Triad 4: Stacking with Triad 1
The Role of Environmental Pollutants in Disrupting Thyroid-Adrenal-Pancreas Relationships
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Module XX-B
Environmental Toxins

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Toxic Exposure

• According to the EPA, more than 4 billion pounds of chemicals were released into the ground in the year 2000, threatening the natural ground water sources.

• The average American unknowingly eats about 124 pounds of additives a year.

• Each year over 2.5 billion pounds of pesticides are dumped on crop lands, forests, lawns, and fields.

Exposure To Toxins Is Increased By

• Eating a diet high in processed foods and fat
• Drinking tap water
• Excessive consumption of caffeine containing beverages
• Excessive alcohol consumption
• Tobacco use
• Chronic use of medication
Exposure To Toxins Is Increased By (Cont.)

• Lack of exercise
• Liver dysfunction
• Kidney problems
• Intestinal dysfunction
• Occupational exposure
• Using pesticides, paint, and other toxic substances without adequate protective gear
• Living or working near areas of high vehicle traffic or industrial plants
Sources of Environmental Toxins

• The large chemical load on the environment is due to many years of chemical exposure from food, water, and contaminated air.

• The EPA since 1976 has conducted a study called the National Human Adipose Tissue Survey (NHATS).
Sources of Environmental Toxins (Cont.)

• In 1982 the EPA expanded its list to look for 54 environmental chemical toxins.

• Five chemicals were present in all of the samples.
  – Octachlorodibenzo-p-dioxin (OCDD)
  – Styrene
  – 1,4, dichlorobenzene
  – Xylene
  – Ethylphenol
    • Ibid., EPA
Sources of Environmental Toxins (Cont.)

- Nine other chemicals were found in more than 90% of the samples.
  - Benzene
  - Toluene
  - Chlorobenzene
  - Ethylbenzene
  - Dichlorodiphenyldichloroethylene (DDE)
  - Three dioxins
  - One furan
    - Ibid., EPA.
Sources of Environmental Toxins (Cont.)

• Also found in the study in greater than 80%  
  – Polychlorinated biphenyl (PCB)  
  – Beta-benzene hexachloride (BHC)  
  • Ibid., EPA.
Sources of Environmental Toxins (Cont.)

- A study from the CDC showed that cadmium, cesium, cobalt, lead, mercury, and thallium were present in almost all of the samples that they took which were from healthy people and had no known exposure to chemicals besides the environment.

Sources of Environmental Toxins (Cont.)

• The load of xenobiotics has also been examined.
• This study tested more compounds in each person than any previous study.
• It tested for 210 xenobiotics and found 167.
• The average number was 91.
  – Houlihan, J., et al., “Body burden, the pollution in people,”
Sources of Environmental Toxins (Cont.)

• Studies looking at chemical residues on foods have not found any foods chemical free.

• Foods with the highest level of DDE
  – Fresh or frozen spinach
  – Butter
  – Collards
  – Pork sausage
  – Lamb chops
  – Canned spinach
Reference

Sources of Environmental Toxins

• DDT and DDE were banned in the U.S. in 1972. Some of the high levels may be due to residual pesticide and some may be contamination from food brought in from other countries.
Common Environmental Toxins

- Organohalogens are chemicals that are very persistent in the environment and in the human body.
- Major sources of organohalogens
  - Organochlorine pesticides e.g., DDT (dichlorodiphenyltrichloroethane)
  - Polychlorinated biphenyls (PCBs)
  - Polybrominated diphenyl ethers (PBDEs)
  - Plastic residues
  - Dioxins
  - Organic byproducts of water chlorination
Reference

Xenobiotics

• A xenobiotic is a chemical which found in an organism which is not usually produced or expected to be present in it.
• The term can also cover substances that are in higher concentrations than what they are usually found.
• The term also refers to toxins such as dioxins and polychlorinated biphenyls.
Mechanisms of Toxic Injury

- Xenobiotic-initiated injury usually affects three targets.
  - Alter, remove or impair the synthesis of specific molecules—e.g., glutathione
  - Alter structural entities—e.g., mitochondria
  - Create disturbances in cell signaling—e.g., cytokines
    - Ibid., Lyon.
Biotransformation

- Many metals, drugs, and xenobiotics undergo biotransformation before being excreted from the body.
- Biotransformation commonly involves phase I and phase II detoxification in the liver.
The Detoxification Process

• Detoxification is a process by which the body transforms toxins and medications into harmless molecules that can be eliminated.
• It takes place primarily in the liver and to a smaller degree in other tissues.
Detoxification Is Accomplished In Two Phases

- Phase I—Certain enzymes change toxins into intermediate compounds
- Phase II—Other enzymes convert the intermediate compounds created in Phase I into harmless molecules that are eliminated by the body.
Phase I

- Enzymes in the cytochrome P-450 system use oxygen to modify toxic compounds, medications, and steroid hormones.
- This is the first line of defense for the detoxification of all environmental toxins, medications, supplements including vitamins, as well as many waste products that the body produces.
FIGURE 104-2
Phase 1 detoxification. P-450, cytochrome P-450.

Phase 1 Detoxification

Alcohol  Environmental Toxins  Drugs

P-450 System

~100 Enzymes

Free Radicals

Neutralized Toxin

Fat Soluble

Antioxidants (Glutathione)

Cleared
Reference

Phase I (Cont.)

- Occurs in the liver and usually involved oxidation
- May also involve demethylation, hydroxylation, or dehalogenation
- If there is increased Phase I clearance without increased Phase II clearance, this can lead to the build up of intermediates that may be more toxic than the original substance.
- Decreased Phase I clearance will cause toxic accumulation in the body.
Phase I (Cont.)

