Liver phases 1 and 2 detoxification pathways

What are the symptoms of a dysfunctional liver?

Abnormal metabolism of fats (lipids) leading to –

• Abnormalities in the level of fats in the blood stream e.g. elevated LDL cholesterol and reduced HDL cholesterol and elevated triglycerides.
• Arteries blocked with fat, leading to high blood pressure, heart attacks and strokes.
• Fatty liver and build up of fat in other body organs.
• Obesity and /or inability to lose weight
• Sluggish metabolism

External signs

• Coated tongue
• Bad breath
• Red palms and soles
• Flushed facial appearance or excessive facial blood vessels (capillaries/veins)
• Acne, Rosacea
• Yellow conjunctiva on the eyes
• Red swollen itchy eyes (allergic eyes)
• Dark circles under the eyes
• Brownish spots and blemishes on the skin (liver spots)
• Rashes and itchy skin (pruritis)

Digestive Problems

• Gall stones and gall bladder disease
• Intolerance to fatty foods
• Intolerance to alcohol
• Indigestion
• Reflux
• Nausea
• Abdominal bloating
• Constipation
• Irritable bowel syndrome
• Haemorrhoids

Nervous System

• Depression
• Mood changes such as anger and irritability
• Poor concentration and "foggy brain"
• Overheating
• Recurrent headaches associated with nausea

Immune dysfunction

• Allergies- sinus, hay fever, asthma, dermatitis, hives, etc.
• Skin rashes and inflammations
• Chemical and food sensitivities
• Auto-immune diseases
• Chronic Fatigue Syndrome and Fibromyalgia
• Recurrent viral, bacterial and parasitic infections

Blood Sugar Problems

• Craving for sugar
• Hypoglycaemia
• Mature onset diabetes is common in those with a fatty liver

Hormonal imbalance

• Intolerance to hormone replacement therapy (e.g. side effects)
• Menopausal symptoms such as hot flushes may be more severe
• Pre-menstrual syndrome may be more severe

Details of Liver Functions

Liver Functions:

The liver has a number of important functions, some of the main ones being:

- Detoxification of potentially toxic chemicals from both inside and outside of the body including drugs, alcohol and toxins from intestinal microbes. Accomplished with antioxidant nutrients and enzymes such as glutathione. The liver detoxifies these harmful substances by a

complex series of chemical reactions. The role of these various enzyme activities in the liver is to convert ***fat soluble toxins*** into ***water soluble substances*** that can be excreted in the urine or the bile depending on the particular characteristics of the end product.
- Storage of sugar as 'glycogen' and regulation of blood sugar levels.
- Production and storage of proteins as well as the regulation of many substances involved in protein metabolism.
- Production of bile which aids in the digestion of fats.
- Production of blood proteins, clotting factors and substances important to the production of red blood cells (erythrocytes)
- Regulation of a number of hormones.
- Neutralization of 'free-radicals' by antioxidants. Free radicals are highly reactive oxygen molecules that can damage tissues.
- Storage of vitamins, mainly iron, copper, B12, vitamins A, D, E and K
- It plays an important role in digestion (breaking nutrients down)
- Involved with assimilation (building up body tissues).
- Red blood cells, which are responsible for carrying oxygen around the body, are recycled in the liver

Many factors determine whether the liver performs its critical functions well. Too much pressure on the liver from overeating rich or poor-quality food, environmental stresses, overwork or emotional stress can cause liver overload, leading to a decreased ability to clear toxins and hormones and manufacture bile. Foods which contain high levels of antioxidants help to protect the liver and keep it healthy while other foods cleanse the liver.

Click **here** to view the different steps of detoxification of a “healthy” or “unhealthy” liver.

The symptoms of a sluggish or overtaxed liver are varied and can include excess weight, liver and gall bladder diseases, headaches and migraines, digestive problems, allergies, immune system problems such as hay fever and asthma, food and chemical sensitivities, constipation, unexplained fatigue, skin itching and irritation, PMS and other menstrual problems.

Foods to Eat for Liver Health:

There are certain foods that help to protect and detoxify the liver itself so that it can perform better to detox the entire body:

- **Apples** contain **pectin** which helps to **bind and excrete heavy metals** right off the intestines. This directly helps to reduce the load of filtration on the liver.
- **Beets, carrots, red onions and aubergine (eggplant)** contain **flavonoids and beta-carotene** which are **potent antioxidants**.
- **Garlic** contains **allicin** and the mineral **selenium**, both **antioxidants**. It assists the **removal of heavy metals** from the liver.
- **Eggs, brown rice and whole grains, broccoli and spinach** contain **B-complex vitamins** which **improve liver function and promote liver decongestion**.
- **Vitamin B12** helps to **metabolize fats and improves liver health**.
- **Cruciferous vegetables** such as **cauliflower, broccoli, cabbage, Brussels sprouts, Bok Choy, kale, radishes, and turnips** contain **glucosinolates** which help the liver produce **enzymes for detoxification**.
- **Grapefruits** are **rich in antioxidants** and help in natural **detoxification of liver**.

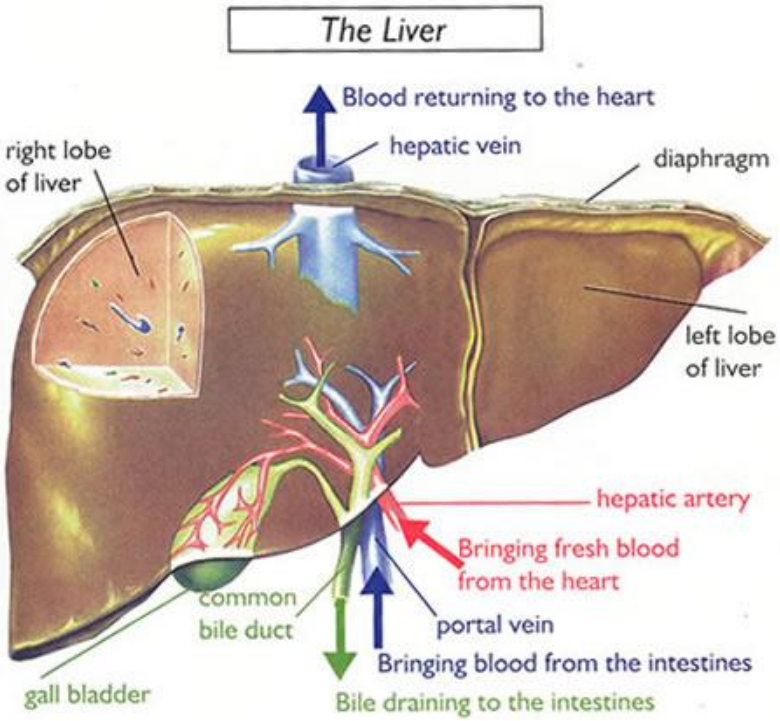
- **Bitter vegetables** such as **bitter gourd, dandelion greens, mustard greens and chicory** promote the **production and flow of bile**.

Tips for a healthy liver:

- Eat organically produced foods as much as possible to avoid toxic chemical residues.
- Avoid artificial flavorings and preservatives.
- Avoid damaged fats such as hydrogenated fats found in many processed foods.
- Use cold pressed oils and do not use them for cooking. Only a little butter, a saturated fat (coconut oil), should be used for cooking. Cooking with olive oil is still controversial. If used then do not heat it to a high temperature and add AFTER food has been removed from heat.
- Make sure your nuts and seeds are really fresh.
- Avoid excess saturated animal fat like sausage, bacon, salami, hot dogs, high fat dairy products like whole milk, ice cream and cheese.
- Alcohol is known to be a powerful toxin that will damage the liver.

Treating your liver well by following the above advice will have a huge impact on your health and longevity.

