



## Clinical Test of Pyrroles: Usefulness and Association with Other Biochemical Markers

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### Abstract

**Background:** Psychiatrists started using urine pyrroles (hydroxyhemopyrrolin-2-one, HPL) to diagnose mental disorders many years ago. The biological origins of HPL are not known, nor are the causes of elevated urinary pyrrole excretion well understood.

**Methods:** In the present study we analyzed the level of pyrroles in 148 patients with schizophrenia, 135 patients with bipolar disorder, 97 patients with depression, and 119 patients with ADHD and compared these data with the results of pyrrole tests for patients with non-mental conditions and healthy volunteers.

**Results:** According to our data, urinary pyrrole concentrations tended to be high in patients with mental illnesses, but elevated level of pyrroles was not specific for only these patients. We found evidence of an allergy related component in the fact that elevated pyrrole levels were significantly more prevalent in subjects with elevated histamine values. A role of intestinal bacteria, or imbalances in intestinal bacterial metabolism, was also suggested based on the found relationship between elevated pyrrole levels and elevations in indicans and urobilinogens. In addition, our data demonstrated that subjects with severely elevated pyrrole levels were deficient in nutrients such as zinc, vitamin B3, and vitamin C.

**Conclusion:** Thus, pyrrole excretion seems to be a component of illness in general and not strictly mental illness.

### Keywords

Mental illness, Pyrroles, Indicans, Urobilinogens, Histamine, Nutrient deficiency

### Introduction

Interest in pyrroles as markers of mental illness started Dr. Abram Hoffer's discovery that "Mauve Factor", a pyrrole named for its lavender appearance in urine chromatograms stained with Ehrlich's reagent [1], was prominent in urine samples from schizophrenics [2,3]. After considerable effort [4-10], Mauve Factor was determined to be the hemopyrrole derivative hydroxyhemopyrrolin-2-one (HPL). Hoffer claimed that HPL tended to decrease when a patient recovered from illness, and increased when illness reappeared; moreover, treatments with vitamin B6 and zinc were reported to decrease HPL levels and were associated with patient recovery

[11]. Some psychiatrists, particularly those with interests in orthomolecular medicine, have used HPL as a clinical tool for diagnosing and following the progression or remission of mental illness [11-17]. Data from these studies suggest that roughly one-third of schizophrenia patients tested had elevated pyrroles, but high urine HPL levels were not limited to schizophrenia, as a variety of conditions and stresses are associated with urine pyrrole excretion.

The biological origins of HPL are not known, nor are the causes of elevated urinary pyrrole excretion understood. Proposed mechanisms for HPL formation and accumulation in the body include intake from dietary sources, heme breakdown, or altered heme biosynthesis, the latter perhaps occurring with the aid of gut flora [18]. Irvine has proposed that HPL is a metabolite of heme synthesis intermediates porphobilinogen and prophyryns, as these are structurally very similar to HPL [19]. Urine HPL levels can be quantified using a colorimetric assay, provided precautions are taken to keep it stable prior to and during the assay. Increases in pyrrole levels and excretion may occur as a result of stress-induced changes in intestinal permeability, which in turn leads to increased pyrrole absorption. To the extent that pyrrole excretion may be an indicator of heme breakdown due to emotional stress, oxidative stress, or nutrient deprivation, a study of the correlation between urinary pyrroles and nutrient levels should be of interest [18,20-22].

At the Riordan Clinic, urinary pyrrole measurements have been part of the protocol for diagnosing mental illnesses and other disorders for decades. Access to the clinic's database has enabled us to examine pyrrole levels in patients with a variety of illnesses and to see how they correlate with the concentrations of other key nutrients or metabolites. The present manuscript describes our analysis and evaluation of these data, and provides some assessment of the potential value of monitoring pyrrole levels in mentally ill patients.

### Materials and Methods

All laboratory tests were conducted by the Riordan Clinic Bio-Center Laboratory (Wichita, KS), a licensed and certified medical laboratory that offers over one-hundred laboratory tests (<http://www.riordanclinic.org/laboratory/catalog.pdf>). Handling of laboratory data by our institute is done in full compliance with HIPAA regulations. Assay methods for the various vitamins, minerals, and lipids for which data are presented here were conducted

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**Table 1:** Mean values of various laboratory test parameters for subject with different types of mental illnesses.

