British Journal of Psychiatry (1994), **164** (suppl. 23), 65–70

II. The Treatment of Schizophrenia

Neuroleptic Treatment of Patients with Schizophrenia
Mechanisms of Action and Clinical Significance

FRITS-AXEL WIESEL

Neuroleptic drugs have been used in the treatment of schizophrenic patients for 40 years. In the 1960s it was proposed that the mechanism of action was a blockade of dopamine receptors; *in vivo* studies give strong evidence that a blockade of D_2 dopamine receptors mediate the antipsychotic effect of classic neuroleptics. However, the antipsychotic effect of neuroleptics is synergistic with family treatment and social-skills training.

Antipsychotic drugs constitute a diverse group of chemical compounds, but the reason for grouping them together is their clinical characteristic of reducing psychotic symptoms. The term 'neuroleptic' was introduced by Delay & Deniker (1957) to characterise compounds which (a) had an antipsychotic effect not due to sedation, (b) reduced psychomotor activity, and (c) induced extrapyramidal symptoms like Parkinsonism or catalepsy. These compounds are effective in the treatment of both toxic and functional psychoses, which demonstrates that they are suitable for all types of psychosis, so that the use of the term 'antischizophrenic drugs' is inappropriate. The schizophrenics are the major patient group treated with neuroleptics. Neuroleptic treatment does not cure the disease, but the course of the illness has become more favourable since the introduction of neuroleptics (Wyatt, 1991). Drug treatment also lends itself to combination with other types of psychiatric treatment (Hogarty *et al*, 1974; Goldstein *et al*, 1978; Falloon *et al*, 1985; Leff *et al*, 1985). The clinical efficacy of antipsychotics is well documented and in acute treatment about 60–70% of patients are described as much improved (Davis *et al*, 1980), but those with a long prodromal phase or duration of psychosis are less sensitive to antipsychotics, and their poorer prognosis may be related to a long delay before the start of treatment (Wyatt, 1991). In general, antipsychotics are considered to be more efficient in the treatment of positive symptoms or increase in psychic functions (prominent thought disturbances, hallucinations, delusions, delusional mood, feeling of being controlled, ideas of persecution), but less efficient with negative symptoms or decrease in psychic functions (poverty and slowness in thinking, affective flattening, anhedonia, avolition, apathy) (Andreasen, 1985).

Patients with brain abnormalities, as shown in computerised tomographic images, benefit less from neuroleptic treatment, but this is probably not related to a higher frequency of negative symptoms in this category of patients (Gattaz *et al*, 1990).

Generally, the choice of a neuroleptic drug for a particular patient is related to its profile of side-effects. There is some evidence that selective D_2 dopamine antagonists are more effective in helping patients with autistic and negative symptoms and that they will produce lesser side-effects than conventional neuroleptics (Härnryd *et al*, 1984*a*). However, a subgroup of chronic schizophrenic patients exists in whom positive psychotic symptoms remain, despite treatment with high doses of neuroleptics; clozapine has been shown to be of special value in these severely ill patients (Kane *et al*, 1988).

It has been proposed that neuroleptics may cause negative or dysmentia-like symptoms (Wilson *et al*, 1983), and some of these reported problems are partly related to treatment with excessively high doses. However, when the neuroleptics were introduced, the way that previously retarded, apathetic, and socially withdrawn patients became activated was astonishing to experienced clinicians. The limitations of therapeutic results should be recognised, but it is also essential to differentiate between side-effects of neuroleptics and symptoms of the disease.

Biochemical and receptor mechanisms

Since the discovery that reserpine, an antipsychotic drug, reduced the levels of the monoamines in the central nervous system, their role in the mechanism of action of antipsychotics has been extensively studied. Dopamine was first thought to play only a precursor role in norepinephrine synthesis, but since the distribution of norepinephrine and dopamine differed, it was suggested that dopamine may also have an independent function in the brain (Carlsson *et al*, 1958). In a pioneering study, Carlsson & Lindqvist (1963) suggested that antipsychotic drugs like chlorpromazine and haloperidol block post-synaptic catecholamine receptors and thereby induce a compensatory activation of the pre-synaptic neuron. It had not been possible for them to

