

# Narcotic Properties of Carbon Dioxide in the Dog

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$P_{aCO_2}$  ranging from 15 mm. to 95 mm. of mercury with arterial pH values from 7.64 to 7.10 had no effect on the minimum anesthetic concentration (MAC) for halothane in dogs.  $P_{aCO_2}$  levels above 95 mm. of mercury with arterial pH below 7.10 were progressively narcotic, and replaced the halothane required to maintain a constant depth of anesthesia. Anesthesia was achieved with  $CO_2$  alone at  $P_{aCO_2}$  of 245 mm. of mercury. The mechanism of  $CO_2$  narcosis correlated well ( $P > 0.05$ ) with the pH changes in the brain as measured in the cisternal CSF, and appeared to be independent of arterial pH,  $P_{aCO_2}$  and cerebrospinal fluid  $P_{CO_2}$ .

In 1820 the narcotic properties of  $CO_2$  were demonstrated by Hickman,<sup>1</sup> and a century later anesthesia was produced in man with 30 per cent  $CO_2$  and  $O_2$ .<sup>2</sup> However, muscle movements and convulsions precluded further investigations of  $CO_2$  as an anesthetic. Because wide fluctuations of  $CO_2$  may occur during general anesthesia and in respiratory failure, this study was undertaken to examine the narcotic effects of  $CO_2$  over a wide range of concentrations in the dog. The first question considered is how  $CO_2$  influences the concentration of an anesthetic gas (halothane) required to maintain a constant depth of anesthesia. Specifically, at what level does  $CO_2$  exert a narcotic effect as determined by a reduction in halothane requirement, and at what concentration does  $CO_2$  behave as an anesthetic as evidenced by its complete replace-

ment of halothane while maintaining the same constant depth of anesthesia? The second question is how does  $CO_2$  produce narcosis? Is it a result of the hydrogen ions produced, or is there an unexplained effect like that seen with the inert anesthetic gases? If  $CO_2$  acts by forming acid then the narcotic effect should correlate best with either arterial or cerebral pH. If it acts as an inert gas then the best correlation should be with  $P_{aCO_2}$ . To distinguish between these possibilities the  $P_{aCO_2}$  and pH were independently altered in blood and brain as represented by cisternal cerebrospinal fluid.<sup>3</sup>

## Methods

The technique of determining the minimum anesthetic concentration (MAC)<sup>4</sup> needed to prevent gross movement in response to a given painful stimulus was employed in all experiments. This provides a constant index of depth of anesthesia below which the animal moves and above which he does not move when stimulated in a standard manner. Although this method has not been previously used for  $CO_2$ , it is known to be stable over a wide range of arterial pH and  $P_{O_2}$ , and constant over periods of 8–10 hours.<sup>5</sup> With this technique one can observe the effect of a given concentration of  $CO_2$  upon a constant level of anesthesia.

Healthy mongrel dogs (15–25 kg.) were anesthetized with halothane and  $O_2$  by mask using a semi-closed circle system including a  $CO_2$  absorber. Their tracheas were intubated, and spontaneous breathing was recorded with an in circuit ventimeter connected to a Gilson polygraph. Catheters were inserted into the femoral artery and vein for blood pressure recording on the polygraph, and for blood gas analysis with appropriate  $p_{O_2}$ ,  $P_{CO_2}$  and  $P_{O_2}$  electrodes. All values were corrected for temperature measured with an esophageal thermometer and maintained between 36° and 38° C.

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Accepted for publication March 27, 1967. This work was supported in part by United States Public Health Service Grants HE 07946-03; CM-K3-17, 685; 5 ROI HE 07946; and 2 TOI GM 00063.

With the dog's head flexed, a plastic canula was placed through the foramen magnum into the cistern for sampling of cerebrospinal fluid. Approximately 2 ml. were drawn into an oiled glass syringe, the dead space rinsed first with cerebrospinal fluid, and immediately analyzed for pH and  $P_{CO_2}$ . In the final group of experiments cerebrospinal fluid bicarbonate was measured with the Van Slyke apparatus. If gross bleeding occurred in the subarachnoid space the sample was discarded and no cerebrospinal fluid was collected.

End-tidal  $CO_2$  and halothane were measured by sampling through respective infrared analyzers. The halothane analyzer was repeatedly calibrated against a cylinder of known halothane concentration. The cross-over effect of  $CO_2$  was determined and halothane concentrations corrected accordingly. Establishment of the MAC for halothane required testing the animals' response to 4 or 5 different concentrations, each level held constant for a minimum of 15 minutes before stimulation. Therefore when the initial or base line MAC was determined, the animal had equilibrated to the extent that expired halothane approached 80 per cent of the inspired.

Elevation of  $CO_2$  was achieved by removing the  $CO_2$  absorber and adding appropriate flows of  $CO_2$  from a cylinder to the halothane-oxygen mixture. Using end-tidal  $CO_2$  recording on the polygraph as a guide, each level of  $CO_2$  was held constant while the halothane MAC was determined. This required at least one hour at each level of  $CO_2$  and at the end of each period samples of arterial blood and cerebrospinal fluid were taken.

