Unexplained Hepatitis Following Halothane


HALOTHANE WAS INTRODUCED into clinical practice in 1956.1 Anecdotal cases of unexplained hepatitis following halothane anesthesia (UHFH)—halothane hepatitis—were first described in 19582,3 and were soon followed by an increasing number of similar reports, predominantly from the United States.4-7 Since then enormous amounts of time, effort, and money have been spent in attempt to unravel the mystery surrounding the existence, incidence, and, more recently, the cause of halothane hepatitis.

The use of halothane has declined markedly in some countries, notably in the United States. While this may have resulted in part from the introduction of alternative agents (enflurane and isoflurane) that may offer certain advantages, undoubtedly a major factor has been the perceived medico-legal consequences of previously healthy patients developing potentially fatal liver damage. Indeed it has been suggested that one should have a positive reason for using halothane in preference to other agents.8 Is halothane destined for obsolescence? If so, is it worth pursuing the cause of hepatic dysfunction following its use so vigorously? Perhaps we should opt to use other volatile agents or alternative techniques with less serious and more predictable side effects?

There are a number of reasons for considering such an attitude unreasonable and unrealistic. First, many authorities agree that halothane is a useful and safe agent.9,10 Second, it is considerably cheaper than enflurane and particularly isoflurane. This may not be an overriding priority in affluent countries, although all physicians should consider the cost-effectiveness of their practice. Third, although diethyl ether continues to be advocated and used for anesthesia in developing countries, it is not an agent that is easy to administer and it precludes the use of electrical cautery.11 An increasing number of anesthesiologists working in these countries have trained in Europe or North America and have little experience with diethyl ether. Halothane is much easier to manage and can be delivered via systems now being advocated for use in this environment.12 It seems certain, therefore, that halothane will play an important role in developing countries for the foreseeable future. Enflurane and isoflurane are also halogenated hydrocarbons and also may have the potential to produce hepatotoxicity.13 Finally, an insight into the cause(s) of halothane hepatitis is necessary in order to predict the likelihood of toxicity with new agents as they are developed.

It seems appropriate at this time to review the published data on UHFH and see how far it has taken us toward answering those questions of concern to the clinical anes-

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Unexplained hepatitis following halothane (UHFH), or as it is commonly defined, "halothane hepatitis," is a very rare complication of halothane anesthesia. Jaundice, i.e., a rise in bilirubin concentration, with or without other changes in liver function tests, is common after anesthesia and surgery. Such changes relate to preexisting liver disease, blood transfusion, infection, viral hepatitis, and the extent of the surgical procedure. These causes are easily diagnosed, and it is extremely unusual for patients with these conditions to have fulminant hepatic failure develop as a primary condition postoperatively. However, if viral hepatitis is responsible, with the exception of non-A non-B hepatitis, serologic testing can distinguish this from other causes of hepatitis.

This review focuses on those patients where all reasonable causes of postoperative hepatitis following halothane anesthesia have been excluded, yet the patient is unwell, and a diagnosis of halothane hepatitis is made.

**History**

Halothane was synthesized by Suckling in 1952 for Imperial Chemical Industries. After preliminary pharmacologic studies by Raventos, it was introduced into clinical practice in 1956. Its many advantages over other agents led to a rapid and widespread increase in its usage.

Initial animal work had indicated either an absence of hepatotoxicity or minor disturbance similar to that seen with diethyl ether. In particular, no hepatic necrosis was observed following halothane administration (cf, chloroform and divinyl ether).

**Early Reports**

Early clinical reports appeared to confirm these animal studies. However, cases of postoperative liver necrosis after use of halothane were published in 1958, and further reports noting the clinical and pathologic similarities between UHFH and chloroform hepatotoxicity followed.

**Retrospective Studies**

The concern provoked by these reports stimulated a number of retrospective surveys of hepatic dysfunction following general anesthesia. Whether hepatic necrosis at postmortem or clinical evidence of liver damage was used as the criterion, no study was able to show a significantly increased incidence of hepatotoxicity following halothane anesthesia. The indelible nature of these conclusions led the National Institute of Health to conduct a large, multicenter review of fatal hepatic necrosis occurring within 6 weeks of anesthesia. The results of the National Halothane Study published in 1969, familiar to most anesthesiologists, are frequently misquoted or misinterpreted. In some 850,000 cases (only 250,000 of whom received halothane) there were 82 cases of fatal hepatic necrosis. Only nine were unexplained on other grounds: of these, seven had received halothane, four on more than one occasion within 6 weeks. The true incidence of unexplained fatal hepatic necrosis following halothane from this study is, therefore, seven in 250,000 (one in 35,000), and not one in 10,000, as frequently quoted. The National Halothane Study concluded that unexplained fever and jaundice in a specific patient following halothane might reasonably be considered a contraindication to subsequent use. Later, Dykes and Bunker noted that there was not a single patient in the National Halothane Study who was jaundiced after administration of halothane and died after a second administration, and who was found at necropsy to have suffered massive or intermediate hepatic necrosis.

In 1970, the suggestion of a link between repeated halothane anesthesia, radiation therapy, and liver damage was made. However, this contention was not always confirmed by others. Indeed the very existence of halothane hepatitis as an entity was still open to debate in the early 1970s. Nevertheless, later studies seemed to confirm that severe hepatic dysfunction did follow halothane anesthesia, albeit rarely, with an incidence of between one in 6000 and one in 20,000. In addition, an association between multiple exposures and both decreasing latency before manifestation and increasing severity of liver dysfunction was identified. However, the well-recognized deficiencies of retrospective analysis led to attempts to further elucidate the issue by other means.

