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Dopamine and Mania: Behavioral and Biochemical Effects of the Dopamine Receptor Blocker Pimozide

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Abstract. Although recent data suggest that pimozide has effects at other neurotransmitter receptor sites, it is one of the more specific neuroleptics in its effects on dopamine receptors. We report that in manic patients pimozide produces substantial clinical improvement with a magnitude and time course similar to that observed with the more routinely used phenothiazines chlorpromazine and thioridazine. Pimozide did not significantly increase probenecid-induced accumulations of the dopamine metabolite homovanillic acid (HVA) compared to pretreatment values. Higher HVA values were observed in manic than in nonmanic patients, however. These clinical and biochemical data add to a growing body of indirect evidence that a dopaminergic alteration may be associated with some components of the manic syndrome.

Key words: Dopamine – Mania – Neuroleptics – Pimozide – Homovanillic acid (HVA)

A number of recent studies in the neuropsychiatric literature have emphasized a possible role of dopamine (DA) in manic symptomatology (Goodwin et al., 1970; Bunney et al., 1971; Murphy, 1972; Gerner et al., 1976; Post, 1978). Randrup et al. (1975) have reviewed the literature noting the efficacy of routine neuroleptics which block DA receptors in manic illness. In a case study of a rapid-cycle manic-depressive patient, an indirect DA agonist (amphetamine) and a direct agonist (piribedil) were associated with the production of manic episodes, while the DA receptor antagonist pimozide was helpful in treating these episodes (Gerner et al., 1976). In addition, low doses of DA receptor agonists, which paradoxically have inhibitory effects on motor behavior (Carlsson, 1975; Strombom, 1976), may have some antimanic effects (Post et al., 1976; Corsini et al., 1977). Inhibition of tyrosine hydroxylase with α-methyl-*P*-tyrosine (AMPT) is associated with antimanic effects in some patients, while inhibition of DA β-hydroxylase is not effective, further implicating DA rather than norepinephrine (NE) (Sack and Goodwin, 1974). Lithium carbonate, the drug of choice for manic-depressive illness, has also been reported to have several effects on dopaminergic metabolism (Corrodi et al., 1969; Friedman and Gershon, 1973; Ho et al., 1970; Segal et al., 1975) and has recently been reported to block development of behavioral and electrophysiological DA receptor supersensitivity following chronic neuroleptics (Pert et al., 1978a, b; Gallager et al., 1978).

A role for DA has been suggested in some patients with depressive illness as well. Several studies report that a directly acting DA receptor agonist, such as piribedil, may have a spectrum of therapeutic effects in depressed patients (Post et al., 1978; Shopsin and Gershon, 1978). Although levodopa is not generally an effective antidepressant (Goodwin et al., 1970), in one study (van Praag and Korf, 1974), those with lower cerebrospinal fluid (CSF) homovanillic acid (HVA) responded well. Evidence now suggests that tricyclic antidepressants have biochemical and possibly behaviorally relevant mechanisms of action through the dopaminergic system (Halaris and Freedman, 1975; Randrup and Braestrup, 1977; Molander and Randrup, 1976a, b). Clearly, the monoamine oxidase inhibitors also affect DA, as well as serotonin (5-HT) and NE metabolism. Alterations in dopaminergic mechanisms have been implicated in the effects of electroconvulsive therapy (Modigh, 1976; Papeschi and Randrup, 1974). The acute mood-elevating and dysphoria-inducing properties of the indirect DA ago-

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nists, such as amphetamine and cocaine (Post, 1975), also provide and indirect pharmacological link to DA (in addition to NE) alterations and affective symptomatology (van Rossum, 1970; Snyder et al., 1974; Scheel-Kruger et al., 1977).

