

Anesthetic Effects on Cerebral Metabolism

B. Raymond Fink, M.D.,* and Richard H. Haschke, Ph.D.†

A discussion of the effects of anesthetics on cerebral metabolism presupposes a reasonably adequate knowledge of the normal state of metabolism of the organ. Unhappily, although considerable advances have been made in the last ten years, our knowledge of normal cerebral metabolism is still small, and understanding of the effects of anesthetics on this metabolism is correspondingly fragmentary. This review begins with human and animal data of greatest interest to the clinician, followed by an account of cellular-level developments. A more complete survey of the latter, to the end of 1968, is available.¹ Aspects of cerebral metabolism relevant to changes in cerebral blood flow were recently the subject of an excellent review by Smith and Wollman.²

Early biochemical studies related to anesthesia were designed to test the hypothesis that interference with energy metabolism was the fundamental cause of insensibility. This idea doubtless arose from the incontrovertible fact that the maintenance of normal mental function does depend on a sufficient supply of oxygen and glucose to the brain. For normal function the waking brain requires³ approximately 3.5 ml of oxygen (156 micromoles)/100 g/min, or a total of about 50 ml/min, extracted from an average normal cerebral blood flow of 57 ml/100 g/min. The importance of oxygen to the normal function of neurons is well illustrated by the effects consequent on temporary retinal ischemia. In the experiment of Carlisle *et al.*,⁴ where pressure was applied to the eyeball, vision was lost within 4 seconds when the oxygen was at ambient atmospheric pressure but persisted for as long as a minute when the oxygen was at

a pressure of 4 atm. But, as Duffy *et al.*⁵ point out, there is a difficulty to this reasoning, because during anoxia brain function fails before there is any significant decrease in ATP or any great change in phosphocreatine. For them the depression is not the result of a power failure, but represents a protective reaction to conserve the slender stores of energy. To the reviewers this seems farfetched, for the protective value of coma has yet to be demonstrated.

Present understanding may be summarized as follows:

1) When the internal jugular venous P_{O_2} is reduced to 28–25 torr there is sufficient underoxygenation of the cerebral tissue to elicit compensatory reactions such as dilatation of cerebral vessels (“reaction threshold”).

2) At a P_{O_2} of 20–18 torr in internal jugular venous blood the oxygen deficiency is sufficient to lower the rate of oxidative phosphorylation, and consciousness is lost (“critical threshold”). However, the critical intracellular P_{O_2} is probably quite different. Experiments *in vivo* and *in vitro* have demonstrated that a P_{O_2} of 1–2 torr or less is sufficient to allow maximal phosphorylation in brain mitochondria.^{6,7}

Hess⁸ estimated that the average human cortical neuron with its processes utilizes 122×10^{-6} μ l of oxygen per hour, or 16–50 times as much as the average neuroglial cell. Rose⁹ concluded that there was little difference between the metabolic rates of neurons and glia, but the most recent data of Ruscak and Ruscakova¹⁰ agree in general with Hess. Metabolic fluxes in single neurons during anesthesia have recently been discussed by Passonneau and Lowry.¹¹

Effects of Anesthetics on CMR_{O_2}

Most general anesthetics and cerebral depressants have been shown to reduce the oxygen consumption of the brain under conditions of clinical anesthesia (table 1). Unfortu-

* Professor, Department of Anesthesiology.

† Assistant Professor, Department of Anesthesiology.

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TABLE 1. Effects of Anesthetics on Oxygen Uptake of the Human Brain

Induction with Thiopental	Anesthetic	CMRO ₂		Reference
		ml/100 g/min	Per Cent Change	
	Thiopental		-36	12
	Thiopental, 0.5-1.6 g		-36	128
	Thiopental, 0.6-1.5 g	2.2	-39	129
	Thiopental, 1-1.5 g		-66	130
	Thiopental	1.5	-55	13
	Ether		-40	30
	Alcohol, 320 mg/100 ml blood	2.2	-31	131
	Alcohol, 6S mg/100 ml blood	2.8	0	131
No	Halothane, 1 per cent, + air	2.2	-27	132
Yes	Halothane, 1 per cent, + N ₂ O, 50 per cent		-27	133
No	Halothane, 1.2 per cent	2.8	-15	15
Yes	N ₂ O (60-80 per cent) with: Halothane, 0.5 per cent Chloroform, 0.5 or 1 per cent Methoxyflurane, 0.5 per cent		-16 -10 -13	36
Yes	N ₂ O (70 per cent) with: Halothane, 0.5 per cent Halothane, 2 per cent		-14 -33	134
No	C ₂ H ₆ , 5 per cent		-30	20
No	Ketamine	2.82	0	135

nately, few of the studies can be normalized, as they lack data on blood levels of anesthetic. For example, Himwich¹² observed that during thiopental anesthesia the oxygen consumption of the human brain diminished, on the average, by 36 per cent. Pierce *et al.*,¹³ in 1962, made measurements in human subjects anesthetized with sodium thiopental and *d*-tubocurarine, the total doses ranging from 10 to 55 mg/kg and from 0.7 to 1.3 mg/kg, respectively, while P_{CO₂} was maintained at an average of 44 torr. In the presence of clinical and electroencephalographic indications of profound anesthesia, the oxygen consumption rate of the brain represented a reduction of approximately 55 per cent below the rate in conscious normal eucapnic subjects. The cerebral respiratory quotient was unchanged, suggesting that cerebral metabolism was not qualitatively altered.

Concerning trichloroethylene, McDowall *et al.*¹⁴ found that the cerebral oxygen uptake

was reduced by 20 per cent in a localized area of the cerebral cortex in dogs. There is general agreement that halothane does reduce oxygen consumption by the brain. Cohen *et al.*¹⁵ observed that in man 1.2 per cent halothane caused a decrease of approximately 15 per cent in cerebral oxygen consumption in the presence of a 1 C fall in body temperature, although for the most part the depression could be accounted for by this fall in temperature. In dogs, Theye and Michenfelder¹⁶ found a 17 per cent reduction in the rate of oxygen consumption by the brain in dogs inhaling 1 per cent halothane in 70 per cent nitrous oxide and oxygen. A comparable depression was recently demonstrated with methoxyflurane¹⁷ a 23 per cent decrease in CMRO₂ with 0.44 per cent end-expired methoxyflurane (about twice the minimum alveolar anesthetic concentration). These authors¹⁸ also showed that nitrous oxide by itself increased rather than decreased the cerebral demand for oxy-

gen. However, Wollman and colleagues¹⁹ concluded that in man 70 per cent nitrous oxide depresses CMR_{O_2} about 15 per cent.

That the effect of nitrous oxide is not a simple stimulation is suggested by the observation of McDowall and Harper²⁰ that nitrous oxide and halothane are synergistic in their effect on cerebral oxygen uptake. Cyclopropane also appears to have a complex effect, characterized as biphasic by Alexander *et al.*²¹ However, the reduction in oxygen uptake with thiopental probably does not occur uniformly throughout the brain. Autoradiographic studies with ¹³¹I-labeled trifluoroiodomethane²² have shown that blood flow through different areas of gray matter is remarkably non-uniform in conscious cats, but that during light anesthesia with thiopental the differences in flow between the various cortical areas become much smaller. Similar data were obtained more recently by Cassano.²³ Perfusion through the regions of highest flow slows down almost to the rate through the more slowly perfused parts. Also pertinent in this connection is Roth's²⁴ demonstration that the concentrations of labeled thiopental in different areas of the brain vary directly with the local rates of blood flow at the time of injection. If cerebral blood flow is autoregulated by metabolic demand, the observations by Landau²² seem to indicate that thiopental reduces oxygen uptake most in those areas where oxygen uptake is highest in the conscious state.

