With regard to the first point, it is quite clear that the ambient ions in the stratosphere will be extensively hydrated (*3*). This follows readily from the use of known laboratory three-body association rate constants (*4*), which lead to hydration times of the order of 10^{-3} second for NO_3^- ions at an altitude of 20 km, for example. The hydration reactions will be so rapid in the stratosphere that one can almost assume a thermodynamic distribution of cluster ions. We estimate that less than 1 percent of NO_3^- ions would be unhydrated at 20 km, based on available thermodynamic data on the clustering of H_2O to NO_3^- (*5*). This is consistent with the observation (*6*) that the terminal NO_3^- ions are hydrated extensively at much higher altitudes (73 to 90 km), where both the total pressure and the water concentrations are much less, so that hydration would be much slower than in the stratosphere. Ruderman *et al.* noted the probability that the longer-lived ions would be hydrated, but assumed that rate coefficients would not be affected by the hydration. However, since the addition of the first water molecule to NO_3^- renders reaction 1 endothermic, it necessarily kills any reactivity (*2*). It is quite possible that hydration at early stages of the negative-ion reaction sequence will prevent formation of NO_3^-, but we do not need to evoke that prospect for the present purpose. It is also possible that as yet unrecognized chemical processes circumvent the production of NO_3^- as a terminal ion in the stratosphere; however this could only further diminish the role of reaction 1.

In regard to the second point, we have examined reaction 1 in our laboratory by using the NOAA (National Oceanic and Atmospheric Administration) flowing afterglow system, which has been extensively applied to atmospheric negative-ion reactions (*7*). We find $k_1 < 10^{-13}$ cm^3 $molecule^{-1}$ sec^{-1} to be a conservative upper limit for this rate constant at 300°K. This makes reaction 1 insufficient for the proposed O_3 removal, even if NO_3^- were a major stratospheric ion reactions (*7*). We find $k_1 < 10^{-13}$ man *et al.*, which required a value of k_1 at least as large as 10^{-12} cm^3 $molecule^{-1}$ sec^{-1} (*1*).

These considerations clearly eliminate the specific reaction mechanism proposed by Ruderman *et al.* (*1*).

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References and Notes

1. M. A. Ruderman, H. M. Foley, J. W. Chamberlain, *Science* **192**, 555 (1976).
2. Ruderman *et al.* give the exothermicity of reaction 1 as 0.8 ev. Recent precise measurements of the electron affinities of NO_2 [E. Herbst, T. A. Patterson, W. C. Lineberger, *J. Chem. Phys.* **61**, 1300 (1974)] and NO_3 (J. A. Davidson, F. C. Fehsenfeld, C. J. Howard, *Int. J. Chem. Kinet.*, in press) lead to the value 0.35 ev.
3. E. E. Ferguson, in *The Natural Stratosphere of 1974* (Report DOT-TST-75-51, National Technical Information Service, Springfield, Va., 1975), pp. 5–43.
4. J. D. Payzant, A. J. Cunningham, P. Kebarle, *Can. J. Chem.* **50**, 2230 (1972).
5. J. D. Payzant, R. Yamdagni, P. Kebarle, *ibid.* **49**, 3308 (1971).
6. R. S. Narcisi, A. D. Bailey, L. Della Lucca, L. Sherman, D. M. Thomas, *J. Atmos. Terr. Phys.* **30**, 1147 (1971).
7. F. C. Fehsenfeld and E. E. Ferguson, *J. Chem. Phys.* **64**, 1853 (1976); *ibid.* **61**, 3181 (1974).

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Dopamine Receptors and Average Clinical Doses

Creese *et al.* (*1*) have convincingly demonstrated that the relative affinities of an extensive series of butyrophenones, phenothiazines, thioxanthenes, and other dopamine antagonists in competing with [^{3}H]haloperidol binding to the dopamine receptor of calf striatal membranes predict their clinical potencies in psychiatric patients as well as pharmacological properties in animal behavioral tests. Their conclusions are based on a correlation coefficient of .87 relating the inhibition constant K_i, the concentration that produces 50 percent receptor occupation, for each drug, to "average clinical dose."

