

# KPU/HPU: A MAJOR PIECE OF THE PUZZLE IN OVERCOMING CHRONIC LYME DISEASE

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Dr. Dietrich Klinghardt MD, PhD is a practicing physician in Kirkland, Washington with a focus on the treatment of chronic neurological conditions such as Lyme disease, autism, and CFIDS. In the many years that he has treated patients with chronic infections, he has observed that, for many, recovery is elusive. Patients may often plateau or find that their recovery is stalled. In other cases, patients may not succeed in their attempts to rid the body of a particular toxic or infectious burden; such as in patients with long-standing or therapy-resistant late stage Lyme disease.

In looking for possible explanations as to why some patients struggle more than others to regain their health, Dr. Klinghardt has found a high correlation between patients with chronic Lyme disease and those with Kryptopyrroluria (KPU), or more precisely Hemopyrrolactamuria (HPU). The condition is alternatively known as the "Mauve Factor" or "Malvaria". HPU may be an inherited condition but it can also be induced by childhood psychological trauma or chronic infections.

The HPU complex is a biochemical marker and neurotoxic substance frequently identified in the urine of patients with autism, learning disabilities, alcoholism, substance abuse, schizophrenia, ADHD, Down syndrome, depression, bipolar disorders, and even criminal behavior. Some estimate the incidence of KPU to be 40-70% in schizophrenia; 50% in autism; 30% in ADHD; and 40-80% in alcoholism and substance abuse.

Dr. Klinghardt has found the incidence of HPU in Lyme disease to be 80% or higher; in patients with heavy metal toxicity (lead, mercury, cadmium, and others) over 75%; and in children with autism over 80%. These are very significant percentages of the patient population with chronic illness that may benefit from a treatment program which addresses HPU. Normal, healthy controls do not test positive for HPU.

## History

In 1958, a psychiatric research program in Saskatchewan, Canada led by Abram Hoffer MD, PhD, the father of orthomolecular psychiatry, was looking for the possible biochemical origin of schizophrenia. One study involved evaluating the urine for certain chemical fractions and evaluating those of schizophrenic patients and those of normal controls. The effort yielded the "mauve factor" - a specific substance that reliably allowed the examiners to identify the schizophrenic patients, as it was not identified in the normal controls.

Early on, the substance was known as "the mauve factor" due to the mauve color that was observed on the stained paper. It was then termed "kryptopyrrole", later identified as hydroxy-hemopyrrolin-2-one (HPL). The researchers first called the disease associated with this condition "Malvaria", but it was renamed by Dr. Carl Pfeiffer MD, PhD to "Pyrolleuria" which was, for no obvious reason, consistently spelled "Pyrroluria" in later publications. In the 1970's, Dr. Pfeiffer created an assay for the condition and was able to show clinical improvement in positive patients with high doses of zinc and vitamin B6.

## Overview

Elevated levels of HPL found in urine are the result of an abnormality in heme synthesis. Hemoglobin is the substance that holds iron in the red blood cells. HPL is a byproduct of hemoglobin - or heme - synthesis and can be identified in the urine. HPLs bind to zinc, biotin, manganese, vitamin B6, arachidonic acid and other important compounds and lead to a significant depletion of these substances in the body.

Turning to the importance of zinc, biotin, manganese, vitamin B6, and arachidonic acid in the body, it becomes clear how widespread the problem may be that is created by this condition.

Zinc deficiency may result in emotional disorders, delayed puberty, rough skin, delayed wound healing, growth retardation, hypogonadism, hypochlorhydria, mental lethargy, short stature, diarrhea, stretch marks or striae (which may be misinterpreted as Bartonella in some patients), white spots on the fingernails, reduction in collagen, macular degeneration, dandruff, skin lesions such as acne, hyperactivity, loss of appetite, reduced fertility, transverse lines on the fingernails, defective mineralization of bone leading to osteoporosis and many others.

Zinc is a powerful anti-oxidant and lower levels of zinc, as found in those with HPU, lead to an increase in oxidative stress. Lower levels of zinc are correlated with low levels of glutathione, an important part of the detoxification system. Zinc is required to support proper immune function. "White blood cells without zinc are like an army without bullets," says Dr. Klinghardt.

