measured against. Unfortunately, the data that he presents do not "support the contention that nearly all the inevitable mishaps . . . that occur during anesthesia can be identified through safety monitoring. . . ." Even Orkin's critical analysis misses three key points that neutralize the usefulness of Eichhorn's conclusion in determining the value of the Harvard standards.

First, Eichhorn only collected data on major intraoperative accidents in healthy patients. By using this extremely narrow time frame, he "excluded from consideration injuries and deaths resulting from events originating during postanesthesia or ICU care, or during transport of a patient." Thus, he deliberately excluded a number of events that would reflect anesthetic errors resulting in deaths. For instance, premature extubation in the PACU resulting in death would not be included in the data set.

Secondly, by failing to look beyond the intraoperative period, he excludes from analysis those anesthesia-related deaths that do not result in an immediate accident. For instance, he states that two deaths due to halothane hepatitis were ignored. Who knows how many fatal cases of hepatitis, pneumonia, congestive heart failure, silent myocardial infarction, or other problems were missed because of this? Although Eichhorn takes the liberty of favorably comparing his study to that of "a British study," he neglects to mention that most British studies base their statistics on death within 30 days of operation, rather than intraoperative deaths. This is a significant difference, since it is known that when looking at surgical deaths, less than 27% of all deaths occur within 3 days.

Third, most of the 11 cases would have been prevented by ongoing correction of the problems listed, even if no other actions had been taken. A critical review of the 11 cases presented reveals that there were three cases associated with old or broken equipment (cases 1, 3, 9), one case associated with a substandard technique (succinylcholine infusion with spontaneous ventilation, case 2), and four cases associated with inadequate supervision of residents and CRNAs (cases 5, 6, 7, 11). Assuming that the hospitals in the survey had a reasonably competent anesthesia service, it is likely that malfunctioning equipment would be replaced and inadequate supervision would be corrected.

Any anesthetic death, whether it arises from an intraoperative accident or not, is a significant one. I do believe that the Harvard standards represent an important tool in decreasing anesthetic mortality. It is unfortunate that Eichhorn's paper not only fails to prove this statistically, but also fails to analyze the overall picture of anesthetic deaths.

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REFERENCES


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In Reply—Dr. Kraft, like Dr. Orkin in his thoughtful editorial, emphasizes some of the acknowledged caveats and limitations I noted in my paper. Also, both make reference to the "Harvard standards." It would be better to focus on the concept of safety monitoring during anesthesia care rather than the standards that served only as a vehicle for codifying the desired monitoring practices.

To maximize its validity, the retrospective review was very deliberately narrow in scope. There are three main reasons: 1) intraoperative anesthesia catastrophes are definable and thus, identifiable; 2) they are precisely what safety monitoring is intended to impact; and 3) expanding to all "anesthesia-related" morbidity and mortality for 30 days postanesthesia creates an unwieldy morass of definitions and judgments that would make an analysis such as used here essentially impossible; other reviewers have noted this problem.

No individual or group of individuals is perfect. Human nature dictates that there always will be some instances of use of malfunctioning equipment, lapses in supervision, or bad judgement. Resulting mishaps are inevitable. The fundamental purpose of safety monitoring is to provide the earliest possible awareness of these mishaps, earlier than often previously available, and thus allow appropriate intervention in time to prevent injury. Safety monitoring is no substitute for vigilance and good judgement, but it can help compensate for failures in vigilance and judgement by facilitating avoidance of catastrophe.

While analysis of "the overall picture of anesthetic deaths" would be desirable and valuable, any such attempt would have to be more diffuse and would involve an even more personal interpretation. Virtually all authors agree that, prior to the most recent developments, unrecognized intraoperative hypventilation was the greatest cause (number and severity) of anesthesia-induced injury. The paper and the concept of safety monitoring are focused on this type of problem and its prevention. While not addressing the total picture, it is a significant start. I sincerely believe that the principles of safety monitoring correctly applied can virtually eliminate this previously major source of patient injury and consequent insurance loss. Parenthetically, the malpractice premium for anesthesiologists insured by Harvard's captive insurance carrier was cut by 38% in 1989 compared to 1988, an action spurred by data suggesting fewer current anesthesia-caused injuries.