differentiate between changes in norepinephrine and in dopamine metabolism, but it was found later that neuroleptics preferentially increase dopamine metabolism (Andén *et al*, 1964; Nybäck & Sedvall, 1968). Electrophysiological studies demonstrated that antipsychotic drugs increase the impulse activity of dopamine neurons, probably by blocking central dopamine receptors (Bunney *et al*, 1973), and biochemical studies showed that dopamine stimulated adenylate cyclase in the brain to form cyclic adenosine monophosphate, which may propagate dopaminergic transmission within the post-synaptic neuron (Kebabian *et al*, 1972). Different classes of antipsychotics were shown to block the stimulatory effect of dopamine on adenylate cyclase, which was thought to be related to the D_1 dopamine receptor (Karobath & Leitich, 1974). However, the *in vitro* actions of the butyrophenones on adenylate cyclase were unexpectedly weak, in comparison with their *in vivo* increase of dopamine turnover. In 1975, binding sites for the butyrophenones were identified in the striatum (Creese *et al*, 1975; Seeman *et al*, 1975). Kebabian & Calne (1979) called these sites 'D_2 receptors', in contrast to the D_1 receptors linked with adenylate cyclase. Most interesting was the observation that the relative affinities of the neuroleptics to the D_2 receptor, but not to other types, were correlated with their clinical potency in the treatment of schizophrenic patients (Peroutka & Snyder, 1980). These findings are of great interest in understanding the pharmacological mechanisms of action of antipsychotics, but their relevance to treatment remained unclear.

Another line of research has been the study of the major monoamine metabolites in the brain, since they have been shown to reflect the functional activity of the monoamine neurons (Roth *et al*, 1976). Neuroleptics, both typical and atypical, have been demonstrated to increase brain levels of the major dopamine metabolite, homovanillic acid (HVA), in experimental animals (Wiesel & Sedvall, 1975). In man, it has not been possible to measure HVA in the brain, but the determination of HVA levels in the cerebrospinal fluid (CSF) was considered to be a possible way to obtain an indirect measure of brain dopamine activity. In fact, the HVA content in human lumbar CSF has been shown to be derived almost exclusively from the brain, and may reflect central dopamine turnover (Wik & Wiesel, 1991). Patients treated with neuroleptics have been found to increase their HVA levels in CSF (Sedvall *et al*, 1975). Both typical and atypical neuroleptics increase the CSF levels of HVA, supporting the notion of a common action of neuroleptics on dopaminergic systems in the human brain (Härnryd *et al*, 1984*b*). In contrast, antidepressants and lithium do not increase HVA levels in CSF (Sedvall *et al*, 1975).

Both the experimental and clinical findings give strong support for the hypothesis of a blockade of dopamine receptors as the major mechanism of action of neuroleptics. However, some antipsychotic drugs also increase central norepinephrine metabolism and block norepinephrine-sensitive adenylate cyclase (Nybäck & Sedvall, 1968; Blumberg *et al*, 1975). The serotonin system may also be of relevance for the mechanism of action of antipsychotic drugs; several studies have demonstrated a functional relationship between dopamine and serotonin neurons and lesions of the serotonin neurons result in a reduced cataleptogenic effect of some neuroleptics (Costall *et al*, 1975). The possible involvement of the serotonin system has also been the basis for the development of serotonin antagonists in the treatment of schizophrenia. However, blockade of D_2 dopamine receptors seems to be the common mechanism of action of antipsychotics. Effects on other receptor types like muscarinic cholinergic, α-adrenergic, serotonin-2 and histamine-1 receptors do not correlate with the average clinical antipsychotic potency of neuroleptic compounds as blockade of D_2 dopamine receptors does (Peroutka & Snyder, 1980).

Clinical considerations

Clinical treatment studies give strong support to the importance of dopamine receptor blockade in the alleviation of psychotic symptoms. In a critical study by Johnstone *et al* (1978), two isomeric forms of flupenthixol were compared with placebo in the treatment of acute schizophrenia. The α-isomer, which blocks dopamine receptors, reduced psychotic symptoms significantly in comparison with both placebo and the β-isomer, which does not block these receptors. The effects of the β-isomer were similar to those of placebo. The importance of the dopaminergic system is further supported by the finding that α-methyltyrosine strengthens the antipsychotic action of subthreshold doses of neuroleptics (Wåhlinder *et al*, 1976). Alpha-methyltyrosine acts as an inhibitor of tyrosine hydroxylase, and decreases the feedback activation of dopamine neurons following dopamine receptor blockade, therefore strengthening the neuroleptic blockade of dopamine receptors (Carlsson, 1974). These findings support the view that the blockade, rather than the increased dopamine turnover which follows, is crucial for the clinical effect of neuroleptic treatment. Other clinical data that also indirectly support the importance of dopamine blockade for the reduction of psychotic symptoms include the successful treatment of

