extradural dosing. The literature is replete with single-drug studies without controls for the parenteral uptake from that site, and with comparisons of drugs that omit sensitivity measures, such as using at least two doses of one of the drugs to see if a measurable difference results. Until these issues are addressed, side-effect incidence comparisons are misleading.

Second, the editorial suggests that use of receptor selective opiates offers the opportunity to maximize pain relief and minimize side effects. We would agree with this in principle. In practice, however, the drug doses used produce concentrations in cerebrospinal fluid (CSF) which are very high, 50,000 nmol/l in lumbar CSF 30 min after lumbar injection of 2.5 mg morphine. It may be that such high concentrations are necessary because drug is bound non-specifically, but at first glance arguing for receptor-selectivity at such levels is unrealistic.

Third, the author suggests that kappa ligands do not produce urinary problems. The difficulty with this argument is that intrathecal injection of kappa ligands may also fail to produce analgesia. In animal behavioral studies, spinal kappa ligands seem to be poor analgesics, particularly in tail-flick studies, although supraspinal analgesic effects can be observed. In electrophysiological tests of analgesic effect, the net result of intrathecal kappa ligands is that they are not analgesic. Until there is convincing evidence that spinal application of kappa ligands does indeed produce clinically relevant analgesia, it is premature to suggest that recourse should be made to kappa-selective drugs to minimize urinary difficulties.

In Reply.—Drs. McQuay and Moore's comments are pertinent, but need to be balanced by the following observations. Certainly few clinical studies have critically examined the relationship between different doses of spinal opiates, the intensity of analgesia, and the occurrence of side effects. Comprehensive studies of this kind would be welcome. However, where comparisons between different drugs have been made using equianalgesic doses, clear differences have been observed in the incidence of urinary retention. This observation suggests the possibility that the mechanisms of opiate-induced analgesia and impaired urinary bladder activity are different. Several other factors may also account for apparent differences between the activities of opiates. These include differences in their pharmacokinetic properties and in their intrinsic pharmacological activity. The relationship between these factors and the relief of pain should be interpreted cautiously. In the example given, it is difficult to weight the significance of the high CSF concentration of morphine, measured 30 min after spinal administration, with analgesia, because adequate pain relief is produced for many hours following a single dose of morphine. During this time, substantial redistribution and clearance of drug occurs. Indeed, a more relevant measurement would be the concentration of morphine at the active site within the spinal cord. This is likely to be a fraction of that present in the CSF. Finally, the specificity and receptor selectivity of spinal morphine can only be defined using a selective antagonist, such as naloxone. This has been shown in a number of studies to reverse the effects of epidural morphine. Finally, the efficacy of spinal kappa ligands as analgesics is indeed questionable from animal studies in which noxious somatic stimulation has been tested. Other studies, however, support the efficacy of kappa ligands against visceral nociception. Clearly, such differences observed in experimental animals require further study, but these findings also invite future clinical evaluation.

REFERENCES