**The Three Phases of Detoxification**

These three steps or phases of removing undesirable or harmful lipid-soluble compounds are performed by three sets of cellular proteins or enzymes, called the phase I (transformation) and phase II (conjugation) enzymes, and the phase III (transport) proteins.

Phase I, II, and III metabolisms have different biochemical requirements and respond to different metabolic signals, but must work in unison for proper removal of unwanted xenobiotics (such as toxins or drugs) or endobiotics (such as excess hormones). Enzymes of the phase I, II, and III pathways have several characteristics that make them well suited for their important roles.19 Unlike most other enzymes, detoxification enzymes; can react with many different compounds broadening the number of toxins a single enzyme can metabolize; are more concentrated in areas of the body that are most directly exposed to the environment (like the liver, intestines, or lungs); are inducible, meaning that their synthesis can be increased in response to toxin exposure.

The liver is the primary detoxification organ; it filters blood coming directly from the intestines and prepares toxins for excretion from the body. Significant amounts of detoxification also occur in the intestine, kidney, lungs, and brain, with phase I, II, and III reactions occurring throughout the rest of the body to a lesser degree.

**Phase I Detoxification** **– Enzymatic Transformation**: Under most circumstances, Phase I enzymes begin the detoxification process by chemically transforming lipid soluble compounds into water soluble compounds in preparation for phase II detoxification. The bulk of the phase I transformation reactions are performed by a family of enzymes called the cytochrome P450s (CYPs).

CYP enzymes are relatively non-specific, each has the potential to recognize and modify countless different toxins; after all, a mere 57 human CYPs must be able to detoxify any potential toxin that enters the body.20However, the cost of this versatility is speed; CYPs metabolize toxins very slowly compared to other enzymes. For instance compare the predominant CYP3A4, which metabolizes 1-20 molecules per second,21to superoxide dismutase (SOD), which metabolizes over a million molecules per second. Major sites of detoxification overcome the slower speed by producing large amounts of CYPs - CYPs may represent up to 5% of total liver proteins, and similar large concentrations can be found in the intestines. CYPs are amongst the most well studied and best characterized detoxification proteins due to their role in the metabolism of prescription drugs, and to their role in metabolizing endogenous biochemicals (for example, aromatase, which transforms testosterone to estradiol, is a CYP.)22

Several other enzymes contribute to the phase I process as well, notably: the flavin monooxygenases (FMOs; responsible for the detoxification of nicotine from cigarette smoke); alcohol and aldehyde dehydrogenases (which metabolize drinking alcohol), and monoamine oxidases (MAO’s; which break down serotonin, dopamine, and epinephrine in neurons and are targets of several older antidepressant drugs)23

**Phase II Detoxification – Enzymatic Conjugation**: Following phase I transformation, the original lipid-soluble toxin has been converted into a more water-soluble form, however, this reactive intermediate is still unsuitable for immediate elimination from the cell for a couple of reasons: 1) phase I reactions are not sufficient to make the toxin water-soluble enough to complete the entire excretion pathway; and 2) in many cases, products from the phase I reactions have been rendered more reactive then the original toxins, which makes them potentially more destructive than they once were. Both of these shortcomings are addressed by the activities of the phase II enzymes, which modify phase I products to both increase their solubility and reduce their toxicity. The activation of the phase II enzymes is responsible for the anti-mutagenic and anti-carcinogenic properties of the metabolic detoxification systems; it is widely accepted that phase II enzymes protect against chemical carcinogenesis, especially during the initiation phase of cancers.24

At the genetic level, the production of most phase II enzymes is controlled by a protein called nuclear factor erythroid-derived 2 (Nrf2), a master regulator of antioxidant response.25 Under normal cellular conditions, Nrf2 resides in the cytoplasm (the liquid inside cells within which the cells components are contained) of the cell in an inactive state.26 However, the presence of oxidative stress (triggered by metabolism of toxins by CYPs) activates Nrf2, allowing it to travel to the cell nucleus.27 In the cell nucleus, Nrf2 turns on the genes of many antioxidant proteins, including the phase II enzymes.28 In this way, Nrf2 “senses” oxidative stress or the presence of toxins in the cell, and allows the cell to mount an appropriate response. Nrf2 regulates the activity of genes involved in the synthesis and activation of important detoxification molecules including glutathione and superoxide dismutase (SOD). It also plays an important role in initiating heavy metal detoxification, and the recycling of CoQ10, a potent antioxidant.29,30,31

Certain dietary constituents (including **sulforaphane** from **broccoli** and **xanthohumol** from **hops**) may also directly activate Nrf2 and stimulate antioxidant enzyme activity; this may partially explain their beneficial effects on detoxification.32

There are several families of phase II enzymes that differ significantly in their activities and biochemistry. In several cases, phase II enzymes exhibit redundancy -- a particular xenobiotic or endobiotic can be detoxified by more than one phase II enzyme.

