RESPIRATORY AND CARDIOVASCULAR EFFECTS
OF FLUOTHANE IN DOGS

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A new anesthetic agent, Fluothane (1) (halothane; 1,1,1-trifluoro-2,2-
bromoethylmethane) is beginning to be used extensively in this country
and abroad. Fluothane is a colorless, volatile anesthetic with a boiling
point of 50.2 C. at 760 mm. of mercury, and a molecular weight of 197.39
(2). It is neither flammable nor explosive when mixed with oxygen in
any concentration. In the presence of light, moisture, and air, it theo-
retically will decompose to form volatile halide acids. This decom-
position, however, can be prevented by storing the liquid in amber
colored bottles in dark places. The addition of 0.01 per cent thymol
stabilizes Fluothane to the decomposing action of light (3). It is
completely stable in the presence of 5 per cent carbon dioxide and soda
lime at 50 C. Fluothane has a pleasant odor.

Over 5,000 patients in the United States have received Fluothane
anesthesia, and at least that many in England and Canada. There has
been very little basic animal research on Fluothane, however, besides
the original work of Raventós in England (2). .

There have been several clinical reports of respiratory and cardio-
vascular depressions with the induction and use of Fluothane (4, 5).
Some investigators have noted a tachypnea with Fluothane anesthesia
in patients who were unpremedicated (6, 7). Some found that small
doses of intravenous opiates such as meperidine or morphine would
abolish the tachypnea and produce slow deep respirations with ade-
quate ventilation (7, 8). Others found this same result but declared
that the minute volume was inadequate and assisted respirations were
necessary (3, 9). Still others reported no change in the respiration.
Many different vaporizers were used by these various investigators
and often the exact concentration of Fluothane in the inspired air was
unknown.

Most investigators reported some hypotension with the induction
of Fluothane anesthesia (4, 9). This ranged from a mild (10 to 20 mm.
of mercury) hypotension to very severe cardiovascular collapse (6).
Again the vaporizers were varied, and in many instances severe cardio-
vascular collapse could have been due to a very high percentage (per-
haps 4 per cent or more) of Fluothane in the inspired air, although this
was not measured.

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Many anesthesiologists reported that the hypotension and bradycardia produced by Fluothane anesthesia could be reversed by the intravenous administration of atropine (8, 10, 11). Another said that bradycardia with Fluothane was not common (4). Indeed, some claimed that the hypotension could be prevented almost completely by adequate atropinization beforehand. In order to do this, the usual premedication of about 0.6 mg. atropine, about an hour before anesthesia, and a second dose from one to ten minutes before induction, was given. Other anesthesiologists noticed severe hypotension even with atropinization (4, 6).

Some observers reported severe arrhythmias with Fluothane, including ventricular tachycardia (6, 12). Careful analysis of the cases in which the more severe arrhythmias were produced, revealed that there were many other factors present. These included such things as inadequate airway, inadequate ventilation, and large doses (500 mg. or more) of thiopental (13). These factors made evaluation of these arrhythmias difficult. Most investigators who monitored the concentration of Fluothane in the inspired air carefully found a surprisingly small incidence of cardiac arrhythmias due to Fluothane (5, 14).

In an effort to unravel some of these discrepancies and to investigate the basic physiology of Fluothane, the following experiment was set up.

**METHOD**

Nine mongrel dogs in good health, unselected as to sex, and weighing from 8.6 to 12.7 kg. were used.

The following physiological parameters were measured:

*Respiratory Pattern.*—Respirations were monitored using an endotracheal nonrebreathing system, with the respiratory gases passing through a wire screen flow meter of the author’s design (fig. 1). The slight pressure drop across the screen was led to a P-97 Statham differential pressure transducer and displayed on a Sanborn rectilinear recorder. The wire screen flow meter produced negligible physiological resistance and recorded accurately fast changes in the respiratory pattern (15).

In order to evaluate the respiratory effect of Fluothane, the dogs were allowed to breathe spontaneously. To eliminate as far as possible the effects of other drugs, the dogs breathed room air. Since the maximum concentration of Fluothane in the inspired air was very small (1 to 3 per cent) it was believed that production of the added complication of hypoxic hypoxia by addition of Fluothane was practically nil.

