29 Xenobiotics: Managing Toxic Metals, Biocides, Hormone Mimics, Solvents, and Chemical Disruptors

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INTRODUCTION

Xenobiotics are biologically active synthetic chemicals, many of which compromise human health. The human cost is a reduction of 8.8 years of life for the average person due to the effects of these toxicants.[1] This is a biological tax of 10% of most people's life span. The direct disease care costs induced by toxic metals (TMs) are calculated, in aggregate, to be in excess of $100 billion annually.[2]

There has been a 1000-fold increase in TMs and persistent organic pollutants (POPs) in our environment over the last 1000 years. Over half of the TMs and POPs burden on the environment has been added within the last century. Bioaccumulation in mammals, including humans, is typically 100,000 to 200,000,000 times that of the environment. This is largely due to most mammals' ready uptake and impaired innate release (detoxification plus excretion) mechanisms when they lose homeostatic and innate antitoxic mechanisms. These innate mechanisms are designed to trap and facilitate the safer elimination of these toxins. Further, these mechanisms are inducible when we come in contact with small amounts of the toxicant and have the healthy resilience to induce elective, protective mechanisms. Today, too many people have lost those protective mechanisms and thus appear to be at greater (genetic) risk than their actual (phenotypic) situation. Still further, we know all too little about the interactions of toxins.

This chapter reviews the impact of better-studied, clinically known toxicant groups on musculoskeletal conditions. In addition, functional tests to determine body toxicant burden and immunotoxic reactivity are included because they improve diagnostic precision and clinical outcomes. Functional procedures such as penicillamine provocation for nutritional and TM status allow a noninvasive clinical window on cellular mineral and cellular buffering competencies. In addition, lymphocyte response assays (LRA) by ELISA/ACT method, late-phase, delayed hypersensitivity reactivities allow for patient-specific diagnostic testing and therapeutic monitoring. Taken together, these approaches to clinical management hasten more predictive, cost-effective, outcome-effective, integrative, and comprehensive clinical care.

Editor's Note

Many anthropogenic, human-sourced intoxicants bioaccumulate in the food chain. Since humans are a part of the food chain and toxins are stored primarily in fat, muscle, and bone, it follows logic that environmental toxins contribute to emerging and severe musculoskeletal conditions. Scientific evidence is also "bioaccumulating" for a clinical imperative to mitigate exposure where possible and to optimize host defenses, generally through strategic nutrition and functional adaptations.

PERSISTENT ORGANIC POLLUTANTS

POPs are a broad category of synthetic chemicals including polychlorinated biphenyls (PCBs), dioxin, chlordane, and DDT. POPs are pervasive chemicals, more of which are being developed on an ongoing basis. They can be categorized as follows:

1. Hormone disruptor biocides (pesticides, fungicides, mitocides)
   - Cholinesterase inhibitor organophosphate pesticides
   - Halogenated pesticides.
2. Solvent residues
   - Chlorinated compounds (chloroform, methylene chloride, ethylene chloride)
   - Other halogenated compounds (brominated, fluorinated, iodinated) used most commonly as artificial food dye colorants, as radiocontrast agents, and art materials.

Even though some POPs have been banned or are restricted in use by some countries, POPs are, as their name suggests, persistent in the environment. They evaporate slowly into the atmosphere and aquifers and disperse around the globe. Living organisms then concentrate these fat-soluble chemicals in fatty tissues.

Adverse effects on human health can begin at thresholds below direct detection. In the case of dioxin, PCB, polybrominated biphenyl (PBB), and related compounds, human health risks emerge at the parts per trillion (ppt) level. This is in contrast to most laboratory tests that are only able to measure down to parts per million (ppm) levels of detection. In other words, we now routinely have biological health effects at amounts of materials in our bodies below our ability to detect them.

TOXIC METALS

While toxic metals with balanced electrons, like metallic lead or mercury, are of low direct human toxicity,[3] their surprisingly ready conversion under physiological conditions to substantially more toxic biologically active forms (e.g., divalent methylmercury, dimethylmercury, mercuric sulfides, and other mercurous or mercuric compounds, ethyl-lead, etc.) continues to be a major public health risk.[4] Biologically active TMs are considered by Nriagu and Pacyna to be the most toxic of all the toxic anthropogenic exposures[5] in the biosphere even when compared with POPs and ionizing, radioactive elements.

The common TMs encountered in North America are lead (Pb^{2+}), mercury (Hg^{2+}), arsenic (As^{2+}), cadmium (Cd^{2+}), nickel (Ni^{2+}), and aluminum (Al^{3+}). Except for trivalent aluminum and exotic multivalent minerals, TMs are divalent. This predicts their transition state biochemistry.

Primary sources of TM exposure in humans include:

1. Medications and devices including amalgams and vaccines.
2. Metallic TMs in occupational or recreational settings.
3. Fungicides in interior environments or in agriculture.
4. Recreational exposures including from leaded glass decanters for beverages or ceramics used for food, ceramic glazes used by artists and commercial glazers, commercial uses of solders and fluxes.
5. Water and aerosol contamination.
6. Dietary sources including fish, fowl, such as commercially raised chicken, beef, and game. Generally, the higher up the food chain, the greater the contamination.

Living in an industrialized society exposes all inhabitants to metals and POPs in the environment. Substantial sources of highly toxic compounds can greatly enrich an environment in a toxicant without public awareness. These largely invisible depositions are bioidentical and just as toxic as the exposures of which we are aware. For example, while 200 to 600 tons of mercurial toxicants are annually added to the American ecosystem from all anthropogenic sources, an additional 100 tons of mercury is derived from trans-Atlantic tiny dust particles. Additional metric tons may be added by the trans-Pacific plumes of aerosol toxicants from the Pacific Rim. These are carried in the upper atmosphere and contain enough mercury and arsenic to qualify as mineable ore if only this dust could be trapped before it reaches the southern United States and Caribbean Basin.[6] This last environmental burden was unknown until as recently as 1990. This illustrates how substantial sources of "high toxic effects compounds" can greatly enrich an environment in a toxicant without general awareness of the influx of that toxicant. These largely invisible depositions are bioidentical and just as toxic as the exposures of which we are aware.

