

## Urinary Pyrrole in Health and Disease

James A. Jackson, M.T., (ASCP), Ph.D., BCLD;<sup>1</sup> Hugh D. Riordan, M.D.;<sup>2</sup>  
Sharon Neathery, M.T.;<sup>2</sup> Neil H. Riordan, PA-C.<sup>2</sup>

Urinary pyrrole, also known as the mauve factor (malvaria), pyrroluria and krypto-pyrrole, was first described in the 1950s. It was found in the urine of patients undergoing experimental LSD treatments. When reacted with Ehrlich's reagent (p-dimethylamino benzaldehyde), several of the urines developed a purple or "mauve" color.<sup>1</sup> This colored compound was first thought to be an indole. In 1961, a study using paper chromatography identified a group of Ehrlich-positive substances in the urine of patients with mental illnesses and showed that these compounds were more associated with pyrroles than indoles.<sup>2</sup>

Hoffer and Mahon, in studies conducted during this same period, confirmed the presence of Ehrlich-positive substances in the urine of patients with schizophrenia. They suggested malvaria as the name for this condition.<sup>3</sup> Other workers also confirmed the presence of Ehrlich positive substances in urine.<sup>4,5</sup>

Sohler, in 1967, using 24-hour urine specimens found malvaria in 60% of chronic schizophrenic patients; it was absent in most normal patients. He postulated that the mauve factor was composed of pyrroles or furans from the breakdown of amino sugars, or the interactions of amino acids and carbohydrates. Such compounds could come from N-acetyl neuraminic acid in the central nervous system.<sup>6</sup> Irvine et al, in 1969, used different extraction techniques and UV-mass spectrophotometer measurements to demonstrate that the mauve factor was a kryptopyrrole (2,4-dimethyl-3-ethylpyrrole).<sup>7</sup> In 1970, Sholer et al, reported that the mauve factor reacted like

kryptopyrrole when examined by thin layer chromatography. They also injected rabbits with kryptopyrrole which caused a distinct sedative effect. They said that this result eliminated the mauve factor as a possible stimulant metabolite; one that produced "over arousal" in schizophrenics.<sup>8</sup> Russell (1972) proposed that the mauve factor was an isomerization and rearrangement of porphobilinogen and was an abnormal side-product in the biosynthetic pathway of porphyrins.<sup>9</sup>

Pfeiffer (1973), reported that kryptopyrrole combined chemically with vitamin B<sub>6</sub> and removes it from the body, similar to the way that penicillamine and INH removes B<sub>6</sub>. He also reported that 50% of schizophrenic patients had the mauve factor in their urine. These same patients responded well to large doses of vitamin B<sub>6</sub>, up to 1600 mg/day, and zinc in dietary doses.<sup>10</sup> However, at this time, there was still controversy as to the exact nature of kryptopyrrole. Sohler, et al (1974), proposed that the most likely endogenous source of kryptopyrrole was bile pigment, rather than a metabolic form of porphyrins. They suggested that pyrroluria may be due to a stress induced condition of abnormal intestinal permeability which allows increased absorption of pyrrole into the systemic circulation.<sup>11</sup>

To further complicate matters, an article published in 1975 stated that neither kryptopyrroles nor hemopyrroles could be detected in the urine of patients with schizophrenia when measured by GC-MS.<sup>12</sup> These findings were confirmed in a report in 1978 by Gendler et al. They also reported failure to detect hemopyrrole or kryptopyrrole in the urine of schizophrenic or normal patients using the GC-MS method.<sup>13</sup> Irvine countered this by reporting that the compound in the urine of schizophrenics was a hydroxyhemo-

1 Department of Medical Technology, Wichita State University, Wichita, KS. 67206-0043

2 The Center for the Improvement of Human Functioning International, Inc, 3100 N. Hillside, Wichita, KS. 67219

pyrrolenone, not krypto-pyrrole or hemopyrrole.<sup>14</sup> Irvine later synthesized 2-hydroxy hemo-pyrrolene-5-one and stated that this compound was found to be identical to the naturally occurring pyrrole found in urine.<sup>15</sup> However, there was still some question that pyrroles were excreted in the urine of schizophrenic patients who manifest the characteristic physical and mental signs and symptoms.

The exact properties of pyrrole and the interaction with vitamin B<sub>6</sub>, zinc and magnesium in the blood probably need further research. We do know that pyrrole serves as a building block of heme and porphyrins. As stated before,<sup>10</sup> there is much evidence of successful treatment of schizophrenic patients who are excessive excretors of urinary pyrroles with vitamin B<sub>6</sub> and zinc.