Walton et al. in 1976 comprehensively reviewed cases of hepatic dysfunction following anesthesia throughout the United Kingdom at the time of report, thus achieving a more thorough and uniform investigation of patients. Two hundred four cases of postoperative jaundice reported were reviewed blindly by a panel of hepatologists, and 76 patients were classified as UHFH. This study reaffirmed the association between UHFH and multiple exposure: 95% of the cases followed multiple halothane anesthesia; 55% followed reexposure within 4 weeks. It also indicated an increased incidence in the obese and in middle-aged women. The demonstration of thyroid autoantibodies in a high percentage of the patients seemed to lend credence to an immune hypothesis for UHFH.

**Prospective Studies**

In reviewing early prospective studies, Little concluded that hepatic dysfunction was no more common after hal-
othane than other available agents. However, none of these studies used halothane-free machines for nonhalothane cases, and repeated anesthesia was not studied.9

In 1975, two studies of multiple halothane anesthesia were published in the United Kingdom.45,46 The first showed that aspartate aminotransferase (AST) levels were higher in urologic patients undergoing repeat halothane anesthesia than those receiving trichloroethylene (from a halothane-free circuit).45 In the second study in patients undergoing multiple anesthesia during treatment for carcinoma of the cervix, alanine aminotransferase (ALT) levels were significantly elevated in four of 18 patients receiving halothane (cf, 0 of 21 controls). Two of these four patients showed a hepatic picture on liver biopsy.

Unfortunately, these findings were not reproduced in subsequent similar studies. McEwan47 found a tendency for AST and ALT levels to be higher in patients receiving nonhalothane anesthesia after previous halothane than those getting repeat halothane. Allen and Downing48 found only minimal elevation in liver enzyme values in patients receiving multiple anesthetics with either halothane or enflurane, although the gap between reexposure was considerably in excess of 28 days.

A further study by Fee et al. from Belfast48 seemed to indicate an increased incidence of liver enzyme abnormalities after multiple halothane anesthesia than with multiple enflurane anesthesia, although no patients had postoperative jaundice develop. But when obese patients and those receiving repeat anesthesia within 6 weeks were excluded, there were no significant differences between agents.49

The rarity of halothane hepatitis means that large studies are necessary to provide useful data. Their cost in both time and money is likely to be prohibitive in the future. When ethical objections are also considered, it is not surprising that recent research has focused on the development of animal models.50–52

Pathology

The early clinical reports of fatal hepatic necrosis following halothane identified no distinguishing pathologic features. However, the similarity to lesions produced by known hepatotoxins, e.g., carbon tetrachloride, was noted.5 Many subsequent reports emphasized the presence of centrilobular necrosis,7,22,25,53–57 The distribution and pattern of this centrilobular necrosis was felt by many to be distinguishable from that seen following viral hepatitis.55,58 The presence of fatty infiltration also was noted by a number of authors.6,7,25,31,54,57,59 However, others have acknowledged difficulties in distinguishing halothane hepatitis from viral hepatitis on light microscopy.6,39,56,57,60,61,63–66 Although the pathologic features suggestive of drug-induced liver injury were outlined in 1974 by an international group of pathologists,57 these features were not found to be helpful in distinguishing halothane-induced hepatitis from other causes of postoperative jaundice.68,41

A few reports have included electron microscopy (EM) of liver biopsy specimens.56,65,69 Distinctive mitochondrial abnormalities were seen by some authors65,68 but not by others.69 The absence of recognizable EM features also was noted by Wills and Walton,68 who concluded that neither light nor electron microscopy had useful diagnostic value in differentiating halothane hepatitis from other causes of postoperative hepatic dysfunction. A later EM study of intraoperative liver biopsies before and after exposure to different anesthetic agents did show an increased incidence of changes with halothane compared with enflurane and narcotic anesthesia.70 However, since no patients in this study had postoperative hepatic dysfunction develop, it is impossible to assess the importance of EM changes in the diagnosis of halothane hepatitis.

Although UHFH can progress rapidly to fatal massive hepatic necrosis, in those patients who recover, repeat histologic examination shows considerable resolution of the lesions.71,72 There are only two cases reporting progression to chronic liver disease: in one, there was recurrent occupational exposure;42 in the other, the diagnosis of chronic active hepatitis was made three months after exposure, and subsequent follow-up was not reported.73

Biochemistry

Although most early reports focused on hepatic necrosis following halothane, a number of later studies have looked at elevation of transaminase and other liver enzymes after halothane.45,46,48 Not all such studies have demonstrated an increased incidence of liver enzyme disturbance after halothane compared with other volatile agents.34,74 The incidence of minor hepatic dysfunction following halothane is unknown,75 and there are many causes of a similar pattern of liver enzyme elevation, notably viral hepatitis.10 Indeed, reversible, minor changes in liver function are common in the postoperative period, regardless of the type of anesthesia.58,76,77 The pitfalls of a diagnosis based on biochemical disturbances have been highlighted by Schemel,78 who found that 11 of 7,620 ASA I patients scheduled for elective surgery had preoperative elevation of liver enzymes. Although surgery was canceled in all cases, three patients had jaundice develop. It is highly likely that the biochemical and clinical hepatic dysfunction detected in these patients postoperatively would have been attributed to the anesthetic agent used, had this been halothane. Routine postoperative screening of liver enzymes to detect those at risk from
subsequent halothane anesthesia has been suggested, but the high cost benefit ratio of such a policy has been emphasized.

The problem of differentiating halothane hepatitis from viral hepatitis presenting in the perioperative period is a real one. It has been estimated that of every million patients anesthetized with all agents, approximately 100 might become jaundiced in the postoperative period because of viral A hepatitis.

