THE GIFT OF THE EARTH TO MEDICINE:

Minerals in Health and Disease

A Source Book for Doctors and Patients
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ZINC

Zn

The all-around multi-purpose essential element

An adult human contains 2-4 g of zinc. We have only slightly less zinc than iron (4-5 g in adults) in our bodies, however, many of us are still unfamiliar with zinc metabolism.

In 1869, zinc was found to be necessary for the growth of a particular mushroom, and in 1934 it was determined to be essential for animals. Carbonic anhydrase was the first zinc-containing enzyme to be isolated from red blood cells (in 1940).

Parakeratosis, a disease affecting pigs, was described in 1955. In 1963, a recurring combination of symptoms was described among children and adolescents of poorer social classes in Iran. These symptoms included general physical and mental developmental delays, testicular atrophy, anemia, liver and spleen enlargement, and skin disorders. The cause was determined to be zinc deficiency. Following zinc supplementation, symptoms were eliminated within a few months! The symptoms had been caused not only by the high phosphate and phytate levels of the Iranian diet, but by the loss of zinc due to excessive sweating in the tropical climate.

A zinc deficiency model can provide the basis for research. For example, cattle with an autosomal recessive A46 mutation have zinc deficiency due to the disruption in zinc absorption from the intestine. Their symptoms are well documented, including the effects of zinc supplementation, which has been shown to reduce immune dysfunction as a result of the deficiency (1993).

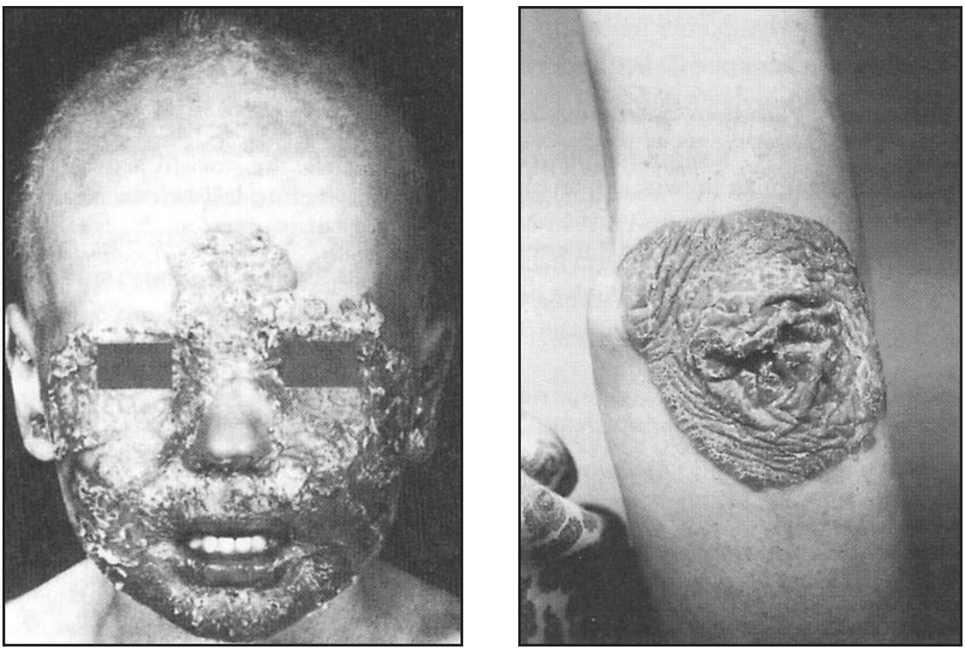
Appendix 1 describes zinc-containing enzymes and the principal functional mechanisms of trace elements. Since zinc enzymes are continually being discovered, the current total of 200 enzymes will continue to increase.