In general, significant cerebral metabolic depression occurs during anesthesia with barbiturates^{13, 25} and narcotics,²⁶ but not with ketamine: Takeshita and colleagues²⁷ report no change in patients; in the dog an increase has been observed.^{28, 29} However, preanesthetic medication with hypnotics and narcotics produces only insignificant effects on total-body oxygen consumption rate. In dogs, pentobarbital, 2 mg/kg, or meperidine, 2 mg/kg, administered during halothane anesthesia depressed CMR_{O_2} an additional 7 and 13 per cent, respectively.³⁰ The neuroleptic, droperidol, 0.3 mg/kg, does not alter CMR_{O_2} in dogs,²⁶ but fentanyl, 0.006 mg/kg, decreases it by 18 per cent. In combination as Innovar, the two together reduce it 23 per cent. Morphine³¹ produces depression of as much as 15 per cent; the effect reaches a plateau at a

cumulative dose of 1.2 mg/kg in the dog and is reversed by nalorphine, 0.3 mg/kg. As regards gaseous anesthetics, no general rule can be invoked (fig. 1). Kety²² has stated that a 40 per cent decrease in CMR_{O_2} occurs with ether anesthesia in man. Cerebral oxygen consumption in man is reduced to approximately 70 per cent of normal during the inhalation of 5 per cent cyclopropane,³² and remains at this level during the inhalation of 13 and 37 per cent cyclopropane, but returns to nearly normal values with the inhalation of 20 per cent. The observation of a large increase in cerebral blood flow with 20 per cent and 37 per cent cyclopropane in the face of a 42 per cent decline with 5 per cent cyclopropane underscores the complexity of the response. Clearly, there is no simple proportionality between the functional and metabolic depression of the nervous system induced by this anesthetic. Such nonproportionality also appears to hold for diethyl ether. It seems that 1.2 times the so-called minimum alveolar concentration (MAC) of ether depresses the CMR_{O_2} to 65 per cent of normal, whereas 2.3 MAC is associated with a CMR_{O_2} of about 88 per cent of normal.¹

Alexander *et al.*³³ suggested that the peculiar biphasic actions of cyclopropane and ether on cerebral blood flow and cerebral metabolic rate for oxygen were due to the property of the agents of enhancing sympathoadrenal activity with increasing concentrations. Support for such a mechanism was adduced by Michenfelder and Theye³⁴ in dogs. Increasing cyclopropane from 5 to 30 per cent in their dogs resulted in no significant change in CMR_{O_2} . They treated one group of dogs with reserpine because reserpine is known to deplete the stores of norepinephrine throughout the body. In the reserpinized dogs the biphasic effect of cyclopropane disappeared, since 13 per cent cyclopropane reduced CMR_{O_2} to 89 per cent of control, and this reduction was maintained as cyclopropane was further increased to 20 and 30 per cent. In other dogs, spinal anesthesia was used as an alternative to reserpine for the purpose of suppressing sympathoadrenal stimulation by cyclopropane. The responses to cyclopropane were the same as in the reserpinized dogs. For good measure, they tested the effects of epi-

nephine and norepinephrine in a dog in the presence of cyclopropane and spinal anesthesia. Both epinephrine and norepinephrine produced large increases in CMR_{O_2} and cerebral blood flow, which were rapidly reversed upon cessation of the catecholamine infusion.

In man, cyclopropane is known to produce a progressive increase in the level of circulating norepinephrine,³⁵ but in the dog the major increase is in the epinephrine fraction.³⁶ By analogy with the dog, it would seem that a dose-related cerebral response to norepinephrine may account for the biphasic effect of increasing cyclopropane concentrations on CBF and CMR_{O_2} in man: at low concentrations the direct cerebral depressant effects of cyclopropane predominate, whereas at higher concentrations sufficient norepinephrine is released to cause increases in both CMR_{O_2} and CBF. At still higher concentrations of cyclopropane this effect is exhausted or outweighed by the direct depressant effect of the anesthetic. Enflurane (Éthrane) is a potent depressor of CMR_{O_2} in man.³⁷ A 50 per cent reduction develops with 3 per cent enflurane. Methoxyflurane, chloroform, and trichloroethylene, tested in dogs only, depress CMR_{O_2} 10–20 per cent.³⁸

In sum, the effect of anesthetic depression on oxygen utilization by the brain as a whole is variable and not directly related to the degree of electrophysiologic depression, although there does appear to be a direct correlation between the anesthetic depression produced by barbiturates and the depression of oxygen uptake.³⁹ Altenburg and Michenfelder²⁵ believe that the effectiveness of thiopental in decreasing CMR_{O_2} is lessened by pretreatment with thiopental as little as two hours previously. The basis for this acute tolerance has not been established. Regional differences probably exist,^{40, 41} but these may be partly due to non-uniformity of blood flow.

Anesthetics and Tolerance to Ischemia

Just how well can brain cells withstand anoxia? The anesthesiologist is interested in the problem and will further ask: Does anesthesia as such protect the patient's neurons against anoxia at all?

To begin with the first question, the widely held view that permanent loss of function follows 3 or 4 minutes of circulatory arrest to the

brain is probably erroneous. If the oxygenation of the heart is maintained during the period of cerebral ischemia, the brain can tolerate an appreciably longer period of total circulatory arrest.⁴²

The significance of maintenance of blood pressure above the critical level is patent in the experiments of Hirsch *et al.*⁴³ in rabbits. Complete ischemia of the brain, produced by inflating a blood pressure cuff around the neck to 300 torr, was tolerated for about 4 minutes at 37 C without neurologic or histologic damage. When the experiments were done with artificial respiration, the revival time was doubled. Studies of electroencephalographic (EEG) recovery in cats subjected to cerebral anoxia but with systemic blood pressure maintained by means of extracorporeal circulation point the same way.⁴⁴ If after cardiac arrest the revival time is so short, this is the result of cardiac failure during recovery and not the short revival time of the brain itself. It is therefore crucial to maintain the blood pressure above the critical level during recovery by means of cardiac massage and infusion of norepinephrine.

Experiments by Webster and Ames⁴⁵ with the rabbit retina *in vitro* interestingly corroborate the animal data. Electron microscopic examination of retinas deprived of oxygen and glucose for only 3 minutes shows generalized swelling of mitochondria and loss of synaptic vesicles. All these changes are completely reversible when the deprivation lasts as long as 20 minutes, but become irreversible by 30 minutes. It is interesting that simple glucose withdrawal produces only minor changes. This may denote the presence of a sizeable intracellular reserve of glycogen, or metabolism of substitute substrates derived from amino acids or fatty acids.

The second question may now be considered: Is the prospect of cerebral recovery improved if the anoxic or ischemic insult takes place in the presence of general anesthesia? At stake is the crucial point whether the reduced cerebral metabolism induced by certain anesthetics can increase the tolerance of the brain for anoxia during neurosurgical interventions on the cerebral vascular system.

Important insights have been gained from studies under controlled conditions *in vitro*.

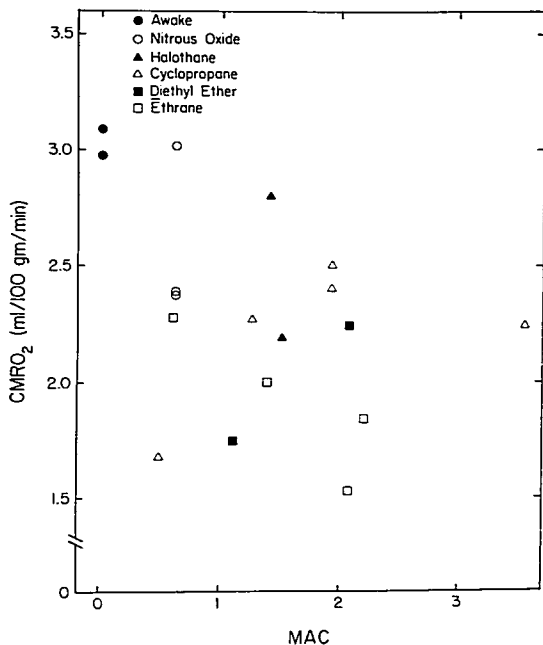


FIG. 1. Cerebral metabolic rate for oxygen as a function of MAC (Smith, AL, Wollman, H, ANESTHESIOLOGY 36:385, 1972).

Detailed discussions are available elsewhere,⁴⁶ and only a few particulars will be given here. It has long been plain that the oxygen uptake of brain slices *in vitro* reflects the basal needs for the maintenance of cellular integrity, and occurs at about half the normal *in-vivo* rate,⁴⁷ or approximately the same rate as in brain deeply depressed by barbiturate anesthesia. The *in-vitro* rate can be doubled by electrical stimulation.⁴⁸ Stimulated excess respiration is inhibited by anesthetics, but this again may reflect a primary effect of the anesthetic on electrical excitability rather than on metabolism. In potassium-stimulated brain slices, 50 per cent cyclopropane or 5 per cent ether causes a significant and reversible decrease of oxygen consumption.⁴⁹ The measurements, of course, do not distinguish between the oxy-

gen consumed by neurons and the oxygen consumed by neuroglia.

