Module 6 * FMDT 551A

The Physiology and Biochemistry of Biotransformation/Detoxification (The Phases of Detoxification)

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Physiology and Biochemistry of Biotransformation and Detoxification

The origin of toxins that are present in our bodies comes from an array of sources. These sources include environmental exposure (exogenous sources); such as in the air we breathe, the food we eat, the water we drink, and medications; and the endogenous sources such as; the products produced by digestion, energy metabolism, tissue regeneration, and end products from the metabolism of hormones, bacterial by-products and other complex molecules.

Detoxification is the process of transforming and removing potentially harmful products from the body\(^1\). The detoxification process has its own energy, nutrient and regulatory requirements\(^1\). The process of transforming toxins into a form suitable for excretion is called biotransformation. Biotransformation is the sum of all chemical processes of the body that modify endogenous or exogenous chemicals.

Biotransformation is not only affected by the type of toxicants, but also by the uniqueness of the individual. Individual factors that affects biotransformation include; age, sex, body composition, pre-existing pathology, concomitant disease, nutritional status, genetic predisposition, diet, environmental factors (home environment and occupational factors), medications, and enzyme induction and enzyme inhibition. Enzymes for biotransformation reactions are found in many tissues of the body with the liver being the primary source. The other tissues include the kidneys, the lungs, the intestines and the skin. Biotransformation of a toxin occurs in several steps.

Although it is the largest organ of the human body, skin is often not considered in discussions of drug metabolism. However, there is growing evidence that most common drug-metabolizing enzymes are expressed in the skin. Evidence for expression of cytochromes P450, flavin monooxygenases, glutathione-S-transferases, N-acetyltransferases, and sulfotransferases in human skin and skin cells are presented. Additional discussion is focused on the evidence of actual metabolism of drugs.\(^2\)

[Xenobiotic is defined as a chemical or molecule that is foreign to the biological system. These chemicals and molecules can originate from the environment, or from food and metabolic by-products.]
There is a significant amount of genetic variation in detoxification and biotransformation function; therefore, defining genetic polymorphism is paramount.

DNA does not directly exert its influence on cells, but merely contains sequences of nucleotides known as *genes* at that serve as *templates* for the production of another nucleic acid known as RNA. The process of reading DNA and writing the information as RNA is termed transcription. The RNA serves as a messenger from the nucleus to the cytoplasm. In the cytoplasm, the RNA is read, and the information is written down as protein. The production of proteins from RNA is termed *translation*.

The overall process looks like this:  

\[
\text{DNA} \rightarrow \text{RNA} \rightarrow \text{protein}
\]

This unidirectional flow equation represents the Central Dogma (fundamental law) of molecular biology. This is the mechanism whereby inherited information is used to create actual objects, namely enzymes and structural proteins. An exception to the Central Dogma is that certain viruses (retroviruses) make DNA from RNA using the enzyme reverse transcriptase.

The genome is the entirety of an organism’s hereditary information. Over 99 percent of the human genome is identical in all humans. It is the other 1 percent that represents the broad variations in human traits, abilities and risk of disease. The gene is the basic unit of inheritance. Genes hold the information to build and maintain the organism’s cells and pass genetic traits to the offspring. Genes are passed from parents to offspring and contain the information needed to specify traits. Genes are arranged, one after another, on the chromosomes. A chromosome is an organized package of DNA found in the nucleus of the cell. Humans have 23 pairs of chromosomes. Each parent contributes one chromosome to each pair so that the offspring get half of their chromosomes from their mother and half from their father. A chromosome contains a single, long DNA molecule, only a portion of which corresponds to a single gene. Humans have approximately 23,000 genes arranged on their chromosomes.
An allele is one of two or more versions of a gene. An individual inherits two alleles for each gene, one from each parent. If the two alleles are the same, the individual is homozygous for that gene. If the alleles are different, the individual is heterozygous.

**Polymorphism**

Polymorphism involves one of two or more variants of a particular DNA sequence. The most common type of polymorphism involves variations at a single base pair. Polymorphisms can also be much larger in size and involve long stretches of DNA.

