

# Cerebral Carbohydrate Metabolism During Hypocarbica in Man

## Studies During Nitrous Oxide Anesthesia

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Brain carbohydrate metabolism was studied in 11 healthy male volunteers during anesthesia induced with intravenous thiopental (5 mg./kg.) and maintained with 70 per cent N<sub>2</sub>O-30 per cent O<sub>2</sub> and *d*-tubocurarine. When arterial P<sub>CO<sub>2</sub></sub> (Pa<sub>CO<sub>2</sub></sub>) was normal, oxygen and glucose consumption were reduced approximately 25 per cent from the normal value in conscious man; but no change in the pattern of glucose utilization was noted. A reduction in Pa<sub>CO<sub>2</sub></sub> below 20 mm. of mercury was accompanied by a decreased aerobic and an increased anaerobic utilization of glucose. Mild, readily reversible changes in the EEG pattern also occurred when Pa<sub>CO<sub>2</sub></sub> was less than 20 mm. of mercury. Clinical implications of these changes are discussed. The validity of several indices of cerebral carbohydrate metabolism is considered.

SINCE deliberate hyperventilation is a widely used anesthetic technique, its effects on the brain should be carefully evaluated. Hypocarbica resulting from overventilation diminishes cerebral blood flow, and the P<sub>O<sub>2</sub></sub> of cerebral tissue decreases.<sup>1, 2, 3</sup> Changes in cerebral function, related to hypocarbica have been noted, including alterations in the electro-

encephalogram and in the response to the flicker fusion test.<sup>4, 5, 6</sup> However, biochemical changes indicative of cerebral hypoxia or anaerobic metabolism have not been demonstrated during hypocarbica and anesthesia. In a previous study, when carbon dioxide tension was lowered to 25 mm. of mercury during halothane-oxygen anesthesia, consistent biochemical evidence of cerebral hypoxia was not noted.<sup>7</sup> The threat of arterial hypotension prevented further elevation of minute ventilation in those subjects. The present study, during 70 per cent nitrous oxide and 30 per cent oxygen anesthesia, was undertaken in order to study brain metabolism in the presence of a greater degree of hypocarbica and a slightly lower arterial oxygen content.

### Methods

*Experimental Design and Measurements.* Following a thiopental induction, measurements were made during N<sub>2</sub>O-O<sub>2</sub>-*d*-tubocurarine anesthesia without operation in 11 healthy fasting adult males ranging in age from 21 to 25 years. The premedication, anesthetic technique, breathing circuit, blood sampling and instrumentation for all subjects are described elsewhere.<sup>2</sup>

In 6 subjects (Group I) cerebral blood flow (CBF) and carbohydrate metabolism were studied during two different steady states: normocarbica (mean Pa<sub>CO<sub>2</sub></sub> = 41.3 mm. of mercury), and hypocarbica (mean Pa<sub>CO<sub>2</sub></sub> = 18.3 mm. of mercury). The level of Pa<sub>CO<sub>2</sub></sub> was controlled by varying the inspired CO<sub>2</sub> tension as described previously.<sup>2</sup>

In 5 additional subjects (Group II) brain carbohydrate metabolism was studied at four

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different levels of arterial carbon dioxide tension ( $P_{aCO_2}$ ). Pulmonary ventilation of these subjects was performed with a Bird Mark 9X Respirator, and measurements were made at mean  $P_{aCO_2}$  levels of 37.2, 25.5, 19.4, and 11.6 mm. of mercury. The order in which these levels were achieved was varied from subject to subject. Pulmonary ventilation was kept constant (mean  $V_E = 25.1$  liters/minute), and  $P_{aCO_2}$  was altered by adding  $CO_2$  to the inspired gas. In all instances inspired  $N_2O$  concentration was maintained at 70 per cent. Blood samples were taken only after end-tidal  $P_{CO_2}$  had been stable for 10–15 minutes and jugular venous thiopental concentration had decreased below 3 mg./liter.

CBF was measured with an inert gas technique, using  $^{85}Kr$ .<sup>2</sup> Blood thiopental concentration was determined by the method of Brodie *et al.*<sup>8</sup> Arterial and jugular venous  $P_{O_2}$ ,  $P_{CO_2}$ , and pH were made with techniques described elsewhere using appropriate electrodes.<sup>2</sup> Blood oxygen content was determined manometrically by the method of Van Slyke and Neill.<sup>9</sup> Arterial and jugular venous blood glucose, lactate, and pyruvate concentrations were determined enzymatically.<sup>7</sup> Eight-channel bipolar electroencephalograms were recorded, and interpreted without knowledge of the existing  $P_{aCO_2}$  level. Each electroencephalogram was rated on a five-point scale (table 1) which is essentially a subdivision of Stage I of the EEG criteria of cerebral hypoxia described by Gastaut.<sup>10</sup>

**Calculations.** The brain uses glucose almost exclusively as its normal substrate for energy production.<sup>11, 12</sup> Furthermore, brain synthesis of glycogen, amino acids and fat is negligible. Therefore, the following relationships were used to calculate the proportion of: (A) glucose being metabolized with oxygen or (B) glucose being metabolized to lactate.

