

Editorial Views

A New Aspect of the Metabolism of Halothane

FOR A HUNDRED YEARS after surgical anesthesia was introduced, inhalation anesthetics were assumed to be unaffected by passage through the body. That inhalation anesthetics actually do undergo biodegradation was reported as early as 1883, when chloroform was shown to be metabolized by man.¹ This observation received little attention at the time, however, and it soon was lost sight of. Later, trichloroethylene was also shown to be metabolized, but although this fact was known to pharmacologists and anesthesiologists, it was regarded as an esoteric feature unique to trichloroethylene and so generally ignored; certainly it was not regarded as typical of other anesthetics.

Metabolism of inhalation anesthetics first became widely recognized in the early 1960's. At that time it was conclusively demonstrated that two popular inhalation anesthetics, halothane and methoxyflurane, undergo substantial biodegradation when administered to man. Since then, anesthetic metabolism has been the subject of a large number of studies, which have taken two directions. One, a biochemical approach, has been principally concerned with the chemical reactions involved, identification of resulting metabolites, and determination of the factors regulating rate and magnitude of metabolism. The other approach, clinically oriented, has been primarily concerned with the clinical significance of anesthetic metabolism. Of special interest has been the possibility that a rela-

tionship might exist between toxicity and metabolism. The aspects of toxicity that have been examined have included teratogenicity and abortifacient activity, but the main emphasis has been on histotoxicity.

That histotoxicity and anesthetic metabolism are closely related was soon shown to be the case with chloroform. The metabolism of chloroform is clearly directly and immediately responsible for its hepatotoxicity. The nephrotoxicity of methoxyflurane has also been shown to be the result of its metabolism. Biodegradation of fluroxene was additionally found to be related to its toxicity, but only in certain experimental animals, not in man.

Equally clear evidence that the metabolism of halothane is related to toxicity has not been forthcoming, despite the expenditure of a tremendous amount of effort, time, and money. The stimulus behind most of these studies has been the attempt to determine whether the putative hepatotoxicity of halothane as manifested by so-called "halothane hepatitis" is in any way related to the fact that a considerable portion of the halothane taken up during clinical anesthesia is subsequently metabolized. One of the possibilities was that the metabolites resulting from the biodegradation of halothane might, as in the case of chloroform, be toxic to the liver, even though only ephemerally present. Most of the support for this has been derived from *in-vitro* laboratory experiments. The evidence

that metabolites of halothane are clinically hepatotoxic remains unconvincing, at least so far. Another possibility, that the metabolites of halothane might indirectly provoke hepatic damage by forming antigens capable of initiating sensitization reactions involving the liver, has also received considerable attention. Again, some experimental data have been obtained to support such a possibility, but the evidence that this is the explanation for the rare case of "halothane hepatitis" remains inconclusive at best, if not wholly negative. Indeed, there is even doubt whether the syndrome of "halothane hepatitis" really exists.

Attempts to define the possible clinical significance of the metabolism of inhalation anesthetics have to date been based almost exclusively on the tacit assumption that histotoxicity is the major, if not the only, potential implication of anesthetic metabolism. Evidence to suggest that the metabolites of inhalation anesthetics may have important effects other than those related to production of morphologic changes in cells has, however, gradually been accumulating. An example of this, and what may well prove to be a watershed in how we perceive toxicity of inhalation anesthetics, is the report by Tinker and his associates in the present issue.² Tinker *et al.* found plasma bromide levels to be significantly elevated in 25 patients following operations performed with halothane anesthesia. This could only be due to metabolic debromination of halothane. By itself, this is not an entirely new observation. Atallah and Geddes³ reported increased blood bromide levels in eight patients after halothane anesthesia. Johnstone *et al.* also found significant elevations of plasma bromide levels in normal volunteers following halothane anesthesia without surgery,⁴ though, happily, no significant change in plasma bromide levels was found in individuals, including anesthetists, occupationally exposed to trace concentrations of halothane.⁵

What is new about the data of Tinker *et al.* is their quantitation of this phenomenon. Plasma bromide levels rose as a function of concentration of halothane administered. They also rose as a function of duration of exposure to halothane. The elevation of plasma bromide was, therefore, directly related to concentra-

tion times duration of exposure, *i.e.*, MAC hours. Peak bromide levels were, however, not achieved in these patients for 48 to 72 hours following anesthesia and operation. Once reached, though, they persisted for days thereafter.