The tidal air of at least 3 breaths was measured by planimetry of the flow meter records and averaged. The respiratory rate was counted from the same record. The minute volume was calculated by multiplying the respiratory rate by the tidal air. The control minute volume was that taken during the “awake” period at the beginning of
a run. The minute volumes and respiratory rates are reported as ratios of "experimental" divided by "control."

Respiratory Blood Chemistry Determinations.—The blood samples were drawn as described below and two or more determinations made for each blood chemistry for each run. The hydrogen ion concentrations were measured with a Cambridge electronic pH meter. Whenever possible the pH meter was maintained at the same body temperature as the dog. In some instances, where this was not possible, a correction for temperature according to Rosenthal (16) was applied. Duplicate readings could be read in most instances as close as ± 0.002 pH unit. The overall accuracy of the method, however, was con-

![Diagram of a wirescreen flowmeter](image)

Fig. 1. A diagrammatic cross-section of the wire screen flowmeter used to measure respiration in these experiments. It is essentially the same as the Lilly flowmeter except for the heating element which is kept at about 40 °C to prevent moisture condensation on the wire screen and, the standard Foregger anesthetic connections.

sidered to be ± 0.02 pH unit. The oxygen content, carbon dioxide content, and oxygen capacity were analysed directly by the method of Van Slyke and Neill. From the oxygen capacity and oxygen content, the per cent of arterial oxygen saturation and the hemoglobin were calculated. Hematocrits by the micro method of McGovern, Jones, and Steinburg (17) and Jones (18) were done on the same blood samples as an additional check on the hemoglobin.

Cardiovascular System.—Blood pressure was monitored by means of a 2 mm. inside-diameter polyethylene catheter inserted through the femoral artery into the abdominal aorta. This catheter was attached to a Statham P-23AA pressure transducer and the system filled with heparinized saline. The pickup from this transducer was also dis-
played on the Sanborn recorder. By means of a three-way stopcock proximal to the pressure transducer, arterial blood samples could be drawn from time to time in the following manner:

Five milliliters of blood were withdrawn, immediately prior to the sampling, in a separate syringe, in order to remove any saline proximal to the stopcock and to insure sampling of fresh aortic arterial blood. This 5 ml. of blood was replaced after the sampling was completed. Ten milliliters of actual blood sample was then drawn into a siliconized syringe containing 0.2 ml. of heparin (2 mg.). Care was taken to avoid introduction of any air bubbles, and the syringe was mercury sealed, gently inverted several times for mixing, and immediately analyzed.

Lead II of the electrocardiogram was recorded continuously. The pulse rate was counted from the blood pressure and electrocardiographic records.

Electroencephalogram.—The fronto-occipital electroencephalogram was also monitored continuously on the Sanborn recorder.

Urine.—A polyethylene catheter was placed in the urinary bladder and the urine output recorded intermittently.

**Procedure**

The dog was anesthetized with a sleeping dose of thiopental and intubated immediately. It was then transferred from the kennels to the laboratory where the endotracheal tube was attached to a non-rebreathing system and light Fluothane anesthesia administered during the surgical procedures. (The total dose of thiopental used ranged from 25 to 40 mg./kg.) The electroencephalographic and electrocardiographic electrodes were placed immediately, and the femoral artery and vein in one leg were exposed and cannulated. Minimal amounts of heparinized saline were used to keep the cannulas free from clots. Through the femoral vein an intravenous drip of 5 per cent glucose in water was maintained, enough to produce an adequate and constant urinary output. This was found to be necessary since, despite the best precautions, some dogs arrived in the laboratory in a dehydrated condition.

When the dog was no longer receiving any stimulation, it was allowed to awaken as much as possible, as long as it did not move enough to disturb the electrodes and catheters. At this time, clinically and by electroencephalographic evidence, the dog was awake and all effects of the last dose of thiopental (which had been administered, on the average, seventy-seven minutes before) had almost completely worn off.

