Treatment of Pyroluric Schizophrenia (Malvaria) With Large Doses of Pyridoxine and a Dietary Supplement of Zinc

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A syndrome is described in the mauve-positive, urinary kryptopyrrole-ex-creting patient which has many distinguishing features, namely: (1) *white spots in nails;* (2) *failure to remember dreams;* (3) *sweetish breath odor; (4) left upper quadrant abdominal pain;* (5) *dysperceptive schizophrenia and neurological-metabolical symptoms. These patients excrete urinary pyrroles at a level above 20 mcg percent. The usual age of onset is 15 to 20 years of age when the patient encounters the stress of senior year high school or first year of college. Kryptopyrrole has been shown to combine chemically with pyridoxal which then complexes with zinc to produce symptoms of vitamin B6 and zinc deficiency. The incidence is 30 to 40 percent in schizophrenics and 5 to 10 percent in normals. The disorder is familial and is responsible for the high incidence of "schizophrenia" in families. Adequate doses of* 86 (up *to 3.0 gm/day) and zinc will relieve the symptoms and reduce the urinary excretion of kryptopyrrole to the normal range. Discontinuation of the B6 - zinc results in a rapid return of serious symptoms within 48 hours. Work is progressing on the biochemical nature of stress-induced formation of kryptopyrrole.*

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BACKGROUND

In our studies on outpatient schizophrenics (Pfeiffer et al., 1969) we have found approximately 50 percent of the patients to be low in blood histamine (histapenic) and high in copper, while 20 percent are high in blood histamine (histadelic) and normal in serum copper. Either group may be low in serum zinc and/or manganese. Diaminoxidase (his-taminase) contains copper. Zinc is needed by the mast cell in order to store histamine. The terminal vesicles of the mossy fibers of the hippocampus are high in zinc which may be needed to store histamine for histaminergic neurotransmission. The patient's blood histamine correlates in a highly significant fashion with the absolute basophil count (Pfeiffer et al., 1972). These two suggested categories, histapenia and histadelia, account for 70 percent of the schizophrenias, and a knowledge of the biochemical defect allows more specific therapy directed at raising or lowering the blood (and presumably the tissue) level of histamine. With specific therapy based on changing low or excess tissue histamine, most problem patients improve.

A remaining group of 30 percent to 40 percent of patients are normal in their blood histamine and normal in serum

copper levels. This is the group which excretes kryptopyrrole (KP) or the "mauve factor." We have now found that these patients respond to large doses of B6 and dietary supplements of zinc because the pyrrole combines with pyridoxal (B6) and then makes a complex with zinc and produces a combined deficiency. Some problem patients may have both the mauve factor and a histamine imbalance. The schizophrenias may truly be a series of three or more biochemical imbalances.

Several workers have confirmed the original observations of Irvine (1961) and Hoffer/Osmond (1963) that abnormal mauve factor is excreted in greater frequency in the urine of schizophrenics. Other workers (Ellmann et al., 1968) have labeled this finding a drug artifact noted only in patients on phenothiazines. Recently Irvine et al. (1969) have succeeded in isolating and identifying the mauve factor as 2, 4 dimethyl-3-ethylpyrrole, an observation confirmed subsequently by Sohler et al. (1970). Neither Irvine or Sohler could find any relationship of KP excretion to phenothiazine medication. Furthermore 5 percent of "so-called" normals, who are not on phenothiazines, excrete the mauve factor.

The dose of B6 needed by the KP-positive patient may be as high as 3,000 mg per day to prevent Psychopathology and keep the urine free of KP. Our present quantitative test for KP measures only the assayable KP since we find that KP combines with the aldehyde of pyridoxal phosphate to form a stable Schiff's base which is then excreted in the urine complexed with zinc. This results in a syndrome of B6 and zinc deficiency.

This clinical entity would undoubtedly have been discovered much earlier if the essential interrelationship of zinc and B6, had been known. We have found that mauve-positive patients excrete in their urine significantly more zinc and coproporphyrin (Table 1).