Michenfelder and Theye⁵⁰ set out to answer the question by examining the ATP and lactate levels in canine brain. They produced cerebral anoxia, or more precisely ischemia, by the time-honored expedient of decapitation, and observed the post-decapitation rates of ATP depletion and lactate accumulation. At 37 C these were uninfluenced either by the presence of halothane or by halothane with thiopental, although the premortem CMR_{O₂} had been reduced 40 per cent below control. Lowering the temperature to 30 C without anesthetic likewise reduced CMR_{O₂} 40 per cent below control, but in this case the post-decapitation ATP depletion and lactate accumulation rates also were reduced 40 per cent. Thus, anes-

thetia and hypothermia had similar effects on CMR_{O_2} , while the dog was alive, but had entirely different effects on the rate of depletion of ATP and lactate accumulation after decapitation. Michenfelder and Theye thought it significant that, anesthetized or not, the cerebral ATP content following decapitation decreased at an approximately constant rate down to 25 or 30 per cent of the pre-decapitation level and thereafter decreased at a much slower rate. They had previously shown that reductions in CMR_{O_2} during anesthesia and hypothermia are accompanied by quantitatively similar reductions in cerebral glucose consumption, indicating continued aerobic energy production. Michenfelder and Theye reasoned, therefore, that reduction in CMR_{O_2} was accompanied by quantitatively similar reductions in the rate of ATP synthesis and the rate of ATP utilization. If similar levels of ATP are obtained during anesthesia and hypothermia, why, then, was there not a similar degree of cerebral protection against anoxia? The answer was that the rate of utilization of the ATP by the decapitated brain was so different in the two states; anesthesia alters only that aspect of ATP utilization responsible for the conscious state but not that required for cellular integrity. Hypothermia reduces both. In the anesthetized brain, once the EEG was abolished by anoxia, the energy requirement for maintenance of cellular integrity would be unaffected by anesthetics.

The results of Michenfelder and Theye have been described in some detail because their conclusions are at variance with the above-discussed survival experiments. Michenfelder and Theye argue that the anoxic brain undergoes irreparable damage within 3 or 4 minutes, whereas the experiments of Schneider *et al.*⁵² have shown that irreparable damage within this time is contingent on failure of the circulation in the recovery phase. When glucose transport to the brain is present after the period of anoxia, the levels of ATP and P-creatine are well maintained.⁵¹ The weakness of the experiments of Michenfelder and Theye is that they do not show that recovery cannot occur after 3 minutes of complete anoxia. They only show that this does not occur in the decapitated dog's head, which is hardly surprising. If the concentration of

ATP is limiting, then the rate of ATP utilization may be decreasing continuously as the ATP level falls. This would account quite well for the published data. By the same token, some caution may also apply to their conclusion that anesthetic reduction of cerebral metabolism does not afford any protection against hypoxia. There is some evidence to the contrary from experiments on living animals. Dhruva *et al.*⁵³ reported that halothane anesthesia could increase the tolerance of the brain to anoxia. Goldstein⁵³ showed that in dogs pentobarbital, 30 mg/kg, extended the tolerance of cerebral ischemia—total interruption of cerebral circulation—by several minutes; however, this study lacked precise temperature control. Cox and colleagues⁵⁴ reported that the addition of halothane to a 3-to-1 nitrous oxide-oxygen mixture markedly increased the tolerance of the rabbit brain to ischemia at normothermia. Bain *et al.*⁵⁵ used the pneumatic tourniquet around the rabbit's neck to produce isolated cerebral ischemia while maintaining artificial ventilation, normal blood gases, and normal temperature. The absence of cortical electrical activity throughout the period of occlusion was considered evidence of cerebral ischemia. The addition of halothane to the standard nitrous oxide-oxygen mixture increased the 24-hour survival rate following 3 minutes of cerebral ischemia from 36 to 95 per cent; survival following 6 minutes of cerebral ischemia increased to 72 per cent (from 21 per cent) with halothane, methoxyflurane, or cyclopropane anesthesia.

This discussion should not persuade anyone to make light of the threat of disaster. Its message is that if a disaster does occur, immediate recovery of effective cardiac function is a generally hopeful portent.

Glucose Metabolism

What is the oxygen consumed by the brain used for? The short answer is, to burn glucose. The complete oxidation by cerebral tissue of glucose to carbon dioxide and water appears to be the principal source of energy metabolism in this organ. Except for glycerol and mannose,⁵⁶ none of the other substrates that have been tested is significantly metabolized. The normal rate of utilization of

glucose amounts to 27.8 nanomoles/100 g brain/min, or about 70 mg/min for the entire brain, and in the process approximately 5.5 millimoles oxygen per millimole glucose are consumed.⁵⁷ After crossing the cell membrane, glucose is immediately phosphorylated, thereby facilitating further glucose entry. Consistent with the conclusion that brain respire almost entirely at the expense of glucose is the observation that hypoglycemia produces a definite decrease in cerebral oxygen consumption and that the decrease correlates well with the arterial blood glucose level and with the mental state. Consciousness lost in hypoglycemia is restored with intravenous administration of glucose.⁵⁸ In brain slices the amount of glucose disappearing is approximately equal to the total expected from the oxygen consumption (assuming complete oxidation) and from the amount of lactic acid formed in anaerobic glycolysis.⁴⁰ It may be noted that dependence of the human brain on glucose is lessened during prolonged fasting, presumably thanks to induction of enzymes capable of oxidizing keto acids.⁵⁹

Some of the glucose entering the brain cells is not metabolized directly, but serves as a precursor of various intermediates. Evidence for this is the observation that when labeled glucose is utilized, the resultant carbon dioxide has a lower specific radioactivity than the original glucose substrate. The glucose label becomes diluted because some of the glucose is initially used to synthesize other compounds such as amino acids and lipids. These are then metabolized together with unlabeled intermediates already in the pool.⁶⁰ In the perfused brain of the cat, glucose is taken up at the rate of 10 mg/min/100 g of tissue^{61, 62} under "resting" conditions; 30-35 per cent of the glucose absorbed is oxidized directly, and another 20-30 per cent is taken up and rapidly transformed into acid-soluble components such as amino acid and lipids. During this time the amount of oxygen consumed by the perfused brain corresponds to that necessary to oxidize all of the glucose to carbon dioxide.

What effect does anesthesia have on the intermediary metabolism and, more particularly, on the metabolism of glucose? Unfortunately, many of the results to be cited have

been obtained at uncertain body temperatures and blood levels of anesthetic, from animals coincidentally suffering from unknown degrees of hypoxia and acidosis. All the more importance attaches to the rare studies in man, such as those of Cohen *et al.*¹⁵ These workers observed a cerebral glucose uptake of 8.1 mg/100 ml blood during inhalation of 1.2 per cent halothane vapor. The normal value is about 9.5 mg/100 ml blood, with 92 per cent of the glucose being oxidized and the rest appearing as lactate. Since glucose appears to be the principal substrate for the metabolism of cerebral tissue, one may assume that oxygen consumption is really an indirect measurement of glucose metabolism.

In vitro, barbiturates stimulate glycolysis by rat brain,⁶³ but so far as is known the human brain does not respond to barbiturates by increased glycolysis. Thiopental anesthesia in man has been shown to reduce the CMR_{O_2} by an average of 55 per cent, but the respiratory quotient was 0.99.¹³ In isolated ganglia, where anesthetics "selectively" inhibit synaptic transmission,^{64, 65} pentobarbital depression of the postganglionic action potential accelerates the rates of glucose consumption and lactate production while decreasing oxygen uptake. Diethyl ether, on the other hand, with a similar reduction in action potentials, has no measurable effect on oxygen uptake. Thus, so far as carbohydrate metabolism is concerned, the results with excised ganglia closely resemble those with slices of brain tissue.⁶⁶ Of the glucose utilized by the ganglia *in vitro*, 64 per cent appears as carbon dioxide and 24 per cent as lactate.⁶⁶ These results are quite similar to those of Geiger⁶¹ with the perfused brain of the cat. One may conclude that the much greater production of lactate by the *in-vitro* preparations compared with the intact brain probably reflects the drastic difference in conditions of oxygenation occasioned by the absence of circulating blood.

One indication of an anesthetic's influence on brain glucose metabolism is a change in the rate of appearance of metabolites from freshly administered glucose. The specific radioactivity of carbon dioxide produced by the brain during continuous infusion of ¹⁴C-labeled glucose has been measured by Barkai and Allweis⁶⁷ in the intact cat narcotized with

pentobarbital (after induction of anesthesia with diethyl ether). At apparent isotopic equilibrium, the relative specific activity of the carbon dioxide produced by the brain amounted to 45 per cent compared with 32 per cent observed in the unanesthetized cat brain. An even larger increase in the specific radioactivity of the CO_2 formed by glucose oxidation was found by Geiger *et al.*⁶⁵; the addition of pentobarbital to the perfusion fluid roughly doubled the amount of label appearing in the CO_2 carbon. Possibly the anesthetic depressed the incorporation of the glucose into other components and therefore made more substrate available for direct oxidation. Experiments by Bachelard *et al.*⁶⁹ indicate that the incorporation of ^{14}C from uniformly labeled glucose into amino acids in the rat brain is significantly retarded by diethyl ether and by pentobarbital (75 mg/kg). On the other hand, experiments with the anesthetized dog have shown that the relative specific radioactivity of the CO_2 produced by the brain remained at 100 per cent for most of the time of the experiment.⁷⁰ At present it is not clear whether the difference between the results with cats and with dogs is due to species or technique. Sacks⁷¹ estimated that in man little more than half the cerebral CO_2 production comes directly from glucose.

