# Functional Strategies for the Management of Gastrointestinal Disorders:

## Principles and Protocols for Healthcare Professionals

**Supporting Core GI Functions • Malabsorption and Low Stomach Acid • Digestive Enzymes and Bile Support**

**Constipation and Natural Laxatives • Support for Liver Detoxification • Supporting the Gut Microbiome**

**Probiotic Therapies for GI Outcomes • Supporting Gut Barrier Functions • Neuroendocrine Functions**

**Protocol Suggestions for Inflammatory Bowel Disease • Irritable Bowel Syndrome**

**Small Intestinal Bacterial Overgrowth • AAD and *C. difficile* • *Helicobacter pylori* • Candidiasis • And much more...**

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Thomas G. Guilliams Ph.D.

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# Functional Strategies for the Management of Gastrointestinal Disorders:

## Principles and Protocols for Healthcare Professionals

By Thomas G. Guilliams Ph.D.

POINT INSTITUTE

STEVENS POINT, WI

The Point Institute was founded by Thomas Guilliams, Ph.D. as an independent research organization focused on examining and disseminating information about the use of natural therapeutic options for treating and preventing chronic disease. Along with therapies generally defined as lifestyle interventions, the Point Institute specializes in the evidence and application of nutraceuticals (dietary supplements, herbs, vitamins, minerals, etc.) as therapeutic and preventative agents in clinical practice.

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# Crossroads in GI Health:
## A Functional Approach for Functional Disorders

Gastrointestinal symptoms are some of the most frequently experienced by all subjects and one of the most common reasons individuals seek medical care. Some of these symptoms are acute and self-limiting, while others linger for years or even decades without resolution. Often, individuals describe seeking the help of numerous physicians and treatment modalities over many years, without significant relief. Unfortunately, millions more suffer silently, believing their symptoms are "normal." As they attempt to avoid foods or situations that trigger their symptoms or self-medicate with antacids, over-the-counter laxatives and analgesics, they always keep one eye on the nearest available restroom.

At the same time, clinicians often find GI complaints to be difficult to diagnose and treat, especially in patients who have experienced years of symptoms and unsuccessful remedies. Many other clinicians are frustrated by the overuse of drugs and surgery in the attempt to relieve GI complaints, as these remedies often have no relationship to the root cause(s) of the dysfunctions experienced by the patient. Clinicians are well-aware that a wide range of GI complaints occur in individuals with no discernable organ dysfunction or disease. In recent decades, conditions such as irritable bowel syndrome have fallen into phenomena deemed "functional bowel disorders" to acknowledge that while no discernable organ or tissue defect has been discovered, some overall dysfunction within the GI tract is present.

In fact, over the past few decades, a whole new designation has been given to a wide-range of GI conditions, now referred to as functional gastrointestinal disorders (FGIDs). These disorders have been divided into different categories (for adults and children) using criteria developed by the Rome Foundation (see Table 2 for Rome IV FGIDs).[1] They are generally classified based on "symptom clusters" that remain consistent across clinical and populations with these disorders.

### Table 2: Rome IV Functional Gastrointestinal Disorders

**Functional Gastrointestinal Disorders**

A. Esophageal Disorders
B. Gastroduodenal Disorders
C. Bowel Disorders
D. Centrally Mediated Disorders of Gastrointestinal Pain
E. Gallbladder and Sphincter of Oddi (SO) Disorders
F. Anorectal Disorders
G. Childhood Functional GI Disorders: Neonate/Toddler
H. Childhood Functional GI Disorders: Child/Adolescent

A1. Functional chest pain
A2. Functional heartburn
A3. Reflux hypersensitivity
A4. Globus
A5. Functional dysphagia
B1. Functional dyspepsia
  B1a. Postprandial distress syndrome (PDS)
  B1b. Epigastric pain syndrome (EPS)
B2. Belching disorders
  B2a. Excessive supragastric belching
  B2b. Excessive gastric belching
B3. Nausea and vomiting disorders
  B3a. Chronic nausea vomiting syndrome (CNVS)
  B3b. Cyclic vomiting syndrome (CVS)
  B3c. Cannabinoid hyperemesis syndrome (CHS)
B4. Rumination syndrome
C1. Irritable bowel syndrome (IBS)
  IBS with predominant constipation (IBS-C)
  IBS with predominant diarrhea (IBS-D)
  IBS with mixed bowel habits (IBS-M)
  IBS unclassified (IBS-U)
C2. Functional constipation
C3. Functional diarrhea
C4. Functional abdominal bloating/distension
C5. Unspecified functional bowel disorder
C6. Opioid-induced constipation
D1. Centrally mediated abdominal pain syndrome (CAPS)
D2. Narcotic bowel syndrome (NBS)/ Opioid-induced GI hyperalgesia
E1. Biliary pain
  E1a. Functional gallbladder disorder
  E1b. Functional biliary SO disorder
E2. Functional pancreatic SO disorder
F1. Fecal incontinence
F2. Functional anorectal pain
  F2a. Levator ani syndrome
  F2b. Unspecified functional anorectal pain
  F2c. Proctalgia fugax
F3. Functional defecation disorders
  F3a. Inadequate defecatory propulsion
  F3b. Dyssynergic defecation
G1. Infant regurgitation
G2. Rumination syndrome
G3. Cyclic vomiting syndrome (CVS)
G4. Infant colic
G5. Functional diarrhea
G6. Infant dyschezia
G7. Functional constipation
H1. Functional nausea and vomiting disorders
  H1a. Cyclic vomiting syndrome (CVS)
  H1b. Functional nausea and functional vomiting
    H1b1. Functional nausea
    H1b2. Functional vomiting
  H1c. Rumination syndrome
  H1d. Aerophagia
H2. Functional abdominal pain disorders
  H2a. Functional dyspepsia
    H2a1. Postprandial distress syndrome
    H2a2. Epigastric pain syndrome
  H2b. Irritable bowel syndrome (IBS)
  H2c. Abdominal migraine
  H2d. Functional abdominal pain - NOS
H3. Functional defecation disorders
  H3a. Functional constipation
  H3b. Nonretentive fecal incontinence

According to the Rome Foundation, the symptoms associated with various FGIDs are related to combinations of physiological phenomena, such as increased motor reactivity, enhanced visceral hypersensitivity, altered mucosal immunity (inflammation), changes in gut microbiota, or altered regulation of the gut by the central nervous system (including psychological and sociocultural factors).[2] FGIDs are the third most common GI diagnosis during an ER visit across the United States, and over 10% of FGID-related emergency visits result in hospitalization.[3] Not surprisingly, it is quite common for a single individual to have symptoms associated with at least two different FGIDs (e.g., IBS-D and functional diarrhea), or an FGID with another gastrointestinal diagnosis (e.g., IBS and IBD or functional dyspepsia and GERD).[4,5,6] This guidebook is not designed to give a detailed review of each FGID, but will discuss the criteria for several as we navigate our way through several topics, including IBS (page 189), functional dyspepsia (page 25), and functional constipation (page 53).

## Functional Medicine

Almost parallel in time with the development of the Rome criteria, a paradigm of medicine has been emerging that acknowledges core body functions (and, therefore, dysfunctions) are ultimately at the root of all complex chronic disease and healing potential. This new paradigm of medicine is generally referred to as "functional medicine," though many others within the broader integrative medical community practice a similar paradigm under different banners.† While defined differently by various groups, functional medicine essentially combines the importance of patient-centered preventative care with the understanding of the complex interconnections between organ systems. This form of medicine allows clinicians to begin to understand the complex network connecting each body system through a web of physiology and biochemistry. No longer is each body system isolated from the other; instead, the emphasis is on what connects the systems together; and what common relationships (and deficiencies) help explain a patient's chronic conditions. In essence, this form of medicine asks, "What are the common threads connecting the symptom patterns seen in a patient experiencing chronic illness?" rather than merely "How can we differentiate one disease from one another?" The result is therapies focused on root causes of complex and chronic disease patterns that are tailored to specific patients.