Zinc-containing enzymes are involved in:

- DNA, RNA and protein metabolism;
- growth and wound healing;
- regulation of sex hormones;
- reproductive gland function and fertility;
- membrane stabilization;
- protection from free radicals via superoxide dismutase and zinc thionine;
- inhibiting intestinal absorption of toxic heavy metals (such as lead and cadmium);

- fatty acid and prostaglandin metabolism;
- regulation of brain neurotransmitters;
- sensory functions (sight, hearing, smell, and taste);
- immune defense (cellular and humoral immunity);
- blood formation.

A milestone for zinc research occurred in 1973 when the cause of acrodermatitis enteropathica, a rare disease relatively unknown in medicine outside of pediatrics, was discovered to be a genetic disturbance of the intestinal zinc absorption mechanism. This condition, which was previously fatal in early childhood, can be treated with zinc supplementation. In the US, acrodermatitis enteropathica was also observed among patients receiving long-term parenteral (intravenous) nutrition. The cause was traced to very low zinc levels in the intravenous solutions, many of which were found to be zinc-free. These patients often experienced complete hair loss. To avoid zinc depletion during long-term intravenous treatment, it is important to monitor zinc levels frequently. Hair loss can be reversed with zinc supplementation.



In zinc-deficient "acrodermatitis enteropathica" the skin develops lesions that look similar to those seen in psoriasis.

Zinc is required for many functions and is found practically everywhere in the human body, although concentrations differ according to location. In blood, 90% of the zinc is found within red and white blood cells and only 10% is contained in the serum (important when assessing zinc measures). In total, 60% of the body's zinc is found in skeletal muscles and 30% is found in bones. Significant concentrations are also found in the prostate, sperm and hair (useful in laboratory analysis).

Zinc content of organs (in mg/kg)

Heart 27	Kidney 37	Liver 38	Muscle 48
Bone 66	Prostate 87	Sperm 125	Hair 175

The distribution of zinc within an organ is not necessarily homogeneous. For example, in the pancreas, the majority of zinc is localized in a complex contained in the hormones insulin and glucagon inside the alpha and beta cells of the islets of Langerhans (zinc levels drop here whenever insulin excretion increases).

In cases of zinc deficiency, blood serum zinc levels drop much faster than those in erythrocytes. Serum levels rise much faster as well. Since zinc content is 10 times lower in serum than in erythrocytes, even a slight amount of hemolysis can lead to elevated serum values.

Individuals at risk for zinc deficiency include:

- pregnant and nursing women, newborns (baby formulas often contain too little zinc);
- people who have unbalanced diets ("fast food") or eat very little, such as adolescents and seniors (sometimes food in retirement homes and hospitals is less than optimal);
- people fed intravenously over prolonged periods or who frequently undergo weight loss diets;
- strict vegetarians (since high phytate levels hinder zinc absorption);
- alcoholics (due to an unbalanced diet and increased loss of zinc through the urine);
- elite athletes (due to excessive sweating and increased zinc requirements);
- those with increased zinc loss due to intestinal or skin disorders, diabetes (with increased urine loss from the kidney), infections (especially chronic), and tissue damage from surgeries, burns, heart attacks, rheumatism, collagenosis, or cancer;
- people taking D-Penicillamine (chelating agent used for rheumatism), tetracyclines, Isoniazid, Phenytoin;
- long-term users of oral contraceptives or cortisone.

Even though zinc content in food fluctuates according to soil zinc levels, there is an association between food cost and zinc content. Animal products are expensive but they are the best sources of zinc, and therefore zinc deficiency has been found frequently in people with low-income status. In Iran, for example, low-income status was associated with reduced animal product intake and, as a result, zinc deficiency symptoms.

Many diseases affect zinc metabolism. Acute and chronic infections, burns, surgery, heart attacks and cancer will lower blood zinc concentrations. This is mainly caused by an increased zinc requirement for the production of proteins (especially acute phase proteins released during stress). As an illness progresses, zinc deficiency can be worsened by reduced food intake, perspiration, wound secretion and diarrhea.