**Occupational Exposure**

Unexplained hepatic dysfunction in medical personnel occupationally exposed to halothane has been reported. The recurrence of liver dysfunction following deliberate reexposure to halothane has been called "the most compelling evidence of the existence of halothane hepatitis." However, certain aspects of these case studies have been criticized; moreover, none of the patients was challenged with any other agent (or placebo). Two further cases have been described: in both individuals halothane-related antibody was detected in the serum.

The frequent observation of an increased incidence of halothane hepatitis after multiple exposures within a short period seems to be at variance with the rare occurrence of hepatitis in personnel repeatedly exposed to trace concentrations of halothane. Cascorbi found an apparent increase in metabolism of halothane in a small group of exposed personnel compared with nonexposed pharmacists, however, a similar larger study by Cascorbi showed no difference. Reinher has shown an increasing metabolism of halothane in one anesthesiologist over a 2-year period of occupational exposure. Some studies have indicated an increased incidence of hepatic disease in exposed anesthesiologists and dentists compared with control populations, although it is not possible to exclude viral hepatitis as a factor in these cases.

**Animal Work**

Most early studies in dogs and monkeys revealed no evidence of hepatic necrosis after halothane and no increased incidence of hepatic dysfunction as compared with diethyl ether. However, positive reports of liver damage were published by some workers, although in the first of these studies, halothane was administered intraperitoneally, resulting in a very high hepatic blood concentration, and in the second, the guinea pig was used. Subsequent work has shown that anesthetic concentrations of halothane cause profound hypotension in this model.

Following Van Dyke's demonstration that halothane undergoes phenobarbital-inducible biotransformation by the mixed-function oxidase (MFO) system in hepatic microsomes, interest in the use of enzyme-induced animal models increased. In 1976, Sipes and Brown demonstrated a high incidence of hepatic necrosis in rats pretreated with a polychlorinated biphenyl (PCB), even in 100% oxygen. However, since PCB can cause morphologic changes in the liver per se, this may not be the most appropriate model. An apparently more reliable model uses phenobarbital (PB)-pretreated rats exposed to halothane in an hypoxic environment. Cousins et al. have demonstrated qualitative and quantitative similarities in the metabolism of halothane in rats and humans and in the histologic lesions produced in the liver. However, claims that this model is valid and relevant to the human situation rely on reductive metabolism being etiologically important in human halothane hepatotoxicity; this contention is not yet supported by direct evidence.

The use of animal models introduces a number of problems because of variations in route and extent of metabolism between species. For example, PB/hypoxic mice do not show hepatotoxicity to halothane. In addition, there are age and sex differences in drug metabolism and toxicity. Even in a species with apparent similarities to humans, e.g., the rat, there are differences between strains in metabolism of halothane (and other agents) and susceptibility to organ toxicity.

Recently the validity of the PB/hypoxic rat as a model of halothane hepatotoxicity resulting from reductive metabolism has come into question. The PB/hypoxic rat model does not always show reproducible hepatotoxicity within the same institution; the incidence of hepatic necrosis varies, depending on the vendor of the animals; and the ease of reproducibility follows a seasonal variation. Hypoxia alone can produce hepatic necrosis in PB-pretreated rats. In addition, enflurane and isoflurane are both capable of producing hepatic necrosis in PB/hypoxic, starved rats. Shingu et al. were unable to distinguish between halothane and other inhalation (enflurane and isoflurane) and intravenous (thiopental and fentanyl) agents in hypoxic (10% O2), enzyme-induced rats. These data suggest an alternative mechanism for hepatotoxicity is more likely, since metabolism of enflurane and isoflurane is low and reductive metabolism nonexistent. In addition, the incidence of hepatic necrosis was higher in PB/hypoxic rats exposed to high concentrations of halothane for short periods as opposed to low concentrations for long periods. Since the metabolism of halothane is proportionally greater at low (subanesthetic) concentrations, this is the converse of what one would expect if metabolites were directly responsible for toxicity. Unfortunately, evaluation of this data is complicated by variations in oxygen concentration, temperature control, source and strain of rats, starvation, and
histologic classification between studies.\textsuperscript{112,120} It may be significant that studies showing hepatotoxicity with other agents have used more severe hypoxia (FiO\textsubscript{2} = 0.06–0.10).\textsuperscript{111,116} since neither enflurane nor isoflurane produce hepatotoxicity in the PB-rat in 14% oxygen.\textsuperscript{121} Development of liver injury with enflurane in the rat requires maintenance of body temperature as well as profound hypoxia, in contrast to halothane, and the time course of development of the lesions resembles that seen with severe hypoxia (5% oxygen) alone, rather than that seen with halothane.\textsuperscript{122} It is possible, therefore, that the two models are distinct.

Extrapolating data from the PB/hypoxic rat model to the human situation is difficult. There is some evidence of a dose–response relationship in the hypoxic rat,\textsuperscript{123} in contrast to the clinical situation. In humans, enzyme induction is not a factor in liver damage.\textsuperscript{115} Clinical hepatotoxicity may be rapidly progressive and often fatal, whereas rats in which hepatotoxicity develops do not die from liver failure and they recover quickly.\textsuperscript{125} In rats there is no increase in incidence or severity of hepatic dysfunction with multiple exposures.\textsuperscript{124} Indeed, Reynolds and Moslen\textsuperscript{125} found a decreasing incidence of liver necrosis with repeated exposure to halothane in their rat model.