psychotic amphetamine abusers with neuroleptics. Schizophrenic patients whose psychotic symptoms have deteriorated after L-dopa or amphetamine treatment are also improved by neuroleptic administration (Gerlach & Luhdorf, 1975; Angrist *et al*, 1980).

Neuroleptic treatment increases dopamine turnover in man, as measured by HVA levels in CSF, and if this effect were relevant for the antipsychotic effect, one might expect a correlation between HVA levels and clinical symptoms. Correlations were indeed found between increased HVA levels and reduction in psychotic symptoms (Sedvall *et al*, 1975; Praag, 1977; Alfredsson *et al*, 1984). However, the correlations were fairly weak and not consistent enough to give more than some support to the view that neuroleptics induce antipsychotic effects in schizophrenic patients in a graded fashion, proportional to the degree of interaction with central dopaminergic mechanisms.

PET studies

The relevance of the *in vitro* correlation between affinities of neuroleptics to the D_2 receptor and clinical average dosages is uncertain, since *in vivo* human brain conditions may give a different result. Positron emission tomography (PET) makes it possible to study the human brain *in vivo* and thereby to identify receptors *in vivo* (Sedvall *et al*, 1986); in studies of D_2 dopamine receptors, the highly selective D_2 dopamine antagonist raclopride, a substituted benzamide, has been used. Raclopride is labelled with ^{11}C, which is a positron-emitting isotope with a half-life of 20 minutes. The radiolabelled ligand is administered as a bolus intravenously, and the accumulation of radioactivity is measured by the positron camera in sections of the brain. In normals and untreated patients, the accumulation of radioactivity in the putamen and caudate is pronounced. In neuroleptic-treated patients, however, the radiolabelled tracer will not accumulate in the caudate and putamen, since the D_2 dopamine binding sites are occupied or blocked by the drug. In our studies, the patients had all been under treatment with conventional doses of an antipsychotic compound for at least one month and had responded well to the treatment. D_2 dopamine receptor occupancy in the basal ganglia was determined by comparing the accumulation of radioactivity in a group of patients without drug treatment and a group of treated patients (Farde *et al*, 1988, 1992). Receptor occupancy was determined in the PET experiment six hours after the morning (last) dose, or in the case of depot neuroleptics, one week after the last injection. With a similar methodology but with another ligand, ^{11}C-labelled SCH-23390, a D_1 dopamine antagonist, D_1 dopamine receptor occupancy was also determined in some patients (Farde *et al*, 1992).

D_2-receptor occupancy

Patients treated with chemically distinct antipsychotic drugs were found to have similar receptor occupancy levels in the brain (Farde *et al*, 1992). In patients treated with conventional neuroleptics ($n = 20$), receptor occupancy levels were in the range 70–89%; haloperidol in moderate doses (4–12 mg), with serum concentrations $\geqslant 9$ ng/ml, resulted in occupancy values which were above 80%; these patients had a high frequency of extrapyramidal side-effects. Sulpiride (400 mg × 2) and remoxipride (200 mg × 2) gave occupancy values of 78% and 71% respectively. The atypical antipsychotic compound clozapine (300–600 mg) ($n = 5$) was found to cause lower occupancy values, 38–63%.

D_1-receptor occupancy

In a limited number of patients ($n = 12$), the receptor occupancy of D_1 dopamine receptors was determined (Farde *et al*, 1992), and it seemed that the chemical structure of the neuroleptic compound determined to what degree the receptors were occupied. Perphenazine and sulpiride did not seem to interact with D_1 receptors. Thioridazine (30%) and flupenthixol (44%) seemed to interact with D_1 receptors, but to a much lower degree than with D_2 receptors. Clozapine showed the highest degree of D_1 receptor occupancy – 36–52%; this drug seemed to differ from the other compounds by having a similar receptor occupancy for both D_1 and D_2 receptors. The fact that clozapine in clinically effective doses had a low D_2 receptor occupancy may explain why this compound does not produce extrapyramidal side-effects. It may be speculated that a similar receptor occupancy of the D_1 and D_2 dopamine receptors is synergistic, and therefore will result in a full antidopaminergic effect, in analogy with the finding that a full behavioural dopaminergic response requires the activation of both D_1 and D_2 dopamine receptors (Longoni *et al*, 1987).

