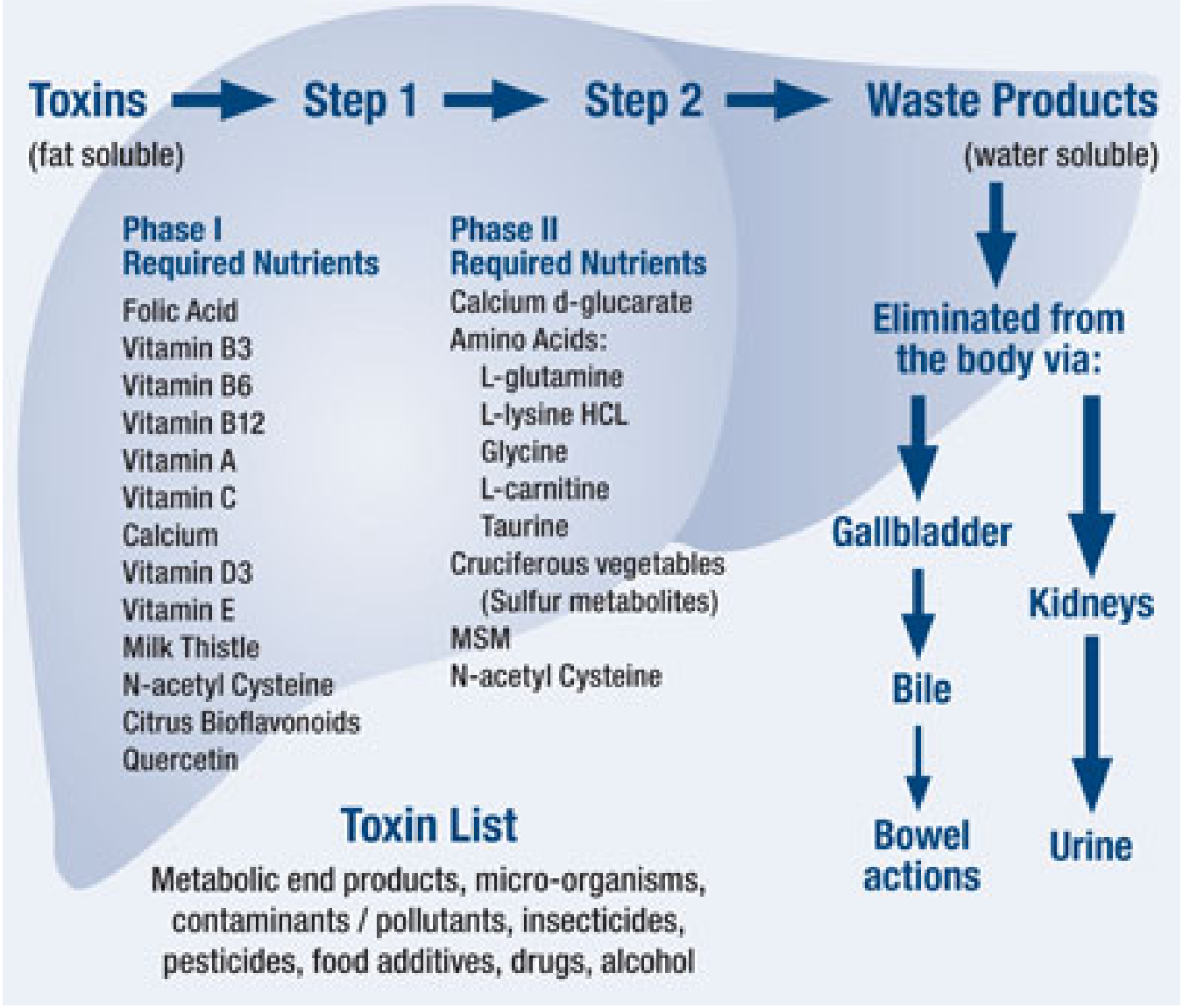
LIVER DETOXIFICATION PATHWAYS

Inside the liver cells there are sophisticated mechanisms that have evolved over millions of years to break down toxic substances; they are called Liver Detox Pathways.

FIG 1. Liver Detoxification Pathways and Supportive Nutrients



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Books:

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***Natural Therapy for Your Liver* by Christopher Hobbs**
***Cleanse and Purify Thyself* by Dr. Richard Anderson**
***Eating for Beauty* by David Wolfe**

Articles:

What Conventional Medicine Won't Dare Tell You About Gallbladder Removal Surgery by Mike Adams

Websites:

www.LivingNetwork.co.za

Audio/Video:

DVD: Crazy Sexy Cancer with Kris Carr
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Publications:

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Conventional:

"You Can't Cleanse the Liver"
Pharmaceuticals
Charcoal-Broiled Meats
Environmental/Industrial Toxins

Terms:

conjugation
Glutathione
Phase-I
Phase-II

LIVER PHASES 1 AND 2 DETOXIFICATION PATHWAYS

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

The liver phases in a nutshell

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).

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 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.

The seven parts (conveyor belts) of the phase 2 **system are called:**

The Glycine pathway
The Taurine pathway
The Glutathione pathway
The Sulphation (sulfation) pathway
The Methylation pathway
The Glucoronidation pathway
The Acetylation pathway

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.

Lab tests

Some labs such as Genova Labs (they used to be known as Great Smokies Lab) used to test the ability of the liver to detoxify substances through its pathways, through their Liver Detoxification Profile, which assessed the pathways by challenging them with specific substances, such as caffeine for the phase 1 pathway. However, since this form of challenge testing only focused on one of the phase 1 enzyme, its clinical significance was of lessor value. It is no longer available and has since been replaced by the DetoxiGenomic® Profile test, which is much more comprehensive in the sense that it looks at your DNA and check for the presence or absence of certain SNP's, which are simply areas of your DNA which code for how you detoxify substances.

Genova says this test, "evaluates SNPs associated with increased risk of impaired detoxification capacity especially when exposed to environmental toxins. It also identifies individuals potentially susceptible to adverse drug reactions." The value of this test is that you only ever have to do it once in your life, as genes do not change. The benefits of its clinical application at this stage are still unknown to us, and we shall report back once we know more.

- *In USA:* Genova Labs for the DetoxiGenomic Profile test.
- *In Europe & the UK:* Contact Genova Europe
- *In South Africa:* Pathcare will be starting an association with Genova Labs towards the end of 2010, whereby some Genova tests will become available. We will let you know when this occurs.

There is a more comprehensive article on the liver pathways here… It is well worth reading.

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 they actually doing what they are supposed to.

To summarise:

- Tackle your gut first. Get a stool test and use pro-biotics, 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 e.g with oral chelation.

PHASE 1 AND 2 LIVER DETOXIFICATION PATHWAYS

Source:
http://www.carahealth.ie/index.php?option=com_content&view=article&id=365%3Aphase-1-and-2-liver-detoxification-pathways&catid=263%3Adetox&Itemid=217&lang=en

Inside the liver cells there are sophisticated mechanisms that have evolved over millions of years to break down toxic substances.

Every drug, artificial chemical, pesticide and hormone, is broken down (metabolised) by enzyme pathways inside the liver cells.

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 made of fatty substances. In these fatty parts of the body, toxins may be stored for years, being released during times of exercise, stress or fasting. During the release of these toxins, symptoms such as headaches, poor memory, stomach pain, nausea, fatigue, dizziness and palpitations may occur. The body's primary defence against metabolic poisoning is carried out by the liver.

The liver has two mechanisms designed to convert fat-soluble chemicals into water soluble chemicals so that they may then be easily excreted from the body via watery fluids such as bile and urine.

How the Liver Detoxifies

There are two major detoxification pathways inside the liver cells, which are called the Phase 1 and Phase 2 detoxification pathways.

Toxin list

- metabolic end products
- micro organisms
- contaminants/pollutants
- insecticides
- pesticides
- food additives
- drugs
- alcohol

Phase One - Detoxification Pathway

Phase one detoxification consists of oxidation reduction and hydrolysis. **Phase one detoxification is catalysed by enzymes referred to as the cytochrome P-450 enzyme group or Mixed Function Oxidase enzymes MFO.** These enzymes reside on the membrane system of the liver cells (called Hepatocytes). Human liver cells possess the genetic code for many isoenzymes of P-450 whose synthesis can be induced upon exposure to specific chemicals. This provides a mechanism of protection from a wide variety of toxic chemicals.

To put it simply, this pathway converts a toxic chemical into a less harmful chemical. This is achieved by various chemical reactions (such as oxidation, reduction and hydrolysis), and during this process free radicals are produced which, if excessive, can damage the liver cells. Antioxidants (such as vitamin C and E and natural carotenoids) reduce the damage caused by these free radicals. If antioxidants are lacking and toxin exposure is high, toxic chemicals become far more dangerous.