**Single Nucleotide Polymorphism (SNP)**

Called a single nucleotide polymorphism, or SNP (“snip”), researchers are studying how SNPs in the human genome correlate with disease, drug response, and other phenotypes. There are approximately 1.42 million SNPs in the human genome\(^1\). SNP’s may or may not have clinical significance. A SNP can change an amino acid in the protein coding sequence, thereby altering an enzyme binding site and / or the substrate binding site, which will affect the overall function.

\[ \text{All DNA is composed of a purine base (adenine and guanine) and a pyrimidine base (cytosine and thymine). The bases combine with the sugar, deoxyribose and phosphate to form the four nucleotides (A, G, C, and T)} \]

Genetic polymorphisms can be the result of chance, or may have been induced external factors, such as radiation or viruses. If a disease process is associated with a polymorphism, it may be termed a genetic mutation. Genetic polymorphisms in biotransformation/detoxification may play a significant role in the pathophysiology of certain diseases.
In the genes coding for certain biotransformation/detoxification enzymes, several polymorphisms have been described, resulting in enzymes with reduced or enhanced activity. As chemical and oxidative stress may be involved in the etiology of Crohn’s disease, polymorphic genes encoding for biotransformation enzymes may be putative candidates for genetic susceptibility to Crohn’s disease.

**Detoxification and Biotransformation Mechanisms**

Mechanisms that protect human tissue from toxicity include barriers to penetration, mobilization and excretion. Metabolic biotransformation produces more easily removed chemicals derivatives via gastrointestinal tract, kidney, skin and lungs.

In its basic form, the way the body processes xenobiotics is illustrated below.
The following illustration outlines the dynamic body systems interaction of toxicants, which include exposure, uptake, transport, storage, metabolism and excretion.

The detoxification process involves the biotransformation of non-polar (lipophilic) toxins into polar (hydrophilic) non-toxic metabolites. These metabolites are eliminated by the liver (bile into the GI tract), kidneys, lungs and skin. The detoxification of toxins occurs in two phases, however a third phase is also said to occur. A system of enzymatic reactions is involved in the process of detoxification.

**Phases of Detoxification/Biotransformation**

**Phase I:**

Phase I adds or uncovers a reactive group on the toxin making it more polar, however it may not be fully water soluble, and therefore ready for elimination. In fact the toxin may be more chemically reactive (reactive intermediate metabolites and/or reactive oxygen species), and therefore more toxic. Phase I reactions consist of oxidation, reduction, dehalogenation, and hydrolysis. These reactions convert molecules into substrates for the Phase II enzymes.

Phase I enzyme system is mainly composed of cytochrome P450 (CYP or CYP450) supergene family. (The P stands for pigment and the 450nm is the wavelength of light absorption). CYP450 is also known as NADPH-CYP450 system because it uses oxygen and the co-factor NADPH. CYP contains an iron protoporphyrin prosthetic group (heme). The cytochromes catalyze a variety of reactions including epoxidation, N-dealkylation, O-dealkylation, S-oxidation and hydroxylation. In addition to detoxification, the cytochromes are important in steroid, cholesterol, and vitamin D synthesis.
The classic reaction is as follows: \[ \text{NADPH} + \text{H}^+ + \text{O}_2 + \text{RH} \rightarrow \text{NADP}^+ + \text{H}_2\text{O} + \text{R-OH} \]
\[\text{(RH is the contaminant)}\]

Cytochromes are primarily located in the smooth endoplasmic reticulum (microsomal fraction) and some are located in the inner mitochondrial membrane. There are numerous isoforms (mixed function oxidases) of CYP450. (An isoform is a cytochrome enzyme variant that derives from a particular gene.) They are classified according to the similarities of the amino-acid sequences. It’s important to note that some cytochrome metabolize very few toxins, while some metabolize multiple. There are over fifty human genes coding for the various cytochrome P450 enzymes. There are several isoforms that are of particular important due to their involvement in metabolism of drugs and other exogenous substances. These include:

