Carlsson, A. (1966). *Handb. exp. Pharmak.*, **19**, 529–592.
Corrodi, H. & Jonsson, G. (1967). *J. Histochem. Cytochem.*, in the press.
Dahlström, A. & Fuxe K. (1964). *Acta physiol. scand.*, **62**, Suppl. 232, 1–55.
Dahlström, A., Fuxe, K. & Hillarp, N.-Å. (1965). *Acta pharmac. tox.*, **22**, 277–292.
Fuxe, K. (1965). *Z. Zellforsch.*, **65**, 573–596.
Fuxe, K. & Jonsson, G. (1967). *J. Histochem. Cytochem.*, in the press.
Fuxe, K. & Ungerstedt, U. (1966). *Life Sci.*, **5**, 1817–1824.
Fuxe, K. & Ungerstedt, U. (1967a). *Z. Zellforsch.*, in the press.
Fuxe, K. & Ungerstedt, U. (1967b). *Europ. J. Pharmac.*, in the press.
Hamberger, B., Malmfors, T. & Sachs, Ch. (1965). *J. Histochem. Cytochem.*, **13**, 147.
Hamberger, B. (1967). *Acta physiol. scand.*, in the press.
Hillarp, N.-Å., Fuxe, K. & Dahlström, A. (1966). In *Mechanisms of release of biogenic amines*, editors, Euler, U.S.von, Rosell, S. & Uvnäs, B., pp. 31–36. London: Pergamon Press.
Sai-Halasz, A., Brunnecker, G. & Szara, S. (1958). *Psychiat. Neurol.*, **135**, 238.

Fenfluramine and critical flicker frequency

SIR,—Fenfluramine hydrochloride (Ponderax) is a recently marketed appetite-suppressant agent which, although having chemical resemblances to amphetamine, does not appear clinically to produce central stimulation (Traherne, 1965; Munro, Seaton & Duncan, 1966). It has been claimed to possess sedative acitivity and has been used for this reason in patients with anxiety states (Raich, Richels & Raab, 1966).

Amphetamine, phenmetrazine and diethylpropion are appetite suppressant agents possessing central stimulant properties, and they have been shown to increase the critical flicker frequency in normal subjects (Smart & Turner, 1966; Turner, 1967). This method is a valuable test of central function which has been shown to be sensitive in assessing the action of several centrally-acting drugs when administered in modest therapeutic doses (Turner, 1967). In a double-blind experiment, identical tablets of fenfluramine 20 and 40 mg and a placebo were administered in random order in a latin square design and at intervals of not less than 3 days to 6 young adult subjects of either sex. The critical flicker frequency was measured before dosing and at 1½ and 3 hr thereafter by a technique (Turner, 1965a; Smart & Turner, 1966) which involved exposing the subjects in random order to intermittent light at 25 and 50 c/sec for 1 min before measuring the ascending and descending thresholds of critical flicker frequency.

The results were submitted to an analysis of dispersion (Rao, 1952) which is the multivariate analogue of the analysis of variance. This permits a more accurate evaluation than does an analysis of variance of the responses to drug and placebo over time.

No significant difference was demonstrated between the effects of fenfluramine 20 and 40 mg and placebo on mean critical flicker frequency at either 1½ or 3 hr. There was a significant difference between ascending and descending thresholds ($P < 0.001$), and between thresholds after adaptation to light at 25 and 50 c/sec ($P < 0.05$), but these were not influenced by either dose of drug or placebo. This is consistent with the stability of these factors which has been previously demonstrated (Turner, 1965b; Turner, Patterson & Smart, 1966).

These findings indicate that fenfluramine in therapeutic doses does not influence the critical flicker frequency, and this is in keeping with the clinical absence of central stimulation associated with its use.

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References

Munro, J. F., Seaton, D. A. & Duncan, L. J. P. (1966). *Br. med. J.*, **2**, 624–625.
Raich, W. A., Richels, K. & Raab, E. (1966). *Curr. Ther. Res.*, **8**, 31–33.
Rao, C. R. (1952). *Advanced Statistical Methods in Biometric Research.* London: Chapman & Hall.
Smart, J. V. & Turner, P. (1966). *Br. J. Pharmac. Chemother.*, **26**, 468–472.
Traherne, J. P. (1965). *Practitioner*, **195**, 677.
Turner, P. (1965a). *J. Pharm. Pharmac.*, **17**, 388–389.
Turner, P. (1965b). M.D. Thesis, University of London.
Turner, P. (1967). *Br. J. Ophthalmol.*, in the press.
Turner, P., Patterson, D. S. & Smart, J. V. (1966). *Nature, Lond.*, **209**, 813–814.

Isolation, aggressiveness and brain 5-hydroxytryptamine turnover

SIR,—Male albino mice submitted to prolonged isolation showed a smaller increase in brain 5-hydroxytryptamine (5-HT) compared with normal animals, when treated with monoamine oxidase inhibitors (Valzelli, 1966). The present report supplies additional quantitative evidence using the method of Tozer, Neff & Brodie (1966) to calculate the turnover of brain 5-HT.

Male Swiss albino mice, 20 ± 2 g, were isolated (1 animal/cage) or grouped (10 animals/cage) for 4 weeks under the conditions previously described (Consolo, Garattini & Valzelli, 1965). At the end of 4 weeks, isolated and grouped animals received an intraperitoneal injection of tranylcypromine (20 mg/kg). Animals were killed at various times after tranylcypromine injection and their brains analysed for 5-HT (Shore, 1959) and for 5-hydroxyindoleacetic acid (5-HIAA) (Giacalone & Valzelli, 1966).

It is evident that while the level of brain 5-HT is comparable in the two experimental conditions (Table 1), there is always a small but significant decrease of brain 5-HIAA in isolated compared with grouped mice.

The administration of tranylcypromine induces an increase of brain 5-HT and a decrease of brain 5-HIAA, which are respectively linear on a normal or on a logarithmic scale (see Fig. 1) in grouped or isolated animals. However the slope of the curves was different, which indicated an increase in the turn-

TABLE 1. LEVELS OF BRAIN 5-HT AND 5-HIAA IN ISOLATED AND GROUPED MICE

Experiment No.	Isolated mice		Grouped mice	
	5-HT	5-HIAA	5-HT	5-HIAA
1	0·65 ± 0·02	0·32 ± 0·01*	0·65 ± 0·03	0·41 ± 0·01
2	0·81 ± 0·03	0·42 ± 0·02**	0·80 ± 0·02	0·51 ± 0·01
3	0·75 ± 0·01	0·41 ± 0·01*	0·76 ± 0·01	0·49 ± 0·01
4	0·70 ± 0·02	0·34 ± 0·01**	0·71 ± 0·02	0·38 ± 0·01

* = $P < 0.01$.
** = $P < 0.05$.
Figures represent μg/g ± s.e.