As this paradigm has been emerging, research has greatly advanced the way we understand gastrointestinal functions and related disorders. For instance, many studies have illuminated the complex interaction of the immune system, neuroendocrine system and microbial environment within the gut, detailing how these newly discovered interactions are fundamentally related to core GI functions. Obviously, these advances in understanding have profound implications on the diagnosis and treatment of gastrointestinal disorders. While older models of gastroenterology defined discreet independent disorders, this new approach defines several shared fundamental functions, to be at the root of many, seemingly unrelated, GI disorders. When we combine these scientific advances along with the understanding of the biological individuality of each patient, we are at the heart of functional and lifestyle medicine. In the end, regardless of the name given to the medical tradition or the diagnostic code placed into the chart, this paradigm allows clinicians to treat patients (rather than diseases) and target root causes (rather than merely their manifesting symptoms).

## Heal the Gut First

The gastrointestinal (GI) tract represents our most intimate contact with the external environment. In our lifetimes we will consume between 30-50 tons of food and host more microbial cells in our gut than human cells in the rest of our body. The GI tract is tasked with the responsibilities of extracting the appropriate nutrients we need to thrive, maintaining an appropriate balance of helpful and harmful microbes, and acting as a conduit for waste removal. At the same time, the healthy GI tract prevents the entrance of harmful substances into the body. Is it any wonder this delicate balance in the gut is often disturbed, leading to GI symptoms, disorders and syndromes for which many seek medical care?

It is not surprising, then, that one of the most common phrases used within naturopathic, functional and related integrative medical communities is "heal

† The Institute for Functional Medicine (IFM) has championed the functional medicine model and has published the Textbook of Functional Medicine to define their perspective on how to practice within this paradigm. The principles and protocols shared within this book are, in our view, generally complimentary to those of IFM or other organizations teaching similar approaches- though they may differ in nomenclature and specific details.

the gut first." This idea reminds clinicians of the front-line role the GI system plays in nearly every facet of health. It is rare to find an individual with any chronic condition without some related GI system dysfunction. Conversely, patients with major GI disorders will manifest symptoms that are systemic. On top of this, all other recommended therapies involving foods, beverages, supplements or drugs require a predictable interface with the GI system and related detoxification pathways. Therapies that may work in a healthy GI environment may be neutralized or even exacerbate the condition for which they are intended to help when GI function is disrupted. "Heal the gut first" is a reminder that GI dysfunction can lead to many, seemingly unrelated, chronic conditions that may be best addressed after (or along with) known GI dysfunctions.

## Core Functions of the GI System

Within this Road map, GI functions will be grouped into five core areas based on function: **Digestion, Elimination, Protective Barrier, Microbial Ecosystem,** and **Neuroendocrine.** These core functions are discrete and different, though most are interrelated and highly dependent upon one another. We will briefly define these core functions here, though each will be expanded greatly throughout this text.

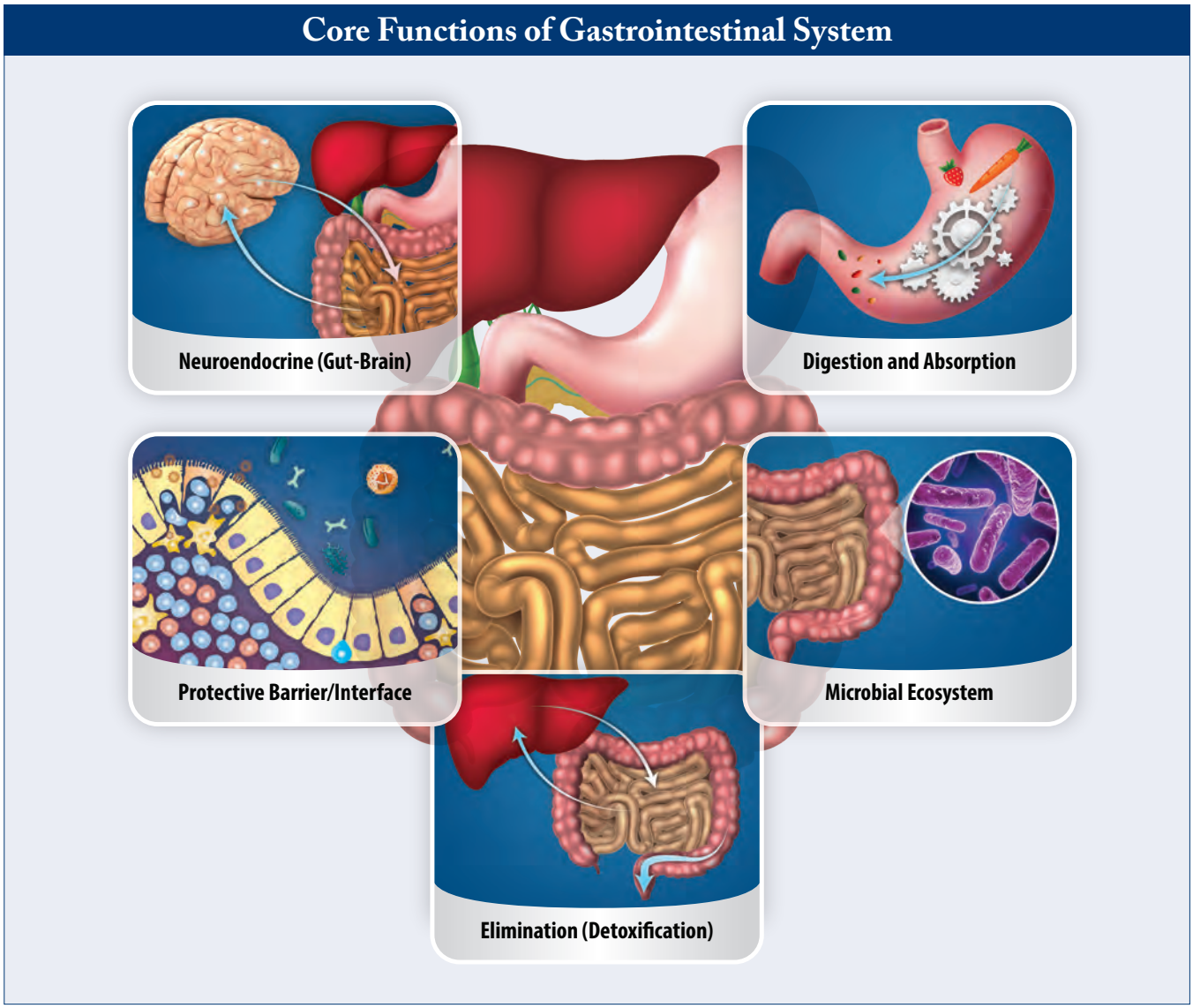



**Figure 4: The five categories of core gastrointestinal functions used within this Road map.** See text for more details.

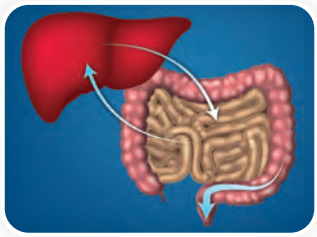
**Digestion (and Absorption)**

Perhaps the most obvious of all its functions, the GI tract is tasked with digesting and absorbing the nutrients within the food and beverages we consume. Through a complex coordination of enzymes, acids, bile salts, peristaltic action, transporters, and microbial biotransformation, our GI tract must take complex foodstuffs and deconstruct them into macronutrients (protein, carbohydrate, fat) and micronutrients (vitamins, minerals, phytonutrients, etc.) that can be transported into the body. Each step in the processes of digestion is important, as it only requires a deficiency in one or a few micronutrients to lead to a metabolic dysfunction.