First, 12 dogs were anesthetized with halothane-oxygen as described, and after the initial halothane MAC, and analyses of arterial blood and cerebrospinal fluid they were hyper-ventilated to reduce the  $P_{ACO_2}$  until a new constant level was attained. After approximately 30 minutes of hypocapnia halothane MAC was determined and arterial blood and cerebrospinal fluid sampled. The dogs then breathed spontaneously until  $P_{ACO_2}$  and halothane MAC returned to the initial resting value. At that point  $CO_2$  was added to the halothane-oxygen mixture in increments of 50 to 75 mm. of mercury, each new level of  $CO_2$

maintained constant while halothane MAC, arterial blood, and cerebrospinal fluid measurements were made. In this manner  $CO_2$  was raised until the halothane MAC approached zero, that is, no movement occurred in response to stimulation when less than 0.15 per cent expired halothane could be detected. As the  $CO_2$ , not halothane, now maintained the same anesthetic depth (MAC) this represented  $CO_2$  narcosis. Because this level of  $CO_2$  narcosis could not exclude the influence of residual halothane, the following experiments were done without halothane.

Six dogs were given  $CO_2$  and  $O_2$ , approximately 50 per cent each, by mask using the same circle system without a  $CO_2$  absorber. When consciousness was lost, cyclopropane was added to the  $CO_2$ - $O_2$  mixture to facilitate tracheal intubation, as well as cisternal, arterial and venous catheterization. Cyclopropane was discontinued and anesthesia maintained with 30-40 per cent inspired  $CO_2$  for 30-60 minutes while cyclopropane was eliminated. At this level of  $CO_2$ , there was no response to painful stimuli, that is, there was complete  $CO_2$  narcosis. By lowering  $CO_2$  in 20-40 mm. of mercury decrement, and keeping each concentration a steady level for 15 minutes before testing, the  $CO_2$  MAC was established, at which time arterial blood and cerebrospinal fluid samples were taken.

To study the problem of how  $CO_2$  produced narcosis an attempt was made to reverse the acidosis that accompanies  $CO_2$  retention, by administering sodium bicarbonate. Six dogs anesthetized with halothane-oxygen were given increasing concentrations of  $CO_2$ , as in the first group of dogs. At the same time  $NaHCO_3$  (30 mEq./kg.) in a 0.1 per cent solution was given intravenously to maintain the arterial pH between 7.1 and 7.3 while the  $CO_2$  concentration was elevated to the point of  $CO_2$  anesthesia. Arterial blood and cerebrospinal fluid samples were taken at each point of elevated  $CO_2$ .

We then attempted to reproduce the changes in arterial pH observed with  $CO_2$  anesthesia without using  $CO_2$ . Eight dogs anesthetized with halothane-oxygen were given 0.3 N hydrochloric acid (30 mEq./kg) into the stomach via an inflated urinary catheter to prevent regurgitation. Over 3-4 hours, arterial

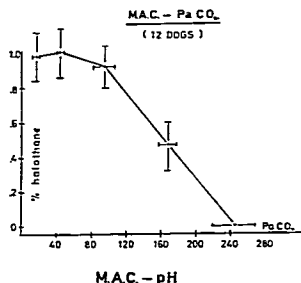


FIG. 1a. Halothane MAC and  $Pa_{CO_2}$  in the first 12 dogs anesthetized with halothane- $O_2$  and given progressively higher levels of  $CO_2$ . From  $Pa_{CO_2}$  15 mm. of mercury to 95 mm. of mercury the MAC is relatively constant, while above 95 mm. of mercury  $Pa_{CO_2}$  MAC declines progressively until the point of  $CO_2$  anesthesia, where MAC is zero. One standard deviation is indicated at each point.

pH fell to an average of 6.90 despite mild spontaneous respiratory compensation ( $Pa_{CO_2}$  fell from 44 to 35). At this point the halothane MAC and arterial blood gas analyses were determined.

Because the arterial acidosis with infusion of HCl had little or no effect on the halothane MAC it was thought that the principal effect of  $CO_2$  was exerted at the central nervous system, and it would be worthwhile to determine whether acid in the brain in the absence of elevated  $CO_2$  could produce narcosis. However, perfusion of the ventricles with acid is impractical as one doesn't know the mass of brain perfused and quantitative assessment of acidosis is impossible. On the other hand, by lowering the cerebrospinal fluid bicarbonate, which is the only buffer, one could expect a greater fall in pH for a given rise in  $P_{CO_2}$ . This can be done by hyperventilation as shown by Severinghaus *et al.*,<sup>6</sup> although the exact mechanism is unclear. Six additional dogs anesthetized with halothane-oxygen were hyperventilated vigorously ( $Pa_{CO_2}$  below 10 mm. of mercury) for 3-4 hours. Cerebrospinal fluid bicarbonate fell from a normal value of 23 mEq./liter to 13 mEq./liter. Simultaneously a small amount of 0.1 hydrochloric acid (8 mEq./liter) was given intravenously to provide a larger gradient for reducing cerebro-

spinal fluid bicarbonate. Hyperventilation was then abruptly terminated, and  $CO_2$  added to the halothane-oxygen mixture in a step-like fashion until the point of complete  $CO_2$  anesthesia was attained. This point could then be compared with the level of  $CO_2$  anesthesia in the first group of dogs whose cerebrospinal fluid bicarbonate was not lowered.

