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.

A child who plays out of sight and hurts himself, typically first starts to run towards the parents, and only after a while begins to cry. Such observations indicate that there is no simple connection between the pain felt and its expression even in children.

In contrast to an idea of naturally expressed pain, is also the fact that children with early infantile autism may hurt themselves without showing any visible reactions. For example, Mahler (1952) reports that an autistic child, seeing his mother light a cigarette with a lighter from the dashboard of the car, seized the lighter and burned his mouth, apparently without feeling any pain. This failure to express pain has been interpreted as a sign that autistic children suffer from some defect in the nervous system which make them insensitive to pain (Rimland, 1964). There is, however, another possibility; that expressing pain is primarily communicative.

Several case histories of autistic children support the idea that expression of pain is linked with communication in a wider sense. If children who show insensitivity to pain improve to the point where they begin to communicate, they typically also begin to express pain. This might be due to some improvement of the nervous condition of these children, but this is not a likely explanation since comparable courses of development are found among the congenitally blind, and children raised in institutions (Keeler, 1958; Provence and Lipton, 1962). These children may fail to show pain at an early age, but at later ages communicate both their pains and pleasures. There is no reason to believe that they share some neurological pathology with the autistics. The children do, however, face difficulties during their development which may hamper the acquisition of communicative skills, indicating that expression of pain may be dependent upon communicative ability.

Furthermore, if the expression of pain depends upon the child's communicative ability, it follows that children who differ in their means of communication should also differ in their expressions of pain. A case which apparently demonstrates this has been brought to our attention. A fifteen-month-old normal hearing boy with deaf parents fell down the stairs and cut his forehead. He bled freely, but did not cry. He did, however, run to his parents pointing demonstratively to his forehead. Thus the boy expressed his pain according to his parents' communicative abilities, and was duly rewarded with attention and care. This happened while the family were on a visit to hearing relatives for a couple of months. The relatives were shocked by the boy's 'unnatural' reactions, and as a consequence of this the deaf parents employed a hearing housekeeper when they returned home. During the stay with his hearing relatives the boy more frequently started to cry when hurting himself.

The case of this boy, as well as the other above mentioned observations makes it a warranted suggestion that pain has no natural expression.

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MORE ON ALCOHOLISM AND DEPRESSION

DEAR SIR,

Galdi and Bonato (*Journal*, August 1977, **131**, pp 221–2) took an interesting epidemiologic approach to elucidate the relation between alcoholism and psychiatric disorder. However, a number of conceptual and methodologic reservations must be raised in addition to those mentioned by them.

Hospital admission rates reflect treated prevalence, not incidence, especially in the case of depression. Over a third of affectively ill patients in Helgasson's epidemiologic study were not admitted to hospital anywhere for their illness (2). This rate is subject to the vagaries of fashion, accessibility, administrative and clinical interest, budgeting, reporting, social attitudes, etc, in addition to actual changes in level of need.

It is noteworthy that admission rates for psychiatric disorders also increased significantly during the six-year period in question. There is evidence that in the long run this rate as well as the prevalence of psychiatric disorders should remain steady (1, 3). Therefore such a marked increase may reflect transitory, atypical trends in Sweden.

Further, patients with so-called depressive spectrum disease (DSD) (6), a depression closely linked to alcoholism familially, have a different rate of hospital