**UDP-glucuronlytransferases (UGTs)** catalyze glucuronidation reactions, the attachment of glucuronic acid to toxins to render them less reactive and more water-soluble. There are several different UGTs that are distributed throughout the body, with the liver being the major location. In humans, many xenobiotics, environmental toxicants, and 40-70% of clinical drugs are metabolized by UGTs.33 The plasticizer bisphenol A34 and benzopyrene (from cooked meats)35 are two notable examples of UGT substrates (a substrate is a molecule upon which an enzyme acts). Intestinal UGTs may affect oral bioavailability of several drugs and dietary supplements, and may be responsible for chemoprevention in this tissue.36

**Glutathione S-transferases (GSTs)** catalyze the transfer of glutathione (a significant cellular antioxidant) to phase I products. GSTs play a major role in the metabolism of several endobiotics, including steroids, thyroid hormone, fat-soluble vitamins, bile acids, bilirubin and prostaglandins.37 GSTs can also function as antioxidant enzymes, detoxifying free radicals38 and oxidized lipids or DNA.39 GSTs are soluble enzymes that are ubiquitous in nature and in humans, forming about 4% of the soluble protein in the human liver and present in several other tissues (including brain, heart, lung, intestines, kidney, pancreas, lens, skeletal muscle, prostate, spleen and testes).40,41 Products of GST conjugation can be excreted via bile, or can travel to the kidneys where they are further processed and eliminated in urine.

**Sulfotransferases (SULTs)** attach sulfates from a sulfur donor to endo- or xenobiotic acceptor molecules. This reaction is important both in detoxification reactions, as well as normal biosynthesis (the addition of sulfate to chondroitin and heparin, for example, is catalyzed by specific SULTs.42) SULTs play a major role in drug and xenobiotic detoxification, and the metabolism of several endogenous molecules (including steroids, thyroid and adrenal hormones, serotonin, retinol, ascorbate and vitamin D).43 SULTs in the placenta, uterus, and prostate are thought to play a role in the regulation of androgen levels.44 In contrast to other phase II enzymes, SULTs can convert a number of procarcinogens (such as heterocyclic amines from cooked meats) into highly reactive intermediates which may act as chemical carcinogens and mutagens.45

While the UGTs, GSTs, and SULTs catalyze the bulk of human detoxification reactions, several other phase II enzymes contribute to the process to a lesser, but still important extent, including:

**Methyltransferase enzymes** catalyze methylation reactions using S-adenosyl-L-methionine (SAMe) as a substrate. COMT (catechol O-methyltransferase) is a major pathway for eliminating excess catecholamine neurotransmitters (such as adrenaline or dopamine). Methylation reactions are one of the few phase II reactions that decrease water solubility46;

**Arylamine N-acetyltransferases** **(NATs)**: NATs detoxify carcinogenic aromatic amines and heterocyclic amines47;

**Amino acid conjugating enzymes**: Acyl-CoA synthetase and acyl-CoA amino acid N-acyltransferases attach amino acids (most commonly glycine or glutamine) to xenobiotics. The food preservative benzoic acid is one example of a toxin metabolized by amino acid conjugation.48

**Phase III Detoxification – Transport**: Phase III transporters are present in many tissues, including the liver, intestines, kidneys, and brain, where they can provide a barrier against xenobiotic entry, or a mechanism for actively moving xenobiotics and endobiotics in and out of cells.49 Since water-soluble compounds require specific transporters to move in and out of cells, phase III transporters are necessary to excrete the newly formed phase II products out of the cell. Phase III transporters belong to a family of proteins called the ABC transporters (for ATP-Binding Cassette50), because they require chemical energy, in the form of ATP, to actively pump toxins through the cell membrane and out of the cell.51 They are sometimes called the Multidrug Resistance Proteins (MRPs), because drug-resistant cancer cells use them as protection against chemotherapy drugs52