Other rat models using triiodothyronine (T\textsubscript{3})\textsuperscript{126–128} or chronic ethanol pretreatment\textsuperscript{129} have been described. T\textsubscript{3} pretreatment results in hepatic necrosis in rats exposed to halothane even in nonhypoxic environments.\textsuperscript{126,128} Hepatic necrosis in T\textsubscript{3} rats was seen with both enflurane and isoflurane by Berman\textsuperscript{130} and with halothane by Wood et al.\textsuperscript{128} Hyperthyroidism does enhance the metabolism of halothane and enflurane\textsuperscript{131} and also enhances the toxicity of other hepatotoxins, including carbon tetrachloride (CCL\textsubscript{4}),\textsuperscript{132} chloroform (CHCl\textsubscript{3}),\textsuperscript{128} and acetaminophen,\textsuperscript{133} which act via toxic intermediate metabolites. Nevertheless, although there is some evidence linking reductive metabolism and hepatotoxicity in the PB/hypoxic rat model, the mechanism in the T\textsubscript{3} rat appears to be different.\textsuperscript{127,128}

It seems more likely that intracellular hypoxia secondary to the increased metabolic rate is involved in this model.\textsuperscript{127,130} Tagaki et al.\textsuperscript{129} reported extensive hepatic necrosis in chronic ethanol-pretreated rats exposed to halothane in 10% O\textsubscript{2}. Chronic alcohol administration causes induction of hepatic microsomal enzymes in rats and humans\textsuperscript{89} and increases susceptibility to hypoxic liver damage.\textsuperscript{134} However, since hypoxia per se can lead to hepatic necrosis,\textsuperscript{114} the relevance of the ethanol pretreatment in this model is unclear. There is no correlation between chronic alcohol ingestion or hyperthyroidism and UHFF in humans.

Recently, Cousins et al.\textsuperscript{156} have revived interest in the use of a guinea pig model.\textsuperscript{135} This model appears to be more relevant to the human situation, since neither enzyme induction nor hypoxia are required for the production of hepatotoxicity. Although similar hypotension occurs in this model with both halothane and isoflurane,\textsuperscript{16} hepatic necrosis is only seen with halothane, suggesting that hypotension is unlikely to be responsible for the liver damage observed.

While these animal models have certainly been important in describing the biotransformation of halothane, it is by no means certain that they have shed much light on the cause of halothane hepatotoxicity in humans.

**Etiology of Halothane Hepatotoxicity**

**BIOTRANSFORMATION**

Following the demonstration of chloroform metabolism,\textsuperscript{137} Van Dyke found biotransformation of halothane in vitro and in vivo and showed that this occurred in the microsomal fraction of the liver, was NADPH-O\textsubscript{2} dependent, and was inducible with PB.\textsuperscript{98–100} Biotransformation in humans was confirmed by Stier,\textsuperscript{138} who detected free bromide (Br) in the urine following halothane anesthesia. The extent of this metabolism was quantified by Rehder et al.,\textsuperscript{89} who recovered 20% of absorbed halothane as urinary metabolites, predominantly Br and trifluoroacetic acid (TFAA). At this stage, attention focused solely on oxidative metabolism. Reductive dehalogenation of the trifluoromethyl moiety of halothane was not considered possible, and fluoride levels in vivo were very low.\textsuperscript{139}

However, neither oral nor intraperitoneal administration of TFAA to rats or mice produced significant hepatotoxicity.\textsuperscript{140–142} Although some evidence for hepatotoxicity due to the precursors of TFAA—trifluoroacetaldehyde and trifluoroethanol—does exist,\textsuperscript{143} other workers have failed to show hepatic necrosis with trifluoroethanol.\textsuperscript{141} The formation of trifluoroethanol, as a metabolite of halothane, although postulated,\textsuperscript{144} has never been demonstrated in humans, and formation of trifluoroacetaldehyde has never been shown in humans or other animals.\textsuperscript{142} Although psychoactive, and near-sedative blood Br concentrations may be reached following halothane anesthesia,\textsuperscript{145–147} there is nothing to link Br formation with hepatotoxicity.

In 1969, using low-temperature, whole-body autoradiography, Cohen\textsuperscript{148} demonstrated that fluorinated, nonvolatile metabolites of halothane were covalently bound to liver macromolecules in mice for 2 weeks after halothane exposure, and this binding was increased by 40% in PB-induced animals.\textsuperscript{149} However, this binding could not be correlated with hepatic necrosis, since no such necrosis was seen. Some workers found evidence suggesting that halothane could induce its own metabolism,\textsuperscript{148,150,151} which seemed relevant, given the clinical association between enhanced toxicity and repeat exposures. However, other workers failed to demonstrate this phenomenon,\textsuperscript{152,153} possibly because of variations in con-
centrations administered. The relevance of reductive metabolism of halothane to the pathogenesis of UHFF was first suggested by the work of Utheleke et al., who showed increased in vitro binding of labeled halothane metabolites to rabbit microsomal protein (from PB-induced animals) under anaerobic conditions.

The binding of halothane metabolites to rat liver microsomes was characterized by Van Dyke et al.; binding occurs in the microsomal fraction, is enhanced by inducers of cytochrome-P450, e.g., PB and PCB, but not by inducers of cytochrome-P448, e.g., 3-methylcholanthrene (3MC), is enhanced in anaerobic conditions, and by decreased perfusion in the isolated, perfused liver, and is reduced by enzyme inhibitors, e.g., metyrapone, carbon monoxide, and SKF-525A. Binding occurs to both lipid and protein fractions, but in anaerobic conditions binding to lipid is greatly enhanced (with an associated massive increase in F release in vivo).

These studies can be compared with the whole animal studies of Gee et al. in rats exposed to halothane, demonstrating increased hepatotoxicity in the presence of inducers of cytochrome-P450 (PB and PCB), and significant protection with pretreatment with the enzyme inhibitors SKF-525A and metyrapone. The sulfadyl donor cysteamine afforded some protection when given up to 8 h after exposure. More recently, cimetidine has been shown to reduce halothane-induced hepatotoxicity in the rat. This apparently results from selective inhibition of the reductive metabolic pathway, although cimetidine can also inhibit oxidative metabolism in normoxic conditions.

