but also the fact that the opposite results previously reported have not been mentioned in their paper.

Is it possible for these authors to throw some light on the discrepancy between their findings and those of all other workers?

Yours faithfully,

J. HOENIG.


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DEAR SIR,

Dr. Hoenig asks us "to throw some light on the discrepancy between our findings (in a clinical trial of amitriptyline) and those of all other workers".

We have checked our results very carefully, and believe that we have excluded any technical or printing error.

The paper of Garry and Leonard described the use of amitriptyline in chronic depressive states, their patients having been ill for a mean period of 7·5 years. We feel that it would serve no purpose to compare their results with ours, as we were dealing with more acute cases.

With regard to the paper of Burt *et al.*, this was published after our paper had been accepted. We did at that time consider putting in an addendum to our paper, but finally decided to let it stand as it was. In comparing these two papers, it is clear that the results in cases of endogenous depression (affective psychosis) differ. Burt *et al.* found improvement in 18 out of 25 cases (72 per cent.) whilst in our series improvement resulted in only 9 out of 19 (45 per cent.). There are, no doubt, many possible causes for this discrepancy, for example, differences in diagnostic formulation or in assessing changes objectively. However, the most important, in our view, is that we compared amitriptyline with a placebo, whereas Burt *et al.* compared it with imipramine, on the basis that imipramine was well-tried and generally regarded as the most effective anti-depressant drug available at that time. We feel that there may well have been a considerable difference in the subjective attitudes of the workers in these two trials. Perhaps we experienced a greater anxiety for those patients with severe depression who were not showing a good response to treatment, because we knew that some of them might be having the placebo tablets. Burt *et al.* knew that every patient in their trial was receiving an anti-depressive drug, either amitriptyline or imipramine. It is possible that they felt more secure and could therefore allow a longer period of time to elapse before having to consider removing a patient from the trial.

Dr. Hoenig suggests that amitriptyline is of marginal value only in cases of reactive depression (psychogenic reaction), and because of the high rate of response in our cases, 13 improved out of 16 (81 per cent.), he questions whether we accidentally got our results switched around. We would point out, however, that Burt *et al.* found improvement in 11 out of 12 cases of reactive depression, that is 92 per cent. It is clear that their improvement rate in these cases was higher than ours. In our paper we mentioned that we gained the impression that amitriptyline had a tranquillizing effect in these patients, and suggested that a trial comparing it with chlorpromazine would appear worthwhile. Such a trial would indicate whether amitriptyline has a specific anti-depressant action or not in cases of reactive depression.

We wonder if Dr. Hoenig is correct when he states that the impressions and experience of *most* clinicians are contrary to our findings. In questioning our colleagues, we find that the majority consider amitriptyline to be one of the less useful drugs in the treatment of endogenous depressive states.

We do not believe that discrepancies in controlled trials are so uncommon. For example, compare the results of two trials on imipramine. Ball and Kiloh (1959) found it superior to a placebo, whilst Roulet *et al.* (1962) were unable to demonstrate any significant differences between the drug and placebo group. (We are aware that Roulet *et al.* were dealing mostly with depressive reactions, and had very few psychotic depressives in their trial.)

The whole subject of double-blind trials is complex, and requires a good deal of re-thinking. Cromie (1963) in his paper "The Feet of Clay of the Double-Blind Trial" considers some of the pitfalls that beset us.

Yours faithfully,

M. W. BROWNE.

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