DETOXIFICATION

What is toxicity?

Toxicity refers to the degree to which a substance is poisonous to our system. Mechanisms of toxicity include:

- Interference with enzymes
- Blockages of receptor sites and cellular transport mechanisms
- Blockage of nutrient absorption
- Oxidative damage
- Mimicking of hormones or neurotransmitters

How can we be exposed to toxins?

We can be exposed to toxins via our lungs and skin, but most often it is via the digestive system. Toxin exposure can be subcategorised into two main groups:

1. **Endotoxins:** Those toxins produced within the body. A major source of toxicity for most people is the products and by-products of their digestive systems. A poor diet consisting of high sugars/fats/preservatives/additives and/or a malfunctioning digestive system can lead to gut dysbiosis, leaky gut and subsequent entry of a variety of toxins into the bloodstream and lymph system.
2. **Exotoxins:** Environmental, industrial and "medical" toxins directly administered to the body (e.g. injection) or absorbed through the skin and mucous membranes, inhaled into the lungs or ingested.

Though an acute exposure to one toxin can cause damage to the body, it is likely that most of the health burden of toxin exposure comes from multiple, low dose exposures, rather than single, large doses. The concept of "total load" describes the sum total of all the influences that impact on patient's physiology.

Contributors to total load include:

- Xenobiotics (e.g. insecticides, herbicides, drugs, solvents, metals)
- Biological toxins (e.g. aflatoxin, lectins)
- Biological inhalants (e.g. moulds, pollen, algae etc)
- Physical phenomena (e.g. ionising radiation, electromagnetic fields)
- Infection
- Hormonal imbalances
- Mechanical problems (e.g. spinal alignment, nasal or intestinal obstruction)
- Lifestyle choices (e.g. alcohol, junk food, smoking, recreational drugs)
- Psychosocial factors (e.g. stress, coping skills, belief systems & trauma)

What protects us against toxins?

Our bodies have several mechanisms to protect us against toxins such as:

- Physical barriers: skin
- Digestive secretions and mucous barriers
- Immune surveillance & enzyme systems (e.g. CYP450 pathways) that process toxins for excretion (via sweat, breath, urine, bile, faeces)
- Storage: if the body is unable to deal with toxins immediately, it will store them in adipose tissue and bone for later detoxification.

What happens when this protection fails?

If any or several of these defence mechanisms become impaired (often as a result of being overloaded by toxic material), levels of toxins can increase in the body with resulting damage being caused to various systems, including the defence systems themselves (e.g. leaky gut, liver damage).

Why do some people get sick from toxicity and some don't?

This depends on the toxins the person is exposed to and the way each person's body deals with it. Some individual's have healthier lifestyles and/or detoxification systems that work more efficiently than others. General factors that influence detoxification include:

- Liver & Kidney function
- Nutrient intake & stores
- Digestion & absorption of food
- Bowel function
- Stress
- Sleep

What symptoms & diseases are generally associated with toxicity?

Just about any disease process can be aggravated by exposure to toxins. Some symptoms and diseases strongly related to toxin exposure include:

- **Symptoms**
  - Recurrent headaches, infections
  - Muscle aching & weakness
  - Paraesthesia's (numbness, pins & needles) & neuralgia (pain - nervous system)
  - Infertility
  - Adverse reactions/sensitivities
  - Chronic fatigue & lethargy
  - Depression, anxiety &/or mood swings
  - Poor short-term memory & concentration
  - Anaemia

- **Diseases**
  - Allergies & Asthma
  - Atherosclerosis
  - Autism
  - Autoimmune diseases
  - Cancer (various types)
  - Chronic Fatigue Syndrome
  - Endocrinopathies (diseases involving the endocrine glands)
  - Fibromyalgia
  - Inflammatory Bowel Disease
  - Multiple chemical sensitivities
  - Neurodegenerative disorders
  - Reproductive disorders