In the earlier experiments before the Flupette vaporizer was available, a Heidbrink Trilene bottle, without wick, was used. The Fluothane in the Heidbrink bottle was carefully weighed before and after each run. From the average minute volume, as recorded by the wire
screen flow meter, the average concentration of Fluothane in the inspired air could then be calculated. There were three major sources of error in this technique: error in weighing, particularly owing to evaporation of Fluothane while being weighed; variations in minute volumes from moment to moment, and possible leaks or regurgitation in the nonrebreathing system. These errors were reduced as much as possible by rapid weighing and a correction for evaporation, by allowing ample time for the dog to arrive at a reasonably steady state, and by inserting two Stephen-Slater valve leaflets in the system. Large variations in concentration were noted with the Heidbrink vaporizer. For example, setting 10 gave percentages from 1.52 to 3.89 per cent at different times.

After the dog was stabilized, nearly awake, Fluothane was introduced at a fixed setting. The induction was then observed until the dog appeared to be in a steady state. This procedure was repeated, giving several inductions for each of the 9 dogs. Respiratory patterns, blood pressures, electrocardiogram and electroencephalogram were recorded during the induction as described above. Some of the dogs received atropine prior to some of the inductions.

Two steady states were observed in each dog, called "light" and "deep," corresponding approximately to plane 1 and plane 3 of stage III anesthesia. Measurements of all of the above-mentioned parameters were taken, including arterial blood samples, after at least twenty-five minutes under a fixed concentration of Fluothane were allowed to elapse. These steady states were achieved by maintaining the inspired Fluothane concentration the same for at least twenty-five minutes. During the last ten minutes of this period there were no changes in respiration, blood pressure, heart rate, urine output, or electroencephalogram. These levels were then considered as nearly physiologically steady states as could be obtained under given planes of anesthesia.

After this part of the experiment was finished, the Fluothane was turned to a lethal setting and the mechanism of the dog's death was observed.

Results

Each dog was made to serve as his own control, in order to reduce the error of large individual variation. Many values, therefore, are expressed as ratios. A ratio is the experimental value divided by the control ("awake") value.

Induction.—Figure 2 shows an example of a typical induction of a dog under Fluothane anesthesia. From table 1 and figure 3 it may be seen that there was a large individual variation between dogs. After five minutes of induction with the Heidbrink Trilene vaporizer at 8 or above, the average heart rate decreased about 10 per cent. During the same time, there was a gradual decrease in blood pressure
### TABLE 1

**Heart Rate and Blood Pressure in 9 Dogs During 25 Fluothane Inductions**

<table>
<thead>
<tr>
<th></th>
<th>Before Induction</th>
<th>With Fluothane</th>
<th>30 Seconds</th>
<th>1 Minute</th>
<th>2 Minutes</th>
<th>5 Minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>152 ± 34*</td>
<td>1.05 ± .14</td>
<td>1.01 ± .15</td>
<td>.95 ± .15</td>
<td>.89 ± .13</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>163 ± 18*</td>
<td>.88 ± .08</td>
<td>.83 ± .11</td>
<td>.77 ± .12</td>
<td>.72 ± .10</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>98 ± 4*</td>
<td>.84 ± .14</td>
<td>.78 ± .16</td>
<td>.70 ± .17</td>
<td>.64 ± .15</td>
<td></td>
</tr>
</tbody>
</table>

None of the dogs received atropine. Ratio indicates experimental divided by control. Asterisk indicates actual value, not a ratio. (See fig. 3).

of about 30 per cent. It is interesting to note that the diastolic pressure decreased more than the systolic pressure, giving a net increase in the pulse pressure.

In the 4 dogs that were given an average of 0.053 mg./kg. of atropine intravenously an average of twenty-four minutes before induction

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**Fig. 2.** An actual record of a Fluothane induction. The top line indicates the standard lead II electrocardiogram, and the second line represents aortic arterial blood pressure. The third line represents respiratory flow with inspiration up and expiration down. The numbers on the graphs indicate tidal air in milliliters. The fourth, or bottom line, represents frontal-occipital electroencephalogram. The arrow at 2:23 p.m. indicates when Fluothane was turned on. Note change in paper speed about forty seconds before Fluothane was turned on, and again about sixty seconds after Fluothane was turned on. The right hand strip indicates the same things three minutes later.
(table 2 and fig. 4), there was an even greater decrease in heart rate, systolic blood pressure, and diastolic blood pressure than in the non-atropinized animals. Again there was a similar increase in pulse pressure.

