LABORATORY OBSERVATIONS WITH FLUOTHANE

C. R. Stephen, M.D., G. Margolis, M.D.
L. W. Fabian, M.D., M. Bourgeois-Gavardin, M.D.

One of the pressing needs in clinical anesthesia is a nonflammable and nonexplosive compound which can be administered in an easily reversible and safe manner to patients. No potent inhalation drug which fulfills these requisites is at present in common usage. With compounds administered intravenously the anesthesiologist is handicapped to a certain extent by lack of control of concentration in the blood stream and slowness in regression of anesthetic action.

The use of fluorinated compounds for anesthesia has been suggested previously. In 1946 Robbins (1) reported on the anesthetic activity of 46 fluorinated hydrocarbons and indicated that four compounds were worthy of further study. Krantz and coworkers in 1953 (2) examined a number of such drugs and suggested that trifluoroethylvinyl ether (Fluoromar) might be of clinical interest. However, this compound is flammable in anesthetic concentrations. More recently, in the laboratories of Imperial Chemical Industries, England, a screening of fluorinated hydrocarbons produced a nonflammable volatile liquid, a simple ethane derivative, which possessed potent anesthetic properties. Fluothane, $CF_3CHBrCl$, boils at 50.2 C., well within the range of practical usefulness, and has a vapor pressure of 243 mm. of mercury at 20 C. and an oil-water solubility ratio of 330. The compound is stable at room temperatures when kept in light-resistant bottles and apparently does not metabolize within the body. The original pharmacologic investigations with this drug were carried out by Raventós (3). It is the purpose of this paper to delineate further some of the pharmacologic properties of this compound, with particular reference to the clinical interests of the anesthesiologist.

Methods of Investigation

A total of 120 acute and chronic experiments were performed in dogs and monkeys. Venous and arterial cutdowns and endotracheal intubation with a cuffed tube facilitated measurement of vital functions. An eight channel Grass electroencephalographic recorder was used to produce permanent records. The electrocardiogram was monitored via needle electrodes and the electroencephalogram via fronto-occipital electrodes specially designed to be inserted directly into the cranial bones. By means of an appropriate demodulator and a Statham transducer the arterial blood pressure was recorded directly. Respiratory

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patterns were visualized in a similar manner with the aid of either a pneumotachograph placed in continuity with the endotracheal tube or a pneumograph fastened about the chest wall.

Several methods were employed to vaporize Fluothane. The boiling point is sufficiently low that administration by the simple "open-drop on a mask" technique was feasible. Employing this method in the dog or monkey, unconsciousness was produced within one to two minutes when 30 to 40 drops per minute were vaporized. A second stage of anesthesia, marked by struggling and irregular respirations, usually ensued and lasted for one to one and a half minutes. Then respirations became regular and machine-like in action, denoting entrance into the third or "surgical" stage of anesthesia. At this point the lash reflex was no longer present, but the corneal reflex was active. If administration of Fluothane was continued unabated, in three or four minutes respirations became shallow and slow in rate, with marked intercostal paresis. In another two or three minutes, respiratory arrest occurred. By slowing the rate of administration to 10 or 12 drops per minute when surgical anesthesia was reached, anesthesia could be maintained in an even plane. The absence of salivary secretions during induction and maintenance was remarkable. Recovery from anesthesia was equally as rapid as induction.

In these experiments the majority of animals were anesthetized by means of a standard anesthetic gas machine (Foregger). Preliminary anesthesia for preparation of the animal was obtained with intravenous thiamylal (Surital), 15 to 20 mg. per kilogram of body weight. An ultra-short-acting barbiturate was employed without premedicant drugs so that minimal residual effect would be present during experiments. Active movement of the extremities, or bucking and coughing on the endotracheal tube, denoting minimal activity of thiamylal, were usually present before Fluothane was administered. With the gas machine oxygen was utilized as the vaporizing medium. A partial rebreathing or nonrebreathing technique was employed. Fluothane was vaporized either by allowing oxygen in varying amounts to bubble through it in the Copper Kettle or by permitting oxygen in varying amounts to pass over the surface of Fluothane placed in a specially designed vaporizer. It was found that concentrations of 1.5 to 2.5 per cent Fluothane were required for induction of anesthesia, whereas maintenance requirements varied between 0.5 and 1.5 per cent in the inhaled atmosphere.

