Great Smokies Diagnostic Laboratory

Functional Liver Detoxification Profile

- *Use a non-invasive test to assess how well the liver detoxifies and eliminates toxic chemicals.*
- *Assess the risk for free radical damage due to impaired liver function.*
- *Monitor effectiveness of detoxification programs.*

  Measure availability of body sulfate and glutathione.

The liver fills a key role in the body's natural self-defense system by converting and "neutralizing" toxins into safe by-products which can then be eliminated.

However, many challenges to this system – repeated exposure to food-borne toxic chemicals, environmental pollutants, endotoxins and other substances – can weaken the liver's primary detoxification function. Various physiological conditions, including altered intestinal permeability (leaky gut), dysbiosis, alcoholism and cirrhosis, increase the liver's detoxification burden; this overload can lead to greater production of free radicals and greater risk of systemic damage to the body.

The Functional Liver Detoxification Profile provides valuable information for patients with:

- **Alzheimer's or Parkinson's Disease**
- **Altered Intestinal Permeability**
- **Autoimmune Disease**
- **Chronic Fatigue Syndrome**
- **Encephalopathy**
- **Food Allergies**
- **Headaches**
- **Hepatitis**
- **Infectious Bowel Disease**
- **Intestinal Toxemia**
- **Multiple Chemical Sensitivities**
- **Pre-Menstrual Syndrome**
- **Occupational exposure to xenobiotics**

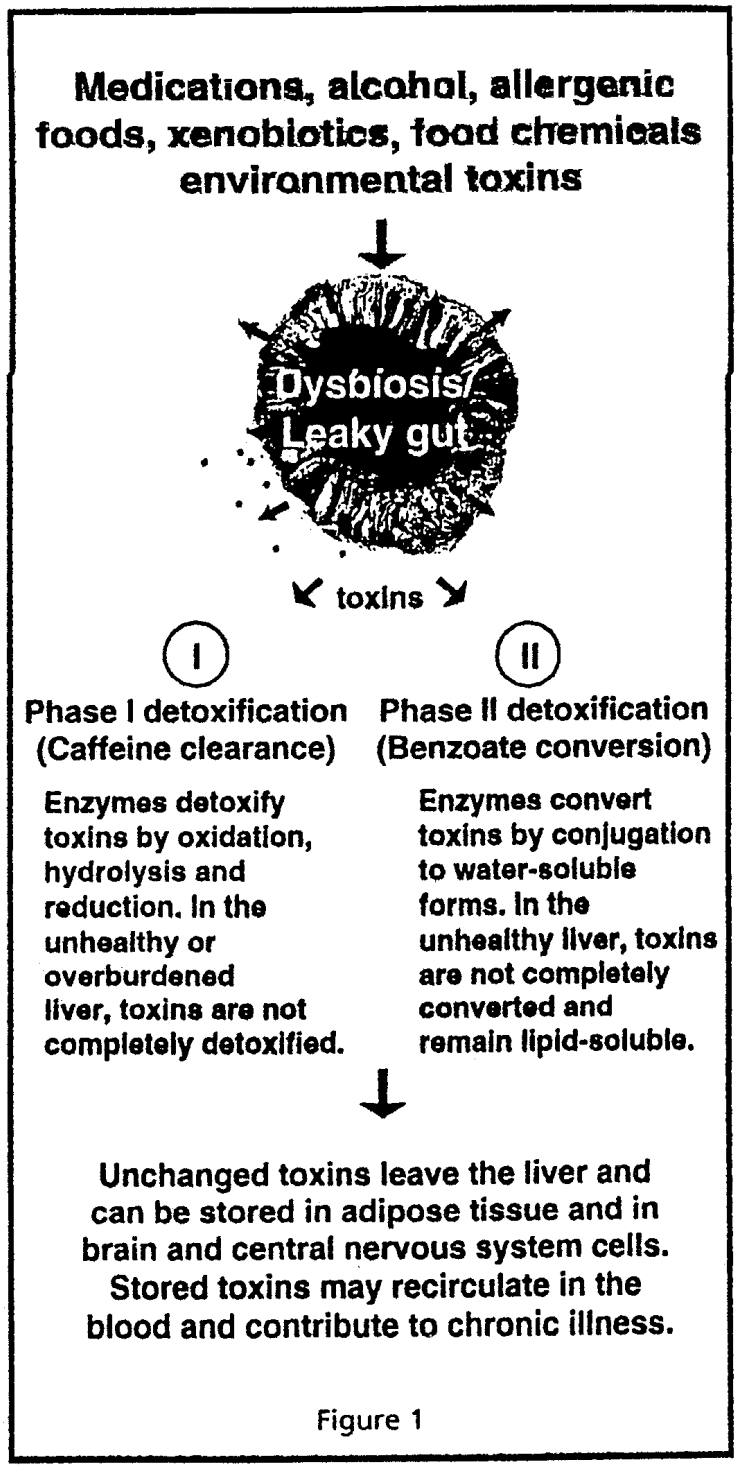

Figure 1

In individuals with dysfunctional livers, toxic wastes accumulate in adipose body tissue, including the brain and central nervous system. Stored toxins also recirculate in the blood and may contribute to long-term health problems.

The *Functional Liver Detoxification Profile* specifically assesses the functional capacity of the liver to carry out detoxification. It evaluates the organ's ability to mobilize metabolic reserves in response to a challenge. Standard laboratory liver tests (such as SGOT, SGPT or bilirubin) only measure existing pathological damage to liver cells.

Clinical Relationships

Increased body burden of toxins is associated with many clinical conditions. The accumulation of metabolic toxins can cause impairment of oxidative phosphorylation and reduced energy production, which at the whole organism level can result in fatigue and poor exercise tolerance. These symptoms are seen in patients with Chronic Fatigue Syndrome (CFS). A recent study reported that many CFS patients had disordered liver detoxification ability and showed signs of increased toxic exposure.[1] Buist suggests that CFS may be a result of xenobiotic or toxin exposure.[2]

Many chronically unwell patients with occasional exposure to chemical agents continue to provoke chemical intolerances or even exacerbate them. The enzyme systems in the body dealing with the detoxification are clearly of importance in such patients, because their total load of xenobiotics may impair or induce such enzymes. A recent study showed that the majority of chemically sensitive patients had impaired hepatic sulfoxidation ability.[3]

The Liver's Role in Detoxification

The enzymatic detoxification process is responsible for converting and "neutralizing" endotoxins and exotoxins into safe by-products for elimination through urine and, to a lesser degree, in feces. Hepatic detoxifying enzymes represent one of the most important defensive mechanisms against the toxic effects of xenobiotics (such as pesticides), endogenous sterols, endotoxins, drugs and alcohol.

Failure of this critical process leads to accumulation of toxic wastes throughout the adipose body tissue including the brain and central nervous system, which can lead to the development of a wide range of systemic complaints and chronic unwellness. Stored toxins recirculate in the blood and may contribute to long-term health problems.

Detoxification Processes

All ingested and microbial-produced toxins are presented to the first-pass clearance system. First-pass clearance involves the biotransformation and clearance of a chemical from the body before it reaches the systemic circulation. This clearance takes place at two major sites: the intestinal mucosal wall and the liver. At the mucosal wall, biotransformation is activated both by microbial and mucosal cell enzymes.