In addition, we have found that in "schizophrenics" compared to "normals" an oral dose of 50 mg of B6 results in the reduction of urinary zinc excretion. In this study the patients of these two groups were not screened for mauve factor or quantitative free KP urinary excretion. This 50 mg oral dose of B6 reduces urinary zinc excretion in both patients and normals while copper excretion is increased in both groups. The decrease in zinc excretion produced by the B6 is greater in schizophrenic patients than in the normals. Iron excretion is decreased in normals. Patients characteristically excrete less copper than the normals. Because of wide individual variation, these changes are not statistically significant (Table 2).

TABLE 1

Urinary Content of Trace Metals and Coproporphyrin in Schizophrenic Outpatients

All means are mcg% ± S.E.

Schizophrenic outpatients	Zn N = 45	Cu N = 45	Fe N = 45	Coproporphyrin N = 27
Mauve positive	49.71 ± 6.95	3.18 ± 0.62	4.07 ± 0.56	121.11 ± 10.49
Mauve negative	N = 35 29.66 ± 4.43	N = 35 3.31 ± 0.56	N = 35 5.20 ± 0.80	N = 12 38.50 ± 7.79

t for Zn = 6.34 ($p < 0.0001$)
t for Coproporphyrin = 5.04 ($p < 0.001$)

Urinary content of trace metals and coproporphyrin in mauve-negative and mauve-positive schizophrenic out patients. All means are mcg% ± standard error of metal or coproporphyrin content in early morning uring sample.
The mauve positivity was determined by the Irvine test before the development of the present quantitative test. Zinc excretion is greater in the mauve positive as is also the coproporphyrin excretion.

ORTHOMOLECULAR PSYCHIATRY, VOLUME 3, NUMBER 4, 1974, Pp. 292 - 300

TABLE 2

Urinary Excretion of Trace Metals After 50 mg Pyridoxine Orally

All numbers are mcg per 6-hour period

	Patients				Normals			
Med-Oral Dose	Trials	Cu	Zn	Fe	Trials	Cu	Zn	Fe
Placebo	18	1.7	152	16	26	4.6	148	20
B_6, 50 mg.	21	3.9	89	15	14	7.4	105	10

Urinary excretion of trace metals in schizophrenic outpatients compared to normals. Patients not separated according to mauve positivity. All means are mcg of metal excreted in a six-hour daily period collected from 8:00 a.m.to 2:00 p.m. Trials were run weekly. The number of patients and normals contributing to the trials exceeded 12 in each group. Statistical analysis shows these differences do not attain significance. However, the trend in both patients and normals is for greater copper and less zinc excretion. Iron excretion decreases in the normals only. Patients characteristically excrete less copper than normals.

Since various pyrroles contribute to the mauve-color reaction, we suggest that "pyroluria" might better designate these patients than "malvaria."

We have now had over three years of experience in diagnosing and treating the mauve-positive schizophrenic. We have seen over 300 pyroluric patients and, in consultation, probably twice that number. The B6 and zinc treatment is usually effective in producing a remission of their psychosis. Symptoms return when the patient goes off the nutrients or runs out of these nutrients. Our first case was puzzling, but most instructive, and therefore a review of Sara's difficulties is appropriate.

First Patient: Sara T. (now aged 19)

Our initial B6 - zinc-deficient patient developed knee joint problems at about puberty which (like her older brother) was diagnosed as inadequate development of the semilunar cartilages with chondromalacia of the patellae. This was probably the first sign of her zinc and manganese - B6 deficiency. (Various animal species get hock disease and slipped tendon when the diet is deficient in either zinc or manganese.) Mental difficulties began in 1966 when she was 11 years. At this time the patient began having daydream-like episodes in which she would lose contact with reality. Later that year she lost insight so that it was difficult for her to distinguish between what was imagined and what was real. In 1968 the patient suffered from chronic insomnia. Her weight was 150 pounds. On a "crash diet" in June of 1969 she lost 35 pounds to a weight of 115 pounds in a five-month period.

In the summer of 1970 (then aged 15) she became delusional, thinking there was a plot to drive her insane. At that time she had the first episode of left-sided muscle spasm in which she thrashed about hitting herself. Friends who first witnessed these episodes mistakenly thought that she had taken LSD and was on a "bad trip." On October 1, 1970, she attempted suicide by hanging. She couldn't recall the incident and doesn't believe that it really happened. After that, she was hospitalized at a general hospital.