Since the GI tract is exposed to 30-50 tons of food in the average lifetime, the types of food we eat are extremely important in maintaining proper GI health. The Standard American Diet, or SAD (sometimes called MUD, the Modern Urban Diet), is associated with nearly every chronic illness discovered, including most chronic GI complaints. Highly processed foods with high amounts of refined carbohydrates, hydrogenated fatty acids, food additives and preservatives, and low in fiber, natural colors and phytonutrients are typical of this dietary pattern. These poor dietary patterns are pro-inflammatory, place a significant burden upon the detoxification reserve capacity, and reduce bowel transit time, all of which can generate a downward spiral of gastrointestinal complaints and dysfunction. On top of this, many individuals have undiagnosed food allergies that continue to mediate ongoing immunological reactivity, further weakening the barrier function of the gut.

We will outline the types of diets and eating patterns known to be beneficial for the prevention and treatment of a range of digestive disorders, including discussions of a variety of ways to specifically improve digestion and absorption of nutrients. In addition, several ways clinicians can test a patient for poor digestive function will be listed.

**Elimination**



The process of elimination can be nearly as important as digestion. Ridding the body of the unusable portions of foods as well as the toxic metabolites stored and produced in the body is a critical function of the GI system. Healthy liver detoxification (biotransformation), bile production and regular bowel movements are hallmarks of a healthy GI tract. Proper elimination also helps regulate bowel transit time, which has an effect on proper digestion and absorption, water and electrolyte balance, and healthy microbial function. Constipation is one of the most common GI symptoms for which people seek a remedy. Stool frequency and morphology have been used to define overall health for millennia.

Details will be given about healthy detoxification and ways in which clinicians can encourage patients to avoid unhealthy toxins and allergens encountered in their diets, as well as nutritional and supplementary strategies to increase detoxification efficiency. We will also review the efficacy and safety of lifestyle and non-pharmacological approaches for preventing and treating constipation.

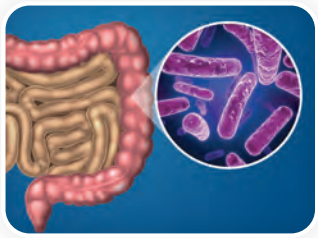
**Protective Barrier**

While we think of the GI tract as a digestive and absorptive organ, maintaining proper mucosal barrier function is vital for both GI and system-wide health. The GI tract is specifically equipped to balance the need for massive absorption of nutrients, while preventing the passage of unwanted particles or organisms into the body. The lumen of the gut contains numerous entities that should never reach the blood stream or lymphatic system, such as large antigenic/allergenic food particles, toxins, harmful microorganisms and their metabolites. The integrity of the mucosal barrier is maintained by a single layer of tightly fitted columnar epithelial cells that comprise a surface area the size of a doubles tennis court. As we shall outline later, greater than 70% of the immune system is closely associated with the GI tract in specialized lymphatic compartments within the mucosa

and in the intercellular space along the epithelium. The barrier protection can be compromised by a number of factors such as dysbiosis, inflammation, food allergies and immune system dysregulation.

We will outline the consequences of barrier disruption that leads to gastrointestinal permeability (i.e., leaky gut), discussing both the common causes and ways to prevent and treat barrier disruptions. We will also describe the role of the gut-associated lymphoid tissue in maintaining the barrier function, describing ways to improve gut-immune function (and overall immune function), a role closely tied to both the microbiome and the neuroendocrine functions of the GI system.

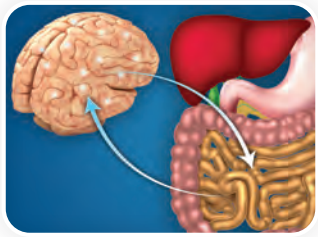
**Ecosystem for Gut Microbiome**



The human GI tract is host to at least 100 trillion individual microorganisms, from at least 1,000 different identified subspecies of bacterial and yeast alone. Over the past decade, research has been uncovering the interrelationship between proper human metabolism and the signals and metabolites that are generated from this internal microbial ecosystem. In fact, by some measures these microorganisms represent one of the most metabolically active systems within the human body— affecting glycemic control, cholesterol and amino acid metabolism, short-chain fatty acid production (e.g., butyrate for colon cell energy), and vitamin synthesis. Proper microbial balance helps regulate immune function and maturation, prevent overgrowth of harmful organisms, and regulate bowel motility.

Dysbiosis, the generic name given to any number of potential imbalances within the gut microbial environment, can lead to a wide range of GI pathologies and create vulnerabilities within the immune and detoxification systems, resulting in system-wide effects. This guidebook will overview the current scientific understanding of the human gut microbiome as it pertains to human metabolism, health and disease, while reviewing the known lifestyle, diet and non-pharmacological approaches (e.g., probiotics and prebiotics) for modulating the gut microbiome in the prevention and treatment of GI-related outcomes.

**Neuroendocrine**



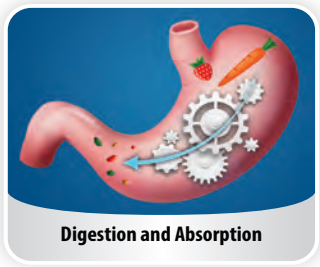
Since the GI system maintains a critical interface with the external environment, there are a number of signaling mechanisms designed to coordinate its function with the rest of the body. The enteric nervous system of the gut interacts in a coordinated fashion with the central nervous system to control a number of gastrointestinal functions. Beyond these basic neuronal connections, a number of endocrine signaling processes occur within the gastrointestinal tract to modulate gastric secretions, mucosal immune functions, microbial signaling, and a collection of functions usually labeled as "gut-brain" interactions. For instance, the strong connection between HPA axis stress and GI function is primarily mediated through the neuroendocrine functions within the GI tract.

As with all the other core functions of the GI system, the neuroendocrine functions of the gut are integrally entwined with the other core functions described above. Throughout the text, we will explain various aspects of the cells and functions which coordinate the neuroendocrine functions of the GI system within the other core functions already mentioned.

## Functional Testing and GI Function

Within the functional and integrative medical community, a wide variety of laboratory tests are performed to help the clinician assess basic GI function within patients and to decipher complex gastrointestinal dysfunctions. Some of these tests are commonly used by a wide range of physicians or GI specialists, while others are more commonly used by clinicians trained within functional or integrative clinical models. Throughout various sections of the text, we will include a discussion of the available laboratory tests that may help a clinician confirm (or rule out) a particular GI dysfunction.

# Functional Support for Digestion and Absorption




The old adage "you are what you eat" was meant to be a reminder that our daily food habits will have an effect (directly or indirectly) on our body composition and health.† As we shall explore, this is partly true, though it is a bit more complicated when we get into the details. Perhaps we might say that we are what we absorb, since eating foods and absorbing or utilizing their nutrients is not always the same thing; especially in subjects with poor digestion. Reduced nutrient absorption, however, is just one facet of poor digestive health. In fact, various symptoms related to the digestive process (i.e., indigestion/dyspepsia) are some of the most commonly experienced by individuals worldwide; and the use of prescription, OTC and dietary supplements to aid digestion or relieve dyspeptic symptoms is rampant in the United States. This section of the guidebook will discuss both the fundamental principles of digestion and absorption, along with the most common dysfunctions related to digesting and absorbing nutrients from dietary sources. We will also review ways in which digestion can be improved through the use of lifestyle changes or dietary supplementation.

## Indigestion and Functional Dyspepsia

Indigestion (i.e., dyspepsia) is one of the most common adverse gastrointestinal conditions experienced by all people—even if only on occasion. The definition of indigestion is somewhat vague, loosely related to an upset stomach or an adverse digestive outcome. Thus, depending on the criteria used to define dyspepsia, chronic indigestion/dyspepsia is experienced by an estimated 10-40% of the general population (estimates are much higher when heartburn is included in the criteria).[1]

On the other hand, functional dyspepsia as a Rome diagnosis is defined a bit differently and, ironically, is mostly *unrelated* to the processes normally associated with digestion. The Rome definition for functional dyspepsia is now divided into two basic syndromes: the epigastric pain syndrome and the postprandial distress syndrome.[2] The epigastric pain syndrome is defined by intermittent pain or burning in the epigastrium at least once per week for six months, while the postprandial distress syndrome is defined by bothersome postprandial fullness occurring after normal-sized meals at least several times per week for six months. Subjects with heartburn/regurgitation are excluded from a diagnosis of functional dyspepsia, according to Rome criteria.

