ethylamine in the urine of two normal subjects did not increase after oral administration of 0·5 g of 3,4-dihydroxy-L-phenylalanine and the amine could not be detected in the urine of two patients with pheochromocytoma. In urine of three groups of five rats each given intramuscular injections of 3,4-hydroxy-L-phenylalanine (100 mg/kg body-wt.), dopamine (10 mg/kg) and norepinephrine (1 mg/kg) respectively, 3,4-dimethoxyphenylethylamine could not be detected. Considering the chemical structure of the amine, an endogenous precursor would probably be either dopamine or 3-methoxytyramine. A large amount of the latter compound was consistently detected in urine from both human subjects and rats after the administration of either 3,4-dihydroxy-L-phenylalanine or dopamine. These results imply that 3,4-dimethoxyphenylethylamine originates from dietary sources or is a product formed by intestinal bacteria.

An amine indicated as No. 6 in Fig. 1 was frequently observed on the chromatograms of urine from schizophrenic patients who had received chlorpromazine. It was purified by a combination of ion exchange chromatography and counter current distribution techniques, and was tentatively identified as 10-(3-aminopropyl)-2-chloro-5-oxyphenothiazine from the results of elemental analysis, infra-red and ultra-violet absorption spectra. The occurrence of this compound in human urine as a metabolite of chlorpromazine was reported by Fishman and Goldenberg[5].

It is of interest that another unidentified compound (Fig. 1, No. 7) was observed more frequently in the urine of schizophrenics (25/62) than in the urine of normal subjects (2/21) and psychoneurotics (2/21). This substance was detected as a purple spot with ninhydrin reaction and did not react with any of several other reagents. This compound might also originate from dietary sources because the amount excreted daily varied widely. It should be mentioned that the R_F value of this amine is similar to that of 3,4-dimethoxyphenylethylamine in the first solvent system, which is the system used by Friedhoff and Van Winkle. Therefore, the metabolite of chlorpromazine and the other unidentified substance might be confused with 3,4-dimethoxyphenylethylamine. The other amines numbered 1–4 in Fig. 1 were observed in all specimens of urine and the amines numbered 8–11 were detected frequently.

Masashi Takesada
Yasuo Kakimoto
Isamu Sano
Ziro Kaneko

Department of Neuropsychiatry,
Osaka University Medical School,
Osaka, Japan.

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The preceding communication confirming the presence of 3,4-dimethoxyphenylethylamine in the urine of schizophrenic patients[1,2] is of considerable interest. The fact that their procedure differed in some respects from ours adds further support to our identification of this compound.

It should be pointed out that interfering compounds have been described by us. We have sometimes found it necessary to resolve 3,4-dimethoxyphenylethylamine by the use of 2 successive solvents. Several satisfactory solvent systems are described in our publications. In general, however, 3,4-dimethoxyphenylethylamine can be distinguished from other chromatographically similar compounds by means of the specific colour reaction for β-phenylethylamines that we have developed[3].

The results of Takesada *et al.* are particularly impressive because of the unusually high percentage of schizophrenic patients who excrete identifiable 3,4-dimethoxyphenylethylamine. Their incidence is higher than that found in our group of patients. This suggests either that their methods are more sensitive than ours or that their diagnostic classification or patient population is somewhat different from ours.

Their detection of 3,4-dimethoxyphenylethylamine in the urine obtained from a normal control group may have resulted from the increased sensitivity of their analytical methods, but it is pertinent that our normal controls were selected with deliberate intention to exclude any subjects with even mild schizoid tendencies. If schizophrenia is a genetically determined disorder, it would be expected that a significant percentage of the 'normal' population would have incomplete penetrance of the disease. It would seem, therefore, to be crucial not only to do qualitative studies but also quantitative determinations of 3,4-dimethoxyphenylethylamine in normal subjects and patients. Also, a specific comparison of patients according to diagnostic criteria should be carried out inasmuch as some cases of schizophrenia in one country would be classified as psychoneuroses in another.

The attempt to synthesize 3,4-dimethoxyphenylethylamine from dihydroxyphenylalanine and dopamine carried out by Takesada *et al.* did not result in the formation of the dimethoxy amine. It should be pointed out that the conversion rate of infused precursors of this compound may be very low. In any event, it seems most fruitful to examine this conversion in schizophrenic patients where the conversion is most likely to occur. Inasmuch as rats do not appear to excrete 3,4-dimethoxyphenylethylamine, it is unlikely that they would form it from precursors. We are now carrying out investigations in schizophrenic patients using tritiated dopamine as a precursor.

The data of Takesada *et al.*, when subjected to simple χ^2 analysis, reveal that their combined schizophrenic group differs significantly from their normal control group ($P < 0{\cdot}001$) in the incidence of 3,4-dimethoxyphenylethylamine in urine. This finding alone plus the pharmacological nature of 3,4-dimethoxyphenylethylamine suggest that many additional investigations of this compound should be carried out. It is of uncommon interest that 3,4-dimethoxyphenylethylamine has profound central effects without appreciable peripheral effect[4]. This is compatible with the symptoms characterizing schizophrenia. In addition, 3,4-dimethoxyphenylethylamine has been shown to produce experimental catatonia in cats[5,6].

Takesada *et al.* have confirmed the presence of a potentially psychotoxic compound in urine. They suggest that this compound is of dietary or microbial origin, but they provide no data to support this.

We feel that considerable caution should be exercised in the interpretation of the relationship of 3,4-dimethoxyphenylethylamine to schizophrenia. At the present time, therefore, it must be concluded that the origin and significance of this compound has not been ascertained. The unusually high incidence of 3,4-dimethoxyphenylethylamine in the urine of the patients studied by Takesada *et al.* should stimulate further interest in investigating the possible significance of this compound in mental illness.

A. J. Friedhoff
E. Van Winkle

Department of Psychiatry and Neurology,
New York University School of Medicine,
New York, 16.

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