"Kettle"-type vaporizers, when in good working order and properly used, will deliver extremely precise concentrations of halothane under free flow conditions. With closed systems and IPPB, these vaporizers are subject to a 30 per cent error in delivered concentration unless a check valve is used, and still subject to a 15 per cent error with an external check valve. The described valve is not only a more efficient remedy, but is the least expensive method suggested to date.

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Halothane and Hepatic Necrosis

To the Editor.—A plague of reports of death and disease following the use of halothane is predictable.

Past and future reports should be scrutinized objectively and with intense care. Reports of liver disease following the use of halothane are utterly inconclusive, unless all of the following criteria are fulfilled:

(1) The time interval between putative cause and effect is reasonable.
(2) All other iatrogenic causes are, as nearly as possible exonerated, including, surgery itself, other anesthetic agents, and non-anesthetic agents.
(3) Indubitable evidence rules out infectious hepatitis, or, failing this:
(4) Careful epidemiologic study demonstrates incidence in time and number and place significantly higher than in a control halothane-free series.
(5) Pre-existing liver disease is, as nearly as possible, ruled out.

The report from Michigan (Brody, G. L., and Sweet, R. B.: ANESTHESIOLOGY 24: 29, 1963) fails in several ways to meet these criteria. For example, no mention is made of the length of time covered in the survey or of the comparative incidence of such liver necrosis in similar cases done without halothane in the same period of time by the same anesthesiologists in the same places. Indeed, we are not even told where the cases were except for one which is acknowledged to have been done in the authors' hospital. Little or no effort is reported to rule out causes of hepatic disease other than halothane. Two of the patients had biliary disease, and it is hardly an improbable leap from there to the liver.

The guilt of halothane is apparently given credence by implication. The authors' words, "These four cases offer no proof that halothane was the direct cause of the massive hepatic necrosis; however, the implications that such is the case are strong" are almost their only bow to the objectivity of the scientific method —scarcely more than a faint nod, really.

Indictment often has the emotional effect of conviction. The circumstantial evidence adduced to date hardly proves guilt, but it tarnishes the innocence of a useful drug.

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To the Editor.—It becomes apparent when one reads the two reports concerning halothane toxicity in the March 7 issue of the *New England Journal of Medicine* that those articles had been submitted *concurrently* with ours, not *sequentially*. This seems to us to indicate that others using halothane have also been concerned about its possible toxicity. None of the articles submitted offers more than circumstantial evidence that halothane can, in rare instances, produce hepatic necrosis and none can be construed to be a *study* of the drug. Rather, our intent was simply to call this problem to the attention of anesthesiologists with the hope that a statistically significant scientific evaluation of halothane might be undertaken. Such a study is now being organized to include several teaching institutions.

We agree with Dr. Friend that circumstantial evidence hardly proves guilt but also believe that unwillingness to consider possible adverse reactions to halothane is unrealistic.

GERALD L. BRODY, M.D.
ROBERT B. SWEET, M.D.
University of Michigan Medical Center
Ann Arbor, Michigan

To the Editor.—It would seem that the rock on which opinions may perish is no longer the heart, but the liver. The recent reports [1-4] of liver necrosis following halothane anaesthesia have cast suspicion on the methods of screening for hepatotoxicity. This is a surprising development as it has been established beyond reasonable doubt that halogenated hydrocarbons which cause liver necrosis in man will readily produce similar lesions in the laboratory animal.[5, 6]

Many liver studies of halothane in several species of animal, some of them conditioned by hypoxia, starvation or selenium, have failed to reveal a necrotising action. Liver function studies in man following halothane anaesthesia did not provide evidence of liver impairment beyond that which follows surgical trauma under conventional anaesthetic methods. Halothane anaesthesia in conditions likely to provoke liver injury—induced hypotension, cardiac and pulmonary surgery, obstetrics, and burn therapy—has not been followed by reports of liver necrosis. It has been used without incident in a series of 33 consecutive and successful porto-caval anastomoses.[7] In the light of this experience it can be stated with confidence that halothane cannot by any stretch of the imagination be described as a true hepatotoxin, like chloroform and carbon tetrachloride.

The authors of the halothane reports have made little or no reference to the fact that postoperative hepato-renal failure is not unknown in circumstances unrelated to halothane. It would therefore seem relevant to refer briefly to some of the other factors which may cause or predispose to liver damage in the surgical patient.

THE SURGICAL OPERATIONS

Hepato-renal failure or the hyperpyrexial 'liver-death' syndrome has been described as "an exceedingly important cause of death in surgery of the biliary tract as well as in thyroid disease, and an important cause of death after the other types of operation." [8] It has been observed after all types of anaesthesia and analgesia.[9, 10] Hypotension due to haemorrhage or ganglion blockade may contribute to the liver damage.[11] Traction on viscera in the upper abdomen may cause up to a 50 per cent decrease in the liver blood flow.[12] Severe or prolonged surgical trauma under light anaesthesia—nitrous oxide, ether and relaxants—may cause centrilobular necrosis and polymorphonuclear infiltration of the liver.[13]

Acute pancreatitis is a complication of upper abdominal and other forms of surgery; [14] and it may be followed by jaundice due to compression of the common bile duct by the swollen pancreas.[15] If this complication is preceded by or associated with liver disease, heart failure, septicaemia, haemorrhage, shock or blood transfusion, it is not improbable that the consequences to the liver will be obvious.[16, 17]

OTHER DRUGS

An interesting commentary on the increasing prevalence of unexplained liver jaundice has indicated that vasopressor and antibiotic drugs may play their part in causing liver damage.[18] An allergic response to penicillin has been held responsible for the death from liver necrosis of a patient shortly after an operation for carcinoma of the breast; [19] penicillin allergy has been cited as the cause of at least one other postoperative death.[20] It is interesting to note that several of the reported hepatic reactions following halothane anaesthesia were associated with the manifestations of allergy: urticarial and erythematous skin reactions, fever, malaise, arthralgia, generalised lymphadenopathy, eosinophilia and hypotension.