Biotin deficiency may be evidenced by rashes, dry skin, seborrheic dermatitis, brittle nails, fine or brittle hair, and hair loss. More importantly, however, it may be associated with depression, lethargy, hearing loss, fungal infections, muscle pain, and abnormal skin sensations such as tingling. Biotin is an important factor in the production of energy in the mitochondria. Biotin is essential for a healthy brain and nervous system. Biotin deficiency is associated with many aspects of the aging process.

Manganese deficiency may be associated with joint pain, inflammation, and arthritis. It may result in a change in hair pigment or a slowing of hair growth. It is essential for normal growth,

glucose utilization, lipid metabolism, and production of thyroid hormone. It may be associated with diseases such as diabetes, Parkinson's disease, osteoporosis, and epilepsy.

Vitamin B6 deficiency is thought to be a rare occurrence. However, in those with HPU, this is not the case. B6 deficiency may lead to nervousness, insomnia, irritability, muscle weakness, poor absorption of nutrients, decrease of key enzymes and cofactors involved in amino acid metabolism, impairment in the synthesis of neurotransmitters, impairment in the synthesis of hemoglobin, seborrheic dermatological eruptions, confusion, and neuropathy. Similar to zinc, B6 is also an anti-oxidant and correlates to levels of glutathione.

Arachidonic acid (from omega-6) deficiency may lead to the impairment of white blood cell function, primarily the leukocytes which may lead to one being more vulnerable to infection. It may lead to neuropathy, neural and vascular complications in preterm babies, skin eruptions, behavior changes, sterility in males, arthritic conditions, dry eyes, growth retardation, dry skin and hair, slow wound healing, hair loss, kidney dysfunction, heart beat abnormalities, and miscarriages.

When one considers the magnitude of potential health problems that may be present when a single condition causes a deficiency in zinc, biotin, manganese, vitamin B6, and arachidonic acid simultaneously, the negative implications on health are almost endless.

### **HPU and Lyme Disease**

Three possible origins of HPU are discussed in the literature: genetics, early childhood trauma, and chronic infections. The connection between HPU and many of the illnesses previously discussed has been known for quite some time. However, never before has a connection been observed or published between HPU and Lyme disease. This discovery has been a key for Dr. Klinghardt to return his patients to a better state of health and wellness. The changes he has observed have been profound.

Dr. Klinghardt has found that 4 of 5 patients with chronic Lyme disease test highly positive for this condition. That suggests that 80% of patients with symptoms of chronic Lyme disease might benefit from a treatment protocol that addresses HPU.

Dr. Klinghardt believes that it is not possible to have chronic symptomatic Lyme disease as an adult without a preceding mold illness or the patient having developed HPU. He postulates that the biotoxins from microbes block one or more of the eight enzymes of heme synthesis. This leads to a significant loss of key minerals in white blood cells which effectively disarms cellular immunity.

One young adult female struggling with Lyme for several years had severe multiple chemical sensitivities (MCS) that were not improved by any previous treatment. After starting the HPU protocol, she noticed improvements in her MCS for the first time since she became ill. Other patients with intractable chronic infections have experienced significant improvements in immune function and a resulting lowering of total microbial body burden.

Dr. Klinghardt has observed numerous patients that have struggled to rid the body of parasitic infestations. In these patients, regardless of the interventions used, the patient continues to expel these parasites on an ongoing basis. Therapy-resistant infections are a hallmark sign of HPU. Dr. Klinghardt has found that once the HPU protocol is put in place, there is often swift

resolution of long-standing infections and infestations. This includes patients who have failed years of antibiotic therapy for chronic or late stage Lyme disease.

Chronic Lyme disease patients often suffer from severe jawbone infections that may require cavitation surgery, which often tends to fail in these patients. When the clients are pre-treated for HPU, the outcome of the surgical procedure is generally much better. In some cases, ozone treatment of the jaw is sufficient to turn things around.

Dr. Klinghardt has followed the interest in HLA genetic typing in regards to biotoxin illnesses such as Lyme disease and mold. Until now, patients with certain haplotypes were considered more difficult to treat as the body could not properly and effectively respond to and remove biotoxins from Lyme disease, molds, or in the worst cases, both. In his experience, once the HPU issue is addressed, these HLA types become far less of a concern in most patients.