With the caveats noted in the paper, the editorial, and Dr. Kraft's letter, it remains that the purpose of the presentation was to define the study group of major intraoperative anesthesia accidents and suggest that safety monitoring would have had, and is now having, a beneficial impact.
In reply—Dr. Kraft takes issue with my editorial,¹ noting that monitoring standards in this country will soon be set by the legal profession rather than physicians. Actually, if such an unfortunate circumstance develops, it will occur only because physicians have not developed meaningful standards for themselves. Development of practice standards requires the same objectivity as we apply to the evaluation of drugs and other forms of medical technology, as I tried to emphasize.

He cites “three key points that neutralize” the validity of Dr. Eichhorn’s conclusions regarding the value of the monitoring standards, which he feels that I overlooked. Two points are related problems with the design of Dr. Eichhorn’s study, that it ignored the universe of anesthetic complications by considering only intraoperative catastrophes and immediate outcomes. Such a narrow focus was probably chosen intentionally because it would emphasize the circumstances in which many believe that monitoring standards would have their greatest impact. Despite this bias, however, the case was weak, at best, obviating the need to consider anesthetic complications more broadly. Yet, I did note that “risk management interest is now shifting appropriately to the postanesthetic recovery room.”

Dr. Kraft’s third point—that correction of inadequacies in supervision of residents and nurse anesthetists and in equipment maintenance would have prevented the adverse events, even in the absence of other actions, such as the imposition of monitoring standards—actually dovetails nicely with my emphasis on the diverse ways in which anesthesia safety may be enhanced, in addition to improved monitoring.

He also highlights an important, unemphasized issue in discussions of sophisticated monitoring equipment. While the pulse oximeter, for example, is capable of detecting subtle changes in arterial oxygen saturation, many seem to view the device as a means of detecting the often less subtle hypoxemia accompanying accidents as a final common pathway. I suspect that further advances in anesthesia safety await our getting beyond narrow monitoring issues and developing a better understanding of accident evolution,² especially the role of human factors.

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Narcotic Analgesics and Debrisoquine Polymorphism

To the Editor—In a recent publication, Henthorn et al.¹ suggested that “a genetic defect may be important for elimination clearance by metabolism for dextropropoxyphene, alfentanil, and fentanyl.” This could contribute to interindividual differences in elimination clearance for these analgesics and therefore complicate their clinical use. The conclusions of Henthorn et al.¹ were based on the interaction of the analgesics with the 2-hydroxylation of desmethylimipramine, a prototype reaction for the debrisoquine polymorphism, in a human liver microsomal preparation. The competitive character of the analgesics was regarded to be decisive to reach their conclusions. We, however, believe that the investigators ignored a second factor that is equally important for the interpretation of kinetic data obtained in competitive inhibition experiments, i.e., the relative values of the inhibition constant Kᵢ versus the Kᵢₑ.

As pointed out by Boobis et al.,² two conditions have to be met in order to conclude that the same form of cytochrome P-450 is involved in the metabolism of two substrates: first, the two substrates should be competitive inhibitors of the metabolism of each other, and secondly, the Kᵢ for inhibition should be the same as the Kᵢₑ for metabolism. In their study, Henthorn et al.¹ found a Kᵢₑ for alfentanil of 176 μM. This Kᵢₑ however exceeds by far the recently published Kᵢₑ for alfentanil, 22.8 μM.³ So, the inhibition by alfentanil of the 2-hydroxylation of desmethylimipramine observed by Henthorn et al.¹ occurs at a high concentration relative to its Kᵢₑ which indicates that the cytochrome P-450 form involved in the debrisoquine polymorphism contributes at most to only a small part of the total metabolism of the drug. Although Henthorn et al.¹ also suggest this may be the case, the authors overemphasize the competitive character of the analgesics as inhibitors and therefore reach faulty conclusions. Recently, we demonstrated that debrisoquine itself is a noncompetitive inhibitor of any of the in vitro metabolic pathways of alfentanil in human liver microsomes, and that the Kᵢ for debrisoquine (2.0–3.2 mM) was much greater than its Kᵢₑ (0.086–0.090 mM).³

From the data summarized above, we may conclude that a genetic