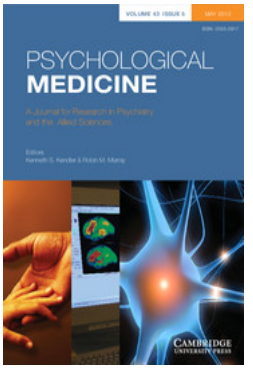

Urinary dimethyltryptamine and psychiatric symptomatology and classification

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Psychological Medicine / Volume 6 / Issue 04 / February 1977, pp 649 - 657
DOI: 10.1017/S0033291700018304, Published online: 09 July 2009

Psychological Medicine, 1976, **6**, 649–657

Urinary dimethyltryptamine and psychiatric symptomatology and classification

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SYNOPSIS The excretion of dimethyltryptamine (DMT) was studied amongst 122 recently admitted psychiatric patients and 20 normal subjects. DMT was detected in the urine of 47% of those diagnosed by their psychiatrists as schizophrenic, 38% of those with other non-affective psychoses, 13% of those with affective psychoses, 19% of those with neurotic and personality disorders and 5% of normal subjects. Ninety-nine patients were interviewed in a semi-standardized fashion, and also categorized according to a variety of operational definitions of the psychoses. The operational definitions failed to reveal any group significantly more correlated with urinary DMT than a hospital diagnosis of schizophrenia, but a discriminant function analysis of symptomatology could be used to define a group of 21 patients of whom 15 (71%) excreted detectable DMT. There was a general relationship between psychotic symptoms and urinary DMT, but specifically schizophrenic symptoms did not appear to be major determinants of DMT excretion.

INTRODUCTION

The notion that some endogenously produced toxic chemical might be implicated in the aetiology of the functional psychoses has a long history. Much biological research into schizophrenia has been characterized by the quest for such a psychotoxic agent, but none has yet been found. Indeed, after an exhaustive review of the literature Wyatt and his colleagues (1971) were able to state: 'To date, no biochemical abnormalities have been consistently and exclusively associated with schizophrenia.' Recent interest in schizophrenia has focused on two hypotheses which are not necessarily mutually exclusive: the dopaminergic hypothesis (Randrup & Munkvad, 1972; Snyder *et al.* 1974) and the transmethylation hypothesis. This paper is concerned with one aspect of the latter.

The transmethylation hypothesis proposes that some psychoses may be caused by the abnormal accumulation of a methylated biogenic amine. This hypothesis, originally suggested by Harley-Mason and Osmond & Smythies in 1952, gained impetus from the demonstration by Pollin *et al.* (1961) that when chronic schizophrenic patients are given a monoamine oxidase inhibitor plus a methyl group donor such as methionine, some will develop an acute psychosis. These workers were unable to determine whether the psychosis was schizophrenic in nature or merely a non-specific toxic reaction. Cohen *et al.* (1974), reviewing ten replication studies, concluded that a third of the 107 patients showed an exacerbation of functional psychosis in the absence of organic signs.

In the search for methylated compounds which might mediate this clinical deterioration, attention was focused throughout the 1960s on methylated products of the catecholamines. 3,4-dimethoxyphenylethylamine was proposed as the supposed pathogenic agent (Friedhoff & van Winkle, 1962). However, this substance is not hallucinogenic in man and initial suggestions that it appeared selectively in the urine of schizophrenic subjects have not been substantiated (Wyatt *et al.* 1971; Boulton, 1971). More recently methylated indoleamines – *N,N*-dimethyltryptamine (DMT), 5-methoxy-*N,N*-dimethyltryptamine and *N,N*-dimethylserotonin

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(bufotenin) – have re-emerged as possible hallucinogenic products of transmethylation.

The most intriguing of these is DMT, which when injected in single doses to human volunteers can mimic some psychotic symptoms (Kaplan *et al.* 1974). Tryptamine, the precursor of DMT, is present in the human brain (Saavedra & Axelrod, 1972), and elevated tryptamine concentrations have been reported in the urine of some schizophrenics (Himwich, 1970). The enzyme which catalyses the transfer of methyl groups of *S*-adenosyl-methionine to tryptamine to yield DMT has been demonstrated in the human lung (Mandel *et al.* 1972) and possibly the human brain (Mandell & Morgan, 1971; Saavedra & Axelrod, 1972), while the *in vivo* formation of DMT has been reported in the brains of rats pretreated with monoamine oxidase inhibitors (Saavedra & Axelrod, 1972; Wu & Boulton, 1973). Wyatt *et al.* (1973) have reported significantly higher levels of DMT forming enzyme in the platelets of acute schizophrenics than normals.

