LETTERS TO THE EDITOR

SIR:

The following statement concerning cyclopropane is made in the Canadian Anaesthetists' Society Journal, vol. 14, no. 6, November 1967, p. 505, par. 3: "It is perhaps too bad that the Toronto group either through timidity or indifference did not go on from there to demonstrate cyclopropane in clinical practice." I am writing to you, the Editor of the Journal, to say I do not know who are included in the "group" in the article "Development of Anaesthesia in Canada" by Dr. Harold R. Griffith. I feel as the only survivor of a group that discovered and experimented with cyclopropane, I must clarify the position of the late Professor V. E. Henderson and the late Dr. W. Easson Brown, who attempted, without success, to conduct clinical trials in the Toronto General Hospital.

Pure cyclopropane, prepared in liquid state in the Department of Pharmacology, was stored in a steel tank at room temperature for over a month to determine whether or not toxic substances would form in it as they did in propylene when it was treated thus. After the purity was established by chemical tests and by laboratory animal experimentation, Dr. W. Easson Brown anaesthetized Professor V. E. Henderson and Alan Brock, the chief technician, using a McKesson anaesthetic machine. I kept close check on the percentage of cyclopropane to which these persons were subjected. Dr. Brown then lightly anaesthetized me. It was our hope that following these demonstrations, Dr. Brown would be permitted to conduct some clinical trials in the Toronto General Hospital. As Dr. Samuel Johnston, chief of the Department of Anaesthesia, had not observed these experiments on humans, Professor V. E. Henderson arranged a special meeting in the Department of Pharmacology, which Dr. Johnston attended and where Dr. Brown deeply anaesthetized Dr. Frederick Banting. However, following this, when Dr. Brown requested Dr. Johnston's permission to conduct some clinical trials with cyclopropane in the Toronto General Hospital, he was flatly refused.

Whether or not Dr. Johnston was influenced by three deaths in the city under ethyl chloride anaesthesia which greatly aroused the city coroners, or was afraid of an inflammable gas such as cyclopropane, or was under pressure of hospital administration not to permit clinical trials with the gas, is a secret which is buried with him.

As the Department of Phamacology had no connection with any other hospitals in Toronto by which it could initiate clinical trials with cyclopropane, experimentation in Toronto with this gas ended and interest in it as a general anaesthetic died in its birthplace. There was no indifference or timidity on the part of those who had discovered it and had carried animal and human experimentation with it to the point where, in the hands of an experienced anaesthetist such as Dr. Brown, it appeared safe for short clinical trials.

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November 20, 1967

SIR:

I wish to comment on some statements that were made in the article entitled Relationship of Metabolic Acidosis and Capillary P_{CO_2} in Cyclopropane and Halothane Anaesthesia, by Gordon F. Clark, M.D., appearing in this journal [*14*: 551 (1967)].

Doctor Clark is obviously not very familiar with the literature on the subject he has written about. Our group has published in this journal, as well as in others, "to compare various anaesthetic agents under identical controlled conditions." Our data showed clearly that, during spontaneous breathing and controlled breathing, diethyl ether is the only commonly used general anaesthetic that might cause metabolic acidosis. The conditions which cause a trend toward metabolic acidosis, with other agents, are haemorrhage (graded) and induced hypoxia (<15% oxygen in the inspired gas). *In the absence of hypoxia or haemorrhage*, hypercarbia—whether due to depressed respiration or to the addition of carbon dioxide to the inspired gas mixture up to 7.5 per cent—does *not* cause metabolic acidosis. The statement made by Bunker, which Doctor Clark quotes, does not mean that metabolic acidosis necessarily follows because bicarbonate falls during anaesthesia. A fall in bicarbonate of 2 mEq./L. is consistent with the fasting state and is within the daily variation in normal humans.

Doctor Clark evidently did not get the point from my correspondence regarding the paper by Papadopoulos and Keats, in which I pointed out that *their data in fact did not show even the slightest metabolic acidosis to occur* under the conditions they studied and reported.

I could not find evidence in Doctor Clark's paper which showed me that his project "was designed to clarify the relationship between anaesthesia, metabolic acidosis, and arterial P_{CO_2}." He neglected altogether to record in his paper the control values from any of the patients in his study, so the reader doesn't know where each patient stood to begin with. He obviously did not measure arterial P_{CO_2} in any of the patients, but only measured the pH of arterialized capillary blood from fingertip or ear-lobe, from which he derived the Pa_{CO_2}, "base excess," and "standard bicarbonate."