After psychiatric consultation she was transferred to a psychiatric hospital. While at this hospital she had the seizure-like episodes previously described at a rate of three per week. Her appetite was poor, and she vomited frequently. Her therapy consisted of group psychotherapy, Trilafon or Thorazine or Stelazine and Dilantin. No improvement was seen. Her menstrual periods ceased in December, 1970.

She had two series of complete neurological studies. These included EEC's, mercury brain scan, skull x-rays, echoencephalograms, and visual field examinations. All were normal. Her PBI was 7.8 and urinalysis and blood chemistry profile were normal. She also had psychological tests as follows: I.Q. Verbal 115, performance 100, full scale 109. **Diagnosis:** Schizo-affective with paranoid features. Adjustment reaction

of adolescence, severe.

On January 7, 1971, after three months at the psychiatric hospital with no improvement, she was transferred to the psychiatric floor of an institute in New York. An EEG taken during one of the seizures was "within normal limits." She was treated with Thorazine and individual psychotherapy.

On January 29, 1971, her blood was tested by our laboratory, and the patient was found to be low in histamine, 26.2 ng/ml (normal 40-70), her spermidine was .45 mcg/ml (normal 0.9), spermine 1.99 mcg/ml (normal 1.3 - 1.5), serum iron 3.0 (normal 1.2), and zinc 2.6 (normal 1.2 p.p.m.). Her score on the Experiential World Inventory (EWI) psychiatric rating test was 78 (normal 15). **Diagnosis at the Institute:** (1) Seizure disorder; (2) Schizophrenia, chronic undifferentiated.

On February 3, 1971, she was transferred to a New Jersey psychiatric hospital. EKG, spine x-rays, and five-hour glucose-tolerance test were normal. A VDRL was non-reactive. On February 10, 1971, she began receiving a trace metal dietary supplement plus vitamins. She was given zinc sulfate 10 percent and manganese chloride 0.5 percent, 4 drops in a.m. and p.m.; folic acid, 2.5 mg in a.m.; Pyridoxine, 25 mg each a.m.; deanol, 100 mg in a.m.; niacin, 100 mg bid.; ascorbic acid, 500 mg bid.; Benadryl, 50 mg h.s. and E12, 1 mg injection once a week. The niacin and ascorbic acid were gradually increased to 1,000 mg t.i.d. on February 12, 1971. After only a few days on this regime,
improvement was noted in that her appetite was better, she had more energy, and was less depressed. The blood tests on this date confirmed the improvement; her histamine had risen to 44.3.

On February 24, 1971, she was referred to group therapy and Navane 1 mg t.i.d. was started. She continued to show steady improvement, and on March 3, 1971, her EWI score had fallen to 44 and histamine was 45.5. The seizures had been in remission for two weeks. Her family requested discharge on March 8, 1971. **Diagnosis:** Schizophrenia acute undifferentiated type. Upon discharge the Navane was discontinued, and on March 10, 1971, her EWI was down to a normal 14, and her histamine had gone up to 62.2. The serum iron was normal at 1.04 p.p.m.

She was continued on folic acid, 2.5 mg in a.m.; deanol 50 mg in a.m.; B6, 25 mg, niacin and ascorbic acid, 500 mg t.i.d.; zinc and manganese, 4 drops a.m. and p.m.; and magnesium chloride, 10 drops a.m. and p.m. Her menstrual period, which was regular since its onset in 1967, skipped three months (December 1970, January, February 1971) and became regular again in March, one month after starting the B6 Zn-Mn dietary supplement. Her MMPI on March 15, 1971, was as follows:

L/F/K	HS	D	HY	PD	MF	PA	Pf	SC	MA	SI
56/58/62	60	49	64	62	41	53	50	60	70	38

Beginning in June, 1971, she showed a syndrome of severe constipation and splenic pain which did not respond to treatment with codeine. She had had this

TABLE 3

KP and Coproporphyrin Urinary Excretion

S.T. aged 16 Urinary Excretion (a.m. Sample)