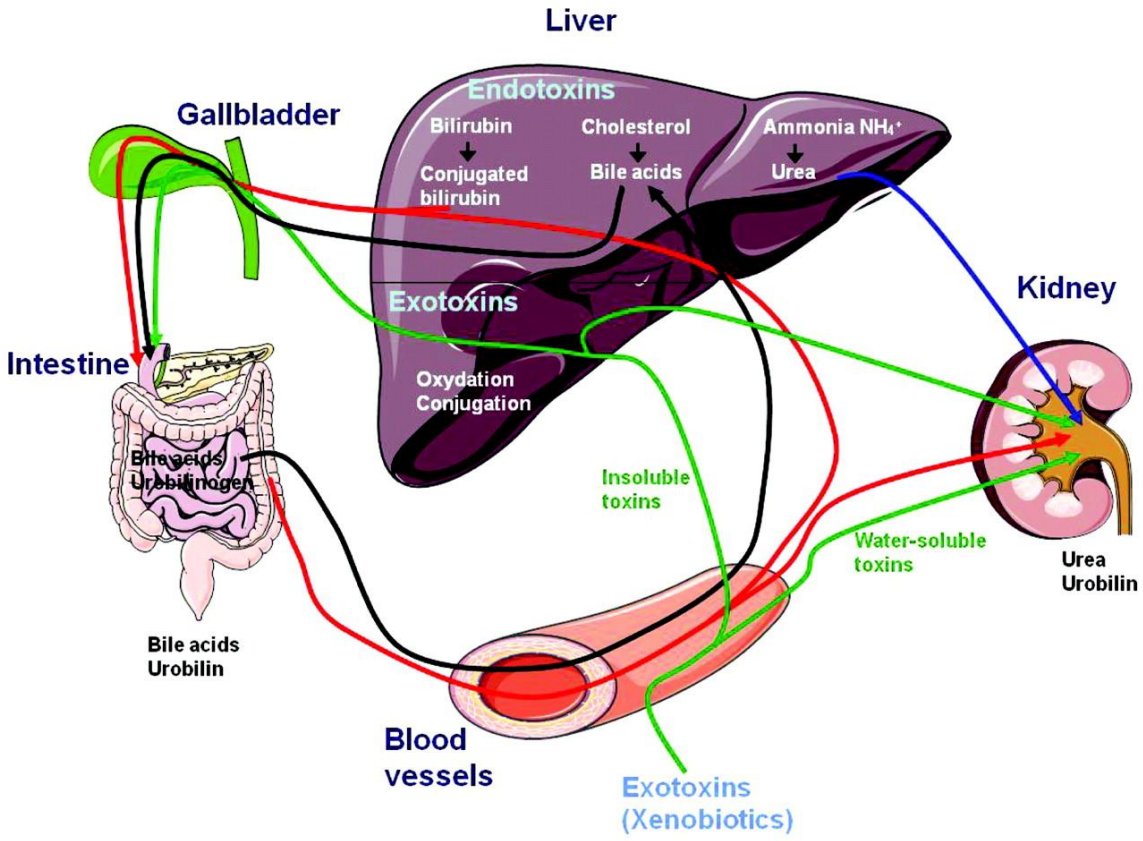
Liver Detoxification



The major percentage of blood being filtered by the liver is from the portal vein, which carries blood from the intestines. The liver can remove a broad spectrum of microorganisms such as bacteria, fungi, viruses and parasites from the blood, which is desirable, as we certainly do not want these building up in the blood and invading deeper parts of the body. Infections and parasites often come from the contaminated water supplies found in large cities, and indeed other dangerous organisms may find their way into your gut and blood stream from these sources. This can cause chronic infections and poor health, so it is important to protect your

liver from these microorganisms. The safest thing to do is drink water that has been filtered and sterilized. High loads of unhealthy microorganisms can also come from foods prepared in conditions of poor hygiene by persons who are carrying bacteria, viruses or parasites on their skin. Foods, especially meats that are not fresh or are preserved, also contain a higher bacterial load, which will overwork the liver if they are eaten regularly.

Many of the toxic chemicals that enter the body are fat-soluble, which means they dissolve only in fatty or oily solutions and not in water. This makes them difficult for the body to excrete. Fat soluble chemicals have a high affinity for fat tissues and cell membranes, which are composed of fatty acids and proteins. In these fatty tissues of the body, toxins may be stored for years, being released during times of exercise, stress or fasting. During the release of these toxins, several symptoms such as headaches, poor memory, stomach pain, nausea, fatigue, dizziness and palpitations can occur.



General Liver Detoxification Nutrients

Foods to aid detoxification:

- Beetroot and artichoke: helps with liver drainage
- Broccoli, cauliflower and other cruciferous vegetables: these aid cytochrome P450 activity
- Protein
- Radish, watercress: rich in sulphur
- Albion family vegetables: garlic, onions
- High fiber foods such as whole grains, psyllium, flax seeds, fruit and vegetables: fiber binds toxins and eliminates them through the GI tract

Supplements to aid liver detoxification:

- B-complex vitamins: necessary co-factors used in Phase 1 detoxification
- Digestive enzymes: may be necessary to ensure that protein is adequately digested and glycine is readily available
- Essential fatty acids
- N-acetyl cysteine (NAC): an immediate precursor to glutathione, a potent antioxidant and among the most import detoxification nutrients for the liver
- Reduced glutathione
- Selenium, zinc, magnesium and manganese; possibly iron and copper if used with caution
- Taurine (a useful combination product is magnesium taurate)
- Vitamins C and E and beta carotene.
- Inositol & Methionine: lipotropic agents (help with the breakdown of fat in metabolism) that work to transport fat out of the liver
- High ORAC vegetable extract blend with polyphenols (a phytonutrient)

Vitamins and minerals – particularly the B vitamins – play a major role, acting as co-factors for many enzyme systems including those of liver detoxification, therefore making sure you consume enough of the B complex group of vitamins is of prime importance for optimum detoxification. Including plenty of whole grains which contain B vitamins in the diet as well as taking a good B complex supplement will aid the liver in this crucial role.

Depletion of vitamin C may also impair the detoxification process; vitamin C also prevents free radical formation. Vitamin C is found in citrus fruits and green leafy vegetables. However, in order to obtain optimum amounts supplementation is required. I recommend at least a few grams a day.

Vitamin E and selenium are co-factors for glutathione peroxidase activity as well as being powerful antioxidants. (Vitamin E also works synergistically with vitamin C.) Today, our diets are very low in selenium due to the depletion of the soil of this vital mineral. Supplementation is therefore important.

Cruciferous vegetables such as broccoli, cauliflower, brussel sprouts and cabbage in the diet have been shown to enhance Phase I activities. I use those when vegetable juicing on a frequent basis.

Zinc is another essential nutrient and acts as a co-factor for many enzyme systems. Zinc deficiency can cause a whole range of consequences. One important role that zinc plays is in the functioning of an enzyme alcohol dehydrogenase involved in the conversion of alcohols to aldehydes in Phase I detoxification. Therefore anyone who drinks alcohol should ensure they have optimum amounts of zinc in their diet.

Liver herbs to aid detoxification (traditionally known as 'blood cleansing' herbs):

- **Dandelion root, beet leaf & Yellow Dock:** cholagogue (stimulates liver secretions and bile flow)
- **Artichoke leaf:** promotes regeneration of the liver and promotes blood flow in that organ, stimulates bile flow

- **Silymarin (bioflavonoid found in Milk Thistle):** according to research, this herbal extract stabilizes the membranes of liver cells, preventing the entry of virus toxins and other toxic compounds including drugs. Supports the protection of the liver and promotes it's regeneration.
- **Turmeric:** a cholagogue like dandelion, but may irritate the gastric mucosa. Its advantages are its cheapness and ability to be used in cookery.

Note: These herbs are best combined with **wild yam**, which helps to prevent liver spasms caused by gall bladder-stimulating herbs. (*Also see Secondary plant metabolites.*)

Coffee Enema Helpful In Liver Detoxification

The use of coffee in enemas for liver detoxification purposes is well known. It is a common herbalogical remedy that has been suggested by holistic and alternative medicine professionals for many years.

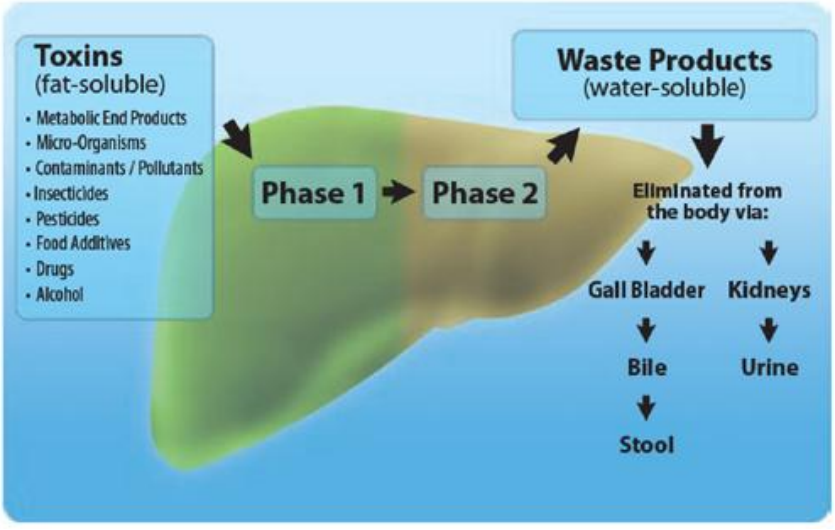
The coffee enema has been used for many years to detoxify the liver. It is a low-volume enema that remains only in the sigmoid colon. There is a duct between the sigmoid colon and the liver called the entero-hepatic circulation system. When the stool reaches this point, it contains many toxins, which are sent to the liver for detoxification.

Coffee Enema For Liver Detoxification

The caffeine that is absorbed into the entero-hepatic system causes the liver ducts, including the bile ducts, to empty into the sigmoid colon and be eliminated. Releasing the toxins in the liver ducts, makes room for toxins from the body to enter the liver for detoxification. The alkaloids in the caffeine stimulate the production of glutathione-S-transferase, which is an enzyme that facilitates the liver detoxification pathways. Coffee enemas will not waste minerals and electrolytes because they have already been absorbed in the previous sections of the intestines. The coffee enema is safe even for people who are sensitive to caffeine because the coffee remains in the sigmoid colon, where it will not be absorbed, provided the proper amount is used and the enema bag is not place too high.

The liver phases in a nutshell

Figure 1 - Detoxification (Biotransformation) Pathways



Phase 1

During the phase 1 pathway, toxin chemicals and metals (from food, water, and air) are converted into less harmful chemicals through many chemicals reactions through the induction of P-450 enzyme.

Does even the smallest bit of caffeine keep you wide awake at night? You could have sluggish phase I detox. Can you guzzle two cups of coffee in the afternoon and sleep just fine? Your phase I enzymes might be over active.

Specially targeted nutrients can do wonders for your liver's detoxifying ability.

Substances that activate or induce Phase 1 detoxification

Note: The term "induce" can be misleading as it refers to anything that fires up the system - those that are harmful which need processing, and those which aren't harmful and activate processing.