Assuming that he worked very carefully, that samples from the finger and the ear were interchangeable or consistently almost identical, that arterialization was done the same way each time, that his measurements were superbly accurate to 3 decimal points for pH and to one-tenth mm. Hg CO_2, and that the Astrup method is the best technique for studying this subject, I examined the tabular data he published to see if his actual data unequivocally "showed metabolic acidosis to develop in both cyclopropane and halothane anaesthesia irrespective of the level of P_{CO_2} *and to be progressive with time.*" In order to fill all these conditions, I felt obliged to examine only the figures in which there was a progression of values for a full 90 minutes of anaesthesia, so that there would be some measure of validity to any conclusions that may be drawn. Table I shows my simple calculation of mean values from his tabular data for pH and P_{CO_2} from which I derived the corresponding plasma bicarbonate values.

It is evident to me that his data does *not* show the slightest metabolic acidosis to occur with halothane and I have to stretch my imagination to consider that it

TABLE I

	½ hour			1 hour			1½ hours			2 hours			Δ
	pH	P_{CO_2}	$[HCO_3^-]$	pH	P_{CO_2}	$[HCO_3^-]$	pH	P_{CO_2}	$[HCO_3^-]$	pH	P_{CO_2}	$[HCO_3^-]$	$[HCO_3^-]$
Cyclopropane, low P_{CO_2} (6 pts.)	7.42	33.6	20.8	7.41	31.8	19.2	7.41	33.2	20.2	7.40	33.1	19.7	1.1
Cyclopropane, high P_{CO_2} (7 pts.)	7.24	59.2	24.1	7.24	57.9	23.5	7.25	59.4	24.7	7.24	55.7	22.8	1.3*
Halothane, low P_{CO_2} (5 pts.)	7.44	29.5	19.4	7.44	30.7	19.9	7.45	28.2	19.9	7.47	26.7	19.0	0.4
Halothane, high P_{CO_2} (5 pts.)	7.36	42.2	22.1	7.33	43.3	21.2	7.31	46.0	22.3	7.30	46.4	21.8	0.3

*Three of these patients also received diethyl ether.

