THE IDENTIFICATION OF DEPRESSED PATIENTS WHO HAVE A DISORDER OF NE METABOLISM AND/OR DISPOSITION

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INTRODUCTION

3-METHOXY-4-hydroxyphenethyleneglycol (MHPG) is a naturally occurring catecholamine metabolite which was initially discovered by AXELROD *et al.* (1959). A number of subsequent reports have shown that MHPG is the major metabolite of brain norepinephrine (NE) (MANNARINO *et al.*, 1963; GLOWINSKI *et al.*, 1965; RUTLEDGE and JONASON, 1967; MAAS and LANDIS, 1968; SCHANBERG *et al.*, 1968a, b; SHARMAN, 1969). In addition it has been shown that either direct stimulation of the locus coeruleus or stress produces an increased turnover of NE and an increase in the sulphate conjugate of MHPG in the rat cerebrum, and that these effects are abolished by ablation of the locus coeruleus suggesting that MHPG in brain may reflect functional activity of central noradrenergic neurons (KORF *et al.*, 1973a, b, c). Finally, there is some evidence which suggests that a significant fraction of urinary MHPG has its origins in the metabolism of NE within brain, whereas urinary NE, normetanephrine (NM), and perhaps 3-methoxy-4-hydroxymandelic acid (VMA) originate in pools of catecholamines outside the central nervous system (GLOWINSKI *et al.*, 1965; MAAS and LANDIS, 1965, 1968, 1971; MAAS *et al.*, 1972b, 1973). It should be noted, however, that while there is general agreement that MHPG is the major metabolite of brain NE, definitive information is not available as to the exact amount of MHPG excreted in urine which is derived from brain (BREESE *et al.*, 1972). Despite this uncertainty there is the possibility that urinary MHPG may reflect directly or indirectly NE metabolism in brain, and for this reason it has seemed that assaying urinary MHPG along with other catecholamine metabolites which have their origins outside the central nervous system might be a reasonable strategy for beginning clinical investigations of the catecholamine hypothesis of the affective disorders (SCHILDKRAUT, 1965; SCHILDKRAUT and KETY, 1967; BUNNEY and DAVIS, 1965). In this paper a brief summary of the results of some clinical studies of depressed patients in which this approach has been used will be noted. In addition, attention will be focussed upon pharmacological and clinical methods by which a subgroup of depressed patients who are thought to have a disorder of NE metabolism and/or disposition may be identified. Finally, reports bearing upon the role which state variables, particularly activity, may have in affecting the excretion of NE and its metabolites into urine by normal subjects and depressed patients will be noted.

DIAGNOSIS AND CATECHOLAMINE METABOLITE EXCRETION

In an initial pilot study of MHPG excretion by depressed patients it was found that depressed patients as a group excreted significantly less MHPG than did normal

subjects, whereas the urinary NM and metanephrine (M) levels for the two groups were the same (MAAS *et al.*, 1968). Subsequently, GREENSPAN *et al.* (1970), BOND *et al.* (1972) and JONES *et al.* (1973c) published data indicating that during periods of depression patients excreted significantly less MHPG than they did during episodes of euthymia or mania. It is also of interest that it has been reported that MHPG in the CSF of depressed patients is significantly less than that of control subjects (GORDON and OLIVER, 1971; POST *et al.*, 1973). However, another group did not find decrements in the CSF MHPG of depressed patients, although they did note a tendency for CSF MHPG levels to be elevated during mania (WILKS *et al.*, 1972; SHOPSIN *et al.*, 1973). More recently, in a study containing more subjects, 19 healthy male subjects, 20 seriously depressed male patients, 21 healthy female subjects, and 48 seriously depressed female patients were compared as to the urinary excretion of NM, M, VMA and MHPG. All groups were age matched, were on a VMA exclusion diet, and were free of medication for at least three weeks prior to the collection of two or more separate 24-hr urine specimens which were assayed for the noted catecholamine metabolites. The value for a given metabolite for each subject was taken as the average of the separate determinations. It was found that while male and female patients and controls did not differ as to urinary NM, M, or VMA, there were statistically significant decrements in MHPG excretion by the patient group. These data are presented in Table 1 (DEKIRMENJIAN *et al.*, 1973). There thus seems to be some agreement among different investigators that some patients do in fact have decrements in MHPG excretion during periods of depression.

TABLE 1.

	Males			Females		
	patients $N = 20$	controls $N = 19$	P	patients $N = 48$	controls $N = 21$	P
M	114 ± 22	86 ± 9	NS	97 ± 6	83 ± 9	NS
NM	172 ± 17	196 ± 17	NS	214 ± 17	223 ± 33	NS
VMA	4601 ± 318	4165 ± 656	NS	4378 ± 257	4612 ± 408	NS
MHPG	1394 ± 89	1674 ± 117	$<.05$	1155 ± 58	1348 ± 65	$<.05$

Values are expressed as μg/24 hr.

