screening study and a cut-off point with high specificity in a study of unambiguous groups of normal, depressed, and Alzheimer patients.

M. G. BINKS

Department of Psychology and
Institute of Human Ageing
Liverpool University, P.O. Box 147
Liverpool L69 3BX

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Caffeine and Panic Attacks

SIR: It has not been clearly shown that caffeine alone can cause panic attacks in normal subjects. I report an adverse reaction which occurred during a normal volunteer study in which caffeine was compared against placebo and rolipram (a CNS phosphodiesterase inhibitor).

Case report: A 21-year-old healthy male volunteer with neither a history of panic attacks nor severe anxiety was given 500 mg of caffeine – equivalent to 5 – 8 cups of coffee – in the form of 1 gm of caffeine citrate in an orange drink. After approximately 20 minutes the subject started to feel an intense dread, which was quickly followed by the somatic symptoms of severe anxiety, including sweating, palpitations, and physical restlessness. He was unable to tolerate staying in the experimental room, and he had fears of impending death. Diazepam (15 mg) was given intravenously, which quelled both the physical and the cognitive changes, but did not remove them entirely. After around 1½ hours the anxiety symptoms returned and further diazepam was required.

This adverse reaction has implications both in theory and in clinical practice. Firstly, the interaction between the benzodiazepines and caffeine is not yet fully understood (File *et al*, 1982); Ghoneim *et al*, 1986). It is known that caffeine is an adenosine receptor antagonist at concentrations found in plasma (Daly *et al*, 1981) and not, as had previously been thought, a phosphodiesterase inhibitor. Diazepam interacts at the benzodiazepine receptor, yet this experiment shows that a benzodiazepine will attenuate the symptoms of anxiety induced by caffeine. This is shown by the return of the anxiety after around 1½ hours, when the diazepam is unbound from the receptor; the plasma half-life of caffeine is of the order of 3–6 hours (or longer) in healthy non-smoking men (Axelrod & Reichenthal, 1953). This would imply that the causation of anxiety might in some way be related to adenosine receptor antagonism. Secondly, it shows that large doses of caffeine can cause severe anxiety in normal people, and therefore an estimation of caffeine intake needs to be part of the assessment of panic attacks. Although this may seem a large dose of caffeine it is not uncommon, as Graham (1978) showed, for people in the general population to drink this quantity in a 24-hour period. Finally, this finding also emphasises the importance of caffeine in the generation of anxiety, which does not amount to panic, in the coffee-consuming general population.

M. W. D. ROWLANDS

Department of Psychological Medicine
St Bartholomew's Hospital
London EC1

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Hyponatraemia and Lofepramine

SIR: Hyponatraemia in psychiatric patients has been variously attributed to compulsive water drinking (Ferrier, 1985), to the primary psychiatric disorder (Singh *et al*, 1985), and to the syndrome of inappropriate secretion of anti-diuretic hormone (SIADH) induced by psychotropic drugs (Sandifer, 1983; Streeten *et al*, 1981). SIADH is a recognised complication of tricyclic antidepressants, and has been reported in association with amitriptyline and desipramine (Sandifer, 1983). We wish to report a case of hyponatraemia which was probably due to SIADH in association with lofepramine.

Case report: A 52-year-old married woman with a history of schizoaffective illness was admitted as an emergency into a medical ward with an acute onset of lethargy, anorexia, vomiting, severe weight loss, and confusion. There were no significant findings on physical examination, but she had repeated abnormal biochemical results. The initial report

was: Na^+ 110 mmol/litre, K^+ 3.3 mmol/litre, urea 1.9 mmol/litre, and creatinine 64 mmol/litre. Her urine sodium and osmolarity were not determined.

She had been off all neuroleptics for six months, but had been prescribed lofepramine (140 mg daily) four weeks before her presentation. The hyponatraemia persisted until her lofepramine was stopped, and within 36 hours it resolved. It is of interest that she had been on fluphenazine, haloperidol, trifluoperazine, iprindole, and amitriptyline in the past without any undue effect.