In 1975, Cohen et al. identified two new urinary metabolites of halothane following intravenous administration of labeled halothane to legally dead heart transplant donors: N-trifluoroacetyl-2-aminoethanol, derived from oxidative metabolism; and a defluorinated mercapturic acid, N-acetyl-S-(2-bromo-2-chloro-1,1-difluoroethyl)-L-cysteine. This latter is thought to derive from the conjugation of 2-bromo-2-chloro-1,1-difluoroethylene (BCDF) with glutathione. Formation of BCDF had been postulated previously by Ulrich and Schnabel in 1973 and has subsequently been demonstrated in humans but only in closed circuit systems, where it appears to form by a reaction between halothane and warm, moist sodium lime. The presence of a defluorinated metabolite in humans indicates that reductive metabolism can occur. However, BCDF is unlikely to be responsible for hepatotoxicity, at least in the rat, since the BCDF conjugate has not been found in this species. Moreover, BCDF is scavenged by glutathione, and glutathione depletion in PB/hypoxic rats exposed to halothane does not lead to increased hepatotoxicity. In addition, mice exposed to BCDF do not show liver damage.

The presence of the trifluoroacetylthanolamide conjugate in human urine is thought to arise by hydrolysis of trifluoroacetyl-phosphatidylethanolamine following binding to phospholipid. However, this metabolite has not been demonstrated in the rat, and Sipes et al. have shown that halothane and 3H-halothane (which undergoes similar reductive but very little oxidative metabolism) produce equal hepatotoxicity in the rat. It seems that reductive metabolism is more important etiologically in this model, and therefore the oxidative product, N-trifluoroacetyl-2-aminoethanol, is unlikely to be a causative agent.

In 1977, Mukai et al. identified 2-chloro-1,1,1-trifluoroethane (CTF) and 2-chloro-1,1-difluoroethylene (CDF) in the expired breath of rabbits exposed to halothane. The formation of these compounds subsequently has been confirmed in both rats and humans. In the enzyme-induced rat, the levels of CTF and CDF are greatly increased in blood, liver, and expired breath. However, it is unlikely that these end products of reductive metabolism are responsible for hepatotoxicity, even in the rat, since different strains show a varying incidence of liver toxicity, despite similar levels of CTF and CDF in the expired breath. Other workers have failed to show liver damage in animals exposed to CDF and CTF, although Brown et al. did show liver damage in rats after injection of CTF in propylene glycol into the portal vein.

Metabolic pathways explaining the formation of the observed metabolites of halothane have been proposed, involving the formation of reactive free-radical and carbamion intermediates. It is known that the classical hepatotoxins CCl₄ and chloroform (CHCl₃) act via reactive, free-radical intermediates. Although free-radicals are trapped during halothane administration in vivo, they also are formed when halothane is administered in 14% oxygen to non-enzyme-induced rats, conditions not normally associated with liver necrosis in this model. Nevertheless, the extent of free radical formation in the rat with different volatile anesthetics does parallel their hepatotoxicity. Eade et al. have shown a decreased frequency of hepatic necrosis in PB rats pretreated with the free-radical scavenger diethyldithiocarbamate. However, there is no direct evidence that free-radicals (or other reactive intermediates) are responsible for halothane hepatotoxicity.

Reactive intermediates could produce liver damage directly or indirectly by causing peroxidative decomposition of fatty acids in the phospholipid portion of the cell membrane, with subsequent damage to vital intracellular structures, e.g., endoplasmic reticulum and mitochondria. Diene conjugate formation (a marker of lipo-peroxidation) in the rat is increased by enzyme induction and hypoxia, conditions associated with...
enhanced hepatotoxicity and reduced by pretreatment with the free-radical scavenger diphenyl-p-phenylenediamine. However, it would appear that lipo-peroxidation is a result, rather than a cause, of halothane-induced hepatotoxicity.

By 1982, it appeared that there was substantial evidence that reductive biotransformation played a crucial role in the production of halothane hepatotoxicity in the PB/hypoxic rat, although none of the identified metabolites had been shown to be toxic in themselves. However, there was no direct evidence to support such an argument in humans. Moreover, the numerous differences between the conditions required for toxicity in the rat, for example, hepatotoxicity, cannot be induced in female or young animals, and the clinical situation in humans left some authors sceptical as to the value of this model in determining the cause of UHFF. During the last 2 years, other workers have produced evidence that brings into question the specificity of the PB rat model. Thus, other inhalation and intravenous anesthetics, hypoxia per se, and interference with hepatic arterial flow or surgical trauma can all produce similar hepatic lesions in the PB rat. Much of this recent data seem to support liver hypoxia as an etiologic factor, at least in the profoundly hypoxic rat model. It has been suggested that the relatively common, mild, transient hepatic dysfunction seen after halothane (and other anesthetics) has a different etiology from the rare, fulminant form. If reductive metabolism is important in humans, it may be in the formation of molecules capable of acting as haptems that provoke a hypersensitivity response and produce the rarer, more severe form.

Hypersensitivity (Immune-Mediated)

Early evidence in support of the idea that a hypersensitivity response to halothane (or more likely to one of its metabolites) was responsible for UHFF included the frequent association with multiple exposures; the observation that mild fever after a first exposure was followed in some cases by frank jaundice on reexposure; the association with fever and eosinophilia; the frequent history of drug allergy or atopy; the positive challenge tests described by Klatkin and Kimber and Belfrage et al., and the demonstration of circulating antibodies to liver kidney microsomes; thyroid, nucleic contents, smooth muscle, and mitochondria. However, the value of an unexplained fever after halothane as an indicator of sensitization has been questioned; the symptoms and signs of severe liver disease of any cause can mimic an immune reaction with fever, rashes, and eosinophilia; and cases of UHFF can follow first exposure.