Vapor Concentrations

Vapor concentrations of Fluothane were determined by collecting in a breathing bag the mixture of gas and vapor resulting from the partial or complete passage of 4 liters of oxygen over or through liquid Fluothane during a 60 second period. This volume was immediately liberated into previously evacuated pyrex vapor traps which were submerged in liquid nitrogen. Immediate solidification of the total Fluo-

thane vapor content occurred. The oxygen was pumped off by re-evacuation of the traps. Following the removal of the pyrex traps from the nitrogen flasks, liquefaction of the Fluothane occurred as the trap warmed to existing room temperature. Measurement of the liquid volume at room temperature and pressure and the substitution of these values into the general gas law equation provided the data necessary for calculating the percentage of vapor in the total volume of gas and vapor collected in the original sample.

An example follows in which 1.2 cc. of liquid was obtained by extraction from 4 liters of oxygen. Room temperature and pressure were 24 C. and 756 mm. of mercury, respectively.

Mol. Wt. Fluothane 197.39
Liquid density Fluothane 1.86 Gm./cc. at STP
Vapor density Fluothane 8.83 Gm./liter at STP. (This value is derived by application of the Avagadro principle where: $\frac{\text{Mol Wt. (Gm.)}}{22.4} = \text{Vapor Density.}$)

$\frac{1{,}000}{\text{vapor density}} \times \text{liquid density} = \text{No. cc. vapor produced by 1 cc. liquid at STP}$

$\frac{1{,}000}{8.83} \times 1.86 = 211 \text{ cc. vapor/cc. liquid at STP}$

$$V_2 = V_1 \times \frac{T_2}{T_1} \times \frac{P_1}{P_2}$$

where V_2 = the amount of vapor produced by total evaporation of liquid yield
V_1 = the product of the volume of liquid obtained in the extraction and the no. cc. vapor-produced by 1 cc. liquid at STP
T_2 = Room temperature in Kelvin degrees (R.T. + 273°)
T_1 = 273° K (0° C.)
P_1 = Barometric pressure during analysis
P_2 = 760 mm. Hg.

$$V_2 = 1.2 \times 211 \times \frac{273 + 24}{273} \times \frac{760}{756}$$

$V_2 = 1.2 \times 226$
$V_2 = 271.2$ cc. vapor
Vol. O_2 = 4,000 cc.
Total gas plus vapor = 4271.2 cc.

$$\text{Per cent vapor} = \frac{271.2}{4271.2} \times 100 = 6.34 \text{ per cent Fluothane}$$

This procedure was utilized for all appropriate settings of the vaporizer control mechanism on the special vaporizers and various flowmeter readings on the Copper Kettle of the Foregger gas machine used in this study.

Chemical Reaction

An important factor in clinical administration is the reactivity of an anesthetic drug with soda lime or baralyme. The production or catalysis of a decomposition reaction involving dehalogenation of saturated fluorocarbons by the carbon dioxide absorbents in clinical use is difficult because of the stability of these fluorinated compounds. Fusion with metallic sodium will occur usually only under conditions of increased temperature (up to 1,300 C.) and pressure (up to 20 pounds per square inch).

However, to eliminate the possibility of toxicity during clinical use, extractions of vapor from baralyme were made essentially as described above, but while maintaining a closed system and a flow of gas initiated by means of a Palmer pump. The resulting liquid was tested for free halogen using the thiocyanate titration method of Volhard (4). In addition the density and boiling point of the liquid yield were checked. These tests revealed no evidence of decomposition of Fluothane even after 14 days of constant vapor contact with baralyme which was heated periodically to 50 C. during the exposure.