Parameter and Units	NR	1SD		Mean and Standard Deviation Values							
		Low	High	ADHD		Schizophrenia		Bipolar		Depression	
Amino Acids				MEAN	STDEV	MEAN	STDEV	MEAN	STDEV	MEAN	STDEV
Homocysteine (uM)		7.5	12.5	6.9	1.6	9.7	3.2	9.1	3.0	9.1	3.0
Tryptophan (umol/dL)		0.9	1.8	1.4	1.0	1.3	1.2	1.3	1.1	1.4	0.9
Tyrosine (umol/dL)		5.1	9.3	7.0	1.9	7.2	1.9	7.0	2.3	6.8	1.8
Phenylalanine (umol/dL)		4.1	7.8	5.6	1.4	6.2	1.8	5.8	1.3	5.6	1.4
Minerals		Low	High	ADHD		Schizophrenia		Bipolar		Depression	
Iron (total) (ug/dL)		40.8	100.3	101.9	51.8	88.7	34.0	88.7	38.3	90.4	35.6
Iron (hair) (ppm)		4.6	10.6	10.3	6.3	10.5	12.6	7.4	3.6	9.9	7.8
Copper (RBC) (ug/dL)		50.1	74.8	64.0	12.6	60.8	13.7	60.1	7.2	61.5	10.6
Copper (serum) (ug/mL)		74.0	118.0	30.4	45.4	94.7	16.5	41.4	55.3	34.0	56.2
Selenium (RBC) (ug/dL)		95.0	219.0	151.5	40.7	143.2	59.9	184.6	97.9	163.2	57.0
Magnesium (hair) (ppm)		56.5	125.5	37.6	39.2	47.7	49.1	75.6	91.6	99.8	143.0
Zinc (RBC) (ug/mL)		9.5	14.9	10.0	2.1	11.7	1.6	11.9	2.0	11.9	1.7
Zn:Cu (ratio)				9.3	5.5	6.5	7.9	11.8	4.6	12.1	5.2
Toxic metals		Low	High	ADHD		Schizophrenia		Bipolar		Depression	
Lead (hair) (ppm)		0.0	1.6	0.9	1.4	3.2	7.2	1.2	3.1	1.4	2.1
Mercury (hair) (ppm)		0.0	1.6	0.2	0.3	0.6	0.5	0.4	0.4	0.6	0.5
Aluminum (hair) (ppm)		0.0	1.4	7.9	7.2	5.5	8.2	5.9	5.7	6.4	9.7
Arsenic (hair) (ppm)		0.0	0.6	0.1	0.2	0.3	0.1	0.2	0.2	0.2	0.2
Cadmium (hair) (ppm)		0.0	0.3	0.1	0.2	0.1	0.1	0.1	0.2	0.2	0.4
Fatty Acids		Low	High	ADHD		Schizophrenia		Bipolar		Depression	
EPA (RBC) (uM/L)		8.0	16.0	9.6	6.9	11.5	4.3	14.1	8.0	12.5	0.7
Arachidonic:EPA (RBC) (ratio)		7.0	11.0	20.0	12.5	16.1	8.6	16.1	10.6	16.7	10.4
O6:O3 (RBC) (ratio)		1.4	3.5	7.6	3.6	5.9	2.7	5.5	2.5	6.4	3.1
Urine Parameters		Low	High	ADHD		Schizophrenia		Bipolar		Depression	
Na:K (urine) (ratio)		0.8	4.0	3.7	3.4	1.8	1.0	4.4	3.5	5.8	6.4
Pyrroles (urine) (ug/dL)		0.0	15.0	29.2		25.4	27.9	19.9	19.7	20.7	20.6

by the Bio-Center Laboratory using standard methodologies. For measurement of urine HPL, urine was stabilized with ascorbic acid (8mL urine added to 500mg of ascorbic acid) and frozen to ensure HPL stability. Pyrroles were then extracted from urine with chloroform and reacted with Ehrlich's aced aldehyde reagent (0.5g of p-dimethylaminobenzaldehyde, 2.5 ml sulfuric acid in 50ml of methanol). This preparation yields a chromophore with an absorption maximum of 540 nm, which is related to HPL concentration using a standard curve. The comparison of the colorimetric assay for HPL with highly sensitive and specific HPL assay, which utilizes high-pressure liquid chromatography mass spectroscopy (HPLC/MS), showed the high level of correlation between these two assays ( $r=0.9$ ;  $P<.0001$ ) [18].