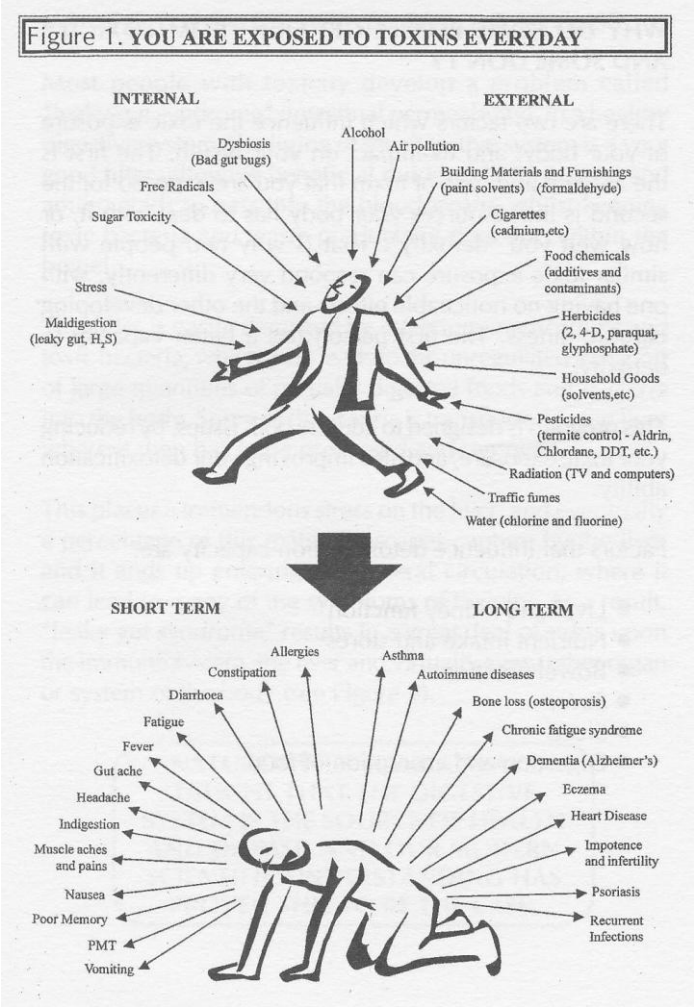

Figure 1: From Metagenics Detox - Patients Manual

How should we go about detoxifying the body?

Detoxification essentially means converting a toxin to a non-toxic, soluble form that can be safely eliminated by the body. Though detoxification is a straightforward process, it requires several steps to complete it effectively. Historically, many Detoxification Programs focus on liver support (the main organ involved in detoxification), but this is really an incomplete approach, as the gut, as mentioned, is a major source of toxic exposure for many individuals. No amount of liver support can help if a patient's system is being constantly overwhelmed with toxic material from the environment or their digestive system. Overall we need to look at:

A. DECREASING TOXIC LOAD

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B. PROMOTING HEALTHY GUT FLORA

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C. REPAIRING THE GUT LINING

⇩

D. SUPPORT DETOXIFICATION PROCESSES

A. DECREASING TOXIC LOAD:

This is a primary consideration when dealing with toxicity. Reducing exposure to toxins reduces the risk of aggravations of symptoms during the process, and the chances of the patient regressing once treatment is complete. Toxic exposure should be assessed when talking to your patient by considering the following possible sources:

- Occupational exposure (e.g. pesticides, organic solvents, radiation etc)
- Chemicals at home (e.g. pesticides, cleaning products)
- Water supply
- Food (e.g. pesticides, lectins. alkaloids, allergens)
- Recreational exposure
- Medications

As the gut is often one of the main sources of toxins; it can be beneficial to follow a healthy diet prior to and/or whilst detoxing. For example (see attached Shopping List Guide Also):

- Avoid packaged and pre-prepared foods as much as possible
- Eliminate foods containing artificial flavours and colours (e.g. Tartrazine: *code 102*), other additives (e.g. MSG: *code 621*) and hydrogenated fats and stabilisers.
- Eliminate foods known to cause a reaction, as well as minimizing common causes of food intolerances e.g. Wheat, dairy.
- Purchase fresh seasonal fruit and vegetables if possible. Organic as well…even better.
- Minimise high sodium, salt and sugar foods. Aim for less than 15g of sugar per serve.
- Fresh vegetable juice can be a great addition. High in nutrients and enzymes to help digestion.
- Prepare easy to digest meals (e.g. vegetable casseroles, soups, stews)

For patients who appear particularly reactive to foods, or where a more restrictive diet may be thought to be beneficial, some of the following options may be included:

- A/B/O Blood Type Diet – reduces exposure to inflammatory stimulating lectins
- Low salicylate/low amine foods lists (refer to Metagenics Detox Manual Appendix A)
- Low reactive/elimination diet (refer to Metagenics Detox Manual Appendix A)

B. PROMOTING HEALTHY GUT FLORA:

Toxic exposure from the gut can come partly from ingested foods and chemicals, but also from the gut flora that constitutes a continuous source of metabolites that reach the systemic circulation.