While these definitions of functional dyspepsia may be helpful for advancing clinical trial inclusion/exclusion criteria, there is still disagreement on their utility in clinical research and practice.[3] As with other functional gastrointestinal disorders (FGIDs), functional dyspepsia often overlaps with other FGIDs such as IBS and/or other GI disorders such as GERD.[4,5,6] Commonly, psychological distress (e.g., anxiety) is associated with functional dyspepsia, although abnormal pain processing or gastric motility and relaxation are also considered to be common as well.[2]

This section will cover the support of "digestive function" within the traditional context of breaking down and absorbing food nutrients. Often, dysfunctional digestion and absorption is called maldigestion/malabsorption to distinguish this from the symptoms that may (or may not) be associated with poor digestion (i.e., dyspepsia/indigestion). We will discuss each phase of digestion first, discussing specific cases of malabsorption along the way.

† This phrase appears to have been popularized in the 1920s by the nutritionist Victor Lindlahr, who promoted what he called the Catabolic Diet. In a 1923 edition of the *Bridgeport Telegraph*, he is quoted as saying "Ninety per cent of the diseases known to man are caused by cheap foodstuffs. You are what you eat." He would later publish a book by this name in 1942.

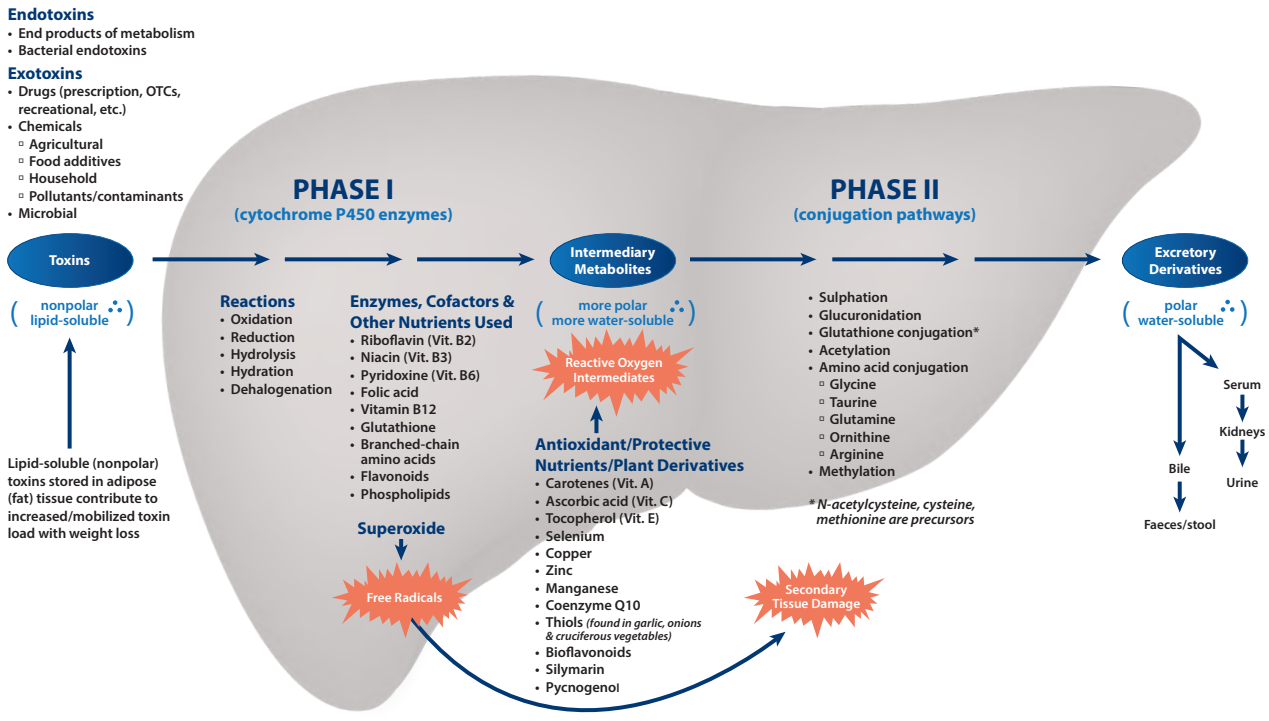
# Detoxification (Biotransformation) Pathways: The Basics

The majority of the toxins that accumulate without rapid excretion are lipid-soluble compounds. In order for these toxins to be safely and efficiently removed from the body, they need to be transformed (i.e., biotransformation) into water-soluble compounds and eliminated via the bile or urine. In humans, this critical function occurs mostly in the liver, through a two-step process involving Phase I and II detoxification pathways (Figure 15). When these pathways are functioning sub-optimally, fat-soluble toxins pass through the liver unmodified or partially modified, and are deposited in various tissues (mostly adipocytes). A general discussion of these pathways is described below and in Figure 15.

**Phase I (Bioactivation):** The Phase I detoxification system, composed mostly of the cytochrome P450 enzyme system, contributes to the metabolism of a variety of exogenous and endogenous compounds such as pharmaceuticals, carcinogens, steroids and eicosanoids. This system is composed of a group of more than 50 enzymes. A vast amount of knowledge of the substrates, cofactors and genomic activation of Phase I detoxification enzymes in the liver has been derived from pharmacokinetic studies, the study of drug metabolism. While a bit of an oversimplification, the purpose of the Phase I enzymes is to form a reactive intermediate that is then ready for a Phase II enzymatic reaction. As is often the case, the intermediate metabolite may actually be more toxic, though it is rarely available for circulation due to the tight coupling of the Phase I and Phase II systems within the liver.

Phase I cytochrome P450 enzyme activities include oxidation, reduction, hydrolysis, hydration, and dehalogenation reactions (see Figure 15). Of these, the most well-known is oxidation, which has been explored in numerous pharmacokinetic studies of certain drugs. In this pathway, a cytochrome P450 enzyme uses oxygen and NADH (as a cofactor) to add a hydroxyl group to the lipid-soluble toxin. As an illustration, estrogens can be metabolized by one of three different CYP450 enzyme pathways, which differ in the reactive intermediate that is generated prior to phase II conjugation. These different

## Figure 15: Liver Detoxification Pathways & Supportive Nutrients



intermediates involve hydroxylation at different sites of the estrogen molecule (positions 2, 4 or 16), performed by different cytochrome P450 enzymes (CYP 1A1, 1B1 and 2C/3A4-respectively); differences that have been shown to confer relatively different estrogenic effects in various tissues.[158]

All three estrogen molecules formed from Phase I (e.g., 2-OH, 4-OH, and 16-OH estrogens) must be further detoxified by Phase II reactions, prior to removal from the body. This occurs mainly through the methylation, sulfation and glucuronidation pathways (discussed in greater detail below). If these intermediate metabolites are not further metabolized by the Phase II enzymes (or are deconjugated by colonic bacterial enzymes and recirculated), they may have the potential to cause damage to proteins, DNA and RNA, leading to carcinogenesis.

| Table 6: PHASE I ENZYMES | |
|---|---|
| **CYP1A & B** | Polycyclic Hydrocarbons, Nitrosoamines |
| **CYP2A-H** | Drugs, Alcohol, Steroids |
| **CYP3A** | Drugs, Antibiotics, Flavonoids |
| **CYP4** | ω-oxidation Fatty Acids |
| **CYP5** | Thromboxane Synthase |
| **CYP7A** | 7α-Hydroxylase, Bile Acids |
| **CYP8A & B** | Prostacyclin Synthase, Bile Acids |
| *** CYP11A & B** | Cholesterol Side-chain Cleavage, Aldosterone Synthesis |
| **CYP51** | Cholesterol Biosynthesis, 14-Demethylase |
| *** CYP40** | Vitamin D3 - 1α-Hydroxylase |
| *** CYP27** | Bile Acid Synthesis |
| **CYP26** | Retinoic Acid Hydroxylase |
| *** CYP24** | Vitamin D Degradation |
| **CYP21** | Progesterone 21-Hydroxylase |
| **CYP19** | Estrogen Biosynthesis, Aromatase |
| **CYP17** | Steroid 17α-Hydroxylase, Steroid C17/21 Lyase |

** Mitochondrial Enzyme*

**Phase II (Conjugation):** The main goal of Phase II detoxification pathways is to conjugate, or attach, specific molecules to the intermediate metabolite formed from Phase I, so it can be excreted through the urine or bile as a water soluble non-toxic substance. Specifically, there are six Phase II conjugation pathways.[159,160] Reactions that occur in these pathways all rely on specific nutrient cofactors that must be replenished either through the diet or nutritional supplementation. In addition, large amounts of energy (i.e., ATP) are used in this process and must be replenished for optimal detoxification function.

