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 *p*H 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 *p*H 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 *p*H changes in the brain as measured in the cisternal CSF, and appeared to be independent of arterial *p*H, P_{aCO_2} and cerebrospinal fluid P_{CO_2}.

In 1820 the narcotic properties of CO_2 were demonstrated by Hickman,[1] and a century later anesthesia was produced in man with 30 per cent CO_2 and O_2.[2] 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 replacement 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 *p*H. If it acts as an inert gas then the best correlation should be with Pa_{CO_2}. To distinguish between these possibilities the Pa_{CO_2} and *p*H were independently altered in blood and brain as represented by cisternal cerebrospinal fluid.[3]

Methods

The technique of determining the minimum anesthetic concentration (MAC)[4] 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 *p*H and P_{O_2}, and constant over periods of 8–10 hours.[5] 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_{H}, P_{CO_2} and P_{O_2} electrodes. All values were corrected for temperature measured with an esophageal thermistor 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; GM-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 *p*H 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 hyperventilated to reduce the $P_{A_{CO_2}}$ 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 $P_{A_{CO_2}}$ 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 *p*H 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 *p*H 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

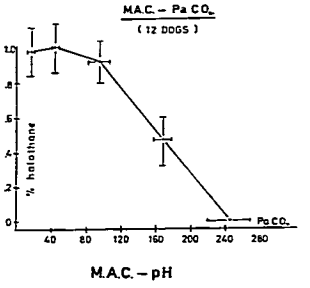

FIG. 1a. Halothane MAC and Pa_{CO_2} in the first 12 dogs anesthetized with halothane-O_2 and given progressively higher levels of CO_2. From Pa_{CO_2} 15 mm. of mercury to 95 mm. of mercury the MAC is relatively constant, while above 95 mm. of mercury Pa_{CO_2} MAC declines progressively until the point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

*p*H 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 *p*H for a given rise in P_{CO_2}. This can be done by hyperventilation as shown by Severinghaus *et al.*,[6] 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 cerebrospinal 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 *p*H 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 *p*H 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

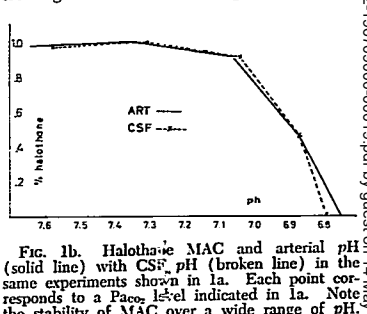

FIG. 1b. Halothane MAC and arterial *p*H (solid line) with CSF *p*H (broken line) in the same experiments shown in 1a. Each point corresponds to a Pa_{CO_2} level indicated in 1a. Note the stability of MAC over a wide range of *p*H. The decline in MAC (onset of narcosis) begins when the *p*H falls below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

of CO_2 anesthesia, when the arterial *p*H was 6.75 and the cerebrospinal fluid *p*H was 6.79.

In the 6 dogs anesthetized with CO_2 and O_2 the point of anesthesia was reached at an average Pa_{CO_2} of 222 mm. of mercury. Figure 2 indicates the response of each dog to a standard painful stimulus at various levels of CO_2. The mean value of the positive and negative responses was considered to be the CO_2 MAC for each animal. At this point average arterial *p*H was 6.76 and the average cerebrospinal fluid *p*H 6.79, identical to arterial and cerebrospinal fluid *p*H in the dogs anesthetized with halothane prior to CO_2 administration. This indicates that at the point of CO_2 anesthesia there was no influence of halothane in the first 12 dogs since any residual effect would have lowered the CO_2 level required to produce narcosis. On the contrary these dogs needed a slightly higher CO_2 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_2, were excluded.

In the 6 dogs given sodium bicarbonate attempting to reverse the CO_2 narcosis there was no change in the Pa_{CO_2} required for CO_2 anesthesia (244 mm. of mercury). Despite the fact that arterial *p*H remained above 7.12 cerebrospinal fluid *p*H fell to 6.87 which demonstrated the well known blood brain

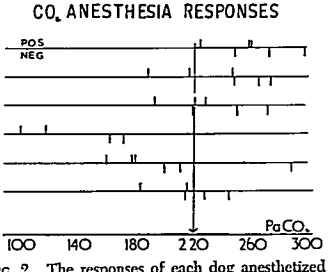

FIG. 2. The responses of each dog anesthetized with CO_2–O_2 to painful stimulation and the Pa_{CO_2} value at which the dog was tested. Positive responses are indicated by a vertical line above and negative responses by a vertical line below each horizontal. The mean CO_2 anesthesia value for all 6 dogs is shown by the arrow. Note the CO_2 MAC value for dog no. 4 is approximately 140 mm. of mercury.