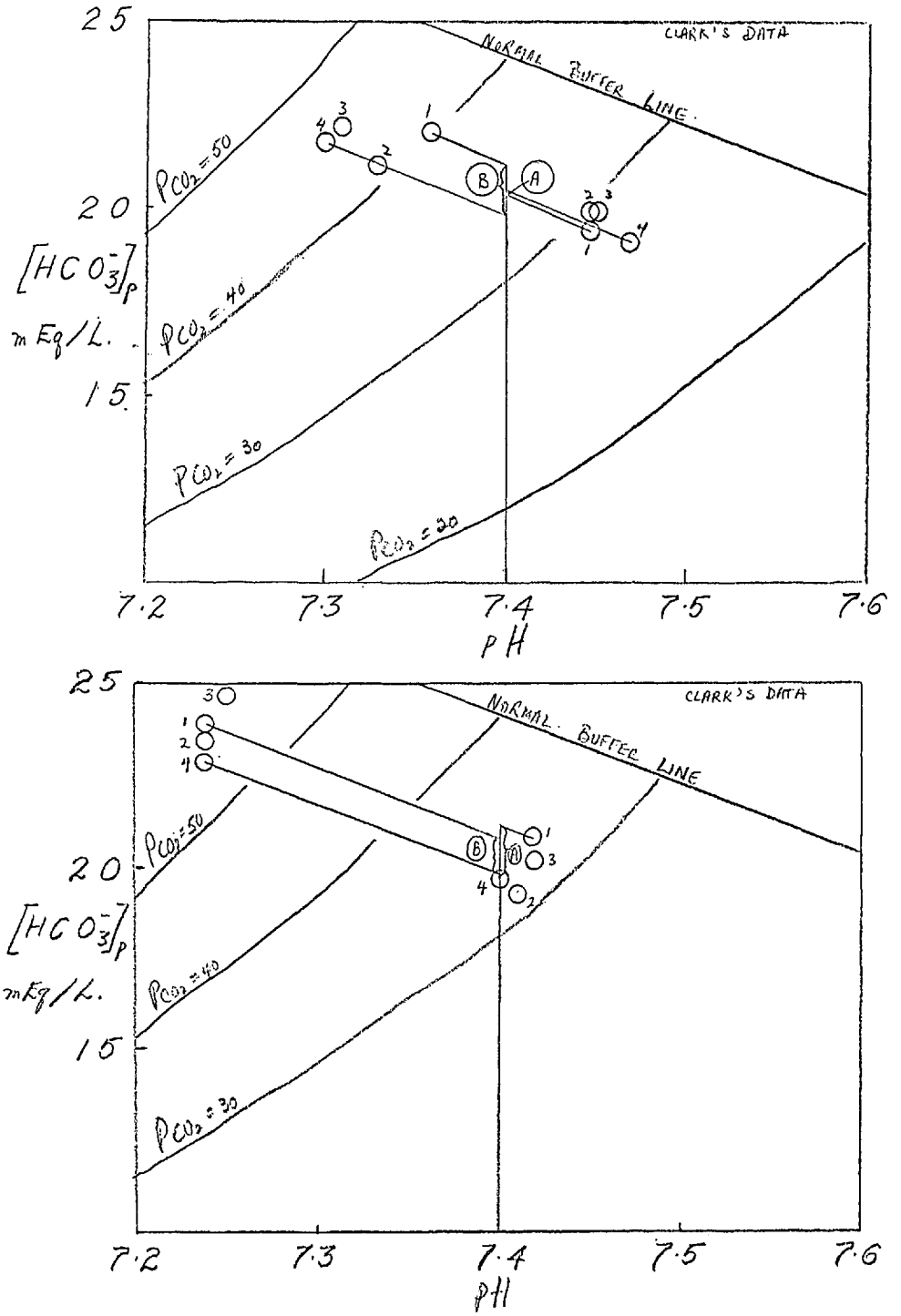

FIGURE 1. Acid-base diagrams. Above: halothane; below: cyclopropane. A = low P_{CO_2}; B = high P_{CO_2}. Anaesthesia times as follows: 1 = ½ hour, 2 = 1 hour, 3 = 1½ hours, 4 = 2 hours.

occurred with cyclopropane. What little change that occurred was obviously *not* progressive with time.

If pulmonary ventilation is augmented so that the alveolar P_{CO_2} remains near normal, metabolic acidosis may be said to occur during anaesthesia when the pH falls approximately 0.1 units for each 2 mEq./L. fall in the plasma bicarbonate. I am quite certain that Doctor Clark will not find such a clear-cut change to occur with *any* of the inhalation anaesthetics properly administered, except perhaps with diethyl ether. [See Fig. 1.]

Metabolic acidosis is a serious derangement which can be fatal to a patient. The anaesthetist should always be aware that it might occur when his patient bleeds or when there are bouts of severe hypoxia from any cause. To incriminate an anaesthetic agent in the primary aetiology of this condition is a serious charge that should be considered with great care and clear evidence. I feel therefore that the author of this paper should take the pains to know what he is doing when he studies this problem further, for we all use these agents for surgical operations that often far exceed two hours' duration. I, for one, would hate to have the added worry of metabolic acidosis developing progressively whenever I administer halothane or cyclopropane to my patients.

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November 17, 1967

SIR:

I have read Dr. Dobkin's letter wherein he offers many points of criticism of my paper published in the Canadian Anaesthetists' Society Journal, November 1967. I shall attempt to answer these in the order in which they appear in his letter.

Dr. Dobkin apparently feels that my failure to acknowledge his paper[1] on metabolic acidosis during anaesthesia published in your Journal indicates "obvious unfamiliarity" with the literature on this subject. His paper deals exclusively with laboratory animals and since my paper deals exclusively with anaesthesia in humans I believe most readers would interpret my observations as referring to humans. There are other data derived from observations on humans which confirm the metabolic acidosis reported in my paper. Both Greifenstein[2] and Papadopoulos and Keats[3] have shown increases in lactic acid during anaesthesia on humans, the former using halothane-oxygen and the latter cyclopropane-oxygen. The interpretation of these data involved a consideration of the part played by carbon dioxide. The point of my paper was to show that this metabolic acidosis, even though small in magnitude and not requiring corrective measures, occurs whether the P_{CO_2} is elevated or depressed—hence the title of my paper.

With respect to his observation that "a fall in bicarbonate of 2 mEq./L. is consistent with the fasting state," this is an acknowledged fact. However, it was clearly stated in my paper that all patients were free of metabolic disorders. It follows, therefore, that all preanaesthetic bicarbonate levels fell within the daily "physiological" variation seen in the mild starvation of the elective surgical case. To derive any meaningful interpretation of the effects of anaesthesia in this parameter, I reported only the changes in base excess from the preanaesthetic level which occurred after each half hour of anaesthesia. Is it reasonable to suppose that the unmistakable and statistically significant change in base excess which occurs during, say, the first half hour of anaesthesia is due simply to a half hour of additional starvation? The writer thinks not.