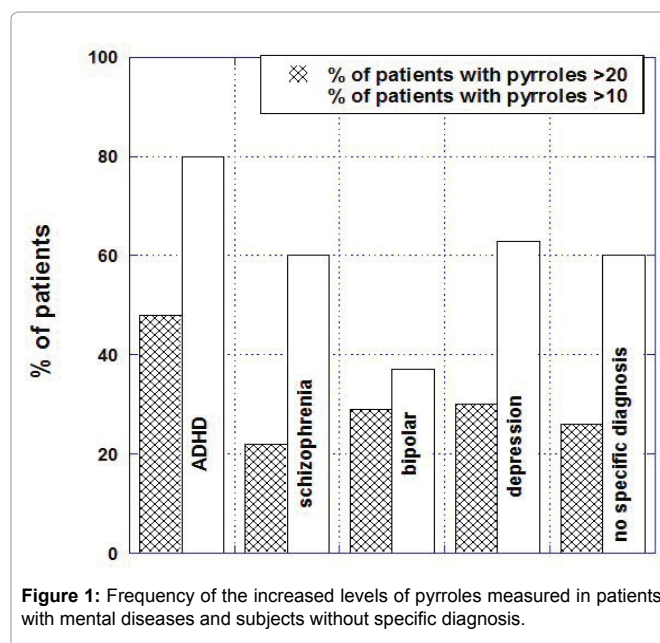
Data from the Bio-Center Laboratory were obtained using the LabNet program (Henry Schein, Melville NJ). Statistical analyses were carried out using the Excel spreadsheet program and graphs, with regression data fits where appropriate, were constructed using the Kalaidagraph program (Synergy Software, Reading PA).

## Results

We analyzed urine pyrrole data in 119 patients with ADHD, 148 patients with schizophrenia, 135 patients with bipolar disorder and 97 patients with depression. We first examined parameters that are key precursors for neurotransmitters (amino acids) or have been cited as being potentially relevant to mental illness, such as toxic metals, essential minerals, and fatty acids. The average values of these tests are shown in Table 1.

Tests for mental illness groupings show elevated average values of hair aluminum, lead (in patients with schizophrenia), iron (total and hair), Arachidonic acid to EPA ratio, omega 3 to omega 6 fatty acid ratios, and urine pyrroles. Deficiencies were found in the levels of essential metals magnesium, zinc and copper (serum). Some deficiencies and the metabolic imbalances in fatty acid, amino acid, mineral, and pyrrole levels in ADHD patients were analyzed previously [19].

The percentage of patients with increased levels of pyrroles in comparison with patients without specific diagnosis (134 healthy subjects) is shown in Figure 1.

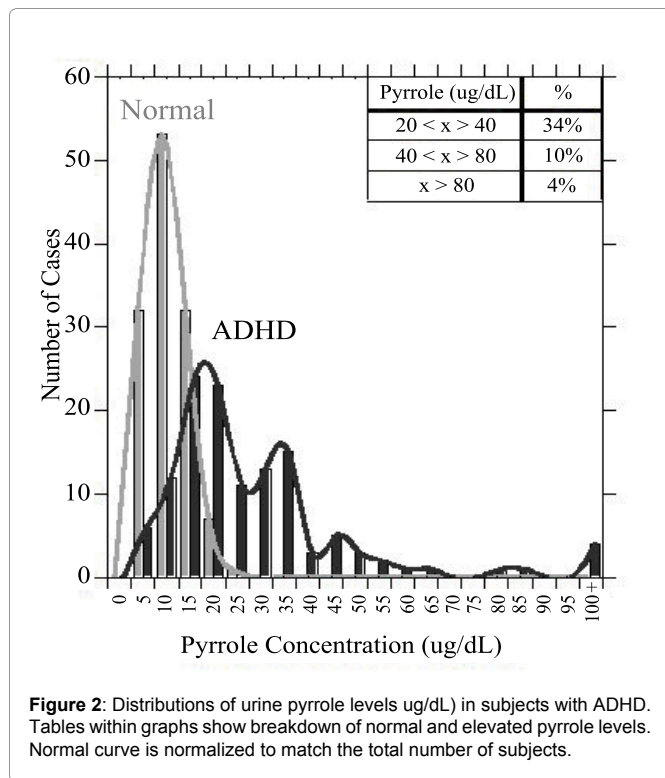


**Figure 1:** Frequency of the increased levels of pyrroles measured in patients with mental diseases and subjects without specific diagnosis.

