This Week's Citation Classic™

CC/NUMBER 43
OCTOBER 22, 1984

Larson C P, Jr., Eger E I & Severinghaus J W. The solubility of halothane in blood and tissue homogenates. *Anesthesiology* **23**:349-55, 1962.
[Dept. Anesthesiology and Cardiovascular Res. Inst., Univ. California Med. Ctr., San Francisco, CA]

Partition coefficients of halothane in blood and body tissue homogenates of man and cattle were determined by equilibrating these substances with known volumes of liquid halothane in closed flasks and analyzing the halothane concentration of the overlying gas phase by infrared analysis. Whole blood coefficient was 2.3 and tissue coefficients ranged from 3.6 for kidney to 8.3 for cerebral white matter. [The *SCI*® indicates that this paper has been cited in over 150 publications since 1962.]

C. Philip Larson, Jr.
Department of Anesthesia
Stanford University School of Medicine
Stanford, CA 94305

July 20, 1984

"Shortly after I began my research fellowship in July 1960, my research advisers, John Severinghaus and Ted Eger, suggested that I attempt to determine the partition coefficient for halothane in blood and other tissues. They thought that it could be done by equilibrating halothane between liquid and gas phases and then measuring the concentration in the gas phase using the newly developed infrared halothane analyzer. From their clinical experience with halothane, they thought that the blood/gas value of 3.6 reported by Raventós[1] might be too high.

"The experiments were conducted in John's laboratory in the Cardiovascular Research Institute at the University of California at San Francisco. I added accurately measured volumes of liquid halothane to known volumes of outdated human blood in sealed flasks and measured the concentration of halothane in the gas phase using a calibrated infrared halothane analyzer. To my surprise, I obtained a consistent value of 2.3 ± 0.1 SD. Using the same experimental model, tissue/gas solubility coefficients were determined for homogenized specimens of whole brain, gray and white matter, liver, kidney, muscle, and fat. Halothane proved to be 1.5 to 3.5 times as soluble in tissues (excluding fat) as in blood, a finding that was at variance with the value of 1.0 that had consistently been found for all other anesthetics studied.

"Because the volume of human tissues from autopsy sources was limited, officials at the Swift and Co. meat-packing plant agreed to donate beef blood and other tissues. On several occasions, I made a 'tissue run' to the south San Francisco butchering plant where I collected buckets of fresh blood, brain, and other tissues immediately after the animal had been killed. An untimely automobile accident on a San Francisco street would certainly have caused an unwelcome sensation.

"Prior to publication of our results, I was invited to present them at a conference on uptake and distribution of anesthetic agents held in New York City under the auspices of the National Research Council and the New York Academy of Medicine. However, of even greater concern, William A.M. Duncan, a coauthor with Raventós of the first publication on the pharmacokinetics of halothane anesthesia,[2] was in attendance. I was certain that Duncan would challenge my findings and produce data to prove me wrong. My fears were unfounded. Duncan, a gentleman throughout, stated that he was able to confirm our findings using a somewhat different methodology.[3]

"In examining why this publication has become a *Citation Classic*, three explanations are possible. First, halothane holds a premier position as the most versatile anesthetic in anesthesia. It has been studied more extensively than any prior anesthetic. Since its physical properties, including solubility, determine its pharmacological actions, frequent reference is made to solubility coefficients. Second, accurate solubility values are essential to predict uptake and distribution characteristics of an anesthetic, so any studies of pharmacokinetics of halothane refer to our solubility studies. Third, and perhaps most important, the technique that we used for determining halothane solubility was a major departure from the traditional extraction methods that had been used for determining the solubility of halothane and other anesthetics. Virtually all studies of the solubility of volatile anesthetics developed after halothane was synthesized have used the technique that we introduced. Our technique has been used recently to determine the solubility of the reductive metabolites of halothane."[4]

1. **Raventós J.** The action of fluothane—a new volatile anaesthetic. *Brit. J. Pharmacol.* **11**:394-410, 1956. (Cited 300 times since 1956.)
2. **Duncan W A M & Raventós J.** The pharmacokinetics of halothane (fluothane) anaesthesia. *Brit. J. Anaesth.* **31**:302-15, 1959. (Cited 90 times since 1959.)
3. **Larson C P, Jr.** Solubility and partition coefficients. (Papper E M & Kitz R J, eds.) *Uptake and distribution of anesthetic agents*. New York: McGraw-Hill, 1963. p. 5-19.
4. **Denson D D & Ford D J.** How reactive are the reductive metabolites of halothane? *Anesthesiology* **51**:S243, 1979.