Final Report of the National Halothane Study

The Final Report of the National Halothane Study conducted by the National Academy of Sciences-National Research Council will be published in the near future. This vast and much publicized enterprise was undertaken as an urgent problem of the practice of anesthesia and an important issue of public health. Its objectives were to compare halothane with other general anesthetics as to incidence of fatal postoperative massive hepatic necrosis and total postoperative mortality. At the completion of the Study it was found that (1) Fatal postoperative massive hepatic necrosis was a rare occurrence. It occurred primarily following operations associated with high death rates and could usually be explained on the basis of circulatory shock, sepsis, or previous hepatic disease. The possible rare occurrence of halothane-induced hepatic necrosis following single or multiple administrations could not be ruled out. (2) Halothane, rather than being a dangerous anesthetic, had a record of safety as reflected in an overall mortality which was lower than that of the study as a whole.

These and other conclusions of the National Halothane Study have already been published in summary form, and for this reason announcement of the forthcoming publication of the full report may not seem big news. But the question of halothane toxicity has remained an open one in many physicians' minds, and accordingly the publication of the complete evidence should be of interest.

A major part of this evidence, the report of the study of hepatic pathology, appears in this issue of ANESTHESIOLOGY. In the course of the pathology study more than 10,000 necropsy reports were reviewed, as a result of which nearly 1,000 microscopic sections were examined. Eighty-two cases of massive hepatic necrosis and 115 cases of "intermediate" (submassive) necrosis were identified.

Most cases of hepatic necrosis were readily attributable to the clinical events which preceded death, such as anoxia, shock, and sepsis, and were reflected in the histologic pattern of hepatic injury associated with these conditions. The few cases of hepatic necrosis for which no clear clinical explanation was available, and which were thought possibly to have been caused by halothane, exhibited a microscopic lesion resembling that of fatal viral hepatitis and some drug-induced forms of hepatitis. However, it was not possible to identify a specific anesthesia-induced microscopic lesion, nor was it possible in these few cases to demonstrate a statistical correlation of hepatic necrosis with the use of halothane. At the same time, neither do the data prove that halothane does not damage the liver, a conclusion which some have incorrectly taken to mean that the study failed in its objective. The statisticians take this limitation as a statistical fact of life, and in the Final Report Drs. Moses, Mosteller, and Gentleman have written an enlightening chapter entitled "On the Basic Unresolvability of Very Small Differences." From a clinical point of view one might paraphrase this to say that in nearly a million cases of general anesthesia there were too few cases of hepatic necrosis to allow statistical comparison of anesthetic agents and too few to be of major clinical concern.

To resolve these final remaining small doubts may be impossible. A larger Study of the variety just completed, or a randomized clinical trial, is almost unthinkable and, in fact, could not be justified at this time; for the incidence of anesthetic-induced fatal hepatic injury has been demonstrated clearly to be very small indeed. Another approach which
has already been initiated is to establish a registry to collect all instances of hepatic necrosis from whatever cause. The interpretation of randomly-collected data in such a registry is fraught with limitations and pitfalls, as already discussed in the final recommendation of the Summary of the National Halothane Study.¹

The possibility of a special risk of hepatic injury after repeated exposures to halothane has attracted widespread interest. Many of the published cases of massive postoperative hepatic necrosis thought to be halothane-induced did follow multiple administrations of halothane. However, in reports of patients who have received 30 or more administrations, no hepatic injury was found. In the National Halothane Study, the incidence of massive hepatic necrosis was higher after two or more general anesthetics when halothane had been used at least twice than when it had not been used. However, many of the clinical situations which were found to be associated with higher incidence of hepatic necrosis (e.g., open-heart surgery and exploratory laparotomy) also frequently require multiple operations. Concerning the selection of anesthetic agent under these circumstances, obviously a matter of critical importance, we have relatively few data.

With the issue unresolved, and perhaps unresolvable, how should one proceed clinically? Certainly it is unwarranted to suggest that halothane anesthesia should not be repeated, for it is under the difficult circumstance of emergency reoperation that a wide choice of anesthetic agents may be needed most urgently. Furthermore, it would not be justifiable to suggest that halothane should not be used for more than one purely elective operation. When, however, a patient has suffered unexplained fever and jaundice after administration of halothane, it is the opinion of some physicians that halothane should not be used for a subsequent operation. The basis for their recommendation is the usual medical doctrine that any treatment followed by ill effects ordinarily should not be repeated. Whatever the merits of such a recommendation, it is remarkable that there was not a single patient in the National Halothane Study who was jaundiced after the administration of halothane and died after a second administration and was found at necropsy to have suffered massive or intermediate hepatic necrosis.

The second major objective of the National Halothane Study was to compare halothane with other general anesthetics as to total postoperative mortality, because it was recognized that, even if halothane were responsible for death from hepatic necrosis more often than were other anesthetics, the incidence probably would be small compared to an overall operative mortality of approximately 2 per cent.

Halothane, rather than being a dangerous anesthetic, had a record of safety, as reflected in an overall mortality of 1.87 per cent, compared with an average for all anesthetic practices of 1.93 per cent. This overall parity of halothane holds up when imbalances in patient populations are taken into account by detailed statistical adjustments. Significant differences among other anesthetics were observed, most notable of which was a death rate following the use of cyclopropane which was higher that that following use of other anesthetics even after statistical adjustment to compensate for differences in the populations exposed to the various agents.

Of special interest and concern were the large differences in postoperative mortality occurring among the participating institutions. These differences could not be accounted for by the variations among hospital populations by any of the criteria measured in the study. This matter is discussed further in the full report, and a statistical consideration of these institutional differences is presented in a recent issue of the Journal of the American Medical Association.²

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References