In the liver, two related processes – known as *Phase I* and *Phase II* – carry out biotransformation. *Phase I* chemically alters substances through oxidation, reduction, sulfoxidation or hydrolysis, using the cytochrome P-450 mixed-function oxidase enzymes. Exposure to a chemical induces different isoenzymes of P-450.[4]

In *Phase II*, a conjugation reaction adds a small polar molecule to the toxin, converting lipophilic substances to water-soluble forms for excretion and elimination. The *Phase II* reaction may follow *Phase I* or proceed independently. The liver uses glutathione, sulfate, glycine, acetate, cysteine and glucuronic acid molecules, among others, to act upon the conjugation molecule and catalyze the reaction step.[4] Adequate amounts of these molecules must be present for proper liver function.

A third process involved in detoxification is sulfation, an important means of converting steroid hormones, drugs and phenolic compounds into less toxic substances. Sulfate is a product of the tripeptide glutathione, an antioxidant. When glutathione reserves are depleted, the liver cannot effectively process and detoxify harmful substances.

Substances which induce P-450 enzymes

- Acetate
- Alcohol
- Barbiturates
- Carbon Tetrachloride
- Charcoal broiled meats
- Dioxin
- Exhaust fumes
- High protein diets
- Niacin
- Oranges
- Organophosphorus pesticides
- Paint fumes
- Riboflavin
- Sassafras
- Saturated fats
- Steroid hormones
- Sulfonamides
- Tangerines

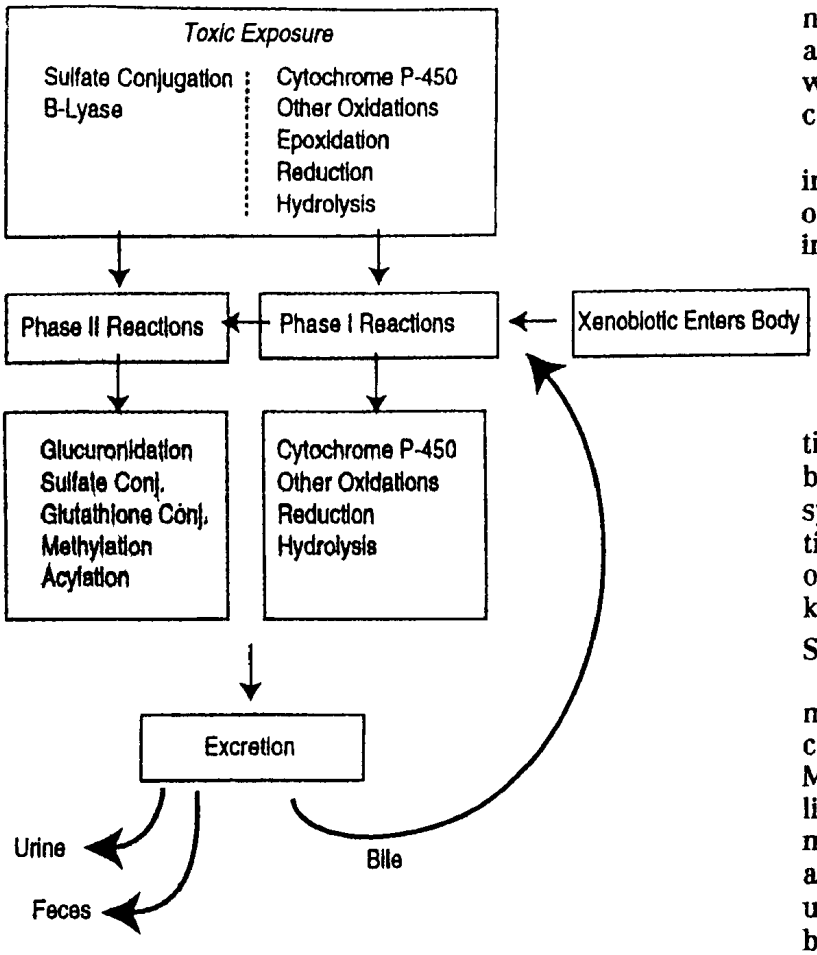

Figure 2

Pathways for Phase I and Phase II reactions in biotransformation of toxins[5]

Research indicates both sulfation capacity and glutathione stores may be evaluated with a urinary sulfate-to-creatinine ratio.[6,7]

Liver Function Assessments

The *Functional Liver Detoxification Profile* uses two common challenge substances to evaluate hepatic detoxifying ability: caffeine, which is primarily oxidatively demethylated by P-450 enzymes, and sodium benzoate, which is conjugated with glycine to produce hippuric acid.[8]

Caffeine Clearance

Measurement of salivary caffeine clearance provides a non-invasive procedure for quantifying hepatic microsomal function regardless of disease.[9,10] Caffeine is almost completely absorbed by the intestine and is metabolized in the liver by P-450 enzymes.[9]

The clinical usefulness of caffeine as a tool for investigating liver function has been aided by the introduction of a rapid and simple enzyme immunoassay. Measurement of salivary caffeine clearance appears particularly suitable for children where quantification of liver function has been cumbersome.[9]

High caffeine clearance values reflect enzyme induction, probably due to exposure to endogenous or exogenous toxins. This also suggests potential increased free radical production due to excessive P-450 activity. Smokers generally have a more rapid caffeine clearance due to the inducing capacity of cigarette smoke on the P-450 system.[11] Vitamin C slightly increases clearance.[12]

A low clearance rate indicates slow, dysfunctional P-450 enzyme activity; this suggests metabolic difficulty in removing toxic chemicals from the system. Endotoxemia, oxidant stress and medications (such as amphetamines, isoniazid, cimetidine, oral contraceptive steroids and ciprofloxacin) are known to reduce caffeine clearance as well.[12-16]

Sodium Benzoate

Benzoate, a commonly-used preservative, is metabolized mainly in the liver through glycine conjugation into hippurate, then excreted in urine. Measuring the amount of urinary hippurate the liver has converted provides a good index to determine hepatic functional reserve and the detoxifying ability of the liver.[17,18] This type of analysis has been used in liver function tests for decades, and has been labeled the most practical measure of liver function.[19]

A slow conversion of benzoate to hippurate after a sodium benzoate challenge is indicative of inadequate Phase II detoxifying reactions.[20]

Caffeine-Benzoate Conversion Ratio

An elevated caffeine clearance to benzoate conversion ratio indicates increased liver cytochrome P-450 activity relative to the *Phase II* conjugation with glycine. These individuals have been termed "pathological detoxifiers." This increased P-450 activity creates an imbalance in the detoxification process which produces an increase in toxic biotransformed intermediate substances, which can exert their own toxic effects through free radical damage. This condition can be caused by nutritional inadequacy, activation of cytochrome P-450 by certain drugs and alcohol, or by significant xenobiotic exposure.

A reduced caffeine clearance to benzoate conversion ratio indicates decreased liver cytochrome P-450 activity relative to the glycine conjugation. These individuals have been termed "slow detoxifiers." Xenobiotic substances and other toxins are less quickly eliminated due to the rate-limiting inhibition of cytochrome P-450 detoxification.

Sulfate-Creatinine Ratio

Urinary sulfate to creatinine ratio indicates the supply of glutathione available for detoxification. A

Interpreting GSDL's *Functional Liver Detoxification Profile*

Low caffeine clearance ***(Phase I)***
Indicates slow P-450 enzyme activity and metabolic detoxification difficulty; may also reflect use of medications such as amphetamines, cimetidine, isoniazid and oral contraceptives.

High caffeine clearance ***(Phase I)***
Reflects excessive P-450 enzyme induction, possibly due to toxin exposure (such as cigarette smoking).

Slow Benzoate conversion ***(Phase II)***
Indicates an inadequate Phase II glycine conjugation detoxification reaction.

Elevated Caffeine/Benzoate Conversion ratio
Indicates increased P-450 enzyme activity relative to Phase II conjugation with glycine.

