CHAPTER 1

OUR DIGESTIVE SYSTEM

Introduction

Our digestive system has **three primary functions**.

1. The digestion and absorption of the nutrients necessary to sustain life.
2. The utilization of specific and non-specific barriers that limit the absorption of non digestible proteins and xenobiotics (everything that is not a nutrient).
3. Direct and indirect actions which decrease the immune mechanism's responsiveness (over-reaction) to the food proteins.

The implementation of these digestive system functions is accomplished by highly specialized mucosal cells located at the lumenal (intestinal wall) surface. **These mucosal cells require a significant input of energy in the form of oxygen and nutrients in order for the digestive system to function at peak performance levels**. Because these mucosal cells are subject to significant physical and chemical tear, their life span is very short. Their importance to the proper functioning of the digestive system requires that they be replaced very rapidly by the enterocytes (first cell layer of the intestine). To accomplish this, the gastrointestinal (GI) system is highly vascularized which provides the energy (**oxygen and nutrients**) required to accomplish the task.

The GI system must also produce mucus, digestive enzymes, transport proteins, protons and ions which are necessary for the proper and complete absorption of nutrients. **This adds to the total energy (oxygen and nutrients) requirements needed by the GI system**.

The smooth muscle of the intestine is in continuous motion to insure the proper mixing and propulsion of the lumenal contents (digesta). **This adds to the total energy (oxygen and nutrients) requirements needed by the GI system**.

Ingestion is the most common method for entry of xenobiotics into the body. Therefore, it can be expected that toxic reactions will occur frequently in the mucosal cells of the GI tract. The micro flora of the GI tract that contributes to digestion, release toxins which can amplify the response symptoms generated by ingested xenobiotics. **These toxic responses in the mucosal cells create yet another demand for energy (oxygen and nutrients)**.

All of this is to say that there is a high demand for energy (oxygen and nutrients) in order for the digestive system to function at peak performance levels. Increased ingestion of toxins increases the overall demand for **energy**. The first demand upon the available **energy** will be to neutralize ingested toxins. Thus, the other essential functions of the digestive system may not have sufficient **energy** to function at peak performance levels. This will reduce the efficiency with which the digestive system absorbs energy (**oxygen and nutrients**). **Eventually, the body's natural immune mechanisms will be adversely affected due to the continued high demand for energy with increasingly less energy being available. This scenario becomes even more critical to those whose immune systems are already at risk**.

Energy Metabolism

Observation of the activities of the parietal cells of the stomach and the enterocytes (submucosal cells) of the intestine quickly reveals a sophisticated and rapid response mechanism to both neural and chemical stimulation. The cellular suborganelles which facilitate the high productivity demands of these cells, i.e., the power supply, are the mitochondria. Both parietal cells and enterocytes are heavily packed with mitochondria. This large number of mitochondria present confirms the tremendous need that these cells have for energy (**oxygen and nutrients**). In particular, **there is a substantial requirement for oxygen in order to maximize the efficiency of these cells**.

Seventy to eighty percent of the blood supplied to the stomach and intestine go to the parietal cells and the enterocytes. This represents a blood flow that is two to ten times higher than that supplied to the muscle layer. Thus, **the availability of oxygen in the mucosal area is good; however, the demand is also great**. The intestinal partial pressure of oxygen at the muscle/submucosal interface (27 mmHg) is twice that measured at the mucosal villi (14 mmHg). During the absorption of nutrients, the availability of metabolized D-glucose increases blood flow. This increases cell respiration and nutrient absorption. **Interference with the demand for oxygen significantly reduces the energy available to the parietal cells and the enterocytes**. **Consumption of pathogens and toxins, which act as oxygen scavengers, significantly reduces energy metabolism, which at the same time, reduces nutrient absorption and immune response effectiveness**.

The systematic arrangement of the vessels in the mucosal villi permit a counter current flow. By this mechanism, the transfer of pathogens and toxins into the body through the mucosa is slowed down. This protective mechanism does have its down side in that it **decreases the oxygen partial pressure and makes the mucosal villi more susceptible to necrosis (cells shut down due to lack of intraluminal oxygen)**.

Isolated mucosal cells of the small intestine show an oxygen consumption rate of approximately 9.5 nmol per million cells per minute. In addition to this supply of oxygen, the blood also supplies glutamine and keto bodies for the production of glucose. Depending on the availability of oxygen (anaerobic vs aerobic conditions) either lactate or pyruvate is produced. The oxidative metabolism of either produces the essential Adenine Triphosphate (ATP). ATP is utilized for the transport of sodium through the membranes and is consumed in biosynthetic reactions. **Reduced oxygen levels, due to ingestion of xenobiotics, will inhibit glucose and/or ion transport resulting in a wide range of deleterious effects to the mucosa**.

