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
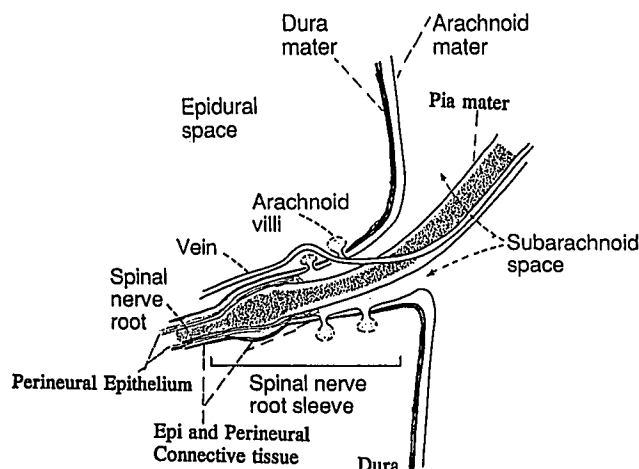
FIG. 1. The root sleeve histology. Note that the dura becomes thin and continue as epi- and perineural connective tissue. The pia–arachnoid continue as perineural epithelium of peripheral nerves. The subarachnoid space, arachnoid villi, and associated veins in the proximal part of the root sleeve.

diffuse from the epidural space to common nerve trunks, nerve roots, and the SAS around the proximal part of the nerve roots and *vice versa*.

1. The flaw in the Bernards and Hill's experiment is not dissecting and isolating the nerve root fibers from the membranous covering (sleeve) of the nerve roots and inserting it in the diffusion cell as shown in cell 2 of our diagram (fig. 2). Instead, these workers inserted the entire nerve root along with sleeve. The nerve fasciculi are enclosed in the root sleeve and add considerable thickness (many folds) to the root sleeve. Such preparations surely will retard the rate of diffusion.

2. The proximal sections of the nerve roots and the dorsal root ganglion have the extension of the subarachnoid space (fig. 1). To make the experiments physiologic, this space should be cre-

ated with the diffusion fluid in it. I do not believe the study took this histologic fact into consideration.

3. To assume that all the nerve roots have arachnoid villi is erroneous. Did they section the roots they used in the diffusion chamber 2 and find out the exact histology of the nerve roots used in the experiments?

4. Pressure changes in cerebrospinal fluid and epidural space due to physiologic conditions of the chest and abdomen and uptake and distribution by blood vessels of the nerve root need to be considered.

I suggest that another series of experiments be repeated using diffusion cell 1 as is. The second diffusion cell should contain the dura and its continuation epi- and perineurium, and pia–arachnoid and its continuation perineural epithelium peeled off from the nerve roots (figs. 1 and 2, diffusion cell 2). Create subarachnoid space by peeling pia mater from the spinal cord. In another series of experiments, use a hollow root sleeve by removing all the nerve fibers and then tying the distal cut end.

It is difficult for me to believe that the thinned dural extension covering the nerve roots as epi- and perineural connective tissue, permeated by arachnoid villi and blood vessels, and its associated subarachnoid space in the proximal segment will not allow any more solutes to diffuse when compared to the dense dura and multilayered arachnoid cell layers covering the spinal cord. If these experiments are repeated using only root sleeve without the nerve fasciculi, they should prove that the nerve root sleeve is one of the most important routes and "the preferred" route for the spread of drugs and other solutes introduced into the epidural space.

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FIG. 2. The diffusions chambers. To prove whether the root sleeve is the preferred site for diffusion of solutes compared to the dura and arachnoid, the sleeve should be dissected in inserted as shown in diffusion chamber 2.

