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# Relationships Between Clinical and Biochemical Effects of Melperone and Thiothixene in Psychotic Women

Lars Bjerkenstedt[2], Bo Gullberg[3], Christer Härnryd[2], and Göran Sedvall[1]

[1] Laboratory of Experimental Psychiatry, Department of Psychiatry (Karolinska Hospital), Karolinska Institutet, S-104 01 Stockholm,
[2] Psychiatric Clinic 2, Beckomberga Hospital, S-161 04 Bromma,
[3] Department of Statistics, University of Lund, S-220 05 Lund, Sweden

**Summary.** Clinical and biochemical effects of melperone (100 mg × 3) and thiothixene (10 mg × 3) were studied in women with psychoses of schizophrenic or paranoid type. Psychotic morbidity and side effects were determined by rating scales. Concentrations of the major monoamine metabolites homovanillic acid (HVA), 4-hydroxy-3-methoxyphenyl-ethylene glycol (MOPEG), and 5-Hydroxy-3-indoleacetic acid (5-HIAA) in cerebrospinal fluid (CSF) were measured by mass fragmentography. Concentrations of prolactin in CSF and plasma were determined by radioimmunoassay (RIA). Measurements were performed before and after 2 and 4 weeks of drug treatment.

The drugs did not differ in antipsychotic effect, but thiothixene treatment caused greater elevation of HVA and prolactin than melperone. The measures of dopaminergic activity did not correlate significantly with therapeutic outcome in either of the treatment groups. Treatment with melperone, but not thiothixene, reduced MOPEG levels, but only during thiothixene treatment was MOPEG reduction related to clinical improvement. In both treatment groups clinical improvement correlated significantly with an increase in the 5-HIAA/MOPEG ratio. Extrapyramidal side effects correlated negatively with HVA and HVA/MOPEG in the thiothixene, but not in the melperone group.

It is concluded that there is no simple relationship between alteration of dopaminergic transmission and therapeutic outcome in drug-treated psychotic patients. In addition to dopamine (DA) receptor blockade, alteration of norepinephrine (NE) mechanisms may play a role in the antipsychotic effect. It is suggested that the balance of activity between central serotonin (5-HT) and NE systems should be considered in the mechanism of action of antipsychotic drugs and the pathophysiology of psychosis.

*Send offprint requests to:* Lars Bjerkenstedt, M. D., Laboratory of Experimental Psychiatry, Department of Psychiatry, Karolinska Hospital, S-104 01 Stockholm, Sweden

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## Introduction

The antipsychotic effect of neuroleptic drugs is generally thought to be related to their interference with central dopaminergic and noradrenergic mechanisms (Carlsson and Lindqvist, 1963). The evidence for this view is based on a number of pharmacological, biochemical, and clinical studies (van Rossum, 1966; Nybäck and Sedvall, 1968; Persson and Roos, 1968; Andén et al., 1970; Sedvall et al., 1974; Seeman et al., 1975; Creese et al., 1976; Greengard, 1976). Therapeutic doses of most of the commonly used antipsychotic drugs elevate levels of homovanillic acid (HVA), the major dopamine (DA) metabolite in the cerebrospinal fluid (CSF). This fact has been shown consistently in recent clinical studies (Post and Goodwin, 1975; Bjerkenstedt et al., 1977a; Wode-Helgodt et al., 1977a). Another biochemical effect, thought to be related to DA receptor blockade by the antipsychotic drugs, is the elevation of prolactin levels in plasma and CSF of drug-treated patients (Sedvall et al., 1975; Frantz and Sachar, 1976; Meltzer and Fang, 1976; Bjerkenstedt et al., 1977b; Wode-Helgodt et al., 1977b). The experimental and clinical studies accordingly indicate that most, if not all antipsychotic drugs interfere with central dopaminergic mechanisms. The quantitative relationship between DA receptor blockade and the antipsychotic effect is still far from clear. Some compounds, like clozapine and melperone, while having antipsychotic effects similar to other neuroleptics, are fairly weak blockers of central DA receptors (Sedvall and Nybäck, 1973; Ackenheil et al., 1974; Gerlach et al., 1974; van Praag et al., 1976; Bjerkenstedt et al., 1977a and b; 1978).