Cell Restitution and Regeneration

The gastrointestinal mucous membrane is constantly being renewed. There are at least two different mechanisms which maintain epithelial integrity. They are restitution and regeneration. Denuding an area of the mucosa may initiate restitution, a migration of surrounding cells to fill in the gap. Alcohol is a common agent which causes a chemical loss of mucosal cells. If a denuded area is exposed too long, inflammation sets in and the process of regeneration becomes necessary for rebuilding the injured area. Xenobiotics (pathogens and toxins) can aggravate inflammation and inhibit the regenerative process.

Mucosal Biotransformation

The process of intestinal absorption and mucosal biotransformation influence the biological fate of myriad nutrients and xenobiotics. Enterocytes form a layer of highly active epithelial cells that are tightly connected to each other and form a barrier to toxins. Once the xenobiotic toxins cross this mucosal barrier, intracellular biotransformation (breakdown of complex organic matter into usable metabolites) may occur. Enterocytes contain appreciable concentrations of most of the enzymes that are involved in these metabolic transformation reactions. This process of biotransformation will affect the eventual deposition of the xenobiotic. The toxins and/or their metabolites can be excreted into the intestinal lumen or transported into the blood for systemic distribution and renal excretion. Thus, the small intestine is a site for pre-systemic elimination of xenobiotics.

Absorbed chemicals may also be transported via the portal vein to the liver where additional first pass effects and biotransformation occur. Obviously, the liver is quantitatively the most important site for xenobiotic biotransformation. However, since the small intestine does contain enzymes with biochemical characteristics similar to those of the liver, it can have a significant influence on the eventual distribution of xenobiotics.

Biotransformation is affected by several factors, including exposure to chemicals, age and nutritional status of the individual. Nevertheless, as society becomes more dependent upon chemicals for maintaining its lifestyle, exposures will increase and alternate measures will be necessary to reduce the stress created by these ingested toxins.

Normal Flora of the Gastrointestinal Tract

The pH of stomach fluids is about 2. The stomach can be viewed as a microbiological barrier against the entry of foreign bacteria into the GI tract. Although the bacterial count of the stomach contents is generally low, the walls of the stomach are often colonized on the order of 100 per gram with acid-resistant bacteria such as Lactobacillus, Serratia and Streptococcus.

The small intestine is separated into three parts, i.e., the duodenum, the jejunum, and the ileum. Adjacent to the stomach is the duodenum which is fairly acidic and resembles the stomach in its micro flora with colony sizes on the order of 10 to 100 per gram of digesta. From the duodenum, the pH gradually becomes more alkaline (pH 4 to pH 5) and bacterial numbers increase. Jejunum populations range from 1,000 to 10,000 per gram while ileum populations range from 100,000 to 10,000,000 per gram. Also, the farther from the stomach that the digesta moves, the more mixed it becomes with regard to bacterial colonization.

In the large intestine (pH 7), bacteria are present in enormous numbers, from 10,000,000,000 to 100,000,000,000 per gram. The colonies are so overwhelming that this region can be viewed as a specialized fermentation vessel. Living within the lumen, the bacteria utilize products of the digestion process as nutrients. Facultative aerobes, Escherichia, are present in relatively small numbers, less than 10,000,000 per gram of intestinal contents. The activities of facultative aerobes include the consumption of any oxygen that may be present. This makes the environment of the large intestine strictly anaerobic and favorable for the profuse growth of obligate anaerobes, Clostridium, Bacteroides and Enterococcus.

Though there are over 400 species of bacteria known to inhabit the GI tract of people around the world, for the individual adult the species type rarely change. The populations are always in flux. Population size is influenced by the rate of passage of digesta, acidity, intestinal contents, changes in diet, intestinal gas, use of drugs and diseases or illness.

A summary of the functions of intestinal micro flora is as follows:

- Bile acids: Biotransformation, i.e., deoxycholic acid will both induce water secretion and prevent its absorption unless acted on by microbes.

- Hydrolysis of Glycosides, Glucuronide, Nitrates, Sulfamates.
- Reduction of Azo compounds, Phenolic acids, Oxidation of Sulfides, Nitrogenous compounds, Phenolic compounds.
- o-Demethylation of Methoxylated Isoflavones; Flavonoids.
- Vitamin synthesis, form non-food sources of thiamin, riboflavin, pyridoxine (B6), B12 and K.
- Gas production: carbon dioxide, methane, hydrogen, nitrogen, hydrogen sulfide, ammonia.
- Odor production: Amines, Indole, Skatole, Butyric acid.
- Organic acids: Acetic, Propionic, Butyric acids.
- Glycosidase reactions.