Brain Levels of Glucose and Glycogen

Glucose is stored in the brain mainly in the form of glycogen. In the mammalian brain the total amount of glycogen is equivalent to 2 g glucose.⁷² This is sufficient substrate for approximately 24 minutes of oxidative metabolism at the normal rate. However, in an animal deprived of oxygen, the glycogen would be used up at five or six times this rate because of the greatly increased rate of glycolysis.⁷³ Since such a rapid exhaustion of substrate may be a principal factor in causing irreversible damage to the brain during circulatory arrest, especially in the newborn,⁷⁴ it is of interest to examine the effect of anesthetics upon this phenomenon in case any protective effect is present. With barbiturate narcosis, a time-dependent increase in cerebral glycogen has been found, six hours of anesthesia producing a two- to threefold increase.^{75, 76, 77} Higher levels of plasma glu-

cose are not a sufficient explanation for this increase in the cerebral levels. Central depression of glycolysis may be involved.⁷⁸

Brunner *et al.*⁷⁹ have observed that the volatile anesthetics affect the intracerebral concentration of glucose in a manner similar to the barbiturates. Upon administration of 4.5 per cent diethyl ether, plasma and cerebral glucose were both elevated. However, the ratio of cerebral glucose to plasma glucose increased. After two hours plasma glucose had increased 40 per cent; cerebral glucose increased 80 per cent, and glucose-6-phosphate increased approximately 56 per cent. Glycogen also increased approximately 80 per cent in two hours, but after four hours began to decrease. All of these substances represent energy stores which accumulate in the brain during general anesthesia. Halothane, methoxyflurane, and enflurane in equivalent concentrations were also studied; their effects on levels of cerebral glucose, cerebral glycogen, and plasma glucose were generally similar to those of diethyl ether. All the general anesthetics depressed the cerebral metabolic rate about 50 per cent and tended to decrease body temperature, but a 10-degree C fall in temperature in the absence of anesthetic did not affect the intracellular concentration of glycogen.

Takemori⁸⁰ has reported that certain depressants like pentobarbital, diethyl ether, and chloroform increase the glucose-6-phosphate dehydrogenase activity in rat cerebral cortex, implying an increased utilization of glucose via the pentose phosphate pathway.

A conflicting note from the laboratory of Biebuyck and Hawkins⁸¹ mentions a reduction in rat brain glucose-6-phosphate, 3-phosphoglycerate, and α -ketoglutarate with pentobarbital (50 mg/kg, intraperitoneal) or halothane (1.5 per cent in oxygen). The divergence probably arises from differences in methodology. Estler⁸² found a small increase in cerebral glycogen in mice after one hour of 4.5 per cent ether anesthesia.

The distribution of glycogen in the brain is not uniform, and neither is the increase occasioned by anesthesia. In unanesthetized animals glycogen levels are higher in the white matter than in the cortex.⁸³ Phenobarbital (200 mg/kg) increases the glycogen more

in layer I than in the remaining layers, but does not change the glycogen content in the subjacent white matter. Glucose and phosphocreatine are also increased. At the electron-microscopic level, prolonged barbiturate anesthesia (6 hours, phenobarbital, 250 mg/kg) produces large increases of particulate glycogen in the astrocytes of the hippocampus and frontal cortex.⁸⁴ Smaller increases occur in cerebellar cortex, but none in the hypothalamus or midbrain reticular formation. Interestingly, in this study glycogen was present only in astrocytes and not in neurons, oligodendroglia, or microglia.

High-energy Phosphates

Oxygen consumption as a measure of the "health" of tissue is somewhat crude and may, in fact, be misleading. The major oxygen consumption of tissues is through the electron-transport system, at a rate controlled by and coupled to the phosphorylation of ADP to ATP. This control may be lost and electron transport, and, thereby, oxygen consumption may be uncoupled from phosphorylation and proceed at an uncontrolled or even super-normal rate. Unreplenished, the cell's store of ATP would soon be depleted and the cell would in fact be dying, although consuming oxygen in abundance.

Interest in the brain levels of high-energy phosphates during anesthesia was stimulated by the hope of casting light on the role of energy metabolism in narcosis. Depleted levels might incriminate inhibition of oxidative metabolism as a primary cause of anesthesia, whereas an excess could suggest that decreased oxidative metabolism is secondary to the primary effect of the anesthetic. Because of the extremely rapid breakdown of labile phosphates during decapitation and complete freezing of the brain, critical importance attaches to the experimental procedure. It is because of this difficulty in technique that much of the earlier work must be critically re-evaluated. An investigation of methodology by Weiner⁸⁵ indicated no change in ATP content with ether or pentobarbital anesthesia, although a higher level of phosphocreatine was found. In the above-cited work of Brunner *et al.*,⁷⁹ it was also found that animals anesthetized with ether, halothane, methoxy-

flurane, or enflurane all had approximately 30–50 per cent increases in brain energy stores. However, these were principally a result of increased glucose and glycogen levels, not large increases in ATP or phosphocreatine. Other workers, using barbiturate anesthetics, also found the cortical levels of ATP and phosphocreatine stabilized or only slightly increased during anesthesia.^{86, 87} The weight of evidence indicates a small increase in phosphocreatine and no change in ATP levels during narcosis.^{88, 89}

The mechanism of the inhibition of oxygen uptake by anesthetics may involve several control points in the energy-generating and energy-utilizing machinery of the cell. Cohen and Marshall⁹⁰ have shown how this can occur at the NAD reductase step in the oxidative phosphorylation system with halothane. In addition to a direct effect of anesthetics on this pathway, Quastel⁴⁶ postulated a model in which a Na⁺-K⁺-linked ATPase in the plasma membrane is seen as one of the possible sites of anesthetic inhibition leading to a decrease of cellular oxygen uptake. Inhibition of ATP breakdown in the plasma membrane would increase the ATP/ADP ratio and consequently decrease the ADP available for phosphorylation. Indirectly, then, the effect is again upon the oxidative phosphorylation system. Ueda and Mietani⁹¹ looked for a direct effect of general anesthetics on the ouabain-sensitive Na⁺-K⁺-linked ATPase of microsomal fractions of rabbit brain. Decreased ATPase activity was demonstrated only with ether and with halothane when the partial pressures were eight to ten times pressures used clinically. However, microsomal ATPase may not be bound to lipoprotein membrane in the same way as the Na⁺-K⁺-sensitive ATPase of plasma membrane. On the other hand, firefly luciferase,⁹² an enzyme with ATPase activity, is inhibited by therapeutic concentrations of diethyl ether and halothane.

Chance *et al.*⁹³ have shown that the site of action of an inhibitor of electron flow can be identified by the crossover point, the point in the respiratory chain where reduced cofactor accumulates upstream and reduced forms are depleted downstream. With barbital and other oxybarbiturates, this crossover point is found between reduced nicotinamide (NADH)

and flavin. Several sites of inhibition may be postulated.⁹⁴ Cohen's study⁹⁰ of the action of halothane on the rate of phosphorylation of ADP in liver mitochondrial preparations is of particular interest. It demonstrated that 50 per cent inhibition is produced by approximately 1.6 per cent halothane. The ability of succinate to reverse the inhibition suggests that halothane may interfere with the oxidation of reduced NADH by flavoprotein. Even greater sensitivity of oxidative metabolism to volatile anesthetics has been observed in certain cell culture strains.⁹⁴ However, a factor often discounted in studies with volatile anesthetics is the possibility of an effect due to the oxygen which is used as carrier gas. Williams and Haugaard⁹⁶ found that 100 per cent oxygen at 1 atmosphere depresses ATP synthesis in rat brain homogenates. This depression occurs earlier than depression of substrate utilization, indicating that oxidative phosphorylation is particularly sensitive to inactivation by oxygen *in vitro*. On the other hand, there is a report⁹⁷ that hyperbaric oxygen (3-6 atm) shortens the sleeping time of mice anesthetized with sodium pentobarbital.

In the above-mentioned studies of high-energy phosphate, the investigators measured only the total concentration of the pool of the various compounds. The study of cerebral levels as such has an inherent limitation. For example, an increase can result from either increased production or decreased utilization. One must also be aware that constancy in the size of a pool of a high-energy compound does not necessarily mean that it is being turned over at a constant rate. An anesthetic could affect the turnover rate without altering the absolute level. It must also be remembered that compartmentalization of high-energy phosphates in various areas of the cell may exist, and that the nucleotide may be displaced from one compartment of the cell to another without any change in the size of the total pool. At present there is no good evidence for or against such compartmentalization.