Inspection of the data presented in the initial report (MAAS *et al.*, 1968), as well as subsequent findings (DEKIRMENJIAN *et al.*, 1973; PRANGE *et al.*, 1971; SCHILDKRAUT *et al.*, in press) and see Table 1), indicate that not every depressed patient excretes less than normal quantities of urinary MHPG. It has been found, however, that those patients who excrete less than normal quantities of MHPG can be identified pharmacologically and clinically. This data may be briefly summarised as follows. In two separate studies ($N = 12$ patients, first study; and $N = 16$ patients, second study), it was found that a low *pretreatment* urinary MHPG predicted a favorable response to treatment with desipramine or imipramine, whereas pretreatment values for NM, M, or VMA were not significantly related to treatment response.* Further, patients

* Patients were not given other specific antidepressant treatments such EST or monoamine oxidase inhibitors, and therefore the relationship of pretreatment MHPG to improvment with these types of therapies is unknown.

who excreted less than normal quantities of MHPG responded with a mood elevation when given *d*-amphetamine, whereas those patients who excreted normal or greater than normal quantities of MHPG had either no response or a worsening of mood after *d*-amphetamine administration. With either *d*-amphetamine, desipramine, or imipramine induced mood elevations, there were modest increments in MHPG excretion, whereas those patients who did not respond had decrements in MHPG excretion (FAWCETT *et al.*, 1972; MAAS *et al.*, 1972a). In contrast, it has been reported that depressed patients who excrete normal or greater than normal quantities of MHPG respond well to amitryptilline (SCHILDKRAUT *et al.*, 1971). These findings are interpreted as being generally consistent with and supportive of the possibility that there is a functional deficiency of central nervous system NE in a subgroup of depressed patients and that these patients may be identified by pretreatment urinary MHPG levels.

While these pharmacological-behavioural methods of identifying patients who excrete less than normal amounts of MHPG are of particular interest in terms of the biochemical genesis of depressive illness, they are time consuming, do not lend themselves readily to use by other investigators, and make large N studies difficult if not impossible. For these reasons, investigations as to the possibility that those patients who excrete less than normal amounts of MHPG might be easily and quickly identified by explicit clinical criteria are of particular interest. The results of studies from our group dealing with this issue of the relationship between clinical classifications of depressed patients and catecholamine metabolite excretion have been presented in detail elsewhere (JONES *et al.*, 1973b) and are summarised in that which follows. The clinical classifications chosen for study were (1) severe agitated and retarded depressions (2) unipolar (single episode and recurrent types) or bipolar illness (types I and II) (3) psychotic or neurotic depressions (with psychosis being defined by the presence of a thought disorder), and (4) the method used by the Washington University group, i.e., primary affective disorder, secondary affective disorder, or affective disorder undiagnosed type (ROBBINS and GUZE, 1971; FEIGHNER *et al.*, 1972; ROBBINS *et al.*, 1972; BAKER *et al.*, 1971). The sample studied consisted of 32 female patients having depressions of sufficient severity to warrant hospitalisation and 21 outpatient, healthy women of approximately the same age who were clinically judged to be free of gross psychopathology and significant depression. All subjects were off medication for at least three weeks prior to study and were maintained on a VMA exclusion diet. A minimum of two separate 24-hr urines were collected and assayed for M, NM, VMA and MHPG without knowledge of diagnosis. It was found that (i) urinary levels of M, NM, or VMA were not significantly different between patients and controls, nor were there significant differences for these metabolites between any of the subgroups. (ii) There were no significant differences in urinary MHPG levels between agitated depressives or retarded depressives in the total sample, and normal subjects. (iii) The presence or absence of a thought disorder per se, i.e., psychosis, does not distinguish patients from controls in terms of MHPG excretion. (iv) The patient group diagnosed as having unipolar illness ($N = 27$) did not differ significantly from control subjects in urinary MHPG. (v) The mean MHPG excretion by the bipolar group ($N = 5$) was 916 ± 43 μg MHPG/24 hr, and that for the control subjects was 1328 ± 85 μg/24 hr, and the difference between these groups is statistically significant ($P < 0{\cdot}025$). This finding is generally consistent with other

data which indicates that bipolar type depressed patients excrete significantly less MHPG than do patients with depressions of a characterological type (SCHILDKRAUT *et al.*, in press). (vi) As noted previously, the *total* patient group excreted less MHPG than did the healthy subjects, but the level of statistical significance was weak ($P < 0{\cdot}05$). In contrast, those depressed patients who had been classified as having a primary affective disorder ($N = 21$) excreted 1032 ± 63 μg MHPG/24 hr, whereas the control subjects ($N = 21$) excreted 1348 ± 65 μg/24 hr, and here the difference was highly significant ($P = 0{\cdot}0005$). When those subjects who were diagnosed as having primary affective disorders were subdivided into bipolar, unipolar recurrent, unipolar single episode types and were compared with healthy subjects by ANOVA, a significant F was obtained, and the use of the Duncan's Multiple Range Test indicates that none of the subtypes of the primary affective disorder group differ from each other, whereas all of them are significantly different from the control group. This data is presented in Table 2.