With the aid of molecular genetics, several new subtypes of dopamine receptors have been identified: the D_3 (Sokoloff *et al*, 1990), D_4 (Tol *et al*, 1991), and D_5 receptor (Sunahara *et al*, 1991). However, the significance of these for the therapeutic effect of antipsychotic compounds is not yet known. The D_4 dopamine receptor may be of special interest, since clozapine has about a tenfold affinity for that subtype than for the other receptors. Recently, genetic polymorphism has been demonstrated for the

D_4 dopamine receptor (Tol *et al*, 1992). The D_4 receptor variants showed different properties to antagonists, and these might underlie individual responses to antipsychotic treatment.

Clinical significance

The available PET results strongly support the view that a blockade of D_2 dopamine receptors mediates the antipsychotic effect. Therefore, they also suggest that monotherapy with neuroleptic compounds should be recommended: a more pronounced antipsychotic effect should not be expected from combining several of them. The main reason to combine neuroleptics is to obtain sedation of the patient in the acute phase, but in many cases this could probably be obtained by the use of benzodiazepines.

Much research has attempted to define a linear relationship between plasma drug concentrations and clinical effects. However, the results have not been able to demonstrate such a relationship convincingly; instead, concentration intervals have been defined (i.e. in most patients who have improved, concentrations are within a defined interval) (Dahl, 1986; Baldessarini *et al*, 1988). With PET, it has been possible to study the relationship between dose, drug concentrations, and receptor occupancy: the results demonstrated a hyperbolic relationship (Farde *et al*, 1988, 1992). In clinical treatment, the receptor occupancy values were in the range 70–89%, which means that the patients are approaching the flat part of the curve. From a clinical point of view, the implication is that a wide range of doses and concentrations will give receptor occupancy values of that order. Determination of plasma drug concentrations will therefore be of limited value, but will have some value in determining compliance and, in special cases (e.g. poor metabolisers), in individualising the treatment.

A relatively large group of patients with schizophrenia do not respond satisfactorily to drug treatment, and there has been much discussion as to whether this may be due to pharmacokinetic or pharmacodynamic reasons. Patients on neuroleptic treatment who have responded poorly have been investigated with PET: receptor occupancy of these patients was found to be similar to that of patients who were responding well (Wolkin *et al*, 1989). Previous studies have excluded pharmacokinetic reasons for resistance to treatment, and a low receptor blockade of D_2 dopamine receptors can now also be excluded. These patients may be helped, however, by compounds interacting with other receptor types; clozapine has been shown to be superior to other compounds in helping 'therapy-resistant' patients (Kane *et al*, 1988). It has been proposed that the mechanism of action of this effect is a blockade of serotonin-2 receptors, or of α-receptors, or interaction with glutamatergic mechanisms (Carlsson & Carlsson, 1990). However, it may also be due to a moderate but similar blockade of both D_1 and D_2 dopamine receptors (*vide supra*). The importance of the D_4 dopamine receptor for the clozapine effect is of course of great interest in this connection.

A pronounced blockade of the D_2 dopamine receptors occurs after the first dose of a neuroleptic (Nordström *et al*, 1992), but the period of time required for the development of the antipsychotic effect seems to range between a few hours and several months. Evaluation of how quickly the antipsychotic effect develops is complicated by the fact that several uncontrolled environmental factors contribute to the reduction of psychotic symptoms (Gottschalk, 1979). Also, sedative properties of the neuroleptic compound are of importance in reducing the intensity of symptoms. Accordingly, Lerner *et al* (1979) failed to find any differences in the reduction of psychotic symptoms following treatment on one day with diazepam or haloperidol. On average, though, the major reduction in clinical symptoms seems to be obtained within 3–4 weeks of drug treatment. In a review of the time-course of the antipsychotic effect, Keck *et al* (1989) found that "the degree of the patients' improvement during neuroleptic treatment was similar regardless of the duration of the study". On the whole, there is a difference between the time-course of receptor occupancy and the time-course of the antipsychotic effect, but this difference is not defined. The great variations that are found in the course of the antipsychotic effect indicate that several factors are of importance in addition to D_2 dopamine blockade in mediating the antipsychotic effect.