Amino-acid and Protein Metabolism

Protein turnover in the living brain takes place at a high rate relative to turnover in liver and in secreting glands. The reason for such high turnover is better understood now

that proteins are known to be exported continuously from the perikaryon to the nerve ending. Such transport occurs at speeds ranging from 1 to 400 mm/day or more. The rapid transport is oxygen dependent but is unaffected during general anesthesia. Lidocaine, 0.4 per cent, inhibits the rapid axonal transport of proteins *in vitro*,⁹⁸ and so does 0.5 per cent procaine (C. Aasheim *et al.*, to be published). The inhibition of transport by lidocaine precedes the loss of microtubules from the axon,⁹⁹ but it is not yet known whether either effect occurs during therapeutic nerve blocks. If found, this will represent a toxic effect rather than a physiologic component of nerve block, since the minimum concentration of local anesthetic blocking protein transport is more than ten times as high as that necessary for conduction block.⁹⁸

As previously mentioned, the amino acids necessary for the functioning of the brain are partially synthesized in the brain cells from glucose and partially transported across the blood-brain barrier. The transport of amino acids into the brain is slow,¹⁰⁰ but rapid turnover inside the brain is maintained by uptake from the free amino acid pool¹⁰¹ derived from the intermediary metabolism of glucose. In the brain of the rat the rate of incorporation of ³⁵S from labeled methionine into the proteins can replace all of the methionine in cerebral proteins in 20 days.¹⁰² The effect of anesthetics on uptake of labeled amino acids was unequivocal. Ether anesthesia in rats maintained at normal body temperature decreased the rate of uptake of intracisternal ³⁵S into brain proteins by 34 per cent. Intraperitoneal injection of pentobarbital, 75 mg/kg, diminished uptake by 24 per cent. The effect was greatest in animals that were most deeply anesthetized. Nechaeva *et al.*¹⁰³ obtained generally similar results with radioactive methionine and glycine.

That the brain can rapidly synthesize amino acids from glucose was first demonstrated in brain slices by Beloff *et al.*,¹⁰⁴ and Barkulis *et al.*¹⁰⁵ confirmed this in cortical slices of perfused cat brain. They reported that narcosis with pentobarbital did not appreciably change the pattern of labeling. However, Tsuji *et al.*¹⁰⁶ observed a decrease in cortical levels of γ -aminobutyric acid (GABA) and

glutamic acid in rat brain after intraperitoneal injection of pentobarbital (30 mg/kg). Cyclopropane, 10–15 per cent, also provoked a decrease in GABA level. The findings are of interest because GABA is a transmitter at inhibitory synapses; nevertheless, it seems doubtful that these changes play any direct part in causing the anesthetic state, since they also occur under certain conditions that do not give rise to anesthesia.

Besides effects of anesthetics on protein biosynthesis in brain, Lajtha and Toth¹⁰⁷ noted that the excitement stage may lower the normal resting level of glutamine. (Malhotra¹⁰⁸ concluded that anesthetic excitement depressed the acetylcholine content of brain.) Apparently, increased activity of the brain generally is associated with a lowering of the glutamine level. Under ordinary conditions, this decrease of glutamine is not noticed because cerebral stimulation also has the effect of liberating ammonia in the brain, which in turn promotes increased *de novo* synthesis of glutamine; in anesthesia it is noticed because anesthesia prevents production of free ammonia in the brain, as does ethanol intoxication. Dobkin¹⁰⁹ has confirmed these observations, adding that the stimulus of decapitation, in itself, significantly decreased the glutamine content of the brain in the rat. However, Biebuyck and Hawkins⁸¹ have noted a 30 per cent increase of the glutamine concentration in rat brain 10–40 minutes after the onset of halothane, pentobarbital or ketamine anesthesia. Here again, technique doubtless plays a determining part. Biebuyck did not decapitate his animals but blew their brains out.

Cremer and Lucas¹¹⁰ have presented evidence that the pool of glutamate is not metabolically homogeneous within the cell and that pentobarbital affects the hypothesized compartments unevenly.

A distinctive effect of halothane on the permeability of brain cells to an enzyme, glutamate oxalacetate-transaminase (GOT), was observed by Amakata and Greene¹¹¹ *in vitro*. Normally the permeability of cellular membranes to this enzyme is very low, and it exists entirely as an intracellular enzyme. Halothane in concentrations of 1 and 2 per cent significantly increased the efflux of GOT from slices of cerebral cortex. This effect was spe-

cific inasmuch as it was not present in mid-brain, heart, and liver slices, and did not occur with ether. While halothane increased membrane permeability, it did not affect GOT activity. The functional significance of the observation is unknown. An interesting sidelight on the modification of protein metabolism by general anesthetics was contributed by Ungar.¹¹² All the common ones inhibited a protease obtained from rat cerebral cortex. The ID_{50} was several times higher than the anesthetic AD_{50} for goldfish, but the correlation was excellent ($r = 0.9911$) and was interpreted as pointing to the combination of anesthetics with structured water surrounding the protein molecules, in other words, supporting the Pauling–Miller microhydrate-crystal theory of anesthesia.

Neurotransmitters

Once the doctrine of chemical transmission of nerve impulses became firmly established, attempts were made to determine whether the cerebral content of neurotransmitters or their precursors varied with the functional state. What is more important, now that labeled precursors are freely available, the rate of turnover of many substances can be determined. Thus, the studies of effects of anesthetics on concentrations in brain, or on regional distribution within the brain, are giving way to measurements of effects on turnover rates. The earliest neurotransmitter to be studied was acetylcholine; more recently, the monoamines have been gaining much attention.

Acetylcholine

Diethyl ether and pentobarbital, examined by Crossland and Merrick,¹¹³ produce little change in the acetylcholine content of various regions of the brain—the cerebral hemispheres, the upper brainstem, the cerebellum (the medulla is an exception)—at least in adult rats. In young rats the results were different. All parts of the young brain underwent an increase in acetylcholine during light anesthesia with either agent and a further increase during deep anesthesia. Schmidt¹¹⁴ reported increases in various regions of the brain with halothane anesthesia, presumably expressing decreased liberation of acetylcholine

from cholinergic neurons secondary to anesthetic depression of cerebral activity. It appears that the acetylcholine content of the brain increases inversely with the state of functional activity and eventually reaches a plateau. The plateau is explained by the limited capacity of the tissue to accumulate the substance. It has been known for many years that acetylcholine is released continuously from the cerebral cortex¹¹⁵ and also from the ventral surface of the cat brain¹¹⁶ and from brain slices.¹¹⁷ The amount of "weeping" of acetylcholine from the cortex decreases with increasing anesthetic depression. In sheep lightly anesthetized with ether, cyclopropane, or pentobarbital, the rate of release of acetylcholine is 1.0-3.54 ng/min/cm² of cortex and is roughly proportional to the electrical activity of the brain.¹¹⁸ In the visual cortex of conscious, free-moving rabbits,¹¹⁹ the rate of release of acetylcholine is also related to the activity and state of arousal; it is three times higher in the free-moving animal than in animals anesthetized with pentobarbital, 30 mg/kg, intravenously.

Monoamines

An interesting new aspect of the influence of anesthetics and narcotics on amino-acid metabolism in brain is their effect on catecholamine and dopamine biosynthesis. Subject to the usual cautions concerning species differences, there is reason to suppose that the narcotic effect of morphine may be bound up with the action of morphine on dopamine metabolism. In normal rats the accumulation of dopamine from tyrosine injected intracisternally is increased in the hypothalamus and striatum approximately 1.3-fold one hour after injection of morphine (60 mg/kg). In rats made tolerant to morphine the increase was more than twofold.¹²⁰ Further arguments for the mediation of the analgesic action of morphine through metabolism of dopamine have been presented by Fukui and Takagi.¹²¹ Analgesic doses of morphine (10 mg/kg, sc) increased the content of the dopamine metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), in the brain of the normal mouse. The time course of the increase of the dopamine metabolites was approximately the same as the

time course of the morphine analgesia. In morphine-tolerant mice, the concentrations of DOPAC and HVA were not different from normal. The next question to be asked is, what is the mechanism of the increase in DOPAC and HVA? There are, as usual, several possibilities: 1) Increased biosynthesis of dopamine, leading to enhanced formation of the metabolites. 2) Impeded resorption of dopamine into the storage form, thereby leaving more available for degradation. 3) Inhibited removal of the dopamine metabolites. We suggest that the work of Smith *et al.*¹²² and Clouet and Ratner,¹²⁰ cited above, favors the first of these possibilities.

