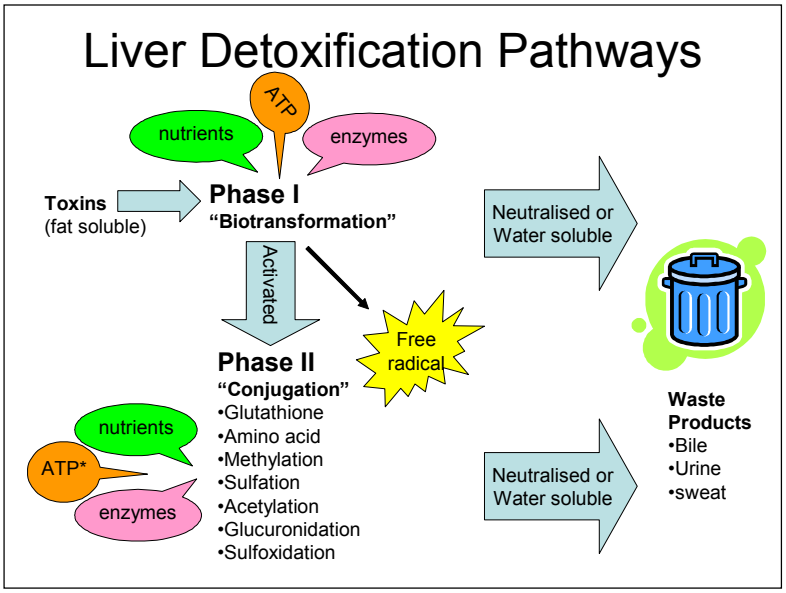
Supporting the Liver's Detoxification Process through Diet and Nutrition

The human body, in its infinite quest for homeostasis, is designed to protect itself from a myriad of internal and external hazards. Some hazards come in the form of toxins. Murray & Pizzorno (1998) define a toxin as "any compound that has a detrimental effect on cell function or structure (p105). Toxins consist of unwanted compounds such as drugs, alcohol, food additives, heavy metals, insecticides, pesticides, micro-organisms as well as normal body metabolite end products such as hormones and inflammatory chemicals (such as histamines) which would become toxic if allowed to build up (Cabot, 2004). It is generally accepted that today's exposure to environmental toxins is high (Murray & Pizzorno, 1998) (Baillee-Hamilton, 2004) (Cabot, 2004) (Williams, 1998).

The body handles these toxins in one of two ways: by eliminating the offending substance or by transforming the toxin to a less harmful substance. (Jeffrey, 2006) The major pathways in the body for detoxification are the gastrointestinal system (including the liver and the large intestine), the urinary system (through the kidneys), the respiratory system (expired through the lungs), the skin (perspired) and the lymphatic system (Williams, 1998). This paper will investigate the liver's detoxification process.

Liver Detoxification Process

One of the liver's primary functions is to filter the blood. In fact, it filters about 1.7 litres of blood every minute. While some blood comes from the hepatic artery to feed the liver with oxygen and nutrients, the majority arrives from the portal vein having gathered through small capillaries surrounding the small intestine, all the ingested nutrients and toxins (Williams, 1998). This blood is sent to the liver to carry out its many functions including breakdown, assimilation and storage of vitamins and minerals, breakdown and inactivation of various hormones and microbes, metabolism of carbohydrates, fats and protein, secretion of bile, and detoxification of drugs and noxious substances (Waugh & Grant, 1998).



Most toxins are fat-soluble and thus difficult for the body to expel through the normal routes. To cope with this, the liver operates a two-stage

enzyme-driven detoxification system to neutralize or convert these toxins to water-soluble for easy excretion, referred to a Phase I and Phase II.