Toxic metals are potent metabolic, hormonal, immune, and gene toxins.[7] For example, continued exposures to TMs that bioaccumulate, above about 1 part per billion (ppb),[8,9] impose long-term human health risks, particularly for increased chronic autoimmune and cardiovascular illnesses.[10]

With regard to lead, the evidence base of pervasive subacute toxicities is particularly well documented and well reviewed elsewhere.[11]

Living in an industrialized society exposes all inhabitants to metals and POPs in the environment. Some minerals are essential for life. To some extent, beneficial minerals are antitoxic in that they block or compete with the TMs. In other words, people with adequate stores of buffering minerals block the uptake and facilitate the excretion of TMs from the body in all excretory pathways. These pathways of excretion include urine, stool, sweat, desquamated skin, hair, nails, and breath. The antitoxic minerals work best when the amounts, balance, and ratios provide ample reserve pools to draw upon. The particular minerals involved are potassium and sodium, calcium and magnesium, zinc and copper, chromium and vanadium, manganese and molybdenum, selenomethionine and iodides, etc.

Some minerals, like selenium, have proper, bioactive form (selenomethionine and selenocysteine) and can form stable, permanent, covalent links with biologically active mercury or arsenic (and probably other divalent TMs), thereby detoxifying them. These stable complexes are not easy to remove and may remain in the body for periods of years to decades. Their "balanced electron" relatively low toxicity reduces the priority placed on their removal from the host. In contrast, other forms of selenium commonly used in supplements do not have this beneficial property, yet are more toxic.

TMs and POPs are an acquired and reversible health risk for over 80 million Americans. The human cost is a reduction of 8.8 years of life for the average person due to the effects of these toxicants.[12] This is a biological tax of 10% of most people's life span. The direct disease care costs induced by TMs are calculated, in aggregate, to be in excess of $100 billion annually.[13]

This means that we could fund a transition from our current symptom-reactive, sick care focus to a proactive, intoxication prevention program out of savings from sick care costs not incurred. The public health risk from TMs is even greater due to observed but not extensively defined or replicated synergies of mineral toxicities.[14] Since TMs and POPs both bioaccumulate and bioconcentrate, the adventitious exposures are likely to increase greatly just at the time that internal reserve mineral and antioxidant protectors are at their highest. Chapter 25 addresses the importance of alkaline balance and of avoiding both metabolic acidosis and catabolic illness.

TMs and POPs are among "nature's mimics" in that they can bring to substantially greater intensity a wide variety of clinical conditions including fibromyalgia, rhabdomyolysis, chronic pain, osteoporosis, birth defects, and autoimmune syndromes. TMs and POPs potentiate these highly diverse conditions due to their common yet variable expressions of free radical pathology, made worse in the face of antioxidant deficits and metabolic acidosis.

Understanding this molecular pathophysiology allows us to enter a new era of clinical medicine where comprehensive, integrative care plays an important role. Identifying the role of clinical chronic subacute (low-level yet persisting) TM and POPs actions is integral to "identify and mitigate the causes rather than focus on relief from the symptomatic consequences" of philosophy of care that differentiates integrative and comprehensive care as a specialty from conventional internal medicine and family practice.

Among the effects of TMs and POPs are the following molecular consequences for cell functions:

1. *Metabolic uncoupler*: Inhibits cytochrome I to coenzyme Q_{10} transfer in the mitochondria, the cells energy producing detoxifying saprophytic organelle. This reduces ATP (high-energy compound) production, thus reducing the functionality of those parts of the cell consuming the most energy; generally, this means the most metabolically active and functionally important component of the cell becomes starved for energy.

2. *Hapten immunotoxins*: Small molecules that bind to and distort the structure of the body's own proteins, from globulins to insulin, from lipoproteins to macroglobulins, thus increasing the probability of autoimmune, chronic illness.
3. *Enzyme inhibitor*: For cell regulatory control kinases and other enzymes with cysteine or thiamine (B1) sulfhydryls at their active site. Phosphodiesterase, superoxide dismutase (SOD), and nucleotide binding protein (NBP) are examples of particularly vulnerable, functionally vital enzyme catalysts.
4. *Anti-antioxidants (pro-oxidants)*: TMs and POPs are pro-oxidants that induce excessive consumption and wasting of glutathione and ascorbate. These two antioxidants are at the center of the antioxidant recycling network that protects delicate cell components from free-radical oxidative damage when we are in physiologic homeostasis and immune tolerance. Once antioxidants are selectively depleted, free-radical damage can run rampant in oxidizing and making important cell systems dysfunctional. Chapter 7 by Harris and Baer addresses this in more detail.
5. *Bioconcentrate*: These toxicants bioaccumulate in critical and most unfortunate places within the body like the choroids plexus where spinal fluid is produced to the loop of Henle where the kidney concentrates toxins for excretion into the urine. This reduces the body's functionality and accelerates biological aging.