In the liver, phase III transporters move glutathione, sulfate, and glucuronide conjugates out of cells into the bile for elimination. In the kidney and intestine, phase III transporters can remove xenobiotics from the blood for excretion from the body.53

**Balance of Phase I and Phase II Reactions**

The products of phase I metabolism are potentially more toxic than the original molecules, which does not present a problem if the phase II enzymes are functioning at a rate to rapidly neutralize the phase I products as they are formed. This, however, is not always the case. Factors which increase the ratio of phase I to phase II activity can upset this delicate balance, producing harmful metabolites faster than they can be detoxified, and increasing the risk of cellular damage. Some of the factors include: diet (some foods and supplements increase phase I enzyme activity), smoking and alcohol consumption (both induce phase I), age (which can decrease phase II UGT, GST, and SULT activity), sex (premenopausal women show 30-40% more phase I CYP3A4 activity than men or postmenopausal women), disease, and genetics (reviewed in 54).

An illustrative (and unfortunately common) example of the consequences of phase I/phase II imbalance is toxicity caused by overdose of the analgesic acetaminophen (paracetamol) – the active ingredient in Tylenol®. Acetaminophen toxicity is the most common cause of liver failure in the US.55 With a normal therapeutic dose of acetaminophen, the drug is predominantly detoxified by the phase II UGT and SULT enzymes. A small amount of the drug is detoxified by a third mechanism: it is first transformed into the toxic metabolite NAPQI (N-acetyl-p-benzoquinoneimine) by phase I CYP enzymes; and this intermediate is detoxified by conjugation with glutathione using the phase II enzyme GST.

During acetaminophen overdose, the UGT and SULT enzymes become quickly overwhelmed. Proportionally more of the drug undergoes the third detoxification mechanism (transformation to NAPQI and conjugation by GST). Eventually, activity of the phase II GST enzyme slows as glutathione stores become depleted56, and NAPQI is produced faster than it can be detoxified. Rising levels of NAPQI in the liver cause widespread damage, including lipid peroxidation, inactivation of cellular proteins, and disruption of DNA metabolism.57Treatment for acetaminophen overdose involves the timely replenishment of glutathione stores through administration of the precursor amino acids for glutathione synthesis (most commonly N-acetyl cysteine58; see below).

**Bile secretion** is a critical digestive process for the absorption of dietary fats and fat-soluble nutrients, but also functions as the major mechanism for moving conjugated toxins out of the liver and into the intestines, where they can be eliminated.

**Antioxidation** is a necessary protective measure against the harsh phase I oxidation reactions, which frequently produce free-radical byproducts. The production of antioxidant enzymes, many of which are under the same genetic regulation (by Nrf2) as the phase II enzymes, is important for minimizing this free-radical damage.

**Heavy metal toxicity** can lead to oxidative damage by direct generation of free radical species and depletion of antioxidant reserves.59 Mercury, arsenic, and lead, for example, effectively inactivate the glutathione molecule so it is unavailable as an antioxidant or as a substrate for xenobiotic detoxification60; lead can also reduce the activity of the enzymes of that recycle glutathione.61 One method for heavy metal removal is their chelation by the cellular proteins metallothioneins (MTs), which have a high capacity to bind various reactive metal ions, such as zinc, cadmium, mercury, copper, lead, nickel, cobalt, iron, gold, and silver.62 One molecule of MT can bind 7–9 zinc or cadmium ions (or any combination of these two), up to 12 copper ions, and up to 18 mercury ions.63 Cellular stress (particularly oxidative stress), turns up MT production, which, like the phase II enzymes, is stimulated by the activity of Nrf2.64

**Prevention of absorption** through trapping of potential toxins (such as surface adhesion to another molecule in the gut, like activated charcoal or kaolin clay65) is an effective means of mitigating exposure; this mechanism has the requirement of some dietary adsorbent to be taken while the toxin is in transit in the GI tract. Uptake of potential toxins and their detoxification by beneficial colonic microflora could have a similar effect.