We would like to point out several problems with the two measures Creese *et al.* have correlated. The calculation of K_i by the formula given in their table 1 does not take into account the fact that most of the neuroleptics are highly absorbed, each having a different tissue solubility (*2*). The formula only holds if the unbound drug concentration is used; thus it is better to report only the experimental 50 percent inhibitory concentration (IC_{50}). The authors' sources for average clinical doses are general review articles [see (*1*)] and they used the averages of midpoint values of listed ranges of daily dose from these sources. Only 8 of the 22 drugs for which the average clinical daily dose is provided are in approved clinical use in the United States. Most of the rest have had limited general use abroad and limited, if any, clinical testing in the United States. Because of the frequently demonstrated enormous interindividual differences in the pharmacokinetics of antipsychotic drugs, it is difficult to make meaningful comparisons between drugs across groups unless the groups are very large. A small group of studies may produce conflicting and misleading results. Thus, there may be significant problems with the dosages for two of the drugs included in the study by Creese *et al.*

The sources consulted by Creese *et al.* indicated that clozapine is clinically half as potent as chlorpromazine (*1*) and that the average clinical dose of chlorpromazine is 12 μmole kg^{-1} day^{-1} (260 mg/day for a 70-kg human), a figure I believe most clinicians would agree is too low. For example, Klein and Davis (*3*) indicate that the average daily dose of chlorpromazine is 692 mg. I checked three clinical studies of clozapine which permit an assessment of the average daily dose; comparing this with an average dose of chlorpromazine of 260 mg/day, the estimated potency of clozapine is 0.6 to 1.25 times the potency of chlorpromazine (*4*). If 692 mg/day is taken as the average dose of chlorpromazine, clozapine is 2.3 to 4.2 times as potent as chlorpromazine. The available data for (+)-butaclamol are also suspect since in most of the limited clinical trials of this drug mixtures of the inactive stereoisomer with the active compound have been used (*5*). The average clinical dose utilized by Creese *et al.* for (+)-butaclamol is markedly greater than that consistent with the regression equation derived from their data. Despite the problems with clozapine and (+)-butaclamol, the Spearman rank-order correlation coefficients for the 8 drugs in general use and the 14 other drugs are virtually identical: .863 and .837, respectively. Thus it is reasonable to conclude that the average clinical dose for at least 12 of the 14 less used drugs are in correct relationship to each other.

The work of Creese *et al.* as well as of others (*6*) strongly supports the role of dopamine blockade in the antipsychotic action of the majority of neuroleptic drugs. However, their work leaves unsettled the mechanism of action of clozapine, which is a weak receptor blocker in their in vitro system (in the 100 n*M* range) and a weak dopamine receptor blocker in vivo (*7*). On the other hand, Seeman *et al.* (*8*) found that clozapine can block haloperidol binding in the range 10 to 20 n*M*. Other evidence points to an effect of clozapine as an inhibitor of dopamine release (*9*).

Finally, I would like to question the desirability of using the method of

Creese *et al.* for screening new phenothiazines, butyrophenones, or thioxanthenes. Measurement of the effect of drugs of these classes on serum prolactin levels in the rat also serves to identify dopamine receptor blockers and is much simpler (*10*). Of greater importance is the fact that there are many drugs of these classes already in clinical use. New drugs of the same type usually differ only quantitatively in potency, sedative effects, and extrapyramidal side effects but do not increase the proportion of patients who will respond, the extent of improvement, or the rapidity of response. Vast numbers of schizophrenics are chronically impaired despite neuroleptic treatment. The real need is to develop entirely different chemical approaches to the prophylaxis and treatment of schizophrenia.