Only one arrhythmia of any type was seen in a total of 43 inductions in 9 dogs. This consisted of an extrasystole ten seconds and another extrasystole fifteen seconds in one dog after the Fluothane was turned on. This dog was not atropinized. The Heidbrink Trilene vaporizer setting in this instance was at 10.

![Graph](image)

**Fig. 3.** This graph represents 25 Fluothane inductions in 9 dogs without atropine. Ratio indicates experimental divided by control. Vertical lines indicate standard deviation. (See table 1.)

*Steady State.*—As can be seen from table 3, both systolic and diastolic pressures were depressed about 15 per cent under light Fluothane anesthesia. Under deep Fluothane anesthesia the depression was between 40 and 50 per cent with a slightly greater depression of the diastolic pressure giving rise to a slightly increased pulse pressure.

Under light Fluothane anesthesia the respiratory rate was essentially unchanged. Under deep Fluothane, however, the respiratory
Fig. 4. This graph represents 17 Fluothane inductions in 4 dogs. Seven inductions after atropinization. Ratio indicates experimental divided by control. (See table 2).

### TABLE 2

**Heart Rate and Blood Pressure During 17 Fluothane Inductions in 4 Dogs**

<table>
<thead>
<tr>
<th></th>
<th>Before Induction</th>
<th>With Fluothane</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>30 Seconds</td>
</tr>
<tr>
<td>Heart rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 Not atropinized</td>
<td>150 ± 39*</td>
<td>1.03 ± .11</td>
</tr>
<tr>
<td>7 Atropinized</td>
<td>.95 ± .15</td>
<td>.96 ± .17</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 Not atropinized</td>
<td>150 ± 12*</td>
<td>.89 ± .06</td>
</tr>
<tr>
<td>7 Atropinized</td>
<td>.97 ± .15</td>
<td>.80 ± .03</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 Not atropinized</td>
<td>101 ± 8*</td>
<td>.86 ± .11</td>
</tr>
<tr>
<td>7 Atropinized</td>
<td>.86 ± .11</td>
<td>.72 ± .00</td>
</tr>
</tbody>
</table>

Ten of these inductions were done before atropine was administered. Seven were done after atropine administration. The average dose of atropine was 0.053 mg./kg., intravenously. The average time that elapsed between atropinization and induction was twenty-four minutes. Ratio indicates experimental divided by control. Asterisk indicates actual value, not a ratio. (See fig. 4.)
TABLE 3
BLOOD PRESSURE, RESPIRATORY RATE AND MINUTE VOLUME RATIOS IN
7 DOGS DURING FLUOTHANE ANESTHESIA

<table>
<thead>
<tr>
<th>Dog Number</th>
<th>Blood Pressure Ratios</th>
<th>Respiratory Rate Ratios</th>
<th>Minute Volume Ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Light Anesthesia</td>
<td>Deep Anesthesia</td>
<td>Light Anesthesia</td>
</tr>
<tr>
<td>1</td>
<td>.87/.95</td>
<td>.53/.46</td>
<td>1.01</td>
</tr>
<tr>
<td>2</td>
<td>1.00/1.00</td>
<td>.54/.44</td>
<td>1.00</td>
</tr>
<tr>
<td>3</td>
<td>.82/.77</td>
<td>.69/.53</td>
<td>.80</td>
</tr>
<tr>
<td>4</td>
<td>.87/.89</td>
<td>.42/.35</td>
<td>.92</td>
</tr>
<tr>
<td>5</td>
<td>.60/.61</td>
<td>.67/.58</td>
<td>.59</td>
</tr>
<tr>
<td>6</td>
<td>.87/.90</td>
<td>.80/.80</td>
<td>1.19</td>
</tr>
<tr>
<td>7</td>
<td>.93/.78</td>
<td>.59/.43</td>
<td>1.25</td>
</tr>
<tr>
<td>Average</td>
<td>.85/.84</td>
<td>.61/.54</td>
<td>.97</td>
</tr>
</tbody>
</table>

Ratios indicate experimental divided by control (awake). Determinations made at the same time as those in Table 4.

rate was decreased almost 40 per cent. The minute volume under light fluothane was decreased about 15 per cent, indicating that the depression was primarily in the tidal air since the rate was unchanged. Under deep fluothane anesthesia the minute volume was decreased 60 per cent of the control value, indicating again that the depression was more in the tidal air than in the rate.