According to these data the percentage of patients with the levels of pyrroles higher than 20ug/dL was 48% for ADHD patients, 22% for patients with schizophrenia, 30% for patients with bipolar and depression and 26% for patients without specific diagnosis.

Pyrrole distributions in subjects with mental illnesses were analyzed by illness category, along with the distribution that would be expected if all subjects were in the normal range. There was skew in the data indicating subjects with elevated pyrrole levels. It is particularly acute in ADHD patients, of whom 48% had levels above the normal range (Figure 2).

The mean of pyrrole values outside the normal range were 47ng/dL for patients with schizophrenia, 43ng/dL for patients with bipolar disorder, 39ng/dL for patients with depression and 44ng/dL for patients with ADHD.



The highest level was measured for a 10-year old boy (481ug/dL). A level of 192ug/dL was found in 5 year old girl and levels of 123ug/dL and 114ug/dL in two boys. The proportion of subjects with pyrroles outside the normal range was similar to those seen in patients with other illnesses (26% of all subjects analyzed had pyrrole levels above 20ug/dL), suggesting that pyrrole levels indicate illness in general and not necessarily mental illness.

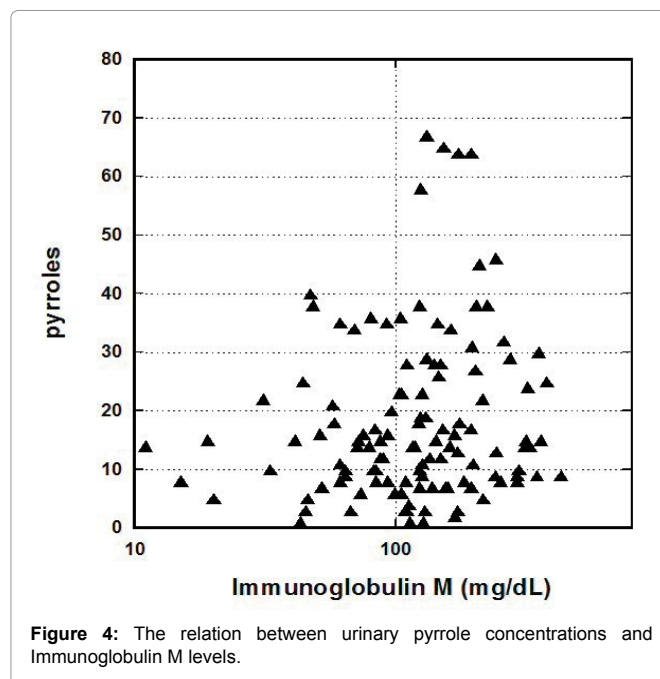
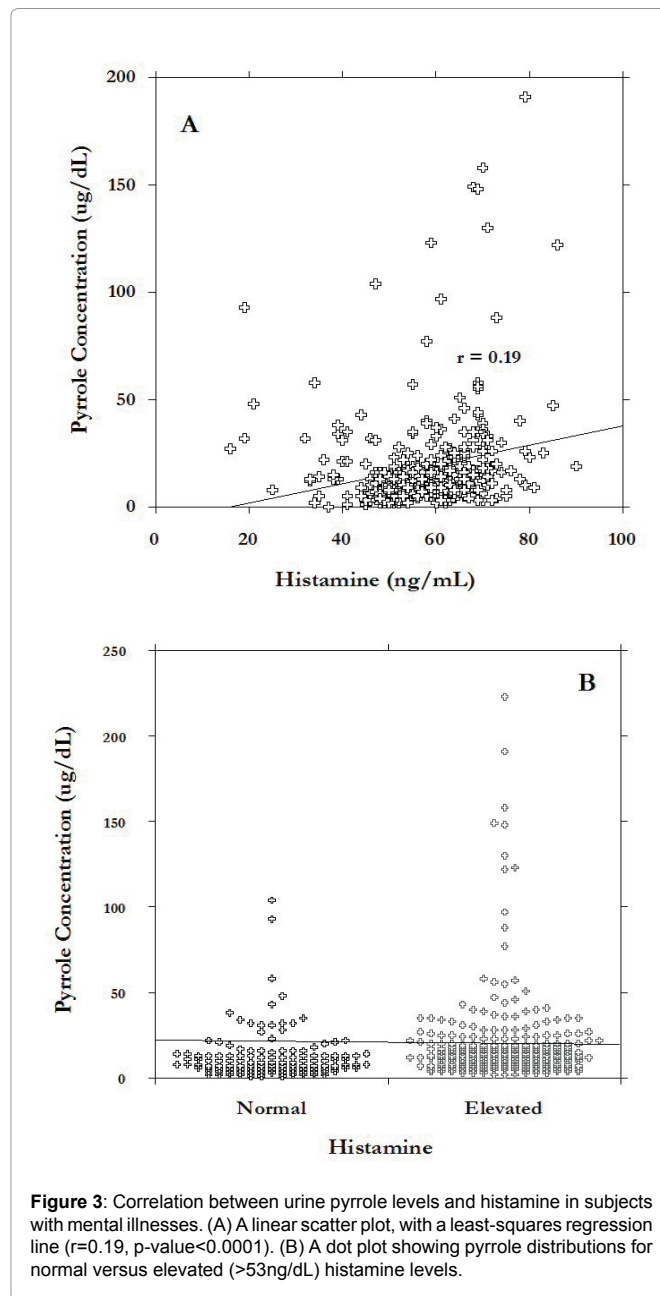
To see if pyrrole levels were related to allergic reactions, we compared pyrrole levels with histamine and immunoglobulin levels. For histamine, data are shown in Figure 3a and Figure 3b.

