962.
2. Eger, E. I., II, and Shargel, R.: Solubility of methoxyflurane in human blood and tissue homogenates, *ANESTHESIOLOGY* 24: 625, 1963.
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**NEONATAL RESUSCITATION** In many maternity units, provision for resuscitating babies is hopelessly inadequate. The necessary equipment is lacking, ineffective and even dangerous measures are used, and the available staff is either untrained or inexperienced in modern methods. The equipment available should include suction tips, nasal catheters, endotracheal tubes, laryngoscopes, airways, ampules of appropriate drugs, and oxygen. With the use of this equipment, a preplanned program of neonatal resuscitation applying tracheal intubation and intermittent positive pressure inflation of lungs can be accomplished. (*Barrie, H.: Resuscitation of the Newborn, Lancet* 1: 650 (Mar. 23) 1963.)

**PLETHYSMOGRAPH** Use of a plethysmograph method to measure the thoracic gas volume of the lungs of newborn infants suggest the following conclusions. (1) Thoracic gas volume and total lung capacity are established within a few hours after birth in normal infants and increase a little during subsequent neonatal life. (2) There is a significant decrease in thoracic gas volume and total lung capacity in newborn infants with hyaline membrane syndrome. (3) This decrease in volume occurs early in the course of the disease. (4) Compliance and total lung capacity or thoracic gas volume are related in sick infants. (5) Trapped gas may exist in the lungs of some normal newborn infants. (*Auld, P. A. M., and others: Measurement of Thoracic Gas Volume in the Newborn Infant, J. Clin. Invest.* 42: 476 (Apr.) 1963.)

**SUCCINYLBOLINE** Severe cardiovascular collapse followed intravenous injection of succinylcholine in two patients. In one case cardiac arrest required internal cardiac massage. Children seem to be particularly susceptible, probably because of their lower cholinesterase activity. Cardiovascular collapse is believed to be due to a cholinergic reaction to succinylcholine, which can be lessened or prevented by higher doses of belladonna drugs. (*Meyer, E., and Huegin, W.: Circulatory Reactions to Succinylcholine, Der Anaesthetist* 12: 65 (Mar.) 1963.)