## Results

The first 12 dogs anesthetized with halothane-oxygen followed by increasing amounts of  $CO_2$  demonstrated no narcotic effect until a  $Pa_{CO_2}$  of 94 mm. of mercury was reached (fig. 1a). Nor was there any stimulant effect of  $CO_2$  which could have raised the halothane MAC. From  $Pa_{CO_2}$  of 94 mm. of mercury to 170 mm. of mercury there was a progressive decline in the halothane MAC as the halothane was replaced by  $CO_2$ . The effect of  $CO_2$  continued to a level of 245 mm. of mercury, when the halothane required for constant depth anesthesia was completely taken over by  $CO_2$ . This represented the point of  $CO_2$  anesthesia. Figure 1b shows the arterial and cerebrospinal fluid pH changes as  $Pa_{CO_2}$  ranged from 15 mm. to 245 mm. of mercury in the same experiments. There was no narcotic effect (no change in halothane MAC) until the pH in both blood and cerebrospinal fluid fell below 7.10. As the blood and brain became more acid there was an increasing narcotic effect of  $CO_2$  until the point

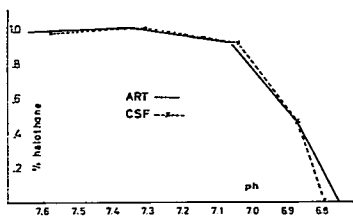


FIG. 1b. Halothane MAC and arterial pH (solid line) with CSF pH (broken line) in the same experiments shown in 1a. Each point corresponds to a  $Pa_{CO_2}$  level indicated in 1a. Note the stability of MAC over a wide range of pH. The decline in MAC (onset of narcosis) begins when the pH falls below 7.10 and reaches the point of  $CO_2$  anesthesia when the pH falls below 6.80.

of CO<sub>2</sub> anesthesia, when the arterial pH was 6.75 and the cerebrospinal fluid pH was 6.79.

In the 6 dogs anesthetized with CO<sub>2</sub> and O<sub>2</sub> the point of anesthesia was reached at an average PaCO<sub>2</sub> of 222 mm. of mercury. Figure 2 indicates the response of each dog to a standard painful stimulus at various levels of CO<sub>2</sub>. The mean value of the positive and negative responses was considered to be the CO<sub>2</sub> MAC for each animal. At this point average arterial pH was 6.76 and the average cerebrospinal fluid pH 6.79, identical to arterial and cerebrospinal fluid pH in the dogs anesthetized with halothane prior to CO<sub>2</sub> administration. This indicates that at the point of CO<sub>2</sub> anesthesia there was no influence of halothane in the first 12 dogs since any residual effect would have lowered the CO<sub>2</sub> level required to produce narcosis. On the contrary these dogs needed a slightly higher CO<sub>2</sub> concentration for anesthesia (245 mm. of mercury versus 222 mm. of mercury). This difference would disappear if dog no. 4, which convulsed while being anesthetized with CO<sub>2</sub>, were excluded.

In the 6 dogs given sodium bicarbonate attempting to reverse the CO<sub>2</sub> narcosis there was no change in the PaCO<sub>2</sub> required for CO<sub>2</sub> anesthesia (244 mm. of mercury). Despite the fact that arterial pH remained above 7.12 cerebrospinal fluid pH fell to 6.87 which demonstrated the well known blood brain

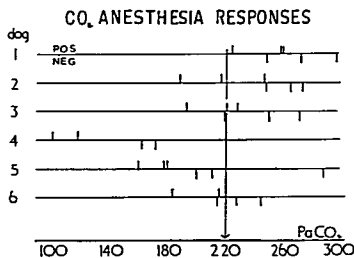


FIG. 2. The responses of each dog anesthetized with CO<sub>2</sub>-O<sub>2</sub> to painful stimulation and the PaCO<sub>2</sub> value at which the dog was tested. Positive responses are indicated by a vertical line above and negative responses by a vertical line below each horizontal. The mean CO<sub>2</sub> anesthesia value for all 6 dogs is shown by the arrow. Note the CO<sub>2</sub> MAC value for dog no. 4 is approximately 140 mm. of mercury.

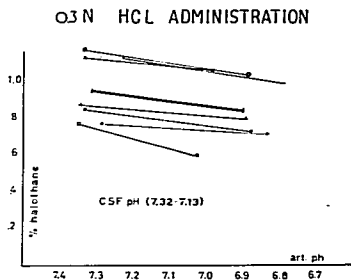


FIG. 3. Halothane MAC and arterial pH in 8 dogs anesthetized with halothane-O<sub>2</sub> and given HCl intragastrically. The heavy dark line indicates both one dog and the average of all the dogs. Note the small change in MAC over a large change in arterial pH. The CSF pH remained between 7.32 and 7.13.

barrier to the passage of ions.<sup>7</sup> Because of the bicarbonate induced diuresis in these dogs there was insufficient cerebrospinal fluid for analysis at the point of CO<sub>2</sub> anesthesia in 2 of the 6 animals. The data from these experiments are plotted in figures 5-8 on the curve labelled metabolic alkalosis.

In the 8 dogs given HCl, arterial pH fell to 6.90 while cerebrospinal fluid pH in 6 of 8 dogs ranged between 7.13 and 7.32. Figure 3 shows the values for each experiment where arterial pH is plotted against the halothane MAC. The mean data are indicated by the heavy line showing that the halothane MAC fell less than 15 per cent over the wide range of arterial pH (7.34 to 6.90). The average dose of HCl was 500 mM over 3-4 hours. One animal whose halothane MAC, declined 50 per cent developed pulmonary edema and expired. There were no serious effects observed in the other seven dogs.