Drugs and Environmental Toxins: acetate, alcohol, barbiturates, carbon tetrachloride, dioxin, exhaust fumes, nicotine in cigarette smoke, organophosphorus pesticides, paint fumes, pesticides,Phenobarbital, steroid hormones, sulphonamides (sulpha drugs)

Bad Foods: charcoal-broiled meats, high protein diets, saturated fats,

Good Foods:

- **Indoles** from cruciferous vegetables: cabbage, broccoli, and brussels sprouts
- Diets adequate in protein (meat, fish and eggs or vegetable protein)

- oranges and tangerines (but not grapefruits)

Nutrients:

- **Vitamins :** Vitamin B1, Vitamin B2 (riboflavin), Vitamin B3 (niacin), Vitamin B6, Vitamin B9 (Folic Acid), Vitamin B12, Vitamin C
- **Lipotrophics** – compounds that break down fat in metabolism (cysteine, methionine, choline, and inositol)
- **Minerals:** Magnesium & Iron
- **Antioxidants:** Glutathione, Flavonoids (such as catechins – found in green tea)

Herbs: caraway, dill seeds, Milk Thistle, sassafras tea

Substances that Inhibit Phase 1 detoxification

Note: In general, inhibition of detoxification is not desired. In the case of Gilbert's Syndrome, there is an exception to Phase 1 inhibitors, as at a certain level it can allow Phase II detox to keep up with it.

Drugs: benzodiazepines; antihistamines; cimetidine and other stomach-acid secretion blocking drugs; ketoconazole; sulfaphenazole

Phytochemicals in Foods: naringenin from grapefruit juice; curcumin from turmeric; capsaicin form chili pepper; eugenol from clove oil; quercetin from onions

Botanicals: curcuma longa (curcumin); capsicum frutescens (capsaicin); eugenia caryophyllus (eugenol); calendula officianalis

Other: aging; toxins from inappropriate bacteria in the intestines

Phase 2

A diet low in protein-all too common in women who are trying to lose weight with a low-fat diet-can dramatically slow phase II detoxification. Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs), including ibuprofen (found in Advil, Nuprin, and other products), also slow phase II detoxification.

Does garlic make you sick? Does your urine have a strong smell after you eat asparagus? Did you suffer from toxemia during your pregnancy? Any of these symptoms may indicate problems with phase II.

The phase 2 detoxification pathway is known as the conjugation pathway. This involves converting the fat-soluble toxic chemical and transforming the toxins into water-soluble chemicals. Then they are passed out through body fluids as such as the bile or urine.

For this 2nd pathway to function efficiently, there are some important substances needed to activate the catalyst for toxin conversion.

Note: There are various combination products available to support liver detoxification with an emphasis on one phase or both phases.

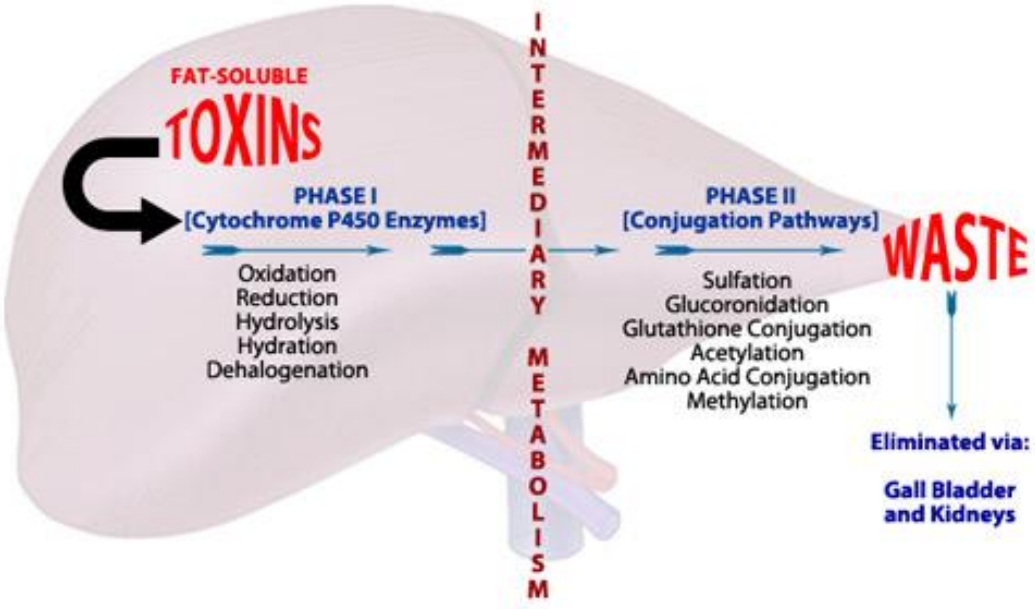
Nutrients which encourage or activate Phase II include:

- Aspartic acid
- Blue green algae
- Bee pollen
- Cruciferous vegetables (broccoli, cabbage, brussels sprouts, cauliflower)
- Glutamine
- Glutamic acid
- Glycine
- Grapefruit juice contains naringenin, a substance which slows down Phase 1 enzyme activity. This increases the half life of some drugs, causing them to remain active longer. If you already have a sluggish Phase 1 and are on medication: **Caution** is advised when taking large doses of grapefruit juice and some drugs.
- Molybdenum
- Sulfur-containing amino acids like Cysteine (or NAC), Taurine or Methionine.
- Sulfur-containing amino acid foods: meat protein, eggs
- Sulphur-containing phytonutrients available from garlic, shallots, onions, etc...
- Vitamin B12

Note: The debate about eating meat to get the amino acids that are needed for other liver detoxification routes goes on. Some authorities maintain that red meat is needed to detoxify chemicals but others say that the vegetarian diet with its complementary proteins such as rice (whole grains) with lentils or beans (legumes) will provide the same amino acids.

After studying metabolic typing I have come to the conclusion that there is not one diet that is right for everyone. Some people **do indeed need meat** and will not thrive on a vegetarian diet.

The 6 detoxification pathways of Phase 2



Click **here** to view a more detailed image than the picture below. (**Note:** There is a typo in the Phase 1 section - **Riboflavin = Vitamin B2 and NOT Vitamin A**)

1- The Sulphation (sulfation) pathway

2- **The Glucoronidation pathway**

3- **The Glutathione conjugation pathway**

4- **The Acetylation pathway**

5- **The Amino Acid conjugation pathway** (glycine, cysteine, glutamine, methionine, taurine, glutamic acid and aspartic acid)

6- **The Methylation** (& Sulfoxidation) **pathway**

Nutrients needed by phase II detoxification enzymes

Sulfation: Molybdenum, Cysteine and its precursor Methionine, co-factors (Vitamin B12, Folic Acid (B9), Methyl Donors, Magnesium, B-6/P-5-P), MSM, S-adenosyl-methionine (SAMe), Taurine

Glucuronidation: Glucuronic acid, Magnesium, B-Vitamins

Glutathione conjugation: Glutathione Precursors (Cysteine, Glycine, Glutamic Acid, and co-factors), Essential Fatty Acids (Black Currant Seed Oil, Flax Seed Oil, EPA), Parathyroid Tissue, Vitamin B6

Acetylation: Acetyl-CoA, Molybdenum, Iron, Niacinamide (B3), Vitamin B2

Amino acid conjugation: Glycine (see Glycination)

- **Glycination:** Arginase Enzyme, Glycine, Gly Co-factors (Folic Acid, Manganese, B-2, B-6/P-5-P)

Methylation: Methionine, Co-factors (Magnesium, Folic Acid, B-12, Methyl Donors), Lipotropic nutrients (choline, methionine, betaine, folic acid, vitamin B12)

Inducers of phase II detoxification enzymes

Sulfation: **Food sources of:** Cysteine, methionine, taurine

Glucuronidation:

- **Good:** Fish oils, limonene-containing foods (citrus peel, dill weed oil, caraway oil)
- **Bad:** cigarette smoking, birth control pills, Phenobarbital

Glutathione conjugation: (Click here to read more about foods that increase Glutathione)

- **Food:** Asparagus, avocados, Brassica family foods (cabbage, broccoli, Brussels sprouts, kale, bok choy, watercress, mustard, horseradish, turnips, rutabagas, kohlrabi), limonene-containing foods (citrus peel, dill weed oil, caraway oil), papaya, red beets, watermelon

Note: Generally fresh fruits and vegetables contain from 25mg up to 750mg glutathione per pound so that is why we see so many detoxification diets recommending an abundance of these foods.

Acetylation: Food sources of: Acetyl-CoA, Molybdenum, Iron, Niacinamide (B3), Vitamin B2

Amino acid conjugation: Food sources of Glycine

Methylation: Food sources of lipotropic nutrients (compounds that help to break down fat in metabolism) - Ex: choline (found in Lecithin), methionine, betaine, folic acid (B9), vitamin B_{12}

Inhibitors of Phase II Detoxification Enzymes

Note: Inhibition of phase II detoxification is not desired, especially in those with Gilbert's Syndrome, as these enzymes are already inhibited.

Sulfation: Non-steroidal anti-inflammatory drugs (e.g. aspirin), tartrazine (yellow food dye), molybdenum deficiency

Glucuronidation: Aspirin, probenecid

Glutathione conjugation: Selenium deficiency, vitamin B2 deficiency, glutathione deficiency, zinc deficiency

Note: The drug Morphine depletes Glutathione levels. We also produce less Glutathione as we age.