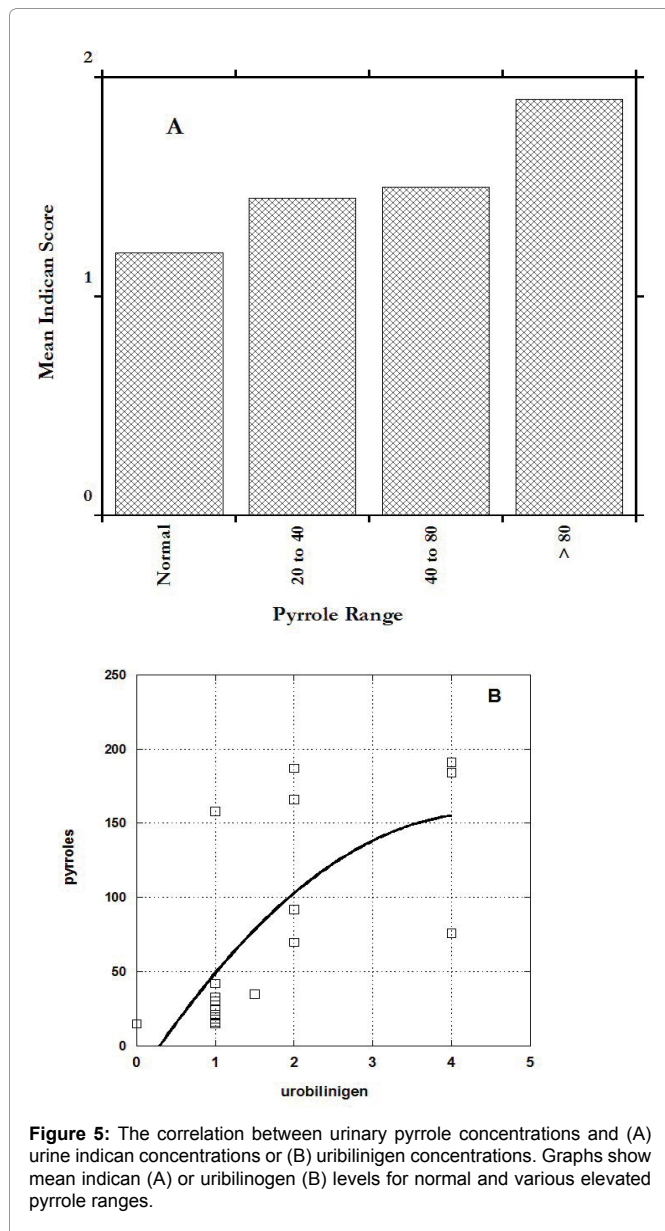
There was a statistically significant correlation ( $p < 0.001$ ) between histamine levels and pyrrole levels, and the vast majority of patients with elevated pyrrole levels showed elevated histamine levels also. For instance, for subjects with histamine levels below 53ng/dL (the upper limit of normal in our laboratory, only 16% of subjects had elevated (>20ug/dL) pyrrole levels, with only 2% having pyrrole values above 40ug/dL and only 2% having values above 80ug/dL. In contrast, 26% of subjects with elevated histamine levels had elevated pyrrole levels, with 9% showing values above 40ug/dL and 4% showing values above 80ug/dL. All subjects with pyrrole levels above 100ug/dL had elevated histamine levels. Similar trends were observed with the immunoglobulins IgM. Relation between IgM and pyrroles is shown in Figure 4.

