J. Psychiat. Res., 1965, Vol. 3, pp. 125–131. Pergamon Press Ltd. Printed in Great Britain.

PSYCHOPATHOLOGY AND 5-HYDROXYINDOLEACETIC ACID EXCRETION

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(*Received* 15 *February* 1965)

(*Revised* 6 *April* 1965)

INTRODUCTION

CONSIDERABLE indirect evidence, associating serotonin with central nervous system function and the actions of important psychotropic drugs, led to suggestions[1,2] of a relationship between serotonin metabolism and schizophrenia. Despite considerable effort, experimental support for this suggestion has been inconclusive. Among studies in this area are those on quantitative excretion, and variability of excretion, of serotonin's major metabolite, 5-hydroxyindoleacetic acid, by various diagnostic populations, and on the relationship between such excretion and clinical symptomatology. Thus, schizophrenics have been reported variously to excrete supernormal,[3–5] subnormal,[6] and normal[7–13] amounts of this metabolite, and to show excessive variability in excretion. More recently a direct relationship between urinary levels of 5-hydroxyindoleacetic acid and other tryptophan metabolites and clinical symptomatology has been reported.[15–18]

As part of a larger multidisciplinary study on the attributes of schizophrenia,† it was possible to examine some of these reports on a large population maintained under controlled conditions.[19,20] The present paper deals with a comparison of the quantitative excretion of 5-hydroxyindoleacetic acid by various diagnostic populations, and an analysis of the correlations between such excretion and pertinent biological and behavioral variables.

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† This investigation was carried out as part of the Schizophrenia and Psychopharmacology Joint Research Project, supported by USPHS MY–1972, MY–4567 and MH–07293–01. The author is indebted to Mr. T. Best for technical assistance, Mr. N. Mattsson for statistical help, and Drs. R. W. Gerard, S. Gershon and E. Geller for their helpful comments.

MATERIALS AND METHODS

Subjects. Schizophrenic and nonschizophrenic subjects 18–50 years of age were drawn from the male population of Ypsilanti State Hospital. Admission to the research ward was contingent upon unanimous concordance on primary diagnosis (obtained independently by three psychiatrists) and the absence of concurrent physical illnesses. All psychiatrists had access to the medical records.

Diagnostic subdivisions into paranoid schizophrenic, non paranoid schizophrenic, nonschizophrenic with chronic brain syndrome, and nonschizophrenic without chronic brain syndrome were established by the majority judgment of the three psychiatrists on the predominant psychiatric and medical state of the subjects. While unanimity was not required, it was achieved in the majority of cases. 123 subjects (63 schizophrenics and 60 nonschizophrenics) were admitted to the research ward in diagnostically mixed groups of five. Medication was terminated two months before testing, and subjects were maintained on an unvarying diet with daily vitamin supplementation throughout their stay on the research ward. A three-week period of dietary adjustment was allowed. Baseline biochemical determinations were made during the fourth week when diet was rigidly controlled and ward observation carried out. Specimens were discarded from subjects failing to consume their diet completely. The mean age of the schizophrenics in this study was 35·8 ± 8·25* years, and they had been hospitalized for 54·4 ± 77·4 months. Psychiatric and ward ratings were carried out using Lorr MSRPP[21] and the Gorham Ward Rating Scale.[22]

Specimens. Urines were collected over 24-hour periods and were refrigerated at 5°C between collections. Analytical determinations were carried out daily. Estimations of 5-hydroxyindoleacetic acid were not carried out on samples having a pH greater than 6·9.

Methods. Urinary 5-hydroxyindoleacetic acid was estimated by the procedure of UDENFRIEND *et al.*,[23] creatinine by a Jaffe reaction[24] and sodium by flame photometry. In most instances individual figures for 5-hydroxyindoleacetic acid and sodium are the average of two samples taken two days apart, while figures for total volume and urinary creatinine are the means for five determinations. Reported values, therefore, are the means of such individual averages. Cross- and intra-correlations were computed from daily individual 24-hour values, rather than pooled mean values, and the variables in question.

RESULTS AND DISCUSSION

Comparisons of the 5-hydroxyindoleacetic acid excretion by various diagnostic populations (Table 1) substantiate those investigations[7–14] concluding that schizophrenics and nonschizophrenics do not differ in 5-hydroxyindoleacetic acid excretions. Non paranoid schizophrenics did differ significantly ($P < 0{\cdot}05$) from both paranoid schizophrenics and nonschizophrenics with chronic brain syndrome in the urinary concentration of 5-hydroxyindoleacetic acid but not in total daily excretion. However, of the 30 cross comparisons

* Mean ± standard deviation.

