Pfeiffer Protocol Explained

Metallothionein (MT) and Heavy Metal Detoxification

Metallothioneins are proteins whose purpose are to metabolise and regulate metals. There are at least ten known closely related metallothionein proteins expressed in the human body. In humans, large quantities are synthesized primarily in the liver and kidneys, however they have been found at a number of other sites as well. Its production is dependent on availability of the dietary minerals zinc and selenium, and the amino acids histidine and cysteine.

In a 2001 presentation to the American Psychiatric Association, Dr. William J. Walsh of the Pfeiffer Treatment Center suggested a potential link between metallotionein disorders and autism. Walsh concluded

> "The absence of Cu and Zn homeostasis and severe Zn deficiency are suggestive of a metallothionein (MT) disorder. MT functions include neuronal development, detoxification of heavy metals, and immune response. Many classic symptoms of autism may be explained by a MT defect in infancy including G.I. tract problems, heightened sensitivity to toxic metals, and abnormal behaviors. These data suggest that an inborn error of MT functioning may be a fundamental cause of autism."

Mammals possess genes for four subfamilies of metallothionein, the ubiquitous MT-1 and MT-2, the brain specific MT-3 and the squamous epithelium specific MT-4.

MT **kills Candida**, and helps regulate bacterial levels in the mucosa.

A genetic metallothionein weakness is consistent with:

1. Casein/gluten intolerance,
2. Presence of dense, undeveloped brain cells evident in autopsy studies,
3. Hypersensitivity to mercury & other toxic metals,
4. High autism incidence after thalidomide,
5. Hypersensitivity to vaccines,
6. Poor immune function,
7. Low stomach acid,
8. Higher incidence in males,
9. Taste/texture sensitivities,
10. Tendency for yeast overgrowth,
11. Leaky gut,
12. Behaviour problems

Measurements of MT-levels, as well as zinc, have been used to indicate zinc deficiency. MT increases rapidly after zinc supplementation and decreases if the diet is deficient in zinc. The zinc from plasma proteins begins to be used up when the body stores are depleted. When plasma zinc levels are below 33 mcg/dL, skin-rash, abdominal pain, diarrhea, loss of appetite and a reduced sense of taste and smell can occur.

The Pfeiffer Treatment Center has developed a nutrient therapy to promote metallothionein in the gastrointestinal tract, brain and elsewhere. Aggressive zinc loading must precede any attempt to promote MT for best results. Each molecule of MT requires 7 atoms of zinc to function properly. Premature synthesis of MT at the intestinal mucosa can temporarily prevent zinc transport into the blood, which can result in severe irritability.

The Pfeiffer MT Promotion protocol is a 2 stage process:

1. Preloading zinc and co-factors (Primer)
2. Metallothionein promoting nutrients (Promoter)

More than 85% of the 41 families that achieved compliance (metallothionein promotion) report impressive gains in cognition, speech, and socialization. More than 20% report irritability and sleep problems, usually coincident with improved cognition or speech. Only 10% of compliant families report zero progress.

Primers

The Primer formula is used for the *phase 1* Pfeiffer Protocol for the biochemical treatment of patients with Autism Spectrum Disorder (ASD). It is a general supplement designed to re-balance the copper: zinc ratio in the body (by decreasing copper and increasing zinc), and to assist in the promotion of metallothionein (MT) proteins in the gastrointestinal tract (important for detoxification), brain and elsewhere. This protocol is based on over 1,200 published articles describing MT synthesis, activation and redox mechanisms.

Promotion of MT proteins within the body provides many benefits to ASD patients including:

1. The removal of toxic heavy metals in the body
2. Protection against future toxic exposures
3. Normalization of the gastrointestinal tract
4. Improved behaviour control
5. Improved immune function, and
6. Enhanced development of brain neurons and synaptic connections.

The first five benefits may be attainable in the first year of treatment, regardless of the age of the patient. However, the rate of formation of new synaptic connections declines rapidly with age, which is why early intervention is critically important for development of speech, cognitive development, etc. Great patience is needed in the treatment of older children who can be expected to progress at a relatively slow rate. Behaviour therapies which shower the brain with impulses and promote neuronal development are especially recommended in conjunction with MT promotion therapy.