For abnormal levels of pyrroles (>2ug/dL), 75% of data were in the range of IgM higher than 100mg/dL. Average level of pyrroles was 30ng/dl  $\pm$  8ng/dl for IgM<100mg/dl and 46ng/dl  $\pm$  40ng/dl for IgM>100mg/dL.

Elevated pyrroles are also thought to be related to intestinal issues. The urine indican test is considered an indicator of intestinal toxemia and overgrowth of anaerobic bacteria (indican is a product of bacterial tryptophan digestion), while urobilinogens are products of intestinal bacteria that can build up if the liver is overburdened. Figure 5 shows how these parameters vary depending on urinary pyrrole levels. In both cases, elevated pyrroles are associated with elevated levels, supporting the hypothesis that intestinal bacteria overgrowth may be associated with excessive pyrrole excretion.

To determine if increased pyrroles secretion is accompanied by nutritional deficiencies, we compared urinary pyrrole concentrations with vitamins and minerals in blood for cases where both were





measured on the same visit. Vitamins are natural barriers against infection and allergic reactions, as well as chemical balance of essential minerals. Examples where a relationship was particularly noticeable are shown in Figure 6.

Vitamin C, vitamin B3, red blood cell zinc, and zinc to copper ratios were found in some mental illness groups to decrease with increasing pyrrole levels. Examining Figure 6, it appears that subjects with very high pyrrole levels (above 40ug/dL) tended toward the left hand side of the horizontal axis, suggesting that data points with very high pyrrole levels had low nutrient values. The potential link between nutrient levels and pyrrole levels deserves further more systematic study.

At the Riordan Clinic, patients with mental illness are sometimes treated by attempting to restore proper mineral balances and correct nutrient deficiencies. In particular, the integrative approach to the treatment of elevated pyrroles includes: intravenous ascorbic acid (5g-15g), Plex IV INF, vitamin B6 IV infusion, fortified flax, super EPA, cod liver oil, zinc boost, lipoic acid, ProEFA, chelated magnesium, DHEA and amino acids (cysteine, glutamine, tyrosine, arginine). Other nutrients were added to assist in pyrroluria include niacinamide, pantothenic acid, manganese, Evening Primrose Oil and digestive enzymes. We examined the database for mental illness patients who underwent this type of therapy (though precise protocol details varied from subject to subject) and compared "initial" to "final" pyrrole values. Results are shown in Table 2.

These data suggest that pyrrole levels decreased during treatment. We have not yet conducted a controlled trial where a consistent treatment is used and patient mental illness (symptom severity) is also monitored over time.

