

Increased Excretion of Dimethyltryptamine and Certain Features of Psychosis

A Possible Association

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• The excretion of the hallucinogen dimethyltryptamine (DMT) and its precursor *N*-methyltryptamine (NMT) was studied among 74 recently admitted psychiatric patients and 19 normal persons. Both compounds were detected in 24-hour urine samples from all subjects. Dimethyltryptamine excretion was greatest in schizophrenia, mania, and "other psychosis" and tended to decline as clinical state improved. Psychotic depressives excreted smaller amounts of DMT more akin to those excreted by neurotic and normal subjects. Urinary NMT excretion was unrelated to psychiatric diagnosis. Ratings on the Present State Examination (PSE) also indicated that increased excretion of DMT was associated with psychotic rather than neurotic psychopathology. Forty-three percent of the variance in urinary DMT levels could be explained in terms of six of the 38 PSE syndromes. Syndromes suggesting elation, perceptual abnormalities, and difficulty in thinking and communicating were most correlated with raised urinary DMT excretion.

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There has been recurrent speculation over a possible etiological role for transmethylation in schizophrenia, and in recent years interest has centered on the indolamine dimethyltryptamine (DMT).¹⁻³ There is ample proof that DMT has hallucinogenic properties⁴⁻⁶ and some, though less satisfactory, evidence that the enzymic pathways for its formation are present in animals and man.⁷⁻¹⁰ But, there remains doubt as to whether DMT is present in greater amounts or metabolized differently in schizophrenic patients.¹¹⁻¹²

Much of this uncertainty stems from the inadequate characterization by many investigators of both the patients studied and the compounds identified. The availability of more reliable means of describing psychiatric symptoms and of determining DMT levels in body fluids has advanced our potential for resolving this controversy. Using a qualitative method with a sensitivity limit of 500 ng/24 hr, Rodnight et al¹³ found DMT in the urine of 47% of schizophrenics, 37% of those with other nonaffective psychosis, and only 5% of normal subjects. However, in an equally stringent study using similar means of case identification, Carpenter et al¹⁴ failed to detect DMT more frequently in the urine of schizophrenics than normals. The reason for the discrepancy between these two studies may be the relative sensitivities of the qualitative methods used, particularly since Oon et al,¹⁵ employing a quantitative method with a sensitivity limit of 20 ng/24 hr, identified DMT in the urine of all 19 normal subjects tested, but only one individual (5%) excreted more than 500 ng/24 hr.

If this explanation is correct, then the use of the more sensitive quantitative technique should demonstrate significant differences in the amount of DMT excreted by psychotic patients and normal individuals. This communication reports the testing of this hypothesis, and the effect of clinical change on the excretion of DMT by psychotic patients.

SUBJECTS AND METHODS

Ninety-three individuals were studied, 74 of whom were patients admitted over a 12-month period to two South London psychiatric hospitals. The ages of the 37 male and 37 female patients ranged from 16 to 65 years. Shortly after admission (mean, nine days), a 24-hour urine sample was obtained from each

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of them. The remaining 19 individuals consisted of seven normal males and 12 normal females from whom urine was collected for control purposes and who have been described in greater detail.¹⁵ None of the individuals studied had received any psychotropic medication other than benzodiazepines in the two weeks prior to the urine collection; 32 patients had received benzodiazepines during this period.