Some may be converted from relatively harmless substances into potentially carcinogenic substances. Excessive amounts of toxic chemicals such as pesticides can disrupt the P-450 enzyme system by causing over activity or what is called 'induction' of this pathway. This will result in high levels of damaging free radicals being produced. The danger is if these reactive molecules are not further metabolised by Phase II conjugation, they may cause damage to proteins, RNA, and DNA within the cell.

Substances that may cause overactivity (or induction) of the P- 450 enzymes

- Caffeine
- Alcohol
- Dioxin
- Saturated fats
- Organophosphorus pesticides
- Paint fumes
- Sulphonamides
- Exhaust fumes
- Barbiturates

The family of P-450 enzyme systems is quite diverse, with specific enzyme systems being inducible by particular drugs, toxins or metabolites. It is this characteristic that has allowed the development of special tests to check the function of the various pathways.

The Substrates (the substance acted upon by the enzyme) of cytochrome P-450 enzymes.

- Theophylline
- caffeine
- phenacetin
- acetaminophen
- Lidocaine
- erythromycin

- cyclosporin
- ketoconazole
- testosterone
- estradiol
- cortisone
- Alprenolol
- bopindolol
- carvedilol
- metoprolol
- propranolol
- Amitriptyline
- clomipramine
- desipramine
- nortriptyline
- Codeine
- dextrometh- orphan
- ethylmorphine
- 4-methoxyamphetamin
- Phenytoin
- ibuprofen
- naproxen
- oxicam drugs
- S-warfarin
- Diazepam
- hexobarbitone
- imipramine
- omeprazole
- alcohol
- chlorzoxazone
- enflurane

Cofactors of P-450 Phase 1 detoxification

NADH, riboflavin, niacin, magnesium, iron, certain indoles from cruciferous vegetables.

Substances that inhibit cytochrome P-450

Many substances inhibit cytochrome P-450. This situation can cause substantial problems as it makes toxins potentially more damaging because they remain in the body longer before detoxification.

Grapefruit

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 P-450 activity by a remarkable 30%.

Curcumin

Curcumin, the compound that gives turmeric its yellow colour, 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 grilled 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.

Phase-I detoxification and aging

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 ageing individuals.

Phase-II Detoxification Pathway

This is called the conjugation pathway, whereby the liver cells add another substance (eg. cysteine, glycine or a sulphur molecule) to a toxic chemical or drug, to render it less harmful. This makes the toxin or drug water-soluble, so it can then be excreted from the body via watery fluids such as bile or urine.

Major Phase-II pathways

- **Glutathione**
- **Sulphate**
- **Glycine**
- **Glucuronide conjugations**

Through conjugation, the liver is able to turn drugs, hormones and various toxins into water soluble excretable substances. Individual xenobiotics and metabolites usually follow one or two distinct pathways. This makes testing of the various pathways possible by challenging with known substances.

Sulphur containing foods and amino acids stimulate phase II detoxification

For efficient phase two detoxification, the liver cells require sulphur-containing amino acids such as taurine and cysteine. The nutrients glycine, glutamine, choline and inositol are also required for efficient phase two detoxification.

Eggs and cruciferous vegetables (eg. broccoli, cabbage, Brussels sprouts, cauliflower), raw garlic, onions, leeks and shallots are all good sources of natural sulphur compounds to enhance phase two detoxification. Thus, these foods can be considered to have a cleansing action.

The phase two enzyme systems include both UDP-glucuronyl transferase (GT) and glutathione-S-transferase (GSH-T).

Glutathione-S-transferase

Glutathione-S-transferase is the most powerful internal antioxidant and liver protector. It can be depleted by large amounts of toxins and/or drugs passing through the liver, as well as starvation or fasting. Phase II reactions may follow Phase I for some molecules or act directly on the toxin or metabolite.

Substrates of the glycine pathway

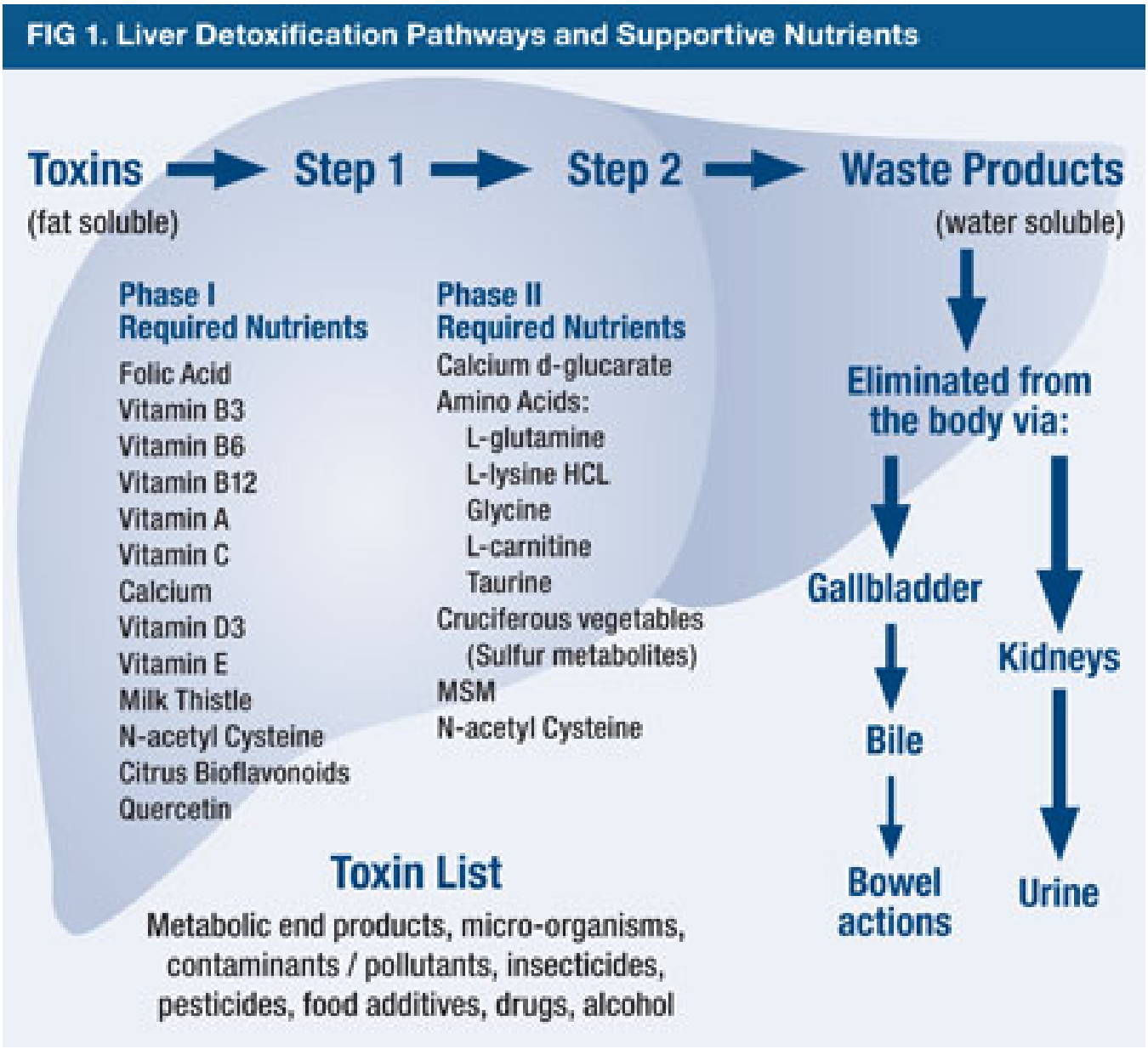
Salicylates and benzoates are detoxified primarily through glycination. Benzoate is present in many food substances and is widely used as a food preservative. Many other substances are detoxified as well via the glycine conjugation pathway. Patients suffering from xenobiotic overloads and environmental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

Substrates of the sulphation pathways

Neurotransmitters, steroid hormones, certain drugs such as Acetaminophen (also known as paracetamol) and many xenobiotic and phenolic compounds.

Substrates of glucuronidation

Polycyclic aromatic hydrocarbons, steroid hormones, some nitrosamines, heterocyclic amines, some fungal toxins, and aromatic amines. It also removes "used" hormones, such as oestrogen and T4 (thyroid hormone) that are produced naturally by the body.



Toxic Overload

If the phase one and two detoxification pathways become overloaded, there will be a build up of toxins in the body. Many of these toxins are fat soluble and incorporate themselves into fatty parts of the body where they may stay for years, if not for a lifetime. The brain and the endocrine (hormonal) glands are fatty organs, and are common sites for fat-soluble toxins to accumulate. This may result in symptoms of brain dysfunction and hormonal imbalances, such as infertility, breast pain, menstrual disturbances, adrenal gland exhaustion and early menopause. Many of these chemicals (eg. pesticides, petrochemicals) are carcinogenic and have been implicated in the rising incidence of many cancers.