Reduced Caffeine/Benzoate Conversion ratio
Indicates "slow detoxifier" P-450 enzyme activity relative to Phase II glycine conjugation.

Low Sulfate/Creatinine ratio
Reflects low amount of glutathione and sulfate available for detoxification.

high ratio suggests adequate supply of glutathione and sulfate, while a low ratio suggests lower amounts of these substances, putting the liver at risk for free radical damage and impaired conjugation.

A low ratio is associated with increased intestinal permeability. The probable pathophysiology in those with permeable bowelsis an increased requirement for dietary sulfur amino acids needed for hepatic detoxification of xenobiotics leaking into the liver circulation.[21]

Measurements of Oxidative Stress

Additional analyses of oxidative stress are available with GSDL's *Functional Liver Detoxification Profile - Oxidative Stress* panel. This panel includes all four components of the liver detoxification profile plus measurement of blood glutathione and lipid peroxides.

Under oxidative stress, an individual's total body redox potential is shifted towards oxidative damage. There are lower amounts of reducing agents in the blood, such as vitamins E and C, carotenes and glutathione, and higher levels of oxidants such as lipid peroxides and other reactive oxygen species.

There are a number of physiological alterations which may be analyzed to evaluate the potential of free radical damage.The whole blood reduced glutathione and lipid peroxides tests measure the body's ability to remove free radicals and provide an accurate evaluation of relative oxidative stress.[22]

The glutathione status of the body is measured by the whole blood reduced glutathione test. Oxidative stress due to xenobiotic detoxification increases the demand for reduced glutathione, an antioxidant.

The lipid peroxides test measures the amount of serum lipid damaged by oxidants which produce lipid peroxide by-products, such as malonaldhyde and other reactive aldehyde products.

Relationship to Intestinal Permeability

The intestinal mucosa is the primary barrier to permeation of toxic compounds and macromolecules. Abnormalities of the intestinal immune system (sIgA) or mechanical barriers (leaky gut) lead to enhanced uptake of inflammatory luminal macromolecules, endotoxins and xenobiotics. With clinical intestinal injury, mucosal absorption of substances that are normally excluded increases dramatically.

These "foreign" chemicals are presented to the liver's detoxifying system for processing and elimination. They can drain the detoxification ability of the liver, or not be processed and remain harmful in a dysfunctional environment. The combined leaky gut access and dysfunctional liver detox system can lead to increased tissue stores of toxic compounds and depressed immune systems.

Using the Functional Liver Detoxification Profile

In the *Functional Liver Detoxification Profile*, hippurate converted to sodium benzoate is measured in a urine sample, and caffeine clearance is measured in two saliva samples. Additionally, the ratio of urinary sulfate to creatinine is calculated to provide information on glutathione reserves.

The *Functional Liver Detoxification Profile* requires the patient to fast overnight, then drink a small amount of a premixed challenge dose. One hour after the challenge drink, the patient collects a single urine specimen. The saliva specimens are collected two and eight hours after the test drink. Addition of the *Oxidative Stress* panel requires whole blood and serum samples. Specimens are sent to Great Smokies for rapid analysis and results are reported to the health care professional.

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Clinical Therapeutics for Liver Detoxification

General therapeutic considerations center around nutritional and herbal support for the liver, tissue saturation of antioxidants and, in certain instances, detoxifying regimes.

- **When the *Phase I* system is induced** (rapid/elevated), it is usually due to increased exposure to toxins. Because free radicals are formed in this process, antioxidants are recommended, such as Vitamins E, C, beta carotene, flavonoids (quercitin, hesperidin), pycnogenol and selenium. Use extreme caution in using any detox program, as the production of free radicals and intermediate metabolites can lead to tissue damage.

- **When the *Phase I* system is decreased** (slow), it indicates a dysfunctional system and increased susceptibility to toxins. A nutritional detox program is usually recommended along with biochemical liver support such as silymarin and lipotropic factors. Nutrients such as iron, molybdenum, magnesium and antioxidants can help to "upregulate" the system.

- **When the *Phase II* conversion is slow**, it indicates a low hepatic functional reserve and decreased glycine conjugation. Liver support with silymarin and lipotropic factors is helpful, as well as conjugating nutrients such as glutathione, N-acetyl cysteine and glycine.

- **An elevated Caffeine-to-Benzoate Conversion Ratio** indicates the individual is a "pathological detoxifier." Antioxidants are recommended for preventing free radical damage to tissue, and the replacement of conjugating nutrients such as N-acetyl cysteine is critical to the rebalancing of the system.

- **A reduced Caffeine-to-Benzoate Conversion Ratio** reflects a dysfunctional system. Liver support and upregulating nutrients may be helpful. Cruciferous * vegetables can help support activity of both *Phase I* and *Phase II*.

- **When the Sulfation Index is decreased**, indicating depletion of glutathione and cysteine stores, supplements of glutathione, N-acetyl cysteine and sulfur-containing foods such as garlic may be helpful.

*korsblomstrede grøntsager

BY JACQUELINE KROHN, MD

DETOXIFICATION PATHWAYS

The body reacts to any substance or condition that is harmful to it as a toxin. A person's susceptibility and response to toxins varies with age, gender, genetic factors, nutritional status, other diseases, exposure pattern, and behavior or lifestyle factors. People whose immune defenses are lowered or whose body defense mechanisms (e.g., skin, lungs, gastrointestinal tract) are impaired are more likely to be affected by toxins. Responses to toxins also vary with the nature of the toxin.

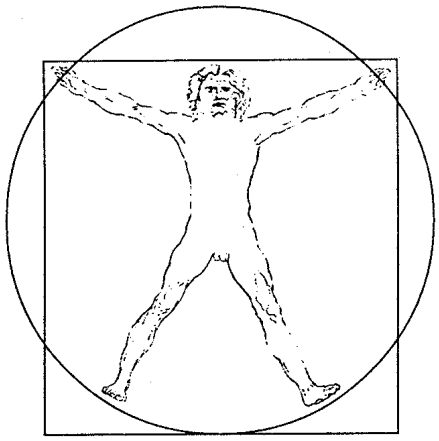
Our bodies have detoxification mechanisms to rid themselves of toxins and chemicals. The skin, lungs, gastrointestinal tract, kidneys, and liver are the organs of detoxification, eliminating foreign chemicals and drugs (Xenobiotics), as well as compounds that the body produces, such as hormones, vitamins, cholesterol, and fatty acids. Many chemicals that the body absorbs tend to remain in the tissues for long periods of time. Most of these chemicals are lipophilic—that is, they dissolve readily in fat, which is one of the main components of cell membranes. These lipophilic chemicals are complex and difficult for the body to break down and excrete.

The detoxification process in the body is composed of two phases, known as Phase I and Phase II. These phases are two different biochemical processes that enable the body to eliminate xenobiotics. Fat-soluble (lipophilic) chemicals, which accumulate in the body, are converted to water-soluble substances, which can then be excreted. These detoxification processes occur in the highest concentrations in the liver, but they also occur in the lungs, skin, and intestines.

PHASE I DETOXIFICATION

Phase I detoxification changes nonpolar, nonwater-soluble chemicals into relatively polar (electrically charged) compounds with the help of enzymes by adding a polar group or a reactive group. These changes are a type of chemical reaction known as biotransformation. Such changes include:

- *desulfuration* – eliminates a sulfur group and adds an oxygen group
- *dehalogenation* – eliminates a halogen (chlorine, fluorine, bromine, or iodine) group and adds an oxygen group
- *oxidation* – loses an electron
- *reduction* – gains an electron after an atom of oxygen is added to the molecule.