In the last few years reliable methods of determining the presence of DMT in human body fluids have become available (Walker *et al.* 1973). But in planning any biochemical investigation into psychosis, one is immediately confronted by the lack of a clear consensus (Cooper *et al.* 1972) among psychiatrists about what they mean by schizophrenia. One way of surmounting this difficulty is by the use of strict operational definitions of schizophrenia and other psychotic conditions. Another method is to ignore diagnostic categories and instead attempt to correlate symptoms and signs, elicited in a standardized fashion, with biological variables. We decided to use both of these methods in a study of the frequency with which DMT was present in the urine of different groups of recently admitted psychiatric patients.

METHODS

SUBJECTS

The study included 122 patients without significant organic disease admitted over a 12-month period to three South London psychiatric hospitals. There were 67 men and 55 women, and their ages ranged from 16 to 83 years; 107 were receiving drugs (20 only benzodiazepines). Shortly after admission (mean 11 days) a 24-hour urine specimen was obtained from each patient and evaporated to 10% of its original volume. For control purposes 24-hour urine samples from 11 normal men and 9 normal women were also obtained.

DETECTION OF DMT

DMT was extracted by the procedure of Narasimhachari *et al.* (1971*b*); further purified by preparative thin layer chromatography on silica, and its presence determined by both gas chromatography and by thin-layer chromatography on cellulose (Baumann & Narasimhachari, 1973). A positive identification of DMT was only made when both these methods were in agreement. The recovery of the extraction procedure (for 2·5 μg) was 32% and the lowest amount detectable was 0·5 μg per 24-hour urine specimen. As a check the area containing putative DMT from the preparative thin-layer plate was further analysed by gas chromatography/mass spectrometry in two patients and in a pooled extract from ten patients; the resultant mass spectra were identical with that of authentic DMT. All analyses were carried out by one of us (M.O.) who had no knowledge of the clinical state of the patients.

INTERVIEWS

The last 99 of the 122 patients were interviewed by one of us (either R.M.M. or I.F.B.) in a semi-standardized fashion using the 9th edition of the Present State Examination (PSE), which has been developed as a reliable means of assessing psychiatric symptomatology (Wing *et al.* 1974). The first 23 patients and the normal subjects were not interviewed. The PSE contains 140 items each representing a probe for a particular symptom or sign. The ratings on certain groups of items can be summed to produce 38 'syndromes', e.g. 'auditory hallucinations' or 'situational anxiety'. Each 'syndrome' has a score comprising the summed scores of its constituent items. The syndromes can then be processed by a computer program named Catego to lead to a standardized diagnostic grouping.

DIAGNOSTIC CRITERIA

At the time of discharge, or after 3 months continuous hospitalization, the hospital notes of all

122 patients were scanned. A note was taken of the diagnosis made by the hospital psychiatrists according to the British Glossary of Mental Disorders (Registrar General, 1968) which is based on the 8th revision of the International Classification of Diseases. For the 99 patients who had been personally interviewed information from the notes and the PSE interviews was then combined enabling the patients to be categorized according to a number of different operational definitions of psychotic illness. The criteria for schizophrenia were Catego class 'S', Schneider's first rank symptoms (Schneider, 1959), Langfeldt (1937), the 'flexible system' of Carpenter *et al.* (1973), the New Haven Schizophrenia Index (Astrachaan *et al.* 1972), and the operational definitions of Feighner *et al.* (1972) and Forrest & Hay (1973). The criteria for schizoaffective psychosis were those of Kasanin (1933), Forrest & Hay (1973) and R. E. Kendell & I. M. F. Brockington (1976, unpublished). The criteria for paranoid psychosis were Catego class 'P', and the operational definition of Forrest & Hay (1973), for mania Catego class 'M', and those of Feighner *et al.* (1972), and for depressive psychosis Catego class 'D'.

RESULTS

DMT was detected in the urine of 38 subjects. Its detection was unrelated to urinary volume or creatinine, age, sex or (for the patients) hospital; neither was it significantly related to the length of psychiatric history, length of present illness, the number of days since admission, nor to the type or length of medication.

