pregnancy in man but the rôle of the 2 diseases in pregnancy is the same and such differences as exist may well be of a generic order. In like manner, there are some differences between the spontaneous and experimental intoxications in the rabbit which may be attributable to the fact that in one case the disease is of gradual evolution while in the other it is precipitated abruptly. The evidence so far obtained is sufficient to warrant further investigations of the possible rôle of the pituitary in the etiology of the human disorder.

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Rate of Elimination of Divinyl Ether.

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We have found that the rate of elimination of divinyl ether from an anesthetized dog does not follow the formula first developed for acetone by Widmark[1,2] $C_t = C_o.e^{-V\lambda t/m}$ where C_o is the original concentration of volatile substance in the blood; C_t the concentration after time t; t, the time; V, the alveolar ventilation; λ, the partition coefficient between air and blood; and m, the "reduced volume". A mathematical treatment has also been applied to the elimination of ethyl ether by Henderson and Haggard.[3,4] Widmark's simplified formula is $C_t = C_o.e^{-\alpha t}$ where α is the "elimination constant" and which in the logarithmic form becomes $\log C_t = \log C_o - \alpha t$. If, therefore, the rate of elimination of a substance which follows this formula is plotted on semi-logarithmic paper with $\log C_t$ plotted against t a straight line should be obtained the slope of which is determined by the elimination constant.

Curve I in Fig. 1 is the typical straight line obtained for ethyl ether with dogs based on the data of Haggard.[4] Curve II, also from Haggard's data, shows the effect of administering carbon dioxide on the rate of elimination by increasing the alveolar ventilation. At point (A) on the curve the administration of carbon dioxide was stopped and the subsequent portion is essentially parallel to Curve I.

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1 Widmark, E. P., *Acta Med. Scandinavica*, 1919, **52**, 57.

2 Winterstein, H., *Die Narcose*, Berlin, 1926, p. 220.

3 Henderson, Y., and Haggard, H. W., *Noxious Gases*, New York, 1927

4 Haggard, H. W., *J. Biol. Chem.*, 1924, **59**, 753.

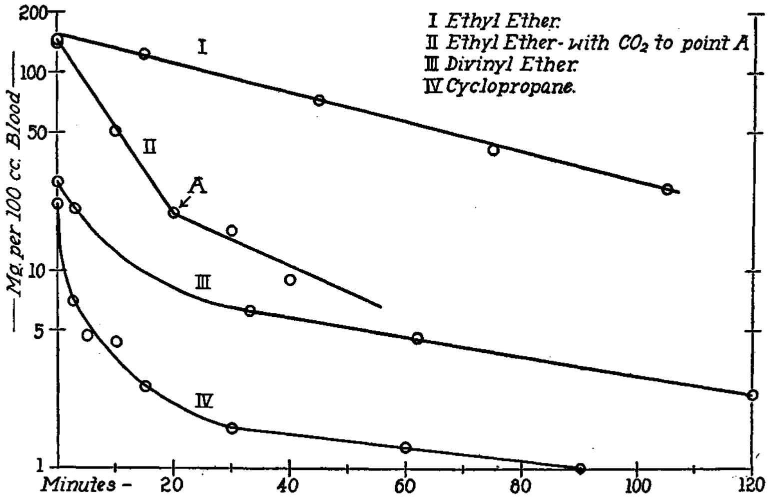

FIG. 1.
Elimination of anesthetics from the blood of anesthetized dogs. Concentration of anesthetic in the blood is plotted on a logarithmic scale against the time in minutes.

Curve III shows a result obtained in our laboratory for divinyl ether (the technic of these blood concentration studies will be published elsewhere). This curve does not become a straight line until after 30 minutes and hence we must infer that some new factor is in operation which is not accounted for by the Widmark expression. Comparing divinyl ether with ethyl ether, it will be seen that the initial rate of elimination of divinyl ether is much greater corresponding to the earlier recovery of consciousness from divinyl ether anesthesia. This could be predicted from the Widmark formula since for divinyl ether λ^1 is 0.76[5] and for ethyl ether 0.065.[4]† Later, however, the rate of elimination of divinyl ether is slower and finally is even less than that of ethyl ether.

The elimination of cyclopropane is shown by Curve IV, which is based on the recent data of Robbins.[6] The remarks made for divinyl ether also apply here. When the results of Nicloux[7] on chloroform are plotted in this way a straight line is obtained over a period of 6½ hours subsequent to the first 30 minutes period. The fact that

[5] Ruigh, Wm. L., and Erickson, A. E., in press.

† Widmark's λ is the reciprocal of λ the Ostwald solubility expression which is numerically equal to the partition coefficient water-air. The differences in values obtained with blood are disregarded.

[6] Robbins, B. H., *Anesthesia and Analgesia*, 1937, **16**, 93.

[7] Cited in Meyer-Gottlieb, *Experimental Pharmakologie*, 8th edition, Berlin, 1933, p. 123.

the elimination of chloroform follows an exponential formula after 30 minutes was first noted by Widmark.[1]

The explanation of this behavior, we believe, can be reached by a consideration of the influence of the lipoid-blood or as actually measured, the olive oil-water partition coefficients of the anesthetics. The partition coefficients of acetone, 0.23,[8] and ether, 3.2,[9] are of a different order of magnitude from those of cyclopropane, 34.2,[9] divinyl ether, 41.3,[5] and chloroform, 100.[10] The overall rate of elimination of the first class, represented by ethyl ether, and the *initial* rate of the second class of lipotropic anesthetics is undoubtedly governed by the factors of alveolar ventilation, pulmonary blood flow and the air-water distribution ratio as stressed by Widmark and Haggard. We believe that the final rate of elimination, after an initial 30 minutes' transition period of the second class of anesthetics, is determined primarily by the slow rate of diffusion of the substance from the masses of depot fat in the body. Such fat has a poor blood supply and acts as a reservoir for the anesthetic. The elimination again follows a logarithmic curve but the causative factors differ from those mentioned earlier.

This concept of the mechanism of elimination is in entire harmony with the observation of Seevers, Meek, Rovenstine and Stiles,[11] that large quantities of cyclopropane are slowly "lost" in closed spirometer experiments with dogs. Their preferred explanation lay in the high lipoid solubility of this gas although they mention the possibility of destruction by metabolism and slow diffusion through the skin.

In conclusion it may be pointed out that with an anesthetic having a high oil-water partition coefficient, the final rate of elimination is governed by 2 practical factors—the duration of the anesthesia and the relative amount of fat present in the body. With the lipotropic anesthetics, chloroform, divinyl ether or cyclopropane, the prolonged administration to obese persons should be undertaken with caution if the long-continued presence of residual anesthetic in the patient be considered undesirable.

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8 *International Critical Tables*, III, p. 425.

9 Orcutt, F. S., and Seevers, M. H., *J. Pharm. and Exp. Therap.*, 1937, **59**, 206.

10 Lindenburg, A., *Compt. rend. soc. biol.*, 1933, **112**, 1524.

11 Seevers, M. H., Meek, W. J., Rovenstine, E. A., and Stiles, J. A., *J. Pharm. and Exp. Therap.*, 1934, **51**, 1.