Phase I

Phase I enzyme activities include oxidation, reduction and hydrolysis. The main active enzymes in this phase are collectively known as *cytochrome P450* (CYP450). This family of enzymes detoxifies xenobiotics as well as assists in the metabolism of nutrients and endogenous molecules such as essential fatty acids, phytonutrients, steroid hormones, and vitamins A and D. (Jeffery, 2006)

When Phase I metabolizes a toxin, referred to as "*biotransformation*", it either:

1. chemically transforms it to a less toxic state,
2. makes it water-soluble, or
3. converts it to a more chemically active form to be passed on to Phase II. (Bland, 2006)

The first option is certainly the most desirable result. This is, for example, what becomes of caffeine. The second is also effective as a water-soluble toxin can easily be excreted. (Murray & Pizzorno, 1998)

The final case is the most common route (Bland, 2006). CYP450 bioactivates the toxin by adding a hydroxyl group to the lip-soluble toxin, using nicotinamine adenosine dinucleotide (NADH) as a cofactor (Liska & Bland, 2006). But the side effect of Phase I is that as toxins are activated, free radicals are produced. (Murray & Pizzorno, 1998)

Phase II

Phase II detoxification involves a process called *conjugation* whereby various enzymes bind protective compounds to the toxin to either neutralize the toxin or to render it water-soluble. Phase II conjugation pathways include:

- glutathione
- amino acid
- methylation
- sulfation
- sulfoxidation
- acetylation
- glucuronidation (Murray & Pizzorno, 1998).

These various pathways process different toxins and nutrients, depending on the chemical structure of their corresponding enzymes. Some toxins may be processed by multiple routes. The commoner substrates as well as some symptoms of dysfunction are listed in Table 1 below.

Glutathione conjugation is the most common Phase II detoxification route (60% of activity (Colert, 2005)) rendering toxins water soluble. Glutathione is a tripeptide composed of amino acids (cysteine, glutamic acid and glycine) and is one of our most important antioxidants also used to attack the free radicals released in Phase I activation. (Murray & Pizzorno, 1998)

System	Some substrates	Some symptoms of dysfunction
Phase I	Caffeine, histamine, hormones, benzopyrene (bbq meat), yellow dyes, insecticides, ibuprofen, lidocaine, codeine, diazepam, alcohol, cortisone, testosterone, warfarin, many common otc and prescription drugs	Caffeine intolerance, chemical sensitivity (eg perfume makes you sick)
Phase II **Glutathione**	Nicotine, organophosphates, heavy metals	Chronic signs of toxicity, lowered immunity, premature ageing
Phase II **Amino acid**	Benzoate (food preservative), aspirin	Hepatitis, alcoholic liver, carcinomas, chronic arthritis, hypothyroidism, pregnancy toxaemia
Phase II **Methylation**	Oestrogen, dopamine, adrenal hormone, histamine	PMS, conditions of excessive oestrogen (eg cholestasis)
Phase II **Sulfation**	Steroid hormones (eg oestrogen), warfarin, phenolic compounds, paracetamol, sulfur food additives, thyroid hormones, neurotransmitters	Some nervous disorders
Phase II **Acetylation**	Sulfa drugs (eg UTI antibiotics), mescaline	Not fully understood
Phase II **Glucuronidation**	Paracetamol, morphine, diazepam, digitalis, menthol, aspirin, synthetic vanilla, benzoates, many common prescription drugs.	Gilbert's disease, jaundice not from hepatitis
Phase II **Sulfoxidation**	Sulfites, food preservatives, asthma drugs, garlic compounds	Reaction to sulfites & garlic, asparagus odour

(Cabot, 2004) (Murray & Pizzorno, 1998)

Several amino acids (glycine, taurine, glutamine, arginine and arithine) are used to combine with and neutralize toxins in *amino acid conjugation*, with glycine the most common. (Murray & Pizzorno, 1998)

Methylation involves methyl groups mostly from S-adenosylmethionine (SAM) which is synthesized from the amino acid methionine. Through methylation, SAM inactivates estrogens. Methionine also promotes the flow of lipids to and from the liver and is a major source of sulfur-containing compounds and amino acids cysteine and taurine. *Sulfation* and *sulfoxidation* target and metabolise various sulfur containing drugs and foods with sulfations as the primary route for the elimination of neurotransmitters. *Acetylation* targets toxins with acetyl CoA and is subject to genetic variation and not fully understood. *Glucuronidation*, combining glucuronic acid with toxins, requires UPD-glucuronyl transferase (UDPGT) and works well in most people, except those with Gilbert's syndrome. (Murray & Pizzorno, 1998)

