above and therefore seems to us predestined to demonstrate that opioids as sole anesthetics are ineffective in blocking hemodynamic and hormonal stress responses.

Despite a "less than ideal anesthetic technique" for blocking stress responses to stimulation, Philbin *et al.*[1] may still have shown that higher plasma concentrations of sufentanil are more effective than lower concentrations at preventing hemodynamic responses to stressful events. If hemodynamic responders with plasma concentrations of sufentanil greater than 10 ng/ml are compared to responders with plasma concentrations of less than 10 ng/ml for all three events (postintubation, poststernotomy, and postcannulation) (fig. 3 in the article by Philbin *et al.*) only 14.3% (6 of 42) of the responders had plasma sufentanil concentrations above 10 ng/ml, *versus* 35.2% (19 of 54) with plasma concentrations below 10 ng/ml. This difference is statistically significant; according to Fisher's Exact test, $P = 0.034$.

The issue addressed by Hug[2] is whether high doses of μ-opioid agonists, because of their limited ability to block autonomic and endocrine responses during surgery, can ever be considered more than incomplete or partial anesthetics. Clearly, opioids seem to produce their anesthetic effects *via* different mechanisms than those causing anesthesia with the classical inhalation and even other intravenous agents. What Philbin and co-workers and Hug have not emphasized is that subtleties in anesthetic technique, including timing of opioid administration, are more important with opioids than with other anesthetics in explaining differences in measured outcomes.

Dr. Hug is incorrect in stating that highly potent opioids such as fentanyl and sufentanil are incapable of preventing movement in all subjects, whether patients or dogs. Bailey *et al*[3] have shown that 100% of unparalyzed dogs receiving 3,000 μg/kg fentanyl did not move in response to a supramaximal tail-clamp stimulus of 30 s. Some readers may suggest that 3,000 μg/kg is an excessively high dose of fentanyl. Undoubtedly, it is excessive in humans, but it is the only dose that Bailey *et al*[3] found that would reliably produce a plasma fentanyl concentration above 500 ng/ml 5 min after injection in the dog. If plasma fentanyl concentrations were above 500 ng/ml, all dogs in Bailey's experiments did not move regardless of the stimulus. If plasma fentanyl concentrations were less than 500 ng/ml, the incidence of movement increased as the plasma concentration decreased.

Published and unpublished data obtained from studies in a variety of animal species have demonstrated that, although within any species individual variability may be extremely large, there is a plasma concentration of all potent μ-receptor agonists that blocks movement in all individuals.[3-7,*,†] The plasma concentration of sufentanil that blocks movement in response to a painful stimulus in "all dogs" has not yet been determined. Likewise, the plasma concentration of fentanyl or sufentanil that blocks undesirable responses (including awareness) to painful stimuli in all human patients also has not been determined. Furthermore, whether there are advantages in attempting to achieve anesthesia with only an extremely high dose of an opioid (and achieving high plasma and CNS concentrations), *versus* using an opioid plus one or more supplements, has not been carefully studied and is unknown.

The upshot of all of this is that while Philbin *et al.*[1] and Hug's[2] contention that suppression of hemodynamic and hormonal stress responses is not related to opioid plasma concentration may be correct, we believe the study has not adequately tested this hypothesis. Unfortunately, despite its popularity in anesthesia, the subtleties of opioid anesthetic actions are still not well known, and therefore, clinical anesthetic techniques with opioids probably are still quite primitive.

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In Reply:—The critical issue underlying our study is the practical limits of the dose–response relationship. Stanley and Bailey assume that higher opioid blood levels, and therefore, timing of periodic doses in anticipation of stimulation, will abolish responses. This also assumes that there is a continuous dose–response relationship that does not plateau. Our data clearly demonstrate that within the dose range tested, such a plateau exists. We could discern no difference in response between patients receiving 50 μg/kg fentanyl and those receiving 40 μg/kg sufentanil plus infusion. Since this latter dose is already well beyond that recommended for clinical use, we have no evidence that changes in or timing of doses predictably decrease response. We stand by our statement that it is unlikely that any *clinically useful dose* will successfully abolish responses in *all patients.*

In addition, Stanley and Bailey have misinterpreted our data in figure

3. Both the text and the legend clearly indicate that after the initial response, therapy was started and no further data points were included for that patient.

We agree that "the plasma concentration of fentanyl or sufentanil that blocks undesirable responses to painful stimuli in all human patients has not been determined." What we question is whether such a concentration exists in a clinically useful dose range. Drs. Stanley and Bailey's description of the enormous doses of fentanyl required to block response to pain in dogs seems to corroborate our opinion.

Further studies with extremely large doses or perhaps even more potent opioids will be necessary to put this issue to rest. Then the related issue of appropriateness of these doses in terms of side effects and cost will have to be addressed. For the present, we remain convinced that in the clinically relevant dose range of available potent opioids, no evidence of a dose–response relationship exists.

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In Reply:—Stanley and Bailey miss the mark in their analysis of the findings by Philbin *et al.* Philbin *et al.* gave a loading infusion along with a constant maintenance infusion of sufentanil in the manner suggested by Wagner[1] as a means of quickly reaching a stable plasma concentration—a highly desirable condition in which to relate drug concentration to effect. The expected consequence of this infusion regimen is an initially very high drug concentration that rapidly declines as the drug equilibrates between plasma and well-perfused tissues (distribution phase). Thereafter, plasma and brain concentrations decline more slowly until a steady state is reached. A delay between the initial loading infusion and measurements of drug concentration and effect is necessary to allow relatively stable conditions to be achieved. The sequence employed by Philbin *et al.* was appropriate to their purpose.

Observations of response/nonresponse were made for sternotomy when the plasma levels of sufentanil were relatively stable. Reliable "anesthesia" (*i.e.*, suppression of hemodynamic responses to a potent noxious stimulus) was *not* evident in the range of 10–16 ng/ml concentrations of sufentanil in plasma. The proportion of responders was virtually the same in the concentration ranges of 2–5 ng/ml (7 of 13), 5–10 ng/ml (7 of 14), and 10–16 ng/ml (4 of 10). I doubt that anyone would be willing to administer the very large doses of sufentanil necessary to produce and maintain plasma concentrations greater than 10 ng/ml and still accept a 40% response rate. And if not 10–16 ng/ml, how much sufentanil is required to use it as a "pure anesthetic"? That is the primary practical point made by Philbin *et al.*

Importantly, de Lange *et al.* did not use "pure" sufentanil to achieve satisfactory anesthetic conditions in their cardiac surgical patients. Their patients were premedicated with a large oral dose of lorazepam (0.08 mg/kg).[2] We have found that this large dose of lorazepam makes it relatively easy to finish the induction of anesthesia and to maintain it with a moderate concentration of opioid in plasma.[3,*]

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Nystagmus Following Epidural Morphine

To the Editor:—We read with great interest the report of Fish and Rosen[1], in which a case of vertical nystagmus in a patient who had received epidural morphine was described. We recently also observed such a case.

A 67-yr-old male, of weight 75 kg and height 168 cm, underwent bilateral total knee replacements for osteoarthritis. His past medical history was unremarkable; specifically, he had no neurologic disease and was taking only a nonsteroidal antiinflammatory medication. His anesthetic was performed with lumbar epidural anesthesia using 0.75% bupivacaine HCl. During the surgical procedure he received midazolam 10 mg. No other hypnotics, sedatives, or analgesics were administered. In the recovery room he received a loading dose of 2 mg preservative-