Normally, the body absorbs only 10-40% of zinc obtained from the diet. Zinc absorption is hindered by phytate, which is abundant in whole grain products. Phosphates, found in soft drinks, also decrease zinc absorption.

Since zinc is primarily found within the outer layers of a grain, zinc content falls according to the extent to which grain products are ground. Correspondingly, white flour contains the lowest amount of zinc. However, if there is sufficient time after milling (for example, when manufacturing sour dough), the phytase enzyme in the grain can dissociate various minerals, including zinc, from the phytate, thus allowing greater zinc absorption.

Zinc absorption decreases in people with albumin deficiency. Albumin is a blood protein that binds zinc (immediately following its absorption from the intestines) and transports it within the circulatory system. Excess production of gall and pancreatic fluids can also lead to zinc loss. These fluids contain elevated amounts of zinc. When they are released into the intestine, zinc is lost. During periods of zinc deficiency (and perhaps in response to high blood sugar levels) intestinal absorption is increased. Zinc is also eliminated to a certain extent through hair, perspiration and skin (especially if a skin disorder is present). Some people excrete zinc through the kidneys when intake is high. In alcoholism, pancreatic dysfunction often plays a role in the development of zinc deficiency. As a result of poor pancreatic function, alcoholics often have insufficient levels of picolinic acid which is required for optimal zinc absorption.

Elevated zinc levels in the body are rare. In some cases, elevated levels of zinc appear in the blood when zinc is mobilized from cells and tissues resulting in deficiency symptoms. By comparison, you can have a transient rise in zinc levels right after experiencing trauma or stress. High zinc intake rarely has a toxic effect since large amounts of zinc often cause intestinal irritation leading to elimination via diarrhea. Only a small amount of zinc is stored in the body's cells and tissues.

Well-intentioned, prolonged intake of higher doses of zinc (without medical supervision or laboratory feedback) is not recommended because of its antagonism with copper and manganese (and molybdenum to a lesser extent). An excess of one of these elements (zinc, copper or manganese) can unintentionally lower any of the other two equally important elements.

The lethal dose of zinc sulfate is reported to be 3-5 g and the lethal dose of zinc chloride is reported to be 6-30 g. Salt is also lethal at 30 g. Zinc overdose symptoms (especially gastric complaints, nausea, and vomiting) have been described with daily doses in excess of 100 mg when taken over a period of several weeks or months.

The following sections describe specific biochemical functions of zinc in the human body.

Zinc in childhood and puberty

Due to its role in protein synthesis and enzyme function, zinc requirements significantly increase during periods of growth. Normally we obtain larger quantities of zinc as we develop in the womb via maternal blood, in infancy via breast milk (contains more zinc than formula), and in childhood and puberty via increased food intake. Children are very sensitive to zinc deficiency. As described earlier, children in Iran and also Egypt experienced general physical, mental, and sexual developmental delays including poor growth and testicular atrophy. Zinc supplementation allowed many of these patients to regain age-related sexual development, including normal pubic hair growth and an acceleration of body growth up to 13 cm in one year. This is extremely significant for someone with halted development! During childhood, adolescence, and adulthood, zinc is important for learning, memory, concentration, and attention.

Zinc and pregnancy

Animal studies have shown that adequate maternal zinc levels are indispensable for conception and normal fetal development (especially during rapid growth in the third trimester). In one study, half of all rats fed a zinc-deficient diet from the beginning of pregnancy miscarried and the other half gave rise to birth defects. The birth defects occurred in various organs, however half involved brain abnormalities. Animals with borderline zinc deficiency had offspring with low birth weights, although none of these had a birth defect. The control group consuming an average diet with sufficient zinc levels (but without zinc supplementation) had offspring with normal birth weights and no birth defects.

In animal studies, zinc deficiency during pregnancy has also been found to weaken the immune system. This effect has been shown to carry over into three subsequent generations – a surprising phenomenon which has yet to be fully explained.