Bitter herbs to improve phase 1 and 2 detoxification

Bitter herbs are the corner stone of herbal medicine. A range of physiological responses occur following stimulation of the bitter receptors of the tongue. The bitter taste stimulates the specific

bitter taste buds at the back of the tongue to stimulate the parasympathetic nervous system to trigger a number of reflexes. These reflexes are important to the digestive process and general health.

Specifically in relation to digestion herbal bitters;

Sialogogues – stimulate saliva to digest carbohydrates.

Orexogenics – stimulate hydrochloric acid to digest protein.

Chologogues – Stimulate bile flow to digest fats.

The stimulation of the flow of digestive juices from the exocrine glands of mouth, stomach, pancreas, duodenum and liver, aid in digestion, absorption and assimilation of foods and nutrients. There is also a very mild stimulation of endocrine activities, especially insulin and glucagon secretion by the Islets of Langerhans in the pancreas therefore used to treat of non-insulin dependent diabetes. By promoting the flow of bile, bitters assists the liver in its detoxifying capacity.

THIS ONE ANTIOXIDANT KEEPS ALL OTHER ANTIOXIDANTS PERFORMING AT PEAK LEVELS

Source: Mercola.com by Dr. Joe Mercola and Ori Hofmekler
http://articles.mercola.com/sites/articles/archive/2010/04/10/can-you-use-food-to-increase-glutathione-instead-of-supplements.aspx

By Dr. Mercola, & Ori Hofmekler

Glutathione is your body's most powerful antioxidant and has even been called "the master antioxidant." It is a tripeptide found inside every single cell in your body.

Antioxidants are crucial in eliminating free radicals from your body. Free radicals are basically very reactive particles that bounce all around the cell damaging everything they touch. Most originate during the process of metabolism but they can also arise from exposure to toxins, irradiation, and toxic metals.

Because free radicals are so destructive, cells have a network of defenses designed to neutralize them. This antioxidant network is composed of numerous components that include vitamins, minerals and special chemicals called thiols (glutathione and alpha-lipoic acid).

Glutathione is comprised of three amino acids: cysteine, glutamate, and glycine.

Glutathione is sometimes confused with glutamine and glutamate due to the similarity in names. Although all three molecules are related, they are different in composition and function. When you are healthy, the three are balanced and do a delicate dance within your body.

In a nutshell, this is the difference between the three:

1. Glutamine: Your body's most abundant amino acid, made in your brain from glutamate; has a major role in various anti-injury processes and muscle repair; a precursor to glutathione.
2. Glutathione (two types, GSH and GSSG): The "master antioxidant"—most powerful antioxidant in your body, present in every cell. Protects cells, and especially important for liver health; breaks down into free glutamate.
3. Glutamate (aka glutamic acid or L-glutamate): Monopeptide amino acid neurotransmitter in your brain—required for synaptic activity. You don't want too much of it—it's an excitotoxin. (See also monosodium glutamate, or MSG)

Glutathione is different from other antioxidants in that it is *intracellular*. It has the unique ability of maximizing the activity of all the other antioxidants, including vitamins C and E, CoQ10, alpha lipoic acid, and the fresh veggies and fruits you (hopefully) eat every day. It removes toxins from your cells and protects you from the damaging effects of radiation, chemicals, and environmental pollutants.

You might think that a miracle molecule such as glutathione might be a good thing to put into supplement form. As usual, science loses to nature when it comes to optimizing this health-promoting little gem.

There is currently a great deal of hype about glutathione supplementation, highly popularized as a "miracle" means to boost health, prevent disease and fight aging.

Let's separate some of the facts from the myths about how glutathione works and look at the right way to build your body's glutathione reserves.

How Glutathione Works

The main function of glutathione is to protect your cells and mitochondria from oxidative and peroxidative damage. As you age, your body's ability to produce glutathione decreases.

Glutathione isn't just an endogenous antioxidant--it is also an essential factor in energy utilization, detoxification, and preventing the diseases we associate with aging. Glutathione deficiency has been linked to:

- Age-related diseases such as Alzheimer's and Parkinson's
- Coronary and autoimmune diseases
- Arthritis, asthma and other inflammatory conditions
- Cancer
- Mitochondrial dysfunction
- Muscle weakness and fatigue

Synthesis of glutathione depends upon adenosine triphosphate (ATP), which is the molecule that provides cellular energy. It follows that glutathione levels are linked to energy deficiency, or low ATP.

This is a major reason why exercise is so beneficial for your overall health—among other things, it boosts your glutathione levels!

If you can enhance internal glutathione production, you will strengthen your immune system in a way that will shield you from many of the adverse effects of aging.

Do Glutathione Supplements Work?

Your body is quite poor at getting glutathione from your digestive system into your blood. Most oral glutathione supplements have been shown to be poorly absorbed and a waste of your hard-earned money.

There has been some success with intravenous glutathione supplementation, but this is certainly not practical and very expensive and should be reserved for extreme situations. Glutathione supplementation can help people with immunodeficiency but only to a certain degree, and only temporarily—kind of like recharging a dead battery.

Ironically, glutathione supplements may actually interfere with your body's own glutathione production.

The human body is programmed to self-produce its own antioxidant enzymes such as glutathione and SOD (superoxide dismutase, the first antioxidant mobilized by your cells for defense). And synthetic supplementation of these compounds actually signal your body to stop its own production – which leaves you dependent on synthetic substances (supplements or drugs).

Glutathione levels can be enhanced somewhat by taking supplements such as alpha lipoic acid, which is known to regenerate glutathione. Alpha lipoic acid also helps to regenerate vitamins C and E so that they remain active longer in your body. Red meat and organ meats are the best dietary source of alpha lipoic acid.

Glutamine can be used as a supplement since it's a direct precursor to glutathione. However, there is quite a bit of evidence it is poorly absorbed.

There is also evidence that vitamin D increases intracellular glutathione. Unless you are a newcomer to my website, you know that I am an enthusiastic fan of vitamin D, and this is yet one more reason it's so important for your health.

Some nutritional authorities recommend taking a form of cysteine known as N-acetyl-cysteine (NAC), but I would advise against using this supplement if you still have mercury amalgam fillings because it could interfere with detoxification of the mercury.

Fortunately, there are natural ways to boost your body's glutathione reserves.

Vitamins and supplements have their uses but are always less desirable than nutrients in their natural form, obtained from the foods you eat. What has been proven beyond a doubt is that whole food based diets--rich in vegetables, fruits, nuts, seeds, and quality protein--promote health and longevity.

What Foods Promote the Highest Glutathione Levels?

Many whole foods contain significant amounts of glutathione or its precursors. Foods richest in sulfur-containing amino acids are usually the best sources of glutathione:

- The overall top food for maximizing your glutathione is high quality **whey protein**. It must be cold pressed whey protein derived from grass fed cows, and free of hormones, chemicals and sugar.
  Quality whey provides all the key amino acids for glutathione production (cysteine, glycine and glutamate) and contains a unique cysteine residue (glutamylcysteine) that is highly bioactive in its affinity for converting to glutathione.

  Glutamylcysteine is a bonded cysteine molecule (cysteine plus glutamate) that naturally occurs in Bovine Serum Albumin – a fragile immune component of the whey. This unique cysteine is exclusive to whey and rarely appears in other protein foods – which makes whey protein the best glutathione-promoting food source.

  Furthermore, whey provides critical co-factors, immunoglobulins, lactoferrin and alpha Lactalbumin (also a great source of cysteine), which together help create the right metabolic environment for high glutathione activity.

- **Raw milk products, raw eggs and meat**: Glutathione occurs in the highest levels in fresh, uncooked meats and raw milk, *but is almost entirely absent in pasteurized dairy products*.

- **Fresh fruits and vegetables** provide excellent glutathione, but once cooked, values become negligible. Spinach, potatoes, asparagus, avocado, squash, okra, cauliflower, broccoli, walnuts, garlic and tomatoes have the highest glutathione per serving.

- The herb **milk thistle** is an excellent source of the antioxidant compound silymarin, which may help to prevent glutathione depletion in the liver. Glutathione is crucial in the liver for detoxification and can become depleted from acetaminophen (Tylenol), alcohol consumption, and general toxic overload.

- **Curcumin** may also be useful for increasing glutathione levels.

Keeping your glutathione levels up is a matter of increasing factors that boost your glutathione and decreasing factors that lower it. The things that deplete your glutathione the fastest are chemicals, toxins and sugar.

The Right Whey

If you want to supplement your diet with whey protein products, you have to be careful because not all whey protein products are created equal. Supermarket and nutrition store shelves are lined with protein powder choices, 99 percent of which are loaded with sugar and chemicals that don't support your health goal.