In our previous lecture on probiotics and the gut, we know there is a variety of beneficial and harmful microflora throughout the intestinal tract. Metabolites from various harmful bacterial and fungal species have been found in the urine of patients with many different pathologies. In addition to harmful metabolites, the cell-wall fragments of bacteria may pass into the bloodstream. These fragments (consisting of lipopolysaccharides and often referred to as endotoxins), are potent stimulators of the inflammatory response. They are detected by Kupffer cells (liver cells) and cause a massive increase in the production of inflammatory mediators such as Tumour Necrosis Factor alpha (TNFα). These can further aggravate pre-existing inflammatory or immune conditions.

Some organisms associated with dysbiosis include:

- *Bacteroides fragilis*
- *Campylobacter jejuni*
- *Candida albicans*
- *Candida tropicalis*
- *Citrobacter freundii*
- *Clostridium difficile*
- *Escherichia coli*
- *Geotrichum spp.*
- *Klebsiella pneumoniae*
- *Proteus vulgaris*

i) Weeding:

Ridding the body of detrimental microbes is often referred to as the "Weeding" stage. This may take anywhere from 2-6 weeks to complete, depending on the person's intestinal state and overall immune system. Various tests (e.g. Indicans, Haemaview, Complete Stool Analysis, Intestinal Permeability etc.) can be performed before starting and along the way to ascertain how the intestinal flora and overall patient health is progressing. There are many herbal medicines that have been shown to have potent antimicrobial actions against these dysbiotic organisms such as:

- Barberry (*Berberis vulgaris*) root bark
- Black walnut (*Juglans nigra*) green hulls
- Chinese wormwood (*Artemesia annua)* herb
- Cinnamon (*Cinnamomum zeylandicum) bark oil*
- Grapefruit (*Citrus x paradise)* fruit
- Olive (*Olea europaea*) leaf, dry
- Oregano (*Origanum vulgare*) oil
- Thyme (*Thymus vulgaris*) oil

There are various pre-prepared products available in the market to help remove pathogenic microflora. Some also contain herbs and nutrients to help stimulate digestion and soothe the gastrointestinal lining. Some examples include:

- Parex (Metagenics)
- Costat (Metagenics) – good for systemic infections
- Paracea Forte (Bioceuticals)
- Wormwood Complex (Mediherb)
- Intestaclear (Orthoplex)

note: Prior to treating with antimicrobial herbal mixtures, many practitioners find that doing a bowel purge for 1-3 days can be useful in removing a large amount of dysbiotic organisms from the intestines, thereby helping to speed the overall "weeding" process.

- 100-200ml of Aloe Vera Juice taken before bed usually has the desired effect.
- 2-4 teaspoons of Epsom salts (Magnesium sulphate) followed by a couple of large glasses of water.
- Some patients may require a combination of Aloe Vera juice and Epsom salts.

Whilst ridding the bowels of detrimental microbes, it is recommended that other nutrients are included to help prevent the binding of detrimental microbes to the intestinal wall and to help "mop-up" the by products of dysbiotic organism breakdown. Some examples include:

- Colostrum: provides a source of immunoglobulins that can bind to dysbiotic bacteria preventing their entry into the bloodstream. It also contains other bioactive proteins including lactoferrin & lactoperoxidase. *note: this product should not be given to individuals with know milk/dairy allergies/intolerances.*
- Selenium, iodine and zinc support the function of these proteins
- Refer to Prebiotics notes (Wk 5 notes, pages 4-5) for other useful bowel substances that can help support bowel function.

Again, there are a variety of products on the market that can fill this role. Some examples are:

- Ultra Probioplex (Metagenics) – contains colostrum so be careful with dairy intolerant individuals.
- Gastro Care Excel (Bioceuticals)- contains colostrum
- Gastro AG (Metagenics) – Arabinogalactans, dairy free.

When the load of dysbiotic organisms living in the digestive system has been reduced, the next main step is to:

ii) Seed: re-inoculate the intestines with beneficial (probiotic) bacteria

Refer to the notes on Probiotics and Prebiotics (Wk 5). There is a large range of probiotics available from reputable companies such as Metagenics (refer to Detox manuals supplied), Bioceuticals, Orthoplex, Blackmores etc. It is fine to start with one type of probiotic then move on to another blend as appropriate.

C. REPAIRING THE GUT LINING

There is not much point putting in good bacteria if the environment they arrive in is not conducive to their growth. For this reason it is also important to:

iii) Feed: feed the good bacteria and support the integrity of the gut lining.

