Reports of Scientific Meetings

Ellis N. Cohen, M.D., Editor

Post Anesthesia Liver Dysfunction

An interdisciplinary symposium on Post Anesthesia Liver Dysfunction took place December 5, 1976, at the Johns Hopkins School of Medicine. The session was attended by approximately 250 specialists from anesthesiology, medicine, and surgery. The meeting was chaired by Dr. Victor McKusick (Johns Hopkins), and participants included Drs. John P. Bunker and Ellis N. Cohen (Stanford), Dr. Willis Maddrey, Dr. John Boitnott, and Mr. Sam Shapiro (Johns Hopkins).

A major question concerned the diagnosis of "halothane hepatitis." Is there such an entity? Is the diagnosis only presumptive, or is it possible to establish definite etiology? Dr. Maddrey pointed out that in order to identify halothane hepatitis one must first exclude all other possible causes of postoperative jaundice, including viral hepatitis, injury to the biliary tract, massive transfusion, intra- or extrabiliary dysfunction, shock, hypoxia, prolonged anesthesia, bleeding, etc. The diagnosis is usually made by exclusion in the case of a patient who has fever, develops hepatitis several days after an operative procedure, and shows impaired hepatocellular function without evidence of hemolysis, pressors, shock, or infection. Direct viral transmission may be considered unlikely due to its short latent period, generally less than seven days. The possibility of subclinical viral hepatitis is, of course, possible. Dr. Maddrey and associates have identified 24 cases of post-halothane jaundice among patients without known pre-existing hepatic disease, blood transfusion, or history of current hepatitis, all of whom were negative for hepatitis B antigen. There was a predominance of females with obesity (75 per cent) in the group. The mortality rate from halothane hepatitis was high compared with viral hepatitis. Generally the latter had a mortality rate of less than 10 per cent whereas for halothane hepatitis the rate would appear to be 25–40 per cent. Many patients had experienced previous exposure to the agent, and there seemed to be a shortened latent period with recurrence of hepatitis on re-exposure. The immunologic aspects were also noteworthy, in that few patients had low-titer antimitochondrial antibodies.

Dr. Cohen felt that although we are unable to define precisely the etiology of halothane hepatotoxicity, there is considerable information supporting a general association between anesthetic metabolism and toxicity. Scholler has reported increased SGOT–SGPT levels and hepatic necrosis in animals receiving chloroform anesthesia following pretreatment with phenobarbital. Animals given disulfiram (an enzyme inhibitor) showed no hepatic change. Thus, if one prevents the metabolism of chloroform one prevents its hepatotoxocity. Similar information has also been produced for fluroxene. Cascorbi exposed mice to fluroxene for one hour, with an 18 per cent mortality rate, whereas animals induced with phenobarbital had a 100 per cent mortality rate. Small doses of carbon tetrachloride administered before fluroxene anesthesia prevented all anesthetic mortality. Methoxyflurane produces nephrotoxicity associated with the production of inorganic fluoride, and animals induced with phenobarbital have increased inorganic fluoride and nephrotoxicity. The antimetabolite SKF-525A reduces nephrotoxicity. Studies with halothane utilizing a radiolabelled molecule show that this anesthetic is extensively metabolized. Experiments in heart-transplant donor subjects indicate that 12.0 per cent of the administered halothane is metabolized within six hours. Drs. Stier and Rehder have demonstrated metabolites as long as 21 days after halothane administration. In heart-transplant donor subjects, the highest concentrations of metabolites appear to be in the liver and bile. However, high concentrations of halothane metabolites are found in the kidney, as well as in the gonads. Metabolites include trifluoroacetic acid, trifluoroacetyl ethanolamine, and bromochlorodifluoroethylcystein. Halothane can be metabolized either oxidatively or reductively. Van Dyke *et al.* have shown that in hypoxic animals there is a marked increase in the amount of serum inorganic fluoride. Oxygen tension thus plays an important role in the route of halothane metabolism. When oxygen tension is low, metabolism proceeds reductively, releasing a highly reactive species of defluorinated compounds. Important in the detoxification of this compound is its conjugation by glutathione. By giving the animals diethylmaleate one can deplete glutathione and increase hepatotoxicity.

Dr. Boitnott's investigations concerned mild halothane hepatitis, as opposed to those patients with massive hepatic necrosis. He presented three patients who had liver biopsies early in the course of the hepatitis (within one week after onset of fever). No patient was jaundiced, although two showed bilirubin elevations. Transaminases were high (2,000), and eosinophilia was prominent. It was usually possible to separate mild halothane hepatitis from viral hepatitis of moderate severity since the latter manifested a diffuse injury pattern throughout the lobule, and confluent small areas of necrosis did not occur, as in mild halothane hepatitis. Comparable cell dropout in viral hepatitis is to be found only in very severe cases. In halothane hepatitis the hepatocytes are shrunken, and eosinophilic and mononuclear cells are in intimate association with healthy looking hepatocytes immediately adjacent. Liver biopsy following an episode of shock and hypoperfusion of the liver shows a marked increase in transaminase and a minimal dropout of cells. Mononuclear inflammation, which characterizes viral hepatitis diffusely and halothane hepatitis focally, is not a feature of this injury. In massive hepatic necrosis the focal hepatitis of the mild halothane type spreads to the entire lobule, and the differential features are largely lost.

