Detoxification and Gastrointestinal Health
Learning Outcomes:

- On successful completion you will be able to do the following:
  - Evaluate the role of the gastrointestinal tract in detoxification
  - Describe the scope of nutritional therapy in the support of gastrointestinal health
  - Explain the detailed functions of the gastrointestinal tract
  - Show awareness of the importance of referral with ‘Red Flag’ symptoms
Detoxification
Gastrointestinal Health

• An important role in determining overall nutritional status
  - imbalance in the gastrointestinal system has implications that extend far beyond GIT symptoms
• The best food intake lacks potential for well-being if the digestive function is suboptimal
• Poor digestion and assimilation of food may lead to malabsorption-induced ill health
• ‘You are what you eat’ is only partially true
  - ‘You are also what you absorb...’

Detoxification

- ‘Toxin’ - the degree to which a substance is poisonous

- Detoxification/biotransformation
  - The process of transforming the toxin from a harmful state to harmless

- The body has inherent detoxification/biotransformation processes which may be lacking due to:
  - interference with enzymes, hormones or neurotransmitters
  - blockage of cellular transport mechanisms or receptor sites
  - oxidative damage

Sources of Toxins

Endogenous

• The majority of toxins originate from the digestive system - the products and by-products of their digestion function
  - Experts vary on the tonnage, but figures range from 30 to 60 tons of food consumed in the lifetime of the average well-nourished adult

• Stress & belief systems

• Oxidative stress

• Mechanical problems - spinal alignment, nasal or intestinal obstruction

Sources of Toxins

Exogenous
• Lifestyle - smoking, alcohol
• Orthodox medications
• Foods - high sugar, trans-fatty acids, dietary lectins
• Environmental - lead from traffic, chlorine and fluorine from water, insecticides, herbicides, solvents, metals...
• Biological inhalants - mould, pollen, algae..
• Radiation - television, computers
• Natural - solanine in potatoes
Source of Toxins

INTERNAL
- Dysbiosis (Bad gut bugs)
- Free Radicals
- Sugar Toxicity (AGEs: Advanced Glycation Endproducts)
- Stress
- Maldigestion (leaky gut, $H_2S$)

EXTERNAL
- Alcohol
- Air pollution
- Building Materials and Furnishings (paint solvents) (formaldehyde)
- Cigarettes (cadmium, etc)
- Food chemicals (additives and contaminants)
- Herbicides (2, 4-D, paraquat, glyphosate)
- Household Goods (solvents, etc)
- Pesticides (termite control - Aldrin, Chlordane, DDT, etc.)
- Radiation (TV and computers)
- Traffic fumes
- Water (chlorine and fluorine)

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Common signs and symptoms of suboptimal detoxification

- Bowel - halitosis, bitter taste, bloating, fatty stools, constipation, diarrhoea, intolerance to fatty foods, tender swollen liver, gallbladder problems...

- Immune - food allergies, skin issues, asthma...

- Hormonal - stress, infertility, PMS, being overweight, depression...

- Nervous system - headaches, dementia, poor memory and concentration
Common signs and symptoms of suboptimal detoxification

• Recurrent headaches
• Muscle aches and weakness
• Paraesthesia and neuralgia
• Recurrent infections
• Infertility
• Adverse reactions or sensitivity to environmental chemicals, odours or nutritional supplements
• Chronic fatigue and lethargy
• Depression, anxiety or mood swings
• Poor short-term memory and concentration
• Anaemia
Detoxification

The five organs of detoxification
GIT Detoxification

• Correction of digestive processes
  - stomach acid
  - pancreatic secretions
  - bile production
• Ensure adequate elimination
• Restore GIT microbial balance
• Repair GIT membrane integrity
• Promote liver detoxification pathways
Digestive System

The Human Digestive System

Digestion
Absorption
Excretion
Function of the Digestive Tract

1. **Oesophagus** - a long muscular tube, which moves food from the mouth to the stomach
2. Abdomen contains all of the digestive organs
3. The **stomach**, situated at the top of the abdomen, normally holds just over three pints (about 1500 ml) of food from a single meal. Here the food is mixed with an acid that is produced to assist in digestion. In the stomach, acid and other digestive juices are added to the ingested food to facilitate breakdown of complex proteins, fats and carbohydrates into small, more absorbable units
4. A valve at the entrance to the stomach from the **oesophagus** allows the food to enter while keeping the acid-laden food from "refluxing" back into the oesophagus, causing damage and pain
5. The **pylorus** is a small round muscle located at the outlet of the stomach and the entrance to the duodenum - the first section of the small intestine. It closes the stomach outlet while food is being digested into a smaller, more easily absorbed form. When food is properly digested, the pylorus opens and allows the contents of the stomach into the duodenum
6. The **small intestine** is about 15 to 20 feet / 4.5 to 6 metres long and is where the majority of the absorption of the nutrients from food takes place. The small intestine is made up of three sections: the duodenum, the jejunum and the ileum.

7. The **duodenum** is the first section of the small intestine and is where the food is mixed with bile produced by the liver and with other juices from the pancreas. This is where much of the iron and calcium is absorbed.

8. The **jejunum** is the middle part of the small intestine extending from the duodenum to the ileum; it is responsible for digestion.

9. The last segment of the intestine, the **ileum**, is where the absorption of fat-soluble vitamins A, D, E and K and other nutrients are absorbed.

10. Another valve separates the small and large intestines to keep bacteria-laden colon contents from coming back into the small intestine.

11. In the large intestine, excess fluids are absorbed and a firm stool is formed. The colon may absorb protein, when necessary.
Digestion in the stomach

Hydrochloric acid
• Secreted by parietal cells in the stomach wall

Actions
• Denatures proteins and enhances nutrient absorption
• Activates pepsin from pepsinogen
  – which renders some minerals e.g. calcium and iron more absorbable
• Inhibit the overgrowth of Candida spp.
• Stimulates secretion of pancreatic juices
• Supports barrier defence against ingested microbes

Digestion in the stomach

Hydrochloric acid

• Overconsumption of fat leads to hyperchlorhydria
• Yet excessive and inappropriate use of H2 blocking antacids results in hypochlorhydria, with proton pump inhibitors only exacerbating the problem

• Low hydrochloric acid results may influence the development of:
  – food allergies, rheumatoid arthritis, acne rosacea, asthma, coeliac disease, chronic autoimmune disorders, eczema, gallbladder disease, hepatitis, hyper and hypothyroidism, lupus erythematosus, osteoporosis, pernicious anaemia, psoriasis...
Digestion in the stomach

Factors lowering hydrochloric acid secretion:

- Ageing
  - > 50% of those over 60 years old have insufficient production
- Chronic inflammation
  - parietal antibodies or autoimmune involvement
- Imbalanced GALT
- Chronic stress

Digestion in the stomach

Common signs and symptoms of low gastric activity

- Bloating, belching and flatulence
  - within one to two hours after meals
- Sensation of ‘fullness’ after eating
- Undigested food in stool
- Foul smelling stools
- Chronic dysbiosis – candida, parasites, abnormal flora
- Indigestion, diarrhoea, constipation
- Iron deficiency, multiple food allergies/sensitivities, nausea after taking nutritional and herbal supplements, post-adolescent acne, weak, peeling and cracked fingernails, dilated capillaries in the cheeks and nose

Digestion in the stomach

Clinical uses

• The relationship between Helicobacter pylori, hypochlorhydria and peptic ulcer has been researched extensively over the past ten years
  – 90% to 100% of patients with duodenal ulcers, 70% with gastric ulcers, and about 50% of people older than the age of 50 test positive for *H. pylori*²

• Hydrochloric acid has an inhibitory effect on H. Pylori, therefore must be optimised

• Hypochlorhydria is also associated with an increase in proximal small intestine pH, small intestine bacterial overgrowth, and decreased secretion of intrinsic factor, which is necessary for adequate absorption of vitamin B12


Digestion in the small intestine

Pancreatic enzyme secretion

• Chyme is pushed through the pyloric sphincter into the duodenum
• Bicarbonate, secreted by the pancreas, neutralises the acidic chyme, and pancreatic enzymes break down carbohydrates, proteins and fats
  – enzymes – cholesterol esterase, chymotrypsinogen/chymotrypsin, collagenase, deoxyribonuclease, lipase, pancreatic alpha amylase, procarboxypeptidase, proelastase, retinyl ester hydrolase, ribonuclease, trypsinogen/trypsin
• Chronic hyposecretion leads to fat and protein maldigestion and also micronutrient deficiencies
  – enzymes are required to separate B12 from its carrier protein

Digestion in the small intestine

Signs and symptoms of low pancreatic enzyme secretion

- Steatorrhoea
  - may be associated with malabsorption of lipid soluble vitamins
- Bloating, discomfort, pain
  - within one hour of eating
- Reflux
- Drowsiness after meals
- Loss of appetite
- Food allergies/sensitivities
- Low zinc, B12 and folate absorption

Digestion in the small intestine

Bile actions

• Acts as an emulsifier to break fat into smaller globules
  – Micelle formation
  – Making the fat more hydrophilic
  – Fats and fat soluble vitamins can then be carried into the intestinal mucosa, absorbed into the lymphatics and finally into the blood

• Detoxify bacterial endotoxins

• From the small intestine, bile acids are absorbed into the portal blood and are taken up by hepatocytes, conjugated with taurine and glycine and resecreted in bile - a process known as enterohepatic circulation

Digestion in the small intestine

Low bile production may be associated with the following:

- Constipation
- Fat malabsorption
- Steatorrhoea
- Floating stool
- Fatty food intolerance
- Gallstones
- Nausea

Digestion in the small intestine

Bile excretion

• Consumption of six to eight glasses of water is necessary each day to maintain the water content of bile
• Hydrochloric acid may increase bile production
• Taurine and phosphatidylcholine are essential components
• Rice fibre has been shown to increase bile excretion
• Olive oil may stimulate the body's secretion of bile due to the cycloartenol content of olive oil

Digestion in the small intestine

Bile excretion

• Choleretics increase bile secretion by the liver
  – Many herbal choleretics have a positive effect on the solubility of bile
    • Dandelion root (*Taraxacum officinale*), silymarin from *Silybum marianum*, globe artichoke (*Cynara scolymus*), and turmeric (*Curcuma longa*)

Digestion in the small intestine

Clinical Use

- The relationship between dietary fat and increased risk of colon cancer is believed to hinge on the excess production of bile acids and the bacterial conversion of conjugated primary bile acids to potentially dangerous unconjugated secondary bile acids.

- Bacterial overgrowth markedly increases the concentration of unconjugated bile acids, and this mechanism may play an important role in the pathophysiology of gut mucososal injury.

GIT Membrane Integrity

• The GI mucosal membrane surface is the largest interface between our internal body and the external world
  – It covers more than 400 square meters, which is over 200-fold greater than the surface area of the skin
• Detoxification is very active in the intestinal mucosa
• Gastric epithelial layer
  – covers the stomach and protects it from damaging stomach acid
  – important role in protecting the stomach from ingested toxins, drugs, alcohol, and pathogens such as infectious bacteria and viruses

In a healthy intestinal tract, the intestine’s tight junctions limit the transport of large molecules (>500 Da) across the epithelium.

In an unhealthy intestine the tight junctions become ‘leaky’ and these large molecules, which can include unprocessed proteins or large amino acids that have intact antigenic sites on them, can then slip into circulation:

– ‘leaky gut’ (increased intestinal permeability)

Commonly seen in patients presenting with intestinal inflammation, food allergies and intolerances, and coeliac disease, after radiation or chemotherapy treatments and is induced by stress.