Again, refer to the notes on Probiotics and Prebiotics (Wk 5). It is recommended that this "seed & feed" phase should be continued for at least 2 weeks. It is better, particularly for patients with a history of intestinal complaints to continue this phase for 4-8 weeks. Some good Prebiotic blends include:

- Intestamine (Bioceuticals)
- GIT 2 (Orthoplex)
- Glutagenics (Metagenics)

It is important to ensure your patient is following their diet well at this stage, as eating the wrong foods can encourage the wrong gut flora to grow back before the Probiotics can establish a decent population. It may also be necessary to provide specific digestive support (e.g. digestive enzymes) to prevent food fermentation in the gut that can lead to bloating and wind.

It may be useful to do an indicans test again at the end of the "seed & feed" stage to ensure decent digestion is taking place.

D. SUPPORT DETOXIFICATION PROCESS

Now the load on the body's waste removal systems has been reduced, the final stage of detoxification is to enhance the capacity and function of these systems. This step will take 2-4 weeks (possibly more) depending on the chronicity and severity of the patient's condition, and the organ reserve available for detoxification. Depending on the toxic load of the body, patients can often feel a little unwell during this stage as toxins are released. It is important to go steadily and include nutrients to help support the body and the "fall-out" of the detoxification process. A single detoxification will likely not remove all the toxins from a patient's body. Several gentle detoxification cycles are much better for the patient than a harsh "all at once" approach.

In summary, the body has 3 major detoxification systems that work mainly through the liver and intestine:

1. Phase 1 detoxification
2. Phase 2 detoxification
3. Phase 3 antiport system lining the intestine

Phase 1 Detoxification: This system is mainly comprised of the cytochrome P450 (CypP450, CYP450) super family of enzymes (*refer to handout on CYP P450's for more detail*). It is the first enzymatic defence against foreign compounds, particularly steroids, drugs and exogenous toxins.

These enzymes either add or expose a functional group to the substrate (toxin); most commonly a hydroxyl group (OH), which then opens up a reactive site that allows the toxin to be conjugated to a substance in phase 2. In general they utilize oxygen and NADH (Activated B3) as follows:

$$\mathbf{NADPH + H^+ + O_2 + RH \rightarrow NADP^+ + H_2O + R\text{-}OH}$$

RH denotes parent drug and R-OH is the oxidized product

The reaction above may actually make the toxin highly reactive, and it can now act as a free radical, potentially damaging proteins, DNA and RNA and causing cellular damage. It is important that the Phase 2 reactions act on this reactive intermediate as quickly as possible to reduce the time available for it to do damage. Therefore, it is critical for effective detoxification that Phase 2 keeps up with Phase 1, so that there is no accumulation of these reactive intermediates.

It is important to realize that Phase 1 Detoxification occurs in various tissues throughout the body. For example CYP1A1 & CYP1B1 in breast tissue; CYP1A2 and CYP3A4 in the liver. Xenobiotic-metabolising CYP's however, are largely expressed within the liver where they play a crucial role in hepatic metabolism, although lower levels have been found in extrahepatic tissues including the lung, kidney, gastrointestinal tract and nasal epithelium. CYP's expressed within these extrahepatic tissues can contribute to overall drug clearance from the body. For ease of explanation however, we will be referring to the liver when discussing detoxification pathways from here on.

Human CYP's responsible for metabolism of pharmaceuticals and environmental toxins are largely concentrated within the CYP 1-3 families, and to a lesser extent the CYP4 family. CYP450 enzymes can either be induced or inhibited (refer to diagram on detox handout). Most patients initially presenting to you will likely have an induced Phase 1 cycle happening due to the intake of coffee, alcohol, nicotine as well as increased levels of stress in their lives.

For this reason it is often useful to first:

- **Inhibit Phase 1 detoxification** in order to reduce the amount of highly reactive intermediates being produced. (refer to list of Phase 1 inhibitors on Detox handout, and Appendix 1 of these notes)
- **Help protect the liver** (i.e. use Hepatoprotectants such as Silymarin & Bupleurum)
- **Include high levels of Antioxidants in the diet** (broad range supplements suggested) to help deal directly with and minimize free radical damage from the high levels of reactive intermediates produced.
- **Support and increase Phase 2 detoxification** to help rid the body of the harmful intermediates (refer to list of Phase 2 support & enhancing nutrients, Detox handout and Appendix 1 of these notes)

Phase 1 activity should only be induced after Phase 2 has had a chance to catch up.