Lymphocyte transformation (LTT) and leukocyte migration inhibition tests (in vitro indicators of cell-mediated immunity) have been used to try and demonstrate hypersensitivity responses in patients with UHFF. Paronetto and Popper demonstrated a positive lymphocyte transformation test in patients with suspected halothane hepatitis, but other workers were unable to confirm this. A positive leukocyte migration inhibition test also has been reported in patients with UHFF, whereas the test had negative results in normal subjects, healthy anesthesiologists, patients with other liver disease, and patients exposed to halothane without sequelae, suggesting that the test might have value in diagnosis and screening. However, a later report indicated that both false-positive and false-negative results can occur.

The demonstration by Uehleke et al. that halothane metabolites could bind covalently to liver macromolecules suggested that these metabolites might act as haptems and thereby provoke an immune response. TFAC protein complexes were shown to be capable of provoking antibody and delayed hypersensitivity (cutaneous) responses in guinea pigs. However, Reeves and McCracken were unable to induce hepatic necrosis in similarly sensitized guinea pigs subsequently challenged with halothane, and Walton et al. were unable to demonstrate a cell-mediated response (lymphocyte transformation test or leukocyte migration inhibition test) to TFAC protein conjugates with the use of serum from patients with UHFF. More recently, Ford and Coyle were unable to demonstrate any increased liver toxicity in PB/hypoxic rats sensitized to TFAC protein complex.

In 1978 Vergani et al. showed in vitro sensitization of leukocytes from patients with UHFF to hepatocytes from rabbits previously exposed to halothane. No such sensitization was seen when liver cells from ether-pre-treated animals were used as the antigen. In 1980 the same group of workers detected circulating antibodies that bound to the surface membrane of halothane-altered rabbit hepatocytes in nine of 14 samples from 11 patients with UHFF. In addition, normal lymphocytes could be induced into becoming cytotoxic to halothane-altered (but not ether-altered) rabbit hepatocytes by incubating them with serum from patients with UHFF. The authors claimed specificity for this test, since serum from patients with acetaminophen-induced liver failure did not render lymphocytes cytotoxic to acetaminophen-pretreated hepatocytes. Nevertheless, the antibodies were detected more frequently in the recovery phase, so it is possible that the test is simply looking at a marker of halothane hepatitis. Dienstag has pointed out that immune markers have been detected even in cases of liver injury caused by known toxins, e.g., CCl4. However, this antibody has not been demonstrated in patients uneventfully exposed to multiple halothane anesthetics or in healthy anesthesiologists. Furthermore, it has not been shown in patients in whom hepatic necrosis developed from other causes after incidental halothane anesthesia. This halothane-related antibody has since been detected in other
patients with UHFH. In contrast to the biotransformation theory, which emphasizes the reductive pathway of halothane metabolism, the halothane-altered membrane antigen is only produced when the oxidative pathway is activated. As yet, there has been no demonstration of sensitization of patients with UHFH to their own hepatocytes.

The biotransformation and hypersensitivity theories of UHFH are not mutually exclusive: metabolism may be responsible for the production of a hapten capable of provoking an immune response. Some authors have suggested that mild hepatic dysfunction may have a toxic (or hypoxic) cause, whereas severe hepatic necrosis might have an additional immune component. In support of this, Davis et al. were unable to detect antibodies to halothane-sensitized hepatocytes in sera from 16 patients with mild hepatic dysfunction following halothane.

**Hypoxia**

The demonstration that hypoxia is a prerequisite for the development of marked hepatotoxicity in the PB rat model, and the correlation between hypoxia and reductive metabolism in this model and other species, led to the hypothesis that enhanced reductive metabolism secondary to hypoxia (with the production of toxic reactive intermediates) might be the cause of halothane hepatotoxicity in humans.

Recently, evidence has accumulated indicating that hypoxia per se might be implicated in the PB rat model. Eger et al. have shown that hypoxia in the absence of halothane can cause similar hepatic lesions. High concentrations of halothane for short periods produced more toxicity than low concentrations for prolonged periods, finding more compatible with liver hypoxia secondary to cardiovascular or respiratory depression. Enflurane and isoflurane, which undergo much less biotransformation than halothane and have no reductive pathway, can produce similar hepatic necrosis in the rat model. Van Dyke also has shown liver damage with enflurane and isoflurane in starved, hypoxic PB rats. Since starvation and hypoxia alone can produce similar damage, it is possible that hypoxia itself is the cause in this situation.

Respiratory depression per se is unlikely to be responsible for liver hypoxia. However, local liver hypoxia arising from an imbalance between oxygen supply and demand may be relevant. Hyperthyroidism, chronic ethanol treatment, and increased body temperature, factors known to increase O2 consumption, are associated with increased halothane hepatotoxicity in the rat. It is possible that enzyme induction, with PB, also may act this way. Decreasing hepatic O2 supply by decreasing perfusion in the isolated rat liver also produces centrilobular necrosis. Harper et al. have shown that ligation of the hepatic artery in the normoxic, PB rat produces comparable lesions to those seen in the PB/hypoxic rat and that upper abdominal surgery is associated with a greater severity of liver damage than lower abdominal or peripheral surgery. Since upper abdominal surgery in humans is associated with a significantly greater decrease in hepatic arterial flow compared with peripheral surgery, this suggests that interference with hepatic blood flow with consequent hepatocellular hypoxia may be important in the production of liver damage. This hypothesis is supported by the work of Gelman et al., showing that liver damage in the PB/hypoxic rat exposed to halothane was correlated with a fall in consumable oxygen. Although celiac plexus block affords no protection in the rat model, suggesting that reflex hepatic artery vasoconstriction is not an important factor, this does not preclude regional intrahepatic alterations in blood flow.