Pimozide has relatively specific effects at DA receptor sites (Andén et al., 1970; Horn and Phillipson, 1976; Hyttel, 1974; Jacobs, 1974; Ettenberg and Milner, 1977; Baudry et al., 1977a, b; Seeman et al., 1976, 1978). However, it does not block DA-induced adenylate cyclase activity as effectively as would be predicted from its receptor binding characteristics or clinical potency (Clement-Cormier et al., 1974; Snyder et al., 1975; Creese et al., 1976a). In addition to its effects on DA receptors, pimozide also blocks NE-induced increases in limbic forebrain cyclic AMP in some preparations (Blumberg et al., 1975; Sawaya et al., 1977) but not others (Horn and Phillipson, 1976). Like several other neuroleptics with relatively low incidences of extrapyramidal side effects (such as clozapine and thioridazine), pimozide displays a high affinity for cholinergic receptors (Yamamura et al., 1976). Pimozide also shows a high affinity for the opiate receptor as measured by ^{3}H-naloxone binding (Creese et al., 1976b). Recent data suggest that DA receptors may exist in multiple forms (Kebabian, 1978) and that most classical neuroleptics block those associated or not associates with adenylate cyclase nonspecifically. One study suggests that pimozide may act more selectively on pre- compared to post-synaptic DA receptors, in contrast to chlorpromazine (CPZ) or thioridazine (TH) which have opposite relative effects (Puech et al., 1978), since pimozide blocked apomorphine-induced decreases in motor activity and hypothermia (presynaptic) better than circling, climbing, and increased motor activity and stereotypy (post-synaptic). In contrast, Gianutsos et al. (1976) suggest that haloperidol is more effective at presynaptic DA receptors than pimozide. Partial agonist-like effects of pimozide were shown by biphasic effects on prolactin secretion in culture rat pituitary cells (Denef and Follebouckt, 1978). Thus, while pimozide may be relatively more specific in its DA receptor blocking properties than many other neuroleptics, it does exert effects on other neurotransmitter receptors, and its precise effects on the kind of DA receptor and its anatomical location remain to be clarified.

In this paper we report that in a small group of manic patients pimozide appears to have therapeutic effects similar in magnitude and time course to routinely used phenothiazines. We also report the effects of pimozide treatment on the DA metabolite HVA, as well as on metabolites of NE and 5-HT, 3-methoxy-4-hydroxyphenyl glycol (MHPG), and 5-hydroxyindoleacetic acid (5-HIAA), respectively.

Materials and Methods

Patients with bipolar manic-depressive or schizoaffective illness in the manic phase, diagnosed by the criteria of Spitzer et al. (1975), were admitted to two psychobiological research units at the National Institute of Mental Health. Other patients with diagnoses of schizophrenia, schizoaffective illness, and acute depressive psychosis were also included in the biochemical data for comparison purposes. All patients gave appropriate informed consent to the research procedures described prior to and during participation in the clinical trial. Patients were studied during a baseline period of approximately 2 weeks prior to pimozide treatment.

Patients were rated twice daily by consenus of trained nursing staff for global depression, mania, psychosis, anger, and anxiety (Bunney and Hamburg, 1963; Murphy et al., 1974). The antimanic response to pimozide was evaluated in comparison to 18 similarly diagnosed manic patients treated with lithium carbonate (900–2400 mg/day) to achieve blood levels greater than 0.80 mEq/l. The group of eight patients was selected from 19 lithium-treated patients so that age, sex, and initial severity of mania matched that of the pimozide group as closely as possible (see 3). This comparison group, which met similar diagnostic criteria, was included only to give a rough guide as to the relative time course and magnitude of the clinical changes. A crossover design in which the same patients were treated with both agents was clinically feasible only in two cases.

The time course of antimanic response to pimozide was also compared to that achieved in nine consecutively treated patients with the more commonly used neuroleptics, i.e., CPZ or TH. The average peak dose of CPZ was 1230 mg/day and for TH, 633 mg/day.

Active treatment was preceded by a placebo period during which baseline ratings and biological evaluations were performed. Pimozide was begun at doses ranging from 1–2 mg/day and increased as tolerated to a final dose of 4–16 mg/day. The average peak dose was 12 mg/day during the clinical trial, which lasted an average of 28 days in these manic patients. Antiparkinsonian medications were not administered during the course of the study, except in one patient for whom biological data were not available.

During a drug-free interval, patients received an initial lumbar puncture following probenecid (100 mg/kg), which was administered in four oral divided doses 18 h prior to a lumbar puncture (approximately 3 p.m.) (Goodwin et al., 1973). Each patient was maintained at bed rest from the night before. The probenecid procedure was repeated during a relatively acute phase of neuroleptic administration (5–10 days) and then during a more chronic phase of neuroleptic administration (16–29 days) when clinically feasible.