The skin, lungs, gastrointestinal tract, kidneys, and liver are the organs of detoxification, eliminating foreign chemicals and drugs (Xenobiotics), as well as compounds that the body produces, such as hormones vitamins, cholesterol, and fatty acids.

The Phase I enzymes are known as the cytochrome P-450 monooxygenase system, and the mixed-function amine oxidase system. The cytochrome P-450 system is the major system. The cytochrome P-450 monooxygenase system is a chain of enzymes in which cytochrome P-450 is the end of an electron-transport chain in adrenal and liver cells. It is important for the detoxification of foreign substances, such as xenobiotic compounds. The mixed-function amine oxidase system is an enzyme system that detoxifies chemical groups called amines, which contain nitrogen and hydrogen.

Many forms of cytochrome P-450 are involved in Phase I reactions. The highest concentration of cytochrome P-450 occurs in the liver, and it is the site of the most active metabolism. Cytochrome P-450 has also been found in the intestines, adrenal cortex, testes, spleen, heart, muscles, brain, and skin. The lungs and the kidneys are secondary organs of biotransformation, having about one-third of the liver's detoxification capacity.

The action of detoxification enzymes depends on the presence of various minerals. For example, alcohol dehydrogenase, which converts alcohols (such as ethanol) to aldehydes, depends on an adequate supply of zinc to function properly. In the next step in alcohol metabolism, aldehyde oxidase changes the aldehyde into an acid that can be excreted in the urine. Aldehyde oxidase depends on an adequate supply of molybdenum and iron.

Usually, these enzymatic reactions

decrease chemical toxicity. However, unless there is a balance with Phase II, toxic or reactive chemicals can form during Phase I metabolism, and these metabolites are more toxic than the original compound. This is known as bioactivation. The following harmful substances can form during bioactivation: teratogens (causing fetus malformation), mutagens (causing cell mutation), and carcinogens (causing cancer). They can adversely affect the liver and other areas of the body. For example, benzo[a]pyrene, a chemical in coal tar and cigarette sidestream smoke, is biologically inert until it is converted by the mixed-function oxidases into a metabolite that can then initiate cancer-causing activity. Many compounds form dangerous reactive free radicals, chemicals with an unpaired electron that can cause tissue damage. Some people are at risk for cancer from a buildup of these free radicals.

Because of the possibility of more toxic compounds forming in the case of an imbalance between Phase I and Phase II, it has been suggested that biotransformation is a more appropriate term than detoxification when describing Phase I and Phase II. When the more toxic compounds form, it is not a detoxification process, but biotransformation. However, this article uses the term detoxification because it is more frequently used in the literature describing the Phase I and Phase II reactions.

Phase I of the detoxification process can be measured with a caffeine metabolism test. A known quantity of caffeine is ingested, and saliva samples are obtained twice after ingestion. Rapid clearance of caffeine shows enzyme induction (increased production), either from xenobiotic exposure or toxins within the body. Low caffeine clearance indicates that the cytochrome P-450 activity in the liver is abnormal. Patients with low caffeine clearance would have difficulty eliminating xenobiotics.

PHASE II DETOXIFICATION

In Phase II detoxification, chemical groups are added, or conjugated, to the chemical. The chemical is now water-soluble and can be excreted through the kidneys. Major conjugation reactions include:

- *acetylation* – Adds acetyl Co-A to form a mercapturic acid conjugate; chief degradation pathway for aromatic (aryl) amines, sulfur amides, and aliphatic amines
- *acylation* – Uses acyl Co-A and amino acids, taurine, glycine, and glutamine to form a peptide conjugation
- *gluconation (glucuronidation)* – Adds a sugar group, using glucuronic acid; the major conjugation reaction for xenobiotics and body chemicals
- *methylation* – Adds a methyl (CH_3) group; uses the amino acid methionine
- *sulfonation* – Adds inorganic sulfate to hydroxyl groups for detoxification; requires high energy.

Phase II of the detoxification pathway can be evaluated by ingesting acetominophen and aspirin and measuring the recovery of the products of glutathione conjugation, sulfation, glucuronidation, and glycine conjugation.

Detoxification of xenobiotics requires large amounts of energy, which comes mainly from the food we eat. If we do not eat enough protein, the body breaks down vital tissue protein to produce the energy it needs. This, in turn, decreases the amounts of Phase I and Phase II enzymes, amino acids, and peptides. This decreases the metabolism of xenobiotics. Vitamins and minerals are also required in the chemical reactions of the detoxification process.

It is very important to provide the body with the nutrients for function, repair, and detoxification. Fresh fruits, vegetables, grains, and meats can supply many of these nutrients. Eat high quality food, fresh food, and when possible organic foods. If there is doubt about food quality, supplementation can be used to assure adequate nutrients. Avoid processed foods and foods high in sugar and fat.

The accompanying tables list vitamins, minerals, and other nutrients that aid in Phase I and Phase II detoxification. ■

Jacqueline Krohn, MD, is the author of The Whole Way to Natural Detoxification, *from which the preceding article was adapted. She is also the author of* The Whole Way to Allergy Relief & Prevention *and practices environmental and occupational medicine and pediatrics in Los Alamos, New Mexico.*

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NUTRIENTS FOR DETOXIFICATION

The following nutrients aid in Phase I and Phase II detoxification.

PHASE I VITAMINS	
Beta-carotene – yellow, red, and green vegetables	Converted in body to vitamin A, which helps to protect lipid portion of the cell membrane. Promotes healthy intestinal mucosa necessary for absorption of other nutrients. Vitamin A is also necessary for conversion of alcohols to aldehydes.
Vitamin B1 (thiamine) – dairy, meats, legumes, whole grains, nuts	Thiamine pyrophosphate, the coenzyme form of thiamine (the form most easily utilized by the body), is necessary for moving an aldehyde group from one molecule to another. It is needed for the enzyme necessary for glutathione regeneration.
Vitamin C – fruits, green vegetables	Increases antioxidant protection and is necessary for electron transport. The action of cytochrome P-450 is dependent on vitamin C.
Vitamin E – vegetable oils, green leafy vegetables, milk, eggs	Antioxidant that prevents formation of peroxides and oxidation of vitamins A and K and of fat-soluble hormones. Helps prevent an overactive cytochrome P-450 system, which can be a source of free radicals.
PHASE I MINERALS	
Copper – meats, seafoods, nuts	Activates several enzymes. In superoxide dismutase.
Iron – beans, meats, dark-green vegetables	Contained in cytochrome P-450.
Magnesium – nuts, legumes, dark-green vegetables	Necessary for glutathione synthesis, ammonia detoxification, and oxidative phosphorylation (produces ATP, the main source of energy for the body).
Manganese – leafy vegetables whole grains, nuts	In the enzymes superoxide dismutase and glutathione synthetase.
Molybdenum – whole grains, legumes, seeds	In aldehyde oxidase, which helps change aldehydes to acids that are excreted in the urine.
Sulfur – garlic, eggs, onions, meats	All glutathione enzymes contain sulfur.
Zinc – shellfish, meats, dairy	In alcohol dehydrogenase, a Phase I enzyme.
OTHER PHASE I NUTRIENTS	
Alpha-ketoglutaric acid— Supplement required	Helps detoxify ammonia. Addition of an ammonia group to this acid forms glutamic acid, which is then transformed to glutamine, providing the major pathway for removing ammonia from the body.
Choline – whole grains, cheese, legumes, meats	When combined with an acetyl group, helps increase intestinal peristalsis (contractions during digestion); this in turn aids in elimination of toxins. Cytochrome P-450 enzymes are dependent on choline.
Fatty acids – flaxseed, soybeans, fish oils	Speed up transit time of the stool, averting buildup of toxins and reducing toxic load for the liver.
Lecithin – legumes, grains, eggs, fish	Used with oils. Its action allows safe transport of fats through the bloodstream.
Methionine – meat, eggs, whole grains	Because of its sulfur content, helps to remove heavy metals from the body; adds a methyl group to xenobiotics that aids in their excretion from the body; precursor for other sulfur amino acids.
Silymarin – Milk thistle	Helps to detoxify the liver of alcohol and various pollutants.
Recommended oils – flaxseed, evening primrose, black currant seed	The body exchanges these oils for contaminated fat, which is eliminated through bile excretion and feces. The oils also decrease plasma cholesterol, encouraging fecal excretion.