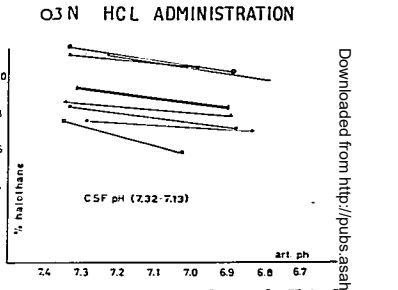

FIG. 3. Halothane MAC and arterial *p*H in 8 dogs anesthetized with halothane–O_2 and given HCl intragastrically. The heavy dark line indicates both one dog and the average of all the dogs. Note the small change in MAC over a large change in arterial *p*H. The CSF *p*H remained between 7.32 and 7.13.

barrier to the passage of ions.[7] Because of the bicarbonate induced diuresis in these dogs there was insufficient cerebrospinal fluid for analysis at the point of CO_2 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 *p*H fell to 6.90 while cerebrospinal fluid *p*H in 6 of 8 dogs ranged between 7.13 and 7.32. Figure 3 shows the values for each experiment where arterial *p*H 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 *p*H (7.34 to 6.90). The average dose of HCl was 500 m*M* 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_2 anesthesia was reached at a Pa_{CO_2} 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_2 narcosis is that the cerebrospinal fluid *p*H was 6.82, very close to 6.79 in the other group, despite the

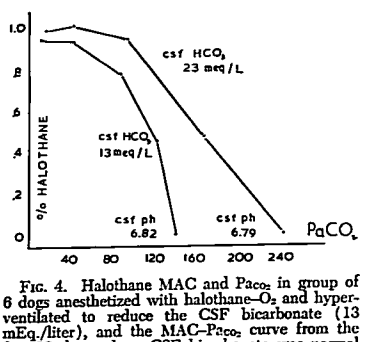

FIG. 4. Halothane MAC and Pa_{CO_2} in group of 6 dogs anesthetized with halothane–O_2 and hyperventilated to reduce the CSF bicarbonate (13 mEq./liter), and the MAC–Pa_{CO_2} curve from the first 12 dogs whose CSF bicarbonate was normal (23 mEq./liter) before CO_2 administration. Note at every level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

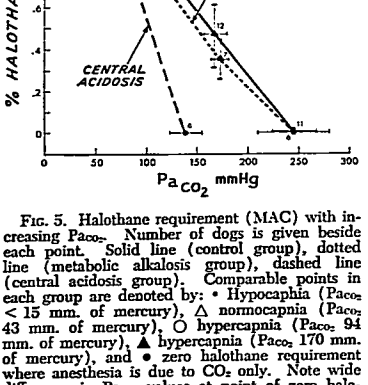

FIG. 5. Halothane requirement (MAC) with increasing Pa_{CO_2}. Number of dogs is given beside each point. Solid line (control group), dotted line (metabolic alkalosis group), dashed line (central acidosis group). Comparable points in each group are denoted by: • Hypocapnia (Pa_{CO_2} < 15 mm. of mercury),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

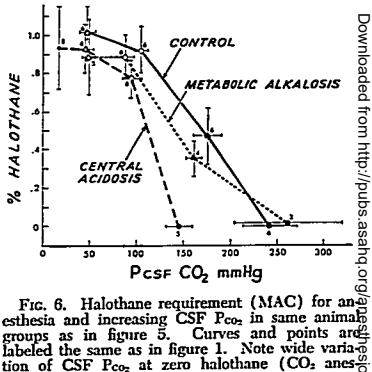

FIG. 6. Halothane requirement (MAC) for anesthesia and increasing CSF P_{CO_2} in same animal groups as in figure 5. Curves and points are labeled the same as in figure 1. Note wide variation of CSF P_{CO_2} at zero halothane (CO_2 anesthesia).

difference in Pa_{CO_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 Pa_{CO_2} values (139 mm. to 245