Over 22 years ago, one of the authors (HDR), successfully treated a female high school sophomore with the triad of schizophrenia, white spots in the finger nails and knee joint pain. The treatment with high levels of B<sub>6</sub> and zinc by mouth resulted in her symptoms disappearing in two weeks. A few years ago, HDR met the parents of this patient and found out that she had gone on to become a champion baton twirler and a symptom-free, well adjusted mother of two. Pfeiffer had previously reported that approximately 20% of schizophrenics presented with this triad of fingernail white spots, knee point pain, and schizophrenia. When The Center's records were examined several years ago, the schizophrenic patients with knee joint pain was 19%, almost exactly as Pfeiffer had reported. We did not systematically assess fingernail white spot status at that time. At the Center, we have found elevated urinary pyrroles in patients with many different physiological and psychological diseases. The highest levels found in our laboratory were from a study done on patients with Down Syndrome (DS). Twenty of 28 patients (71.4%) with DS were high pyrrole

excretors: two male subjects, both 24 years of age, had levels of 165 and 434 ug/dL, respectively (normal < than 20 ug/dL). None of the patients in this study had a vitamin B<sub>6</sub> deficiency. Five patients (24%), however, showed a vitamin B<sub>1</sub> deficiency.<sup>16</sup> Zinc and magnesium levels were not measured. The lack of a vitamin B<sub>6</sub> deficiency in such high urine pyrrole excretors is puzzling. Perhaps it is the degree of B<sub>6</sub> that is excreted, and not an absolute. That is, high pyrrole excretors could have blood B<sub>6</sub> levels at the low end of the normal range without being completely deficient. Also, none of these patients were schizophrenic. To investigate this relationship further, 100 cases were randomly selected from our patient files from 1996. Most all patients had multiple diagnoses. Common complaints from many of the patients were arthritis, chronic fatigue syndrome, "easy bruising," heart disease, allergies, hypertension, irritable bowel syndrome, and migraine headaches. Forty three percent of these patients had elevated urine pyrroles; 57 percent had normal (< 20 ug/dL) urine pyrroles. None of the patients with pyrroluria were deficient in vitamin B<sub>6</sub>, or RBC zinc: two patients (5%) had low RBC magnesium. None of the high pyrrole excretors were diagnosed as schizophrenic. The highest pyrrole measured was 41 ug/dL, or about two times the normal range.

The data would tend to support a theory that many different types of physiological and/or psychological stresses, other than schizophrenia, can cause the excretion of abnormal amounts of pyrrole in the urine. In some cases, it may be the first clue that these conditions exist in a patient. Also, according to data from this small group of patients, high urine pyrroles does not necessarily result in a deficiency of vitamin B<sub>6</sub>, zinc or magnesium in the patient.

For the past twenty years, the BioCenter Laboratory has measured urine

pyrrole at the request of The Center's physicians. They are particularly happy when someone with the diagnosis of schizophrenia also has pyrroluria, because they know that there will be a high likelihood that treatment with vitamin B<sub>6</sub> and zinc will be useful to that patient.

## References

1. Hinshaw CT: Urinary Pyrrole, Mauve Factor, Malvaria, Pyrroluria, and Kryptopyrrole. *Review*, 1991; No. 1.
2. Irvine DG: Apparently Non-Indolic Ehrlich-Positive Substances Related to Mental Illness. *J Neuropsychiat*, 1961; 2: 292-305.
3. Hoffer A, Mahon M: The Presence of Unidentified Substances in the Urine of Psychiatric Patients. *J Neuropsychiat*, 1961; 2: 331-397.
4. O'Reilly EM, Hughs G: The Incidence of Malvaria. *Brit J Psychiat*, 1965; 111: 741-744.
5. Yuwiler A, Good MH: *Psychiat Res*, 1962; 1: 215-277.
6. Sohler A, Renz RH, Smith S, Kaufman J: Significance of Hydroxyskaatole and Mauve Factor Excretion for Schizophrenia. *Int J Neuropsychiat*, 1967; 4:327-331.
7. Irvine DG, Bayne W, Miyashita H, Majer JR: Identification of Kryptopyrrole in Human Urine and its Relationship to Psychosis. *Nature*, 1969; 224:811-813.
8. Sohler A, Beck R, Noval JJ: Mauve Factor Re-identified as 2-4-Dimethyl-3-ethylpyrrole and its Sedative Effect on the CNS. *Nature*, 1970; 228:1318-1329.
9. Russell CS: Biosynthesis of Phorphyrins and the Origin of the "Mauve Factor." *J Theor Biol*, 1972; 35:277-283.
10. Pfeiffer CC, Lliev V: Pyrroluria, Urinary Mauve Factor, Causes Double Deficiency of B-6 and Zinc in Schizophrenics. *Fed Proc*, 1973; 32:276.
11. Sohler A, Holsztynaks E, Pfeiffer CC: A Rapid Screening Test for Pyrroluria: Useful in Distinguishing a Schizophrenic Subpopulation. *Orthromol Psychiat*, 1974; 3:273-279.
12. Jacobson SJ, Rapoport H, Ellman GL: The Nonoccurance of Hemo- and Kryptopyrrole in Urine of Schizophrenics. *Biol Psychiat*, 1975; 10:91-93.
13. Gendler PL, Dunham HA, Rapoport H: Hemopyrrole and Kryptopyrrole are Absent from the Urine of Schizophrenics and Normal Persons. *Clin Chem*, 1978; 24:230-233.
14. Irvine DG: Hydroxy-Hemopyrrolenone, not Kryptopyrroles in the Urine of Schizophrenics and Phorphyrins. *Clin Chem*, 1978; 14:1069-1070.
15. Irvine DG: Pyrroles in Neuropsychiatric and Porphyric Disorders: Confirmation of a Metabolite Structure by Synthesis. *Life Sci*, 1978; 23:983-990.
16. Jackson JA, Riordan HD, Neathery S: Vitamin, Blood Lead and Urine Pyrrole Levels in Down Syndrome. *Amer Clin Lab*, 1990; Jan-Feb: 8-9.