Acetylation: Vitamin B2, B5, or C deficiency

Amino acid conjugation: Low protein diet

Methylation: Folic acid or vitamin B12 deficiency

The liver phases in detail

Your liver is your most important organ of detoxification and continuously processes all forms of substances, from your digestive tract and the rest of your body, throughout the day. It has to deal with all these compounds, some of which are very toxic and others which are beneficial, and decide what to do with them. Your liver is very good at deciding what needs to be kept and what needs to be removed. It functions like a massive chemical plant that manufactures certain compounds, detoxifies dangerous compounds, and directs substances all over the body for use, storage or excretion. Your liver makes use of two pathways in order to carry out its detoxification work – **phase 1** and **phase 2 pathways**. You can think of **phase 1** as being responsible for **breaking things down** and then sending the raw materials to **phase 2**, which **builds new substances** from the raw material by adding molecules to them (this is called conjugation).

You need to supply the 'special conjugation substances' via your diet or the production lines come to a halt. If one conveyor belt stops because it is missing its 'special substance', the other conveyor belts are equipped to deal with some of these jammed items that need conjugation. But certain compounds are restricted to only go down a specific pathway and production must wait until more of the 'special substance' is provided. Even still, **phase 1** does not stop production and it just keeps on going.

Since many of these 'special substances' can be derived from big proteins that you eat, it shows why regular protein meals are vital for ill people. Sometimes your body is unable to go through all of the specific steps it needs to, in order to break complex proteins down fully and thereby provide **phase 2** some of the seven particular 'special substances'. For example, sulphur (sulfur foods) are metabolized down through several steps in order to produce sulphate (sulfate), but some people are unable to complete the conversion of sulphur into sulphate, or they do it poorly, due to faulty or poisoned enzymes. In order to keep the Sulphation pathway moving, they must supply sulphate to the body via supplements taken on a daily basis, such as Magnesium sulphate (Epsom Salts) or Glucosamine sulphate. Different people will have different problems with different pathways.

You can think of the toxic metabolites from **phase 1** as many freshly laid and fragile eggs from different birds that are churned out every second in the **phase 1** factory. These eggs need to be quickly organised and sent down the correct conveyor belt or they will back-up and create a huge mess. Chicken eggs must go down the chicken egg conveyor belt, and geese eggs down the geese egg conveyor belt. So the eggs are swiftly organized onto specific conveyor **phase 2** belts where workers (phase 2 enzymes) add certain 'special substances', to create boxes and bubble wrap (taurine, glycine,sulphate) which stabilizes them and makes them ready for transport.

In Multiple Chemical Sensitivity (MCS) the **phase 1** birds are making way to many eggs, while the **phase 2** workers are overwhelmed and can't keep up with the packing. This creates a bottle-neck at the beginning of the **phase 2** conveyor belt and the eggs spill over and make a huge mess. When this happens in the body, the toxic metabolites that are bottle-necked at the beginning of **phase 2** start to circulate and cause a lot of damage throughout the system. So when a person with MCS encounters certain compounds like perfumes or paint that need to be detoxified by the **phase 2** system and it is not working, then they get a lot of symptoms. These individuals need help to slow down **phase 1** pathways, with phase 1 inhibitors such as **niacinamide (**500-1000mg/day) or **grapefruit juice** (250ml 3-4 times per day) or **oregano oil**, this also kills intestinal yeast and dosages vary) and support/speed up **phase 2** pathways (e.g. with substances like sulphate or methyl groups).

Grapefruit juice and curcumin (in tumeric, though people with high plasma cysteine and sulfur problems are cautioned by Andy Cutler, in Amalgam Illness, as curcumin raises plasma cysteine further) are able to accomplish both of these tasks by slowing down **phase 1** and speeding up **phase 2** simultaneously. Here is a chart that shows the substances metabolised in the phase 1 pathways, and inducers and inhibitors of the specific enzymes.It takes quite a bit of personal experimentation to find out where exactly in your liver pathways you are having trouble.

Phase 1 & Phase 2 must be in balance

In some people the detoxification pathways (Phases I and II) are out of balance. For example, if Phase I is more active than Phase II, a build up of reactive intermediate metabolites can occur

which in turn can lead to tissue damage and disease. These people are referred to as "Pathological Detoxifiers".

Pathological detoxifiers can be identified as those individuals who are highly sensitive to fumes - Ex: paints and perfumes, react adversely to various pharmaceutical drugs and may have a reaction to drinking caffeine.

There is now an extensive body of evidence indicating that diet plays a crucial role in modifying the body's detoxification pathways. Even in allopathic medicine grapefruit juice is utilised for transplant patients as grapefruit contains naringenin, a substance which slows down Phase I enzyme activity.

This enables such drugs as cyclosporin – which is given to prevent organ rejection – to stay in the system for longer prior to the drug being detoxified. Pathological detoxifiers may also find it useful to include grapefruit juice in their diet.

Phase 1

Phase 1 uses many, many enzymes to break substances down. This phase as the 'SUBTRACTION' phase of metabolism, where the enzymes work to subtract molecules from substances and break them up into smaller more useful units, just like the process of food digestion does so in the gut. **Phase 1** is utterly dependent on these ENZYMES, whose speed of metabolism is in turn affected by things like genetics, exercise and the presence or absence of certain substances/supplements in the diet that can either speed them up (induce them) or slow them down (inhibit them). After the enzymes have broken down some of the substances, some very toxic end products (metabolites) remain and they must quickly be shunted to **phase 2** pathway in order to make them safer for the body to use. Heavy metals in particular can make these enzymes dysfunctional.

Phase 1 is carried out by the cytochrome P 450 enzyme system and consists of oxidation and reduction reactions. Various nutrients are required in order for the Phase I detoxification system to be carried out efficiently. Cytochrome P450 reactions generate free radicals and this can cause secondary damage to cells. An adequate supply of key antioxidants is therefore essential to prevent tissue damage. Reduced glutathione, superoxide dismutase and additional nutrients such as beta carotene, vitamin E, selenium and N-acetyl-cysteine (NAC) will act as antioxidants.

Other nutrient co-factors required for cytochrome P450 reactions include riboflavin, niacin, magnesium, iron and certain phytonutrients such as indoles from cruciferous vegetables and quercetin have been shown to support Phase I of liver detoxification.

Cytochrome P450 is induced by some toxins and by some foods and nutrients. Obviously, it is beneficial to improve phase I detoxification in order to eliminate toxins as soon as possible. This is best accomplished by providing the needed nutrients and non-toxic stimulants while avoiding those substances that are toxic. However, stimulation of phase 1 is contraindicated if the patient's phase II systems are underactive.

Drugs and environmental toxins activate P450 to combat their destructive effects, and in so doing, not only use up compounds needed for this detoxification system but contribute significantly to free radical formation and oxidative stress. Among foods, the brassica (cruciferous) family – Ex: cabbage, broccoli, and Brussels sprouts, contains chemical

constituents that stimulate both phase 1 and phase 2 detoxification enzymes. One such compound is indole-3-carbinol, which is also a powerful anti-cancer chemical. It is a very active stimulant of detoxifying enzymes in the gut as well as the liver. The net result is significant protection against several toxins, especially carcinogens. This helps to explain why consumption of cabbage family vegetables protects against cancer.

Oranges and tangerines (as well as the seeds of caraway and dill) contain limonene, a phytochemical that has been found to prevent and even treat cancer in animal models. Limonene's protective effects are probably due to the fact that it is a strong inducer of both phase I and phase II detoxification enzymes that neutralize carcinogens.

The metabolites from this detoxification process are often potentially more harmful than their original toxic compounds and it is important for health that these toxic compounds do not build up. This is where Phase II of liver detoxification comes in.

Inhibition of Phase 1:

Many substances inhibit cytochrome P450. This situation can cause substantial problems as it makes toxins potentially more damaging because they remain in the body longer before detoxification. For example, grapefruit juice decreases the rate of elimination of drugs from the blood and has been found to substantially alter their clinical activity and toxicity. Eight ounces of grapefruit juice contains enough of the flavonoid naringenin to decrease cytochrome P450 activity by a remarkable 30%.

Curcumin, the compound that gives turmeric its yellow color, is interesting because it inhibits phase I while stimulating phase II. This effect can be very useful in preventing certain types of cancer. Curcumin has been found to inhibit carcinogens, such as benzopyrene (found in charcoal-broiled meat), from inducing cancer in several animal models. It appears that the curcumin exerts its anti-carcinogenic activity by lowering the activation of carcinogens while increasing the detoxification of those that are activated. Curcumin has also been shown to directly inhibit the growth of cancer cells. As most of the cancer-inducing chemicals in cigarette smoke are only carcinogenic during the period between activation by phase I and final detoxification by phase II, curcumin in the turmeric can help prevent the cancer-causing effects of tobacco. Those exposed to smoke, aromatic hydrocarbons, and other environmental carcinogens will probably benefit from the frequent use of curry or turmeric.

The activity of phase I detoxification enzymes decreases in old age. Aging also decreases blood flow through the liver, further aggravating the problem. Lack of the physical activity necessary for good circulation, combined with the poor nutrition commonly seen in the elderly; add up to a significant impairment of detoxification capacity, which is typically found in aging individuals. This helps to explain why toxic reactions to drugs are seen so commonly in the elderly.

Phase 2

Phase 2 is the **ADDITION** or **CONJUGATION** phase where new substances are added/conjugated to the toxic and good metabolites produced in **phase 1** in order to make them easier to transport, more stable and/or more functional for the body.
You can think of the **phase 2** pathways like you would seven conveyor belts in constant motion extending outwards from a central point, where the phase 1 pathways empty their byproducts. Specific substances are shunted towards a specific conveyor belt where particular enzymes are available for the addition of a ‘special substance’ to create a new substance. Mostly these

'special substances' are amino acids like glycine and taurine, and other substances, like glutathione, sulfate, and methyl. Each conveyor belt adds/conjugates a specific substance.