Increased intestinal permeability - ‘leaky gut’
Increased intestinal permeability - ‘leaky gut’

Risk factors:

• Alcohol
• Cancer - radiation and chemotherapy
• Corticosteroids
• Excessive stress
• Excessive simple sugar consumption
• Fasting
• Food allergies
• Gastrointestinal infections
• NSAIDs
• Nutrient insufficiencies
• Premature birth
• Whole food exposure before the age of four months

Increased intestinal permeability - ‘leaky gut’

Symptoms associated with increased intestinal permeability

• Abdominal distention and pain
• Arthralgias
• Cognitive and memory deficits
• Diarrhoea
• Fatigue and malaise
• Fevers of unknown origin
• Food intolerances
• Myalgias
• Poor exercise tolerance
• Shortness of breath
• Skin rashes

Increased intestinal permeability—‘leaky gut’

Associated conditions:

- Inflammatory bowel disease
- Coeliac disease
- Food allergy
- Diabetes mellitus
- Inflammatory joint disease
- Rheumatoid arthritis
- Ankylosing spondylitis
- Reiter’s syndrome
- Alcoholism

Increased intestinal permeability-‘leaky gut’

Associated conditions:

• Acne
• Autism
• Childhood hyperactivity
• Hepatic dysfunction
• Multiple food and chemical sensitivities
• Pancreatic insufficiency
• Psoriasis and eczema
• Urticaria

Gut associated lymphoid tissue (GALT)

- Composes approximately 25% of the mucosal mass of the intestine
- 60% of the immune system and more than 80% of the immunoglobulin-producing blasts and plasma cells are located within the mucosa of the GIT
- First line of defence against exogenous substrates
  - e.g. food antigens and pathogenic bacteria
- Important in the development of oral tolerance
- Therefore mandatory to optimise mucosal integrity

Covered in more detail in the Immune lecture

Microflora

• The number of bacteria in the large bowel alone is greater than 100 billion - more than all of the human cells in the body

• The bacteria constitute a ‘chemical factory’ that have important effects on the body

• They produce toxins and antitoxins, alter chemical composition of food and drugs, produce and degrade vitamins, produce short-chain fatty acids from fibre, degrade dietary toxins and inhibit the growth of certain pathogens
Microflora

• The beneficial symbiotic microflora that reside primarily in the large intestine have a direct impact on:
  • promoting a healthy GI tract barrier
  • development and support of GALT function
  • digestion of large carbohydrates - such as fibres that escape hydrolysis in the stomach and small intestine
  • feedback effect on transit time
  • an environment resistant to colonisation by pathogens, including competitive inhibition for bacterial adhesion sites
    • For example, lactobacillus acidophilus has been shown to inhibit adhesion of several enteric pathogens to human intestinal cells
Functions of commensal microflora

Metabolic processes:
• fermentation
• vitamin synthesis
• energy production

Trophic stimulation:
• epithelial cell differentiation
• immunomodulation

Pathogen protection:
• competing for nutrients, space, adherence
• producing bacteriocidins

Dysbiosis

• *Dysbiosis* – an imbalance in the colonies of the bowel flora, and the effects that their chemical products have on human physiology

• Bacterial by-products can:
  – inactivate brush border and pancreatic enzymes
  – deconjugate bile salts
  – hydrolyse bile acids

• In addition, microbial translocation across the intestinal barrier can cause a role in the systemic immune inflammatory response

Major Causes of Intestinal Dysbiosis

- Poor diet/nutritional status
- Stress
- Antibiotic/other drug therapy
- Decreased immune status
- Decreased gut motility
- Maldigestion
- Intestinal infection
- Xenobiotics
- Increased intestinal pH
- Diabetes, scleroderma
- Gastrointestinal tract surgery

Dysbiosis

Published research has implicated intestinal dysbiosis as contributing to:

- vitamin and amino acid deficiencies
- malabsorption of carbohydrates
- inflammatory bowel disease
- autoimmune arthropathies
- colon and breast cancer
- obesity
- low grade systemic inflammation

Liver function

Five major functions and many minor:
1. Detoxification
2. Normalisation of blood fats
3. Synthesis and normalisation of blood proteins
4. Manufacture of bile
5. Synthesis and storage of glycogen

Liver function

Symptoms of compromised liver function:

- Fatigue
- Weakness
- Neurological symptoms
- Elevated blood cholesterol
- Anorexia
- Steatorrhoea
- Bloating
- Oedema
- Jaundice

Liver detoxification

The biotransformation of a lipophilic compound, not able to be excreted in urine or bile, to a water-soluble compound

• Phase I:
  – Primes a binding site on the toxin for conjugation
    • Uses oxygen to form a reactive site
  – primarily via Cytochrome P450 enzymes

• Phase II:
  – Conjugates resulting toxin with a conjugating agent for excretion via the kidneys or bowel

• Phase III:
  – Antiporter activity - an energy dependent efflux pump which pumps xenobiotics out of the cell therefore reducing intracellular concentration of xenobiotics

Liver Detoxification Phase I & II

Toxins
- Endotoxins: end products of metabolism, bacterial endotoxins
- Exotoxins: drugs (prescription, OTC, recreational, etc.), chemicals
  - Agricultural
  - Food additives
  - Household
  - Pollutants/contaminants
- Microbial

Reactions
- Oxidation
- Reduction
- Hydrolysis
- Hydration
- Dehalogenation

PHASE I [cytochrome P450 enzymes]
- Enzymes, Cofactors & Other Nutrients Used:
  - Riboflavin (vit B2)
  - Niacin (vit B3)
  - Pyridoxine (vit B6)
  - Folic acid
  - Vitamin B12
  - Glutathione
  - Branched-chain amino acids
  - Flavonoids
  - Phospholipids

Intermediary metabolites
- More polar, more water-soluble

PHASE II [conjugation pathways]
- Excretory derivatives
  - Sulfation
  - Glucuronidation
  - Glutathione conjugation
  - Acetylation
  - Amino acid conjugation
  - Glycine
  - Taurine
  - Glutamine
  - Ornithine
  - Arginine
  - Methylation
  - N-acetylcysteine, cysteine, methionine are precursors

Antioxidant/Protective Nutrients/Plant Derivatives
- Carotenoids (vit A)
- Ascorbic acid (vit C)
- Tocopherols (vit E)
- Selenium
- Copper
- Zinc
- Manganese
- Coenzyme Q10
- Thiols (found in garlic, onions, cruciferous vegetables)
- Bioflavonoids
- Silmarin
- Oligomeric proanthocyanidins (OPCs)

Free Radicals
- Superoxide
- Secondary tissue damage

Phase I

- Cytochrome P450 supergene family of enzymes (CYP450)
  - involve oxidation, reduction or hydrolysis
  - adding or exposing a functional group to the molecule – frequently a hydroxyl (OH)
  - reactive molecules which may be more toxic than the parent molecule are produced
  - if not further metabolised by Phase II conjugation, they may cause damage to proteins, RNA, and DNA within the cell

- Associations between induced Phase I and/or decreased Phase II activities and an increased risk of disease, such as cancer, systemic lupus erythematosus, and Parkinson’s disease and adverse drug responses

Inhibitors of Phase I
• Curcumin
• Watercress
• Naringenin
• Garlic
• Echinacea
• Kava-kava

Inducers of Phase I
• Hypericum
• Alcohol
• Nicotine
• Caffeine
• Stress
• Various toxins
## Nutrients to support Phase I

<table>
<thead>
<tr>
<th>Nutrient(s)</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niacin, riboflavin, zinc, magnesium, thiamine, quercetin, folic acid, vitamin B6, vitamin C</td>
<td>Regulates Phase I liver detoxification activities. B vitamins are co-factors for Phase I detoxification enzymes</td>
</tr>
<tr>
<td>Cysteine, glycine, glutamine, vitamin C</td>
<td>Precursor nutrients for glutathione production. Counteracts free radicals produced through Phase I detoxification</td>
</tr>
<tr>
<td>Vitamin A, vitamin E, zinc, selenium, magnesium, manganese, quercetin</td>
<td>Antioxidant nutrients to counteract and neutralise free radicals produced during Phase I detoxification</td>
</tr>
<tr>
<td>Rosemary</td>
<td>Enhances both phase I and phase II activity</td>
</tr>
<tr>
<td>Turmeric</td>
<td>Provides antioxidant support to counteract and neutralise free radicals produced during Phase I detoxification</td>
</tr>
</tbody>
</table>

Liver detoxification

### Phase II phytonutrients
- Brassica
- Curcumin
- Apiaceae
- Silymarin
- Green tea
- Limonene

### Phase II conjugation substrates
- Glutathione
- Glycine
- Sulphate
- Glutamine
- Cysteine
- Methionine
- Glucuronide
- Taurine
- Choline
## Nutrients to support Phase II

<table>
<thead>
<tr>
<th>Nutrient(s)</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnesium</td>
<td>Support glucuronidation pathway</td>
</tr>
<tr>
<td>Glycine, glutamine</td>
<td>Supports glycination pathway</td>
</tr>
<tr>
<td>Cysteine, taurine, vitamin A</td>
<td>Supports sulphation pathway</td>
</tr>
<tr>
<td>Vitamins B6, B12, folic acid</td>
<td>Supports methylation pathway</td>
</tr>
<tr>
<td>Cysteine, glutamine, glycine, selenium, vitamin B6, vitamin B12, folate</td>
<td>Supports glutathionation pathway and glutathione production</td>
</tr>
<tr>
<td>Cysteine, carnitine, vitamin B5</td>
<td>Supports acetylation pathway</td>
</tr>
<tr>
<td>Rosemary, Bupleurum</td>
<td>Support phase II activity and protect liver</td>
</tr>
</tbody>
</table>

Green Tea Polyphenols

Enhancement of Antioxidant and Phase II Enzymes by Oral Feeding of Green Tea Polyphenols in Drinking Water to SKH-1 Hairless Mice: Possible Role in Cancer Chemoprevention

Following the oral feeding of a polyphenolic fraction isolated from green tea (GTP) in drinking water, an increase in the activities of antioxidant and phase II enzymes in skin, small bowel, liver, and lung of female SKH-1 hairless mice was observed. GTP feeding (0.2%, w/v) to mice for 30 days significantly increased the activities of glutathione peroxidase, catalase, and quinone reductase in small bowel, liver, and lungs, and glutathione S-transferase in small bowel and liver. GTP feeding to mice also resulted in considerable enhancement of glutathione reductase activity in liver. In general, the increase in antioxidant and phase II enzyme activities was more pronounced in lung and small bowel as compared to liver and skin. The significance of these results can be implicated in relation to the cancer chemopreventive effects of GTP against the induction of tumours in various target organs.