(A) The aerobic oxidation of one mole of glucose to carbon dioxide and water requires 6 moles of oxygen. Therefore, the percentage of glucose oxidized (Aerobic Index) can be calculated from the equation:

\* The word "venous" when used subsequently refers to blood from the superior bulb of the jugular vein.

TABLE 1. Electroencephalographic Changes During Hypocarbica in Lightly Anesthetized Man

Level	Beta Activity	Theta Activity	Delta Activity
0	Present	None	None
I	Present	Fewer than 5 waves per 10 seconds	None
II	Present	More than 5 waves per 10 seconds	None
III	Present	More than 5 waves per 10 seconds; Increased amplitude	Fewer than 5 waves per 10 seconds
IV	Present	More than 5 waves per 10 seconds; Increased amplitude	More than 5 waves per 10 seconds; Increased amplitude

Aerobic Index (AI)

$$= \frac{(A - V)_{O_2} \times 100 \text{ per cent}}{6 \times (A - V)_{\text{glucose}}}$$

where  $(A - V)_{O_2}$  and  $(A - V)_{\text{glucose}}$  represent the arteriovenous differences in oxygen and glucose content in mM/liter.

(B) When glucose is metabolized anaerobically, 2 moles of lactate are produced from each mole of glucose. The percentage of glucose converted to lactate (Anaerobic Index) can be calculated from the equation:

Anaerobic Index (ANI)

$$= \frac{(A - V)_{\text{lactate}} \times 100 \text{ per cent}}{2 \times (A - V)_{\text{glucose}}}$$

where  $(A - V)_{\text{lactate}}$  is the arteriovenous difference in lactate concentration in mM/liter.

An estimate of cerebral anaerobiosis was sought in the calculation of excess lactate (XL) as described by Huckabee,<sup>13</sup> using the formula:

$$XL = (L_V - L_A) - (P_V - P_A) \frac{L_A}{P_A}$$

where L and P represent the blood lactate and pyruvate concentrations in mM/liter, and the

TABLE 2. Cerebral Metabolism During Thiopental-N<sub>2</sub>O-O<sub>2</sub> Anesthesia of Man. Mean Values in 6 Subjects of Group I

	Normocarbica (Mean PaCO <sub>2</sub> = 41.3 mm. Hg)		Hypocarbica (Mean PaCO <sub>2</sub> = 18.3 mm. Hg)		Significance of Difference ( <i>P</i> )
	Mean	SE <sub>m</sub>	Mean	SE <sub>m</sub>	
Rectal temperature (°C.)	36.5	0.4	36.5	0.3	>0.5
CMR <sub>glucose</sub> (mg./100 g./min.)	3.31	0.22	3.82	0.24	>0.2
CMR <sub>O<sub>2</sub></sub> (ml./100 g./min.)	2.39	0.19	2.50	0.20	>0.5
CMR <sub>lactate</sub> (mM/100 g./min.)	2.55*	0.94	6.61*	1.62	>0.1
Aerobic metabolic index (%)	98.3*	8.4	87.6	3.6	>0.2
Anaerobic metabolic index (%)	7.4*	2.6	15.0	3.2	>0.1
Excess lactate (mM/liter)	0.04*	0.04	0.04	0.08	>0.5
Glucose accounted for (%)	102.5*	8.15	103.5	2.8	>0.5

\* Data available from only 5 subjects; *t*-tests done using only five pairs.

† Matched pairs *t*-tests.

subscripts A and V denote arterial and venous blood.

Cerebral metabolic rates for glucose (CMR<sub>glucose</sub>), lactate (CMR<sub>lactate</sub>), and oxygen (CMR<sub>O<sub>2</sub></sub>) were calculated for the subjects in Group I. These were computed as the product of CBF and the appropriate arteriovenous content difference.