Once all of the bodily systems are back online and functioning properly, a few months after introducing the HPU protocol, patients are essentially made invulnerable to Lyme disease, to molds, and even to heavy metals. Their bodies are now much better equipped to deal with these conditions when they have appropriate levels of zinc, biotin, manganese, vitamin B6, and arachidonic acid to support optimal functioning of numerous bodily processes.

### **HPU and Multiple Sclerosis**

Dr. Klinghardt has treated many patients with Multiple Sclerosis. All of the MS patients that he has tested have been highly positive for HPU. Over time, he has come to the conclusion that HPU can lead to MS in some patients. He has found that patients with MS respond favorably to HPU treatment.

In patients with HPU, histamine levels are almost always low. The treatment for MS patients with HPU should include histamine in addition to the HPU protocol outlined later in this article. Treatment with histamine may be either with oral or transdermal products. Prokarin is a transdermal patch which delivers histamine and has been used by some in the treatment of MS.

### **HPU and Heavy Metal Toxicity**

As mentioned earlier in this article, both zinc and vitamin B6 deficiencies - important cofactors in the methylation cycle - reduce levels of glutathione in the body. Glutathione is important for the detoxification of heavy metals. When HPU is an issue and zinc and vitamin B6 are depleted, the detoxification pathways are overwhelmed and ineffective. Replacing missing zinc and vitamin B6 increases glutathione. This in turn increases the rate of detoxification of heavy metals and other body burdening toxins.

However, it is also the case that incorporating the HPU protocol will liberate additional heavy metals in the body. This aspect of the HPU protocol is discussed later in this article and is of utmost importance for the practitioner to understand before beginning to treat patients for the condition.

### **Evaluation and Testing**

HPL levels can be measured from urine through the laboratory Health Diagnostics (Formerly Vitamin Diagnostics). The [test](#) costs approximately \$55 dollars. [A lab kit is ordered](#) and the

urine sample is returned to the lab by the patient. It is important that the patient follow the instructions as Dr. Klinghardt outlines and not the directions that come with the test kit from the lab.

Until recently, Health Diagnostics (Formerly Vitamin Diagnostics) offered a test for the related compound called kryptopyrrol only. Recently, they began to offer a test for the hydroxy-hemopyrrolin-2-one (HPL) compound. When filling out the requisition, the practitioner can now select HPL in addition to kryptopyrrol. The HPL test results in a much higher yield.

Dr. Klinghardt finds that in order to get the best possible insight into the patient's condition, it is best to avoid all supplements, especially those containing zinc, biotin, and vitamin B6, for 5-7 days before the urine sample is collected. He suggests that patients use a 24-hour urine collection as opposed to first morning urine as the release of HPL complex into urine is not consistent and might be missed in a single urine collection. The sample should be shielded from light. 500mg ascorbic acid should be added to each liter of urine as a preservative. To further maximize the benefit of testing for the condition, it is best for the patient to be under stress at the time the test is being performed as HPL excretion is known to increase during times of stress.

Dr. Klinghardt has found that Health Diagnostics (Formerly Vitamin Diagnostics) has the [best test for HPU available in the United States](#). In some circumstances, however, patients may still test negative even when the condition is suspected. In those cases, an empiric trial of the HPU protocol may still be warranted.

#### **Other laboratory results that may be suggestive of HPU include:**

- WBC < 5000/mcL (due to low levels of zinc)
- High LDL / Low HDL
- Low normal alkaline phosphatase (<60U/L)
- Low omega-6 fatty acids in red cell membrane test
- Low taurine in amino acid profile
- High MCV
- WBC and RBC zinc and manganese levels may be normal while biopsies from bone and CNS are completely deficient
- Bone biopsies are a reliable predictor of HPU. Severe deficiencies of zinc, manganese, lithium, calcium, magnesium, and molybdenum are often found

#### **Treatment**

Hemopyrrolactamuria is a severe, but reversible deficiency of zinc, biotin, manganese, vitamin B6 (or P5P), and arachidonic acid.

