Cerebral Carbohydrate Metabolism in Man During Halothane Anesthesia

Effects of Pa_{CO_2} on Some Aspects of Carbohydrate Utilization

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Cerebral blood flow and carbohydrate utilization were measured in healthy adult male volunteers during anesthesia produced by 1.2 per cent halothane in oxygen during hypocarbia, normocarbia, and mild hypercarbia. Cerebral oxygen consumption was unaffected by the rate of cerebral blood flow but was diminished by approximately 15 per cent in the presence of a 1° C. fall in body temperature. Metabolic alterations induced by 1.2 per cent halothane were slight or absent. Increased anaerobic metabolism was not demonstrated when cerebral blood flow was diminished during hypocarbia. Slight alterations in the pathways of glucose and oxygen metabolism were shown to be produced by changes in Pa_{CO_2}.

DELIBERATE hyperventilation during anesthesia is commonly used in the hope of "potentiating" anesthesia. Some investigators [1-6] have proposed that hypocarbia, acting to diminish cerebral blood flow (CBF), may result in cerebral hypoxia and that the "potentiation" of anesthesia noted during hyperventilation may be a result of such hypoxia. Others[7-9] are of the opinion that the effects of hyperventilation result directly from the diminution of P_{CO_2} in cerebral tissue and that no hypoxic injury results from the technique.

This laboratory has examined the effects of hyperventilation during halothane anesthesia on human cerebral metabolism of glucose, oxygen, and lactic acid. The decrease in CBF produced by decreased Pa_{CO_2} was not associated with evidence of cerebral hypoxia. In addition, normocarbia and mild hypercarbia of a degree sufficient to increase CBF were also studied. Cerebral metabolism of glucose, oxygen, and lactate during halothane anesthesia was little changed from that of awake man.

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Methods

Eighteen measurements of whole brain blood flow and carbohydrate metabolism were performed on ten fasting healthy adult male volunteers ranging in age from 22 to 41 years. They were studied without premedication or operation during the inhalation of 1.2 per cent halothane in oxygen. Intravenous normal saline was infused in volume sufficient to replace blood removed for samples. Six measurements were made during hypocarbia, six at normal Pa_{CO_2}, and six during mild hypercarbia. All but two of the subjects were studied at two levels of Pa_{CO_2}; the selection of Pa_{CO_2} was randomized. The anesthetic procedures, breathing, sampling and recording systems are described elsewhere.[10] Measurements of CBF, blood *p*H, P_{CO_2}, P_{O_2}, and oxygen content were made with techniques described in the same work.

Arterial and cerebral venous * blood lactate and pyruvate contents were determined enzymatically [11] in a system employing lactic dehydrogenase and reduced or oxidized diphosphopyridine nucleotide. Glucose content was also determined enzymatically [11] with commercially available reagents.† All determinations were done in duplicate. Cerebral meta-

* All reference to "venous blood" implies sampling from the superior bulb of the internal jugular vein.

† Glucostat (Worthington).

TABLE 1. Cerebral Blood Flow and Carbohydrate Metabolism During Halothane Anesthesia: Conditions

	Hypocarbia		Normocarbia		Hypercarbia	
	Mean	S.E.m	Mean	S.E.m	Mean	S.E.m
Age (years)	25.0	1.1	24.7	1.2	25.8	3.1
End-tidal halothane concentration (%)	1.03	0.04	1.03	0.03	0.96	0.05
$\dot{V}_E$ (liters/minute)	12.18	0.67	13.08	0.94	11.48	0.47
V_T (ml.)	801	39	847	59	803	44
f (breaths/minute)	15.4	1.0	15.7	1.1	14.4	0.6
Mid-esophageal temperature (°C.)	36.2	0.4	36.4	0.4	36.0	0.6

V_E = Minute ventilation; V_T = Tidal volume; f = Respiratory rate.

bolic rates for glucose ($CMR_{glucose}$), lactate ($CMR_{lactate}$), and oxygen (CMR_{O_2}) were obtained as the product of CBF and arterial-venous difference in content. An estimation of anaerobic metabolism was obtained with the calculation of excess lactate as described by Huckabee.[12] Positive values of excess lactate indicate an increased lactate : pyruvate ratio and suggest the presence of significant anaerobiasis.