Pharmacologic Reactions

The most striking factor in the administration of Fluothane was the rapidity and potency of its action. By the same virtue, the quick reversibility of its effects was remarkable. To what extent these properties are dependent on the high oil-water solubility ratio, it is difficult to say. Regardless of the explanation, this drug must be administered with careful control of concentration.

Figures 1 and 2 illustrate the effects of Fluothane in the dog on respiration, cardiovascular action and the electroencephalogram. During the induction excitement stage, respirations were irregular and associated with breath-holding. The over-all effect seemed to be one of stimulation. During the third stage of anesthesia, a progressive diminution of respiratory exchange or ventilation occurred. Intercostal paresis was noted first and was followed by intercostal paralysis and lessened diaphragmatic activity. Complete cessation of respiratory activity occurred several minutes before cardiac failure. The progressive respiratory depression was somewhat similar to that noted with increasing concentrations of ether vapor, except that with Fluothane it developed much more rapidly. The rate of respiration was also slowed with increasing depth of anesthesia. The diminution in tidal volume and the slow rate of respiration in combination produced a respiratory acidosis (fig. 1). With discontinuance of Fluothane, ventilation returned to normal within a few minutes, unless a toxic overdosage of the drug had been administered.

The cardiovascular actions of Fluothane in the dog and monkey were relatively consistent. A moderate bradycardia occurred with increasing depth of anesthesia (fig. 1). Of greater importance was the

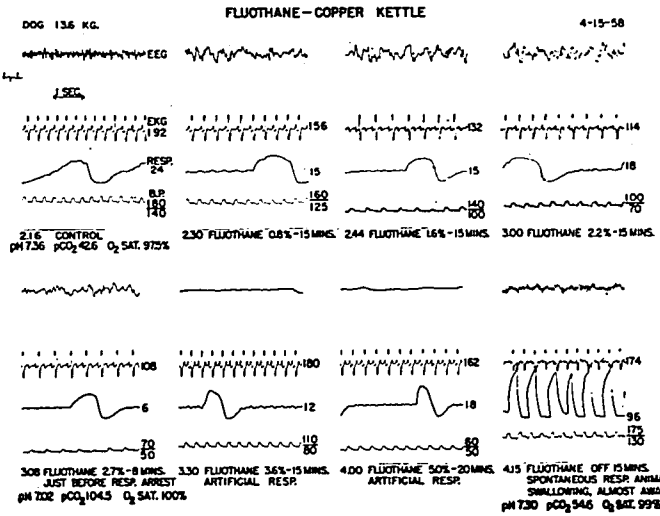

FIG. 1. Recordings from Grass electroencephalograph. From above downwards: electroencephalogram (50 μv. standardization at extreme upper left), electrocardiogram, respiration (pneumotachograph), arterial blood pressure. (Paper speed, 30 mm. per second.) To show effects of increasing concentrations of Fluothane and rapid recovery from anesthesia. Note at 3.08, respiratory acidosis secondary to inadequate ventilation; at 3.30, beneficial effect of artificial respiration, and at 3.30, inactivity and flattening of electroencephalogram.

hypotension which was seen almost invariably with the onset of third stage anesthesia. The decrease in blood pressure was so consistent that the degree of hypotension could be considered a measure of the depth of anesthesia. When maintenance concentrations of Fluothane had been established, the blood pressure was maintained at a level somewhat lower than the control (20 to 40 mm. of mercury in the dog). A reduction in pulse pressure usually was associated with the hypotension.