Electron microscopic studies revealed specific mitochondrial alterations. Fat droplets were common in halothane

hepatitis, in contrast to viral hepatitis, where fat accumulation is usually absent. Another feature is the alternating dark and light cells with striking and bizarre mitochondrial changes, including crystalloid inclusions. Glycogen depletion, which is common to viral hepatitis, is remarkably absent in halothane hepatitis. The ultra-structural comparison of viral hepatitis and halothane hepatitis thus shows crystalloid inclusions present in both, although quantitatively greater with less injured cells in halothane injury. Glycogen depletion is less prominent, and lipid accumulation is more prominent, in halothane hepatitis. The increase in smooth endoplasmic reticulum (ER) is of considerable interest, and might correlate with induction of microsomal enzymes and production of potentially toxic metabolites. There are, however, data that favor an immune mechanism, including an idiosyncratic reaction. Arthralgia and rash are common in drug allergies and do not seem prominent in halothane hepatitis. If it were a cell-mediated immunity, the inflammatory infiltrate should be predominately mononuclear, and the cells show a lack of evidence of lysosomal enzyme increase. Polyribosomes should be prominent, indicating active metabolism. Thus, the morphologic changes found in mild halothane hepatitis are characteristic, remarkedly constant, and in several important respects different from those of acute viral hepatitis, ischemic hepatitis, and toxic hepatitis due to other halogenated hydrocarbons. The nature of the inflammatory infiltrate is compatible with cell-mediated immunologic injury. The cell-mediated attack seems directed toward hepatocytes, and presumably these hepatocytes have been altered in some way by exposure to halothane.

Dr. McKusick noted that in considering a rare medical event, the immunologists think of allergy and the geneticists think of a constitutional or a genetic peculiarity. With the phenomena of succinylcholine sensitivity and malignant hyperthermia, we have classic examples of pharmacogenetically-dependent conditions. In the nonanesthetic area there are other examples, such as INH. Previous work on the genetics of INH metabolism show that slow inactivation is due to a mendelian recessive trait. There may be a parallel between INH hepatitis and halothane hepatitis. If so, this would favor a metabolic pathway, since metabolism of INH determines susceptibility to INH hepatitis. The immunologic hypothesis and genetic hypothesis may not be mutually exclusive. In examining the altered metabolic pathways, one might look in siblings of patients who have halothane hepatitis for genetic deficiencies in glutathione synthesis. This is a rare syndrome usually accompanying hemolytic anemias.

Mr. Shapiro, as an epidemiologist, examined the issues from a different point of view. He emphasized the relationship between benefit and risk for the particular agent under consideration. In such an investigation one first examines the relationship between the number of adverse events and the number of people who are at risk. There is still uncertainty in our ability to differentiate between viral hepatitis and halothane hepatitis. Circular reasoning may be involved, since we arrive at the characteristics of a particular type of hepatitis and then put it into the causal category of halothane. The error factor by which a definition of halothane hepatitis can be arrived at has yet to be resolved.

If we assume 14 million persons undergoing surgical procedures, a halothane hepatitis rate of 1/40,000, two-thirds of procedures using halothane, we should estimate approximately 200 cases of halothane hepatitis per year. The literature seems not to support this rate. With respect to the denominator, the gross number of halothane administrations is known within reasonable limits? However, if we attempt to calculate the associated risk with characteristics of patients, we find that we really know very little about the denominator. For instance, obesity may accurately reflect an elevated risk. Again, the issue of repeated exposure may correlate with repeated operation and not with the anesthetic agent. There does not seem to be sufficient information in the literature comparing risks associated with halothane with those associated with other anesthetics. What is needed is a definition of the universe of misadventures, their frequency, totality, and that which is causal for the agent.

Dr. Bunker reviewed his experience with cyclopropane and ether during the period 1940–1960. When these agents were used for spleenorenal and portacaval shunt procedures, hepatic failure occurred occasionally, and a possible contribution of the anesthetic agent was discussed. Halothane was subsequently associated with hepatic necrosis, and the National Halothane Study reviewed more than 850,000 cases. Eighty-two cases of hepatic failure were identified. The autopsy slides were examined blindly by a group of pathologists, and the etiology of massive hepatic necrosis could not be identified by this means alone. All 82 patients died, but only nine deaths were not explained by the prolonged shock, massive transfusions, sepsis, or other factors. Of the nine patients who died, seven had received halothane; thus, the incidence of unexplained massive hepatic necrosis following halothane may be roughly one of 100,000. The study therefore neither proved nor excluded the possibility of halothane hepatitis.

The panel closed with summations by the participants, but with only partial agreement as regards the specificity of diagnosis. Causal factors, specific etiology and recommendations were equally divided.

EUGENE NAGEL, M.D.
Professor and Chairman
Department of Anesthesiology
Johns Hopkins University
Baltimore, Maryland