Absence of Evidence is not Evidence of Absence

With regard to POPs and possible interactions among chemicals, of the 104,000 chemicals introduced into the environment through made-made novel synthesis, barely 4000 have been studied at all and barely a handful have been studied for their interactive toxicities. The absence of data is not a basis for assuming the data of absence exists.[15]

An example of absence of evidence is the immune system's response to toxins, even once removed. There are T-helper lymphocytes that are involved with delayed allergy reactions to haptenic* immunotoxins such as TMs. Clinically, this can be functionally measured by a classic memory enzyme linked immunosorbed assay (MELISA) modification of thymidine incorporation or by the LRA by ELISA/ACT tests that assay kinase activation prior to inducing thymidine incorporation and cell mitotic division. These technologies show us that even tiny amounts of internal or environmental exposure to a substance that induces an immunotoxic hypersensitivity reduces immune defense abilities and induces

* Haptenic substances (or haptens) are small molecules which, while not large enough to be recognized as foreign by the body, bind to the body's own proteins. This binding distorts the innate structure, rendering them "foreign" and immunoreactive in the body.

deferral of immune repair. When this becomes the usual condition, we become hospitable to "whatever is going around."

Another example of absence of evidence is the toxin's damage to energy production. Among the effects of TMs and POPs when they bioaccumulate in cells is apoptosis of mitochondria. After mitochondria commit this programmed cell suicide, the cell's overall death is not far off. In contrast, protection and rehabilitation of mitochondria is central to lifelong health maintenance, restoration, or enhancement.

The effects of TMs and POPs are more destructive when low cellular minerals (particularly potassium and magnesium) predispose the cell to metabolic acidosis. Intracellular depletion of potassium and magnesium can cause metabolic acidosis regardless of how well compensated the blood pH may be. The combination of metabolic acidosis and TMs and POPs accelerates mineral leaching from bone to buffer the excess acids the kidney needs to concentrate and excrete without damaging itself, to the extent possible. This means that osteopenia and osteoporosis are accelerated. Among the other effects are shifts within cells from elective production of structural proteins and metallothionines to a survival mode for the cell such that only actions needed for the cell to avoid death are performed.

Elective and protective elements are no longer produced. Toxic effects of TMs are further potentiated in this situation. Unhealthy hormone metabolites may accumulate rather than be excreted owing to toxic damage or lack of cell energy required to "pump" toxicants out of the body and into urine, stool, and sweat while healthier hormone products, in contrast, may not be made. Further, we know too little about the interactions of low-level persistent TMs. What little we do know suggests there is synergy of toxic effects when two or more TMs are concurrently present.[16]

Risk of Bioaccumulation of Toxicants: A Matter of Balance and Homeostasis

Bioaccumulation of TMs or POPs is a function of intake and output balance.

$$\text{Intake} - \text{Output} = \text{Residual (remainder in body)}$$

The integral of this simple input–output model determines individual body burden. For example, if

$$\text{Intake (high)} - \text{Output (low)} = \text{Increase in toxic burden}$$

1. Intake (high) − Output (high) = Steady state, high risk state
2. Intake (low) − Output (high) = Decrease in toxic burden
3. Intake (low) − Output (low) = Low exposure

$$\text{Goal: Intake (low)} - \text{Output (high)} = \text{Body burden reduction}$$

It is possible to reduce, but not avoid, intake as discussed earlier. It is also possible to increase output to reduce the residual, or total body burden. In other words, low intake and high capacity to excrete toxins is a feasible clinical evidence-based goal.

Note that high output is associated with elective synthesis of metallothionines, polypeptides made largely of glycine and cysteine with zinc or magnesium as the counterion. When these biological detoxifiers are produced, substantial TM trapping capacity is observed in the gut, the plasma, and the cerebrospinal fluid.

Increasing Output to Reduce Bioaccumulation

William Walsh of the Pfeiffer Treatment Center, Wheaton, IL, reports a link between the above basic science genetic and phenotypic data, suggesting a hereditary or xenobiotic pseudogenetic predisposition to mercury toxicity and T-lymphocyte hypersensitivity (DTH). The emerging data make thimerosal exposure at times of distress or impaired detoxification particularly troublesome. Thimerisal typically contains 5 to 7.5 μg of ethylmercury per vaccination dose.

High output of toxins from the human body is associated with elective synthesis of metallothionines. Under normal circumstances, there is a large concentration of the protein metallothionine waiting in the intestines, as a sentinel, to interact with the mercury or other TM and detoxify it before it enters the body.

Each metallothionine molecule has binding sites for seven atoms of zinc plus variable amounts of magnesium, selenomethionine, and glutathione. Structurally, it is a linear protein of 61 amino acids with 20 or more cysteine or cystine-active sulfhydryls. Its job is TM detoxification. It is present in high concentration in the GI tract and in the liver, but it is present in every cell in the body. When present, it protects the GI tract from all of the nasty things that TMs like mercury can do. However, its production is elective. Metallothionine production occurs only when the body is healthy, alkaline buffered, and in homeostatic equilibrium. In states of hormonal, neurochemical, or immune distress, metallothionine production can be substantially downregulated.

> If you take somebody whose metallothionine system is working well, however, the mercury forms covalent links to other, active sulfhydryl groups. The sulfhydryl groups in active site of certain enzymes in the gastrointestinal tract include the enzymes that break down casein from cow milk and gluten from wheat and other grains. A metallothionine disorder, therefore, is often associated with major digestive and dysbiosis problems as well. Most typically, wheat and casein intolerances and other delayed T cell mediated allergic hypersensitivities occur. These individuals are also prone to intestinal inflammation and enteropathy.
>
> Metallothionine is a family of four proteins (1,2,3, and 4). Metallothionines 1 and 2 are ubiquitous and present in every cell in the body. Metallothionines carry out innate antioxidant functions and deliver zinc wherever it is needed.[17]

Metallothionine is also responsible for homeostasis between copper and zinc. These trace elements, in turn, are related to production of specific hormones, cytokines, and neurotransmitters. For example, for the zinc or copper requiring enzyme catalysts to convert the right amount of dopamine into norepinephrine, copper to zinc balance and sufficiency are required. This is discussed in more detail in Chapter 13.