TABLE 1. MEAN EXCRETION OF 5-HYDROXYINDOLEACETIC ACID BY VARIOUS DIAGNOSTIC POPULATIONS

	N	Mean μg/ml	S.D. μg/ml	Mean mg/24h	S.D. mg/24h
Schizophrenics	63	4·47	2·58	4·46	2·35
Paranoid	22	3·86	1·70*	5·28	2·62
Nonparanoid	41	4·79	2·92*	4·02	2·08
Nonschizophrenics	60	4·36	2·34	5·06	2·76
CBS†	22	4·65	2·59*	5·54	3·49
Non CBS	38	4·23	2·26	4·69	2·27

* Nonparanoid schizophrenics differ from paranoid schizophrenics $P < 0{\cdot}05$, and from nonschizophrenics with chronic brain syndrome $P < 0{\cdot}05$.
† Nonschizophrenics with chronic brain syndrome.

TABLE 2. RELATIONSHIP BETWEEN SELECTED PSYCHIATRIC FACTORS AND 24 h 5-HYDROXYINDOLEACETIC ACID EXCRETION BY SCHIZOPHRENICS

Psychiatric item definition	*N*	*r**	*P*†	*P*‡	S–NS§
Lorr A—Depression vs excitement	60	+0·176	NS	<0·001	+
Lorr B—Compliance vs resistiveness	61	−0·027	NS	<0·05	+
Lorr C—Paranoid projection	59	−0·095	NS	<0·001	+
Lorr D—Activity (under vs over)	60	+0·067	NS	<0·01	−
Lorr E—Melancholy agitation	60	+0·110	NS	<0·01	−
Lorr F—Perceptual distortion	60	−0·085	NS	<0·001	+
Lorr G—Motor disturbance	61	−0·227	NS(<0·1)	<0·001	+
Lorr H—Submissive vs belligerent	61	+0·030	NS	<0·001	−
Lorr I—Withdrawal (more vs less)	61	+0·413	<0·001	<0·001	−
Lorr J— Self depreciation vs grandoise expansion	61	−0·107	NS	NS	+
Lorr K—Conceptual disorganization	60	−0·222	NS(<0·1)	<0·001	+
Gorham 1—Activity level	61	+0·180	NS	<0·01	−
Gorham 2—Anxiety level	61	−0·104	NS	<0·001	+
Gorham 3—Mental disorganization	61	−0·262	<0·05	<0·001	+
Gorham 4—Mood (depressed vs euphoric)	61	+0·114	NS	<0·01	−
Gorham 5—Interpersonal relations (less vs more withdrawn)	61	−0·373	<0·01	<0·001	+
Gorham 6—Anger	61	+0·076	NS	NS	+

* Pearson correlation coefficient.
† Probability of the correlation; NS signifies not significant.
‡ Distinguish between schizophrenics and nonschizophrenics at the indicated probability level.
§ + Mean for schizophrenics greater than mean for nonschizophrenics.
− Mean for schizophrenics less than mean for nonschizophrenics.

between schizophrenics, nonschizophrenics, and their various sub-populations in this analysis, one and one-half differences of the 0·05 level would be expected by chance alone, and it is unlikely that the two statistical differences observed had clinical significance.

It is also of interest that the variance was nearly identical for schizophrenics and nonschizophrenics; and ranges of individual values for 24-hour excretion was also comparable between these groups. The extreme values for schizophrenics ranged from 1·09 mg/24 h (a non paranoid schizophrenic) to 12·79 mg/24 h (a paranoid schizophrenic) while the extremes among nonschizophrenics were 1·11 mg/24 h to 11·69 mg/24 h (two nonschizophrenics without chronic brain syndrome). Thus, it would appear that schizophrenics do not show greater variability than nonschizophrenics on this measure when both are maintained under similar environmental conditions.

It has been suggested[17] that 'exacerbations of schizophrenic activity in terms of aggravations of hallucinatory and delusional experiences as well as agressiveness and hostility' are accompanied by increased urinary excretion of tryptamine, indole-3-acetic acid, and 5-hydroxyindoleacetic acid. Correlations between 5-hydroxyindoleacetic acid excretion and various pertinent behavioral and biological variables were analyzed, therefore, to assess the validity of the postulated relationship for this compound. The correlations between metabolite excretion and LORR[21] and GORHAM[22] rating factors, presented in Table 2, not only fail to support this suggested relationship, but even suggest the opposite trend, of *decreasing* psychopathology with increasing 5-hydroxyindoleacetic acid excretion. Excretion of 5-hydroxyindoleacetic acid correlated significantly with withdrawal on both the Gorham 5 and Lorr I in the direction of less withdrawal with higher excretion, and with the Mental Disorganization Factor, Gorham 3, in the direction of less mental disorganization with higher excretion. Correlations with other rating factors failed to reach statistical significance, but, with the exception of the Lorr A, all were in the direction of decreased schizophrenic psychopathology with increased 5-hydroxyindoleacetic acid excretion. The Lorr I and the Gorham 5 in this study correlated remarkably well for these types of measures ($r = 0{\cdot}764$, $P = 0{\cdot}001$, $N = 99$) so that both factors seem to be estimating similar phenomena. Although single rating factors may not fully reflect global pathology, 15 of the 17 Lorr and Gorham scale items distinguished schizophrenics from nonschizophrenics in this study and 10 did so at $P < 0{\cdot}001$.