Phase 2 Detoxification: The processing of reactive intermediates into water soluble, non-toxic compounds requires two steps:

- A conjugating substance
- An enzyme to catalyse the reaction

Conjugation Reactions	Enzyme	Conjugating substance
Acetylation	N-acetyl transferases	acetyl-CoA
Amino acid conjugation	Amino acid transferases	Glycine, taurine, glutamine, arginine, ornithine
Glucoronidation	Glucoronyl transferases	Glucoronic acid
Glutathionation	Glutathione transferase	Glutathione
Methylation	N & O-methyl transferases	Methyl groups (mainly SAM: S-adenosylmethionine)
Sulfation	Sulfotransferases	Sulphur containing compounds, taurine, glutathione

Phase 2 reactions are more vulnerable to defects, as they require both an adequate supply of conjugants (amino acids and other nutrients), plus adequate enzyme function. Phase 2 pathways are also down regulated by inflammation. Typically then, many patients will present with elevated Phase 1 activity and reduced Phase 2 activity, leading to an accumulation of reactive intermediates, with consequent tissue inflammation and damage. This is a major factor in how toxicity drives disease processes.

Studies performed in the UK have proved a link between a deficiency in the sulphation conjugation pathway of patients with Parkinsons, Motor Neurone Disease and Alzheimer's, indicating toxic stress as a major predisposing factor in degenerative disease of the nervous system. Similarly, 50% of the general population and 80% of chemically sensitive people are slow acetylators (Referenced from *Get a Life* website).

As mentioned before, always include an antioxidant mix in any detoxification protocol. There are a variety of prepared mixes available that support the appropriate balance between Phase 1 & Phase 2 detox. Some of these include:

- Phyto Pro (Metagenics)
- Thermo Phase Detox (Metagenics)
- RejuvenX (Bioceuticals)
- XenoClear (Bioceuticals)
- LM1 (Orthoplex)

Phase 3 Antiporter Intestinal Detoxification System:
As the gastrointestinal tract represents the first barrier met exogenous compounds of food or orally ingested drugs and toxins, it is not surprising that intestinal cells have a coupled detoxification system known as the antiporter.

The antiporter is an energy dependent efflux pump that pumps xenobiotics out of the cell into the intestinal lumen, thereby decreasing intracellular concentration of xenobiotics. This activity seems to be co-regulated with the intestinal phase 1 Cyp3A4 enzyme.

The maintenance of the gut mucosal integrity is essential for this antiport system to work, so all the more reason the clean up the gut before continuing with the Phase 1 & 2 detoxification. A compromised gut mucosal barrier will allow xenobiotics to migrate into the circulation without the opportunity for detoxification.

Additional Notes of Interest:

Chelation: for patients with significant toxic metal or chemical exposure, adding one or both of chelating agents Lipoic Acid or Glutathione during detoxification may help to reduce their symptoms and significantly increase toxin excretion.

Nutrients to Support Kidney Excretion:

- Water: needed to keep substances in solution and able to be excreted. Avoiding dehydration is essential.
- Vitamin A, B6, C, Lipoic acid, magnesium and potassium help the kidneys operate more efficiently during waste removal.

Options for helping the body excrete toxins during a detox:

- Dry skin brushing – remove dead cells to allow better toxin excretion through skin
- Spa treatments – encourage waste excretion through sweat, detox wraps etc.
- Lymphatic drainage massage – mobilise toxins into and out of the lymph system

Exercise:

- Help get the blood and lymph moving to move toxins to sites for excretion. (Not too much earlier on in the detox when the person's body is already under strain coping with excess toxins being processed).

Avoiding toxins in the environment and emotions:

- Reduce chemical exposure by limiting pesticide use, antiperspirants, bad foods etc
- Minimise toxic thoughts and individuals from your life. Stress and unhappiness can release many toxins in the body.

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Appendix 1: Substances that Effect Phase 1 & 2 Detoxification

Taken from Tuberose.com website, Liver Cleansing and Support Products:
http://www.tuberose.com/Liver_Detoxification.html

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**: niacin; vitamin B_1; vitamin C
- **Herbs**: caraway and dill seeds
- **Environmental toxins:** carbon tetrachloride; exhaust fumes; paint fumes; dioxin; pesticides

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

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, B-6/P-5-P), MSM
- **Acetylation:** Acetyl-CoA, Molybdenum, Iron, Niacinamide, B-2
- **Glucuronidation**: Glucuronic acid, Magnesium
- **Glycination**: Arginase Enzyme, Glycine, Gly Co-factors (Folic Acid, Manganese, 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