The acid metabolites of DA and 5-HT, HVA, and 5-HIAA were measured in CSF by fluorimetric techniques as described elsewhere (Goodwin et al., 1973). MHPG was measured by gas chromatography with the method of Gordon and Oliver (1971).

Results

As illustrated in Table 1 and Fig. 1, patients with a manic or schizoaffective manic diagnosis responded well to treatment with the relatively specific DA receptor antagonist pimozide. Seven of eight patients studied showed substantial clinical improvement, usually within the first 2–5 days of treatment. One patient showed no response to pimozide in doses of up to 14 mg/day for 6 weeks. It is noteworthy that this patient also subsequently failed to respond to treatment with CPZ or with low doeses of piribedil during a second

Table 1. Demographic and pimozide response data in manic patients

Patient Number	Diagnosis[b]	Age	Sex	Peak dose (mg/day)	Mania ratings[a]		Psychosis ratings[a]	
					Baseline	Pimozide	Baseline	Pimozide
018	BPI	46	M	14	2.9	1.2	3.1	2.7
014	SA(M)	22	M	16	5.4	2.8	6.7	1.0
020	BPI	29	F	4	3.1	1.5	1.0	1.0
023	BPI	50	F	14	5.9	1.1	4.6	2.9
121	BPI	20	F	12	7.7	1.8	2.0	1.0
081	BPI	22	F	14	6.6	7.2	8.7	7.1
117	BPI	27	M	10	13.8	1.5	6.8	1.0
128	BPI	33	M	9	8.4	3.1	7.8	2.7
Means ± SEM		31.1±4.0		11.6±1.4	6.7±1.2	2.5±0.7	5.1±1.0	2.4±0.7

[a] Mania and psychosis ratings represent means of approximately 7 days on placebo and during the third week on pimozide.
[b] All patients were bipolar I (BPI, i.e., a history of hospitalization for a manic episode) except one patient who met criteria for schizoaffective, manic type (SA[M])

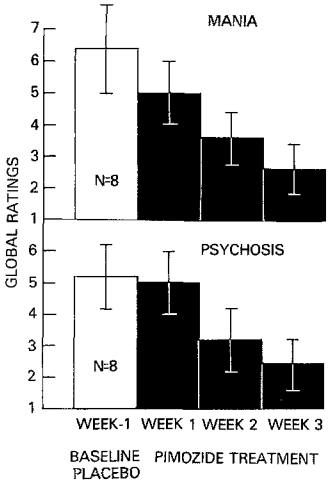

Fig. 1. Improvement in both manic and psychotic components of affective episodes treated with the dopamine receptor blocker pimozide. Mania ratings were significantly decreased by week 1, whereas psychosis ratings decreased significantly by week 2

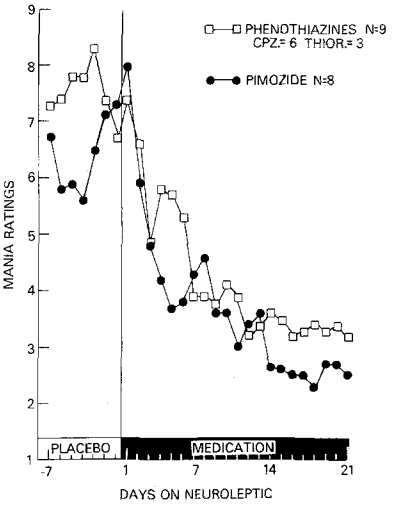

Fig. 2. Similar time course of antimanic effects in patients treated with pimozide and the more routinely used phenothiazines chlorpromazine (CPZ) and thioridazine (Thior.). Average peak daily dose of pimozide was 11.6 mg/day, while that of CPZ was 1230 mg/day and Thior. 633 mg/day

hospitalization, although she responded well to lithium carbonate.