Penicillin [21] and other antibiotics [22-24] are now recognised to be capable of producing allergy and liver necrosis. It is not improbable that patients who survive the initial anaphylac-

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tic response will develop liver damage similar to the Arthus reaction stated to be due to the formation of antigen-antibody thrombi in the portal capillaries.[19]

Viral Hepatitis

This disease may complicate the recovery from surgery either as the result of preoperative infection or by the transmission of the virus via blood transfusion or other hypodermic injections. Preoperative subclinical infection may become manifest within twenty-four hours of the operation, the writer having had a particularly narrow escape from this trap in the first weeks of the initial clinical trial of halothane.[25] Transmission of the virus by blood transfusion may be followed by malignant hepatitis in three or four weeks; [26] and by postnecrotic cirrhosis any time thereafter.[27] One of the more disturbing features of this disease is that a person may remain capable of transmitting it for at least seventeen years after acquiring it.[26]

Chemotherapy is not always therapeutic. Nowadays, so many drugs are used simultaneously in the treatment of disease that it is often difficult to identify the one responsible for a given reaction. If confusion is to be avoided in the assessment of effect it would seem that it will become necessary to apply criteria reminiscent of those postulated by Kock to define the pathogenicity of bacteria. Klatskin [28] has clearly defined the features of a true hepatotoxin and they are certainly not those of halothane. Compounds which indirectly cause liver injury by an allergic or hypersensitive response are much more difficult to assess in this respect, but it is clear that several in the antibiotic and tranquillizer groups are suspect. It remains to be determined whether halothane affects this response, adversely or otherwise.

It might even be inferred from recent pharmacological investigations that halothane may be the anaesthetic of choice for patients with liver disease. It has been observed in dogs that most, if not all the cardiovascular effects of halothane are due to blockade of the sympathetic outflow from the brain.[29] Others have demonstrated in rats that blockade of the sympathetic outflow from the brain confers complete protection from the hepatotoxic action of carbon tetrachloride.[30]

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To the Editor.—I was very interested in your editorial comments in ANESTHESIOLOGY, concerning halothane and liver damage.

The interest to me lies not so much in the possibility of liver damage being caused by halothane, but why these cases should be occurring in the U.S.A. and not in Britain.* No British anesthetists have reported any cases, and on a personal note, I have used halothane since 1956 with no abnormal findings in the liver postoperatively. (I was one of Dr. M. W. Johnston's Juniors, when he carried out his clinical trials.)

Which brings me back to why these cases occur in U.S.A. and not Britain. May I put forward a possible line of thought—and I would add that I have no concrete evidence to support my view—merely a theory. Could there be a build-up of CO_2 during anesthesia? —and could this, in association with halothane, cause the liver damage?

I have spoken to Dr. Raventós—he assures me that he has been unable to produce liver damage in his animals, no matter how high the CO_2 level—but would this of necessity hold in human beings?

I was able to observe methods in the U.S.A. at close quarters. I was privileged to be a Special Fellow in Anesthesiology at the Cleveland Clinic, Cleveland, Ohio, from February 1960–February 1961. One marked difference in technique which I noticed, was that we use much higher flows than our U.S.A. colleagues —*e.g.*, on semi-closed circuits we use 6 litres of O_2, 2 litres of N_2O or 5:3—usually a total flow of 8–9 litres (for adults—less for children.) This high flow is sufficient to wash out CO_2, even without an absorber. In U.S.A., people seemed to use a much lower flow—2:2 —but of course with an absorber. Suppose, however, the absorber was not acting efficiently, *e.g.*, soda lime stale—there would be a CO_2 build-up. It would be interesting to find out whether there was any CO_2 build-up in the cases reported.

I'm not for a moment implying any wrong or bad technique from the anesthesiologists concerned, but it seems so strange for cases to occur in U.S.A. and not here, yet we use the same halothane. So a feasibility must be technique, and you must agree that with a high flow and no absorber there is less chance of CO_2 build-up than with a low flow and inefficient absorber. A possible explanation of why cases on one side of the Atlantic only??

DR. MERTON SEIGLEMAN
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To the Editor.—I have been most interested in the article by G. L. Brody and R. B. Sweet and your own editorial comment on the subject of necrosis of the liver following anesthesia in which halothane is administered.

It occurs to me to inquire whether in the cases reviewed, halothane concentration was determined by monitoring the mixture actually delivered to the patient or whether it is merely inferred from the settings of the vaporizers used. In the latter case certain techniques can of course result in a substantially different concentration reaching the patient from that which is actually set on the vaporizer. I would not suggest, of course, that the concentration would be so grossly inaccurate as to cause obvious disparities at the time of the operation, but in matters like the present, where one is seeking the cause of an observed serious effect the academic details can be important.

My interest in this matter arises from the fact that my Company specializes in the development and manufacture of the Vaporizer for volatile anaesthetic agents. We are always striving to provide the practitioner with the most accurate control possible so that any indication that particular conditions require an especially sensitive control of the agent are of prime importance in planning and developing vaporizers of tomorrow.

J. A. JEPHCOTT
Longworth Scientific Instrument Co. Ltd. England

* Since my original letter, reports have appeared in the *British Medical Journal.*