Biochemical Methods

Urine was collected in plastic containers without the addition of preservative. The pH and total creatinine level were measured immediately on receipt of the samples, which were then frozen at -15°C and stored pending analysis. Urinary DMT and N-methyltryptamine (NMT) levels were measured by a procedure with a limit of detection of $20\text{ ng}/24\text{ hr}^{-1}$ for DMT, and $50\text{ ng}/24\text{ hr}^{-1}$ for NMT.¹⁶ Of each 24-hour sample, 50% was concentrated in a rotary evaporator to 70 mL and extracted with toluene at alkaline pH. The resulting extract was purified by preparative thin-layer chromatography and injected into a gas chromatograph fitted with a nitrogen-sensitive detector. An internal standard of 5-methyldimethyltryptamine was added to the concentrated urine to account for variations in recovery. Recovery of added DMT or 5-methyldimethyltryptamine ($1\mu\text{g}/500\text{ mL}$ of urine) was of the order of 40%; there was no evidence that the internal standard was differentially recovered from urine samples from different groups of subjects. As described elsewhere,^{15,16} the specificity of the method was validated for ten urine samples by gas chromatography/mass spectrometry using the technique of mass fragmentography. For these samples, excellent qualitative and quantitative agreement between the two methods was obtained.

Psychiatric Assessment

All the patients were interviewed by one of the authors (R.M.M.) in a semistandardized fashion using the ninth edition of the Present State Examination (PSE), which has been developed as a reliable means of assessing psychiatric symptoms.¹⁷ The ratings on the 140 PSE items are grouped to produce 38 syndromes (eg, auditory hallucinations or situational anxiety), each with a score comprising the summed scores of its constituent items, and syndrome scores are processed by a computer program named Catego to lead to a standardized diagnostic grouping. We slightly modified the PSE to cover only the preceding week, and not the preceding month, as the instructions stipulate. Thus, the psychopathology ratings in this study refer to a period closer to the date of the urine collection than those in our previous work.¹³

At the time of discharge, the hospital notes of all the patients were scanned and a note was taken of the diagnosis made by the hospital psychiatrists according to the *British Glossary of Mental Disorders*.¹⁸ Information from the notes and from the PSE interviews was then combined, enabling the patients to be categorized according to the operational criteria of the American DSM-III.¹⁹

Statistics

Both parametric and nonparametric methods were used to assess associations and differences among variables. Parametric methods were applied to the natural logarithms of DMT and NMT whenever these variables were used. This was to counteract the skewed distribution of the raw scores for these two variables and to equalize variances in the analysis of variance procedures as checked by the Bartlett homogeneity of variance test statistic.

The results presented are those of the parametric analyses such as Pearson product moment correlations, and analysis of variance with Tukey range tests for subsequent comparisons between pairs of groups. Where possible, these analyses were repeated using a suitable nonparametric alternative, and in such cases, the signifi-

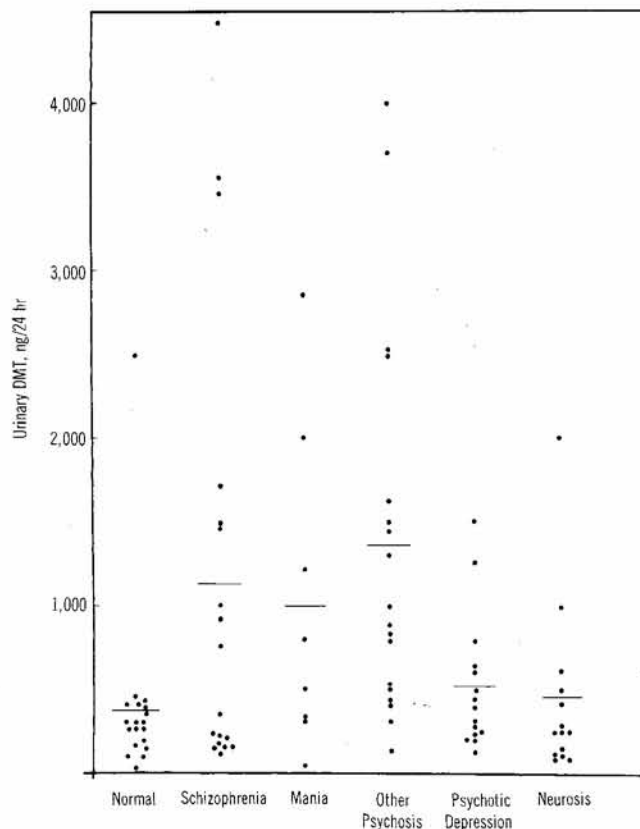


Fig 1.—Urinary dimethyltryptamine (DMT) excretion and hospital diagnosis. Horizontal lines represent mean values.

cant results presented are for those tests where the two analyses agreed.

