ON THE CLINICAL RESPONSE/PLASMA LEVEL RELATIONSHIP FOR CLOMIPRAMINE

DEAR SIR,

In a recent paper in this Journal (Della Corte *et al*, 1979), for the full WSH group of 30 orally clomipramine-treated patients, no significant correlation between clinical outcome and any plasma level parameter involving either clomipramine (CI) or its main metabolite DMCI was found. A statistically significant correlation was reported between the ratio DMCI/CI and DMCI ($r = 0.68$, $P < .01$). At the end of treatment (day 21), there were 17 responders and 13 non-responders. A responder here is a patient with at least a 50 per cent reduction in severity of depress in (% Ham-D $\downarrow \geqslant 50$ per cent) assessed by the depression scale of Hamilton, 1960.

From Figs 4 and 5 of their paper, a raw data table for the 30 WSH patients can be constructed, with some minor uncertainties, in terms of % HAM-D$\downarrow$ and the four plasma level parameters DMCI, CI, total plasma (DMCI+CI) and ratio (DMCI/CI). Using the methods in Dutt (1981a and b), the 17 responders can be broken into two mutually exclusive subgroups:

I: 15 for which (DMCI/CI > 1)
II: 2 for which (DMCI/CI < 1)

Group II is, of course, too small for evaluation but an analysis of Group I reveals a significant correlation between clinical response and CI (Spearman $r = 0.65$, $P < .01$) which was confirmed by a second calculation (Pearson $r = 0.63$, $P < .02$). Confirmed significant correlations were also found between DMCI and ratio ($r = 0.82$, $P < .001$), DMCI and total plasma ($r = 0.92$, $P < .001$), ratio and total plasma ($r = 0.58$, $P < .025$) and, CI and total plasma ($r = 0.66$, $P < .005$). Significant but weaker correlations were also found with the alternative definition of responder (% Ham-D$\downarrow \geqslant 40$ per cent) employed by Dutt (1981a and b).

In the full WSH study group, there are several factors which appear to reduce the likelihood of finding a significant clinical response/plasma level relationship. The high proportion 13 of non-responders in the full group of 30 patients makes the population non-homogeous. Although these were in-patients, there were no stated minimal intake Hamilton criteria, as well as no evidence that steady state was reached on day 21, the minimal time normally needed to assess efficacy of tricyclics. In fact, as the authors noted, DMCI levels had already doubled by day 21. Moreover, the curvilinear response for the full group of patients might suggest that dosage adjustment was necessary, (Vandel *et al*, 1978).

For these reasons, therefore, it was not surprising that with the full group of patients a significant clinical response/plasma level relationship was not found by the authors. It should be reassuring, however, that with the (DMCI/CI > 1) responder subgroup, such a significant relationship was found with CI. This conforms to the pattern observed for other tricyclics (Dutt, 1981a and b).

Unfortunately, as the authors noted, the present response rate with tricyclic treatment is about 60 per cent which means a high proportion of non-responders that tend to make the study population heterogeneous. The difficulty in establishing the clinical response/plasma level relationship will tend to remain until patients can be selected who in fact can respond to the drug (Glassman *et al*, 1977). The Feighner criteria (Feighner *et al*, 1972), important as they are, are not sufficient to ensure large numbers of responders.

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