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Nutritional Medicine and Gastrointestinal Health Issues

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Key References For This Course:

1. Integrative Medicine (textbook) David Rakel M.D. Elsevier-Saunders – 2012

2. The Encylcopedia of Natural Medicine (textbook- 3rd edition) Michal Murry ND & Joseph Pizzorno ND – Atria Paperback - 2012

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Topics Covered

1. Review of Digestion and GI Function
2. Lactose Intolerance
3. Fructose Intolerance
4. Food Allergies and Intolerances
5. Cankers
6. Gastritis
7. GERD and Barrett's esophagus
8. Peptic Ulcers
9. Gallstones- Cholelithiasis
10. Celiac Disease
11. Non-Celiac Gluten Sensitivity
12. IBS
13. Inflammatory Bowel Disease: Crohn's disease and Ulcerative Colitis
14. Diverticulosis
15. Simple Constipation (Functional Constipation)
16. Colon Cancer Prevention

1. Review of Digestion And Absorption:

This is important as advice given to patients about nutrition and supplementation demands an in-depth understanding of how the gastrointestinal tract processes and absorbs nutrients, in addition to health conditions that commonly affect GI-tract, and Nutritional Medicine interventions that can help prevent these problems, and provide complementary management to improve patient outcomes.

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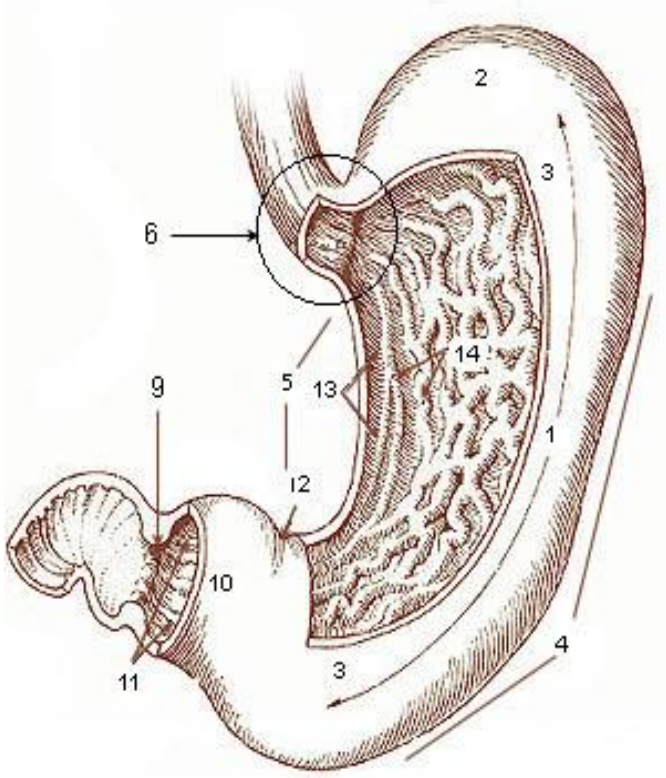
Stomach is highly elastic and holds up to 2 Quarts of food, beverages and stomach juices:

We make less stomach acid as we age, which inhibits absorption of many minerals (iron and calcium most notably), as well as decreased vitamin B12 due to decreased intrinsic factor release. Women, especially, are prone to hypochlorhydria, and those taking antacids, H2-blockers and most notably proton-pump inhibitors -



Stomach Emptying –1-4 hours depending upon:

- Volume of food
- Type of food (fat moves slower)
- Stress (stress slows down movement into intestinal tract) - 2-4 hours longer on game day for athletes for stomach emptying to occur.

- So, relaxed state is helpful to reduce bloating and improve digestion, as are small, frequent meals, and low fat food choices.

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Stomach

- **Some water, alcohol** (especially on an empty stomach), aspirin and other weak acids get absorbed directly into bloodstream from stomach (alcohol on empty stomach gets absorbed much faster)

- **Liquids** leave stomach first to enter the small intestine (duodenum)

- **Carbs** leave ahead of protein, which leave ahead of fats (CPF) – so a lower fat meal is easier to digest and causes less bloating

- **Mixed together**, the presence of fat slows down gastric emptying of carbs and protein, as they all mix and travel together in a semi-liquid state from secretions of stomach juices - mixture is 50% water (chyme) – like vomit

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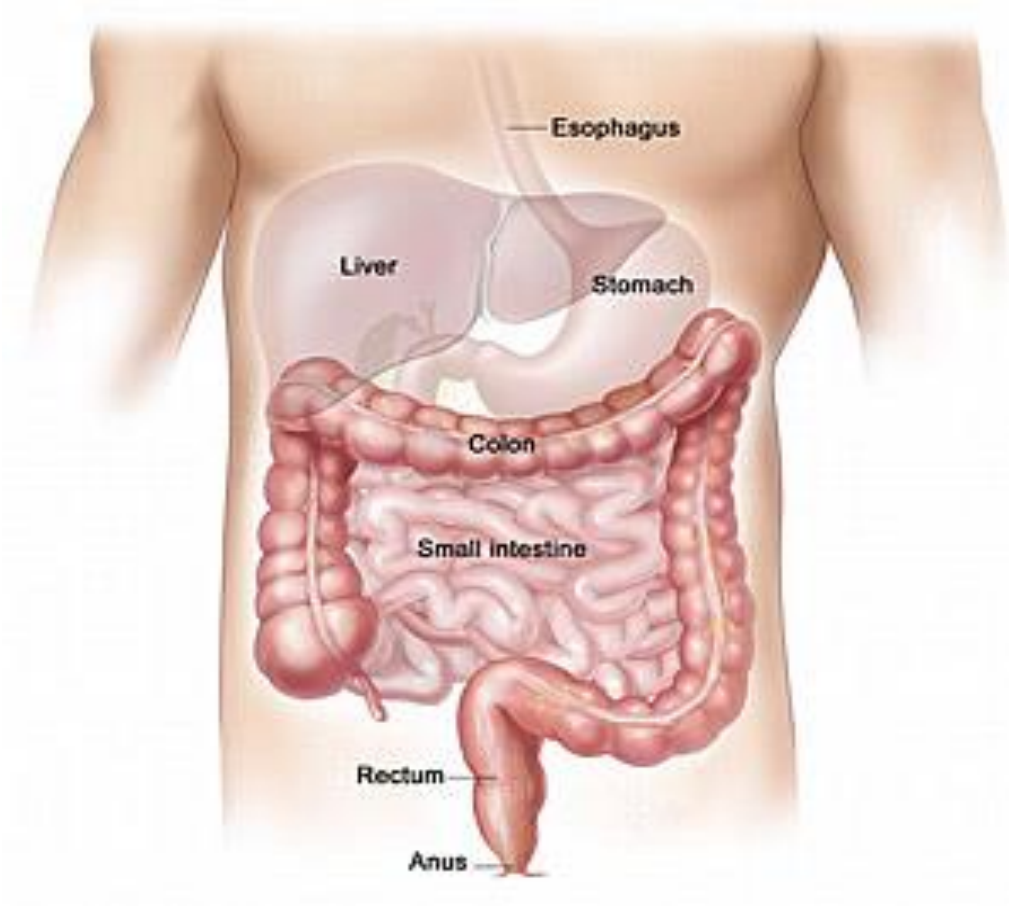
Intestinal Tract Overview



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Mean While Back In The Stomach

- Large meal takes longer for stomach to empty

- Stomach also secretes:

    1. Mucus

    2. Hcl (women secrete less Hcl to breakdown protein and thus, need more enzymes to digest protein, but actually make less)

    3. Intrinsic factor - which decreases with age (may need more vit B12)

- Decreased acid in small intestine also results in decreased absorption of certain **minerals** (iron, calcium, zinc, selenium)

- Therefore, vitamin C can help – hence a high potency multiple vitamin with your two biggest meals – 500 mg each of vitamin C (not ester C, that is a mistake)

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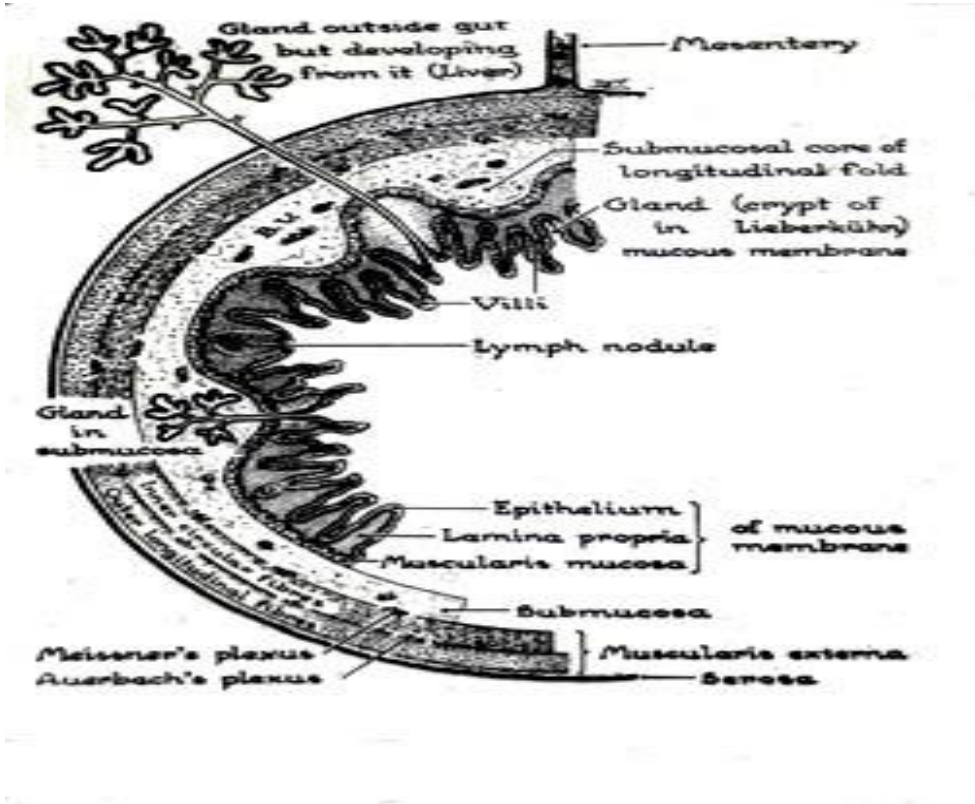
Small Intestine: Duodenum, Jejunum, Ileum

- **90%** of carbs, protein and fat absorbed in **small intestine** (if working properly).

- **Water** is also absorbed here, as is **alcohol**

- **Vitamins and Minerals** absorbed here, dependent on varying factors:
  - Fiber
  - Lactose
  - Acidity or alkalinity
  - Competing minerals
  - Presence of food
  - Fat required for fat-soluble vitamins to be absorbed
  - Intrinsic factor for vit B12
  - Vitamin D status affects calcium absorption, etc).

The small intestine – 10 feet long, but presence of microvilli enlarge (convoluted) absorptive surface area by 600 times (compared to smooth surface), creating 200 square meters of absorptive surface – ***the surface area of a tennis court***



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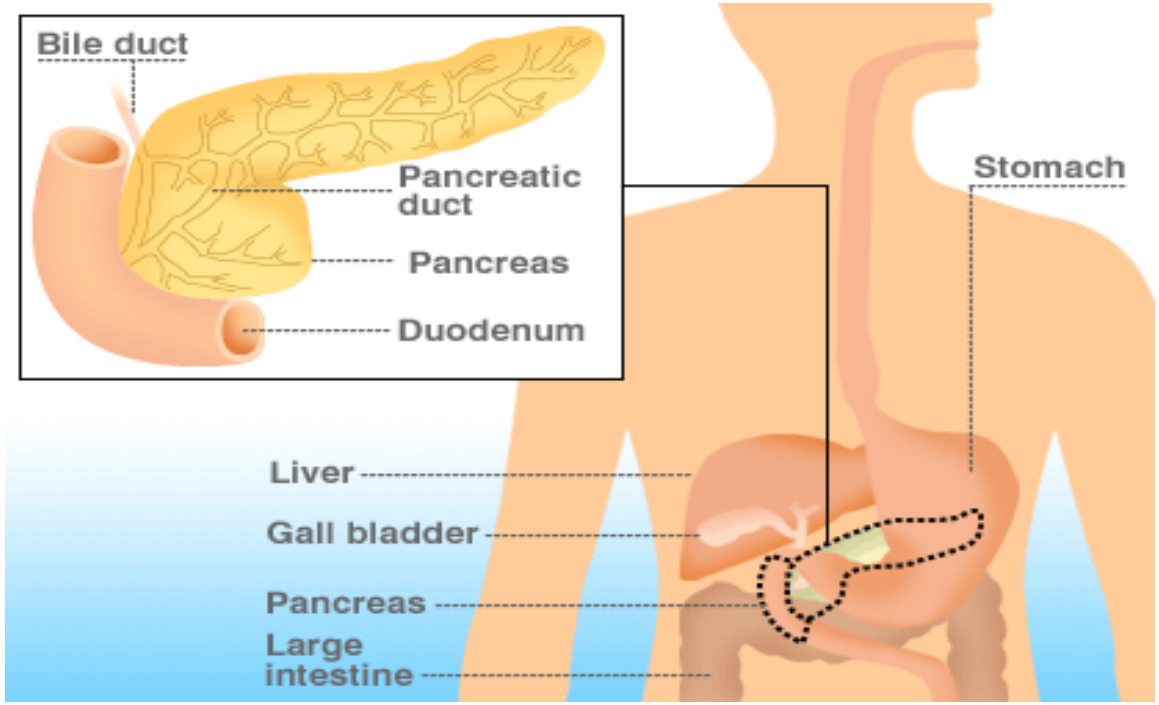
The Pancreas and the Intestinal Epithelial Cells - Secrete Digestive Enzymes, which break food down into singular molecules, allowing absorption through intestinal cells into the bloodstream or lymphatics. With aging many people secrete lower amounts of digestive enzymes, which is more common in women. This leads to more abdominal discomfort, with gas, distension, bloating etc. Digestive enzyme supplements can often help in these cases



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Intestinal Epithelial Cells

- **Intestinal Epithelium** – replaces itself every 2-3 days (highly intelligent – pregnancy increases iron absorption by 30%; safe guards against iron toxicity, calcium binding protein under direction of vitamin D and parathyroid hormone, responds to body need, helps to decrease mineral toxicities).

- **Secrete digestive enzymes** as final step in digestive process. These cells require nutrition or won't work well and have high demand (turn over rate) such that a high potency multiple vit and min makes these cell more efficient, so they can manufacture more enzymes themselves, alleviating some bloating and improving overall nutritional status.

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Complement of Digestive Enzymes

Stomach

1. Pepsin (a peptidase) breaks down proteins into smaller peptide fragments

2. Gelatinase, degrades type I and type V gelatin and type IV and V collagen, which are proteoglycans in meat.

3. Gastric amylase degrades starch, but is of minor significance.

4. Gastric lipase acts almost exclusively on tributyrin, a butter fat enzyme

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Complement of Digestive Enzymes

Pancreatic enzymes

1. Trypsin and Chymotrypsin break down peptides in the small intestine
2. Steapsin degrades triglycerides into fatty acids and glycerol
3. Carboxypeptidase splits peptide fragments into individual amino acids
4. Several elastases that degrade the protein elastin and some other proteins
5. Several nucleases that degrade nucleic acids, like DNAase and RNAase (beans, peas, seeds contain DNA and RNA)
6. Pancreatic amylase breaks down glycogen and starch (Long-branching chains of glucose)
7. Bile from the liver, which emulsifies fat, allowing more efficient use of lipases in the duodenum; in converting lipids to their component fatty acid and glycerol molecules

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Final Digestive Phase By Intestinal Epithelial Cells

Small Intestine Epithelial Cells Secrete:

1. Several peptidases – break down remaining peptides into individual amino acids

2. Carbohydrate digesting enzymes that degrade disaccharides into simple sugars:

Sucrase - breaks down sucrose into glucose and fructose
Maltase - breaks down maltose into glucose plus glucose
Isomaltase - breaks down maltose and isomaltose
Lactase - breaks down lactose into glucose and galactose

3. Intestinal lipase - breaks down triglyceride (fats)

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Functions of Large Bowel

- Holding chamber for fecal matter (spends 24 hours here or more) and contains bile and food remnants, fiber
- Contains microflora, which metabolize certain nutrients and produce certain vitamins
- Some soluble fiber metabolized to SCF and other products, which decrease colon cancer risk (slow replication rate of colon cells) – healthy microflora critical
- SCF absorbed here and have effects of breast cancer prevention
- Some bacteria make vitamin K and biotin

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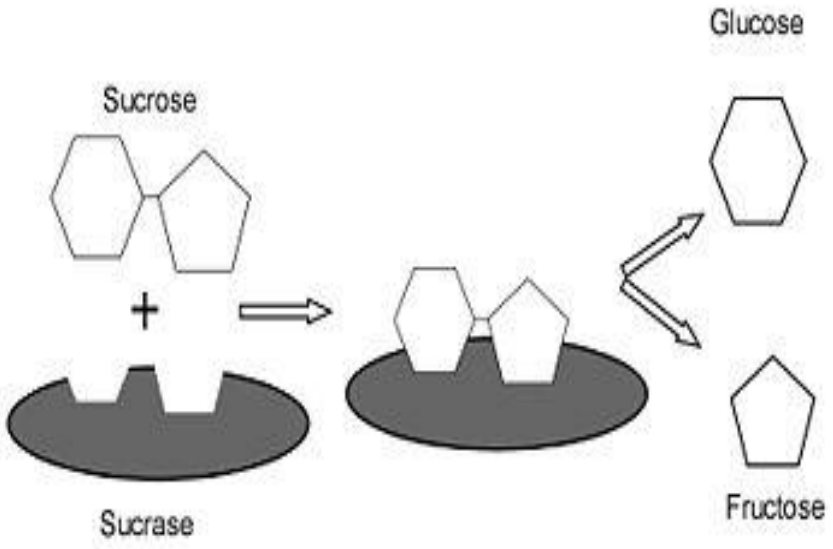
Functions Of Large Bowel Contd

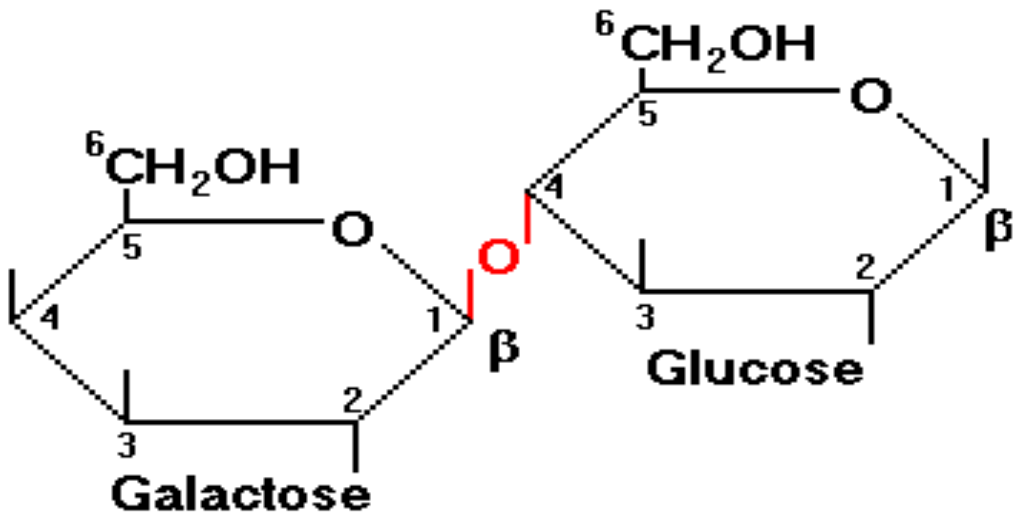
- Some nutrients absorbed here after bacterial transformation (isoflavones, phytonutrients, enterolactone, enterodiol etc), but healthy microflora is critical function

- Water is absorbed here as well, as well as sodium and chloride. If it fails to do this then diarrhea results

- *Thus, microflora of large bowel is critical to overall health and prevention of colon cancer/breast cancer*

Disaccharides: Sucrose and Lactose





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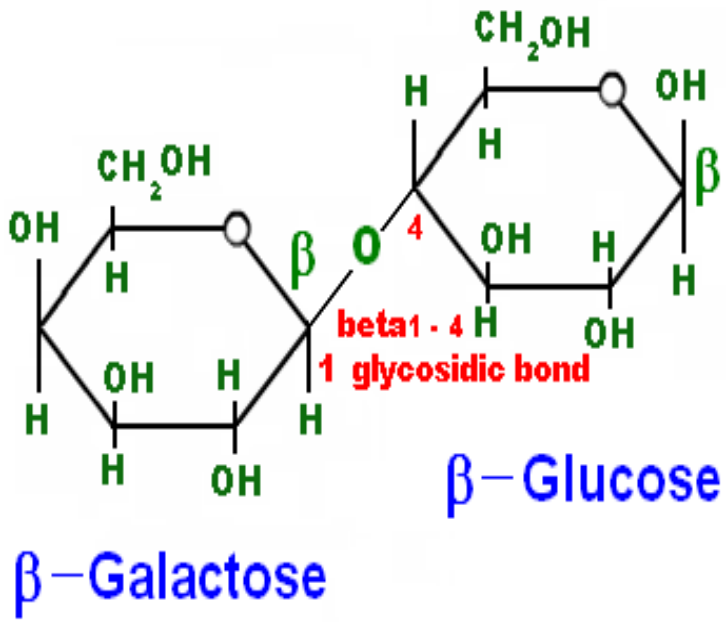
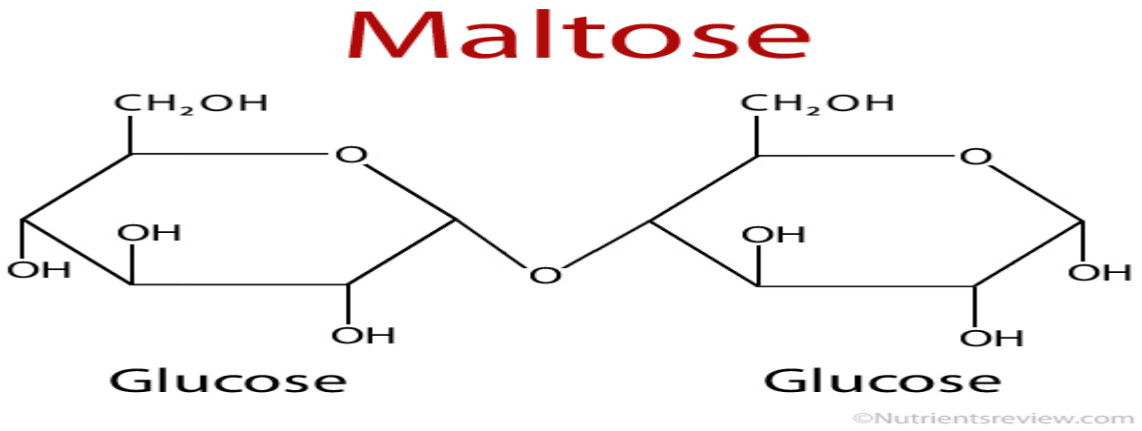
Disaccharides: Lactose and Maltose





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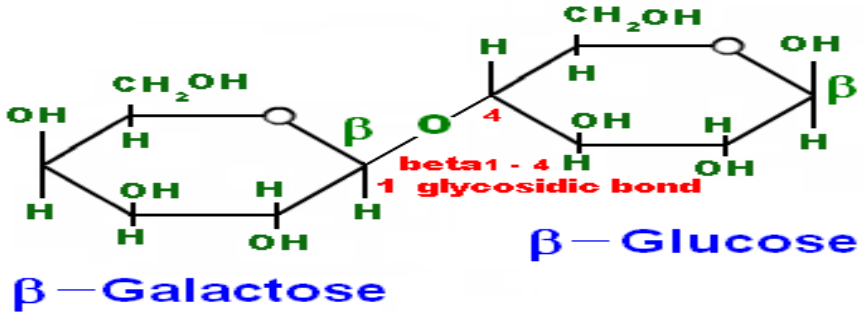
2. Lactose Intolerance:

Lactase normally synthesized by intestinal epithelial cells

- Deficiency in lactase enzyme that breaks up lactose into two simple sugars: galactose and glucose.

- It is estimated that 70% of adult humans develop some degree of lactose intolerance as they age



- Without lactase, lactose remains in the intestines. Enteral bacteria adapt to the relative abundance of this undigested sugar and quickly switch over to lactose metabolism, which produces copious amounts of gas via fermentation.

- This also causes abdominal symptoms, including stomach cramps, bloating, flatulence and diarrhea.

- The lactose raises the osmotic pressure of the colon contents, preventing the colon from reabsorbing water, thereby adding a laxative effect to the excessive gas production as well as watery stools

Nutritional Medicine Management:

1. Avoid lactose-containing products. Lactose is found in milk, yogurt, cream, butter, ice cream and cheese. But it's also in some breads and baked goods, pancake mixes, ready-to-eat breakfast cereals, instant soups, candy, cookies, salad dressings, deli meats, drink mixes and margarine.
2. If mild intolerance, can usually handle Greek yogurt – has less lactose than regular yogurt and other dairy products
3. Lactase enzymes also helpful in cases of mild intolerance, allowing more dairy-based foods to be consumed
4. Lactose-free milk and many other lactose-free products are available

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3. Fructose Intolerance

Fructose Intolerance: a digestive disorder of the small intestine in which the fructose carrier in enterocytes is deficient. As a result concentrations of fructose in the intestine are increased. Fructose malabsorption is found in approximately 30-40% of the population of Central Europe, with about half of the affected individuals exhibiting symptoms.

Typical symptoms:

1. Bloating (because of fermentation in the small and large intestine)
2. Diarrhea and / or constipation
3. Flatulence
4. Stomach pain (due to muscle spasms)

- Medical Testing Available (Fructose Intolerance Testing)

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4. Food Allergy and Food Intolerances

Food Allergy

A True Food Allergy is an adverse **immune response** to a food **Protein**

These allergic reactions have an acute onset (from seconds to one hour) and may include:

1. Angioedema: soft tissue **swelling**, usually involving the eyelids, face, lips, and tongue. A severe swelling of the tongue as well as the larynx (voice box) and trachea, result in upper airway obstruction and difficulty breathing.
2. Hives
3. Itching of the mouth, throat, eyes, skin
4. Nausea, vomiting, diarrhea, stomach cramps, and/or abdominal pain. This group of symptoms is termed gastrointestinal hypersensitivity
5. Rhinorrhea, nasal congestion
6. Wheezing, scratchy throat, shortness of breath, or difficulty swallowing
7. Death from Anaphylaxis: a severe, whole-body allergic reaction that can result in death – airway become totally consticted

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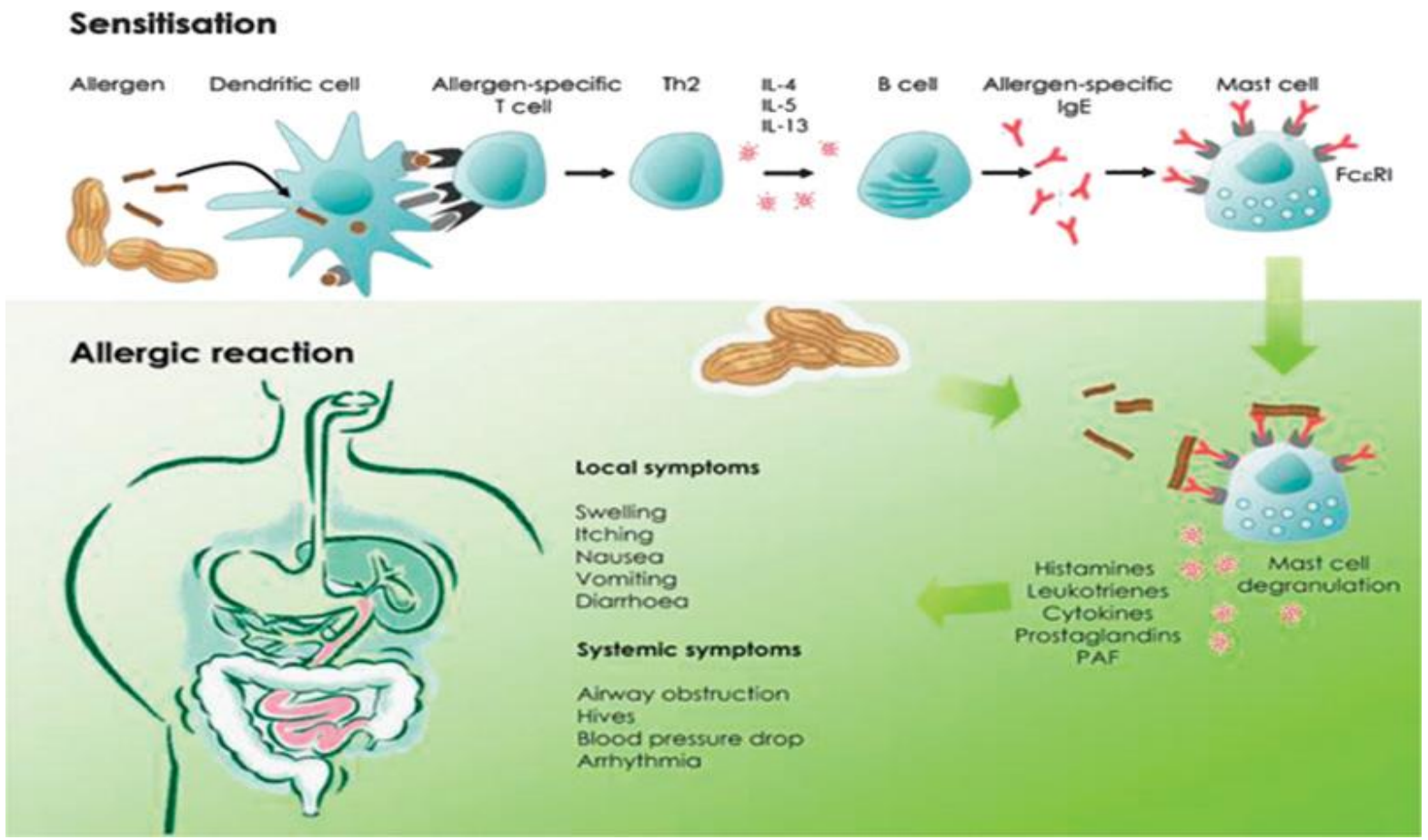
IgE-Mediated Food Allergy



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The Big Eight: 90% of food allergies in North America from:

1. Milk allergy
2. Egg allergy
3. Peanut allergy
4. Tree nut allergy
5. Seafood allergy
6. Shellfish allergy
7. Soy allergy
8. Wheat allergy

An allergist can test for these (MD specialist)

Important differential diagnoses include:

- **Lactose intolerance:** this generally develops later in life but can present in young patients in severe cases. Common in Non-Western People
- **Fructose intolerance:** 30-40 of individuals from Central Europe – have trouble absorbing fructose
- **Celiac disease**: this is an autoimmune disorder triggered by gluten proteins such as gliadin (present in wheat, rye and barley). It is a non-IgE mediated food allergy by definition. Symptoms include chronic diarrhea, weight loss or failure to thrive (in children) and fatigue.
- **Non-Celiac Gluten Sensitivity:** up to 5% of the population whose intestinal and other symptoms improve upon elimination of gluten
- **Irritable bowel syndrome (IBS**): often the diagnosis of elimination, and where stress and fibromyalgia may also be a factor
- **Intestinal Parasites**- that have damaged the intestinal lining i.e. (Giardiasis), where stool samples are required to make diagnosis

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Food Intolerance

- **Food Intolerance:** is a reaction to a food that may or may not be related to the immune system – not really a food allergy. It can be caused by deficiency of specific digestive enzymes, or to the body's responses to certain food constituents (chemicals) both natural or artificial.

- **Symptoms:** any combination of gas-bloating, intermittent diarrhea, constipation, irritable bowel syndrome, skin rashes, migraine headaches, unproductive cough.

- **Diagnosis:** elimination diet and challenge testing (RD, RNC, ND, ROHP, RNCP).

- **Treatment:** can involve avoidance, and re-establishing a level of tolerance **(Digestive Enzymes and Prebiotics are often very helpful in food intolerance problems)**

- *Therefore, if you test negative for food allergy, lactose intolerance and celiac disease, you may still have a food intolerance*

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FOOD ALLERGY FACTS

- Food allergy is not common but can be serious.
- Food allergy differs from food intolerance, which is far more common.
- The more frequent types of food allergies in adults differ from those in children.
- Children can outgrow their food allergies, but adults usually do not.
- The diagnosis of food allergy is made with a detailed history, the patient's diet diary, or an elimination diet.
- Food allergy is treated primarily by dietary avoidance.

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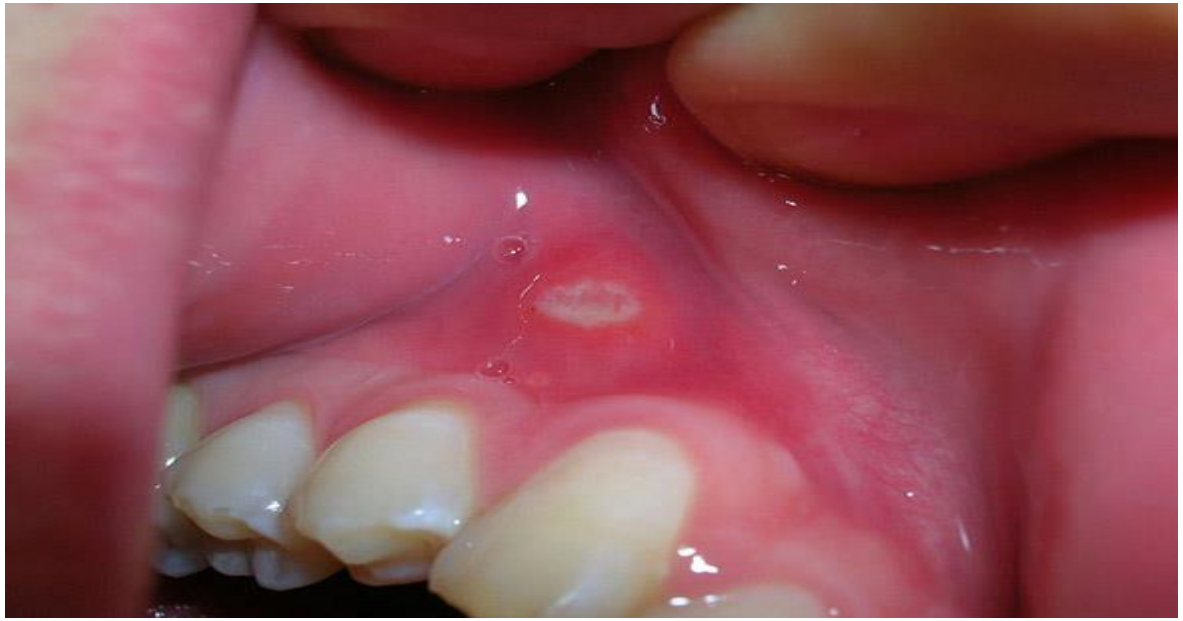
4. Cankers (Canker Sores)
Recurrent Apthous Stomatitis (RAS)

Canker sores are small, painful ulcers on the inside of the mouth, tongue, lips, or throat – affecting 20% of population

A canker sore looks like an ulcer, usually with a depression in the center. The middle of the canker sore may appear white, gray, or yellow, and the edges are red



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Causes of Cankers:

Multiple factors may cause canker sores, including injury to the mouth, acidic or spicy foods, vitamin deficiencies, hormones, stress, lack of sleep, or autoimmune disorders. The common link appears to be an immune factor susceptibility.

Certain Food Allergies: Milk and Gluten- also implicated as causes of cankers, with associated IgE antibodies and higher levels of white blood cells (mast cells and basophils)

Low Levels of Various B-Vitamins and Iron- linked to increases incidence of RAS. (B1, B2, B6, B12 and iron)

Canker sores are not the same thing as fever blisters (cold sores), which are caused by a herpes virus(Herpes simplex I). This is not the case with canker sores.

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Canker Sore Treatments:

1. **Salt:** Mix one teaspoon of salt in one cup of lukewarm water and stir it well.

Use the solution to rinse your mouth. Swish the solution around for at least 30 seconds and then spit it out. ...

After completing your rinse, put a pinch of salt directly on the canker sore. ...

Repeat the process four or five times a day.

2. **DGL Mouth Rinse:** Deglycyrrhizinated licorice (DGL) – 200 mg powdered DGL dissolved in 200 ml of warm water, four times per day – shown to speed healing in clinical trial

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Canker Sore Prevention and Supportive Treatment:

1. Eliminate or Reduce Offending Foods (citrus fruits, spices, gluten, dairy etc.)

2. Immune System Modulation – Medicinal Mushrooms, Astragalus and L-Glutamine – 2gm per day

3. Sublingual Vitamin B12 – 1,000 mcg, 1x week for prevention (and 5,000 mcg every other day during early signs of canker sore onset, until resolved)

4. High Potency Multiple Vitamin (B-50 complex, 15 mg zinc, etc.)

5. Probiotics

Primary Reference: Reference No. 2

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6. Gastritis

Gastritis is inflammation of the lining of the stomach. It may occur as a short episode or may be of a long duration. There may be no symptoms but, when symptoms are present, the most common is upper abdominal pain. Other possible symptoms include nausea and vomiting, bloating, loss of appetite and heartburn.

Incidence: Gastritis is believed to affect about half of people worldwide. As people get older the disease becomes more common. Gastritis, along with a similar condition in the first part of the intestines known as duodenitis, resulted in 50,000 deaths in 2015.

Complications: may include bleeding, stomach ulcers, and stomach tumors. When due to autoimmune problems, low red blood cells due to not enough vitamin B12 may occur, as in Pernicious Anemia.

Most Common Causes: include infection with *Helicobacter pylori* and use of nonsteroidal anti-inflammatory drugs (NSAIDs).

Other causes: include alcohol, smoking, cocaine, severe illness, autoimmune problems, radiation therapy and Crohn's disease.

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Assessment: Endoscopy, Upper GI imaging, blood tests, and stool tests may help with diagnosis.