A similar mechanism of action of antipsychotics may explain the difficulties in finding clinically relevant differences among the neuroleptic compounds. The hyperbolic curve of receptor occupancy may also explain why Baldessarini *et al* (1988) did not find any major differences between patients who had been given low (<250 mg chlorpromazine equivalent/day), moderate (300–600 mg chlorpromazine equivalent/day), or high doses of neuroleptics (>800 mg chlorpromazine equivalent/day). This suggests that high doses increase the risk for the development of side-effects more than they produce further improvement in the patient's psychosis. So far, it has not been possible to define with any certainty a threshold for the antipsychotic effect; dose–response studies have only given rather broad guidelines. In such a study by Clark *et al* (1972), placebo was compared with 150 mg, 300 mg, and 600 mg chlorpromazine daily for 12 weeks. The dose

of 150 mg was superior to placebo, but both 300 mg and 600 mg daily gave better results than the 150 mg dose level; however, side-effects were more common in the high-dose group. Wode-Helgodt *et al* (1978) compared three doses of chlorpromazine – 200 mg, 400 mg, and 600 mg per day – over four weeks. Their findings did not demonstrate a dose–response relationship, but there were more drop-outs in the lower-dose groups, because of insufficient efficacy. Extrapyramidal and other side-effects, including somnolence, were more frequently observed in the patients taking the highest dose (600 mg). These clinical findings are in line with the view that doses resulting in a receptor occupancy above 70% induce an antipsychotic effect.

Haloperidol, however, results in a high receptor occupancy at doses considered by some to be too low to be effective. Our own experience is that haloperidol is a very potent antipsychotic compound, and there are now several studies which demonstrate that in doses around 5 mg per day, haloperidol is effective in the treatment of schizophrenia (Putten *et al*, 1985; McEvoy *et al*, 1991). However, the antipsychotic effect of neuroleptic treatment is multidimensional; this has been convincingly demonstrated in maintenance treatment studies in which relapse rates were lowered by family treatment, group treatment, and social training (Goldstein *et al*, 1978; Falloon *et al*, 1985; Leff *et al*, 1985; Hogarty *et al*, 1991).

Even if the primary effect of antipsychotics could be related to dopamine blockade, complex interactions among several different neuronal systems in various regions also have to be considered in this connection. In addition to effects on dopamine systems, neuroleptics also interact with several other neuronal transmitter systems, including the neuropeptides, but evaluation of the clinical importance of these other systems in relation to the mechanism of action of antipsychotics remains incomplete.

How a psychosis is brought about and how a blockade of dopamine receptors can relieve patients from the psychotic symptoms is in principle unknown. Schizophrenic patients are not cured by antipsychotics, since there is a high risk of relapse with discontinuation of drug treatment. Moreover, a fairly high proportion of schizophrenic patients are insufficiently improved by antipsychotics. It is evident that too little is known about the pathophysiological mechanisms leading to psychotic disorders, but such knowledge must be the basis for improved treatment in the future.

Acknowledgements

Ms A. Liberg is gratefully acknowledged for preparing the manuscript. The study was supported by grant 8318 from the Swedish Medical Research Council.

References

ALFREDSSON, G., BJERKENSTEDT, L., EDMAN, G., *et al* (1984) Relationships between drug concentrations in serum and CSF, clinical effects and monoaminergic variables in schizophrenic patients treated with sulpiride or chlorpromazine. *Acta Psychiatrica Scandinavica*, **69** (suppl. 311), 49–74.

ANDÉN, N.-E., ROOS, B.-E. & WERDINIUS, B. (1964) Effects of chlorpromazine, haloperidol and reserpine on the levels of phenolic acids in rabbit corpus striatum. *Life Sciences*, **3**, 149–158.

ANDREASEN, N. C. (1985) Positive vs. negative schizophrenia: a critical evaluation. *Schizophrenia Bulletin*, **11**, 380–389.