- Adverse drug reactions can be due to decreased clearance of Phase I.
- Within the genetic makeup are variations called single nucleotide polymorphisms, (SNPs).
- SNPs code for a particular enzyme that can increase or decrease the activity of that enzyme.
- Therefore, SNPs may increase or decrease the clearance rate. Both can be toxic.
References

– Ibid., Lyon.
Phase I Detoxification Requires

- Niacin
- Magnesium
- Copper
- Zinc
- Vitamin C
- Vitamins B2, B3, B6, B12
- Folic acid
- Flavonoids
Phase II

• In this phase large water-soluble molecules are added to toxins, usually at the reactive site formed by Phase I reactions.
• After Phase II modifications, the body is able to eliminate the transformed toxins in the urine or the feces.
Phase 2 Detoxification

Conjugation

Neutralized Toxin

<table>
<thead>
<tr>
<th>Phase II System</th>
<th>Fat Soluble</th>
<th>Required Nutrients</th>
</tr>
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<tbody>
<tr>
<td>Glutathione</td>
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<td>Amino Acid</td>
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<td>Methylation</td>
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<td>Glucuronidation</td>
<td></td>
<td>Glucuronic Acid</td>
</tr>
</tbody>
</table>

Toxin Prepared for Excretion

Water Soluble

Bile/Intestines → Urine/Kidneys

Reference

– Ibid., Fortney.
Phase II Detoxification Has Six Phases

- Glutathione conjugation
- Amino acid conjugation
- Methylation
- Sulfation
- Acetylation
- Glucuronidation
Glutathione Conjugation

• Glutathione is the strongest antioxidant that the body makes
• Requires glutathione and B6
• Conjugates with organic xenobiotics and heavy metals to eliminate them from the body
• Makes toxic substances more water soluble and allows them to be excreted via the bile or kidney.
Glutathione Conjugation (Cont.)

• If mercury accumulates in the hepatocytes, the excretion of mercury and other toxic substances is decreased.
Glutathione Conjugation (Cont.)

• Supplementing with alpha lipoic acid increases the level of intracellular glutathione if there is adequate sulfur amino acid intake present.
  – Ibid., Lyons.
Glutathione Conjugation (Cont.)

• Undenatured whey protein which is rich in glutathione precursors can increase cellular plasma glutathione.
  – Ibid., Lyon.
Amino Acid Conjugation

- Requires glycine, taurine, and glutamine
Methylation

• Needed for many reactions in the body
• Requires folic acid, choline, methionine, trimethylglycine, s-adenosylmethionine (SAMe)
Sulfation

- Requires cysteine, methionine, and molybdenum
Acetylation

• Requires acetyl CoA
Glucuronidation

• Requires glucuronic acid
References

Upregulation of Phase II

- Cruciferous vegetables significantly increase phase 2 enzyme activity.
  - Ibid., Lyon.
Antioxidants and Liver Detoxification

• Antioxidants also play a major role in liver detoxification by decreasing oxidative stress which results from phase I activity and preventing glutathione consumption by ROS.
  – Milk thistle
  – Curcumin
  – Green tea
    • Ibid. Lyon.
References


Toxic Response

• Nutritional and environmental factors also can modify a patient's susceptibility to environmental toxins.

• These factors for detoxification may be very modifiable when it comes to nutrition, environment, and lifestyle factors.

— Ibid., Lyon.
Toxic Response (Cont.)

• High carbohydrate diets downregulate P450 system which may decrease the reduction in the metabolism of drugs and hormones.
Other Nutritional Factors and Detoxification

- Intestinal dysbiosis inhibits the P450 system.

- Supplementing with probiotics reduces the effects of bacterial endotoxins on the liver along with decreases gut permeability.
• Some dietary fibers enhance the activity of both phase I and phase II.
Other Nutritional Factors and Detoxification (Cont.)

• Fiber also decreases stool transit time which aids in the sequestration of conjugated xenobiotics and endobiotics located in the bile and reduces the amount of bacterial deconjugating enzymes in the stool.

• All of these reduce the recycling of xenobiotics and endobiotics throughout the enterohepatic circulation.
References

– Ibid., Lyon.


Exercise and Detoxification

- Exercise, along with adequate calories and protein, has been shown to increase detoxification.
- Exercise has also been shown to increase antioxidant enzymes.
- Exercise also increases reduced glutathione.
  – Ibid., Lyon.
References


Exercise and Detoxification

- Exercise also mobilizes extracellular fluid and lymph where xenobiotics may tend to accumulate after being released from the cells.
- Sweating also increases the detox mechanisms of the liver.
- Exercise also aids in the elimination of organic and metallic toxicants.
  - Ibid., Lyon.
References


Exercise and Detoxification

• Exercise may be helpful to accelerate the movement of mercury from the extracellular fluid through the lymph and into the bloodstream.
  – Ibid, Lyon.

• Hyperthermic therapy with a sauna may also help mobilize mercury.
  – Ibid., Lovejoy.
Toxic Response

• There are a significant number of genetic polymorphisms that determine the patient's ability to detoxify.
  – This subject will be covered fully in module XXII: Genomics and Proteonomics.

• Some toxins act in a simple manner, where others are multifunctional with a large pattern of induction and inhibition, or both, of several phase I and phase II enzyme systems.
Summary of Phase I and Phase II

- Phase I and Phase II enzymes are the engines that run the detoxification process.
- They are fueled by vitamins, minerals, and other key food components.
- Therefore, if one is undernourished or lacks key vitamins or nutrients, they may not be able to adequately detoxify.
Toxic Exposure History

• Community
  – City and neighborhood air quality, noise, electromagnetic fields

• Home
  – Home heating and ventilation, cleaning chemicals, pesticides, paints, carpets, building materials, molds, allergens, water

• Hobbies
  – Toxic chemicals, paints, solvents, metal fumes
    • Ibid., Lyon.
Toxic Exposure History (Cont.)

• Occupation
  – Workplace air quality, toxic chemicals

• Personal habits
  – Smoking, drinking, drug use, sun exposure exercise, stress management

• Diet
  – Overall quality of diet, amount of food consumed, organic or not, fast foods, snacks, deep-fried foods, fish or seafood, meat or not, food allergies, or intolerances, leaky gut syndrome, abnormal gut flora
  • Ibid., Lyon.
Toxic Exposure History (Cont.)

- Drugs
  - Prescription, OTC, recreational

- Dental
  - Amalgams placed and removed, extractions, root canals

- Development
  - Mother’s pregnancy and exposures, childhood exposures
    - Ibid., Lyon.
Symptoms of Dysfunctional Detoxification

• The symptoms of a dysfunction of the body’s ability to detoxify may be vague and not specific.