If you're going to supplement, you should only use a high quality whey protein that provides all the necessary nutritional elements for NATURALLY boosting glutathione and also preventing its decline.

Be sure your whey protein supplement has the following features:

1. The whey comes from grass-fed cows that are not treated with pesticides or hormones
2. Cold processed, since heat destroys whey's fragile molecular structure
3. Whey protein concentrate, not protein isolates
4. Sweetened naturally, not artificially, and low in carbohydrates
5. Highly digestible—look for medium chain fatty acids (MCTs), not long chain fatty acids

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LIVER DETOXIFICATION

Source: http://www.tuberose.com/Liver_Detoxification.html

THE LIVER

The liver is the most hard-working organ in the human body. It performs many functions that are vital to life. It plays an important role in digestion (breaking nutrients down) and assimilation (building up body tissues). It is the storage site for many essential vitamins and minerals, such as iron, copper, B_{12}, vitamins A, D, E and K. Red blood cells, which are responsible for carrying oxygen around the body, are also produced in the liver and Kupffer cells help to devour harmful micro-organisms in the blood so helping to fight infection.

The liver is one of the most important organs in the body when it comes to detoxifying or getting rid of foreign substances or toxins, especially from the gut. The liver plays a key role in most metabolic processes, especially detoxification. The liver detoxifies 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. 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.

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 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.

The liver neutralizes a wide range of toxic chemicals, both those produced internally and those coming from the environment. The normal metabolic processes produce a wide range of chemicals and hormones for which the liver has evolved efficient neutralizing mechanisms. However, the level and type of internally produced toxins increases greatly when metabolic processes go awry, typically as a result of nutritional deficiencies. These non-end-product metabolites have become a significant problem in this age of conventionally grown foods and poor diets.

Many of the toxic chemicals the liver must detoxify come from the environment: the content of the bowels and the food, water, and air. The *polycyclic hydrocarbons* (DDT, dioxin, 2,4,5-T, 2,3-D, PCB, and PCP), which are components of various herbicides and pesticides, are on example of chemicals that are now found in virtually all fat tissues measured. Even those eating unprocessed organic foods need an effective detoxification system because all foods contain naturally occurring toxic constituents.

The liver plays several roles in detoxification: it filters the blood to remove large toxins, synthesizes and secretes bile full of cholesterol and other fat-soluble toxins, and enzymatically disassembles unwanted chemicals. This enzymatic process usually occurs in two steps referred to as *phase I* and *phase II*. **Phase I either directly neutralizes a toxin, or modifies the toxic chemical to form activated intermediates which are then neutralized by one of more of the several phase II enzyme systems.**

Proper functioning of the liver's detoxification systems is especially important for the prevention of cancer. Up to 90% of all cancers are thought to be due to the effects of environmental carcinogens, such as those in cigarette smoke, food, water, and air, combined with deficiencies of the nutrients the body needs for proper functioning of the detoxification and immune systems. The level of exposure to environmental carcinogens varies widely, as does the efficiency of the detoxification enzymes, particularly phase II. High levels of exposure to carcinogens coupled with slow detoxification enzymes significantly increases susceptibility to cancer.

When optimum nutrition is provided the liver operates efficiently. A great many people however, do not eat the right kinds of foods to provide the liver with everything it needs for the elimination of the extra toxins bodies are exposed to daily. If nutrition is compromised through poor dietary and lifestyle habits, this will impede detoxification processes, and other organs will suffer as the body retains these toxins.

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.**

Bile Excretion

The liver's second detoxification process involves the synthesis and secretion of bile. **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.

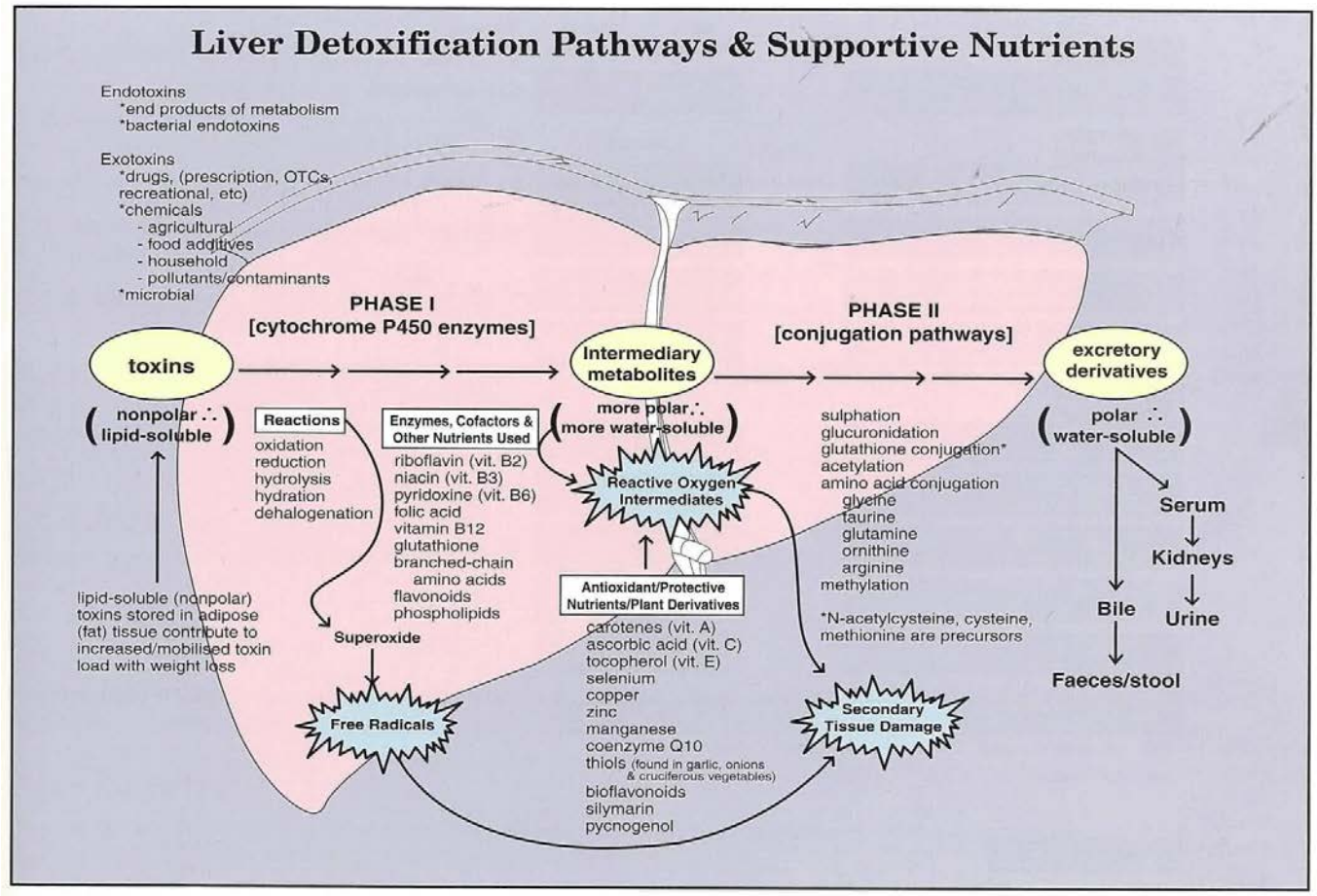
Gall Stones

"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."

Phase I Detoxification

The liver's third role in detoxification involves a two-step enzymatic process for the neutralization of unwanted chemical compounds. This pathway converts a toxic chemical into a less harmful chemical. This is achieved by various chemical reactions (such as oxidation, reduction and hydrolysis), and during this process free radicals are produced which, if excessive, can damage the liver cells. Antioxidants reduce the damage caused by these free radicals. If antioxidants are lacking and toxin exposure is high, toxic chemicals become far more dangerous. Some may be converted from relatively harmless substances into potentially carcinogenic substances.

The effects of exposure to toxins varies from individual to individual. Some people are highly sensitive to different endogenous and exogenous toxins. Others, because their bodies are more resilient and their livers can detoxify more efficiently, aren't as sensitive.. Excessive amounts of toxic chemicals such as pesticides can disrupt the P-450 enzyme system by causing hyper activity or what is called 'induction' of this pathway. This will result in high levels of damaging free radicals being produced. Substances that may cause hyperactivity of the P- 450 enzymes: Caffeine, Alcohol, Dioxin, Saturated fats, Organophosphorus pesticides, Paint fumes, Sulfonamides, Exhaust fumes, Barbiturates.



If the phase II detoxification systems are not working adequately, these intermediates can cause substantial damage, including the initiation of carcinogenic processes. Each enzyme works best in detoxifying certain types of chemicals, but with considerable overlap in activity among the enzymes.