Importance of Bifunctional Balance

One can now begin to see the implicit interdependencies. Firstly, it is important that Phase I works efficiently and effectively. If Phase I is unable to keep up with the inflow of toxins, either because it is defective or because inflow is too great, these toxins will be left to circulate in the blood. As they are fat-soluble, they will be stored in body fat for later processing. In fact, Murray & Pizzorno (1998) suggest that those who typically develop cancer are either exposed to a lot of carcinogens or are whose CYP450 isn't working well. We know that CYP450 activity varies individually (Liska & Bland, 2006), possibly accounting for the variety of outcomes, such as why a heavy smoker may never get lung cancer while another does from passive smoke.

Another scenario is one where Phase I is working appropriately, but deficiencies are found in Phase II. In this case activated intermediates, often more toxic than the original toxin, along with free radicals released during activation, begin to build up and circulate awaiting Phase II. Williams (1998) likens this situation to cleaning asbestos out of the attic by dragging it openly through to house, into the windy garden and off to the bin collectors! Additionally, the key antioxidant for neutralizing Phase I free radicals is glutathione, also a major enzyme for Phase II. Thus, when the toxic exposure is high, GSH can become used up leaving none available for Phase II, also enhancing toxin exposure. (Liska & Bland, 2006)

Signs and symptoms of liver overload

Liver function tests exist to evaluate the various pathways discussed, but damage is normally significant before a malfunction is evident (Baillee-Hamilton, 2004). Some early signs, however, may become evident, including:

- abnormalities in the *metabolism of fats* such as elevated LDL cholesterol, reduced HDH cholesterol and elevated triglycerides, cellulite, lumps of fat in the skin (lipomas), abdominal weight gain and signs of a fatty liver (Cabot, 2004)
- hyperglycemia and *unstable blood sugar levels* related to fatty liver (Cabot, 2004)
- *immune dysfunction* such as increased allergies, asthma, autoimmune diseases) such as chronic fatigue syndrome and fibromyalgia) and increased viral/bacterial infections. This may occur because the body's detoxification system is overwhelmed and becomes oversensitive to toxins which it would otherwise have fought off (Balliee-Hamilton, 2004)
- *digestive problems*, especially IBS and IBD, gall stones, food intolerances, abdominal bloating, constipation, pain over the liver (Cabot, 2004)
- *skin problems* such as acne, psoriasis and eczema (Hobbs (2002)
- nervous system disorders, especially *depression*. Some believe that the primary cause of most depression is liver dysfunction. The build up of toxins enter the nervous system and directly interfere with brain and central nervous system, leading to feelings of apathy, lethargy and often depression. (Ballentine, 1978) Moodiness and anger is also linked to liver problems (Hobbs, 2002)
- *hormonal imbalances*, such as HRT or contraceptive pill intolerances and severe menopausal and PMS symptoms (Cabot, 2004).
- *Arthritis* and weak tendons, ligaments and muscles (Hobbs, 2002)
- General external signs including: coated tongue, bad breath, dark circles under eyes, red eyes, liver spots, red palms and soles, (Cabot, 2004) blurring eyes, bitter taste in the mouth (Hobbs, 2002).

In addition, toxins that have been stored in body fat and are later released during times of stress, exercise or fasting can present symptoms of toxicity including headaches, dizziness, poor memory, stomach pain, nausea, fatigue, and palpitations (Baillee-Hamilton, 2004).