***The Six Phase II Detoxification Pathways:***

- **Sulfation**: Sulfation is the conjugation of toxins with sulfur-containing compounds. Neurotransmitters, steroid hormones (such as cortisol), certain pharmaceuticals (such as acetaminophen), food additives, and many xenobiotic and phenolic compounds utilize this pathway as a primary route of detoxification.
- **Glucuronidation**: The UDP-glucuronosyltransferase (UGT) enzyme plays a critical role in this pathway. The reaction catalyzed by the UGT enzyme involves the conjugation of glucuronic acid to xenobiotics. This pathway is considered an important detoxification mechanism when sulfation or glycination activity is impaired or saturated, and is upregulated in obese patients.[161] In particular, glucuronidation helps to detoxify certain medications (aspirin), food additives (benzoates), preservatives, reproductive and adrenal hormones (esp. estrogen), and bilirubin. It is also known that this reaction can be reversed by beta-glucuronidase enzyme activity by certain species of the gut microbiota. It is speculated that increased beta-glucuronidase activity may be partly responsible for the development of estrogen-dominant conditions such as fibrocystic breast disease, breast cancer, and prostate cancer, though the evidence for such influence is limited.
- **Glutathione conjugation**: The attachment of glutathione to toxins helps to detoxify and eliminate many harmful electrophilic compounds (either xenobiotics or their metabolites). This conjugation step is mediated by the enzyme glutathione transferase (GST). Glutathione is an important nutrient with powerful antioxidant and detoxification properties. Since glutathione is composed of the amino acids cysteine, glutamic acid and glycine, it is important that these nutrients are in adequate supply.
- **Acetylation**: The conjugation of acetyl Co-A to toxins occurs via the N-acetyl transferase enzymes. This, in turn, helps to detoxify xenobiotics, such as tobacco smoke. Individuals with slow acetylation activity have a higher toxic burden, while rapid acetylators add acetyl groups rapidly, which may result in increased levels of toxic intermediate metabolites. Both slow and rapid acetylators are at increased risk for toxic overload if they are exposed to environmental toxins. While not much is known

about how to directly improve the detoxification activity of this system, it is known that acetylation is dependent on thiamin, pantothenic acid and vitamin C.

- **Amino acid conjugation**: Conjugation of toxins to amino acids such as glycine, taurine, glutamine, arginine, and ornithine are additional means to prepare intermediate metabolites for excretion. Of these amino acids, glycine is the most common. In normal adults, there is a wide range in the measures of activity through the glycine conjugation pathways due to known genetic variation of the enzymes catalyzing these reactions and bioavailability of glycine in the liver.
- **Methylation**: Methylation consists of conjugating methyl groups to active intermediates through one of several methyl transferase enzymes. Magnesium, SAMe, vitamin B12, folates and choline are required as co-factors in this pathway.

## Supporting Detoxification: Principles and Protocols

Even in the absence of overt signs and symptoms from harmful exogenous toxins, the human body is tasked with enormous biochemical and physiological challenges. When we consider the need to perform these functions while buffering and neutralizing a vast amount of toxins encountered within the environment, the cells performing these important functions are quickly challenged. Unfortunately, the combined burden of our environment, diet, lifestyle, and metabolic processes upon these processes each day can overwhelm the detoxification capacity of many individuals, leading to a wide range of dysfunctions. Additionally, nutritional deficiencies can reduce the liver's capacity to transform and eliminate toxins, exacerbating nutrigenomic and toxicogenomic susceptibilities.

### The Clinician's Dilemma

Patients experiencing elevated levels of toxic burden often present with a complex clinical picture. Ironically, these patients will seldom present with a history of overt toxic exposure, and will experience symptoms that manifest from different organ systems. For the conventionally trained clinician, toxin exposure can be difficult to detect since most conventional laboratory tests are designed to discover extreme measures of toxin exposure. For this reason, many clinicians overlook the possibility of toxic burden unless patients present with overt signs of toxicity, or have a specific health history involving a known toxic environment. Currently, the use of detoxification therapy and testing (among conventional medical practitioners) is largely limited to patients who have drug and/or alcohol dependency. Once a clinician understands how even small accumulation of toxins can burden the health of patients in diverse ways, the benefit of removing these toxins will increase in priority. In addition, several specialized laboratories now offer a variety of testing options that can help determine levels of a particular stored toxin (such as solvents, pesticides, heavy metals, etc.).

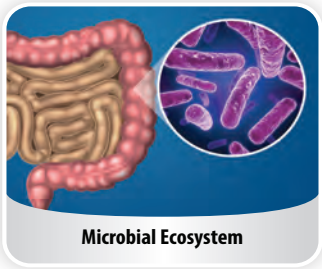
While any subject with a chronic disease is a candidate for toxin exposure testing and detoxification, certain patients are commonly considered to have a higher likelihood of toxic burden or sensitivity. Such patients may present with the following "cardinal" signs and symptoms related to toxicity:

- Chronic fatigue syndrome
- Multiple chemical sensitivities
- Fibromyalgia and similar pain-type syndromes
- Immune disorders
- Neuropsychiatric disorders and cognitive disturbances

### Conditions or Lifestyles That May Benefit from Detoxification

- **Exposure to tobacco products, alcohol, caffeine, pharmaceutical medications and industrial chemicals:** Patients who are frequently exposed to these substances are at an increased risk for an imbalanced Phase I/Phase II liver detoxification. These substances can induce or up-regulate Phase I liver detoxification, causing an inability for Phase II pathways to conjugate and neutralize the increase in intermediary metabolites formed from Phase I pathways. The activated intermediates and free radicals react with and damage cellular proteins, RNA, and DNA, leading to poor cell signaling.
- **Obesity/overweight:** Since most exogenous (and some endogenous) toxins are fat-soluble, the volume of fat mass has been related (either as a cause or effect) of toxic burden. A buildup of toxins is also commonly thought to affect a patient's ability to

# Supporting the Microbial Ecosystems in the Gut


Microbial Ecosystem

One of the greatest paradigm shifts in medicine over the past few decades has been the unfolding discoveries revealing the metabolic influence of the human microbiome, especially that which resides within the gastrointestinal tract. Indeed, it is difficult to find a medical discipline that is not actively investigating the potential role played by the gut microbiome in human health and disease. This explosion of knowledge has been welcome news for many healthcare providers, though keeping up with the published research, changing nomenclature and therapeutic ramification of this information has been a difficult task. Our goal in this chapter is not to provide a comprehensive review of all the current literature (though we provide updated references for those who want to investigate this further†); instead, we will overview the fundamental and clinically-relevant aspects of the human GI microbiota, focusing our attention on modifiable behaviors and therapies that have been shown to alter these organisms, their environment and influence (good or bad). In addition, we have specifically attempted to answer, with the best available evidence, the most frequently asked questions clinicians have posed to us related to these issues.

## Nomenclature Related to GI Microbes

Basic definitions and common terms used to describe features of the gastrointestinal microbial community. As indicated, many of these terms are interchangeable (practically), even if they represent different features (technically).