PHASE II VITAMINS	
Folic acid – dark green leafy vegetables, cabbage family, organ meats	Coenzyme form is an intermediate carrier for methylation.
Vitamin B1 (thiamine) – dairy, meats, legumes, whole grains	Needed for glutathione regeneration. Provides energy for conjugation.
Vitamin B2 (riboflavin) – milk, meat, dark-green leafy vegetables	Needed for the enzyme glutathione reductase.
Vitamin B3 (niacin) – meat, eggs, poultry, fish, whole grains	Needed for recycling glutathione.
Vitamin B5 (pantothenic acid) – meats, whole grains	Pantothenic acid is bound to coenzyme A, a carrier of acetyl groups. This combination is essential in acetyl conjugations of several classes of chemicals. It is also important in transamination processes.
Vitamin B6 (pyridoxine) – meats, vegetables, whole grains	Required for metabolism of methionine for glutathione. A deficiency of B6 slows conjugation.
Vitamin B12 (cobalamin) – meat, dairy products, eggs	Coenzyme form participates in reactions in which methyl groups are transferred.
PHASE II MINERALS	
Germanium – garlic, shiitake mushroom, onions	Helps with toxic metal detoxification. Raises glutathione levels for Phase II detoxification, increases oxygen utilization at cell levels, and is a free-radical scavenger.
Magnesium – nuts, legumes, dark-green vegetables	Needed for glutathione production. Is a mineral activator for many detoxification enzymes. Methyl transferase requires magnesium.
Manganese – leafy vegetables, whole grains, nuts	Required for glutathione production, as well as for enzymes necessary to detoxification pathways.
Molybdenum – whole grains, legumes, seeds	Helps in synthesis and use of sulfur amino acids, is a component of detoxification enzymes, and is necessary for utilization of vitamin C at cell level.
Selenium – brewer's yeast, garlic, liver, eggs	Is in glutathione peroxide.
Sulfur – garlic, eggs, onions, meats, cabbage family	In the form of sulfates, with the enzyme sulfotransferase, enables the conjugation process of sulfonation. This process results in products that are less toxic and more easily excreted than the original compound. Because of its high sulfur content, garlic is very helpful in removing heavy metals.
Zinc – shellfish, meats, dairy	In enzymes necessary for conjugation.
OTHER PHASE II NUTRIENTS	
Cysteine – eggs, meats, onion family	Detoxifies pesticides, plastics, hydrocarbons, and other chemicals.
D-Glucarate – vegetables	Helps in major conjugation reaction in converting xenobiotics to polar water-soluble compounds.
Glycine – whole grains, meats, dairy	Stimulates production of glutathione. Also aids in detoxification of benzoic acid and phenol.
L-glutathione (reduced form) – produced in the body from cysteine, glutamic acid, and glycine	An antioxidant that conjugates with metabolites of xenobiotics to increase their water solubility, enabling excretion by the kidneys.
N-acetyl cysteine – precursor to glutathione; must be supplemented	Converted by the body to cysteine, which along with vitamin C detoxifies pesticides, plastics, hydrocarbons, and other chemicals.
Taurine – meats, seafood	Helps peptide conjugation of xenobiotics.

Den medfølgende liste angiver de vitaminer, mineraler og andre næringsstoffer, som medvirker i Fase I og II afgiftningen.

Fase I vitaminer:
beta-karoten, vitamin B1, C og E

Fase I mineraler:
kobber, jern, magnesium, mangan, molybdæn, svovl og zink

Andre Fase I næringsstoffer:
alpha-ketoglutarsyre (tilskud)
cholin - hele korn, ost, grønsager, kød
fedtsyrer - hørfrø, soyabønner, fiskeolier
lecithin - grønsager, korn, æg, fisk
methionin - kød, æg, hele korn
silymarin - Marietidsel
anbefalede olier - hørfrø, natlys, solbærfrø

Fase II vitaminer:
folinsyre, vitamin B1, B2, B3, B5, B6, B12

Fase II mineraler:
germanium, magnesium, mangan, molybdæn, selen, svovl, zink

Andre Fase II næringsstoffer:
cystein - æg, kød, løgfamilien
D-glucarat - grønsager
glycin - hele korn, kød, mælkeprodukter
L-glutathion - dannes i kroppen af cystein, glutaminsyre og glycin
N-acetyl cystein - tilskud
taurin - kød, fisk

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Kroppens afgiftningsmekanismer

Kroppen reagerer på ethvert stof, som er skadeligt for den, som på et giftstof (toksin). En persons modtagelighed over for toksiner afhænger af alder, køn, genetiske faktorer, ernæringstilstand, andre sygdomme, eksponeringsmønster og adfærds- og livsstilfaktorer. Mennesker, hvis immunsystem er svækket eller hvis kropslige forsvarsmekanismer, dvs. hud, lunger og mave-/tarmsystem, er skadet, har større sandsynlighed for at blive påvirket af toksiner. Reaktionen på toksiner varierer også med arten af giftstofferne.

Vores krop har afgiftningsmekanismer, som skiller kroppen af med giftstoffer og kemikalier. Huden, lungerne, mave-/tarmsystemet, nyrerne og leveren er afgiftningsorganer. De fjerner medicin og fremmede kemikalier (xenobiotics) såvel som stoffer, kroppen selv producerer, f. eks. hormoner, vitaminer, kolesterol og fedtsyrer.

Mange kemikalier, som kroppen optager, har tendens til at blive i kroppen i lang tid. De fleste af disse kemikalier er lipofile, dvs. de opløses nemt i fedt, som er en af hovedbestanddelene i cellemembranerne. Disse lipofile kemikalier er vanskelige for kroppen at nedbryde og udskille.

Fase I og II afgiftningen
Afgiftningsprocessen i kroppen foregår i to faser, kendt som Fase I og Fase II. Disse faser er to forskellige biokemiske processer, som gør kroppen i stand til at nedbryde fremmede kemikalier. Fedtopløselige kemikalier, som ophobes i kroppen, omdannes til vandopløselige stoffer, som derefter kan udskilles. Disse afgiftningsprocesser foregår i de største koncentrationer i leveren, men de foregår også i lungerne, huden og tarmene.

Fase I afgiftningen ændrer neutrale, ikke-vandopløselige kemikalier til elektrisk ladede stoffer. Denne form for kemisk reaktion kaldes biotransformation. Den sker ved hjælp af enzymer, som tilfører kemikaliet en elektrisk ladet gruppe.

Fase I enzymerne kaldes "cytokrom P-450 monooxygenase systemet" og "mixed-function amin oxidase systemet". Amin oxidase systemet er et enzymsystem, der afgifter de kvælstof- og brintholdige stoffer, som kaldes aminer. Cytokrom P-450 systemet er det vigtigste. Det er en kæde af enzymer, i hvilken cytokrom P-450 er afslutningen på en elektron-transportkæde i binyre- og levercellerne. Den har betydning for afgiftningen af fremmede kemikalier. Mange former for cytokrom P-450 er involveret i Fase I reaktioner. Den højeste koncentration af cytokrom P-450 findes i leveren, og den er stedet for den mest aktive stofomdannelse. Lungerne og nyrerne er sekundære organer i biotransformationen, og de har omkring en tredjedel af leverens afgiftningskapacitet.