RESULTS

General

Both DMT and NMT were detected in the urine samples of all the subjects tested. The mean excretion rates among the normal subjects were $386\text{ ng}/24\text{ hr}$ for DMT and $856\text{ ng}/24\text{ hr}$ for NMT; in 18 of the 19 normal subjects, the DMT excretion rate was below $500\text{ ng}/24\text{ hr}$ and in 16 of the 19, the NMT rate was below $1,000\text{ ng}/24\text{ hr}$. The distribution of values for DMT is shown in Fig 1. In neither the normal subjects nor the patients were the excretion rates of DMT and NMT related to age, urinary volume, pH, or creatinine level, and the rates for the monomethylated and dimethylated compounds were not intercorrelated. When DMT excretion was examined in relation to sex for the total group, men excreted significantly more than women ($P < .025$). This, however, was due to the unequal sex distribution among the various diagnostic categories. When DMT excretion was examined in relation to sex within these categories, the apparent sex difference disappeared.

Diagnosis

Individuals considered by the hospital psychiatrists to have a psychotic illness had significantly higher levels of urinary DMT than did normal subjects ($P < .05$), but those with neurotic illness did not. There was a trend for those

Table 1.—Urinary Indoleamine Levels in Relation to Catego Diagnosis

Catego Diagnosis	Catego Class	No. of Subjects	Mean Dimethyltryptamine Level, ng/dL	Mean Monomethyltryptamine Level, ng/dL
Schizophrenic and paranoid psychosis	S ⁺ , P ⁺	26	1,223	678
Manic psychosis	M ⁺	10	1,022	897
Uncertain "other psychosis"	0	4	1,656	816
Uncertain schizophrenia and paranoid psychosis	S?, P?	7	640	340
Depressive psychosis	D ⁺ , D?	4	319	501
Retarded depression	R ⁺	9	487	613
Neurotic conditions	N ⁺ , A ⁺ , X	14	604	684
Normal subjects	...	19	386	856

with schizophrenia, mania, or "other psychosis" to excrete larger amounts of DMT than the normal subjects (Fig 1), but this difference reached significance only for those categorized as "other psychosis" ($P < .05$).

Similar findings resulted when urinary DMT excretion was compared with the diagnosis made by the Catego program on the basis of PSE scores (Table 1). Individuals classified as having nonpsychotic illness (R⁺, N⁺, A⁺, X) did not differ in their DMT excretion from normals, but those with psychotic illness did ($P < .05$). Within the broad category of psychosis, patients with schizophrenia and paranoid psychosis (S⁺, P⁺), mania (M⁺), and uncertain "other psychosis" (0) had high levels of urinary DMT, whereas those with depressive psychosis (D⁺, D?) had levels no higher than those of neurotic and normal individuals.

Twenty-two patients satisfied the DSM-III criteria for schizophrenia. When these patients were subdivided according to the DSM-III categories for course of illness and for types of illness, there were no significant differences in DMT excretion either between subgroups or between any subgroup and normals.

No matter by which means patients were classified, urinary NMT levels were not related to psychiatric diagnosis. Neither was there any relationship between the DMT/NMT ratio and diagnosis.