• It is important to rule out a serious medical condition causing that may cause these symptoms as well.
Symptoms of Dysfunctional Detoxification (Cont.)

- Fatigue with sleep disruption and brain fog
- Mood disturbance, especially depression, anxiety, fear, and anger
- Muscle aches and joint pain
- Sinus congestion, dark circles under the eyes, and postnasal drip
- Headaches with neck and shoulder pain
- Bloating and gas
- Irritable bowel, foul-smelling stools and dark urine
- Weight changes and loss of muscle tone

— Ibid., Fortney.
Symptoms of Dysfunctional Detoxification (Cont.)

- Heartburn
- Infertility and low libido
- Premature aging and weakness
- Fluid retention and excess weight
- Rash and canker sores
- Bad breath
- Body odor
- Recurrent colds and persistent infections
- Recurrent colds and persistent infections

— Ibid., Fortney.
Detoxification Testing

- Detoxification of Phase I and Phase II can be measured.
- SNPs can be evaluated.
  - For example, CYP3A4, affects an enzyme that the body uses to detoxify over 50% of all drugs.
  - These medications include many antidepressants, steroid hormones, and cholesterol lowering medications.
Heavy Metal Intoxication

- Toxic metals like cadmium, mercury, lead, aluminum, and nickel poison the intracellular enzymatic systems that keep the body working optimally.
- They are not biodegradable.
- They have a high affinity for sulfhydryl (SH) groups and consequently displace essential metals like zinc and selenium from the active sites of proteins.
Heavy Metal Intoxication (Cont.)

• Enzymatic dysfunction can occur (e.g., GSH-Px) with suppression of the following
  – Protein synthesis
  – Inhibition of mitochondrial enzymes
  – Production of free radicals
Heavy Metal Intoxication (Cont.)

• Heavy metal intoxication also
  – Destroys the architecture of cell membranes and mitochondria which may result in the following
    • Increase in DNA damage and cancer
    • Neuron decay and cognitive decline
    • Mitochondrial decay with accelerated aging and degenerative diseases
      – Ibid., Grober.
Sources of Heavy Metals

- Vehicle exhaust fumes (lead)
- Lead piping
- Aluminum-based antacids
- Aluminum pots and pans
- Sachets of instant coffee
- Canned food
- Fish
- Mussels
- Shellfish
- Pesticides
- Dental amalgams (mercury)
- Cigarettes (cadmium)
  - Ibid., Grober.
Toxicity of Heavy Metals

• Furthermore, metals that are not nutrient may bind to molecular areas where they are involved in inappropriate catalytic activities including the generation of free radicals.
  – Ibid., Lyons.
Reference

Toxins and the Thyroid Gland
PCBs, Dioxins, Furans

- Are all highly persistent, lipophilic, organochlorine pollutants.
- About 90% of exposure from intake—mainly meat, fish, dairy
- Breast feeding accounts for 12%-14% of exposure
- Can affect the ability to convert T4 to T3
Reference

Polybrominated Biphenyls (PBBs)

• An increase in rate of primary hypothyroidism has been shown in a group of workers exposed to PBBs.
TCDD

• In another study, elevated levels of free T4 index were seen in workers with exposed to the highest body burdens of 2,3,7,8-TCDD which is a dioxin-like compound.
Polychlorinated Biphenyls

• Hydroxylated metabolites of various polychlorinated biphenyls compete with endogenous ligands for non-receptor transport proteins

• Binds transthyretin which disrupts thyroid homeostasis
  – Ibid., Luderer.
Thiocyanates and Perchlorates

• Thiocyanates and perchlorates inhibit thyroid synthesis by blocking iodine uptake into the thyroid gland.
  – Ibid., Luderer.

• Perchlorate contamination of drinking water
  – Reduced T4
  – Increased TSH in newborns
Lithium

• Suppresses thyroid hormone release
• Inhibits cyclic AMP-mediated effects of TSH
  – Ibid., Luderer.
Inhibit Organification of Iodine

• Cobalt
• Cyclic organic compounds
  – Substituted phenols
    • Ibid., Luderer.
Thiocyanate

• Chronic cyanide exposure seen in electroplating workers caused an accumulation of thiocyanate.
  – Decreases free T3
  – Decreases free T4
  – Elevates TSH

Compounds Associated with Hypothyroidism

• Lead
• Carbon disulfide
• Polybrominated biphenyls (PBBs)
• Polychlorinated biphenyls (PCBs)
  – Enhances T4 glucuronidation which increases excretion of thyroid hormone
  – Binds to serum thyroid hormone transport proteins
• Dioxins
• DDT
  – Enhances T4 glucuronidation which increases excretion of thyroid hormone
Compounds Associated with Hypothyroidism (Cont.)

- Furans
  - Ibid., Luderer.
- Chloroacetanilides (herbicides)
  - Enhances T4 glucuronidation which increases excretion of thyroid hormone
- Methoxychlor (organochlorine insecticide)
  - Inhibition of peripheral T4 deiodination
References

– Ibid., Luderer.


PBBs

• Accidental exposure to PBBs in Michigan in farming communities in the 1970s revealed an increase in non-goitrogenic thyroid dysfunction.
  – Had increase in thyroid antibodies
PCBs

• Study people exposed to PCBs (‘Yusho rice oil’) contaminated with PCBs 16 years earlier.
  – Elevated free T3
  – Elevated free T4
  – TSH normal
  – Normal thyroid antibodies
PCBs (Cont.)

• Human studies are conflicting.
• Recent study of employees in a former PCB plant showed an increase in thyroid volume and increase in positive antibodies.
• No difference in free T4 or TSH was seen.
PCBs (Cont.)

• Animal studies there is no conflicting data.
• Studies show a decrease of free T4 by PCBs.
  – Ibid., Cheek.
PCBs (Cont.)

• Study on children revealed a negative relationship between serum PCB levels and serum levels of free T3.

• The same study revealed a positive correlation with TSH.

PCBs (Cont.)

• Animal study showed that maternal PCB exposure caused lower T4 and T3 levels in fetal brains.
• Motor deficits and impaired learning were also recognized.
PCBs and Dioxins

• Study showed a positive correlation between breast milk PCBs and dioxins and neonatal TSH, but there was no correlation with TSH.
Dioxins

• Study with people exposure to TCDD showed a positive correlation with T4 and free T4 index, but not TSH or thyroid disease.