The activity of the various cytochrome P450 enzymes varies significantly from one individual to another, based on genetics, the individual's level of exposure to chemical toxins, and his or her nutritional status. Since the activity of cytochrome P450 varies so much, so does an individual's risk for various diseases. This variability of cytochrome P450 enzymes is seen in the variability of people's ability to detoxify the carcinogens found in cigarette smoke and helps to explain why some people can smoke with only modest damage to their lungs, while others develop lung cancer after only a few decades of smoking.

Patients with underactive phase I detoxification will experience caffeine intolerance, intolerance to perfumes and other environmental chemicals, and an increased risk for liver disease, while those with an overactive system will be relatively unaffected by caffeine drinks. One way of objectively determining the activity of phase I is to measure how efficiently a person detoxifies caffeine. Using this test, **a surprising fivefold difference in the detoxification rates of apparently healthy adult has been discovered.**

When cytochrome P450 metabolizes a toxin, it chemically transforms it to a less toxic form, makes it water-soluble, or converts it to a more chemically active form. Caffeine is an example of a chemical directly neutralized by phase I. Making a toxin water-soluble allows its excretion by the

kidneys. Transforming a toxin to a more chemically reactive form makes it more easily metabolized by the phase II enzymes.

A significant side-effect of phase I detoxification is the production of *free radicals* as the toxins are transformed--**for each molecule of toxin metabolized by phase I, one molecule of free radical is generated.** Without adequate free radical defenses, every time the liver neutralizes a toxin exposure, it is damaged by the free radicals produced.

The most important antioxidant for neutralizing the free radicals produced in phase I is *glutathione*. In the process of neutralizing free radicals, however, *glutathione* (GSH) is oxidized to *glutathione disulfide* (GSSG). Glutathione is required for one of the key phase II detoxification processes. When high levels of toxin exposure produce so many free radicals from phase I detoxification that the glutathione is depleted, the phase II processes dependent upon glutathione stop, producing oxidative stress or liver damage.

Glutathione is Magnesium-Dependent

Glutathione protects the cells from oxidative-stress-induced apoptosis and **glutathione levels are magnesium dependent! Glutathione is a very important detoxifying agent**, enabling the body to get rid of undesirable toxins and pollutants. **It forms a soluble compound with the toxin that can then be excreted through the urine or the gut. The liver and kidneys contain high levels of glutathione** as they have the greatest exposure to toxins. **The lungs are also rich in glutathione** partly for the same reason. **Many cancer-producing chemicals, heavy metals, drug metabolites etc. are disposed of in this way.**

Glutathione (glū'tə-thī'ōn') is a polypeptide, C10H17N3O6S, of glycine, cysteine, and glutamic acid.

***Glutathione synthetase* requires *γ-glutamyl cysteine, glycine, ATP*, and *magnesium* ions to form glutathione.** In magnesium deficiency, the *ss y-glutamyltranspeptidase* is lowered. **There is a direct relationship between cellular magnesium, GSH/GSSG ratios, and tissue glucose metabolism. Magnesium deficiency causes glutathione loss** and this is unwelcome as the clouds of radiation are touching down across the northern hemisphere. Magnesium deficiency causes glutathione loss, which is not at all healthy because **glutathione helps to defend the body against damage** from cigarette smoking, exposure to radiation, cancer chemotherapy, and toxins such as alcohol and just about everything else.

According to Dr. Russell Blaylock, **low magnesium is associated with dramatic increases in free radical generation as well as glutathione depletion** and this is vital since **glutathione is one of the few antioxidant molecules known to neutralize mercury. "For every molecule of pesticide that your body detoxifies, you throw away or use up forever a molecule of glutathione, magnesium and more,"** says Dr. Sherry Rogers who goes on to say that, "Your body uses nutrients to make this glutathione and it uses up energy as well. **Every time we detoxify a chemical, we use up, lose, throw away forever, a certain amount of nutrients."**

The toxins transformed into activated intermediates by phase I are substantially more reactive than the phase I toxins were. Unless quickly removed from the body by phase II detoxification mechanisms, they can cause widespread problems, especially *carcinogenesis*. Therefore, the rate

at which phase I produces activated intermediates must be balanced by the rate at which phase II finishes their processing. People with a very active phase I detoxification system coupled with slow or inactive phase II enzymes are termed *pathological detoxifiers*. These people suffer unusually severe toxic reactions to environmental poisons. A liver detoxification test can pinpoint exactly how efficiently your liver is carrying out the detoxification process and if you are a pathological detoxifier.

An imbalance between phase I and phase II can also occur when a person is exposed to large amounts of toxins or exposed to toxins for a long period of time. In these situations, the critical nutrients needed for phase II detoxification are depleted, which allows the highly toxic activated intermediates to build up.

An efficient liver detoxification system is vital to health and in order to support this process it is essential that many key nutrients are included in the diet. Vitamins and minerals – particularly the B vitamins – play a major role, acting as cofactors for many enzyme systems including those of liver detoxification, therefore ensuring a plentiful supply of the B complex group of vitamins is of prime importance for optimum detoxification..Depletion of vitamin C may also impair the detoxification process; vitamin C also prevents free radical formation. Vitamin E and selenium are cofactors for glutathione peroxidase activity as well as being powerful antioxidants. Other nutrients which play vital roles in the Phase II pathway include amino acids glycine, cysteine, glutamine, methionine, taurine, glutamic acid and aspartic acid. Grapefruit juice, which contains *naringenin,* slows down Phase I enzyme activity.

Recent research shows that the cytochrome P450 enzyme systems are also found in other parts of the body, especially the brain cells. Inadequate antioxidants and nutrients in the brain result in an increased rate of neuron damage, such as seen in Alzheimer's and Parkinson's disease patients. As with all enzymes, **the cytochrome P450s require several nutrients to function,** such as copper, magnesium, zinc and vitamin C. A considerable amount of research has found that various substances *activate* cytochrome P450 while others *inhibit* it.

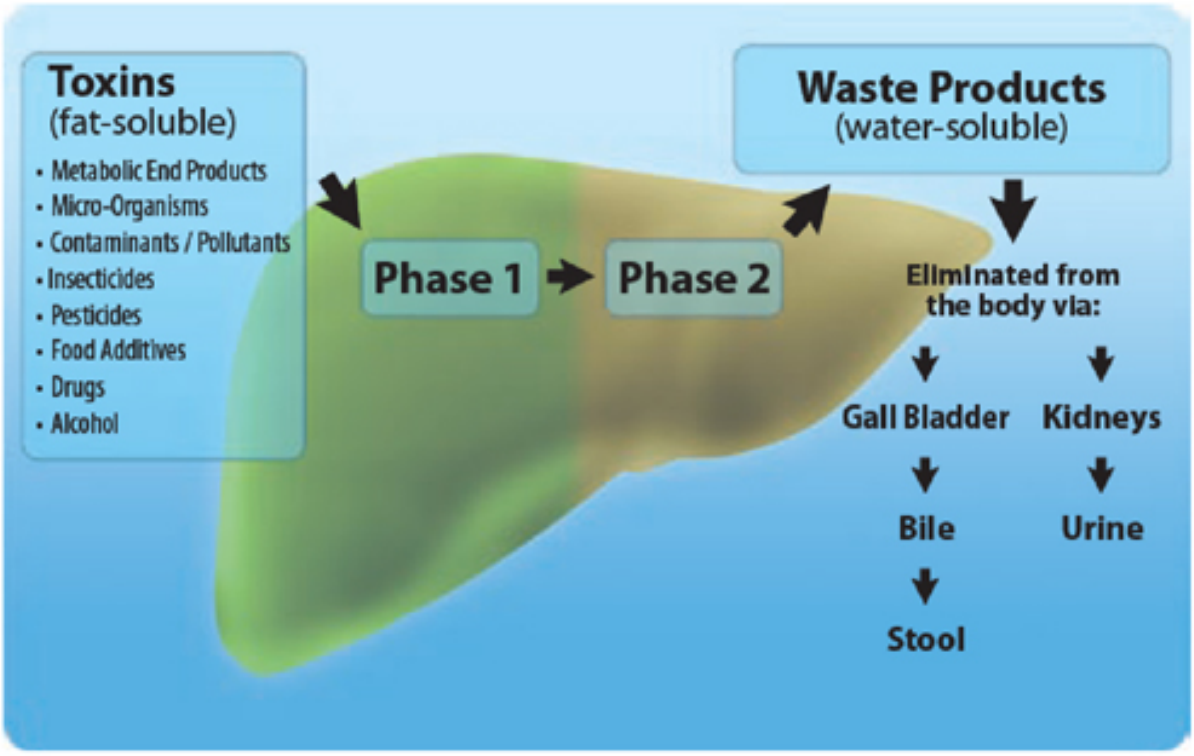
Inducers of phase I detoxification

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 I 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 family, i.e. cabbage, broccoli, and Brussels sprouts, contains chemical constituents that stimulate both phase I and phase II 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.