- CYP3A4
- CYP3A5
- CYP2D6
- CYP2C9
- CYP2C19
- CYP2C8
- CYP1A2
- CYP2E1
- CYP2A6

![Cytochrome Isoform Diagram]
The activity of the cytochrome enzymes may differ due to genetic polymorphisms. From a clinical perspective, the differences can have profound clinical consequences when prescribing pharmaceutical, botanical and supplements. A genetic polymorphism can cause reduction in the ability to detoxify a certain chemical or chemicals. The term “slow metabolizers” has been applied to these individual. (There can also be polymorphisms in the Phase II enzymes). Patient with polymorphisms usually have difficulty clearing medications. This may factor into the numerous adverse drug reactions. The end result of Phase I metabolites are:

- Inactive
- Equally active
- More active
- Toxic
- Activated (pro-drug)

**Phase II**

Phase II reactions involve the process of conjugation of the Phase I molecules making them water-soluble, and therefore amenable for elimination. These products are then excreted into the bile and urine.

Phase II conjugation reactions include:

- Glucuronidation
- Glutathione transferases
- S-Methylation
- N-Methylation
- Acetylation
- Sulfotransferases
- Thioltransferases
- Glycination (peptide bond formation) (Amino acid conjugation)

All of these reactions require energy (ATP) and cofactors to proceed.
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**Phase I**
(cytochrome P450 enzymes)

Toxins
(non-polar)

Intermediary metabolites (reactive)
(somewhat polar)

Secondary tissue damage (DNA, RNA, protein)

Reactive oxygen species (e.g., superoxide)

**Phase II**
(conjugation pathways)

Excretory derivatives
(polar)

bile

serum

kidneys

feces

urine
TABLE 8.18 — CONJUGATION PATHWAYS USED FOR SPECIFIC COMPOUNDS

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Xenobiotics</th>
<th>Drugs</th>
<th>Natural Compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutathione conjugation</td>
<td>Styrene Acrolein Ethylene oxide Benzopyrenes Methyl parathion Chlorobenzene Anthracene Toxic metals Petroleum distillates Naphthalene</td>
<td>Acetaminophen Penicillin Ethacrynic acid Tetracycline</td>
<td>Bacterial toxins Alfatoxin Lipid Peroxides Ethyl alcohol Quercitin N-Acetylcysteine Prostaglandins Bacterial toxins Bilirubin Leukotriene A4</td>
</tr>
<tr>
<td>Sulfation</td>
<td>Aniline Pentachlorophenol Terpenes Amines Hydroxylamines Phenols</td>
<td>Acetaminophen Methyl dopa Minoxidil Metaraminol Phenylephrine</td>
<td>DHEA Quercitin Bile acids Saffrole Tyramine Thyroxine Estrogens Testosterone Cortisol Catecholamines Melatonin 3-Hydroxy coumarin 25-Hydroxy vitamin D Ethyl alcohol CCK Cerebrosides</td>
</tr>
<tr>
<td>Gycine conjugation</td>
<td>Napthylacetic acid Alphatic amines</td>
<td>Salicylates Nicotinic Acid Chlorpheniramine Brompheniramine</td>
<td>Bile acids Cinnamic acids PABA Plant Acids Benzoic acid Phenylacetic acid</td>
</tr>
<tr>
<td>Taurine conjugation</td>
<td>Propionic acid Caprylic acid</td>
<td></td>
<td>Bile acids Stearic acid Palmitic acid Myristic acid Lauric acid Decanoic acid Butyric acid</td>
</tr>
<tr>
<td>Glucuronidation</td>
<td>Aniline Carbamates Phenols Thiophenol Butanol N-Hydroxy-2-naphthylamine</td>
<td>Salicylates Acetaminophen Morphine Meprobamate Benzodiazepines Clofibr acid Naproxen Digoxin</td>
<td>Phenybutazone Valproic acid Steroids Lorazepam Cimadol Propranolol Oxazepa Bilirubin Estrogens Melatonin Bile acids Vitamin E Vitamin A Vitamin K Vitamin D Steroid hormones</td>
</tr>
<tr>
<td>Acetylation</td>
<td>2 Aminofluorene Aniline</td>
<td>Clonazepam Dapsone Mescaline Isoniazid Hydralazine</td>
<td>Procaainamide Benzidine Sulfonylamides Promizole</td>
</tr>
<tr>
<td>Methylaion</td>
<td>Paraquat Beta-carbolines Isoquinolines Mercury Lead Arsenic Thallium Tin Pyridine</td>
<td>Thiouracil Isothairine Rimterol Dobutamine Butanehine</td>
<td>Elouphed Morphine Levaphanol Nalorphine Histamine Epinephrine Dopamine Norepinephrine L-Dopa Apomorphine Hydroxyestadiols</td>
</tr>
</tbody>
</table>