Under Fase II afgiftningen tilføres kemikaliet nye kemiske forbindelser. Kemikaliet bliver nu vandopløseligt, og det kan udskilles gennem nyrerne.

Bioaktivering
Normalt vil disse enzymreaktioner i kroppen formindske stoffernes giftighed. Men medmindre der er balance med Fase II, kan giftige og reaktive kemikalier dannes under Fase I. Disse stofskifteprodukter er mere giftige end de oprindelige kemiske forbindelser. Dette kaldes bioaktivering. Følgende skadelige stoffer kan dannes under bioaktivering: teratogener, mutagener og carcinogener. De kan forårsage hhv. fosterskader, celleforandringer og kræft, og de kan påvirke leveren og andre kropsdele negativt.

For eksempel er benzopyren, et kemikalie i tjære og tobaksrøg, biologisk inaktivt, indtil det er omdannet af "mixed-function amin oxidase" enzymerne til stofskifteprodukter, som kan sætte kræftdannende aktiviteter igang. Mange stoffer danner også reaktive, frie radikaler, som kan forårsage vævsødelæggelse.

Funktionen af afgiftningsenzymerne er afhængig af tilstedeværelsen af forskellige mineraler. F. eks. kræver nedbrydningen af alkohol en passende mængde zink i det første trin for at fungere ordentligt. I det næste trin af alkoholomdannelsen er molybdæn og jern nødvendige, inden alkoholen kan udskilles som en syre i urinen.

Afgiftningstests
Fase I i afgiftningsprocessen kan måles ved en koffeinstofskifte test. En kendt mængde koffein indtages, og spytprøver tages to gange efter indtagelsen. En langsom renselse af spyttet for koffein tyder på, at cytokrom P-450 aktiviteten i leveren er unormal. Patienter med langsom kooffeinudrensning vil have vanskeligt ved at nedbryde fremmede kemikalier og medicin i kroppen

Fase II i afgiftningsprocessen kan bedømmes ved at indtage aspirin og acetominophen og måle genvindingen af nedbrydningsprodukterne.

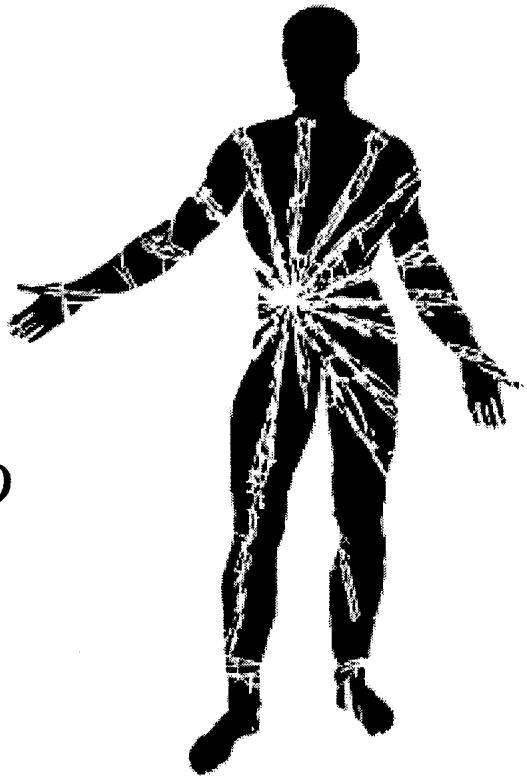
Fødens betydning
Afgiftningen af fremmede kemikalier kræver store mængder energi, som først og fremmest kommer fra den mad, vi spiser. Hvis vi ikke får nok protein, nedbryder kroppen livsvigtigt vævsprotein for at producere den energi, den behøver. Dette mindsker til gengæld mængden af Fase I og II enzymer, aminosyrer og peptider. Og dette mindsker nedbrydningen af fremmede kemikalier. Vitaminer og mineraler er også nødvendige for de kemiske reaktioner i afgiftningsprocessen.

Det er meget vigtigt at forsyne kroppen med næringsstoffer til funktion, reparation og afgiftning. Friske frugter, grønsager, korn og kød kan levere mange af disse næringsstoffer. Spis føde af høj kvalitet, frisk føde og om muligt økologisk. Hvis der er tvivl om madens kvalitet, kan kosttilskud anvendes for at sikre de nødvendige næringsstoffer. Undgå forarbejdede fødevarer og mad med højt sukker- og fedtindhold.

BY LOUISE KOSTA

Leaky Gut Syndrome

An interview with Leo Galland, MD



[*A Fellow in the American College of Physicians and the American College of Nutrition and a member of the American Academy of Environmental Medicine, Dr. Galland is certified by the American Board of Internal Medicine. His faculty appointments have included New York University School of Medicine and Albert Einstein College of Medicine in New York, the State University of New York at Stony Brook, and the University of Connecticut. Dr. Galland practices internal medicine in Manhattan. His most recent book is* Power Healing, *Random House 1998.*]

LK: What is leaky gut syndrome?
LG: Any condition associated with increased permeability of the intestinal tract is a leaky gut syndrome. The intestinal tract is huge: it's 30 feet long and has the surface area of a doubles tennis court. It's important that the contents of the intestinal tract *stay* in the intestinal tract — it's the most toxic mixture most of us will ever encounter. Although the intestinal tract is inside the body, its inner surface is actually best thought of as outside the body. We rely on it to be intact and to protect us from the toxicity of the gut contents.

It's important to remember that the content of the gut includes nutrients as well as the toxic materials I've been talking about, such as bacterial toxins. The normal microflora of the gut, bacteria and so on, survive in this internal environment. The problem comes when the gut permits materials in the gut to enter the body in an unregulated fashion.

LK: How so?
LG: The normal intact gut is protected by a thick mucous coating and a dense lining of cells. The cells of the gut lining absorb materials in the gut and release them into the bloodstream. This is a vital function, because some of these materials are nutrients from the foods we eat. Interestingly, some of the materials absorbed by the cells and released into the bloodstream are also allergens, which enable the body to "learn" to recognize allergens.

Leakiness occurs when the lining of the intestinal tract becomes damaged. This damage consists of microscopic leaks so small that it is easy to miss them when looking at tissue samples using a regular lab microscope. Examination under an electron microscope will usually pick them up, however.

When this damage occurs, one of the body's defense systems breaks down. The cells in the normal gut wall process the gut contents, releasing some of them into the bloodstream in an orderly fashion and keeping others from being absorbed. But when the gut wall is damaged, the gut contents begin to squeeze out into the bloodstream *between* the gut wall cells. There is no regulation, and then problems can occur.

LK: What kinds of problems?
LG: These problems arise because of what happens next: Most of the materials that enter the bloodstream from the gut go directly to the liver. The liver is responsible for screening these materials before they are released into general circulation within the body. A normal intact gut wall will prevent the liver from being deluged with materials. But a leaky gut wall permits much larger quantities of materials to enter the bloodstream, and this creates much more work for the liver.

In effect, the liver has to work overtime to process all the materials sent to it from the gut. The liver then has trouble handling other toxic materials encountered by the body through other exposure routes, like the lungs and the skin.

