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(Accepted for publication April 2, 1992.)

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77:218, 1992

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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(Accepted for publication April 2, 1992.)