any factor which is known to influence response to therapy should either be equally divided between the two drug groups or eliminated. On page 817, the authors discuss the significance of delusions and they point out that patients who are frankly deluded do badly on imipramine and they also offer evidence that these patients will probably respond less well to amitriptyline. The initial efforts to ensure that relevant factors were distributed equally between the two drug groups were both rigorous and reasonable and it was indeed very bad luck that "chance" was so unfair as to place seventeen of the frankly depressively deluded patients into the imipramine group and only six into the other.

Since delusions in a depressed patient foretell a poor response to treatment with imipramine (and possibly amitriptyline) this particular study was loaded against imipramine from the start unless one excludes the deluded patients. If one does this, the results would read:

	No ECT	ECT	Total
Imipramine	37	14	51
Amitriptyline	54	9	63
Total	91	23	114

Chi-square now becomes 3·0332 and $P>0·05$, *no longer statistically significant.*

It would seem, therefore, that the statistical superiority of amitriptyline over imipramine in this study appears to be due to the fortuitous distribution of deluded patients in the two treatment groups.

J. G. Domenet,

Medical Department,
Geigy Pharmaceutical Co. Ltd.

Dear Sir,

On behalf of myself and my colleagues, I should like to reply to the comments made by Dr. Domenet of the Geigy Pharmaceutical Company.

It is quite true, as you could personally confirm, that for the purpose of publication in the *British Journal of Psychiatry*, we had to shorten the second paper describing our investigation. However, a lengthier, more detailed account will soon be available as part of a monograph, "Depressive States: A Pharmacotherapeutic Study." Written by myself in collaboration with Dr. Burt and Mr. Holt, this book is shortly to be published by Charles Thomas, of Springfield, Illinois.

Dr. Domenet correctly points out that in our second paper we used the ultimate need for ECT as the index for the success or failure of treatment. We concluded that the overall results of the in-patient phase of the trial strongly favoured amitriptyline, to which 81 per cent. of patients responded, rather than imipramine, to which only 54 per cent. responded. Dr. Domenet, however, believes that our conclusion is invalid, since chance, he thinks, unluckily resulted in a disproportionately large number of deluded patients entering the imipramine group; this, he alleges, "loaded the study against imipramine from the start unless one excludes the deluded patients."

I am sure that this was not so and that Dr. Domenet is mistaken in his assumption. In the first place, the results given in our second paper were obtained by combining the findings of two consecutive yet independent in-patient phases of the investigation. In 73 patients in the first phase, which we described in our first paper (*J. Ment. Sci.*, 1962, **108**, 711–730), the response rates were: amitriptyline 78 per cent., imipramine 58 per cent. In 64 patients in the second phase, the corresponding rates were: amitriptyline 84 per cent., imipramine 50 per cent. These results correspond quite closely. If chance, as Dr. Domenet believes, has been responsible for placing a disproportionately large number of deluded patients in the imipramine group, the similarity of these results would imply that the same disproportionate allocation of such patients to imipramine occurred by chance in each of the two quite separate in-patient phases of the trial, a rather unlikely occurrence. Further, in our monograph we provide evidence that the samples of patients in the two drug groups who, after stratification by age and severity of illness, were blindly and randomly allocated to one or other drug, did not differ significantly in socio-economic or psychiatric background. The two samples were similar in age. They were initially almost identical in total "pathology scores" on the Hamilton scale for depression (amitriptyline group, n=69, mean score 48·82; imipramine group, n=68, mean score 48·68) and they did not differ significantly in the initial severity of any of the 17 Hamilton scale symptoms, some of which in their most extreme form actually correspond to unequivocal delusions. In view of these considerations and the fact that, as page 822 of our second paper observes, our results are in line with those obtained by other investigators using imipramine in severely depressed patients, it is straining credulity to suppose that our two drug groups were biased initially in regard to the inclusion of deluded patients. All the evidence points to the contrary.