Note: The symptoms of gastritis may be a presentation of a **myocardial infarction**. Other conditions with similar symptoms include inflammation of the **pancreas, gallbladder problems, and peptic ulcer disease.**

Prevention: by avoiding things that cause the disease. Reducing NSAIDs use by substituting natural anti-inflammatory agents is a major consideration

Medical Treatment:

- Includes medications such as antacids, H2 blockers, or proton pump inhibitors.
- During an acute attack drinking viscous lidocaine may help.
- If gastritis is due to NSAIDs these may be stopped.
- If *H. pylori* is present it may be treated with a combination of antibiotics such as amoxicillin and clarithromycin.
- For those with pernicious anemia, vitamin B12 supplements are recommended either by mouth or by injection.
- People are usually advised to avoid foods that bother them.

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Natural Remedies:

1. Most critical is to avoid offending agents (smoking, alcohol, NSAIDs, stress, food irritants etc.), and to support intestinal epithelial cells with high potency multiple vitamin and correct any underlying nutrient deficiencies (B12, Vitamin C, Iron, Vitamin D, Calcium)

2. **DGL Tablets:** Licorice is a demulcent or muco-protective agent (forms a soothing film over a mucous membrane, relieving pain and inflammation of the membrane) used to treat gastritis and peptic ulcers (stomach and duodenum)

Dosage: 2-4, 380 mg DGL tablets, chewed up and mixed with saliva, ingested 30 minutes before a meal.

3. **Slippery Elm Root Bark Powder** (also a demulcent used for irritated esophagus or gastric mucosa)

Dosage**:** 1-2 tablespoons of powder, mixed with a glass of water before meals and/or at bedtime. Can be sweetened with honey or other substance to make it more palatable.

Note - demulcents can interfere with absorption of some drugs and thus, drugs should be taken at least 2-3 hours before or after demulcent use if possible.

4. Oil of Oregano – may help to kill H. pylori bacteria (always take a probiotic when using oregano supplements

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5. Reference No 1

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7. GERD and Barrett's Esophagus
Gastroesophageal Reflux Disease

GERD: digestive disorder affecting the lower esophageal sphincter (LES), the ring of muscle between the esophagus and stomach. However, malalignment of the gastroesophageal junction can also cause GERD, but there is usually some level of abnormal tone in the LES.

Causes of Decreased LES Tone:

A. Medications:

- Aminophylline -bronchodilator
- Anticholinergics calm the parasympathetic NS – motion sickness, peptic ulcers, diarrhea, ulcerative colitis, diverticulitis, vomiting, respiratory disorders like asthma, chronic bronchitis, and calming involuntary movements.
- Beta-adrenergic agents
- Calcium-channel blockers
- Nitrates
- Phosphodiesterase inhibitors, including sildenafil
- Smoking

B. Supplements:

- L-Arginine – via increased nitric oxide production
- Peppermint.
- High dose Essential Oils

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D. Foods and Beverages:

- Alcohol
- Chocolate – methylxanthines
- Coffee (caffeinated more than decaffeinated)
- Cow's Milk
- Fat
- Orange Juice
- Spicy foods
- Tea
- Tomato Juice

E. Other:

- Esophagitis
- Surgical Damage
- Scleroderma-like diseases
- Pyloric Obstruction
- Increased intra-abdominal and gastric pressure: Obesity, Pregnancy, Ascites, even Tight Clothing
- Gastric Contents near GE junction: Recumbent position, bending over or hiatus hernia
- Any condition decreasing production of saliva (i.e. some medications, TCH) – as saliva helps neutralize acid.
- Stress (tends to exacerbate this condition)
- In Children – primary cause is esophageal disease (regurgitation, choking, irritation-pain, gagging etc. with or after meals), often caused by allergy to cow's milk – symptoms improve when cow's milk avoided.

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GERD: Signs and Symptoms:

- Retrosternal burning
- Acid regurgitation
- Nausea
- Vomiting
- Chest Pain
- Laryngitis
- Cough
- Dysphagia difficulty swallowing

Assessment:

- Endoscopy
- Imaging
- Ambulatory pH Assessment

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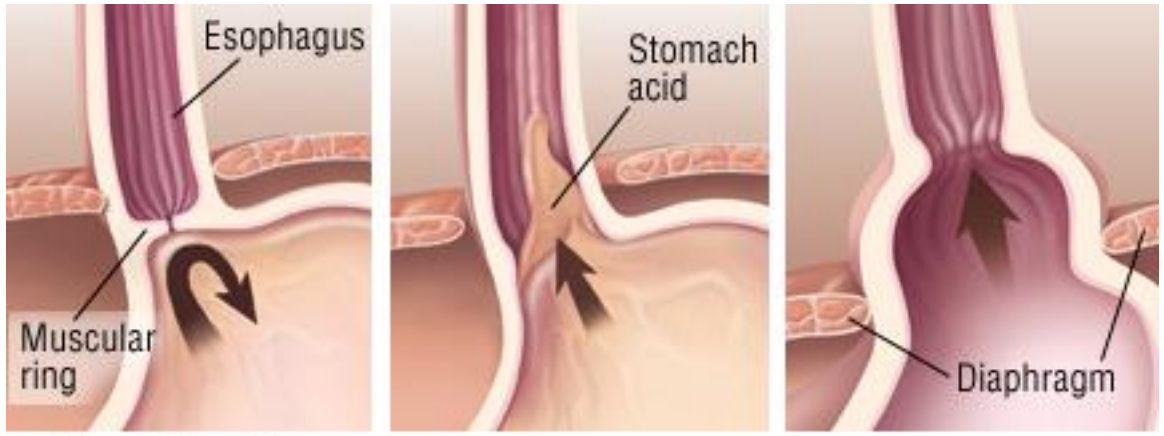
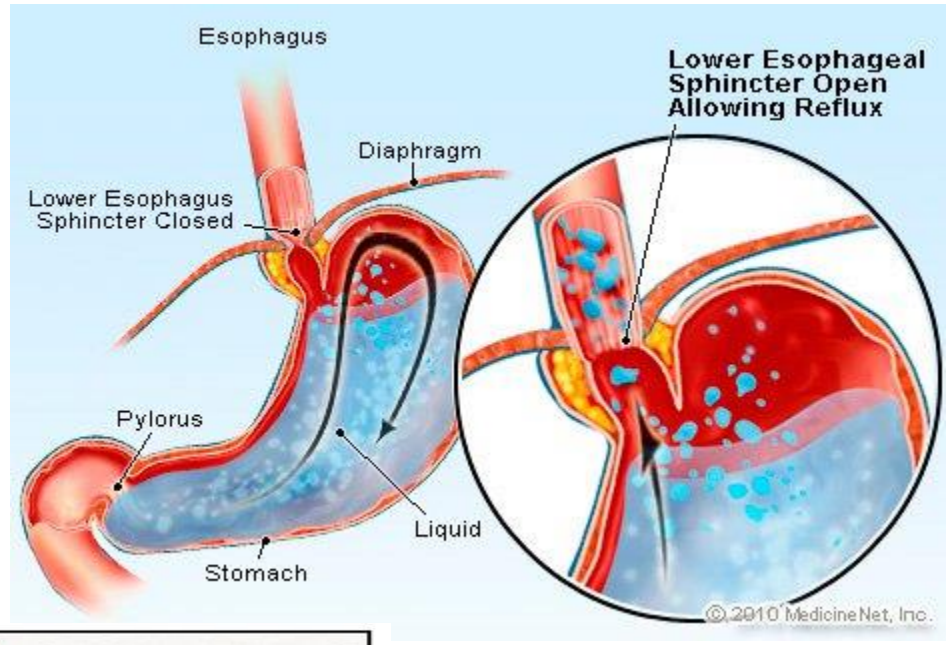
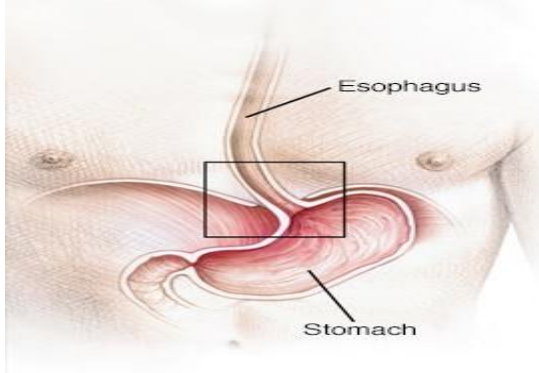
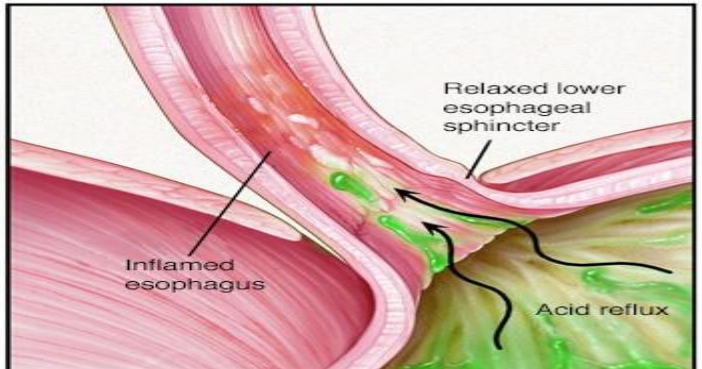
GERD Images









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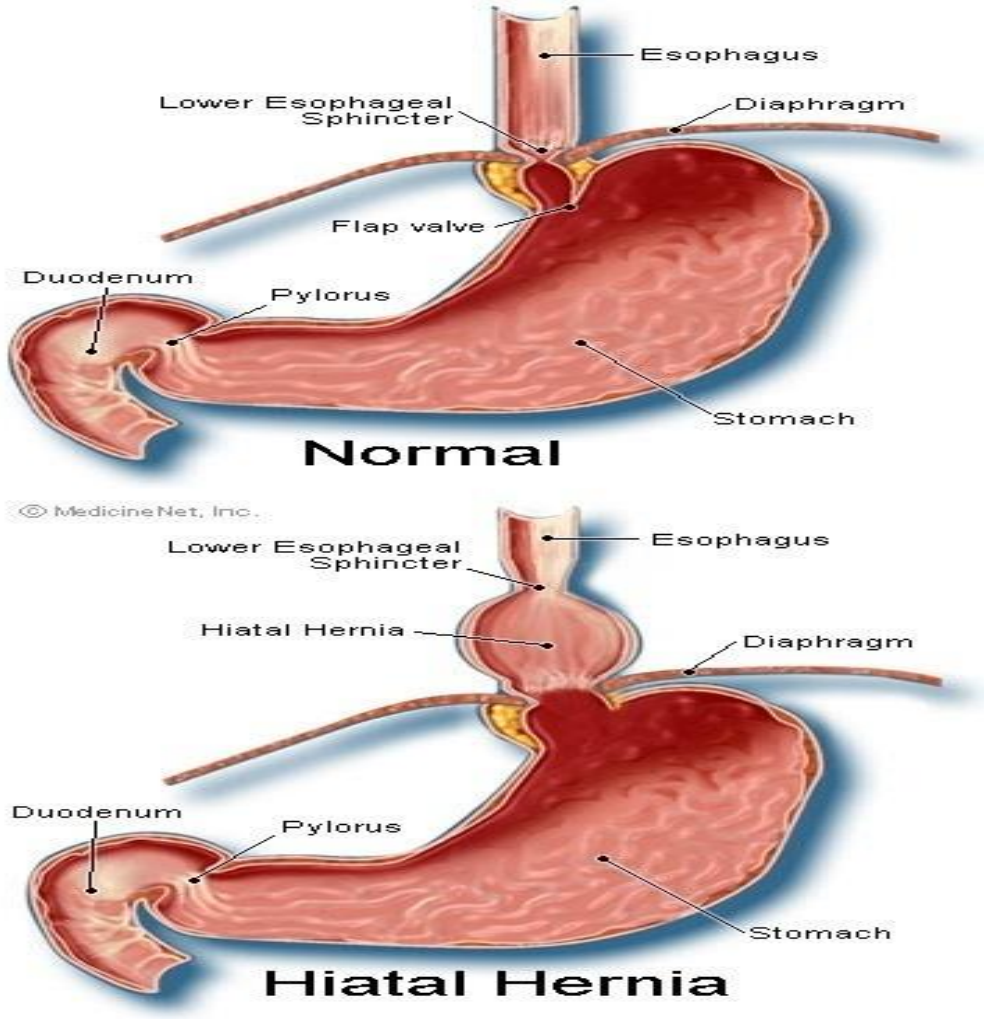
Hiatus Hernia – From Weight Gain or Pregnancy: GERD Can Develop



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Medical Treatment: Proton Pump Inhibitor

Lifestyle Management:

1. Weight Loss
2. Smoking Cessation (alcohol also strongly linked to esophageal cancer – squamous cell cancer vs adenocarcinoma - Barrett's Esophagus)
3. Avoid Offending Foods and Supplements (and medications, if possible)
4. Avoid Eating Large Meals or Consuming Large Amounts of Fluids with Meals
5. Elevate Head by 6-8 inches at Night if Night-time Symptoms Prevalent, by raising bed posts (not by using pillows, which compress abdomen and increase intra-abdominal pressure – thereby exacerbating symptoms)

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Natural Remedies:

1. **DGL Tablets:** Licorice is a demulcent or muco-protective agent (forms a soothing film over a mucous membrane, relieving pain and inflammation of the membrane) used to treat gastritis and peptic ulcers (stomach and duodenum)

Dosage: 2-4, 380 mg DGL tablets, chewed up and mixed with saliva, ingested 30 minutes before a meal.

2. **Slippery Elm Root Bark Powder** (also a demulcent used for irritated esophagus or gastric mucosa)

Dosage**:** 1-2 tablespoons of powder, mixed with a glass of water before meals and/or at bedtime. Can be sweetened with honey or other substance to make it more palatable.

Note - demulcents can interfere with absorption of some drugs and thus, drugs should be taken at least 2-3 hours before or after demulcent use if possible.

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Incidence of GERD:

15-20% of US Population suffers from GERD with 7% having daily symptoms. Incidence increasing due to obesity epidemic

Complications:

Esophageal cancer. In very serious cases, untreated GERD (and subsequent **Barrett's esophagus**) can lead to cancer of the esophagus – adenocarcinoma

Esophageal cancer is 7th most common cancer site for men and 14th among women, but 4th most common cause of cancer death in men and 6th in women. Squamous cell carcinoma (linked to smoking and drinking) are key risk factors in Western world. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4113043 Journal Gut and Liver 2014)

As such, Endoscopy is very important when patients have signs and symptoms of GERD to assess histology of esophageal lining.

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Barrett's esophagus: involves metaplasia in the cells of lower esophagus. It is characterized by replacement of normal stratified squamous epithelium lining by simple columnar epithelium with goblet cells (which are usually found lower in the gastrointestinal tract).

Barrett's esophagus is considered a premalignant condition, which can lead to very lethal adenocarcinoma quite often.

The main cause of Barrett's esophagus is thought to be an adaptation to chronic acid exposure from reflux esophagitis.

The condition is found in 5–15% of patients who seek medical care for heartburn (gastroesophageal reflux disease), although a large subgroup of patients with Barrett's esophagus do not have symptoms

The incidence in the United States among Caucasian men is eight times the rate among Caucasian women and five times greater than African American men. Overall, the male to female ratio of Barrett's esophagus is 10:1.

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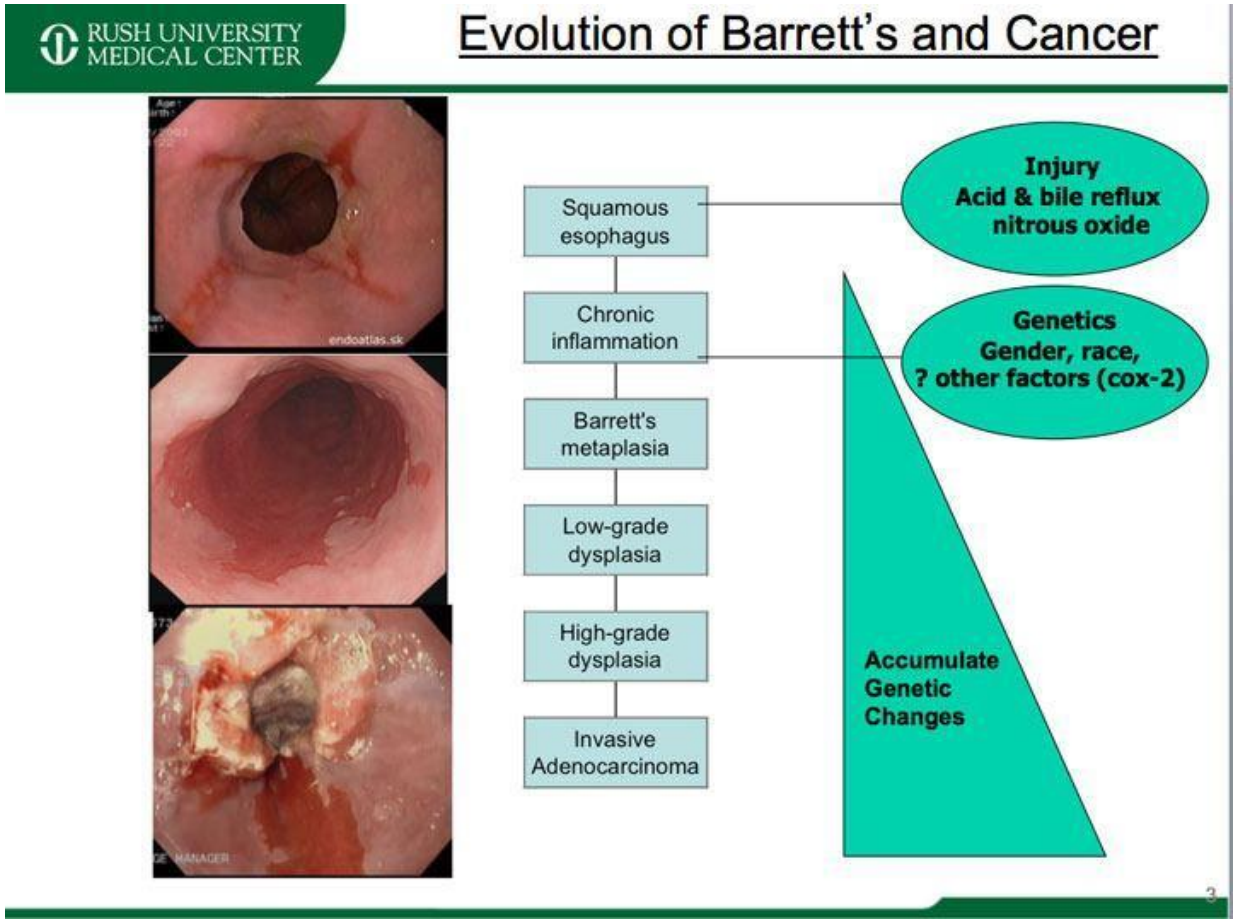
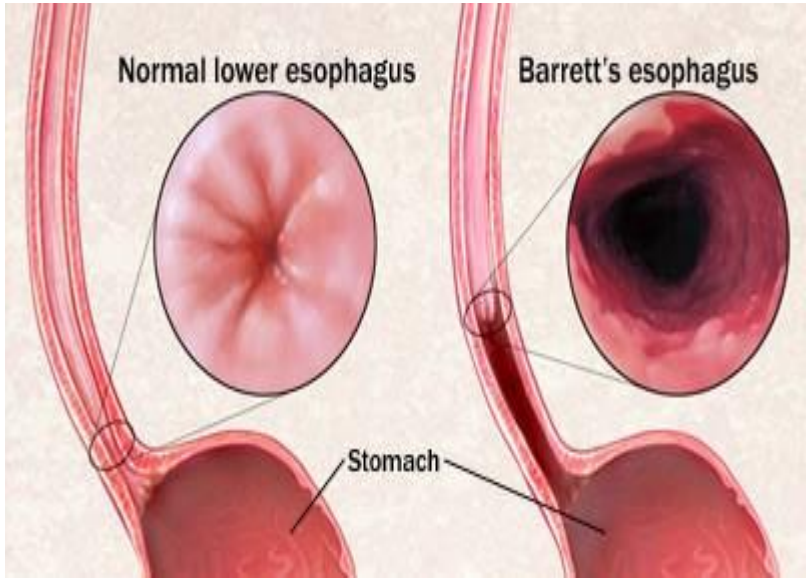
Barrett's esophagus: Prevalence: about 1.5% (lifetime occurrence)





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Barrett's esophagus Risk factors:

- **Chronic heartburn and acid reflux.** Having GERD that doesn't get better when taking medications known as proton pump inhibitors or having GERD that requires regular medication can increase the risk of Barrett's esophagus.

- **Age -** Can occur at any age but is more common in older adults.

- **Being a man -** Men are far more likely to develop Barrett's esophagus.

- **Being white -** White people have a greater risk of the disease than do people of other races.

- **Being overweight -** Body fat around abdomen further increases risk.

- **Current or past smoking.**

- **Family History –** although no genetic markers have been identified yet (7% correlation with BE in family member)

- **Low intake of Vegetables and high intake of Red Meat** have also been correlated with increased risk of BE. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4113043 Journal Gut and Liver 2014)

These patients, and patients with a family history, should avoid smoking and alcohol

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References: GERD and Barrett's Esophagus

1. Reference No 1

2. Mayo Clinic: https://www.mayoclinic.org/diseases-conditions/gerd/symptoms-causes/syc-20361940

3. https://www.ncbi.nlm.nih.gov/pubmed/16211720

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8. Peptic Ulcer

Pathology: Occurs with loss of protective mucosal barrier – in stomach or duodenum, with equal distribution btw men and women.

Men – more duodenal ulcers

Women – more gastric ulcers

Signs and Symptoms:

- Epigastric pain – especially a few hrs after meals (gnawing, burning, cramp-like, aching or as heartburn-type pain. Eating and taking antacids provides great relief
- Bloating
- Nausea
- Early satiety
- Altered bowel habits
- Heartburn
- Pain is often relieved by eating or antacids

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Incidence: 500,000 diagnosed with peptic ulcers each year in U.S.

6-12% of Adult U.S. population is lifetime occurrence

Was once twice more common in men, but now equal incidence

Etiology:

H. Pylori infection and NSAIDs medication account for most peptic ulcer problems

H. Pylori Infection – increases risk of peptic ulcers by 4x, by directly damaging the protective mucus lining – so more acid damage occurs.

H. pylori also triggers immune response causing damaging inflammation to intestinal lining.

However, only 10-20% of people with H. pylori infection develop peptic ulcers

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NSAIDs – NSAIDs use increases risk of peptic ulcers up to 5x, as well as risk of bleeding. Conservative calculations estimate that approximately 107,000 patients are hospitalized annually for nonsteroidal anti-inflammatory drug (NSAID)-related gastrointestinal (GI) complications and at least 16,500 NSAID-related deaths occur each year among arthritis patients alone. The figures of all NSAID users would be overwhelming, yet the scope of this problem is generally under-appreciated." (http://americannutritionassociation.org/newsletter/deadly-nsaids)

NSAIDs inhibit the COX1 enzyme used by intestinal epithelial cells to synthesize protective mucus barrier

Patients with peptic ulcers or history of peptic ulcers should avoid NSAIDs

But more than 80% of NSAIDs users do not develop ulcers

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Other Causes:

Radiation

Zollinger-Ellison tumors

Carcinoid syndrome

Other Drugs

Cytomegalovirus

Systemic Mastocytosis

Assessment:

Endoscopy

Barium GI Series

Check for Blood in Stool

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Medical Treatment:
2 Antibiotics Plus Proton Pump Inhibitor:

Typically: Amoxicillin + Clarithromycin + Omeprazole

Success Rate: Historically, 80-90% eradication of H. pylori infection and healing of ulcer. But H.pylori antibiotic resistance is on the rise, so success rates are dropping to 50% in some studies, thus integrative measures are important to add to treatment protocol

Complications: Bleeding and Perforation (can lead to peritonitis) – these are both serious and life-threatening

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Nutrition: Certain foods have anti-H. pylori properties:

- Carotenoids from carrots, spinach, mango, sweet potatoes, apricots
- Flavonoids from berries and grapes and green tea, onions, parsley
- Sulforaphanes from cruciferous vegetables, especially high in broccoli sprouts
- Foods containing Capsaicin (chili)
- Honey and Garlic
- Cranberry and Pure Cranberry Juice
- Drinking Fresh Cabbage Juice (1 liter per day) was shown to help heal ulcers in study performed in the 1950's.

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Avoid Milk - milk increases peptic ulcer risk, likely via increased acid production, but yogurt and other probiotic-containing foods help to protect against H. pylori infection

Avoid Alcohol – alcohol damages mucosal lining and heavy drinking especially, increases ulcer risk by up to 4x

Physical Activity – regular physical activity decreases risk of peptic ulcers and is a good adjunctive treatment and prevention of relapse

Sleep – adequate sleep is important to prevent peptic ulcers – likely via increased cortisol (stress hormone)

Stress – stress and high cortisol (causing GI erosion and ulceration) is a well established cause of peptic ulcers. Therefore, meditation, exercise, progressive relaxation etc., are key part of therapy and prevention for certain patients

Tobacco Cessation – smoking increases peptic ulcer risk by up to 4x.

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Supplements:

- **Probiotics** – increase mucus formation, compete with H. pylori for binding sites and produce anti-H. pylori compounds (especially Lactobacillus strains and Saccharomyces boulardii)

- **Vitamin C –** 500 mg, 2x daily (help kill H. pylori and linked to decreased peptic ulcer development)

- **Zinc** – 40 mg daily for 4 weeks: Clinical trial showed faster ulcer healing (3-4x faster than placebo)

- **Essential Fatty Acids** (EPA-DHA, ALA and GLA) - exhibit anti-H. pylori effects and clinical trials show eradication of H. pylori infection by 50% in 8 weeks (1 gm fish oil plus 1 gm GLA-containing oil)

- **L-Glutamine** – 400 mg, 4x per day - clinical trials show it prevents and cure peptic ulcers via repair of intestinal epithelial cells and primary fuel for these cells

- **Turmeric**– 600 mg whole Turmeric, 5x per day has anti-H. pylori effects and clinical trials have shown its ability to resolve peptic ulcers

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Chewable DGL Tablets – shown to protect the mucus barrier via prostaglandin synthesis and other mechanisms (H2 blocker).

Chewable DGL Tablets – also shown to prevent ulcer relapse

Dosage:

Active Treatment Dosage: 380 mg, three times per day (20 mins before meals) – very important that it mix with saliva before swallowing. Continue treatment for 8-16 weeks after ulcer has healed to prevent future relapse

Mastic (resin from Pistacia lentiscus) **–** when chewed this resin (mastic gum) it has resolved duodenal ulcers and reduced pain in two small placebo-controlled clinical trials (1 gm per day)

Aloe Vera Juice – may help suppress stomach acid

References:

Reference No. 1

Reference No. 2

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9. Cholelithiasis (Gallstones)

- Gallbladder Disease Incidence: 20 million people in US
- 20-70% incidence among various population – ethnicity is a factor
- Two to four times more prevalent in women than men (Female, Fat, Fertile, Forty plus Profile, as well as high estrogen, ERT or tamoxifen therapy)
- Vegetarians show very low risk of gallstone formation and gallbladder problems
- Lifestyle is Main Culprit

Bile: made in the liver bile is composed of bile acids, cholesterol and phospholipids. It is stored in the gallbladder and released upon stimulation from cholecystokinin-causing release.

Gallstones: they form with supersaturation of bile with free cholesterol, decreased bile acids that dissolve cholesterol, excess mucus production, and gallbladder dysmotility and stasis. **Cholesterol stones account for up to 85% of stone type.** Most people with gallstones remain asymptomatic, but about 20% develop biliary symptoms (pain in upper right quadrant, often radiating to back or shoulder. 1-2% develop complications requiring surgery

Bile

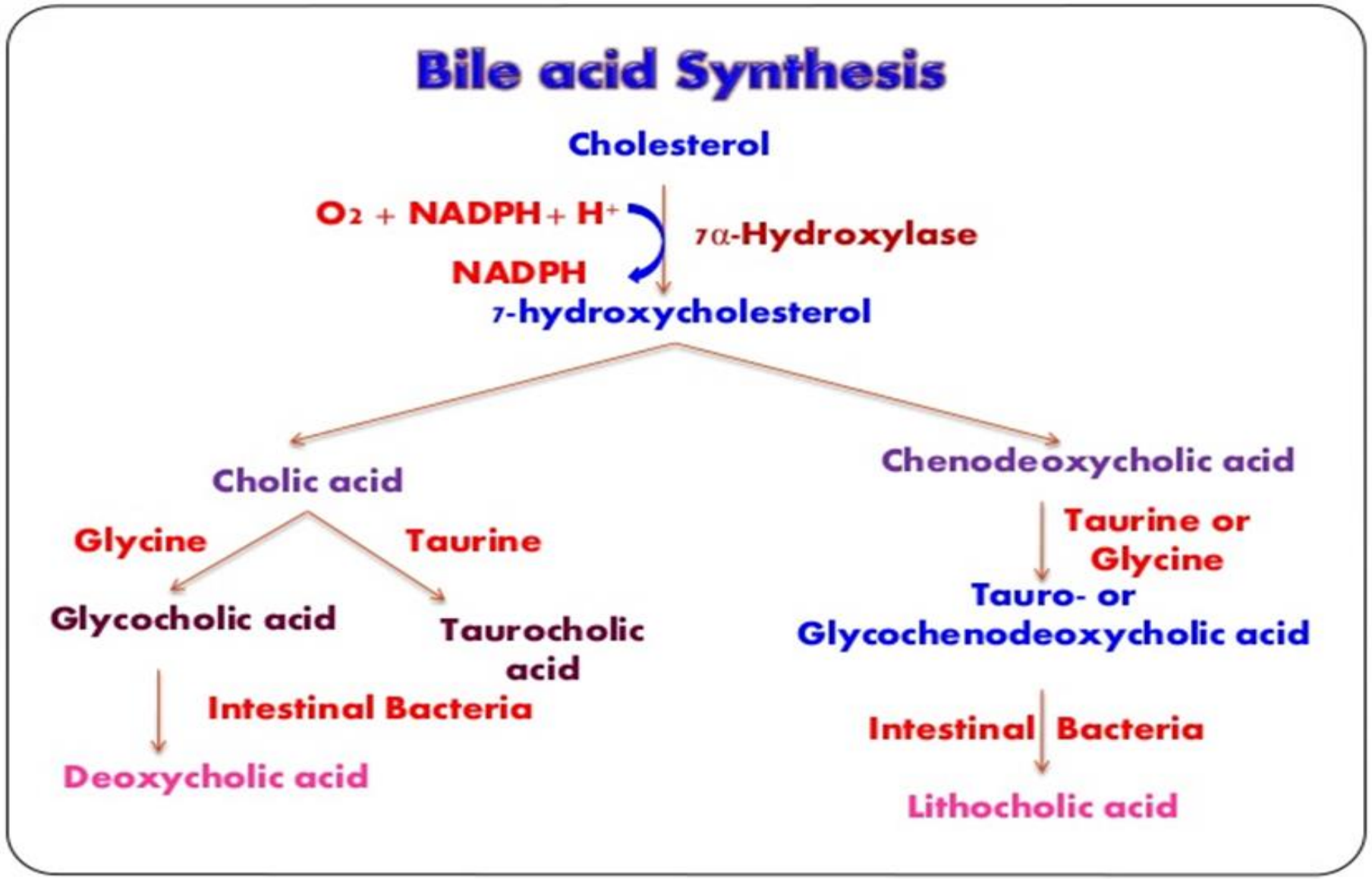
- **bile** – yellow-green fluid containing minerals, cholesterol, neutral fats, phospholipids, bile pigments, and bile acids

  - **bile acids (bile salts)** – steroids synthesized from cholesterol
    - **bile acids** and **lecithin**, a phospholipid, aid in fat digestion and absorption
  - **gallstones** may form if bile becomes too concentrated

  - **80% of bile acids are reabsorbed** in ileum & returned to liver
  - **20% of the bile acids are excreted in the feces**
    - this is the body's only way of eliminating excess cholesterol

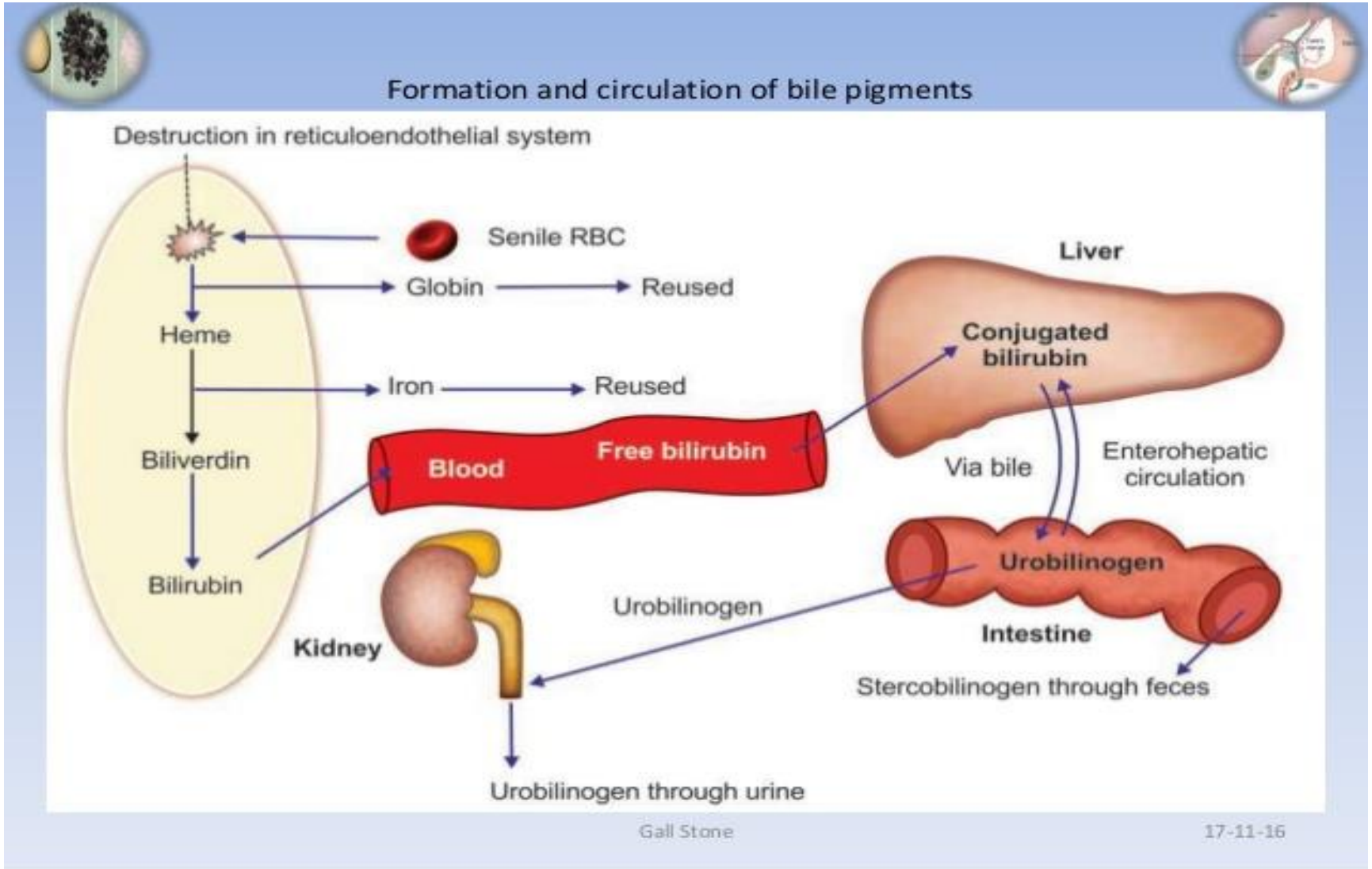
Cholelithiasis

- Bile salts & phospholipids are responsible for keeping the cholesterol in bile in a soluble state.
- Due to bile salts & phospholipids deficiency (particularly bile salts), cholesterol crystals precipitate in the gall bladder often resulting in cholelithiasis- cholesterol gall stone disease.
- Cholelithiasis may be due to defective absorption of bile salts from the intestine, impairment in liver function, obstruction of biliary tract etc.


Bile acid Synthesis
Cholesterol
O2 + NADPH + H+
NADPH
7α-Hydroxylase
7-hydroxycholesterol
Cholic acid
Chenodeoxycholic acid
Glycine
Taurine
Taurine or
Glycine
Glycocholic acid
Taurocholic acid
Tauro- or
Glycochenodeoxycholic acid
Intestinal Bacteria
Intestinal Bacteria
Deoxycholic acid
Lithocholic acid

Functions of phospholipid

- Constitutes cell membrane
- Membrane PL provides arachidonic acid to synthesize eicosanoids
- In bile, solubilize cholesterol & prevent gall stone formation
- Helps in coagulation (cephalin)
- 2nd messenger for hormones


Formation and circulation of bile pigments
Destruction in reticuloendothelial system
Senile RBC
Globin
Reused
Heme
Iron
Reused
Biliverdin
Bilirubin
Blood
Free bilirubin
Liver
Conjugated bilirubin
Via bile
Enterohepatic circulation
Urobilinogen
Intestine
Stercobilinogen through feces
Kidney
Urobilinogen
Urobilinogen through urine
Gall Stone
17-11-16

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Risk Factors for Gallstones:

1. Overweight – especially abdominal fat. Also rapid weight loss increases stone formation via cholesterol and bile salts stasis, thus safe weight loss rate is 1.5 kg (3.3 lbs) per week maximum.
2. Exercise – regular exercise is strongly associated with decreased risk of gallstones
3. High Saturated Fat Diet – increases cholesterol saturation of bile leading to stone formation (some studies show up to 40% increased risk)
4. Healthy Fats Decrease Stone Formation – monounsaturated fat and omega-3 fats shown to inhibit stone formation, by decreasing cholesterol saturation and increasing bile flow (preventing stasis)

5. Fiber Reduces Risk – Soluble fiber reduces reabsorption in gut of secondary sterol (deoxycholic acid), which increases stone formation. Thus ground flaxseed, fruits and vegetables, possibly legumes and nuts, all shown to reduce risk.

6. Excess Simple Sugars – increase cholesterol saturation of bile, increasing stone formation and reducing the ratio of beneficial cholic acid to deoxycholic acid. High correlation between glucose intolerance and gallstone formation, as **hyperinsulinemia** may cause supersaturation of cholesterol in the bile as well as gallbladder dysmotility.

