

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.

DANIEL M. PHILBIN, M.D.  
CARL E. ROSOW, M.D.  
ROBERT C. SCHNEIDER, M.D.  
GREG KOSKI, M.D.  
MICHAEL N. D'AMBRA, M.D.  
*Department of Anesthesia  
Massachusetts General Hospital  
Boston, Massachusetts 02114*

(Accepted for publication November 2, 1990.)

Anesthesiology  
74:390, 1991

*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<sup>1</sup> 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).<sup>2</sup> 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.<sup>3,\*</sup>

CARL C. HUG, JR., M.D., PH.D.  
*Professor of Anesthesiology and Pharmacology  
Emory University School of Medicine  
Director, Cardiothoracic Anesthesia  
The Emory Clinic  
Atlanta, Georgia 30322*

#### REFERENCES

1. Wagner JG: A safe method for rapidly achieving plasma concentration plateaus. *Clin Pharmacol Therap* 16:691–700, 1974
2. de Lange S, Boscoe MJ, Stanley TH, Pace N: Comparison of sufentanil-O<sub>2</sub> and fentanyl-O<sub>2</sub> for coronary artery surgery. *ANESTHESIOLOGY* 56:112–118, 1982
3. Hug CC Jr, Hall RI, Angert KC, Reeder DA, Moldenhauer CC: Alfentanil plasma concentration vs effect relationships in cardiac surgical patients. *Br J Anaesth* 68:435–440, 1988

(Accepted for publication November 2, 1990.)

\* Hug CC Jr, Moldenhauer CC: Pharmacokinetics and dynamics of fentanyl infusions in cardiac surgical patients. *ANESTHESIOLOGY* 57: A45, 1982

Anesthesiology  
74:390–391, 1991

## Nystagmus Following Epidural Morphine

*To the Editor:*—We read with great interest the report of Fish and Rosen<sup>1</sup>, 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-