### Phase II Conjugation Pathways

<table>
<thead>
<tr>
<th>Table Entry</th>
<th>Details</th>
</tr>
</thead>
</table>
| **Glutathione conjugation** | **Tripeptide antioxidant – glycine, cysteine, glutamine**  
Nicotine, organophosphates (insecticides), epoxides (carcinogens)  
Vital to detoxification – provides protection for reactive species  
Asparagus, walnuts, cabbage, broccoli, avocados, Brussels sprouts, dill, caraway seeds |
| **Amino Acid conjugation**  | **Requires glycine**  
Salicylates and benzoate  
Affected by protein deficiency |
| **Sulphation conjugation**  | **Requires L-cysteine and methionine**  
Neurotransmitters, thyroid hormones, steroid hormones, certain drugs and many xenobiotic and phenolic compounds  
Sulphur containing compounds – red pepper, garlic, onions, broccoli, Brussels sprouts, egg yolk |
# Phase II Conjugation Pathways

<table>
<thead>
<tr>
<th>Phase II Conjugation</th>
<th>Dependant on acetyl-CoA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylation conjugation</td>
<td>Detoxify sulphur drugs – Sulphonamides (antibiotics)</td>
</tr>
<tr>
<td></td>
<td>Requires Vitamins B1, B5 and Vitamin C</td>
</tr>
<tr>
<td></td>
<td>Whole grains, vitamin B and C rich foods, cabbage, red peppers</td>
</tr>
<tr>
<td>Glucuronidation conjugation</td>
<td>Requires glucuronic acid and EFAs</td>
</tr>
<tr>
<td></td>
<td>Important when sulphation or glycination is diminished or saturated</td>
</tr>
<tr>
<td></td>
<td>Important pathway for many pharmaceuticals</td>
</tr>
<tr>
<td></td>
<td>Sulphur rich foods, dill, caraway, citrus</td>
</tr>
<tr>
<td>Methylation conjugation</td>
<td>Methionine is synthesised from choline</td>
</tr>
<tr>
<td></td>
<td>Vitamin B12 and folic acid to produce SAMe → oestrogen detoxification</td>
</tr>
<tr>
<td></td>
<td>Green leafy vegetables (folic acid), B6, B12, grains and legumes</td>
</tr>
</tbody>
</table>
Antioxidants

Antioxidant defence is essential as free radical production is a by-product of biotransformation

– Vitamin E
– Glutathione
– Quercetin
– Rutin
– Lipoic acid
– Vitamin C

Phase III

- Generally sulphate, glucuronide and glutathione metabolites are too hydrophilic to diffuse passively out of hepatocytes
- Carrier-mediated processes are required to transport these phase II conjugates across the membrane
- Expressed on the brush border membrane of the intestinal enterocytes
- Requires glutathione
- Inflammation inhibits - TNFα
Phase III

Includes:

• organic cation transport proteins (OCTPs)
• organic anion transport proteins (OATPs)
• P-glycoprotein (P-gp)
• breast cancer resistance protein (BCRP)
• multidrug resistance-associated proteins (MRPs)

• If the antiporters are not functioning optimally, the metabolised toxins cannot be excreted out of hepatocytes and may cause damage to the mitochondria and DNA within these cells
Liver detoxification

**Phase III inducers**
- Broccoli sprouts
- Alkalisers
  - Potassium citrate

**Phase III requirements**
- Glutathione
  - Glycine
  - Glutamine
  - Cysteine
Endogenous antioxidant detoxification systems

Antioxidants can be divided into three main groups:

1. antioxidant enzymes
2. chain breaking antioxidants
3. transition metal binding proteins

Endogenous antioxidant detoxification systems

**Figure 2** Antioxidant defences against free radical attack. Antioxidant enzymes catalyse the breakdown of free radical species, usually in the intracellular environment. Transition metal binding proteins prevent the interaction of transition metals such as iron and copper with hydrogen peroxide and superoxide producing highly reactive hydroxyl radicals. Chain breaking antioxidants are powerful electron donors and react preferentially with free radicals before important target molecules are damaged. In doing so, the antioxidant is oxidised and must be regenerated or replaced. By definition, the antioxidant radical is relatively unreactive and unable to attack further molecules.
Antioxidant enzymes

**Catalase**

- Catalyses the two stage conversion of hydrogen peroxide to water and oxygen

\[
\text{catalase–Fe(III) + H}_2\text{O}_2 \rightarrow \text{compound I}
\]

\[
\text{compound I + H}_2\text{O}_2 \rightarrow \text{catalase–Fe(III) + 2H}_2\text{O + O}_2
\]

Antioxidant enzymes

• consists of four protein subunits, each containing a haem group and a molecule of NADPH (niacin is a precursor)

• largely located within cells in peroxisomes, which also contain most of the enzymes capable of generating hydrogen peroxide

• the greatest activity is present in liver and erythrocytes but some catalase is found in all tissues

Antioxidant enzymes

Glutathione peroxidases and glutathione reductase

• Glutathione peroxidases catalyse the oxidation of glutathione at the expense of a hydroperoxide - which might be hydrogen peroxide or another species such as a lipid hydroperoxide

\[ \text{ROOH} + 2\text{GSH} \rightarrow \text{GSSG} + \text{H}_2\text{O} + \text{ROH} \]

• Requires selenium at the active site

Antioxidant enzymes

• Highest concentrations are found in liver
  – although glutathione peroxidase is widely distributed in almost all tissues

• The predominant subcellular distribution is in the cytosol and mitochondria
  – suggesting that glutathione peroxidase is the main scavenger of hydrogen peroxide in these subcellular compartments

• The activity of the enzyme is dependent on the constant availability of reduced glutathione

• The ratio of reduced to oxidised glutathione is usually kept very high as a result of the activity of the enzyme glutathione reductase: $\text{GSSG} + \text{NADPH} + \text{H}^+ \rightarrow 2\text{GSH} + \text{NADP}^+$

Antioxidant enzymes

**Superoxide dismutase**

- Catalyse the dismutation of superoxide to hydrogen peroxide:
  \[ O_2^- + O_2^- + 2H^+ \rightarrow H_2O + O_2 \]
- The hydrogen peroxide must then be removed by catalase or glutathione peroxidase
- There are three forms of superoxide dismutase in mammalian tissues, each with a specific subcellular location and different tissue distribution

Antioxidant enzymes

1. Copper zinc superoxide dismutase (CuZnSOD):
   • CuZnSOD is found in the cytoplasm and organelles of virtually all mammals
   • It has two protein subunits, each containing a catalytically active copper and zinc atom

Antioxidant enzymes

2. *Manganese superoxide dismutase* (MnSOD):
   - MnSOD is found in the mitochondria of almost all cells
   - It consists of four protein subunits, each probably containing a single manganese atom
3. Extracellular superoxide dismutase (ECSOD):

- A secretor enzyme of copper and zinc
- Synthesised by only a few cell types, including fibroblasts and endothelial cells
- The major SOD detectable in extracellular fluids
- May play a role in the regulation of vascular tone
  - endothelial derived relaxing factor (nitric oxide or a closely related compound) is neutralised in the plasma by superoxide

Antioxidant enzymes

- Uric acid is also an effective free radical scavenger
- Albumin and albumin bound bilirubin also can act as antioxidants in the body

The chain breaking antioxidants

• Whenever a free radical interacts with another molecule, secondary radicals may be generated

• These can react with other targets to produce yet more radical species (ROS)

• The chain of ROS can be broken when a molecule can accept or donate an electron without needing to rectify its gain or loss

The chain breaking antioxidants

Chain-breaking antioxidants can be divided into fat soluble or water soluble and include:

– Vitamin E and the tocopherols
– Vitamin A and carotenoids
– Polyphenols
– Ascorbic acid
– Flavonoids

Metallothionein

- Metallothioneins (MTs) are intracellular, low molecular, low molecular weight, cysteine-rich proteins
- MTs have unique structural characteristics to give potent metal-binding and redox capabilities
- A primary role has not been identified, and remains elusive, as further functions continue to be discovered

Metallothionein

- The most widely expressed isoforms in mammals, MT-1 and MT-2, are rapidly induced in the liver by a wide range of metals, drugs and inflammatory mediators
- In the gut and pancreas, MT responds mainly to Zn status
- A brain isoform, MT-3, has a specific neuronal growth inhibitory activity and appetite suppressant activity

Metallothionein

- These include involvement in Zn homeostasis, protection against heavy metal (especially Cd) and oxidant damage, and metabolic regulation via Zn donation, sequestration and/or redox control.

The 4R program

• A comprehensive approach for the normalisation of gastrointestinal function

• It comprises four steps:
  1. Remove
  2. Replace
  3. Reinoculate
  4. Repair

Step 1: Remove

• The remove phase of the program focuses on removing pathogenic bacteria, viruses, fungi, parasites, allergens and toxins from the GIT thereby decreasing the ‘toxic load’

• Incorporates removing food allergens
  – Food allergy and intolerance testing can be helpful to identify adverse food reactions (IgG, IgE and lactose intolerance tests)
  – Tailored food protocol which may include full elimination diet depending on the severity of symptoms
  – Not all food reactions are immunologically based, for example a lactase insufficiency which causes lactose intolerance, so removing the ‘usual suspects’ for the period of the program may be beneficial
Step 2: Replace

- Replenish digestive enzymes and other digestive factors that may be lacking

- Enzymes and other factors that may need to be focused on include:
  - proteases, lipases, cellulases, sacchridases, hydrochloric acid, pepsin, intrinsic factor and bile

Step 2: Replace

• Hydrochloric Acid (betaine hydrochloride)
  – Used to help raise stomach acid
  – Zinc and B6 are important cofactors

• Digestive enzymes
  – Used to help digestion in the small intestine, from insufficient pancreatic or brush border enzymes
  – Normally well tolerated and without side effects
Prescribing HCl Supplements

- Use supplements with at least 600mg of betaine hydrochloride per capsule/tablet
- Start with one right at the beginning of starting to eat
- At every meal, consume one more pill until you reach a total of five or until a ‘warmth’ in the stomach occurs first
- The warm feeling means too many were consumed so cut one pill back
- Smaller meals will need a lesser amount of pills
- Those that need five capsules/tablets or more should spread them throughout the meal
- As the program continues and gut repair happens, clients will often need less tablets as their own HCl increases
- Cut down the use of tablets as necessary when they get that warmth

Prescribing digestive enzymes

• Are available from plant or animal sources

• Use two to three at the beginning or middle of a meal

• Look for a formula containing at least
  – Protease 100 000 USP units
  – Lipase 20 000 USP units
  – Amylase 100 000 USP units

Prescribing digestive enzymes

• Vegetarians should use a formula containing
  – Amylase 100 000 USP units
  – Protease 100 000 USP units
  – Lipase 10 000 USP units
  – Lactase 1600 Lase

• The sources are often from pineapple (bromelain) or papaya (papain) or cultured on Aspergillus fungus

Prescribing digestive bitters

• Digestive bitters are an alternative to enzyme replacement

• 10-20 drops are often taken in water before a meal for the ‘bitter principle’ effect via the stimulation of the vagus nerve

• These may include Swedish bitters or herbal extract formulas containing gentian, dandelion root or artichoke
Step 3: Reinoculate

• Reintroduction of beneficial bacteria (probiotics)
Normal colonisation of GIT

• Human infants are born with a sterile GIT until an infant ingests vaginal and faecal microflora at delivery
• The population of microflora in the infant GI tract is further enhanced by feeding
• The breastfed infant contains a colon population of 90% Bifidobacteria with some Enterobacteriaceae and Enterococci but virtually no Bacteroides, Staphylococci, Lactobacilli or Clostridia
• In contrast Bifidobacteria do not predominate in the bottle-fed infant
  – Breastfed infants switched to cow’s milk or solid foods colonise Bifidobacteria, Clostridia, Lactobacilli, Bacteroides, Streptococci and enterics

Normal colonisation of GIT

- The type and number of microflora increase distally along the length of the GIT

- Gastric acid suppresses the growth of large colonies in the stomach, even thought there is some bacterial growth there

- The flora of the upper intestine generally numbers less than 105 colony forming units (cfu) per millilitre (mL); the mid ileum the population increases to 107 cfu/mL

Probiotics

- Favourable characteristics found in probiotics are exhibited by *Lactobacillus plantarum, L. rhamnosus, L.reuteri, and L. Agilis*
- These *Lactobacilli* species are scarce in people living in industrialised nations
- *L. plantarum* is carried by 25% of the general population in the US in comparison to nearly 100 percent of the population in Africa and Asia
- The most significant reason is that a Western diet contains drastically decreased amounts of Lactobacilli