In a recent clinical study we compared the clinical effects of melperone and thiothixene, two neuroleptic drugs for which the experimental and clinical evidence indicate a marked difference in central DA receptor blocking potency. With respect to antipsychotic effects, the two drugs did not differ significantly (Bjerkenstedt et al., 1978), but thiothixene was much more potent in elevating levels of HVA in CSF and prolactin levels in both CSF and plasma. Moreover, melperone but not thiothixene caused a significant reduction of the level of 4-hydroxy-3-methoxyphenyl-ethylene glycol (MOPEG), the major norepinephrine (NE) metabolite, in CSF (Bjerkenstedt et al., 1977a and b).

The clinical study mentioned was performed according to a design allowing simultaneous quantitative evaluation of the clinical and biochemical changes in the drug-treated patients. In the present paper the relationships obtained between the clinical and biochemical effects of thiothixene and melperone are described in detail.

## Material and Methods

### *Subjects*

Psychotic women served as subjects. The procedure for patient selection has been described in detail in previous communications (Bjerkenstedt et al., 1978; Wode-Helgodt et al., 1978). A

total of 81 acutely admitted women were selected from the emergency ward. All of these patients exhibited symptoms that satisfied WHO diagnostic criteria for schizophrenic or paranoid type psychosis (World Health Organization, 1973). In the present study the following narrower set of criteria was selected from these.

*Inclusion Criteria.* Presence of thought disorder, delusions, or auditory hallucinations.

*Exclusion Criteria.* Presence of organic brain disorder, somatic disease, alcohol and drug abuse, manic or depressive psychosis, or borderline symptomatology. Those admitted in a confused state were excluded if their psychotic symptoms did not persist when the confusion had cleared up.

Due to dropouts, anticholinergic treatment, and loss of samples the present calculations regarding relationships between the morbidity measure used (Σ6, see below) and the biochemical measures are based on data from 49 patients at most.

A variance analysis indicated that neither dropouts, anticholinergic treatment, or sample loss preferentially affected any of the treatment groups or had any significant influence on biochemical or morbidity measure or the relationships between them.

*Administration of Drugs*

During the first week one tablet of active compound (melperone 100 mg; thiothixene 10 mg) was given at 8 a.m. and at 4 p.m. After the first week the dose was increased to three tablets per day of the active compound, the additional tablet given at 12 a.m. During the remaining part of the study, i.e. 3 weeks, this dose (melperone 300 mg and thiothixene 30 mg per day) was kept constant. The drugs were administered according to the 'double-dummy' technique (Bjerkenstedt et al., 1977a). Melperone was given to 25 patients and thiothixene to 24. For sleep induction and sedation diazepam (Stesolid, Dumex AB, Sweden) was prescribed to 15 patients during active neuroleptic treatment (melperone = 8, thiothixene = 7). The diazepam-treated patients did not differ significantly from the rest of the group in any of the measures.

*a) Rating of Psychopathology.* Each patient was rated by two psychiatrists (L.B. & C.H.) using the Comprehensive Psychopathology Rating Scale (CPRS) (Åsberg et al., 1978). The mean of the scores from the two raters were used for the evaluation of treatment effects. (For further details concerning the rating procedure see Bjerkenstedt et al., 1978.)

From the CPRS data several morbidity measures were constructed. One of the morbidity measures, Σ6, includes six separate CPRS items considered typical of schizophrenia (Bleuler, 1911). These items are: (1) ideas of reference and persecution; (2) disrupted thoughts; (3) illusions and hallucinations; (4) withdrawal; (5) incongruity of affect; and (6) incoherent speech. This morbidity measure reflects the severity of schizophrenic symptomatology. Moreover the Σ6 was the morbidity measure that was most consistently related to the biochemical measures. For these reasons, this measure was generally used in this paper.