Levorphanol is about ten times more potent than morphine in its ability to increase locomotor activity and to deplete cerebral catecholamines.¹²³ The analgesic action supposedly results from a decrease in the brain catecholamine concentration which results in a corresponding increase in the amount of dopamine. Chlordiazepoxide (Librium) and diazepam are reported to decrease norepinephrine turnover in the thalamus-midbrain, cortex, and cerebellum, and dopamine turnover in the striate region.¹²⁴ However, the dosage of the drugs, 10 mg/kg injected subcutaneously, seems remarkably high by human standards, and the suggestion of the authors that the mode of action of these minor tranquilizers involves catecholamines in the central nervous system can hardly be accepted on this basis.

The effect of general anesthesia on brain monoamine content is much less striking than that of the narcotics. Bonnycaeste and colleagues,¹²⁵ using a biological assay, reported finding increases in 5-hydroxytryptamine after the administration of a variety of central nervous system depressants, including pentobarbital, thiopental, diethyl ether, ethanol, meperidine, and morphine. However, Diaz *et al.*,¹²⁶ using a more refined spectrofluorimetric method, could find little effect in the cerebral level of serotonin (5-HT) with 15 per cent cyclopropane, 3 per cent diethyl ether, or 0.75 per cent halothane. The main metabolite of 5-HT, 5-hydroxyindoleacetic acid (5-HIAA), was increased, presumably because its removal was prevented. They concluded that these anesthetics probably block the 5-HIAA transport mechanism; there was no evidence of

inhibition of monoamine oxidase activity. Sung¹²⁷ reported that ketamine, 40 mg/kg, in the rat produces in the brain a significant increase in serotonin and a decrease in norepinephrine concentration. Thiopental did not affect the concentration of the monoamines. The turnover rate of cerebral serotonin was markedly depressed after ketamine. Gardier¹²⁸ examined *in vitro* the effect of cyclopropane on catecholamine-O-methyltransferase, but found little effect. On the whole, there is still little to suggest that an effect on neurotransmitter metabolism is important in the establishment or maintenance of general anesthesia.

A metabolic basis for the anesthetic state is at present a discredited idea because electrical excitability at synapses becomes a casualty at concentrations of anesthetic that have had little or no demonstrable metabolic effect *in vitro*.

Efforts are presently being made to link impairment of mitochondrial pumping of Ca⁺⁺ with the presence of a "clinical" concentration of anesthetic.¹²⁹ Such an effect could produce hyperpolarization of the neuronal membrane and reduce excitability,¹³⁰ and would represent an effect at a lipoprotein membrane, that of the mitochondrion, but whether this is merely another of the multitudinous correlations with lipophilic properties of anesthetic molecules or the key to anesthetic depression of the nervous system remains entirely unsettled.

References

1. Fink BR: Effects of anesthetics on metabolism of brain. *Handbuch der exp Pharmacol* 30:387-408, 1972
2. Smith AL, Wollman H: Cerebral blood flow and metabolism: Effects of anesthetic drugs and techniques. *ANESTHESIOLOGY* 36:378-400, 1972
3. Sokoloff L: Local cerebral circulation at rest and during altered cerebral activity induced by anesthesia or visual stimulation, *Regional Neurochemistry*. Edited by SS Kety, J Elkes. New York, Pergamon Press, 1961
4. Carlisle R, Lanphier EH, Rahn H: Hyperbaric oxygen and persistence of vision in retinal ischemia. *J Appl Physiol* 19:914-918, 1964
5. Duffy TE, Nelson SR, Lowry, OH: Cerebral carbohydrate metabolism during acute hypoxia and recovery. *J Neurochem* 19: 959-977, 1972
6. Chance B, Hollunger C: Inhibition of electron and energy transfer in mitochondria. *J Biol Chem* 278:418-431, 1963
7. Lübberts DW: Tissue hypoxia: Cellular oxygen requirements with special regard to the *in vivo* pO₂ of the brain. *Scand J Lab Clin Invest suppl* 102:11:A, 1968
8. Hess III: The rates of respiration of neurons and neuroglia in human cerebrum, *Regional Neurochemistry*. Edited by SS Kety, J Elkes. New York, Pergamon Press, 1961
9. Rose SPR: Preparation of enriched fractions from cerebral cortex containing isolated, metabolically active neuronal and glial cells. *Biochem J* 102:23, 1967
10. Ruscak M, Ruscakova D: Metabolism of the Nerve Tissue in Relation to Ion Movements In Vivo and In Situ. Baltimore, University Park Press, 1971, pp 21-28
11. Passonneau JV, Lowry OH: Metabolite flux in single neurons during ischemia and anesthesia, *Recent Advances in Quantitative Histo- and Cytochemistry*. Bern, Hans Huber, 1971
12. Himwich WA, Homburger E, Maresca R, et al: Brain metabolism in man: Unanesthetized and in penthalo narcosis. *Am J Psychiatry* 103:689-696, 1947
13. Pierce EC, Lambertsen CJ Deutsch S, et al: Cerebral circulation and metabolism during thiopental anesthesia and hyperventilation in man. *J Clin Invest* 41:1664-1671, 1962
14. McDowall DG, Harper AM, Jacobson I: Cerebral blood flow during trichloroethylene anesthesia: A comparison with halothane. *Br Anaesth* 36:11-18, 1964
15. Cohen PJ, Wollman H, Alexander SC, et al: Cerebral carbohydrate metabolism in man during halothane anesthesia. *ANESTHESIOLOGY* 25:185-191, 1964
16. Theye RA, Michenfelder JD: The effect of halothane on canine cerebral metabolism. *ANESTHESIOLOGY* 29:1113-1118, 1968
17. Michenfelder JD, Theye RA: Effects of methoxyflurane on canine cerebral metabolism and blood flow. *ANESTHESIOLOGY* 38:123-127, 1973
18. Theye RA, Michenfelder JD: The effect of nitrous oxide on canine cerebral metabolism. *ANESTHESIOLOGY* 29:1119-1124, 1968
19. Wollman H, Alexander SC, Cohen PJ, et al: Cerebral circulation during general anesthesia and hyperventilation in man. *ANESTHESIOLOGY* 26:329-334, 1965
20. McDowall DG, Harper AM: Blood flow and oxygen uptake of the cerebral cortex of the dog during anesthesia with different volatile agents. *Acta Neurol Scand suppl* 41: 146-151, 1965
21. Alexander SC, James FM, Colton ET, et al: Effects of cyclopropane anesthesia on cerebral blood flow and carbohydrate metab-