It is likely that her condition was precipitated by lofepramine. However, we were unable to confirm this conclusively, since it would have needed a challenge test to do so. However, we hope that this case will draw attention to the possibility of a drug-induced hyponatraemia in psychiatric patients.

DEREK O'SULLIVAN
FEMI OYEBODE

John Conolly Hospital
Birmingham B45 9BD

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Clomipramine and Flupenthixol – Additive Antidepressants?

SIR: The possibility that flupenthixol and tricyclics would have an additive antidepressant effect was first suggested by Reiter (1969), although the combination has never been specifically evaluated. This report shows the effect of manipulating flupenthixol dose when a stable tricyclic regime is being given concurrently.

Case report: A 31-year-old female with a severe, recurrent, unipolar, depressive psychosis met RDC criteria (Spitzer *et al*, 1977) for major depressive disorder, endogenous, psychotic, and retarded sub-types. She was non-delusional, but had suicidal and homicidal hallucinations. She was a DST non-suppressor, and had a Hamilton score of 38. In the first 25 months of her third episode, she was refractory to treatment with tricyclic antidepressants, lithium/tricyclic, tricyclic/antipsychotic, and lithium/tricyclic/antipsychotic combinations, carbamazepine and ECT. Marital therapy, cognitive-behaviour therapy, light-exposure and an exclusion diet were similarly ineffective.

At that time, her medication was changed to clomipramine (300 mg/day), L-tryptophan (1 g b.d.) and thioridazine (100 mg t.i.d.) but, despite four weeks on this regime, her mental state deteriorated and remained refractory to six further ECTs. Her hallucinations were prominent, she was sleeping only two or three hours a night, showed virtually no diurnal variation, and had become increasingly agitated. We decided to add flupenthixol to her regime, the depot form being chosen because of previous non-compliance: 20 mg was given initially and 40 mg three days later. Five days later she began to improve rapidly, with marked attenuation of hallucinations, sleep disturbance, and social withdrawal. Twenty-four hours later she was expressing optimism regarding the future, the first such emotion in over two years. Fortnightly injections were planned. Three days after her next injection she suddenly relapsed, but eight days later she improved. Two further cycles of eight days well and eight ill followed. We attempted to rationalise her medication by replacing thioridazine with flupenthixol, but, despite increasing flupenthixol, we were unable to reduce her thioridazine. Indeed, a pattern of decreased well-being on increased doses of flupenthixol developed, no symptomatic relief being obtained on 80 mg flupenthixol fortnightly.

At this stage further injections were withheld, in the expectation of clinical improvement. Nine days later (23 days after 80 mg flupenthixol had been administered) improvement began. The following day 20 mg was administered. Improvement continued until seven days later, when she claimed to be "as well as I have ever been". A regime of 20 mg fortnightly was adopted. On this regime, withdrawal of thioridazine and L-tryptophan and halving the dosage of clomipramine had no adverse effect on her mental state, and she remained free from affective symptomatology until her discharge six weeks later. Three weeks after discharge she began to deteriorate, hallucinations returning after a further three weeks and re-admission occurring one week later. She admitted not taking her clomipramine after discharge, although she had received flupenthixol injections as planned. Six days after reintroduction of clomipramine (150 mg/day) she began to improve.

Since the patient's medication regime was uncontrolled, it is not possible to draw firm conclusions about her response. However, improvement occurred only when flupenthixol and clomipramine were given in combination, and was maintained only with a dose of flupenthixol not normally considered antipsychotic. Indeed, beneficial effects were lost at higher doses. It is therefore unlikely that improvement was due to either agent alone. The close relationship between her mental state and manipulation of her medication make spontaneous fluctuation unlikely. Johnson & Malik (1975) describe mood elevation in the seven days following flupenthixol injection – our patient did not show this pattern.

It is likely that her response is unrelated to the antipsychotic effects of flupenthixol. It has been