**Microbiota:** The total microbial organisms within the gut (or other defined ecosystem). This generally includes friendly and unfriendly organisms: bacteria (bacteriome), fungi (mycobiome) and virus (virome). To date, with the exception of a few fungal species, our study of the microbiota is almost entirely focused on bacteria.

**Microflora:** Considered (and favored) by many to be equivalent to "microbiota" (i.e., "microbial flora"), though others consider it to be an incorrect term remnant of the days when bacteria and fungi were considered part of the plant kingdom. Nonetheless, the term is still common in both scientific and popular writings.

**Microbiome:** This term is considered by many to be interchangeable with "microbiota," though it is often used to describe the total microbial community with its environment (i.e., biome). Others use this term exclusively to describe the total genomic information contained in these microbes (i.e., microbial genome). We prefer and will use the first definition throughout this chapter, and use "metagenome" to describe the second.

**Metagenome:** This term refers to the total non-human genetic material (bacterial, fungal, viral) that can be isolated from humans (e.g., identifiable genomic material from GI bacteria, etc.). Additional "omic" terms such as metatranscriptome, metaproteome, metametabolome are equivalent terms used to describe non-human transcripts, protein expression and metabolites found in or on humans.

**Operational Taxonomic Unit (OTU):** This operational definition of species is used when only genetic material (DNA or RNA) is analyzed to distinguish one species from another. Since many bacteria within the gut microbiome cannot be isolated, grown and investigated in a laboratory

† A growing list of references related to the microbiome can also be found at http://americangut.org/publications/

# The Human Gut Microbiome: The Basics

As most are now aware, the human GI tract is a host to countless microbes (some estimate 100 trillion bacteria alone) that have a powerful impact on human health. This impact extends well beyond the gut lumen, and has been implicated in nearly every facet of human physiology and metabolism.[1,2,3] In fact, the gut microbiome is now commonly viewed by many as a semi-autonomous symbiotic organ or organ-like system within the GI tract. However, while our knowledge of the microbiome within the human gut has greatly expanded in just the past few years, there is much we still do not know about this complex ecosystem, especially as it pertains to modifying its structure and metabolic functions to favor a healthy outcome for the host.

Our knowledge of the commensal gut microbiota is heavily weighted toward bacterial species, though there is a growing base of knowledge on GI-resident viruses, bacteriophages (viruses that infect bacteria), fungi, and protozoa. Recent technological advances that allow for the recovery, amplification and sequencing of genetic material from the gut have given us exponentially more information than the plating/growth technologies of the past, allowing for the identification of more than 1,300 different bacterial species in humans worldwide (identified primarily by ribosomal RNA sequences).[†4,5]

Acknowledging that the human GI tract is a highly complex network of microbes is one thing, understanding the important features within this complexity has been much more daunting. This is partly due to the fact that the primary tool used to study the gut microbiome in humans is the analysis of fecal microbiota (from stool samples), which we now know is only a rough approximation of the many microbial niches found within the GI tract. However, since this is how most of the data is generated, we will start our discussion there.

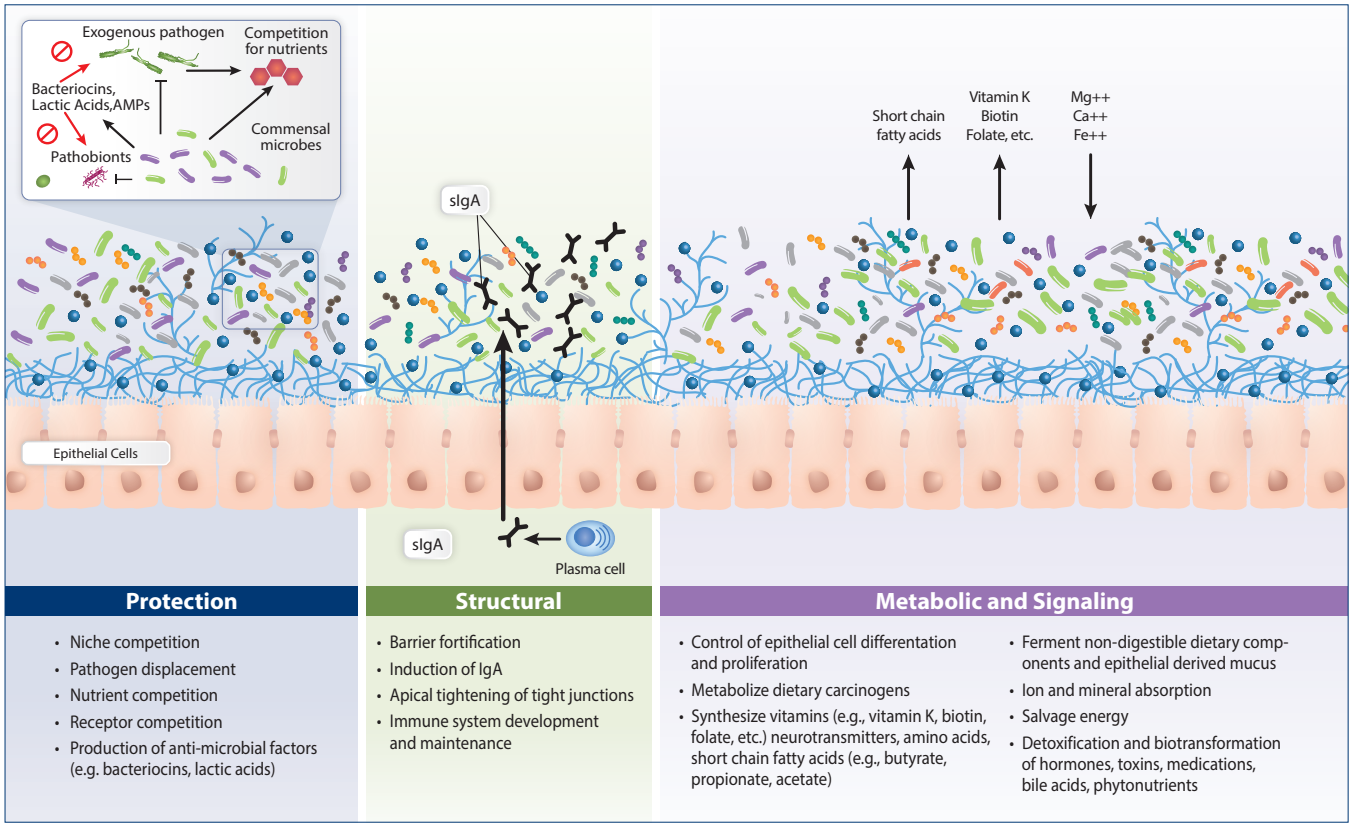
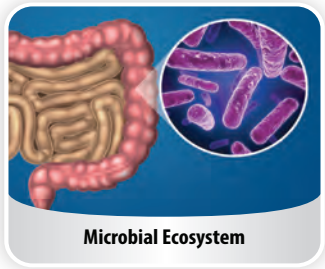



**Figure 16: Basic Function of the Commensal Gut Microbiota.** From the perspective of the host, this figure illustrates the three basic functional categories performed by the commensal gut microbiota. Some of these activities are also provided by certain probiotic organisms. See text for more details.

† There is some debate about the number of species identified with the global human microbiome based on the definition of a species and the techniques used to identify genetic differences. This number continues to expand as better genetic tools become available and larger populations are sampled.

# Probiotics: Therapeutic Agents for Dysbiosis and Beyond


Microbial Ecosystem

The use of probiotics to help re-establish a healthy gut microbiome is now a well-accepted practice across the globe. Research into various types, combinations and doses of probiotics for nearly every potential outcome is expanding at a rapid pace, making it difficult for clinicians to assess the validity of the products that are available for their use or recommendation. In this section, we will outline critical information clinicians should know about using probiotics within the clinical setting, focusing on those factors that may help distinguish one particular product from another. Here, we will also discuss the use of probiotics for basic therapies such as dysbiosis and microbiota maintenance; however, specific recommendations for probiotic therapies will be left to their respective sections.