There are five main conjugation categories, including acetylation, acylation (peptide conjugation with amino acids), sulphur conjugations, methylations and conjugation with glucuronic acid. Some substances enter Phase II detoxification directly, others come via Phase I pathways. Conjugation involves the combining of a metabolite or toxin with another substance which adds a polar hydrophilic molecule to it, converting lipophilic substances to water-soluble forms for excretion and elimination. Individual xenobiotics and metabolites usually follow a specific path, so whereas caffeine is metabolized by P450 enzymes, aspirin-based medications are conjugated with glycine, and paracetamol (acetaminophen) with sulphate.

During phase II detoxification, activated substances from phase I–otherwise known as intermediates–are altered further. Seven different major biochemical reactions occur in this phase, known as glutathione conjugation, amino acid conjugation, methylation, sulfation, acetylation, glucuronidation, and sulfoxidation. Each of these reactions works on specific types of intermediates and needs specific nutrients in order to proceed to successful completion. Basically, these reactions work by adding a molecule to the intermediate from phase I, making it less toxic and soluble in water. Then the final product can be flushed out of the body in either the urine or the bile, another product of the liver. Bile leaves the body as part of solid waste.

The nutrients required for phase II fall into two categories. The first are the amino acids, which donate molecules that are attached to phase I intermediates. These include the sulfur donors, among which are the amino acids methionine, taurine, cysteine, and N-acetylcysteine. Other, non-sulfur-containing amino acids are also required: glycine, taurine, glutamine, ornithine, and arginine. The antioxidant amino acid glutathione is also required for phase II detoxification.

6 detoxification pathways in detail:

1- Sulphate conjugation (sulphation)

This is the pathway where toxins attach with sulphur-containing compounds. This is the main liver detoxification pathway that neutralizes the stress hormone cortisol, as well as some commonly-prescribed pharmaceuticals, food additives, aspartame, toxins produced by intestinal bacteria, neurotransmitters, steroid hormones, certain drugs such as Acetaminophen (also known as Paracetamol or Tylenol) , environmental toxins, and many xenobiotic and phenolic compounds (Some phenols are germicidal and are used in formulating disinfectants. Others possess estrogenic or endocrine disrupting activity - **Bad ones:** hormone disruptors (xenoestrogens, Bisphenol A) – **Good ones:** some flavonoids and other fat-soluble anti-oxidants, neurotransmitters). Sulfation is also used to detoxify some normal body chemicals and is the main pathway for the elimination of steroid (glucocorticoids, mineralocorticoids, androgens, estrogens, and progestagens) and thyroid hormones.

Sources of sulphur include the sulphur-bearing amino acids such as methionine and cysteine, in addition to the nutritional product methylsulfonylmethane (MSM). Many factors influence the activity of sulfate conjugation. For example, a diet low in methionine and cysteine has been shown to reduce sulfation. Sulfation is also reduced by excessive levels of molybdenum or vitamin B6 (over about 100 mg/day). In some cases, sulfation can be increased by supplemental sulfate, extra amounts of sulfur-containing foods in the diet, and the amino acids

taurine and glutathione. Large doses of N-acetyl-cysteine (NAC) are a standard treatment for Tylenol (paracetamol or acetaminophen) overdose.

Since sulfation is also the primary route for the elimination of neurotransmitters, dysfunction in this system may contribute to the development of some nervous system disorders. Steventon at Birmingham University (UK) has found that many sufferers from parkinsonism, motor neurone disease and Alzheimer's disease as well as environmental illness, tend to have a reduced ability to produce sulphate from the amino acid cysteine in their body, and instead accumulate cysteine. Sulphate may be ingested from food, but is also produced by the action of the enzyme cysteine dioxygenase on cysteine. This process is known as sulphoxidation. The body's ability to conjugate toxins with sulphate is 'rate limited' by the amount of sulphate present; if there is inadequate sulphate, toxins and metabolites can accumulate, perhaps building up to levels which cause degeneration of nervous tissue after several decades. Steventon's findings are a matter for serious concern. How many individuals are given the opportunity to find out whether they are poor sulphoxidizers and to reduce their chances of developing the above mentioned diseases by improving their sulphoxidation ability?

Glucuronidation

Glucuronidation, the combining of glucuronic acid with toxins, requires the enzyme UDP-glucuronyl transferase (UDPGT). Glucuronidation is a major inactivating pathway for a huge variety of exogenous and endogenous molecules such as pollutants, fatty acid derivatives, retinoids (similar to Vitamin A), bile acids and bilirubin. Many of the commonly prescribed drugs or medications (such as aspirin) are detoxified through this pathway. This pathway also helps to detoxify food additives (such as benzoates), aspartame, menthol, vanillin (synthetic vanilla) and preservatives, in addition to reproductive and adrenal hormones such as androgens, estrogens, mineralocorticoids and glucocorticoids.

Glucuronidation requires magnesium, B-Vitamins. Glucuronic acid is a metabolite of glucose. It can conjugate with chemical and bacterial toxins such as alcohols, phenols, enols, carboxylic acid, amines, hydroxyamines, carbamides, sulphonamides and thiols, as well as some normal metabolites in a process known as glucuronidation.

For most individuals glucuronidation is a supplementary detoxification pathway. It is a secondary, slower process than sulphation or glycination, but is important if the latter pathways are diminished or saturated. Obese people seem to have an enhanced capacity to detoxify molecules that can use the glucuronidation pathway. However, damage to the capacity for oxidative phosphorylation, which takes place in the mitochondria, is likely to diminish the capacity for glucuronide conjugation.

If the liver's detoxification pathways are excessively stimulated and overly utilized, they eventually become depleted or begin to respond poorly - being suppressed by toxic chemicals. Once breakdown of the main pathways occurs as a result of pollutant overload, toxins are shunted to lesser pathways, eventually overloading them, and disturbing orderly nutrient metabolism. Chemical sensitivity may then occur, followed by nutrient depletion and finally a "fixed-name disease".

Glucuronidation appears to work well, except for those with **Gilbert's syndrome** - a relatively common syndrome characterized by a chronically elevated serum bilirubin level (1.2-3.0 mg/dl).

Previously considered rare, this disorder is now known to affect as much as 5% of the general population. The condition is usually without serious symptoms, although some patients do complain about loss of appetite, malaise, and fatigue (typical symptoms of impaired liver function). The main way this condition is recognized is by a slight yellowish tinge to the skin and white of the eye due to inadequate metabolism of bilirubin, a breakdown product of hemoglobin. The activity of UDPGT is increased by foods rich in the monoterpene limonene (citris peel, dill weed oil, and caraway oil). **Methionine, administered as SAM, has been shown to be quite beneficial in treating Gilbert's syndrome.**

Glutathione conjugation:

A primary phase II detoxification route is conjugation with glutathione (a tripeptide composed of three amino acids--cysteine, glutamic acid, and glycine). **Glutathione conjugation** helps to detoxify and eliminate poisons in the liver, lungs, intestines, and kidneys. The attachment of glutathione to toxins helps to detoxify and eliminate fat soluble toxins, especially heavy metals like mercury, cadmium and lead. Glutathione-S-transferase (GST) also detoxifies other fat-soluble environmental toxins such as many solvents, herbicides, fungicides, polycyclic aromatic hydrocarbons and lipid peroxides. Decreased glutathione conjugation capacity may incrase toxic burden and increase oxidative stress. Glutathione-S-tranferase affords protection against oxidative stress (especially by reducing hydrogen peroxide and by regenerating oxidized vitamins C and E).

Glutathione is a very important antioxidant and anti-cancer agent in the body. Its production requires the presence of amino acids such as cysteine, glutamic acid and glycine. Nutrients that help to increase glutathione levels include Vitamin C, alpha-lipoic acid, whey protein, and the amino acids glutamine and methionine.

The elimination of fat-soluble compounds is dependent upon adequate levels of glutathione, which in turn is dependent upon adequate levels of methionine and cysteine. When increased levels of toxic compounds are present, more methionine is utilized for cysteine and glutathione synthesis. Methionine and cysteine have a protective effect on glutathione and prevent depletion during toxic overload. This, in turn, protects the liver from the damaging effects of toxic compounds and promotes their elimination.

Exposure to high levels of toxins depletes glutathione faster than it can be produced or absorbed from the diet. This results in increased susceptibility to toxin-induced diseases, such as cancer, especially if phase I detoxification system is highly active. Disease states due to glutathione deficiency are not uncommon. A deficiency can be induced either by diseases that increase the need for glutathione, deficiencies of the nutrients needed for synthesis, or diseases that inhibit its formation.

Smoking increases the rate of utilization of glutathione, both in the detoxification of nicotine and in the neutralization of free radicals produced by the toxins in the smoke. If you smoke, stop. Avoid exposure to herbicides, fungicides, insect sprays and industrial solvents.

Glutathione is available through two routes: diet and synthesis. Dietary glutathione (found in fresh fruits and vegetables, cooked fish, and meat) is absorbed well by the intestines and does not appear to be affected by the digestive processes. Consumption of colorful vegetables and fruits, vitamin C, N-Acetyl-Cysteine and Milk Thistle. Liberally consume cruciferous vegetables

(broccoli, cauliflower, kale, cabbage, bok choi, etc...) and allium vegetables (onions, garlic, shallots, etc.). Vitamin E supplementation may also be helpful.

Dietary glutathione in foods appears to be efficiently absorbed into the blood. However, the same may not be true for glutathione supplements.