Electrocardiographic arrhythmias were uncommon with Fluothane administration, but nodal rhythms and ventricular arrhythmias were occasionally observed in both dog and monkey. Usually these arrhythmias were associated with deep levels of anesthesia and they disappeared spontaneously when the Fluothane concentration was reduced. As noted also by Krantz *et al.* (5), in surgical planes of anesthesia inversion of the T wave was seen in some animals. However, the T wave frequently reverted to normal with artificial respiration (fig. 1). With overdosage of the drug and in terminal stages, the electrocardiogram showed a complete heart block (fig. 2). However, even in such terminal stages, provided normal ventilation had been preserved arti-

ficially, recovery of the animal was possible sometimes by doing nothing more than discontinuing the Fluothane and maintaining ventilation (fig. 2).

The electroencephalogram in dogs showed a gradual reduction in electrical activity with increasing concentrations of the drug (figs. 1, 2 and 3). In surgical planes of anesthesia slow, high voltage waves were predominant. In deep planes of anesthesia electroencephalographic activity was abolished almost completely (figs. 1 and 2). Return to a control level of activity was rapid following discontinuance of the drug.

As mentioned previously, the lack of salivary secretions was remarkable in these unpremedicated animals. When induction was accomplished with Fluothane only, laryngospasm was not observed. About three minutes after the establishment of third stage anesthesia, relaxation of the jaw was present and the reflexes of the pharynx and larynx so obtunded that an endotracheal tube could be inserted without reaction.

Compatibility with Drugs

In clinical anesthesia, where several drugs may be introduced into the blood stream simultaneously, it is important to determine the influence of two or more compounds acting together. Figure 3 illustrates the action of several compounds on the vital functions of a dog anesthetized with Fluothane.

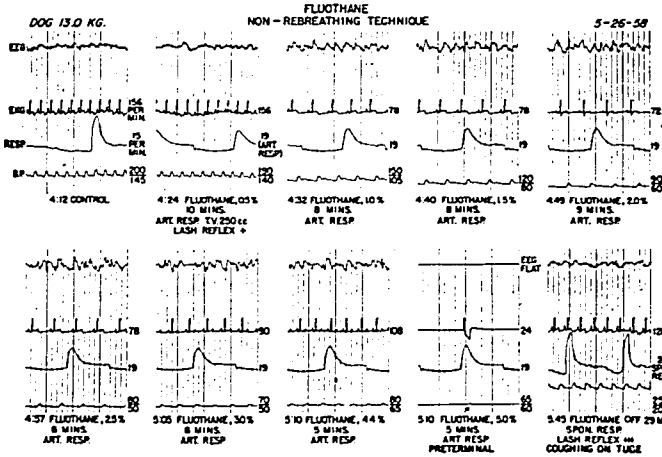

Fig. 2. Recordings from Grass electroencephalograph (standardization and paper speed as in fig. 1). To show effect of increasing concentrations of Fluothane on vital functions. Note early institution of artificial ventilation (Palmer pump) to avoid effects of hypoventilation and recovery of animal despite profound myocardial and cerebral depression at 5:10.

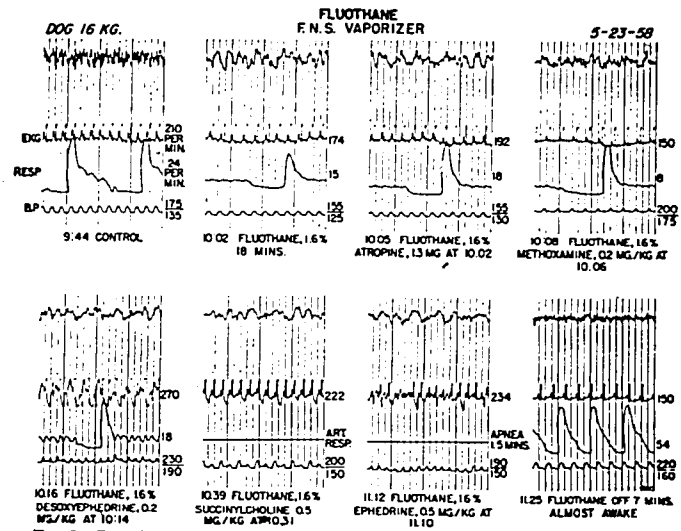

FIG. 3. Recordings from Grass electroencephalograph (standardization and paper speed as in fig. 1). To show reaction of Fluothane with atropine, methoxamine, desoxyephedrine, succinylcholine, and ephedrine.