Psychopathology

The scores on the individual PSE syndromes were summed to give a global measure of the degree of psychiatric disturbance of each patient, and this total score compared with the log of the urinary DMT and NMT levels by means of Pearson's correlation coefficient. Total PSE score was significantly correlated with urinary DMT levels ($r = .25$, $P = .012$), but not with urinary NMT levels. The 38 PSE syndromes can also be divided into four groups, and the scores for the syndromes in each group summed. Neither summary scores for specific neurotic syndromes or for nonspecific neurotic syndromes were related to urinary DMT or NMT levels. However, summary scores for syndromes of delusions and hallucinations (DAH) and for syndromes of speech and behaviour abnormalities (BSO) were both highly correlated with urinary DMT excretion ($r = .27$, $P = .007$), though not with urinary NMT excretions.

Twenty of the PSE syndromes are usually associated with psychosis, and 18 more frequently associated with neurosis. Figure 2 illustrates the mean DMT levels for

patients in whom the various syndromes were either present or absent. In 18 of the 20 psychotic syndromes, the mean DMT level was higher for those patients in whom the syndrome was present, while this situation occurred in only eight of the 18 neurotic syndromes. When scores on individual syndromes were related to the excretion of the DMT, the following were significantly correlated: grandiose and religious delusions ($r = .35$, $P < .001$), delusions of persecution ($r = .31$, $P < .002$), nonspecific psychosis ($r = .30$, $P < .003$), organic impairment ($r = .29$, $P < .004$), auditory hallucinations ($r = .27$, $P < .007$), self-neglect ($r = .27$, $P < .007$), and doubtful interview ($r = .30$, $P < .01$). Only organic impairment was significantly related ($r = .27$, $P < .001$) to urinary NMT excretion.

It was theoretically possible that some of the seven syndromes significantly correlated with urinary DMT excretion might have been so because of their close relationship with another syndrome genuinely related to DMT excretion. An analysis of partial correlations showed that the correlations between the above variables and DMT levels remained almost unaffected when each of the remaining variables in this set were controlled.

A stepwise linear regression analysis revealed that 35% of the variance in urinary DMT levels could be explained in terms of the syndromes of grandiose and religious delusions, organic impairment, and delusions of persecution, and 43% when self-neglect, doubtful interview, and auditory hallucinations were also considered.

Repeat Measurements

An attempt was made to obtain repeat 24-hour urine samples following significant recovery from patients who had been initially diagnosed by Catego as psychotic; significant recovery was defined as a score on the combined DAH/BSO index that had fallen to 33% or less of the original score. For a variety of reasons (eg, early discharge or failure to recover sufficiently), this was only possible in 22 patients (43%). Figure 3 shows that DMT excretion had fallen in 14 of these 22, remained relatively static in four, and increased in four. Dimethyltryptamine excretion fell in 14 of the 15 patients whose original excretion was greater than 500 ng/24 hr, but nine of the total 22 patients still excreted more than 500 ng/24 hr following significant recovery. While the total PSE scores of those whose repeat DMT levels were greater or less than 500 ng/24 hr were similar, the mean combined DAH/BSO score of the former was 2.7, compared with 1.25 for the latter.