7. Coffee – stimulates cholecystokinin release and improves bile flow and decreases stone formation. Some studies show up to 40% reduction in gallstones in men drinking 2-3 cups of coffee today (but no preventive effective from other caffeinated substances – like tea, soft drinks or chocolate

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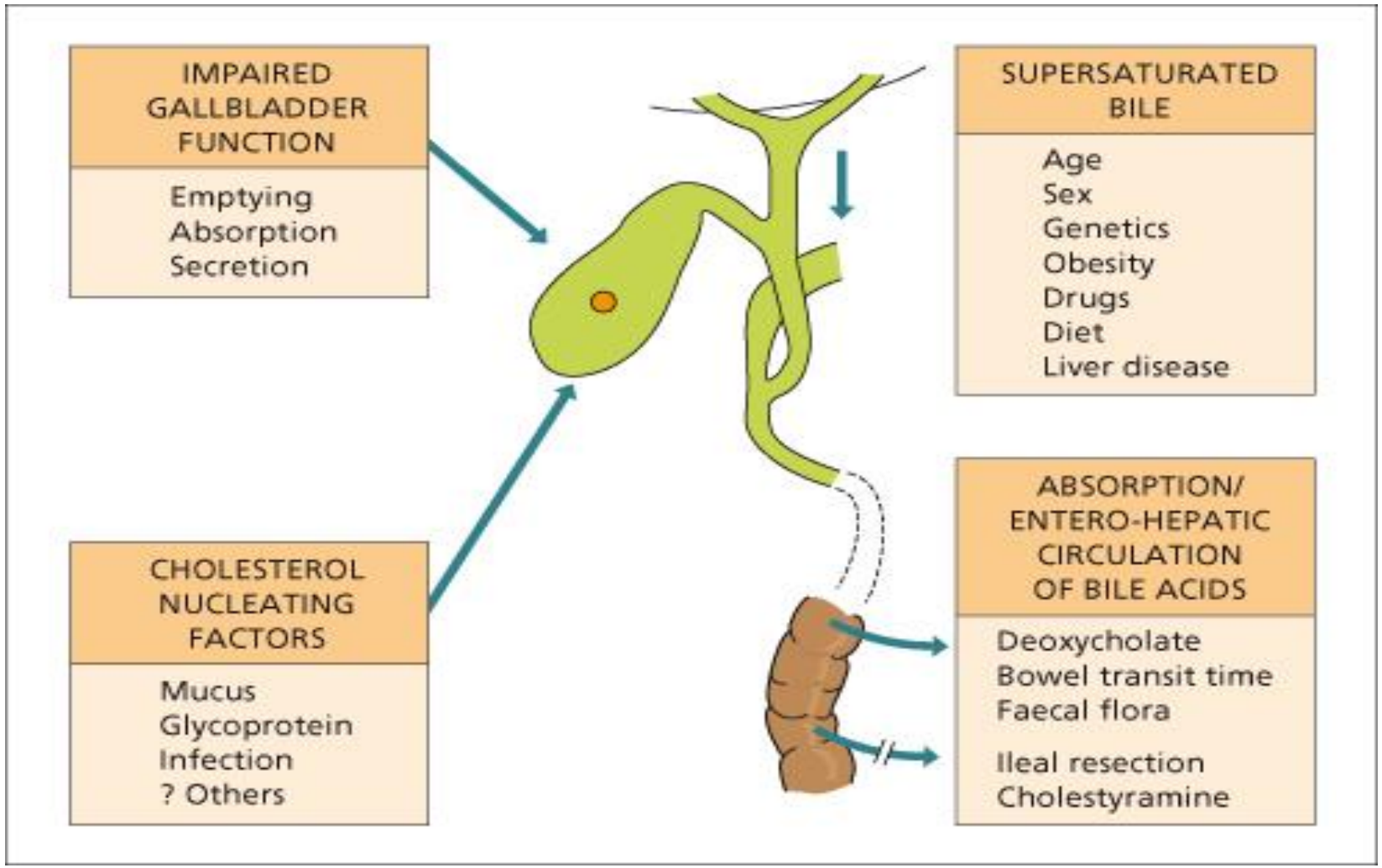
8. Water – 6-8 cups of water per day helps to ensure adequate water content of bile, helping to prevent crystal agglomeration

9. Alcohol- moderate alcohol consumption linked to decreased gallstone formation in various studies.

9. Food Allergies – a study back in 1940's showed linked between food allergies and gallstones, and when offending substance was eliminated impressive results were seen (100% response rate in patients with postcholecystectomy syndrome). Foods most commonly evoking problem included: eggs, pork, onions, fowl, milk, coffee, citrus, corn, beans and nuts. Thus, an elimination diet to test effect of eliminating one food at a time may be warranted, in addition to reducing bad fats in the diet.

10. Stress – some evidence (including animal studies) point to stress as etiological factor. Thus exercise, meditation etc.

11. Estrogen Replacement Therapy – increases gallstone formation (both oral and patch) by increasing cholesterol saturation of bile and decreasing cholesterol nucleation time in bile formation.


IMPAIRED GALLBLADDER FUNCTION
Emptying
Absorption
Secretion
SUPERSATURATED BILE
Age
Sex
Genetics
Obesity
Drugs
Diet
Liver disease
CHOLESTEROL NUCLEATING FACTORS
Mucus
Glycoprotein
Infection
? Others
ABSORPTION/ ENTERO-HEPATIC CIRCULATION OF BILE ACIDS
Deoxycholate
Bowel transit time
Faecal flora
Ileal resection
Cholestyramine

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Supplements:

1. **Vitamin C –** involved in conversion of cholesterol to bile acids. 500 mg. 4x per day has slowed cholesterol crystal formation in 2 week study

2. **Magnesium** – low magnesium intake linked to increased gallstones. Ensure 200-300 mg per day from food and/or supplements

3. **Vitamin E** – animal studies show gallstones form in vitamin E deficiency state, and when vitamin E administered along with high-fat diet the vitamin E prevented gallstone formation (consider 400 IU vitamin E per day)

4. **Lecithin** – phospholipids (lecithin) increases solubility of biliary cholesterol. Lecithin supplementation shown to increase biliary phospholipids and decrease free cholesterol. Many people fail to ingest adequate choline and lecithin, thus lecithin supplementation should be considered at 500-1,000 mg per day (often see 1200 mg capsules)

5. **Calcium –** calcium helps to prevent reabsorption of secondary sterols (deoxycholic acid), which is helpful (daily calcium intake of 1000 -1500 mg per day is usually best target)

6. **Cholerectic Herbs** – certain botanical substances improve bile flow and increase bile production and solubility. The main ones include Gum guggul, Dandelion, Milk thistle, Globe Artichoke and Curcumin (from Turmeric). Supplement companies often combine these together (along with peppermint oil) as a biliary or gallbladder and liver support formula.

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- Gum guggul – increases LDL-C clearance by liver, and increases conversion of cholesterol to bile, and up-regulates bile acid pump for improved biliary flow

- Dandelion stimulates bile flow

- Milk thistle (silymarin) – shown to repair damaged liver cells and increase detoxification ability of hepatic cells (https://www.ncbi.nlm.nih.gov/books/NBK11896/)

- Artichoke – increases conversion of cholesterol to bile in liver and increase bile flow

- Curcumin – shown to decrease cholesterol absorption and synthesis, and improve bile flow, and protect liver and bile duct against various toxic agents (http://gallbladderattack.com/blog/turmeric-benefits-and-your-gallbladder-health /)

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Natural Treatment:

Olive Oil Flush (Dangerous) – the gallbladder flush, as it is commonly known, combines high-dose olive oil with lemon juice and apple juice. This combination stimulates gallbladder contractions and many stones are often found in stool after this procedure.

However, these stones have been shown to be saponified complexes of olive oil, minerals and lemon juice. Even if it stimulates stones to be expelled there is a significant risk that a stone can get lodged in the bile duct producing serious pain and side effects. Ideally this approach is avoided until ultrasound reveals size and number of stones in gallbladder.

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Medical Treatment: usually laparoscopic cholecystectomy

Nutritional Medicine – best evidence is for prevention of gallstones via:

1. Weight Management
2. Exercise
3. Stress-reduction
4. Nutrition
5. Supplementation – vitamins and minerals, and essential fatty acids
6. Botanicals (gum guggul, dandelion, milk thistle, artichoke, curcumin)

References:
Reference No 1

Reference No 2

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10. Irritable Bowel Syndrome (IBS)

IBS is a functional disorder of the intestinal tract. It is the diagnosis of exclusion. Must first rule out other causes of abdominal pain, bloating, bowel changes (constipation, diarrhea, alternating constipation and diarrhea) including:

- Colon Cancer
- Intestinal Parasites (giardiasis, amebiasis)
- Disturbed bacterial microflora from antibiotic or antacid use
- Diverticular Disease
- Inflammatory Bowel Disease (Crohn's disease and Ulcerative Colitis)
- Intestinal Candidiasis
- Lactose or Fructose Intolerance
- Laxative Abuse
- Celiac Disease and Non-Celiac Gluten Intolerance
- Mechanical Causes (fecal impaction)
- Metabolic Disorders (Adrenal Insufficiency, Diabetes, Hyperthyroidism)
- Overconsumption of Tea, Coffee, Carbonated Beverages

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Incidence: 30-50 million Americans affected presently (2:1 Female to Males)

Prevalence: 10-18% of U.S. Population

Cost:

$10.5 billion per year on medical costs U.S.

$20.0 billion per year on indirect medical costs U.S.

$20.0 billion per year additional cost is cost of absenteeism from IBS (U.S.)

IBS patients visit physician 3x more than non IBS patients for symptoms not related to GI-tract (U.S.). IBS often occurs with chronic fatigue syndrome, fibromyalgia, rheumatic conditions.

IBS accounts for 30-50% of referrals to gastroenterology clinics in U.S.

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Rome III Criteria for Diagnosis of IBS:

Symptoms present for at least 3 days per month in past 3-months (with symptom onset at least 6 months previously) with at least two of the following:

- Pain improved with defecation
- Onset of pain associated with change in stool frequency
- Onset of pain associated with a change in stool form

70% of patients report a worsening of symptoms after meals. The opposite of peptic ulcers.

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Multi-Modal Etiological Factors:

- Visceral Hypersensitivity
- Neuroendocrine Dysfunction
- Psychosocial Factors
- Stress
- Enteric Infection
- Altered GI Flora
- Food Sensitivities or Food Allergies

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Gut Microflora and Inflammation – studies have shown that 25-30% of patients will develop IBS after enteric infection, often with great deal of mucosal inflammation involvement as part of pathology. This activates visceral perception, motility, and hypersensitivity even after initial infection has cleared. (Residual inflammation with IBS symptoms)

Probiotics have been used with some success to improve IBS, especially in cases of overgrowth of unfriendly bacteria, where 41% of patients reported improvement. Bacterial overgrowth may contribute to distension and bloating symptoms.

Dysbiosis is very common due to:

1. Antibiotic use in humans
2. Antibiotic use in animals (food, water)
3. Birth Control Pills – leading to candida
4. Lack of Fiber Intake
5. Decreased reliance on pickled or fermented foods
6. Caesarian births – decreased inoculation of child with mother's microbiome
7. Decreased breast feeding

Most people have some dysbiosis due to modern day living. As such, require support for friendly bacteria:

Prebiotics – FOS and Inulin – increase replication of friendly gut bacteria, crowding out unfriendly bacteria & yeast (Reference For This Page: Blaser MJ. Missing Microbes (HarperColins Publishers Ltd): 2014)

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Stress – has been shown to increase IL-6 and signs of intestinal inflammation, as well as higher morning cortisol levels.

Emotional factors appear to play some role in IBS and psychotherapy, hypnosis and cognitive behavioural therapy have shown great benefit in some studies

Stress and emotions are strongly linked to gut (the second brain). IBS patients show higher serotonin levels (synthesized in the gut), which alters gastric emptying, increases small bowel contractions – faster, smaller bowel transit time and altered pain perception.

Gut microflora can affect brain chemistry via Vagus nerve, but brain (emotions) can affect gut microflora and release of serotonin and cortisol. 95% of serotonin in the body is synthesized by gut enterochromaffin cells, not brain.

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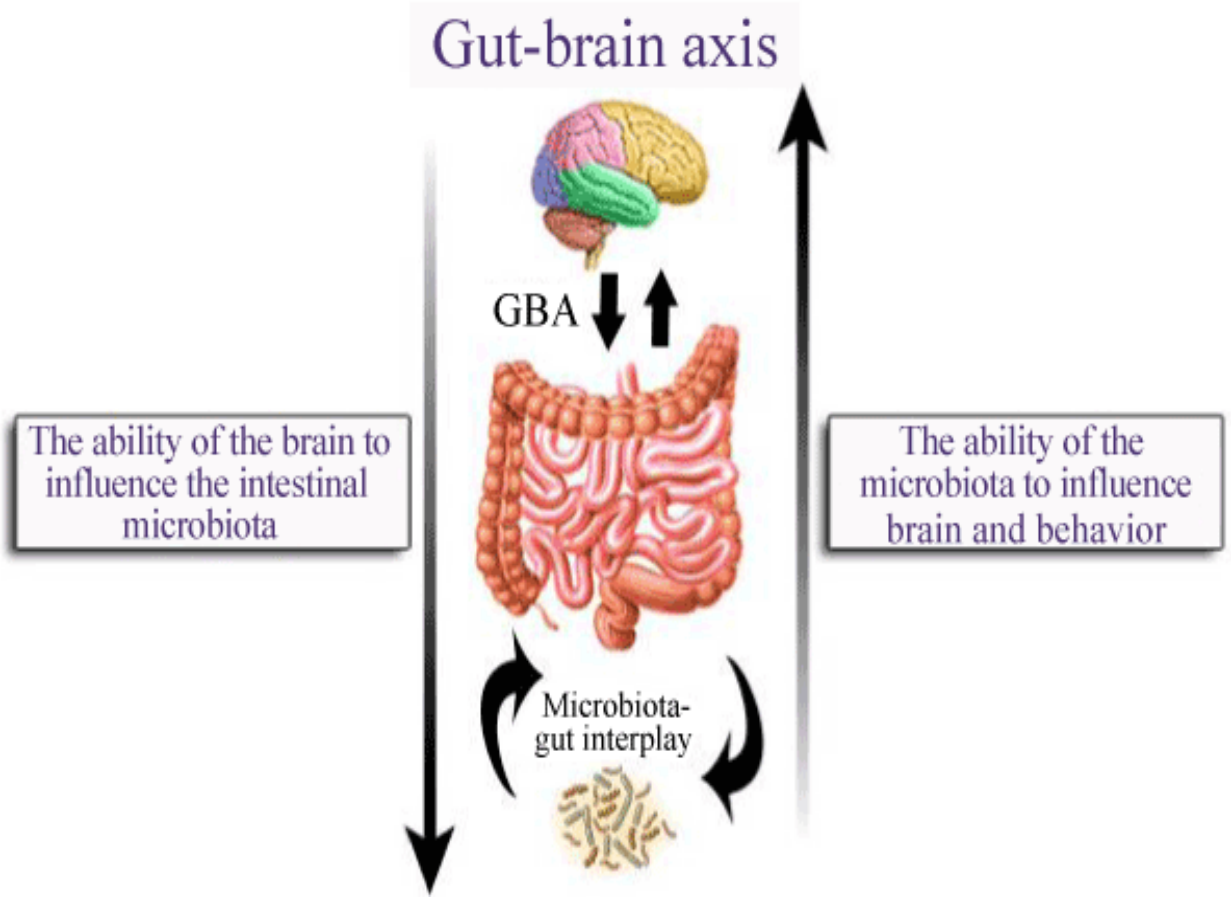
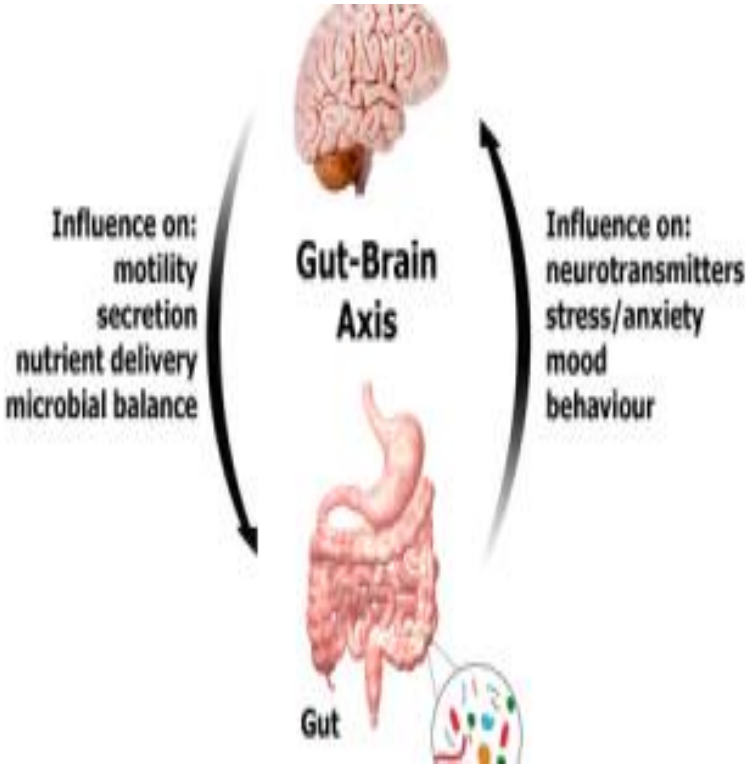
Gut-Brain Axis





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Food Allergies and Food Sensitivities: Some research suggests that food allergies (positive IgE blood test) or food sensitivities (positive IgG blood test) can exacerbate or cause IBS for about 8% of IBS patients. **Dairy products and Grains have been the two most commonly found food allergies linked to IBS.**

Based on Positive IgG Test, a 26% decrease in IBS symptoms occurred when patients consumed the therapeutic diet guided by the IgG positive findings. Symptoms returned when resuming unrestricted foods.

Gluten Sensitivity – approximately 4-5% of IBS patients test positive for Celiac disease and patients with negative Celiac blood test, but positive IgG test for gluten show improvement in IBS symptoms when gluten removed from diet

Lactose and Fructose Intolerance – 25% of adults have lactose intolerance, which increases in age and affects 35-40% of patients with IBS. Many IBS patients also show intolerance to fructose or have carbohydrate malabsorption issues, whereby symptom resolution occurs in 40% of these patients after removing or reducing offending sugars. Sorbitol-containing chewing gum can be a common trigger or IBS.

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IgG Food Sensitivity Testing: Rocky Mountain Labs; Great Plains Labs etc.

- **IgG Food Sensitivity Testing** - In an IgG reaction, the IgG antibodies attach themselves to the food antigen and create an antibody-antigen complex. These complexes are normally removed by macrophages. However, if they are present in large numbers and the reactive food is still being consumed, the macrophages can't remove them quickly enough. The food antigen-antibody complexes accumulate and are deposited in body tissues. Once in tissue, these complexes release inflammation causing chemicals, which may play a role in numerous diseases and conditions.

Why Test IgG Food Sensitivity?

- There is a growing body of evidence to support the clinical benefits of eliminating IgG reactive foods from the diet. IgG food sensitivities have been implicated in migraine headaches and **irritable bowel syndrome**
  https://www.ncbi.nlm.nih.gov/pubmed/?term=Atkinson+J.+et+al.+Gut+2004%3B53%3A1459%E2%80%931464

- Because IgG food reactions take hours or days to develop, this makes it difficult to determine which food is responsible for the reaction without doing testing.

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Fermentable Carbohydrates: The FODMaPs Restricted Diet (short-chain CHO's that are easily fermentable):

Restricting fermentable oligosaccharides, disaccharides, monosaccharides, and polyols found in:
Apples, Pears, Dried Fruit, Sugar, Alcohol, Mushrooms, Avocado, Milk, Cheese, Wheat, Rye, Onions, Artichokes, Beans, Peas, Lentils, Cabbage and Brussels Sprouts – these all contain short-chain carbohydrates that can produce gas, bloating and promote overgrowth of unfriendly bacteria in state of dysbiosis.

Soluble Fiber - the addition of soluble fiber has been shown to be helpful to spur the proliferation of gut-friendly bacteria, especially psyllium husk fiber and guar gum (Ispaghula). But don't ingest soluble fiber supplements on empty stomach.

Insoluble fiber (especially corn and wheat bran) tends in make IBS worse.

Exercise – has been shown to help prevent and improve IBS

Sleep – poor quality sleep further aggravates IBS

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Nutritional Medicine Approach to IBS Treatment: (10 Steps)

After ruling out other causes of diagnoses:
1. Consider Food Allergy, Foods Intolerance, Celiac, Non-Celiac Gluten Sensitivity, Lactose Intolerance, Fructose Intolerance (Allergist, IgG Test, Physician – Lactose, Fructose, Celiac Testing)

2. Probiotics and Prebiotics (Various Lactobacillus and Bifidus strains, and Propioniobacterium, and Saccharomyces boulardii – have shown good results)

3. Low FODMaps Diet and reducing refined sugars

4. Psyllium Husk Fiber – 1-3 teaspoons per day (and soluble fiber rich fruits)

5 Avoid insoluble fiber foods (wheat bran, corn, rice bran, peas and beans)

6. Digestive Enzymes – 20% of IBS patients shown to have pancreatic enzyme defect

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7. Peppermint Oil – has antispasmodic effects on GI tract, and shown to help in some IBS cases (79% improvement in one study). Dosage: 200-400 mg Enteric Coated Capsules, 3x per day – MUST BE ENTERIC COATED OR CAN WEAKEN CARDIAC SPHINCTER CAUSING HEARTBURN AND GERD

8. Fennel – is also antispasmodic on GI and has been shown to help some IBS patients. Dosage: 1 teaspoon per day, or in capsule form

9. Psychotherapy – biofeedback, stress reduction, hypnosis, meditation etc.

10. Regular Sleep and Exercise

References

Reference No 1

Reference No 2

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Van Vorous Dietary Management of IBS

- Having soluble fiber foods and supplements, substituting dairy with soy or rice products, being careful with fresh fruits and vegetables that are high in insoluble fiber, and eating regular small amounts can all help to lessen the symptoms of IBS (Van Vorous 2000).

- Foods and beverages to be avoided or minimized include red meat, oily, fatty and fried products, dairy (even when there is no lactose intolerance), solid chocolate, coffee (regular and decaffeinated), alcohol, carbonated beverages, especially those also containing sorbitol, and artificial sweeteners (Van Vorous 2000).

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11 Celiac Disease

- Celiac disease is an autoimmune inflammatory condition of the small intestine. It is also known as non-tropical sprue, endemic sprue, gluten enteropathy or gluten-sensitive enteropathy, and gluten intolerance. It is important to keep in mind that while the disease is caused by a reaction to wheat proteins, it is not the same as wheat allergy.

- Celiac disease is caused by a reaction to the ingestion of gliadin, a polypeptide component of wheat, rye, barley and oat flour. Upon exposure to gliadin, the enzyme tissue transglutaminase modifies the protein, and the immune system cross-reacts with the small-bowel tissue, causing an inflammatory reaction.

Gluten is combination of two proteins found in wheat and some other grains:

1. Gliadin
2. Glutenin

It's the Gliadin protein that causes the problem in Celiac Disease

- Celiac disease affects nearly 1% of the population.

In the body transglutaminase enzymes normally help form extensively cross-linked, insoluble protein polymers, which are necessary for the body to create barriers and stable structures. Examples are blood clots (the synthesis of coagulation factor XIII), as well as skin and hair**.** In celiac disease antibodies to tissue transglutaminase are found, which play a role in the small bowel damage in response to dietary gliadin.

Pathophysiology

Upon ingestion, gliadin binds to receptor protein on enterocyte surface producing an antigenic autoimmune inflammatory response in the small intestine with blunted villi (villous atrophy) and enhanced crypt mitosis.

With destruction of villi the disaccharidase enzymes and dipeptidase and tripeptidase enzymes are decreased producing lack of macronutrient absorption with weight loss and gastrointestinal symptoms and other symptoms, which range from mild to severe.

The intestinal damage leads to a truncating of the villi lining of the small intestine (called villous atrophy), which further interferes with the absorption of nutrients, as the intestinal villi are responsible for absorption.

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Signs and Symptoms Of Celiac Disease

The most common signs and symptoms of celiac disease include:

- Abdominal cramping and Diarrhea
- Growth Failure and Weight Loss
- Anemia
- Signs of nutrient deficiencies
- Life threatening electrolyte losses
- Osteomalacia and bone pain in children
- Secondary hyperparathyroidism from decreased absorption of calcium and vitamin D
- Dermatitis herpetiformis – a pruritic pattern of recurrent blisters over elbows and knees (disappears with gluten – free diet)

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Testing For Celiac Disease

- A blood test is now available to help diagnose celiac disease. Of interest is the fact that celiac disease can be asymptomatic and therefore the blood test is recommended for family members of celiac patients.

- The blood test (serology for anti-transglutiminase antibodies) is highly sensitivity (99%) and specific (>90%) for identifying the disease.

- Endoscopy can also be used to confirm the diagnosis. Typically, an upper endoscopy with biopsy of the duodenum or jejunum is performed. The physician normally obtains multiple samples (four to eight) from the duodenum.

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Testing for celiac disease involves a simple blood test, but requires confirmation via intestinal biopsy.

Blood Tests: Recommended by the Canadian Celiac Association

- tTG – IgA class test - Tissue transglutaminase antibody (tTG), IgA class
- IgA test
- EMA - Anti-endomysial antibodies (Clinical Nutrition April 2015. http://www.clinicalnutritionjournal.com/article/S0261-5614(14)00218-0/fulltext)

- Testing for wheat allergy should also be included

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At Risk Populations

Celiac disease is found in higher frequency in peoples of North and Western Europe (Basque Country - northern Spain, and Ireland – showing highest frequencies) as well as portions of Africa and India.

It also occurs more frequently in South and Central America.

People of African, Japanese and Chinese descent are rarely diagnosed with celiac disease.

Population studies suggest that a large proportion of celiac sufferers remain undiagnosed. This is due to many clinicians not screening for the condition as indicated.

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Treatment:

- The primary treatment for celiac disease is a gluten-free diet.

Hidden Gluten in Common Foods and Dietary Management

- It is the gluten in flour that helps bread and other baked goods bind and prevent crumbling. This application has made gluten an attractive addition to many processed and packaged foods. As such, celiac patients need to read the labels of all packaged and processed foods to ensure they are gluten-free. This is especially true for soups, luncheon meats and sausages.

- This is important as the only meaningful treatment for celiac disease is to maintain a strict gluten-free diet for life. If celiac disease is diagnosed early and treated with a gluten-free diet, the damaged tissues can heal and the risk of developing many of the long-term complications of this disease, including osteoporosis, lymphoma, and infertility can be reduced (1).

- The following food chart assembled by Shelley Case is an excellent reference to the understanding of gluten-containing foods:

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Gluten-Containing Ingredients To Be Avoided Reference:

Shelley Case, B.Sc., RD - ISBN 1-894022-79-3

(See reference 3 below at end of this Celiac subsection)

GLUTEN-CONTAINING INGREDIENTS TO BE AVOIDED		
Barley	Graham Flour	Rye
Bulgar	Kamut*	Semolina
Cereal Binding	Malt**	Spelt (Dinkel)*
Couscous	Malt Extract**	Triticale
Durum*	Malt Flavouring**	Wheat
Einkorn*	Malt Syrup**	Wheat Bran
Emmer*	Oats***	Wheat Germ
Filler	Oat Bran***	Wheat Starch
Farro*	Oat Syrup***	
* Types of Wheat		
** Derived from barley		
*** Information about eating oats appears below		

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Oats

“The safety of oats in individuals with celiac disease has been extensively investigated. Clinical evidence confirms that consumption of pure, uncontaminated oats is safe in the amount of 50 to 70 grams per day (1/2 – 3/4 cup dry rolled oats) by adults and 20 to 25 grams per day (1/4 cup dry rolled oats) by children with celiac disease.

Studies looking at the consumption of oats over five years have confirmed their safety. However, the studies looking at safety of oats in celiac disease have involved a small number of subjects, the oats used were pure, free of gluten contamination and the amount allowed per day was also limited”. (Shelley Case - see reference)

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Foods Allowed On A Gluten-Free Diet

- Amaranth
- Arrowroot flour
- Baking soda Bean flour Buckwheat
- Cassava (Manioc flour)
- Chick pea flour
- Corn flour
- Cornmeal
- Cornstarch (Masa farina)
- Cream of tartar
- Dal or Dahl (Legume from India)

- Flax
- Gelatin
- Green pea flour
- Gums:
  - Acacia (Gum Arabic)
  - Carob bean gum
  - Carrageenan
  - Cellulose
  - Guaica
  - Guar
  - Karaya
  - Locust bean
  - Tragacanth
  - Xanthum

- Invert Sugar
- Kudzu
- Lecithin
- Legumes: Seeds of plants which include
  - Channa
  - Chick peas
  - Gram
  - Lentils
  - Peanuts
  - Peas
  - Soya

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Other Health Conditions Associated With Celiac Disease

Even with a gluten-free diet celiac disease patients show a higher incidence of future development of:

- Intestinal lymphoma and colon cancer
- Rheumatoid arthritis
- Diabetes
- Thyroid disease
- Ulcerative colitis
- Schizophrenia

As such, routine screening for colon cancer and intestinal lymphoma is recommended, as well as blood glucose levels, tests for thyroid function (TSH). Joint inflammatory symptoms require investigation for rheumatoid arthritis.

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Key Points To Keep In Mind:

- Celiac disease is often under diagnosed by the medical profession.

- Practitioners should be aware of signs and symptoms that may suggest celiac disease, especially in ethnic groups who are most genetically predisposed to this condition, and encourage family members of celiac disease patients to undergo the simple, but highly accurate, blood test for celiac disease.

- In cases of diagnosed celiac disease practitioners should strongly encourage patients to follow a gluten-free diet, as outlined meticulously by the work of Shelly Case.

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References:

1 Current Therapy In Nutrition. Jeejeebhoy KN Editor (B.C. Decker Inc Publisher. 1988):121-134

2. Quick Reference To Clinical Nutrition 2nd edition. Halpern S Editor (J.B. Lippincott Company Publisher. 1987): 201

3. Gluten-Free Diet: A Comprehensive Resource Guide. Shelley Case. Centax Books & Distribution.

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Landmark Studies Shows Importance of B-Vitamin Supplementation in Celiac Management

- Damage to the intestinal lining reduces the ability for celiac patients to absorb various nutrients including, iron, folate, calcium, Vitamin D, protein, fat and other food compounds.

- A 2009 study published in the *World Journal of Gastroenterology* showed that celiac disease patients commonly have sub-optimal nutritional status of certain B-vitamins (folic acid, vitamin B6, vitamin B12). As these vitamins are required to keep homocysteine in a safe range, many celiac patients have high blood levels of homocysteine, which increases their risk for heart disease, stroke and other vascular complications (2).

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The body relies on vitamin B6, folic acid and vitamin B12 to recycle homocysteine back to methionine or to serine within our cells. This keeps homocysteine blood levels in the ideal range.

Thus, even marginal deficiencies in these B-vitamins can result in higher homocysteine levels, with resulting increased risk of vascular disease (3, 4).

Homocysteine is a chemical made in all body cells which, if left unchecked, diffuses into the bloodstream and causes damage to the blood vessel wall – setting the stage for plaque development with resulting increased risk for heart attack, stroke and other vascular problems.

Some reports suggest that at least 10% of all heart attacks in the U.S. each year are attributable to high homocysteine levels (3, 4).

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- In the 2009 study, researchers gave a sub-group of celiac disease patients a B-vitamin supplement (including vitamin B6, folic acid, vitamin B12), only to discover that their blood homocysteine levels declined into the normal and safer range.

- As celiac patients are known to be prone to high homocysteine levels they should pay heed to the findings of this study from the standpoint of helping to reduce risk of heart attack and stroke, as an important factor in the long term management of their health (1).

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- In my view, this study emphasizes the need for celiac patients to take a high potency multiple vitamin and mineral that includes a B-50 complex.

- A supplement of this nature would also help to improve their nutritional status of all important micronutrients (vitamins and minerals), and reduce risk of premature vascular disease by helping to keep homocysteine within the desired range (under 6.3 micromoles per liter).

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References:

1. http://www.hc-sc.gc.ca/fn-an/securit/allerg/cel-coe/index-eng.php
2. Hadithi et al. Effect of B vitamin supplementation on plasma homocysteine levels in celiac disease**.** *World Journal of Gastroenterology*, 2009; 15 (8): 955
3. Boushey CJ, Beresford SA, Omenn GS, Motulsky AG. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease: probable benefits of increasing folic acid intakes*. JAMA* 1995;274:1049-57.
4. Kang SS, Wong PW, Malinow MR. Hyperhomocyst(e)inemia as a risk factor for occlusive vascular disease. *Ann Rev Nutr* 1992;12:279-98.

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Some Final Notes On Celiac Disease: Reference No. 2

High correlation of Celiac disease with positive HLAB27 antigen Test – seen in 85-95% of celiac patients (compared to 20-25% of normal subjects). Also high correlation with genetic marker – DRw3 –also appears on cell surface.

People in central and northern and north-west part of Europe, show high prevalence of HLAB27 antigen, and in these parts of Europe the introduction of wheat is a relatively newer phenomenon - about 1,000 BC. And prevalence of disease is higher in people with these genetic roots.

The early introduction of cow's milk is also linked to increased risk of Celiac disease, whereas breastfeeding and delayed administration of cow's milk and cereal grains are the primary preventive steps that can greatly reduce the risk of developing Celiac disease.

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A study conducted between 1969-2008 showed earlier mortality in associated with gluten-sensitivity:

- 39% increased early death rate in full-blown celiac disease, compared with controls
- Those with inflammation of the intestine, but not full-blown celiac disease had a 72% increased risk compared to controls
- Those with gluten-sensitivity (elevated gluten antibodies, but negative intestinal biopsy) had a 35% increased risk of early mortality compared to controls

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Celiac disease and gluten-sensitivity have correlation with:

- IBS
- Inflammatory Bowel Disease
- Anemia
- Migraines
- Epilepsy
- Fatigue
- Canker sores
- Osteoporosis
- Rheumatoid Arthritis
- Lupus
- Multiple Sclerosis
- Other Autoimmune diseases
- Multiple Food Allergies, Lactose Intolerance and Increased Intestinal Permeability

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In one double-blind study with celiac patients the administration of:

Folic acid – 800 mcg

Vitamin B12 – 500 mcg

Vitamin B6 – 3 mg

Reduced elevated homocysteine in celiac patients by 34%, with significant improvements in:

- Feelings of wellbeing
- Reduced anxiety
- Improved mood

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In my experience, I suggest that Celiac patients take:

1. A high potency multiple vitamin and mineral supplement
2. An essential fatty acid supplement containing borage seed, flaxseed and fish oil
3. A digestive enzyme supplement, which also contains the prebiotics FOS and Inulin.
4. A glutamine supplement (500 mg, twice daily)

These nutrients work synergistically to help form healthier intestinal cells, aid in digestion, immune regulation of the gut immune system, and help to minimize local and systemic inflammatory responses via their effects on prostaglandin (eicosanoid) synthesis.

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12. Non-Celiac Gluten Sensitivity

This condition, officially recognized in 2012 is a condition that mimics the symptoms of Celiac disease, but blood tests and biopsy tests do not show presence of antibodies or celiac damage to the intestinal tract.

Researchers estimate that about 6% of the population have gluten sensitivity.

In these case avoidance of gluten containing foods improves GI symptoms, such as:

- Post meal bloating
- Frequent diarrhea
- Cramping pain or discomfort
- Associated joint pain and fatigue

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- Gluten Sensitivity is very common in people who also have irritable Bowel Syndrome, and avoidance of gluten in these cases helps to reduce IBS symptoms.

- But not all IBS is linked to gluten sensitivity. People with IBS should create a trial for themselves where they avoid all gluten-containing foods and see if their symptoms improve.

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- Some evidence also suggests that gluten sensitivity may trigger symptoms in some patients with schizophrenia or Autism Spectrum Disorder. It might be only a small percentage of patients who benefit, but it worth a simple trial to see if avoiding gluten enhances the treatment of schizophrenia and/or improves the symptoms of autism.

- For everyone else, if they have the abdominal symptoms mentioned outlined in this section and the doctor has run all the battery of tests and can't find anything, then it may be gluten-sensitivity. In which case it would make sense to avoid gluten-containing foods to see if it helps.

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But remember that between celiac disease, wheat allergy and gluten sensitivity subjects, together they account for less than 10% of the entire population. So for most of us, gluten is not a problem. Spending effort on locating gluten-free foods is really not necessary for most people, according to the literature.

However, keep in mind that 1% of population have a wheat allergy. They can't eat wheat, but can eat other gluten-containing foods.

These people typically have atopic symptoms like:

- Hay fever
- Hives
- Eczema
- Asthma

And these conditions are made worse from eating wheat. There is a simple blood test for wheat allergy that is often included in the Celiac testing profile to help distinguish simple wheat allergy from Celiac disease.

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- And know that to make gluten-free foods, they often have to add extra fat and carbohydrate calories to replace the gluten so the foods won't crumble and fall apart.

- Those extra fat and sugary calories are likely to do more harm than gluten, if you're truly not gluten sensitive or have Celiac disease.

- So there is a lot of hype about gluten these days, as being a food toxin that destroys health. This appears to be true for less than 10% of the population. For the rest of us it doesn't seem to be a problem.

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References:

- Primary Reference: Clinical Nutrition April 2015. http://www.clinicalnutritionjournal.com/article/S0261-5614(14)00218-0/fulltext

- Wheat Allergy Information: http://acaai.org/allergies/types/food-allergies/types-food-allergy/wheat-gluten-allergy

Consider reading the book “Wheat Belly” by Dr. William Davis M.D. (Deckle Edge 2012)

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13. Inflammatory Bowel Disease: Crohn's disease and Ulcerative Colitis

Incidence: In U.S, about 1.4 million people have Inflammatory Bowel Disease (IBD)

Most common age of onset: 15-35 yrs

Females affected slightly more than males

Caucasians have 2-4x incidence than African-American or Asian Americans

Jewish heritage have 3-6X higher incidence than non-Jews

Crohn disease – granulomas usually found in the ileum of small intestine, but may also be present in mucosa of mouth, esophagus, stomach, duodenum, jejunum and colon.