It should be noted that although prior reports suggest that pimozide was a relatively nonsedating neuroleptic of less clinical efficacy in patients with acute psychomotor agitation (Denijs and Vereecken, 1973; Bobon et al., 1970; Sugerman, 1971; Kolivakis et al., 1974; Claghorn, 1974; Yaryura-Tobias et al., 1974; Riding and Munro, 1975; Goldberg and Kurland, 1974), the drug produced rapid improvement in manic behavior within the first 2–5 days of treatment (Figs. 1 and 2). This amelioration of acute manic symptomatology appeared to follow a relatively similar time course to that observed in similarly diagnosed patients following TH or CPZ. Although double-blind ratings of drowsiness or sedation were not available, it was our clinical impression that sedative side effects with pimozide were not prominent during this acute response phase and that motor and verbal components of the manic syndrome decreased in a parallel manner. The

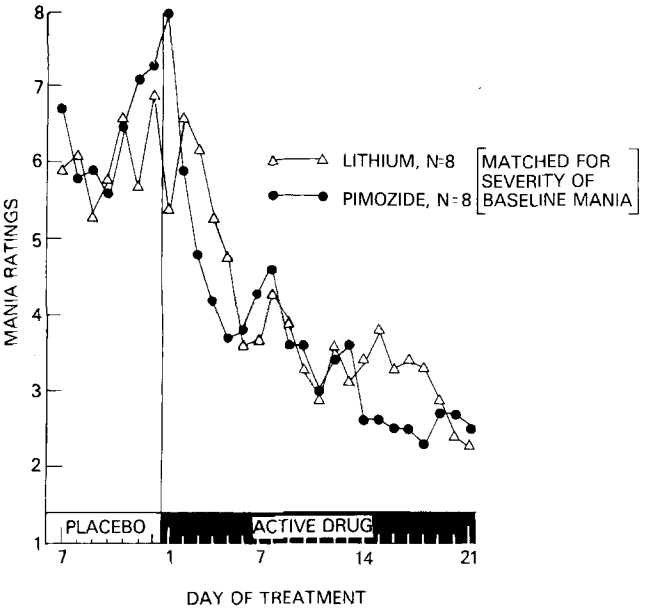

Fig. 3a. In patients approximately matched for equal severity of baseline mania ratings, the onset and course of pimozide effects are at least as rapid and substantial as those of lithium carbonate

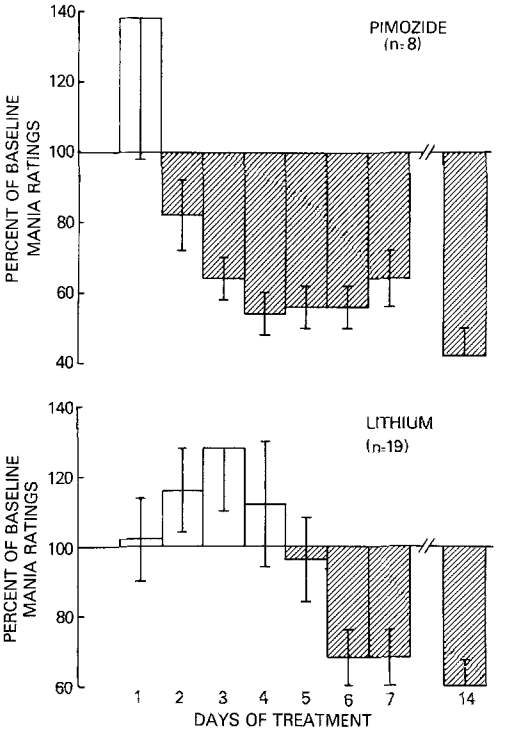

Fig. 3b. Onset of antimanic effects to pimozide by the second day of treatment are compared with the slower onset responses generally observed following lithium carbonate

onset of antimanic effects in the first 2–5 days is somewhat faster than that seen following lithium administration in 19 patients with similar diagnostic presentations or in eight patients roughly matched for initial severity of mania (Fig. 3). It is also noteworthy that ratings of manic symptomatology (Fig. 1) appeared to decrease relatively more rapidly than those of psychosis during the initial phase of pimozide treatment, although there was substantial improvement in both symptom clusters.