Because of digesta motility, bacteria is constantly being lost, about one third the weight of feces. To replace lost populations, depending on the species, bacteria will double their populations 1-6 time per day.

When an antibiotic is given orally, it will usually inhibit the growth of normal flora as well as pathogens. Continuous movement of intestinal contents leads to the loss of preexisting bacteria and the virtual sterilization of the GI tract. As the result of intestinal sterilization, several physiologic changes take place that are not yet totally understood. The observed changes include the following:

- Increased Caecum results in less responsiveness to mechanical and biologic stimuli.
- Reduced muscular activity of the smooth muscle of the intestinal wall produces a decrease in spontaneous contractions, resulting in constipation.
- The threshold dose of required biologically active amines (chemical agents that regulate propulsion) that control relaxation and contraction of digesta increases.
- Prolonged transit time of digesta.
- Increase in fecal pH and total nitrogen.

Sterilization of the intestine poses an immediate medical concern, i.e., the establishment of opportunistic microorganisms such as resistant Staphylococcus, Proteus, Salmonella and Yeast before the normal flora can become reestablished.

Little is known about the interrelationships among intestinal microbes. What is known is that their presence has a positive influence on stimulating motility, enhancement of response to bioactive amines and that the organic acids produced inhibit adjacent colony growth and contribute to the resistance to pathogens. However, when a population becomes hyperactive, their toxins can cause diarrhea, nausea, vomiting, bleeding, intestinal lesions, fever, etc.

Intestinal Gas

A false assumption is that the intraluminal space of the intestine is mostly anaerobic and that intestinal gas is not significant to the functions of digestion and the overall health of the intestinal tissues. Of the five principal gases found in the GI tract (nitrogen, oxygen, carbon dioxide, hydrogen, methane), only nitrogen and oxygen are present in degree in atmospheric air. Oxygen and nitrogen enter the digestive tract with swallowed air. They may also gain entrance in charged beverages and in foods whose preparation incorporates air, such as whipped foods and soufflés or in foods that contain air (e.g., an apple contains 20% gas by volume). In addition, some nitrogen may be contributed by diffusion from the blood or from bacterial breakdown of amino acids.

Composition of Gastrointestinal Gas

Gas	Stomach %	Colon %
Nitrogen	79	23-80
Oxygen	17 (6 ppm)	0.1 - 2.3 (0.05 - 0.9 ppm)
Carbon Dioxide	4	5 - 29
Hydrogen	-	0.1 - 47
Methane	-	0 - 26

Carbon dioxide is generated in large amounts in the duodenum from the interaction between hydrochloric acid and bicarbonate present in the duodenum (this reaction neutralizes the acid, increasing the pH). It is also formed as a product of the reaction of bicarbonate with fatty acids resulting from the digestion of triglycerides in the duodenum by pancreatic lipase. Hydrogen is derived from the action of bacteria on fermentable substrates. Nearly all the bacterial activity takes place in the colon, but some may occur in the small intestine when bacterial overgrowth affects this segment of the gut or when there is bacterial colonization of an ileostomy.

Because of its greater partial pressure in the bowel lumen, hydrogen, more or less, constantly diffuses into the blood perfusing the gut. The blood transports it to the lung; here it is excreted in expired air. Methane is generated and excreted in the same manner as hydrogen. Because its formation is species specific, and that the necessary flora appears to be an inherited family trait, only one third of adults will have it.

The substrates on which the bacteria act to form hydrogen, methane and carbon dioxide represent the residue of foodstuffs that were consumed but were not fully digested or absorbed in the small intestine. Intestinal disorders that reduce pancreatic exocrine secretion, denude or destroy the mucosa, obstruct lymphatic drainage or in other ways impair digestion and absorption, increases bacterial nutrients which greatly increases bacterially produced gases. What stands out from this brief discussion on intestinal gas is that oxygen is rapidly consumed by the mucosal epithelial cells, and in the absence of oxygen, pathogens and toxins readily invade the intestinal tissues.

Conclusion

The above discussion reveals that oxygen is extremely important for the following reasons.

- **Energy metabolism requires oxygen.**
- **Cell restitution and regeneration requires oxygen.**
- **Biotransformation of toxins requires oxygen.**
- **The control of pathogen overgrowth requires oxygen.**
- **Maintaining the mucosal barrier against xenobiotics requires oxygen.**
- **The health of the mucosa requires oxygen.**
- **Efficient glucose absorption requires oxygen.**
- **Preventing the absorption of bacterial endotoxins requires oxygen.**