Ulcerative Colitis – involves lining of colon

Both conditions are associated with increased risk of colon cancer

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Predisposing Factors In IBD

1. Genetics
2. Antibiotic Use – dysbiosis
3. Western Diet – dysbiosis
4. Stress (emotions) – inflammation/immune alterations
5. Ultra-hygienic conditions – dysbiosis

Increasing incidence IBD in developed countries

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Major Disease Features

1. Immune Dysregulation/Inflammation
2. Small Intestine Permeability (Leaky gut)
3. Dysbiosis (cause or consequence?)
4. Stress Hormones (psychological-emotional connection – can trigger onset and relapses
5. Oxidative Stress

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The Goals of Lifestyle Medicine: Multi-faceted

1. Reverse Dysbiosis
2. Modulate Immune Function – biological response modulators
3. Reduce inflammation
4. Improve digestion and nutrient absorption
5. Improve Gut Barrier – rebuilding healthy intestinal cells and lining
6. Reduce oxidative stress
7. Manage Stress Response and Emotional Wellbeing

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Timing is Everything

Due to hyper-gut sensitivity in IBD, its important to not shock the GI tract.

Thus, nutrition and supplementation strategies should be staged-in slowly over time, and introduced only during periods of remission.

The use of TNF-inhibitor drugs, which control inflammation, have made it easier to rebuild the health of the gut, reverse dysbiosis and improve immune function, during concurrent drug use

The long-term goal is to reduce requirement for medications to manage the disease, if possible.

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1. Dysbiosis: The Gut Microflora

- Complex ecosystem that consists of bacteria and other microorganisms (archaea, yeasts, planctomycetes and filamentous fungi and viruses, such as Senegal virus).

- Estimated number of species in gut is more than 1,000 species.

- 10 times more microbial cells in gut than number of human cells in our bodies, and they contain in total 150 times as many genes as our own genome.

Gut microbiota (microflora) modulates expression of genes involved in:

1. Immunity
2. Nutrient absorption
3. Energy metabolism
4. Intestinal barrier function

http://www.jscimedcentral.com/Pharmacology/pharmacology-2-1016.php

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Other Functions of Microflora

- Helps protect body against pathogens
- Metabolizes complex lipids and polysaccharides that otherwise would be inaccessible nutrients
- Neutralizes drugs and carcinogens
- Modulates intestinal motility
- Affects visceral perception – release neurotransmitters and other agents that influence brain function
- Synthesizes vitamin K and biotin

- http://journal.frontiersin.org/article/10.3389/fnint.2013.00070/full

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Antibodies to Microbial Antigens In Crohn’s disease

- Presence of antibodies to gut bacteria antigens in Crohn's Disease supports theory that one aspect of Crohn's Disease pathology involves an abnormal immune response to otherwise normal intestinal flora

http://www.crohns.net/page/C/CTGY/LifeStyle_Chane

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Other Studies Suggest Dysbiosis

Infectious Pathogens Implicated in Crohn's Disease:

- Escherichia coli
- Listeria monocytogenes
- Yersinia enterocolitica
- Mycobacterium avium subspecies paratuberculosis
- Measles virus

Reducing antigens from these agents may help tame the immune-inflammatory response

http://www.crohns.net/miva/education/articles/Microbial_Factors.shtml

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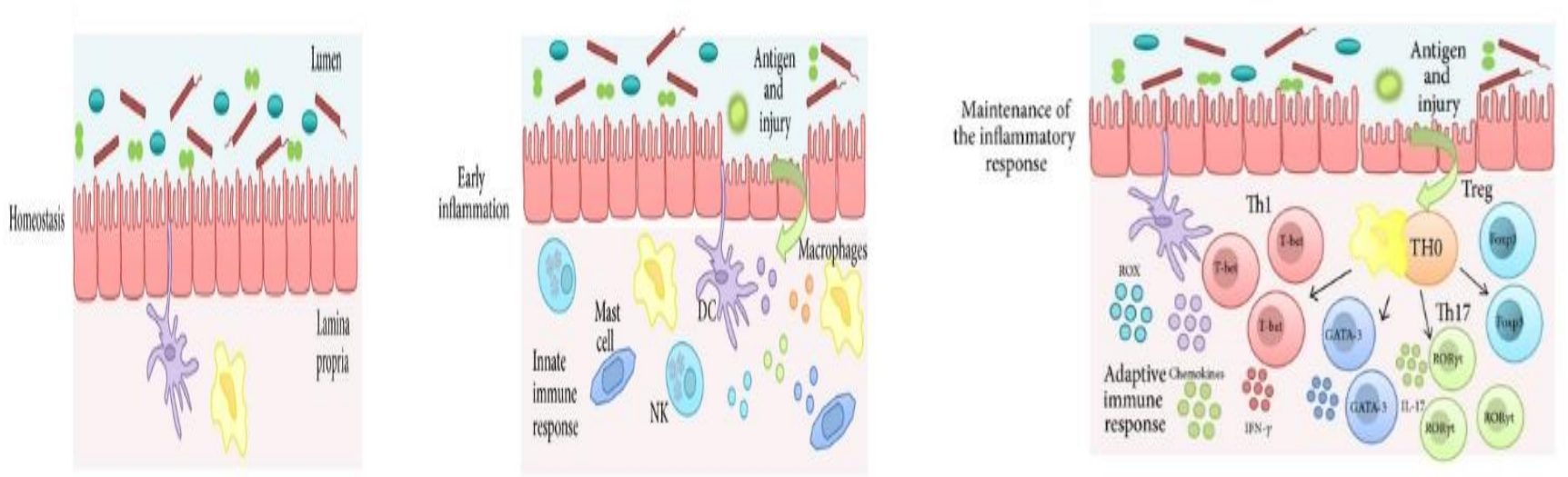
Sequence of Events

During early inflammation, foreign antigens activate the different innate immune cells located in the intestine, including natural killer cells, mast cells, neutrophils, macrophages, and dendritic cells.

A maintained inflammatory reaction promotes the activation of the adaptive immune response. Abnormally activated effector T helper (Th) cells synthetize and release different inflammatory mediators that generate the vicious circle of inflammation that leads to chronic tissue injury and epithelial damage

http://www.hindawi.com/journals/isrn/2014/928461



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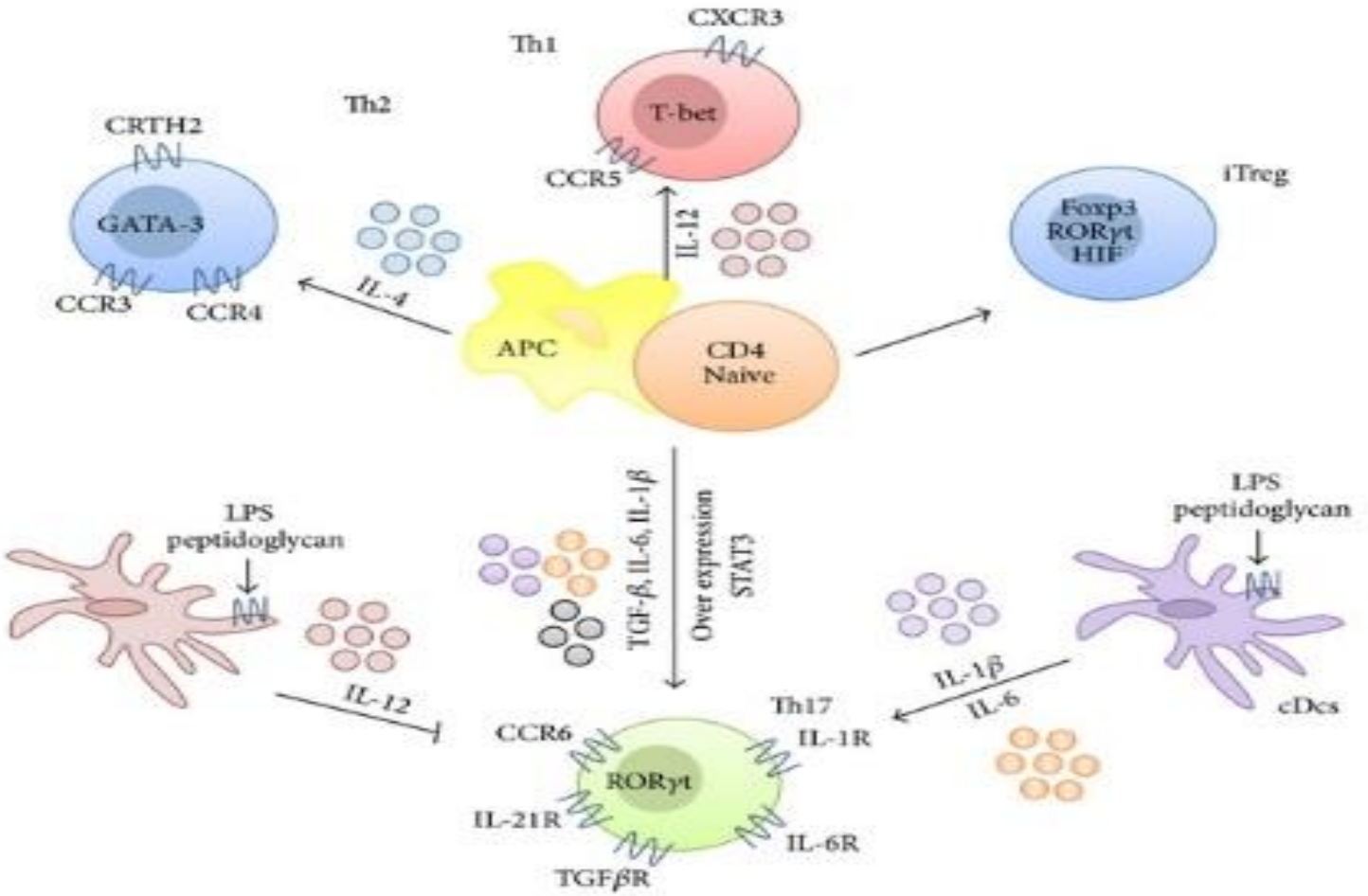
CD4 cells morph into CD17 cells

http://www.hindawi.com/journals/isrn/2014/928461



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Th17

- Th17 cells massively infiltrate the inflamed intestine of IBD patients, where they produce interleukin- (IL-) 17A and other cytokines, triggering and amplifying the inflammatory process.

- http://www.hindawi.com/journals/isrn/2014/928461

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Probiotic Supplementation

Lessons From C. difficile Infection:

Clinical studies show that administration of probiotic supplements to patients on antibiotics has prevented Antibiotic-associated Diarrhea (AAD) and *C. difficile*-associated diarrhea (CDAD) .

10–25% of cases of AAD caused by bacterium *Clostridium difficile*. CDAD is particularly important in elderly hospitalized patients - subpopulation with highest risk for problem.

Probiotic supplements prevent AAD and CDAD by restoring healthy intestinal microflora, enhancing immune response, and clearing pathogens and their toxins from the intestinal tract

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Animal Studies: Lactobacillus and Bifidus

The probiotic combination supplement shown to improve intestinal barrier function in animals with colitis included a commercial supplement that contains:

Lactobacillus casei, Lactobacillus plantarum, Lactobacillus acidophilus, and Lactobacillus delbrueckii subspecies bulgaricus, Bifidobacterium longum, Bifidobacterium breve, Bifidobacterium infantis, Streptococcus salivarius subspecies thermophilus

References:

1.Wallace TC et al. Human gut microbiotica and its relationship to health and disease. Nutrition Reviews 2011. Vol 69 (7):392-403

2.S Pietro Pozzoni MD; Alessia Riva MD; Alessandro Giacco Bellatorre MD; Maria Amigoni MD; Elena Redaelli MD; Anna Ronchetti MD; Mariangela Stefani MD; Rosangela Tironi MD; Edoardo Ennio Molteni MD; Dario Conte MD; Giovanni Casazza PhD; Agostino Colli MD. S*accharomyces boulardii* for the Prevention of Antibiotic-Associated Diarrhea in Adult Hospitalized Patients: A Single-Center, Randomized, Double-Blind, Placebo-Controlled Trial. The American Journal of Gastroenterology. 2012;107(6):922-931.

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Probiotic and Prebiotic Studies

- Emerging therapies for IBD include probiotics and prebiotics.
- There is good animal data to support the beneficial effects of many commensal bacteria on immune function and mucosal integrity.
- **Probiotics** - Positive Results seen in Pouchitis Prevention
- **Prebiotic therapy** - Colonic growth of *Bifidobacteria* strains promoted by regular consumption of certain indigestible carbohydrates such as fructooligosaccharides (FOS) and inulin, found at high concentrations in specific vegetables.

http://www.jscimedcentral.com/Pharmacology/pharmacology-2-1016.php

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Probiotic Therapy

1. Kissing - Kiss Someone with a Health Microbiota: Spouses have similar microbiota compared to parent-offspring microbiota
   (http://journal.frontiersin.org/article/10.3389/fnint.2013.00070/full)

2. Probiotic Supplementation

3. Foods with Active Bacterial Culture

4. Fecal Microbiota Transplantation (FMT) – impressive results in CDAD cases

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Live Bacterial Culture Foods

- Low fat yogurt
- Sauerkraut
- Kefir
- Miso
- Pickles
- Tempeh
- Kimchi (Korean sauerkraut)

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J of Crohn's and Colitis 2014

Systematic Review of FMT in IBD

- 18 human studies, involving 122 patients were described (79 ulcerative colitis. 39 Crohn's disease; 4 IBD unclassified).

- Overall, 45% of patients achieved Clinical Remission (CR) during follow-up.

- Among the cohort studies, the pooled proportion of patients that achieved CR was 36.2%.

Conclusions

This analysis suggests that FMT is a safe, but variably efficacious treatment for IBD. More randomized controlled trials are needed and should investigate frequency of FMT administration, donor selection and standardization of microbiome analysis

http://www.sciencedirect.com/science/article/pii/S1873994614002438

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Dysbiosis Test

- Organix Dysbiosis Profile by labs such as Metametrix or Great Plains Laboratory is a urine organic acid test measuring the by-products of microbial metabolism, and is particularly useful in detecting the presence of pathogenic microbial overgrowth.
  https://www.gdx.net/product/organix-dysbiosis-test-urine

Cost: about $300.00 US https://www.directlabs.com/akhil/OrderTests.aspx

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Prebiotics: FOS Sources

- Bananas
- Onions
- Chicory root
- Garlic
- Asparagus
- Jicama
- Leeks,
- Jerusalem artichoke
- Agave
- (and Wheat and Barley)

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Prebiotics: Inulin Sources

- Agave
- Banana/Plantain
- Chicory
- Dandelion
- Garlic
- Globe artichoke
- Jerusalem artichoke
- Jicama
- Onion
- Wild yam

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Supplementation with Digestive Enzymes & Prebiotics

- **Digestive Enzymes** help reduce partially digested food from producing hyperosmolarity in bowel leading to diarrhea
- Also improve nutrient absorption and utilization to build healthier body and intestinal cells
- **Prebiotics** increase number of friendly bacteria, which regulate gut immune system, elimination process and digestive process.

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2. Immune Modulation

A. Vitamin D and IBD:

- IBD patients tend to have low vitamin D levels, even at time of diagnosis
- Immune cells and intestinal cells have vitamin D receptors.
- **In IBD, vitamin D shown to reduce TNF release by immune cells**
- **Patients with high vitamin D levels and/or who take vitamin D supplements (2000-5000 IU per day) show better disease management in many studies, compared to placebo.**
- **And have fewer complications, including hospitalizations, surgeries, infections, and colon cancer.**
- More research is required to make definite statements about vitamin D in IBD – but taking vitamin D has not been shown to make IBD worse (but requires doctor's consent)

http://www.vitamindcouncil.org/health-conditions/inflammatory-bowel-disease

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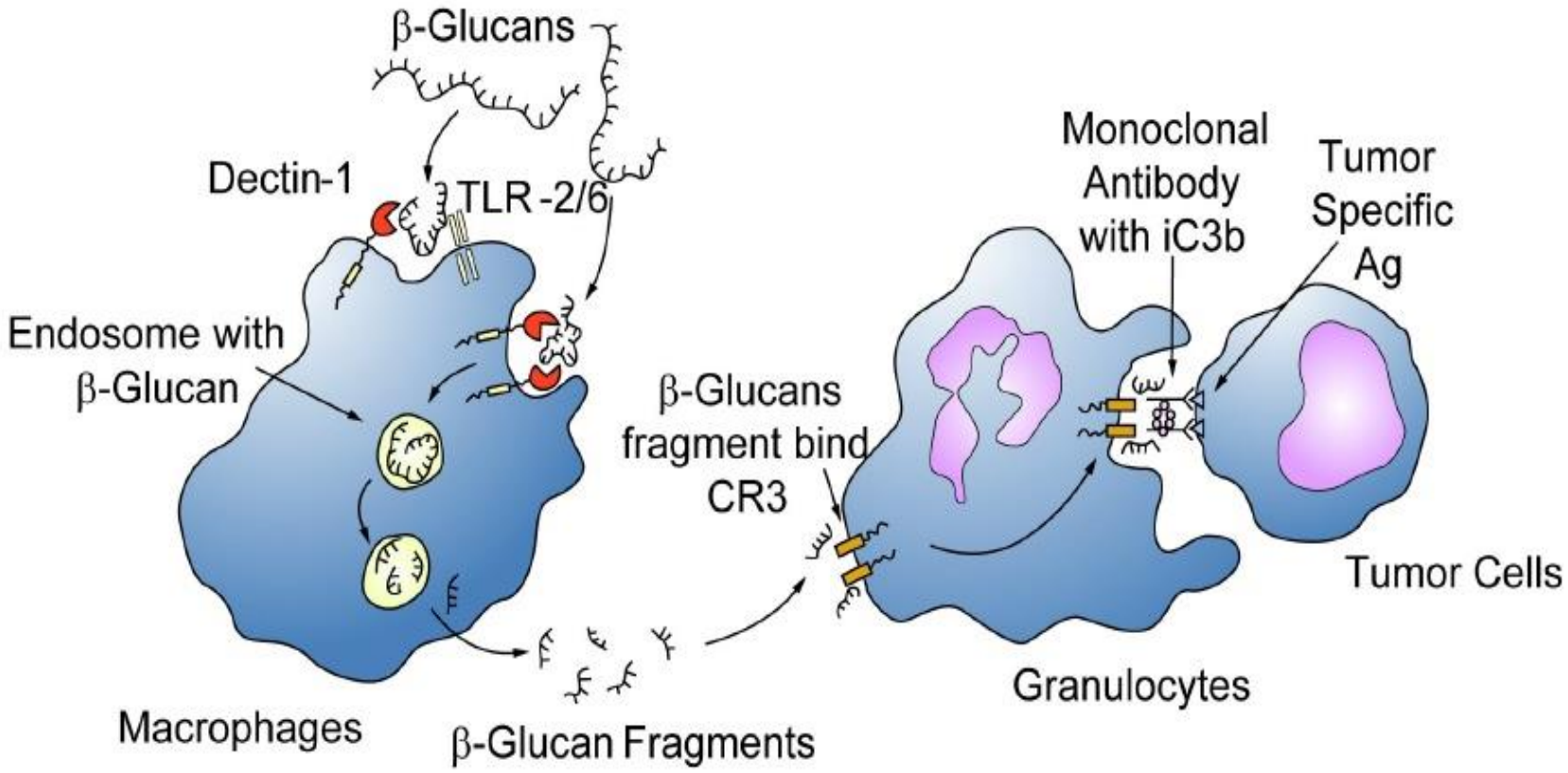
B. Beta-glucans – from Medicinal Mushrooms:

Biological Response Modulators



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3. Reducing Inflammation & Irritation

1. Inflammatory Foods

2. Essential Fatty Acids

3. Natural Anti-inflammatories

4. Food Allergies/Sensitivities

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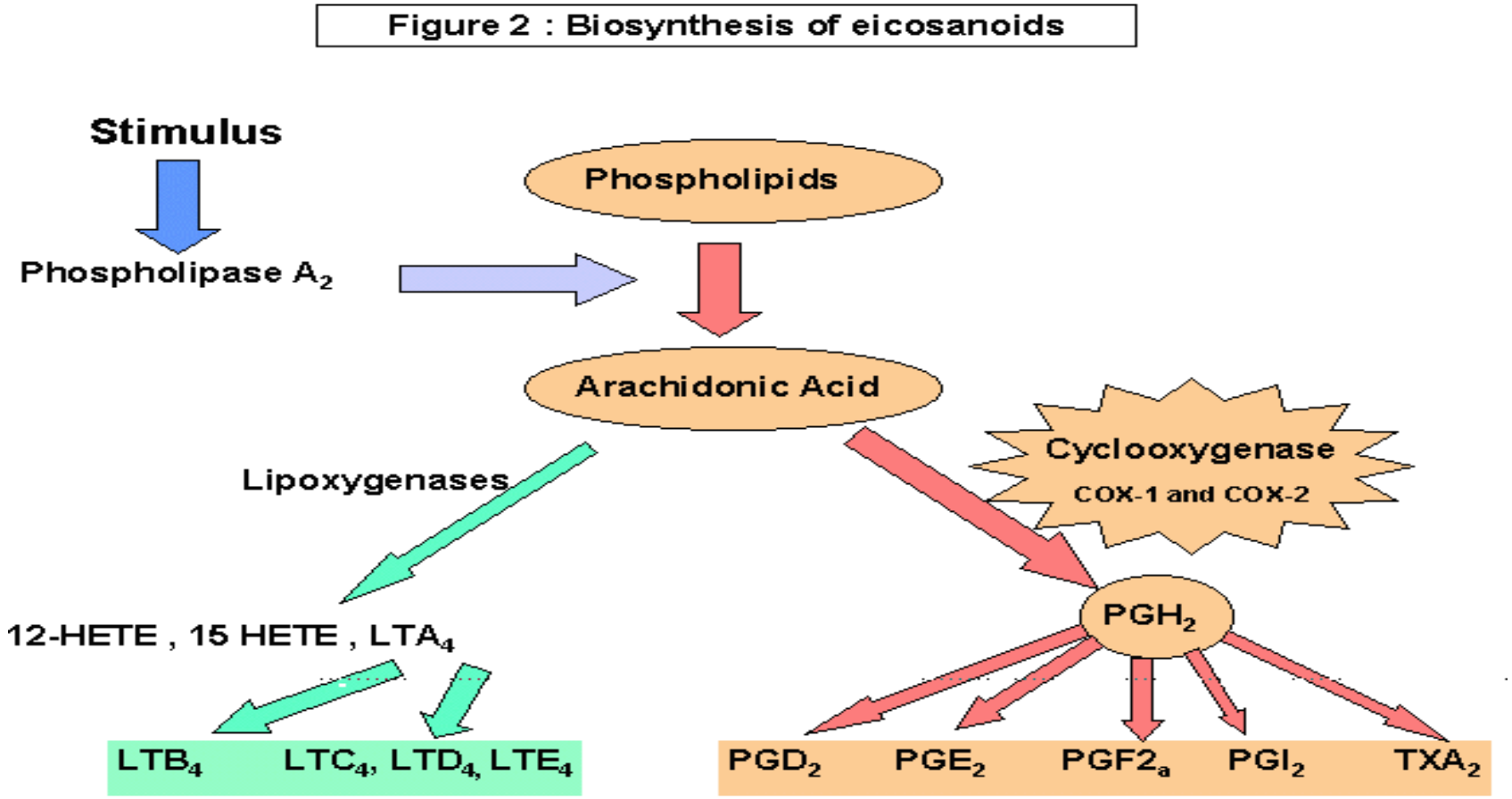
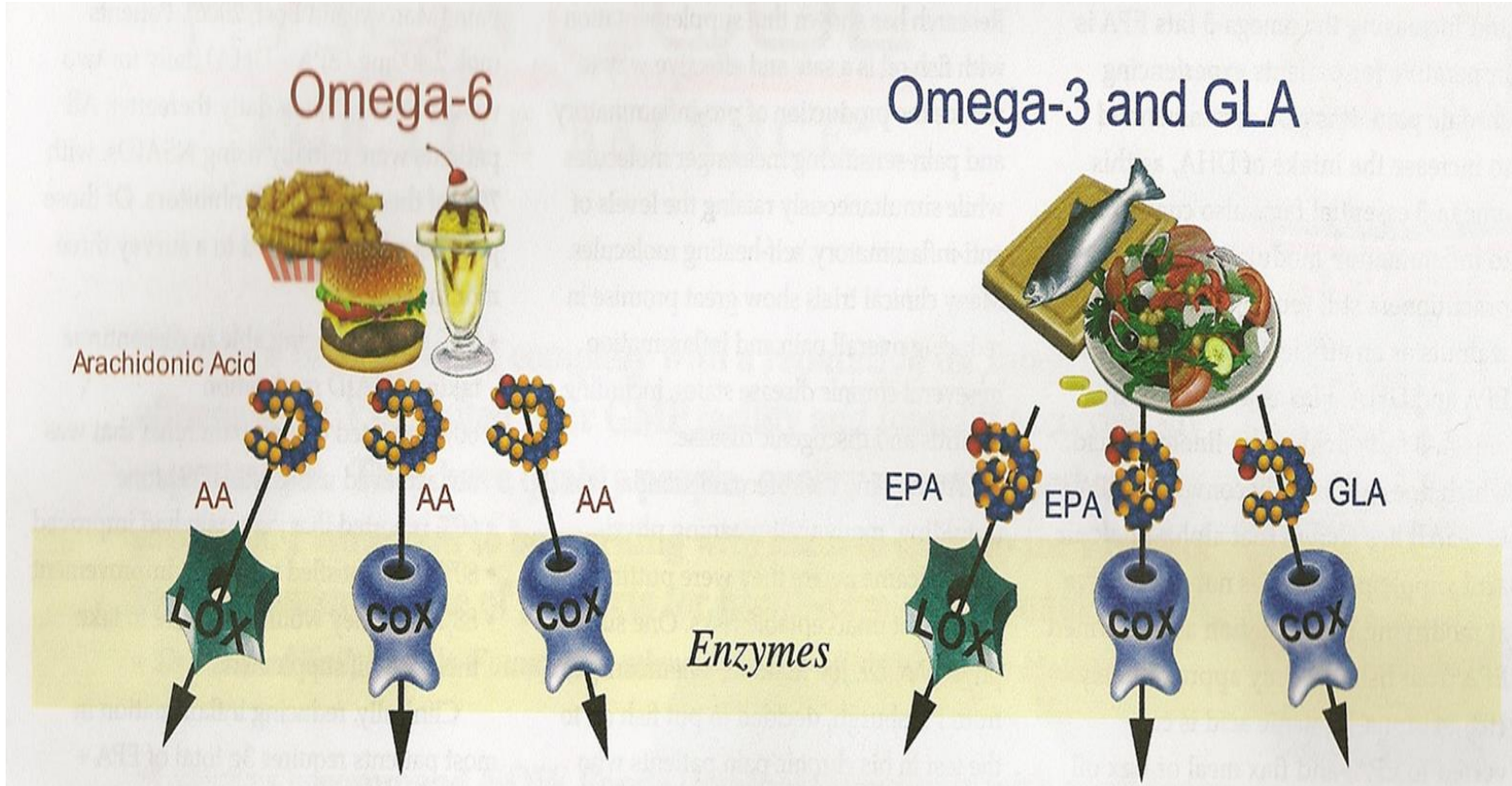
Inflammatory Foods: **Bad Fat (Arachidonic acid)** Causes Inflammation Via Increasing COX and LOX pathways (PG-2 Synthesis)





LTB-4
Leukotrienes-4 series

- Promotes inflammation
- Constricts airways
- Prolongs duration of inflammation

TXA-2
Thromboxane-A2

- Constricts blood vessels
- Constricts airways
- Increases blood clotting
- Reduces circulation

PGE-2
Prostaglandin-E2

- Increases sensitivity to pain
- Increases swelling
- Induces fever
- Constricts blood vessels

LTB-5
Leukotriene-5 series

- Relaxes blood vessels
- Increases circulation
- Relaxes airways
- Promotes anti-inflammatory response

PGE-3
Prostaglandin-E3

- Improves circulation
- Decreases sensitivity to pain
- Relaxes blood vessels
- Promotes anti-

PGE-1
Prostaglandin-E1

- Relaxes muscles spasms
- Reduces blood clotting
- Increases protective stomach secretions
- Improves circulation

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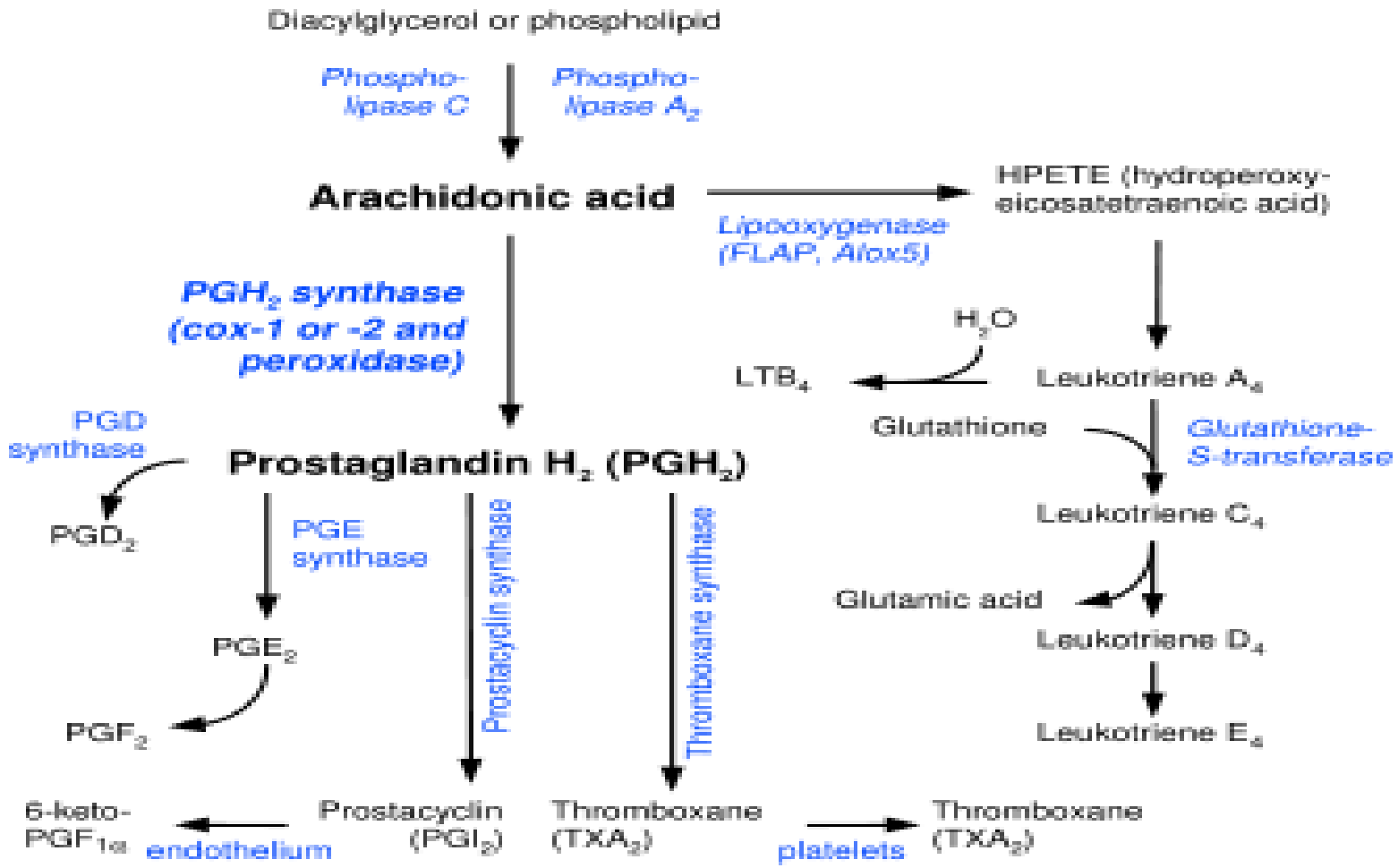
Arachidonic Acid Promotes Inflammation



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Foods With The Inflammatory Fats

1. Red meat, lamb, duck, pork
2. Organ Meats
3. Milk or Yogurt (2% or higher) 14% vs 36% (under 20% is okay)
4. Cheese (4% or higher) – most 80-95% fat (calcium issue)
5. Other Dairy - cream, whipped cream, cream cheese, ice cream – double/double, triple/triple –

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6.Regular Chocolate Products

7. Palm or Coconut Oil – Containing foods, candies or pastries

8. Egg Yolks (250 mg of cholesterol per yolk)

9. Alcohol - converts other calories into fat

10. Pastries (cheese cake, cookies, donuts etc) – include hydrogenated fatty foods as well (creamy salad dressings, fried foods etc)

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Low Fat Protein Foods

1. Chicken Breast
2. Turkey Breast
3. Cornish Hen
4. Fish – max 2X/wk (be careful with seafood)
5. Soy milk, soy cheese, tofu
6. Non fat or 1% Milk or Yogurt
7. Egg Whites
8. Cheese less than 4% MF
9. Protein Shakes (whey, egg white, soy, pea) – 20-25 gm/scoop

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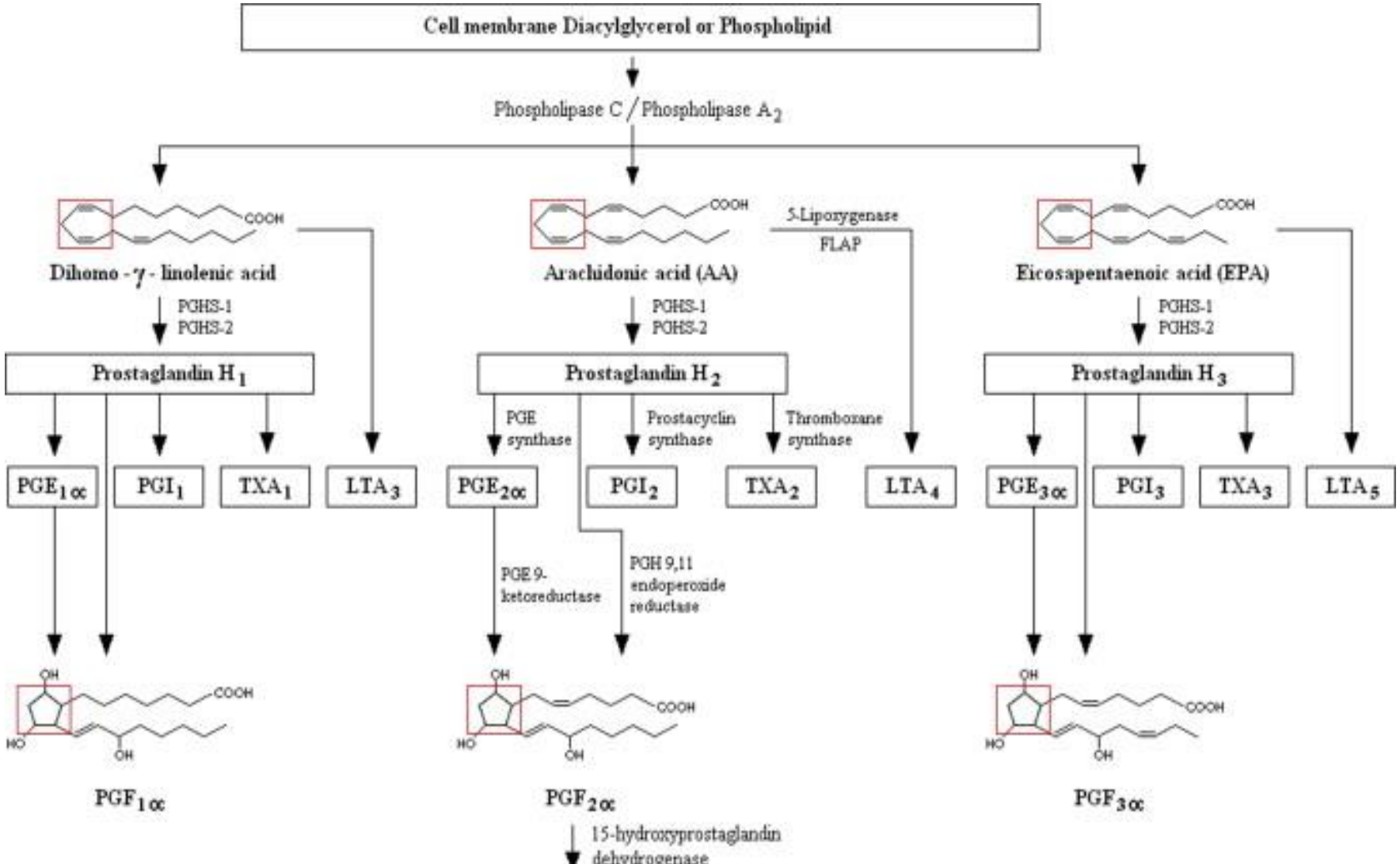
Anti-inflammatory Prostaglandins 1 & 3



