memory deficits" (added words are italicized). Our original sentence,[3] though correct, is vague and may lead some readers to infer that Dundee and Pandit studied aspects of memory other than retrograde amnesia.

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Amrinone in Patients Undergoing Cardiac Surgery

To the Editor:—Bailey *et al.*[1] conducted an excellent study of the pharmacokinetics of amrinone during cardiac surgery. However, I disagree with their conclusions regarding the inadequacy of low-dose amrinone (a 0.75-mg/kg intravenous loading dose and a 10-$\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion) for providing inotropic support after cardiopulmonary bypass (CPB).

We[2] administered a loading dose of amrinone 0.75 mg/kg, followed by an infusion of 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (combined with norepinephrine to maintain afterload), to patients during the immediate post-CPB period. The mean cardiac index increased by 65%. When a second dose of 0.75 mg/kg amrinone was given 30 min later and the infusion rate doubled, no additional increase in cardiac index occurred. We initially studied 7 patients but have since found this regimen to be predictable and effective in more than 200.

The finding that a linear dose relationship exists between plasma concentration and cardiac output in patients with chronic congestive heart failure[3] cannot be extrapolated to patients needing inotropic support immediately after CPB. Postbypass myocardial dysfunction is multifactorial, acute, and unpredictable with respect to severity. The plasma concentration of 1.7 $\mu g/ml$ is considered by some to be a threshold therapeutic level in a stable environment. However, blood levels and, presumably, intracellular levels are likely to fluctuate in the postbypass phase of hemodynamic instability and cannot be depended on to serve as rational guides to dosage choice.

Wilson *et al.*[4] demonstrated a counterclockwise hysteresis in patients with chronic congestive heart failure when cardiac index, corrected for baseline values, was plotted as a function of plasma concentration of amrinone. They observed a lack of concordance between the time course of changes in cardiac index and plasma concentration. The authors suggested that the site of action of amrinone is pharmacokinetically distinguishable from the plasma and from the tissues in instantaneous equilibrium with the plasma. The instability of the immediate post-CPB state would certainly enhance the disjunction between plasma levels and response to amrinone.

Bailey *et al.* incorrectly cited the work of Butterworth *et al.*[5] to support their conclusion that low-dose amrinone is inadequate in the immediate postbypass phase. The study described in the abstract of Butterworth *et al.* was done 24–36 h postoperatively and has little relevance to the optimal dosage in the immediate postbypass period.

Clearly, multiple factors affect heart function at separation from CPB. The appropriate dose of amrinone in patients separating from CPB is best determined by examining the therapeutic end-points of improved hemodynamic characteristics and cardiac indices. Although knowledge of pharmacokinetics is useful, we must avoid treating a blood level and remember that more is not necessarily better.

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In Reply:—We agree with Lathi that the relationship between amrinone plasma levels and therapeutic effect in cardiac surgical patients immediately after cardiopulmonary bypass is unknown. A controlled study of this question is certainly needed. However, we do not believe

that the observation of Lathi *et al.*[1] represents such a study. They reported that cardiac index did not increase when a second 0.75-mg/kg bolus dose of amrinone was given 30 min after therapy was initiated with a 0.75-mg/kg bolus dose and 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion. This observation was made in seven patients, five of whom were also receiving norepinephrine, a potent β_1 agonist, as needed to maintain blood pressure.

It is difficult to interpret their observations on cardiac index since neither amrinone nor norepinephrine were administered in a controlled fashion. Administering a β_1-adrenergic agent in combination with a cyclic AMP–specific phosphodiesterase inhibitor creates a complex interaction that makes it impossible to identify the contribution of amrinone to any change (or lack of change) of contractility. Lathi's statement that they "initially studied seven patients but have since found this regimen to be predictable and effective in more than 200" represents an anecdotal comment. Furthermore, we would predict on the basis of our pharmacokinetic data that Lathi *et al.* did not significantly alter amrinone plasma concentrations by administering a second 0.75-mg/kg dose 30 min after the initial dose. Taking data from table 4 of our paper, we can predict, using standard pharmacokinetic calculations, that the initial average amrinone plasma concentration would be 5.6 $\mu g/ml$ and that the second bolus dose would only transiently increase this to 7.1 $\mu g/ml$.[2] Using the data of Edelson *et al.*,[3] this small increment of amrinone plasma concentration would increase cardiac output by only 10%, which is not large enough to be measured reliably by routine thermodilution and among all the other variables in patients after cardiopulmonary bypass. Lathi has seemingly ignored one of the major points of our article—specifically, that despite a relatively long elimination half-time, plasma levels of amrinone will decrease rapidly after a bolus dose, even when an infusion is also given, due to distribution of amrinone to body tissues.

We also believe that Lathi has overstated the case for a lack of concordance between the time course of changes in cardiac index and plasma amrinone concentrations, suggested by the data of Wilson *et al.*[4] This was based on a *single* time point after oral administration and is hardly conclusive. Also, we are perplexed that although Lathi objects to our extrapolating the data of Edelson *et al.*[3] from patients with chronic heart failure, he is doing the very same thing in citing the work of Wilson *et al.*,[4] which was also drawn from patients with chronic congestive heart failure.

Finally, Lathi suggests that we have incorrectly cited the work of Butterworth *et al.* because the study of Butterworth *et al.* in cardiac surgical patients was performed 24–36 h postoperatively.[5] There are, however, other studies that also demonstrate the inadequacy of 0.75 mg/kg as a loading dose to improve cardiovascular function at the end of cardiopulmonary bypass.[6]

Cardiac index or cardiac output is a complex physiologic parameter that depends on several variables (preload, afterload, contractility), each of which is altered by amrinone. By providing new information regarding previously undescribed pharmacokinetics, we hope that our report[2] will facilitate the additional pharmcodynamic studies needed to explore fully the role of amrinone in the management of cardiac surgical patients.

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Spinal Nerve Root Is One of the Preferred Routes for Transfer of Drugs to the Nerve Roots and Spinal Cord from the Epidural Space

To the Editor:—The recent paper by Bernards and Hill[1] does not give proper attention to the histologic structure of the spinal root sleeve. Figure 1 in their publication shows the pia–arachnoid mater ending at the proximal part of the root sleeve. Our studies have shown that the leptomeninges on the root continue as perineural epithelium covering the entire peripheral nervous system, including almost all the sensory and motor end organs.[2–5] As the dura mater continues distally as epi- and perineural connective tissue on the spinal nerve root, its thickness is considerably reduced. The pia and arachnoid mater join at the proximal segment of the dorsal root ganglion and continue as perineural epithelium (fig. 1) on peripheral nerves.[4] Furthermore, the arachnoid villi are found in less than 40% of the nerve roots sectioned.[4,6] These villi have intercellular spaces that open to the subarachnoid space on the proximal part of the nerve roots (fig. 1).[4,6,7] These histologic features make the root sleeve the weakest, and the specialized section through which the solutes and small particulate matter can