Walsh and colleagues have used the plasma zinc–copper ratio as an indicator of properly functioning metallothionine. They use it as an indicator of "toxic-coping ability." They report that, if you have a population of:

1. Obsessive–compulsive (OC) individuals, the ratio between plasma zinc and serum copper will be around 0.8.
2. The healthy range, based on nearly 100,000 individuals, is about 1.0.
3. Walsh et al. have examined 5700 individuals with attention-deficit disorder and the mean ratio is 1.17.
4. For children who exhibit violent behavior, the ratio is typically > 1.4.

Walsh suggests that impaired homeostasis for copper and zinc correlates with poor metallothionine function. The detailed influence of supplementation on normalizing these ratios and their impact on function and performance are, as yet, unreported.[18]

Reducing Iatrogenic Input

If you study people with amalgams, many of them show few adverse effects. Similarly, most children who receive vaccinations containing thimerosal go through this experience without many notable adverse effects. Perhaps these are the individuals with adequate ascorbate and glutathione, magnesium and zinc, selenomethionine and sulfur from dietary sources (including breast milk from mothers whose antitoxic levels are high). These individuals are protected and are at relatively low risk. When zinc, selenomethionine, and magnesium are marginal or deficient, metallothionine loses functionality.[19] Such individuals are sensitive and at high risk of the adverse consequences of TMs and POPs.

The Swedish experience is the most rigorous and extensive regarding toxicity from dental materials, particularly mercury amalgam. Lindh pioneered research using nuclear probe microscopy for minerals in biomedical analysis.[†] Neutrophil (granulocyte) mercury was compared between patients with mercury amalgams who were sick and controls (i.e., people with mercury amalgams who were not sick).

[†] Nuclear microscopy or PIXE is an advanced analytical tool that allows for the measurement of trace elements in small objects, such as the nucleus of the neutrophil granulocyte (with a detection limit of 0.5 μg/g dry substance). This is done by bombarding the cells and their organelles with protons (hydrogen atoms). Because each trace element has its own characteristic emission fingerprint, it is then possible to determine the amounts of a particular element in the various regions of the cell. This was based on the earlier work of Jaffe, Smith, and Costa.

The results showed that the patients who had amalgams and who were sick had detectable mercury in their cells and that the controls did not show bioaccumulation of mercury.

In addition, the concentrations of other elements such as magnesium, calcium, manganese, iron, and zinc were more than one standard deviation below in the patients and not in the asymptomatic controls. Examination of elements in the nucleus showed a maldistribution of zinc, which correlated with the presence of mercury in the nucleus of the neutrophils. There is a typical zinc distribution in the nucleus of the neutrophil granulocyte. In contrast to this normal situation, the patients who had mercury burdens showed an abnormal distribution and an invasion of mercury into delicate nuclear or nucleolar centers. Mercury in the nucleus correlated with the decreased zinc in those areas. Whether mercury caused the mineral aberrations or if preexisting mineral deficiencies predisposed to mercury remains to be determined. In summary, by using sensitive[‡] probes, Lindh clearly demonstrated the presence of mercury in the cells of patients who had amalgams and who were sick, and the absence of mercury above threshold levels in the cells of asymptomatic controls with amalgams.

The majority of metals that are used in dentistry belong to the transition group in the periodic table. A general characteristic of these elements is that they have an uncompleted electron shell, either in the natural or oxidative state. Since electrons always exist in pairs, transition metals form strong complexes with both organic and inorganic ligands. The memory cells are long-lived and can be detected in the blood of sensitive individuals, prior to the appearance of objectively documented clinical symptoms.

Stejskal and Lindh, elucidated the immune response that mercury may trigger. The research agrees that T lymphocytes play a role in all types of allergic and autoimmune reactions.[20] This makes them evident candidates as markers for metal-induced sensitivity. After contact with an antigen, T- and B-lymphocytes that are antigen-specific for that substance correlate with inflammatory reactions that lead to cell damage when repair is delayed or blocked. Repeated exposure with the same or a chemically similar cross-reacting antigen will immediately induce a faster, secondary immunological reaction initiated by the memory cells. Cytokine release will activate other cell types and the result is either beneficial for the body when repair is facilitated or, in the case of repair deficient autoimmune diseases, a pathological consequence. Human lymphocytes can be stimulated *in vitro* with various foreign substances called mitogens. The lymphocyte stimulation test has been used for 30 years as routine analysis for evaluation of

[‡]Nuclear microscopy or PIXE is an advanced analytical tool that allows for the measurement of trace elements in small objects, such as the nucleus of the neutrophil granulocyte (with a detection limit of 0.5 μg/g dry substance). This is done by bombarding the cells and their organelles with protons (hydrogen atoms). Because each trace element has its own characteristic emission fingerprint, it is then possible to determine the amounts of a particular element in the various regions of the cell. This was based on the earlier work of Jaffe, Smith, and Costa.

cellular immunity and clinical immunology, as well as for diagnoses of allergic reactions to medicines, metals, and other substances. Specific stimulation is based on the fact that every person's immune system remembers the antigen that it has previously been programmed to remember.[21] Such a reaction gives rise to memory T- and B-lymphocyte cells that circulate in the bloodstream and defend as needed the individual against foreign substances including:

1. Xenobiotics and other synthetic small molecules (mostly haptens).
2. Partially digested, immunoreactive food digestive remnants.
3. Pathogens including bacteria, parasites, viruses, or anything recognized by an individual as foreign to their immune system.