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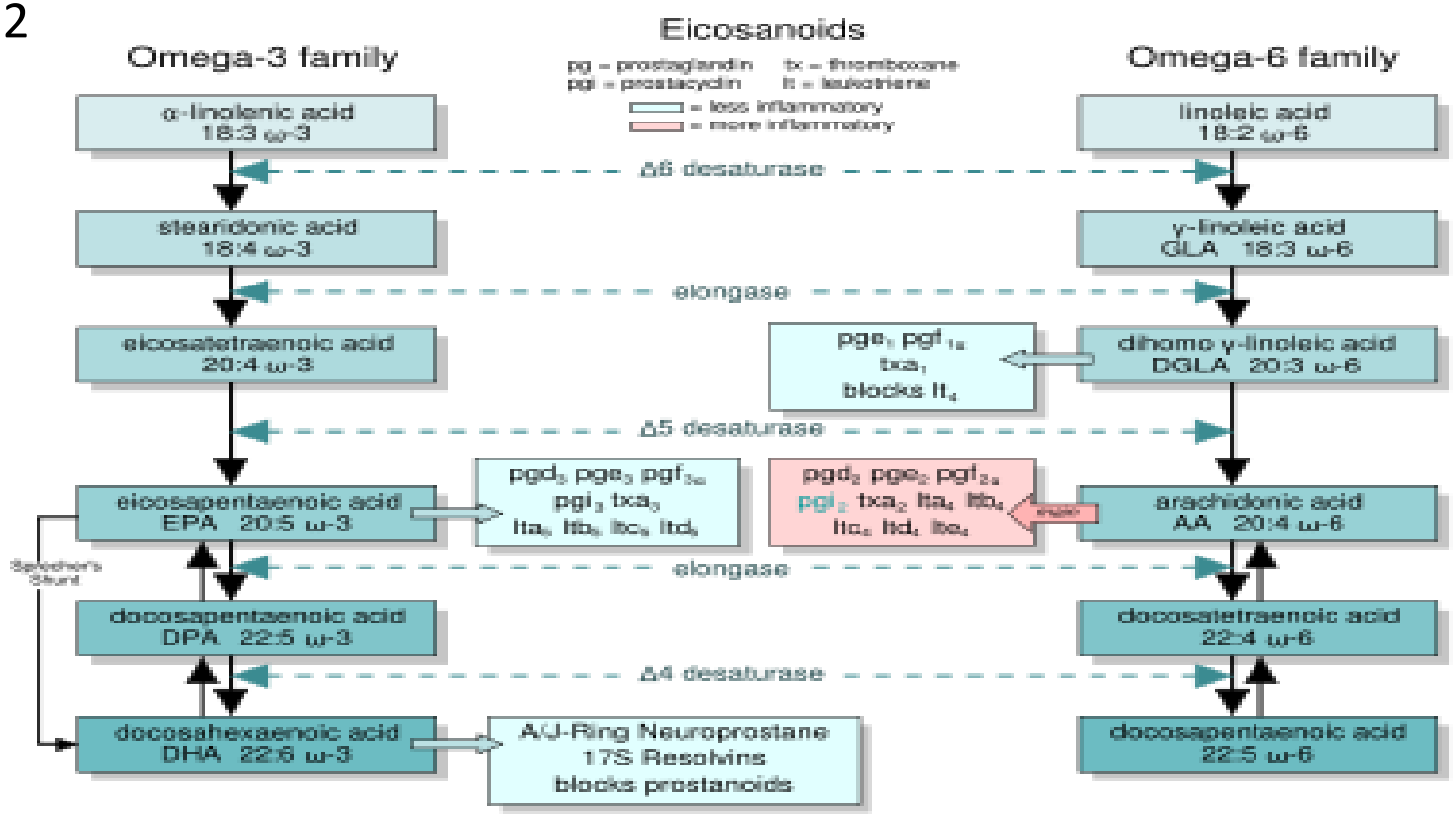
Essential Fatty Acid Supplementation

Fish oil supplementation (2.7-5.1 gm per day) demonstrated an ability to prevent or delay relapse of in both Crohn's disease and Ulcerative Colitis

Reference No. 2



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Example of Essential Fatty Acid Supplement

One capsule contains:

1. Fish Oil – 400 mg **(30% EPA/20% DHA** = 50% EFA)
2. Flaxseed Oil – 400 mg (58% ALA)
3. Borage Seed Oil – 400 mg (22% GLA)

Dosage: 3 capsules/d for maintenance

4-6 capsules/d for therapeutic purposes

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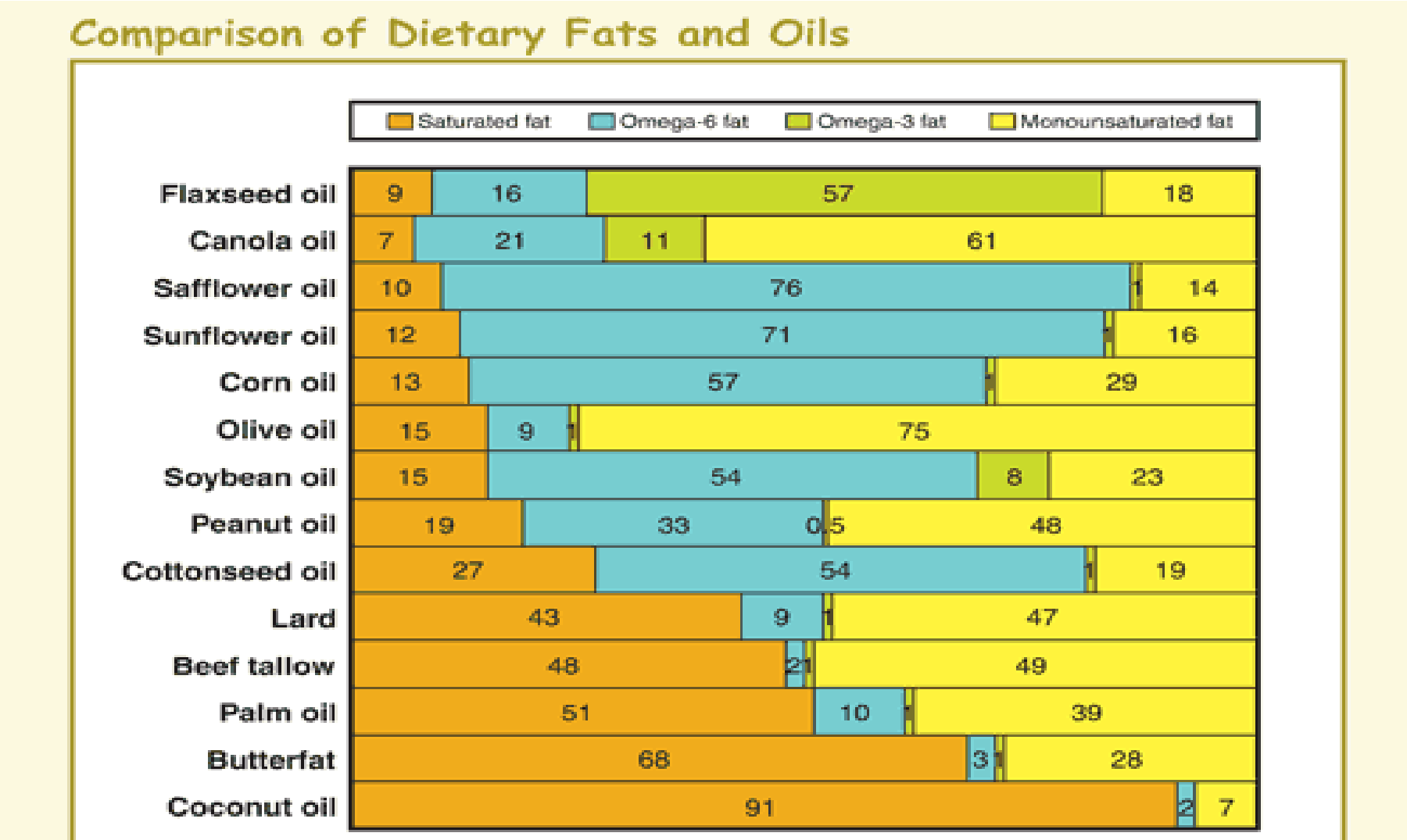
Olive Oil & Canola Oil have most monounsaturated fat



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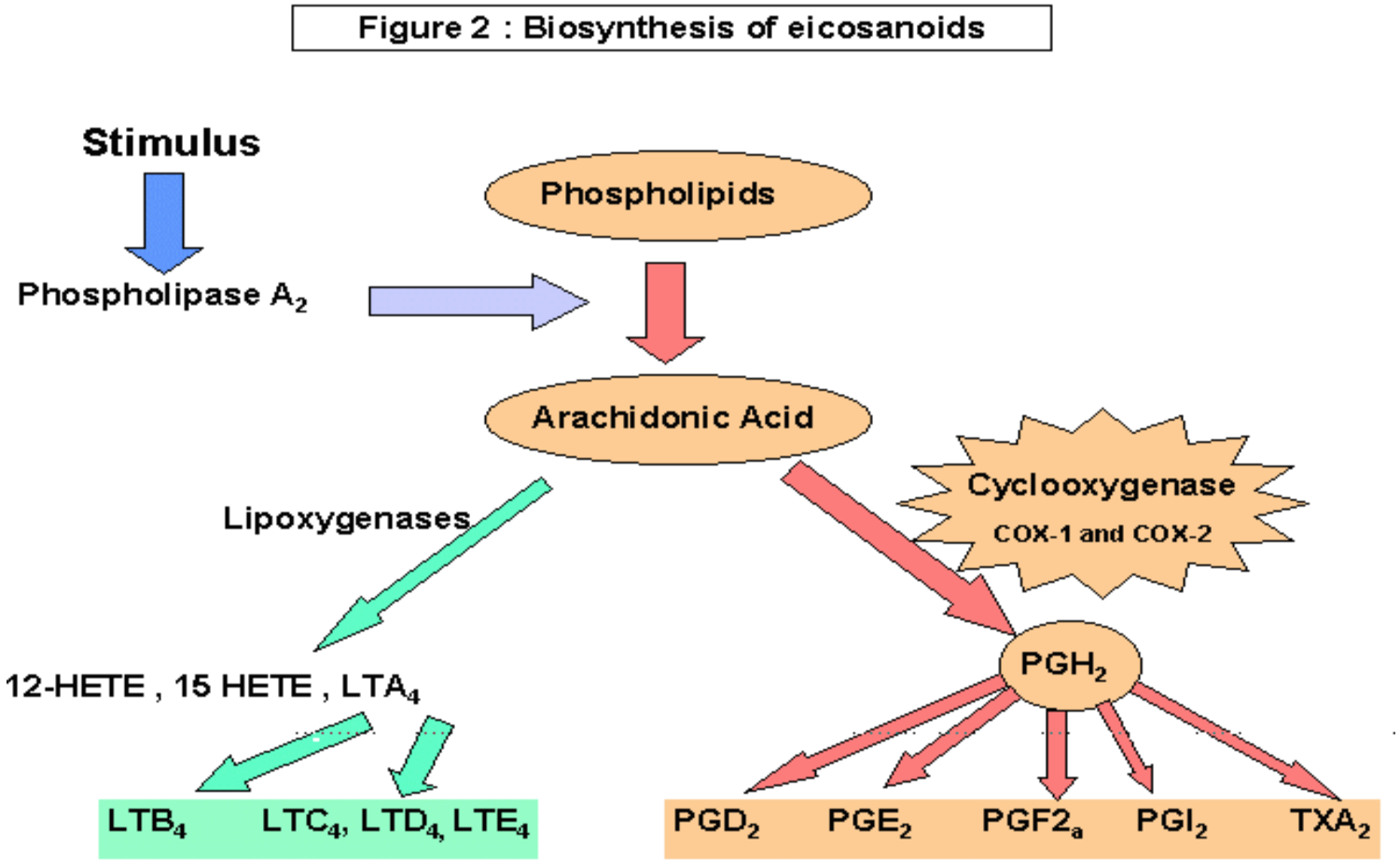
Certain natural agents block COX and LOX without producing GI irritation, bleeding, liver or kidney damage



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Natural Anti-inflammatory Agents

Curcumin – Small open trial with curcumin supplementation 5 UC patients and 10 CD patients:

9/10 CD patients showed significant improvement

4/5 UC patients reduced or eliminated their need for medication.

A Larger study with UC patients (no=89) showed that 1,000 mg curcumin, 2x daily resulted in clinical improvement and a decreased relapse rate

Boswellia – 350 mg, Boswellia, 3x daily showed similar efficacy as anti-inflammatory drug sulfasalazine (1,000 mg, 3x daily) in reducing symptoms or lab abnormalities of patients with UC. Rate of remission was 82% with boswellia extract and 75% with sulfalsalazine

Another study showed similar efficacy of boswellia extract compared to mesalazine in CD patients.

Reference No 2

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Example of Natural Anti-inflammatory Supplement:

1. Curcumin - (COX and LOX and TNF) – 600 mg
2. White Willow Bark Extract (15% salacin) - (COX) – 100 mg
3. Ginger - (5% gingerols) (COX and LOX)– 150 mg
4. Boswellia – (70% boswellic acids) (LOX) – 600 mg

Dosage: – 2-8 capsules/day

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GI Irritation From Food Allergies/Sensitivities

Food Allergy Testing by Allergist (MD):

•**Blood tests** – RAST and Elisa food testing for IgG + IgE food antibodies

•**Skin tests** – small punctures made with needles containing tiny amounts of allergens.

The most common food allergens include the big 8:

1. peanuts
2. milk
3. eggs
4. tree nuts
5. fish
6. shellfish
7. soy
8. wheat

These foods account for about 90% of all allergic reactions

.

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Other Tests

Celiac Profile Test:

Tissue Transglutaminase Antibodies (tTG-IgA) – The tTG-IgA test will be positive in about 98% of patients with celiac disease who are on a gluten-containing diet. If positive then must avoid wheat, barely, rye products, and many processed foods containing gluten.

Electrodermal Screening - For Food Sensitivities:
Tests sensitivity to over 300 of the most common foods

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3. Improve Gut Barrier – rebuild healthy intestinal cells and lining

How?

- Reduce Inflammation – food and supplements
- Improve Digestion – digestive enzymes, prebiotics, probiotics
- Eliminate Irritation Foods – allergy/sensitivities/gluten
- L-Glutamine Supplementation
- B-Vitamins (B-50 Complex)
- Protein Requirement
- Reduce Foods Linked to IBD

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L- Glutamine

L-Glutamine – the primary food for intestinal cells (energy)

L-glutamine supplementation shown support health of intestinal tract lining (even in chemo and radiation patients).

L- Glutamine also strengthens immune function (decreasing URT in overtraining athletes

L Glutamine supplementation also increases glutathione levels – an important cellular antioxidant and detoxification agent

Dosage: 2000 – 5000 mg per day (can be added to protein shake or juice)

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Blood-based Nutrient Deficiencies Common in IBD:

- Iron deficiency – 40%
- Vitamin B12 – 48%
- Folic Acid – 54-64%
- Magnesium – 14-33%
- Potassium – 6-20%
- Retinol – 21%
- Vitamin C – 12%
- Vitamin D – 25-65%
- Zinc – 40-50%

Reference No 2

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B-Vitamins (B-50 Complex)

Energy Production in Intestinal Cells:

Requires: Vitamin B1, B2, B3 (niacin) Pantothenic acid, Biotin

DNA and RNA Synthesis For New Cells:

Folic acid, Vitamin B12

Blood Tests: RBC Folate (erythrocyte folate)

Serum Vitamin B12

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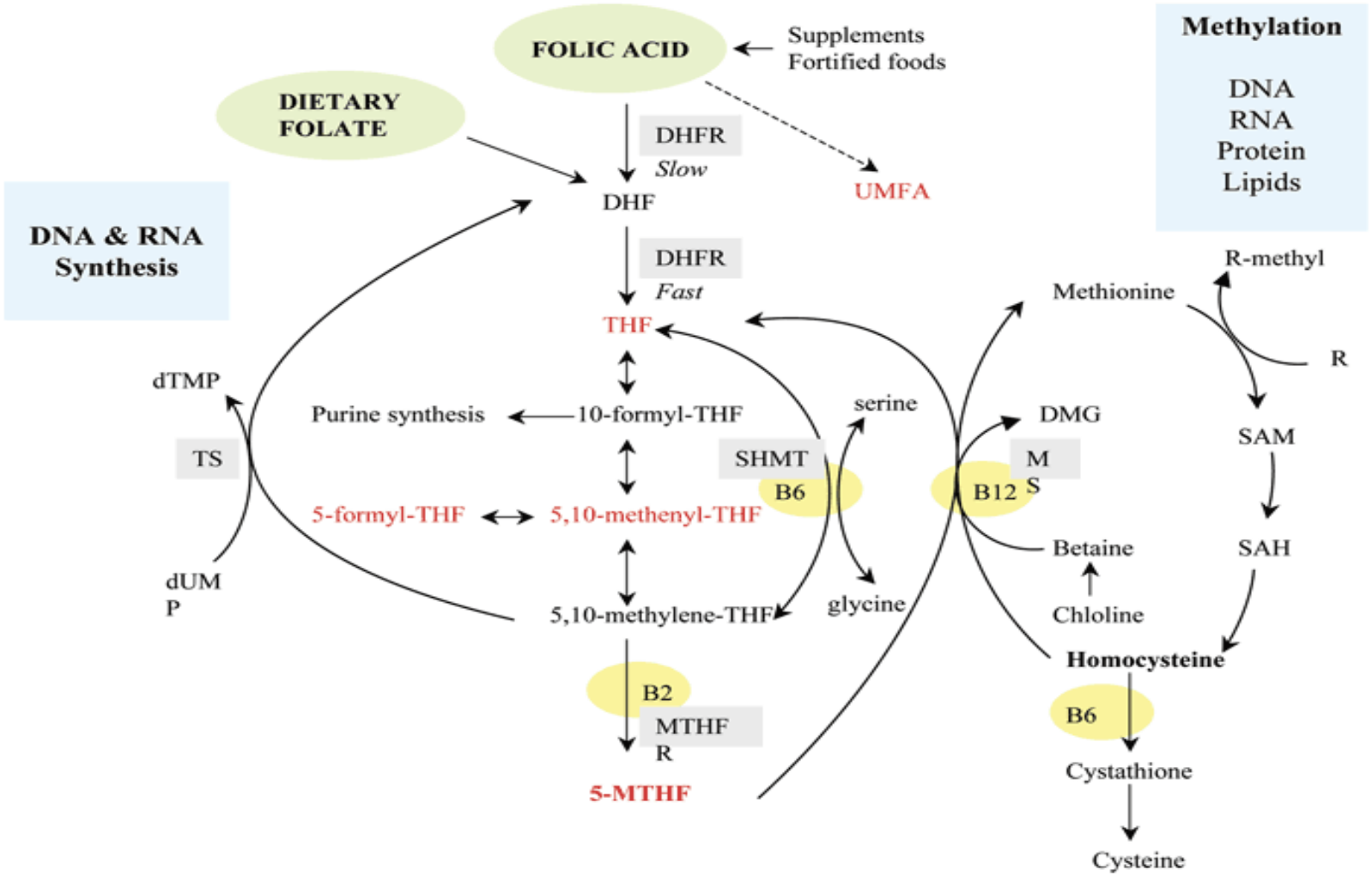
Folic Acid and Methyl Folate Considerations



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Antioxidants

Antioxidant supplementation suppresses production of inflammatory prostaglandin hormones via COX and LOX suppression

Cell Maturation – Vitamin A, Vitamin D, and Carotenes – required for normal cell development (maturation)

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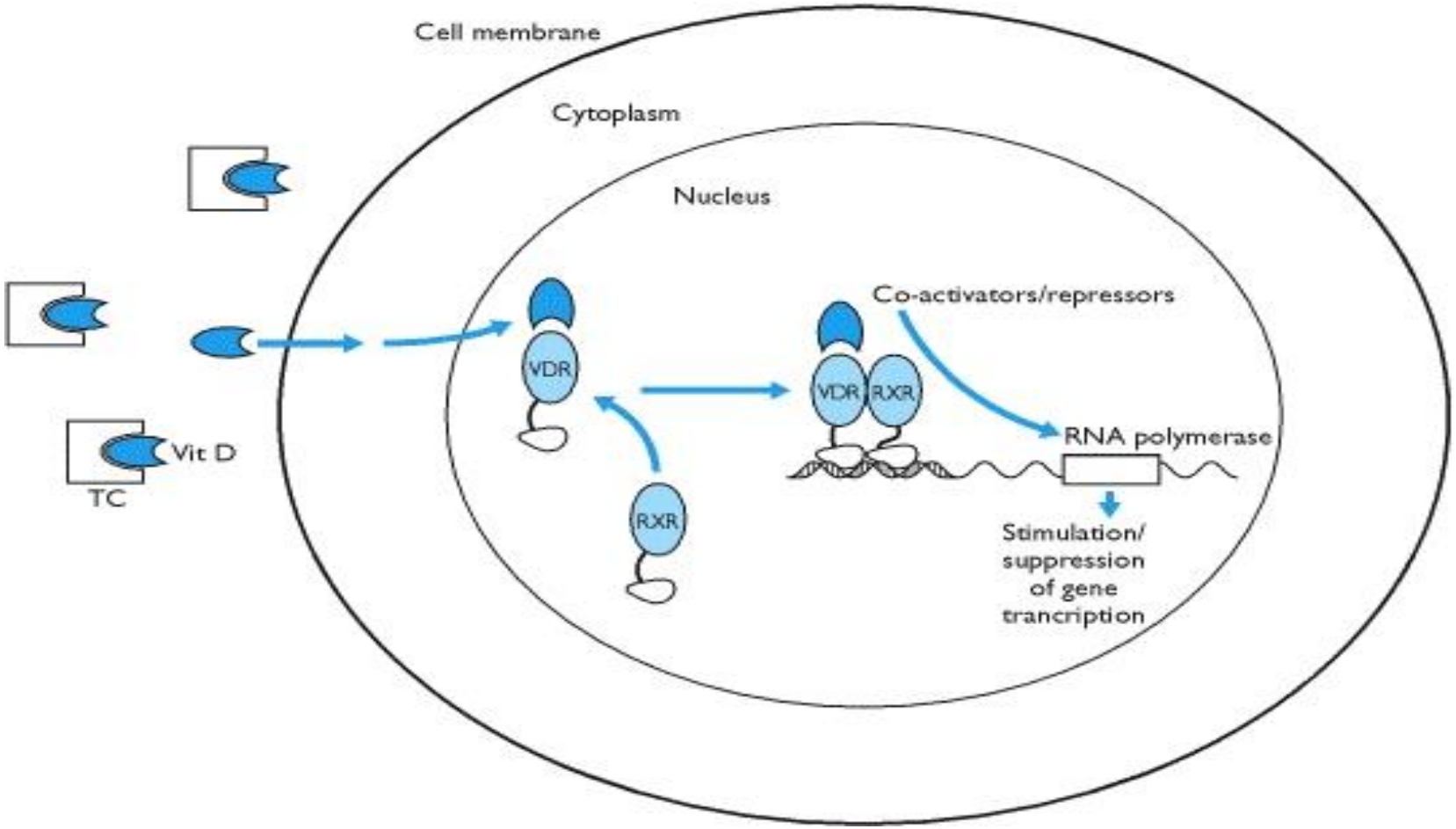
Vitamin D and Vitamin A Slow Rate Of Cell Division and Increase Maturation



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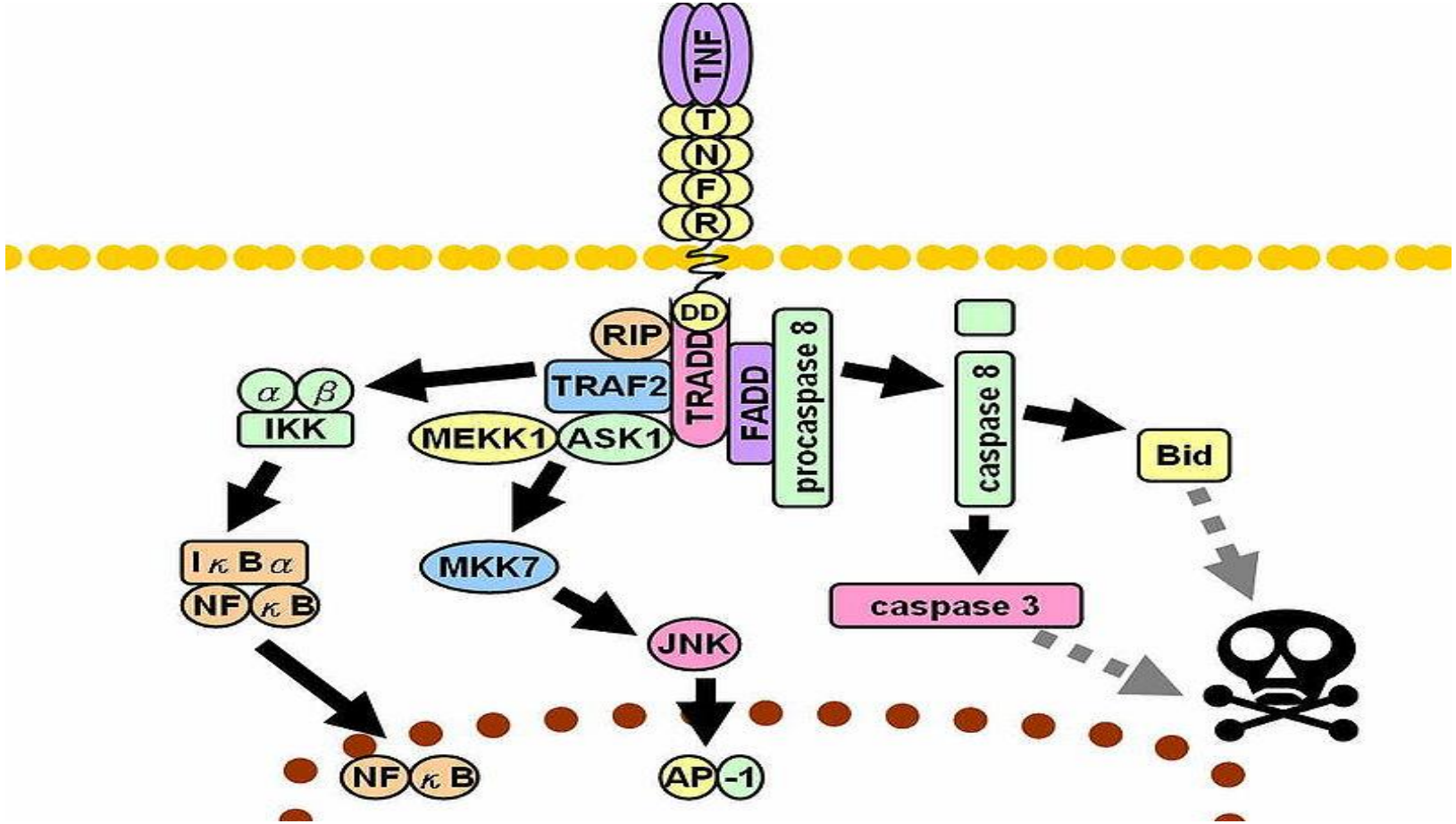
4. Oxidation and Inflammation via TNF: The role of antioxidants (vitamins C, E, beta-carotene, selenium)



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Example of High Potency Multiple Vitamin and Mineral

Multiple Vitamin and Mineral		
Vitamin A		2,500 I.U.
Beta Carotene		15,000 I.U.
Vitamin C		1,000 mg
Vitamin D		1000 I.U.
Vitamin E	succinate	400 I.U. (natural)
Thiamin		50 mg
Riboflavin		50 mg
Niacin		50 mg
Vitamin B-6		50 mg
Folic Acid		400 mcg
Vitamin B-12	methylcobalamin	50 mcg
Biotin		300 mcg
Pantothenic Acid		50 mg

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High Potency Multiple Vitamin and Mineral Continued

Multiple Vitamin and Mineral Continued		
Calcium		500 mg
Iron		6 mg
Magnesium		200 mg
Zinc		15 mg
Selenium		200 mcg
Copper		2 mg
Manganese		5 mg
Chromium		50 mcg
Molybdenum		50 mcg
Bioflavonoids		50 mg
Lutein		6 mg
Lycopene		6 mg

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Protein Requirement

25-80% of patients with IBD shown to ingest less than required protein (Reference No 2)

Protein Required for:

1. Lean mass
2. Bone mass
3. Immune System – immunoglobulins, cytokines, antibodies
4. Tissue repair and regeneration

Requirement = 1.0 – 1.25 gm of protein for each kg you weigh

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Meet Your Protein Requirement

Low Fat Protein Sources:

Chicken Breast, Turkey Breast (3 oz) ----------25 gm

Most Fish (3 oz) ----------15-20 gm

3 Egg Whites ---------- 21 gm

Cottage Cheese (3 tablespoons) ----------10 gm

Non Fat or 1% Milk or Yogurt (8 oz) ----------9 gm

Kidney beans (1/2 cup) ----------7.5 gm

Most beans and peas (1/2 cup) ---------- 4–6 gm

Cooked Pasta (1 cup) ---------- 7 gm

Cooked Rice (1 cup) ---------- 4 gm

Soy Milk (1 cup) ---4 gm; Soy Cheese (1 oz) ------7 gm

Bread (1 slice) -----2–3 gm: Bagel (1) ----------7 gm

Most Fruit and Vegetables (1/2 cup) ----------1-3 gm

Protein Shake Mix ----------20-25 gms per scoop
(whey, egg white, soy)

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Reduce Foods Linked to IBD

- It has been hypothesized that changing diets are altering the gut microbiota towards dysbiosis and may thus be driving an increase in the incidence of inflammatory diseases.

- Dietary factors apparently associated with dysbiosis in animal models include **high-fat, high-carbohydrate, and low-fibre diets.**

- These diets are associated with lower levels of short-chain fatty acids (SCFAs), produced by the microbiota, leading to inflammation

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5. Stress & Emotions in IBD

- Stress and emotions can influence the microbial composition of the gut through the release of stress hormones or sympathetic neurotransmitters that influence gut physiology and alter the habitat of the microbiota.

http://journal.frontiersin.org/article/10.3389/fnint.2013.00070/full

- Cortisol can alter gut permeability and barrier function, and thus contribute to variations in gut microbiota composition

O'Mahony et al., 2011.

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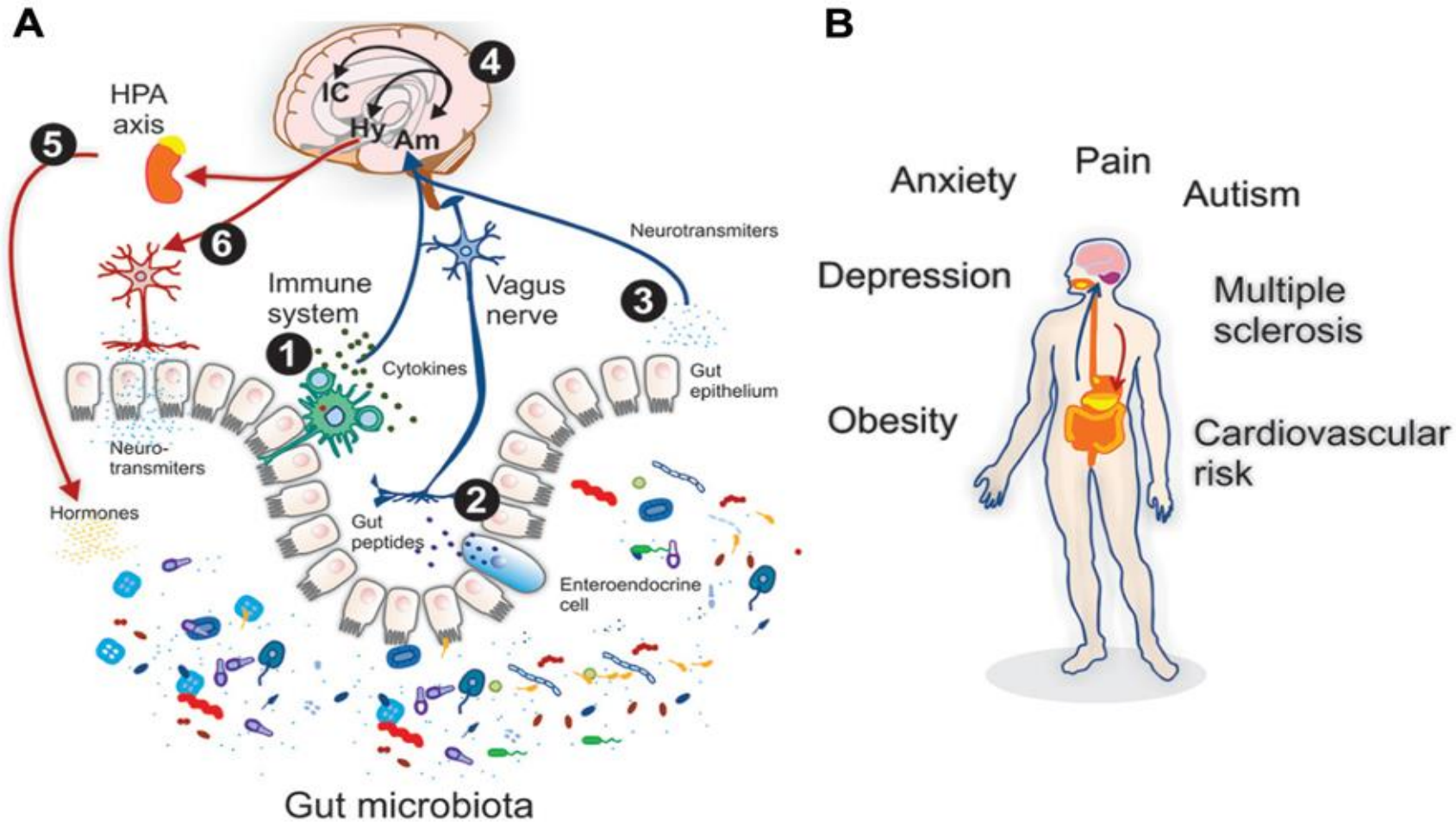
Stress and Emotions in IBD



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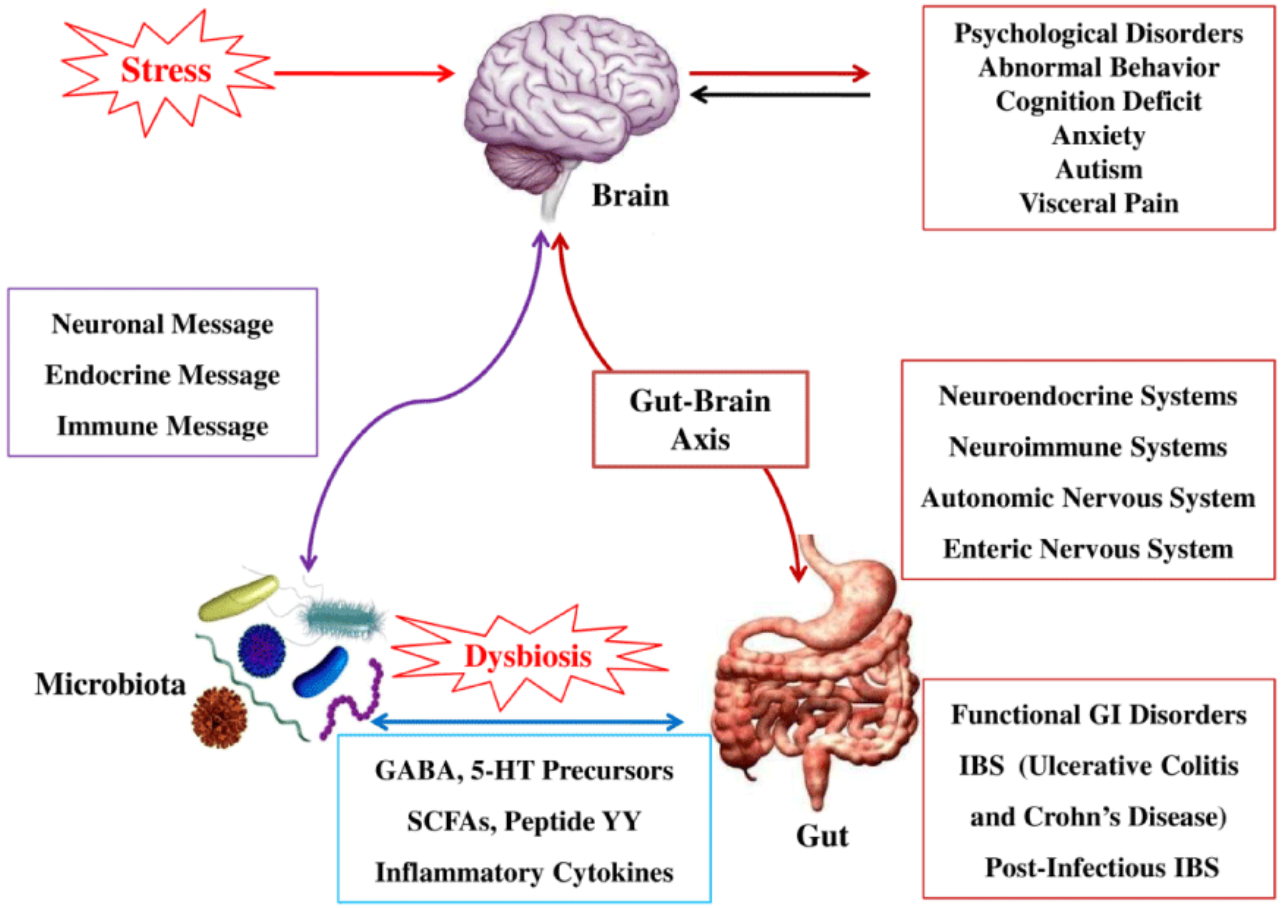
Stress and Dysbiosis/Inflammation



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Stress and IBD

- Studies show strong evidence that exposure to stress, and release of catecholamines and norepinephrine into the GI tract during stress may be responsible for the dysregulation of the gut-brain axis, via changing the GI motility, secretion of mucus and epithelial cells, thus leading to the different diseases of the gut.

Animal Studies - stress during the early maturity life in animals produces microbiota changes associated with inflammatory cytokines and increased levels of corticosterone

- http://www.jscimedcentral.com/Pharmacology/pharmacology-2-1016.php

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Harvard Gazette- May 2015

http://news.harvard.edu/gazette/story/2015/05/meditation-may-relieve-ibs-and-ibd

Meditation/Progressive Relaxation:

A pilot study has found that participating in a nine-week training program including elicitation of the relaxation response had a significant impact on clinical symptoms of the gastrointestinal disorders irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) and on the expression of genes related to inflammation and the body's response to stress.