ANGRIST, B., ROTROSEN, J. & GERSHON, S. (1980) Responses to apomorphine, amphetamine, and neuroleptics in schizophrenic subjects. *Psychopharmacology*, **67**, 31–38.

BALDESSARINI, R., COHEN, B. M. & TEICHER, M. H. (1988) Significance of neuroleptic dose and plasma level in the pharmacological treatment of psychoses. *Archives of General Psychiatry*, **45**, 79–91.

BLUMBERG, J. B., TAYLOR, R. E. & SULSER, F. (1975) Blockade by pimozide of a noradrenaline sensitive adenylate cyclase in the limbic forebrain: possible role of limbic noradrenergic mechanisms in the mode of action of antipsychotics. *Journal of Pharmacy and Pharmacology*, **27**, 125–128.

BUNNEY, B. S., WALTERS, J. R., ROTH, R. H., *et al* (1973) Dopaminergic neurons: effect of antipsychotic drugs and amphetamine on single cell activity. *Journal of Pharmacology and Experimental Therapeutics*, **185**, 560–571.

CARLSSON, A. (1974) Antipsychotic drugs and catecholamine synapses. *Journal of Psychiatric Research*, **11**, 57–64.

———, LINDQVIST, M., MAGNUSSON, T., *et al* (1958) On the presence of 3-hydroxytyramine in brain. *Science*, **127**, 471.

——— & ——— (1963) Effect of chlorpromazine or haloperidol on formation of 3-methoxy-tyramine and normetanephrine in mouse brain. *Acta Pharmacologica et Toxicologica*, **20**, 140–144.

——— & CARLSSON, A. (1990) Interactions between glutamatergic and monoaminergic systems within the basal ganglia – implications for schizophrenia and Parkinson's disease. *Trends in Neuroscience*, **13**, 272–276.

CLARK, M. L., RAMSEY, H. R., RAHHAL, D. K., *et al* (1972) Chlorpromazine in chronic schizophrenia: the effect of age and hospitalization on behavioral dose–response relationships. *Archives of General Psychiatry*, **27**, 479–483.

COSTALL, B., FORTUNE, D. H., NAYLOR, R. J., *et al* (1975) Serotonergic involvement with neuroleptic catalepsy. *Neuropharmacology*, **14**, 859–868.

CREESE, I., BURT, D. R. & SNYDER, S. H. (1975) Dopamine receptor binding: differentiation of agonist and antagonist states with ^{3}H-dopamine and ^{3}H-haloperidol. *Life Sciences*, **17**, 993–1002.

DAHL, S. (1986) Plasma level monitoring of antipsychotic drugs. Clinical utility. *Clinical Pharmacokinetics*, **11**, 36–61.

DAVIS, J. M., SCHAFFER, C. B., KILLIAN, G. A., *et al* (1980) Important issues in the drug treatment of schizophrenia. *Schizophrenia Bulletin*, **6**, 70–87.

DELAY, J. & DENIKER, O. (1957) Characteristiques psychophysiologiques des medicaments neuroleptiques. In *The Psychotropic Drugs* (eds J. Garattini & V. Ghetti), pp. 485–501. Amsterdam: Elsevier.

FALLOON, J. R. H., BOYD, J. L., MCGILL, C. W., *et al* (1985) Family management in the prevention of morbidity of schizophrenia. *Archives of General Psychiatry*, **42**, 887–896.

FARDE, L., WIESEL, F.-A., HALLDIN, C., *et al* (1988) Central D_2-dopamine receptor occupancy in schizophrenic patients treated with antipsychotic drugs. *Archives of General Psychiatry*, **45**, 71–76.

———, NORDSTRÖM, A.-L., WIESEL, F.-A., *et al* (1992) Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine. *Archives of General Psychiatry*, **49**, 538–544.

GATTAZ, W. F., KOHLMEYER, K. & GASSER, G. (1990) Computer tomographic studies in schizophrenia. In *Searches for the Cause of Schizophrenia* (eds H. Häfner & W. F. Gattaz), pp. 242–256. Berlin: Springer.

GERLACH, J. & LUHDORF, K. (1975) The effect of L-dopa on young patients with simple schizophrenia, treated with neuroleptic drugs: a double-blind cross-over trial with Madopar and placebo. *Psychopharmacologia*, **44**, 105–110.