Special attention to the signs of zinc deficiency should be given to pregnant women who are diabetic, or alcoholic, as well as pregnant teens who have higher growth-related zinc requirements than adults.

Zinc deficiency plays an important role in the development of fetal alcoholic syndrome. Elevated hormone levels during pregnancy also contribute to zinc deficiency and copper excess. This excess of copper is associated with post-partum depression and autism.

Zinc and the immune system

Significant zinc deficiency often leads to a weakened immune system. This is apparent in patients with acrodermatitis enteropathica (described above), where zinc deficiency contributes to the following: a reduction in the size of lymph nodes, thymus and spleen; a decrease in T-lymphocytes and their activity against tumor cells; and the fall of immunoglobulin G levels.

In cancer clinics, zinc deficiency was repeatedly observed among patients treated with agents that retard cell activity and replication. Zinc supplementation significantly improved patients' general well-being. This included faster wound healing, less hair loss and improvements in other conditions involving skin and mucous membranes.

Zinc and athletic performance

Zinc increases muscular strength and endurance since it is required to increase muscle mass. Athletes often have a high carbohydrate diet that is relatively low in zinc. While a normal person loses about 1.5 mg of zinc daily through perspiration, this can rise up to 6 mg (four times the normal amount!) during strenuous physical activity. Similar observations have been made among heavy laborers and even those accustomed to hot working conditions.

Zinc promotes wound healing

Since antiquity, zinc ointments have been known to improve wound healing. The zinc content of skin around a wound is higher than normal. Lower leg abscesses are often chronic conditions that can last for several years. They usually occur as a result of circulatory problems in arteries and/or veins. In addition to treating the underlying problem, zinc supplementation was beneficial for patients who did not respond to conventional treatment. A controlled study involving 104 hospital patients of various ages was conducted. They received identical capsules containing either 220 mg of zinc sulfate or 220 mg of lactose (placebo). The average healing time for patients in the zinc treatment group was 32 days versus 77 days for those in the placebo group.

Wound healing can also be promoted by zinc supplementation after surgical operations or burn trauma. It has been estimated that the average daily zinc loss following surgery is approximately 30 mg (possibly up to 600 mg). In all surgical facilities (especially in burn and emergency units), this should be taken into consideration as a preventive measure to reduce complications during and after surgery.

Zinc has also been used in the treatment of skin disorders including acne, psoriasis, hair loss (especially alopecia areata), and skin changes associated with diabetes.

Zinc has proven to be important for the metabolism of cysteine, an amino acid found in skin and hair (especially in keratin). There is also a key zinc-dependent enzyme involved in the lipid synthesis of skin cells. Patients with atopic dermatitis (includes eczema) benefit from using zinc because they often have altered skin lipid composition.

Zinc and aging

Zinc deficiency is common in older people. Several factors likely contribute to this: unbalanced diet/eating habits; increased zinc requirements; and increased loss due to illness. Seniors often have an increased need for zinc but unfortunately their ability to absorb zinc is compromised.

Zinc and the brain

Research literature has reported neurological and psychiatric conditions as a result of, or in association with, zinc deficiency. Zinc concentrations differ in various regions of the brain.

One of zinc's functions as a component of various enzymes is to regulate the synthesis and degradation of neurotransmitters (especially the amino acid-based neurotransmitters glutamate and GABA). Zinc acts as a modulator for amino acid receptors, particularly NMDA receptors. Zinc can lower excitability by moderating the NMDA receptor release of the excitatory neurotransmitter glutamate – significant in strokes (CVA's) and hyper-stimulated states with convulsions (epileptic seizures).

Zinc modulates the activity of glutamate decarboxylase, which is necessary for the production of gamma aminobutyric acid (GABA). GABA is the most important inhibitory brain neurotransmitter. GABA levels are low when zinc levels are low, resulting in reduced inhibition and prevailing nerve cell stimulation.