Nutritional support for detoxification

To work effectively, Phase I and II enzyme systems require nutrition. In fact, the different pathways have specific nutritional needs. When these needs are not met, the pathway will not function properly and subsequently not process the related toxins effectively. Metabolic energy is also essential and if the liver cells' mitochondria are not functioning with sufficient amounts of energy in the form of adenosine triphosphate (ATP), due to magnesium deficiency or lack of exercise, Phase II detoxification will slow down leading to a build-up of toxic intermediates. (Liska & Bland, 2006)

Nutrients for Phase I

To assist activation:
- vitamins B2, B3 and B6,
- iron,
- magnesium,
- manganese,
- molybdenum,
- zinc

Protect against side effects
- vitamins A, C and E,
- beta-carotene,
- flavonoids,
- proanthocyanidins
- selenium
- co-enzyme Q10
- omega-3 oils
- MSM sulfate

(Williams, 1998) (Baillee-Hamilton, 2004) (Murray & Pizzorno, 1998)

Table 2 lists the nutrients useful to assist Phase I activation as well as anti-oxidants useful to protect the body from introduced free radicals. B vitamins are required for generation of NADH (used by CYP450) (Liska & Bland, 2006). Foods that ensure that Phase I is working well include:

- Brassica-family foods (such as cabbage, broccoli and Brussels sprouts). This family has constituents that stimulate both Phase I and II enzymes such as indole-3-carbinol, considered a powerful anticancer compound. (Murray & Pizzorno, 1998)
- Vitamin B-rich foods (such as nutritional yeast and whole grains) to assist Phase I activation.
- Vitamin C-rich foods (such as peppers, cabbage and tomatoes) as antioxidants to protect during Phase I.
- Citrus foods such as oranges and tangerines (not grapefruit) as well as caraway and dill seeds contain limonene, a strong inducer of both Phase I and II enzymes. (Note that grapefruit reduces CYP450 activity by as much as 30%, thereby reducing the rate of detoxification).
- Turmeric, containing curcumin which inhibits Phase activation while stimulating Phase II, thereby increasing detoxification of activated toxins. (Cabot, 2004)
- High antioxidant foods, including:
    - Green tea
    - Proanthocyanidins found in grape juice and red wine

- Quercetin, found in green and black tea, red wine, garlic, tomatoes, peppers (green and cayenne), broccoli, grapes, berries and apples. (Cabot, 2004)

Table 3 provides a summary of the nutrients recommended to support Phase II.

- Glutathione, essential to the majority of the detoxification, and can be found in fresh fruit and vegetables, especially asparagus, avocados and fresh meat. (Baillee-Hamilton, 2004). Vitamin C has been found to increase levels (500mg Vitamin C daily increased level by 50%) (Murray & Pizzorno, 1998) Artichoke has also been found to reduce glutathione loss (Liska & Bland, 2006).

System	Nutrients (Murray & Pizzorno, 1998) (Cabot, 2004) (Baillee-Hamilton, 2004)
Phase II Glutathione	Brassicas, limonene, asparagus, avocado, walnuts, vitamin C
Phase II Amino acid	Protein-rich foods especially in times of chronic toxin stress, glycine
Phase II Methylation	Lipotropic nutrients: choline, methionine, betaine, folic acid, B12
Phase II Sulfation	Sulfur contain foods (egg yolks, red peppers, garlic, onions, shallots, brocolli & Brussels sprouts), cysteine, methionine, taurine
Phase II Acetylation	Thiamine (B1), pantothenic acid (B5) and vitamin C
Phase II Glucuronidation	Limonene (citrus peel, dill & caraway seed oil), sulfur-rich foods, citrus fruits (not grapefruit)
Phase II Sulfoxidation	Molybdenum (legumes & whole grains)

- Lipotropic nutrients (including choline, betaine, methione, B6, folic acid and B12) promote the flow of fat and bile to and from the liver, and feed both methylation (SAM) and glutathione pathways. (Cabot, 2004). Specific foods include: beets, egg yolks, soy beans, grains and nuts.
- High sulfur foods, such as garlic, cabbage, onions, leeks, shallots, seafood, asparagus and eggs feed the sulfation, glucuronidation and sulfoxidation pathways.
- High quality protein as a source of amino acids. (Liska & Bland, 2006)

And finally, are foods that are considered biofunctional modulators, meaning that they support optimal detoxification balance by modulating Phase I, inducing several Phase II activities, and minimizing damage by active reactive molecules. Examples include: ellagic acid (found in pomegranates and many berries), catechins (found in green tea and red grapes) and glucosinolates (found in brassicas such as broccoli and watercress). (Liska, & Bland, 2006)