## Probiotics: Definitions and Distinctions

Within the context of this discussion, probiotics describe microorganisms that are intentionally consumed for an intended health benefit, usually to help re-establish a healthy gut microbiome. We specifically distinguish the term "probiotics" from both foodborne microbes (e.g., from soil on vegetables) and microbes used in the production of foods (for fermentation, etc.).[1] While both of the latter can be important influences on a person's gut microbiota over time, the overwhelming majority of research on probiotics in human health is based on commercially-prepared products derived from concentrated bacterial strains. In some cases, these probiotics are added to fermented foods in order to deliver added benefits to the consumer (e.g., yogurt, kefir).

It is also import to establish that commercial probiotics should not be confused with commensal (or indigenous) organisms and, therefore, the therapeutic use of probiotics should not be strictly viewed as "re-inoculating" or "re-colonizing" the gut (see 4R model on page 22). Instead, probiotics should be viewed as highly domesticated varieties of a very limited subset of the "wild" population of microbes living in the human gut. Depending on the strain, probiotics retain some of their "wild-type" characteristics, allowing them to confer benefit alongside the commensal organisms, though they usually lack other characteristics that would permit them to become permanent residents within the host (discussed further below). Probiotics, then, can benefit the host by direct (but transient) effects, and/or by modifying various gut micro-environments that benefit commensal organisms (limiting pathogenic or pathobiont organisms, altering pH, signaling immune cell function, etc.).

From a regulatory standpoint, probiotics are controlled based on the type of products in which they are contained (food, dietary supplement, investigational drug, etc.), based on the types of claims made for those products. In the United States, probiotics are sold mainly as dietary supplements or foods, though the definition of a dietary supplement in the Dietary Supplement Health and Education Act (DSHEA) does not specifically include probiotics. Probiotic research in the United States is often complicated by these definitions since the FDA (or institutional review boards) can require an Investigational New Drug (IND) application prior to conducting research involving certain disease-related endpoints or patient types.[2] This can stall important research or cause researchers and probiotic marketers to go outside the United States to perform their clinical trials.

The definition of a probiotic assumes two other features: they are "live" organisms and they have a defined health benefit. While both of these are prominently part of the agreed-upon definition of a probiotic "*live microorganism that, when administered in adequate amounts, confer a health benefit on the host*," they are not as easily defined, and even more difficult to regulate.[3] As we shall discuss further in this section, "live" is a relative term when it comes to probiotics,

# Supporting the Barrier Function of the Gut


It is often difficult to conceive of the gut lumen as being "outside" the body, but there is an intricate set of barriers designed to ensure it remains so. Therefore, the barrier/permeability functions of the gut represent one of the most important interfaces between a person and the external environment. However, we should not imagine this barrier function as simply a means to keep things out, but as a sophisticated system to communicate with, and allow selective entry of, certain contents from the gut lumen into the body. This requires a tightly controlled, but thin barrier of tissues and secretions ***intentionally designed for close proximity to the gut lumen***. This proximity permits the absorption of available nutrients and physiological interaction with trillions of non-human microbes and their metabolites and signals, but also creates a vulnerability to those same microbes, toxins and immunologically reactive components from the gut lumen. In this section, we will briefly overview the main features of the gut barrier, the functions and dysfunction of intestinal permeability, and how breaches in barrier function contributes to various GI dysfunctions and diagnostic phenomena. We will also review ways in which the barrier function of the gut can be measured and supported in patients with these conditions.

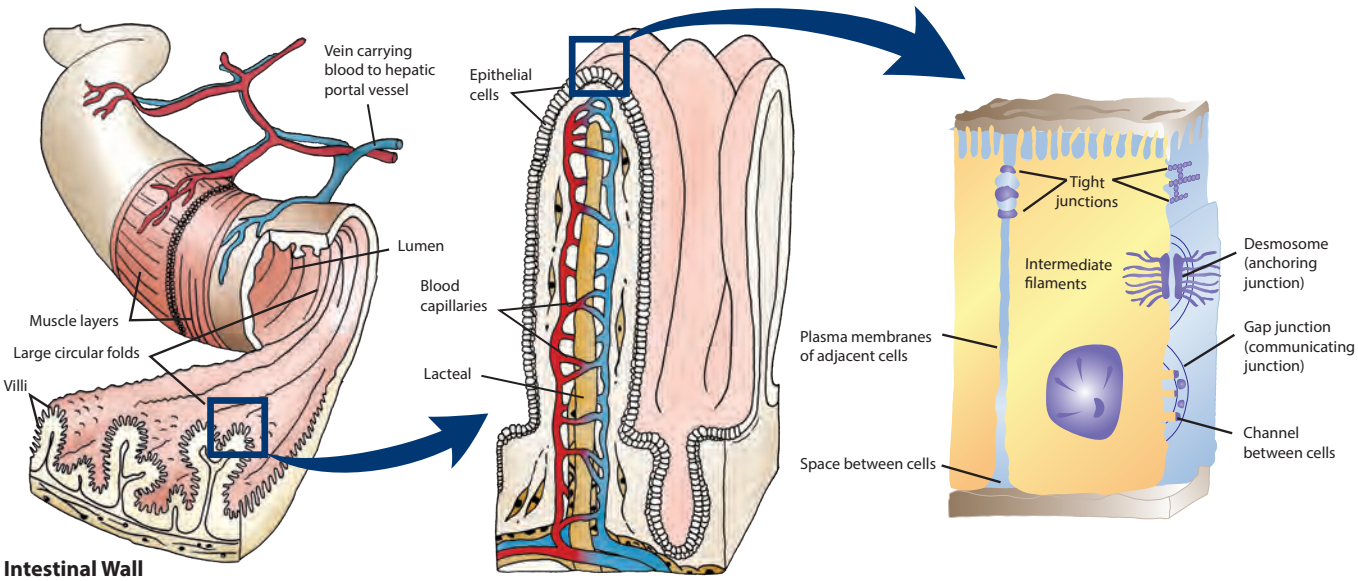



**Figure 29: Expanding Surface Area of the GI tract.** The intestinal wall uses large folded surfaces containing many individual villi (center). These villi are lined with a single layer of epithelial cells with access to both the blood supply (capillaries) and the lymphatic system (lacteal). Each epithelial cell is joined to the adjacent cell by the formation of tight junctions, preventing particles from the gut lumen from passing between the epithelial cells.