HOSPITAL DIAGNOSIS

As shown in Table 1, DMT was found more frequently in the patients than in the normal controls ($\chi^2 = 4{\cdot}41$, $P<0{\cdot}05$). Detection of DMT was then compared with the diagnoses ascribed to the patients by the hospital psychiatrists. DMT was found in 31 of the 90 (34%) diagnosed as psychotic as against 6 out of the 32 (19%) said to be suffering from neurosis or personality disorder; this difference was not significant. DMT was detected significantly more frequently in the urine of schizophrenics than of normals ($\chi^2 = 9{\cdot}16$, $P<0{\cdot}01$), of those with neurosis and personality disorder ($\chi^2 = 6{\cdot}64$, $P<0{\cdot}05$), and of those with affective psychosis ($\chi^2 = 9{\cdot}26$, $P<0{\cdot}01$). The only group in which DMT was detected almost as frequently as among schizophrenics were the 18 individuals with 'other non-affective' psychosis. These 'other psychotics' included 3 patients with probable drug-induced psychosis, 2 with involutional paraphrenia and 1 each with epileptic and puerperal psychosis. In the remaining 11 patients the diagnosis remained in doubt with schizophrenia one possibility in 9 of these; detection of DMT was not especially associated with this latter group.

OTHER DIAGNOSTIC CRITERIA

Table 2 shows the results of applying different operational definitions of the psychoses to the 99 interviewed patients and the relationship of the groups thus defined to the detection of DMT. The number categorized as schizophrenic varied widely with the different criteria, e.g. only 13 patients met Forrest & Hay's criteria, while 39 met those of Astrachaan *et al.* (1972). Furthermore, criteria which produced similar numbers of schizophrenics did not necessarily include the same patients; of the 32 patients diagnosed as schizophrenic by the hospital psychiatrists and 33 so diagnosed by Catego, only 21 patients were common to both groups.

The percentage of patients with detectable DMT in their urine ranged from 33% of those meeting the criteria of Carpenter *et al.* (1973) to 53% of those meeting Forrest & Hay's (1973) criteria. To ascertain whether DMT was associated with some core group of schizophrenics, its detection was analysed in relation to the number of criteria which a patient satisfied for schizophrenia. Twenty-one per cent of those who satisfied one or two criteria were DMT positive, rising to 50% of those who satisfied four or five, and falling to 20% of those who satisfied seven or eight criteria. The relationship between the various operationally defined psychoses and the excretion of detectable DMT was measured by Cohen's kappa coefficient; this is interpreted as a measure of agreement over and above that due to chance and is to be preferred to the correlation

TABLE 1

RELATIONSHIP BETWEEN HOSPITAL DIAGNOSIS AND URINARY DMT

	Schizophrenia	Affective psychosis	'Other' psychoses	Neurosis and personality disorder	Normal
No. of subjects	42	30	18	32	20
Mean age ± SD (years)	30·0±11·5	45·3±14·7	28·0±13·4	36·5±13·0	32·5±11·6
No. of subjects in whom DMT detected	20	4	7	6	1
% of subjects in whom DMT detected	47	13	38	19	5

TABLE 2

URINARY DMT IN RELATION TO DIFFERENT CRITERIA FOR SCHIZOPHRENIA APPLIED TO 99 PATIENTS

	Hospital psychiatrists	Catego (S)	Schneider's first rank symptoms	Feighner's criteria	Langfeldt's poor prognosis	Carpenter's criteria (6 present)	New Haven schizophrenia index	Forrest & Hay's criteria	Consensus diagnosis (4 out of 8 definitions satisfied)
No. of patients	32	33	26	18	26	20	39	13	33
No. of patients in whom DMT detected	15	13	11	8	12	6	18	7	12
% of patients in whom DMT detected	47	39	42	44	46	33	46	53	36
Kappa coefficient ± SD	0·26±0·11	0·14±0·11	0·17±0·12	0·15±·013	0·22±0·12	0·01±0·13	0·29±0·10	0·19±0·13	0·23±0·11

TABLE 3

URINARY DMT IN RELATION TO DIFFERENT CRITERIA FOR SCHIZOAFFECTIVE PSYCHOSIS, PARANOID PSYCHOSIS AND AFFECTIVE PSYCHOSIS IN 99 PATIENTS