TABLE 2.

	Primary affective disorders			
	Bipolar ($N = 5$)	Unipolar recurrent ($N = 9$)	Unipolar single epsiode ($N = 7$)	Comparison group ($N = 21$)
MHPG (μg/24 hr)	916 ± 152	1066 ± 86	1073 ± 140	1348 ± 65

No statistically significant differences between the primary affective disorder group or any of its subtypes and control subjects for VMA, NM, or M were found. The primary affective disorder group did not differ significantly from the control subjects in age [patients 48 ± 3 (range 24–62) and controls 42 ± 2 (range 21–59)]. Within this primary affective disorder depressed group there were 7 patients who were markedly agitated and 10 patients who were retarded. The former group excreted 1030 ± 108 μg MHPG/24 hr, and the latter 986 ± 65 μg MHPG/24 hr. An ANOVA in which these two groups and healthy subjects were compared indicated statistically significant differences, with the agitated and retarded groups both being significantly different from the controls but not from each other. Finally, those depressed patients who as a group were diagnosed as having affective disorders, undiagnosed type ($N = 11$) excreted 1322 ± 174 μg MHPG/24 hr. The variance for the undiagnosed group is quite large, and their mean is not significantly different from the means of either the primary or control groups. As measured by Nurse's depression ratings, Hamilton scores, or an item on the BPRS, there were no differences in the severity of depression between the primary and undiagnosed affective disorder groups.

In brief, those patients who were classified as having primary affective disorders, depressed type, had levels of urinary MHPG which were clearly and consistently less than normal. This relationship between the diagnosis of primary affective disorders and low urinary MHPG has implications for both improved treatment and biochemical studies of depression.

THE PROBLEM OF STATE VARIABLES AND ARTIFACTUAL RESULTS

Data presented elsewhere indicate that age, smoking, 24-hr urine volume, height, weight, body surface area, and creatinine are not significantly related to urinary MHPG (24-hr specimens) in patients or controls (DEKIRMENJIAN *et al.*, 1973). There are sex differences in MHPG excretion, as well as pharmacological effects of tricyclic drugs (DEKIRMENJIAN *et al.*, 1973; PRANGE *et al.*, 1971; MAAS *et al.*, 1972a; SCHILDKRAUT *et al.*, 1965). All patients and control subjects in the study reported above were free of medication for three weeks, however, and in these summarised clinical classification studies (JONES *et al.*, 1973b) all subjects were females, and for this reason it seems unlikely that the above variables are operative in producing the cited results.

It has been reported that activity may alter urinary MHPG levels (EBERT *et al.*, 1972), but our data which indicates that this variable cannot alone account for the cited relationship between urinary MHPG and certain types of depression may be summarised as follows. (i) Five healthy, young male subjects were exercised for 2 hr on two of three consecutive days using standardised isometric and isotonic exercse procedures. The exercise protocols were moderately severe in that marked fatigue was produced in all subjects. Urinary levels of NE, NM, M and MHPG and plasma MHPG were measured for the two hour periods before, during and after exercise. A 3- to 5-fold increase in urinary NE was present after both exercise procedures. No increase in urinary MHPG or M was observed during or 2 hr after exercise. Slight increases of plasma MHPG and urinary NM were observed during one of the two exercise periods compared to the 2 hr preceding exercise (GOODE *et al.*, in press) (ii) As noted above, agitated and retarded depressed patients were chosen for study as to MHPG excretion. Only retarded patients who were clinically judged to be free of an agitation component to their illness were selected. One patient was classified as having an agitated stupor and one a retarded stupor. No significant differences in urinary quantities of MHPG between these two types of patients within the group as a whole or within the primary affective disorder group were found (JONES *et al.*, 1973a, b). (iii) A patient who shifted from depression into mania on two occasions and from mania into depression once has been followed longitudinally in terms of 24-hr urinary MHPG or NM levels. It was found that the increments in MHPG and possibly NM preceded by as much as four days the shifts from a retarded depression into a hyperactive manic state (JONES *et al.*, 1973c).

SUMMARY

The data given here lead us to conclude that in a subgroup of depressed patients who may be identified clinically (primary affective disorders), biochemically (low MHPG), and pharmacologically (good response to desipramine, imipramine and amphetamine), there is a significant alteration in the metabolism and/or disposition of NE which is integral to the depressive illness *per se*.

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