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References and Notes

1. I. Creese, D. R. Burt, S. H. Snyder, *Science* **192**, 481 (1976).
2. P. Seeman, A. Staiman, M. Chau-Wong, *J. Pharmacol. Exp. Ther.* **190**, 123 (1974).
3. D. F. Klein and J. F. Davis, in *Diagnosis and Treatment of Psychiatric Disorders* (Williams & Wilkins, Baltimore, 1969), p. 61.
4. M. Ackenheil, H. Beckmann, W. Greil, G. Hoffmann, E. Markianos, J. Raese, in *The Phenothiazines and Structurally Related Drugs*, I. Forrest, C. J. Carr, E. Usdin, Eds. (Raven, New York, 1974), p. 647; I. Gerlach, P. Koppelhus, E. Helweg, A. Monrad, *Acta Psychiatr. Scand.* **50**, 410 (1974); G. Chouinard and L. Annable, *J. Clin. Pharmacol.* **16**, 289 (1976).
5. D. H. Mielke, D. M. Gallant, T. Oelsner, C. M. Kessler, W. K. Tomlinson, G. H. Cohen, *Dis. Nerv. Syst.* **36**, 7 (1975); L. E. Hollister, K. L. Davis, P. A. Berger, *Psychopharmacol. Commun.* **1**, 492 (1975).
6. P. Seeman, M. Wong, T. Lee, *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **33**, 246 (1974); P. Seeman, *J. Pharmacol.* **5** (Suppl. 2), 91 (1974).
7. G. Bartholini, H. H. Keller, A. Pletscher, *J. Pharm. Pharmacol.* **27**, 439 (1975).
8. P. Seeman, T. Lee, M. Chau-Wong, K. Wong, *Nature (London)* **261**, 717 (1976).
9. H. Y. Meltzer and V. S. Fang, *Life Sci.* **17**, 229 (1975); J. Hyttel, *Acta Pharmacol. Toxicol.* **38** (No. 4), 358 (1976).
10. J. A. Clemens, E. B. Smalstig, B. D. Sawyer, *Psychopharmacologia* **40**, 123 (1974). H. Y. Meltzer, S. M. Paul, and V. S. Fang (*Eur. J. Pharmacol.*, in press) have demonstrated a high correlation for (+)- and (−)-butaclamol, *cis*- and *trans*-flupenthixol, and chlorpromazine metabolites between effects on dopamine-dependent behavior and serum prolactin levels.
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We agree with Meltzer that determining the "mean" effective clinical dose of an antischizophrenic drug is a difficult process, since dosage requirements vary tremendously from patient to patient. Using the clinical doses for chlorpromazine, clozapine, and (+)-butaclamol suggested by Meltzer, we have recalculated the correlation between affinity for dopamine receptors and clinical potency (Fig. 1) and found the same high correlation coefficient (r = .87) observed previously with different doses for these three drugs (*1*). Employing the IC_{50} value (concentration that inhibits receptor binding by 50 percent) rather than the apparent K_i (inhibition constant, indicating 50 percent receptor occupation), as recommended by Meltzer, does not influence correlations between the drugs' affinities for the receptor and clinical efficacy, since the K_i is obtained from the IC_{50} value by multiplying IC_{50} for each drug by the constant factor 0.5 in these experiments.

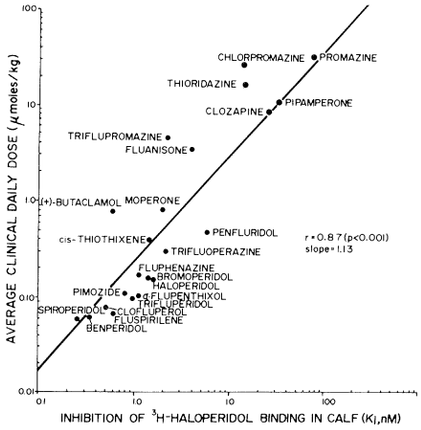

Fig. 1. Antischizophrenic drugs: correlation between affinity for [³H]haloperidol binding and clinical potency.