- olism of man. ANESTHESIOLOGY 29:170, 1968
22. Landau WM, Freygang WH, Roland LP, et al: The local circulation of the living brain: Values in the unanesthetized and anesthetized cat. *Trans Am Neurol Assoc* 80:125-129, 1955
 23. Cassano GB, Chetti B, Gliozzi E, et al: Autoradiographic distribution study of "short acting" and "long acting" barbiturates: ^{35}S -thiopentone and ^{14}C -phenobarbitone. *Br J Anaesth* 39:11-20, 1967
 24. Roth LJ: *In Uptake and Distribution of Anesthetic Agents*. Edited by EM Papper, RJ Kitz. New York, McGraw-Hill, 1963, p 155
 25. Altenburg BM, Michenfelder JD, Theye RA: Acute tolerance to thiopental in canine oxygen consumption studies. ANESTHESIOLOGY 31:443-448, 1969
 26. Michenfelder JD, Theye RA: Effects of fentanyl, droperidol, and Innovar on canine cerebral metabolism and blood flow. *Br J Anaesth* 43:630-635, 1971
 27. Takeshita H, Okuda Y, Sari A: The effects of ketamine on cerebral circulation and metabolism in man. ANESTHESIOLOGY 36: 69-75, 1972
 28. Dawson B, Michenfelder JD, Theye RA: Effects of ketamine on canine cerebral blood flow and metabolism: Modification by prior administration of thiopental. *Anesth Analg (Cleve)* 50:443-447, 1971
 29. Kreuzer H: *Die Hirndurchblutung unter Neuroleptanaesthesia*. Berlin, Springer-Verlag, 1967
 30. Messick JM Jr, Theye RA: Effects of pentobarbital and meperidine on canine cerebral and total oxygen consumption rates. *Can Anaesth Soc J* 16:321-330, 1969
 31. Takeshita H, Michenfelder JD, Theye RA: The effects of morphine and N-allylnormorphine on canine cerebral metabolism and circulation. ANESTHESIOLOGY 37:605-612, 1972
 32. Kety SS: Circulation and metabolism of brain. *Am J Med* 8:205-217, 1950
 33. Alexander SC, Colton ET, Smith AL, et al: The effects of cyclopropane on cerebral and systemic carbohydrate metabolism. ANESTHESIOLOGY 32:236-245, 1970
 34. Michenfelder JD, Theye RA: Effects of cyclopropane on canine cerebral blood flow and metabolism: Modification by catecholamine suppression. ANESTHESIOLOGY 37:32-39, 1972
 35. Hamelberg W, Sprouse JH, Mahaffey JE, et al: Catecholamine levels during light and deep anesthesia. ANESTHESIOLOGY 21:297-302, 1960
 36. Bagwell EE, Woods EF, Durst GG Jr: Influence of reserpine on cardiovascular and sympatho-adrenal responses to cyclopropane anesthesia in the dog. ANESTHESIOLOGY 25:148-155, 1964
 37. Wollman H, Smith AL, Hoffman JC: Cerebral blood flow and oxygen consumption in man during electroencephalographic seizure patterns induced by anesthesia with Ethrane. *Proc Fed Am Soc Exp Biol* 28:365, 1969
 38. McDowall DG, Harper AM: Blood flow and oxygen uptake of the cerebral cortex of the dog during anesthesia with different volatile agents. *Acta Neurol Scand suppl* 14: 146-151, 1965
 39. Gleichmann U, Ingvar DH, Lassen NA, et al: Regional cerebral cortical metabolic rate of oxygen and carbon dioxide related to the EEG in the anesthetized dog. *Acta Physiol Scand* 55:82-94, 1962
 40. Dixon TF, Meyer A: Respiration of brain. *Biochem J* 30:1577-1582, 1936
 41. Elliott KAC, Heller IH: *Metabolism of neurons and glia, Metabolism of the Nervous System*. Edited by D Richter. New York, Pergamon Press, 1957
 42. Schneider M: Blood pressure in the cerebral circulation, Selective Vulnerability of the Brain. Edited by JP Schade and WH Menemeny. Philadelphia, Davis, 1963, pp 7-20
 43. Hirsch H, Bolte A, Schaudig A, et al: Über die Wiederbelebung des Gehirns bei Hypothermie. *Pfluegers Arch* 265:328-336, 1957
 44. Hossmann K-A, Sato K: Recovery of neuronal function after prolonged cerebral ischemia. *Science* 168:375-376, 1970
 45. Webster HdeF, Ames A 3d: Reversible and irreversible changes in the fine structure of nervous tissue during oxygen and glucose deprivation. *J Cell Biol* 26:885-909, 1965
 46. Quastel JH: Effects of drugs on metabolism of the brain *in vitro*. *Br Med Bull* 21:49-56, 1965
 47. Elliott KAC: *Brain tissue respiration and glycolysis, The Biology of Mental Health and Disease*. New York, Hoeber, 1952
 48. McIlwain H: Metabolic response *in vitro* to electrical stimulation of sections of mammalian brain. *Biochem J* 49:382-393, 1951
 49. Matteo RS, Hoeh GP Jr, Hoskin FCC: The effects of cyclopropane and diethyl ether on tissue oxygen consumption and anaerobic glycolysis of brain *in vitro*. ANESTHESIOLOGY 30:156-163, 1969
 50. Michenfelder JD, Theye RA: The effects of anesthesia and hypothermia on canine cerebral ATP and lactate during anoxia produced by decapitation. ANESTHESIOLOGY 33:430-439, 1970
 51. Broniszewska-Ardelt B: Effect of hypoxia on substrate levels in the brain of the adult mouse. *J Neurochem* 18:2237-2240, 1971

52. Dhruva AJ, Javeri FM, Parulkar GB, et al: Fluothane as an anaesthetic adjuvant for prevention of hypoxic brain damage. *J Exp Med Sci* 5:1-7, 1961
53. Goldstein A, Wells BA, Keats AS: Effect of anesthesia on the tolerance of dog brain to anoxia. *ANESTHESIOLOGY* 25:98-99, 1964
54. Cox JMR, Catton DV, Spoerel WE: The effect of halothane on cerebral ischemia in rabbits. *ANESTHESIOLOGY* 26:242-243, 1965
55. Bain JA, Catton DV, Cox JMR, et al: The effect of general anaesthesia on the tolerance of cerebral ischaemia in rabbits. *Can Anaesth Soc J* 14:69-78, 1967
56. Ghosh AK, Mukherji B, Sloviter HA: Metabolism of isolated rat brain perfused with glucose or mannose as substrate. *J Neurochem* 19:1279-1285, 1972
57. Kety SS: The general metabolism of the brain *in vivo*, Metabolism of the Nervous System. Edited by D Richter. New York, Pergamon Press, 1957
58. Tews JK, Carter SH, Stone WE: Chemical changes in the brain during insulin hypoglycemia and recovery. *J Neurochem* 12: 679-693, 1965
59. Smith AL, Satterthwaite HS, Sokoloff L: Induction of brain D(-)- β -hydroxybutyrate dehydrogenase activity by fasting. *Science* 163:79-81, 1969
60. Sacks W: Cerebral metabolism of doubly labeled glucose in humans *in vivo*. *J Appl Physiol* 20:117-130, 1965
61. Geiger A: Correlation of brain metabolism and function by the use of a brain perfusion method *in situ*. *Physiol Rev* 38:1-20, 1958
62. Allweis C, Magnes J: The uptake and oxidation of glucose by the perfused cat brain. *J Neurochem* 2:326-336, 1958
63. Webb JL, Elliott KAC: Effects of narcotics and convulsants on tissue glycolysis and respiration. *J Pharmacol Exp Ther* 103: 24-34, 1951
64. Larrabee MG, Posternak JM: Selective action of anesthetics on synapses and axons in mammalian sympathetic ganglia. *J Neurophysiol* 15:91-114, 1955
65. Larrabee MG, Holaday DA: Depression of transmission through sympathetic ganglia during general anesthesia. *J Pharmacol Exp Ther* 105:400-408, 1952
66. Larrabee MG, Klingman JD: Metabolism of glucose and oxygen in mammalian sympathetic ganglia at rest and in action, *Neurochemistry*. Second edition. Edited by KAC Elliott, III Page, JH Quastel. Springfield, Charles C Thomas, 1966
67. Barkai A, Allweis C: The contribution of blood glucose to the carbon dioxide produced by the narcotized brain of the intact cat. *J Neurochem* 13:23-33, 1966
68. Geiger A, Kawakita Y, Barkulis SS: Major pathways of glucose utilization in the brain in brain perfusion experiments *in vivo* and *in situ*. *J Neurochem* 5:323-338, 1960
69. Bachelard HS, Gaitonde MK, Vrba R: The effect of psychotropic drugs on the utilization of glucose carbon atoms in the brain, heart and liver of the rat. *Biochem Pharmacol* 15:1039-1043, 1966
70. Gainer H, Allweis CL, Chaikoff IL: Precursors of metabolic CO₂ produced by the brain of the anesthetized intact dog: The effect of electrical stimulation. *J Neurochem* 10:903-908, 1963
71. Sacks W: Cerebral metabolism of isotopic glucose in normal human subjects. *J Appl Physiol* 10:37-43, 1957
72. Kerry SE, Ghantus M: The carbohydrate metabolism of brain. II. The effect of varying the carbohydrate and insulin supply on the glycogen, free sugar, and lactic acid in mammalian brain. *J Biol Chem* 116:9-10, 1936
73. Mark J, Codin Y, Mandel P: Glucose and lactic acid content of the rat brain. *J Neurochem* 15:141-143, 1968
74. Lowry OH, Passonneau JV, Hasselberger FX, et al: Effect of ischemia on known substrates and cofactors of the glycolytic pathway in brain. *J Biol Chem* 239:18-30, 1964
75. Nelson SR, Schulz DW, Passonneau JV, et al: Control of glycogen levels in brain. *J Neurochem* 15:1271-1279, 1968
76. Mayman CI, Gatfield PD, Breckenridge BM: The glucose content of brain in anesthesia. *J Neurochem* 11:483-487, 1964
77. Goldberg ND, Passonneau JV, Lowry OH: Effects of changes in brain metabolism on the levels of citric acid cycle intermediates. *J Biol Chem* 241:3997-4003, 1966
78. Gey KF, Rutishauser M, Pletscher A: Suppression of glycolysis in rat brain *in vivo* by chlorpromazine, reserpine, and phenobarbital. *Biochem Pharmacol* 14:507-514, 1965
79. Brunner EA, Passonneau JV, Molstad C: The effect of volatile anesthetics on levels of metabolites and on metabolic rate in brain. *J Neurochem* 18:2301-2316, 1971
80. Takemori AE: Effect of central depressant agents on cerebral glucose 6-phosphate dehydrogenase activity of rats. *J Neurochem* 12:407-415, 1965
81. Biebuyck JF, Hawkins RA: The effect of anaesthetic agents on brain tissue metabolite patterns. *Br J Anaesth* 44:226, 1972
82. Estler C-J: Der Glykogengehalt des Gehirns weisser Mause unter der Einwirkung von Phenobarbital und seine Beziehungen zu Blutzucker und Korper Temperatur. *Med Exp (Basel)* 4:30-36, 1961