Figure 1 - Detoxification (Biotransformation) Pathways



Substances That Activate Phase I Detoxification

Drugs: alcohol; nicotine in cigarette smoke; Phenobarbital; sulfonamides; steroids
Foods: cabbage, broccoli, and brussels sprouts; charcoal-broiled meats; high-protein diet; 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 and dill seeds, milk thistle, sassafras tea
Environmental toxins: carbon tetrachloride; exhaust fumes; paint fumes; dioxin; pesticides

Inhibitors of Phase I Detoxification

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.**

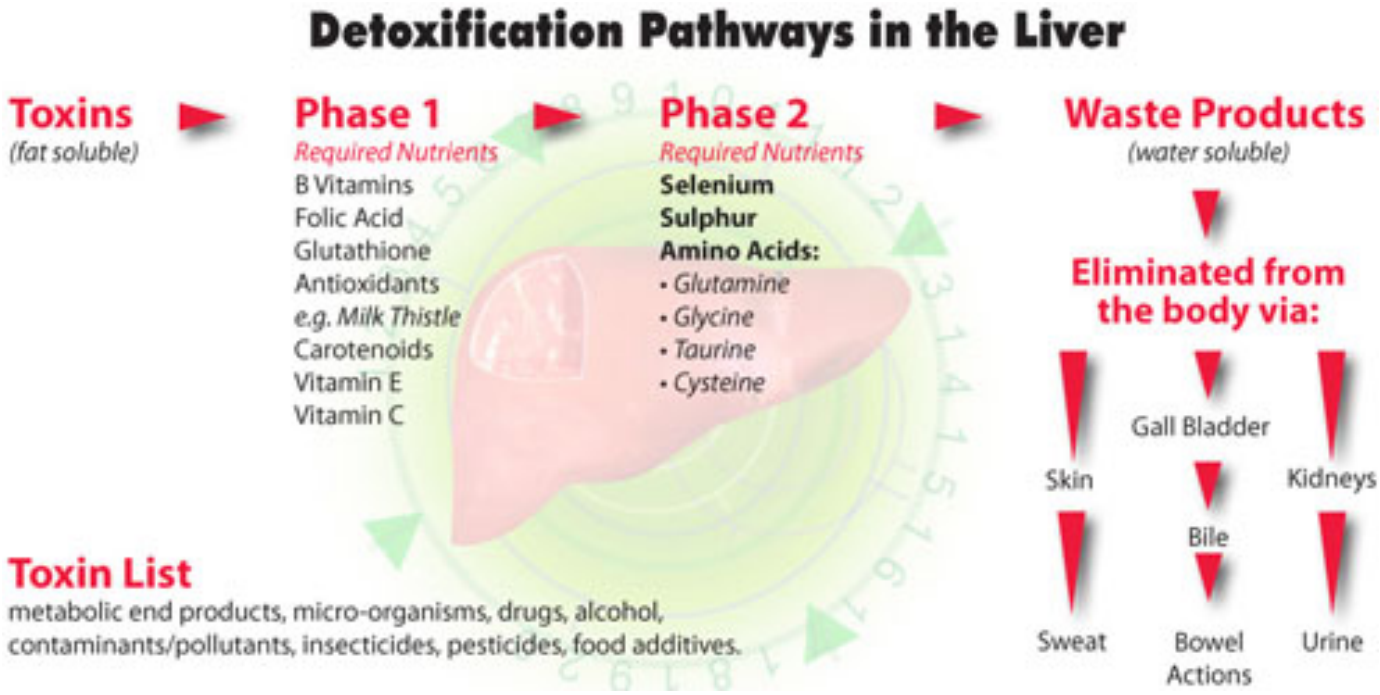
As most of the cancer-inducing chemicals in cigarette smoke are only carcinogenic during the period between activation by phase I and final detoxification by phase II, curcumin in the turmeric can help prevent the cancer-causing effects of tobacco. Those exposed to smoke, *aromatic hydrocarbons*, and 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.

Substances That Inhibit Phase I Detoxification

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



This is called the *conjugation pathway*, whereby the liver cells add another substance (eg. cysteine, glycine or a sulphur molecule) to a toxic chemical or drug, to render it less harmful. This makes the toxin or drug water-soluble, so it can then be excreted from the body via watery fluids such as bile or urine. Individual xenobiotics and metabolites usually follow one or two distinct pathways. There are essentially six Phase-II detoxification pathways:

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

The conjugation molecules are acted upon by specific enzymes to catalyse the reaction step. Through conjugation, the liver is able to turn drugs, hormones and various toxins into excretable substances. **For efficient phase two detoxification, the liver cells require sulphur-containing amino acids** such as taurine and cysteine. The nutrients glycine, glutamine, choline and inositol are also required for efficient phase two detoxification.

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 produces water-soluble *mercaptates* which are excreted via the kidneys.** The elimination of fat-soluble compounds, especially heavy metals like mercury and lead, 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.

Glutathione is also an important antioxidant. This combination of detoxification and free radical protection, results in glutathione being one of the most important anticarcinogens and antioxidants in our cells, which means that a deficiency is cause of serious liver dysfunction and damage. **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. 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. Dietary glutathione in foods appears to be efficiently absorbed into the blood. However, the same may not be true for glutathione supplements.

In healthy individuals, a daily dosage of 500 mg of vitamin C may be sufficient to elevate and maintain good tissue glutathione levels. In one double-blind study, the average red blood cell glutathione concentration rose nearly 50% with 500 mg/day of vitamin C. Increasing the dosage to 2,000 mg only raised red blood cell (RBC) glutathione levels by another 5%. Vitamin C raises glutathione by increasing its rate of synthesis. In addition, to vitamin C, other compounds which can help increase glutathione synthesis include *N-acetylcysteine* (NAC), *glycine*, and *methionine*. In an effort to increase antioxidant status in individuals with impaired glutathione synthesis, a variety of antioxidants have been used. Of these agents, only *Mega H-*, vitamin C and NAC have been able to offer some possible benefit.

Over the past 5-10 years, the use of NAC and glutathione products as antioxidants has become increasingly popular among nutritionally oriented physicians and the public. While supplementing the diet with high doses of NAC may be beneficial in cases of extreme oxidative stress (e.g. AIDS, cancer patients going through chemotherapy, or drug overdose), it may be an unwise practice in healthy individuals.

Amino Acid Conjugation

Several amino acids (*glyucine, taurine, glutamine, arginine*, and *ornithine*) **are used to combine with and neutralize toxins.** Of these, glycine is the most commonly utilized in phase II amino acid detoxification. Patients 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 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.

Methylation

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, the active form of B_{12} *--methyl cobalamin*, and the active form of folic acid *--5-methyltetrahydrofolate*.** 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.

Sulfation

Sulfation is the conjugation of toxins with sulfur-containing compounds. The sulfation system is important for detoxifying several drugs, food additives, and, especially, toxins from intestinal bacteria and the environment. In addition to environmental toxins, sulfation is also used to detoxify some normal body chemicals and is the main pathway for the elimination of steroid and thyroid hormones. 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.

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 B_6 (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.**

Acetylation

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. While not much is known about how to directly improve the activity of this system, it is known that **acetylation is dependent on thiamine, pantothenic acid, and vitamin C.**

Glucuronidation

Glucuronidation, the combining of *glucuronic acid* with toxins, in Phase II can be reversed by Beta glucuronidase enzymes produced by pathological bacteria and cause toxins to be reabsorbed increasing toxicity. Many of the commonly prescribed drugs are detoxified through this pathway. It also helps to detoxify aspirin, menthol, vanillin (synthetic vanilla), food additives such as benzoates, and some hormones. Calcium d-glucurate, a natural ingredient found in certain vegetables and fruits can inhibit beta glucuronidase activity resulting in increased elimination of toxins.