Probiotics

To qualify as a beneficial microflora the following criteria must be met:

– acid and bile resistant
– metabolically active in the GI tract
– able to adhere to the GI tract
– possess antimicrobial activity toward pathogenic bacteria
– reduce colon pH

<table>
<thead>
<tr>
<th>Microflora</th>
<th>Associated Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteroides species</td>
<td>Chronic colitis, gastritis, arthritis (increased bacterial urease activity in chronic juvenile arthritis)</td>
</tr>
<tr>
<td><em>Bifidobacterium animalis</em></td>
<td>Decreases <em>Candida albicans</em> systemic dissemination in euthymic or athymic beige mice</td>
</tr>
<tr>
<td>Bifidobacteria species</td>
<td>Reduced incidence of neonatal necrotizing enterocolitis</td>
</tr>
<tr>
<td><em>Enterococcus faecium</em> SF 68 or <em>Escherichia faecium</em> SF 68</td>
<td>a. Decreased duration of acute diarrhea from gastroenteritis</td>
</tr>
<tr>
<td><em>Escherichia coli</em> nonpathogenic strain (serotype O6:D5:H1)</td>
<td>b. No benefit in diarrhea due to <em>Vibrio cholerae</em> and <em>Escherichia coli</em></td>
</tr>
<tr>
<td><em>Lactobacillus</em> strains</td>
<td>a. Administration of multiple organisms, predominantly <em>Lactobacillus</em> strains shown to be effective in ameliorating pouchitis</td>
</tr>
<tr>
<td></td>
<td>b. Lactose digestion improved, decreased diarrhea and symptoms of intolerance in lactose intolerant individuals, children with diarrhea, and in individuals with short-bowel syndrome</td>
</tr>
<tr>
<td></td>
<td>c. Microbial interference therapy – the use of non-pathogenic bacteria to eliminate pathogens and as an adjunct to antibiotics</td>
</tr>
<tr>
<td></td>
<td>d. Improved mucosal immune function, mucin secretion, and prevention of disease</td>
</tr>
</tbody>
</table>

| Lactobacillus acidophilus | a. Significant decrease of diarrhea in patients receiving pelvic irradiation  
|                        | b. Decreased *Candida albicans* systemic dissemination in euthymic or athymic beige mice  
|                        | c. Decreased polyps, adenomas, and colon cancer in experimental animals  
|                        | d. Prevented urogenital infection with subsequent exposure to three uropathogens *E. coli, K. pneumoniae, P. aeruginosa*  
|                        | e. Lowered serum cholesterol levels  
| Lactobacillus GG | a. Reduced duration and/or risk of rotavirus diarrhea  
|                   | b. Decreased polyps, adenomas, and colon cancer in experimental animals  
|                   | c. Reduced duration of acute diarrhea most often caused by gastroenteritis  
|                   | d. Reduced diarrheal illness in formula-fed toddlers  
|                   | e. Reduced occurrence of *Clostridium difficile* diarrhea  
|                   | f. When co-administered with antibiotics in children, non-*Clostridium difficile* antibiotic-associated diarrhea is reduced  
|                   | g. Reduced risk of traveler’s diarrhea  
|                   | h. Reduced severity of pneumonia in children with cystic fibrosis  
|                   | i. Decreased *Candida albicans* systemic dissemination in euthymic or athymic beige mice  
|                   | j. Increased IgA-specific antibody secreting cells to rotavirus and reduced the duration of diarrhea  
|                   | k. Increased IgA secretion in Crohn’s disease  
|                   | l. Prevented recurrent, chronic vaginitis  
|                   | m. Lactobacillus vaginal suppositories effective in reducing the incidence of recurrent urinary tract infections  
|                   | n. Reduced food allergies and atopic dermatitis  
|                   | o. Increased interleukin-10 production in atopic children  

<table>
<thead>
<tr>
<th>Microflora</th>
<th>Associated Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Lactobacillus fermentum</em> strain KLD</td>
<td>Traveler’s diarrhea—no effect</td>
</tr>
<tr>
<td><em>Lactobacillus plantarum</em></td>
<td>Produced and preserves key nutrients, vitamins, and antioxidants; eliminated toxic components from food; protected food from decay; eradicated pathogens such as Enterobacteriaceae, <em>S. aureus</em>, and Enterococci</td>
</tr>
</tbody>
</table>
| *Lactobacillus plantarum* (299v and DSM 9843) | a. Reduced incidence of diarrhea in daycare centers when administered to only half of the children  
b. Especially effective in reducing inflammation in inflammatory bowel; e.g., enterocolitis in rats, small bowel bacterial overgrowth in children, pouchitis  
c. Reduced pain and constipation of irritable bowel syndrome  
d. Reduced bloating, flatulence, and pain in irritable bowel syndrome in controlled trial  
e. Positive effect on immunity in HIV+ children |
| *Lactobacillus reuteri*            | a. Shortened the duration of acute gastroenteritis  
b. Decreased *Candida albicans* systemic dissemination in euthymic or athymic beige mice  
c. Prevented development of methotrexate-induced and acetic acid-induced colitis in rats  
d. Shortened acute diarrhea |
<table>
<thead>
<tr>
<th><strong>Lactobacillus rhamnosus (HN001)</strong></th>
<th>Enhanced cellular immunity in healthy adults in controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lactobacillus salivarius</strong></td>
<td>Suppressed and eradicated <em>Helicobacter pylori</em> in tissue cultures and animal models by lactic acid secretion</td>
</tr>
</tbody>
</table>
| **Saccharomyces boulardii (yeast)** | a. Reduced recurrence of *Clostridium difficile* diarrhea  
b. Effects on *C. difficile* and *Klebsiella oxytoca* resulted in decreased risk and/or shortened duration of antibiotic-associated diarrhea  
c. Shortened the duration of acute gastroenteritis  
d. Decreased only functional diarrhea, but not any other symptoms of irritable bowel syndrome  
e. Decreased duration of diarrhea induced by tube feedings  
f. Ineffective for small intestinal bacterial overgrowth  
g. May reduce HIV-related chronic diarrhea  
h. Childhood diarrhea  
i. Extends remission time of Crohn’s disease  
j. Increased IgA anti-toxin A responses in pretreated mice |
| **Saccharomyces cerevisiae** (a yeast containing sucrase) | Enhanced digestion of sucrose load was shown in infants with sucrase deficiency |

Forms of Probiotics

Fermented foods

• Fermented yoghurt
  – cultured with *L. delbrueckii* ssp. *bulgaricus* and *S. thermophilus* are responsible for the taste, consistency, and smell that we associate with yoghurt yet these species lack the ability to survive in the human GIT

• Yoghurt manufacturers now routinely add additional probiotic species of bacteria to yoghurt in an attempt to enhance its therapeutic effects
  – Primarily *Lactobacillus acidophilus* and *Bifidobacterium bifidum*

Forms of Probiotics

Fermented foods

Sauerkraut and kimchi

- *L. plantarum* are involved in the final stages of fermentation in both kimchi and sauerkraut, and they typically reach populations of $>10^8$ bacteria/ml by the end stages of fermentation.

Quality

The quality of probiotic supplements depends on two main factors:

1. the characteristics of the strains contained in the supplement

2. adequate viability so that sufficient numbers of bacteria are viable at the time of consumption

Quality

- Bacterial strains used in probiotic supplements should as a minimum at least survive transit through the stomach and proximal small intestine
- Viability at consumption depends on a number of factors
  - proper manufacturing and the "hardiness" of the strain, as well as packaging and storage of the product in the right amount of moisture and at the correct temperature
- Many strains of lactobacilli and bifidobacteria do not respond well to freeze-drying (lyophilisation), spray drying, or conventional frozen storage, and too high a temperature during packaging or storage can dramatically reduce viability
- Unless the product has been shown to be stable, refrigeration is necessary during storage and ideally during transport
- Some products may not have to be refrigerated until after their container has been opened

Probiotic dosage

• Supplements are best consumed with meals in order to take advantage of the greater alkalinity of the gastric environment.

• A dosage of \(10^8\) **bacteria per sitting** is often mentioned in the probiotic literature as the minimum quantity of bacteria needed to produce therapeutic effects.

• Most of the successful probiotic research has utilised more than \(10^9\) **bacteria per dose**.
## Prebiotics

<table>
<thead>
<tr>
<th>Prebiotic compound</th>
<th>Food sources</th>
<th>Targeted microorganisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-glucooligomers</td>
<td>Oats</td>
<td><em>Lactobacillus</em> spp., <em>Bifidobacterium</em> spp.</td>
</tr>
<tr>
<td>Raffinose</td>
<td>Legumes, beets</td>
<td><em>Lactobacillus</em> spp.</td>
</tr>
<tr>
<td>Galactooligosaccharides</td>
<td>Cow's milk, yoghurt; human milk</td>
<td><em>Bifidobacterium</em> spp.</td>
</tr>
<tr>
<td>Xylooligosaccharides</td>
<td>Oats</td>
<td><em>Bifidobacterium</em> spp.</td>
</tr>
<tr>
<td>Galactosyl lactose</td>
<td>Human milk</td>
<td><em>Bifidobacterium</em> spp.</td>
</tr>
<tr>
<td>Fructooligosaccharides</td>
<td>Asparagus, banana, barley, burdock, chicory, dandelion, garlic, globe artichoke, Jerusalem artichoke, leek, onion, rye, maple syrup, beer, honey</td>
<td><em>Lactobacillus</em> spp.</td>
</tr>
</tbody>
</table>

Step 4: Repair

Direct nutritional support for the structure and function of the intestinal wall structure

– The antioxidants – alpha and beta-carotene, C, E
– Minerals - Zn and Mg
– Amino acids - N-acetylcysteine, glutamine
– Carbohydrates - inulin and fructooligosaccharides
– Pantothenic acid is often used due to its role in collagen formation

Another analogy for detox: the weed, seed, feed program

Step 1: Prepare and Weed

Prepare - Day 1

• For an optimal pre-protocol 24-hour fast, advise the patient to exclude all food and beverages other than purified water

• Vegetable juices and broths are acceptable in moderation

The weed, seed, feed program

Weed – Eradicate Dysbiotic Organisms using Garlic

Days 2–3

- The main components of garlic are the sulphur compounds, including alliin. Allicin is produced from alliin (via the action of the enzyme alinase) when garlic is crushed or chopped

- If fresh garlic is used in this protocol, it should be crushed first and taken with enough water to flush the garlic through the stomach quickly so the antimicrobial substances can act in the intestine

Other broad spectrum antimicrobial herbs can be used here, depending on the need:

- Pau D’Arco (*Tabebuia avellandae*) - antifungal and immune enhancing
- Goldenseal (*Hydrastis canadensis*) - broad antimicrobial
- Oregano oil (*Origanum vulgare*) - antimicrobial and anti-parasitic
- Caprylic acid

The weed, seed, feed program

Step 2: Feed (Days 4–15)

Step 2a: Provide prebiotics to feed the bowel with FOS and resistant starch rich foods

• The growth of endogenous beneficial bowel flora can be encouraged by administering prebiotics

• Prebiotics include herbs and foods containing mucilages, polysaccharides and fructooligosaccharides (FOS)

Slippery Elm

• The most common mucilage-containing herb historically used for GIT disorders is slippery elm (Ulmus rubra)

• It is a demulcent, emollient and nutrient and provides a simple physical soothing action

The weed, seed, feed program

Step 2b: Inhibit the regrowth of Pathogenic Flora

• Use selective gastrointestinal antiseptics to restore normal bowel flora, such as green tea and grape seed extract