### Results

Cerebral metabolic parameters are listed in table 2 for the 6 anesthetized subjects of Group I, at mean PaCO<sub>2</sub> levels of 41.3 and 18.3 mm. of mercury. Cerebral glucose consumption was 27 per cent lower than the value measured in this laboratory in the awake state; *i.e.*, 3.31 as compared to the normal value of 4.54 mg./100 g. minute (*P* of difference < 0.01). The CMR<sub>O<sub>2</sub></sub> at normocarbica was 23

per cent lower than the value obtained in this laboratory in conscious man, a phenomenon which was discussed in an earlier work.<sup>2</sup> When PaCO<sub>2</sub> was normal, the cerebral production of lactate (CMR<sub>lactate</sub>), and values of excess lactate (XL), jugular venous P<sub>O<sub>2</sub></sub> (Pv<sub>O<sub>2</sub></sub>), Aerobic Index (AI) and Anaerobic Index (ANI) were not significantly different from the levels noted in conscious man in this laboratory.

When PaCO<sub>2</sub> was lowered to a mean of 18.3 mm. of mercury, CMR<sub>glucose</sub> and CMR<sub>O<sub>2</sub></sub> were not altered further. However, three indices of cerebral metabolism: CMR<sub>lactate</sub>, ANI, and AI changed in a direction indicative of increased anaerobiosis. Although none of these changes was statistically significant, values in 4 of 5 subjects changed in an anaerobic direction. The mean cerebral excess lactate value did not change, and in only one subject did a significantly large value appear during hypocarbica.

In both normocarbica and hypocarbica phases approximately 100 per cent of the (A - V)<sub>glucose</sub> difference was accounted for as the sum of (1) aerobic utilization (*i.e.*, combination with O<sub>2</sub>), (2) anaerobic utilization (*i.e.*, conversion to lactate), and (3) conversion to pyruvate.

During hypocarbica the EEG level changed in a "hypoxic" direction in each subject (table 3). These small but definite changes in the EEG, together with the suggestive but inconclusive changes in CMR<sub>lactate</sub>, ANI, and AI, suggested further exploration of the pos-

TABLE 3. Electroencephalographic Levels in 6 Subjects of Group I During Normocarbica and Hypocarbica

Subject	EEG Levels	
	Normocarbica (Mean PaCO <sub>2</sub> = 41.3 mm. Hg)	Hypocarbica (Mean PaCO <sub>2</sub> = 18.3 mm. Hg)
301	0	II
303	0	III
304	0	I
305	0	III
306	0	II
307	1	II
Median EEG level	0	II