GOLDSTEIN, M. J., RODNICK, E. H., EVANS, J. R., *et al* (1978) Drug and family therapy in the aftercare of acute schizophrenics. *Archives of General Psychiatry*, **35**, 1169–1177.

GOTTSCHALK, L. A. (1979) A preliminary approach to the problems of relating the pharmacokinetics of phenothiazines to clinical response with schizophrenic patients. In *Pharmacokinetics of Psychoactive Drugs* (ed. L. A. Gottschalk), pp. 63–81. New York: Spectrum.

HÄRNRYD, C., BJERKENSTEDT, L., BJÖRK, K., *et al* (1984*a*) Clinical evaluation of sulpiride in schizophrenic patients – a double-blind comparison with chlorpromazine. *Acta Psychiatrica Scandinavica*, **69** (suppl. 311), 7–30.

———, ———, GULLBERG, B., *et al* (1984*b*) Time course for effects of sulpiride and chlorpromazine on monoamine metabolite and prolactin levels in cerebrospinal fluid from schizophrenic patients. *Acta Psychiatrica Scandinavica*, **69** (suppl. 3), 75–92.

HOGARTY, G. E., GOLDBERG, S. C. & SCHOOLER, N. R. (1974) Drug and sociotherapy in the aftercare of schizophrenic patients. *Archives of General Psychiatry*, **31**, 609–618.

———, ANDERSSON, C. M., REISS, D. J., *et al* (1991) Family psycho-education, social skills training, and maintenance chemotherapy in the aftercare treatment of schizophrenia. *Archives of General Psychiatry*, **48**, 340–347.

JOHNSTONE, E. C., CROW, T. J., FRITH, C. D., *et al* (1978) Mechanism of the antipsychotic effect in the treatment of acute schizophrenia. *Lancet*, *i*, 848–851.

KANE, J., HONIGFELD, G., SINGER, J., *et al* (1988) Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. *Archives of General Psychiatry*, **45**, 789–796.

KAROBATH, M. & LEITICH, H. (1974) Antipsychotic drugs and dopamine-stimulated adenylate cyclase prepared from corpus striatum of rat brain. *Proceedings of the National Academy of Sciences*, **71**, 2915–2918.

KEBABIAN, J. W., PETZOLD, G. L., GREENGARD, P. (1972) Dopamine-sensitive adenylate cyclase in caudate nucleus of rat brain, and its similarity to the 'dopamine receptor'. *Proceedings of the National Academy of Sciences*, **69**, 2145–2149.

——— & CALNE, D. B. (1979) Multiple receptors for dopamine. *Nature*, **277**, 93–96.

KECK, P. E., COHEN, B. M., BALDESSARINI, R. J., *et al* (1989) Time course of antipsychotic effects of neuroleptic drugs. *American Journal of Psychiatry*, **146**, 1289–1292.

LEFF, J., KUIPERS, L., BERKOWITZ, R., *et al* (1985) A controlled trial of social intervention in the families of schizophrenic patients: two year follow-up. *British Journal of Psychiatry*, **146**, 594–600.

LERNER, Y., LWOW, E., LEVITAN, A., *et al* (1979) Acute high-dose parenteral haloperidol treatment of psychosis. *American Journal of Psychiatry*, **136**, 1061–1064.

LONGONI, R., SPINA, L. & DICHIARA, G. (1987) Permissive role of D-1 receptor stimulation for the expression of D-2 mediated behavioral responses: a quantitative phenomenological study in rats. *Life Sciences*, **41**, 2135–2145.

MCEVOY, J. P., HOGARTY, G. E. & STEINGARD, S. (1991) Optimal dose of neuroleptic in acute schizophrenia. *Archives of General Psychiatry*, **48**, 739–745.

NORDSTRÖM, A.-L., FARDE, L. & HALLDIN, C. (1992) Time course of D_2-dopamine receptor occupancy examined by PET after single oral doses of haloperidol. *Psychopharmacology*, **106**, 433–438.

NYBÄCK, H. & SEDVALL, G. (1968) Effect of chlorpromazine on accumulation and disappearance of catecholamine formed from tyrosine ^{14}C in brain. *Journal of Pharmacology and Experimental Therapeutics*, **162**, 294–301.