Zinc plays a role in the storage of biogenic amines (such as histamine) in nerve cell synaptic vesicles and is involved in rapid axonal transport. Histamine, a brain neurotransmitter, regulates electrical activity in the nucleus accumbens – an area of the brain responsible for behavior responses, filtering incoming sensory information, and communicating with the hypothalamus, ventral tegmentum, and amygdala.

Decreased zinc levels have been observed in depression, psychosis, senile dementia, and mental retardation.

Zinc is a significant calcium antagonist. Calcium antagonism is an important mechanism of action for several drugs that act on the brain, promote circulation and activate metabolic functions.

It is suspected that zinc regulates the binding of encephalins at receptor sites, protecting against fatty acid peroxidation (which causes nerve cell injury).

Anorexia nervosa and chronic alcoholism are associated with diminished zinc concentrations in the brain hippocampal area. This suggests that zinc has a role in the limbic system (emotion center) and hormonal processes of the hypothalamus and hypophysis.

Alcohol-dementia and Alzheimer's disease share similar symptoms. Zinc-dependant liver enzymes are compromised in alcohol-dementia. These same enzymes are found in the brain and, when compromised, can alter brain function and cause dementia. From this we can argue that zinc deficiency has a major role in Alzheimer's disease. In classic hepatic encephalopathy, a liver disease (usually alcohol-induced) that causes dementia, compromised liver enzyme activity as a result of zinc deficiency is suspected as follows: by reduction of glutamine neurotransmitters normally destroyed by glutamate dehydrogenase; by diminished urease production as a result of diminished ornithine carbamoyl transferase; and by diminished glutamine production as a result of diminished glutamine synthetase (this causes ammonium levels to rise, which is as damaging to the brain as diminished urease production). All of these enzymes and their activities are localized within the brain, liver and muscles.

Zinc, sensory organs and vitamin A

Zinc is important for the senses of taste and smell. Disturbances in these senses are typically accompanied by zinc deficiency. These symptoms are often overlooked by medical practitioners due to their slow and subtle development. If the taste or smell disturbance is caused by zinc deficiency alone, then zinc supplementation can normalize these senses.

Vitamin A metabolism is disrupted when zinc is deficient. Zinc is required to mobilize vitamin A from the liver and transport it through the circulatory system to the retina. The retinol-binding protein required for vitamin A transport is a zinc-dependent protein produced in the liver. In the retina, zinc assists in vitamin A metabolism. The production of retinaldehyde from retinol requires alcohol dehydrogenase – a zinc-dependent enzyme. It is well known that vitamin A deficiency causes night blindness. Zinc deficiency plays an integral role in this process.

In some cases, zinc deficiency may play a role in optic nerve damage. This observation was made in patients with acrodermatitis enteropathica (mentioned above). When these patients were treated with zinc supplementation, optic nerve damage no longer occurred.

Miscellaneous information

Zinc deficiency has been observed during acute and chronic infections, acute and chronic tissue injuries, collagenosis and rheumatoid arthritis.

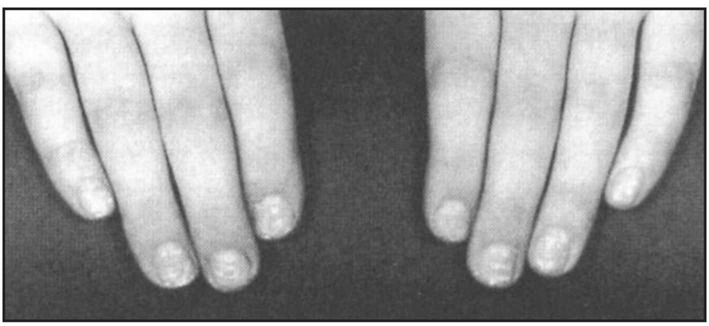
Mild zinc deficiency has been found in dialysis patients. In these patients, a diminished sense of taste was often the earliest sign. Zinc supplementation resulted in increased alkaline phosphatase activity (suggesting improved kidney function).