Date		Coproporphyrin	Kryptopyrrole	(Sohler Method) (Normal 0-50 mcg%)
2/8/72	Control	225 mcg%	1046 mcg%	
2/9/72	R_x B_6	75 mcg%	45 mcg%	
2/10/72	R_x B_6	48 mcg%	127 mcg%	
2/11/72	R_x B_6	76 mcg%	0 mcg%	
2/12/72	R_x B_6	52 mcg%	32 mcg%	
2/13/72	After Control	370 mcg%	141 mcg%	

trouble intermittently since the age of 11, but the syndrome was disregarded because of her mental state and seizure syndrome. We found her KP excretion to be 4+ (coproporphyrin 225 *v*g %) and found further that both abnormalities decreased with zinc and B6, therapy. Her urine was consistently negative tor homocysteine by the nitroprusside test.

Her parents sent her again to the New York institute, but this time the diagnosis of acute intermittent porphyria (AIP) was raised. The doctors reviewed the history and tested her urine which was negative, but they agreed that AIP might be the basic problem.

The B6 dosage was doubled, and we found that 400 mg of B6, morning and night - 800 mg per day when taken with zinc - manganese dietary supplement-would keep all mental and abdominal symptoms away. After making up her missed schooling, she is currently a second-year college student at a Midwestern university.

Summary of First Case

This 15-year-old upper middle-class patient (now 19 after study for four years) represents a case of nutrient deficiency in which vitamins (specifically B6) and the trace minerals manganese and zinc were inadequate for the development of normal knee joints and normal brain function. The deficiency was sufficiently severe at its peak to cause prolonged psychosis, atypical seizures, arthritis, amenorrhea, constipation, and splenic pain. The pain is probably due to hemolytic crises in which red cell fragments engorge the Kupfer cells of the spleen and liver, extend the capsule, and cause pain. The double deficiency is produced by the formation of KP which

TABLE 4

Metabolic B_6 and Zinc Deficiency

Inspection:

China doll complexion
White spots in nails
Crowded upper incisors
Coarse hairs in eyebrows
Look-alike siblings
Sweet aldehyde odor to breath

History:

Stress-induced disorder - onset 17-21 yrs.
Inability to tan: itching with sunlight
Low dream recall
Constipation
Upper quadrant acute pain (spleen - hemolytic crises)
Unexplained chills and fever
Morning nausea (can't eat breakfast)
Dysperceptive schizophrenia (but better affect)
Knee joint aches
Neurol: Amnesia, tremor, shaking, muscle spasms, convulsions
Impotence, amenorrhea, anovulation
Barbiturate and tranquilizer intolerance
Anemia - nonresponsive to iron therapy

Tests:

"Kryptopyrrole" in urine above 20 mcg%
Stretch marks (stria)
Hypoglycemia
Decrease in KP with B_6 and zinc treatment
Low serum zinc or extremely high (B_6 deficiency)
Normal levels of copper and histamine

TABLE 5

Six-hour Urinary Excretion of Trace Metals after Various Oral Medications

	mcg./6 hrs. Urinary Excretion							
	Patients				Normals			
Med. Oral Dose	Trials	Cu	Zn	Fe	Trials	Cu	Zn	Fe
Placebo	18	1.7	152	16	26	4.6	148	20
Zinc Ac. 35 mg	13	3.7	108	22	10	3.6	138	15
$MnCl_2$ 3 mg	11	5.5	137	47	10	1.2	325	12
$ZnSO_4$/Mn 50/3 mg	12	11.0	147	15	12	9.1	154	15
Zn/Mn/B_6 50/S/50	14	20.0	224	16	13	3.0	186	6
Penicillamine 500 mg	11	174	526	16	8	178	300	9
CPZ 150 mg.	27	9.3	122	19	-	-	-	-

combines with pyridoxal and zinc. The syndrome is close to acute intermittent porphyria in that coproporphyrin excretion is also increased. The history is given in detail to show the difficulty a patient with a biochemical imbalance may have in seeking adequate diagnosis and treatment.