Nutrients Needed by Phase II Detoxification Enzymes

Glutathione conjugation: Glutathione Precursors (Cysteine, Glycine, Glutamic Acid, and co-factors), Essential Fatty Acids (Black Currant Seed Oil, Flax Seed Oil, EPA), Parathyroid Tissue
Amino acid conjugation: Glycine
Methylation: Methionine, Co-factors (Magnesium, Folic Acid, B-12, Methyl Donors)
Sulfation: Molybdenum, Cysteine and precursor (Methionine), Co-factors (B-12, Folic Acid, Methyl Donors, Magnesium, Vitamin B-6/P-5-P), MSM
Acetylation: Acetyl-CoA, Molybdenum, Iron, Niacinamide, Vitamin B-2
Glucuronidation: Glucuronic acid, Magnesium
Glycination: Arginase Enzyme, Glycine, Gly Co-factors (Folic Acid, Manganese, Vitamins B-2, B-6/P-5-P)

Inducers of Phase II Detoxification Enzymes

Glutathione conjugation: Brassica family foods (cabbage, broccoli, Brussels sprouts); limonene-containing foods (citrus peel, dill weed oil, caraway oil)
Amino acid conjugation: Glycine
Methylation: Lipotropic nutrients (choline, methionine, betaine, folic acid, vitamin B_{12})
Sulfation: Cysteine, methionine, taurine
Acetylation: None found
Glucuronidation: Fish oils, cigarette smoking, birth control pills, Phenobarbital, limonene-containing foods

Inhibitors of Phase II Detoxification Enzymes

Glutathione conjugation: Selenium deficiency, vitamin B_2 deficiency, glutathione deficiency, zinc deficiency
Amino acid conjugation: Low protein diet
Methylation: Folic acid or vitamin B_{12} deficiency
Sulfation: Non-steroidal anti-inflammatory drugs (e.g. aspirin), tartrazine (yellow food dye), molybdenum deficiency
Acetylation: Vitamin B_2, B_5, or C deficiency
Glucuronidation: Aspirin, probenecid

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

One of the primary routes for the elimination of modified toxins is through the bile. However, 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 or pregnancy) and *Gilbert's syndrome*.

Acetyl Glutathione

The antioxidant glutathione, known as *GSH*, is arguably **the most important antioxidant the body makes,** and most certainly **the most powerful intracellular antioxidant.** In its *reduced* form it plays a pivotal role in **DNA repair, immunity, flushing of toxins, removal of heavy metals, quenching of free radicals,** and **recycling of other antioxidants** such as vitamins C and E. Glutathione supports **detoxification in the lining fluid of the lung and intestines**, **enhances macrophage function**, and **slows virus production**.

Low levels of glutathione are associated with an astonishing range of diseases, from diabetes to Parkinson's to asthma to kidney problems, and many other conditions. Unfortunately, **oral supplementation of glutathione has proven tricky and sometimes ineffective,** since the molecule, **when taken orally, is not able to effectively reach and be absorbed into the intracellular space** where it is needed. Optimal exposure to the potential benefits linked to GSH have been achieved with IV therapy but it is expensive and inconvenient, and has only short-term benefits, and so needs to be repeated frequently.

The contribution of GSH deficiency in many pathologies has stimulated a number of researchers to find new potential approaches for maintaining or restoring GSH levels. One novel formulation of the molecule, ***S-acetylglutathione*** (S-GSH), is **surprisingly well absorbed by cells** and of great potential benefit. **It crosses the cell membrane more easily than GSH itself, and is easily de-acetylated in the cell, becoming active GSH. S-GSH can be effectively absorbed by cells after an oral dose** and has great potential in comparison to IV therapy.

S-GSH proved **a significant anti-viral agent** both *in vitro* and in *animal* studies in a 2005 study from Johann Wolfgang Goethe University Hospital in Germany. Remarkably, it was **stable in plasma and taken up directly by cells** with subsequent conversion to *GSH* (the active, reduced form). In cell culture, **S-GSH efficiently restored intracellular glutathione,** and in mice, **S-GSH but not *plain* glutathione, significantly decreased virally induced mortality.** This novel form of glutathione was active and stable.

S-GSH has also been **shown to cause the death of certain cancer cells.** In a study in the *International Journal of Oncology*, **S-GSH induced significant cell death in three human lymphoma cell lines.** It did not have the same effect on normal lymphocytes. The researchers concluded that **"S-acetyl glutathione specifically activates programmed cell death in lymphoma cells."** In fact, their analysis showed that this form of glutathione **depleted intracellular glutathione in the cancer cells,** in a *selective* effect that was **the opposite of its action in normal cells.**

Finally, in mice infected with a viral complex, S-GSH was **able to reduce spleen viral content by 70% and lymph node viral content by 30%--**and to do so **at half the concentration of GSH.** As the Italian researchers note in Molecules, glutathione analogues such as S-GSH "may offer a promising therapeutic alternative for reducing the GSH functional loss related to many human diseases."

Why Our Health Depends on Methylation and Glutathione

In the simplest terms, **maintaining life can be viewed as the ability to resist oxidation**. Oxygen is essential to life, but oxygen is like fire. It can be very damaging and needs to be controlled by antioxidants, known as "reducing" molecules. **Balancing reduction and oxidation**—or *redox*—**is the fundamental challenge of life**. What's great about that word, *redox*, is that it shows that **they are profoundly linked and we need both**. Once you understand this relationship, it leads to all kinds of new insights.

From the very moment of conception, life can be sparked by the unique redox environment created when a sperm fertilizes an egg. **The sperm is extremely rich in proteins containing the mineral *selenium*, which is a potent reducing agent for glutathione, the most important antioxidant molecule in cells. The egg, on the other hand, is very rich in *glutathione*.** Bring these two potent antioxidant strategies together, and you create an exceptionally reduced cell that can initiate life and promote development using the power of redox. That reducing power provides a metabolic spark as new life begins its journey, allowing the rapidly dividing cells to safely maintain a high rate of oxidation. The same metabolic challenge continues as the embryo develops. The entire nervous system and the shaping of gene activity are profoundly influenced by this redox balance as well. Aging is essentially a process of gradual oxidation, and our health as we age depends on successfully quenching that oxidation. Finally, innumerable diseases are linked to high levels of oxidation and low levels of glutathione—from schizophrenia to major depression, autism, chronic fatigue syndrome, fibromyalgia, and most chronic autoimmune and chronic inflammatory diseases.

Glutathione is made from *cysteine, glycine,* and *glutamic acid*. **You can get cysteine from the diet, in meat, eggs, garlic, onions, red pepper, broccoli and other foods**. Cells in the gut lining, aided by transporter molecules, will bring it into the body. **Both *gluten*** (found in grains such as wheat) **and *casein*** (milk protein) **can inhibit the uptake of cysteine**, which the body needs to make glutathione. So many children with autism, or adults with autoimmune disorders, do better when they eliminate wheat and milk from their diet. It's due to a redox mechanism.

Both casein and gluten are broken down into certain peptides that are relatively stable. The protein *casein* is broken into *casomorphins*. The "morphins" are so named because, like morphine, **they act on the opiate receptors**. The most famous one, *beta casomorphin 7* (BCM7), has seven amino acids. Our recent research shows that BCM7 first *stimulates* the uptake of cysteine, but then *inhibits* it. However, the *human* BCM7 is markedly different than *bovine* BCM7 from the cow. It turns out that the **BCM7 from a cow inhibits cysteine at least twice as much as the BCM7 from a human mother**. The implications for health are profound if you start thinking about formula feeding and all the dairy products from cows in our diet. **Breastfeeding is clearly regulating the redox system of newborns.** A diet high in dairy from cows can promote a decrease in our antioxidant capacity, our ability to make enough glutathione.

The peptide from sheep's milk behaves more like human milk. Similarly, the protein in gluten is known as *gliadin*, and it also creates a seven amino acid peptide, like BCM7. We already know that **gliadin can trigger celiac disease**, **and can also lead to gluten intolerance and sensitivity**. These problems reflect the ability of gluten peptides to inhibit cysteine uptake, perhaps **contributing to chronic inflammation**, although we have more to learn about that. Of course, not everybody who eats diary or wheat has poor antioxidant capacity, and milk and wheat are important sources of

nutrition. There are probably genetic vulnerabilities that bring some people closer to a critical point for oxidative stress, while for others it is a non-issue. Overall, though, **this is an issue to consider in any chronic inflammatory disease or neuro-immune disease**.

***Methylation* and *glutathione* are very tightly intertwined**. There is a critical metabolic intersection—a fork in the road—where cells must decide to either make more *glutathione*, or support more *methylation*. **The overall balance between these two options is crucial to health**.

Your body can take homocysteine and convert it back to cysteine. Homocysteine is a metabolite of the essential amino acid methionine, and elevated levels have been associated with vascular disease. **Homocysteine is created when methionine donates its methyl group to another molecule in a process known as *methylation***.

Methylation is a fundamental process of life which is intimately linked to redox status. In chemistry, a *methyl group* is a hydrocarbon molecule, or *CH3*. When a substance is *methylated*, it means that **a CH3 molecule has been added to it**. **Methylation can regulate gene expression, protein function, even RNA metabolism**. **It can suppress viruses, even latent viruses or cancer viruses we are born with and can help us handle heavy metals**. In the liver in particular, methylating a toxin helps change it to a form of the compound that can be more easily processed and excreted.

Methylation is an extremely broad and fundamental action that nature uses to regulate all kinds of processes. It regulates *epigenetic* changes—**changes to gene expression that occur because of environmental factors**—by affecting how DNA unravels during development. **Some changes can be permanent for the whole lifespan and can even be passed down as many as three generations**. That shows that the environment, through the process of methylation, can be quite a profound influence. **There are 150-200 *methyl transferase* enzymes**, and **each enzyme can methylate multiple targets**. So you can imagine methylation as **a spider's web within each cell**, and that web branches out in many directions.