• This study was done on workers that were exposed to TCDD 15 years earlier.
  • Ibid., Luderer.
Another study showed an association between serum TCDD concentration and T4 but not TSH in chemical workers.

Dioxins (Cont.)

• Yet another study—this one done on Vietnam veterans exposed to TCDD in Agent Orange.
• Free T4 index did not show any change.
  – Ibid., Calvert.
Cobalt

• Studies were done on women that were exposed to cobalt-based paints.
  – Dose-related elevation of T4
  – Dose-related elevation of free T4
  – Dose-related elevation of the T4-to-T3 ratio.
  – No change in TSH or pituitary function was seen

• Results suggest reduced peripheral deiodination of T4 to T3.
References


Other Chemicals

• Thyroid dysfunction has been seen also related to the following chemicals
  – Organophosphates
  – Carbamates
  – Organochlorines
  – Fungicides
  – Food colorants
  – Mercury

Mercury

• Is one of the most toxic substances
• When mercury enters the cell it becomes covalently bound to the sulfhydryl groups found in glutathione.
• Mercury binds to a less amount to
  – Cysteine
  – Biotin
  – Lipoic acid
  – Coenzyme A
    • Ibid., Lyon.
Mercury (Cont.)

• Causes a reduction in glutathione production and glutathione peroxidase activity
• Glutathione is very important in liver detoxification.
• Also causes free radical production
Outcomes

• No long-term studies have been done to look at the potential reversibility of thyroid dysfunction.

• Lead workers removed from exposure appear to have an improvement of depressed T4 levels.
Toxins and The Thyroid

• The following toxins decrease T4 and T3 and increase TSH since they are competitive inhibitors of iodine transport.
  – Thiocyanates
  – Perchlorates
  – Pertechnetates
Toxins and The Thyroid (Cont.)

- The following are compounds that inhibit thyroid peroxidase which is needed in the second step of thyroid synthesis.
  - Thiourea
  - Thiouracil
  - Propylthiouracil
  - Carbimazole
  - Aniline derivatives
  - Para-aminobenzoic acid
  - Substituted phenols like resorcinol
  - Phloroglucinol
    - Ibid., Crinnon.
Toxins and The Thyroid (Cont.)

• Iodine and lithium block thyroid hormone release from the thyroid.
  – Ibid., Crinnion.
Toxins and The Thyroid (Cont.)

• Low levels of thyroid hormone have been seen with exposure to the following
  – Lead
    • Due to problem with hypothalamus
  – Carbon disulfide
  – PBBs
    • Ibid., Crinnion.
Lead

• Mild depression in thyroid function has been seen in adult patients chronically and heavily exposed to lead without substantial effects on lower levels.
  – Ibid., Luderer.
Reference

Lead Toxicity

- Study showed that the bones of humans today contain lead at 1,000 x greater than humans of the pre-industrial era.
Toxins and The Thyroid (Cont.)

• These substances are suggested to adversely affect thyroid function.
  – Organophosphates
  – Carbamates
  – OCCs
  – Fungicides
  – Food coloring
  – PCBs
  – Mercury (animal studies)
    • Ibid., Crinnion.
Inducers of hepatic cytochrome P450 cause an alteration in thyroid structure and decrease in T4

- Phenobarbital
- Benzodiazepines
- Calcium channel blockers
- Steroids
- Retinoids
- Chlorinated hydrocarbons
- Polyhalogenated biphenyls
Reference


– Ibid., Crinnion.
Mitochondrial Disruptions

• Toxic metals and many xenobiotics also may target the membranes of the mitochondria.
• This can result in alterations in energy metabolism and subsequent thyroid function.
  – Ibid., Lyon.
Toxins and Adrenal Function
Toxins and Adrenal Function

• There are not many studies that look at toxins and adrenal function.
• The zonae reticularis and fasciculata are the main targets for xenobiotic chemicals.
• The adrenal cortex is predisposed to toxic affects due to adrenocortical cell storage of lipids which allows lipophilic compounds to accumulate.
Toxins and Adrenal Function (Cont.)

• The lipophilic compounds have enzymes including enzymes of the cytochrome P450 system that are capable of biotransforming xenobiotics.

• May cause increase or decrease in toxicity

• Most chemicals that affect adrenal function do so by altering steroidogenesis.

  – Ibid., Haschek.
PCBs

- Transformer repairmen were studied that were exposed to PCBs (former and current workers).
- Urinary 17-hydroxycortisone excretion was observed to be lower.
- Also, urinary 17-hydroxycortisone was negatively correlated with fat cell PCB concentration.
- Serum levels were not measured.
Toxins and Adrenal Function

- The lower urinary 17-hydrocortisone levels may be reflective of a suppressive effect of PCBs on adrenal glucocorticoid secretion or synthesis which would results in low serum glucocorticoid levels.
  - Ibid., Luderer.
Paraquat

• Is a herbicide
• Is an inhibitor of aldosterone synthesis
• Action similar to spironolactone and metyrapone
• A decrease in aldosterone was seen in animals
  – Ibid., Luderer.
Organophosphates

• Malathion and diazinon both organophosphates have been shown to interfere with adrenomedullary function.
  – Increases production of E and NE
  – Results in hyperglycemia
  – Glycogen deposition in the liver
  – Exhaustion of adrenal stores of these amines
Reference


– Ibid., Luderer.
Mirex, Toxaphene, and Dioxin

- All have been shown to cause suppression of glucocorticoid synthesis by the adrenals.
- Results in hypoglycemia that is reversible by cortisone.
Reference

– Ibid., Luderer.
1, 1, 1-trichloroethane

• 1,1,1-trichloroethane is a solvent.
• It suppresses plasma corticosterone and ACTH concentrations
• May have an effect on hypothalamic corticotropin-releasing hormone (CRH) in animals.
Testing for Toxins
Testing for Toxins

• History of exposure
• Extensive panels are now available to measure the level of organic toxins via blood, urine, or adipose biopsy.
  – PCBs
  – Organochlorine pesticides
  – PBDE fire retardants
  – Furans
  – Dioxins
Treatment
Treatment