Because of the difficulty in specifying clinical state and environmental conditions precisely it is conceivable that the negative relationship between 5-hydroxyindoleacetic acid and psychopathology observed in this cross-sectional study and the positive relationship reported in longitudinal studies may reflect extraneous influences on 5-hydroxyindoleacetic acid excretion. For example, the nine schizophrenic subjects studies by BERLET *et al.*[17] ranged in age from 39–59 years (mean 53) and were hospitalized for from 6–28 years (mean 19). The schizophrenics in our study were younger (35·8 $\pm$ 8·2 years of age) and had been hospitalized for a lesser period (4·53 $\pm$ 6·45 years). However, in our study, hospitalization (but not age) correlated negatively with 5-hydroxyindoleacetic acid excretion ($r = -0{\cdot}381$; $P < 0{\cdot}01$), so that neither experimental difference alone appears to account for the differences in the findings. As expected, hospitalization and, to a lesser extent, age correlated positively with increasing psychopathology (Table 3).

TABLE 3. RELATIONSHIP AMONG SCHIZOPHRENICS BETWEEN PSYCHIATRIC RATING FACTORS, AGE AND HOSPITALIZATION, URINE VOLUME AND URINARY CREATININE

Rating factor	Age		Hospitalization		Urine volume		Creatinine	
	r*	P†<	r	P<	r	P<	r	P<
Lorr A		NS		NS	+0·238	0·05	+0·268	0·01
B		NS	+0·237	0·05	−0·202	0·05	−0·271	0·01
C		NS		NS		NS		NS
D		NS	−0·222	0·05	+0·248	0·05		NS
E	−0·231	0·05	−0·251	0·05	+0·201	0·05		NS
F		NS		NS		NS	−0·257	0·05
G		NS		NS		NS	−0·268	0·01
H	−0·272	0·01	−0·194	0·05		NS		NS
I	−0·236	0·05	−0·514	0·001	+0·406	0·001	+0·485	0·001
J		NS		NS		NS		NS
K		NS	+0·268	0·01		NS	−0·382	0·001
Gorham 1		NS	−0·199	0·05	+0·250	0·05	+0·220	0·05
2		NS		NS		NS	−0·212	0·05
3	+0·189	0·05	+0·521	0·001	−0·265	0·01	−0·445	0·001
4		NS		NS	+0·240	0·05		NS
5	+0·264	0·01	+0·399	0·001	−0·364	0·001	−0·444	0·001
6	−0·191	0·05	−0·231	0·05		NS		NS

* Pearson correlation coefficient.
† Probability of the correlation; NS signifies not significant.

The most reasonable remaining explanation of these findings is that 5-hydroxyindoleacetic acid reflects physical changes resulting from or accompanying psychopathology. Thus, and in agreement with the findings of BERLET *et al.*[26], 24 h creatinine excretion correlated with 5-hydroxyindoleacetic acid excretion ($r = +0{\cdot}588$; $N = 61$; $P < 0{\cdot}001$), as did 24 h urine volume ($r = +0{\cdot}399$; $P < 0{\cdot}001$), 24 h urinary sodium ($r = +0{\cdot}506$; $P < 0{\cdot}001$), and 24 h urinary potassium excretion ($r = +0{\cdot}404$; $P < 0{\cdot}001$). Further, these latter variables also generally correlated with psychiatric items in the direction of decreasing values with increasing psychopathology (Table 3), the opposite direction from that reported by BERLET *et al.*[26] As anticipated, creatinine excretion, in this study, correlated positively for both schizophrenics and nonschizophrenics with such anthropometric measures as body weight, calf girth and lean body weight. Hospitalization, however, correlated negatively with the creatinine excretion of schizophrenics and positively with excretion by nonschizophrenics. A possible interpretation is that this reflects a gradual physical deterioration among schizophrenics during chronic hospitalization, in contrast to a physical restoration among nonschizophrenics, particularly sociopaths, during their shorter hospitalization. Chronic schizophrenic psychopathology, then, would be accompanied by a continued loss of muscle mass, reflected in decreased creatinine excretion, and decreased 5-hydroxyindoleacetic acid excretion. Transitory exacerbations of psychopathology superimposed on this basic pattern could temporarily hasten this degenerative process, increasing creatinine excretion during rapid loss of muscle mass, as suggested by BERLET *et al.*, and concommitantly heighten excretion of 5-hydroxyindoleacetic acid. This interpretation, while reconciling

these apparently discrepant findings, also suggests that 5-hydroxyindoleacetic acid excretion is more closely related to physical state than to psychopathology: however, a direct relationship between psychopathology and indole excretion is not excluded particularly since 5-hydroxyindoleacetic acid is considered a less sensitive indication of behavioral change than is tryptamine or indole-3-acetic acid.

SUMMARY

Schizophrenics and nonschizophrenics do not differ in urinary excretion of 5-hydroxyindoleacetic acid on either a concentration or 24 h basis, nor do they differ in variability of excretion. Although a pattern was observed of decreasing psychopathology with increasing 5-hydroxyindoleacetic acid excretion, this pattern may be related to alterations in physical state accompanying psychopathology rather than to psychopathology *per se*.

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