The final experiments on 6 dogs whose cerebrospinal fluid bicarbonate was lowered by hyperventilation showed the most significant results. As seen in figure 4 the point of CO<sub>2</sub> anesthesia was reached at a PaCO<sub>2</sub> of 139 mm. of mercury compared with 245 mm. of mercury in the dogs whose cerebrospinal fluid bicarbonate was not lowered. The remarkable fact about this point of CO<sub>2</sub> narcosis is that the cerebrospinal fluid pH was 6.82, very close to 6.79 in the other group, despite the

## CENTRAL ACIDOSIS

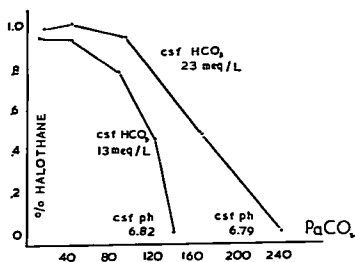


FIG. 4. Halothane MAC and  $P_{aCO_2}$  in group of 6 dogs anesthetized with halothane- $O_2$  and hyperventilated to reduce the CSF bicarbonate (13 mEq./liter), and the MAC- $P_{aCO_2}$  curve from the first 12 dogs whose CSF bicarbonate was normal (23 mEq./liter) before  $CO_2$  administration. Note at every level of  $CO_2$  a greater fall in MAC in the group with lowered CSF bicarbonate. At the point of  $CO_2$  anesthesia ( $P_{aCO_2}$  139 versus 245) however, the CSF pH was almost the same in both groups.

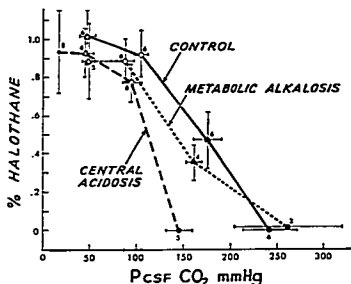
HALOTHANE REQUIREMENT VS.  $P_{CSF} CO_2$ 

FIG. 6. Halothane requirement (MAC) for anesthesia and increasing CSF  $P_{CO_2}$  in same animal groups as in figure 5. Curves and points are labeled the same as in figure 1. Note wide variation of CSF  $P_{CO_2}$  at zero halothane ( $CO_2$  anesthesia).

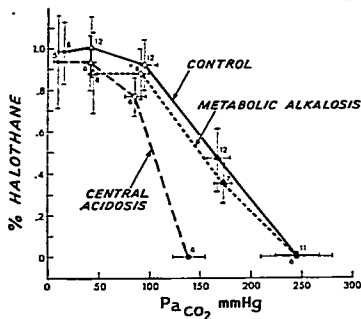
HALOTHANE REQUIREMENT VS.  $P_{aCO_2}$ 

FIG. 5. Halothane requirement (MAC) with increasing  $P_{aCO_2}$ . Number of dogs is given beside each point. Solid line (control group), dotted line (metabolic alkalosis group), dashed line (central acidosis group). Comparable points in each group are denoted by: • Hypocapnia ( $P_{aCO_2}$  < 15 mm. of mercury),  $\Delta$  normocapnia ( $P_{aCO_2}$  43 mm. of mercury),  $\circ$  hypercapnia ( $P_{aCO_2}$  94 mm. of mercury),  $\blacktriangle$  hypercapnia ( $P_{aCO_2}$  170 mm. of mercury), and  $\bullet$  zero halothane requirement where anesthesia is due to  $CO_2$  only. Note wide difference in  $P_{aCO_2}$  values at point of zero halothane ( $CO_2$  anesthesia).

difference in  $P_{aCO_2}$ . Figures 5-8 compare arterial pH,  $P_{CO_2}$ , cerebrospinal fluid pH and  $P_{CO_2}$  in this group labelled as central acidosis, with the first 12 dogs referred to as controls, and the metabolic alkalosis group. Figure 5 shows that  $CO_2$  narcosis may occur over a wide range of  $P_{aCO_2}$  values (139 mm. to 245

## ANESTHETIC REQUIREMENT VS. ARTERIAL pH

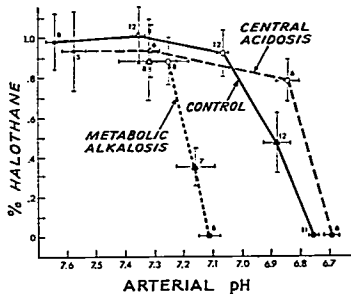


FIG. 7. Anesthetic requirement (MAC) for halothane and arterial pH in same experiments as in figure 5 (increasing hypercapnia). Points are also marked as in figure 5. Note that alkalosis (pH > 7.6) had no effect on anesthesia required. Again note wide scatter in arterial pH where  $CO_2$  begins to reduce anesthetic requirement and at zero halothane ( $CO_2$  anesthesia).

ANESTHETIC REQUIREMENT VS. CSF pH

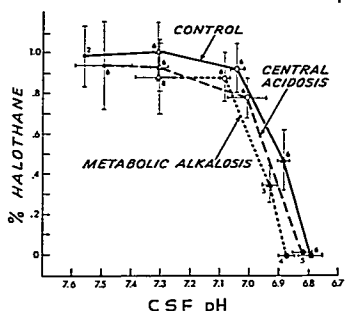


FIG. 8. Anesthetic requirement (MAC) for halothane and CSF pH. Points represent the same  $P_{CO_2}$  as in figure 5 (increasing hypercapnia). Note striking similarity of curves and points at each level of CSF pH. Halothane requirement was zero when CSF pH fell below 6.90 ( $CO_2$  anesthesia).

mm. of mercury), and figure 6 shows a similar scatter for cerebrospinal fluid  $P_{CO_2}$  (146 mm. to 262 mm. of mercury). The  $P_{CO_2}$  in cerebrospinal fluid parallels  $P_{aCO_2}$  but is normally about 9 mm. of mercury higher.<sup>8</sup> Figure 7 shows the same curves plotted for arterial pH which varied from 6.75 to 7.11 at the point of  $CO_2$  narcosis. Figure 8 demonstrates the similarity of all three curves in terms of pH. At the point where  $CO_2$  began to substitute for halothane cerebrospinal fluid pH ranged between 7.01 to 7.08, and the same narrow range of pH was found at the point of total halothane replacement or  $CO_2$  anesthesia (6.79 to 6.87).