	Number of patients	Number of patients in whom DMT detected	% patients in whom DMT detected	Kappa coefficient ±SD
Schizoaffective psychosis				
Hospital psychiatrists	5	4	80	+0·16±0·14
Kendell & Brockington	29	10	34	+0·05±0·12
Kasanin	7	0	0	−0·13±0·15
Forrest & Hay	8	1	12	−0·08±0·15
Paranoid psychosis				
Catego 'P'	6	1	17	−0·05±0·15
Forrest & Hay	11	5	45	+0·18±0·12
Mania				
Hospital psychiatrists	10	1	10	−0·12±0·15
Catego 'M'	4	3	75	+0·05±0·15
Feighner *et al.*	6	1	17	−0·04±0·15
Psychotic depression				
Hospital psychiatrists	14	2	14	−0·12±0·14
Catego 'D'	8	2	25	−0·02±0·14

TABLE 4

MEAN PSE SYNDROME SUMMARY SCORES FOR 99 PATIENTS IN RELATION TO URINARY DMT

	Total summary score	Syndromes of delusions and hallucinations	Syndromes of speech and behaviour abnormalities	Specific neurotic syndromes	Non-specific neurotic syndromes
Patients in whom DMT detected	25·1	6·1	4·4	4·4	10·1
Patients in whom DMT not detected	26·6	4·9	3·8	6·2	11·7

coefficient in this situation. Its variance can be calculated approximately from the equation:

$$\text{var}(\kappa) = \frac{P_o(1-P_o)}{N(1-P_c)^2}.$$

The value of κ can be compared with its standard deviation and the result referred to the normal distribution (Everitt, 1968). Only three agreements were significant at the level $P<0{\cdot}05$. These were those between DMT excretion and a hospital diagnosis of schizophrenia, schizophrenia as defined by the criteria of Astrachaan *et al.* (1972), and a consensus diagnosis of schizophrenia, i.e. four out of eight definitions satisfied.

The 99 interviewed patients were also categorized according to various definitions of schizoaffective psychoses, paranoid psychosis, mania and depressive psychosis (Table 3). None of these criteria revealed groups highly associated with DMT with the exception of a hospital diagnosis of schizoaffective disorder and a Catego diagnosis of mania; both of these criteria produced very small numbers of patients.

PSYCHOPATHOLOGY

The data derived from PSE interviews were then further examined in relation to urinary DMT. First the scores on the individual syndromes were summed to give a measure of the degree of psychiatric disturbance of each patient. The mean summary score of the patients in whom DMT was detected was 25·1 and for DMT negative patients it was 26·6. Thus, urinary DMT was not related merely to the number of symptoms present.

The 38 PSE 'syndromes' can be divided into four groups, and the scores for the 'syndromes' in each group summed (Table 4). DMT positive patients achieved a higher mean summation score than DMT negative patients on those