83. Folbergrova J, Lowry OH, Passonneau JV: Changes in metabolites of the energy reserves in individual layers of mouse cerebral cortex and subjacent white matter during ischaemia and anaesthesia. *J Neurochem* 17:1155-1162, 1970
84. Phelps CH: Barbiturate induced glycogen accumulation in brain: An electron microscopic study. *Brain Res* 39:225-234, 1972
85. Weiner N: The content of adenine nucleotides and creatine phosphate in brain of normal and anesthetized rats: A critical study of some factors influencing their assay. *J Neurochem* 7:241-250, 1961
86. King LJ, Lowry OH, Passonneau JV, et al: Effects of convulsants on energy reserves in the cerebral cortex. *J Neurochem* 14:599-611, 1967
87. Williams S, Paterson RA, Heath H: The effect of β,β' -iminodipropionitrile and anaesthesia on some adenine nucleotides of rat brain and retina. *J Neurochem* 15:227-233, 1968
88. Nilsson L, Siesjö BK: The influence of nitrous oxide and barbiturate anaesthesia upon the energy and the acid-base metabolism of the brain in normoxia and hypoxia. *Acta Anaesth Scand suppl* 37:143-144, 1970
89. Oja SS, Sarajas IISS: Cerebral energy metabolism in young rats during anaesthesia and hypothermia. *Ann Med Exp Biol Fenn* 49:29-34, 1971
90. Cohen PJ, Marshall BE: Effects of halothane on respiratory control and oxygen consumption of rat liver mitochondria. *Toxicity of Anesthetics*. Edited by BR Fink. Baltimore, Williams and Wilkins, 1968, pp 24-36
91. Ueda I, Mietani W: Microsomal ATPase of rabbit brain and effects of general anesthetics. *Biochem Pharmacol* 16:1370-1374, 1967
92. Ueda I: Effects of diethyl ether and halothane on firefly luciferin bioluminescence. *ANESTHESIOLOGY* 26:603-606, 1965
93. Chance B, Williams GR, Holmes WF, et al: Respiratory enzymes in oxidative phosphorylation. V. A mechanism for oxidative phosphorylation. *J Biol Chem* 217:439-451, 1955
94. Fahmy AR, Ibrahim HH, Talaat M: Inhibitory effect of thiopentone on the pyruvic dehydrogenase in brain. *Can J Biochem Physiol* 40:477-483, 1962
95. Fink B, Kenny GE: Metabolic effects of volatile anesthetics in cell culture. *ANESTHESIOLOGY* 29:505-516, 1968
96. Williams CD, Haugaard N: Toxic effects of oxygen on cerebral metabolism. *J Neurochem* 17:709-720, 1970
97. Jamieson D: Effect of high pressure oxygen on the duration of anaesthesia in mice. *J Pharm Pharmacol* 18:319-320, 1966
98. Fink BR, Kennedy RD, Hendrickson AE, et al: Lidocaine inhibition of rapid axonal transport. *ANESTHESIOLOGY* 36:422-432, 1972
99. Byers MR, Hendrickson AE, Fink BR et al: Effects of lidocaine on axonal morphology, microtubules and rapid transport in rabbit vagus nerve *in vitro*. *J Neurobiol* 4:125-143, 1973
100. Richter D: Factors influencing the protein metabolism of the brain. *Br Med Bull* 21:76-80, 1965
101. Gaitonde MK, Richter D: The uptake of 35 S into rat tissues after injection of (35 S) methionine. *Biochem J* 59:690-696, 1955
102. Gaitonde MK, Richter D: The metabolic activity of the proteins of the brain. *Proc R Soc Lond [Biol]* 145:87-99, 1956
103. Nechaeva GA, Sadikova NV, Skvortsevich VA: Renewal of amino acids of protein under different functional states. *Chem Abstr* 53:1500, 1959
104. Beloff-Chain A, Catanzaro R, Chain EC, et al: Fate of uniformly labelled 14 C glucose in brain slices. *Proc R Soc Lond [Biol]* 144:22-28, 1955
105. Barkulis SS, Geiger A, Kawakita Y, et al: Study on the incorporation of 14 C derived from glucose into the free amino acids of the brain cortex. *J Neurochem* 5:339-348, 1960
106. Tsuji H, Balagot RC, Sadove MS: Effect of anesthetics on brain γ -aminobutyric and glutamic acid levels. *JAMA* 183:133-135, 1963
107. Lajtha A, Toth J: The effects of drugs on uptake and exit of cerebral amino acids. *Biochem Pharmacol* 14:729-738, 1965
108. Malhotra CL, Pundlik PG: The effect of some anaesthetics on the acetylcholine concentrations of different areas of dog brain. *Br J Pharmacol* 24:348-351, 1965
109. Dobkin J: Effects of excitation and anaesthesia on the glutamine content of the rat brain with a reference to the administration of glutamine. *J Neurochem* 19:1195-1202, 1972
110. Cremer JE, Lucas HM: Sodium pentobarbitone and metabolic compartments in rat brain. *Brain Res* 35:619-621, 1971
111. Amakata Y, Greene NM: Effect of halothane and ether on glutamic-oxalacetic transaminase efflux from brain slices. *Biochem Pharmacol* 18:1239-1241, 1969
112. Ungar G: Inhibition of a brain protease by general anesthetics. *Nature* 207:419, 1965
113. Crossland J, Merrick AJ: The effect of anaesthesia on the acetylcholine content of brain. *J Physiol* 125:56-66, 1954

114. Schmidt KF: Effect of halothane anesthesia on regional acetylcholine levels in the rat brain. *ANESTHESIOLOGY* 27:788-792, 1966
115. Mackintosh FC, Oborin PE: Release of acetylcholine from intact cerebral cortex. *Abstr 19 Int Physiol Congr, Montreal, 1953*
116. Beleslin D, Polak RL, Sproull DII: The release of acetylcholine into the cerebral subarachnoid space of anaesthetized cats. *J Physiol* 177:420-428, 1965
117. Kalant H, Grose W: Effects of ethanol and pentobarbital on release of acetylcholine from cerebral cortex slices. *J Pharmacol Exp Ther* 158:386-393, 1967
118. Mitchell JF: The spontaneous and evoked release of acetylcholine from the cerebral cortex. *J Physiol* 165:98-116, 1963
119. Collier B, Mitchell JF: The central release of acetylcholine during consciousness and after brain lesions. *J Physiol* 188:83-98, 1967
120. Clouet DH, Ratner M: Catecholamine biosynthesis in brains of rats treated with morphine. *Science* 168:854-855, 1970
121. Fukui F, Takagi H: Effects of morphine on the cerebral contents of metabolites of dopamine in normal and tolerant mice: Its possible relation to analgesic action. *Br J Pharmacol* 44:45-51, 1972
122. Smith CB, Villarreal JE, Bednarczyk JH, et al: Tolerance to morphine induced increases in [¹⁴C] catecholamine synthesis in mouse brain. *Science* 170:1106-1108, 1970
123. Smith CB, Sheldon MI, Bednarczyk JH, et al: Morphine induced increases in the incorporation of [¹⁴C] tyrosine into [¹⁴C] dopamine and [¹⁴C] norepinephrine in the mouse brain: Antagonism by naloxone and tolerance. *J Pharmacol Exp Ther* 180:547-557, 1972
124. Taylor KM, Lavery R: The effect of chlor-diazepoxide, diazepam and nitrazepam on catecholamine metabolism in regions of the rat brain. *Eur J Pharmacol* 8:296-301, 1969
125. Bonnycastle DD, Bonnycastle MF, Anderson EG: The effect of a number of central depressant drugs upon brain 5-hydroxytryptamine levels in the rat. *J Pharmacol Exp Ther* 135:17-20, 1962
126. Diaz PM, Ngai SH, Costa E: The effects of cyclopropane, halothane and diethyl ether on the cerebral metabolism of serotonin in the rat. *ANESTHESIOLOGY* 29:959-963, 1968
127. Sung YF, Frederickson EL, Holtzman SC: Effects of intravenous anesthetics on brain monoamines in the rat. *Abstracts of Scientific Papers, Annual Meeting, American Society of Anesthesiologists, 1972*, pp 283-284
128. Gardier RW, Hamelberg W: Effects of anesthetics on catecholamine biotransformation, Toxicity of Anesthetics. Edited by BR Fink. Baltimore, Williams and Wilkins, 1968, pp 209-219
129. Miller RN: The effects of methoxyflurane on electron transfer, oxidative phosphorylation and calcium uptake by isolated rat liver and pigeon heart mitochondria. *Abstracts of Scientific Papers, Annual Meeting, American Society of Anesthesiologists, 1972*, pp 141-142
130. Krnjevic K, Lisiewicz A: Injections of calcium ions into spinal motoneurons. *J Physiol* 225:363-390, 1972