*b) Rating of Side Effects.* A modified version of the Simpson and Angus scale (1970) for extrapyramidal symptoms was used for the evaluation of side effects. Here also each item was rated by the two psychiatrists. The classical parkinsonian side effects reflected in the first three items of the scale were measured by the subscale Σ3 (Bjerkenstedt et al., 1978). The items included are: (1) gait, (2) elbow rigidity and (3) tremor.

*c) Biochemical Measures.* Concentrations of HVA, MOPEG, and 5-hydroxyindoleacetic acid (5-HIAA), the major serotonin (5-HT) metabolite, in lumbar CSF were determined by a mass fragmentographic method (Swahn et al., 1976). Prolactin concentrations in the CSF and serum were measured by radioimmunoassay (RIA) (Bjerkenstedt et al., 1977b).

*d) Statistical Methods.* Two-sided Spearman's rank correlation tests were used.

## Results

### *Effects of Melperone and Thiothixene Treatment on Psychotic Morbidity and Concentrations of HVA and Prolactin in CSF*

In previous reports of this project we described in detail changes in the clinical condition of the patients and some biochemical measures associated with melperone or thiothixene treatment (Bjerkenstedt et al., 1977a and b; 1978).

Figure 1 summarizes the effect of the drugs on psychotic morbidity and biochemical measures related to dopaminergic mechanisms. Psychotic morbidity was reduced similarly in both treatment groups. The concentrations of HVA and prolactin were increased significantly more in the thiothixene group than in the melperone group. These results indicate that with the fixed doses used, the drugs have similar therapeutic effects, but that the central DA receptors are blocked to a greater extent by thiothixene than by melperone.

### *Correlations Between Morbidity Scores and Biochemical Measures in Psychotic Women Before Treatment*

*Monoamine Metabolites in CSF.* Before treatment there were no significant correlations between psychotic morbidity (CPRS Σ6) and the baseline concentrations of HVA, MOPEG, or 5-HIAA. In spite of the fact that the concentration of 5-HIAA was significantly higher in this group of patients than in that of a healthy control group (Sedvall et al., 1977a), there was no significant correlation between the 5-HIAA concentration and psychotic morbidity. The ratio 5-HIAA/MOPEG was significantly correlated to the pretreatment morbidity ($r = -0.30$, $P < 0.05$). The correlation was negative, i.e., a low ratio was related to high morbidity.

*Prolactin Concentrations in Plasma and CSF.* There were no significant correlations between prolactin concentrations and psychotic morbidity before treatment.

### *Relationships Between Changes in Psychotic Morbidity and Biochemical Measures During Melperone or Thiothixene Treatment*

*Monoamine Metabolites.* There were no significant correlations between the changes of the levels of HVA or 5-HIAA and the change in psychotic morbidity.

A high and significant correlation was found between the reduction in the MOPEG concentration and the reduction of the morbidity score in the thiothixene group after 4 weeks of treatment (Fig. 2) ($r = 0.65$, $P < 0.01$). However, the MOPEG concentration was not significantly altered by thiothixene treatment (Bjerkenstedt et al., 1977a). The relationship found indicates that there was a reduction in the MOPEG concentration of those patients that improved.

In the melperone-treated patients, the MOPEG concentrations were reduced after four weeks of treatment (Bjerkenstedt et al., 1977a). But this effect was not correlated to psychiatric improvement.

There was no correlation in either of the treatment groups between the reduction in MOPEG and the change in motor activity as measured by two CPRS items, Overactivity (55) and Agitation (57) (Bjerkenstedt et al., 1978).