Some ENT (ear, nose, and throat) clinics recommend zinc supplementation for sensory deafness. It was discovered that the inner ear was more sensitive to sound under zinc deficiency. Zinc-based synapses were found in a group of nerve cells of the inner ear called the nucleus cochlearis. Positive results have also been reported in the treatment of age-related deafness and tinnitus (ringing in the ear).

Due to the high zinc content of seminal fluid, it seems possible that an existing or borderline zinc deficiency can be worsened by frequent sexual intercourse. More serious zinc deficiency leads to a decrease in testicular size and lower sperm counts.

Gynecologists are now reporting that zinc plays a role in female hormone levels and fertility. Several hormones (including the hypophysial gonadotropins LH and FSH that are important for women) form dissociable zinc-protein-hormone complexes through which hormonal activation takes place.

Both male and female sex organs contain large amounts of zinc. Low zinc levels are often found in women and these levels plummet further with oral contraceptive use. Low zinc levels can become more problematic when a woman is pregnant (due to vomiting) or breastfeeding. One gynecologist commented on the "fascinating idea that zinc is so closely connected to the propagation of life."



Fingernail white spots are a sign of zinc deficiency

Positive results with zinc supplementation have been found in patients with low blood pressure, cold extremities, menstrual complaints and Wilson's disease (a rare copper storage disease).

After a 1967 discovery that arthritis-like symptoms appeared in chicks with zinc deficiency, several reports on polyarthritis patients were found describing zinc supplementation reducing morning stiffness and joint swelling which enabled greater walking distances. Similar results were observed in cases of psoriatic-arthritis. To a certain extent, lab results also indicate a decline in arthritic inflammatory immunoglobulin reactions. Zinc is suspected to play a role in the following: improving blood sugar utilization in cells, resulting in better energy levels; stabilizing membranes, especially those of lysosomes; increasing cellular immunity and anti-inflammatory effects via the regulation of prostaglandin synthesis.

Prolonged zinc supplementation is often paired with copper supplementation (sometimes with a time separation) in order to prevent copper levels from dropping. The beneficial effects of zinc are enhanced when copper is present. Even so, copper supplementation is not always advised, especially when treating patients with potential copper excess problems (associated with hormonal depression, paranoia, and fatigue).

Zinc deficiency hinders insulin activity. Some substances (such as Alloxan) can form insoluble compounds with zinc which may trigger diabetes. Low zinc levels have not been found in diabetics except in those cases where arteriosclerosis is also present.

Like vitamin E, zinc stabilizes cellular membranes and protects cells from peroxidative damage. Within cells, zinc thionein and superoxide dismutase (SOD) provide important protection against free radicals.

Zinc impedes the damaging effects of cadmium, lead and mercury in part by contributing to their increased elimination.

Zinc-finger molecules (zinc containing proteins with finger-like structures) regulate the proliferation and differentiation of cells and tissues by influencing gene expression. Zinc is required for the binding of zinc-finger-containing transcription factors to DNA and for hormone-receptor interactions (especially those involving estrogen, glucocorticoids, and thyriod hormones).

Zinc and acid-base balance

Zinc deficiency influences the activity of carbonic anhydrase (CA) in the lungs, kidneys, placenta and liver. CA, a particularly well-known zinc-dependent enzyme, facilitates the following chemical reaction in a split-second:

$$\mathbf{CO_2 + H_2O \longleftarrow CA \longrightarrow H_2CO_3 \longleftrightarrow H^+ + HCO_3^-}$$

Without CA, this reaction would take about 100 seconds to occur spontaneously. If CO_2 is removed from the equation, H_2CO_3 (carbonic acid) falls and the amount of available hydrogen (H^+) ions decreases. With CA, this reaction proceeds quickly and allows the body to eliminate CO_2 and to lower H+ ion concentration!

