FLUOTHANE

To the Editor.—In his last paper published in your journal (A., 19: 38, 1957). Dr. Krantz and his collaborators state that the therapeutic ratio of Fluothane (Halothane) is significantly smaller than that of diethyl ether when examined on several animal species. In all my experiments, however, which have included mice, rats, rabbits, dogs and monkeys, I found that the therapeutic ratio of this compound was about twice that of ether, irrespective of the animal species used in the experiment.

I think that the differences between Dr. Krantz's results and my own can be explained by differences in the methods used in the two laboratories for the examination of volatile anesthetics and in the criteria used for the assessment of their action.

When I started my researches on the anaesthetic properties of fluorinated hydrocarbons I tried the methods described by Dr. Krantz in his article on cyclopropane methyl ether (J. Pharmacol. & Exper. Therap. 69: 207, 1940) but I found that, in my hands, they were not altogether reliable and so I developed the techniques described in my original paper on Fluothane (British J. Pharmacol. Chemotherp. 11: 394, 1956) that permit of the exposure of animals to vapour mixtures of known concentration.

My own objections to Dr. Krantz's methods are as follows:

(1) *Methods for Experiments on Mice.*—In the two methods described by him and his collaborators (J. Pharmacol. & Exper. Therap. 69: 207, 1940 and THIS JOURNAL 18: 250, 1957) mice are placed in an exposure chamber which has some cotton wool or some soda lime in the bottom of it, and the agent is introduced either as a liquid or as a vapor (1957). Because of the uncontrollable variables in these methods, i.e., the body-volume of the mice, the volume of the cotton wool, or that of the soda lime, which together represent a fair percentage of the total volume of the chamber, it is impossible to calculate with accuracy the final concentration of anaesthetic in the chamber.

A further objection is that with this method the vapours of volatile compounds, as their density is greater than that of air, will tend to accumulate at the bottom of the chamber forming a layer of high concentration of agent which will mix with the air only very slowly, by diffusion, and by the turbulence created by the movements of the mice.

By my method, on the other hand, the mice are exposed to mixtures of vapor of known concentration that are passed through the chamber at a constant rate of 1 or 2 liters/minute. In this way the animals are exposed to homogeneous mixtures without running the risk of moving into pockets of mixtures of different concentrations.

(2) In my experiments I have assessed the anaesthetic and lethal concentration (v/v per cent) after 30 minutes exposure instead of the 5 minutes recommended by Dr. Krantz. With these longer times of exposure, I think that in most cases the concentration of anaesthetic in the blood will then be in equilibrium with that of the mixture in the chamber and give a better idea of the therapeutic ratio under test.

I feel also that with Dr. Krantz's methods one may use larger amounts of anaesthetic than I do and that some of the deaths recorded after 5 minutes are perhaps due to side effects of the agents.

(3) With the long inhalation periods that I use it is possible to find out if the compounds have some delayed toxicity that probably would not be apparent after the short anaesthesias recommended by Dr. Krantz. For instance, with this method it is impossible to demonstrate the delayed toxic action of chloroform, but its toxic action on the liver can be seen with regularity if the animals are kept in the chamber for 1 hour.

(4) *Methods for Experiments on Dogs and Monkeys.*—In the method used by me for these experiments the animals inhale vapor mixtures of known concentrations (v/v per cent) in an open circuit until anaesthesia and respiratory arrest are obtained. Also by changes in the concentration of agent one can measure with accuracy the induction concentration that will produce surgical anaesthesia in 5 minutes, the concentration that will maintain anaesthesia, and the concentration that will kill the animals by

respiratory arrest in 2 hours. I calculate the therapeutic ratio from the lethal and maintenance concentrations.

By the method of the Baltimore workers, the animals are anaesthetized with a closed-circuit apparatus (McKesson). Two centimeters of the agent are injected under the mask at the start of the experiment and are followed by further doses of 0.5 cc. each every minute. In this method, as in any closed-circuit technique, it is practically impossible to know what the concentration of the agent is, and this is even more difficult to determine if one injects the material under the mask because it will tend to create very high concentrations around the nostrils of the animal. Also the rate of evaporation and therefore the concentration of the agent, may be influenced by the respiratory minute volume and tend to increase when the respiration is depressed.

That it is possible in this way to produce very high and toxic concentrations of Fluothane is shown by the fact that Dr. Krantz found some difficulty in restoring spontaneous respiration in some of his animals and others could not be revived after respiratory arrest. In my own experiments, working with concentrations of between 4 and 6 per cent I have NEVER lost an animal because of apnoea. In every case spontaneous respiratory movements returned after a few minutes of artifical respiration with air. The danger of the inhalation of high concentrations of Fluothane in closed-circuit has been shown in the fatality reported some months ago by Dr. Foster in a letter to the Lancet, which started a very interesting correspondence among the anaesthetists of this country.

(5) Most anaesthetists are now using anaesthetics with a higher degree of accuracy than they did some years ago, measuring the concentrations of their agents in terms of v/v per cent; it is surprising therefore, to find that Dr. Krantz calculates the anaesthetic and lethal doses of the agents in his his experiments on large animals in terms of cc./kg. body weight. Undoubtedly this is a handy laboratory yardstick, but it has several disadvantages: firstly, it can be confusing for the practical anaesthetist; secondly, it cannot be used with gases, making their comparison with volatile agents somewhat difficult and thirdly, as the volume of vapor produced by 1 cc. of liquid is different for each compound and depends on its M.W. and S.G., it is impossible to know the concentration of the inhaled mixture, even if the volume of O_2 in the closed-circuit is kept constant and the liquid volatilizes completely after each successive administration.

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To the Editor.—Dr. Raventós has very kindly sent us a copy of his letter to ANESTHESIOLOGY in which he has criticized the work of Krantz *et al.* on Fluothane. To his specific comments we wish to reply as follows:

(1) In our article (Krantz, Park, Truitt and Ling, ANESTHESIOLOGY 10: 38 (Jan.-Feb.) 1958) we state specifically: "We did not find this agent (Fluothane) to have an anesthetic index twice that of diethyl ether, as did Raventós, but found it to be only slightly safer than chloroform when measured under our experimental conditions and methods of calculations." This we believe to be true.

We have no apologies to make for the method employed, using mice in the partially evacuated anesthetic chamber. The agent in a vapor form was introduced at the top of the chamber, and being heavier than air diffuses throughout the volume of the vessel in accordance with the concept of the kinetic theory of gases, and has been confirmed by equal induction times of animals stationed at different levels in the anesthetic jar. We are not willing to accept the criticism that it will rapidly settle as a layer at the bottom of the container. The volumes occupied by the soda lime and mouse are constant errors of negligible magnitude and do not vitiate comparative results.

Thus by our method the anesthetic index of diethyl ether was found to be 2.67 (AD_{50} 6.08 and LD_{50} 16.20). Mörch, Ayerigg and Berger (J. Pharm. Exp. Therap. 117: 184, 1956) found 6 and 18 volumes per cent of diethyl ether for the anesthetic and lethal concentrations respectively, giving an index of 3.00. However, Raventós found