This formula contains much needed zinc (as picolinate, the most easily absorbed form of zinc), as well as activated B6 (Pyridoxal-5-Phosphate), manganese gluconate and essential antioxidants (vitamins C and E). *Aggressive zinc loading must precede full scale MT promotion therapy* for best results, since each molecule of MT requires 7 atoms of zinc for proper functioning. Primer is often used as the first step in nutritional supplementation of patients with ASD, particularly for those patients with low zinc levels and high copper levels.

The best clinical outcomes have been achieved using the two-phase protocol of:

Phase 1 - preloading with zinc and augmenting nutrients (i.e. the *Primer*), followed by

Phase 2 - cautious, gradual introduction of MT promotion nutrients

In treating ASD this should be part of a comprehensive treatment program.

Aggressive supplementation with zinc and augmenting nutrients is recommended for at least 4 to 8 weeks, but can be up to 6 months or more. Sensitive patients may require a gradual build up of zinc dosages. It is also important to remember that **Primer must never be taken on an empty stomach**, as this may cause nausea (even though zinc is best absorbed on an empty stomach).

Our Primer formulas

Primer SD 25mg (SD= Small Dose)	**Primer 50mg**
Vitamin C (Ascorbic Acid- Corn Free) 125mg	Vitamin C (Ascorbic Acid- Corn Free) 250mg
Pyridoxine Hydrochloride (B6) 25mg	Pyridoxine Hydrochloride (B6) 50mg
Pyridoxal-5-Phosphate 12.5mg	Pyridoxal-5-Phosphate 25mg
Magnesium (as oxide) 11mg	Magnesium (as oxide) 22mg
Vitamin E (as succinate) 50IU	Vitamin E (as succinate) 100IU
Manganese (as gluconate) 3.75mg	Manganese (as gluconate) 7.5mg
Zinc (as picolinate) 25mg	Zinc (as picolinate) 50mg
Overmethylating Primer	**Undermethylating primer**
Vitamin C (Ascorbic Acid- Corn Free) 250mg	Vitamin C (Ascorbic Acid- Corn Free) 250mg
Pyridoxine Hydrochloride (B6) 50mg	Pyridoxine Hydrochloride (B6) 50mg
Pyridoxal-5-Phosphate 25mg	Pyridoxal-5-Phosphate 25mg
Magnesium (as oxide) 22mg	Magnesium (as oxide) 22mg
Vitamin E (as succinate) 100IU	Vitamin E (as succinate) 100IU
Manganese (as gluconate) 7.5mg	Manganese (as gluconate) 7.5mg
Zinc (as picolinate) 50mg	Zinc (as picolinate) 50mg
Niacinamide 500mg	**Methionine 750mg**
Folinic Acid 840mcg	**Folinic Acid 840mcg**
Thiamine (B1) 10mg	**Thiamin (B1) 10mg**
Riboflavin-5-phosphate 5mg (active vitamin B2)	**Riboflavin-5-phosphate 5mg (active vitamin B2)**
Calcium pantothenate (B5) 25mg	**Niacinamide (B3) 10mg**
	Calcium pantothenate (B5) 25mg

Overmethylating Primer

This supplement contains the same nutrients as the *Primer* with the addition of high dose **Niacinamide (B3)**, along with other supporting **B vitamins**.

The additional nutrients within this formulation help to repair damaged methionine synthesis pathways i.e. **methylation**.
"Methylation reactions are those reactions in our metabolism that involve the transfer of a methyl group (a carbon with three hydrogens attached) from one compound to another. These reactions are required for many of the most vital pathways in our metabolism. The building or repair of every cell in our bodies requires methylation." (Cynthia Schneider, MD)

Two of the most effective biomarkers for methylation are:

1) Whole blood **histamine** ** (an important protein involved in many allergic reactions), and
2) Absolute **basophils** (one type of cell in the leukocyte or white blood cell family)

Low whole blood histamine, coupled with low absolute basophil readings are indicative of **OVERMETHYLATION.**

Overmethylation is the result of an "*imbalanced methylation*" pathway, which leads to higher levels of methyl groups. It is the biochemical opposite to undermethylation.