LK: What kinds of symptoms does this cause?
LG: There may be general gastrointestinal symptoms like pain, bloating, constipation, or diarrhea. Then there is a group of other symptoms that are characteristic of leaky gut problems: fever, fatigue, muscle aches, skin problems, and joint pain.

LK: That sounds like chronic fatigue syndrome!
LG: Yes. I've found that about 70 percent of both chronic fatigue and multiple chemical sensitivity patients have leaky guts.

LK: Are there any tip-offs that a patient may have a leaky gut?
LG: Yes. If the patient's history includes regular alcohol use or the use of anti-inflammatory drugs like aspirin or ibuprofen (but not acetaminophen) and the patient has the symptoms I mentioned, there's a good chance that leaky gut is a problem. In addition, if there is a

history of food allergy and/or a history of intestinal parasite infection, leaky gut could be a problem. Patients who have celiac disease or Crohn's disease are also apt to develop leaky gut problems.

LK: Does intestinal candida *infection make leaky gut problems likely?*
LG: Interestingly, not necessarily. It turns out that half of all patients who have chronic intestinal *candida* infections have normally permeable small intestines. We think that *candida* may make people sick in three different ways. Two of them might lead to leaky gut problems, but the third does not.

When *candida* invades the tissues of the gut lining, it can damage the gut wall. This could lead to leaky gut problems. Similarly, allergic reactions inside the gut could damage the gut wall and lead to leaky gut. But the third way *candida* seems to make people sick is by producing toxic materials that are readily soluble and can pass directly through the intact gut wall lining. These materials make people sick, but they don't cause direct damage to the gut wall.

LK: How is leaky gut syndrome diagnosed?
LG: There's a test called the Intestinal Permeability Test. We think about doing this if the patient has the symptoms I described and has a history that suggests that damage to the gut wall might have occurred. The test measures how much of a substance gets out of the patient's gut and ends up in his or her urine.

The patient drinks a substance that is not well-absorbed by the healthy intact gut. There are several different kinds of substances used: One test uses lactulose and mannitol, another uses polyethylene glycol, another uses EDTA. These materials have predetermined normal ranges in which they show up in urine. If a patient's urine contains greater than normal amounts of the test substance, we know that the gut leaked.

This test can be done with the patient fasting, to show how much of the substance gets through to the urine. If the amount is greater than normal, the patient's gut leaked. If food allergy is suspected, the test can be done again after the patient eats a suspect food on an empty stomach. If the amount of the test material that shows up in the urine after the food is greater than the amount that showed up when the test was done fasting, we have good evidence that allergy to the suspect food made the patient's gut leak, or leak more.

A doctor has to order these tests. A few labs around the country process them.

LK: How is leaky gut treated?
LG: There are three steps.
Step one is to identify the cause and eliminate it if possible. This means identifying and treating any parasitic infection, stopping alcohol use, stopping aspirin use. If food allergy is a problem, eliminating the offending food or foods is ideal. For patients with many food allergies, this may not be possible. We find that some allergic reactions in the gut can be stopped by the use of oral cromolyn sodium or the use of quercetin supplements.

The next step is to heal the gut. We find that glutamine and essential fatty acids found in fish oils and evening primrose oils are very helpful. The antioxidant gamma oryzanol from rice bran oil is very promising. It's been tested successfully in Japan for stomach ulcers. Epidermal growth factor, which is found in saliva and other tissues, is also promising. All of these are discussed in my book, *Power Healing.*

In addition to using substances to directly heal the gut, it is also important to support overall gut health. For many patients, this means the use of dietary fiber and the use of probiotics, particularly *lactobacilli* species. It appears that the normal bacteria residing in the gut have a protective effect on the integrity of the gut wall.

The final step is to continue to promote gut health through the use of fiber and probiotics if necessary, in conjunction with food allergen avoidance and avoidance of substances that can promote gut-wall damage.

LK: It's been common in the past for some critics to say that health problems attributed to the gut and its contents are not physical at all, but are mostly neurotic — in people's heads. How do you respond?
LG: This type of thinking hasn't proved to be productive. Critics who use it are using a framework for discussing health that does not capture the things that matter most about health. This is a problem that goes back to the 19th century. At that time, it became common to think about the mind and the body as if they were entirely separate. The body was viewed as a type of machine, and the mind was viewed as not being "real" in the same sense. This had never been done before in the West, and it still isn't done in Chinese medicine.

* * *

"If medicine is to regain its Hippocratic roots, preserving and restoring health, then physicians must learn the science of preserving and restoring normal intestinal permeability." Leo Galland MD, Alternative and Complementary Therapies, *August 1997* ■

For more information . . .

For more information about topics discussed in this article see:

■ Galland, Leo. *Power Healing.* New York: Random House, 1998.

■ Galland, L. Intestinal toxicity: New approaches to an old problem. *Alternative & Complementary Therapies*, August 1997, pp. 288-295. (Reprints available; contact K. Ballen, *Alternative & Complementary Therapies*, Mary Ann Liebert, Inc., 2 Madison Ave., Larchmont, NY 10538-1962. Phone 914/834-3100.)

Also:

■ Andre, C. Food allergy: Objective diagnosis and test of therapeutic efficacy by measuring intestinal permeability. *Presse Medicale* 15:105-108, 1986.

■ Andre, C. Measurement of intestinal permeability to mannitol and lactulose as a means of diagnosing food allergy and evaluating effectiveness of disodium cromoglycate. *Annals of Allergy* 59:127-130. 1987.

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Advocacy, Information, Research and Encouragement for the CFIDS Community

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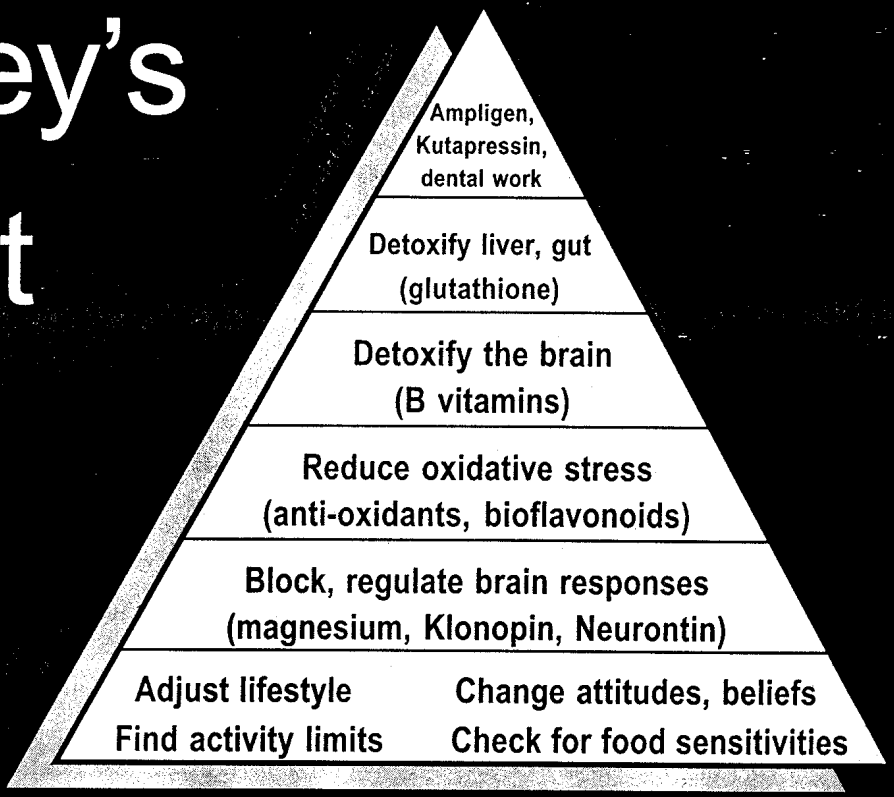
Chron

THE BI-MONTHLY PUBLICATION OF THE CHRONIC FATIGUE AND IMMUNE DYSFU

Dr. Cheney's Treatment Pyramid



Details on page 13, with 16 pages on research and treatment

Also:

- ✔ Show us the money! Keeping the pressure on the CDC (page 27)
- ✔ Ampligen trials move to phase III (page 22)
- ✔ New school, new hope for teen (page 35)
- ✔ Vacation time with Nan Talbot (page 41)

Treatment at the Cheney Clinic

Dr. Paul Cheney

The first steps are basic: finding limits, making adjustments

By David Hoh

The foundation of treatment at Dr. Paul Cheney's clinic in Charlotte, N.C., involves four steps that cost little or nothing and that nearly everyone should be able to do. One of them even has "home run potential."