The data from dogs anesthetized with  $CO_2$  alone are not shown in figures 5-8 because these are plots of halothane MAC at constant depth anesthesia. The data when  $CO_2$  alone was given fell within the ranges ( $P_{CO_2}$  and pH of arterial blood and cerebrospinal fluid) seen in the three curves plotted in figures 5-8 and are presented in table 1 together with all  $CO_2$  values for narcosis.

The systemic effects of elevated  $CO_2$  are well known resulting from sympathetic and respiratory stimulation. Figure 9 demonstrates the respiratory and circulatory responses in the dogs anesthetized with  $CO_2-O_2$

TABLE 1. pH and  $P_{CO_2}$  at MAC for  $CO_2$  Anesthesia

Groups	Arterial		CSF	
	$P_{CO_2}$	pH	$P_{CO_2}$	pH
$CO_2$ alone	222 ±46 (6)	6.762 ±0.100 (6)	245 ±56 (6)	6.794 ±0.098 (6)
Halothane and $CO_2$	245 ±30 (12)	6.752 ±0.019 (12)	242 ±29 (6)	6.794 ±0.045 (6)
Metabolic alkalosis and $CO_2$	244 ±18 (6)	7.110 ±0.029 (6)	262 ±58 (3)	6.872 ±0.027 (4)
Central acidosis and $CO_2$	139 ±16 (6)	6.696 ±0.024 (6)	146 ±17 (5)	6.821 ±0.037 (5)

Note large differences in arterial  $P_{CO_2}$ , pH and CSF  $P_{CO_2}$  values among the 4 groups of experiments and the small differences in CSF pH values. One standard deviation and the number of experiments are given below each figure.

only. Peak responses occurred when  $P_{aCO_2}$  was between 200 mm. and 250 mm. of mercury. At higher  $P_{aCO_2}$  there was a decline in ventilation and systolic pressure corresponding

SYSTEMIC RESPONSES TO HYPERCAPNIA

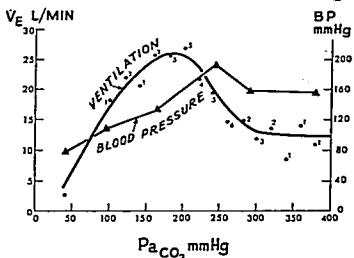


FIG. 9. Ventilation and blood pressure responses to  $CO_2$  in 6 dogs administered  $CO_2-O_2$  only. After establishing MAC  $CO_2$  was raised and lowered to obtain ventilation data. Dots represent 20 mm. of mercury elevations in  $CO_2$  and average ventilation for number of dogs indicated. Curve represents best fit for all points. Solid triangles indicate average systolic blood pressures at  $P_{aCO_2}$  levels of 90, 160, 240, 290 and 380 mm. of mercury. Values for ventilation and blood pressure at normocapnia were taken from previous observations on healthy, awake dogs in this laboratory.

with the narcotic effects of  $\text{CO}_2$ . Between  $\text{Pa}_{\text{CO}_2}$  300 mm. and 400 mm. of mercury however, the ventilation and systolic pressure remained constantly higher than the control values. Tachycardia developed in all dogs with elevated  $\text{CO}_2$  and the course paralleled that of the blood pressure. Arrhythmias of supraventricular origin were seen with higher concentrations of  $\text{CO}_2$  in several animals, but were not serious.

Other aspects of  $\text{CO}_2$  anesthesia included labored respiration, characterized by little change in frequency but marked increase in tidal volume, increased muscle tone and muscle twitching. Convulsions occurred in approximately one-fourth of the animals during the period of highest  $\text{CO}_2$  concentration. They were unsustained and untreated, and apparently did not affect the ability to make a purposeful movement in response to painful stimuli at  $\text{CO}_2$  levels below  $\text{CO}_2$  narcosis.

### Discussion

These results showed that  $\text{CO}_2$  exerts a narcotic influence in dogs at a concentration above 95 mm. of mercury and at a level of 245 mm. of mercury  $\text{CO}_2$  produces anesthesia. This effect correlated well with changes in pH in the brain which, presumably are reflected in the cisternal cerebrospinal fluid.  $\text{CO}_2$  anesthesia was found over a wide range of  $\text{Pa}_{\text{CO}_2}$ , cerebrospinal fluid  $\text{P}_{\text{CO}_2}$  and arterial pH values but was always associated with acidosis (pH 6.79 to 6.87) of the cerebrospinal fluid. Thus it appears that  $\text{CO}_2$  narcosis is not a result of any inert or toxic property of the gas, nor is it a result of peripheral acidosis.