Other types of white blood cells are dendritic cells such as monocytes and macrophages, endothelial cells and fibroblasts, astrocytes and Kupfer cells. These cells perform various functions such as presentation of processed antigens to naive unprogrammed lymphocytes and removal of toxic substances; thus, they are termed "scavenger" or dendritic cells. They are short-lived with a typical life span of 8 to 12 h in the body. Tests that employ changes in short-lived granulocytes are not using contemporary technology for functional immune system predictive response. At best they are looking "through a glass darkly" and overinterpreting aggregate particle changes as lymphocyte-specific changes, which they probably are not. The possibility to diagnose delayed allergy (hypersensitivity) with the help of lymphocyte stimulation tests rests on the fact that in the case of low molecular weight substances (haptens), antigen-specific memory cells are present in patients with allergy symptoms, but not in healthy exposed individuals. Further, since memory cells circulate through the body, the sensitization or allergy is always a systemic phenomenon. The term local allergy often used in the case of oral mucosal changes indicates ignorance of modern immunological principles. The majority of the lymphocytes that operate in cell-mediated reactions are T-lymphocytes. T-lymphocytes play a key role in the development of all types of allergic and autoimmune disorders. The identification of the antigenic structures (epitopes) involved in allergy and autoimmunity is a "hot field" in current research. One method of autoimmunity is that metals bind to the sulfhydryl groups on proteins and alter their three-dimensional structure. The immune system recognizes the altered proteins as foreign and an autoimmune process starts, often with condition-specific imbalances in Th1 and Th2 populations of lymphocytes. TMs and POPs can affect the immune system in several ways. In the oral cavity, high concentrations of metal ions may suppress the immune response and result in immunosuppression. This could explain why the oral mucosa contains only a low number of cells with the capability to present antigen to T-lymphocytes. This may also be why mucosal changes adjacent to metal fillings are rarely seen. Higher concentrations of metals can also upregulate immune reactions (called the polyclonal or nonspecific stimulation) and such responses are seen in individuals with intact immunity.

In contrast, in some hereditarily predisposed individuals, TMs may act as haptenic immune reactors. To be able to use the conventional lymphocyte stimulation test for diagnosis of metal-induced allergy, it was necessary to modify the test in such a way that only the antigen-specific reaction was measured. This was achieved by reducing the concentrations of the metals added to cultures. Since antigen-specific memory cells in the blood are relatively few, the number of lymphocytes in the metal cultures was increased, and the number of other cells that could affect the lymphocyte proliferation negatively was reduced. This version of the lymphocyte stimulation test is called MELISA. Another advanced lymphocyte response assay is the LRA by ELISA/ACT tests system.

In short, MELISA or LRA by ELISA/ACT enables individuals who are immunoreactive to mercury and other metals to be identified. Furthermore, after the removal of amalgam and replacement with nonmetal composites or the systematic reduction in immunoreactive exposures, the lymphocyte stimulation test often reverts to nonreactive. This "resetting" of immune responses typically takes 6 to 18 months. These changes parallel the decrease in concentrations of mercury inside the neutrophil granulocyte. The dental research in this regard in Sweden is well documented by Hudecek, a capable biological dentist. Following dental amalgam(s) removal, his data showed that 76% of patients reported long-term health improvement, 22% reported unchanged health, and 2% reported a worsening of symptoms.

Recently, Lindvall reported that at 1 to 2 years following amalgam removal, about a quarter of the patients had completely recovered from their chronic autoimmune or immune dysfunction syndromes, half were substantially improved, one fifth showed no change, and one twentieth (5%) were worse off than before. This latter group was mostly patients who had improper or premature amalgam removal.[22]

QUANTIFYING INDIVIDUAL EXPOSURE

Evaluation of a person suspected of chronic clinical metal toxicity and heavy metal sensitivity or POPs burden[23] can be based clinically on the following:

1. Determining the body exposure and burden of the TMs, POPs, and the relevant nutritional antitoxic metals on an appropriately provoked specimen is the current state of the art of testing and determining probably (?) clinical body burden at a sufficient level of precision to warrant clinical management based on the provoked urine quantitative information. In addition, unprovoked urine may be employed as a preprovocative testing screening assessment but is not routinely, clinically necessary.
2. Penicillamine (D-Pen™, Cupramine™) is an example of a mineral binding or chelating compounds that has been standardized for provocative testing and therapeutic monitoring. Penicillamine has

been standardized as a challenge agent for cellular toxic and nutritional mineral content. Other chelators are in development, while a variety of selective chelators are currently available, varying with local regulatory practices.

3. Further, the timing of detoxification is best accomplished when host systems for sequestration and rapid elimination of toxin are facilitated. For example, removal of mercury containing amalgams (if needed) should follow a systematic program to enhance dietary intake of detoxifying foods and to reduce the mobilizable burden of TMs or POPs. Examples of "detox" foods are garlic, onions and ginger, brassica sprouts, and eggs. Each of them can block uptake and bind (thereby detoxifying) TMs, most POPs, and other sources of biologically active sulfur compounds to accomplish the same effects. Individualized therapy by clinically experienced professionals is needed to guide supplementation, lifestyle changes, and attitudinal healing.

Confirmatory, follow-up testing is encouraged at 3 to 6 months following the initiation of therapy. In many cases, otherwise unexpected additional toxicants or essential nutritional mineral deficits will be revealed. It is cost-effective to engage these elements of comprehensive and integrative care. This reduction in human morbidity can be linked to the reduction of biologically active TMs/POPs and the enhancement of antioxidant, antitoxic stores in the person.

Removing TMs and POPs

Now we will look at the practical aspects of identifying nutritional and TM body burden by provocation testing using penicillamine as an example of a validated oral protocol.