**The treatment that Dr. Klinghardt uses for HPU is as follows (dosages for adults):**

**Before Breakfast:**

Zinc 27-40mg elemental zinc per day (as [Picolinate](#), [Gluconate](#) or Sulfate; liquid is more effective). Initially, up to 240mg of elemental zinc may be used under the care of a doctor in those with metal toxicity and chronic infections. Nausea after zinc supplementation may be a sign of hypochlorhydria or low stomach acid. This tends to resolve after 2-4 months on the protocol.

[Manganese](#) 5mg per day (initially up to 20mg per day in those patients with joint and ligament weakness)

**With Breakfast:**

Arachidonic acid from Omega-6 oils ([Ghee](#), [Evening Primrose Oil](#), [Black Currant](#), [Borage](#), [Pumpkin](#); 4-6 capsules of Evening Primrose Oil per day is commonly used)

[Fish oil](#) 1 teaspoon per day

**Before Bedtime:**

[Vitamin B6](#)/P5P 25mg B6 per day and 50mg P5P per day (Most patients do better with a [combination of both B6 and P5P](#). Some require P5P. Approximately 10% do not tolerate P5P at all. Initially, up to 750mg per day may be used, especially in those with seizure disorders.)

Magnesium ([Glycinate](#) or [Malate](#)) 600-2000 mg per day - or titrate to bowel tolerance

[BioPure MicroMinerals](#) 1 tablespoon per day

[Biotin](#) 10mg per day for brain, skin, hair, and nails

This is the core treatment for HPU.

**Optional:**

- [Niacinamide](#) 1000mg three times per day for psychiatric symptoms
- [Taurine](#) 500mg three times per day for brain-related symptoms such as seizures, brain fog, and memory loss. Supports elimination of neurotoxins, improves bile quality, increases glutathione, and normalizes brain rhythms
- [Lithium Orotate](#) or [Aspartate](#) 60mg-240mg per day
- [Chromium](#) 500 mcg per day (initially up to 2 mg, especially in certain brain disorders and hypo/hyperglycemia and insulin resistance)
- [Molybdenum](#) 300 mcg (initially much higher, especially with sulfur reactivity)

- [High Gamma Vitamin E](#) 400 IU per 40lbs of body weight per day (Unique E is the brand often used)
- HPU clients are also often deficient in silica, iodine, and boron.

In Europe, "Depyrrol" is a product which contains Zinc, Manganese, and a mix of vitamin B6 and P5P. It is used as a method of treating HPU. The more complete US product "[Core](#)" is available from BioPure Healing Products. Omega-6 oils must be supplemented in addition to Depyrrol or [Core](#), but these products provide the patient the convenience of getting the key components of the protocol in one product. One potential consideration is that some patients may not tolerate both vitamin B6 and P5P; both of which are contained in Depyrrol and [Core](#). As a result, it is occasionally necessary for patients to take each component of the HPU program separately.

It is critically important to monitor mineral levels during this treatment. Copper levels should be assessed using a red cell mineral test. [Copper](#) replacement is often necessary at a dose of 2-4mg per day due to the high zinc dosage. This is evaluated and introduced when necessary after the treatment has begun, often between months four and six. Zinc, manganese, and vitamin B6 are copper antagonists. Thus, monitoring levels of copper and supplementing where needed is an important part of the treatment protocol. Zinc and copper should not be taken at the same time of day.

Copper deficiency can lead to hemorrhoids, varicose veins, fatigue, edema, hair loss, anorexia, skin problems, osteoporosis, cardiovascular disease, aneurisms, and many other undesired conditions. Current nutritional teachings are misinformed on the topic of copper toxicity. The immune system uses copper and iron to fight infections associated with Lyme disease. As a result, oxidized copper is displaced in the connective tissue and may appear as though the patient is copper toxic by some testing methods when in fact copper supplementation may be appropriate. High dose [Vitamin C](#) has the effect of changing copper to a form that can be reused by the body.

### **Detoxification and Course of Treatment**

For many patients, the course of treatment will not be an easy one. This is a treatment that should be done only under the care and supervision of a doctor as patients often experience a worsening in their condition before they improve. According to Dr. Klinghardt, many of our metabolic enzymes use zinc as part of their molecular makeup. However, in patients with HPU, there is not enough zinc available to satisfy the need. In these cases, lead, mercury and other 2-valent metals bind to these sites instead in a poor attempt to fulfill the role of zinc.