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Meal Plan Ideas: Two Staple Nutrition System – Protein and Complex Carbs

At Each Meal Include:

- 1 Low Fat Protein Selection
- 2-3 Carbohydrate Selections

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Example

Breakfast:

Low Fat Protein: Low Fat Yogurt

Complex Carbohydrate: With High Fiber Cereal with a few berries

Or: Whey Protein Shake with added ground flaxseed powder, berries and/or other fruits, low fat plain yogurt, water and ice cubes

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Lunch:

Low Fat Protein: Chicken Burger (or veggie burger) or Turkey Sandwich

Complex Carb: Whole Wheat Bun and Tomato and lettuce

Complex Carb: Small Salad (oil and vinegar dressing) - optional

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Dinner:

Low Fat Protein: Broiled Salmon

Complex Carbs: Broccoli or other cruciferous vegetable

Complex Carb: Small Fruit Salad

Plus: a Solution-Substitution at critical points in the day

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Consider Functional Foods

1. Live Bacterial Culture Foods – low fat yogurt, sauerkraut, kefir, miso, pickles, tempeh, kimchi (Korean sauerkraut)

2. 14 mushroom blend – 2 teaspoons/d (www.mushroomharvest.com)

3. Vegetables with FOS and Inulin

Also - Try removing highly allergenic foods such as wheat, corn, and non-fermented dairy products, and ensure adequate fiber and low sugar and refined carbohydrates

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Supplement Considerations

1. Probiotic
2. Prebiotics with Digestive Enzymes
3. Essential Fatty Acids (borage, flax, fish oils)
4. Natural Anti-inflammatory (curcumin etc.)
5. High Potency Multiple Vitamin (antioxidants B-vitamins, vitamin D, vitamin A etc.)
6. Additional Vitamin D (2000 – 5000 IU/d)
7. L-Glutamine (2,000 – 5,000 mg/d)

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Mind/Body

To reduce release of stress hormones and calm the nervous system:

- Meditation
- Progressive Relaxation
- Yoga

- Physical Exercise – moderate (if you push too hard you'll secrete too much cortisol)

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14. Diverticular Disease

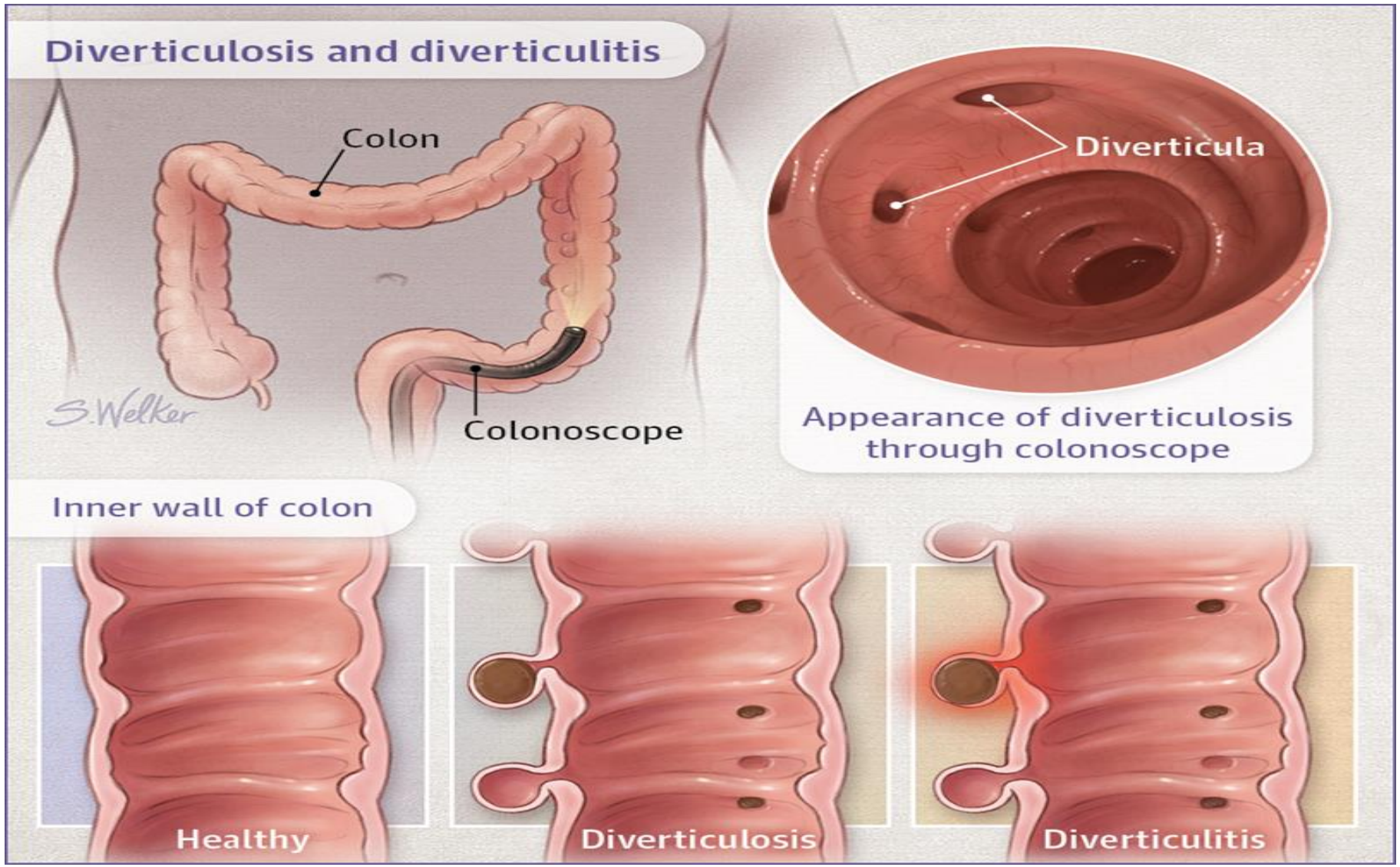
- **Diverticulosis:** Diverticulosis is a term used to describe the presence of colonic diverticula, small sac-like outpouching of mucosal and submucosal layers of the colonic wall. Diverticular disease is a term used to include diverticulosis and diverticulitis.

- The two most common and well-recognized complications are acute episodes of bleeding and diverticulitis. **Reference**: Boynton W, Floch M. New strategies for the management of diverticular disease: insights for the clinician. Therap Adv Gastroenterol 2013 6(3):205-21 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3625022/

- This is uncommon before the age of 40 and increases in incidence after that age (10% of the population over 40) Helps DD from IBD

- Diverticula are thought to be caused by increased intra-colonic pressure secondary to constipation leading to weaknesses in the colon wall giving way to diverticula. Other causes *may* include colonic spasm due to dehydration or low-fiber diets

- Fiber causes stools to retain more water and become, softer and easier to pass.


Diverticulosis and diverticulitis
Colon
Colonoscope
S.Welker
Diverticula
Appearance of diverticulosis through colonoscope
Inner wall of colon
Healthy
Diverticulosis
Diverticulitis

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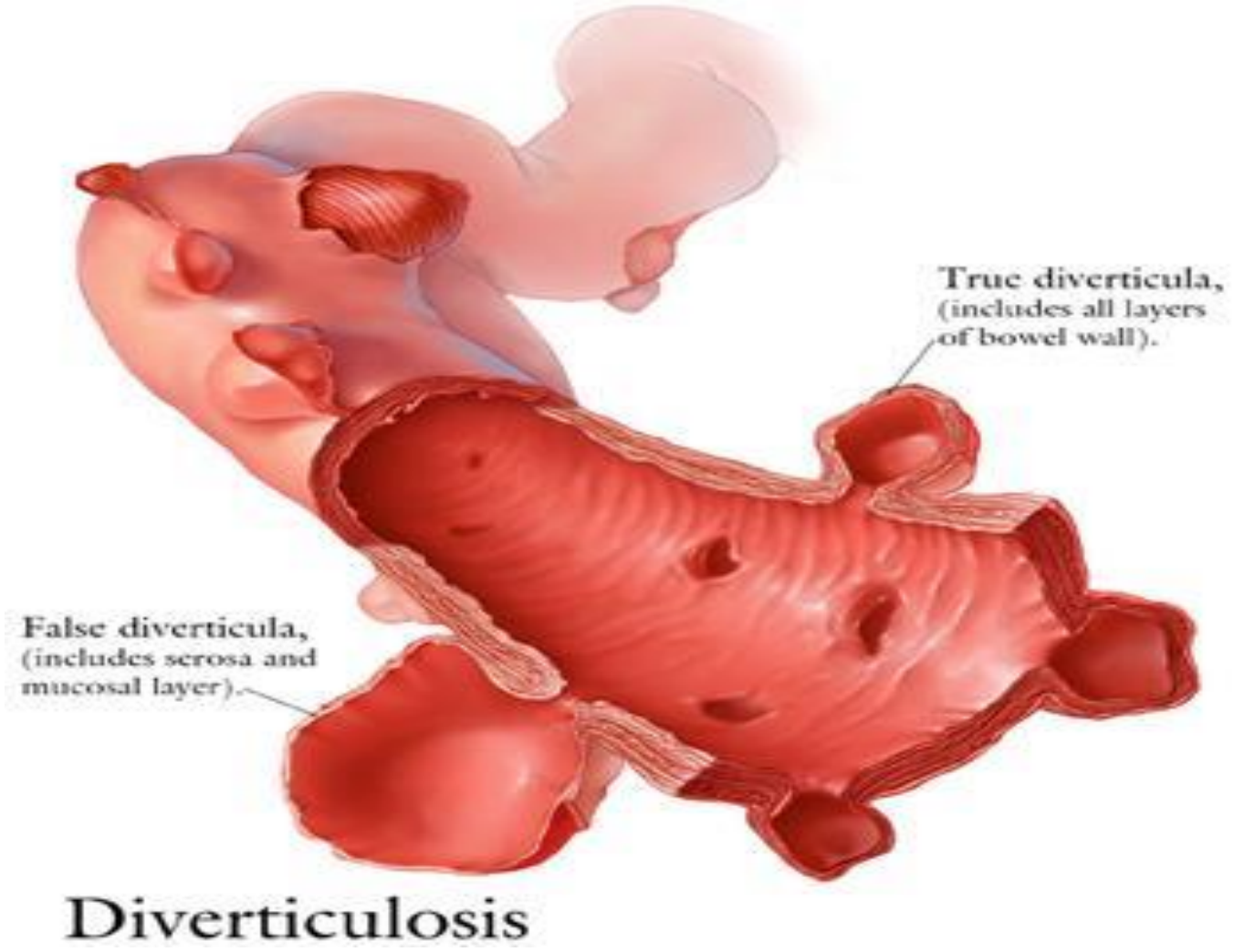
Colonic Diverticula



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Diverticular Disease

Symptoms: Overview

1. Bleeding from the bowel (variable amounts)
2. Bloating
3. Abdominal pain/cramping after meals in the left lower abdomen
4. Changes in bowel movements (diarrhea or constipation).
5. Sometimes, symptoms include nonspecific chronic discomfort in the lower left abdomen

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2012 Systematic Review of high-fiber therapy in diverticular disease

C, Daniels L, Vrouenraets BC, Boermeester MA. A systematic review of high-fiber therapy in diverticular disease. Int J Colorectal Dis. 2012 4:419-427 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3308000/

Historical Perspective: The Fiber Hypothesis

- While Burkitt was in Uganda, he found that diverticulitis was virtually nonexistent in rural Africa. He investigated fibre intake, stool weight and transit time, by comparing a rural Ugandan population to an English population. The Ugandan population had a lower average transit time and a lower stool volume compared to the English population who had a diet with higher refined sugar and lower dietary fibre.

- The hypothesis is that decreased dietary fibre intake results in decreased intestinal contents and smaller size of the lumen. This in turn results in the transmission of muscular contraction pressure to the wall of the colon rather than to the contents of the lumen.

- The result of increased pressure on the wall is the formation of diverticula at the weakest point in the wall, namely the sites of penetration by blood vessels, called vasa recta

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- The initial hypothesis of Burkitt and Painter in 1971, which was based on a fibre deficiency as crucial factor in the aetiology of diverticular disease, has weaknesses in the evidence when one considers the populations under study.

- The increased lifespan of western populations throughout the twentieth century may parallel the increasing prevalence of diverticulosis. In the epidemiological studies, life expectancy has improved in the last 80 years in the Western world.

- On the African continent, life expectancy remains low. The World Health Organisation data report a life expectancy of 51 years for both South Africa and Kenya, the African countries from which necropsy data were referenced by Burkitt and Painter.

- The prevalence of diverticular disease increases with age to up to 50–66% in patients older than 80 years

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- The fibre hypothesis was studied in a large prospective follow-up study consists of a cohort of 51,529 male US health professionals, enrolled and interviewed in 1986 and interviewed about developing diverticular disease in 1990 and again in 1992.

- Fibre intake of individual participants has been measured before development of diverticular disease. **In this cohort, fruit and vegetable intake, cellulose, hemicellulose and lignin are inversely associated with the risk of symptomatic diverticular disease**.

- **Insoluble fibre reduces the risk of diverticular disease by 37% and cellulose by 48%**. Epidemiological and observational studies have been the two predominant approaches to illuminate the role of diet and lifestyle in the prevalence of diverticular disease.

- The epidemiological approach is currently confounded by the lack of available up-to-date data on prevalence in different populations.

- Despite the lack of evidence, high-fibre diet as treatment for symptomatic diverticular disease, has been recommended in several guidelines.

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- However, intracolonic pressures have been recorded in patients with diverticulosis. Segmentation of the colon can generate excessively high pressures favoring herniation. The hypothesis is that diverticula develop due to high intracolonic pressure at points of weakness in the muscular wall where the vasa recta insert [West and Losada, 2004].

- It has been proposed that the chronic inflammation in diverticular disease is similar to that in inflammatory bowel disease (IBD) Di Mario *et al*. 2006

- The role of bacterial flora has been investigated in the pathogenesis of diverticular disease. Alteration of bacterial flora occurs as a result of slow colonic transit and stagnation of fecal material in the diverticula seen in colonic diverticulosis, which in turn triggers intestinal inflammation by impairing mucosal barrier function and upregulating inflammatory cytokine release [Tursi *et al*. 2007].

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- Low fiber diet is also associated with changes in colonic flora with significant increase in anaerobic counts. Since diverticulosis is associated with low fiber diet, dysbiosis is probably common in patients with diverticular disease. Probiotics may restore the balance of gut flora by decreasing pathogenic gram negative bacteria [Bengmark, 1998] and have been proposed to be used in diverticular disease to prevent inflammation.

- There is evolving evidence that inflammation, dysbiosis, visceral hypersensitivity and colonic dysmotility may all play a potential role in the etiology of diverticular disease. Multiple clinical trials are ongoing to evaluate a few agents that act on these factors.

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Acute Diverticulitis - Medical management includes dietary modification and use of antibiotics targeting common gut bacteria, which is successful in 70–100% of acute uncomplicated diverticulitis [West and Losada, 2004; Di Mario *et al*. 2006; Tursi *et al*. 2007; Rafferty *et al*. 2006].

Large diverticular abscesses (>3 cm) should undergo percutaneous drainage under radiological guidance.

However, surgical management is reserved for patients with signs of bowel obstruction, perforation, peritonitis or hemodynamic instability, or those who fail medical management.

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Managing Chronic Diverticular Disease:

- **Fiber**

The National Diverticulitis Study Group (NDSG) has made a level 1 recommendation for dietary fiber greater than 10 g/d and preferably between 20 and 30 g/d for all patients with diverticular disease except for those suffering from an acute attack.

The effectiveness of fiber for managing chronic diverticular disease symptoms still needs to be confirmed with high quality randomized clinical trials.

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- **Anticholinergic/Antispasmotic agents**

The rationale for using anticholinergic and antispasmotic agents is based on the observed hypermotility of the sigmoid colon in many patients with symptomatic disease [Bassotti *et al*. 2004].

Patients with diverticulosis were found to have higher resting, postprandial and neostigmine-stimulated pressures in the colon compared with controls [Huizinga *et al*. 1999].

Altered motility is thought to contribute to symptoms of chronic diverticular disease although the definite correlation is yet to be established.

- **Non- absorbable Antibiotic:**

Rifaximin is a poorly absorbed antibiotic used for hepatic encephalopathy and traveller's diarrhea in the United States. It is effective against Gram-positive and Gram-negative bacteria and has high bioavailability in the gastrointestinal tract.

It has been shown that rifaximin could be useful in irritable bowel syndrome and small bowel bacterial overgrowth by reducing bloating, abdominal pain, flatulence and loose stools

- **Anti-inflammatory agent: mesalamine**

Mesalamine has been investigated in multiple studies as a single agent to achieve and to maintain remission.

Studies suggest that mesalamine is not only effective in achieving remission but also in maintaining remission in patients with recurrent symptomatic diverticular disease if given continuously.

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- **Probiotics**

They have been used in the management of various colonic conditions including constipation, diarrhea, bloating, *Clostridium difficile*colitis, irritable bowel syndrome, inflammatory bowel disease and diverticulitis.

The rationale for the use of probiotics is based on the theory that endogenous intestinal microflora play a crucial role in the pathogenesis of these disorders [Quigley, 2007].

The use of probiotics will restore the normal intestinal flora that may have been altered in diverticular disease due to stasis and reduced colonic transit time.

There are few data available about the use of probiotics in diverticular disease. Most studies were small and uncontrolled. In one prospective open trial by Fric and Zarovral, *Escherichia coli* strain Nissle 1917 was administered to 15 patients with uncomplicated diverticular disease [Fric and Zarovral, 2003]. These patients had longer periods of remission and improved abdominal symptoms after receiving probiotic compared to before treatment.

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C, Daniels L, Vrouenraets BC, Boermeester MA. A systematic review of high-fiber therapy in diverticular disease. Int J Colorectal Dis. 2012 4:419-427 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3308000/

- Diverticulosis of the colon is an acquired condition resulting from herniation of the mucosa through defects in the muscle layer of the bowel wall. The condition is rare in developing countries but common in Western and industrialized countries.

- Approximately 60% of humans over age 60 living in westernized countries will develop colonic diverticula.

- In the great majority of cases, the condition is asymptomatic with only 10% to 25% of affected individuals developing symptoms.

- Symptomatic diverticular disease results in an annual hospitalization rate of 130,000 in the USA.

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JAMA Patient Page: Diverticulosis and Diverticulitis
https://jamanetwork.com/journals/jama/fullarticle/2552211

Most people who have diverticulosis do not have any symptoms. When diverticulosis causes symptoms, it is called diverticular disease. Symptoms can include constipation, cramps, bloating, and painless bleeding from the rectum. Diverticular disease also includes diverticulitis.

Diverticulitis occurs when diverticula become inflamed or infected. Symptoms include abdominal pain (usually on the left side), fever, nausea, vomiting, cramps, and constipation. Possible complications include

- Abscess
- Stricture (narrowing of part of the colon)
- Perforation (tear)
- Peritonitis (abdominal inflammation that can occur after a perforation)
- Fistula (abnormal connection between the colon and the bladder, small intestine, vagina, or skin)

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Diagnosis

- Because it does not usually cause symptoms, diverticulosis is often found when a test such as a colonoscopy is done for an unrelated reason. Diverticulosis and diverticular disease can also be diagnosed with a barium enema (x-ray scan).

- Diverticulitis is usually diagnosed with a computed tomography scan of the abdomen.

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Prevention

- Eating foods high in fiber can help prevent constipation and may decrease the risk of developing diverticulosis. High-fiber foods include whole grains and fresh fruits and vegetables.

- For many years, doctors recommended that patients with diverticulosis and diverticular disease avoid eating nuts, popcorn, and seeds. Eating these foods was thought to cause symptoms and lead to diverticulitis. A study published in the August 27, 2008, issue of *JAMA*, however, showed that this is not the case. The study found that eating nuts, corn, and popcorn does not increase the risk of diverticulitis or diverticular bleeding.

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Treatment

- Many cases of mild diverticulitis are treated at home with antibiotics and a few days of a liquid diet. If symptoms are severe or complications develop, may need to be treated in hospital.

- Treatment in the hospital might include intravenous antibiotics, bowel rest (no eating or drinking), or surgery.

- Surgery may also be an option if have diverticular bleeding that does not stop on its own or recurrent episodes of diverticulitis.

- **Colon Cancer:** 1:67 patients diagnosed with acute diverticulitis were shown to have colon cancer in follow-up colonoscopy. As such, recommended colonoscopy at 6-8 wks after an episode of acute, uncomplicated diverticulitis to rule out misdiagnosed colorectal cancer (**Peery AF. Colonic diverticula and diverticular disease: 10 Facts**
- **North Carolina Medical Journal. 2016 77(3):220-222** http://www.ncmedicaljournal.com/content/77/3/220.full)

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Peery AF. Colonic diverticula and diverticular disease: 10 Facts.

North Carolina Medical Journal. 2016 77(3):220-222 http://www.ncmedicaljournal.com/content/77/3/220.full

Risk Factors For Diverticular Disease

- **Low Fiber Diet** – debate still exists, but still considered good evidence, as higher fiber intake linked to fewer hospital admissions for diverticulosis and diverticulitis. The exact pathogenesis of diverticular disease of the sigmoid colon is not well established. However, the hypothesis that a low-fibre diet may result in diverticulosis and a high-fibre diet will prevent symptoms or complications of diverticular disease is widely accepted. (C, Daniels L, Vrouenraets BC, Boermeester MA. A systematic review of high-fiber therapy in diverticular disease. Int J Colorectal Dis. 2012 4:419-427 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3308000/)

- **Family History –** 3x greater incidence if sibling with diverticular disease compared to general population
- **Smoking** – dose-dependent relationship
- **Obesity** – increases risk by 80%
- **Lack of Physical Activity –** Physical activity reduces risk by 25%
- Nuts, corn, and popcorn intake **are not** associated with an increased risk of diverticulitis

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Reinhard T. Diverticular Disease. Today's Dietician 2014 16(3):46
http://www.todaysdietitian.com/newarchives/030314p46.shtml

Risk Factors Continued:

- **Aging** - The strong association of age with the presence of diverticular disease argues for the important role of the aging process in the disease. Aging causes an increase in collagen in the colonic wall, with a concomitant reduction in tensile strength, that makes herniation more likely. Slower motility results in higher colonic water reabsorption and harder feces, which causes excessive straining and higher intraluminal pressure.

- Another factor in aging that makes herniation more likely is the reduction in neurons containing nitric oxide in the myenteric plexus. These nerve cells play a role in receptive relaxation, a vago-vagal reflex.

- These reflexes control muscular contraction to propel food through the gastrointestinal tract, and colonic receptive relaxation is important in allowing for expansion to accommodate and propel the fecal mass with lower intraluminal pressure. In addition, the residual nitric oxide–containing neurons may be less functional.

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Risk Factors Continued:

- **Chronic Use of Laxatives** - Chronic use of laxatives over a long period of time could potentially damage the colon, a condition gastroenterologists have dubbed the “cathartic colon,” making it more susceptible to diverticular disease and other gastrointestinal disorders.

- **IBS -** In addition to being important for a differential diagnosis, IBS appears to significantly increase the risk of diverticular disease. A 2009 cross-sectional survey reported that subjects with IBS were much more likely to have diverticulosis than were subjects without IBS, and **subjects aged 65 and older with IBS had a nine-fold increased risk of diverticulosis**.
- Although the reason for the association is unclear, the authors suggested several possible mechanisms. Noting the higher risk in older individuals, they posited that IBS may act in conjunction with the aging-related changes in smooth muscle and neurons to promote the development of diverticular disease.

- Another possible mechanism is that **bacterial overgrowth,** a consequence of diverticula-induced stasis of colonic contents, may cause **chronic low-grade inflammation**. In turn, inflammation sensitizes afferent neurons, giving rise to visceral hypersensitivity and hypermotility, which are hallmark features of IBS.

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Risk Factors Continued:

- **Red Meat Consumption**
- **Higher Socioeconomic status** – these may correlate with more meat, less exercise, fewer plant foods etc.
- **Hypertension**
- **Number of Pregnancies** – higher parity increases risk
- **Inflammatory Foods** - Some foods, such as fruits and vegetables, lower the level of plasma inflammatory markers, while other foods and cooking methods increase these markers. Foods that promote inflammation are those containing significant amounts of starch and sugar but small amounts of fiber. The grilling method of cooking meats, poultry, and fish also promotes inflammation by forming advanced glycation end products. Even without more evidence, as with fiber and physical activity, foods that lower systemic inflammation also are associated with a reduced risk of several chronic diseases

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Reinhard T. Diverticular Disease. Today's Dietician 2014 16(3):46
http://www.todaysdietitian.com/newarchives/030314p46.shtml

Acute Cases: Medical Treatment:

- The rate of surgical intervention in complicated diverticulitis dropped from 17.4% to 14.4% from 1999 to 2005, with more emphasis on conservative treatment when possible.
- Conservative treatment for simple diverticulitis consists of consuming a low-fiber diet and taking oral antibiotics on an outpatient basis.
- If abdominal pain and tenderness are more severe, the patient will require hospitalization, particularly if the patient can't tolerate oral feedings and continues to experience a fever. In this case, treatment includes bowel rest, IV fluids, and antibiotics.
- Surgery may be required for serious complications such as obstruction, major perforations, abscesses, fistula, and phlegmon

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- The medical nutrition therapy for acute diverticulitis consists of instructing the patient to follow a low-fiber diet (10 to 15 g/day) for a short time after the attack and then increase fiber gradually to reach and maintain a high-fiber diet with adequate hydration.

- The current recommendation for daily fiber intake is 25 g for most adult women and up to 38 g for men.

- This actually represents a high fiber intake, as the average male and female consume approximately 50% and 62%, respectively, of the recommended level.

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Summing Up: Nutritional Medicine Management of Diverticular Disease:

Acute Diverticulitis – requires medical management with help of hospital dietician – antibiotics, anti-inflammatory GI drugs, liquid and/or low-fiber foods etc. (do not recommend high-fiber during acute flare-up)

Chronic Diverticular Disease and Prevention:

- Fiber – gradually increase fiber to RDA level (plus water)
- Probiotics
- Avoid high-fat meat and other inflammatory foods
- More Fruit and Vegetables
- Achieve Ideal Body Weight
- Exercise
- Smoking Cessation
- Avoid Simulant Laxatives as much as possible

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15. Simple Constipation

Simple Constipation implies constipation not caused by pathology, but rather a functional problem, only.

Transit Time – 24-72 hours (more fiber speeds it up) emotions, exercise, medications and illnesses can affect transit time as well

Incidence: Estimated to affect 28% of population (U.S.)

Rome II Criteria for Functional Constipation: 2 or more of the following must be present:

1. Straining during at least 25% of defecations
2. Lumpy or hard stools in at least 25% of defecations
3. Sensation of incomplete evacuation for at least 25% of defecations
4. Manual maneuvers to facilitate at least 25% of defecations
5. Fewer than 3 defecations per week

The most important secondary cause of constipation is **hypothyroidism**, as well as medications that can cause constipation.

Medications Causing Constipation:

- Aluminum-containing antacids
- Diuretics
- Calcium-channel Blockers
- Beta-blockers
- Antidepressants
- Antihistamines
- Anticholinergics
- NSAIDs
- Iron supplements
- Opioid drugs (morphine etc.)
- Anticonvulsants

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Other Causes of Constipation:

- Laxative abuse
- Ignoring urge to have a bowel movement

Other Health Conditions:

- Stroke
- MS
- Diabetes
- Kidney Disease
- **Hypothyroidism**
- Pituitary disorders
- Diverticulosis
- IBS
- Colon Cancer

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Treating Functional Constipation

Physical Activity – physical activity speeds up transit time and is associated with improved bowel function and decreased incidence of constipation

Fiber – patients should be encouraged to ingest at least 20-25 gm of fiber (staging it in so the body can adjust to higher intakes) by eating whole grains, breads, unrefined cereals, plenty of fruit and vegetables. Also ground flaxseed, flax meal or bran.

Insoluble fiber – acts like a sponge to bulk up developing fecal matter, increasing peristalsis and decreasing transit time. The higher water concentration also softens to stool allowing easier elimination and dilution of bowel carcinogens. Very important to drink plenty of water to assist function of insoluble fiber

Foods High In Insoluble Fiber

1. Wheat Bran (breads, breakfast cereals – 8-13 gm per serving)
2. Corn Bran (corn, popcorn)
3. Rice Bran (whole grain rice)
4. Psyllium Husk Fiber (2 teaspoons per day)
5. Ground Flaxseeds (2 tablespoons per day)
6. Beans and Peas

Act Like A Sponge, Bulking Effect, Increase Motility

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Fiber Supplements:

Bulking Agents – Psyllium Husk Fiber (i.e. Metamucil) shows most impressive results in clinical studies. But also methylcellulose (i.e. Citrucel) and polycarbophil (i.e. FiberCon) show positive results.

Ground Flaxseed – contains significant amount of insoluble and soluble dietary fiber (a personal preference of mine)

Bulking Agents can be used daily, as they work to support normal function of bowel

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Probiotics: very strong evidence supports the use of a full-spectrum (lactobacillus and bifidobacterial) probiotic daily supplement to improve functional constipation problems.

I have seen this work in very difficult cases when added to use of magnesium supplements (300-900 mg per day – staged in as explained in upcoming slides).

Prunes and Prune Juice – very good evidence support use of 8 fl oz pure prune juice daily (for stubborn cases) or consumption of 5-10 prunes

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More Dramatic Interventions:

Stimulant Laxatives: stimulate intestinal motility and secretion of water to stools (take 6-12 hours to take effect). Can cause abdominal cramping and diarrhea. Examples are senna-containing laxatives (i.e. Ex-Lax and Senokot) and Bisacodyl.

They can produce dependency and cathartic bowel (bloating, pain and incomplete bowel evacuation).

These agents should be used only occasionally if necessary and use more than 3-times per week increases risk of cathartic bowel syndrome.

Senna may potentiate the action of digoxin and other heart medications, owing to potassium depletion. The same is true for diuretics and corticosteroid drugs.

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Osmotic Laxatives – magnesium products (i.e. Milk of Magnesia and magnesium supplements – magnesium citrate) and lactulose are common osmotic laxatives that cause secretion of water into intestinal lumen.

Magnesium Citrate Protocol – 150 mg capsules: 2 capsules at bedtime and 2 capsules in morning. After 4-days, add 1 capsule at bedtime (3 in total). Then add 1 capsule to evening dose every 4 days until soft stool is produced each morning. (STOP AT 8 CAPSULES, up to 6 at bedtime)

One of the first side effects of too much magnesium is diarrhea to prevent magnesium over-dose.

Use magnesium laxatives carefully in those with congestive heart failure and any degree of kidney disease due to risk of electrolyte imbalance.

Stool Softeners – these agents act by lowering surface tension, allowing water to enter the bowel more readily – adding moisture to stools to allow strain-free bowel movements. Examples include Docusate Sodium (Docusate)

Emollient Laxatives – mineral oil is most common one, which coats and softens stools. This agent decreases absorption of fat-soluble vitamins (and CoQ10) and runs risk of aspiration in older adults and children

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Other Considerations:

Don’t Ignore Bowel Movement Urges

Garlic and Coffee have mild laxative effect in some people (and it’s not due to caffeine as decaffeinated coffee also works)

Mind-body – relaxation therapies have been shown to be helpful in some instances. Hypnotherapy has also showed some promise

Aloe Vera – anthroquinones in aloe act as stimulant laxative (50 mg of aloe extract taken at bedtime) But, may create dependency and cathartic bowel, so exercise caution

Cow’s Milk and Dairy Products may induce constipation in some children. In these cases a 4-16 week cow’s milk and dairy-free diet should be tried to see if it helps

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Primary Nutritional Medicine Strategies: Summing Up

1. More fiber-containing foods (especially insoluble fiber) and fluids
2. Exercise
3. Ground Flaxseed (or other fiber supplement- Psyllium Husk Fiber shows most impressive results)
4. Probiotics
5. Magnesium supplementation
6. Prune Juice (8oz) or 5-10 prunes
7. Don’t ignore bowel movement urges
8. Add more garlic too food
9. 3-4 cups of coffee per day (no milk)
10. Mind-body approaches

References:

Reference No 1

Reference No 2

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15. Colon Cancer Prevention

Colon CA – second leading cause of cancer death in North America (usually occurs after 50 yrs. old)

- Colon cancer often causes no symptoms until it has reached a relatively advanced stage. When symptoms do occur, they depend on the site of the lesion. Generally speaking, the nearer the lesion is to the anus, the more bowel symptoms there will be, such as:

1. Change in bowel habits
   - change in **frequency** (constipation and/or diarrhea)
   - change in the **quality** of stools
   - change in **consistency** of stools
2. **Bloody stools or rectal bleeding**
3. Stools with mucus
4. **Feeling of incomplete defecation (sensation of pressure)**
5. Reduction in diameter of feces
6. Bowel obstruction (rare)

- Thus, if 50 yrs. and older, periodic screening with fecal occult blood testing and **colonoscopy.** Remember that with colonoscopy polyps can be removed during the procedure to prevent their further progression into malignant tumors (adenocarcinoma) and to biopsy the polyps to ensure they are benign in their present state. Almost all cancers found in the colon and the rectum are adenocarcinomas, which arise from adenomas (adenomatous polyps)

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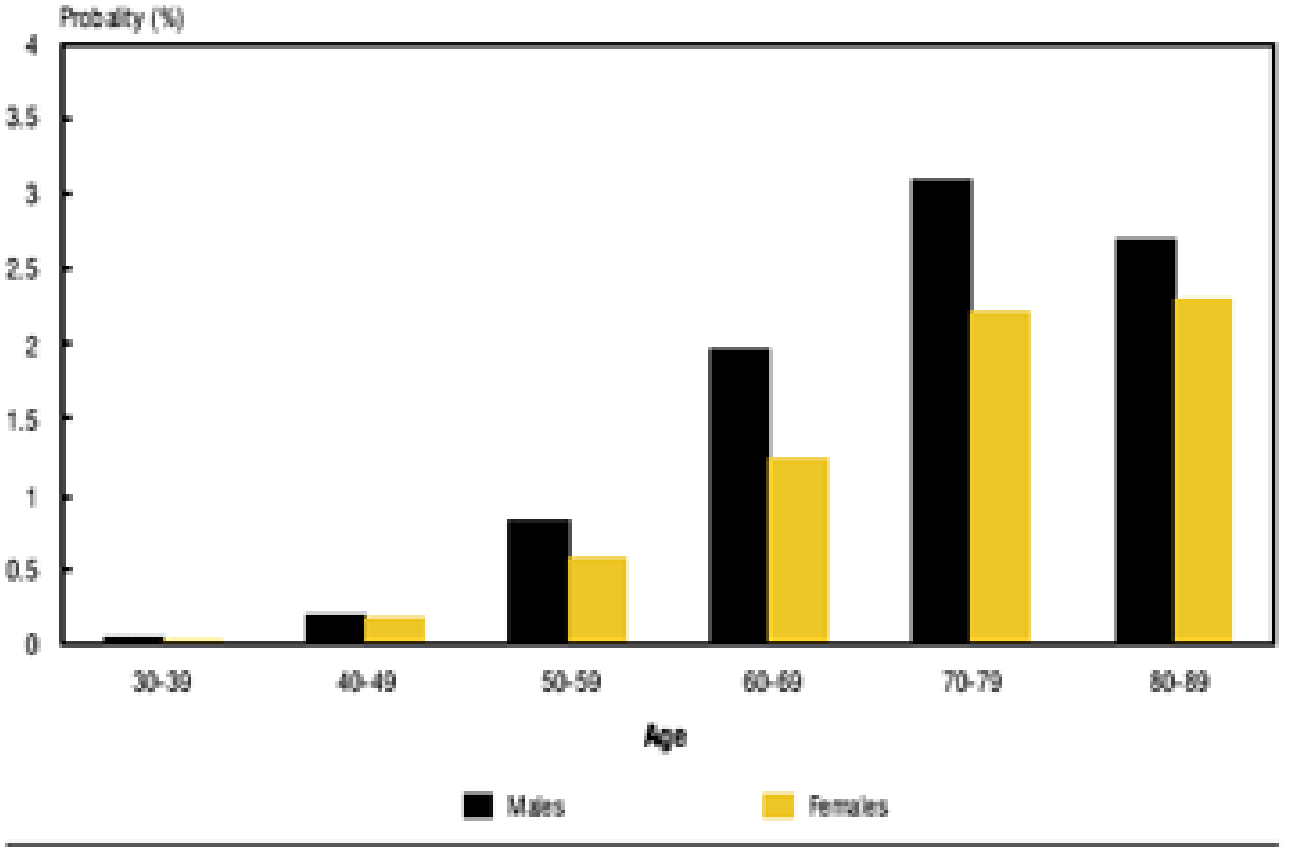
Colon CA Increases After 50

Figure 10.6

Probability (%) of Developing Colorectal Cancer in the Next 10 Years by Age, Canada



Source: Cancer Bureau, CCDPC, Health Canada

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CRC and Genetics

A small percentage of colon cancer cases are attributed to inherited genes that greatly increase risk of this disease. Between **2% to 5%** of all colon cancers arise in the setting of well defined inherited syndromes, including **Lynch syndrome**, **familial adenomatous polyposis (FAP),** MUTYH-associated polyposis, and certain hamartomatous polyposis conditions.

Familial Adenomatous Polyposis: a genetic condition. It is diagnosed when a person develops more than 100 adenomatous colon polyps. An adenomatous polyp is an area where normal cells that line the inside of a person's colon form a mass on the inside of the intestinal tract. The average age for polyps to develop in people with FAP is in the mid-teens. Most people with FAP will have multiple colon polyps by age 35. If FAP is not recognized and treated, there is a very high likelihood that a person will develop colorectal cancer. FAP and attenuated FAP are caused by **germline mutations in *APC*, which encodes a tumor suppressor that is part of the WNT signaling pathway**.

Lynch Syndrome: an autosomal dominant genetic condition that has a high risk of colon cancer as well as other cancers including endometrial cancer (second most common), ovary, stomach, small intestine, hepatobiliary tract, upper urinary tract, brain, and skin.

Reference: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3057468/

Lynch syndrome is the result of a germline mutation in a class of genes involved **in DNA Mismatch Repair System (MMR)**. The MMR system is necessary for maintaining genomic stability by correcting single-base mismatches and insertion-deletion loops that form during DNA replication.

Reference: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3057468/

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Diet and Colon Cancer: Overview

70-90% Cases Avoidable via Diet and Lifestyle:

1. Low animal fat (except fish)
2. Increase fiber
3. Calcium 1500 mg/day
4. Vitamin D 1,000 IU per day
5. Antioxidants (Vitamin C and Vitamin E)
6. Folic Acid and B12
7. Decrease Alcohol
8. Selenium
9. Cruciferous Vegetables
10. Avoid Nitrate, Charred, Smoked Foods and Other Carcinogens
11. Smoking (Long-term Smoking) (American Cancer Society): https://www.cancer.org/cancer/colon-rectal-cancer/causes-risks-prevention/prevention.html
12. Obesity – especially abdominal Obesity (American Cancer Society): https://www.cancer.org/cancer/colon-rectal-cancer/causes-risks-prevention/prevention.html

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Journal of National Cancer Institute 1996

*(Willet, W. Estimates of cancer deaths avoidable by dietary change. J National Cancer Instit.1996; 86,14:948)

In Total – 70-90% of cancer shown to be preventable

Estimates of cancer deaths avoidable by dietary change			
	Percent avoidable		
Type of Cancer	**Doll-Peto (1981)**	**Willett (1994)**	**Range (1994)**
Lung	20	20	10-30
Colon/Rectum	90	70	50-80
Breast	50	50	20-80
Prostate	*(with other)*	75	20-80
Pancreas	50	50	10-50
Stomach	35	35	30-70
Endometrium	50	50	50-80
Gall bladder	50	50	50-80
Larynx, bladder, cervix, mouth, pharynx, esophagus	20	20	10-30
Other	10	10	-
Overall estimate	**35**	**32**	**20-42**

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1. High Animal Fat Diet: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5228679/

2017 Update: Kim J Oh SW, Kim JS et al. Association between dietary fat intake and colorectal adenoma in Korean adults. Medicine 2017 96(1):e5759

- Epidemiologic studies have suggested that among various environmental factors, diet may play the most important role in the risk of colorectal cancer. The Health Professionals Follow-up cohort study showed that high red meat intake was associated with an elevated risk of colon cancer.