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| **What You Need to Know about Metabolic Detoxification:**   * Detoxification is the metabolic process of removing unwanted lipid-soluble compounds from the body. * These “unwanted” compounds can be foreign (such as an environmental toxicants) or endogenous (toxins; such as excess hormone) in nature. * Detoxification reactions occur throughout the body, with the liver being the predominant detoxifying organ. * Detoxification reactions follow three steps or “phases” that have the ultimate goal of converting the toxin into an inert, water-soluble form for excretion:   **Phase I** reactions transform the toxin into a chemical form that can be metabolized by the phase II enzymes. Phase I reactions are performed primarily by the cytochrome P450 enzymes.  **Phase II** reactions conjugate (attach) the toxin to other water-soluble substances to increase its solubility. Each of the different types of phase II enzymes catalyzes a different type of conjugation reaction.   * + UDP-glucuronlytransferases (UGTs) catalyze the glucuronidation of most clinical drugs, and several environmental toxins   + Glutathione-S-transferases (GSTs) conjugate toxins with the antioxidant glutathione; they can also directly detoxify free radicals   + Sulfotransferases (SULTs) catalyze sulfonation reactions; they may also be important for controlling sex hormone levels   Other types of phase II reactions that are used less frequently include methylation and amino acid conjugation reactions.  **Phase III** detoxification involves the transport of the transformed, conjugated toxin into or out of cells. Different phase III transport proteins work in concert to shuttle toxins from different parts of the body into bile or urine for excretion.  Following detoxification reactions, the toxins are removed from the body by excretion:  **A)** Products of liver detoxification often leave the body by being secreted into the intestines in bile, but can sometimes be transported into the bloodstream for processing by the kidneys. **B)** The cells that line the intestines can detoxify toxins as they are absorbed, and release them back into the intestinal lumen.  **C)** The kidneys can filter and further process toxins from circulation, excreting them from the body as urine. |

**Dietary Modification of Metabolic Detoxification**

Given the sheer number of diverse enzymes and transport proteins involved in metabolic detoxification and its related pathways, it is no surprise that detoxification depends on, and is sensitive to, a large number of dietary factors.

Macronutrient and micronutrient intake influences phase I and II systems. Protein deficiency decreases CYP metabolism, while high protein diets increase it.66 The opposite effects are observed for carbohydrates; the effects of lipids on CYP metabolism are unclear. Efficient phase I reactions require sufficiency in several micronutrients; deficiencies in vitamins A, B2 and B3, folate, C, E, iron, calcium, copper, zinc, magnesium, selenium have all been shown to decrease the activities of one or more phase I enzymes, or slow the transformation of specific drugs.67

The diverse set of phase II enzymes require an equally diverse set of essential nutrients, especially B vitamins, as cofactors.

The reduced glutathione for GST conjugation depends on adequate dietary sulfur-containing amino acids (methionine or cysteine), vitamin B6 for the conversion of methionine to cysteine, as well vitamins B2 and B3 for the activity of glutathione reductase, which recycles oxidized glutathione.

The methylation reactions use **SAMe**as a substrate; which, in turn, is synthesized through folate- and vitamin B12-dependent enzymatic reactions.

The conjugation reactions of the NAT’s and amino acid acyltransferases use the cofactor acetyl-coenzyme A (acetyl-CoA), which is synthesized from vitamin B5, using enzymes that themselves depend on multiple B vitamins.

Several phase II reactions require the energy molecule ATP in some fashion. For example, the chemical cofactors for the phase II methylation, sulfonation, glucuronidation, and glutathione conjugation reactions are all made using ATP; these ATP mediated reactions are magnesium-dependent.

**Flavonoids** have been extensively studied in vitro and in animal models for their ability to lower the activity of CYPs, and increase phase II enzyme activities (except for SULTs, which they tend to inhibit.68) The inhibition of CYP activity by naringenin (the principle flavonoid in grapefruit) has been well documented in humans69; hence the recommendation to avoid grapefruit when taking prescription drugs. Other flavonoids that have demonstrated mild inhibition of multiple CYPs in animal models include genistein, diadzein, and equol from soy,70,71 and theaflavins from black tea.72

**Green tea extracts** and the **quercetin** derivatives isoquercetin and rutin are an exception to most other flavonoids; green tea tannins can increase CYP activity in vivo73, but also increase phase II activity (GST and UGT). Similarly, the quercetin derivatives were demonstrated to increase intestinal and liver CYPs in rats; quercetin had no effect on CYPs in this experiment.74