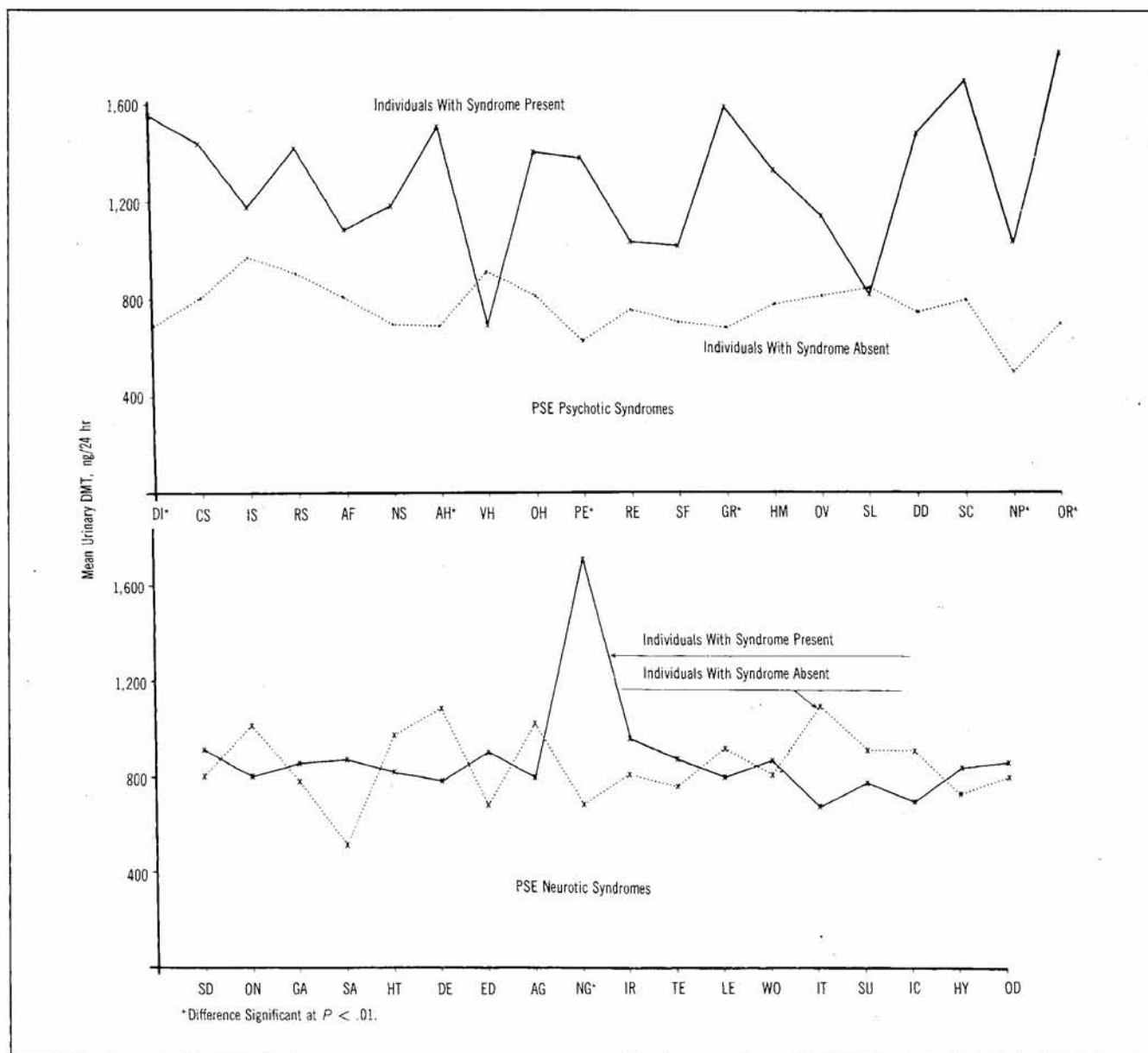


Fig 2.—Relationship between urinary dimethyltryptamine (DMT) excretion and presence or absence of specific psychopathology by Present State Examination (PSE). AF indicates blunt affect; AG, agitation; AH, auditory hallucinations; CS, catatonic syndrome; DD, depressive delusions; DE, depersonalization; DI, doubtful interview; ED, special features of depression; GA, general anxiety; GR, grandiose/religious delusions; HM, hypomania; HT, hysteria; HY, hypochondriasis; IC, loss of interest/concentration; IR, ideas of reference; IS, incoherent speech; IT, irritability; LE, lack of energy; NG, self neglect; NP, nonspecific psychosis; NS, nuclear syndrome; OD, other symptoms of depression; OH, olfactory hallucinations; ON, obsessional neurosis; OR, organic impairment; OV, overactivity; PE, delusions of persecution; RE, delusions of reference; RS, residual syndrome; SA, situational anxiety; SC, subcultural delusions/hallucinations; SD, simple depression; SF, sexual/fantastic delusions; SL, slowness; SU, social unease; TE, tension; VH, visual hallucinations; and WO, worrying.

