Correspondence

Fluroxene in the Rat and Man

To the Editor:—Harrison and Smith, in the article, "Massive Lethal Hepatic Necrosis in Rats Anesthetized with Fluroxene, after Microsomal Enzyme Induction" (ANESTHESIOLOGY 39:619–625, 1973), draw rather sweeping, and what I consider inaccurate, conclusions from their data. These investigators note that in rats fluroxene caused hepatic damage which was increased by pretreatment with the enzyme-inducing drug, phenobarbital. From this they concluded, "Speculation aside, the clinical implication of our observation is clear. Fluroxene anesthesia should not be used for any patient who is on a regimen of treatment with a drug that has enzyme-inducing properties."

I believe the point at which Drs. Harrison and Smith have erred is in making a direct transposition of the results of an animal study to clinical practice. It is well known that there are great variations in the metabolism and pharmacologic effects of many drugs among different species of animals. For this reason, it is an accepted pharmacologic principle that animal toxicity studies have relevance for investigation of drug toxicity in man only if the animal model and man share similar metabolic pathways and toxic manifestations. Specifically, with regard to fluroxene anesthesia in man, there does not appear to be a higher incidence of hepatic dysfunction following its administration than with any other anesthetic agent. Also, it is known that there are major differences in the products of its metabolism between dogs, mice, and rats on the one hand and man on the other; the markedly hepatoxic substance, trifluoroethanol, is a major end-product of the metabolism of fluroxene in the animal species but not in man. Therefore, it is not unexpected that treatment with an enzyme-inducing drug would increase the amount of toxic metabolite in the animals and would exacerbate any adverse reaction the metabolite might produce. Since trifluoroethanol is only a very minor product of the metabolism of fluroxene in man, there is no reason to suspect that enzyme induction would lead to hepatic damage in man. Therefore, it is apparent that the animal model proposed by Harrison and Smith is inappropriate, *i.e.*, the metabolic pathways are different and the toxic manifestation is not common to both species. Their conclusion, then, is speculation, and almost certainly incorrect.

RICHARD I. MAZZE, M.D.
Department of Anesthesia
Stanford University School of Medicine
Stanford, California 94305

(Accepted for publication August 28, 1974.)

To the Editor:—I have every sympathy with the views expressed by Dr. Mazze, for I confess my own initial reaction to the observations reported in our paper[1] were similar. Indeed, this crucial question of the applicability to man of drug research in animals was extensively discussed with particular reference to fluroxene in a recent Editorial in ANESTHESIOLOGY.[2]

However, I thought that we had made it clear in our paper that we considered that the publication of a report of a human fatality from a similar lesion following fluroxene anesthesia[3] and in circumstances analogous to that pertaining in our experimental animals gave our observations immediate clinical relevance. Since that time ANESTHESIOLOGY has published another report of a similar fatality.[4] In addition, there have been two recent reports of postoperative jaundice immediately following fluroxene anesthesia, although in these circumstances no cause–effect relationship can be strictly validated.[5,6]