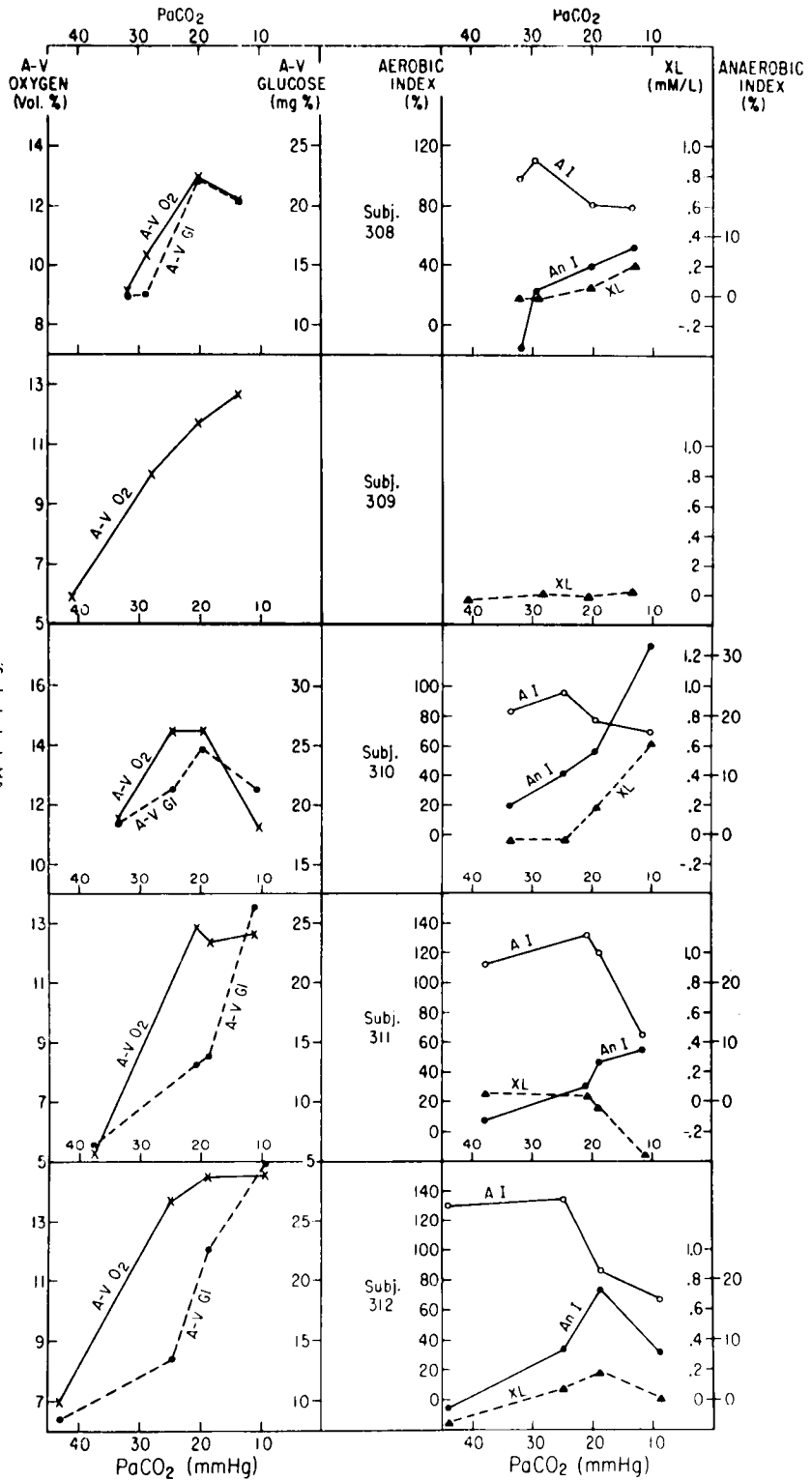


FIG. 1. The effects of progressive hypocarbia on brain oxygen extraction, glucose extraction, Aerobic Index, Anaerobic Index and "excess lactate" in 5 subjects.

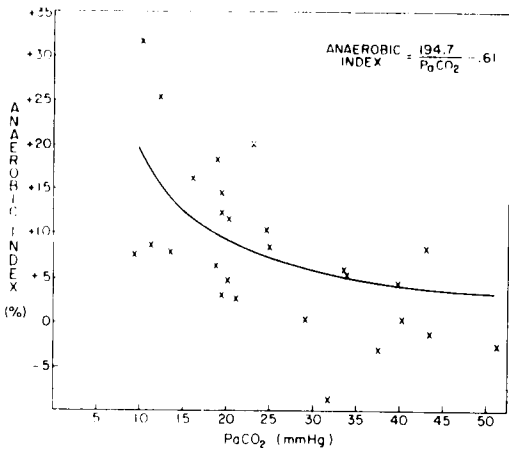


FIG. 2. Cerebral Anaerobic Index as a function of  $\text{PaCO}_2$ .

sible changes in brain metabolic pattern during even more marked hypocarbia (Group II).

$\dot{V}_E$  (25.1 liters/minute) was considerably greater in the subjects of Group II than in Group I (14.9 liters/minute); and the lowest  $\text{PaCO}_2$  (mean 11.6,  $\text{SE}_{\text{m}}$  0.9 mm. of mercury) in Group II was 6.7 mm. of mercury below that achieved in Group I. Among the four phases of Group II there were no significant differences in  $\dot{V}_E$ , jugular venous thiopental concentration, rectal temperature, or interval from the induction of anesthesia to the time of measurement.

The effects of decreasing  $\text{PaCO}_2$  on  $(A - V)_{\text{O}_2}$ ,  $(A - V)_{\text{glucose}}$ , AI, ANI, and cerebral excess lactate in the 5 subjects of Group II are

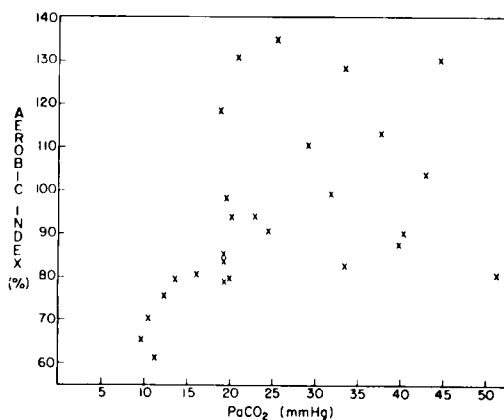


FIG. 3. Cerebral Aerobic Index as a function of  $\text{PaCO}_2$ .

shown in figure 1. As  $\text{PaCO}_2$  was lowered to about 20 mm. of mercury,  $(A - V)_{\text{O}_2}$  increased in all subjects. Only in subject 309 did oxygen extraction continue to increase with further lowering of  $\text{PaCO}_2$ ; in the remaining individuals the  $(A - V)_{\text{O}_2}$  values reached a plateau or were decreased with further hypocarbia. Glucose extraction continued to increase in subjects 311 and 312 at those  $\text{PaCO}_2$  levels at which oxygen extraction had become fixed. In subject 310, oxygen extraction failed to increase below a  $\text{PaCO}_2$  of 24.5 mm. of mercury, while glucose extraction increased until a  $\text{PaCO}_2$  of 19.2 mm. of mercury was reached; in this man both oxygen and glucose extraction were then markedly reduced when  $\text{PaCO}_2$  was further lowered to 10.2 mm. of mercury. Brain glucose and oxygen extraction decreased simultaneously below a  $\text{PaCO}_2$  of 19.9 mm. of mercury in subject 308.