The anticholinergic drugs, atropine and Antrenyl, produced only a moderate increase in pulse rate. The vasopressors, methoxamine and phenylephrine, produced a substantial rise in blood pressure without any alteration in cardiac rhythm except a relative bradycardia. On the other hand, desoxyephedrine, ephedrine, norepinephrine and epinephrine, in addition to their hypertensive action, produced ventricular arrhythmias. Figure 4 shows marked arrhythmias associated with norepinephrine and ventricular fibrillation induced with epinephrine. Like cyclopropane and trichlorethylene, Fluothane sensitizes the conduction mechanism of the heart to vasopressor drugs which have a direct stimulating action on the heart. Epinephrine appears to be the most dangerous of these compounds.

The effect of combining Fluothane and muscle relaxant drugs was interesting. The depolarizing compound, succinylcholine, exerted no unusual action in the presence of Fluothane. In the dog an intravenous injection of succinylcholine, 0.5 mg. per kilogram of body weight, produced apnea for the anticipated 10 to 15 minutes, with return to normal spontaneous respirations in a further 8 to 10 minutes (fig. 3). No alterations in blood pressure were noted during the period of effective relaxant action. The arrhythmia seen in figure 3 was due to the prior administration of desoxyephedrine.

When anesthetized with Fluothane, the reaction of the dog to the injection of *d*-tubocurarine chloride was variable. The muscle relaxant action, as determined by respiratory paresis, was of the expected degree when *d*-tubocurarine, 0.15 mg. per kilogram of body weight, was injected, although the effect persisted longer under Fluothane than under thiamylal. The variability occurred with the cardiovascular changes. In some dogs the administration of *d*-tubocurarine chloride was associated with a profound hypotension, whereas in other animals little if any disturbance of the blood pressure occurred. Further work concerning the relationship between these two drugs is in progress and will be reported more completely in the future.

Chronic Toxicity Studies

In order to determine the effects of prolonged Fluothane administration, seven dogs and two monkeys were anesthetized to surgical planes of narcosis three hours a day for five consecutive days. Liver function as determined by the Bromsulphalein test was investigated on the third and fifth days, while kidney function with the phenolsulfonphthalein test was estimated on the second and fourth days in the dogs. At the conclusion of the final anesthetization, the animals were sacrificed rapidly to avoid terminal hypoxia and autopsies were performed

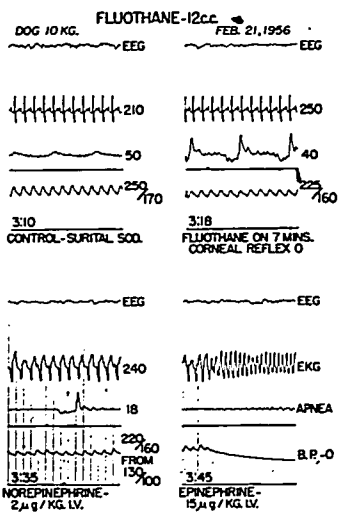

Fig. 4. Recordings from Grass electroencephalograph (standardization and paper speed as in fig. 1). To show electrocardiographic arrhythmias associated with norepinephrine and epinephrine.