• Avoid toxin

• Supplements to support detoxification and antioxidant protection

• Reducing body burden of xenobiotics
  – Ibid., Crinnion.
Avoid

• Solvents
• Paints
• Exhaust fumes
• Perfumes
• Hair sprays
• New furniture
• Carpeting and cabinetry
• Plastics
• Gas or oil heat
  – Ibid., Crinnion.
Things to Do

• Eat organic foods
• Use organic cleaners
• Use organic pesticides if pesticides are needed
• Drink purified water
• Use nature air purifiers
  – Charcoal or high-efficiency particulate air filters
  – Many plants in home
Plants That Clean The Air

• The following plants have been shown in a study done by NASA to clean the air.
  – Mass cane (Dracaena massangeana)
  – Pot mum (Chrysanthemum morifolium)
  – Gerbera daisy (Gerbera jamesonii)
  – Warnecki (Dracaena deremensis “Warnecki”)
  – Ficus (Ficus benjamina)
    • Ibid., Crinnion.
Reference

Nutritional Support

• Nutritional support for detoxification has been focused on two areas.
  – Cofactors for enzymatic biotransformation of xenobiotic compounds
  – Antioxidants
Effects of a Low-Protein Diet on Detoxification

- Decreased cytochrome P450 content of liver, secondary to decreased quantity of microsomal protein
- Decreased NADPH-cytochrome P450 (c) reductase
- Decreased cytochrome b5
- Decrease in hepatic GSH
- Increased liver UDP-glucurononlytransferase (phase 2)
  - Ibid., Crinnion.
Protein Deficiency

• An increase in chemical toxicity and drug toxicity have been seen with protein deficiency.

• Inadequate protein intake decreases the activity of liver mixed function oxidase (MF0) systems which can result in an increase ½ life of drugs and toxic chemicals. It may also increase drug action and toxicity.
  – Ibid., Crinnion.
Protein Deficiency (Cont.)

• The quality and quantity of protein can alter phase I and phase II detoxification of drugs.
• The toxicity of the following agents has been increased several fold by protein deficiency.
  – OCCs
  – Acetylcholinesterase inhibitors
  – Herbicides
  – Fungicides
    • Ibid., Crinnion.
Protein Deficiency (Cont.)

• Other items that suppress MFO activity
  – Methionine deficiency
    • Also affects selenium metabolism by making less selenium available for glutathione peroxidase biosynthesis
  – Cysteine deficiency
  – Folic acid deficiency
  – Choline deficiency
    • Ibid., Crinnion.
Avoid Sugar

• High sugar levels have been shown to reduce the clearance of some chemicals from the liver.
  – Ibid., Crinnion.
Vitamin E

- Stabilizes membranes and helps provide a good environment for the making and activity of membrane-associated enzymes that protect against damage due to toxins.
- Is an antioxidant.
- Helps prevent CCL4 hepatotoxicity.
- Pretreatment with vitamin E before exposure to ozone and nitrous oxide provides partial protection against toxicity.

— Ibid., Crinnion.
Vitamin A and Beta-Carotene

• Beta-carotene is needed for epithelial cell differentiation and regulation of membranes.
• Decreases singlet oxygen species
• Is necessary for normal estrogen cycle
• Protects against singlet oxygen-induced damage
  — Ibid., Crinnion.
Deficiency of Vitamin A

• Is associated with elevated binding of benzo(a)pyrene to tracheal epithelia
• Toxins that decrease vitamin A in liver which increases their toxic effect
  – Organophosphates
  – DDT
  – PCBs
    • Ibid., Crinnion.
Other Things That Lower Vitamin A

- Alcohol
- Coffee
- Cold weather
- Cortisone
- Diabetes
- Excessive iron
- Infections
- Laxatives
- Liver disease
- Mineral oil
- Nitrates
- Sugar
- Tobacco
- Vitamin D deficiency
- Zinc deficiency

– Ibid., Crinnion.
Thiamin

• Thiamin depletion can be due to the following
  – Excessive formaldehyde exposure
  – Alcohol (increases aldehydes)
  – Candida (increases aldehydes)

• The coenzyme of thiamin pyrophosphate (TPP) is needed to metabolize the aldehyde group as is magnesium.

• Also a coenzyme (TPP) for pyruvate DH and alpha-ketoglutarate DH
  – Ibid., Crinnion.
Thiamin (Cont.)

- Used in phase II pathways
- Needed to restore oxidized GSH
- Thiamin deficiency increases the toxicity of the following. They also can lead to lead to thiamine deficiency which further increases their toxicity.
  - PCBs
  - Dieldrin
  - Heptachlor
  - Aniline dyes
    - Ibid., Crinnion.
Riboflavin

• Component of the coenzymes in flavoprotein enzymes needed for oxidation/reduction reactions
• Liver microsomal flavoprotein reduced nicotinamide adenine dinucleotide phosphate (NADPH)-cytochrome reductase supplies reducing equivalents to cytochrome P450.
  — Ibid., Crinnion.
Riboflavin (Cont.)

• These are very important for the functioning of phase I biotransformation.
• Riboflavin helps destroy azo dyes in the liver by MFO which protects against azo dye-induced cancer.
• The GSH reductase pathways also use riboflavin. They work with superoxide dismutase to block the production of free radicals.
  — Ibid., Crinnion.
Niacin

• Nicotinamide is a part of NAD and NADP.
• Both of these are oxidized to NAD+ and NADP+ and are reduced to NADH and NADPH.
• Needed for phase I detoxification.
• Used in the deamination of amino acids, fatty acids, and beta-oxidation of fatty acids.
• Used in steroid formation and drug metabolism.
Pyridoxine

• Exposure to carbon disulfide, PCBs, and penicillamine all can disrupt the optimal function of vitamin B6 and chronic exposure can cause B6 deficiency.

• Chemically sensitive patients are commonly deficient in pyridoxine even if they are taking supplemental B6.

Pyridoxine (Cont.)

• Low levels of pyridoxine can cause low levels of taurine.

• If the patient’s taurine is low, extreme sensitivities to the following may may occur.
  – Chlorine
  – Chlorite (bleach)
  – Aldehydes
  – Alcohols
  – Solvents
  – Ammonia
    • Ibid., Crinnion.
Pyridoxine (Cont.)