Halothane anesthesia in the dog produces a fall in total liver blood flow paralleling a fall in cardiac output. Normally hepatic artery flow is regulated in response to changes in portal venous flow. A number of animal studies have shown that, not only is portal venous flow significantly reduced by inhalation anesthesia, but with halothane hepatic artery flow is also reduced. Recent work in both dogs and rats has shown that, whereas halothane significantly impairs the autoregulation of hepatic artery flow in response to changes in portal venous flow, isoflurane and enflurane produce no such effect. It would seem that an imbalance between hepatic O2 supply and demand is more likely with halothane than with other agents. Cousins et al. showed similar hypotension in the nonhypoxic guinea pig with halothane and isoflurane, but only the halothane group showed liver damage. They argued that this supported a metabolic rather than hypoxic cause for the observed hepatotoxicity. However, an alternative explanation for their findings is that the response of the hepatic circulation to the hypotension was different with the two agents, and liver hypoxia still may be a factor in this model.

Although hypoxia per se can reduce liver blood flow and produce centrilobular necrosis in humans, the incidence of primary liver failure in patients with normal prevenet liver function, following recognized frank hypoxia, is excessively rare. More frequently, primary myocardial, cerebral, or renal damage is followed by secondary liver damage, often as a terminal event. Also, fatal hepatic necrosis can follow halothane for minor surgery with no evidence of intraoperative hypoxia or hypotension. Nevertheless, a marked fall in hepatic artery flow has been demonstrated radiographically in humans during halothane anesthesia, and one of these patients subsequently had hepatic dysfunction develop. Thus, in addition to the evidence in support of an hypoxic cause for hepatic injury in the PB/hypoxic rat model, there seems to be some evidence to implicate regional hypoxia in the
development of the mild, transient liver dysfunction seen following halothane in humans. However, the fulminant, often-progressive form may involve different or additional etiologic factors.105

PHARMACOGENETICS

Differences in susceptibility to the toxic effects of halothane have been shown both between species105 and between different strains of a species.110 A wide variation in the rate and extent of halothane metabolism also has been shown in humans.88,147 Cascorbi123 has demonstrated a decreased variation in halothane metabolism in identical twins compared with fraternal twins, further suggesting a genetic influence. More recently, Hoit et al.232 have presented a review of UHFH in three pairs of closely related women in whom environmental factors were apparently excluded. In a small series, no significant link between UHFH and particular HLA antigens was identified.232 The evidence seems to indicate that, at most, pharmacogenetic factors are simply one variable in a multifactorial cause.209,224

Clearly an interaction of two or more of the factors discussed may be involved in the development of halothane-induced hepatic dysfunction. The mechanisms involved may vary from patient to patient, or they may be different for mild and severe forms of hepatotoxicity.107,129,130 Metabolites may be implicated as direct toxins or in the production of a harmful immune response or in producing physical effects, e.g., changes in organ perfusion. On the other hand, metabolism may play no role, and any apparent correlation may be masking physiologic effects of the parent compound (combined with surgery).111

Which Patients Are at Risk?

SEX

A number of studies of hepatic damage in humans have shown a female:male ratio of approximately 2:1,58,39,41,205 although male patients apparently have a worse prognosis.39,41 In contrast, in the PB/hypoxic rat the female rat is extremely resistant to hepatic necrosis.129 This has been attributed to different levels of activity in the mixed function oxidase system resulting from the differing effects of androgens and estrogens on this system. This is supported by the lack of a sex difference in prepubertal rats.103 Also, the different incidence between male and female rats can be reversed by treatment with the opposite sex hormone.103 Alternatively, this observation may result from a greater degree of enzyme induction in response to PB in the male rat.235 It seems curious that an opposite sex difference is found in rats and humans if metabolism is the sole etiologic factor in both cases.

AGE

An association between posthalothane hepatic dysfunction and middle age has been noted by many authors, whereas it is unusual at the extremes of age.9 Severe hepatic dysfunction following halothane is extremely rare in children.236,237 Isolated cases have been recorded,238-240 but in a number of these the data were incomplete and open to alternative interpretation. In the most recently reported case207 the patient was shown to have the halothane-related antibody, already referred to earlier,200,201 Perhaps children do not have either the metabolic and/or immunologic mechanisms necessary for halothane to cause liver damage.

PREEXISTING LIVER DISEASE

There is no evidence that patients with preexisting, compensated liver disease are at any greater risk of having halothane hepatitis develop. However, there is a very strong case for avoiding anesthesia (with or without halothane) and surgery in patients with active hepatitis from any cause unless absolutely essential, since they may undergo a severe deterioration in hepatic function postoperatively, resulting in fulminant hepatic failure.81

OBESITY

Many reports have indicated an increased incidence of UHFH in obese patients.39,41,48,49,205 Obesity also appears to be associated with a poor prognosis.39,41 Young and Stoelting139 showed increased fluoride levels in obese patients, indicating increased reductive biotransformation, whereas other workers have shown an increase in both reductive (fluoride) and oxidative (bromide) metabolites in the morbidly obese.241

An increased fat store may act as a "reservoir" for halothane with prolonged, slow release into the circulation and an increase in total metabolite production.75 Alternatively, the well-recognized association between obesity and postoperative hypoxemia may offer an explanation, either through enhanced reductive metabolism or liver hypoxia per se.10

TYPE OF SURGERY

Several studies have indicated an increased incidence of UHFH in patients undergoing repeat anesthesia for radium implantation therapy in the treatment of gynecologic malignancy.32,46,64 Other studies have shown no increased risk with halothane in these patients.52,34,47,242 Gamma radiation can break down halothane to dichloroethane fluorobutene, but mice exposed to halothane and gamma radiation show no increased incidence of liver damage245—although the mouse is not a good model.151