In conscious man, glucose utilization by the brain involves oxygen consumption and lactate production.[13-15] Six moles of oxygen are required for the conversion of one mole of glucose to CO_2 and water. When no oxygen is available, two moles of lactic acid are produced from one mole of glucose. Cerebral glucose and oxygen consumption as well as lactate production were measured in the present experiments. The above assumptions were used to determine the percentage of glucose combining with oxygen as well as that percentage converted to lactic acid as follows:

$$\text{Percentage of glucose converted to lactic acid} = \frac{CMR_{lactate}}{CMR_{glucose} \times 2} \times 100$$

$$\text{Percentage of glucose oxidized} = \frac{CMRO_2}{CMR_{glucose} \times 6} \times 100$$

TABLE 2. Cerebral Blood Flow and Carbohydrate Metabolism During Halothane Anesthesia: Blood Analyses

	Hypocarbia		Normocarbia		Hypercarbia	
	Mean	S.E.m	Mean	S.E.m	Mean	S.E.m
Arterial						
P_{CO_2} (mm. Hg)	25.1	1.0	37.3	0.8	51.1	1.3
P_{O_2} (mm. Hg)	558	35	566	15	573	19
*p*H	7.595	0.022	7.449	0.019	7.363	0.005
O_2 content (vol. %)	20.6	0.4	20.4	0.3	20.5	0.2
Lactate (m*M*/l.)	1.573	0.188	1.103	0.071	1.413	0.125
Pyruvate (m*M*/l.)	0.113	0.020	0.086	0.007	0.102	0.011
Glucose (mg. %)	118.6	6.2	121.7	6.4	123.2	9.7
Venous						
P_{CO_2} (mm. Hg)	39.2	0.8	45.8	1.2	58.3	1.5
P_{O_2} (mm. Hg)	30.9	3.9	53.7	5.1	63.5	4.8
*p*H	7.488	0.016	7.399	0.015	7.333	0.004
O_2 content (vol. %)	10.5	0.8	14.9	0.2	16.6	0.2
Lactate (m*M*/l.)	1.736	0.208	1.187	0.071	1.491	0.166
Pyruvate (m*M*/l.)	0.141	0.029	0.092	0.009	0.104	0.011
Glucose (mg. %)	101.0	6.7	113.6	6.3	118.1	10.0

TABLE 3. Cerebral Blood Flow and Carbohydrate Metabolism During Halothane Anesthesia: Indices of Cerebral Circulation and Metabolism

	Hypocarbia		Normocarbia		Hypercarbia	
	Mean	S.E.m	Mean	S.E.m	Mean	S.E.m
CBF (ml./100 g./min.)	25.9	2.4	50.8	2.7	63.8	3.2
CMR_{O_2} (ml./100 g./min.)	2.65	0.40	2.80	0.23	2.45	0.17
$CMR_{glucose}$ (mg./100 g./min.)	4.51	0.65	4.15	0.51	3.20	0.13
$CMR_{lactate}$ (μM/100 g./min.)	3.99	0.61	4.21	2.39	5.16	3.83
Percentage of glucose converted to lactate	8.3	1.1	8.1	5.2	10.7	11.4
Percentage of glucose combining with oxygen	80.0	7.4	92.4	4.0	108.3	11.0
Excess lactate (mM/l.)	−0.163	0.154	0.021	0.059	0.045	0.067

Statistical analyses were performed by analysis of variance.[16] The significance of the linearity and deviation from zero of the slope of all regression lines was likewise tested.[17]

Results

Conditions of the study are presented in table 1. No significant differences in any of these variables were present among the three groups: hypocarbia, normocarbia, and hypercarbia.