Dr. Dobkin objects that I "neglected altogether to record the control values so that the reader could know where the patient stood to begin with." While it is true that these values were not given, it is a matter of elementary arithmetic to derive them from the data given. Since it was the *change* in acid-base status on which I wished to focus attention it seemed reasonable to report only the changes. Dr. Dobkin, who apparently deplores this method of presenting data, follows it studiously in his own paper.[1]

With reference to the correspondence between Dr. Dobkin and Drs. Papadopoulos and Keats, the reader is referred to page 721 of the September 1959 issue of Anesthesiology. Since the correspondence deals with metabolic acidosis during anaesthesia in humans it sheds light on Dr. Dobkin's present criticisms.

With respect to Dr. Dobkin's criticism of my method of investigation and interpretation of results, may I point out that measurement of P_{CO_2} on arterial blood and arterialized capillary blood have been proven to be comparable[4,5] and that indirect analysis of P_{CO_2} by the Astrup technique is comparable to direct measurement by P_{CO_2} electrode.[6] Dr. Dobkin has presented some interpretations based on certain limited data from my paper. From pH and P_{CO_2} values quoted on five cases, he has calculated corresponding bicarbonate values, taken arithmetic means of these values, and plotted them on a pH-bicarbonate diagram. While I have no objection to this diagram as an expression of the Henderson-Hasselbalch equation, it is not as easy to plot values accurately on this diagram as it is on the Siggaard-Andersen nomogram. To attempt to plot average values, derived as Dr. Dobkin has derived them, on either, can lead to some confusion, because these mean values for pH, P_{CO_2}, and $[HCO_3^-]_p$ may not fit the Henderson-Hasselbalch equation. In any case Dr. Dobkin completely ignores the change in bicarbonate during the first half hour of anaesthesia. He ignores the evidence presented on anaesthetics which lasted 90 minutes and chooses only those which lasted 2 hours; but on these he represents the observations at the end of one half hour of anaesthesia as referring to the start of anaesthesia. Despite the reservations on the pH-bicarbonate diagram and the very small sample which Dr. Dobkin has selected, I have done the calculations he claims to have done on the reported "anaesthetics using halothane where P_{CO_2} was depressed" starting with the preanaesthetic values. I have done the same on an additional 14 cases where the data were collected under identical circumstances, and I have plotted these on the pH-bicarbonate diagram (see Table I and Fig. 1). Both of these curves confirm the conclusions I reported in my paper.

TABLE I

	Preanaesthetic (resting level)			½ hour			1 hour			1½ hours			2 hours			Δ
	pH	P_{CO_2} (mm.)	$[HCO_3^-]$ (mEq./L.)	pH	P_{CO_2} (mm.)	$[HCO_3^-]$ (mEq./L.)	pH	P_{CO_2} (mm.)	$[HCO_3^-]$ (mEq./L.)	pH	P_{CO_2} (mm.)	$[HCO_3^-]$ (mEq./L.)	pH	P_{CO_2} (mm.)	$[HCO_3^-]$ (mEq./L.)	Δ $[HCO_3^-]$ (mEq./L.)
Halothane, low P_{CO_2} (5 patients)	7.395	34.2	20.3	7.442	29.5	19.5	7.437	30.7	20.0	7.450	28.1	18.8	7.462	26.7	18.4	1.9
Halothane, low P_{CO_2} (19 patients—5 above + 14 additional)	7.395	38.8	22.2	7.436	30.6	20.0	7.431	30.0	19.3	7.427	30.5	19.3	7.437	28.5	17.8	4.6

Bicarbonate derived from published[5] and unpublished data during anaesthesia for two hours with halothane and P_{CO_2} depressed.