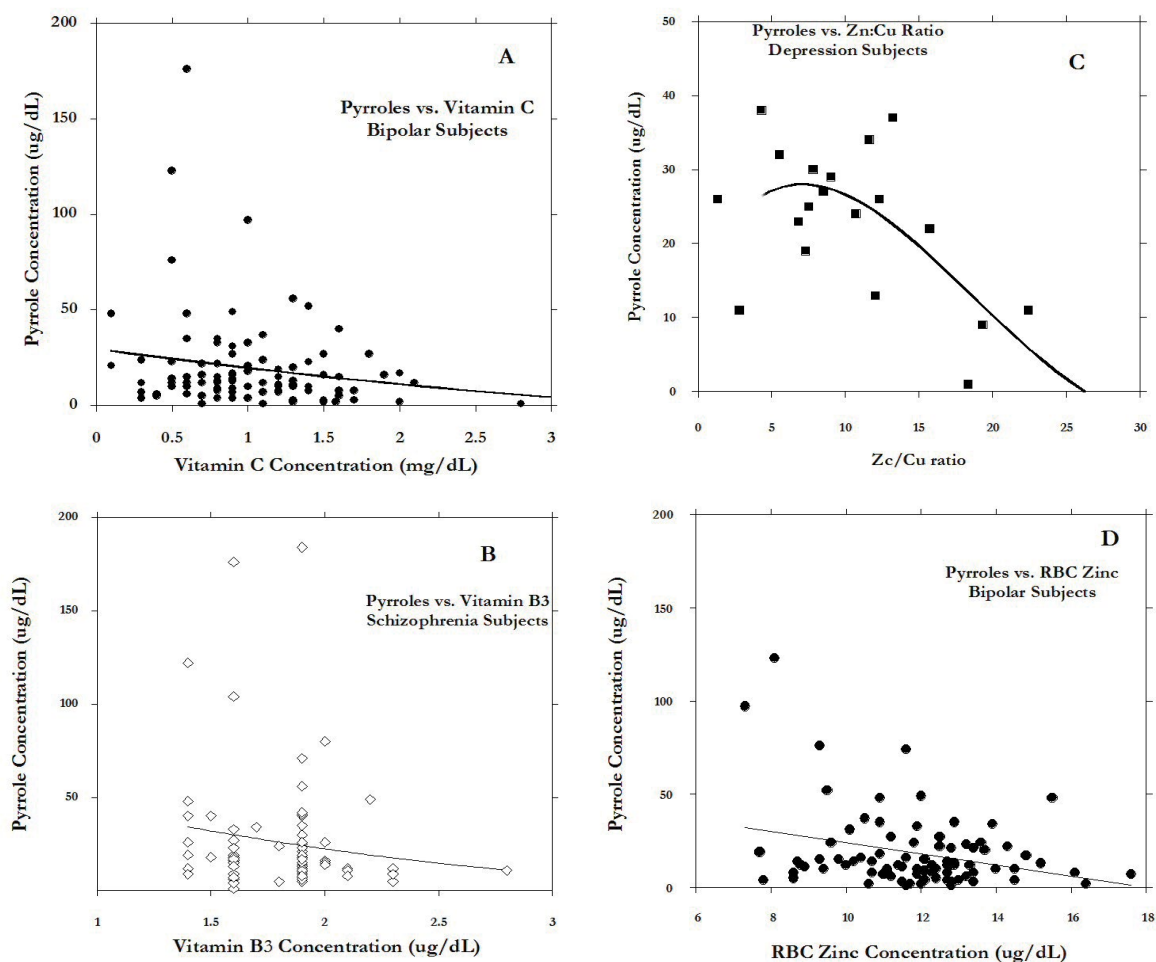
## Discussion

The Riordan Clinic has been measuring nutrients, minerals, toxins and urine pyrrole concentrations as a diagnostic tool for over forty years. In examining laboratory parameters that are thought to be important in maintaining proper neurological function (Table 1), we found several potential trouble signs in patients with various types of mental illnesses. In particular, the tests demonstrated the elevated average values of aluminum, lead (in patients with schizophrenia), iron, arachidonic acid to EPA ratio, omega 3 to omega 6 fatty acid ratios, and urine pyrroles. Deficiencies were found in the levels of essential metals magnesium, zinc and copper (serum). Urinary pyrrole concentrations also tended to be high in these patients. We investigated these elevated pyrroles further, finding that nearly half of the patients diagnosed with ADHD had pyrrole concentrations above the normal limit (20ug/dL) in urine. The proportion was roughly one-third in subject with depression, bipolar disorder, or schizophrenia. Interestingly, that elevated level of pyrroles was not specific for only patients with mental illnesses. When we analyzed patients without mental diseases all together as a whole (with illnesses ranging from cancer to arthritis, fibromyalgia, and chronic fatigue, among others) and subjects without specific diagnosis, roughly a quarter of them have elevated urinary pyrrole levels. Thus, pyrrole excretion seems to be a component of illness in general and not strictly mental illness. We are struck, though, by how high urine pyrroles can be in mentally ill subjects, with roughly ten percent having values above 40ug/dL and, in the case of schizophrenics and ADHD sufferers, nearly 5% of subjects having values above 80ug/dL. We saw some patients with levels over 200ug/dL.

Our examination of the Riordan Clinic database confirms some of the conventional wisdom about pyrrole excretion. We find evidence of an allergy component in the fact that elevated pyrrole levels were significantly more prevalent in subjects with elevated histamine values (Figure 3). Immunoglobulins also appear to correlate with pyrroles (IgM vs pyrroles).