Penicillamine Protocol for Determining Toxic and Nutritional Mineral Status in Cells by Noninvasive Provocation into the Urine

Purpose: Determine the body's burden of mobilizable, potentially toxic metals and the divalent minerals altered when toxins are present.
Method: A 24 h urine test during a short noninvasive provocation using oral d-penicillamine (Cupramine, D-Pen, dimethylcysteine, mercaptovaline) or acetyl-penicillamine, prescribed by a physician.
Protocol:

- The average-sized adult is prescribed 500 mg of penicillamine or *N*-acetyl-penicillamine with each meal and before bed for 3 days. Generally, two capsules of 250 mg each are taken four times a day. This is a total of 2 g each day. The dose is based on 30 mg/kg body weight. If weight is under 100 or over 300 lb, calculation of dose is

recommended. For example, a 100 lb adult weighs 45.5 kg. A daily dose of 1590 mg (~1500 mg) is recommended. This would most easily be achieved by giving 2 × 250 mg capsules with breakfast, dinner, and at bedtime (2 capsules TID). By comparison, a 350 lb person weighs 160 kg. At 30 mg/kg, this calculates to a daily dose of 4800 mg (~4750 mg). This means taking 5 × 250 mg capsules with each of three meals plus 4 × 250 mg capsules at bedtime.

- This short course of penicillamine avoids the rare but important side effects of longer-term therapeutic doses of the drug as discussed in the *Physicians Desk Reference*. Inform patients to discontinue taking the medication until otherwise instructed if there is an adverse effect.
- Begin urine collection on the morning of the second day. This is 24 h after initiating the penicillimine. Collect all urine in a heavy metal-free container, which is usually provided by the doctor or the laboratory. Urine must be collected for a full 24 h cycle. If a urine sample is missed, the collection is incomplete and the protocol should be resumed 1 week later. Urine collected in an incomplete sample may be poured out and the same collection container reused.
- Take the completed urine collection to the laboratory promptly. The total volume is an important part of the information to be sent to the analytic laboratory. It is desirable, although not necessary, to keep the urine refrigerated during the collection period.
- Analyze the results. Typical penicillamine provocation reference ranges are included in Table 29.1.
- Please note that a third-day collection cannot be compared with the standardized second-day collection results. Because the specimen is provoked by d-penicillamine, it should not be used for mineral balance studies. The specimen may be used to check kidney function and to analyze for most hormones and neurotransmitter metabolites.
- If substantial total TM tissue burdens are documented, oral pulse therapy (2 days/week) with penicillamine is recommended. Use 7.5 mg/kg QID, on the two days each week for 3 months. After 3 months, retest the urine by the penicillamine provocation test to determine the residual TM being eliminated as well as for comparison of nutritional mineral status. For example, are they assimilating what is being given or do they have enteropathy with consequent reduction in mineral uptake? Do they have a particularly high need for particular minerals for their unique metabolic balance state, type, or condition based on functional tests?

This short course of penicillamine avoids the rare but important side effects of longer-term therapeutic doses of the drug as discussed in the *Physicians Desk Reference*. Patients should be advised to discontinue taking the medication if any adverse response is observed until otherwise instructed by a clinician.

TABLE 29.1
Mineral value ranges for nutritional and toxic minerals in the second-day 24 h urine after d-penicillamine provocation, 7.5 mg/kg QID for 3 days (*N* = 200)

Mineral element	Reference range mg/g creatinine	Reference range mg/24 h sample
Nutritional		
Calcium	310–620	400–900
Magnesium	250–550	350–700
Zinc	0.8–1.3	1.1–1.5
Copper	0.04–0.06	0.06–0.08
Iron	0.20–0.30	0.24–0.36
Manganese	0.005–0.007	0.006–0.008
Molybdenum	0.11–0.14	0.13–0.19
Boron	4.1–5.6	5.8–6.7
Chromium	0.19–0.30	0.21–0.33
Cobalt	0.04–0.06	0.05–0.07
Selenium	0.25–0.31	0.24–0.35
Vanadium	0.02–0.03	0.03–0.04
Toxic		
	μg/gm creatinine	ug/24 h sample
Lead	<20	<25
Mercury	<7	<9
Arsenic	<120	<175
Nickel	<16	<25
Cadmium	<4	<6

Note: Values lower than the reference range in provoked specimens suggest deficiency of the above-needed essential minerals. Adequacy of supplemental intake to replenish deficits can be monitored by repeat d-penicillamine provocation every 3 months.

Interpretation and Substantiation of Penicillamine Protocol

Each laboratory has an applicable reference range for each mineral assayed. Elevation above the range reported by that laboratory is indicative of increased tissue stores of that heavy metal. Tissue status of nutritional minerals may also be assessed in this way. Typical penicillamine provocation reference ranges are included in Table 29.1.

Managing Modest Amounts of Provoked TMs

Patients are advised to follow the alkaline way diet. Eighty percent of this diet comprises alkaline-forming foods. Alkaline-forming foods add bicarbonate

rather than hydrogen ions. One way patients can assess results of their diet is by monitoring urine pH. Refer to Chapter 25 for the alkaline way diet protocol.

This diet should be combined with sufficient amounts of antioxidants plus minerals (potassium, calcium, magnesium, and zinc as their fully ionized, fully soluble ascorbates, aspartates, citrates, malates, succinates, fumarates glycinates, or other fully soluble, nonallergenic mineral salts) to displace the TMs. Adequate herbal tea, mineral water, or spring water helps to "wash out" these toxins.

A repeat provocative urine minerals test after 3 to 6 months is recommended to confirm the reduction in available TMs.

Managing More Than Modest Amounts of Provoked TMs

Use penicillamine twice a week (e.g., Mondays and Thursdays) for 30 to 60 days at 7.5 mg/kg taken QID (500 mg/QID for most adults) with supplemental calcium, magnesium, and zinc particularly on the nonpenicillamine days to replace these minerals (which penicillamine will chelate along with the other divalent [double charged] minerals along with toxic or heavy metals).