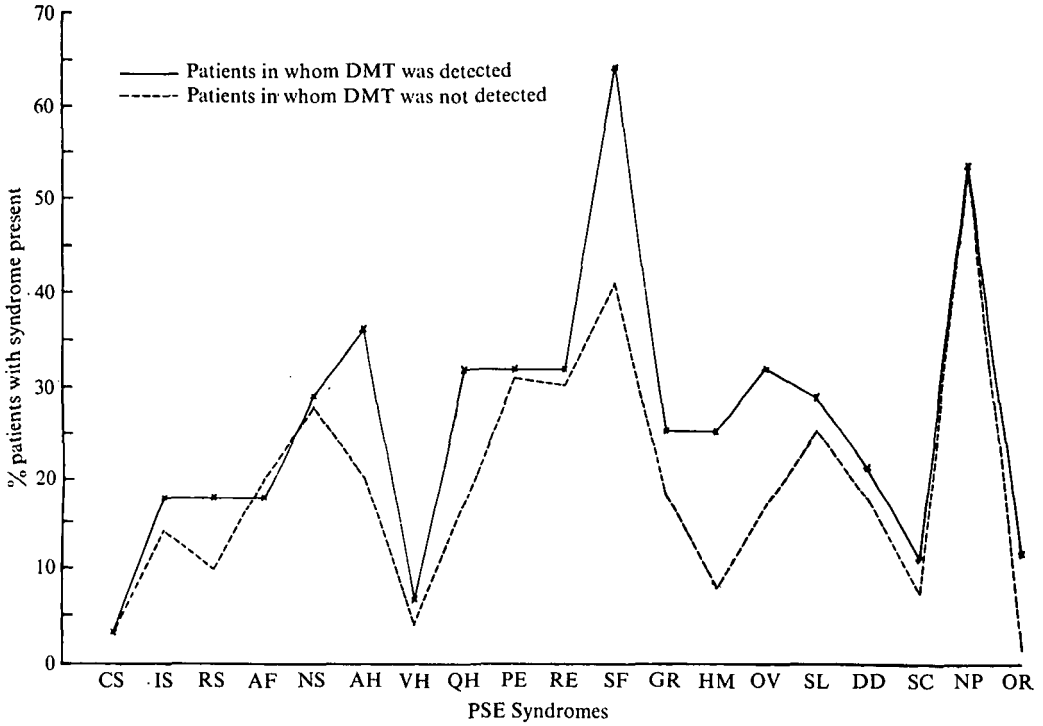

FIG. 1. Relationship between DMT excretion and PSE psychotic 'syndromes'. CS, Catatonic syndrome; IS, incoherent speech; RS, residual syndrome; AF, affective flattening; NS, nuclear syndrome; AH, auditory hallucinations; VH, visual hallucinations; QH, Olfactory hallucinations; PE, delusions of persecution; RE, delusions of reference; SF, sexual and fantastic delusions; GR, grandiose and religious delusions; HM, hypomania; OV, overactivity; SL, slowness; DD, depressive delusions and hallucinations; SC, 'subcultural' delusions and hallucinations; NP, non-specific psychosis; OR, organic impairment.

'syndromes' pertaining to delusions and hallucinations (6·1 as against 4·9), and also on those 'syndromes' concerned with behaviour and speech abnormalities (4·4 as against 3·8). On the other hand, DMT negative patients obtained a higher mean summation score than DMT positive patients on specific neurotic 'syndromes' (6·2 compared with 4·4) and to a lesser extent on non-specific neurotic 'syndromes' (11·7 compared with 10·1). Statistical tests on these summed syndrome scores are of little value because of the error introduced in combining categorical syndrome scores.

From the 38 'syndromes' of the PSE, 19 can be extracted which are usually associated with psychosis. Fig. 1 illustrates the 'psychotic' profile of the DMT positive and negative patients. In 16 of the 19 'psychotic syndromes' the percentage of patients with the syndrome present is smaller for DMT negative patients than DMT positive patients. Compared with a random distribution hypothesis, such a result is very highly significant ($P<0·001$). There was a non-significant trend towards the remaining syndromes being present more frequently in the DMT negative patients.

The PSE data were also analysed in relation to presence or absence of hallucinations or delusions. Seventeen of the 28 (60%) patients in whom DMT was detected were categorized as being hallucinated compared with only 20 of the 71 (28%) in whom DMT was not detected; this difference was highly significant ($\chi^2 = 9·09$; $P<0·01$). Twenty-two of the 28 patients (78%) in whom DMT was detected were categorized as deluded as against 45 of the 71 patients (63%) in whom DMT was not detected; this difference failed to reach statistical significance ($\chi^2 = 2·12$). When individual syndromes were related to detection of DMT it was found that

differences reached minimal statistical significance for only two 'syndromes': 'sexual and fantastic delusions' were more frequently found in those with detectable DMT ($\chi^2 = 4{\cdot}42$, $P < 0{\cdot}05$), as was 'hypomania' ($\chi^2 = 4{\cdot}82$, $P < 0{\cdot}05$). The apparent association of these 'syndromes' with excretion of DMT may be spurious, due to the large number (38) of chi-squared tests carried out.

DISCRIMINATION ANALYSIS

A discriminant function analysis was carried out using the 27 Catego 'syndromes' which distinguished best, on the basis of chi-squared tests, between the DMT positive and DMT negative patients. The resulting distribution of z scores was clearly unimodal but a z score of 0·90 could be used to separate 21 patients from the rest of the sample of whom 15 excreted detectable DMT. This is a higher proportion than any category produced by the operational definitions (Table 2), as shown by a Cohen's kappa coefficient of 0·47. However, it should be emphasized that this is a maximum figure which would certainly be lower if repeated in a second population. Patients with z scores below 0·90 did not correspond with patients fulfilling four out of eight definitions of schizophrenia ($\kappa = 0{\cdot}20$; not significant at the 0·05 level). In addition, the multiple correlation coefficient between the best set of variables and DMT excretion at only 0·43 was also not significant at the 0·05 level.