Dr. Cheney, who has been treating CFIDS since the outbreak in Incline Village, Nev., in 1984, discussed his treatment approach for members of the Charlotte CFIDS Support Group at a meeting in May. He described it as a multi-layered pyramid and said all patients need to commit themselves to working hard at the foundation layer in order for any treatment to be successful. The treatments in the layers above the foundation depend on an individual patient's symptoms and the results of various tests. The smaller the layer, the fewer patients for whom the treatment would be recommended.

The foundation layer includes lifestyle adjustment, setting activity limits, changing attitudes and beliefs, and a modified elimination diet.

The first three pieces of the foundation are closely related. Dr. Cheney said he tells patients to get out and find the boundaries of what they can do in terms of daily life, and then to stay within those boundaries. Trying to do too much *or* pulling back and doing too little, he said, is counterproductive.

By activity limits, Dr. Cheney means exercise. He cautioned against aerobic exercise — any kind of sustained activity, such as running or walking or swimming, designed to raise the heart rate and increase oxygen flow throughout the body. Aerobic exercise beyond a certain point can damage the mitochondria, the key structure involved in producing energy within cells. That system appears to be malfunctioning in CFIDS patients and vulnerable to excessive aerobic exercise.

An anaerobic prescription

However, he said, the anaerobic system appears to be in much better shape. This allows patients to maintain muscle tone and strength with such exercises as weightlifting, isometrics and stretching. He recommended a routine of 10 seconds of activity followed by 60 seconds of rest.

One particular activity he has found to be useful for CFIDS patients is rebounding or bouncing, using a bungee cord contraption called a bounce-back chair. The rebounding concept was researched by NASA in 1980 to help astronauts counter the effects of the weightlessness of space travel. Its benefit seems to be related to the philosophy in Chinese medicine of balancing body systems, as it seems to help restore the autonomic nervous system balance that is out of whack in CFIDS patients.

Gaining perspective

Attitudes and beliefs about one's life and about chronic illness can be impediments to treatment, Dr. Cheney said. A workaholic attitude, for instance, where a person measures his or her worth by how much can be accomplished, can result in anger and loss of ego when the ability to work at that level is taken away by CFIDS. Similarly destructive are beliefs such as hopelessness about the possibility for improvement or an attitude that "my illness allows me to control others." Acceptance of one's illness and finding new ways to view oneself as a contributing member of society are critical to setting the stage for medical treatment.

To help guide patients to the necessary attitude adjustments, Dr. Cheney recommends two tapes: "The Power of Myth," by Joseph Campbell with Bill Moyers, and "Why People Don't

Heal and How They Can," by Carolyn Myss. Both are available from most local bookstores.

The final piece of the treatment foundation is a modified elimination diet, and this, Dr. Cheney said, has "home run potential." The goal here is to determine if the patient has an allergy or sensitivity to a certain type of food. Because the body's reaction to food is often delayed 24 to 72 hours after eating, it's important to follow the recommended regimen carefully and keep accurate records of what is eaten and when and what symptoms are experienced in the one to three days afterward.

"Home run potential"

"In a few cases, the patient will identify a certain food that is causing the symptoms, and eliminating that from the diet will clear up the problem," Dr. Cheney stated. The possibility of dramatic improvement is not great, but it's good enough to make the effort worthwhile, especially since there can often be no cost involved. What is more likely is that a variety of food sensitivities might be identified as provoking part of the symptom problems, and dietary changes could offer some improvement and contribute to the overall treatment.

Following the foundation, Dr. Cheney targets "neural protection" as the second level of his treatment pyramid. The injured brain, he explained, "fires at lower stimuli or at a lower threshold." This apparently natural survival mechanism is out of control in CFIDS, so the body needs something to block these responses. One substance that may block this type of brain response is magnesium, although Dr. Cheney said it is not easily absorbed by cells. Klonopin and Neurontin will also act to raise the sensitivity threshold, although the dosage of Klonopin that will be effective for an individual needs to be carefully determined by trial and error. Nicotine, narcotics and certain antihistamines have an positive indirect effect on this process, as well.

Attacking toxins

The third level of Dr. Cheney's treatment pyramid involves reducing oxidative stress, the cellular damage caused by excessive free radicals or electrically charged oxygen atoms in the body. These may be produced by physical or emotional stress, and by injury, infection and toxins. Dr. Cheney said fatigue can be viewed as a defense mechanism by the body to allow its natural systems to reduce oxidative stress. He prescribes a combination of antioxidants and bioflavonoids, explaining that antioxidants alone can't do the job. Specifically, he suggested patients generally avoid multivitamin combinations containing copper and iron and make sure that magnesium and selenium are included.

Megadoses of B-12

Next on the pyramid are vitamins B-6 and B-12. The latter, particularly, is a potent detoxifier of the brain, Dr. Cheney said. The most recent experience with B-12 in England suggests that it needs to be given in megadoses in the range of 10,000 micrograms or more per day, given before bedtime, to be effective, he said. The British version of B-12 is hydroxycobalamin and is superior to cyanocobalamin as a brain detoxifier.

The top layers of the pyramid include glutathione support to help detoxify the liver and therapy to improve gut functions, the antiviral Kutapressin, targeted treatments for xenobiotic toxins, removal of root canal teeth that can harbor toxins, and finally Ampligen for patients who are highly positive for the newly discovered, low molecular weight RNaseL enzyme.

Commenting on the hope many patients have for Ampligen, Dr. Cheney cautioned that 85% of his patients who took Ampligen relapsed after the treatment was stopped. He noted that the manufacturer of the drug, Hemispherx Biopharma, has not disclosed the relapse rate in their most recent trials, but he suspected his experience was typical. "Maybe if patients are treated longer, they will have a lower relapse rate. That's something we don't know yet."

For more information on elimination diets

Check with your own doctor for recommendations on an elimination diet. A basic outline was included in the Spring 1996 *Chronicle* with an article by William G. Crook, MD. (For a free copy of that article, send a SASE marked "Spring '96, pages 46/47" with 32 cents postage to the Association.) Dr. Crook provides an in-depth discussion of the elimination diet in his books, *CFS and the Yeast Connection* (1996, Professional Books) and *The Yeast Connection and the Woman* (1995, Professional Books). Detailed discussions of elimination diets can also be found in *Optimal Wellness*, by Ralph Golan, MD (1995, Ballantine), and in numerous other books about diet, nutrition and health. These books are available through your local bookstore or online booksellers and these and others may also be available through your public library.

Cheney Clinic relocates

Dr. Cheney is moving his practice this summer from Charlotte to Bald Head Island, along the coast of North Carolina. For more information about Dr. Cheney's practice and treatment of CFIDS, visit his website at http://fnmedcenter.com/ccis.