Secondly, there is a likelier explanation for the disproportionate numbers of patients noted to be deluded in the groups on amitriptyline and imipramine. When the study had been in progress for some months, two of our nursing sisters pointed out that

patients with overt delusions were responding poorly to drug treatment. Struck by this observation, Dr. Burt and Dr. Gordon, in collaboration with these nursing sisters, retrospectively assessed the presence of delusions in those patients who had completed the in-patient phase of the trial. None of the assessors knew which drug the patients had received; and the assessment referred to on page 817 of our second paper was made on the existence of delusions *during the period of hospitalization*, i.e. not at the initial interview. Throughout the remainder of the trial, deluded patients were identified according to the same criteria, i.e. the presence of delusions during their period of hospitalization. In view of the fact that four out of ten unequivocally deluded patients responded to amitriptyline versus none out of 17 to imipramine, and that the two groups of patients were so evenly matched on entry to the trial, it seems not unlikely that amitriptyline, a more powerful antidepressant, might have prevented the emergence of delusions in some patients, while imipramine allowed them to emerge or to persist unchecked. This seems more probable than that two large groups of patients nearly identical in every other initial respect actually contained unequal numbers of cases later noted to be deluded.

Incidentally, the figures Dr. Domenet gives in his table are incorrect. He has omitted four "dubiously" but nevertheless unequivocally deluded patients who received amitriptyline. The table he sets out should read:

	No ECT	ECT	Total
Imipramine	37	14	51
Amitriptyline	52	7	59
Total	89	21	110

χ^2 is 4·30, which is significant ($P < \cdot 05$).

It is clear therefore that even if the assumption mentioned in the preceding paragraph is disregarded, thus loading the study not against imipramine but against amitriptyline, and the analysis is confined to non-deluded depressives, amitriptyline still emerges as the more effective agent.

Finally, one is obliged to point out that though the investigation demonstrated that amitriptyline is a much more effective antidepressant than imipramine, particularly in women between 50 and 70 years of age hospitalized with severe endogenous depressive illnesses, the principal value of the study lies in drawing attention to the possibility of predicting outcome with amitriptyline from first-week treatment response and in showing that after six months the results of amitriptyline therapy are comparable with ECT (*Brit. J. Psychiat.*, 1964, **110**, 641–647). Such prediction, as our second paper notes, is much less feasible with imipramine, an older, less effective, more dangerous drug.

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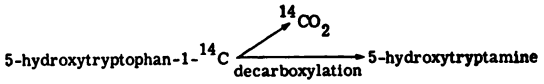
CHANGES IN 5-HYDROXYTRYPTOPHAN METABOLISM IN DEPRESSION

DEAR SIR,

As part of an investigation into trytophan metabolism in depressive illness we have developed a technique for measuring the rate of decarboxylation of 5-hydroxytryptophan (5-HTP). As far as we know the method has not been used before in man although a similar technique has been employed in the study of amine metabolism in animals (Hansson and Clark, 1962; Hansson, Fleming and Clark, 1964). The method, which is relatively simple and causes little discomfort to the patient, measures the expiratory rate of $^{14}CO_2$ following the injection of 5-HTP labelled with ^{14}C in the carboxyl group. This isotope is expensive and difficult to obtain, but we have now completed a small pilot study on 4 patients who were tested before and after recovery from a depressive illness. The results are sufficiently promising to warrant a preliminary report of our findings.



The pathway concerned is shown above. Ten ml. of a solution containing 20μc 5-HTP-1-^{14}C (1–2 mc/mM) was injected intravenously and the expired air was collected for 6 consecutive periods of 5 minutes. The subject was provided with a closely fitting face mask and the expired air was passed via an expiratory valve and two-way tap to a Douglas Bag. The two-way tap enabled the expired air to be diverted to the appropriate bag at the end of each five minute period. The CO_2 in 1 litre from each 5 minute sample of expired air was taken up in 20 ml. of a carbon dioxide absorbent and the volumes remaining in the Douglas Bags were determined with a spirometer. Activity from ^{14}C was estimated in a liquid scintillation counter.

The patients were in a basal condition before the test which was performed between 9 and 10 a.m. They had had no previous treatment before admission.