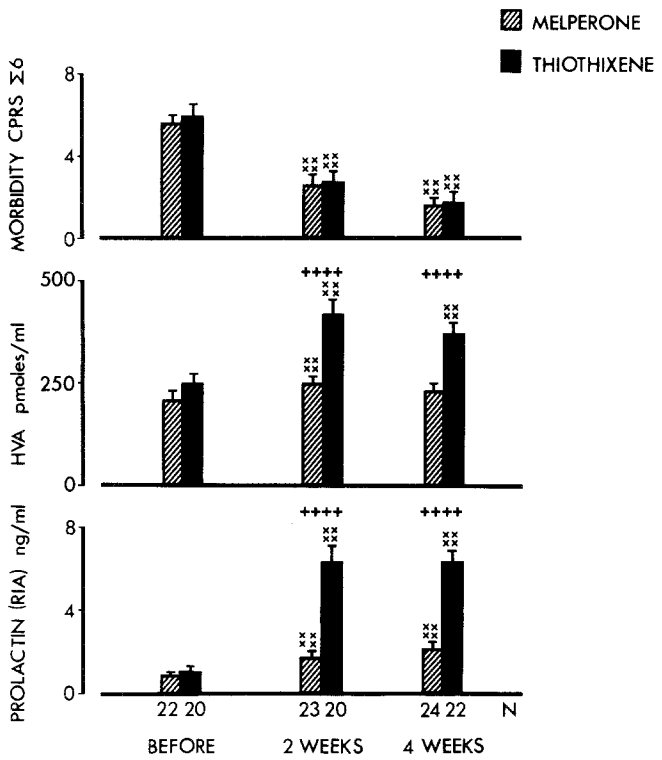


**Fig. 1.** Effects of melperone of thiothixene treatment on morbidity scores and concentrations of HVA and prolactin in CSF of psychotic women

Of the different metabolite ratios constructed, only the change in the 5-HIAA/MOPEG ratio was significantly correlated with the change in psychotic morbidity. Thus, in both treatment groups at 4 weeks, the percentage of change in the 5-HIAA/MOPEG ratio was significantly positively correlated with the reduction of the morbidity scores (Fig. 3) (melperone $r = 0.52$, $P<0.025$; thiothixene $r = 0.60$, $P<0.01$). In neither treatment group was the change in the 5-HIAA/MOPEG ratio related to the change in motor activity.

*Prolactin Concentrations in Plasma and CSF.* There were no significant correlations between clinical improvement and elevation of prolactin concentration either in plasma or CSF in either of the treatment groups.

### *Relationship Between Side Effects and Biochemical Measures During Melperone or Thiothixene Treatment*

*Monoamine Metabolites.* The extrapyramidal side effects ($\Sigma 3_P$) were significantly negatively correlated with the HVA level after both 2 and 4 weeks of thiothixene treatment ($r = -0.39$, $P<0.025$; $r = -0.37$, $P<0.05$). In the same treatment group the extrapyramidal symptoms were positively correlated with the MOPEG level after 2 weeks' treatment ($r = 0.44$, $P<0.01$). In the melperone group there was a lower frequency of extrapyramidal symptoms, and they were not correlated with metabolite levels.

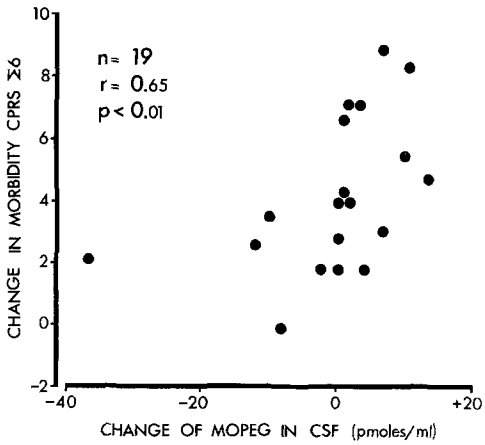


Fig. 2. Relationship between reduction in morbidity score and reduction in MOPEG concentration in CSF in psychotic women after four weeks of thiothixene treatment