Conclusions and Recommendations

The liver's detoxification system is a bit like the motorway network around London. What is important to understand, however, is that in order to keep our carcinogenic exposure down, it is important that this system run both efficiently and effectively. In order to do so, several recommendations are appropriate:

- Keep your exposure to unnecessary toxins down (for example smoking, alcohol,
- Don't overeat! It over burdens the liver. (Ballentine, 1978)

- Drink plenty of water (1.5-3 litres/day) to help the kidneys flush out toxins. (Cabot, 2004)
- Eat plenty of soluble fiber, such as beans, pulses, oats, apples and oranges (supplemented as ground psyllium seeds, fruit pectins and gums) which bind to toxins traveling through the gut, helping excretion. (Baillee-Hamilton, 2004)

If you feel, for whatever reason, that you have an excess of toxins in your system, nourish your liver's detoxification system! If you plan to diet, which will necessarily release stored toxins from your fat, nourish you liver's detoxification system! Many of today's detoxification nutritionalists NO LONGER support water fasts (Liska & Bland, 2006) (Jefferies, 2006) (Baillee-Hamilton, 2004). Murray & Pizzorno (1998) only support a three day juice fast. In fact all authors suggest taking large supplements during any time when detoxification or weight loss is planned (but supplements are another topic).

Food for Liver Detoxification

- Brassica family (broccoli, cabbage, watercress, Brussels sprouts)
- High sulfur-containing foods (garlic, onions, eggs, leeks)
- Citrus fruits (lemons, oranges, tangerines, not grapefruit)
- Water-soluble fibres (pears, oat bran, apples, legumes)
- Protein (such as fish, nuts, soy, legumes)
- Artichoke, avocados, asparagus, red grapes, pomegranates, beets, turmeric, green tea, caraway & dill seeds apples, tomatoes, peppers, berries , bean sprouts, carrots, olive oil, yeast, whole grains

But remember, that the liver's detoxification system is multifaceted and it is important that all its pathways are functioning well – both Phase I and II. Eat a well-rounded mix of nutrients!

References

1. Baillie-Hamilton, P, 2005, *Stop the 21st century killing you,* London: Vermilion

2. Ballentine, R, 1978, *Diet & nutrition,* Pennsylvania: Himalayan Institute

3. Bland, J, 2006, "Managing Biotransformation: Introduction and Overview", *13th International Symposium of The Institute for Functional Medicine,* pp85-87

4. Cabot, S, 2004, *The liver cleansing diet",* New York: HarperCollins

5. Colbert D, 2005, "Nutrients for the liver: your body's natural detox system" in *Share Guide,* Jan/Feb 2005, available at http://web.ebscohost.com.ezproxy.library.wales.ac.uk:2048/ehost/pdf?vid=10&hid=114&sid=ded6ad49-4241-4d92-98fe-4382dee5328c%40sessionmgr109 [accessed 18 April, 2007]

6. Hobbs, C, 2002, *Natural therapy for your liver,* 2nd ed., New York: Avery

7. Jeffrey, EH, 2006, "Detoxification Basics" and "Diet and Detoxification Enzymes",, *13th International Symposium of The Institute for Functional Medicine,* pp96-99

8. Liska, DJ.& Bland, JS, 2006, "Emerging clinical science of bifunctional support for detoxification" in *Townsend Letter for Doctors & Patients,* Jul2006 Issue 276, p96-101, 6p; available at http://web.ebscohost.com.ezproxy.library.wales.ac.uk:2048/ehost/pdf?vid=9&hid=114&sid=ded6ad49-4241-4d92-98fe-4382dee5328c%40sessionmgr109 [accessed 18 April, 2007]

9. Murray M & Pizzorno J, 1998, *Encyclopedia of natural medicine,* 2nd ed, New York: Three Rivers Press

10. Waugh A & Grant A, 1998, *Anatomy and physiology,* 9th ed., Edinburgh: Elsevier

11. Williams, X, 1998, *Liver detox plan,* London: Vermilion