**Nrf2 activators:** A wide variety of dietary components have been shown in vitro or cell culture to activate Nrf2 and directly increase activity of phase II enzymes; these include epigallocatechin gallate (EGCG)75, resveratrol76, curcumin77 and its metabolite tetrahydrocurcumin, which has greater phase II activity78, cinnamaldehyde79, caffeic acid phenyethyl ester, alpha lipoic acid80, alpha tocopherol81, lycopene82, apple polyphenols (chlorogenic acid and phloridzin)83, gingko biloba84, chalcone85, capsaicin86, hydroxytyrosol from olives87, allyl sulfides from garlic88, chlorophyllin89, and xanthohumols from hops90. The beneficial effects of these phytochemicals have been demonstrated in numerous animal and human studies, particularly their chemopreventative and antioxidant abilities; these effects may be explained by their indirect stimulation of antioxidant enzyme production and phase II detoxification through Nrf2 signalling.91

**Isothiocyanates** derived from **glucosinolates** are reactive sulfur compounds with potent chemopreventive properties; the prototypical member is sulforaphane, a constituent of broccoli that is the subject of several human cancer trials.

Isothiocyanates such as sulforaphane and indoles such as indole-3-carbinol (I3C) are among the most potent natural inducers of phase II detoxification enzymes.92 Sulforaphane and a derivative of I3C both directly activate Nrf293, which increases the production of several protective enzymes, including GSTs, UGTs, glutamate-cysteine ligase (which synthesizes glutathione), and NQO1.94 I3C derivatives are also strong inducers of many phase I & II enzymes, and thus are among the most well studied phytochemicals for detoxification, as well as cancer prevention.95,96,9798,99

Compounds from the Japanese horseradish **Wasabi** japonica100,101, and benzyl isothiocyanate (*BITC*102) from **cruciferous vegetables** similarly stimulate phase II enzyme activity via Nrf2 activation. Both sulforaphane and HITC also lower CYP activity.103

**Sulfur constituents from garlic** are inhibitors of various*CYP*s104, andinduce GST and NQO1 activity in gastrointestinal tissues in rats.105 By activatingNrf2, components in garlic were able to reverse the depletion of antioxidant enzymes caused by a toxic metal compound in the livers of laboratory rats106

**D-limonene** (from citrus oil) has been investigated for anticancer activity in uncontrolled human trials and animal studies with some success107; part of this chemopreventive activity is due to the induction of phase I and phase II enzymes. In rats, D-limonene has been shown to increase total CYP activity108, intestinal UGT activity109 and liver GST and UGT activity110,111.

**Calcium D-glucarate** is present in many fruits and vegetables, and can be produced in small amounts in humans.112 When activated in the gut, it functions as an inhibitor of beta-glucuronidase, an enzyme produced by colonic bacteria and intestinal cells. In the intestines, beta-glucuronidase removes (deconjugates) glucuronic acid from neutralized toxins -- essentially reversing the reaction catalyzed by UGTs. Deconjugation reverts the toxin to its previous dangerous form, and allows it to be reabsorbed. Elevated beta-glucuronidase activity has been associated with increased cancer risk.113

**Chlorophyllin**is a chlorophyll derivative114 that inhibits CYP activity115, and stimulates GST activity in cell culture and rodent models.116 The unique chemical structures of chlorophyllin and chlorophyll enable them to bind and “trap” toxins in the gut preventing their absorption. In animal models, chlorophyllin and chlorophyll lower the bioavailability and accelerate the excretion of several environmental carcinogens.117,118,119 Toxin trapping may partly explain the results of a human trial of residents of Qidong, China, an area with a high incidence of liver cancer due to exposure to aflatoxin (a toxin produced by species of the fungus Aspergillus). Among the 180 people who took 100 mg of chlorophyllin three times daily, urinary levels of DNA-aflatoxin conjugates (a marker for DNA mutation) went down 55% compared to untreated people.120

**Probiotics**: Certain strains of probiotic bacteria may minimize toxin exposure by trapping and metabolizing xenobiotics or heavy metals.121 Examples include the detoxification of aflatoxin and patulin (two toxins produced by Aspergillus, a type of mold)122, the metabolism of heterocyclic amines and dimethylhydrazine 123, and the binding of lead and cadmium.124 Additionally, the production of the short chain fatty acid butyrate by lactic acid bacteria (from the fermentation of dietary fiber) has been shown to stimulate GST production in intestinal cell culture; this may also contribute to some of the anticarcinogenic properties of dietary fiber.125