Bromide has long been recognized as a sedative. Its effectiveness as a gentle but nonetheless effective central nervous system depressant is amply testified to by the popularity that over-the-counter and prescription compounds containing bromide have enjoyed for many decades. The amount of bromide in the blood required to produce sedation remains, however, hard to define. To a large extent this is because of the rapid development of tolerance. Most of the published data attempting to relate plasma bromide levels to subjective responses have been derived from subjects who had been taking bromides for relatively long periods and who were, therefore, at least partially tolerant. Nevertheless, the peak plasma bromide levels in Tinker's patients, 0.65 to 2.25 mEq/l, are in the range where central nervous system effects would be expected, especially in non-tolerant surgical patients who have not been taking bromides.

The potential for sedation persisting into the postanesthesia period after elimination of an anesthetic because of the formation and retention of depressant metabolites was demonstrated more than 20 years ago for another anesthetic, trichloroethylene. The trichloroethanol into which trichloroethylene is metabolized is as effective a sedative as the trichloroethanol into which chloral hydrate is metabolized, which is largely responsible for the hypnotic effect of chloral hydrate. When trichloroethylene was more widely used than it is today, prolonged sedation was recognized by anesthetists as a possible complication when the anesthetic was administered for more than two hours, or when it was administered repeatedly to the same individual. It now appears that trichloroethylene may not be alone in its ability to cause prolonged sedation following anesthesia. The same thing may also occur after halothane, especially when administered for long periods at high concentrations. Bromide levels remained abnormally elevated in Tinker's patients for as

long as 22 days following anesthesia. Especially interesting is their patient who had halothane anesthesia for repair of an intracranial aneurysm. Though the operation was successful, the patient failed to regain consciousness for nine days. Consciousness was regained only as the plasma bromide levels started to decrease. While other factors may have contributed to the delayed recovery of this patient, the data reported by Tinker *et al.*, plus those reported by others, clearly indicate the potential for prolonged sedation following halothane anesthesia exists. The clinical significance of halothane may well lie more in this side-effect of halothane than in possible histotoxic responses to the metabolites of halothane.

Additional studies are needed to define more fully the risk of prolonged sedation following halothane anesthesia. In the meantime the prudent anesthesiologist would do

well to bear in mind the data of Tinker *et al.* We may need to adjust our present concepts of the indications for and contraindications to halothane.—N.M.G.

References

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Theories of Anesthesia

CEREBRAL METABOLISM AND HALOTHANE Although many anesthetics have been demonstrated to interfere with mitochondrial respiration *in vitro*, there is a considerable body of data suggesting that normal clinical anesthesia is not associated with decreased cerebral energy stores. Because of major circulatory depression, higher than normal concentrations of halothane have not been studied *in vivo*. Extracorporeal circulation permitted the administration of high concentrations (to 9 per cent) of halothane to the intact dog. When 2.3 per cent halothane was exceeded, a dose-related diminution of cerebral oxygen uptake occurred. This did not depend upon whether the EEG was active or silent. Indeed, cerebral oxygen consumption continued to decline even after the EEG had become isoelectric. Although cerebral oxygen delivery remained adequate, a progressive decrease in brain ATP and phosphocreatine developed at concentrations exceed-

ing 2.3 per cent. This was accompanied by increased brain lactate and an increase in the lactate/pyruvate ratio. These findings, indicative of anaerobic metabolism and diminished brain energy reserves, were reversed when halothane administration ceased. At the same time cerebral oxygen uptake was greater than normal. (Michenfelder JD, Theye RA: *In vivo toxic effects of halothane on canine cerebral metabolic pathways. Am J Physiol* 229: 1050-1055, 1975.) **ABSTRACTER'S COMMENT:** These data indicate similarity between *in vivo* and *in vitro* anesthetic effects. However, they cannot be extrapolated to all agents. The results differ significantly from those the authors observed previously when thiopental was examined (*ANESTHESIOLOGY* 41:231-236, 1974). With this drug, once the EEG became silent no further diminution of cerebral oxygen uptake was found. In addition, at no time was there evidence of decreased cerebral energy reserves.