• Deficiencies of pyridoxine may lead to a decreased ability to conjugate E and serotonin.
  – Ibid., Crinnion.
Vitamin C

• Is a cellular antioxidant
• Scavenges free radical superoxides and hydroxyl radicals
• Protects against the following toxicities
  – Phenol
  – Phenylqumotin
  – Carboxylic acid
  – Barbiturate toxicity
    • Ibid., Crinnion.
Vitamin C (Cont.)

• Also protects against
  – Ozone-reduced pulmonary edema
  – O2 toxicity
  – CCL4 toxicity
• Reduces the toxicity of the following
  – Pesticides
  – Heavy metals
  – Hydrocarbons
  – PCB
  – Acetaminophen
  • Ibid., Crinnion.
Vitamin C (Cont.)

- Increases MFO activity since there is decreased cytochrome P450 activity with vitamin C deficiency
- Increases the incorporation of iron into heme
- Prevents nitrosamine formation from nitrites in the GI tract
- Protects against lead and cadmium toxicity
  – Ibid., Crinnion.
Vitamin C (Cont.)

• Higher levels of vitamin C may help facilitate the breakdown of xenobiotics by liver MFO (mixed function oxidase).

• Also xenobiotics increase vitamin C excretion in the urine.
  – Ibid., Crinnion.
Iron

• Help is important for cytochrome P450 and hemoglobin since they are both heme containing.
• Aniline metabolism is very sensitive to low iron levels and increases susceptibility to lead toxicity.
  – Ibid., Crinnion.
Magnesium

• In a study done on chemically sensitive patients, low magnesium was found in 40%.
  – Ibid., Rea.

• Magnesium deficiency can lead to low
  – Cytochrome P450
  – NADPH cytochrome reductase
    • Both of these are needed for phase I detoxification
    • Magnesium supplementation reverse this process
  – Ibid., Crinnion.
Magnesium (Cont.)

• Magnesium deficiency can also lead to decreased hydroxylation of aniline and demethylation of aminopyrine.
  – Magnesium supplementation can reverse this process
  • Ibid., Crinnion.
Selenium

• GSH peroxidase helps to maintain the integrity of cellular and subcellular membranes and selenium is a component of GSH peroxidase.
• Selenium is also important for phase 2 xenobiotic conjugation.
• GSH peroxidase levels can also be increased by NAC and L-cysteine.
  – Ibid., Crinnion.
Selenium (Cont.)

• Decreases the toxicity of lead
• Increases biliary excretion of cadmium
• Increases biliary excretion of mercury
• Prevents cadmium-induced decrease of Cytochrome P450
• Low selenium levels increases the toxicity of several xenobiotics.
  – Ibid., Crinnion.
Zinc

• The metabolism and detoxification of xenobitoics is affected both by low and excessive levels of zinc.

• Low zinc levels decrease enzyme function

• Low zinc levels reduce GSH levels

• High zinc levels decrease cytochrome P450 levels

  – Crinnion.
Glutathione

- GSH
  - Needed for GSH conjugation in phase II
  - Needed to quench lipid peroxide molecules
- GSH levels can be increased by
  - Selenium
  - NAC
  - Vitamin A
  - Vitamin E
    - Ibid., Crinnion
Glutathione (Cont.)

- Milk thistle also can increase GSH levels
- Inhibits GSH depletion and lipid peroxidation after endrin exposure
  - Vitamin E
  - Vitamin C
  - Cysteine
Botanicals

• Used to treat chemical toxicity
  – Silybum marianum (milk thistle)
  – Curcuma longa (turmeric)
Depuration/Detoxification

• Depuration is the removal of impurities from the body.
• To methods of xenobiotic removal have been described in the literature.
  – Hubbard Purification Rundown
    • Exercise
    • High-temperature saunas
    • Increasing doses of niacin
    • Electrolyte replacement
    – Ibid., Crinnion.
References


Detoxification

• Two methods of xenobiotic removal have been described in the literature (cont.).
  – Fasting
    • Study on people poisoned by PBB-contaminated rice bran cooking oil in Taiwan
Crinnion Depuration Protocol

• Used to treat environmentally poisoned patients

• Developed by Walter Crinnion, ND
  – Used for 20 years
  – Outcome study for various problems treated with this protocol, 83% of patients rated their results as good or great.

• Crinnion, W., “Results of a decade of naturopathic treatment for environmental illness,” Jour Nat Med 1977; 7:21-8/
Crinnion Depuration Protocol (Cont.)

• Testing for chlorinated pesticides, PCBs, and solvents using the depuration protocol showed a reduction of body burden.

• Many had a complete clearance of PCBs from the serum.
  – Crinnion, W., unpublished data.
Crinnion Depuration Protocol

• Exercise daily using exercycle, rebounder, or brisk walking to start lipolysis and diaphoresis.

• Thermal Chamber
  – Up to three 60-minute “sauna” sessions with temperatures from 120F to 135F with cool-down periods in between
    • Not to be used in patients with CHD or arrhythmias
    • Glass bottle spring water and electrolyte replacement
    • Increases the rate of lipolysis in the adipose tissue which releases the lipophilic xenobitoics into the bloodstream
    • Substances in the subcu fat pads are mobilized through sweat, as well as into the blood
Crinnion Depuration Protocol (Cont.)

• Constitutional hydrotherapy
  – Use of alternating hot and cold towels with sine wave stimulation
    • Stimulates body self healing properties
    • Increases the amount of toxin-laden bile dumped from the liver into the intestines
  – Herbal therapy to increase choleretic and cholagogue action on the liver
    • Capsule of a combination of Chelidonium, Chionanthus, Taraxacum, Arctium lappa, Silybum marianum, and Urtica dioca
Crinnion Depuration Protocol (Cont.)

• Colonic irrigation
  – Gravity-fed machines are used to gently introduce triple-filtered water into the large intestines which provides a method for toxic bile and liver byproducts to leave the body
  – Chlorinated pesticides have been found in the effluent

• Constitutional homeopathy

• Counseling
  – Helps to eliminate emotional toxins
  – Helps to eliminate physical toxins
Crinnion Depuration Protocol (Cont.)