• The use of polyphenols and oligomeric proanthocyanidins from grape seed extract and green tea selectively inhibit the regrowth of pathogenic bowel flora

<table>
<thead>
<tr>
<th>Day</th>
<th>Protocol</th>
<th>Dietary Guidelines</th>
</tr>
</thead>
</table>
| Day 1 | Prescribed medicines and supplements are to be taken as normal if the patient is currently on a protocol | - Fasting – no food and plenty of water; if the patient cannot fast, recommend to eat light, fresh meals of vegetables and salads only.  
- No consumption of yeast, sugar or starches is essential. This includes fruits. Vegetable juices and broths are acceptable.  
- No alcohol or caffeine.  
- If cravings for carbohydrates are interfering with patient compliance, add Gymnema tablets (3 per day) into the protocol for blood sugar regulation. |
| Day 2 and Day 3 | ▪ Garlic: 1–2 fresh crushed cloves of garlic twice daily or 2 high quality, enterically-coated garlic tablets.  
If fresh garlic is used, it should be taken with a copious quantity of water. This has the effect of flushing the fresh garlic quickly into the small intestine.  
▪ Golden seal could be taken here as well: 4 tablets containing at least 500 mg of root per day | ▪ Fasting is ideal; if the patient cannot fast, recommend very light, fresh meals of vegetables and salads.  
▪ No consumption of yeast, sugar or starches is essential. This includes fruits and fruit juices. Vegetable juices and broths are acceptable.  
▪ No alcohol or caffeine. |
| Days 4 to 15 | ▪ Slippery elm powder: 1–2 heaped teaspoons of slippery elm powder with copious (240 mL) water, to allow it to swell in the GIT.  
▪ Herbal antioxidant (green tea, grape seed extract, turmeric, rosemary): 2 tablets at night before bed or on an empty stomach, at least 2 hours away from food | ▪ Gradually introduce clean, fresh foods  
▪ Daily consumption of green tea |
| Day 15 | Repeat protocol for another 14 day cycle if desired                      |                                                                                      |
Gastrointestinal Health
Peptic Ulcers

- Peptic ulcers are defects in the gastric or duodenal mucosa that extend through the muscularis mucosa.

- Under normal conditions, a physiologic balance exists between peptic acid secretion and gastroduodenal mucosal defence.

- Mucosal injury and thus, peptic ulcer occur when the balance between the aggressive factors and the defensive mechanisms is disrupted.
  - Aggressive factors, such as NSAIDs, H. pylori, alcohol, bile salts, acid, and pepsin, can alter the mucosal defence by allowing back diffusion of hydrogen ions and subsequent epithelial cell injury.

Peptic Ulcers

• Prevalence

• Lifetime prevalence is approximately 11-14% for men and 8-11% for women

• Roughly matches age
  • i.e. 20% at age 20, 30% at age 30, 80% at age 80 etc.

• Greater in men than women

Peptic Ulcers

Common symptoms

• Epigastric pain (the most common symptom)
  – Gnawing or burning sensation
  – Occurs two to three hours after meals
  – Relieved by food or antacids
  – Patient awakens with pain at night
  – May radiate to the back (consider penetration)
• Nausea
• Vomiting, which might be related to partial or complete gastric outlet obstruction
• Dyspepsia, including belching, bloating, distention, and fatty food intolerance
• Heartburn
• Chest discomfort
• Anorexia, weight loss
• Haematemesis or melena resulting from gastrointestinal bleeding
• Dyspeptic symptoms that might suggest PUD are not specific because only 20-25% of patients with symptoms suggestive of peptic ulceration are found on investigation to have a peptic ulcer

Peptic Ulcers

Diagnostic summary

- Epigastric distress 45 to 60 minutes after meals or nocturnal pain; both relieved by food, antacids, or vomiting
- Epigastric tenderness and guarding
- Symptoms chronic and periodic
- Gastric analysis shows acid in all cases, with hypersecretion in about half the patients with duodenal ulcers
- Ulcer crater or deformity usually occurring at the duodenal bulb (duodenal ulcer) or pylorus (gastric ulcer) on radiograph or fiberoptic examination
- Positive test for occult blood in stool

Peptic Ulcers

Complications

- GIT bleed - is the most common complication. Sudden large bleeding can be life threatening. It occurs when the ulcer erodes one of the blood vessels.

- Perforation - a hole in the wall - often leads to catastrophic consequences. Erosion of the gastro-intestinal wall by the ulcer leads to spillage of stomach or intestinal content into abdominal cavity. Perforation at the anterior surface of stomach leads to acute peritonitis, initially chemical and later bacterial peritonitis. Often first sign is sudden intense abdominal pain. Posterior wall perforation leads to pancreatitis; pain in this situation often radiates to back.

- Penetration - if ulcer continues into adjacent organs such as liver and pancreas.

- Scarring and swelling due to ulcers causes narrowing in the duodenum and gastric outlet obstruction.

- Patient often presents with severe vomiting.
Peptic ulcers

- **Helicobacter pylori**
  - 70% of gastric and up to 90-100% of duodenal ulcers
    - 50% people over 50 test positive for yet 80% never develop ulcers
- Gastric acid is extremely corrosive with a pH of 1 to 3
  - Mucin is produced to protect against ulcers. In addition, the constant renewing of intestinal cells and the secretion of factors that neutralise the acid are produced
- H. pylori colonisation increases due to the increased gastrin
  - Several bioactive factors are produced and released that may directly affect the stomach's parietal cells
  - The increase in acid can contribute to the erosion of the mucous leading to ulcer formation
  - Gastric acid and pepsin enter gastric mucosa

Helicobacter pylori
— the bacterium causing peptic ulcer disease

Infection
Helicobacter pylori infects the lower part of the stomach, antrum.

Duodenum
Pylorus
Antrum

Inflammation
Helicobacter pylori causes inflammation of the gastric mucosa (gastritis). This is often asymptomatic.

Ulcer
Gastric inflammation may lead to duodenal or gastric ulcer. Severe complications include bleeding ulcer and perforated ulcer.

Increased acid secretion
Duodenal ulcer

Inflammation

Bleeding ulcer

Gastric ulcer
Inflammation

© The Nobel Committee for Physiology or Medicine
Peptic ulcers

- **Helicobacter pylori**
- Transmitted oral to oral or fecal to oral
- Determining the level of antibodies to *H. pylori* in the blood or saliva or by culturing material collected during an endoscopy, as well as measuring the breath for urea
- Low antioxidant status and low gastric output may predispose to colonisation

Peptic Ulcers

Aetiology/Risk Factors

- **NSAIDs** – nonsteroidal anti-inflammatory medications
  - the gastric mucosa protects itself from gastric acid with a layer of mucus which is stimulated by certain prostaglandins. NSAIDs block the function of cyclooxygenase 1 (COX-1), which is essential for the production of these protective prostaglandins
- Aspirin – thins gastric mucosa
- Alcohol
- Smoking - ischaemia
- Glucocorticoids
  - Corticosteroids alone do not increase the risk for PUD; however, they can potentiate the ulcer risk in patients who use NSAIDs concurrently
- Overuse of laxatives
- Family history – especially O blood type
Peptic Ulcers

Allopathic treatment

- Proton pump inhibitors – which inhibit and suppress acid production: omeprazole, lansoprazole, rabeprazole, esomeprazole or pantoprazole
- Antibiotics – to kill bacteria: a combination of metronidazole, tetracycline, clarithromycin, or amoxycillin
- Check your BNF for details

Peptic Ulcers Treatment

Lifestyle

- Stress and emotions
  - The medical literature is controversial, and every substantial attempt to examine this assumption has been fraught with methodologic errors
  - Data suggests that it is not simply the amount of stress, but rather the patient's response to it that is the significant factor
  - Psychologic factors are probably important in some patients with peptic ulcer disease, but not in others. As a group, ulcer patients have been characterised as tending to repress emotions. At the least, patients should be encouraged to discover enjoyable outlets of self-expression and emotions

Peptic Ulcers Treatment

• **Smoking**
  • Increases frequency, decreases responsiveness to treatment and increases mortality associated with peptic ulcers
    • 3 hypotheses:
      • Decreases pancreatic bicarbonate secretion
      • Increases reflux of bile salts into stomach
      • Accelerates gastric emptying
  • Smoking increases histamine levels which, in turn, stimulate the H2-receptor
  • Nicotine reduces gastric mucosa prostaglandin generation, thereby leaving the mucosa more susceptible to ulceration

Peptic Ulcers Treatment

- **Food sensitivities**
  - Allergy or food sensitivities suspected
  - IgE has been found localised in peptic ulcers
  - Defects in the gastric or duodenal epithelial barrier can allow proteins to pass with IgE production in the submucosa
  - Elimination diet
  - Avoid milk – increases likelihood of ulcer as increases stomach acid production

- **Fibre**
  - Increased fibre linked with reduced duodenal ulcers
  - Delays gastric emptying of chyme therefore slowing the movement into the duodenum
    - Supplemental fibres: pectin, guar gum, psyllium
    - Increase plant foods

Peptic Ulcers Treatment

- Raw cabbage juice
- ‘Substance U’ – stimulates mucin production
- One litre per day in divided doses
- Contains high levels of glutamine
  - Glutamine 1.6 g qid (four times a day)

- Flavonoids
- Counteract histamine production and secretion
- Catechin shown to provide anti-ulcer activity
  - 1000 mg five times a day

Peptic Ulcers

Dr G. Cheney, of Stanford University, performed a study in which he treated 100 peptic/duodenal ulcer patients with four glasses of raw cabbage juice daily.

In most cases, the patient's pain disappeared within five days and the ulcers healed by the end of two weeks.

A study by Dr Saxon Graham revealed that individuals who never eat *cabbage* were three times more likely to develop colon cancer than those who include it in their meals at least once a week

- contains indoles, which neutralise metabolic toxins
- stimulates liver enzyme systems, which inhibit the activity of carcinogens
- can also be protective against polycyclic aromatic hydrocarbons, which have been linked to cancerous development

Peptic Ulcers
Peptic Ulcers Treatment

- Avoid hot/spicy foods
- Avoid alcohol, coffee, tea and sugar
- Avoid aspirin containing analgesics
- Five to six small meals per day
- Include bananas
  - Contain surface active phospholipid than maintains the protective layer on the gastric mucosa
- Zinc
  - Increases mucin production in vitro
- Deglycyrrhizinated *Glycyrrhiza glabra* (licorice) – DGL
  - Stimulates differentiation to glandular cells and mucus formation
  - Contains several flavonoids that inhibit H. pylori

Gastroesophageal reflux disease - GORD

- Gastroesophageal reflux disease, heartburn, acid reflux, dyspepsia
- An amount of gastric juice that refluxes into the oesophagus exceeds the normal limit, causing symptoms with or without associated oesophageal mucosal injury
- An abnormal oesophageal exposure to gastric juice is probably present in 20-40% of this population, meaning 20-40% of the people who experience heartburn do indeed have gastroesophageal reflux disease
- Maximum frequency during pregnancy – 25% experience daily
- Increases the risk of oesophageal cancer

Gastroesophageal reflux disease - GORD

• **Pathophysiology**

  A functional - frequent transient lower oesophageal sphincter (LOS) relaxation or mechanical - hypotensive LOS – problem with the sphincter pressure

• Certain foods (e.g. coffee, alcohol), medications (e.g. calcium channel blockers, nitrates, beta blockers, diazepam, morphine, theophylline), or hormones (e.g. progesterone, dopamine) can decrease the pressure of the LOS

• Obesity is a contributing factor, probably because of the increased intra-abdominal pressure