In table 2 are presented values of arterial and cerebral venous blood constituents and the results of blood gas analyses. All three groups showed significant differences from each other in arterial and venous P_{CO_2} and pH ($P < 0.01$) and in the oxygen content of the venous blood ($P < 0.05$). Arterial lactate and pyruvate contents were elevated during both hypocarbia and hypercarbia although this elevation was not of statistical significance. Blood glucose content was higher than normal, a phenomenon of unknown mechanism very likely related to the anesthetic agent employed. There was no significant difference in arterial glucose content among the three groups; venous glucose content rose with increasing Pa_{CO_2}, reflecting increased CBF.

Indices of cerebral circulation and metabolism are given in table 3. The CBF in each of the three groups is significantly different from that in the other two groups ($P < 0.05$); the effects of Pa_{CO_2} upon CBF have been fully discussed.[10] Over the range of CBF presented in the study, oxygen consumption did not vary significantly when Pa_{CO_2} was changed. Similar findings were made with respect to the rate of glucose consumption although there appears to be a trend relating a decrease in $CMR_{glucose}$ to an increase in Pa_{CO_2}. There were no significant alterations in either the rate of cerebral lactate production or the presence of excess lactate at any level of Pa_{CO_2}. At all levels of CBF, the percentage of glucose converted to lactic acid remained constant. These findings indicate the absence of any changes in the rate of anaerobic metabolism occurring

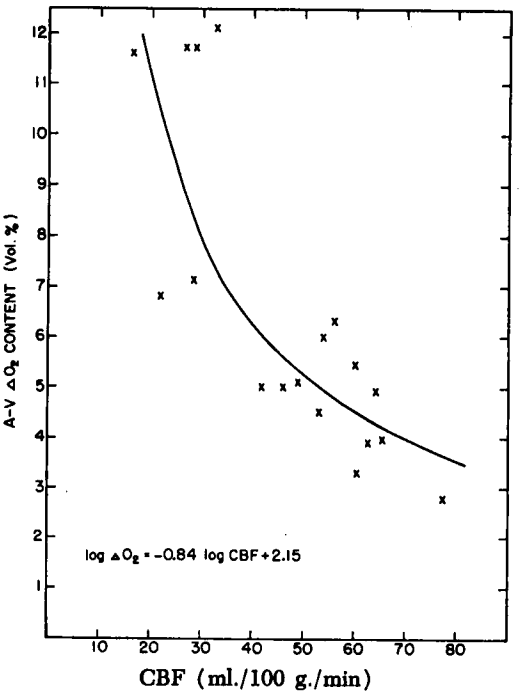

FIG. 1. Arterial-venous oxygen difference as a function of cerebral blood flow during halothane anesthesia.

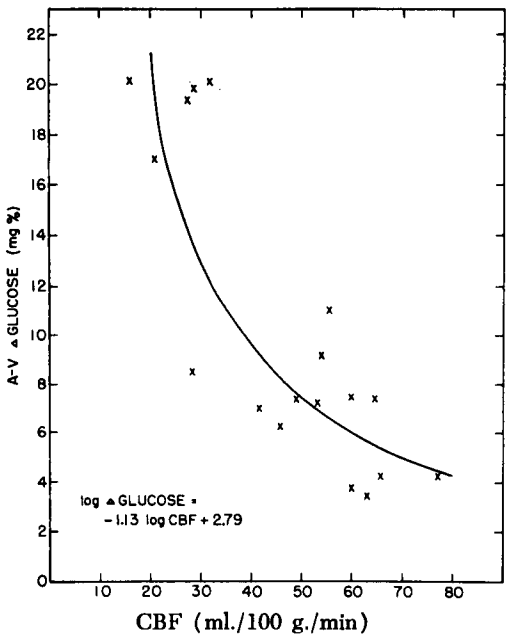

FIG. 2. Arterial-venous glucose difference as a function of cerebral blood flow during halothane anesthesia.

with variation in CBF. Although there were no statistically significant changes among the three groups in the percentage of glucose combining with oxygen, there is a tendency for this percentage to increase with increasing Pa_{CO_2}.