Biochemical Results. As illustrated in Table 2, acute and chronic administration of pimozide was not associated with significant alterations in HVA accumulations following probenecid in a heterogenous group of manic, depressive, and schizophrenic patients. However, probenecid-induced HVA accumulations during acute and chronic pimozide were significantly ($P < 0.01$) greater in manic patients compared to depressed or schizophrenic patients without manic ratings (Fig. 4). This finding is consistent with that observed following chronic phenothiazine treatment; manic patients had significantly ($P < 0.05$) higher HVA accumulations (296.5 ± 27.2 ng/ml, $n = 6$) than nonmanic patients (164.8 ± 40.6 ng/ml, $n = 6$) who received similar doses for treatment of their depressive or schizophrenic psychosis.

As illustrated in Fig. 5, the accumulations of 5-HIAA was reduced in nine of ten patients ($P < 0.05$, sign test) during acute pimozide treatment. Following more chronic pimozide treatment, 5-HIAA levels remained nonsignificantly lower than premedication values ($P < 0.10$, paired t-test). MHPG levels in CSF decreased nonsignificantly during pimozide treatment (16.1 + 2.6 ng/ml, $n = 10$) compared to baseline (20.0 ± 2.4 ng/ml) (Fig. 6).

Probenecid levels in CSF during pimozide treatment (20.72 ± 0.85, $n = 7$) were not significantly different than those in the medication-free state (24.10 ± 2.94, $n = 8$). Moreover, HVA accumulations during acute and chronic pimozide treatment were only weakly correlated with CSF probenecid levels ($r = 0.27$ and $r = 0.39$, respectively). HVA concentrations were not significantly correlated with doses of pimozide acutely ($r = -0.10$) or chronically ($r = 0.06$). Pretreatment HVA accumulations or those following pimozide were not significantly different in the six patients who developed extrapyramidal side effects from those who did not.

Discussion

These data in acutely manic patients suggest that the relatively specific DA receptor blocker pimozide may

Table 2. CSF HVA[a] accumulations following acute and subacute pimozide in manic and nonmanic patients

Patient number[b]	Sex	Diagnosis	Age	Medication-free	Acute (5–10)	Subacute (16–29)
Mania present:						
117	M	BPI	27	283	–	382
121	F	BPI	20	269	429	–
014	M	SA	22	190	332	268
081	F	BPI	22	385	435	453
020	F	BPI	29	281	385	351
064	F	Undiagnosed	39	223	–	429
Means ± SEM				271.8 ± 27.1	395.3 ± 23.8[c]	376.6 ± 32.5
No mania present:						
027	M	SA	40	198	133	169
095	M	S	37	300	–	370
021	M	SA	18	286	231	286
016	F	S	32	340	129	308
077	M	BPII	46	105	39	–
017	M	Undiagnosed	29	297	348	248
025	F	BPII	22	314	257	268
Means ± SEM				263.9 ± 31.2	189.5 ± 45.1	274.8 ± 27.2
Total group means ± SEM				267.0 ± 20.1 (13)	271.8 ± 43.4 (10)	321.1 ± 25.5 (11)

[a] Nanograms/ml ± SEM following probenecid (100 mg/kg orally) in four divided doses

[b] The first six patients received pimozide for treatment of their manic syndrome, as evaluated by two physicians and double-blind nurses' daily global mania ratings. The last seven patients showed no evidence of mania prior to and during treatment for their depressive or schizophrenic psychosis. All patients are included in Fig. 4 where differences from medication-free values during acute and chronic pimozide are plotted

[c] HVA accumulations during acute pimozide were significantly higher ($P < 0.001$) in manic compared to nonmanic patients. Doses of pimozide were not significantly different in the two groups and there was no correlation ($r = -0.10$) between pimozide dose and HVA accumulation during acute or chronic ($r = 0.06$) treatment

be clinically efficacious and provide further indirect evidence of a dopaminergic involvement in manic symptomatology. Moderate to substantial antimanic responses were observed in seven of eight acutely ill patients. The magnitude and time course of decreases in global mania ratings following treatment with pimozide were similar to that observed following treatment with the more routinely used and less selective neuroleptics CPZ and TH. The antimanic response was at least as rapid (and possibly more rapid) than that observed in a comparison group of patients treated with a conventional regimen (no loading doses) of lithium carbonate.

