addition to the nine cases cited in your review a case has been described by Vourc'h and his colleagues.

You also say that although halothane may be suspected as an important contributory cause in these cases it is possible that as a potent hepatotoxin it may be completely absolved. Previous work has tended to promote the view that its noxious effects on the liver are relatively slight. In addition, as with chloroform, it is possible that various extraneous factors such as hypercarbia or hypotension may play a more or less important contributory role.

I agree entirely with the view expressed that the sooner a definitive evaluation of the hepatotoxic effect of halothane as used in clinical practice is reached the better. Accordingly, in this Centre I have, with colleagues, instituted a clinical trial aimed chiefly at this evaluation. The trial, mainly for ethical reasons, is of the sequential type, is strictly controlled, and will among other things compare quantitatively the effect on the liver of halothane and chloroform under standard conditions. We propose to assess liver function by measuring serum glutamic pyruvic transaminase activity.

We endorse the view that the equivocal position of halothane with regard to its toxic effects on the liver must be resolved as quickly as possible, and it is hoped our present trial may be helpful.

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To the Editor.—Drs. Brody and Sweet's interesting article [1] fails to answer questions that must have been foremost in many reader's mind: assuming that halothane is justly implicated in these fatalities, what is the incidence of such complications and what can be done to minimize their risk?

In an attempt to furnish an approximation to the first question we have searched the records of our hospital, a 1,000 bed teaching institution, from January 1, 1959 to January 1, 1963, for fatalities occurring from hepatic failure within six months following an anesthetic in subjects whose hepatic status was considered normal before anesthesia. During the four years in question 88,000 patients were admitted to our hospital and close to 50,000 anesthetics were administered—35,000 of the latter were by conservative estimate halothane–nitrous oxide. It ought to be added that during the past two years there was a distinct epidemic of virus hepatitis in the Montreal area, which might influence our findings.

We have found six charts that satisfied the stated requirements—five women and one man, four of the women past the menopause. Five subjects were anesthetised with halothane–nitrous oxide, one had a spinal. Their operation and immediate recovery was uneventful, their subsequent course paralleled the description in Brody and Sweet's article.[1] In two subjects, later analysis of the charts turned up possible signs that they were anesthetised during the prodromal stage of a hepatitis, in the other four even this much evidence was lacking.

In our hospital then the incidence of fatal hepatic complications following anesthesia has been of the order of 1 in 8,000. While this may not appear unacceptable, let it be remembered that in numerous statistics in the past [2] *all* deaths following chloroform were around 1 in 3,000—the change is not impressive.

Concerning the ratio of five halothane anesthetics to one other anesthetic in this series we believe that fatal hepatic complications cannot be completely avoided just by eliminating all the inhalation anesthetics. Other factors are also involved, such as the obvious oxygenation of the patient and the maintenance of a reasonable cardiac output. Beyond these, there must also be considered the maintenance of adequate blood-flow through the liver at all times. This parameter is poorly defined during anesthesia while the abdomen is closed; what effect an enthusiastically applied retractor might have, we can only wonder, yet five of our six fatalities followed intraperitoneal procedures.

The predominance of post-menopausal women in Brody and Sweet's patients [1] and in our series points towards the particular vulnera-

bility of this group. Should the slightest doubt arise about the competency of liver function in such a patient, it might be prudent to chose some other anesthetic than halothane for her.

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2. Sykes, W. S.: Essays on the First Hundred Years of Anesthesia. London, E & S Livingstone Ltd., 1961, vol. 2, p. 49.

To the Editor.—Your Editorial in the January–February 1963 issue of ANESTHESIOLOGY invited comment relating to halothane (Fluothane) and possible hepatotoxicity, and I believe that I should give what information we, the manufacturers, have, and state our views on the subject.

Experimental evidence from animals has unanimously bracketed halothane with ether and cyclopropane as being relatively free from hepatoxicity. Where halothane has been compared with chloroform under similar experimental conditions the difference has been striking.[1-10] Liver function tests have been carried out after operation by a number of investigators [11-19]; and as you stated, they have not shown halothane to be different from ether or cyclopropane, in the effect it has on these tests.

We estimate that upwards of 20 million halothane anesthetics have now been given, and the number of deaths from liver damage reported has been extremely small. We are aware of nine fatal cases. It is probable that jaundice without death has usually not been considered worth reporting, but it is interesting that Barton,[20] who reported two cases and invited other anaesthetists to report their own experiences, only provoked one reply which was a negative one.[21] We, the manufacturers, have had private reports of suspected liver-toxicity from United Kingdom and Europe only three times. Two of the private reports concerned one case each, but the third dealt with 11 cases of jaundice over a seven-year period, and in two of the cases there was no obvious possible reason for the jaundice other than the anaesthetic. Pichlmayr and Stich [26] reported and subsequently published an account of 41 cases of jaundice of which 29 had received halothane. This "epidemic" was investigated and concluded to be due to the transfusion of stale blood.

In trying to assess the cause of postoperative liver damage a number of factors have to be considered, and much basic information is still required. A number of drugs, including penicillin [22] have been incriminated. The once-in-prominence "hepato-renal syndrome" (Boyce, 1941—The Role of the Liver in Surgery, Springfield, Ill.) seems to have been largely forgotten, but it is noteworthy that four out of the nine reported fatal halothane cases underwent operations involving the biliary tract. It is interesting that in 1932 Guthrie and Robertson [23] published a paper entitled: "Is ether a cause of liver death following gall-bladder surgery? Review of 434 gall-bladder and duct operations." What is it which precipitates the injury? Calvert and Brody [24] have shown that even with carbon tetrachloride it is impossible to cause liver changes experimentally unless the sympathetic nervous system is intact.[24] Do certain types of surgery and certain conditions of anaesthesia result in reflex vaso-constriction of the hepatic artery? That hepatic artery constriction provoked by the increasing use of catecholamines could be a cause of hepatic necrosis was suggested by Brunson *et al.*[25] These authors incidentally drew attention to the apparent mounting incidence of hepatic necrosis in their group of hospitals. This was prior to the introduction of halothane.

Finally you discussed the chances of infective hepatitis coinciding with the postoperative period. Using similar arguments to yours our statistical department has calculated that more than 200 cases of infective hepatitis could have occurred postoperatively following 20 million anaesthetics. These cases of infective hepatitis would have been expected to have been scattered throughout the postoperative period, as has been the case in the nine reported deaths.

In conclusion, there seems to be no real indication that halothane is toxic to the liver. All the experimental and the clinical circum-