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Phase III (The Antiporter System)

Phase III has also been called the antiporter system. A transmembrane protein pump called p-glycoprotein appears to be responsible for “pumping” xenobiotics out of the cell in an effort to decrease their intra-cellular concentration. Antiporter activity has also been associated with the Phase I enzyme CYP3A in the intestines. The antiporter system in the intestine pumps xenobiotics back into the intestinal lumen for elimination. The system has also been associated with multiple drug resistance.

<table>
<thead>
<tr>
<th>Biotransformation Class</th>
<th>Example Enzyme or Set</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen Radical Conversion</td>
<td>Superoxide dismutase</td>
</tr>
<tr>
<td></td>
<td>Catalase</td>
</tr>
<tr>
<td></td>
<td>Glutathione peroxidase</td>
</tr>
<tr>
<td>Ammonia Removal</td>
<td>Urea cycle enzymes</td>
</tr>
<tr>
<td></td>
<td>Renal citrate synthetase</td>
</tr>
<tr>
<td>Immunocompetence</td>
<td>Cyclooxygenase</td>
</tr>
</tbody>
</table>

| Mixed Function Oxygenase Systems         |                                                                                      |
| (Phase I)                               |                                                                                      |
|                                         | Microsomal cytochrome P450                                                           |
|                                         | Microsomal flav-containing monooxygenase                                              |
|                                         | Other oxidation-reduction systems                                                    |
|                                         | Aldehyde and ketone oxides and reductases                                             |
|                                         |                                                                                      |
|                                         | Glucuronidation                                                                       |
|                                         | Glutathione transferases (mercaptans)                                                 |
|                                         | S-Methylation                                                                        |
|                                         | N-Methylation                                                                        |
|                                         | Acetylation                                                                           |
|                                         | Sulfotransferases                                                                    |
|                                         | Thioltransferases                                                                    |
|                                         | Peptide bond formation (glycination)                                                  |

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The Regulation of Detoxification

The activity of the enzymes involved in detoxification are either induced or inhibited by a number of factors which include genetics, diet, environment toxins, medication, and nutritional status.

Induction (inducers) of Detoxification

Certain substances can cause the upregulation of Phase I enzymes without the corresponding upregulation of the Phase II enzymes. If Phase I enzymes are upregulated or induced without an increase in Phase II activity, the result will be an increase in oxidative stress due to the fact that the intermediate metabolite can be more toxic that the original compound that activated the Phase I enzymes. An example of this is the polycyclic hydrocarbons from cigarette smoke that induce CYP1A2. Another example is the drug phenobarbital, which induces CYP2B6.

Substances that induce Phase I include:

- Drugs; nicotine, alcohol, phenobarbital, steroids, sulfonamides
- Foods; cabbage, broccoli, high protein diet,
- Environmental toxins; exhaust fumes, paint fumes, dioxin, pesticides, charbroiled meats
- Nutrients ; see list below

Inhibitors of Detoxification

The enzyme systems of Phase I and Phase II can be inhibited by several mechanisms, which include medications, foods, nutrient deficiency and botanicals. An example of a food causing inhibition of detoxification is grapefruit, which inhibits CYP3A4.

Substances that inhibit Phase I:

- Drugs; see list below
- Foods; grapefruit (naringenin), curcumin(also stimulates Phase II)
- Bowel dysbiosis

The following is a list of CYP450 Substrates, Inhibitors and Inductors:
(A substrate is a molecule upon which an enzyme acts)
## CYP450 SUBSTRATES