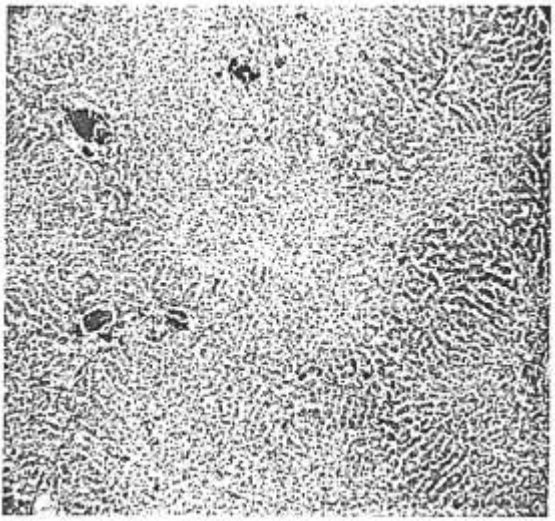

FIG. 5. Section of liver of dog following chronic Fluothane administration. Note the centrilobular fatty alteration and glycogen depletion. (Magnification × 80.)

immediately. Gross and histologic studies were made on all the major organs and tissues, including heart, lungs, liver, kidneys, pancreas, adrenals, spleen, lymph nodes, bone marrow, gastrointestinal tract, striated muscles, central nervous system and peripheral nerves.

Employing a similar protocol, 6 dogs were anesthetized on five consecutive days for three hours daily with chloroform and then sacrificed. The same procedures were repeated in six dogs employing ethyl ether. The three drugs were vaporized by means of oxygen, utilizing a nonrebreathing technique. Particular efforts were made to avoid hypoxia or carbon dioxide retention.

The animals which were anesthetized repeatedly with Fluothane and ethyl ether maintained a good appetite and appeared to be in good health. Both liver and renal function tests remained within normal limits for each animal. On the other hand, the chloroform animals became progressively more ill with each day of anesthesia. Two animals were found dead in their cages on the fourth day of the experiment. Bromsulphalein dye retention became markedly abnormal after the second day of anesthesia in each dog.

The anatomic studies of the Fluothane treated animals revealed no gross pathologic changes attributable to the anesthetic drug. At a histologic level mild to moderate hepatic changes and minimal renal

alterations were found. The characteristic hepatic lesion consisted of a centrilobular fatty alteration and glycogen depletion. This change at its mildest involved a small central zone, and spread peripherally in more severe injuries to involve the central two-thirds of the liver lobules (fig. 5). In the most advanced lesions scattered necrotic parenchymal cells were present. Even in the absence of recognizable necrobiotic changes, mitotic activity of the parenchymal cells was increased. The kidney alteration consisted of a minimal and variable dilatation of the proximal convoluted tubules, without evidence of necrosis or degenerative changes. These alterations were of the same order of severity as those described by Raventós (3), and are considered to be of doubtful significance.

The anatomic studies of the chloroform treated animals demonstrated a hepatic injury of severe degree. At a gross level this organ appeared tawny yellow and swollen, and in some livers the centrilobular zones were reddened and collapsed. Histologic sections revealed a severe fatty infiltration involving essentially all of the liver lobule. In two of the six animals there was a broad zone of necrosis affecting the central zone of the lobule (fig. 6). Mitotic activity was considerably enhanced in the peripheral zone of the lobule. No other significant anatomic changes were observed.

In the animals anesthetized with ethyl ether, the only observable alteration occurred in the liver. This change consisted of a slight centrilobular glycogen depletion and a minimal fatty change. These alterations were of less severity than in the Fluothane treated animals. No recognizable necrobiotic changes or nuclear alterations were observed (fig. 7).

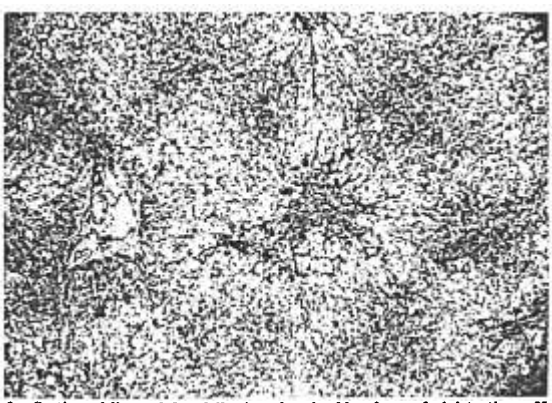

FIG. 6. Section of liver of dog following chronic chloroform administration. Note broad zone of necrosis about central zone of lobule, surrounded by severe fatty infiltration. (Magnification × 80.)