Table 4 shows the respiratory blood chemistry determinations drawn at the same time that the above-mentioned blood pressures and respiratory rate and minute volumes were measured. Under light fluothane anesthesia, where the minute volume was decreased about 15 per cent, the average arterial pH was 7.31, the carbon dioxide con-

TABLE 4
CARBON DIOXIDE CONTENT, OXYGEN SATURATION AND pH OF ARTERIAL BLOOD
DURING FLUOTHANE ANESTHESIA IN 7 DOGS

<table>
<thead>
<tr>
<th>Dog Number</th>
<th>pH</th>
<th>CO₂ Content Volumes (per cent)</th>
<th>Oxygen Saturation (per cent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.49</td>
<td>7.30</td>
<td>33</td>
</tr>
<tr>
<td>2</td>
<td>7.31</td>
<td>7.13</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>7.22</td>
<td>7.05</td>
<td>47</td>
</tr>
<tr>
<td>4</td>
<td>7.38</td>
<td>7.19</td>
<td>43</td>
</tr>
<tr>
<td>5</td>
<td>7.18</td>
<td>7.11</td>
<td>47</td>
</tr>
<tr>
<td>6</td>
<td>7.25</td>
<td>7.13</td>
<td>42</td>
</tr>
<tr>
<td>7</td>
<td>7.36</td>
<td>7.22</td>
<td>50</td>
</tr>
<tr>
<td>Average</td>
<td>7.31</td>
<td>7.16</td>
<td>44</td>
</tr>
</tbody>
</table>

All blood samples were from the abdominal aorta.
Fig. 5. Lethal concentration of Fluothane in dog. A, B, and C are excerpts from a continuous recording. The top line represents standard electrocardiogram lead II; the next line represents arterial blood pressure; the next line represents respiratory flow (inspiration up); and the bottom line represents fronto-occipital electroencephalogram. Note change in paper speed at thirty-one minutes and again at one hundred and twenty-four minutes.

At time zero Fluothane was turned on, 2 per cent; at twenty-six minutes this increased to 3 per cent. Note apnea, which occurred just before thirty-one minutes, after which only cardiac pulses are seen in the respiratory tracing. Except for the last few breaths, the main depression is in the respiratory tidal air, not in the rate. Note some activity of electroencephalogram even at apnea. The electrocardiogram shows only T-wave inversion. Just after excerpt A, Fluothane was turned off, artificial respiration was given, and the dog recovered. At time one hundred and twelve minutes Fluothane was turned on, 4 per cent. The inspiration just before the decrease in paper speed at one hundred and twenty-four minutes was the last spontaneous respiratory effort; at one hundred and twenty-four minutes and eight seconds, as can be seen by the timer artifact, the Fluothane was turned off. Artificial respiration was given but the blood pressure continued to decrease and spontaneous respirations did not return this time.

Excerpt C at one hundred and twenty-six minutes shows a slow heart rate with a relatively normal electrocardiogram. The blood pressure is negligible, there is no respiratory effort, and the electroencephalogram has become flat. Subsequent to this, the heart slowed to 15 beats per minute and then stopped at one hundred and twenty-nine minutes. At autopsy the heart appeared to have stopped in diastole.

tent was 44 volumes per cent and the oxygen saturation was 77 per cent. Under deep Fluothane anesthesia, when the minute volume was decreased 60 per cent of the control value, the average arterial pH was 7.16, the carbon dioxide content was 52 volumes per cent and the oxygen saturation was 43 per cent.