<table>
<thead>
<tr>
<th>1A2</th>
<th>2B6</th>
<th>2C19</th>
<th>2D6</th>
<th>3A4</th>
</tr>
</thead>
<tbody>
<tr>
<td>amitriptyline</td>
<td>selegiline</td>
<td>amitriptyline</td>
<td>tranylcypromine</td>
<td>amitriptyline</td>
</tr>
<tr>
<td>clomipramine</td>
<td></td>
<td>clomipramine</td>
<td>mecloberemide</td>
<td></td>
</tr>
<tr>
<td>imipramine</td>
<td></td>
<td>imipramine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>fluvoxamine</td>
<td>methadone</td>
<td>diazepam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>duloxetine</td>
<td></td>
<td>phenytoin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mirtazapine</td>
<td></td>
<td>phenobarbital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>chlorpromazine</td>
<td></td>
<td>citalopram</td>
<td></td>
<td></td>
</tr>
<tr>
<td>fluphenazine</td>
<td></td>
<td>escitalopram</td>
<td></td>
<td></td>
</tr>
<tr>
<td>perphenazine</td>
<td></td>
<td>fluoxetine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>clozapine</td>
<td></td>
<td>escitalopram</td>
<td></td>
<td></td>
</tr>
<tr>
<td>olanzapine</td>
<td></td>
<td>paroxetine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ziprasidone</td>
<td></td>
<td>venlafaxine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ropinirole</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALL methylxanthines</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PPIs:
- duloxetine
- venlafaxine
- trazodone
- chlorpromazine
- fluoxetine
- trazodone
- ziprasidone
- triazolobenzodiazepines
- zaleplon
- zolpidem
- zopiclone
- carbamazepine
- valproic acid
- buprenorphine
- codeine
- fentanyl
- hydrocodone
- meperidine
- tramadol
- statins
- exceptions
- pravastatin
- and rosuvastatin
- antiarrhythmics
- CCBs
- beta blockers
- macrolide
- azithromycin
### CYP450 INHIBITORS

<table>
<thead>
<tr>
<th>1A2</th>
<th>2B6</th>
<th>2C19</th>
<th>2D6</th>
<th>3A4</th>
</tr>
</thead>
<tbody>
<tr>
<td>amitriptyline</td>
<td>fluoxetine</td>
<td>amitriptyline</td>
<td>All TCAs</td>
<td>nefazodone</td>
</tr>
<tr>
<td>imipramine</td>
<td>imipramine</td>
<td>imipramine</td>
<td>norfluoxetine</td>
<td>fluoxetine</td>
</tr>
<tr>
<td>fluvoxamine</td>
<td>fluoxetine</td>
<td>fluvoxamine</td>
<td>fluoxetine</td>
<td>fluvoxamine</td>
</tr>
<tr>
<td>duloxetine</td>
<td>paroxetine</td>
<td>paroxetine</td>
<td>citalopram</td>
<td></td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>duloxetine</td>
<td>flurazepam</td>
<td>venteril</td>
<td></td>
</tr>
<tr>
<td>norfloxacin</td>
<td>norfluoxetine</td>
<td>fluoxetine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ofloxacin</td>
<td>fluoxetine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cimetidine</td>
<td>fluoxetine</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. **PPIs†**
   - ketoconazole
   - lansoprazole is the most potent in vitro inhibitor of 2C19

2. **3A4**
   - nefazodone
   - norfluoxetine
   - fluoxetine
   - fluvoxamine
   - haloperidol
   - pimozide
   - ciprofloxacin
   - norfloxacin
   - keto- and itraazole
   - diltiazem
   - verapamil
   - cimetidine
   - protease inhibitors
   - NNRTIs
   - Grapefruit

3. **3A4**
   - quinidine
   - ritonavir
   - cimetidine
   - diphenhydramine
   - Vistaril

   Metoclopramide
### CYP450 INDUCERS

<table>
<thead>
<tr>
<th>1A2</th>
<th>2B6</th>
<th>2C19</th>
<th>2D6</th>
<th>3A4</th>
</tr>
</thead>
<tbody>
<tr>
<td>modafinil</td>
<td>phenobarbital</td>
<td>carbamazepine</td>
<td>No Inducers!</td>
<td>carbamazepine</td>
</tr>
<tr>
<td>cruciferous vegetables</td>
<td>cyclophosphamide</td>
<td>valproic acid</td>
<td>oxcarbazepine</td>
<td>oxicarbamazepine</td>
</tr>
<tr>
<td>charbroiled foods</td>
<td>phenobarbital</td>
<td>phenytoin</td>
<td>topiramate</td>
<td>200mg</td>
</tr>
<tr>
<td>cigarette smoke</td>
<td>phenytoin</td>
<td>rifampin</td>
<td>rifampin</td>
<td>rifampin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>efavirenz</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>St. John's Wort</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>modafinil</td>
</tr>
</tbody>
</table>
Nutrients that Support Detoxification