The *Primer Overmethylating* formulation contains:

-**Niacinamide** → to "mop-up" excess methyl groups
-**Folinic acid** → (NOT folic acid) this nutrient is absolutely essential for the operation of the methionine **methylation cycle**. It is also required for the formation of the molecules that transfer energy for cellular functions
-**B vitamins** → including Thiamine (B1), Riboflavin-5-phosphate (active B2), Niacinamide (B3) and Calcium pantothenate (B5); to support **neurotransmitter synthesis** and the **Krebs Cycle** (primary method by which energy is made available for use by the body)

An *overmethylating* patient will exhibit the following characteristics:

- *Poor achiever and low motivation*
- *Artistic/musical ability*
- *High anxiety/panic*
- *Low libido and overweight*
- *Easily frustrated*
- *Sleep disorder and paranoia*
- *Depression and self isolation*
- *Self mutilation and nervousness*
- *Tinnitis (ringing in the ears)*
- *Food/chemical sensitivities*
- *High pain threshold*
- *Past history of ADHD*
- *Hyperactive psychosis*
- *Grandiosity*
- *Nil family history*

COMMON BIOCHEMISTRY OF AN OVERMETHYLATING PATIENT

1) Low blood histamine **
2) Low plasma zinc
3) Elevated copper
4) Low basophil count
5) Elevated levels of the neurotransmitters serotonin, dopamine and norepinephrine

Conditions which are commonly associated with *Overmethylators* include: Anxiety/ Panic disorders, anxious depression, hyperactivity, learning disabilities, low motivation, "space-cadet" syndrome, paranoid schizophrenia and hallucinations.

Ingredients (per daily dose):
Zinc (Picolinate) 50mg
Pyridoxine-5-phosphate 25mg (active vitamin B6)
Pyridoxine HCL (B6) 50mg
Manganese (Gluconate) 7.5mg
Vitamin E 100mg
(Mixed tocopherols)
Ascorbic Acid – Corn Free (*Vitamin C*) 250mg
Magnesium as Oxide 22mg
Niacinamide 500mg
Folinic Acid 840mcg
Thiamin (B1) 10mg
Riboflavin-5-phosphate 5mg (active vitamin B2)
Calcium pantothenate (B5) 25mg

PLEASE NOTE: These doses are standard and can be adapted to suit your individual needs. Because of the need of medical supervision, this formulation is presently available by prescription only. Undermethylating patients will typically require several months treatment to see good results.

** = whole blood histamine is a marker for innate methylation tendency, but is not an indicator of wellness or the degree to which undermethylation has been overcome. Undermethylated patients can become quite well without their histamine lab results changing at all.

Undermethylating Primer

Primer Undermethylating contains the same nutrients as the *Primer* with the addition of **methionine** and supporting **B vitamins**

As with our *Primer* supplement, the main use of the *Primer Undermethylating* formulation is in the biochemical treatment of patients with Autism Spectrum Disorder (ASD). *However, the *Primer Undermethylating* formulation is not solely used in the ASD domain. This supplement has also shown very positive results in children and adults with general symptoms of *undermethylation*.

The additional nutrients within this formulation, such as methionine and folinic acid (among others) enable it to help repair damaged methionine synthesis pathways i.e. **methylation**.

"Methylation reactions are those reactions in our metabolism that involve the transfer of a methyl group (a carbon with three hydrogens attached) from one compound to another. These reactions are required for many of the most vital pathways in our metabolism. The building or repair of every cell in our bodies requires methylation." (Cynthia Schneider, MD)

Two of the most effective biomarkers for methylation are:

1) Whole blood **histamine** ** (an important protein involved in many allergic reactions), and
2) Absolute **basophils** (one type of cell in the leukocyte or white blood cell family)

Elevated histamine and/or elevated basophils readings are indicative of *UNDERMETHYLATION*.

Undermethylation is defined as a dysfunctionally low availability of methyl groups for the many vital biological processes that require them.

The *Primer Undermethylating* formulation contains:

- The amino acid **methionine → primary methyl source**
- **Folinic acid** (the **active form** - NOT folic acid, therefore not dependent on *5-methyltetrahydrofolate reductase*) → **this nutrient is absolutely essential for the operation of the** methionine **methylation cycle**. It is also required for the formation of the molecules that transfer energy for cellular functions
- **B vitamins → including Thiamine** (B1), Riboflavin-5-phosphate (active B2), Niacinamide (B3) and Calcium pantothenate (B5); to support **neurotransmitter synthesis** and the **Krebs Cycle** (primary method by which energy is made available for use by the body)

An *undermethylating* patient will exhibit the following characteristics:

· *Addictive behaviour*	· *Calm demeanour, high inner tension and social isolation*
· *High achiever and strong will*	· *Low pain tolerance*
· *Self motivated through school*	· *Sparse hair growth*
· *High achiever before illness*	· *Family history*
· *High motivation*	· *Delusional and phobias*
· *High libido and energy*	· *Diagnoses of OCD/ODD*
· *Difficultly with transitions*	· *Frequent headaches*

· *Seasonal allergies*	· *Denial of illness and non compliance*

COMMON BIOCHEMISTRY OF AN UNDERMETHYLATING PATIENT

1) High blood histamine **
2) Low plasma zinc
3) Elevated copper
4) High basophil count
5) Low homocysteine
6) High heavy metals
7) Low levels of the neurotransmitters serotonin, dopamine and norepinephrine

As stated earlier, methyl groups are involved in many important biochemical reactions in the body, such as genetic expression, neurotransmitter synthesis and metabolism. Methylation is a major factor in the rate-limiting step of serotonin, dopamine, and norepinephrine synthesis in the brain. This is why *undermethylated* persons tend to be depleted in these three essential neurotransmitters.

Ingredients (per daily dose):

Zinc (Picolinate) 50mg
Pyridoxine-5-phosphate 25mg (active vitamin B6)
Pyridoxine HCL (B6) 50mg
Manganese (Gluconate) 7.5mg
Vitamin E (Mixed tocopherols) 100mg
Ascorbic Acid – Corn Free (*Vitamin C*) 250mg
Magnesium as Oxide 22mg
Methionine 750mg
Folinic Acid 840mcg
Thiamin (B1) 10mg
Riboflavin-5-phosphate 5mg (active vitamin B2)
Niacinamide (B3) 10mg
Calcium pantothenate (B5) 25mg

PLEASE NOTE: These doses are standard and can be adapted to suit your individual needs. Because of the need of medical supervision, this formulation is presently available by prescription only. Undermethylating patients will typically require several months treatment to see good results.

** = whole blood histamine is a marker for innate methylation tendency, but is not an indicator of wellness or the degree to which undermethylation has been overcome. Undermethylated patients can become quite well without their histamine lab results changing at all.

MT Promoters

The *Promoter* provides the building blocks of the metallothionein (MT) protein*. The idea of this supplement is to boost MT function in a *natural* way, thus allowing the body to then detoxify (or chelate) itself *naturally*. This may also self-correct some of the other dysfunctions that are present based on MT abnormalities. Many ASD children use this supplement with anecdotal evidence of positive effects.

MT proteins are made up of 14 amino acids and zinc. Many Autism Spectrum Disorder (ASD) patients are unable to efficiently cleave dietary proteins into the individual amino acids needed for the MT synthesis. The *Promoter* formulation provides all 14 amino acids, in the proportion found in MT proteins. The large amounts of cysteine required for MT synthesis are provided in the form of oral glutathione (GSH) which breaks down in the gastrointestinal tract with minimal side effects.

The glutathione works with selenium (also found in the *Promoter*) to enhance:

i) the delivery of zinc to the cells, and
ii) the sequestering of mercury and other heavy metals

Unfortunately, the *Promoter* may also deplete the body of essential minerals, especially zinc. Therefore, aggressive zinc loading must precede full scale MT Promotion therapy for best results.*

The primary ingredient in this supplement is glutathione; with each capsule containing 200mg of oral GSH.

Glutathione is a *tripeptide,* (i.e. a peptide consisting of three amino acids – *cysteine, glutamic acid* and *glycine*, joined together by peptide bonds) and is the **most powerful naturally occurring antioxidant** in human cells.

Glutathione is highly active in many organ systems and tissues, and is an essential cofactor for many enzymes. It has a critical role in protecting our cells from oxidative stress and maintaining the immune system. In normal health the body uses its enormous glutathione stores to detoxify and remove toxins (e.g. mercury) from the body.

MT Promoter

Selenium (as picolinate) 20mcg

Proprietary Blend – 350mg

(Glutathione, L-Lysine Hcl, L-Serine, L-Alanine,

L-Glutamic Acid HCl, Glycine, L-Threonine,

L-Proline, L-Methionine, L-Aspartic acid,

L-Asparagine, L-Glutamine, L-Isoleucine, L-Valine)

PLEASE NOTE: These doses are standard and can be adapted to suit your individual needs. The Promoter is also available in a 350mg, 175mg and 87.5mg standard dosage.