A role of intestinal bacteria, or imbalances in intestinal bacterial metabolism, is also suggested based on the relationship between elevated pyrrole levels and elevations in indicans and urobilinogens (Figure 5). Indicans can be an indicator of protein digestion efficiency [18]. Patients with high urine indicans can be expected to have issues such as insufficient gastric hydrochloric acid, insufficient digestive enzymes, adverse food reactions, infection, or bacterial overgrowth. These problems are also consistent with elevated urobilinogens. Elevated urine pyrroles, as they correlate with these other stress factors, may simply be an indicator of metabolic stress in the body. It also appears to be a general rule that subjects with severely elevated pyrrole levels were deficient in nutrients such as nutrients zinc, vitamin B3, vitamin C (Figure 6). The stress factors described above (infection, toxicity, etc.) may be factors in causing nutrient deficiency, or may be caused by nutrient deficiency. Vitamin C in particular is important for innate and cell mediated immunity, as it protects neutrophils from oxidative damage. The zinc to copper ratio is also an indicator of oxidative stress. This redox variable is commonly outside its normal range in mentally ill subjects, and appears to correlate in some cases with pyrrole excretion.

At the Riordan Clinic, mentally ill subjects are sometimes treated with supplements (including injections of B-vitamins, and intravenous infusions of vitamin C) to replenish depleted nutrient stores and provide for rejuvenation of the immune system. We were thus interested in how these treatments affected pyrrole levels. While we have not conducted a rigorous clinical study in this regard, we were able to extract from the database a group of subjects who had similar treatments and for whom pyrrole analyses before and after extended treatment was available. The results, shown in Table 2, seem



**Figure 6:** Effect of various nutrient levels on pyrrole excretion: (A) plasma vitamin C levels in bipolar subjects; (B) plasma vitamin B3 levels in schizophrenia subjects; (C) zinc:copper ratios in RBCs of depression subjects; and (D) RBC zinc levels in bipolar subjects. The lines represent linear (D) or quadratic (A, B, C) data fits, and are for illustration purposes only.

**Table 2:** Changes in urine pyrrole concentrations in subjects treated with prolonged nutrient supplementation at the Riordan Clinic. Data show the maximum value of measured pyrroles, period of treatment and the measured value at the end of the indicated period.

Subjects	Pyrrole (max)	Pyrrole (end value)	Days of treatment	Diagnosis	Subjects	Pyrrole (max)	Pyrrole (end value)	Days of treatment	Diagnosis
subject 1	40	26	130	Schizophrenia	subject 18	31	9	22	depression
subject 2	85	20	150	Schizophrenia	subject 19	77	32	200	depression
subject 3	40	17	82	Schizophrenia	subject 20	41	17	150	depression
subject 4	100	30	110	Schizophrenia	subject 21	75	10	80	depression
subject 5	30	12	64	Schizophrenia	subject 22	52	30	50	depression
subject 6	130	23	380	Schizophrenia	subject 23	58	40	100	depression
subject 7	44	3	50	Schizophrenia	subject 24	35	15	150	depression
subject 8	48	29	200	bipolar	subject 25	150	75	30	depression
subject 9	48	16	372	bipolar	subject 26	200	10	250	depression
subject 10	97	56	379	bipolar	subject 27	30	12	60	depression
subject 11	52	31	50	bipolar	subject 28	45	5	80	depression
subject 12	49	21	177	bipolar	subject 29	48	32	167	ADHD
subject 13	123	19	102	bipolar	subject 30	41	19	95	ADHD
subject 14	35	8	90	depression	subject 31	34	16	80	ADHD
subject 15	46	19	300	depression	subject 32	112	14	90	ADHD
subject 16	93	50	73	depression	subject 33	481	35	25	ADHD
subject 17	50	24	400	depression					

to suggest that pyrrole concentrations are reduced after prolonged supplementation therapy. This may be an interesting topic to explore with more rigorous controlled studies.

In summary, our analysis of the Riordan Clinic patient database suggests that pyroluria is relevant to a variety of stress and illness conditions, and, to the extent that these stresses are relevant in mental illness, is relevant to many mentally ill subjects. Abnormal pyrrole

excretion appears to be an indicator of oxidative stress, infection, intoxication, or improper digestion. Moreover, our data suggest that it may be possible to reduce pyroluria using a supplementation treatment regimen such as that employed at the Riordan clinic.

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