Phase I

- Thiamine
- Riboflavin
- Niacin
- Folic acid
- Vitamin C
- Flavonoids
- Phospholipids
- Indoles
- Pyridoxine
- Cobalamin
- Iron, zinc, selenium, magnesium

Nutrients that support intermediate metabolites (between Phase I and Phase II)

- Antioxidants in general (vitamin A, C, E)
- Flavonoids
- Coenzyme Q10

Phase II

- Flavonoids
- Indole-3 carbinol
- Carnosic acid
- Isoflavinones
- Ellagic acid
- Garlic

Specific Phase II nutrients, (Inducers) and [inhibitors];

- Glutathione conjugation – glutathione, B6, NAC (Inducers - Brassica family, dill, caraway); \[Inhibitors – deficiencies of selenium, B12, zinc and glutathione\]
- Amino Acid conjugation – glycine (Inducers – glycine); \[Inhibitors – low protein diet\]
- Methylolation – S-adenosyl-methionine (Inducers - Lipotropic nutrients – choline, methionine, betaine, folic acid, and B12); \[inhibitors – deficiency of B12 or folic acid\]
- Sulfation – cysteine, methionine, molybdenum (Inducers - cysteine, methionine, taurine); \[inhibitors – NSAIDS, molybdenum deficiency, tartrazine(yellow food dye)\]
- Acetylation –Acetyl-CoA, B5 \[inhibitors – deficiency of B2, B5, or C\]
- Glucuronidation – glucuronic acid (inducers- fish oils); \[inhibitors – probenicid, aspirin\]

[note that the Brassica family (broccoli, cabbage and brussel sprouts) stimulate both Phase I and Phase II]
TABLE 8.20 — DETOXIFICATION FUNCTIONS OF SPECIFIC NUTRIENTS

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin C</td>
<td>Increased mobilization, toxic metal binding, and antioxidant protection</td>
</tr>
<tr>
<td>B-complex vitamins</td>
<td>Hepatic enzyme cofactors</td>
</tr>
<tr>
<td>Lipoic acid</td>
<td>Hepatic protection and antioxidant regeneration</td>
</tr>
<tr>
<td>N-acetylcysteine (NAC)</td>
<td>Glutathione formation and direct complexation</td>
</tr>
<tr>
<td>Cysteine</td>
<td>Sulfur amino acid</td>
</tr>
<tr>
<td>Methionine</td>
<td>Methyl donor and sulfur supply</td>
</tr>
<tr>
<td>S-Adenosylmethionine (SAM)</td>
<td>Active form of methionine</td>
</tr>
<tr>
<td>Glycine</td>
<td>Hepatic conjugation</td>
</tr>
<tr>
<td>Free-form essential amino acid mixture</td>
<td>Mitochondrial energy production</td>
</tr>
<tr>
<td>Sulfate</td>
<td>Hepatic conjugation</td>
</tr>
<tr>
<td>Calcium</td>
<td>Lead protection</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Multiple hepatic and other effects</td>
</tr>
<tr>
<td>Selenium</td>
<td>Glutathione regeneration and mercury protection</td>
</tr>
<tr>
<td>Manganese</td>
<td>Glutathione regeneration</td>
</tr>
<tr>
<td>Copper</td>
<td>Glutathione regeneration</td>
</tr>
<tr>
<td>Zinc</td>
<td>Glutathione regeneration and cadmium protection</td>
</tr>
</tbody>
</table>

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Summary

The detoxification/biotransformation process is extremely complex. The interacts between Phase I and Phase II, as well as, the biochemical unique of the patient are the most important factor to address when evaluating your patient’s ability to detoxify. Optimal health requires a balance between all of the phases of detoxification, as well as optimal gastrointestinal function.
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