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Minipigs, Microsomes, Metabolism, and Maupassant

"O, ma pauvre, Mathilde! Le mienne était fausse."
The Necklace, Guy de Maupassant

The article by Sawyer *et al.* in this month's issue of ANESTHESIOLOGY must generate much food for thought. Only six years ago pharmacology students were taught categorically that, almost unique among drugs, inhalation anesthetics entered and left the lungs essentially unaltered by cohabitation with the body's biochemical machinery. At that time the golden era of study of uptake and distribution of these agents was in progress. Numerous computer-programmed multicompartmental analyses concerned with the uptake of anesthetics appeared, based primarily on the variables of blood flow and partition coefficients. There was no "sink" programmed for metabolism—it just did not exist.

Then, in swift succession, several investigators determined this view of metabolic inertness of anesthetics was untenable. Van Dyke, Chenoweth and Van Poznak[1] found that ether, methoxyflurane (Penthrane), and halothane (Fluothane) were metabolized to a considerable extent in animals, a finding documented and investigated further by Cohen[2] and others. The magnitude of halothane metabolism in man was determined by Rehder *et al.*[3] This group of German investigators found that as much as 20 per cent of absorbed halothane was metabolized, a surprise indeed. Like the denouement of a de Maupassant short story, Holaday and coworkers[4] topped this by discovering that 50 per cent of absorbed me-

thoxyflurane was converted to metabolic products in man!

The observation that halothane acutely inhibits its own metabolism, presented in this issue by the University of California group, will prevent the "uptake and distributioners" from chopping their *y*-axes by a 20–50 per cent factor and retracting a dozen or more papers. For this reason alone, this article is significant. But of greater long-range scientific merit is the confirmation that inhalation anesthetics (at least halothane) are capable of inhibiting their own hepatic metabolism. The time of maximal hepatic concentration of halothane (presumably the anesthetic period) is, therefore, a time of minimal metabolism. The influence of this evidence on future experimentation will be great. As examples, delination of enzymatic pathways of anesthetic metabolism by *in vitro* studies may well be hampered if the anesthetics are not metabolized to a great extent during acute administration; if hepatic damage is produced by metabolism and/or metabolites of anesthetics, this effect may occur only when the total level of anesthetic is declining. Assuming this hypothesis, hepatic damage would not necessarily be acutely dose-related, but would be potentially greater with agents of greater lipid solubility. These are just a few insights derived from this paper.

"Concentration Dependence of Hepatic Halothane Metabolism" is a highly informative work, and a major contribution. If any criticism is to be made, it is that the hepatic halothane concentration differences observed were only *assumed* to be the result of metabolic extraction. This article would have been a complete "wrap-up" if metabolic products of halothane had been quantitively assayed. Determination of these metabolic products in microgram and submicrogram quantities, however, is extremely difficult technically.

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