Figures 1 and 2 illustrate the relationship of the arterial-venous differences in glucose and oxygen content to the rate of CBF. As CBF decreases, the extraction of these substances by the brain increases so that a normal rate of consumption is maintained.

Figure 3 illustrates the effects of changes in Pa_{CO_2} on the ratio of arterial-venous oxygen difference to arterial-venous glucose difference. The data indicate that there is a direct relationship between Pa_{CO_2} and the $\frac{\text{A–V oxygen}}{\text{A–V glucose}}$ ratio.

Figure 4 indicates the effect of temperature upon the rate of cerebral oxygen consumption. Solution of the equation of the regression line for a temperature of 37° C. yields a value of 2.96 ml./100 g./minute, which may be compared with the value of 3.09 ml./100 g./minute found in conscious man in this laboratory. A regression line derived from the work of Bering [18] is presented for comparison.

Discussion

A diminished rate of $CMRo_2$ during hypothermia has been demonstrated in animals [18, 19] and in man.[20] Although the present results were obtained over a fairly small range of temperature, there is a good correlation of the rate of cerebral oxygen consumption with body temperature as illustrated in figure 4. These data would indicate that most of the 15 per cent depression of $CMRo_2$ seen in this study results from the lowered body temperature of the subject. A small reduction of

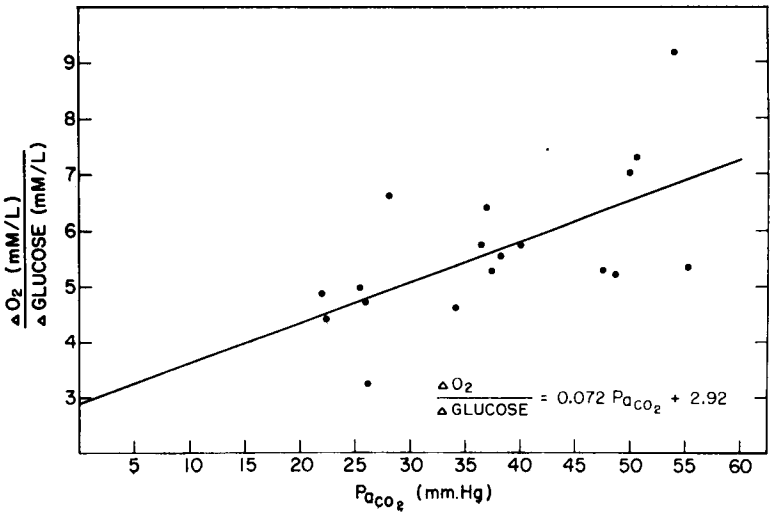

FIG. 3. Ratio of arterial-jugular venous difference of oxygen: glucose as related to Pa_{CO_2} during halothane anesthesia.

$CMRo_2$ by the anesthetic agent itself cannot be ruled out. Furthermore, the effects of other concentrations of halothane on $CMRo_2$ are not now known.

That $CMRo_2$ does not decrease in conscious man during hypocarbia was suggested by Kety and Schmidt.[21, 22] Pierce *et al.*[23] have shown that although cerebral oxygen consumption is lowered following large doses of thiopental, the diminished CBF produced by hyperventilation results in no further changes in oxygen consumption. However, in both of these studies, where the N_2O method was used for estimation of CBF, there are systematic errors in the calculation [24] which would tend to overestimate the CBF and consequently the $CMRo_2$. This overestimation becomes increasingly significant as CBF is diminished. This criticism cannot be applied to the Kr^{85} method of determining CBF as employed in the present investigation.[25]

In this study, cerebral oxygen utilization remained stable at the three specified levels of Pa_{CO_2} (table 3). The lack of effect of Pa_{CO_2} on $CMRo_2$ is further illustrated in figure 1 which demonstrates that over a considerable range of cerebral blood flows, the brain retains its ability to extract sufficient oxygen from the perfusing blood to maintain normal consumption.