Acetylation:

In this pathway, Acetyl Co-A is attached to toxins to make them less harmful and easy to excrete. In order for this pathway to work at its optimal level, Vitamin B5 (Pantothenic Acid), Thiamine (B1) and Vitamin C are needed.

Conjugation of toxins with acetyl-CoA is the primary method by which the body eliminates sulfa drugs. This system appears to be especially sensitive to genetic variation, with those having a poor acetylation system being far more susceptible to sulfa drugs and other antibiotics.

Acetylation is the chief degradation pathway for compounds containing aromatic amines such as histamine, serotonin, PABA, P-amino salicylic acid, aniline and procaine amide. It is also a pathway for sulphur amides, aliphatic amines and complex hydrazines.

N-acetyl Transferase detoxifies many environmental toxins, including tobacco smoke and exhaust fumes. A proportion of the general population - perhaps up to 50 per cent - are slow acetylators. This rises to as high a level as 80 per cent among the chemically sensitive population. Their N-acetyltransferase activity is thought to be reduced, and this prolongs the action of drugs and other toxic chemicals, thus enhancing their toxicity. **Slow** acetylators have a build up of toxins in the system and **rapid** acetylators add acetyl groups so rapidly that they make mistakes in the process. Both slow and rapid acetylators are at increased risk for toxic overload if they are exposed to environmental toxins. If the toxin exposure is reduced, the risk is reduced. Urinary bladder cancer appears to have the most consistent association with low acetyleation. **Minimizing Risks**: If you smoke, stop. Your risk of lung cancer is substantially higher than someone with normal NAT activity. Even occasional smoking or exposure to second hand smoke is harmful.

Liberal consumption of most vegetables and fruits but especially cruciferous vegetables (broccoli, Brussels sprouts, cauliflower, watercress, and cabbage), garlic, onions, soy, grapes and berries will increase Phase II efficienty, including acetylation.

Amino acid conjugation:

The conjugation of toxins with amino acids occurs in this pathway. The amino acids commonly used in this pathway include glycine, taurine and glutamine, but arginine, and ornithine are also used.These amino acids help to excrete many toxic chemicals, called xenobiotics, from the environment. Amino acids are found in protein-rich foods if they are eaten in adequate amounts.

Acylation (peptide conjugation with amino acids)

Acylation uses acyl CO-A with the amino acids **glycine, glutamine and taurine**. Conjugation of bile acids in the liver with glycine or taurine is essential for the efficient removal of these potentially toxic compounds. Disturbed acylation by pollutant overload decreases proper levels

of bile in the gastrointestinal tract, resulting in poor assimilation of lipids and fat-soluble vitamins, and disturbed cholesterol metabolism.

Glycination Pathway

Salicylates and benzoate are detoxified primarily through glycination. Benzoate is present in many food substances and is widely used as a food preservative. Many other substances are detoxified as well via the glycine conjugation pathway. Patients suffering from xenobiotic overloads and environmental toxicity may not have sufficient amounts of glycine to cope with the amount of toxins they are carrying.

People suffering from hepatitis, alcoholic liver disorders, carcinomas, chronic arthritis, hypothyroidism, toxemia of pregnancy, and excessive chemical exposure are commonly found to have a poorly functioning amino acid conjugation system. For example, using the benzoate clearance test (a measure of the rate at which the body detoxifies benzoate by conjugating it with glycine to form hippuric acid, which is excreted by the kidneys), the rate of clearance in those with liver disease is 50% of that in healthy adults

Even in apparently normal adults, a wide variation exists in the activity of the glycine conjugation pathway. This is due not only to genetic variation, but also to the availability of glycine in the liver. Glycine, and the other amino acids used for conjugation, become deficient on a low-protein diet and when chronic exposure to toxins results in depletion.

Toluene, the most popular industrial organic solvent, is converted by the liver into benzoate, which, like aspirin and other salicylates, must then be detoxified by conjugation with the amino acid glycine (glycination). Large doses of glycine and N-glycylglycine are used in treating aspirin overdose. Benzoate is present in many food substances and is widely used as a food preservative.

Glycine is a commonly available amino acid, but the capacity to synthesize taurine may be limited by low activity of the enzyme cysteine-sulfinic acid decarboxylase. Damage can occur to this enzyme directly by pollutants, or by overload/over-use resulting in depletion.

Both taurine- and glycine-dependent reactions require an alkaline pH: 7.8 to 8.0. Environmental medicine specialists may alkalinize over-acidic patients by administering sodium and potassium bicarbonate in order to facilitate these reactions.

Methylation:

Involves conjugating methyl groups to toxins. This pathway is used to detoxify many steroid hormones, including estrogen. The principle amino acid methionine drives this pathway, which requires co-factors Vitamin B12, Folic Acid (B9) and Choline to function properly. Methylation eventually yields usable sulfate with the help of the trace mineral molybdenum.

Sulfoxidation transforms toxic sulfite molecules into sulfate with the assistance of the mineral molybdenum. This is the last part of the methylation process (see above). Sulfites are compounds that are added to some foods to preserve freshness. For example, they are often found in wine, dried fruit, dehydrated foods, seasonings, and salad dressings. Many restaurants use them on salad bar foods. Ironically, sulfites, which can be highly allergenic and can interfere with breathing in those who are sensitive to them, are also added to some asthma medications.

Methylation involves conjugating methyl groups to toxins. Most of the methyl groups used for detoxification come from S-adenosylmethionine (SAM). SAM is synthesized from the amino acid methionine, a process which requires the nutrients choline, vitamin B12, and folic acid. SAM is able to inactivate estrogens (through methylation), supporting the use of methionine in conditions of estrogen excess, such as PMS. Its effects in preventing estrogen-induced cholestasis (stagnation of bile in the gall bladder) have been demonstrated in pregnant women and those on oral contraceptives. In addition to its role in promoting estrogen excretion, methionine has been shown to increase the membrane fluidity that is typically decreased by estrogens, thereby restoring several factors that promote bile flow. Methionine also promotes the flow of lipids to and from the liver in humans. Methionine is a major source of numerous sulfur-containing compounds, including the amino acids cysteine and taurine.

According to environmental medicine specialist William Rae, the process most often disturbed in the chemically sensitive involves methylation reactions catalysed by S-adenosyl-L-methonine-dependent enzymes. Methionine is the chief methyl donor to detoxify amines, phenols, thiols, noradrenaline, adrenaline, dopamine, melatonin, L-dopa, histamine, serotonin, pyridine, sulphites and hypochlorites into compounds excreted through the lungs. Methionine is needed to detoxify the hypochlorite reaction. The activity of the methyltransferase enzyme is dependent on magnesium, and, due to the frequency of magnesium deficiency, supplementation with this nutrient will often stabilize chemically sensitive patients.

Catechol-O-methyl transferase is the enzyme primarily responsible for breaking down the neurotransmitters dopamine, epinephrine, and norepinephrine. Catechol-O-methyltransferase inactivates catecholamines, catechol estrogens, and catechol drugs such as L-DOPA. A polymorphism in COMT results in reduced COMT activity, thus decreased degradation of these compounds. Risk may be increased for some neuropsychiatric disorders, imparied estrogen metabolism, increased sensitivity to pain, and late-onset alcoholism. **Note**: Epinephrine is the same as adrenaline, and norepinephrine is the same as noradrenaline.

Minimizing Risks: Avoid excessive alcohol consumption; seek help if alcohol consumption is a health issue. Minimize sustained mental and environmental stress (stress hormones require COMT for their degradation, thus can decrease the methylation of estrogen compounds). Ensure adequate intake of B vitamins, magnesium, and protein.

Other liver functions in detail

Filtering the Blood

One of the liver's primary functions is filtering the blood. Almost 2 quarts of blood pass through the liver every minute for detoxification. Filtration of toxins is absolutely critical as the blood from the intestines contains high levels of bacteria, bacterial endotoxins, antigen-antibody complexes, and various other toxic substances. When working properly, the liver clears 99% of the bacteria and other toxins during the first pass. However, when the liver is damaged, such as in alcoholics, the passage of toxins increases by over a factor of 10.

Sulfoxidation

Sulfoxidation is the process by which the sulfur-containing molecules in drugs and foods are metabolized. It is also the process by which the body eliminates the sulfite food additives used

to preserve many foods and drugs. Various sulfites are widely used in potato salad (as a preservative), salad bars (to keep the vegetables looking fresh), dried fruits (sulfites keep dried apricots orange), and some drugs. Normally, the enzyme *sulfite oxidase* metabolizes *sulfites* to safer *sulfates*, which are then excreted in the urine. Those with a poorly functioning sulfoxidation system, however, have an increased ratio of sulfite to sulfate in their urine. The strong odor in the urine after eating asparagus is an interesting phenomenon because, while it is unheard of in China, 100% of the French have been estimated to experience such an odor (about 50% of adults in the U.S. notice this effect). This example is an excellent example of genetic variability in liver detoxification function. Those with a poorly functioning sulfoxidation detoxification pathway are more sensitive to sulfur-containing drugs and foods containing sulfur or sulfite additives. This is especially important for asthmatics, which can react to these additives with life-threatening attacks. Molybdenum helps asthmatics with an elevated ratio of sulfites to sulfates in their urine because sulfite oxidase is dependent upon this trace mineral.

Bile Excretion

The liver's second detoxification process involves the synthesis and secretion of bile for the elimination of modified toxins. Each day the liver manufactures approximately 1 quart of bile, which serves as a carrier in which many toxic substances are dumped into the intestines. In the intestines, the bile and its toxic load are absorbed by fiber and excreted. However, a diet low in fiber results in inadequate binding and reabsorption of the toxins. This problem is magnified when bacteria in the intestine modify these toxins to more damaging forms.