COMMENT

This study confirms our previous finding¹¹ of significant differences in the excretion of DMT between acutely psychotic and normal subjects. It is now clear that these differences are quantitative, rather than qualitative, and that normal people do excrete DMT, but in smaller amounts than many acute psychotics. Moreover, such differences are not absolute, in that some normal or neurotic individuals can excrete relatively large amounts of DMT without evidence of present or past psychosis.

Additional evidence that increased excretion of DMT need not be associated with psychosis comes from our previous demonstrations that elevated urinary DMT levels occurred during treatment with a monoamine oxidase inhibitor,¹⁵ and in some patients with liver failure.²⁰ Urinary DMT does not originate in diet or intestinal bacteria, but appears to reflect endogenous production.¹⁵ The increase in the excretion of DMT in liver failure suggests that urinary DMT originates elsewhere than in the urinary tract, which in any case is not well endowed with the necessary

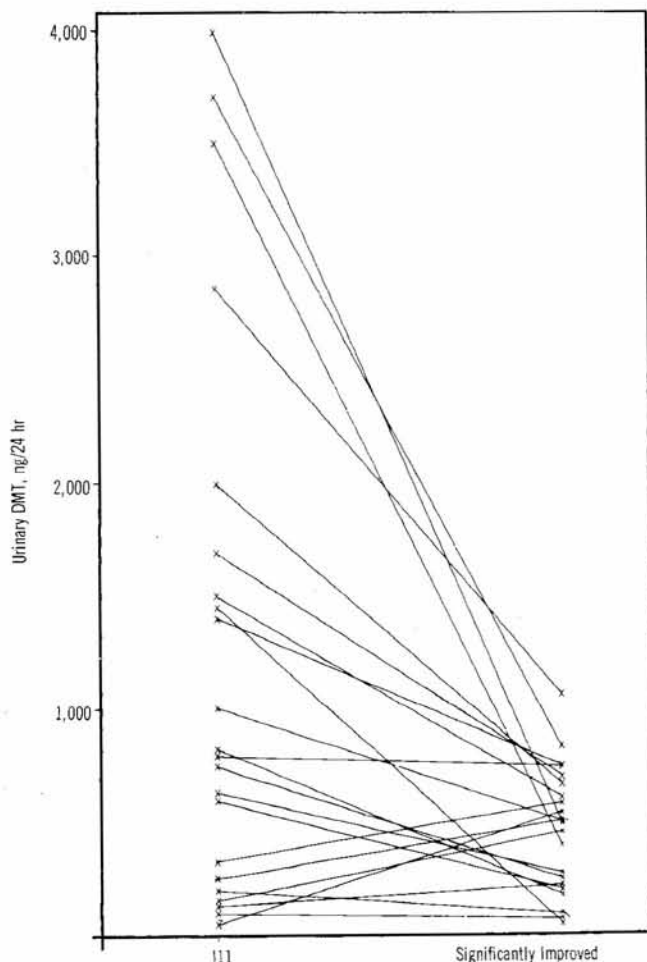


Fig 3.—Urinary dimethyltryptamine (DMT) excretion in 22 psychotic patients before and after significant improvement (significant improvement defined as decrease in combined delusions and hallucinations/behavior and speech abnormalities index to 33% or less of original score).

methyltransferase enzyme. Thus, increased circulating DMT is not necessarily accompanied by psychosis, and therefore cannot be considered as a single or inevitable cause of schizophrenia or other psychoses. Similarly, the fact that 44% of schizophrenics and 43% of all psychotic patients in our study excreted no more than 500 ng of DMT per 24 hours shows that increased circulating DMT is not a necessary causal factor for psychosis in general or for schizophrenia in particular.