The stability of oxygen consumption as CBF diminishes does not, in itself, rule out the presence of cerebral hypoxia. It is conceivable that changes in $CMRo_2$ may occur in specific areas of the brain and not be detected by measurement of the rate of *whole brain* oxygen consumption. In addition, the *demand* for oxygen by the brain could change with variation in Pa_{CO_2} even if the rate of oxygen *consumption* remained constant. Thus, other criteria for the presence of cerebral hypoxia have been employed in this investigation and may now be considered. Many workers [26-31] have called attention to the biochemical changes occurring in the hypoxic brain. These consist of an increase in lactic acid and inorganic phosphate with a decrease in phosphocreatine and adenosine triphosphate. Recent unpublished work by this laboratory indicates that the inhalation of 7.5 per cent oxygen, while normocarbia is maintained, produces no alteration of human cerebral oxygen

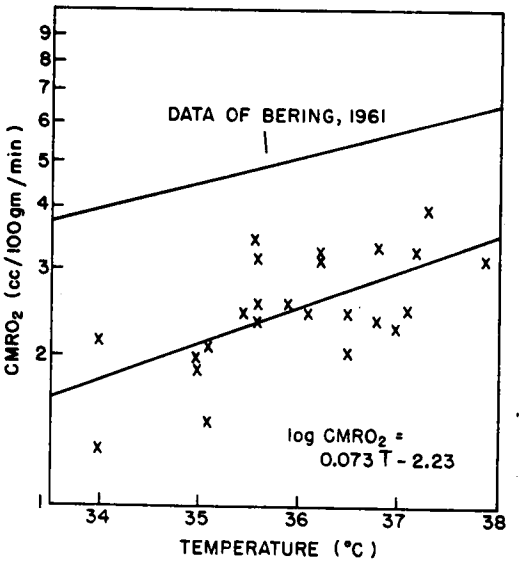

FIG. 4. Effect of temperature on $CMRo_2$ during halothane anesthesia.

consumption. At the same time, however, excess lactate is produced and the percentage of glucose converted to lactic acid increases markedly. In the present study, excess lactate did not accumulate nor was the fraction of glucose converted to lactic acid altered at any level of CBF. The present findings suggest that the lowering of CBF caused by a decrease in Pa_{CO_2} does not produce biochemical evidence of cerebral hypoxia. These findings are similar to those of Cain [32] who demonstrated that excess lactate was not produced by the brain of the anesthetized (pentobarbital 30 mg./kg.) hyperventilated dog.

Although the consumption of oxygen by the brain was unaltered by changes in Pa_{CO_2}, the ratio of $CMRo_2 : CMR_{glucose}$ did vary significantly with Pa_{CO_2} (figure 3, table 3). This is of some interest as it may indicate alternate pathways of glucose utilization, none of which reflects the presence of cerebral hypoxia. In this study, at normal levels of Pa_{CO_2} all of the glucose consumed by the brain was either oxidized or appeared as lactate. During *hypocarbia,* a small fraction of glucose (10 per cent) was neither oxidized nor converted to lactate but may have entered into other phases of glucose metabolism. In contrast, during *hypercarbia,* about 10 per cent more oxygen

than was necessary to oxidize glucose was taken up by the brain and may have oxidized substances other than glucose. The work of Geiger[33] has demonstrated that glucose is rapidly transformed into amino-acids by the perfused animal brain. In addition, it has been shown in animals[33] and in man[34] that CO_2 is produced in the brain from substances other than glucose. It would thus appear that changes in Pa_{CO_2} may slightly alter the pathways of glucose and oxygen metabolism while glucose and oxygen continue to be utilized by the brain in amounts sufficient to maintain the integrity of cerebral function.

Summary

Eighteen measurements of whole brain blood flow and carbohydrate utilization were performed on adult males during the inhalation of 1.2 per cent halothane in oxygen. Measurements were made during hypocarbia ($Pa_{CO_2} = 25$ mm. of mercury), normocarbia ($Pa_{CO_2} = 37$ mm. of mercury), and hypercarbia ($Pa_{CO_2} = 51$ mm. of mercury). The rate of cerebral oxygen consumption was depressed by 15 per cent, a phenomenon ascribed largely to a lowered body temperature. A small depression of $CMRo_2$ due to the direct effect of the anesthetic agent cannot be ruled out. Effects of other concentrations of halothane are not known at the present time.

