of the stereospecificity of the antipsychotic effect in man. Illnesses comparable with schizophrenia have not been identified in animals although some drug-induced models are available.

Enna *et al.* state that "α-flupenthixol and *cis*-thiothixene are much more potent clinically and in animals than their geometrical isomers β-flupenthixol and *trans*-thiothixene respectively. Similarly (+)-butaclamol is much more potent than its optical isomer (−)-butaclamol". These statements are supported by references which include data from animal behavioural experiments but no clinical findings. Therefore there seems to be a risk that the argument will be accepted that data obtained from an animal model of psychosis (for example amphetamine-induced abnormal behaviours) can provide definitive information concerning the nature of schizophrenia or its response to drugs. We suggest that such information can only be obtained from studies on patients with the disease, although this is difficult and time consuming.

If such studies can be designed to include not only a comparison of one isomer with another but of both with a placebo-treated group they can, however, in spite of the difficulties emphasised by Enna *et al.*, yield information beyond that relating to the *in vitro* receptor systems recently studied. If, for example, it can be shown that α-flupenthixol is clinically more active than the β-isomer and the latter is more active than placebo we may conclude on the basis of the data of Enna *et al.* not only that blockade of the dopamine, and possibly 5-HT, receptor may be relevant to the mechanism of action but that another action is also involved. If, on the other hand, the α-isomer is potent and the β-isomer is no more active than placebo, it seems safe to conclude that actions on those receptors on which the two isomers have been shown to be equally active (for example cholinergic, adrenergic and opiate receptors) are not relevant to the therapeutic effect.

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1 Enna, S. J., Bennett, J. P., Burt, D. R., Creese, I. & Snyder, S. H. *Nature* **263**, 338–341 (1976).

Enna *et al.* reply—Crow *et al.*[1] rightly pointed out the importance of clinical studies in establishing for certain whether drugs, such as isomers of neuroleptics, possess anti-schizophrenic activity. It is commonly assumed that neuroleptics act therapeutically in schizophrenic patients by blocking dopamine receptors so that the isomer which fails to act on dopamine receptors would be anticipated to lack clinical effectiveness. This is only a presumption, which must be directly examined in clinical studies. If supposedly inactive isomers have therapeutic effect, one might assume that they exert part of their action through a system which does not display stereospecificity.

Table 1 Neuroleptic stereoselectivity at α-noradrenergic receptor binding sites in rat brain

	Affinity for α-receptors	
	K_i (nM)	Relative stereoselectivity
(+)-Butaclamol	35	
(−)-Butaclamol	2,500	70-fold
cis-Thiothixene	6.6	
trans-Thiothixene	150	23-fold
α-Flupenthixol	10	
β-Flupenthixol	36	3.6-fold

α-Receptors in membranes from whole rat brain were labelled by binding of the potent α-antagonist ^{3}H-WB-4101 (2-([2′, 6′-dimethoxy] phenoxyethylamino) methyl benzodioxan) subtracting as blank values binding in the presence of 100 μM (-)-noradrenaline. Inhibition constants (K_i) were determined by measuring the effects of 3–4 concentrations of each drug in triplicate.

Matters Arising

Matters Arising is meant as a vehicle for comment and discussion about papers that appear in *Nature*. The originator of a Matters Arising contribution should initially send his manuscript to the author of the original paper and both parties should, wherever possible, agree on what is to be submitted. Neither contribution nor reply (if one is necessary) should be longer than 300 words and the briefest of replies, to the effect that a point is taken, should be considered.

The focus of our paper[2] was that some neuroleptics are stereospecific at 5-HT as well as dopamine receptors so that a stereospecific pharmacological action does not necessarily involve only dopamine synapses. Recently we have succeeded in identifying α-noradrenergic receptor binding in brain membranes using an agonist ^{3}H-clonidine or antagonist ^{3}H-WB-4101 (refs 3,4). Several neuroleptics have very high affinities for the α-noradrenergic receptor, often similar to their affinities for dopamine receptors[5]. But, the relative potencies of neuroleptics differ in competing for α receptors and dopamine receptors. Affinity for α receptors parallels closely pharmacological tests of α-noradrenergic blockade and tends to correlate with the ability of neuroleptics to elicit sedation and orthostatic hypotension[5]. We have now found that neuroleptics display marked stereoselectivity at α-adrenergic receptor sites. The extent of stereoselectivity for the butaclamol isomers is as great at α-noradrenergic receptors as at dopamine receptors (Table 1). The potency of *cis*-thiothixene at α-noradrenergic receptors is similar to its potency at dopamine receptors, though the 23-fold stereoselectivity is somewhat less than that at dopamine receptors. The extent of stereoselectivity of flupenthixol isomers at α receptors is substantially less than at dopamine receptors. As some clinical improvement in psychiatric patients, including schizophrenics, could be associated with 'tranquilizing' effects secondary to α receptor blockade, these receptors and their stereoselective interactions with neuroleptics represent yet another neurotransmitter system which should be taken into account in explaining neuroleptic pharmacology.

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1 Crow, T. J., Deakin, J. F. W. & Johnstone, E. C. *Nature* **267**, 183–184 (1977).
2 Enna, S. J., Bennett, J. P., Burt, D. R., Creese, I. & Snyder, S. H. *Nature* **263**, 338–341 (1976).
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4 U'Prichard, D. C., Greenberg, D. A. & Snyder, S. H. *Molec. Pharmac.* (in the press).
5 Peroutka, S. J., U'Prichard, D. C., Greenberg, D. A. & Snyder, S. H. *Neuropharmacology* (in the press).