The lack of significant pimozide effect on HVA accumulation during acute administration (Table 2) in our mixed group of psychiatric patients is somewhat puzzling. It is possible that the doses administered were not substantial enough to produce accumulations in HVA, since van Praag (1977a) and Wode-Helgodt et al. (1977) have shown dose-response-related increases in HVA during treatment with a variety of neuroleptics, although Bowers (1978) has observed an inverse relationship of HVA with dose during chronic treatment. However, pimozide was used in clinically effective doses which should have been sufficient to increase HVA. In four patients treated with pimozide, we did observe increases in CSF prolactin levels both acutely and chronically even when HVA was not elevated (Jimerson et al., 1976), a finding consistent with pimozide's in vivo effect at least on pituitary DA receptors in this dose range.

It is intriguing that greater probenecid-induced accumulations of HVA were observed in manic patients treated with the same dose range of pimozide than in nonmanic patients. These data are consistent with the idea that there is an increased presynaptic response, possibly by activation of tyrosine hydroxylase, following DA receptor blockade produced by the neuroleptics (Carlsson and Lindqvist, 1963; Carlsson, 1978). It is possible that, in comparison to the manics, the depressed and nonactivated schizophrenic patients had relatively less (or a less sustained) increase in DA synthesis, as reflected by the lack of significant increases in CSF HVA. In a group of 11 schizophrenic

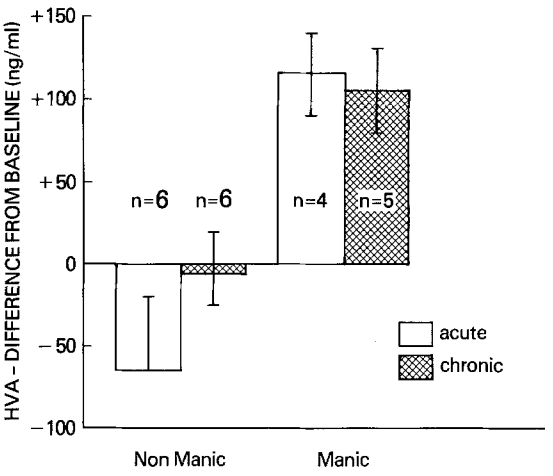

Fig. 4. During pimozide treatment manic patients showed increases in HVA accumulations compared to medication-free values while non-manic patients did not. This differential response in the manics compared to the non-manics was observed during both acute and chronic pimozide treatment

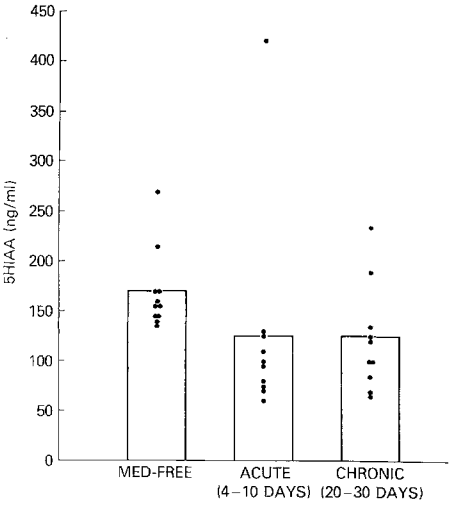

Fig. 5. CSF 5HIAA decreased in nine of ten patients during acute pimozide treatment and tended to remain low during chronic treatment

patients studied by van Kammen and Marder (unpublished data) a similar lack of significant effect of pimozide (average daily dose 11 mg for 40 days) on HVA was observed.

Due to the lack of consistent effect of acute pimozide on HVA, we were unable to adequately evaluate possible tolerance effects of HVA accumulation. Our group (Post and Goodwin, 1975), that of Sedvall et al. (1974), Gerlach et al. (1975), and van Praag (1977b) have suggested that CSF HVA increases in patients treated acutely with neuroleptics may be attenuated with more chronic treatment. Of five patients who showed increases in HVA during acute pimozide administration, four appeared to show less substantial increases or actual decreases in HVA accumulation, compared to baseline, following more chronic treatment. Further work needs to be done before a definitive statement can be made about tolarance to the effects of pimozide on HVA accumulations, however.