When the excretion of bile is inhibited (i.e. *cholestasis*), toxins stay in the liver longer. Cholestasis has several causes, including obstruction of the bile ducts and impairment of bile flow within the liver. The most common cause of obstruction of the bile ducts is the presence of gallstones. Currently, it is conservatively estimated that 20 million people in the U.S. have gallstones. Nearly 20% of the female and 8% of the male population over the age of 40 are found to have gallstones on biopsy and approximately 500,000 gall bladders are removed because of stones each year in the U.S. **The prevalence of gallstones in this country has been linked to the high-fat, low-fiber diet consumed by the majority of Americans.**

Impairment of bile flow within the liver can be caused by a variety of agents and conditions. These conditions are often associated with alterations of liver function in laboratory tests (*serum bilirubin, alkaline phosphatase, SGOT, LDH, GGTP*, etc.) signifying cellular damage. However, relying on these tests alone to evaluate liver function is not adequate, since, in the initial or subclinical stages of many problems with liver function, laboratory values remain normal.

Among the symptoms people with enzymatic damage complain of are: Fatigue; general malaise; digestive disturbances; allergies and chemical sensitivities; premenstrual syndrome; constipation.

Perhaps the most common cause of cholestasis and impaired liver function is alcohol ingestion. In some especially sensitive individuals, as little as 1 ounce of alcohol can produce damage to the liver, which results in fat being deposited within the liver. All active alcoholics demonstrate fatty infiltration of the liver.

Methionine, taken as SAM, has been shown to be quite beneficial in treating two common causes of stagnation of bile in the liver--***estrogen excess*** (due to either oral contraceptive use, estrogen overload from xenoestrogens or pregnancy) and ***Gilbert's syndrome***.

Gall Stones

"Fatty Liver" affects more than 50% of people over the age of 50! Common causes are incorrect diet, excessive alcohol intake, adverse reactions to drugs and toxic chemicals, and viral hepatitis. The gallbladder operation is the most common operation in North America. Every year, more than half a million people in the United States and more than 50,000 people in Canada undergo surgery to remove their gallbladders because of gallstones. 90% of people have gallstones. 80% of people do not know that they have gallstones. 50% of children have gallstones. Approximately 80% of all gallstones show no symptoms and may remain "silent" for years."

So where do I start?

One of the most important principles of detoxification is that you need to clean your bowels first and replenish its normal ecology through the eradication of pathogens and the reintroduction of good bacteria through pro-biotics. The phrase: “You need to clean downstream before you can clean upstream”, implied that you should clean your bowels first, otherwise you will be sending dirty water from the gut to a clean chemical plant at the liver! This is a common cause for so called detoxification-illness.

Practically that means assess the ecology of the bowels with a **stool test**. Thereafter follow these common gut-cleaning principles:

First, **Weed** (remove offending foods and pathogens), then
Seed (take appropriate pro-biotics), and thereafter
Feed (eat the correct foods for your body).

Many people will have developed a **leaky gut** by the time they are ill, and so often the gut lining needs to be repaired during the initial **weeding** phase by using certain products containing glutamine, DLG (DeGlycerized Licorice so as to remove the cortisol retaining properties) and aloe (with the laxative properties removed). An example of a good product that can achieve this is **Glutagenics** by Metagenics.

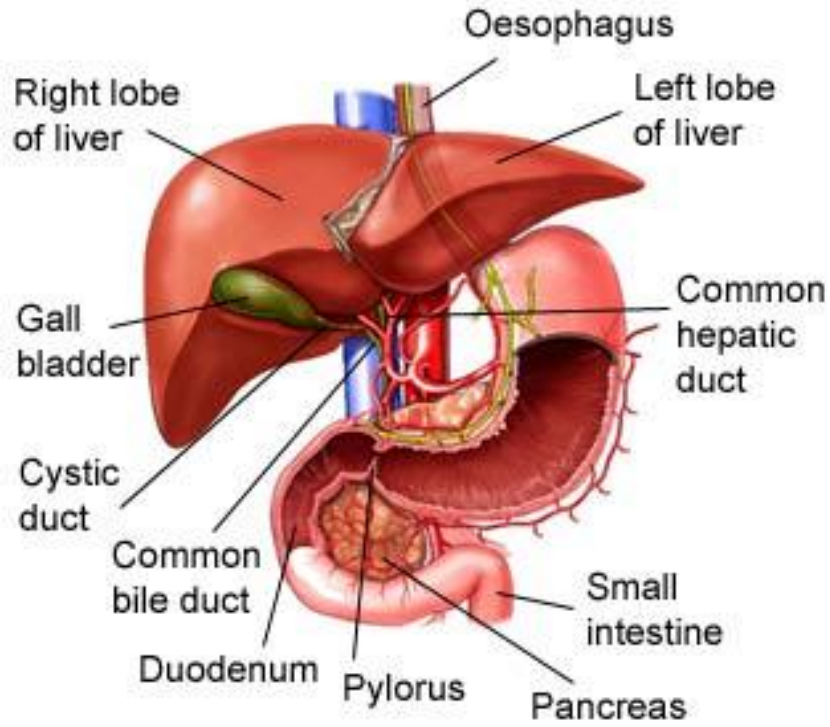
Make sure you get your gut health better before taking compounds to assist your liver pathways. This is a vital step not to miss out!

Another vital consideration before beginning a detoxification program is to ensure that your metabolism is up to the task, by addressing your adrenals and thyroid. Your body temperature indicates just how well your adrenal and thyroid hormones are having an effect at a receptor level. You need your daily average (based on three oral temperatures taken around 9am, 12noon and 3pm) to measure 98.6 degrees F/37 degrees C and stable for good health. If they are higher one day and lower the next, it indicates adrenal problems – because the adrenals control the *stability* of internal temperature. If they are low but stable, it indicates thyroid problems – because the thyroid hormones (T3 in specific) lift the temperature. Saliva testing of the adrenals by DiagnosTechs Labs, and temperature testing and thyroid blood tests, will help you figure out if these glands are making sufficient adrenal and thyroid hormones to keep you healthy.

The thyroid labs will measure the **glandular output** (how much hormone is been secreted by the glands in the blood), while temperatures will measure the effectiveness of the hormones at a **receptor level** i.e. are the actually doing what they are supposed to.

To summarise:

- Tackle your gut first. Get a stool test and use probiotics, diet, and supplements to heal the gut lining.
- Look into your hormonal system. **Important:** work on your adrenals first, and thereafter look towards your thyroid, via thyroid support, in order to begin moving your body temperature, closer towards 37 degrees C (98.6F) and towards stability.
- Address your liver pathways if necessary (as above), and:
- Continue down your detoxification path to remove offending metals – Ex: with oral chelation.



Interesting facts:

- Dr William Rae of the Environmental Health Centre in Dallas says that the most severely ill chemically sensitive patients not only have abnormally low antipollutant enzymes in addition to toxic suppression and nutrient depletion, but in some instances antibodies are produced against cytochrome P450 and these may inhibit or decrease its effectiveness.
- Environmental medicine specialists have found that almost 35 per cent of chemically sensitive patients are deficient in intracellular sulphur. Not only can this hinder the detoxification of some sulphur-containing and other toxic chemicals, it can enhance the harmful effects of exposure to cyanide from foods such as cassava and almonds as well as from tobacco products. The hereditary disease known as Leber's optic atrophy involves a genetic defect in the ability to detoxify cyanide, and leads to sudden, permanent blindness on first exposure to cyanide in small amounts such as those ingested from smoking cigarettes.

- Many practitioner multimineral supplements in the UK omit iron and copper due to theories that individuals may already be overloaded with these nutrients. However if no overload is present, an unbalanced supplement may promote depletion of the minerals. The Environmental Health Centre in Dallas finds that intravenous infusions to replenish iron stores brings dramatic improvements for the chemically sensitive patient as part of their detoxification process. Copper is also found to help catalyze the cytochrome systems. (NB: self-supplementation with iron and copper should be cautious, to avoid iron and copper overload conditions).
- Although the liver microsomal system is the primary site for oxidation of xenobiotics, the cytochrome P450 system is found in other tissues that are exposed to environmental compounds like the skin, lungs, gastrointestinal tract, kidneys, placenta, corpus luteum, lymphocytes, monocytes, pulmonary alveolar macrophages, adrenals, testes and brain, in both the mitochondria and in the nuclear membrane.
- Always rinse your washing-up carefully. Pollutants in the form of solvents and detergents can damage and penetrate the cell membrane and damage the contents of the cell.
- Vitamin B3 has been shown to accelerate the clearance of aldehydes in some chemically sensitive patients.
- Molybdenum, although an essential element, competes with sulphate in its activation step to the important enzyme PAPS and can thus lower sulphate levels and impair sulphation ability. Environmental medicine experts warn that molybdenum supplementation may be contraindicated in individuals with poor sulphation ability.
- The substance naringenin, found in grapefruit, can significantly inhibit Phase I detoxification, as can grapefruit itself. This may prove clinically useful in some situations where Phase I activity is too high, (as shown in liver function tests available from nutritional therapists).
- Persons who have been exposed to toxic chemicals, drugs and other xenobiotics (foreign substances), have increased requirements for some vitamins. Functional nutritional assays for vitamins B1, B2, B3, B6, B12 and folate, and serum levels of vitamins A, D, C and beta carotene were performed in a random sample of 333 environmentally-sensitive patients prior to treatment. 57.8% were found to be deficient in B6, 37.7% in vitamin D, 34.9% in B2, 32.2% in folate, 27.7% in vitamin C, 21.4% in niacin, 14.9% in B12, 5.6% in vitamin A and 4.6% in beta-carotene. *(Ross GH et al: Evidence for vitamin deficiencies in environmentally-sensitive patients. Clinical Ecology 6(2):60-6, 1989.)*

