magnetic resonance, so that subtle differences in outcome can be detected.

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Lithium, Imipramine and Hydroxytryptophan in Resistant Depression

SIR: Hale *et al* (*Journal*, August 1987, **151**, 213–217) reported "the unique efficacy of the triple combination of lithium, clomipramine, and tryptophan" in seven endogenous depressive patients resistant to several other forms of treatment. One of these patients had previously been treated with imipramine and lithium, and another with imipramine and tryptophan, but without success. I would like to report the case studies of two patients with major depression who did not respond satisfactorily to standard doses of imipramine plus hydroxytryptophan (OH-try), but readily and completely did so when lithium was added.

Case reports: (i) Mr G. L., a 48-year-old married man, was referred to our out-patient service for a 16-month depressive episode. His mother committed suicide during a depressive episode at the age of 39. The patient had a 23-year history of depressive recurrences, with a mean inter-episode interval of 3 years. In his previous episodes he had responded adequately to standard antidepressant treatments. During the present episode, however, he failed to respond to several antidepressants (amitriptyline, nortriptyline, mianserine, amineptine, nomifensine and tranylcypromine) at doses and for periods similar to those of previous episodes. When examined, he was a DST non-suppressor and his Hamilton score was 21. Imipramine (150 mg/day) plus OH-try (300 mg/day) was administered. During the following 6 weeks, a slight but unsatisfactory improvement was evident (Hamilton score = 16). Then, lithium carbonate (900 mg/day) (plasma level 0.41 mEq/l) was added. His mood substantially improved by the following week, with a Hamilton score drop to 5. He recovered completely and returned to his job during the following two weeks.

(ii) Mr D. D., aged 20, was referred to our out-patient service during his military service because of a severe depressive episode and manifest suicidal thoughts. He was a DST non-suppressor, and his Hamilton score was 31. He was administered imipramine (75 mg/day) for two weeks, which was then increased to 150 mg/day plus OH-try (400 mg/day) for the following four weeks. During this time his mood did not change substantially, and the Hamilton score decreased by no more than 20%. Lithium carbonate (900 mg/day) (plasma level 0.52 mEq/l) was added, and an improved mood was immediate. By the following week his Hamilton score had decreased by 80%, and he had a complete recovery during the subsequent two weeks.

These case studies suggest that: (a) the administration of lithium and OH-try is also synergistic with imipramine, and not only with clomipramine as Hale *et al* seem to suggest; (b) the addition of lithium to a tricyclic antidepressant and OH-try show that it is clinically efficacious in a period of time shorter than that of other drug treatments for drug-resistant depressives; (c) the clinical efficacy and rapidity of action of this combined treatment manifests itself even without administration of maximal doses of the tricyclic antidepressant. This might depend on the fact that tryptophan is hydroxylated and thus bypasses the limiting step of tryptophan hydroxylation and is readily metabolised to serotonin by neurons.

This combined treatment might be considered one of first choice in the management of drug-resistant major depressive patients. In fact, the canonical increase of the tricyclic antidepressant dose to the point that intolerable side-effects appear generally does not have clinical efficacy until two to three weeks pass. Moreover, this often may be impractical in elderly patients and those particularly sensitive to side-effects. Finally, it would seem to be good clinical practice to avoid the risks associated with the administration of high tricyclic doses unless such doses are an absolute necessity.

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Two-Stage Screening

SIR: We read with interest the paper by Sen *et al* (*Journal*, July 1987, **151**, 33–38) which described the success of the two-stage screening procedure for identifying psychiatric morbidity in primary health clinics in Calcutta (India) and Sao Paulo (Brazil).

We used this methodology in Kenya (Dhadphale *et al*, 1983). The SRQ was locally validated and a 7/8 cut-off point was used. Our Department of Psychiatry has now adopted this methodology as a standard procedure for screening psychiatric morbidity in various settings; for example a traditional healer's clinic, during a follow-up study of post-natal women, and in infertility studies. By July 1987, five major epidemiological studies were planned and successfully completed by our postgraduate psychiatric students for their dissertations for the Masters degree in psychiatry.

Although we are generally happy and satisfied with this two-stage methodology, some of the shortcomings of the procedure are: (a) we find only 11 questions of clinical significance; (b) psychotic questions (21 and 23) are too vague and equivocal, especially in our local cultural setting; and (c) inclusion of the brief MAST is important, as both the SRQ and CIS do not appear to be very sensitive instruments for picking up alcohol-related psychiatric disorders. Hence, we have appended the brief MAST to our research protocol.

In a paper based on our extensive experience in East Africa (in preparation), we have discussed these and other parts more critically. We have also translated our research instruments in Kiswahili and other languages.

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Khat-Induced Paranoid Psychosis

SIR: Gough & Cookson (*Journal*, February 1988, **152,** 294) mentioned that in our description of the patient F. K. with khat-induced paranoid psychosis (*Journal*, February 1987, **150,** 247–249), the urine test was not in keeping with the diagnosis, because it was positive for morphine and dihydrocodeine but not for amphetamines.

We were not able to explain the presence of morphine and dihydrocodeine in the sample, as we mentioned in the original description. We also stated that the urine sample in question was taken nine days post-admission, at which stage breakdown products of khat, which might have registered a postitive test for amphetamine-like substances (depending on the specificity of the actual test used) would no longer have been present in the urine. In this case the diagnosis was made on clinical grounds and was confirmed by the patient bringing in the khat that she had been using, which was then identified by the Regional Poisons Laboratory.

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Down's Syndrome with Mania

SIR: Singh (*Journal*, March 1988, **152,** 436–437) responded to our previous case report (*Journal*, February 1987, **150,** 249–250) of DSM–III-diagnosed mania in a young adult with Down's syndrome with several points which we believe require further discussion.

Firstly, our report did not claim that the case was severe enough to require seclusion. However, it is our understanding that 'seclusion' has never been one of the diagnostic criteria for mania. That notwithstanding, the reported case meets the criteria for mania. However, we would hasten to add that developmental considerations *per se* might modify the clinical presentation of mania, and particularly the necessity for seclusion or other means of physical restraint.

Secondly, our discussion of Prange's hypothesis was not meant to suggest a heightened association of Down's syndrome with mania in the absence of clinical data. To the contrary, the intention of that discussion was to highlight the current lack of support for an association, in either direction, between any mental disorder and any physical disorder on the basis of current knowledge of neurochemistry.

Most importantly, Dr Singh presented the literature pertaining to catecholamines by writing that "post-mortem studies of the brains of patients with Down's syndrome clearly show the cell loss in the noradrenergic system of locus coeruleus and dorsal motor vagus, not only in the middle-aged, but also in younger patients." Careful review of the cited references reveals that only two Down's syndrome patients below the age of 48 had been studied: Yates *et al* (1983) found a decrease in hypothalamic but not caudate norepinephrine in one 27-year-old Down's syndrome patient, and Mann *et al* (1985) found decreased cell count in the locus coeruleus but not dorsal motor vagus in the brain of a 31-year-old patient with Down's syndrome. Thus, these are limited studies which do not lend themselves to the broad conclusions suggested by Singh.

Indeed, the study of affective disorders in patients with Down's syndrome may clarify relationships