Lethal Dose.—When the Fluothane was administered in higher concentrations (from 2.6 to 4.0 per cent), in every case the respiratory depression became more and more severe, primarily in the tidal air, until respiratory arrest occurred. If the dogs were promptly re-
suscititated at the time of respiratory arrest, they returned to normal easily and quickly. Five dogs were reversibly taken to apnea a total of 12 times. If resuscitation was not attempted, the heart slowed and finally stopped in diastole. In no case were any arrhythmias seen until long after apnea. Although no detailed quantitative analyses were made of the terminal state, all of the dogs behaved in qualitatively the same manner. Figure 5 shows a reversible apneic state and a typical terminal state under Fluothane anesthesia.

Discussion

It is immediately apparent that Fluothane is a very potent anesthetic agent. For this reason the accurate monitoring of the percentage of Fluothane in the inspired gas is of the utmost importance. In later experiments where the Flutec vaporizer was used, much more consistent levels of anesthesia could be obtained.

It is of interest that the dogs in this series, as well as those in subsequent experiments, did not exhibit the severe hypotensions nor cardiac arrhythmias that were observed during induction by other investigators. The explanation for this is, perhaps, that the inductions reported here were slower and utilized a maximum of 2 to 3 per cent Fluothane in the inhaled vapors. It is strongly suggested that, in the clinical use of this drug, one does not try to take too much advantage of its potency by pushing extremely rapid inductions. The difference between three minutes and five to six minutes is very little, and perhaps many of the dangers reported with the use of this drug can be eliminated by taking a little more time with inductions. The use of any vaporizer incorporated in series in a circle filter circuit, particularly with the closed system, precludes the accurate monitoring of the concentration of this drug. This is because of the passage of the respiratory gases through the vaporizer more than once, adding to the concentration of the Fluothane each time, and the dependence of the gas flow (hence the vaporization rate of Fluothane) upon the minute volume of the patient. It is recommended, therefore, that Fluothane be used only in nonrebreathing systems or introduced through a T-connection into a circle system at a carefully monitored concentration. In this institution, the former technique is used for children and the latter technique for adults.

It should be emphasized that the authors believe that these “steady state” experiments show the relative effects of Fluothane anesthesia on the respiratory and cardiovascular systems much better than do rapidly changing states such as fast inductions. In the latter case, such rapid changes are occurring in electrolyte and reflex systems that it is very difficult to discern the direct effect of any drug on any particular mechanism. In these steady state experiments, however, the concentration of Fluothane and of all of the physiological parameters
were essentially unaltered from ten to twenty-five minutes. Therefore, a more accurate comparison of the above mentioned effects can be achieved, even though these may be "abnormal" or "compensated" steady states.

During the steady state experiments under light Fluothane anesthesia, only 1 dog showed a blood pressure ratio of less than 0.8 and the average was 0.85/0.84 (ratio indicates experimental/control). This average would be equivalent to a blood pressure drop from 120/80 to 100/70 and could be termed a "slight" to "moderate" hypotension. Under deep Fluothane anesthesia an average ratio of 0.63/0.56 would be equivalent to a blood pressure drop from 120/80 to 60/40. This could be termed a "moderate" to "severe" hypotension. It is interesting to note that atropine did not prevent the hypotension seen with Fluothane anesthesia in dogs.

If one looks at the minute volume, however, one will see that under light Fluothane anesthesia the ratio was the same as that of the blood pressure, whereas under deep Fluothane anesthesia the minute volume decrease was almost twice that of the blood pressure drop. This suggests a respiratory depression out of proportion to the cardiovascular depression.

It is interesting to note that the tidal air was decreased more than the respiratory rate was under Fluothane anesthesia. The respiratory center of a patient under Fluothane anesthesia might attempt to compensate for this decreased tidal air by producing an increased respiratory rate. If this was so, it would be in concurrence with other investigators who reported a relative tachypnea with Fluothane anesthesia in human patients. Since the principal depressant action of Fluothane seems to be respiratory rather than cardiovascular, it is suggested that Fluothane anesthesia can be reasonably safe if it is carried at light enough levels for the patient to breathe spontaneously, with an adequate minute volume. This point establishes the probability of great usefulness in anesthesia for neurosurgical procedures where spontaneous respiration is desirable and deep anesthesia is not needed.