In all of the 4 subjects in whom complete data are available, there was a decrease in AI beginning at  $\text{PaCO}_2$  values of approximately 20 mm. of mercury. ANI increased as the  $\text{PaCO}_2$  was reduced from normal, although in subject 312 this trend was reversed when  $\text{PaCO}_2$  reached 9.4 mm. of mercury, the lowest level attained in any subject.

In this laboratory, cerebral excess lactate values in normocarbic man normally range between  $\pm 0.15$  mM/liter. In the present study only six values were recorded outside this range; one was in Group I and five in Group II. Five of these abnormal values were elevated and one (subject 311) was low ( $-0.36$  mM/liter). All six were measured at  $\text{PaCO}_2$  values below 20 mm. of mercury, and in general, the degree of abnormality was inversely related to the  $\text{PaCO}_2$  level. However, disparate values of XL were present in only 6 of the 13 measurements made at  $\text{PaCO}_2$  levels below 20 mm. of mercury.

The calculated values of ANI for all subjects in Group I and II have been plotted as a function of  $\text{PaCO}_2$  (fig. 2). As  $\text{PaCO}_2$  was reduced, ANI tended to increase. A hyperbolic regression curve and an equation describing the relation between these two parameters are shown.

The AI of all subjects has been plotted as a function of  $\text{PaCO}_2$  (fig. 3). There is considerable scatter in the values of AI at levels of

TABLE 4. Electroencephalographic Levels in 5 Subjects of Group II with Changes in  $P_{aCO_2}$

Subject	EEG Levels			
	Mean $P_{aCO_2}$ 37.2 mm. Hg	Mean $P_{aCO_2}$ 25.5 mm. Hg	Mean $P_{aCO_2}$ 19.4 mm. Hg	Mean $P_{aCO_2}$ 11.6 mm. Hg
308	I	0	II	III
309	0	0	II	I
310	0	I	I	II
311	0	I	I	III
312	I	0	II	II
Median EEG Level	0	0	II	II

$P_{aCO_2}$  greater than 20 mm. of mercury. In contrast, there is a distinct tendency for AI to decrease progressively at lower levels of  $P_{aCO_2}$ .

The effect of alterations in  $P_{aCO_2}$  on  $P_{vO_2}$  in the subjects of Group II is shown in figure 4. As expected,  $P_{vO_2}$  decreased as  $P_{aCO_2}$  was lowered, but tended to approach a plateau at  $P_{aCO_2}$  levels below 20 mm. of mercury.

The electroencephalographic response to alterations of  $P_{aCO_2}$  in the men of Group II is presented in table 4. Although there was considerable variation in both the  $P_{aCO_2}$  level at which changes first occurred and in the degree of change, alterations occurred in every subject as  $P_{aCO_2}$  was lowered. In only two instances was an EEG level of III produced. These occurred at  $P_{aCO_2}$  values below 14 mm. of mercury.

Despite the alterations in metabolic pattern and in the EEG, all subjects regained consciousness promptly and their mental state appeared grossly normal during the postanesthetic observation period of about 18 hours.

**Discussion**

*Validity of Cerebral Metabolic Indices.* All of the metabolic indices utilized in this investigation are derived from arterial-jugular venous differences of various substances. Zierler has discussed the problems inherent in the use of such differences.<sup>14</sup> For a single A-V difference from any organ to be interpretable, the venous blood draining it must be in equilibrium with the tissue. We believe that this condition was met in the present investigation for both oxygen and glucose.<sup>12, 15</sup> Therefore, A-V oxygen and glucose differences reflect

cerebral utilization, and values of  $CMR_{O_2}$ ,  $CMR_{glucose}$ , and AI are accurate indices of brain metabolism.