No correlation between duration, site, or severity of
surgery, including biliary tract procedures, and UHFF has been shown in humans. In fact, it is a feature of UHFF that it can follow apparently uneventful anesthesia for minor surgery.205

ENZYME INDUCTION

Despite the enormous volume of data showing hepatic necrosis in the hypoxic, enzyme-induced rat, there is no real evidence implicating preoperative enzyme induction in humans.244

MULTIPLE EXPOSURE

A number of studies have revealed an increased incidence of UHFF following multiple exposures to halothane. Cumulative data from almost 400 cases revealed a mean incidence of multiple exposure of 84%.245 Multiple exposures within a short period are associated with an increased frequency of both mild45,46,48 and severe47,59,41,205 hepatic dysfunction following halothane. Dysfunction is more severe and latency before presentation is shorter following reexposure.57,203 Most studies have shown a maximum incidence where reexposure has occurred within 28 days.37,39,41,205 although cases occasionally may follow reexposure several years after the initial halothane anesthetic.205 However reexposure in a patient with previous UHFF does not always result in a further episode.41

OTHER INHALATION AGENTS

ENFLURANE

A number of case reports of alleged enfurane hepatotoxicity have been published.246-252 Some patients had histories of previous anesthesia with halothane247,248,252 or enfurane,250,251 Lewis et al.13 reviewed 58 such cases reported to the Food and Drug Administration (FDA) and accepted 24 of them on clinical and pathologic grounds as being "enfurane hepatitis." However, Dykes255 has questioned the validity of this "diagnosis by exclusion." He has indicated that the existence of enfurane hepatotoxicity apparently hinges on a single patient who showed liver damage after each of two enfurane anesthetics.251 Given the known hepatotoxicity of other inhalation agents, it is not entirely surprising that enfurane was incriminated in many of the reported cases. The difficulties associated with diagnosing viral hepatitis presenting postoperatively are well known. This is illustrated by a case attributing postoperative hepatic dysfunction to enfurane when the true cause was viral infection.254

Prospective studies of hepatic function after repeated enfurane anesthesia have shown insignificant54 or minor changes46,72 with no evidence of increased disturbance with each exposure.48

In May 1984 the Gastroenterology Drug Advisory Committee of the FDA reviewed the available information in the United States of America (USA) which allegedly linked enfurane with postoperative liver damage. This committee came to the conclusion that there was a link between enfurane and liver damage and as a result, Anaquest, the manufacturers of enfurane, have altered their package insert to read as follows: "Unexplained mild, moderate and severe liver injury may rarely follow anesthesia with enfurane. Serum transaminases may be increased and histologic evidence of injury may be found. The histologic changes are neither unique nor consistent. In several of these cases, it has not been possible to exclude enfurane as the cause or as a contributing cause of liver injury. The incidence of unexplained hepatotoxicity following the administration of enfurane is unknown, but it appears to be rare and not dose related." It should be noted that this package insert only applies to the United States and is not included in other countries. Notwithstanding the deliberations of the FDA, we believe that presently the case against enfurane remains unproven,169,255 and it should continue to be used in any anesthetic where its properties are advantageous to patient well-being.

ISOFLURANE

No clinical reports of isofurane hepatotoxicity have appeared as of yet. McLaughlin and Eger285 have described a patient given repeated isofurane anesthetics in the presence of abnormal liver enzyme tests. These were ascribed to ascending cholangitis and passage of a gallstone; isofurane was not implicated. Indeed liver function improved during the course of the anesthetics. Currently, there seems no reason to avoid the use of isofurane in any patient for fear of hepatotoxicity.

Conclusion

At the outset of this review we asked whether the role of halothane could be defined with regard to patient population and potential risk of hepatotoxicity. We have concluded the following: 1) Halothane may be used repeatedly in children and has a very low-risk potential for liver damage in this group of patients. 2) There is no contraindication to the use of halothane in the presence of preexisting, compensated liver disease, providing this does not relate to a previous anesthetic. Outcome will be determined by the degree of preoperative liver dysfunction and the extent of the surgical procedure. However, if the liver disease is in an acute phase, anesthesia (with any agent) and surgery may be contraindicated.61 3) Severe liver damage is unlikely to follow a single exposure to halothane in a previously healthy individual. 4) Repeated exposure to halothane in adult humans, particularly in
obese, middle-aged women and over a short period of time (probably 4–8 weeks), may result in severe liver damage. However, there is no means of predicting this, and the “safe time interval” is unknown; the incidence of UHFH is probably of the order of one in 10,000 anesthetics. It is of interest that this figure is also quoted as the overall risk of death solely as a result of anesthesia, and the incidence of serious neurologic sequelae after epidural anesthesia. If repeated halothane anesthesia is contemplated, the anesthesiologist should document, for medico-legal purposes, on the patient’s anesthetic record, the reason for using halothane on the second occasion. In addition, before embarking on the second halothane anesthetic, one should first ascertain, from the patient’s records wherever possible, that there were no unexplained detrimental changes in liver function following the first exposure. Should there have been any such problems after the first anesthetic, halothane should not be administered subsequently. 6) The cause of UHFH is unclear. It seems unlikely to be a metabolic mechanism alone and most probably involves an immunologic response in addition. Although in animal models enzyme induction, starvation, hypoxia, and hypotension contribute to halothane-associated liver damage, there is no proof that this is the case in humans. 7) At present there is no test that is specific for halothane-induced liver damage. Therefore, the diagnosis of UHFH may only be made by excluding all other causes of postoperative liver dysfunction.

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