- A pooled analysis of case-control studies suggested that high fiber intake was inversely associated with risk of colorectal cancer.

- Some case-control studies have shown that high saturated fatty acid (SFA) intake is associated with increased risk of colorectal cancer or adenoma. In addition, animal fat intake showed a positive association with risk of colorectal cancer.

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- Recently, the incidence of colorectal cancer has sharply increased in South Korea. This trend may be because of the transition of risk factors as well as the effect of colorectal cancer screening.

- The major change in dietary pattern in South Korea includes a large increase in the consumption of animal food products and a fall in total cereal intake.

- Most colorectal cancers arise from benign adenomas that develop over several years through an adenoma-carcinoma sequence.

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- Previous studies showed a positive association between total fat intake and risk of colon cancer; this was usually attributable to fat from an animal source or SFA.

- Some case-control studies have suggested that animal fat intake shows a positive association with risk of colorectal cancer; moreover, other studies have shown that high SFA intake is associated with increased risk of colorectal cancer or adenoma.

- Our study (South Korea Study) analyzed both animal fat and SFA intake; only SFA intake was positively associated with colorectal adenoma, in part consistent with the results of prior studies.

- An early animal study demonstrated that tumor-promoting effects of dietary fat might be partly independent to its caloric density.

- With respect to SFA, a previous study suggested that diglycerides containing SFA chains induce mitogenesis of adenomas and some carcinomas in the colon, and may enhance the invasive capacity of carcinomas.

- Another experimental study demonstrated that SFA, essential for lipopolysaccharide (*LPS*) and toll-like receptor 4 (*TLR*4) activation, induces nuclear factor B activation, as well as expression of cyclooxygenase-2 (*COX*-2) and other inflammatory markers.

- Our study results suggested that high SFA intake was positively associated with colorectal adenoma, but there was no significant association between monounsaturated fat (MUFA) or polyunsaturated fat (PUFA) and colorectal adenoma.

- Recent studies have shown variable effects of specific subtypes of PUFA, such as eicosanopentaenoic acid (EPA), on colorectal cancer. It is suggested that substituting food for high medium-chain fatty acids, arachidonic acids, or an EPA-rich diet may contribute to reduced risk of colorectal cancer.

- Also, increased consumption of EPAs and docosahexaenoic acids was associated with reduced risk of colorectal cancer.

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Farhana L, Nangia-Makker P, Arbit et al. **Bile acid: a potential inducer of colon cancer stem cells**

Stem Cell Res **2016** 1:181

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5134122/

Secondary Sterols:
Lithocholic acid (LCA) and deoxycholic acid (DCA), formed from the bacterial transformation of bile acids made in the liver, are considered to be risk factors for colorectal cancer

Epidemiological studies have revealed that the incidence of colorectal cancer (CRC) among populations migrating from low-incidence to high incidence countries changes rapidly. Within one generation, the incidence of CRC reached its highest level in people migrating from Japan to Hawaii. This has been thought to be largely due to changes in diet.

This inference comes from the observation that large increases in both meat and fat-enriched diet are associated with a rise in CRC. Additionally, populations with high incidence of colon cancer also show an increase in fecal concentrations of bile acids.

These observations suggest that increased exposure of the colonic lumen to high levels of bile acids may play a role in the natural course of development of CRC and certain bile acids have been categorized as potential tumor-promoting agents, particularly for colon cancer

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- Higher levels of secondary bile acids in feces and an increased incidence of colorectal cancer (CRC) were observed in patients that consumed high-fat/low-fiber diets.

- Several epidemiological studies have also revealed an association between bile acids and CRC. The presence of CRC has been associated with a higher fecal LCA/DCA ratio and with elevated fecal secondary bile acids levels.

- Although the precise mechanism(s) by which bile acids induce colon carcinogenesis is poorly understood, DCA and chenodeoxycholic acid (CDCA)-mediated genotoxicity in normal human colonic epithelial cells as well as in tumor cells has been found to be due to DNA oxidative damage

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Conclusions

- Taken together, our current data show that certain secondary bile acids, specifically DCA and LCA, which are known for their co-carcinogenic activity, are able to induce CSCs in colonic epithelial cells.

- This is evidenced by the observation that DCA or LCA are not only able to stimulate the expression of several surface epitopes (part of antigen recognized by antibodies and immune cells for binding purposes) of colon CSCs but also the markers of EMT (The epithelial–mesenchymal transition is a process by which epithelial cells lose their cell polarity and cell-cell adhesion, and gain migratory and invasive properties to become mesenchymal stem cells; EMT is seen in the initiation of metastasis and in cancer progression.)

- These increases (epitopes and EMT) are associated with increased spheroid formation, a rise in the expression of multiple drug resistance transporter genes, and drug exclusion. DCA/LCA induction of colon carcinogenesis is found to be regulated by M3R (Muscarinic Receptor-3), which up-regulates Matrix metalloproteinases (MMP) –see next slide

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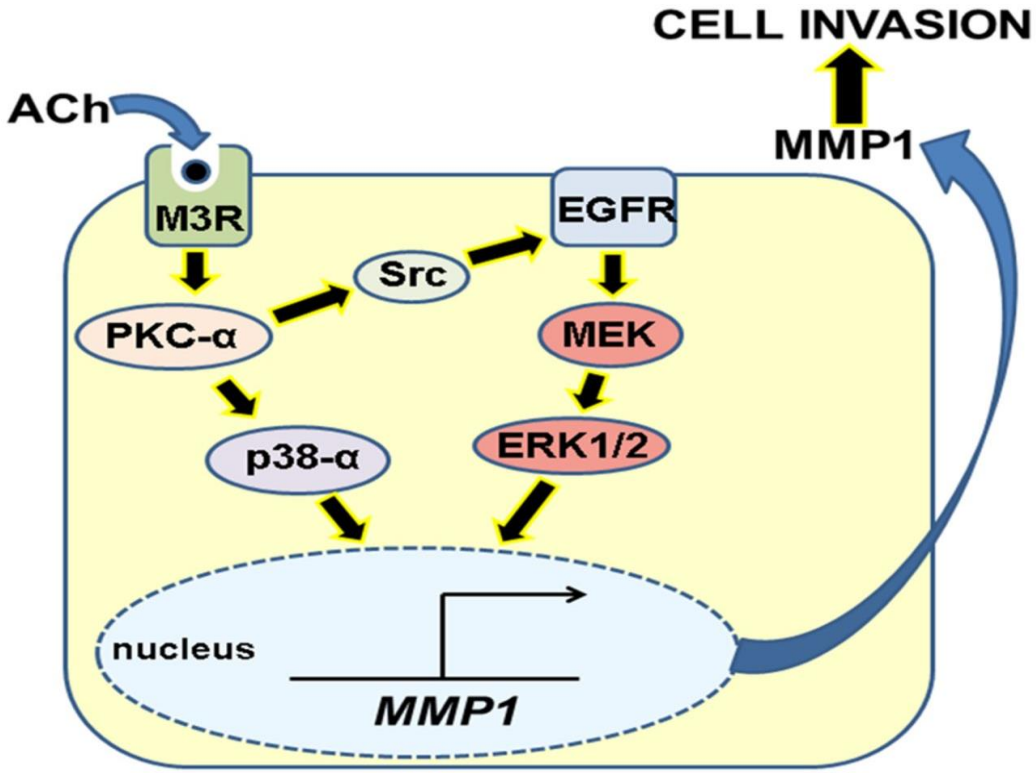
M3R Up-regulation increases MMP1

- Matrix metalloproteases (MMP) are a family of enzymes that contribute to the degradation of the extracellular matrix. The destruction of the extracellular matrix eventually leads to tumour invasion, metastasis and angiogenesis.



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2014 Update: Bile Acids and CRC- World J Surg Oncol

- Bile acids were first proposed as carcinogens in 1939. Since then, accumulated evidence has linked exposure of cells of the gastrointestinal tract to repeated high physiologic levels of bile acids as an important risk factor for gastrointestinal cancers.

- High exposure to bile acids may occur in a number of settings, but most importantly, is prevalent among individuals who have a high **dietary fat intake.** A rapid effect on cells of high bile acid exposure is the generation of reactive oxygen species and reactive nitrogen species, disruption of the cell membrane and mitochondria, induction of DNA damage, mutation and apoptosis, and development of reduced apoptosis capability upon chronic exposure.

- https://www.ncbi.nlm.nih.gov/pubmed/24884764/ 2014 Review

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2. Increasing Fiber: 2015 Update

Kunzmann AT, Coleman HG, Huang W et al. Dietary fiber intake and risk of colorectal cancer and incident recurrent adenoma in **Prostate, Lung, Colorectal and Ovarian Screening Trial**. Am J Clin Nutr 2015 102(4):881-890 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4588743/

- Dietary fiber was first hypothesized as being of potential etiological importance for colorectal cancer in the early 1970s by Burkitt, who observed lower rates of colorectal cancer among Africans who consumed a diet high in fiber

- Several biologically plausible mechanisms have been postulated to explain the link between fiber and prevention of colorectal cancer. Increased fiber intake may lead to a dilution of fecal carcinogens, reduced transit time, and bacterial fermentation of fiber to short-chain fatty acids with anticarcinogenic properties

- Questions still remain about which food sources of dietary fiber may be most beneficial against colorectal cancer development and at which stages along the adenoma-carcinoma pathway fiber may act

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- Overall, the results of this large prospective cohort of screened individuals showed an inverse association between intakes of dietary fiber, **particularly cereal and fruit fiber, and risk of incident adenoma.**

- Importantly, the reduction was **also evident for advanced adenoma, which may be more likely to progress to colorectal cancer.**

- No associations were observed between dietary fiber and recurrent adenoma risk, apart from a reduced risk of rectal adenoma among individuals with **higher cereal fiber intakes**.

- A modest inverse association was found between total fiber and colorectal cancer risk, which was statistically significant for distal colon cancer.

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- To our knowledge, this was the first study to assess the association between dietary fiber and incident adenoma risk in a population-based screening trial.

- Unlike most previous studies, individuals in this adenoma study were systematically screened at baseline, had no evidence of distal polyps on the baseline screen, and received a second screen 3 or 5 y later as part of the trial

- The inverse association between dietary fiber and incident adenoma risk observed in our study is consistent with findings from case-control studies of prevalent adenoma

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- Interestingly, a stronger protective association was also observed between total fiber intakes and risk of colorectal cancer among individuals with higher processed meat intakes.

- Whereas the results of this subgroup analysis should be interpreted cautiously, it is biologically plausible. Fiber could reduce exposure of the colorectal passage to carcinogenic *N*-nitroso compounds produced on processed meat consumption.

- Given the elevated risk of colorectal cancer for those consuming high intakes of processed meat, this novel finding suggests that fiber may reduce some of that excess risk and therefore warrants further investigation

- The findings of stronger reductions in colorectal neoplasm risk associated with cereal and fruit fiber, but not for vegetable or legume fiber, are largely consistent with the literature.

- Possible biological reasons for the observed differences in risk may stem from the type of fiber, with cereals being particularly high in insoluble fiber, which binds carcinogens and reduces transit time to a greater extent.

- Alternatively, the beneficial effects of cereal fiber could be attributable to higher intakes of fiber-rich whole grains rather than to intakes of cereal fiber per se, particularly because the previous systematic review suggested a stronger protective effect of whole grains than of cereal fiber for colorectal cancer risk

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- Nevertheless, the consistent reductions in risk associated with cereal fiber suggest that there are health benefits of high-fiber, whole-grain cereal products.

- Similarly, the reductions associated with fruit fiber may relate to the type of fiber or to other components of fruit or a synergistic interaction between fiber and other components.

- **In conclusion,** in this large prospective study, in which all individuals underwent the same colorectal screening protocol, we found evidence that high fiber intakes, particularly from cereals or grains and fruit, are associated with a reduced risk of incident colorectal adenoma and cancer. This study provides more evidence that dietary fiber may act early in the adenoma-carcinoma sequence and reduce both the risk of adenoma and cancer.

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SCFA's in CRC Prevention

- Short-chain fatty acids contain 2-5 carbon atoms and are mainly produced during fermentation by anaerobic gut bacteria of soluble dietary fiber. There is evidence to suggest that SCFA's help reduce risk of CRC, which would indicate that higher intakes of peas, beans, pectin fiber (from various fruit) may have CRC protective properties. (Nutrient Review.com http://www.nutrientsreview.com/lipids/short-chain-fatty-acids-scfa.html)

- In terms of bacteria playing a positive role in the colon, bacteria such as *Lactobacillus* and *Bifidobacter*species have beneficial effects in the gut.

- The by-products of their fermentation activities are short chain fatty acids (SCFAs), such as acetate, n-butyrate, propionate, and valerate.

- These SCFAs are utilized by epithelial cells in the gut and/or excreted in stool. Butyrate has anti-proliferative properties *in vitro* and anti-cancerous properties in mouse models.

- Thus, the influence of diet on the composition of the microbiota as well as the exposure to metabolites produced by gut bacteria (such as SCFAs), thereby influences the intestinal epithelium in ways that could reduce or increase CRC risk

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- There is also strong epidemiological evidence linking high fat consumption to high risk of colon cancer. Epidemiological data continues to suggest that African Americans have higher risk of developing colon cancer than others.

- It is possible that lower SCFAs in African Americans might explain why African Americans have higher risk of colon cancer and higher CRC mortality as well.

- Additionally, SCFAs reduce the pH of stool, and a recent study by Ohigashi et al. found that the stool from CRC patients had lower levels of acetic acid, butyric acid, propionic acid, and valeric acid and significantly higher pH than the stool of healthy controls.

- Interestingly, we observed here that the stool SCFA content is lower and pH is higher for African Americans than for participants of other races/ethnicities.

Reference: World Journal Gastroenterology 2015 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4351229/

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Legumes and CRC Risk – 2015 Meta-analysis

Scientific Reports 2015

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4350074/

We conducted a meta-analysis based on prospective cohort studies to investigate the association between dietary legume consumption and risk of CRC.

Fourteen cohort studies were finally included, containing a total of 1,903,459 participants and 12,261 cases who contributed 11,628,960 person-years.

We found that higher legume consumption was associated with a decreased risk of CRC (RR, relative risk = 0.91).

Subgroup analyses suggested that higher legume consumption was inversely associated with CRC risk in Asian (RR = 0.82) and soybean intake was associated with a decreased risk of CRC (RR = 0.85)

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- The mechanism underlying a possible protective effect of legume intake on CRC risk might be complex because of a great variety of anti-carcinogens in legumes.

- The most important anticancer composition of legume food is flavonoids, especially isoflavones. Flavonoids from legume food not only inhibit the growth of tumor cells, but also induce cell differentiation.

- The inhibitory effects of flavonoids on the growth of malignant cells might be a consequence of their interference with the protein kinase activities involved in the regulation of cellular proliferation and apoptosis.

- In addition, legumes are rich in dietary fiber, which may increase stool bulk, decrease transit time and dilute potential carcinogens in the gastrointestinal tract. Further, fiber from legume stimulates bacterial anaerobic fermentation which results in production of short-chain fatty acids, such as butyrate, which inhibits growth, induces apoptosis and cell cycle arrest, and promotes differentiation in CRC cells.

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- Furthermore, legumes are good sources of dietary protein, vitamin E, vitamin B, selenium, and lignans with potential cancer-preventive effects. Legumes have a high content of vitamin B6 and vitamin B6 intake was reported to reduce risk of colorectal cancer.

- In addition to its direct cancer preventive effects, legume intake may affect disease risk indirectly as well. For example, higher intake of legumes may replace other sources of protein in the diet such as meat.

Opinion: I believe it is a good idea to increase legume consumption, compared to typical North American levels of intake. They also contain protease inhibitors, which exhibit important anti-cancer properties, and are a good source of both soluble and insoluble dietary fiber. Ground flaxseed is also a good source of both soluble and insoluble dietary fiber, as well as phytoestrogen precursors (SDA and MD)

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3. Calcium

- Over the past 25 to 30 years studies have suggested that calcium may confer protection against colorectal cancer. Animal studies have shown this effect, and many epidemiological studies have shown a strong correlation between higher calcium intake and lower incidence of colorectal cancer. (1-5)

- A meta-analysis published in 2014 in the International Journal of Cancer has provided additional evidence that higher calcium intake, including calcium supplements, is associated with a significant reduction in risk of colorectal cancer.

- More specifically, the data showed that for every 300 mg increase in calcium from supplements there was an associated 9% reduction in risk of colorectal cancer, and that for every 300 mg increase in total calcium there was an associated reduction in risk of 8%.

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- Thus, whether the individual relied on food or supplements as their source of calcium, both showed a similar reduction in risk of colorectal cancer, such that for every 300 mg of calcium consumed there was a corresponding colorectal cancer risk reduction of 8-9%.

- Accordingly, ingesting 1200 mg of calcium per day from food and/or supplements (typical for someone striving to maintain optimal bone density) would confer a 32-36% reduction in colorectal cancer risk.

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- This has important clinical application, as the 2003 to 2006 U.S. National Health and Nutrition Examination Survey showed that the median total calcium intake of adults aged over 50 years was only about 650 mg/day for non-calcium-supplement users and 1,000 mg/day for calcium-supplement users.

- The National Health and Nutrition Examination Survey is a nationally representative cross-section survey in the United States. The 2014 meta-analysis suggests that benefit of calcium intake in preventing colorectal cancer would be expected to increase with continued calcium intake beyond 1,000 mg/day, not only for non-supplement users, but that supplement users may further reduce their risk of colorectal cancer through additional calcium intake (e.g. additional supplementation).

- The researchers conclude that both dietary and supplementary calcium intake may continue to decrease colorectal cancer risk beyond 1,000 mg/day. (6)

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Calcium Supplements Have Prevented Colon Cancer Recurrence

- These observations are further supported by the published results in 2004 of the Calcium Polyp Prevention Study, which was a randomized, double-blind, placebo-controlled chemoprevention trial among patients with a recent colorectal adenoma.

- Nine hundred thirty (930) patients were randomly assigned to calcium carbonate (1200 mg/day) or placebo. Follow-up colonoscopies were conducted approximately 1 and 4 years after the qualifying examination.

- The results showed that group receiving the calcium supplementation (1200 mg per day) had showed pronounced anticancer effects on advanced colorectal lesions compared to the placebo group. (7)

- Other studies, including randomized clinical trials, have also shown that supplementation with calcium is associated with a decreased risk of colorectal adenoma recurrence and colorectal cancer. (8, 9)

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How Does Calcium Reduce Risk of Colon Cancer

- Calcium has been shown to exhibit protection against colorectal cancer through various biological mechanisms. Animal studies suggest that calcium binds to **secondary bile acids and fatty acids** in the colonic lumen, thereby diminishing the potential proliferative stimulus of these compounds on the colonic mucosa.

- Calcium may also reduce the risk of colorectal cancer by direct effects on cells that line the colon (epithelial cells) by slowing the rate of cell division, promoting cellular differentiation and inducing apoptosis (programmed cell death) of cells with genetic damage.

- All of the mechanisms are shown to be important in cancer prevention. Animal studies and some, although not all, clinical trials have shown that increased calcium and dairy food intakes can decrease colonic epithelial cell proliferation. (8)

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- As for an increased risk for cardiovascular disease from higher calcium intakes, this has largely been dismissed by recent research investigations. (10)

- Although it is important in my view to ensure that the patient is also receiving adequate magnesium, as calcium intakes increase and that blood levels of vitamin D remain at or above 30 ng/ml (75 nmol/L) throughout the course of the entire year.

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4. Vitamin D

Overview:

Vitamin D has been shown to suppress cancer cell proliferation, induce cancer cell apoptosis (programmed cell death), and differentiation, demonstrating a strong potential role in the prevention and management of colon, breast and prostate cancer.

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Ng K. **Vitamin D for prevention and treatment of colorectal cancer: What is the evidence?**
Curr Colorectal Cancer Res **2014** 10(3):339-345. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4159193/

Highlights from 2014 Update: Vitamin D and Colorectal Cancer:

- Vitamin D insufficiency is highly prevalent in the U.S., particularly among colorectal cancer (CRC) patients.
- Prospective observational studies suggest that higher vitamin D levels are associated with lower risk of incident CRC as well as improved survival in patients with established CRC, and randomized clinical trials are desperately needed to establish causality
- Epidemiologic and scientific research indicates that diet and lifestyle factors have a significant influence on the development of colorectal cancer (CRC).

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- While the most well-studied function of vitamin D is control of calcium and phosphate metabolism to maintain skeletal health, research over the last several years has revealed that 1α-hydroxylase and VDR are actually present in most cells of the body, including CRC cells, and that VDR also regulates target genes involved in induction of differentiation and apoptosis, and inhibition of proliferation, angiogenesis,[8] and metastatic potential.

- These anti-neoplastic actions of vitamin D, the presence of VDR diffusely in normal and cancer cells, and the extrarenal distribution of 1α-hydroxylase all suggest that calcitriol can be synthesized locally within cancer cells to yield high concentrations within the tumor for intracrine and autocrine anti-cancer effects.

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- The Endocrine Society recommended target 25(OH)D levels of ≥30 ng/mL, (75nmol/L) with levels <20 ng/mL (50nmol/L) considered deficient.

- Preclinical studies show that well-differentiated CRC cell lines have higher VDR expression, and the anti-proliferative effects of vitamin D seem to be greatest in cell lines that express high levels of VDR, consistent with the hypothesis that local production of calcitriol may be directly involved in cancer pathogenesis.

- Vitamin D inhibits growth and promotes differentiation of CRC cell lines and xenografts, and rats maintained on a diet enriched in calcitriol develop fewer intestinal tumors and metastases compared to control animals.

- Moreover, treatment of Apc^{Min} mice with vitamin D or a synthetic analog reduces the size of intestinal adenomas, which is increased in $Apc^{+/Min}$;$VDR^{-/-}$mice.

- Beyond direct effects on proliferation, cell differentiation, apoptosis, and metastatic potential mentioned above, several intriguing studies show that vitamin D can counteract aberrant WNT-β-catenin signaling, which is a known etiologic alteration in the development of CRC, by inhibiting nuclear translocation of β-catenin, sequestering β-catenin at the membrane, and increasing levels of extracellular WNT inhibitors DICCKOPF1 and DICKKOPF4.

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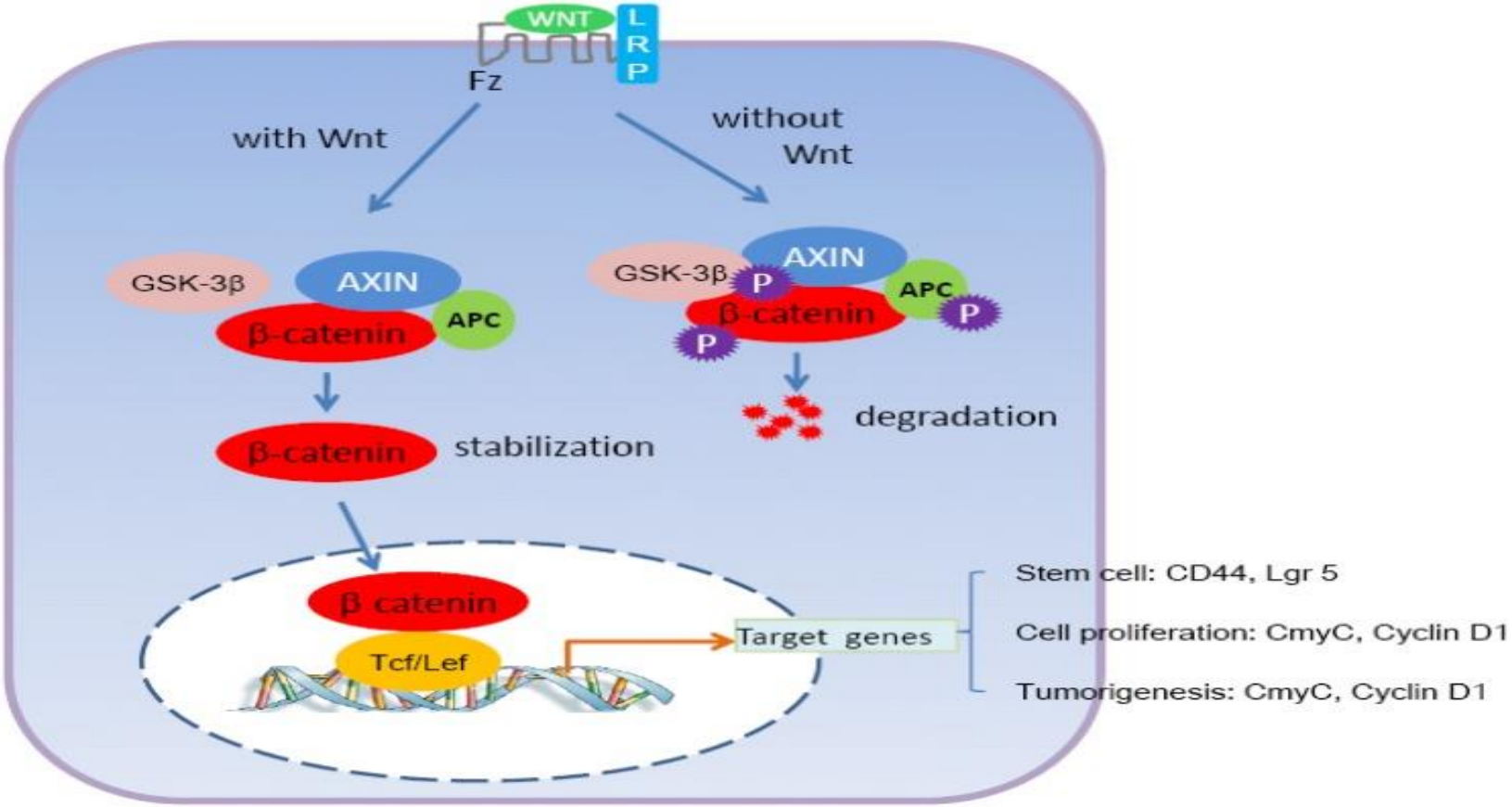
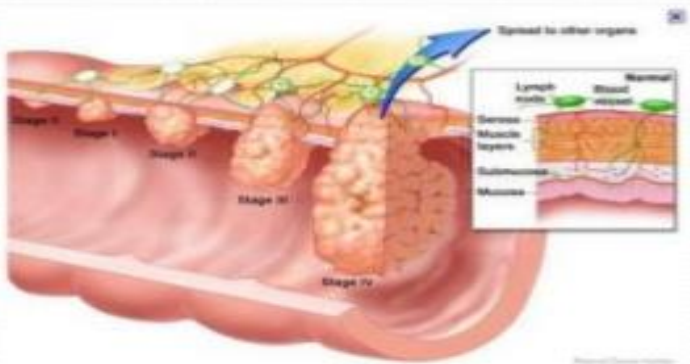
Wnt Pathway Activation in Colorectal Cancer



Things can go wrong: Cancer!

- The APC protein also functions as a tumor suppressor (Korinek et al 1997)
- Colon cancer may occur when APC genes are mutated (Korinek et al 1997)
- APC can no longer keep β-Catenin out of the nucleus (Korinek et al. 1997; He et al. 1998)
- Once inside the nucleus β-Catenin can bind with other proteins including SMADs, CtBP, Groucho and CBP to upregulate proteins for cell division.
- This can lead to uncontrolled proliferation
- Ultimately can lead to tumor formation, more mutations, invasion and metastasis.



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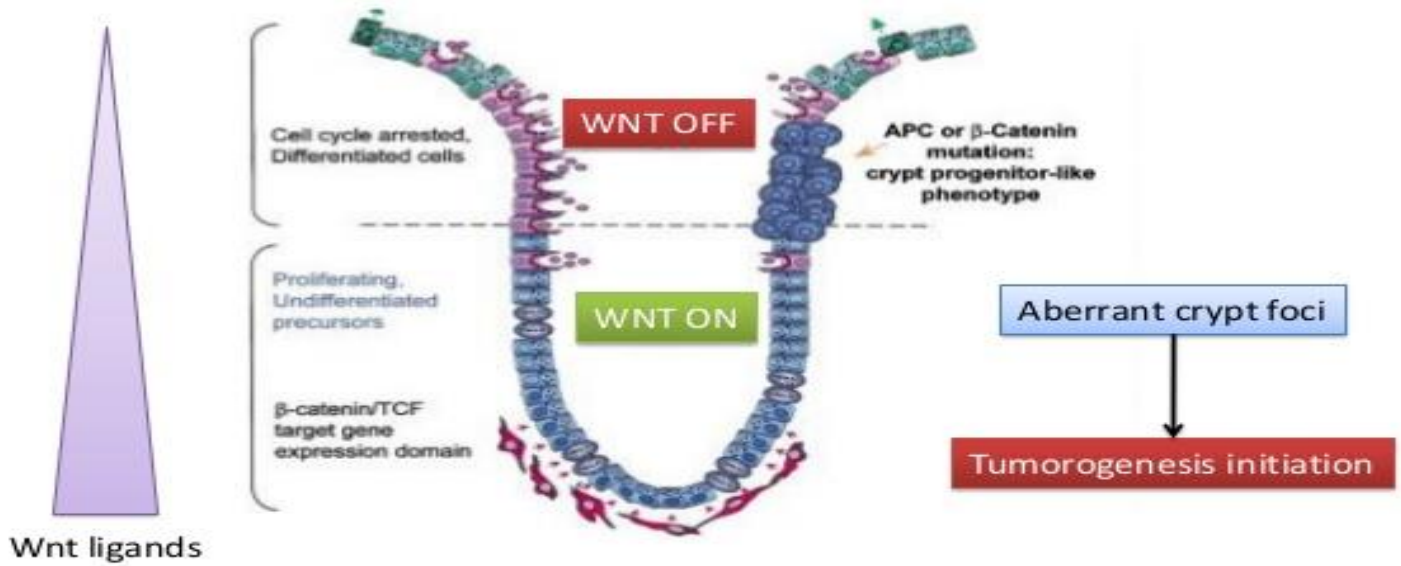
Wnt pathway along the colon crypt



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- Chronic inflammation is also a known risk factor for development and progression of CRC, and vitamin D exerts several anti-inflammatory effects through down-regulation of nuclear factor (NF)-κB activity, increase in production of anti-inflammatory interleukin (IL)-10, and decrease in production of pro-inflammatory IL-6, IL-12, interferon-γ, and tumor necrosis factor (TNF)-α.

- **Moreover, vitamin D inhibits cyclooxygenase (COX) expression** and decreases prostaglandin signaling, which not only suppresses inflammation but also decreases prostaglandin E_2-induced hypoxia-inducible factor (HIF)-1α expression, leading to inhibition of angiogenesis.

- Vitamin D also directly reduces expression of vascular endothelial growth factor **(VEGF),** and *VDR*-null mice demonstrate increased expression of pro-angiogenic factors such as VEGF, HIF-1α, and platelet-derived growth factor (PDGF).

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- In a meta-analysis of five epidemiologic studies, individuals with serum 25(OH)D level ≥33 ng/mL had a 50% lower risk of CRC compared to those with levels ≤12 ng/mL.

- Another meta-analysis of 18 prospective studies showed that individuals with both higher dietary and supplemental intake of vitamin D, as well as higher plasma levels of 25(OH)D, have a significantly reduced risk of developing CRC, with pooled relative risks (RRs) of 0.88 and 0.67, respectively.

- Moreover, a significant dose-response relationship was observed, with each 10 ng/mL increment in plasma 25(OH)D level associated with a RR of 0.74 for CRC.

- Consistent with these findings, a report from the Third National Health and Nutrition Examination Survey (in which 16,818 participants were enrolled from 1988–1994 and followed through 2000) demonstrated an inverse relationship between serum 25(OH)D levels and CRC mortality, with levels 32 ng/mL or higher associated with a 72% risk reduction, compared with levels <20 ng/mL.

- Two other randomized, placebo-controlled trials of vitamin D supplementation designed primarily to look at fracture risk have reported results of secondary endpoints of cancer risk or mortality.

- In the first trial, 2,686 subjects were randomized to receive 100,000 IU of vitamin D_3 versus placebo every four months, and an age-adjusted RR of 0.62 for colon cancer mortality was found with vitamin D compared to placebo (7 versus 11 colon cancer deaths, respectively).

- The second randomized trial evaluated the combination of vitamin D 1,100 IU/day + calcium 1,400–1,500 mg/day versus calcium alone versus placebo in 1,179 healthy post-menopausal women living in Nebraska, and demonstrated a 60% decrease in all-cancer risk (including CRC) in favor of the vitamin D-containing arm.

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- The VITamin D and OmegA-3 TriaL (VITAL) is such an ongoing phase III clinical trial that recently completed its planned accrual of 25,875 healthy subjects aged 50 years and older (ClinicalTrials.gov identifier NCT01169259).

- VITAL involves a 2×2 randomization to vitamin D3 2,000 IU/day or fish oil 1 g/day compared to placebo for five years, with primary endpoints of cancer, cardiovascular disease, and stroke.

- Results are not anticipated for several years.

Opinion: Maintain a vitamin D blood level above 75 nmol/L

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5. Antioxidants: Vitamin C and Vitamin E

- The effect of supplemental ascorbic acid and α-tocopherol on fecal mutagenicity was examined in 2 studies involving 20 healthy human donors aged 22–55 years.

- The vitamins were given at a dose of 400 mg daily each.

- In the first study, with a single donor on a controlled diet, the fecal mutagenicity decreased on treatment to 21% of control.

- In the second study, with 19 donors on free-choice diets, the mutagenicity in producers on treatment decreased to 26% of control.

Reference: Original 1982 Published Data https://www.sciencedirect.com/science/article/pii/0165121882901434

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Vitamin C and Vitamin E Inhibit Nitrosation Reactions

https://www.sciencedirect.com/science/article/pii/0027510788901947

- Although the proof that *N*-nitroso compounds (NOC), a versatile class of carcinogens in animals, are also carcinogenic in man is lacking, humans are exposed through ingestion or inhalation to preformed NOC in the environment and through the endogenous nitrosation of amino precursors in the body.

- Activated macrophages can synthesize nitrate, nitrite and nitrosating agents that can form NOC. A number of bacterial strains isolated from human infections can produce NOC enzymatically from precursors at neutral pH.

- As a consequence endogenous nitrosation may occur at various sites of the body such as the oral cavity, stomach, urinary bladder, lungs, and at other sites of infection or inflammation.

- Since the demonstration by Mirvish et al. (1972) showing that ascorbate can reduce tumor formation in animals following feeding of nitrite plus amine, numerous substances to which humans are exposed have been identified and shown to inhibit formation of NOC in vitro, in animal models and in humans.

- Such inhibitors of nitrosation include vitamins C and E, phenolic compounds, and complex mixtures such as fruit and vegetable juices or other plant extracts.

- Nitrosation inhibitors normally destroy the nitrosating agents and thus act as competitors for the amino compound that serves as substrate for the nitrosating species.

- Independently, epidemiological studies have already established that fresh fruits and vegetables that are sources of vitamin C, other vitamins and polyphenols have a protective effect against cancers at various sites and in particular gastric cancer.

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- Although the evidence that endogenously formed NOC are involved in human cancers is far from conclusive, it is suggestive and justifies preventive measures for reducing exposure to NOC.

- Studies in experimental animals which showed that inhibition of endogenous NOC synthesis leads to a reduction of toxic, mutagenic and carcinogenic effects.

- Vitamin C supplementation (3,000 mg/d) was also shown to reduce the recurrence of colon polyps by 35% compared to only 23% in the placebo group, in a 2.5- year study of polyp sufferers. Reference: Bussey HJR, DeCosse JJ, Deschner EE, et al. A randomized trial of ascorbic acid in polyposis coli. Cancer 1982;50:1434–9. https://onlinelibrary.wiley.com/doi/pdf/10.1002/1097-0142%2819821001%2950%3A7%3C1434%3A%3AAID-CNCR2820500733%3E3.0.CO%3B2-F

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Vitamin C and Vitamin E Supplement Use and Colorectal Cancer Mortality in a Large American Cancer Society Cohort

http://cebp.aacrjournals.org/content/10/1/17 2001 Study

- With respect to colorectal cancer, vitamin C and E inhibit colorectal cancer in rodent models, and supplementation with vitamin C or E decreases fecal mutagenicity in humans.

Conclusion (following over 500,00 adults with 14-yr follow-up)

- In this large prospective study, we found little association between use of either vitamin C or E supplements and risk of colorectal cancer, despite being able to examine long-term supplement use.

- Our generally null results are important given that some recent study results have suggested a substantial protective effect of these antioxidant supplements. For example, vitamin E supplement use was associated with a 50% decrease in risk of colon cancer in the Iowa Women's Health Study .

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- Our results for both vitamin C and E supplement use are consistent with results from randomized trials examining the occurrence of new colorectal polyps after colonoscopy.

- Although an Italian trial found combined vitamin A, C, and E supplementation was associated with decreased risk of colorectal polyps , a Canadian trial and a large United States trial found no reduction in risk after combined supplementation with vitamin C and vitamin E.

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- Some recent epidemiological studies have suggested that use of vitamin C or vitamin E supplements, both of which are important antioxidants, may substantially reduce the risk of colon or colorectal cancer

- We examined the association between colorectal cancer mortality and use of individual vitamin C and E supplements in the American Cancer Society's Cancer Prevention Study II cohort.

- During the 14 years of follow-up, 4404 deaths from colorectal cancer occurred.