There is some doubt, however, that the above criterion is fulfilled for arteriovenous differences of lactate and pyruvate. Eichenholz and his associates demonstrated that in dogs rendered hypocarbic ( $P_{aCO_2} = 10$  mm. of mercury)<sup>16</sup> arterial lactate and pyruvate concentrations were not stable, but continued to rise at an appreciable rate for over four hours. Furthermore, the "blood-brain barrier" is known to impede the movement of ionized substances to and from the central nervous system, and there is little information on the transit times of these two metabolites from the brain.<sup>17</sup> Despite the fact that indices calculated from arteriovenous lactate differences are theoretically liable to give unreliable estimates of brain anaerobiosis, approximately 100 per cent of the glucose extracted by the brain can usually be accounted for as being metabo-

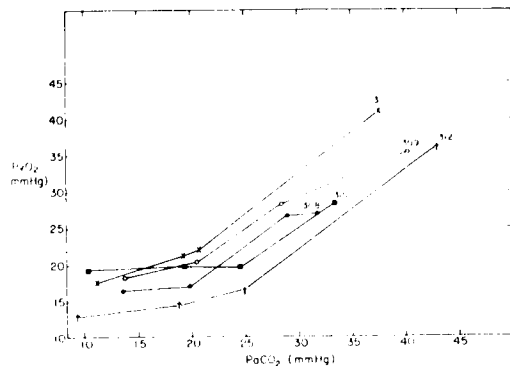


FIG. 4. Jugular venous  $P_{vO_2}$  as a function of  $P_{aCO_2}$ . Individual data in 5 subjects.

lized with oxygen or converted to lactate and pyruvate (table 2).

A rise in  $CMR_{lactate}$  or ANI indicates increased anaerobic metabolism. However, a failure of  $CMR_{lactate}$  or ANI to increase could be due to a disequilibrium of lactate between brain and venous blood. In this situation, more reliable indices ( $CMR_{O_2}$ ,  $CMR_{glucose}$ , and AI) might still indicate decreased cerebral aerobic metabolism.

Uncertainties are compounded when cerebral "excess lactate" is calculated, for this value depends on A-V differences of pyruvate as well as lactate. Inherent in the calculation of XL is the assumption that both lactate and pyruvate cross the blood-brain barrier at equal and rapid rates. Such an assumption may not be valid and has apparently not been tested. Olson has recently raised other more fundamental objections to the interpretation of excess lactate values.<sup>17</sup> In the present investigation, when hypocarbia was extreme, and other metabolic indices changed consistently in an anaerobic direction, changes in XL were more variable. Attention is called to the observations of Cain who noted no increase in cerebral excess lactate in the dog with  $Pa_{CO_2}$  of 9.5 mm. of mercury.<sup>18</sup> For all these reasons cerebral XL appears to be an unreliable indicator of anaerobiosis in the brain.

*Cerebral Metabolic Alterations with Progressive Hypocarbia.* Although cerebral glucose and oxygen consumption were diminished when  $Pa_{CO_2}$  was normal during anesthesia, there were no changes in the pattern of glucose utilization. Thus brain metabolic pathways were apparently unaltered during nitrous oxide anesthesia and normocarbia.

During hypocarbia in the subjects of Group I (mean  $Pa_{CO_2}$  = 18.3 mm. of mercury) no metabolic measurements differed significantly from those made in the normocarbic state (table 2). However, a reduction of  $Pa_{CO_2}$  below this level produced definite alterations of metabolic pathways in the individual subjects of Group II (fig. 1). As can be seen in pooled data for all subjects (fig. 2), as  $Pa_{CO_2}$  was diminished below normal levels, there was an increase in the proportion of glucose converted to lactate (ANI). An exception to this trend is seen in subject 312 (fig. 1) in whom a reduction in  $Pa_{CO_2}$  from 18.7 to 9.4 mm. of mer-

cury was accompanied by a decrease in ANI. This decrease might be attributed to a failure of brain lactate level to reach equilibrium with jugular venous blood, as discussed above.

Further evidence of an alteration in brain metabolism when  $Pa_{CO_2}$  is lowered below approximately 20 mm. of mercury is shown in figure 3. There is considerable scatter in values of AI at  $Pa_{CO_2}$  levels greater than 20 mm. of mercury, but below this value the variation is greatly diminished and AI decreases progressively with further lowering of  $Pa_{CO_2}$ . At the six lowest values of  $Pa_{CO_2}$  (mean = 12.0 mm. of mercury), mean  $Pv_{O_2}$  was 17.0 mm. of mercury and the mean AI value was 73.7 per cent. A different pattern is seen in the measurements made at the six next lowest values of  $Pa_{CO_2}$  (mean = 19.2 mm. of mercury). Their average  $Pv_{O_2}$  was 19.0 mm. of mercury and the average AI value was 90.8 per cent. The marked difference in values of AI between  $Pv_{O_2}$  levels of 19.0 and 17.0 mm. of mercury indicates that the "threshold" for this anaerobic shift in brain metabolism was, for these subjects, at a jugular venous oxygen tension between 17 and 19 mm. of mercury. This "threshold" value agrees quite well with the findings of Hirsch who noted a diminished oxygen uptake of the perfused dog brain when blood flow was decreased until  $Pv_{O_2}$  reached 20 mm. of mercury.<sup>19</sup>