GORD

Symptoms
• Heartburn is the most common typical symptom
discomfort or pain – ‘burning’ behind the breastbone in the upper chest.
Generally worse lying or bending down or after eating
• Regurgitation
• Dysphagia – a sensation that food is stuck

Allopathic treatment
• Proton pump inhibitors
• Histamine H2-receptor antagonists
  reversible competitive blockers of histamine at the H2 receptors, particularly those
  in the gastric parietal cells where they inhibit acid secretion
• Antacids to control the symptoms

(Accessed at: 24 August 2009)
GORD

Aetiology/Risk Factors

Food associated with the reduction in oesophageal sphincter pressure:

• Chocolate
• Alcohol
• Carminatives – peppermint, spearmint
• Citrus juices
• Tomato products
• Coffee
• Salicylate-rich foods
• Also - smoking

Aetiology/Risk Factors

- Hypothesis - poor gastric digestion
  - undigested food → ferment → produce gas → increase gastric pressure → raise cardiac region of the stomach upward → pressure on heart = ‘heartburn’

- A sliding hiatus hernia would present with similar symptoms
GORD

Diet & Lifestyle Treatment

- Five to six small meals per day – last meal three to four hours before bed
- Avoid lying down post meals
- Elevate head of the bed by approximately six inches
  - decreases acid exposure of the oesophagus during sleep
- Cessation of smoking
- Test for H.pylori
- Avoid fatty foods, chocolate, alcohol, coffee, salicylate-rich foods
- Ascertain if food intolerance/sensitivity
  - Elimination/rechallenge or serum testing
# Salicylate-containing foods

<table>
<thead>
<tr>
<th>FOOD</th>
<th>NEGLIGIBLE</th>
<th>LOW</th>
<th>HIGH</th>
<th>VERY HIGH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fruit</td>
<td>Pear (peeled)</td>
<td>Pawpaw, Apple (Golden Delicious), Pomegranate</td>
<td>Passion fruit, Mulberry, Tangelo, Grapefruit, Avocado, Peach, Mandarin, Apple (Granny Smith), Nectarine, Watermelon, Lychee, Kiwi fruit, Apple (Jonathan)</td>
<td>Sultana (dried), Prune, Raisin (dried), Currant (dried), Raspberry, Redcurrant, Grape, Loganberry, Blackcurrant, Youngberry, Cherry, Orange, Blueberry, Plum, Pineapple, Boysenberry, Guava, Apricot, Blackberry, Cranberry, Date, Strawberry, Rockmelon</td>
</tr>
<tr>
<td></td>
<td>Banana (Cavendish)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vegetables</td>
<td>Potato (peeled)</td>
<td>Beans (green), Cabbage (red), Brussels sprouts Mung bean sprouts, Peas (green), Leek, Shallot, Chive, Choko</td>
<td>Eggplant, Watercress, Cucumber, Bean (broad), Alfalfa sprouts</td>
<td>Tomato products, Gherkin, Endive, Champignon, Radish, Olive, Capsicum, Zucchini, Chicory, Pepper (hot)</td>
</tr>
<tr>
<td></td>
<td>Lettuce, Celery, Cabbage, Bamboo shoot, Swede, Beans (dried), Peas (dried), Lentils (brown/red)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nuts/Seeds</td>
<td>Poppy seed</td>
<td>Cashews</td>
<td></td>
<td>Almond, Water chestnut</td>
</tr>
<tr>
<td>Sweets</td>
<td>Sugar (white), Maple syrup, Cocoa, Carob</td>
<td>Golden syrup, Caramels</td>
<td></td>
<td>Licorice, Peppermints, Honey</td>
</tr>
<tr>
<td>Herbs/Spices</td>
<td>Vanilla, Garlic, Parsley, Saffron, Vinegar (malt), Soya sauce, Tandoori</td>
<td>Cinnamon, Cardamon, Pepper (black), Pimento, Ginger, Allspice, Clove, Nutmeg, Caraway, Vinegar (white), Bay leaf, Pepper (white)</td>
<td>Cayenne, Aniseed, Sage, Mace, Curry, Paprika, Thyme, Dill, Turmeric, Worcestershire sauce, Vegemite, Marmite, Rosemary, Oregano, Garam masala, Herbs (mixed), Cumin, Canella, Tarragon, Mustard, Five spice, Mint</td>
<td></td>
</tr>
<tr>
<td>Beverages</td>
<td>Coffee, Decaffeinated, Other: Aktavite, Milo, Alcohol (Gin, Whiskey, Vodka)</td>
<td>Coffee (Harris /Bushells instant, Turkish, Robert Timms instant), Tea (Chamomile), Cereal Coffee (Dandelion, Ecco, Bambu)</td>
<td></td>
<td>Tea (all brands, Peppermint), Cereal Coffee, Alcohol (Liqueur, Port, Wine and Rum)</td>
</tr>
</tbody>
</table>
**GORD**

**Nutritional Therapy**

- Digestive enzymes – facilitate the digestion of food
- Betaine Hydrochloride
- Slippery Elm (*Ulmus fulva*) – 9-30mg
  - Coating and “smoothing” the irritated area - demulcent
- Increase fibre intake to reduce the occurrence of hiatus hernia
- Vitamin A, silicon and Mg-rich foods
- Cabbage juice if ulceration suspected
- *Lactobacillus acidophilus* – to reduce gastric distention
- Barley grass or potassium citrate – alkalise
- Glutamine, carnitine, arginine
**Bristol Stool Chart**

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Separate hard lumps, like nuts (hard to pass)</td>
</tr>
<tr>
<td>2</td>
<td>Sausage-shaped but lumpy</td>
</tr>
<tr>
<td>3</td>
<td>Like a sausage but with cracks on its surface</td>
</tr>
<tr>
<td>4</td>
<td>Like a sausage or snake, smooth and soft</td>
</tr>
<tr>
<td>5</td>
<td>Soft blobs with clear-cut edges (passed easily)</td>
</tr>
<tr>
<td>6</td>
<td>Fluffy pieces with ragged edges, a mushy stool</td>
</tr>
<tr>
<td>7</td>
<td>Watery, no solid pieces. <em>Entirely Liquid</em></td>
</tr>
</tbody>
</table>

[http://thewvsr.com/bristolstoolchart.htm](http://thewvsr.com/bristolstoolchart.htm)
Constipation

• **Quantity and Quality**
  
  Divided, with considerable overlap, into issues of stool consistency - hard, painful stools – though soft bulky stool may also be associated

  and issues of defecatory behaviour - infrequency, difficulty in evacuation, straining during defecation

• Frequency may range from several times per day to once per week

• Severe cases may be associated with faecal impaction which may result in diarrhoea, ulceration of the colon and intestinal obstruction


(Accessed at: 24 August 2009)

Constipation

Aetiology/Risk Factors

- Insufficient fibre intake
- Insufficient fluid intake
- GIT dysbiosis
- Decreased liver/bile function
- Lack of exercise
- Anxiety
- Pregnancy
- Hypothyroidism, diverticular disease, Irritable Bowel Syndrome, colonic carcinoma
- Side effects from pharmaceutical medications
  - Opiates, anticholinergics, iron supplements, anticonvulsants, antacids, antidepressants, calcium channel blockers

Constipation

Aetiology/Risk Factors

• Neurotransmitters and GIT motility
  • Serotonin is a critical signalling molecule in the GIT
  • Initiates peristalsis, secretions, vasodilation and vagal and nociceptive reflexes

Constipation

Complications

• Haemorrhoids
  • which are caused by straining to have a bowel movement

• Anal fissures
  • tears in the skin around the anus

• Rectal prolapse
  • small amount of intestinal lining pushing out from the anal opening

• Loss of bladder control by weakening the pelvic floor muscles as a result of straining
Constipation

Nutritional Therapy

• Increase fluid intake – minimum two litres per day – and avoid all caffeinated drinks due to diuretic action
• Regulate the eating habits to enable body to regulate elimination and respond to urge to stool
• Increase fibre intake
  • whole grains, raw or lightly cooked fruit and vegetables
  • include legumes into daily food intake – high fibre for weight
• Rice bran – increase stool mass
• Psyllium seed husks (*Plantago ovata*) – 15-30 g/day plus
  • minimum of one glass of water on top of required fluids or may cause blockage of oesophagus or colon
• Natural laxatives – prunes, figs, apricots, rhubarb
• Lipotropes – methionine, choline, inositol – to increase bile flow

Constipation

Nutritional Therapy

• Aloe vera juice (*Aloe vera barbadensis*) –
  • whole leaf concentrate – anthraquinones 100mg/kg = laxative effect
  • stimulate peristalsis in the ileum plus increase in fluid intake
• EPA/DHA – increase bile flow
• Probiotics may:
  • improve intestinal motility
  • reduce faecal enzyme activity
• Magnesium - laxative effect and nervous system relaxant
  • especially magnesium citrate
• Vitamin C – laxative effect
• Vitamin B5 – stimulate peristalsis
• Minerals – chronic constipation may result in Ca, Mg, K deficiency

....slow down and create the habit
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Diarrhoea

• Frequent passage of loose, watery stools; generally the result of increased motility in the colon
• Complications can be serious, even fatal, particularly in infants and elderly patients
• Primarily a symptom of an underlying condition with acute diarrhoea is usually self-limiting – two to three days
• Chronic diarrhoea – two to three weeks or more in duration
  • requires appropriate assessment and management
• It is important in these cases to attempt to determine the cause
Diarrhoea

Four types:

1. Osmotic
   - Laxatives
   - Excess vitamin C
   - Presence of disaccharides/lactose intolerance
   - Motion is usually acidic
     - due to bowel fermentation of unabsorbed carbohydrates

Diarrhoea

2. Secretory diarrhoea
   - Watery movement – fluid, electrolytes and other substances
   - Commonly caused by laxative abuse, antibiotics, alcohol or excessive coffee intake
   - Certain bacteria, clostridia difficile, pseudomembranous enterocolitis and shigella (cholera) - overgrowth of anaerobic bacteria in the upper intestine
     - May deconjugate bile salts → poor fat absorption or damage to mucosa
     - → free fatty acids inhibit absorption of salt and water → diarrhoea
   - Fat or blood in the stool may suggest infectious, parasitic or inflammatory disease or processes
Diarrhoea

3. Defective ion diarrhoea
   • Failure of the GIT to absorb actively an important ion such as chloride

4. Motor diarrhoea
   • Abnormal rapid movement through small bowel and colon
   • Mucus may be present

Pus in stool
   - suggests inflammatory bowel disease or infection. May be associated with certain malignancy or gall bladder disease

Diarrhoea

Ascertained relationship with diarrhoea and events

• Intake of milk
  • May indicate lactase deficiency or sensitivity to milk protein

• Emotional upheaval

• Travel
  • May indicate bacterial infection, amoebiasis or giardiasis

Diarrhoea

Common signs and symptoms:
- Frequent and loose, watery stools
- Mucus and/or blood in the stools
- Abdominal discomfort, cramping and/or pain
- Flatulence and/or bloating
- Vomiting and/or nausea
- Fever - if related to infection
- Increased thirst
- Nutrient malabsorption
- Weight loss - in chronic diarrhoea
- Dehydration
Diarrhoea

Possible causes

- Microbial infection/dysbiosis
- Recent antibiotic use
- Nervous anxiety and/or other emotional disturbances
- Irritable Bowel Syndrome
- Inflammatory Bowel Disorders
- Inadequate bile secretion
- Teething (in children)
- Food allergies and/or sensitivities – lactose, gluten, wheat, sugar
- AIDS and other immune disorders
- Hyperthyroidism
- Laxative abuse
- Bowel tumours
- Iatrogenic causes, including medications - antibiotics, antacids, diuretics, antihypertensives, anti-inflammatories
Diarrhoea