RESULTS ON OTHER PATIENTS

After finding a practical antidote to Sara's illness we have successfully applied the same principles of treatment to over 300 problem patients who have the general symptoms of schizophrenia but are unresponsive to antipsychotic drugs, electroshock, or insulin coma therapy. A careful review of these patients gave the following signs and symptoms. Some, but not necessarily all, of these symptoms may be present in a given patient (Table 4).

Manganese may be needed in addition to zinc and B6. We have used a dietary supplement of zinc sulfate 10 percent and manganous chloride 0.5 percent at the rate of six drops a.m. and p.m. This supplement provides in a positive fashion two-thirds of the zinc and manganese which should be contained in a normal daily diet. Many schizophrenic patients are high in serum copper, and this combination of trace metals antagonizes copper and iron to provide greater copper and iron excretion.

These exploratory data are presented without standard errors, etc., since they are used only to make several tentative points. Copper excretion is increased progressively by the combination of zinc, manganese, and B6. This is inferior to the effect of penicillamine but more biological and safer. The antipsychotic drug chlorpromazine (CPZ) in a large oral dose tends to remove copper from the body (Table 5). Other drugs require large doses of B6, (Table 6). The comparison of pyroluric patients with others is given in Table 7.

TABLE 6

Human Requirements for Pyridoxine

Disorder	Dosage/day
Normal	2 mg
B_6-dependent child	5 - 10 mg
INH Therapy	50 mg
Hydralazine Rx	50 mg
Contraceptive pill (+Zn)	50 mg
Homocystinuria	25 - 500 mg
D-penicillamine Rx	500 mg
Metabolic pyroluria	2.0 gm
Acute Intermittent Porphyria	?

The normal need for B6 is 2 mg/day. Infants born of mothers given large doses of B6 may need large doses of 5 to 10 mg per day. Patients on drugs which combine with pyridoxal require large but finite doses of B6 depending on the dose of the drug. Patients with metabolic pyroluria require enough B6 to eliminate free kryptopyrrole excretion, or alternately enough B6 to allow them to remember their nightly dreams. The Acute Intermittent Porphyric patients excrete large amounts of kryptopyrrole (D. Irvinel and zinc. They might therefore respond to large daily doses of B6 and zinc.

TABLE 7

Blood Histamine Nanogram/ml + S.D.

		Number			
Normal	Male	(19)	46.3 ± 18		
	Female	(10)	41.7 ± 14.5		
Pyroluric	Male	(27)	52.8 ± 23.8		
	Female	(27)	46.1 ± 11.7		
Low Histamine	Male	(28)	20.2 ± 10.4	t* = 6.3	p = < 0.001
	Female	(29)	27.6 ± 8.1	t* = 2.3	p = < 0.05
High Histamine	Male	(29)	110.7 ± 16.5	t* = 12.8	p = < .001
	Female	(26)	107.3 ± 24.4	t* = 7.9	p = < .001
Hypoglycemic	Male	(35)	43.4 ± 25.1		
	Female	(71)	49.3 ± 21.1		

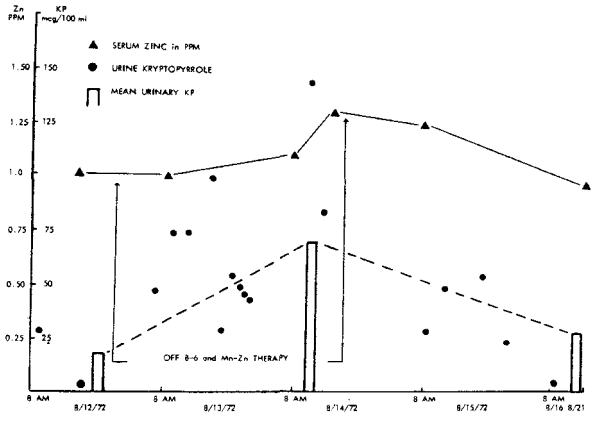
'Compared to normal group

Comparison of blood histamine levels in normals and hypoglycemic patients with that of three types of schizophrenic patients means + standard deviation. The means of normals, pyroluric and hypoglycemic patients are similar and not significantly different.