As might be predicted from the changes in minute volume under light Fluothane anesthesia, a moderate respiratory acidosis with a pH of 7.31 and carbon dioxide content of 44 volumes per cent, and a borderline hypoxia with an oxygen saturation of 77 per cent was found. Again, as might be expected, under deep Fluothane anesthesia there was severe respiratory acidosis with a pH of 7.16 and a carbon dioxide content of 52 volumes per cent, and a severe hypoxia with an arterial oxygen saturation of 43 per cent. One might wonder if the carbon dioxide content should not be higher with this low a pH. It should be mentioned that this was a reasonably steady state and that the dogs' urinary output was remarkably good even under deep anesthesia. This might suggest an attempted compensation for the respiratory
acidosis by the kidney, or the exchange of other acid metabolites for the carbon dioxide. Perhaps a hypoxic stimulus or a direct effect of the excess carbon dioxide under deep Fluothane anesthesia counteracted, to some extent, the hypotensive effect of Fluothane. At any rate, it is surprising that the animals were able to maintain as good a blood pressure as they did with this degree of asphyxia, even if it was a compensated blood pressure.

It is believed that the mechanism of death in dogs under very deep Fluothane anesthesia was almost invariably respiratory in origin. As Fluothane anesthesia could be carried to respiratory arrest and the animal then resuscitated successfully, Fluothane is probably not as cardiotoxic as believed by some investigators. It is interesting to note that no severe arrhythmias occurred until long after respiratory arrest, even though severe asphyxia of the heart must have existed and the concentration of Fluothane in the heart must have been very high.

If Fluothane is as cardiotoxic as some observers believe, it is difficult to explain how an animal, such as dog 8 in figure 5 C, could have had complete apnea, no blood pressure, and still exhibit a relatively normal electrocardiogram. Perhaps one could say that the severe asphyxia with a concomitant electrolyte change protects against the cardiotoxicity of Fluothane, but the authors believe this very unlikely.

The possible mechanisms of hypotension under Fluothane anesthesia are quite complex. The findings, however, of (1) the hypotension not being effected by atropine, (2) only moderate hypotension occurring with severe asphyxia, (3) an increased pulse pressure existing with the hypotension, and (4) the lack of severe arrhythmias occurring even with asphyxia suggest a ganglionic blocking action rather than a cardiotoxic or even vasomotor center action of Fluothane.

Further work will be reported on the effect of Fluothane on the heart.

**Summary**

Fluothane, a potent, volatile, nonexplosive, anesthetic drug was administered to 9 dogs. Various physiologic parameters were measured with emphasis on the respiratory and cardiovascular systems.

Induction with Fluothane produced a moderate hypotension but a net increase in the pulse pressure. Atropine did not prevent the hypotension. Only one mild arrhythmia was seen in 43 inductions.

Under a steady state of Fluothane anesthesia, moderate hypotension was seen, the degree being proportional to the depth of anesthesia. No arrhythmias were seen. There was a respiratory depression proportional to the depth of the anesthesia. The depression of the tidal air was greater than the depression of the respiratory rate. There were profound alterations in the respiratory blood chemistries indicating asphyxia long before a moderate to severe hypotension occurred.

The dogs were intentionally deepened to the lethal level and died.
a respiratory death. After respirations ceased, the heart stopped in diastole. Prompt resuscitation after respiratory arrest would easily return the dog to normal. No severe arrhythmias were seen until long after respiratory arrest.

Fluothane is a safe anesthetic if used with extreme caution and meticulous attention to the respiratory and cardiovascular signs. In dogs, the prime depression is in the respiratory, not the cardiovascular system. Fluothane is extremely potent and the concentration of its vapors in the inspired air should be carefully monitored with an accurate vaporizer.

We wish to acknowledge the generous supply of Fluothane used in this study from Dr. John B. Jewell, Medical Director of Ayerst Laboratories, and to thank Dr. C. Ronald Stephen of Duke University for his kind help and inspiration in initiating this study.

REFERENCES