Therapeutic doses of antioxidants are beneficial as described. They include:

1. Buffered ascorbate based on ascorbate calibration to determine physiological ascorbate need.[24] Flavonoid/flavanol combinations (e.g., a total of 1 to 30 g daily of quercetin dihydrate and soluble OPC) potentiate the benefits of buffered ascorbate. Their need increases in proportion to buffered ascorbate need as noted in the ascorbate calibration document.
2. Natural vitamin E (mixed tocopherols) 200 to 1600 IU/d with tocotrienols (polycosanols) and selenomethionine.
3. A balanced, high-potency, high-activity B complex including para-aminobenzoic acid (PABA) and selenomethionine.
4. A comprehensive micromineral supplement is recommended since micromineral deficits are pervasive. From magnesium and potassium to chromium and vanadium, from manganese and molybdenum to zinc and copper we can measure the relationships of these key nutritional minerals. Selenomethionine is the most active mineral form for combining with and inactivating TMs.
5. Sulfhydryl-rich foods such as garlic, ginger, and onions; eggs; and brassica vegetables (e.g., broccoli, cabbage, etc.). Make fresh ginger tea (with raw honey to taste) a staple beverage. A thumb-size piece of fresh ginger, finely chopped and steeped in hot water for 5 min contains over 5000 μg of TM-trapping sulfhydryl compounds. Ginger tea may be made up ahead of time and may be drunk cool or cold if preferred.
6. Probiotics (8 to 20 Bn/day) containing multiple human strains that have been cultured, harvested, and lyophilized (freeze dried) for maximum activity and potency.

7. Carotenoids (e.g., 25 to 100 mg daily of the carotenoid family including alphacarotene, betacarotene, lutein, cryptoxanthin, and pseudoxanthin) and vitamin D (600 to 2400 IU daily) for enhanced cell regulation and resilience.
8. Adequate beneficial, essential fats (e.g., 0.5 to 5 g daily of total omega 3 fatty acids intake) including conjugated linoleic acid, docosahexaenic acid, and eicosapentenoic acid (EPA) as discussed in detail in the chapter by Mary Enig.

Enhancing antioxidant levels is demonstrated to improve flowing blood in metabolically and hormonally active cells, the blood–brain barrier and the choroid plexus, the enterocytes in the digestive tract, metabolically active nerve, endocrine, immune and hepatic cells, sexual function, and skin.

Penicillamine in Clinical Practice

Penicillamine was found to bind copper in the body and safely mobilize it for excretion in the urine (and stool and sweat) of patients with Wilson's disease[25] for which it has remained the treatment of choice for almost half a century. Walsh has reported the safe and successful use of penicillamine in pregnant women, infants, the elderly, and the infirm.

In nonhuman species, lead in bone seems to be even more effectively mobilized by penicillamine than lead in soft tissues.[26,27] However, CaNa2 EDTA is reported to be a more effective lead chelator than penicillamine *in vitro* in tissue culture.[28] Questions have been raised about the safety of using any agent for low-level TM detoxification because some animal studies report that lead may redistribute into soft tissues such as the choroid plexus (where spinal fluid is produced) or the urine concentrating loop of Henle in the kidney after $CaNa_2$ EDTA therapy.[29] Concerns of this type have been raised about all oral chelators although less with regard to penicillamine than any other substance because of the tight bond between TMs and penicillamine.

Lead, Mercury, Arsenic, Cadmium, and Nickel Mobilization by Penicillamine

Clinical benefits of penicillamine are described by Sachs et al.[30] and Vitale et al.,[31] but not by Marcus[32] (who administered penicillamine while the study subjects continued to live in lead exposed environs). This may well explain the less dramatic decline in blood lead levels in the Marcus study.

In Chisholm's study, children removed from further exposure and treated with penicillamine showed more rapid decline in blood lead levels and in the reversal of hematologic toxicity than the decline in toxicities resulting solely from eliminating the lead exposure sources.[33] In contrast, the study by Rogan et al.[34] did not confirm these findings. This study has been criticized as flawed in method because

the environment of the children studies was not mitigated for continued TM exposure during the study period.[35] In other words, simple use of a chelator is insufficient if you leave the person in the intoxicated environment without mitigation.

In addition to lead, penicillamine also mobilizes and facilitates the safer excretion of TMs[36] including mercury,[37–44] arsenic,[45–50] cadmium,[51–53] and nickel.[54] Inconsistent reports of efficacy have been published. On balance, these may reflect lack of attention to sufficient reducing substance (ascorbate) to enhance TM mobilization and excretion while maintaining the more effective reduced form of penicillamine rather than its disulfide. An additional factor that reduces TM mobilization is metabolic cellular acidosis. Correction of magnesium buffering deficit aids directly (by displacement) and indirectly (by correcting cellular acidosis) enhanced TM mobilization. Magnesium, as the second most prevalent mineral inside healthy mammalian cells, is a major contributor to cellular buffering and its absence induces cellular metabolic acidosis.[55]

The toxicity of penicillamine has been described based on its use for several indications in both adults and children. Toxicity of the racemic mixture used years ago to treat chronic arthritis in adults may account for the severity of some of these symptoms and should never be used. In children, nausea and vomiting appear more often at doses exceeding 60 mg/kg/d and may respond to a decrease in dosage.[56] This protocol uses 30 mg/kg doses for just 3 days for provocation.

