Halothane and Hepatic Necrosis

A report by Brody and Sweet, in this issue of the JOURNAL, of massive hepatic necrosis in patients anesthetized with halothane will undoubtedly evoke considerable concern and, it is hoped, further scrutiny of the problem. This should not provide the occasion for acrimonious debate because the writers have merely presented the available facts in an unbiased manner. They conclude that hepatic complications, though rare, can conceivably occur with the use of halothane and that it is strongly implicated as an etiological agent. Perhaps a recounting of the short history of this anesthetic will help to clarify the issue.

Going back to chloroform, the first detailed description of liver damage by Fraenkel in 1892,² and Whipple and Sperry's investigation of chloroform poisoning in dogs which emphasized the importance of nutritional factors,³ one can understand the later dictum that chloroform anesthesia is synonymous with chloroform poisoning.⁴ Fear of hepatic damage resulting from anesthetics, particularly the halogenated hydrocarbons, was heightened by the subsequent discovery of hepatotoxic properties inherent in divinyl ether (the role of anoxia was noted here), tribromethanol, and trichloroethylene.

It is safe to say that no anesthetic has been introduced to practice with more favorable theoretical properties, animal testing and clinical trial than halothane, a tribute to the initiative of the drug industry, and to modern chemical synthesis. Halothane, a fluorinated paraffin, is chemically inert because the three fluorine atoms attached to the carbon create a strong bond and reduce the reactivity of chlorine and bromine on the adjacent carbon atom in the molecule.⁵ The drug is said to be 99.95 per cent pure by reason of chromatographic and mass-spectrophotometric separation and testing. Stability is further assured by the addition of thymol although the compound will attack rubber and plastics under special circumstances. For these reasons it was believed that halothane would be lacking in hepatotoxicity. Experiments on animals and trials in man with the usual conglomeration of liver function tests seemed to bear out predictions. Halothane produced no greater alterations than ether or cyclopropane; compared to chloroform it was most benign. However, several qualifications must be borne in mind. Hepatic studies in man were performed only on several small groups of patients under optimal circumstances and histological studies were not performed. It has been said that liver function tests are no more infallible than the people who use them. Furthermore, because of appearance of fatty change in the livers of animals and the slight, but still present, changes in liver function in man, the cautious observer may reason that halothane is capable of damaging the liver even though no more than ether.

Now we learn of four cases of hepatic necrosis. Brody and Sweet refer to four other instances and there is still another case described by Temple and his co-workers.⁶ However, the relationship between halothane and the liver changes has by no means been proved. There is little need to repeat the points made in Brody and Sweet's excellent discussion. One of the major difficulties, they suggest, is the inability to distinguish morphologically among the several common causes of hepatic necrosis. The liver is a target for many injurious substances and infectious agents because of its location in the circulation and its detoxifying function. The response to injury is somewhat stereotyped, starting in the central zone of the lobule with fatty infiltration and coagulation necrosis followed by breakdown, scavenger activity and ultimately regeneration of the liver cells. Hence gross or ordinary microscopical examination is not very
helpful. The belief is that toxins may affect mitochondria to interfere with oxidative processes or that vasoconstriction and ischemia may be the chief factors in the production of cell death. Though halothane is thought to induce splanchnic vasodilation this has not been confirmed by measurement of splanchnic blood flow. Many of the known toxins are fat solvents, but fatty changes in the liver can be explained by any of several mechanisms. Finally, with the application of ultramicroscopic, histochemical and biochemical techniques, attempts to reduce clinical symptoms to involvement of specific cellular components have not succeeded and the application of substructural hepatic pathology to human disease is a goal yet to be achieved.

What conclusions can be drawn and what must be the course of action? At first one is tempted not to use halothane, and this applies as well to the other recently introduced fluorinated hydrocarbons, if the favorable properties and lack of flammability are vitiating by development of hepatic necrosis, no matter how rare. Immediate investigation is called for in as many clinics as possible for we cannot afford to wait as long as our forebears did to discover the facts about chloroform. Perhaps after further study halothane will be completely absolved, or a specific set of circumstances, extraneous factors, or a peculiar hepatic sub-stratum will be found to permit the anesthetic to be used under the best conditions. The editorial board of Anaesthesiology welcomes constructive comments and studies on either side of the argument that will help to settle this serious problem.

LEROY D. VANDAM, M.D.

References

Cybernesthesia

Many people seem to be possessed with the idea that machines can do their thinking for them. Data derived from machines are fed into machines which are programmed to provide answers. Often overlooked is the fact that the machines can provide answers only on the basis of a relatively fixed pattern; a pattern established in advance. The answer (which can be obtained with miraculous speed) is still an answer that is possible only by prior arrangement of mechanical processes and the supply of data acceptable within the pattern. The answer is uninfluenced by all the abstract, intangible but often pertinent elements that enter into the thinking processes of the human brain and the considered judgment that results.

In the practice of anesthesia, there is always a strong tendency to become mechanical. More and more equipment is being developed which is capable of providing reasonably precise data on various functions of the human organism. Cybernetics, or the use of thinking machines, has not yet dominated the practice of anesthesia although machines have been used to inject drugs in response to the electrical output of the brain. What is disturbing is the trend toward feeding data obtained from machines into brains that function as machines. Brains functioning in this manner steadily but inexorably deteriorate into nothing more than biological computers. "Atrophy of disuse" develops in those portions of the brain that had the capacity to correlate experience, the input