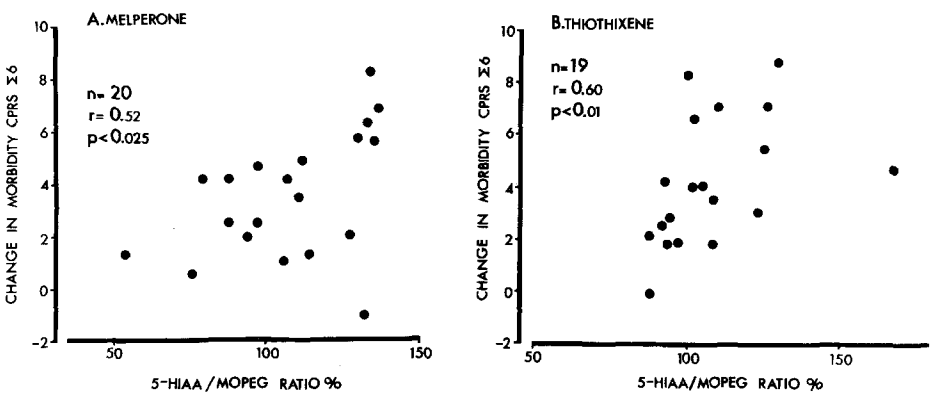


Fig. 3 A and B. Relationship between change in morbidity scores and percentage of change of the 5-HIAA/MOPEG ratio in psychotic women after four weeks of treatment with melperone (A) and thiothixene (B)

| | 2 weeks | 4 weeks |
|---|---|---|
| Melperone | 0.32 | 0.37 |
| Thiothixene | 0.45*** | 0.23 |

*** $P<0.01$

Table 1. Correlation between somnolence and the 5-HIAA/MOPEG ratio

The HVA/MOPEG ratio was significantly negatively correlated with extrapyramidal symptoms in the thiothixene group after both 2 and 4 weeks' treatment ($r = -0.58$, $P<0.01$; $r = -0.50$, $P<0.01$). The 5-HIAA/MOPEG ratio was also negatively correlated with $\Sigma 3_P$ in the thiothixene group after 2 and 4 weeks ($r = -0.47$, $P<0.01$; $r = -0.40$, $P<0.05$).

In the melperone group there were no significant correlations between the extrapyramidal symptoms and the ratios of the monoamine metabolites in CSF.

The side effect somnolence was not significantly correlated with the level of any of the metabolites. In the thiothixene group the 5-HIAA/MOPEG ratio was significantly positively correlated with somnolence after 2 weeks' treatment (Table 1). In neither group were there such correlations after 4 weeks.

*Prolactin Concentrations in Plasma and CSF.* The only correlation between prolactin concentrations and side effects concerned the plasma prolactin level at 4 weeks and extrapyramidal symptoms in the melperone group ($r = 0.65$, $P < 0.025$).

## Discussion

### *Therapeutic Effect*

On the basis of the DA hypothesis, the drug effects of biochemical variables reflecting DA receptor blockade would be expected to correlate with clinical improvement in psychotic patients. Previous studies on patients indicated that the HVA elevation in CSF and the prolactin elevation in plasma may be positively related to therapeutic outcome (Meltzer and Fang, 1976; Sedvall et al., 1976; Sedvall et al., 1977b; van Praag, 1977; Wode-Helgodt, 1977). However, these relationships were fairly weak and not consistently significant.

Previous studies in this project indicate a marked difference between melperone and thiothixene in DA receptor blocking potency. This view was based on animal experiments (Wiesel et al., 1978) and confirmed by data on patients (Bjerkenstedt et al., 1977a and b). The effect evaluation in patients was based on CSF and plasma analysis for HVA and/or prolactin after long-term treatment by the drugs. The CSF was sampled 16 h after the last drug intake. For a quantitative measure an estimate of the response relationships for the metabolite changes in CSF during 24 h is required. But serial CSF sampling is not possible to perform in this type of investigation. The time of day used here for sampling, i.e., in the morning before the first tablet, was selected since at this time there are no rapid changes in drug concentrations such as those which occur later during the day. Ideally one should have biochemical estimates performed repeatedly and use the area under the curve (AUC) for each chemical parameter as indicator for effect. Plasma prolactin was determined at 12 time points throughout the 24 h period in the drug-treated patients (Bjerkenstedt et al., 1977b). All the quantitative data obtained demonstrated that thiothixene induces the greater change in the biochemical measures related to DA receptor blockade. The data gave no indication that melperone could have a stronger effect than thiothixene at any point of the time effect curve. The marked difference between melperone and thiothixene in DA receptor blocking potency gave an opportunity to further explore the relationship between dopaminergic transmission and therapeutic effects of neurologic drugs.