**N-acetyl cysteine**: N-acetyl cysteine can provide an alternative source of sulfur for glutathione production. It is a free radical scavenger on its own, effective at reducing oxidative stress, particularly due to heavy metal toxicity.126 Because it can directly replenish glutathione stores, NAC is more effective than methionine at preventing liver damage,127 and is the current treatment for acetaminophen toxicity. It is an effective treatment for acute liver failure due to non-acetaminophen drug toxicity as well.128

**Milk Thistle** (Silybum marianum), the most well-researched plant in the treatment of liver disease129, contains a mixture of several related polyphenolic compounds called **silymarin**. Silymarin promotes detoxification by several complementary mechanisms. The antioxidant capacity of silymarin can lower the liver oxidative stress associated with toxin metabolism, particularly lipid peroxidation130, which has the effect of conserving cellular glutathione levels.131 Like NAC, silymarin can protect against acetaminophen toxicity (possibly by the similar mechanism of preserving glutathione levels). Silymarin, however, may be a more effective antidote than NAC for acetaminophen toxicity if the treatment is delayed (in an animal model, it was effective when administered up to 24 hours after overdose).132

**Phase III transporters**, while important for removing toxins from healthy cells, can also decrease the effectiveness of pharmaceutical therapies by increasing their clearance. This can be especially problematic with chemotherapy drugs, to which phase III transporters enable cancer cells to become resistant. Therefore, stimulation of phase III activity may not always be desirable.

Dietary factors can have differing effects on phase III transporters. For example, apple polyphenols133, and sulforaphane (at levels equivalent to about two servings of broccoli)134 both stimulate the activity of the phase III proteins. In contrast, the curcumin metabolite tetrahydrocurcumin decreases the activity of the phase III transporters in human cervical carcinoma and breast cancer cell lines.135 Resveratrol decreases phase III protein synthesis which prevented acute myeloid leukemia cells from becoming resistant to the chemotherapy drug doxorubicin in cell culture.136 **Silibinin**, the chief constituent of milk thistle137, is also a phase III inhibitor, both in vitro and in vivo.138

**Bile flow:** As a major carrier of toxins from the body, proper bile flow is a critical final step in the metabolic detoxification process. Impairment of bile flow (cholestasis), resulting from dysfunction within the liver or blockage of the bile duct, can result in the buildup of liver toxins and liver injury. Cholestasis can also be the result of the detoxification process itself; there is increasing evidence that the detoxification and excretion of clinical drugs into the bile can produce cholestatic liver disease.139 **Artichoke** has been used for centuries in folk medicine as a liver protectant and to stimulate bile flow (choleresis), and is the best-studied herbal choleretic agent.

Artichoke contains several antioxidants that can protect against oxidative liver damage, as well as caffeoylquinic acids, which have been shown to stimulate bile flow in animal models.140 Caffeoylquinic acids may also be responsible for the choleretic properities of yarrow141,142, fennel143, and dandelion.144Andrographis, garlic, cumin, ginger, ajowan (carom seed), and curry and mustard leaf have also been shown to stimulate bile flow or bile acid production in rodent models.145,146,147,148

***Disclaimer and Safety Information***

*This information (and any accompanying material) is not intended to replace the attention or advice of a physician or other qualified health care professional. Anyone who wishes to embark on any dietary, drug, exercise, or other lifestyle change intended to prevent or treat a specific disease or condition should first consult with and seek clearance from a physician or other qualified health care professional. Pregnant women in particular should seek the advice of a physician before using any protocol listed on this website. The protocols described on this website are for adults only, unless otherwise specified. Product labels may contain important safety information and the most recent product information provided by the product manufacturers should be carefully reviewed prior to use to verify the dose, administration, and contraindications. National, state, and local laws may vary regarding the use and application of many of the treatments discussed. The reader assumes the risk of any injuries. The authors and publishers, their affiliates and assigns are not liable for any injury and/or damage to persons arising from this protocol and expressly disclaim responsibility for any adverse effects resulting from the use of the information contained herein.*

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