• Body therapies
  – Massage
  – Shiatsu
  – Craniosacral
  – Visceral, spinal, and joint adjustment
Crinnion Depuration Protocol (Cont.)

• Protocol is used daily for 4-8 weeks (5 times a week) with the assistance of their health care provider in the office.
• Therapies are then continued at home for one year.
  – Crinnion.
Treatment Overview of Crinnion Protocol for Environmental Toxins

• Avoidance of further chemical exposure through air, food, and water
• Nutrient support for transformation, elimination, and antioxidant pathways
• Depuration protocol
  – Ibid., Crinnion.
Nutritional Support

- Vitamin C: 6,000 to 12,000 mg/day
- Vitamin E: 400-1,200 units of D-alpha-tocopherol daily
- B complex: once daily
- Vitamin A: 25,000 to 50,000 units/day (unless patient is a smoker or at risk of pregnancy)
- NAC: up to 500 mg/day
- Selenium: 300-600 micrograms /day
Nutritional Support (Cont.)

• Silybum marianum (standardized): 100 mg BID to TID
• Adequate protein in diet with each meal
• Magnesium: 300 to 600 mg/day
• Psyllium husks powder: begin with 0.5 tsp in water nightly (to bind bile in the intestines)
Testing Methods

• Urine—most accurate
• Stool---more of a representation of exposure than actual toxic load
• Hair analysis---not viewed by many authors as accurate
Urine Testing

• The best available way to estimate the amount of toxic metals in the body is a urine test after the administration of a chelating agent.

• Studies have been done since the 1970s on provocation testing for toxic metals determined this was an accurate testing method.
References


References (Cont.)


Measurement of Toxic Metal Levels

• 6-hour or 24-hour urine challenge test.
• See handout.
Provocation Chelating Agents

• Most commonly used provocation chelating agents for toxic metal screening currently are
  – Ca-Na2-EDTA
  – DMPA
  – DMSA
Provocation Chelating Agents (Cont.)

• Since most mercury is excreted through the stool and urine as a glutathione conjugate, patients who have had a toxic burden with mercury for a long time (and therefore depleted glutathione production) may NOT show an elevated level of mercury if a challenge test is NOT done.
Ca-Na2-EDTA

• Has been approved by the FDA and used IV for years as the provoking item and therapeutic treatment of choice for patients exposed to lead.

• Can also increase excretion of iron, copper, nickel, cadmium, and manganese.
Ca-Na2-EDTA (Cont.)

• Will also chelate out zinc if not carefully used
• Check creatinine and GFR before using since Ca-Na2-EDTA moved metals are cleared through the kidney.
• Should attend chelation course before using
• Not as effective chelator of mercury
  – Ibid., Rozema.
DMPS

• DMPS (Dimaval, -(R,S)-2,3-dimercapto-propane-1 sulfonate) is a dithiol.

• Most productive agent to mobilize mercury
DMPS (Cont.)

• Study done on college students
• Subjects with and without mercury fillings were given 300 mg DMPS (PO) and urine was collected.
• A positive correlation was seen between the amount of mercury excreted after the DMPS challenge and amalgam surface area.
  – Ibid., Quig.
Reference

DMPS

• Another study also support the value of using DMPS as a provoking agent in patients exposed to mercury vapors.
• Also concluded that a post-DMPS urinary mercury levels were better indicators of exposure and retention than unprovoked urinary mercury levels.
  – Ibid. Quig.
Reference

DMPS

• The pharmacokinetics of DMPS have been well defined.
  – Ibid., Aposhian.
DMPS (Cont.)

• Efficacy of DMPS as a chelating agents has been found for the following
  – Mercury
  – Arsenic
  – Lead (pediatric)
References


DMPS

• Not approved by the FDA
• Is registered in Germany with the German Drug Regulatory Authorities and is available without a prescription
• In the US, DMPS is available by prescription only from compounding pharmacies for oral, IV, and IM use.
• Suggested to take chelation course and use a consent form since it is not FDA approved in US
DMPS (Cont.)

• Side effects are rare but could include
  – Nausea
  – Weakness
  – Vertigo
  – Chills
  – Fever
  – Cutaneous reactions/itching/erythema multiforme
  – Elevations of transaminases
References

– Ibid., Quig.
– Ibid., Aposhian.
– Ibid., Aposhian.
– Ibid., Wax.
– Ibid., Heyltex.
DMPS Provocation Protocol

• PO detailed provocation protocol can be found
  – Ibid., Aposhian.

• IV detailed provocation protocol – see handout.
Common DMPS Provocation Protocol

• Patient is instructed to fast overnight and to collect a urine specimen.
• In the am, fasting, after the bladder is emptied, the patient is given 300 mg (or 10 mg/kg) DMPS PO.
• All the urine is collected for the next 6 hours
• A light meal can be eaten in fours hours that does not contain sea food.
• Encourage fluid intake
References

– Ibid., Quig.
– Ibid., Aposhian.
DMPS Effective Chelator of These

- Bismuth
- Mercury (organic and inorganic)
- Copper
- Lead
- Arsenic
- Antimony
- Cadmium

- Nickel
- Tin
- Tungsten
- Thallium
- Gold

– Ibid., Quig
DMPS is NOT an Effective Chelator

• Aluminum
• Uranium
  – Ibid., Quig.
DMPS Chelation

• Mercury is the metal that is predominantly excreted after DMPS chelation
• Copper levels will be elevated after chelation and this is normal.
• As mercury levels go down post chelation, then urinary levels may rise of lead, cadmium, and tin with subsequent challenges.

– Ibid., Quid.
DMPS Chelation (Cont.)

• The pattern may shift of different metals excreted.
  – This is based on a combination of affinities of DMPS for the different metals.
  – This is based on the mass competition for metal binding sites.
    • Ibid., Quid.
DMPS Chelation (Cont.)

• There are no established guidelines for the interpretation of the results of a DMPS challenge test.

• Studies have been done to give a range that may be since in your practice.
  – Ibid., Heyltex.
DMPS Chelation (Cont.)

- Conclusions about toxicity cannot be made from the DMPS test by itself.
  - Symptoms
  - History
  - Physical examination
- Results of the DMPS challenge test can be used to compare later challenge tests to evaluate how the treatment is working.
  - Ibid., Quig.
DMPS Chelation (Cont.)