With  $\text{Pa}_{\text{CO}_2}$  between 15 and 95 mm. of mercury, there was little or no alteration in the halothane MAC. This was contrary to expectations for it has been a clinical impression that severe hypocapnia deepens the level of anesthesia, though much of the published data are conflicting. Previous studies showed a correlation between respiratory alkalosis (pH > 7.50) and slow wave EEG activity suggesting a narcotic effect which could be reversed by adding 12 per cent  $\text{CO}_2$ .<sup>9</sup> The influence of hypocapnia on pain thresholds is unsettled, as both an increased<sup>10</sup> and a decreased threshold have been demonstrated.<sup>11</sup> Many authors be-

lieve that the effect of hyperventilation on cerebral blood flow is the critical factor. Specifically, the lowered  $\text{P}_{\text{CO}_2}$  produces cerebral vasoconstriction and may lower cerebral oxygen tension.<sup>12</sup> In the present studies however, halothane may have increased cerebral blood flow<sup>13</sup> and thereby attenuated any ischemic consequences of hypocapnia.

It was of interest that moderate elevation of  $\text{CO}_2$  ( $\text{Pa}_{\text{CO}_2}$  40-90), more likely to be seen clinically, had no effect on the halothane MAC. Elevated  $\text{CO}_2$  augments reticulo-cortical activity, increases excitability and awareness of the environment<sup>14</sup>; therefore one might expect moderate hypercapnia to increase the requirement for halothane. However, there is also evidence that moderately increased  $\text{P}_{\text{CO}_2}$  is a central nervous system depressant.<sup>15-17</sup> Confusion and irritability are seen in healthy subjects breathing 5 to 12 per cent  $\text{CO}_2$ , which if inhaled long enough, leads to loss of consciousness. Qualitative studies on the influence of 5 to 10 per cent  $\text{CO}_2$  added to ether have shown a deepening of the anesthetic level<sup>18,19</sup> but this has not been found in the present study with halothane. It has also been reported that small concentrations of  $\text{CO}_2$  decrease the amount of nitrous oxide necessary to produce loss of consciousness.<sup>20</sup>

With higher concentrations of  $\text{CO}_2$  ( $\text{P}_{\text{CO}_2}$  > 95 mm. of mercury) in the present study there was a progressive narcotic effect as  $\text{CO}_2$  supplanted the halothane needed to maintain constant depth anesthesia. Though the  $\text{CO}_2$  levels were chosen arbitrarily, the lowering of halothane MAC continued in linear fashion (fig. 1a) as the  $\text{CO}_2$  concentration increased, to the point of  $\text{CO}_2$  anesthesia where the halothane requirement was zero. The point of complete  $\text{CO}_2$  narcosis occurred at an average  $\text{Pa}_{\text{CO}_2}$  of 245 mm. of mercury, which agrees with the observations of Leake and Waters on  $\text{CO}_2$  narcosis in rabbits.<sup>2</sup> Thus  $\text{CO}_2$  appears much more potent than nitrous oxide whose physical properties are identical, and less potent than halothane whose MAC in the dog is 0.9 per cent or 7 mm. of mercury.

Using  $\text{CO}_2$  alone, anesthesia occurred at a  $\text{Pa}_{\text{CO}_2}$  of 222 mm. of mercury (fig. 2). EEG activity was not recorded, therefore it is difficult to evaluate the effects of convulsions on the narcotic process. Seizure activity occurred

in at least 25 per cent of the dogs, although it was noted only randomly among the different experimental groups.

Brooks and Eccles and others have shown that inhalation of  $\text{CO}_2$  above 10 per cent produces direct depression of post-synaptic responses and prolongs synaptic delay within the spinal cord.<sup>21</sup> With  $\text{CO}_2$  narcosis a delayed and decreased response to motor nerve stimulation was noted (unpublished data), but there was no evidence of paralysis. The influence of depressed neuromuscular function on the MAC technique is uncertain; however positive responses to painful stimuli were elicited up to the level of  $\text{CO}_2$  narcosis, and the strength of these responses was no less than those observed at lower  $\text{CO}_2$  levels. Therefore it seems that a painful stimulus, if applied long enough, produces a useful qualitative response under conditions of severe hypercapnia and acidosis, providing of course that convulsions do not occur during the time of testing.

From the data presented it is clear that the narcotic properties of  $\text{CO}_2$  are related to hydrogen ions, and that because of rapid diffusion of  $\text{CO}_2$  into all tissues, an acid pH change occurs throughout the organism. Cerebral pH can be assessed by the pH of the fluid bathing it which approaches equilibration with arterial and jugular venous changes in  $\text{P}_{\text{CO}_2}$  within 15 minutes.<sup>22</sup> Cerebrospinal fluid bicarbonate rises with  $\text{CO}_2$  administration, though this rise may be less than<sup>23</sup> or greater than<sup>24</sup> the rise in plasma bicarbonate. The rise in arterial and cerebrospinal fluid  $\text{P}_{\text{CO}_2}$  however, is greater than the bicarbonate rise, with a resulting increase in hydrogen ion concentration. At higher  $\text{CO}_2$  concentrations, the rise in bicarbonate is proportionately less, hence an even greater fall in pH—both arterial and cerebrospinal fluid.

The discrepancy between pH of blood and cerebrospinal fluid during infusion of HCl demonstrates the influence of cerebrospinal fluid pH on the development of narcosis, or the reduction in halothane MAC (fig. 3). Because the cerebrospinal fluid pH did not fall below 7.13, there was no significant change in the halothane requirement, despite marked arterial acidosis. In the other direction, the administration of sodium bicarbonate had no

effect on the cerebrospinal fluid pH (metabolic alkalosis, figure 8); consequently  $\text{CO}_2$  narcosis and anesthesia occurred regardless of the arterial pH which remained above 7.12.