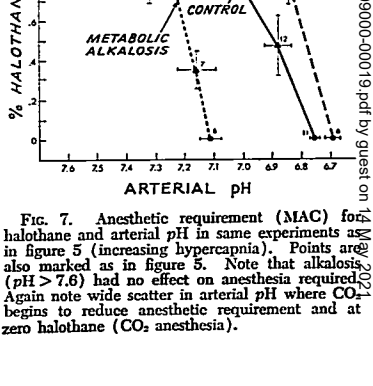

FIG. 7. Anesthetic requirement (MAC) for halothane and arterial *pH* in same experiments as in figure 5 (increasing hypercapnia). Points are also marked as in figure 5. Note that alkalosis ($pH > 7.6$) had no effect on anesthesia required. Again note wide scatter in arterial *pH* where CO_2 begins to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

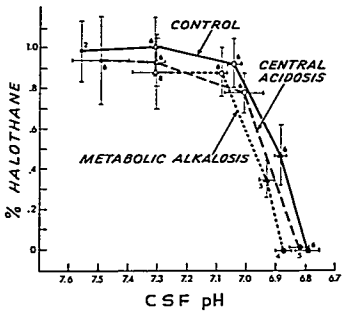

FIG. 8. Anesthetic requirement (MAC) for halothane and CSF *p*H. Points represent the same P_{CO_2} as in figure 5 (increasing hypercapnia). Note striking similarity of curves and points at each level of CSF *p*H. Halothane requirement was zero when CSF *p*H fell below 6.90 (CO_2 anesthesia).

TABLE 1. *p*H and P_{CO_2} at MAC for CO_2 Anesthesia

Groups	Arterial		CSF	
	P_{CO_2}	*p*H	P_{CO_2}	*p*H
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}, *p*H and CSF P_{CO_2} values among the 4 groups of experiments and the small differences in CSF *p*H values. One standard deviation and the number of experiments are given below each figure.

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 Pa_{CO_2} but is normally about 9 mm. of mercury higher.[8] 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 *p*H ranged between 7.01 to 7.08, and the same narrow range of *p*H 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 *p*H 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 only. Peak responses occurred when Pa_{CO_2} was between 200 mm. and 250 mm. of mercury. At higher Pa_{CO_2} there was a decline in ventilation and systolic pressure corresponding

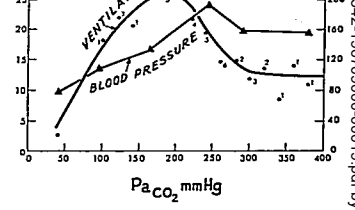

FIG. 9. Ventilation and blood pressure responses to CO_2 in 6 dogs administered CO_2–O_2 only. After establishing MAC CO_2 was raised and lowered to obtain ventilation data. Dots represent 20 mm. of mercury elevations in CO_2 and average ventilation for number of dogs indicated. Curve represents best fit for all points. Solid triangles indicate average systolic blood pressures at Pa_{CO_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 CO_2. Between Pa_{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 CO_2 and the course parallelled that of the blood pressure. Arrythmias of supraventricular origin were seen with higher concentrations of CO_2 in several animals, but were not serious.

Other aspects of 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 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 CO_2 levels below CO_2 narcosis.

Discussion

These results showed that 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 CO_2 produces anesthesia. This effect correlated well with changes in *p*H in the brain which, presumably are reflected in the cisternal cerebrospinal fluid. CO_2 anesthesia was found over a wide range of Pa_{CO_2}, cerebrospinal fluid P_{CO_2} and arterial *p*H values but was always associated with acidosis (*p*H 6.79 to 6.87) of the cerebrospinal fluid. Thus it appears that 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 Pa_{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 (*p*H > 7.50) and slow wave EEG activity suggesting a narcotic effect which could be reversed by adding 12 per cent CO_2.[9] The influence of hypocapnia on pain thresholds is unsettled, as both an increased [10] and a decreased threshold have been demonstrated.[11] Many authors believe that the effect of hyperventilation on cerebral blood flow is the critical factor. Specifically, the lowered P_{CO_2} produces cerebral vasoconstriction and may lower cerebral oxygen tension.[12] In the present studies however, halothane may have increased cerebral blood flow [13] and thereby attenuated any ischemic consequences of hypocapnia.