- After adjustment for multiple colorectal cancer risk factors, regular use of vitamin C or E supplements, even long-term use, **was not associated with colorectal cancer mortality.**

- Reference: 2001 Study: http://cebp.aacrjournals.org/content/cebp/10/1/17.full.pdf

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Opinion:

Animal and preclinical studies suggest that vitamin C and vitamin E exert impressive anti-cancer effects against colorectal cancer.

Vitamin C and vitamin E also block nitrosamine formation and reduce fecal mutagens, which are impressive biological functions

Some prospective studies have shown that vitamin C and/or vitamin E supplementation are associated with reduced risk of colorectal cancer, but the majority of studies have not shown an association or the risk reduction has been very modest.

It's likely that vitamin C and vitamin E supplementation are not premiere agents in the prevention of colorectal cancer, but may play a supportive role when combined with high intake of fruits and vegetables, adequate calcium, vitamin D, folic acid and fiber, and avoidance of known carcinogens and other dietary factors shown to promote CRC development (i.e. beef and high-fat animal products, alcohol etc.)

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6. Folic Acid

- Much epidemiological evidence supports the hypothesis that insufficient folic acid supply favors the development of colorectal tumors, particularly prospective studies have supported this connection.

- However, the data from case-control studies are less consistent. Functional polymorphisms in folate-metabolizing genes, especially the methylenetetrahydrofolate reductase (MTHFR) are capable of modifying the risk of colorectal cancer.

- Observational studies show that individuals with the homozygote genotype for the MTHFR (677C-->T) polymorphism are at higher risk when folic acid supply is low.

Reference: https://www.ncbi.nlm.nih.gov/pubmed/15870856

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Folic Acid Supplementation in Patients with Colorectal Adenoma: Ground-breaking 2008 Study

- A ground-breaking study, published in the *World Journal of Gastroenterology* in 2008, demonstrated that a daily dosage of 5 mg of folic acid resulted in a significant reduction in the recurrence of colorectal adenoma.

- Among the 94 subjects who completed the study (49 in folic acid group and 45 in placebo group), there was a threefold increase in polyp recurrences in the placebo group, compared to the group receiving folic acid supplementation.

- The mean number of recurrent polyps (adenomas) at 3-years was 0.36 (SD, 0.69) for the folic acid treated group compared to 0.82 (SD, 1.17) for the placebo treated group. Of note was the fact that patients under 70 years of age and those with left-sided colonic adenomas, or advanced adenomas, responded the best to folic acid supplementation. (1)

- The mechanisms by which folic acid exerts its chemoprevention effects in colorectal carcinogenesis appear to be multi-faceted.

- Due to folic acid's key role in DNA methylation and cellular homeostasis, folate deficiency (or marginal deficiency) may result in misincorporation of uracil for thymidine during DNA synthesis, which is shown to increase the potential for spontaneous mutation, as well as chromosomal abnormalities and errors in DNA synthesis. (1)

- Moreover, folic acid supplementation, at supraphysiological doses (e.g. 5 mg per day), has been shown to restore DNA methylation status in patients with colorectal neoplasms.

- Other studies have examined the influence of folic acid on a variety of genes involved in colon cancer development.

- In a one-year study where patients took either 5 mg of folic acid or placebo, folate supplementation was shown to prevent the loss of heterozygosis (LOH) of the DCC gene in 5 out of 5 patients who demonstrated baseline heterozygosis, whereas 2 out of 4 placebo treated patients with baseline heterozygosis, demonstrated complete allelic loss. (7, 8)

- The DCC gene (deleted in colorectal cancer) is an important tumour suppressor gene in the colon cancer model. In this study mucosal protein levels of DCC were also reduced in 70% of placebo treated patients compared to only 10% of folate treated patients (7).

- In 70% of colon cancer cases DCC allelic losses in chromosome 18q.21 is a common finding. (8)

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- Cell culture studies have further demonstrated that supplemental folic acid and its metabolite 5 methyltetrahydrofolate (5-MTF**) inhibit Epidermal Growth Factor-receptor** (EGFR) promoter activity in colon cancer HCT-116 cells, by enhancing methylation. (9)

- Over-expression of EGFR is known to play a critical role in the development and progression of a large number of epithelial cancers, including colorectal cancer. (1)

- As such, supplemental folic acid may also attenuate the downstream events of EGFR signal transduction pathways that are critically involved in modulating growth-related processes.

- Clinical support of this hypothesis comes from the findings of patients who have undergone colon polyp removal (polypectomy), whereby folic acid supplementation (5 mg) for one-year lead to a decreased activation of several transcription factors that are commonly over expressed in cancer cells.

- More specifically, folic acid supplementation was shown to decrease the activation of nuclear translocation of β-catenin, which interacts with the T-cell factor 4 (TCF-4) transcription factor to induce expression of specific target genes, including cyclin D1, VEGF (vascular endothelial growth factor) and c-myc. Together these transcription and growth factors are known to promote cell growth and proliferation of many forms of cancer. (1,10)

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Patients at Risk for Folate Deficiency and Folate Status

- A low serum folic acid serum level (<4ng/ml of serum) is where chromosome breaks have been seen. (11)

- The normal range for serum folate is range 7-40 nmol/L, and the normal red blood cell folate reference range is 360-1400nmol/L, which is a direct measure of tissue folate stores. (12)

- Individuals at high risk for folic acid deficiency or marginal deficiency include women of childbearing age and non-Hispanic black women. Even when intake of folic acid from dietary supplements is included, 19% of female adolescents aged 14 to 18 years and 17% of women aged 19 to 30 years do not meet the Estimated Average Requirement (EAR) for folic acid intake.

- As well, 23% of non-Hispanic black women have inadequate total intakes, compared with 13% of non-Hispanic white women. (13). Research has also shown that certain drugs such as methotrexate, levopoda, niacin, phenytoin (Dilantin), carbamazepine, and theophylline can markedly reduce folate levels in the body. (14,15,16). Other well-documented factors that deplete folic acid include alcohol intake (even moderate amounts) and cigarette smoking. (17, 18)

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- The researchers of the 2008 study conclude, “Our data, for the first time, show that the daily consumption of a high dose of folic acid over a period of 3 years prevents the recurrence of colorectal adenomas.”

- As well, “none of the patients in the folate treatment group were found to have histologically aggressive adenomas or carcinoma at final endoscopy.”

- They further indicated that the marked reduction in adenoma recurrence seen in this study could not be attributed to differences in other dietary or lifestyle factors, as all patients completed a detailed lifestyle questionnaire and nutritional assessment with both study groups demonstrating statistically similar caloric, fiber, fat and protein intake as well as similar baseline BMI, folate, B12 and calcium status.

- Additionally, the groups were similar with regard to aspirin use and the number and type of adenoma at baseline.

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- The recent evidence that supraphysiological doses of folic acid (3-5 mg per day) has been shown to reduce recurrence of colorectal adenoma and improve outcomes for patients with cervical dysplasia and other health problems (e.g. high homocysteine) has opened up an new application for the therapeutic administration of folic acid.

- In patients who have had previous colorectal adenoma, the ground breaking 2008 study, by R. Jaszweski et al (1) suggests that supplementation with 5 mg per day of folic acid can help prevent colorectal adenoma recurrence by threefold, compared to placebo.

- This research should be brought to the attention of all patients with a history of colorectal adenoma (those who have had colon polyps removed), as well as their attending physician or oncologist.

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- Finally, it is worth noting that prior to the folic acid food fortification program that commenced in January 1998, 15% of the US adult population was shown to ingest less than the EAR for folic acid on a daily basis.

- The folate food fortification program has improved folate status significantly in recent years, but various groups remain at risk for sub-optimal folate status, which may affect their risk of colorectal cancer. (11, 19)

- It is also mentioning that a 19% reduction in neural tube defect birth prevalence occurred following folic acid fortification of the US food supply. However, some researchers have noted that factors other than fortification may have contributed to this decline, although folic acid fortification is likely a main factor. (19)

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Opinion:

Folic acid deficiency increases risk of cancer, including colorectal cancer

It appears to be the best of interest of individuals to ensure optimal red blood cell levels of folic acid

In cases of high homocysteine, when folic acid intake and supplementation are present, it may be wise to include additional supplementation with Methyl-Folate (500-1,000 mcg/d) to over come 5MTHFR defect. Recheck homocysteine to see it's working (or maybe methionine synthase defect, or vitamin B6-transulfuration defect, or lack of vitamin B12 – check serum vitamin B12 as well)

In general, a supplement containing 400 mcg of folic acid day, in addition to food consumption, should allow for optimal RBC folate levels.

For patients with a history of colorectal adenoma(s), evidence suggests that 5 mg per day of folic acid maybe helpful in preventing their recurrence, and RBC folate, homocysteine and serum B12 should be evaluated in these patients.

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7. Alcohol

- Alcohol intake is one of the primary risk factors for many human cancers, and is strongly associated with cancers of oral cavity, pharynx, larynx, oesophagus, liver, breast, and notably the colon and rectum.

- A systematic review with meta-analysis, published in 2014, provided an update regarding the association between alcohol consumption and risk of colorectal cancer. The meta-analysis included twenty-three case–control studies and two cohort studies.

- The results showed that “all drinkers were associated with 17% increased risk for colorectal cancer, compared with non-drinkers or occasional alcohol drinkers.

- The dose–response analysis demonstrated that for drinkers of 10, 25, 50 and 100 g/day alcohol consumption, the estimated relative risks of colorectal adenoma were 1.02 (95% CI 0.89–1.16), 1.06 (95% CI 0.92–1.20), 1.16 (95% CI 1.02–1.33) and 1.61 (95% CI 1.42–1.84) respectively, in comparison with non-/occasional drinkers. One alcoholic drink is 14 gm of alcohol.

- The risks were consistent in the subgroup analyses of gender and site of adenoma, while it was stronger in European studies than the studies in the US and Asia”. (1)

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Mechanism of Alcohol Damage in Colorectal Cancer

- Alcohol consumption may increase risk of colorectal cancer via a number of documented mechanisms.

- Alcohol intake may lead to folic acid deficiency in the colon and rectum, via folate malabsorption. Folate is required for the synthesis of certain DNA bases and to methylate DNA structure. Marginal deficiencies of folate are known to increase the risk of DNA hypomethylation, DNA mutations and strand breaks, which are shown to increase cancer risk, including colorectal cancer. (3-10)

- As well, intestinal bacteria, which have high activity of the alcohol dehydrogenase enzyme, could oxidise ethanol in the colon and rectum and generate a considerable level of acetaldehyde, which is known to initiate and promote cancer via several mechanisms. (1,11)

- In addition, alcohol may inhibit DNA repair enzymes, suppress immune surveillance to tumour, alter the composition of bile acids and induce the expression of liver cytochrome P-450 enzymes, all of which may contribute to adenoma development. (1)

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- The researchers go on to suggest that screening guidelines for colorectal cancer should possibly be adjusted for individuals who have lifestyle and environmental risk factors that place them in a higher risk category, such as smoking, obesity, (or higher body mass index), lack of exercise, frequent alcohol consumption, etc.

- Early screening for colorectal cancer (colonoscopy) is proven to be a valuable tool to detect early stage cancerous and precancerous lesions, and as a therapeutic intervention, allows physicians to remove suspicious polyps, preventing their progression to malignant lesions

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8. Selenium

- Selenium is an essential nutrient for humans; it fulfills the physiological requirements for more than 13 human enzymes and proteins. (1)

- Its most well known function relates to the activation of the enzyme, glutathione peroxidase, which accounts for selenium's antioxidant role in the reduction of hydrogen peroxide to water and organic hydroxyperoxides to alcohol.

- The form of selenium in all selenoproteins is an amino acid, L-selenocysteine. Both inorganic (e.g., selenite and selenate) and organic (seleno amino acids) forms of selenium have shown impressive cancer – chemopreventive effects in humans and in animal models. (2)

- The nutritional requirement for selenium for the synthesis of L-selenocysteine is considered to be 55 micrograms per day. However, selenium consumed as a dietary supplement, beyond levels attainable from food, at up to 200 mcgs per day is associated with reduced incidence of lung, colorectal and prostate cancer in humans.

- Animal studies also strongly indicate that supraphysiological levels of selenium significantly reduces cancer incidence in various test models. (1)

- Many cancer researchers now propose that the level of selenium intake required to reduce cancer risk exceeds the intake level (55 mcgs), which is required to maximize the synthesis of L-selenocysteine, upon which the RDA is based.

At supraphysiological levels of intake, selenium has been shown to exhibit a number of anti-cancer properties beyond the activation of the antioxidant enzyme, glutathione peroxidase. These general mechanisms include:

- Apoptosis – programmed cell death of cancer cells
- Growth-inhibitory effects of cancer cells
- Induction of p53 tumor suppressor gene, which gives rise to proteins that arrest cell cycle division when DNA mutations occur, allowing DNA repair enzymes to correct the error.
- Protects against DNA damage
- Anti-promotional agent, discouraging cancer cell division.
- The induction of apoptosis (a very important chemopreventive function) is detectable towards the upper limit of plasma selenium concentrations (approximately 5 micromoles per liter) [3,4,5]

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- The present view is that selenium metabolites (i.e., methylated forms of selenium), rather than simply the saturation of L-selenocysteine synthesis alone, are key factors in selenium's cancer preventive effects. (5)

- At physiological levels of intake, dietary selenium (inorganic and organic forms) is reduced to hydrogen selenide (H_2 Se). From H_2 Se selenium is phosphorylated and incorporated into proteins such as L-selenocysteine.

- During periods of supraphysiological intake (supplementation), once L-selenocysteine levels are saturated, H_2 Se is rapidly methylated to dimethyl selenide and other methylated forms including the monomethylated form, and trimethylselenonium.

- Experimental studies highlight the fact that these methylated forms of selenium (metabolites) possess direct and indirect chemopreventive effects that are not attainable by the action of glutathione peroxidase acting alone.

- Thus, selenium supplementation (100-400 mcg per day) increases the levels of methylated selenium metabolites that appear to account for many of selenium's cancer preventive effects. (1,5)

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- As reported by Combs, B., et al, selenium plasma levels of approximately 120 ng/ml (1.5 umol/ml) may be optimal for cancer prevention in general.

- The most recent estimates suggest that women require a minimum of 96 micrograms per day and men require at least 120 micrograms per day to support plasma levels at 120 ug/ml for Americans. These levels are 175% and 218%, respectively, of the revised RDA. (6)

- In terms of specific cancers that may be prevented through selenium supplementation, colorectal cancer has received much attention in both human and animal studies and is the focus of this review. (3)

- More recently a study by Dr. Mark Russo and associates at The University of North Carolina (Chapel Hill) further supported a role for selenium in the prevention of colon and rectal cancers.

- In their study patients who were referred for a colonoscopy assessment also had blood tests performed. As reported by these authors, lower blood levels of selenium were associated with multiple cancerous lesions in the colon.

- The average blood level for patients with cancerous lesions was 107 micrograms per liter vs. 120 micrograms per liter for the cancer free subjects. (25)

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The Protective Effects of Selenium

- As noted, there are several ways that selenium is thought to reduce cancer risk. Selenium enhances antioxidant defenses by increasing activity and levels of the powerful antioxidant enzyme known as Glutathione Peroxidase.

- Glutathione Peroxidase is considered a strong anticancer agent within the body.

- Selenium supplementation also decreases the formation of certain cancer permissive eicosanoids, of the prostaglandin E2 series. Prostaglandin E2 has been shown to increase the rate of cell division of various cancer cells. Animal studies have demonstrated these effects quite extensively.

- Selenium metabolism itself may initiate changes that lead to programmed cell death of cancer cells and pre-cancerous cells. [26,27,31,32] It is important to note, that other human studies by Dr. Willett, and Dr. Salonen, also reported, a 2 and 3 fold increased risk for colon and intestinal cancer respectively, in patients presenting with low blood selenium levels when compared to patients with higher blood levels of selenium. [28,29]

- In line with these observations is the emerging evidence that selenium metabolites (methylated forms) exert a broad range of anti-cancer influences on the cell, including colonic epithelial cells, and that higher levels of selenium intake is required to produce protective levels of these methylated selenium compounds [3,4,5].

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Current Trends and Practical Application

- The average intake of selenium from food sources is shown to be between 50-70 micrograms daily. Is it adequate?

- The evidence suggesting that selenium can reduce the risk of certain cancers indicates that ingesting additional selenium from a supplement may be a prudent strategy. Many health conscious physicians now recommend a supplement containing 50-200 micrograms of selenium daily as part of a preventative health strategy. [30,33]

- As for safety, toxicity of selenium begins at doses starting at 1,000 micrograms per day, but doses as high as 2,000 mcgs per day have been shown to be non toxic is some individuals. [6,30,33,34]

- Most clinical applications have used 100-500 mcg of selenium per day [28, 34]

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Can Selenium Levels Act as a Marker of Colorectal Cancer Risk? BMC-Cancer 2013 Study

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3641950/

The efficacy of selenium is related to a “U” shaped curve in terms of the health benefits.

The low levels of selenium is associated with an increased risk of malignancy. Too much selenium (selenosis) is also linked to higher occurrence of common diseases, such as type 2 diabetes and has also been shown to be linked with increased incidence of lung malignancy.

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- It has been reported that patients with fasting levels of selenium below 128 µg/l are much more likely to present with one or more adenomatous polyps (OR 4.2).

- The same characteristics has been confirmed in number of other studies. However, other studies do not support a protective role for selenium against the risk of colorectal cancer.

- The recent SELECT trial also indicated that supplementation with selenium did not provide any immediate benefit and indeed could result in increased prostate cancer incidence.

- The critical factor in the SELECT trial is the average selenium level for each of the participants. In North America the average reported selenium level ranged from 122.4 µg/l – 151.8 µg/l.

- In Eastern Europe the average selenium level is ~70 µg/l, which is likely to have significant consequences when manipulated by supplementation.

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- The results of this study (European) supports the consistent evidence of inverse correlation of selenium with colorectal cancer risk in countries with low endogenous levels of selenium i.e. lower circulating selenium levels being associated with the greatest risk of malignancy.

- A similar pilot study, examining a larger cohort of patients with colorectal lesions (colorectal adenomas) that included 451 cases where 69% have Se concentrations <140 µg/l and 31% with >140 µg/l, suggested a reduced prevalence of colorectal adenomas at higher selenium levels.

- The other studies published in 1977 on selenium dietary intakes and CRC are derived from Schrauzer and colleagues. In these studies comprising 27 countries evaluation of the content of selenium in the diet showed an inverse correlation between the amount of selenium intake and mortality caused by cancer, including cancer of the colon and rectum.

- In the same study similar inverse correlations were found between cancer mortalities and the selenium concentrations in whole blood collected from healthy human donors in the U.S. and different countries. The most fundamental results on the role of selenium supplementation in cancer prevention, including prevention of CRC, have been achieved in NPC study (Nutritional Prevention of Cancer).

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- This was a randomized clinical trial designed to evaluate the effect of selenium supplementation of 200 µg daily selenized yeast in cancer prevention among 1312 residents of the Eastern United States.

- In this study statistically significant decrease in the incidence of cancers has been demonstrated only for subgroup of subjects with baseline selenium concentration <105 µg/l.

- It was observed also that the effective prevention on selenium supplementation depends not only on its initial level in the body but also on the cancer site. Selenium supplementation was associated with decreased risk of prostate, colon and lung cancers but reverse effect of increased risk was observed for breast cancers.

- The further study performed by these researchers demonstrated that selenium supplementation was associated with a significantly reduced risk of prevalent colorectal adenoma, but only among subjects with a low baseline selenium level (<105,5 ng/ml, OR-0,27, p= 0,01).

The subsequent studies coming from U.S.A. has been reported that patients with fasting levels of selenium below 128 µg/l are much more likely to occur with one or more adenomatous polyps (OR 4.2). The other study conducted at University of North Carolina on a relatively small group of participants (37 cases, 36 non-cases) showed that lower plasma selenium levels were associated with occurrence of multiple adenomas but not with adenoma size or location. These reports are in agreement with our findings.

Opinion: Ideally, having a baseline serum selenium level would be helpful in deciding the level of selenium supplementation to recommend to a patient. As CRC is the second leading cause of cancer death in North America and most developed countries, many anti-aging doctors continue to recommend 100-200 mcg per day of selenium supplementation as a general target for prevention. Future studies are required to make definitive statements about selenium supplementation and cancer.

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9. Cruciferous Vegetables

2013 Meta-analysis (Annals of Oncology)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3603442/

Epidemiological studies have reported inconsistent associations between cruciferous vegetable (CV) intake and colorectal cancer (CRC) risk. To our knowledge, a comprehensive and quantitative assessment of the association between CV intake and CRC has not been reported.

Conclusions

- Findings from this meta-analysis provide evidence that high intake of CV was inversely associated with the risk of CRC and colon cancer in humans. Further analysis on other specific CV, food preparation methods, stratified results by anatomic cancer site, and subsite of colon cancer should be extended in future study.

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- Cruciferous vegetables (CV) contain a variety of bioactive components such as folate, vitamin C, tocopherols, and carotenoids. However, the most frequently attributable anticancer constituent of CV is glucosinolates (GLS), the precursors of isothiocyanates (ITCs) as well as indole-3-carbinol (I3C), which may contribute to reduce risk of CRC.

- Evidence from animal studies has indicated that the joint induction of phase I (i.e. cytochrome P450s) and phase II enzymes (e.g. glutathione *S*-transferases, GST) by a variety of CV results in a favorable metabolic profile for the elimination of certain chemical carcinogens.
- On the other hand, CV as a good source of dietary fiber which can prevent CRC by several plausible mechanisms, including increased fecal bulk and dilution of carcinogens in the colonic lumen, reduced transit time, and bacterial fermentation of fiber to short-chain fatty acids

- In an updated report from the World Cancer Research Fund and the American Institute for Cancer Research (WCRF/AICR), dietary fiber intake has been upgraded as a convincing protective dietary factor for CRC.

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- In summary, this meta-analysis suggested that high intake of CV can decrease risk of CRC and colon cancer. More in-depth studies are warranted to report more detailed results, including other specific vegetables within the CV family, stratified results by anatomic cancer site, subsite of colon cancer, food preparation methods, or adjustment for potential confounders.

Opinion: Higher intake of cruciferous vegetables is associated with a reduction in risk of various cancers, including prostate, colorectal, lung cancer and breast cancer, in published studies over the years.
(National Cancer Institute: https://www.cancer.gov/about-cancer/causes-prevention/risk/diet/cruciferous-vegetables-fact-sheet)

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10. Nitrates, Heterocyclic Amines, Polycyclic Aromatic Hydrocarbons

- Experimental chemical carcinogenesis in the digestive tract is based mainly on information obtained in the laboratories of the National Cancer Center Research Institute.

- It is generally accepted that cancer is the outcome of DNA damage, resulting in mutation, loss, amplification and recombination of genes.

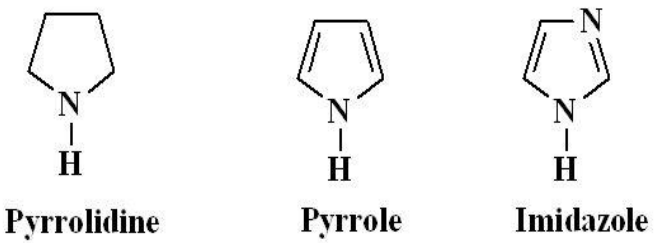
- Gastric cancer is no exception. It was shown very early that cancer of the glandular stomach can be produced in rats by administration of *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine (MNNG), a widely used mutagen.

- With regard to cancer in humans, our finding that cooked proteinaceous foods can give rise to a series of **heterocyclic amines (HCAs)** is of major significance. 2-Amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP), one of the most abundant, causes colon cancers in male rats, whereas in females it induces breast cancers.

Reference: https://academic.oup.com/jjco/article/28/3/163/915564

Heterocyclic Amines

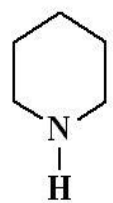
- **In a heterocyclic amine, a five- or six-atom ring contains one or more nitrogen atoms.**



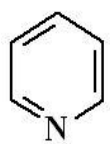
Pyrrolidine

Pyrrole

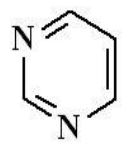
Imidazole



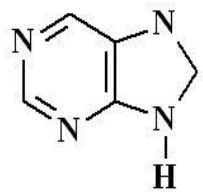
Piperidine



Pyridine



Pyrimidine



Purine

Carcinogens in food

- PAHs and heterocyclic amines from high cooking temperature
- N-nitroso compounds which are result from nitrate or nitrite added during processing and formed endogenously from haem iron
- Food contaminants
- Mycotoxins (aflatoxins)

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PAH and Digestive Cancers: 2011 Review.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3247201/

- Though several environmental chemicals have been implicated as the contributing factors to CRC in humans, one group of chemicals, the **polycyclic aromatic hydrocarbons** have generated the most interest as they are formed in red meat cooked at high temperatures.

- Not only are these chemicals formed during cooking at high temperatures, but also contaminated from several environmental sources, thus making PAHs a single large family of compounds that have the potential to contribute significantly to dietary contamination, human intake and development of CRC.

- Polycyclic aromatic hydrocarbons in fish and shellfish are a result of contamination of fresh and coastal waters.

- Processed food (through smoking;) and cooked food (charcoal cooked;) also contribute substantially to the intake of PAHs.

- The type of cooking, cooking temperature, time, amounts of fat, and oil influence the formation of PAHs.

- Grilled vegetables contain high PAH concentrations due to pyrolysis of organic matter at high temperatures.

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- Findings from a clinic-based case-control study bolster the hypothesis that dietary intake of PAHs is associated with CRC risk. This study created a B(a)P (as a surrogate for PAHs) database using a wide range of food items and linked it to a FFQ. Increased risk of colorectal adenomas with high intake of B(a)P was found from total diet and from meat intake only.

- Using the same study design and a sample size of about 4,000 adenoma cases, this research group also showed that consumption of **well-done red meat was associated with increased risks for adenoma of the descending colon and sigmoid colon for B(a)P.**

- Hence it is conceivable that CRC are promoted by the increased intake of PAHs through dietary fat. Similar to the above mentioned studies, another sigmoidoscopy based study (275 CRC cases and 312 controls) reported an association **among high intake of barbecued red meat, B(a)P, and colorectal adenomas.**

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- Microsatellite mutations have also been found in PhIP-induced colon tumors, as in human hereditary non-polyposis colorectal cancer cases.

- Since carcinogenesis proceeds with accumulation of genetic alteration, often involving genomic instability, exposure to any kind of carcinogenic substances, either xeno- or autobiotics, needs to be reduced as far as possible, taking account of inconvenience at the individual and socio-economical levels.

Opinion: Most cancer researchers suggest reducing intake of smoked foods, red meat cooked at high temperatures or charred meat or fish, as well as BBQ-foods, where smoke is allowed to rise up into the meat, fish or poultry.

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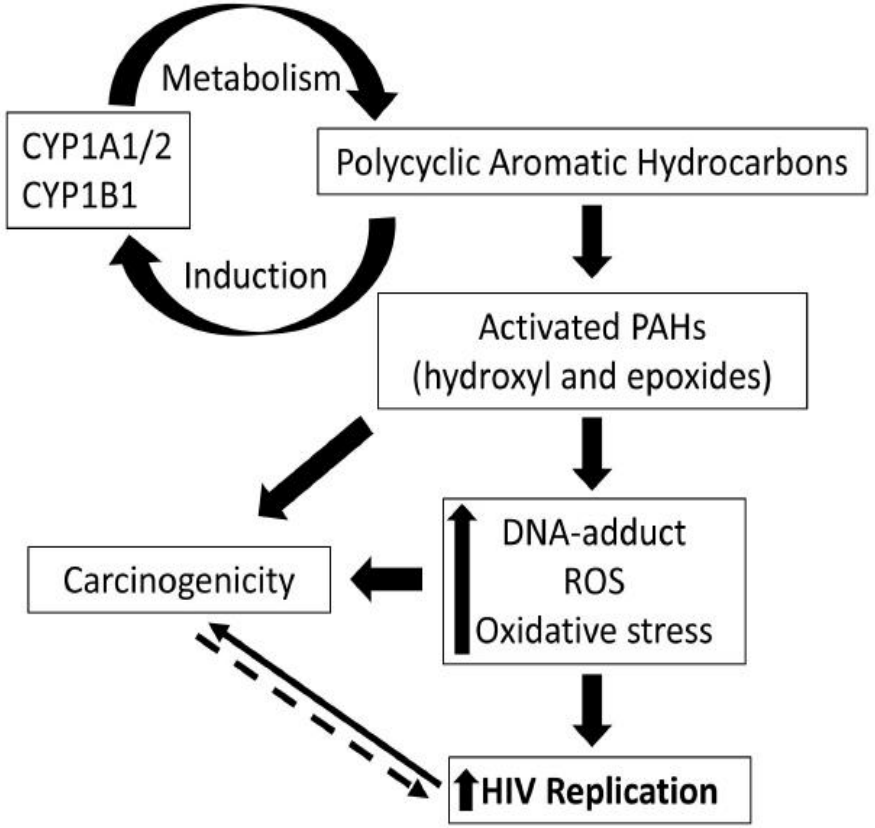
PAH Exposure and Metabolism



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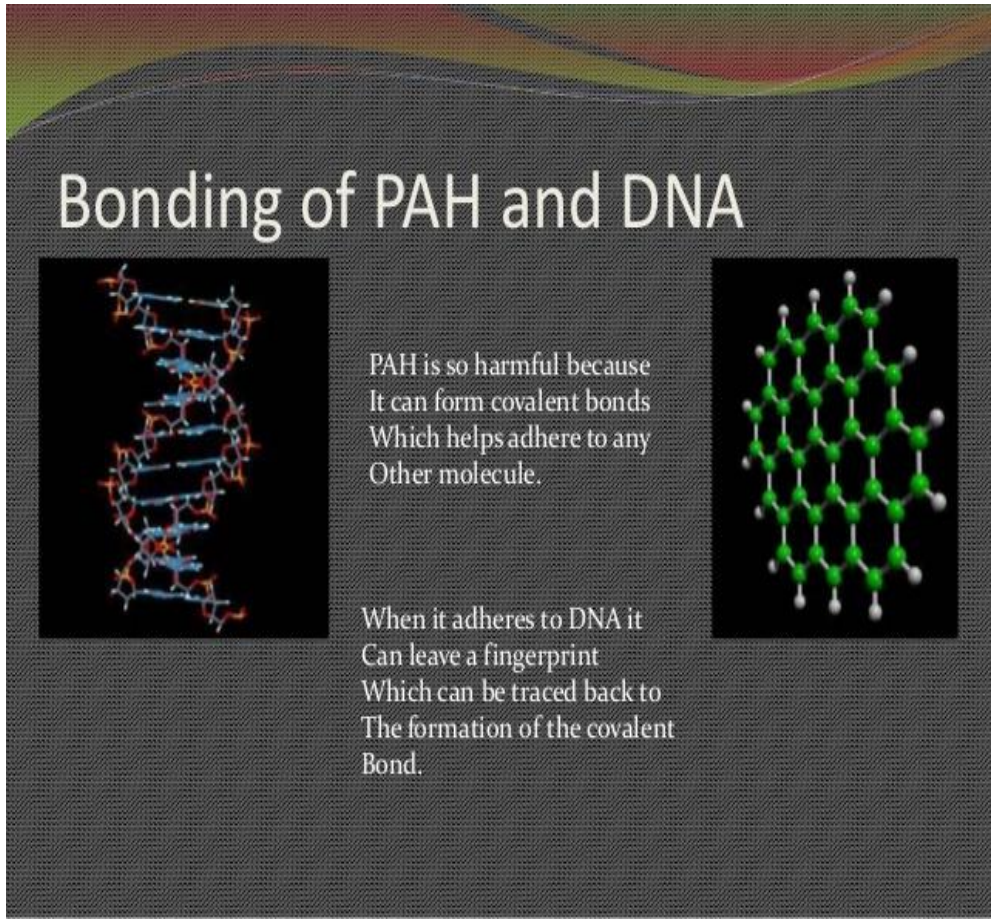
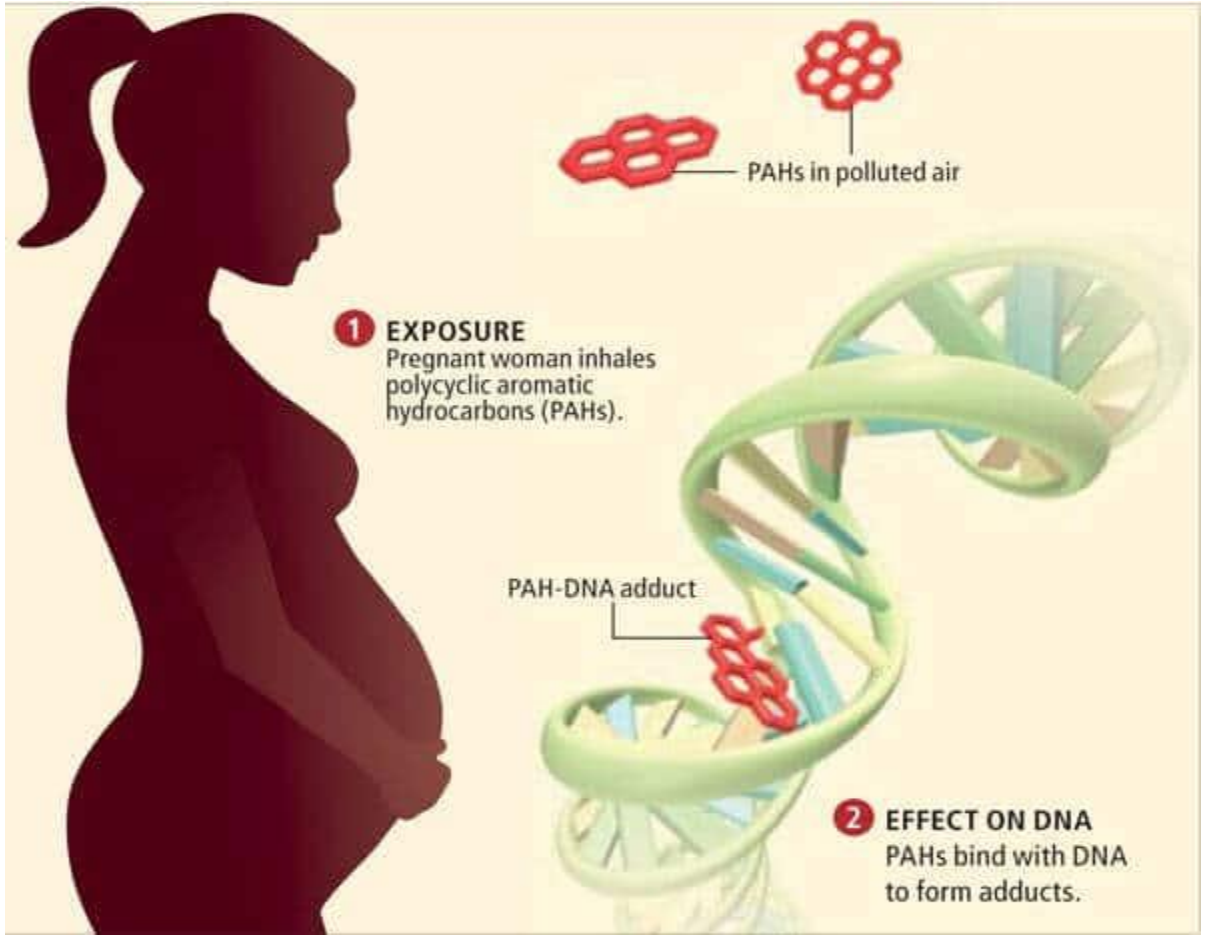
DNA Adducts formed from PAH Linked to Cancer





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Preventing Colon Cancer: Summary
15 Important Considerations

1. **Colonoscopy** beginning at age 50, or sooner if in higher-risk category. With increases in obesity and type2 diabetes across the population some health authorities are suggesting that early detection (colonoscopy) should begin earlier than 50 years of age. Most people should start screening tests for colon and rectal cancers at age 45, rather than waiting for age 50, as long recommended, the American Cancer Society (May 30, 2018)

- Other expert groups still recommend starting at age 50. That's the stance of the influential U.S. Preventive Services Task Force, which last reviewed the issue in 2016.

- But the shift by the cancer society is based on new information about the rise in colon and rectal cancer among younger adults, said Andrew Wolf, an associate professor of medicine at the University of Virginia. He led the group writing the new recommendations.

- Colon and rectal cancers have increased 51% among adults under age 50 since 1994, the cancer society said.

Reference: American Cancer Society: https://www.usatoday.com/story/news/2018/05/30/american-cancer-society-colon-cancer-screening-45/651959002

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2. Diet Low in Long-chain Saturated Fats, Trans-fats, Deep-fried and Breaded and Battered Foods
(replaced by omega-3 fats, monounsaturated fat and even medium-chain triglycerides)

3. High Fiber Diet: emphasizing whole grain cereals, fruits and legumes

4. Ensure Serum Vitamin D level of at least 75 nmol/L (30 ng/mL)

5. Ensure Serum RBC Folate level: Adults: 140-628 ng/mL, or 317-1422 nmol/L

6. Ensure Serum vitamin B12 level: 200 to 900 picograms per milliliter (pg/mL)

7. Ensure Homocysteine Level below 6-8 umol/L (if above this levels may have MTHFR enzyme defect, requiring Methyl-Folate Supplementation)

7. Serum Selenium level: above 128 ug/L

8. Adequate Calcium Intake: 1,000 – 1500 mg per day

9. Be very careful with Alcohol consumption (less than 3 drinks per week is a good target if you drink)

10. Consider vitamin C - 500 mg, twice daily and vitamin E-400 IU/d

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11. Consume Cruciferous Vegetables at least 3 times per week

12. Avoid Processed Meats Containing added Nitrates and Nitrites, as well as cooking foods to High Temperatures, Charring or Smoking Meats and other Foods

13. Don't Smoke

14. Remain at Ideal Weight

15 Have a Regular Exercise Program: "Increasing your level of activity lowers your risk of colorectal cancer and polyps. Regular moderate activity (doing things that make you breathe as hard as you would during a brisk walk) lowers the risk, but vigorous activity might have an even greater benefit. **Increasing the intensity and amount of your physical activity may help reduce your risk."**- American Cancer Society: https://www.cancer.org/cancer/colon-rectal-cancer/causes-risks-prevention/prevention.html