In the present experiments (fig. 1b) an average  $\text{Pa}_{\text{CO}_2}$  of 95 mm. of mercury produced a lowering of cerebrospinal fluid pH from 7.32 to 7.02 corresponding to the onset of  $\text{CO}_2$  narcosis, or a fall in halothane MAC. This is similar to the cerebral pH threshold (jugular venous blood) for EEG slowing resulting from  $\text{CO}_2$  inhalation, reported by Meyer,<sup>25</sup> and similar to the cerebrospinal fluid pH associated with loss of consciousness in respiratory failure, reported by Posner.<sup>26</sup> This value for cerebrospinal fluid pH (7.02) was similar in all groups given  $\text{CO}_2$  (fig. 8). A cerebrospinal fluid pH of 6.80 appears to represent the critical level of cerebral pH associated with lack of responsiveness to painful stimuli in all the experiments. That pH is independent of  $\text{P}_{\text{CO}_2}$  or arterial pH and  $\text{P}_{\text{CO}_2}$  can be seen in figures 4-8 and in table 1. In studies on monkeys with cortical surface electrodes, Mayer<sup>27</sup> demonstrated EEG changes indicating severe depression when the brain pH was reduced below 6.9 to 6.6.

The curious state of  $\text{CO}_2$  narcosis wherein respiration, blood pressure, and muscle tone are increased while consciousness and pain perception are decreased suggest a differential action of  $\text{CO}_2$  within the brain. Gelhorn<sup>28</sup> has shown that  $\text{CO}_2$  affects various synaptic relays within the brain depending upon the level of  $\text{CO}_2$ . Thus, inhalation of 10 per cent  $\text{CO}_2$  depressed local responses of cortical neurones to acoustic and visual stimuli but enhanced those of neurones in the hypothalamic region of the brain stem. Increasing  $\text{CO}_2$  to 20-25 per cent, depressed responsiveness of the brain stem neurones as well as depressing cortical responses further. It is of interest that as  $\text{CO}_2$  exceeded the narcotic level (fig. 9) the respiratory and circulatory stimulus declined, suggesting brain stem depression. Other investigators have observed apnea when the  $\text{Pa}_{\text{CO}_2}$  exceeded 300 mm. of mercury.<sup>29</sup>

Since the central nervous system depressant influence of  $\text{CO}_2$  results from its hydrogen ion effect,  $\text{CO}_2$  narcosis in pathological conditions may be modified by bicarbonate in cerebrospinal fluid. Intrathecal bicarbonate has been



used successfully to reduce the hyperventilation consequent to subarachnoid bleeding (Crampton-Smith, personal communication). Intolerance to hypercapnia may be anticipated in subjects whose cerebrospinal fluid bicarbonate has been lowered by hyperventilation or by treatment with carbonic anhydrase inhibitors. In respiratory failure narcosis is seen over a wide range of  $P_{aCO_2}$ . This variation may be explained by coexisting factors, such as hypoxia, drug therapy, and cerebrovascular disease which may render some areas of the brain more sensitive narcosis by  $CO_2$ . The common denominator in all these cases, however, is probably the cerebrospinal fluid pH.

### Summary

The data presented show that  $CO_2$  in concentrations from 15 mm. to 95 mm. of mercury has no influence on halothane anesthesia in the dog. At higher levels,  $CO_2$  behaves as a narcotic as it reduces the halothane requirement for constant depth anesthesia. At a partial pressure of 245 mm. of mercury  $CO_2$  becomes a narcotic and eliminates the need for halothane.

The mechanism of  $CO_2$  narcosis is closely related to a fall in cerebrospinal fluid pH; this can occur independent of arterial pH,  $P_{CO_2}$  or cerebrospinal fluid  $P_{CO_2}$ . The narcosis begins when cerebrospinal fluid pH falls below 7.10 and reaches a maximum when the cerebrospinal fluid pH approaches 6.80. We conclude that the narcosis resulting from  $CO_2$  inhalation results solely from its hydrogen ion effect.

The assistance of Richard Shargel and Brigit Anderson, and the helpful advice of Drs. John Severinghaus and Robert Mitchell are gratefully acknowledged. The authors also thank Ayerst Laboratories for the supply of halothane (Fluothane).