Once zinc is reintroduced into the body, heavy metals are displaced from these sites. Zinc is once again highly supportive of human health. However, the patient now has dislodged heavy metals circulating throughout the body. These are either competing for the already overtaxed detoxification pathways or are redistributed to places where they may be more harmful.

For this reason, it is wise to have detoxification and binding agents on board at all times while implementing the HPU protocol. In fact, starting a heavy metal detoxification protocol several months prior to beginning the HPU treatment is strongly advised. Heavy metal detoxification agents may include [chlorella](#), [BioPure MicroSilica](#), [BioPure Phospholipid Exchange](#) (NaEDTA), [Detoxamin](#) (CaEDTA) suppositories, fiber, green and red clays, zeolites, pectins,

beta-sitosterol, DMSA, DMPS, OSR, and other agents to mop up the mobilized heavy metals.

Generally speaking, about two to six weeks after the treatment begins, it is important for the practitioner to be ready to deal with symptoms of acute metal toxicity. This healing crisis continues in waves for months. The severity is not to be underestimated. Hair analysis can be used to monitor the client. Strong metal detoxification agents are often needed. Supplementing zinc liberates 2-valent metals such as Mercury, Cadmium, Aluminum, and Lead. Patients express symptoms of acute heavy metal toxicity, which have to be addressed. At this stage of the protocol, the patient generally will require treatments addressed at heavy metal detoxification such as binding agents, chelators, colonics, liver/gallbladder flushes, castor oil packs, sauna and other heavy metal detoxification modalities. The practitioner may opt for the old workhorses such as DMPS, DMSA, EDTA, and IV Glutathione to address detoxification of metals. Freeze-dried garlic and vitamin E have a protective effect.

To increase the body's ability to detoxify, sound-wave enhanced chlorella at a dose of 15 tablets three times per day with meals is often used. To mobilize heavy metals from their binding sites and provide glutathione precursors and binding-peptides, nanonized chlorella (BioPure Matrix Metals) at 5-6 sprays twice daily and energized cilantro tincture at 15 drops three times daily are used. To assist in shuttling metals from the intracellular environment to the liver, BioPure Phospholipid Exchange (alpha-lipoic acid, phospholipids, and magnesium) is used.

One approach is to start the patient on agents that will first support removal of metals from the gastrointestinal tract such as chlorella and BioPure MicroSilica. Rectal EDTA (Detoxamin) may be used next followed by BioPure Phospholipid Exchange. Most patients will require a number of different agents. It is critical to support the kidneys with specific drainage remedies in order to optimize the removal of heavy metals. BioPure Matrix Electrolytes at two tablespoons daily mixed with a capful of M-Water in water and a teaspoon of agave syrup supports kidney function.

In some cases, the rate of detoxification may need to be slowed in order to improve patient tolerance and comfort. Consideration may be given to both lowering the dosages of the protocol as well as to agents that will alkalinize the body. Detoxification of heavy metals occurs only in an acidic environment. However, in such an environment, these metals are also highly reactive. Thus, the practitioner may alkalinize the patient in order to slow down process underway. The saliva and urine pH is monitored and used in determining if an alkalinizing protocol may be appropriate.

The next stage of the treatment response is often the appearance of fevers as the immune system wakes up and begins to respond to previously ignored or under-addressed infections. As soon as the nutritional losses of HPU are corrected, the previously intractable chronic Lyme patient tends to respond to much milder and more biological antimicrobial interventions. Dr. Klinghardt prefers the use of plant peroxides from ozonated plant oils such as Rizol Gamma, Rizol Zeta, and BioPure Quintessence.

An interesting observation has been that patients with HPU often get worse when an attempt is made to incorporate detoxification agents or antimicrobial agents prior to having first addressed the HPU condition. Once HPU has been addressed, these other treatment options are much more effective and better tolerated.