Although the cerebral blood flow was markedly influenced by Pa_{CO_2}, the rate of oxygen consumption was not altered when CBF and Pa_{CO_2} were changed. Measurements of cerebral lactic acid and glucose metabolism gave no evidence for the occurrence of hypoxia when CBF was diminished during hypocarbia.

Changes in Pa_{CO_2} during halothane anesthesia may result in slight alterations in the pathways of glucose and oxygen metabolism, although none of these changes could be ascribed to the presence of cerebral hypoxia.

References

1. Clutton-Brock, J.: The cerebral effects of overventilation, Brit. J. Anaesth. **29**: 111, 1957.
2. Sugioka, K., and Davis, D. A.: Hyperventilation with oxygen—a possible cause of cerebral hypoxia, ANESTHESIOLOGY **21**: 135, 1960.
3. Allen, G. D., and Morris, L. E.: Central nervous system effects of hyperventilation during anesthesia, Brit. J. Anaesth. **34**: 296, 1962.
4. Malette, W.: Cerebral anoxia resulting from hyperventilation, Surg. Forum **9**: 208, 1958.
5. Malette, W. G., and Eiseman, B.: Cerebral anoxia resulting from hyperventilation, J. Aviat. Med. **29**: 611, 1958.
6. Davis, H., and Wallace, W. M.: Factors affecting changes produced in the electroencephalogram by standardized hyperventilation, Arch. Neurol. Psychiat. **47**: 606, 1942.
7. Bonvallet, M., and Dell, P.: Reflections on the mechanism of the action of hyperventilation upon the EEG, Electroenceph. Clin. Neurophysiol. **8**: 170, 1956.
8. Robinson, J. S., and Gray, T. C.: Observations on the cerebral effects of passive hyperventilation, Brit. J. Anaesth. **33**: 62, 1961.
9. Gibbs, E. L., Gibbs, F. A., Lennox, W. G., and Nims, L. F.: Regulation of cerebral carbon dioxide, Arch. Neurol. Psychiat. **47**: 879, 1942.
10. Wollman, H., Alexander, S. C., Cohen, P. J., Chase, P. E., Melman, E., and Behar, M.: Cerebral circulation of man during halothane anesthesia: Effects of hypocarbia and of *d*-tubocurarine, ANESTHESIOLOGY **25**: 180, 1964.
11. Bergmeyer, H. U., Ed.: Methods of Enzymatic Analysis. (Verlag Chemie), New York, Academic Press, 1963.
12. Huckabee, W. E.: Relationships of pyruvate and lactate during anaerobic metabolism; coronary adequacy, Amer. J. Physiol. **200**: 1169, 1961.
13. Himwich, H. E., Ed.: Brain Metabolism and Cerebral Disorders. Baltimore, Williams & Wilkins Co., 1951.
14. Gibbs, E. L., Lennox, W. G., Nims, L. F., and Gibbs, F. A.: Arterial and cerebral venous blood. Arterial-venous differences in man, J. Biol. Chem. **144**: 325, 1942.
15. Himwich, W. A., and Himwich, H. E.: Pyruvic acid exchange of the brain, J. Neurophysiol. **9**: 133, 1946.
16. Tate, M. W., and Clelland, R. C.: Nonparametric and Shortcut Statistics. Danville, Illinois, Interstate Printers and Publishers, 1957, p. 119.
17. Batson, H. C.: An Introduction to Statistics in the Medical Sciences. Minneapolis, Burgess Publishing Co., 1956, pp. 58–60.
18. Bering, E. A., Jr.: Effect of body temperature change on cerebral oxygen consumption of the intact monkey, Amer. J. Physiol. **200**: 417, 1961.
19. Rosomoff, H. L., and Holaday, D. A.: Cerebral blood flow and cerebral oxygen consumption during hypothermia, Amer. J. Physiol. **179**: 85, 1954.