The results indicated that the higher degree and longer duration (Bjerkenstedt et al., 1977b; Wiesel et al., 1978) of DA receptor blockade in the thiothixene-treated patients were not associated with greater therapeutic improvement than that effected by melperone that caused a weaker DA receptor blockade. These results are compatible with the DA hypothesis only if:

1. A weak and/or intermittent DA receptor blockade is sufficient for therapeutic effects, or
2. The biochemical indicators of DA receptor blockade used in the present project are not reflecting the activity of the particular dopaminergic mechanism involved in the antipsychotic action of these drugs.

The first possibility is unlikely since there were no correlations between the antipsychotic effect and the HVA and prolactin concentration in either of the treatment groups. Thus some of the patients showed marked improvement without any indications of DA receptor blockade. The lack of correlation between prolactin levels and clinical improvement may have been due to the fact that women served as subjects in this project. Previous studies showed such correlation in men but not in women (Meltzer et al., 1977; Wode-Helgodt, 1977). The fluctuation of estrogen secretion in women increases the variation in prolactin levels (Wiedeman et al., 1976), possibly masking the drug effects.

It may be argued that the general lack of correlation found in this study between clinical outcome and the biochemical measures of dopaminergic activity may be due to the heterogeneity of the patient group despite the fairly strict inclusion criteria used. However, the finding of fairly strong correlations with other biochemical measures, as will be discussed below, contradicts this possibility.

The second possibility, that of a specific DA receptor with a high sensitivity to the effect of the drugs, cannot be excluded by the present findings. However, not a single antipsychotic drug has been introduced as yet which completely lacks the capacity to block receptors of the striatal or the tubero-infundibular DA neurons that the present biochemical measures reflect. Therefore, even if a different DA receptor mediates the antipsychotic effect, a correlation was expected with the biochemical measures used here that reflect other types of dopaminergic activity.

In conclusion, the present results support the view that antipsychotic drugs in clinical doses interfere with central dopaminergic mechanisms by setting the transmission to a lower level. However, no quantitative relationship could be established between biochemical measures reflecting receptor blockade in the nigrostriatal or tubero-infundibular DA systems and the clinical effectiveness of these drugs. This indicates that in addition to changing DA transmission, other mechanisms play a role in the therapeutic effect of the neuroleptic drugs.

Thiothixene treatment did not alter the concentration of MOPEG, the major NE metabolite, in CSF. However, interestingly, in the thiothixene treated patients there was a positive correlation between clinical improvement and the reduction in MOPEG at the end of treatment. Such a correlation was not found in the melperone-treated patients, while in this group MOPEG declined significantly during treatment. It is unlikely that these effects are due to a change in the motor behavior of the patients, since the effects were not correlated to measures of motor activity in the CPRS.

The findings concerning MOPEG in the treatment reponses to both drugs, therefore, suggest that alteration of noradrenergic transmission is also important in the mechanism of action of antipsychotic agents and/or the pathophysiology of psychosis. The direction of change in MOPEG suggests that improvement in the patient's condition is associated with a reduced noradrenergic transmission.

Similar results and conclusions were reached in studies on patients given chlorpromazine (Wode-Helgodt, 1977) or electroconvulsive treatment (Härnryd et al., 1979). A role for central NE receptors in the mechanism of action of neuroleptics was early postulated by Carlsson and Lindqvist (1963). The present study presents clinical evidence for this view.