Orthodox Treatment

- Opioid analgesics or antagonists - slow down peristalsis and cause the stool to become firmer e.g. Loperamide (Imodium)
- Adsorbents - clay-like substances reduce the water content of stools and make the loose stool firmer
- Bulk-forming medications - water-soluble fibres absorb water from the stools and make the loose stool firmer
- Antimicrobials - if the diarrhoea is due to bacterial, viral or parasitic infection antimicrobial treatment is used - e.g. antibiotics, antivirals, antifungals, antiprotozoal drugs, anthelmintics
- Electrolyte replacement formulations – to correct losses
Diarrhoea

Saccharomyces boulardii

• Infectious types such as rotaviral diarrhoea in children, diarrhoea caused by bacterial overgrowth in adults, traveller's diarrhoea, and diarrhoea associated with enteral tube feedings
• Prevent and treat antibiotic-associated diarrhoea
• Also used orally for general digestion problems, irritable bowel syndrome (IBS), inflammatory bowel syndrome (IBD, Crohn's disease, ulcerative colitis), Lyme disease, relapsing Clostridium difficile colitis, and bacterial overgrowth in short bowel syndrome. It is also used orally for lactose intolerance, urinary tract infections (UTIs), vaginal and candida-related (yeast) infections, high cholesterol levels, hives, fever blisters, canker sores, and adolescent acne

Diarrhoea

• **Saccharomyces boulardii in diarrhea**

  **BACKGROUND:** Interest to probiotics for the prevention and treatment of antibiotic-associated diarrhea is increasing gradually. The most promising seems to be *Saccharomyces boulardii*. Using a double-blind controlled study, we investigated the preventive effect of *S. boulardii* on the development of antibiotic-associated diarrhea in patients under antibiotherapy but not requiring intensive care therapy.

  **MATERIAL/METHODS:** All the patients were hospitalized at the Gulhane Military Medical Academy, Department of Infectious Diseases and Clinical Microbiology. *S. boulardii* was given twice daily during the course of antibiotic therapy and application was initiated in all patients as late as after 48 hours of antibiotic therapy. A total of 151 patients completed the study.

  **RESULTS:** The antibiotic-associated diarrhea development ratio in placebo group was 9% (7/78) and in the study group 1.4% (1/73) (p < 0.05). Stool samples from the patients with antibiotic-associated diarrhea were stored at -70 degrees C and Clostridium difficile toxin A assay was performed using Enzyme Immune Assay as late as in seven days. *C. difficile* toxin A assay yielded positive results in two (2/7) stool samples from the patients with antibiotic-associated diarrhea in the placebo group and a negative result in the only patient who developed antibiotic-associated diarrhea in the study group.

  **CONCLUSIONS:** The results implied that **prophylactic** use of *Saccharomyces boulardii* resulted in **reduced**, with **no serious side effects**, antibiotic-associated diarrhea in hospitalized patients.

Diarrhoea

Malabsorption:

- Chronic diarrhoea can be associated with malabsorption – protein, B12, C, A, Cu, Fe, Mg, K, Na and Zn – therefore supplementation should be considered

Excessive supplementation of the following may be responsible for diarrhoea:

- Vitamin C
- Magnesium
- 5-HTP
- Taurine
- Fish oils
- Ginsengs
- Raw garlic
Irritable Bowel Syndrome

- Colon syndrome, intestinal neurosis, irritable colon syndrome, mucous colitis, nervous indigestion, RBS (reactive bowel syndrome), spastic bowel, spastic colon
- One of the most common GIT presentations yet poorly understood
- Intestines contain no structural or pathologic abnormalities
- Diagnosed by exclusion
  - No tests for confirmation therefore need to rule other differentials ‘out’ vs IBS ‘in’
- Age of onset – late teens to early 30s
- Women > men 2:1
Irritable Bowel Syndrome

Diagnosis

• The Manning criteria to distinguish irritable bowel syndrome from organic bowel disease

1. Onset of pain associated with more frequent bowel movements
2. Onset of pain associated with looser bowel movements
3. Pain relieved by defecation
4. Visible abdominal bloating
5. Subjective sensation of incomplete evacuation more than 25% of the time
6. Mucorrhoea more than 25% of the time

(Accessed at: 24 August 2009)
Irritable Bowel Syndrome

Extraintestinal symptoms:

- Sexual dysfunction
- Fibromyalgia
- Dyspareunia
- Urinary frequency and urgency
- Poor sleep
- Menstrual difficulties
- Lower back pain
- Headache
- Chronic fatigue
- Insomnia

All of which may increase in number with severity of IBS

Irritable Bowel Syndrome

Conditions that may mimic IBS

- Gastrogenic dietary factors such as excessive tea, coffee, carbonated beverages, and simple sugars
- Infectious enteritis such as amebiasis and giardiasis
- Inflammatory bowel disease
- Lactose intolerance
- Laxative abuse
- Intestinal candidiasis
- Disturbed bacterial microflora as a result of antibiotic or antacid usage
- Malabsorption diseases such as pancreatic insufficiency and coeliac disease
- Metabolic disorders such as adrenal insufficiency, diabetes mellitus, and hyperthyroidism
- Mechanical causes such as faecal impaction
- Diverticular disease
- Tumours

Irritable Bowel Syndrome

Pathophysiological considerations

• Brain gut connection
  • Brain and gut develop from the same part of the human embryo therefore share many nerve endings and chemical transmitters
  • This may help explain the GIT symptoms resulting from emotional stimulants
  • Nearly every chemical that controls the brain has been identified in the GIT
    • Serotonin plays a role in peristalsis, secretion, sensation
      • GIT contains over 95% of the body’s serotonin
      • Defects in serotonin signaling in the GIT may underlie the altered function
        • Serotonin 5-HT4 agonists – constipation prominent
        • Serotonin antagonists – diarrhoea prominent

Irritable Bowel Syndrome

Pathophysiological considerations

• Altered stress mechanisms
  • Once again relating to the brain-gut connection
  • Theory is that IBS patients respond to stress differently
    • Non IBS— stress slows stomach emptying and can cause diarrhoea but terminates quickly via cortisol negative feedback mechanism
    • IBS – alterations in feedback may lead to prolonged stress response

• Food sensitivities, intolerance or allergy
  • Most commonly implicated (in descending order):
    • dairy, onions, wheat, chocolate, coffee, eggs, nuts, citrus fruits, tea, rye, potatoes, barley, oats and corn

• Dysbiosis due to recent infection
  • *Blastocystis hominis* - protozoa

Irritable Bowel Syndrome

Nutritional Therapy

• Optimise fibre intake – especially with constipation predominant
  • Psyllium husk - soluble fibre providing a bulk-forming laxative - 20-30g per day
  • Partially hydrolysed guar gum (PHGG)
  • Vegetables, fruit, legumes rather than cereals

• Food allergy (IgE) or intolerance (IgG)
  • Recognised in the aetiology since the early 1900s
  • Foods rich in carbohydrates, fatty food, coffee, alcohol and hot spices
  • Dairy (40-44%) and grains (40-60%)

Irritable Bowel Syndrome

Nutritional Therapy

• Avoid high refined sugar
  • When blood glucose levels rise too rapidly, GIT peristalsis slows, especially in the duodenum and jejunum

• Enteric coated peppermint oil (ECPO)
  • Inhibits GIT smooth muscle action
  • 0.2ml – 0.4ml twice a day between meals

• 5-hydroxy tryptophan (5-HTP)
  • relationship with serotonin, a neurotransmitter that is produced in both the digestive tract and the brain

Irritable Bowel Syndrome

Nutritional Therapy

- Melatonin improves irritable bowel syndrome
- The amino acid L-tryptophan or its metabolic derivative, 5-hydroxy-L-tryptophan (5-HTP), has been considered for treating irritable bowel syndrome (IBS), owing to the relationship with serotonin and melatonin, neurotransmitters that are produced in both the digestive tract and the brain. Because co-morbidity of psychiatric conditions such as depression and anxiety, as well as sleep disturbance, is highly correlated with IBS-coupled with the fact that serotonin and melatonin are involved in the regulation of gastrointestinal motility and sensation-modulation of serotonin and melatonin activity with the use of L-tryptophan, 5-HTP, or melatonin seems logical. At this time the only clinical investigation of these three substances in IBS is a double-blind study conducted with melatonin. Forty patients with IBS and sleep disturbances were randomly assigned to receive either melatonin 3 mg or placebo at bedtime for 2 weeks. The conclusion of the study was that taking melatonin significantly reduced abdominal pain and reduced rectal pain sensitivity. Surprisingly, the study did not show melatonin improved sleep disturbance or psychological distress. These findings suggest that melatonin's effects in improving IBS are exerted on the gastrointestinal tract, highlighting its physiological role in motility and sensation.

Irritable Bowel Syndrome

Nutritional Therapy

- Digestive enzymes
  - Optimise digestion and anti-inflammatory – especially bromelain
- L-glutamine
  - 1-2g per meal
- Probiotics
  - L. plantarum 299v, L. acidophilus, B. bacterium
- Ginger
  - Antispasmodic, mild anti-inflammatory, reduces nausea
- Turmeric
- Exercise and stress reduction techniques
Inflammatory Bowel Disease

- A group of chronic inflammatory disorders of the bowel
  - Ulcerative colitis (UC)
  - Crohn’s disease (CD)
  - 10% with a typical relapsing state in which the differentiation can not be made
- UC more common yet CD is increasing in prevalence
- First-degree relatives have a 5- to 20-fold increased risk of developing IBD
- Increases the risk of colonic carcinoma
- Any age – predominately 15-35 years
- Female to male ratio equal
- Angelo esp. Jewish > African or Asian

Inflammatory Bowel Disease

Symptoms

Ulcerative colitis

• Bloody diarrhoea
• Pain is uncommon but may occur – mild cramping lower abdominal area
• Fatigue, which is often related to the inflammation and anaemia

Crohn’s disease

• Abdominal pain and diarrhoea
• Pain is particularly common, especially when some degree of obstruction is present
  • Almost anywhere within the abdominal cavity, although the classic location is the lower abdomen or right lower quadrant (like appendicitis)
• Fatigue, which is often related to the pain, inflammation, and anaemia

Inflammatory Bowel Disease

Ulcerative Colitis

- Predominantly colon and rectal mucosa
- Predominantly think food allergy/intolerance or bacterial infection

Crohn’s Disease

- Any portion of GIT – mouth to anus
- Predominantly small bowel – especially terminal ileum [SI joins LI]
- May present with strictures and narrowing of the lumen thus impair intestinal flow
- Frequently associated with Fe, B12, folate deficiency
- Secondary lactase deficiency may be present
- Pancreatic digestive enzymes lowered in 80%

Inflammatory Bowel Disease

Pathophysiology

- The pathophysiology of IBD not fully understood
  - The common end pathway is inflammation of the mucosal lining of the intestinal tract leading to ulceration, oedema, bleeding, and fluid and electrolyte loss

- Genetic predisposition (or perhaps susceptibility) for the disease

- The triggering event for the activation of the immune response has yet to be identified
  - Possible factors related to this event include a pathogenic organism (as yet unidentified), an immune response to an intraluminal antigen (e.g. protein from cow’s milk), or an autoimmune process whereby an appropriate immune response to an intraluminal antigen and an inappropriate response to a similar antigen is present on intestinal epithelial cells (i.e. alteration in barrier function)