20. Stone, H. H., Donnelly, C., and Frobese, A. S.: The effect of lowered body temperature on the cerebral hemodynamics and metabolism of man, Surg. Gynec. Obstet. 103: 313, 1956.
21. Kety, S. S., and Schmidt, C. F.: The effects of active and passive hyperventilation on cerebral blood flow, cerebral oxygen consumption, cardiac output, and blood pressure of normal young men, J. Clin. Invest. 25:107, 1946.
22. Kety, S. S., and Schmidt, C. F.: The effects of altered arterial tensions of carbon dioxide and oxygen on cerebral blood flow and cerebral oxygen consumption of normal young men, J. Clin. Invest. 27: 484, 1948.
23. Pierce, E. C., Jr., Lambertson, C. J., Deutsch, S., Chase, P. E., Linde, H. W., Dripps, R. D., and Price, H. L.: Cerebral circulation and metabolism during thiopental anesthesia and hyperventilation in man, J. Clin. Invest. 41: 1664, 1962.
24. Alexander, S. C., Wollman, H., Cohen, P. J., Chase, P. E., and Behar, M. G.: The cerebral vascular response to $Paco_2$ during halothane anesthesia in man, J. Appl. Physiol. In Press.
25. Lassen, N. A., and Munck, O.: The cerebral blood flow in man determined by the use of radioactive krypton, Acta Physiol. Scand. 33: 30, 1955.
26. Stone, W. E., Marshall, C., and Nims, L. F.: Chemical changes in the brain produced by injury and by anoxia, Amer. J. Physiol. 132: 770, 1941.
27. Thorn, W., Scholl, H., Pfleiderer, G., and Mueldener, B.: Metabolic processes in the brain at normal and reduced temperatures and under anoxic and ischemic conditions, J. Neurochem. 2: 150, 1958.
28. Lolley, R. N., and Samson, F. E.: Cerebral high-energy compounds; changes in anoxia, Amer. J. Physiol. 202: 77, 1962.
29. Gurdjian, E. S., Stone, W. E., and Webster, J. E.: Cerebral metabolism in hypoxia, Arch. Neurol. Psychiat. 51: 472, 1944.
30. Gurdjian, E. S., Webster, J. E., and Stone, W. E.: Cerebral constituents in relation to blood gases, Amer. J. Physiol. 156: 149, 1949.
31. Biddulph, C., Van Fossan, D. D., Criscuolo, D., and Clark, R. T.: Lactic acid concentration of brain tissues of dogs exposed to hypoxemia and/or hypocapnia, J. Appl. Physiol. 13: 486, 1958.
32. Cain, S.: An attempt to demonstrate cerebral anoxia during hyperventilation of anesthetized dogs, Amer. J. Physiol. 204: 323, 1963.
33. Geiger, A.: Correlation of brain metabolism and function by the use of a brain perfusion method in situ, Physiol. Rev. 38: 1, 1958.
34. Sacks, W.: Cerebral metabolism of isotopic glucose in normal human subjects, J. Appl. Physiol. 10: 37, 1957.

MANNITOL DIURESIS Studies on the mechanism of mannitol diuresis have been carried out in dogs, in man, and *in vitro*. Systemic administration of mannitol produces a fall in hematocrit, a decrease in renal vascular resistance, and an increased renal blood flow. Regional perfusion of the kidney with mannitol produces similar qualitative and quantitative effects, thereby ruling out primary extrarenal mechanisms in the mediation of mannitol diuresis. The primary effect of mannitol is to produce a fluid shift from both red blood cells and extravascular compartments which alters the plasma and red blood cell volume relation. (*Lilien, O. M., Jones, S. G., and Mueller, C. B.: Mechanism of Mannitol Diuresis, Surg. Gynec. Obstet. 117: 221 (Aug.) 1963.*)