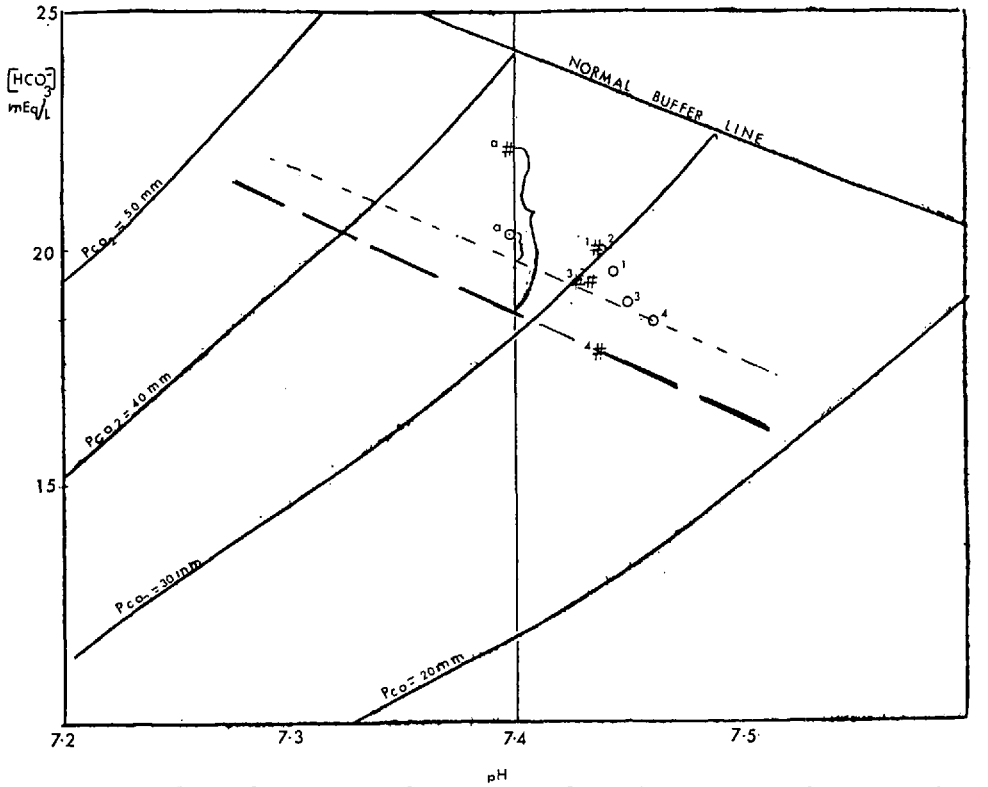

FIGURE 1. Acid-base diagram. ○ = five cases quoted in publication. # = above cases plus 14 others. *a* = preanaesthetic, 1 = ½ hour, 2 = 1 hour, 3 = 1½ hours.

Dr. Dobkin states, "If pulmonary ventilation is augmented so that the alveolar P_{CO_2} remains near normal, metabolic acidosis may be said to occur during anaesthesia when the pH falls approximately 0.1 units for each 2 mEq./L. fall in plasma bicarbonate." If I read this correctly, Dr. Dobkin is saying in effect that if the P_{CO_2} remains near normal (40 mm Hg.) there is a linear relationship between $[HCO_3^-]_p$ and pH, and a fall of 0.1 pH units relates to a fall of 2 mEq./L. $[HCO_3^-]_p$. This is of course not true and it should not be necessary to point this out.

In summary, there are no points in Dr. Dobkin's letter which, in my view, have any validity or which suggest a change in the conclusion presented in my paper.

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December 6, 1967

1. DOBKIN, A. B.; BYLES, P. H.; & NEVILLE, J. F. Neuroendocrine and Metabolic Effects of General Anaesthesia during Spontaneous Breathing, Controlled Breathing, Mild Hypoxia, and Mild Hypercarbia. Canad. Anaesth. Soc. J. *13*: 130 (1966).
2. GREIFENSTEIN, F. E. Excess Lactate during Halothane-Oxygen and Halothane-Nitrous-Oxide-Oxygen Anaesthesia. Anesth. & Analg. *45*: 39 (1966).
3. PAPADOPOULOS, C. N. & KEATS, A. S. The Metabolic Acidosis of Hyperventilation Produced by Controlled Respiration. Anesthesiology. *20*: 156 (1959).
4. GAMBINO, S. R. Collection of Capillary Blood for Simultaneous Determinations of Arterial ph, CO_2, content P_{CO_2}, and Oxygen Saturation. Am. J. Clin. Path. *35*: 175 (1961).
5. CLARK, G. F. Relationship of Metabolic Acidosis and Capillary P_{CO_2} in Cyclopropane and Halothane Anaesthesia. Canad. Anaesth. Soc. J. *14*: 551 (1967).
6. WINTERS, R. W. The Validity of the Astrup Technique for the Measurement of Acid-base Status of Blood. Bulletin no. AS 36, Radiometer, Copenhagen.