When given daily and for prolonged periods (which we never recommend) adverse blood and skin effects seem to be idiosyncratic hypersensitivity reactions and are not dose related. Reversible leukopenia or mild thrombocytopenia is reported in less than 10% of children in one study,[57] but not with similar dosages in two other larger series.[58] This may have resulted from interaction between penicillamine and pyridoxine (B-6).[59] Supplemental B-6 is now routinely recommended as part of penicillamine therapy (not provocation). Eosinophilia (defined as $>18\%$ eosinophils) has been noted in one fifth of high-risk children treated daily for an extended duration with the older, less pure preparations of d-penicillamine.[60]

Angioedema, urticaria, or maculopapular eruptions that require discontinuation of drug therapy are reported at a rate of 0.5 to 1%.[61] Still less commonly reported reactions are proteinuria, microscopic hematuria, and urinary incontinence.[62] All of these relate to increased tissue permeability due to inhibition of connective tissue cross-links when penicillamine is given on a continuing daily basis and not when it is given in the pulsed manner recommended here. All these problems are much less common today because of the higher purity of d-penicillamine and improved understanding of its mechanisms of action and how to separate them for clinical benefits.

Distribution in the body of penicillamine is widespread. Like amino acids such as cysteine of which penicillamine is the dimethyl analog, as also is mercaptovaline, it moves freely inside cells, subcellular organelles like the mitochondria and into deep tissue sites like the brain.[63–70]

Reactive foods or intestinal irritants such as ferrous sulfate[71] may reduce the peak level of penicillamine in blood by a third or more.[72] Antacids or functional

hypochlorhydria[73] decreases penicillamine absorption by as much as two thirds.[74] As with all amino acids, peak blood levels are achieved when the amino acid is given on an empty stomach. For provocation and for therapy, mean blood levels are more important than peak blood levels. Thus, taking the penicillamine with food is acceptable. Compliance with this regimen, individually as suggested above, is high.

The recommended dose and duration of therapy with penicillamine have been empirically derived. Doses have ranged from 100 mg/kg/d (in earlier studies) to 20 to 40 mg/kg/d. Far fewer side effects are reported at the lower dosage range used in provocation and TM mobilization. The duration of the pulse therapy herein recommended is typically on Monday and Thursday for 3 to 6 months, depending on the pretreatment provoked urine TM concentration. When used in this pulsed fashion, penicillamine has become a first-line comprehensive care treatment of choice over the several decades of its increasingly widespread use.

Penicillamine has the additional benefit of serving as a source of nitric oxide, which facilitates cellular communication and improved vascular compliance.[75]

In addition, if substantial total TM tissue burdens are documented, oral pulse therapy (2 days/week) with penicillamine is recommended. Use 7.5 mg/kg QID, on the two days each week for 3 months. After 3 months, retest the urine by the penicillamine provocation test to determine residual TM being eliminated as well as comparison of nutritional mineral status. For example, are they assimilating what is being given or do they have enteropathy with consequent reduction in mineral uptake? Do they have a particularly high need for particular minerals for their unique metabolic balance state, type, or condition based on functional tests?

CONCLUSION: DIAGNOSING AND MANAGING MUSCULOSKELETAL CONDITIONS

This chapter focuses on TMs and POPs with emphasis on their clinical effects, their diagnostic assessment, and their safer detoxification. This is particularly true for the health of the body's frame (structure; bones, joints, and extracellular matrix), for metabolic balance (weight, obesity risk, insulin resistance), for managing such "mystery syndromes" as fibromyalgia or myofascial pain syndromes, as rhabdomyolosis or polymyalgica rheumatica, as chronic fatigue immune dysfunction syndrome (CFIDS) or adult failure to thrive syndrome; and for better ergonomic function (athletic ability and injury risk).

With regard to bone health, toxic metals intercalate in bone matrix, decreasing bone strength and falsely elevating apparent bone density. Further, many pollutants adjust pH downward, away from homeostasis and into cellular metabolic acidosis. As a consequence bone is dissolved to buffer and maintain serum acid–alkaline balance even at great metabolic cost to cells and body structures.

With regard to metabolic balance and weight management (obesity, leptin deficiency), TMs and POPs exacerbate the metabolic syndrome (syndrome X,

insulin resistance). This is discussed in more detail in Chapter 14. Since most POPs are fat soluble (lipophilic), as one loses fat weight, toxins are released into the circulation. Increased toxin burden and inflammatory markers have been measured in clinically important amounts. The interaction (synergies) of these toxicants is largely unstudied.

With regard to fibromyalgia and myofascial pain syndromes, rhabdomyolosis (often induced by medications such as HMG-CoA reductase inhibitors or "statins") and polymyalgica rheumatica, CFIDS and adult failure to thrive syndrome — can be induced or exacerbated by TM excess, POPs. TMs and POPs are among nature's mimics in that they can bring to substantially greater intensity a wide variety of clinical conditions. This has been well demonstrated in "metal fume fever" in arc welders. Mitochondrial destruction leads to cell apoptosis.

With regard to ergonomics, ergogenics, and sports medicine, peak performance is decreased when muscle mitochondria are damaged or intoxicated (metabolically uncoupled). This makes the physical body more susceptible to repetitive motion injury or pain from a less than ideal office chair to sit in during the workday. This antiergonomic results links commonly with an antiergogenic effect. Some sports may even lead to increased toxicity when protective antioxidants and buffering minerals are insufficient to respond to the exercise challenge. An example is lead exposure and bioaccumulation in Motocross racers. In other cases, the artist or the draftsman, the computer programmer or the gardener get exposed to chemicals that inhibit muscle repair.

Our established presumption of safety deserves to give way to a prudent cautionary principle as is now being evolved in Europe and the Pacific Rim. This means that the burden of proving safety is with the innovator. This is in contrast to our current presumption of safety and after-market surveillance to identify risks or toxicities. The potency, prevalence, and predictable interactions of modern synthetics/toxicant candidates, based on what we now know, has outstripped the ability of after-market surveillance to adequately protect public health and safety in a timely and cost-effective manner.

The informed clinician now remains the patient's advocate and safety net. As has often been said, first of all we must do no harm and, second, think of nutrition and detoxification as first-line comprehensive care fundamentals of practice.

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