In reply—Dr. Kraft takes issue with my editorial, 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, especially the role of human factors.

FREDICK K. ORKIN, M.D.
Associate Professor of Anesthesia
University of California, San Francisco,
School of Medicine
UCSF Surgery Center A-3
San Francisco, CA 94143–0368

REFERENCES

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Narcotic Analgesics and Debrisoquine Polymorphism

To the Editor—In a recent publication, Henthorn et al. 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. were based on the interaction of the analgesics with the 2-hydroxylation of desmethylipramine, 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 $K_i$ versus the $K_m$.

As pointed out by Boobis et al., 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 $K_i$ for inhibition should be the same as the $K_m$ for metabolism. In their study, Henthorn et al. found a $K_i$ for alfentanil of 176 μM. This $K_i$ however exceeds by far the recently published $K_m$ for alfentanil, 22.8 μM. So, the inhibition by alfentanil of the 2-hydroxylation of desmethylipramine observed by Henthorn et al. occurs at a high concentration relative to its $K_m$, 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. 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 $K_i$ for debrisoquine (2.0–3.2 mM) was much greater than its $K_m$ (0.086–0.090 μM).

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