increase the plasma clearance of antipyrine or phenylbutazone in women (Carter, Bressler, Hughes, Haussler, Christian & Heine, 1975). Previously, O'Malley, Stevenson & Crooks (1972) had shown an impairment of drug metabolising capacity in a large group of women taking mainly contraceptives containing 50 µg oestrogen. Thus, the present results suggest the absence of marked liver enzyme induction during administration of contraceptive pills containing 50 µg or less of oestrogen.

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SINGLE-DOSE EFFECTS OF TRANLYCYPROMINE ON PSYCHOPHYSIOLOGICAL MEASURES IN NORMALS

Despite the clinical and biochemical interest in the monoamine oxidase inhibitors (MAOIs), relatively little is known of their actions on the human CNS. Tranlycypromine produces a mild stimulation with marked amphetamine-like effects in patients after overdoses or in normal volunteers after single large doses (1.5 mg/kg) (Kinross-Wright, 1959). Its effects are believed to depend on MAO inhibition but more basic knowledge on this relationship is needed to clarify its mechanism of action.

We administered two single oral doses (10 and 20 mg) of the racemic drug and placebo at 2-week intervals to twelve normal volunteers, using a balanced cross-over design with double-blind procedures. On each experimental day, before, 1 and 3 h after drug ingestion, blood samples for platelet MAO and amine uptake activity were drawn (Gentil, Alevizos & Lader, 1978). At this time a battery of physiological and psychological measures was taken including computer-analysed electroencephalogram and electroencephalographic auditory responses, finger tremor, palmar sweating, pupil size, blood pressure, pulse rate, reaction time, tapping rate, digit symbol substitution test, symbol copying test, cancellation

task and a variety of subjective mood and bodily symptom ratings (Greenwood, Lader, Kantameneni & Curzon, 1975). The EEG was analysed both in terms of average rectified voltage in the four clinical wavebands and as power-spectra in computed wavebands.

MAO activity was significantly decreased by both doses of tranlycypromine, reaching a peak inhibition (about 70%) after 3 h, remaining at this level for at least 24 h, and returning to pre-treatment levels after 1 week. No significant *in vivo* inhibition of platelet uptake of amines was detected after the treatments.

In contrast to the potent MAO inhibition, tranlycypromine had small and sometimes inconsistent effects on the various tests. The resting EEG was affected differently by the two doses of the drug: both produced some initial increase in the power frequencies between 6.5 and 9 Hz at the first hour after treatment ($F=3.03$, 4.40 df, $P<0.05$), while only the 10 mg dose decreased these frequencies (Figure 1a) and the 9.5–12 Hz factor ($F=5.03$, 4.40 df, $P<0.005$, Figure 1b). This reduction agrees with previously reported decreases in alpha activity after tranlycypromine and other MAOIs (Fink, 1975), but

Figure 1 Effects of 10 mg (●) and 20 mg (△) tranylcypromine as compared with placebo (□) on two wavebands of the EEG power spectrum. (a) Factor 2 (6.5–9.0 Hz); (b) Factor 3 (9.5–12.0 Hz). The vertical line at time 0 represents the 0.05 critical difference; means further apart than this value are significantly different at the 0.05 level of confidence or beyond.

it is not clear why the larger dose was without sustained effect. On the other hand, only the 20 mg dose affected the power of fast frequencies (12.5–32 Hz), which was increased in 10 out of the 12 subjects.

Tranylcypromine seems therefore to have complex time- and dose- related actions on the EEG, with low concentrations producing initial increases in slow-wave activities (slight sedation) followed by decreases; higher concentrations affect more the faster frequencies whose power is increased. This effect has been described for amphetamine, LSD-25, and other stimulating drugs, and probably reflects increased arousal or alertness.

After an initial tendency to decrease, the lower dose of tranylcypromine significantly increased both power and dominant frequency of the finger tremor at the third hour. Increases in tremor power are found in acutely-provoked and chronic anxiety, and the apparent biphasic effects are consistent with an early sedative followed by a stimulant action of low concentrations of the drug. The higher dose, however, failed to significantly affect the tremor.

The only consistent behavioural effects of tranylcypromine were the significant decreases in the time taken to complete the attention (cancellation) task; the number of errors was also smaller after the two doses than after placebo. This suggests that both

Table 1. Within-treatment correlates of platelet MAO activity

		MAO Activity		
		Placebo	Tranylcypromine 10 mg	20 mg
Variables				
EEG: voltage: waveband	7.5–13.5 Hz	— (NS)	—	–0.67***
	13.5–26.0 Hz	—	—	–0.58**
EEG: power spectrum: waveband	6.5–9.0 Hz	—	—	–0.57**
	9.5–12.0 Hz	—	—	–0.52**
	12.5–32 Hz	—	—	–0.49*
Cancellation task			0.65***	0.59**
df=22	* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.			

doses improved attention and contradicts the evidence for an early sedative effect of the lower dose. Unfortunately subjective ratings were not systematically altered and do not help to resolve these discrepancies.

We attempted to correlate the biochemical and psychophysiological variables. Firstly we looked for within-treatment correlates of platelet MAO activity (Table 1). Decrease in MAO activity after 20 mg of the drug is associated with an increase in EEG voltage and power, and a shortening of performance time in the cancellation task. The biphasic effects of the lower dose on most CNS variables explains the solitary correlation here as platelet MAO was markedly and rapidly inhibited without any biphasic time-course.

To check for possible correlations between these two systems independently of the treatments we computed the between-subjects correlation for the pre-treatment values of the first experimental day, and for the mean values of the placebo occasion for each subject. Despite the small sample, several significant correlations were found: the highest correlations suggested that among these twelve subjects, those with highest platelet MAO activity tended to have the greatest amount of fast ($r=0.90$; 10 df; $P<0.001$) and medium frequency EEG activity ($r=0.74$; $P<0.01$), but lowest amounts of slower activity ($r=0.67$; $P<0.05$). This fits well with previous reports of correlations between CNS variables and human plasma or platelet amine oxidases (e.g. Vogel, Broverman, Klaiber & Kobayashi, 1975) and with previous suggestions that platelet MAO activity may be under the influence of some general factors such as levels of arousal or hormones (Gentil, McCurdy, Alevizos & Lader, 1976).

In conclusion tranlylcypromine effects after single therapeutic doses to normal volunteers are complex and minimal. It may be that higher doses will accentuate the trend towards stimulant effects. This would be consistent with animal experiments showing

that amphetamine-like effects of this drug occur at higher doses than those required for MAO inhibition.

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