J.L.W. is an MRC scholar. The transformation analysis was performed by Dr C.D. Frith.

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Stereochemical specificity in the antipsychotic effects of flupenthixol in man

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Deniker (1960) suggested that ability to induce extrapyramidal side-effects was related to the therapeutic action of chlorpromazine in schizophrenia. Drugs with antipsychotic effects exert actions on central dopaminergic mechanisms (Carlsson & Lundqvist, 1963; O'Keefe, Sharman & Vogt, 1970) and studies of the sensitive adenylate cyclase in the corpus striatum suggest that ability to block the dopamine receptor correlates well with the therapeutic effects of these drugs (Miller, Horn & Iversen, 1974). It has been demonstrated that the two isomers of the thiaxanthene flupenthixol differ widely in their ability to block the dopamine receptor (Miller *et al.*, 1974) although they resemble each other in several other pharmacological properties (Enna, Bennett, Burt, Creese & Snyder, 1976). We have investigated whether these two isomers differ in their therapeutic effects.

Forty-five patients with acute schizophrenic illnesses diagnosed according to Present State Examination criteria were randomly allocated to α-flupenthixol, β-flupenthixol and placebo in a dose of 6 mg for 6 days followed by 9 mg for 22 days. All patients received orphenadrine HCl (50 mg) three times a day, and where additional medication was urgently required chlorpromazine (100 mg). Mental state ratings were made before and at weekly intervals during the trial. All patients showed a decrease in total symptoms over the trial period. This decrease was significantly greater in the group of patients treated with α-flupenthixol, than in the groups treated with β-flupenthixol and placebo. The overall improvement on placebo was slightly greater than on β-flupenthixol.

These findings demonstrate that the therapeutic potency of flupenthixol is confined to the α-isomer and therefore on the basis of *in vitro* receptor studies (Miller *et al.*, 1974; Enna *et al.*, 1976) eliminate the possibilities that the antipsychotic effects are related to blockade of acetylcholine, noradrenaline, GABA, glycine or opiate receptors.

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