It was of interest that moderate elevation of CO_2 (Pa_{CO_2} 40–90), more likely to be seen clinically, had no effect on the halothane MAC. Elevated CO_2 augments reticulo-cortical activity, increases excitability and awareness of the environment [14]; therefore one might expect moderate hypercapnia to increase the requirement for halothane. However, there is also evidence that moderately increased P_{CO_2} is a central nervous system depressant.[15–17] Confusion and irritability are seen in healthy subjects breathing 5 to 12 per cent CO_2, which if inhaled long enough, leads to loss of consciousness. Qualitative studies on the influence of 5 to 10 per cent CO_2 added to ether have shown a deepening of the anesthetic level [18, 19] but this has not been found in the present study with halothane. It has also been reported that small concentrations of CO_2 decrease the amount of nitrous oxide necessary to produce loss of consciousness.[20]

With higher concentrations of CO_2 ($P_{CO_2} >$ 95 mm. of mercury) in the present study there was a progressive narcotic effect as CO_2 supplanted the halothane needed to maintain constant depth anesthesia. Though the CO_2 levels were chosen arbitrarily, the lowering of halothane MAC continued in linear fashion (fig. 1a) as the CO_2 concentration increased, to the point of CO_2 anesthesia where the halothane requirement was zero. The point of complete CO_2 narcosis occurred at an average Pa_{CO_2} of 245 mm. of mercury, which agrees with the observations of Leake and Waters [2] on CO_2 narcosis in rabbits.[2] Thus 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 CO_2 alone, anesthesia occurred at a Pa_{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 CO_2 above 10 per cent produces direct depression of post-synaptic responses and prolongs synaptic delay within the spinal cord.[21] With 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 CO_2 narcosis, and the strength of these responses was no less than those observed at lower 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 CO_2 are related to hydrogen ions, and that because of rapid diffusion of CO_2 into all tissues, an acid *p*H change occurs throughout the organism. Cerebral *p*H can be assessed by the *p*H of the fluid bathing it which approaches equilibration with arterial and jugular venous changes in P_{CO_2} within 15 minutes.[22] Cerebrospinal fluid bicarbonate rises with CO_2 administration, though this rise may be less than [23] or greater than [24] the rise in plasma bicarbonate. The rise in arterial and cerebrospinal fluid P_{CO_2} however, is greater than the bicarbonate rise, with a resulting increase in hydrogen ion concentration. At higher CO_2 concentrations, the rise in bicarbonate is proportionately less, hence an even greater fall in *p*H—both arterial and cerebrospinal fluid.

The discrepancy between *p*H of blood and cerebrospinal fluid during infusion of HCl demonstrates the influence of cerebrospinal fluid *p*H on the development of narcosis, or the reduction in halothane MAC (fig. 3). Because the cerebrospinal fluid *p*H 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 *p*H (metabolic alkalosis, figure 8); consequently CO_2 narcosis and anesthesia occurred regardless of the arterial *p*H which remained above 7.12.

In the present experiments (fig. 1b) an average Pa_{CO_2} of 95 mm. of mercury produced a lowering of cerebrospinal fluid *p*H from 7.32 to 7.02 corresponding to the onset of CO_2 narcosis, or a fall in halothane MAC. This is similar to the cerebral *p*H threshold (jugular venous blood) for EEG slowing resulting from CO_2 inhalation, reported by Meyer,[25] and similar to the cerebrospinal fluid *p*H associated with loss of consciousness in respiratory failure, reported by Posner.[26] This value for cerebrospinal fluid *p*H (7.02) was similar in all groups given CO_2 (fig. 8). A cerebrospinal fluid *p*H of 6.80 appears to represent the critical level of cerebral *p*H associated with lack of responsiveness to painful stimuli in all the experiments. That *p*H is independent of P_{CO_2} or arterial *p*H and P_{CO_2} can be seen in figures 4–8 and in table 1. In studies on monkeys with cortical surface electrodes, Mayer [27] demonstrated EEG changes indicating severe depression when the brain *p*H was reduced below 6.9 to 6.6.

The curious state of CO_2 narcosis wherein respiration, blood pressure, and muscle tone are increased while consciousness and pain perception are decreased suggest a differential action of CO_2 within the brain. Gelhorn [28] has shown that CO_2 affects various synaptic relays within the brain depending upon the level of CO_2. Thus, inhalation of 10 per cent CO_2 depressed local responses of cortical neurones to acoustic and visual stimuli but enhanced those of neurones in the hypothalmic region of the brain stem. Increasing 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 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 Pa_{CO_2} exceeded 300 mm. of mercury.[29]

Since the central nervous system depressant influence of CO_2 results from its hydrogen ion effect, 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 Pa_{CO_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 *p*H.

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 *p*H; this can occur independent of arterial *p*H, P_{CO_2} or cerebrospinal fluid P_{CO_2}. The narcosis begins when cerebrospinal fluid *p*H falls below 7.10 and reaches a maximum when the cerebrospinal fluid *p*H 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).

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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 chloropromazine 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.*)