• DMPS does not provide direct information as to the level of mercury in the CNS.
• GFR must be evaluated before beginning chelation therapy.
• Metals chelated out are excreted mostly from the kidney and a small amount from the liver and biliary/fecal system.
  – Ibid., Aposhian.
DMSA

• DMSA (meso-2,3-dimercaptosuccinic acid) is a dithiol like DMPS.
• Widely used for provocating test
• Used as a chelating agent for the following
  – Lead
  – Mercury
  – Arsenic
  – Antimony
References

– Ibid., Quig.
DMSA

• Approved by the FDA for lead intoxication and is the method of choice for children and adults.
• Used PO
• About 20% of orally given DMSA is available after one dose.
  – Ibid., Quig.
DMSA (Cont.)

• In animal studies DMSA has been shown to effectively remove lead and mercury from the brain.
References


DMSA

• DMSA is usually well tolerated
• Periodic testing of liver enzymes should be done during the course of prolonged treatment
• Possible mild side effects of DMSA
  – GI bloating and gas
  – Occasional loose stools
  – Skin rash
    • Ibid., Quig.
DMSA (Cont.)

• There are several reviews of DMSA protocols.
  – Ibid., Crinnion.
  – Ibid., Aposhian.
  – Ibid., Aposhian.
  – Ibid., Quig.
DMSA (Cont.)

• There is a significant difference between DMSA protocols for acute lead poisoning and chronic low level lead retention.
  – Ibid., Physicians Desk Reference.
  – Ibid., Quig.
Protocol for DMSA Provocation Testing

• There are various protocols.
  – Ibid., Crinnion.

• Common DMSA provocation protocol
  – 10 mg/kg PO TID for three consecutive days
  – 24 hour urine collection on day 3
Protocol for DMSA Provocation Testing (Cont.)

• Most common and convenient protocol
  – Single dose of DMSA PO (30 mg/kg) on an empty stomach and then collect the urine for 6 hours
    • Ibid., Quig.
  – Alternative is DMSA 1,000 mg as a single dose and collect urine for 6 hours
    • LaValle, J., Module VII.
Reference

– Ibid., Quig.
Protocol for DMSA Provocation Testing

• Some authors suggest if using the single day provocation test that the DMSA leaves behind some metals that have been mobilized but not excreted so consider giving DMSA 10 mg/kg TID for the next two days to clean up the metals that are left behind.
  – Ibid., Quid.

• Urine will have a transiently foul, sulfurous odor from the use of DMSA. Let the patient know.
Treatment of Toxic Metals

• Chelation
  – Suggested best agents
    • Arsenic: DMPS excellent
    • Lead: Ca-Na2-EDTA excellent, DMSA and DMPS good
    • Inorganic mercury: DMSA or DMPS excellent
    • Organic mercury: DMSA or DMPS excellent
    • Tin: DMSA or DMPS good
    • Nickel: Ca-Na2-EDTA good
      – Ibid., Quig.
Toxic Metals as Chemical Competitors

- Toxic metals can act as “chemical competitors” with trace metals.
  - Cadmium competes with zinc
  - Lead competes with calcium
  - Mercury competes with selenium
    - Ibid., Lyon.
Toxic Metals as Chemical Competitors (Cont.)

• This may result in high levels of nutritional depletion of competitive metals.
• May also result in inhibition (or overactivation) of metal-dependent systems such as enzymes.
  – Ibid., Lyon.
Micronutrients to Treat Toxic Metal Exposure

- Selenium: AM (4 weeks) 200-300 ug and long-term 100-300 ug
- Zinc: Evening (4 weeks) 25-50 mg and long-term 15-25 mg
- Alpha lipoic acid: 600-1,200 mg (may affect thyroid function)
- Vitamin C: 500-3,000 mg
- L-Glutathione: IV 600 mg 2-3x/week x 6 weeks
- NAC: 200-600 mg
- Vitamin E: 200-500 IU
Micronutrients To Treat Toxic Metal Exposure (Cont.)

- Coenzyme Q-10: 60-200 mg
- Vitamin B complex
- Folic acid: 400-1,000 ug
- B12: 1,000-2,000 ug methylcobalamin
- Taurine: 500-2,000 mg
- Magnesium: 300-600 mg
- Calcium 600-1,000 mg
  – Ibid., Gorber.
Nutrition and Toxic Metal Detox

- Nutrition status has a great influence on absorption, retention, toxicity, and excretion of toxic metals.
  - Ibid., Lyon.
Nutrition and Toxic Metal Detox (Cont.)

• Examples
  – Absorption of lead and cadmium are increased if iron or calcium levels are low (also iron deficiency can lead to increased intestinal permeability)
  – Low levels of some minerals leads to increased retention of toxic metals.
    • Calcium deficiency increases both lead and cadmium body burden
    • Selenium deficiency increases mercury retention
      – Ibid., Lyon.
Other Lifestyle Modifiers of Toxins

• Moderately high-protein diets up regulate the cytochrome P450 system which decreases the patient’s susceptibility to pesticides and other xenobiotics.

• Low protein diets increase pesticide toxicity because they down regulate cytochrome P450.
  – Ibid., Lyon.
Other Lifestyle Modifiers of Toxins (Cont.)

- Cigarette smoking not only increases oxidative stress but also biotransforms some xenobiotics into potent cancer causing agents.
  - Ibid., Lyon.
Other Lifestyle Modifiers of Toxins (Cont.)

• The following also help detoxify the body
  – Onions and garlic
  – Cruciferous vegetables
  – Chlorophyll
  – Terpenoids
    • Citrus
    • Ginkgo biloba
    • Menthol
    • Camphor
Other Lifestyle Modifiers of Toxins (Cont.)

• The following also help detoxify the body (cont.)
  – Bioflavonoids
    • Citrus
    • Pine bark
    • Grape seed
    • Green tea
      – Ibid., Lyon.
The Detoxification Lifestyle

• The mnemonic **A NERD** helps the patient remember how to lead a detoxification lifestyle.
  – Avoid exposure
  – Nutrition
  – Exercise
  – Rest
  – Detoxification
    • Ibid., Lyon.