DISCUSSION

We are aware of the potential pitfalls in this type of research (Wyatt *et al.* 1971; Rodnight, 1975). Biochemical processes in the brain may bear scant relation to the composition of peripheral body fluids, which in turn may be affected by age, sex, dietary and nutritional history, as well as medication and chronic hospitalization. All our patients had been admitted only recently when studied, and the excretion of DMT did not appear to be related to either age or sex, or to the length or type of medication. All were eating comparable hospital food, but we did not study or control their diet. However, excluding all preformed indoleamines from the diet of one subject did not appear to affect excretion of DMT.

Since the rapid metabolism of DMT renders it only transiently detectable in blood, we decided to use a 24-hour specimen as a pool for total body excretion. There are, however, disadvantages to this. First, the source of urinary DMT is unknown. Secondly, Kaplan *et al.* (1974) found that at most only 0·16% of an injected dose of DMT was recovered in the urine over 6 hours. Thirdly, it is possible that alterations in urine pH may affect the excretion of DMT, as may changes in bowel status. In unpublished studies we have found that within physiological limits acidification or alkalinization of the urine had negligible effects on the excretion of DMT, as did sterilization of the gut.

Previous studies of DMT in human body fluids have been contradictory. Narasimhachari *et al.* (1971*a*) claimed to find DMT in the serum of 15 of 22 acute schizophrenics, but only 2 of 20 non-schizophrenics. Mandel (1974) found DMT in the whole blood, plasma or serum of 4 out of 46 chronic schizophrenics and 3 out of 66 patients with other psychotic disorders. Bidder *et al.* (1974) found DMT in the urine of 7 out of 39 psychiatric patients; Narasimhachari and his colleagues (1972) reported that 4 out of 6 drug free chronic schizophrenics sporadically excreted DMT while 7 normals did not.

On the other hand, Carpenter *et al.* (1975) found no differences in the frequency with which DMT was detected in the urine of 12 acute schizophrenics and 9 normal subjects. Their patients were all acute and 'generally had adequate work and social function before admission'. American psychiatrists are more prone to diagnose schizophrenia than their British counterparts (Cooper *et al.* 1972). However, Carpenter and his colleagues interviewed their patients using the PSE, and the majority were assigned to either a schizophrenic or paranoid psychosis category by the Catego computer program. Unfortunately, they do not state the proportion of the patients who were assigned to each group. This information may be important since 39% of our patients diagnosed as schizophrenic by Catego were DMT positive as opposed to 17% of those so diagnosed as paranoid psychosis.

A further possible explanation as to why our two studies have reached contradictory results concerns the relative sensitivities of the respective methods of detecting DMT. As Wyatt *et al.* (1971) pointed out, in a situation where a substance exists in greater concentration amongst a patient group than in normals, a very insensitive method may not detect it in either group, a moderately sensitive method may detect it only in patients, while a very sensitive method may detect it equally frequently in both groups. It may be that our method of detecting urinary DMT corresponds to the second of these alternatives, while that of Carpenter *et al.* to the third. Quantitative methods of estimating DMT are needed to resolve the discrepancy in the two studies.

The original work of Narasimhachari *et al.* (1972) claimed a specific relationship of DMT excretion with schizophrenia. Superficially our study appears to confirm this in that a significant excess of patients with schizophrenia excreted detectable DMT whether the diagnosis of schizophrenia was made by the patients' clinicians or based on various operational definitions. However, a study of the detailed psychopathology did not suggest that specifically schizophrenic symptoms, either singly or in combination, were major determinants of DMT excretion. 'First rank symptoms', auditory hallucinations, and affective flattening were not statistically associated with DMT excretion, nor did they figure prominently in the discriminant function seeking an optimal prediction of the presence of DMT. The search for a specific clinical syndrome associated exclusively with the excretion of detectable DMT was unsuccessful; if the PSE results showed anything it was a general link between DMT detection and a range of psychotic 'syndromes'.

We are currently carrying out a replication study using a quantitative method for detecting DMT some ten times more sensitive than that used in this investigation. Results so far suggest that DMT is excreted by normal subjects in amounts generally below the detection level of the method employed in the investigation reported here. Even if this study confirms that DMT is excreted in larger amounts in some psychoses, it is important to emphasize that this does not imply causality.

Our thanks are due to the medical and nursing staff of the Bethlem Royal, Maudsley and St Francis Hospitals, and especially to Professor R. E. Kendell, D. Carrera, S. Wainwright, and L. Fergusson. This research was supported by grants from the Medical Research Council, the Research Fund of the Bethlem Royal and Maudsley Hospitals and the Wellcome Trust.

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