mouth (colchicine, Houde Laboratories, Paris, France) the time-concentration curve was similar to those found by Wallace & Ertel (1973) after oral administration of a single [^{14}C]colchicine dose (Fig. 2). There was a peak 2 h after the drug had been taken (C_{max} of 6 ng ml^{-1}) and rapid distribution processes because the concentration decreased to <1 ng ml^{-1} by 8 h. The 24 and 48 h concentrations confirmed the prolonged excretion of colchicine and the existence of a long elimination half-time not found by Ertel et al (1976) who described a mean elimination half-time of 58 $\pm$ 20 min. Recently, Bourdon & Galliot (1976, 1979), with a fluorimetric technique and by the Sigma-Minus method, described a terminal half-time of 548 min for ten patients after an oral dose of 1 mg. Our findings agree with this observation and conflict with those of Jarvie et al (1979) who, using the pharmacokinetic data of Wallace & Ertel (1973), give a method for estimating the dose taken in cases of colchicine overdose.

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LETTERS TO THE EDITOR

Why does sulpiride not block the effect of dopamine on the dopamine-sensitive adenylate cyclase?

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Sulpiride is a clinically-effective antipsychotic agent (Mielke et al 1977) which both resembles and differs from classical neuroleptics of the phenothiazine, thioxanthine and butyrophenone types (Spano et al 1979; Jenner & Marsden 1979). One of the major differences between sulpiride and the classical neuroleptics is that the former does not block the effects of dopamine on the dopamine-sensitive adenylate cyclase (Trabucchi et al 1975). This has led to the suggestion that there are two types of dopamine receptor in the brain, a D1 receptor linked to adenylate cyclase and unaffected by sulpiride, and a D2 receptor blocked by sulpiride but not linked to an adenylate cyclase (Kebabian & Calne 1979). Domperidone is a peripheral dopamine antagonist that is similarly a very weak antagonist on the dopamine-sensitive adenylate cyclase (Laduron & Leysen 1979). Domperidone has been used in binding studies as a D2 antagonist (Watling et al 1979).

We suggest an alternative explanation for the lack of effect of sulpiride and domperidone on the dopamine-sensitive adenylate cyclase. It is postulated that for a compound to act as a dopamine antagonist on the adenylate cyclase, a high degree of membrane penetration must be achieved. Thus only those drugs with a sufficiently high oil/water partition coefficient will function as dopamine antagonists in this system. Both sulpiride and domperidone penetrate poorly into the brain following peripheral administration (Honda et al 1977; Woodruff & Andrews 1979; Laduron & Leysen 1979). We point out that the poor penetration of these compounds into the brain might be linked to their poor penetration into membranes in the adenylate cyclase assay. In fact a direct estimate of the lipid solubility of sulpiride has shown this to be very low compared with classical neuroleptics. Thus Norman et al (1979) reported log P (n-octanol–aqueous buffer partition coefficient) values of $-$ 0·5 for sulpiride and 4·25 for *cis*-flupenthixol. We do not envisage that high lipid solubility is the sole criterion for dopamine-blocking activity on the adenylate cyclase, since, for example, the (+)- and (−)-enantiomers of butaclamol have identical octanol–aqueous phase partition coefficients (Norman et al 1979), but differ greatly in their effects on the dopamine-sensitive adenylate cyclase. Rather we suggest that to block the effects of dopamine on the adenylate cyclase, a compound must be a dopamine receptor antagonist and have a sufficiently high degree of lipid solubility. In support of our hypothesis, the substituted benzamide *N*-(1-benzyl-3-pyrollidinyl)-5-chloro-2-methoxy-4-methylaminobenzamide (YM-08050) is chemically closely related to sulpiride, yet it is

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a potent dopamine antagonist on the dopamine-sensitive adenylate cyclase (Usuda et al 1979). YM-08050 has potent behavioural actions following peripheral administration (Usuda et al 1979), indicating that this compound does penetrate readily into the brain. Thus again there is a link between membrane penetration and blocking activity on the adenylate cyclase.

If our hypothesis is correct it might help clarify what, to us, is one of the anomalies of the D1 and D2 receptor hypothesis. That is that, apart from its lack of effect on the adenylate cyclase, sulpiride has a very similar spectrum of activity to that of the classical neuroleptics. Thus sulpiride, like classical neuroleptics, is a potent stimulant of prolactin secretion (Iwasaki et al 1976), is a potent antiemetic (Laville & Magarit, 1968) and is a potent antagonist of electrophysiological responses to dopamine (Woodruff & Andrews 1979; Pinnock et al 1979). Sulpiride, like other neuroleptics, is also very potent, when applied directly into the rat nucleus accumbens, in blocking the locomotor stimulation produced by dopamine receptor agonists (Woodruff & Andrews 1979).

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Some observations on the pharmacological activity of MIF (Pro-Leu-Gly-NH_2)

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We wish to report some observations on the pharmacological activity of MIF (Pro-Leu-Gly-NH_2) with particular reference to the recent communication of Bjorkman et al (1980) in which they reported the lack of activity of MIF against oxotremorine, fluphenazine and amphetamine-induced behaviour in rats and mice. In common with other workers, including Bjorkman et al, we have failed to confirm the original observations of Plotnikoff & Kastin (1974) that MIF would antagonize the effects of oxotremorine. Nor have we found any antagonism of tremor induced by harmaline (10 mg kg^{-1} i.p.). However, in contrast to Bjorkman et al, we have been able to confirm the observations of Voith (1977) that MIF will antagonize neuroleptic-induced catalepsy in mice. The timing of the MIF injections appear to be critical in this experimental situation.

A just supramaximal dose of haloperidol (10 mg kg^{-1} i.p.) was injected into groups of mice and the presence or absence of catalepsy was assessed 30 min later by placing the mice on a string-wrapped rod (see Zetler 1968; Doggett 1973). When animals were also given MIF (100 mg kg^{-1} s.c.) 10 min before, together with, or 10 min after the haloperidol, there was a 60–80% reduction in the number of animals exhibiting catalepsy in comparison with 0·9% NaCl-treated controls. If the MIF was injected outside this narrow time limit, then no antagonism of haloperidol was seen. 50 mg kg^{-1} s.c. MIF was not effective under similar conditions.

In conclusion, the failure of Bjorkman and his colleagues to find any antagonism of fluphenazine-induced catalepsy may be related to the time-effect course of MIF.

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