DISCUSSION

To definitely establish the etiology of this syndrome as a double-deficiency of zinc and B6, one needs additional data. What are the total levels of B6, activity in the untreated patient, and what are the excretory products of B6? Within the year we should have tentative answers to these questions.

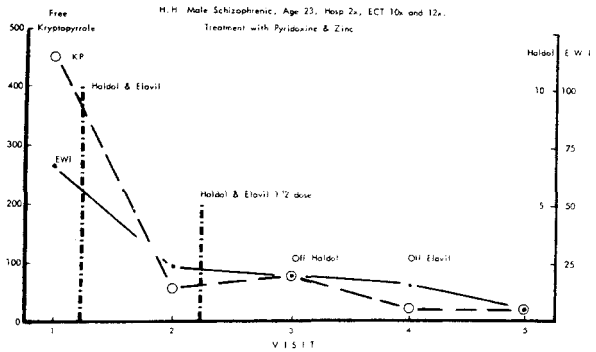
Alternatively, one might substitute identical placebo doses for the B6 and zinc therapy. We have tried this in two patients with such alarming results that we advise **"The large dose of B6 should never be discontinued abruptly."** This may result in catatonia, muscle weakness, or chills with fever. The withdrawal should be under careful guidance of the investigator and should be gradual (i.e., 10 percent per day). Because of the need for B6, these patients should have a vial of B6 and a sterile syringe for use in the continued treatment when nausea and vomiting occurs with other illnesses. With anorexic states, the patient must be taught that B6 takes precedence over other medications. We have also used chlorpromazine suppositories to decrease vomiting in order to absorb the B6.



Forty-eight hour abstinence from zinc and pyridoxine in Sara T., aged 17. Changes in urinary-free kryptopyrrole and serum zinc. Serum zinc, triangular dots, rose with abstinence as did the urinary-free KP. Before (2 urines) 17.5 mcg% average, during (11 urines) 64.5 mcg% and after (5 urines) 31.0 mcg%. The serum zinc remained constant until the severity of the clinical symptoms necessitated discontinuation of the abstinence. These symptoms were progressive muscle weakness, diplopia, loss of affect, severe left upper quadrant abdominal pain, and drop in body temperature with chills. All symptoms disappeared two hours after the administration of 400 mg pyridoxine and 50 mg of zinc sulfate.

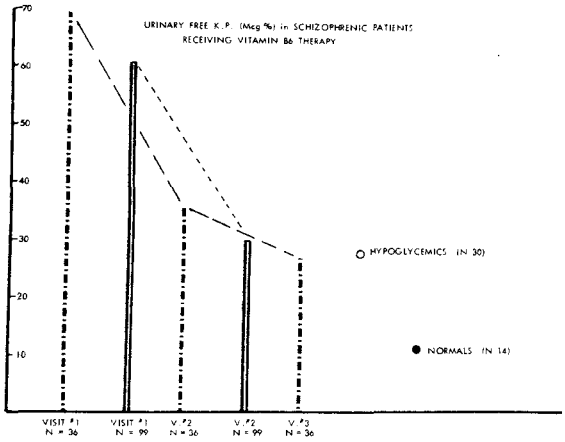
Figure 1

Figure 2



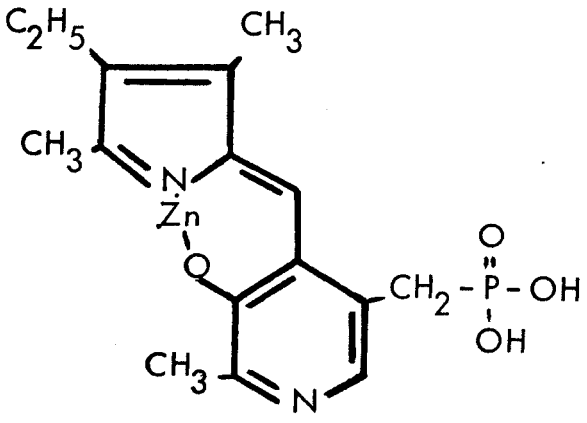
H.H. male patient, aged 23. Onset of dysperception at age 15. Hosp. 10 ECT, 1965. Hospitalized again 1972, 12 ECT. Treatment was ineffective, patient still had paranoia, depression, and insomnia. First seen 6/1/72. Seen monthly thereafter. Patient was doing poorly on 10 mg Haldoperidol and 100 mg Amitriptyline per day. History and physical examination gave the following findings pertinent to possible pyroluria: history of abdominal pain, chronic constipation, breath odor, white spots in nails, impotency, and edematous obesity. Venipuncture was difficult because of poor peripheral circulation. The urinary KP level was high as was the Experiential World Inventory. Therapy was initiated with 200 mg of B_6, a.m. and p.m. plus Vicon Plus, a source of zinc and manganese. The specific tranquilizers Haldoperidol and Amitriptyline were discontinued by the fourth monthly visit. Patient well 11 months later.