Possible factors responsible for the shift of cerebral metabolism toward anaerobiosis during extreme hypocarbia include: (1) a lowering of CBF below a "critical" value, (2) a decrease in oxygen transfer from blood to tissue secondary to respiratory alkalosis (Bohr effect), or (3) a specific effect of hypocarbia or cerebral alkalosis on brain metabolic pathways. The role of each of these factors is a subject for future investigation.

*Clinical Implications.* There were electroencephalographic alterations below  $Pa_{CO_2}$  levels of 20 mm. of mercury in all subjects; but these were both minimal and rapidly reversible. Similar EEG patterns were noted during anesthesia and hyperventilation by Geddes and Gray and also by Hughes and his co-workers.<sup>4,5</sup> These minimal EEG changes are consistent with a mild hypoxic pattern but do not establish a diagnosis of cerebral ischemia. Upon return of consciousness, no gross changes

were noted in the mental function of the healthy young subjects of this investigation, although no attempt was made to elicit more subtle changes described by others.<sup>6</sup> Although a level of hyperventilation sufficient to produce a sustained reduction of  $P_{aCO_2}$  to 20 mm. of mercury will rarely be achieved in clinical practice, a reduction of  $P_{aCO_2}$  to this level seems permissible in healthy young patients during anesthesia. Since the effects of a sustained reduction of  $P_{aCO_2}$  below this level (e.g., during a 4-6 hour operation) are unknown, caution should be used in producing a more extreme degree of hypocarbia.

Hypocarbia even to levels above 20 mm. of mercury could conceivably produce cerebral damage in two types of patients: (1) those with diminished rates of cerebral perfusion and (2) those with increased cerebral metabolic requirements. Thus, the effects of hypocarbia in the presence of arterial hypotension, cerebrovascular disease, or advanced age could be deleterious. Likewise, the febrile patient, whose cerebral metabolic rate is thereby increased, could be harmed by a reduction in  $P_{aCO_2}$ . Therefore, only minimal hypocarbia should be produced in patients with reduced rates of CBF or with increased cerebral metabolism.

### Summary

Studies of brain carbohydrate metabolism were performed in 11 healthy male volunteers during anesthesia induced with thiopental and maintained with 70 per cent nitrous oxide and *d*-tubocurarine. During normocarbia, cerebral oxygen and glucose consumption were reduced from the normal value in conscious man, but there was no evidence to indicate an alteration in the pattern of glucose utilization.

Lowering of  $P_{aCO_2}$  to approximately 20 mm. of mercury, produced no consistent change in brain metabolic pathways, while  $P_{aCO_2}$  levels below 20 mm. of mercury were associated with a decreased aerobic utilization and an increased anaerobic utilization of glucose. All subjects had mild, readily reversible changes in EEG pattern with  $P_{aCO_2}$  levels below 20 mm. of mercury. Consistent changes in cerebral "excess lactate" were not observed during hypocarbia, and this measurement was concluded to be an unreliable estimate of brain

anaerobiosis. No gross changes in mental function were noted.

Possible mechanisms for the observed changes in brain glucose utilization are suggested. Clinical implications of these observations were discussed.