LIVER REFERENCES - PHASE 1

1. Ross A. McKinnon and Michael E. McManus (1996). Localization of Cytochromes P450 in Human Tissues: Implications for Chemical Toxicity, Pathology, 28, 148 - 155.
2. Michael Murray and Gordon F. Reidy (1990). Selectivity in the Inhibition of Mammalian Cytochromes P450 by Chemical Agents, Pharmacological Reviews, 42/2, 85 -101.
3. Uwe Fuhr, Kristina Klittich & A. Horst Staib (1993). Inhibitory effect of grapefruit juice and its bitter principle, naringenin, on CYP1A2 dependant metabolism of caffeine in man.
4. MA Kall and J Clausen (1995). Dietary effect of mixed function P450 1A2 activity assayed by estimation of caffeine metabolism in man, Human & Experimental Toxicology, 14, 801 - 807.
5. F Peter Guengerich (1995). Influence of nutrients and other dietary materials on cytochrome P-450 enzymes, Am J Clin Nutr, 61 (suppl), 651S - 8S.
6. Karl Ludwig Rost, MD, and Ivar Roots, MD (1993). Accelerated caffeine metabolism after omeprazole treatment is indicated by urinary metabolite ratios: Coincidence with plasma clearance and breath test, Clinical Pharmacology & Therapeutics, 55/4, 402-411.
7. F Peter Guengerich (1995). Influence of nutrients and other dietary materials on cytochrome P-450 enzymes, AM J Clin Nutr, 61(suppl), 651S-8S.

8. Yan Li, Erija Wang, Chris J. Patten, Laishun Chen, and Chung S. Yang (1994). Effects of Flavonoids on Cytochrome P450-Dependent Acetamophen Metabolism in Rats and Human Liver Microsomes, Drug Metabolism and Disposition, 22/4, 565-571.
9. Werner Kalow, MD and Bing-Kou Tang, PhD (1991). Caffeine as a metabolic probe: Exploration of the enzyme-inducing effect of cigarette smpking, Clin Pharmacol Ther, 49/1, 44-48.
10. Atholl Johnston (1995). Effect of grapefruit juice on cyclosporin concentration, The Lancet, 346, 122-123.
11. Gary C Yee, Denise L Stanley, Lisa J Pessa, Teresa Dalla Costa, Susan E Beltz, Jorge Ruiz, David T Lowenthal (1995). Effect of grapefruit juice on cyclosporin concentration, The Lancet, 345, 955-956.
12. J A G Agundez, M C Ledesma, Prof J Benitez, J M Ladero, A Rodriguez-Lescure, E Diaz-Rubio, M Diaz-Rubio (1995). CYP2D6 genes and risk of liver cancer, The Lancet, 345, 830-831.
13. Agneta Rannug, PhD, Anna-Karin Alexandrie, BSc, Irene Persson, BSc, Magnus Ingelman-Sundberg, PhD, BScM (1995). Genetic Polymorphism of Cytochromes P450 1A1, 2D and 2E1: Regulation and Toxicological Significance, JOEM, 37/1, 25-36.
14. Daniel W. Nebert, David R. Nelson, Minor J. Coon, Ronald W. Eastbrook, Rene Feyereisen, Yoshiaki Fujii-Kuriyama, Frank J. Gonzalez, F. Peter Guengerich, Irwin C. Gunsalus, Eric F. Johnson, John C. Loper, Ryo Sato, Michael R. Waterman and David Waxman (1991). The P450 Superfamily: Update on New Sequences, Gene Mapping, and Recommended Nomenclature, DNA and Cell Biology, 10/1, 1-14.
15. Brent A. Neuschwander-Tetri, MD (1995). Common blood tests for liver disease. Which ones are most useful? Postgraduate Medicine, 98/1, 49-63.
16. Ross A. McKinnon and Michael E. McManus (1996). Localisation of Cytochromes P450 in Human Tissues: Implications for Chemical Toxicity, Pathology, 28, 148-155.
17. Yan Li, Erija Wang, Chris J. Patten, Laishun Chen, and Chung S. Yang (1994). Effects of Flavonoids on Cytochrome P450-Dependant Acetaminophen Metabolism in Rats and Human Liver Microsomes, Drug Metabolism and Disposition, 22/4, 566-571.
18. Nathalie Roland, Lionelle Nugon-Baudon, Jean-Pierre Flinois and Philippe Beaune (1994). Hepatic and Intestinal Cytochrome P-450 Glutathione-S-Transferase and UDP-Glucuronosyl Transferase Are Affected by Six Types of Dietary Fibre in Rats Inoculated with Human Whole Fecal Flora, J Nutr., 124, 1581-1587.
19. K. D. R. Setchell, Mary Beth Welsh, Marquelle J. Klooster and W. F. Balistreri (1987). Rapid High-Performance Liquid Chromatography Assay for Salivary and Serum Caffeine Following an Oral Load, Journal of Chromatography, 385, 267-274.
20. William D. Parsons, MD, and Allen H. Neims, MD., PhD. (1978). Effect of smoking on caffeine clearance, Clin Pharmacol Ther., 24/1, 40-45.
21. Steven N Lichtman, John Keku, John H. Schwab, and R. Balfour Sartor (1991). Hepatic Injury Associated With Small Bowel Bacterial Overgrowth in Rats Is Prevented by Metronidazole and Tetracycline, Gastroenterology, 100, 513-519.

LIVER REFERENCES: PHASE II

1. Tory M. Hagen, Grazyna T. Wierzbicka, Barbara B. Bowman, Tak Yee Aw, and Dean P. Jones (1990). Fate of dietary glutathione: disposition in the gastrointestinal tract, Am J. Nutr., 259, G530-G535.
2. A. J. Hutt, J. Caldwell and R. L. Smith (1986). The metabolism of aspirin in man: a population study, Xenobiotica, 16/3, 239-249.
3. Gerhard Levy (1986). Sulfate conjugation in drug metabolism: role of inorganic sulfate,

Federation Proceedings, 45/8, 2235-2240.
4. Margie L. Clapper, Christine E. Szarka, Gordon R. Pfeiffer, Todd A. Graham, Andrew M. Balshem, Samuel Litwin, Eric B. Goosenberg, Harold Frucht, and Paul F. Engstrom (1997). Preclinical and Clinical Evaluation of Broccoli Supplements as Inducers of Glutathione S-Transferase Activity, Clinical Cancer Research, 3, 25-30.
5. Sonia M. F. De Morais, Jack P. Uetrecht, and Peter G. Wells (1992). Decreased Glucoronidation and Increased Bioactivation of Acetaminophen in Gilbert's Syndrome, Gastroenterology, 102, 577-586.
6. M Thomas Heafield, Simon Fearn, Glyn B. Steventon, Rosemary H. Waring, Adrian C. Williams and Steven G. Sturman (1990). Plasma cysteine and sulphate levels in patients with Motor neurone, Parkinson's and Alzheimer's disease, Neuroscience Letters, 110, 216-220.
7. A. Temellini, S. Mogavero, P.C. Giulianotti, A. Pietrabissa, F. Mosca and G. Pacifici (1993). Conjugation of benzoic acid with glycine in human liver and kidney: a study on the interindividual variability, Xenobiotica, 23/12, 1427-1433.
8. M. M. Reicks and D. Crankshaw (1993). Effects of D-limonene on hepatic microsomal monooxygenase activity and paracetamol-induced glutathione depletion in mouse, Xenobiotica, 23/7, 809-819.
9. Marion Man-Ying Chan, Chi-Tang Ho, Hsing-I Huang (1995). Effects of three dietary phytochemicals from tea, rosemary and turmeric on inflammation-induced nitrite production, Cancer Letters, 96, 23-29.
10. Elizabeth A. Offord, Katherine Mace, Ornella Avanti, Andrea M. A. Pfeifer (114). Mechanisms involved in the chemoreceptive effects of rosemary extract studied in human liver and bronchial cells, Cancer Letters, 114, 275-281.
11. Seif O Shaheen, Jonathan A C Sterne, Christina E Songhurst, Peter G J Burney (2000). Frequent paracetamol use and asthma in adults, Thorax, 55, 266-270.
12. Chandradhar Dwivedi, Wendy J. Heck, Alan A. Downie, Saroj Larroya, and Thomas E. Webb (1990). Effect of Calcium Glucarate on ß-Glucoronidase Activity and Glucarate Content of Certain Vegetables and Fruits, Biochemical Medicine and Metabolic Biology, 43, 83-92.

Sources:

http://livingnetwork.co.za/chelationnetwork/food/liver-detox-pathways/

http://www.positivehealth.com/articles/weight-loss/548

http://www.articlesbase.com/diseases-and-conditions-articles/an-integrative-approach-to-the-prevention-and-treatment-of-postpartum-depression-ppd-and-postpartum-anxiety-disorder-ppa-3002403.html

http://www.life-enthusiast.com/index/Articles/Cabot/Liver_Detoxification

http://phyto-homeopathy.blogspot.com/2007/04/blog-post_8689.html

http://gut.bmj.com/content/58/12/1690.abstract

http://www.biomatrixone.com/support_liver.html

http://www.suite101.com/content/foods-that-detox-the-liver-a145910

http://tuberose.com/Liver_Detoxification.html