

In these comparative studies, the anesthetic agents themselves become chemical probes of brain maturation.

In the context of these comments, the study of Vannucci and Wolf provides us with several important and interesting results. First, the fetuses of dams anesthetized with nitrous oxide showed changes in cerebral phosphocreatine and ATP consistent with inhibition of aerobic metabolism. There were no such effects in maternal brains. In the fetal brains, there was no increase in lactate as would occur in the ischemic mature brain, perhaps because of the inability of the immature brain to increase markedly the rate of glycolysis under these conditions. The mechanism of this selective effect of nitrous oxide on the fetal brain is not clear, as stated by the authors. Perhaps this agent is altering fetal cerebral blood flow or is acting directly on a maturationally changing cerebral biochemical system. The second important observation in this study is the effect of high doses of pentobarbital in protecting the fetal brain from ischemic changes. Pentobarbital has been shown to protect the fetal monkey brain from metabolic deficit states.⁹ Its use is presently being advocated for clinical states of acute brain dysfunction.¹⁰ These animal studies argue for its use in the hypoxic or neurologically compromised newborn. It is important to learn the specific mechanisms of action and long-term effects of this drug in both immature and mature brain. A better understanding of these mechanisms, including effects on oxidative metabolism, will allow us to predict in which clinical situations and in which age groups use of pentobarbital may be beneficial, and in which it could be deleterious.

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New Implications of Fasting

IN THE ATTEMPT to bring the patient scheduled for an elective surgical procedure to anesthetic induction with an empty stomach, "NPO after midnight" has virtually become a dictum in most clinical situations. In the past, we have been made aware that such a practice may predispose our patients to some undesirable side effects of the surgical and anesthetic experience. For instance, there is evidence that anesthetics and operation produce considerably more depression of renal function when hydration is not maintained by parenteral means overnight.¹ There has been the suggestion that patients who have fasted for as little as 24 hours prior to elective anesthesia and operation may have depleted hepatic glycogen content and perhaps be at greater risk for the production of hepatic

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toxicity.² Now, Miletich *et al.* have reported that the metabolic changes accompanying fasting in the rat result in a lower threshold for epinephrine-stimulated arrhythmias during halothane anesthesia.³

Does this observation have clinical implications? A 12-hour fast in the rat resulted in a threefold increase in plasma free fatty acid (FFA) concentration. Fasting increases FFA in man, but a 24-hour duration is usually necessary.⁴ Although "fed" concentrations were not measured, preanesthetic FFA concentrations in a group of patients "NPO after midnight" were relatively low.⁵ Halothane anesthesia resulted in a two-to-threefold increase in serum FFA in the same study. Whether the same effect would be seen in "fed" patients is not known. In addition, since the arrhythm-

mic threshold for epinephrine was not tested, no conclusion can be drawn from that study concerning the transfer of data from the rat to man.

What is the mechanism of the FFA-halothane-epinephrine interaction in producing ventricular arrhythmias? The observations that stimulated this study were made entirely in ischemic heart preparations.⁶ The observed effect of fatty acids in ischemic and non-ischemic hearts to increase the oxygen cost of work may well explain this effect in the ischemic heart,⁷ although other studies have not confirmed FFA arrhythmia production.⁸⁻¹⁰ Increased sensitivity to epinephrine-induced arrhythmias was observed,⁹ but there is no evidence of a defect in oxygenation in the halothane-anesthetized heart, even at very high concentrations.¹¹ There is some evidence that the route of energy production in the heart may be important in terms of electrical stability of the cardiac cell membrane. It is possible that ATP produced by glycolysis may be more important for this function than the ATP from other energy sources.¹² In addition, halothane appears to interfere with the glycolytic process in heart muscle.¹³ Since increased FFA levels also shift the metabolic processes in heart muscle from glycolytic to lipolytic pathways,¹⁴ the combination of the two might produce the situation where the cell membrane would be more sensitive to beta-adrenergic stimulation. One way of looking at this problem would be to use the cultured heart cell preparation. In fact, Strong *et al.* reported that cultured heart cells in which glycolysis was completely inhibited by the addition of 2-deoxyglucose to the medium were much more sensitive to the negative inotropic effects of halothane than cells in which glycolysis was maintained intact.¹⁵ Whether this inotropic effect also pertains to the effect on the rhythmicity of the cell remains to be determined. Finally, the FFA-albumin ratio appears to be important. At high ratios (>3.0), arrhythmias were produced in perfused rat hearts.¹⁶ The authors speculate that the negative results of other studies⁹ might be related to low FFA-albumin ratios. Miletich *et al.* did not report FFA-albumin ratios.

This report, then, should stimulate further investigation in two directions. First, is the effect specific to the small rodent investigated, or can it be reproduced in higher mammals, especially man? Second, more definitive investigation directed toward elucidating the mechanism of the action must be performed. This is necessary to indicate whether, in fact, the effect of fasting to lower the cardiac cellular membrane threshold for epinephrine-induced arrhythmias during halothane anesthesia is related to the metabolism of the heart cell or whether the increased fatty

acids are a reflection of some other more generalized effect. A further question relates to the specificity of the effect. Perhaps other arrhythmias are also sensitive to FFA. Only after these questions are answered may the results of the investigations of Miletich *et al.* stimulate a change in the preanesthetic preparation of the patient.

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