LH Formula

What is histamine and why is it so important? Carl Pfeiffer studied more than 20,000 people with schizophrenia and determined that 90% of them fell into three bio-chemical subgroups: high histamine, low histamine, and pyrroluria - hence the term "The Schizophrenia's" (Pfeiffer, 1970; Walsh, 1997b). Histamine is integral in balancing the electrical activity of the nucleus accumbens, which is an area of the brain responsible for behavioral responses, filtering incoming sensory information, and communicating with the hypothalamus, ventral tegmentum, and amygdala (Shoblock & O'Donnell, 2000; Otake & Nakamura, 2000; Chronister et al, 1982).

A plethora of research has determined that people with schizophrenia have poor ability to filter incoming sensory information. It has also been reported that 15-20 % of people with schizophrenia have high whole blood histamine levels and another 30-40 % of people with schizophrenia have low whole blood histamine levels (Heleniak, 1999; Pfeiffer, 1988; Heleniak, 1985; Chronister & DeFrance, 1982; Rauscher et al, 1977; Pfeiffer, 1972a).

A person with schizophrenia who has high histamine is under-methylated (Walsh, PTC- Ref. B; Heleniak & Frechen, 1989). A person with schizophrenia who has low histamine is over-methylated (Walsh, PTC- Ref.B; Heleniak & Frechen, 1989).

Taking detailed patient histories is key (Jackson et al, 1998; Edelman, 1996; Jaffe & Kruesi, 1992; Pfeiffer, 1988; Walsh, PTC- Ref.B). People with high histamine have been found with typical symptoms of high intelligence, thought blanking, low grade hallucinations and thought disorder, perfectionism, competitiveness, obsessions, compulsions, suicidal and seasonal depression, defiance, and phobia. High histamine individuals have low serotonin levels and therefore usually benefit from drugs that increase serotonin such as Zoloft, Prozac, and Paxil (Walsh, PTC- Ref.B). High histamine individuals typically have a history of seasonal allergies.

High histamine individuals are inherently high in folic acid. Although folic acid is used along with B-12 in the production of methionine it is also involved in histamine production along with B-12. Consequently B-12 and folic acid are strictly avoided in high histamine patient care. These patients need to avoid multi-vitamins.

People with low histamine have been found with typical symptoms of under-achievement, more severe thought disorder and hallucinations, paranoid thoughts with less pronounced obsessions, suicidal depression, cyclic or suicidal depression, and anxiety (Jackson et al, 1998; Edelman, 1996; Jaffe & Kruesi, 1992; Pfeiffer, 1988; Walsh, PTC- Ref.B).

Excess copper and zinc deficiency, discussed below under heavy-metal overload, are typical low histamine traits that need to be adressed (Sandstead, 1994; Wallwork, 1987; Pfeiffer & Braverman, 1982; Walsh, PTC- Ref.B).

LH (Low Histamine) Formula

Vitamin C (Ascorbic Acid- Corn Free) 175mg

Niacin (as Niacinamide) 175mg

Folic Acid 800mcg

Vitamin B12 (as Cyanocobalamin) 500mcg

Article written by William J. Walsh, PhD, in chemical engineering from Iowa State University; researcher, group leader, and section head at Argonne National Laboratory for over 20 years; holder of six patents and author of more than 200 scientific articles and reports; volunteer in Illinois prisons for almost 20 years; and founder in 1974 of the Prisoner Assistance Project. In 1981, the United Way named him "Prison Volunteer of the Year" for metropolitan Chicago. In 1989 he founded, was the first president, and is now the senior scientist of the Health Research Institute and the Pfeiffer Treatment Center in Warrenville, Illinois. He has made numerous presentations on his research at institutions such as the American Psychiatric Association, the U.S. Senate, the Society for Neuroscience, and the National Institutes of Mental Health. The Pfeiffer Treatment Center is a not-for-profit outpatient clinic specializing in treatment of behavior disorders, learning disabilities, attention deficit disorder (ADD), autism, depression, bipolar disorders, and schizophrenia. Their web page address is: www.hriptc.org

1Walsh, W., A. Usman, and J. Tarpey, "Disordered Metal Metabolism in a Large Autism Population," *New Research Abstracts, No. NR823*, page 223, American Psychiatric Association Annual Meeting, New Orleans, Louisiana, May 2001.