This reaction takes place during the elimination of CO_2 in the lungs. Red blood cells take only one second to flow through the smallest blood vessels in the lungs! In cases of CA deficiency, the elimination of CO_2 is diminished, leading to acid build-up within the body (respiratory acidosis). This build-up is enhanced by physical activity. The same reaction takes place during pregnancy in the placenta. Zinc deficiency makes CO_2 exchange from the fetus to the mother more difficult (in this case acidosis develops in the unborn child).

This reaction is also important in the kidneys for the elimination of H^+ ions. To compensate for sodium loss, one Na^+ ion is absorbed for every H^+ ion released into the urine. Zinc deficiency therefore increases sodium, potassium and magnesium loss which can lead to serious heart muscle problems.

CA is also used to form acid salts in the gastric mucosa. Zinc deficiency, and therefore CA deficiency, causes insufficient gastric acid production. Gastric acid loss is especially consequential for protein digestion. Without adequate gastric acid, many foods remain in the stomach longer, creating a full sensation or nausea. Due to insufficient acidity, residual bacteria will induce unnecessary fermentation which often leads to bloating. The resulting loss of appetite is a classic symptom of zinc deficiency. Fullness or nausea followed by bloating and a loss of appetite can continue in a cyclical pattern if you are zinc-deficient. In these cases, if you avoid protein – which is rich in zinc – to prevent digestive problems, then you are at risk of further depleting zinc.

Since CA is also utilized in the urease cycle (urea and ammonia removal) in the liver, zinc deficiency can contribute to elevated ammonia concentrations which are damaging to the brain (hepatic encephalopathy). Zinc supplementation in this case results in improved metabolism and psychological brain function.

Lab zinc values

Other than hair mineral analysis (and the examples given in the lab chapter), two additional lab tests are particularly important when measuring this trace element. One test involves monitoring alkaline phosphatase (a zinc-dependent enzyme) levels before and after zinc supplementation. An increase of these levels after zinc administration indicates possible zinc deficiency. Another sensitive method involves the determination of serum binding capacity for zinc. Binding capacity rises with zinc deficiency.

METALLOTHIONEIN, ZINC, AND HEAVY METALS

Zinc and metallothionein (MT) are intimately involved in metal regulation. Toxic mercury, for example, can bind inside the “s” configuration of MT where it would no longer be free to do harm. MT can bind up to 13 ions of copper providing a regulatory mechanism to balance zinc and copper levels. MT has the greatest affinity for mercury followed by copper, cadmium, silver, and zinc. Glutathione disulphide helps to release and exchange zinc for other metal ions. MT is found in high concentrations where heavy metals are detoxified - in the kidney, liver, and intestines.

The ‘signal’ to manufacture/induce the thionein component is provided by zinc, copper, cadmium, mercury, bismuth, gold, and other non-metallic compounds. Reduced glutathione found predominantly in the liver, kidney, spleen, and pancreas, helps to load zinc into thionein so it can be ‘preloaded’ with zinc to form active MT. Emotional stress, injury, and nuclear radiation can also induce the manufacture of MT. MT proteins are found in all cells and help us to protect from toxic metals circulating in the blood.

MT is also found in brain tissue as a factor that inhibits neuronal growth. MT has a role in brain cell pruning important in the nerve cell development and connectivity. If MT proteins are compromised, especially during development, it would be difficult to maintain optimal neurotransmitter levels. MT also has a role in behavior as the amygdala (the socialization and emotional memory area) and the hippocampus (involved in memory, learning, and behavior) have high concentrations of MT.

MT is found in the intestines, pancreas, and epithelial cells of the upper digestive tract and skin. MT prevents intestinal yeast overgrowth and intestinal inflammation. When MT binds to toxic metals in the intestinal lining it prevents them from entering the bloodstream. MT allows optimal zinc availability in the intestine to help breakdown casein and gluten. MT is important for the immune system, is involved in stomach acid manufacture, and plays a role in the discrimination of taste.

Zinc, selenium, glutathione, vitamin A and cysteine are important nutrients to promote MT formation and function.