DEAR SIR,

Drs Schiff and Stevenson correctly restate our results. There are sound reasons, both pharmacological and clinical, for sampling at times similar to those chosen by Braithwaite and associates (1974). Pharmacologically, single and multiple dose studies have demonstrated that the pharmacokinetics of the tricyclics follow a two compartment open model with a biexponential disappearance curve and are not dose dependent (Gram and Christiansen, 1974; Alexanderson, 1972). Equilibrium between the central and peripheral compartments is not established until 8–20 hours after an oral dose. It is after this time, during the β or elimination phase that plasma samples would most closely reflect drug concentration in the peripheral compartment. On a once-daily bedtime dosage schedule, elimination phase samples could be drawn from the morning through the evening. On a thrice-daily schedule, only the sample collected in the morning prior to the first oral dose would represent an elimination phase sample. However, our results and those reported by Braithwaite and associates (1974) indicate that in the majority of patients on a thrice daily schedule the rise in plasma levels in the hours after administration of one-third of the usual daily dose is not large enough to be clinically significant, that is greater than ±15–20 per cent of the usual steady state levels (Ziegler *et al*, in press). Clinically, we feel this is an important point since it demonstrates that samples can be collected in out-patients on different dosage schedules, who are being seen throughout the day without special efforts to control for the pharmacokinetic phases of adsorption, distribution and elimination. We would also like to comment on the second portion of the author's letter, although it does not concern amitriptyline, the subject of our report. We are not familiar with the combination of nortriptyline and fluphenazine that they studied but have extensive experience with nortriptyline. We feel their statement that the nortriptyline concentration increased 300 per cent over the pre-dose correlation four hours after the administration of 30 mg of nortriptyline and 1·5 mg of fluphenazine, although correct, is probably misleading for many readers. After an oral dose of nortriptyline the rise in plasma concentration is relatively constant for a given dose in an individual. A 30 mg dose usually produces a 5 to 20 ng/ml increase in plasma concentration. If the predose concentration is 5 ng/ml a 300 per cent increase, in fact occurs, but at the usual steady state therapeutic levels 50 to 150 ng/ml, this is closer to a 10–20 per cent increase and is not clinically significant. As for their speculation that peak plasma levels within the therapeutic range may produce an adequate response, we have no information, but wish to point out that none of the studies of nortriptyline we are aware of, measured peak levels. Sampling has been confined properly to the β elimination phase. That peak plasma levels within the now well defined 50 to 150 ng/ml therapeutic range result in a similar therapeutic response awaits documentation.

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A NOTE ON THE NATURAL EXPRESSION OF PAIN

DEAR SIR,

There is a common belief that pain has some natural or inborn expression. However, expressions of pain differ from one culture to another, and some cultures even train their members to suppress these as well as other signs of distress. Also, within the same culture pain may be expressed in a variety of ways. A person who is physically hurt may, for example, make grimaces, cry out loud, or swear. Thus, when the reactions of adult members of a culture are considered, there seems to be no way that pain can be linked with any specific expression. Neither does there seem to be any clear-cut relation between intensity of the pain felt and the magnitude of the pain reaction. Thus, if pain has some natural expression this should be sought early in the ontogenesis.

Everyday observations of children show that they are more apt to cry when they know someone is watching them than if they believe themselves alone.

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