Nevertheless, the excretion of DMT is raised in certain psychotic conditions, and often declines after recovery from psychosis. At the time of significant recovery, three quarters of the patients were receiving antipsychotic medication, whereas none were at the time of the initial collections. It could, therefore, be argued that the decrease of DMT excretion was a direct consequence of the administration of neuroleptics. The effects of neuroleptics on the pharmacological actions of DMT in animals have been investigated.^{21,22} Although neither of these studies shed any light on the effects of neuroleptic drugs on the formation or excretion of DMT, we have previously found

Table 2.—Dimethyltryptamine Excretion and Psychiatric Diagnosis in Our Present and Previous Studies*

Hospital Diagnosis	% (No.) of Patients	
	Rodnight et al, ¹² 1976	Present Study
Schizophrenia	47 (42)	56 (18)
"Other psychosis"	38 (18)	67 (18)
Mania	10 (10)	50 (8)
Psychotic depression	14 (10)	33 (15)
Neurosis	19 (32)	29 (14)
Normal	5 (20)	5 (19)

*Percentage of patients excreting more than 500 ng of dimethyltryptamine per 24 hours.

no relationship between antipsychotic medication and urinary DMT levels.^{11,17}

Table 2 shows the percentage of subjects from the various diagnostic categories in this and our previous study who excreted more than 500 ng of DMT per 24 hours (the approximate detection limit in the first study). A higher proportion of subjects excreted more than 500 ng of DMT per 24 hours in all diagnostic categories in the second study than in the first, but otherwise, there were considerable similarities. In both studies, schizophrenics and "other psychotics" excreted relatively large amounts of DMT, and psychotic depressives, smaller amounts more akin to those excreted by neurotic patients. The major disparity between the two studies was that a hospital diagnosis of mania was much more closely associated with raised DMT excretion in the second study than in the first. However, in the first study, three out of four patients given a Catego diagnosis of mania had raised DMT levels, and hypomania was the PSE syndrome most closely related to elevated urinary DMT excretion.

Although the PSE ratings in the present study referred to a shorter period than in our first study, increased DMT excretion was once again associated with syndromes pertaining to delusions and hallucinations and behaviour and speech abnormalities, rather than with those concerned with neurotic psychopathology.

On present evidence, it seems unlikely that DMT is causally related to schizophrenia or to other traditional psychotic disease entities. Alternative explanations include the possibility that increased DMT could be an intermediary factor produced by some sick individuals, thus exacerbating certain features of their psychosis, ie, be related to symptom pathogenesis, rather than central etiology. The similarity between the syndromes associated with DMT excretion in our two studies and the symptoms known to be induced by extraneous DMT¹¹ suggests that the possible role of DMT as a mediator of specific symptoms should be further examined. A less likely possibility is that increased DMT could be a chemical marker suggesting increased transmethylation and the increased circulation of as yet undetected psychotoxin. It is perhaps more likely that DMT production increases as a consequence of some psychoses. There are parallels between our results and the findings of raised creatinine phosphokinase levels in the blood of some acute psychotics²³ and in retrospect, it would have been valuable to have estimated this in our patients to

assess whether the two measures might covary.

The mechanism whereby urinary DMT excretion is increased remains uncertain. Monoamine oxidase is the major catabolic enzyme for DMT and NMT, as well as their precursor, tryptamine.²⁴ Individuals with intrinsically low levels of monoamine oxidase might not only have decreased catabolism of DMT and NMT, but also, increased biosynthesis through the blocking of the catabolism of tryptamine by increasing its N-methylation. Some psychotic patients appear to have abnormally low levels of platelet monoamine oxidase,^{25,26} but as this enzyme is largely under genetic control and does not vary significantly during psychotic illness,²⁶ it could not by itself explain the increase in urinary DMT excretion, seen in acute psychosis. Furthermore, when we administered the monoamine oxidase inhibitor iproniazide to a subject, we observed an increase in both urinary DMT and NMT excretion,¹³ whereas in the present study, psychosis was not associated with increased excretion of NMT.

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