Inflammatory Bowel Disease

Pathophysiology

- Autoimmune
  - T helper 1 dominant - ‘tissue specific’ autoimmunity
    - (covered further in the Immune lecture)
  - Substances found to balance Th1 dominance include:
    - Curcumin, fish oils, vitamin E, D, bromelain, glycine and L. acidophilus
- Vitamin D
  - Modulate autoimmune responses
  - 1alpha 25 (OH) 2D3
    - Vitamin D3 analogue produced by activated macrophages may activate a negative feedback loop at sites of inflammation

Inflammatory Bowel Disease

Pathophysiology

- Microbial infection
- Still much debated – Viruses - rotavirus, Epstein-Barr virus, cytomegalovirus, and an uncharacterised RNA intestinal cytopathic virus-and mycobacteria suspected
- Antibiotic exposure is being linked
- Before the 1950s, Crohn's disease was found in selected groups with a strong genetic component. Since this time there has been a rapid climb in developed countries
- Food factors
- The incidence of Crohn's disease is increasing in cultures consuming the Western diet, but it is virtually non-existent in cultures consuming a more primitive diet
- One researcher found that before the onset of disease, patients with Crohn's disease had eaten cornflakes more frequently than controls. Although other researchers could not verify this specific finding, cornflakes are high in refined carbohydrates and are derived from a very common allergen (corn)
Inflammatory Bowel Disease

**Therapeutic considerations**

Reduce production of proinflammatory mediators
- Reduce or eliminate beef, liver, pork, lamb, and milk/dairy products
- Reduce consumption of omega 6 fatty acid
- Increase consumption of omega 3 fatty acids
- Quercetin - inhibits cyclooxygenase and lipoxygenase – 400 mg 20 min before meals
- Foods rich in mucopolysaccharides to reduce inflammation
  - aloe, tripe, oats, onions and slippery elm (*Ulmus fulva*)
- Remove carrageenans
  - used by food industry to stabilise and suspend agents especially milk protein – ice cream, cottage cheese, milk chocolate

- Food sensitivities/allergies
- Food antigens may contribute to GIT inflammation in Crohn’s disease
  - Wheat exacerbates in approximately 70% and dairy between 20 to 50%

Inflammatory Bowel Disease

Therapeutic considerations

Causes of Malnutrition in Inflammatory Bowel Disease

- Decreased oral intake
- Disease induced (pain, diarrhoea, nausea, anorexia)
- Iatrogenic (restrictive diets without supplementation)
- Malabsorption
  - Decreased absorptive surface due to disease or resection
  - Bile salt deficiency after resection
  - Bacterial overgrowth
  - Drugs (e.g. corticosteroids, sulfasalazine, cholestyramine)
- Increased secretion and nutrient loss
- Protein-losing enteropathy
- Electrolyte, mineral, and trace mineral loss in diarrhoea
- Increased utilisation and increased requirements
  - Inflammation, fever, infection
  - Increased intestinal cell turnover

Inflammatory Bowel Disease

Nutritional Therapy

- Optimise **protein** intake with fish being the preferred source

- Optimise **glutathione** levels due to increased reactive oxygen species leading to increased tissue injury
  - Cysteine 1-2 g/d, glutamine 1-2 g/meal, alpha lipoic acid 600mg

- **Zinc** – 50 mg per day
  - Deficiency in approx 45% of patients due to low dietary intake, poor absorption, and excess faecal losses

- **Iron**
  - Deficiency common
  - Prescribe once serum iron and ferritin levels have been ascertained

Inflammatory Bowel Disease

Nutritional Therapy

Additional nutrients

• Calcium
  • Due to loss of absorptive surfaces, steatorrhoea, corticosteroid use, vitamin D deficiency
• Potassium
  • Due to diarrhoea
• Vitamin A
  • Low serum in approximately 20% of Crohn’s patients
• Vitamin D
  • Common deficiency
• Vitamin E
• Vitamin K
• Folic acid
• Vitamin B12
• Ascorbic acid
Coeliac Disease

Non-tropical sprue, gluten-sensitive enteropathy, coeliac sprue

Diagnosed

- 8-12 months
- Third to fourth decades
- The mean age at diagnosis is 8.4 years (range, 1-17 years)
- Approximately 20% of patients with coeliac disease are older than 60 years
- Slightly higher incidence in females than in males
- Most prevalent in Western Europe and the United States with the incidence increasing in Africa and Asia

Coeliac Disease

Diagnostic summary

• A chronic intestinal malabsorption disorder caused by an intolerance to gluten
• Abnormal small intestine structure that reverts to normal on removal of dietary gluten
• Bulky, pale, frothy, foul-smelling, greasy stools with increased faecal fat
• Weight loss and signs of multiple vitamin and mineral deficiencies
• Increased levels of serum gliadin antibodies
• Diagnosis confirmed by jejunal biopsy

Coeliac Disease

Gluten – protein

The major components in the family of Gramineae that trigger Coeliac

- Wheat – gliadins (polypeptide derivative of gluten)
- Rye – secalins + prolamines
- Barley – hordeins + prolamines
- Oats – avenins + prolamines
- Triticale – a hybridised strain (cross-breed) of these cereals

Remove all:

- Wheat - durum, semolina, spelt, kamut, einkorn, and farro
- Rye, barley, triticale, or oats
- Buckwheat and millet are often excluded as well
  - Although buckwheat is not in the grass family and millet appears to be more closely related to rice and corn, buckwheat and millet contain prolamins with similar antigenic activity to the alpha gliadin of wheat

Coeliac Disease
Coeliac Disease

Hidden sources

- Sausages (fillers), soy sauce, hydrolysed plant/vegetable modified food starch, vinegars, ‘natural flavourings’, seasonings, gravies, sauces, ice cream, soup, beer, wine, vodka, whisky, malt

Non-gluten grains

- Rice, corn, quinoa, amaranth, millet

Coeliac Disease

Pathogenesis

• Abnormal immune response to gliadin
  • Leading to both humoral and cell-mediated immunity

• Anti-endomysial antibody (AEA)
  • Used to screen and provide positive diagnosis

• Tissue transglutaminase (tTG)
  • Autoantigen for AEA release in response to tissue wounding

Coeliac Disease

Pathogenesis

• Breastfeeding appears to have a prophylactic effect
  • Decreased risk of development
  • Breastfeeding, and resultant delay in introduction of cow’s milk and cereal grains is considered primary preventative steps
  • Even more pronounced if breastfed after dietary gluten was introduced

Coeliac Disease

Symptoms

- Chronic diarrhoea
- Steatorrhoea
- Abdominal bloating or cramps
- Flatulence
- Weight loss
- Fatigue
- Anaemia
- Bleeding diathesis
- Osteopenia
- Seizure disorders
- Stunted growth

Coeliac Disease

Nutritional Therapy

• Eliminate all sources of gliadin
• Eliminate dairy products initially
• Correct underlying nutritional deficiencies
• Treat any associated conditions
• Determine and eliminate all food allergens

• If the patient does not begin to respond within one month, reconsider the diagnosis and search for hidden sources of gliadin

Coeliac Disease

Oats

• Some research suggests that oats in themselves are gluten-free, but that they are virtually always contaminated by other grains during distribution or processing.

• However, recent research indicated that a protein naturally found in oats (avenin) possessed peptide sequences closely resembling wheat gluten and caused mucosal inflammation in significant numbers of coeliac disease sufferers.

• Some examination results show that oats are very dangerous to certain coeliacs, while not very harmful to others.

• Given such conflicting results, excluding oats is the only risk free choice for coeliac disease sufferers.
Chronic Candidiasis

• Candida is a genus of usually benign yeast-like detrimental fungi including Candida albicans, Candida glabrata, Candida krusei, Candida parapsilosis, Candida tropicalis... over 200 species identified thus far

• Candida is normally found in the GIT and vagina
  • In the healthy individual, beneficial bacteria keep detrimental fungi to controllable levels

• The overgrowth of *C. albicans* is believed to cause a wide variety of symptoms in virtually every system of the body, with the GIT, genitourinary, endocrine, nervous, and immune systems being most susceptible

• Any condition which may weaken the immune system may increase susceptibility to Candida overgrowth

Chronic Candidiasis

**Diagnosis**

- **Stool Analysis**
  - Rather than simply culture a stool sample for the presence of *C. albicans*, the comprehensive digestive stool analysis (CDSA) is more clinically useful.
    - This battery of integrated diagnostic laboratory tests evaluates digestion, intestinal function, intestinal environment, and absorption by carefully examining the stool. It is a useful tool in determining the digestive disturbance that is likely to be the underlying factor responsible for *C. albicans* overgrowth. In addition, the CDSA may determine that the symptoms are not related to *C. albicans* overgrowth but rather to conditions such as small intestinal bacterial overgrowth and the leaky gut syndrome.

- **Antibody and Antigen Levels**
  - Measures the level of antibodies to *Candida* or the level of antigens in the blood.
  - Can be used as a way of monitoring therapy.

Chronic Candidiasis

Predisposing factors to *Candida albicans* proliferation

- Decreased digestive secretions
- Dietary factors
  - sugars, milk and other dairy, mould and yeast-containing foods, food allergies
- Impaired immunity
- Nutrient deficiency
- Drugs - particularly antibiotics
- Impaired liver function
- Underlying disease states
- Altered bowel flora
- Prolonged antibiotic use

Chronic Candidiasis

Nutritional therapy protocol:

• Step 1. Identify and address predisposing factors:
  – Where possible reduce/eliminate prescription medications under the supervision of client’s GP
  – Perform a CDSA
  – Address any predisposing factors such as dietary factors, impaired immunity, impaired liver function, or an underlying disease state

• Step 2. Recommend the *C. albicans* control diet:
  – Eliminate refined and simple sugars
  – Eliminate milk and other dairy products
  – Eliminate foods with a high content of yeast or mould including alcoholic beverages, cheese, dried fruit, melons, and peanuts
  – Eliminate all known or suspected food allergies

Chronic Candidiasis

Nutritional therapy protocol:

• Step 3. Provide nutritional support:
  – A high-potency multiple vitamin and mineral formula
  – Additional antioxidants

• Step 4. Support immune function:
  – Promote a positive mental attitude
  – Help patients deal with stress by teaching positive stress-coping techniques
  – Recommend avoiding alcohol, sugar, smoking
  – Recommend plenty of rest and good sleep

Chronic Candidiasis

Nutritional therapy protocol:

• Step 5. Promote detoxification and elimination:
  – Recommend 3 to 5 g of a water-soluble fibre source such as guar gum, psyllium seed, or pectin at night
  – If necessary, recommend lipotrophic factors and Silymarin to enhance liver function

• Step 6. Recommend probiotics:
  – Dosage: 5 to 10 billion viable L. acidophilus and B. bifidum cells daily

• Step 7. Use appropriate anti-yeast therapy:
  – Ideally, use the recommended nutritional or herbal supplements, or both, to help control against yeast overgrowth and promote a healthy bacterial flora
  – If necessary, use prescription anti-yeast drugs appropriately

Chronic Candidiasis

Anti-yeast therapies

- Berberine containing herbs – *Hydrastis canadensis, Berberis vulgaris, Coptis chinensis*
- Olive leaf (*Olea europaea*) – inhibit replication of viruses
- *Pau-D’Arco* - apthoquinones including lapachol have strong fungicidal effects
- Caprylic acid – natural fatty acid antifungal - is incorporated into the membranes which then rupture killing the Candida – 1000-2000 mg with meals
- Oregano, thyme, peppermint and rosemary oils
- Garlic – allicin content 10 mg or one fresh clove
- *Saccharoymces boulardii*
- Lactoferrin and lactoglobulin – to ‘mop up’ die off (Herxheimer)
- Nystatin – considered quite safe and non-toxic (from GP)