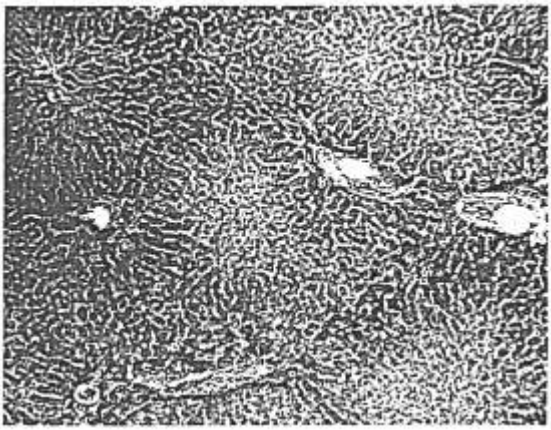

FIG. 7. Section of liver of dog following chronic ethyl ether administration. Note minimal glycogen depletion and fatty change about central lobule. (Magnification × 80.)

These comparative studies indicate that Fluothane, like chloroform, is capable of producing liver injury. The toxicity of this drug, however, is of a much lower order than that of chloroform. On the other hand it appears that Fluothane has more hepatotoxic effect than ethyl ether. More exacting studies comparing the relative hepatotoxic effect of these and other anesthetic agents are now under way.

DISCUSSION

The rapidly developing respiratory depression and associated respiratory acidosis noted in animals with increasing concentrations of Fluothane have been recorded also in humans (6). However, in man the respiratory rate is said to increase in surgical planes, apparently in an attempt to compensate for the diminished tidal volume, whereas in animals the rate of respiration slows in combination with a reduction in tidal volume.

The hypotension associated with the administration of Fluothane has been ascribed to a ganglionic-blocking action (3) to a central depression of vasomotor mechanisms (7), or to a direct depression of the myocardium (8). The rapid return of blood pressure to normal levels as concentrations of the drug are reduced would indicate the lack of any permanent damage to the cardiovascular system. In our experimental work, when overdosage of drug was induced purposely, respiratory failure always preceded cardiac failure by a recognizable margin.

Electrocardiographic arrhythmias with Fluothane are rare in animals until toxic concentrations are reached. However, alterations in

the electrical pattern, with particular reference to inversion of the T wave, have been noted in the literature (5). These changes also were seen in this study, but reverted to normal with the institution of adequate ventilation (fig. 1), or failed to appear in a significant manner when hypoventilation was avoided (fig. 2). It is possible that such alterations are due to factors other than Fluothane *per se*.

Hepatotoxicity might be expected in a highly halogenated compound like Fluothane. However, with relatively prolonged exposure of animals to chloroform or Fluothane under similar circumstances, the degree to which the liver was spared with exposure to Fluothane, when compared with chloroform, was remarkable. In the only published report of a histological examination of the liver of man following repeated exposures to Fluothane, no evidence of hepatotoxicity was noted (9).

Summary

Fluothane is a potent, volatile anesthetic compound allowing rapid induction and early return of consciousness following administration to animals. Depth of anesthesia can be altered with several respirations. Progressive respiratory depression occurs in third stage anesthesia, due in animals to a reduction in tidal volume associated with a slowing of the rate of respiration. Respiratory arrest precedes cardiac arrest by a recognizable margin. The drug produces moderate to severe hypotension in surgical planes of anesthesia. In toxic concentrations complete heart block precedes cardiac asystole. In moderate concentrations Fluothane sensitizes the myocardium to epinephrine and other vasopressor compounds which have a direct cardiac stimulant action. A mild hepatotoxic action has been observed with Fluothane in chronic toxicity studies, but the degree of liver injury has been of a much lower order than that observed with chloroform.

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