Figure 4



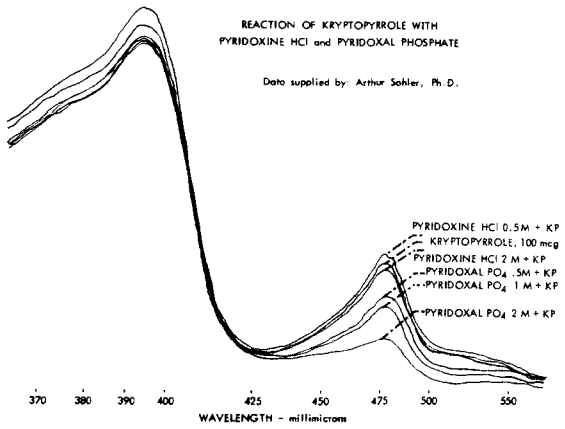
Urinary-free kryptopyrrole (KP) mcg% in schizophrenic or hypoglycemic patients and normals. The urinary level of KP is significantly different from normals and decreases with each monthly visit as the symptoms subside. Some hypoglycemic patients have pyroluria as part of their illness.

Figure 3

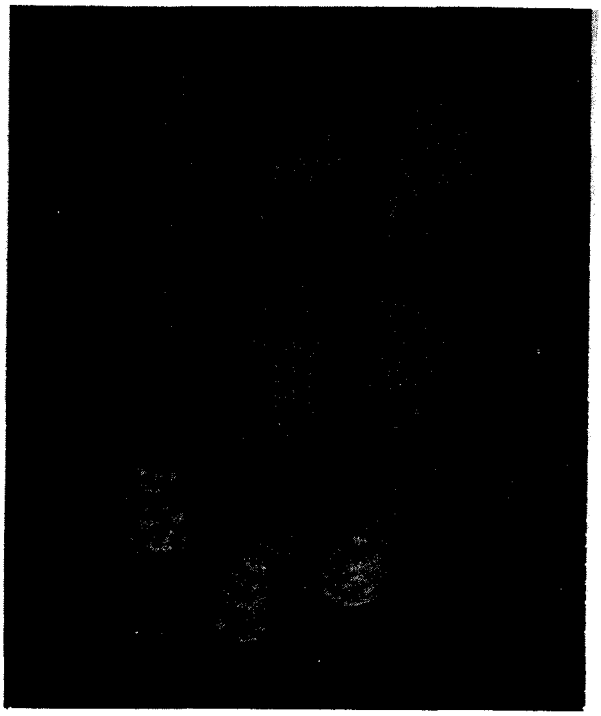


Suggested structural formula for the zinc-kryptopyrrole (KP) pyridoxal chelate. KP is a highly reactive substance. Such pyrroles react with aldehydes at the 5 position of the 5 membered ring. Dipyrroles would probably be equally active. The final product with zinc could form the ring structure drawn above. This type of compound has been made in the laboratory.

Figure 5



Reaction of Kryptopyrrole with pyridoxal phosphate. Addition of pyridoxal phosphate reduced the peak of KP at 480 millimicrons. The greatest reduction occurs with 2 mols of pyridoxal. Pyridoxine does not react with KP.



White spots in fingernails of pyroluric patients as a sign of zinc deficiency. These spots no longer occur when patient receives adequate zinc and B_6.

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