Methylation and glutathione are very tightly intertwined. There is a critical metabolic intersection—a fork in the road—where cells must decide to either make more *glutathione*, or support more *methylation*. **The overall balance between these two options is crucial to health**, and this occurs with homocysteine. **When methionine gives away its methyl group, we're left with homocysteine**. And the body has to decide, should homocysteine be methylated, and go back into *methionine*, or should it be converted into *cysteine*, so that the body can make more of the antioxidant glutathione? This fundamental decision is made again and again by the body, and the overall balance is crucial to health. **Too little glutathione and we will end up with free radical, oxidative damage**. **Not enough methylation, and many genes and viruses will not be properly regulated**. Excess homocysteine, and the risk of vascular disease goes up.

It's important to understand that multiple factors impinge on the same system. What's so important here is that **the glutathione antioxidant system is a common target for so many different environmental toxins and infections**. Every single one of them impinges on the glutathione system. It's not that each molecule of mercury or lead picks off one glutathione molecule. No. It's that in general, **environmental assaults inhibit the enzymes that are responsible for keeping the**

glutathione in its reduced antioxidant state, where it can do its job. The potent ability of mercury to inhibit selenium-containing enzymes is a good example.

Some people sail through these stressors and remain healthy, while others stumble and fall. Though many molecules and nutrients are important, **the active forms of vitamin B12** (*adenosyl*B12 and *methyl*B12) **and the active form of folate** (*methylfolate*) **are essential to this process**. Once you have the raw material to make glutathione or to methylate, you need cofactors like methylfolate and methyl B12 to complete the process. **If we don't make enough of these active forms, we will not be able to smoothly and fluidly shift between methylation and glutathione**.

Nature allows, and even encourages, genetic variation, and the bottom line is that some people have genetic variations that render this process less functional. Even with a less functional genetic legacy, you might be fine if you are not stressed by the environment—in particular by chronic infections or toxic assaults. Stress brings out limitations in genes that otherwise are latent and not problematic. That's a general truth. So yes, with proper testing by a doctor to see if there is a functional deficiency, supplementation with active forms can help. For example, there is a test that measures levels of *methylmalonic acid* (MMA) in the urine; if the levels are high, you are not making enough of the two active forms of B12. **Your serum B12 may be perfectly normal—you just aren't converting enough of it to the active form**.

We ourselves cannot make B12, also known as *cobalamin*. **Bacteria make it for us**, and since vegetables don't carry those bacteria, **vegans can be deficient in B12**. B12 is such a precious material for the body that if, for instance, you eat a piece of rib eye steak, **the B12 released from the proteins is instantly bound right there in the GI tract** and chaperoned as if in a football handoff to be carried to cells, transported inside and then processed into the two active forms. **Nature knows this is a precious material for life**, and a critical indicator of cellular oxidation status.

There are several natural forms of B12 which need to be converted into the active forms, *adenosyl*B12 and *methyl*B12. *Cyano*B12, the form in most vitamin supplements, **is not active and is less useful than the active forms for treating deficiency states**. **Glutathione itself is needed for converting other forms of B12 to the *active* forms**. Indeed, there is a type of cobalamin called *glutathionylcobalamin* that is an intermediate for making the active forms.

There are two enzymes in the human body that require active B12 as a cofactor. One is called *methylmalonyl CoA mutase*, and it needs adenosylB12. It is **an enzyme that is necessary for the mitochondria**—the energy powerhouse of your cell—**to function**. The other enzyme that requires active B12 is the enzyme *methionine synthase*, which requires methyl B12.

MethylB12 is constantly recycled. It donates its methyl group to homocysteine, which then turns into methionine. Once B12 is missing its methyl group, it needs to get a fresh one. And that's where methylfolate comes in. **Methylfolate is in essence a methyl donor for methionine synthase**. That's its job in life. **It is the only molecule than can donate a methyl group to B12**. Once it does that, the rest of the folate is available to go out and support all kinds of other reactions in the body that need plain folate.

When your level of methylB12 is low, homocysteine builds up and this can have adverse health effects. **High homocysteine levels in the blood reflect low activity of the enzyme *methionine***

synthase, and this has been linked to an increased risk of atherosclerosis and coronary artery disease. It is also well known that **homocysteine levels are increased in Alzheimer's disease**, which suggests a role for impaired methylation in this neurodegenerative disorder. Of course low B12 levels are classically associated with **pernicious anemia** and with **peripheral neuropathy**.

Low levels of folate are also classically associated with **anemia, heart disease, fetal abnormalities** such as spina bifida, as well as **neuropathies** and these have been **specifically linked to a deficiency in methylfolate**. In addition, recognition of the important role of methylfolate and vitamin B12 in supporting D4 dopamine receptor methylation links their deficiency to impaired attention such as *attention-deficit hyperactivity disorder* (ADHD). **People with genetic polymorphisms in the enzyme that makes methylfolate are particularly vulnerable to a deficiency.**

Some research has shown that synthetic folic acid can build up when supplemented, and a few studies have suggested this may even be linked to cancer in high doses.

In addition to vitamin B12 and methylfolate, **there are several other nutritional supplements whose actions are critical for redox and methylation pathways**. Vitamin B6 (*pyridoxal-5-phosphate* or P5P) is **an essential cofactor for the two enzymes that sequentially convert homocysteine to cysteine**, namely *cystathionine-beta-synthase* and *cystathionine-gamma-lyase*. Together these two B6-dependent enzymes comprise the *transsulfuration pathway* that promotes glutathione synthesis. The common supplement form of vitamin B6, ***pyridoxine*, must be converted to the active form**, and **in some disorders, such as autism, this conversion is impaired**, so the P5P form may be more effective. *N-acetylcysteine* (NAC) provides a supplementary source of cysteine. **NAC can cross into the cell cytoplasm where the cysteine is released and allowed to promote glutathione synthesis**. *SAMe* is an active, methyl-donating derivative of the essential amino acid methionine, and during oxidative conditions its levels may be low, due to low methionine synthase activity. **SAMe has shown particular benefit in treating depression**.

These examples of the interrelationship between *oxidation* and *methylation* are just the tip of the redox iceberg. Nature has learned to harness the power of oxidation as a signaling mechanism to control cellular activity. **When more antioxidant is made available, cells can safely undertake a higher level of metabolic activity**. There is a lot more to learn, and the real challenge will be to convert this evolving knowledge about redox and methylation into new, more effective treatment strategies.

LIVER DETOXIFICATION SUPPORT

Nutritional Factors

Antioxidant vitamins like vitamin C, beta-carotene, and vitamin E are obviously quite important in protecting the liver from damage as well as helping in the detoxification mechanisms, but even simple nutrients like B-vitamins, calcium, and trace minerals are critical in the elimination of heavy metals and other toxic compounds from the body. The lipotropic agents, choline, betaine, methionine, vitamin B_6, folic acid, and vitamin B_{12}, are useful as they promote the flow of fat and bile to and from the liver. Lipotropic formulas have been used for a wide variety of conditions by nutrition-oriented physicians including a number of liver disorders such as hepatitis, cirrhosis, and chemical-induced liver disease.

Lipotropic formulas appear to increase the levels of SAM and glutathione. Methionine, choline, and betaine have been shown to increase the levels of SAM.

Botanical Medicines

There is a long list of plants which exert beneficial effects on liver function. However, the most impressive research has been done on ***silymarin***, the flavonoids extracted from *silybum marianum* (milk thistle). These compounds exert a substantial effect on protecting the liver from damage as well as enhancing detoxification processes. Silymarin prevents damage to the liver through several mechanisms: by acting as an antioxidant, by increasing the synthesis of glutathione and by increasing the rate of liver tissue regeneration. **Silymarin is many times more potent in antioxidant activity than vitamin E and vitamin C.** The protective effect of silymarin against liver damage has been demonstrated in numerous experimental studies. Silymarin has been shown to protect the liver from the damage produced by such liver-toxic chemicals as *carbon tetrachloride, amanita toxin, galactosamine*, and *praseodymium nitrate*.

One of the key mechanisms by which silymarin enhances detoxification is by preventing the depletion of glutathione. Silymarin not only prevents the depletion of glutathione induced by alcohol and other toxic chemicals, but has been shown to increase the level of glutathione of the liver by up to 35%, even in normals. Inhuman studies, silymarin has been shown to have positive effects in treating liver diseases of various kinds, including cirrhosis, chronic hepatitis, fatty infiltration of the liver, and inflammation of the bile duct. The standard dosage for silymarin is 70-210 mg three times/day.

LIVER DETOXIFICATION PATHWAYS: REFERENCES AND CLINICAL RESEARCH

Source: http://www.tuberose.com/Liver_Detoxification.html

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