Diffusion Cell 1   Diffusion Cell 2
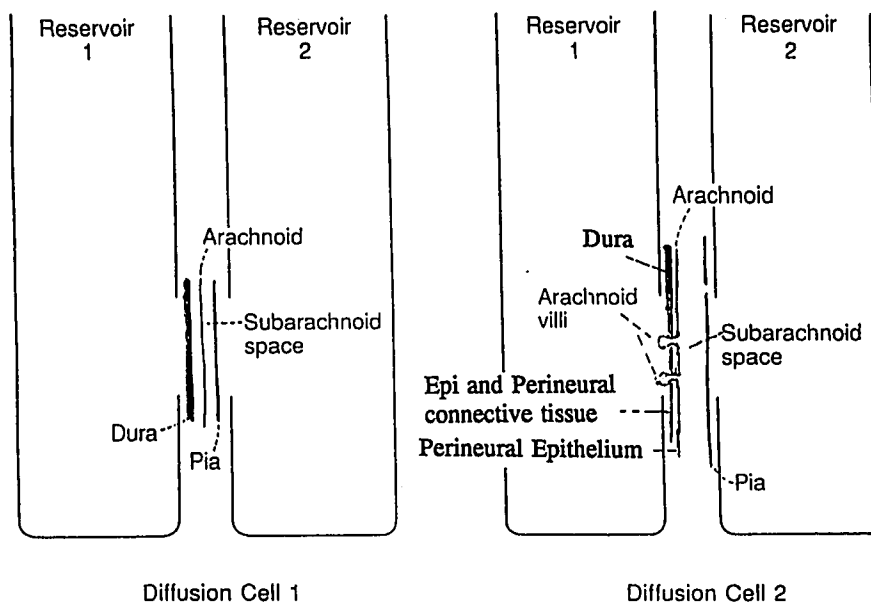
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In Reply:—I thank Shantha for his comments regarding our paper. However, I must disagree with his assertion that our study does not give proper attention to the histologic structure of the spinal nerve root sleeve. The purpose of our study was to investigate diffusion through the spinal nerve root cuff in a model as close to the *in vivo* situation as possible. To that end, we studied sections of spinal nerve and associated meninges extending from the spinal cord to the intervertebral foramen. These specimens, therefore, included all of the relevant histologic structures (*e.g.,* root cuff, spinal nerve, dorsal root ganglion, perineural epithelium) in their normal anatomic relationships. This intact anatomically correct preparation is a strength of our model, not a weakness as suggested by Shantha in his first numbered comment. In fact, to dissect the nerve fascicles from the meninges, as suggested, would produce a highly artificial system, the results of which could not be applied to the intact tissue.

In response to Shantha's second point, as depicted in our paper (fig. 1), the preparation does include the extension of the subarachnoid space into the region of the dorsal root ganglion, and this extension is filled with cerebrospinal fluid (CSF). The subarachnoid space is bounded by the pia mater and does not communicate with the diffusion cell reservoirs in our model, because *in vivo* the pia mater lies between the subarachnoid space and the spinal cord. To remove the pia mater and allow the subarachnoid space to communicate with the fluid reservoirs would yield data on permeability between the epidural space and the subarachnoid space. However, as the title of our paper makes clear, we were interested in movement of drugs between the epidural space and the spinal cord. In addition, as we have shown previously,[1] the arachnoid mater accounts for nearly 90% of the resistance to diffusion through the meninges. Thus, removal of the pia mater to allow direct communication between the subarachnoid space and the fluid reservoirs would have little effect upon the results.

In response to point three, it is true that only 40% of root cuffs have arachnoid villi. Therefore, if the presence of arachnoid villi does in fact increase permeability through the root cuff, then 5 of the 13 root cuff specimens we studied should have had permeability coefficients significantly greater than specimens without a root cuff. However, not one was significantly more permeable than tissue that did not include a root cuff.

In response to point four, it is true that our model does not mimic epidural–CSF pressure gradients or include blood flow. However, drug redistribution *via* radicular artery blood flow is an issue separate from spinal nerve root cuff diffusion and thus is not a limitation of our model. Pressure across arachnoid villi can increase their permeability but only at pressures far greater than normal.[2] Therefore, the absence of a pressure gradient would not seem to be a limitation.

In his closing paragraph, Shantha expresses disbelief that solute permeability through the "thinned dural extensions" covering the nerve roots and through the arachnoid villi penetrating the dura is not greater than in other areas of the meninges. As we explained in our paper, the "thinness" of the dura is immaterial because the arachnoid mater is the overwhelming barrier to diffusion across the meninges.[1] The presence of arachnoid villi is ineffective in increasing permeability because: 1) their surface area is extremely small compared to the rest of the meninges (flux is proportional to surface area); 2) more contemporary studies have established that pores through the arachnoid villi exist only in pathologic states of markedly increased CSF pressure[2,3]; and 3) transport across arachnoid villi has been shown to occur by micropinocytosis and has only been observed to occur in one direction—from the CSF out into the epidural space, not from the epidural space into the CSF.[4]

In conclusion, I believe that our model accurately reflects the *in vivo* anatomy of the spinal nerve root cuff and that our conclusions are valid. In addition, the nonanatomic experiments proposed by Shantha are so removed from normal anatomy and histology that I cannot envision how they would be helpful.

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