It is of interest that 5-HIAA accumulations tended to decrease following acute and chronic pimozide administration. These data are consistent with those of Wode-Helgodt et al. (1977) reporting decreases in 5-HIAA (and MHPG) during CPZ treatment. However, Gallager and Aghajanian (1976) have reported that CPZ and pimozide do not inhibit serotonergic raphe unit firing in the rat as do other neuroleptics. In their preparations, the effects on raphe firing appeared to be indirect effects secondary to DA receptor blockade, although interpretation of effects on serotonergic mechanisms must await clarification of the recent findings that ^{3}H-spiroperidol labels 5-HT receptors in rat frontal cortex and hippocampus (Creese et al., 1978).

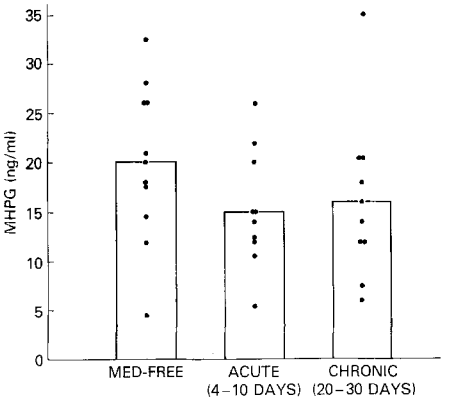

Fig. 6. Pimozide did not significantly alter probenecid-induced accumulations of the norepinephrine metabolite MHPG

The lack of significant effects on CSF MHPG values is consistent with the study of Sedvall et al. (1978) who reported that CPZ and melperone, but not the 'atypical' neuroleptics thiothixene, sulpiride, or clozapine, descreased MHPG. Sternberg et al. (1979) reported that pimozide decreased CSF NE in nine schizophrenics and that the degree of decrease in these patients was positively correlated with the improvement in psychosis.

There are a wide variety of data suggesting that dopaminergic mechanisms are intimately associated with the psychomotor activation in animals, such as hyperactivity and stereotypy, as well as other be-

havioral symptoms often associated with the manic syndrome, including sexuality, decreased need for sleep, increased arousal, altered memory function, and aggression. However, in a parallel way, alterations in serotonergic as well as noradrenergic function have been similarly related to these parameters, and we do not suggest an exclusive role for DA in manic illness. It may be that dopaminergic balance in relation to a variety of neurotransmitter systems is important and that a dopaminergic mechanism is only one link in the path to the final common pathway of increased activated behaviour, as well as lability of mood and the other symptoms of mania. During two separate hospitalizations, one patient in our series responded poorly to three different attempts to treat her symptoms by altering DA receptor function (with pimozide, CPZ, and low-dose piribedil), yet she responded well to lithium. Another patient who was a lithium nonresponder, was extremely sensitive to manipulations of the DA system; during depressed phases he became manic on amphetamine and piribedil and responded to pimozide (Gerner et al., 1976). These two patients may exemplify two separate groups of patients differing not only in pharmacological responsiveness, but also in the degree of dopaminergic involvement in the psychophysiology of their mania. The differences could also reflect different dopaminergic mechanisms or degrees of receptor sensitivity.

In addition, we should reemphasize that dopaminergic mechanisms may be quite different areas of the brain which are in turn associated with different behavioral symptoms. Thus, CSF HVA techniques appear to largely measure alterations in dopaminergic function in the striatum, while neuroendocrine alterations may represent more hypothalamic-pituitary substrates. Alterations in dopaminergic mechanisms in limbic system areas have been previously reported to affect animal hyperactivity and exploratory behavior (Pijnenburg et al., 1976; Costall and Naylor, 1977; Creese and Iverson, 1974; Scheel-Kruger et al., 1977; Kelly and Iverson, 1975; Ljungberg and Ungerstedt, 1977, 1978); their possible relevance to manic symptoms remains to be explored. Similarly, alterations in cortical dopaminergic mechanisms may be critically important for a variety of cognitive memory and language functions which appear to be altered by the illness. The time course of neuroleptic effects on DA metabolism in mesocortical compared to other dopaminergic areas may be more closely associated with clinical effects which do not to show tolerance as rapidly as in the striatum (Glowinski, 1975; Bowers and Rozitis, 1976; Scatton et al., 1976, 1977). While the locus of pimozide action on the type and location of dopaminergic receptors related to its clinical effects is unknown, the efficacy of pimozide in mania suggests that dopaminergic mechanisms at some brain sites play a role in the manic syndrome.

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