

## References and Notes

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## Gut Flora and Urinary Phenylacetic Acid

Sabelli *et al.* (1) suggested that urinary phenylacetic acid (PAA), a metabolic product of phenylethylamine, may be a marker for the diagnosis of some major depressive disorders. These researchers strengthened their argument that urinary PAA reflects metabolism in the body rather than in the gastrointestinal tract by including a number of references, one of which (2) reports a personal communication that ingestion of neomycin, which kills intestinal flora, did not reduce significantly the total urinary PAA excretion. Seakins (3) reported that less than 0.4 percent of an ingested 7-g sample of L-phenylalanine was recovered as urinary PAA. However, when 600 mg of phenylalanine was taken in an enteric-coated capsule, the increase in PAA output corresponded to 22 percent of the ingested dose. Noting the wide range in results on normal subjects, Seakins concluded (3, p. 129) that PAA excretion was affected by "variations in fecal flora, transit time, efficiency of digestion as well as variations in the intake of dietary protein and its digestibility."

We obtained 46 24-hour urine samples from 12 healthy volunteers. The samples were analyzed by the method of Sabelli *et al.* (1) with the exception that 2-phenylbutyric acid was used as an internal standard instead of phenylpropionic acid. The PAA outputs of these individuals were consistent with those reported in (1).

In addition to the volunteers, we obtained urine samples from an individual who was under medical care and was ingesting cloxacillin (8 g per day). Twenty-four-hour urine samples collected on days 25, 26, 27, and 30 of treatment contained 38.4, 24.5, 25.7, and 29.0 mg of PAA, respectively. On days 25, 39, and 46 after the cessation of treatment, the respective PAA values were 121.9, 161.6, and 217.4 mg.

Two of the 12 volunteers were also subsequently placed on antibacterial medication after which their PAA outputs dropped significantly. Prior to receiving medication, one of these indi-

vidual's four consecutive 24-hour urine samples contained 175.6, 134.2, 106.0, and 76.7 mg of PAA. For 4 days this individual ingested penicillin V (1.5 g per day) and then for 5 days cephalexin (Keflex) (1 g per day); urine collected on days 8 and 9 of treatment contained, respectively, 24.0 and 36.2 mg of PAA. The other subject excreted 134.1, 138.8, 188.0, and 160.1 mg of PAA in four sequential 24-hour urine samples; on days 5, 6, 7, and 8 of treatment with ampicillin (1 g per day), the PAA values were 127.0, 83.4, 113.0, and 44.3 mg, respectively.

These results lead us to conclude that urinary PAA values seem to be influenced by the condition of the gut flora. The involvement of the gastrointestinal tract would indicate that the PAA output may also be affected by diet. These findings would limit the use of PAA as a marker for major depressive disorders.

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In our studies we have proposed that a deficit in brain phenylethylamine (PEA), an amphetamine-like substance that was first identified in the brain (1), causes depressive illness. More recently, we reported a reduction in the PEA metabolite phenylacetic acid (PAA) in the urine (2, 3) and blood (4) of depressed subjects. These individuals were otherwise healthy and untreated. In these reports we made no claims that PAA excretion could not also be altered in other illness-

es or with drug treatment. Many factors affect any biochemical variable, and the most important of these should be known before a biochemical measurement is used as a diagnostic test. Thus, the contribution of Hryhorczuk *et al.* is of value to researchers. Some cautionary remarks are, however, in order.

1) Hryhorczuk *et al.* report no measures of mood or any other clinical variable in the patients. Was there diarrhea? What was the protein intake? Many patients with viral illnesses show depressive-like symptoms.

2) There is no evidence presented by Hryhorczuk *et al.* indicating that antibiotics reduce urinary PAA by reducing its dietary absorption. Many antibiotics affect protein metabolism systemically (5). Earlier reports demonstrated that drugs that do not affect the gut flora, such as amphetamines and antidepressants, rapidly modify PAA excretion (6). Changes brought about by antidepressants appear to correlate with therapeutic response.

3) The considerations about diet are highly speculative. Karoum *et al.* (7) have shown that marked dietary manipulations fail to affect PAA excretion. On the other hand, we have found that loading with L-phenylalanine, the amino acid precursor of PEA and PAA, ameliorates depression and can even terminate an episode in bipolar subjects (8). These therapeutic studies strengthen, in our view, the importance of pursuing the study of PEA and PAA in affective disorders.

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