Because of the imprecision in establishing clinical doses, we examined the relationship of neuroleptic affinity for the dopamine receptor and pharmacological activity in several animal behaviors that depend on dopamine receptor blockade (*1*). We observed close correlations with blockade of [³H]haloperidol binding and neuroleptic inhibition of apomorphine-induced stereotyped behavior in rats (r = .94), prevention of apomorphine-induced vomiting in dogs (r = .93), and inhibition of amphetamine-induced stereotyped behavior in rats (r = .92).

Meltzer suggests that screening effects of neuroleptic drugs on serum prolactin levels may be simpler and more meaningful than measuring their affinity for the dopamine receptor. Such prolactin studies require several groups of animals and multiple doses, thus consuming many rats and much drug. Moreover, drugs can influence blood prolactin levels by many mechanisms other than blockade of dopamine receptors. By contrast, a few micrograms of a drug and a few milligrams of brain tissue suffice for dopamine receptor assays; up to 100 drugs can be screened in a morning, providing precise molar affinities of each drug for the dopamine receptor.

However, binding studies of the dopamine receptor (*1, 2*) were not undertaken only to develop a cheap method for screening new drugs. Earlier evidence that antischizophrenic neuroleptic phenothiazines and butyrophenones block dopamine receptors derived largely from studies with intact animals, in which drug effects on other systems may only indirectly alter dopamine activity. Studies of an adenylate cyclase that is stimulated selectively by dopamine (*3*) provided a biochemical means of screening neuroleptic drugs in vitro. Although phenothiazine potencies based on the dopamine-sensitive adenylate cyclase correlate with in vivo pharmacological data, the correlation is quite poor for butyrophenones; some workers even suggested that butyrophenones do not act by dopamine receptor blockade (*4*). Direct labeling of the dopamine receptor with [³H]haloperidol has provided impressive predictions of the clinical and pharmacological activities of both butyrophenones and phenothiazines, affording a novel unequivocal demonstration that pharmacological actions of these drugs are mediated at synaptic receptors for dopamine. Dopamine is an important neurotransmitter in the brain, whose activity has been implicated in numerous diseases including Parkinson's disease and schizophrenia. We feel that biochemical characterization of the dopamine receptor will find its greatest contribution in elucidating molecular mechanisms that regulate synaptic transmission in normal and diseased states.

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References

1. I. Creese, D. R. Burt, S. H. Snyder, *Science* **192**, 481 (1976).
2. ———, *Life Sci.* **17**, 993 (1975); *ibid.*, p. 1715; P. Seeman, M. Chau-Wong, J. Tedesco, K. Wong, *Proc. Natl. Acad. Sci. U.S.A.* **72**, 4376 (1975); D. R. Burt, S. J. Enna, I. Creese, S. H. Snyder, *ibid.*, p. 4655; S. H. Snyder, I. Creese, D. R. Burt, *Psychopharmacol. Commun.* **1**, 663 (1975); S. H. Snyder, D. R. Burt, I. Creese, *Neurosci. Symp.* **1**, 28 (1976); S. H. Snyder, I. Creese, D. R. Burt, in *Neurotransmitters and Hypotheses of Psychiatric Disorders*, E. Usdin, J. Barchas, D. Hamburg, Eds. (Oxford Univ. Press, New York, in press); D. R. Burt, I. Creese, S. H. Snyder, *Mol. Pharmacol.* **12**, 631 (1976); *ibid.*, in press; P. Seeman, T. Lee, M. Chau-Wong, K. Wong, *Nature (London)* **261**, 717 (1976).
3. J. W. Kebabian, G. L. Petzold, P. Greengard, *Proc. Natl. Acad. Sci. U.S.A.* **72**, 4376 (1975); Y. C. Clement-Cormier, J. W. Kebabian, G. L. Petzold, P. Greengard, *ibid.* **71**, 1113 (19 → M. Karobath and H. Leitich, *ibid.*, p. 2915; R. J. Miller, A. S. Horn, L. L. Iversen, *Mol. Pharmacol.* **10**, 759 (1974).
4. P. Seeman and T. Lee, *Science* **188**, 1217 (1975).

13 August 1976