### References

- Hickman, H. H. (cited by Thompson): *Brit. Med. J.* 1: 843, 1912.
- Leake, C. D., and Waters, R. M.: Anesthetic properties of carbon dioxide, *J. Pharmacol. Exp. Ther.* 33: 280, 1928.
- Fencel, V., Miller, T. B., and Pappenheimer, J. R.: Studies on the respiratory response to disturbances of acid-base balance, with deductions concerning the ionic composition of cerebral interstitial fluid, *Amer. J. Physiol.* 210: 459, 1966.
- Eger, E. I., II, and Merkle, G.: A comparative study of halothane and halopropane anesthetic, including a method for determining equipotency, *ANESTHESIOLOGY* 24: 346, 1963.
- Eger, E. I., II, Saidman, L. J., and Brandstater, M. B.: Minimum alveolar concentration (MAC); a standard of anesthetic potency, *ANESTHESIOLOGY* 26: 756, 1965.
- Severinghaus, J. W., and Mitchell, R. A.: Evidence for active transport regulation of cerebrospinal fluid pH and its effect on the regulation of respiration, *J. Clin. Invest.* 42: 977, 1963.
- Robin, E. D., Whaley, R. D., Crump, C. H., Bicklemann, A. G., and Travis, D. M.: Acid-base relations between spinal fluid and arterial blood with special reference to control of ventilation, *J. Appl. Physiol.* 13: 385, 1958.
- Mitchell, R. A., Carman, C. T., Severinghaus, J. W., Richardson, B. W., Singer, M. M., and Shnider, S.: Stability of cerebrospinal fluid pH in chronic acid-base disturbances in blood, *J. Appl. Physiol.* 20: 443, 1965.
- Geddes, I. C., and Gray, T. C.: Hyperventilation for maintenance of anesthesia, *Lancet* 2: 4, 1959.
- Clutton-Brock, J.: The cerebral effects of overventilation, *Brit. J. Anaesth.* 29: 3, 1957.
- Rossett, J.: The experimental production of rigidity, of abnormal involuntary movements and of abnormal states of consciousness in man, *Brain* 47: 293, 1924.
- Sugioka, K., and Davis, D. A.: Hyperventilation with oxygen—a possible cause of cerebral hypoxia, *ANESTHESIOLOGY* 21: 135, 1960.
- Alexander, S. C., Wollman, H., Cohen, P. J., Chase, P. E., and Behar, M.: Cerebrovascular response to  $P_{aCO_2}$  during halothane anesthesia in man, *J. Appl. Physiol.* 19: 561, 1964.
- Wyke, B.: *Principles of General Neurophysiology Relating to Anesthesia and Surgery.* London, Butterworths, 1960.
- Brown, E. W.: The physiological effects of high concentrations of carbon dioxide, *U. S. Navy Med. Bull.* 28: 721, 1930.
- Dripps, R. D., and Comroe, J. H., Jr.: Respiratory and circulatory responses of normal man to inhalation of 7.6 and 10.4 per cent  $CO_2$  and maximal voluntary hyperventilation, *Amer. J. Physiol.* 149: 43, 1947.
- Seevers, M. H.: The narcotic properties of carbon dioxide, *New York J. Med.* 44: 597, 1944.
- Kleindorfer, G. B.: The effect of carbon dioxide on ether, ethylene and nitrous oxide anesthesia, *J. Pharmacol. Exp. Ther.* 43: 445, 1931.

19. Clowes, G. H. A., Kretchmer, H. E., McBurney, A. W., and Simeone, F. A.: The electroencephalogram in the evaluation of the effects of anesthetic agents and carbon dioxide accumulation during surgery, *Ann. Surg.* 138: 558, 1953.
20. McAleavy, J. C., Way, W. L., Altstatt, A. H., Guadagni, N. P., and Severinghaus, J. W.: Effects of  $P_{CO_2}$  on the depth of anesthesia, *ANESTHESIOLOGY* 22: 260, 1961.
21. Brooks, C. McC., and Eccles, J. C.: A study of the effects of anesthesia and asphyxia on the monosynaptic pathway through the spinal cord, *J. Neurophysiol.* 10: 349, 1947.
22. Bradley, R. D., Semple, S. J. G., and Spencer, G. T.: Rate of change of carbon dioxide tension in arterial blood, jugular venous blood and cisternal cerebrospinal fluid on carbon dioxide administration, *J. Physiol.* 179: 442, 1965.
23. Bleich, H. L., Berkman, P. M., and Schwartz, W. B.: The response of cerebrospinal fluid composition to sustained hypercapnia, *J. Clin. Invest.* 43: 11, 1964.
24. Swanson, A. G., and Rosengren, H.: Cerebrospinal fluid buffering during acute experimental respiratory acidosis, *J. App. Physiol.* 17: 812, 1962.
25. Meyer, J. S., Gotoh, F., and Tomita, M.: Acute respiratory acidemia, *Neurology* 16: 463, 1966.
26. Posner, J. B., Swanson, A. G., and Plum, F.: Acid-base in cerebrospinal fluid, *Arch. Neurol.* 12: 479, 1965.
27. Meyer, J. S., Gotoh, F., and Ebihara, S.:  $CO_2$  narcosis, an experimental study, *Neurology* 11: 524, 1961.
28. Gelhorn, E.: Experimental contribution to the duplicity theory of consciousness and perception, *Pflug. Arch. Physiol.* 255: 75, 1952.
29. Graham, G. R., Hill, D. W., and Nunn, J. F.: Toleranz und "Supercarbo," *Anaesthetist* 9: 70, 1960.

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### Drugs

**DELIRIUM TREMENS** Acute alcohol withdrawal syndrome may lead to death from aspiration, pneumonia, physical exhaustion, hyperpyrexia, coexisting injuries, hypovolemic shock, and serum electrolyte imbalance. Psychomotor agitation is the characteristic manifestation of the acute withdrawal syndrome. Besides the general measures of restraint, supplying fluid, vitamin, and caloric replacement, treatment consisted of "keeping the patient quiet" by giving a combination of chlorpromazine with either chlordiazepoxide or diazepam. The following dosage schedules were used: chlorpromazine 300 mg. intramuscularly initially and 50 to 100 mg. every six hours for at least 72 hours; chlordiazepoxide 100 mg. intramuscularly initially and repeating this dosage every eight hours; and diazepam orally in dosages of 10 to 40 mg. every eight hours. In addition, supplemental orders of the medication were given on a prn basis. Methylphenidate was given intravenously for oversedation. (*Hoagland, R. J.: Treatment of Delirium Tremens, South. Med. J.* 59: 1041 (Sept.) 1966.)