PEROUTKA, S. J. & SNYDER, S. H. (1980) Relationship of neuroleptic drug effects at brain dopamine, serotonin, alfa-adrenergic, and histamine receptors to clinical potency. *American Journal of Psychiatry*, **137**, 1518–1522.

PRAAG, H. M. VAN (1977) The significance of dopamine for the mode of action of neuroleptics and the pathogenesis of schizophrenia. *British Journal of Psychiatry*, **130**, 463–474.

PUTTEN, T. VAN, MARDER, S. R., MAY, P. R. A., *et al* (1985) Plasma levels of haloperidol and clinical response. *Psychopharmacological Bulletin*, **21**, 69–72.

ROTH, R. H., MURRIN, L. C. & WALTERS, J. R. (1976) Central dopaminergic neurons: effects of alterations in impulse flow on the accumulation of dihydroxyphenylacetic acid. *European Journal of Pharmacology*, **36**, 163–171.

SEDVALL, G., ALFREDSSON, G., BJERKENSTEDT, L., *et al* (1975) Selective effects of psychoactive drugs on levels of monoamine metabolites and prolactin in cerebrospinal fluid of psychiatric patients. In *Proceedings of the Sixth International Congress of Pharmacology* (ed. H. Airaksinen), pp. 255–267. Forssa: Forssan Kirjapaino Oy.

———, FARDE, L., PERSSON, A., *et al* (1986) Imaging of neurotransmitter receptors in the living human brain. *Archives of General Psychiatry*, **43**, 995–1005.

SEEMAN, P., CHAU-WONG, M., TEDESCO, J., *et al* (1975) Brain receptors for antipsychotic drugs and dopamine binding assay. *Proceedings of the National Academy of Sciences*, **72**, 4376–4380.

SOKOLOFF, P., GIROS, B., MARTRES, M.-P., *et al* (1990) Molecular cloning and characterization of a novel dopamine receptor (D_3) as a target for neuroleptics. *Nature*, **347**, 146–151.

SUNAHARA, R. K., GUAN, H.-C., O'DOWD, B. F., *et al* (1991) Cloning of the gene for a human dopamine D_5 receptor with higher affinity for dopamine than D_1. *Nature*, **350**, 614–619.

TOL, H. H. M. VAN, BUNZOW, J. R., GUAN, H.-C., *et al* (1991) Cloning of the gene for a human dopamine D_4 receptor with high affinity for the antipsychotic clozapine. *Nature*, **350**, 610–614.

———, WU, C. M., GUAN, H.-C., *et al* (1992) Multiple dopamine D4 receptor variants in the human population. *Nature*, **358**, 149–152.

WÅHLINDER, J., SKOTT, A., CARLSSON, A., *et al* (1976) Potentiation by metyrosine of thioridazine effects in chronic schizophrenics. *Archives of General Psychiatry*, **33**, 501–505.

WIESEL, F.-A. & SEDVALL, G. (1975) Effect of antipsychotic drugs on homovanillic acid levels in striatum and olfactory tubercle of the rat. *European Journal of Pharmacology*, **30**, 364–367.

WIK, G. & WIESEL, F.-A. (1991) Regional brain glucose metabolism: correlations to biochemical measures and anxiety in patients with schizophrenia. *Psychiatry Research: Neuroimaging*, **40**, 101–114.

WILSON, J. C., GARBUTT, J. C., LANIER, C. F., *et al* (1983) Is there a tardive dysmentia? *Schizophrenia Bulletin*, **9**, 187–191.

WOLE-HELGODT, B., BORG, S., FYRÖ, B., *et al* (1978) Clinical effects and drug concentrations in plasma and cerebrospinal fluid in psychotic patients treated with fixed doses of chlorpromazine. *Acta Psychiatrica Scandinavica*, **58**, 149–173.

WOLKIN, A., BAROUCHE, F., WOLF, A. P, *et al* (1989) Dopamine blockade and clinical response: evidence for two biological subgroups of schizophrenia. *American Journal of Psychiatry*, **146**, 905–908.

WYATT, R. C. (1991) Neuroleptics and the natural course of schizophrenia. *Schizophrenia Bulletin*, **17**, 325–351.

Frits-Axel Wiesel, MD, PhD, *Professor of Psychiatry, Chairman, Department of Psychiatry, Uppsala University, Ulleråker, S-750 17 Uppsala, Sweden*