The concentration of 5-HIAA in the CSF of the present group of patients before treatment was high in comparison to a healthy control group (Sedvall et al., 1977a), indicating possible disturbances in central 5-HT transmission in some psychotic patients. The 5-HIAA levels, however, did not correlate with psychotic morbidity or with therapeutic outcome. Therefore, the role of the high 5-HIAA levels in the pathophysiology of psychosis is still unclear.

Before treatment there was a negative, but low correlation between the 5-HIAA/MOPEG ratio and psychotic morbitidy. Interestingly, of all the biochemical measures studied here, this metabolite ratio showed the strongest correlation to clinical improvement. Thus, in both treatment groups the improvement in the patient's condition was significantly related to an elevation of the 5-HIAA/MOPEG ratio. These results may indicate that the balance of activity between central 5-HT and NE pathways is related to psychotic morbidity and/or drug-induced improvements.

The 5-HIAA/MOPEG ratio was not significantly altered in any of the treatment groups, whereas the other metabolite ratios, i.e, HVA/5-HIAA and HVA/MOPEG, were markedly elevated (Bjerkenstedt et al., 1977a). Thus most patients had marked elevations of the HVA/MOPEG ratios indicating a substantial pharmacodynamic response to the drug, but the 5-HIAA/MOPEG ratio tended to be elevated only in patients showing marked improvement. This fact raises the question whether the relation found between the 5-HIAA/MOPEG ratio and morbidity results from secondary rather than primary effects of drug treatment, i.e., if the change in the ratio is associated with the improvement itself rather than being caused directly by the drugs.

The present study demonstrated the existence of a biochemical correlate to clinical improvement in both treatment groups. Whether this relationship reflects causal or secondary association with improvement will have to be clarified by further research. This question is of great importance. If it is a causal relationship, it may increase our understanding of the pathophysiology of psychosis and may help in designing new treatment modalities. If it is secondary to the improvement, it may illustrate some of the biochemical events occurring in the central nervous system of patients during remission.

### *Side Effects*

The extrapyramidal side effects were negatively correlated to the level of HVA in CSF after both two and four weeks of thiothixene treatment. Extrapyramidal side effects are believed to result from receptor blockade in the nigrostriatal DA pathway. To explain the negative correlation found, it may be suggested that there was an appearance of extrapyramidal side effects in patients who have a relative functional deficit in the dopaminergic innervation of the basal ganglia.

These patients may lack the capacity to accelerate DA metabolism in response to the drug.

In addition to the dopaminergic mechanisms, the NE system may also be involved in the manifestation of extrapyramidal effects. Both the HVA/MOPEG and 5-HIAA/MOPEG ratios were fairly strongly negatively correlated to the extrapyramidal side effects after two and four weeks of thiothixene treatment. The relationship of NE metabolism to the appearance of the extrapyramidal side effects was opposite in direction to that of DA metabolism. High MOPEG levels were related to the appearance of extrapyramidal side effects. These findings indicate the need for taking into consideration both DA and NE transmission in the causation of extrapyramidal side effects.

In the melperone-treated patients somnolence was negatively correlated with psychotic morbidity after two weeks of treatment ($r = -0.42$, $P<0.05$). In the thiothixene group, and at four weeks in the melperone group, there was no such correlation. At the end of treatment there was no relationship between this side effect and the final therapeutic outcome in either of the treatment groups. These findings contradict the possibility that the correlation between the 5-HIAA/MOPEG ratio and therapeutic outcome found in this study is due to sedation.

It has often been suggested that the antipsychotic effects of neuroleptic drugs are related to their tendency to procedure extrapyramidal side effects (Haase et al., 1969). It has also been alleged that these drugs produce their antipsychotic effect partly through sedation. The correlation found in this study between the different biochemical variables, the side effects, and clinical improvement clearly indicate that the different types of clinical effects can be independent of each other and that each one of them has a specific pattern of biochemical correlates. These findings suggest that the different clinical effects of the neuroleptic drugs are not causally related, but they do seem to be mediated by different mechanisms in the central nervous system.

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