### References

1. Kety, S. S., and Schmidt, C. F.: Effects of altered tensions of carbon dioxide and oxygen on cerebral blood flow and cerebral oxygen consumption of normal young men, *J. Clin. Invest.* 27: 484, 1948.
2. Wollman, H., Alexander, S. C., Cohen, P. J., Smith, T. C., Chase, P. E., and Vander Molen, R. A.: Cerebral circulation during general anesthesia and hyperventilation in man, *ANESTHESIOLOGY* 26: 329, 1965.
3. Sugioka, K., and Davis, D. A.: Hyperventilation with oxygen: A possible cause of cerebral hypoxia, *ANESTHESIOLOGY* 21: 135, 1960.
4. Geddes, I. C., and Gray, T. C.: Hyperventilation in the maintenance of anesthesia, *Lancet* 2: 4, 1959.
5. Hughes, J. R., King, B. D., Cutler, J. A., and Markello, R.: The EEG in hyperventilated, lightly anesthetized patients, *Electroenceph. Clin. Neurophysiol.* 14: 274, 1962.
6. Allen, G., and Morris, L. E.: Central nervous system effects of hyperventilation during anesthesia, *Brit. J. Anaesth.* 34: 296, 1962.
7. Cohen, P. J., Wollman, H., Alexander, S. C., Chase, P. E., and Behar, M. G.: Cerebral carbohydrate metabolism in man during halothane anesthesia, *ANESTHESIOLOGY* 25: 185, 1964.
8. Brodie, B. B., Mark, L. C., Papper, E. M., Lief, P. A., Bernstein, E., and Rovenstine, E. A.: The fate of thiopental in man and a method for its estimation in biological material, *J. Pharmacol. Exp. Ther.* 98: 85, 1950.
9. Van Slyke, D. D., and Neill, J. A.: The determination of gases in blood and other solutions by vacuum extraction and manometric measurement, *J. Biol. Chem.* 61: 523, 1924.
10. Gastaut, H., Bostem, F., Fernandez-Guardiola, A., Naquet, R., and Gibson, W.: *In: Cerebral Anoxia and the Electroencephalogram*, Meyer, J. S. and Gastaut, H. (Editors). Springfield, Ill., Charles C Thomas, 1961, Ch. 32, p. 343.
11. Gainer, H., Allweis, C. L., and Chaikoff, I. L.: Precursors of metabolic  $CO_2$  production by the brain of the anesthetized, intact dog: The effect of electrical stimulation, *J. Neurochem.* 10: 903, 1963.
12. Sokoloff, L.: *In: Handbook of Physiology, Section 1: Neurophysiology, Volume III*, Washington, American Physiological Society, 1960, Cha. LXXXVII, p. 1843.



13. Huckabee, W. E.: Relationships of pyruvate and lactate during anaerobic metabolism: Coronary adequacy, *Amer. J. Physiol.* **200**: 1169, 1961.
14. Zierler, K. L.: Theory of the use of arterio-venous concentration differences for measuring metabolism in steady and non-steady states, *J. Clin. Invest.* **40**: 2111, 1961.
15. Tschirgi, R. D.: *In: Handbook of Physiology, Section 1: Neurophysiology, Volume III, Washington, American Physiological Society, 1960, Ch. LXXVIII, p. 1865.*
16. Eichenholz, A., Mulhausen, R. O., Anderson, W. E., and MacDonald, F. M.: Primary hypocapnia: A cause of metabolic acidosis, *J. Appl. Physiol.* **17**: 283, 1962.
17. Olsen, R. E.: Editorial, *Ann. Intern. Med.* **59**: 960, 1963.
18. Cain, S. M.: An attempt to demonstrate cerebral anoxia during hyperventilation of anesthetized dogs, *Amer. J. Physiol.* **204**: 323, 1963.
19. Hirsch, H., Gleichmann, U., Kristen, H., and Magazinovic, V.: Über die Beziehung zwischen O<sub>2</sub>-Aufnahme des Gehirns und O<sub>2</sub>-Druck im Sinusblut des Gehirns bei uneingeschränkter Durchblutung, *Pflüger. Arch. ges. Physiol.* **273**: 213, 1961.

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**CARBON MONOXIDE POISONING** Accumulation of carbon monoxide in man is related to the concentration of gas in the air, the duration of exposure and the rate and depth of respiration. When a 1 per cent carbon monoxide concentration is present in the inhaled air a lethal concentration may be reached in the blood in less than ten minutes. The elimination of carbon monoxide from the blood is slower than its intake, since only half of the carbon monoxide in the blood may be eliminated in two to four hours by breathing air. This elimination rate is increased by breathing oxygen, so that the same amount can be eliminated in fifteen to thirty minutes. Generally, carbon monoxide poisoning leads to a fatal outcome when hemoglobin becomes more than 50 per cent saturated. (*McBay, A. J.: Carbon Monoxide Poisoning, New Engl. J. Med.* **272**: 252 (Feb. 4) 1965.)

**ADRENAL FUNCTION** Glucocorticoid function of the adrenal cortex in 54 patients and 25 dogs was assessed from the level of 17-oxycorticosteroids in blood plasma under the influence of different types of anesthesia and operation, and also following ACTH and hydrocortisone dosage. Changes in the glucocorticoid function were analogous in ether-oxygen and nitrous oxide-plus-oxygen anesthesia with muscle relaxants, as well as in combined ether-oxygen and halothane anesthesia without muscle relaxants. A high blood level of 17-oxycorticosteroids during anesthesia and operation does not necessarily indicate an increased content of biologically active hydrocortisone in the body. (*Usvator, Y. A., and others: Changes in the Glucocorticoid Function of the Adrenal Cortex in Connection With Anaesthesia and Operation (Russian), Soviet Medicine* **27**: 54, 1964.)