## **Additional Considerations**

Many patients with chronic Lyme disease have issues with sulfur intolerance. This leads to a patient being unable to effectively utilize a number of detoxification agents such as alpha-lipoic acid, DMSA, DMPS, and glutathione as well as supplements such as garlic. This may be related to genetics, but some of the enzymes involved in sulfur metabolism (CBS and others) are heme and B6 dependent - both of which are depleted in HPU. As patients are treated for HPU, these sulfur tolerance issues may resolve. Dr. Klinghardt has found that molybdenum at a dose of 300mcg per day may correct sulfur intolerance in patients with HPU; as molybdenum may also be lost in these patients. Ammonia is generally high in patients with HPU. As HPU is treated, high levels of ammonia tend to normalize.

## **Final Thoughts**

Once patients are on the HPU protocol and mobilized metals have been addressed, the body begins to respond to backlogged infections and significant improvements in the patient's condition are often observed. Hormonal status often improves without supplementation. Some patients who have been on thyroid medication for years may even become hyperthyroid as the body begins to function more optimally. Other patients may lose weight. All symptoms directly related to low levels of zinc, biotin, manganese, vitamin B6, and arachidonic acid resolve.

Just as homes are built by first laying a solid foundation, addressing HPU and the deficiencies in zinc, biotin, manganese, vitamin B6, and arachidonic acid are key pieces of the puzzle in addressing the complexities of chronic Lyme disease and many other conditions.

Evaluation for HPU is now one of the first things that Dr. Klinghardt pursues in working with patients with chronic illnesses. For those that test positive, implementing the HPU protocol often yields progress that had not previously been possible and patient recovery is accelerated in a very deep and profound way.

## **24 Hour Urine Test for HPU Directions**

- No vitamins five days prior to test; especially B vitamins and minerals
- Exposure to normal daily stress is needed
- Use clean, large orange juice or milk carton for collection and later to fill the transport tube provided by the lab
- Add 500 mg of ascorbic acid per liter of urine to stabilize pyrroles
- Wrap aluminum foil around collection container and transport-tube to prevent breakdown of pyrroles which results from exposure to light
- Keep the collection container in the refrigerator
- Collect urine for a full 24 hour period; best collected under dim light

- Once the 24 hour collection is complete, shake the container and pour into the collection tube
- Briefly freeze the tube in order to break up tetrapyrroles
- Ship Monday - Wednesday only
- Contact the lab to ensure that the sample is kept in the refrigerator or freezer until they perform the test

### **Statement Concerning KPU/HPU from Dr. Klinghardt**

Dr. Klinghardt believes that the KPU/HPU issue is a significant one, hence he has explored and used various treatments for the condition. He believes that a combination of zinc, manganese, vitamin B6 and certain other constituents is for many patients an effective combination based on his own clinical experience and also based on what he has gathered from its use in Europe.

Dr. Klinghardt also believes that if someone is proceeding without a practitioner to undertake a KPU/HPU protocol of any kind, caution must be exercised. Generally it is better to start slowly and at low doses in order to determine what is tolerable. It may be that large doses, particularly of zinc, may be required to remedy deep mineral deficiencies. In the presence of large doses, however, one must be aware of possible toxicity, for example in context of the zinc/copper balance. And there may be specific conditions, such as Parkinson's disease and its possible relationship to manganese, that deserve cautious application of KPU/HPU protocols.

Dr. Klinghardt believes in the basic chemistry underlying mineral supplementation to treat KPU/HPU but the key point is caution should be the rule.

*\*\*Disclaimer: This is a treatment that should be done only under the care and supervision of a doctor.*

### **Resources**

The following resources are intended for practitioners. Treatment of HPU should not be done without the guidance of a healthcare practitioner. Attempts to self-treat the condition may result in unintended negative consequences.

BioPure Healing Products, LLC can be found at <http://www.BioPureUS.com>. M-Water is available from BioPure.

Detailed information on Dr. Klinghardt's HPU Treatment Protocol can be found at <http://www.klinghardtneurobiology.com/KPUprotocol.pdf>.

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## **Other Reading**

Discerning the Mauve Factor, Woody R. McGinnis, MD, October 1, 2006 [http://web.mac.com/autismprotocols/Site/Pyroluria\\_files/woodymcginnis.pdf](http://web.mac.com/autismprotocols/Site/Pyroluria_files/woodymcginnis.pdf) (Last Accessed January 17, 2010)

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