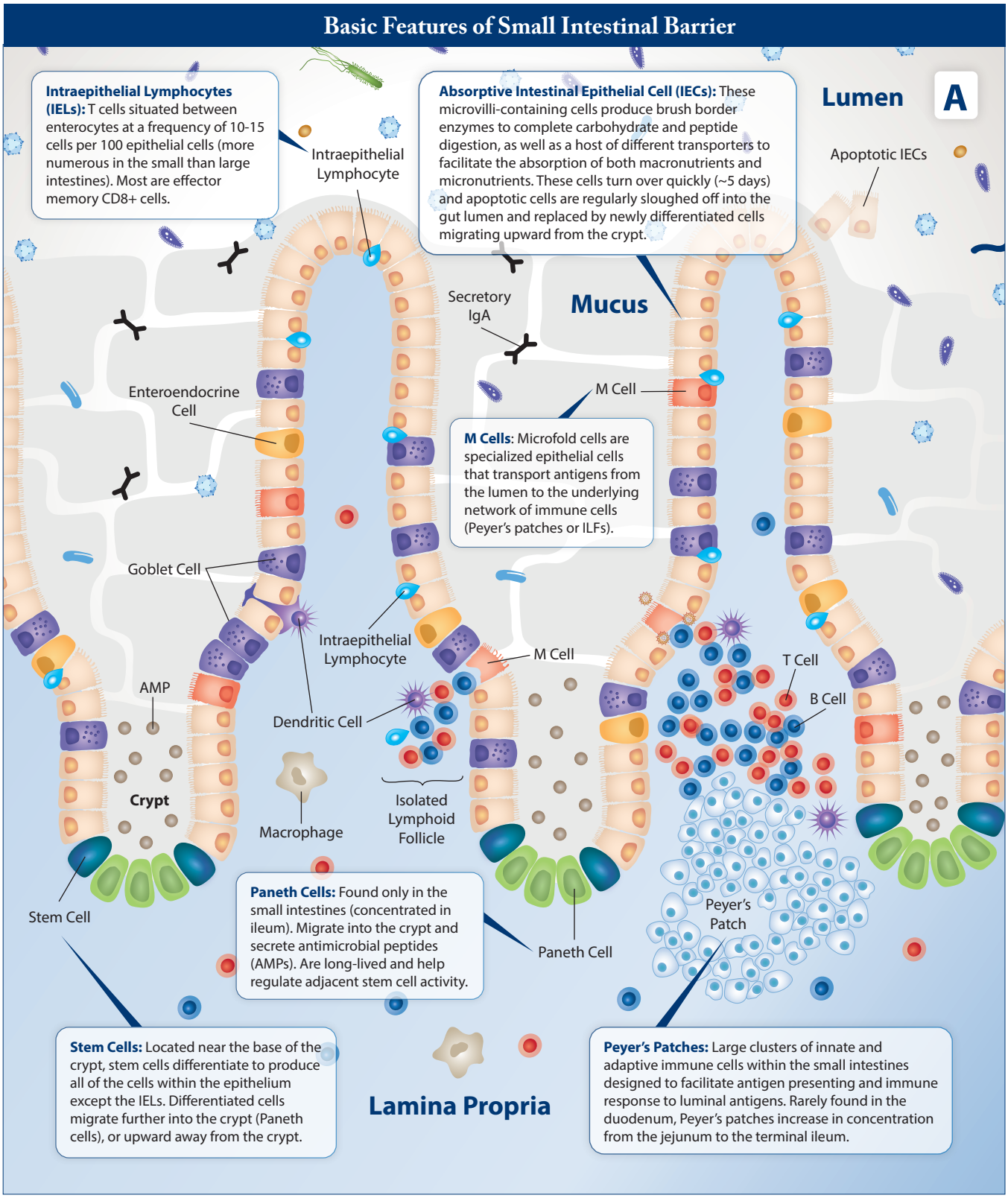
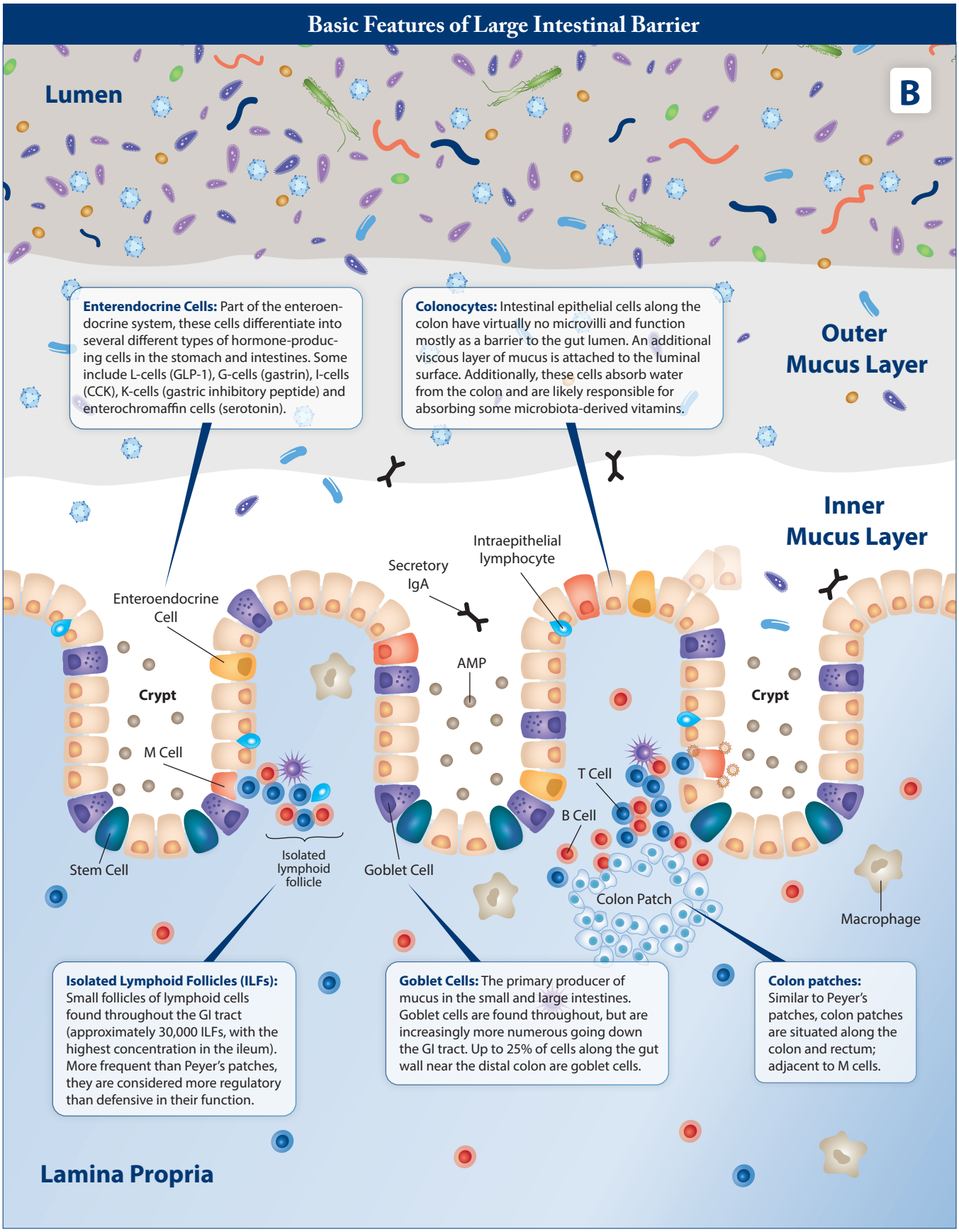



**Figure 30: Basic Features of Small (A) and Large (B) Intestinal Barrier.** Shown here are the basic cells and architecture of the gut barrier in both small and large intestines. Note that the large intestines lacks villi (and microvilli), but contains an additional thick layer of mucus. The associated circulatory and lymphatic systems are not shown. See text for more details.


Basic Features of Large Intestinal Barrier
Lumen
B
Enterendocrine Cells: Part of the enteroendocrine system, these cells differentiate into several different types of hormone-producing cells in the stomach and intestines. Some include L-cells (GLP-1), G-cells (gastrin), I-cells (CCK), K-cells (gastric inhibitory peptide) and enterochromaffin cells (serotonin).
Colonocytes: Intestinal epithelial cells along the colon have virtually no microvilli and function mostly as a barrier to the gut lumen. An additional viscous layer of mucus is attached to the luminal surface. Additionally, these cells absorb water from the colon and are likely responsible for absorbing some microbiota-derived vitamins.
Outer Mucus Layer
Inner Mucus Layer
Intraepithelial lymphocyte
Secretory IgA
Enteroendocrine Cell
AMP
Crypt
Crypt
M Cell
T Cell
B Cell
Stem Cell
Isolated lymphoid follicle
Goblet Cell
Colon Patch
Macrophage
Isolated Lymphoid Follicles (ILFs): Small follicles of lymphoid cells found throughout the GI tract (approximately 30,000 ILFs, with the highest concentration in the ileum). More frequent than Peyer's patches, they are considered more regulatory than defensive in their function.
Goblet Cells: The primary producer of mucus in the small and large intestines. Goblet cells are found throughout, but are increasingly more numerous going down the GI tract. Up to 25% of cells along the gut wall near the distal colon are goblet cells.
Colon patches: Similar to Peyer's patches, colon patches are situated along the colon and rectum; adjacent to M cells.
Lamina Propria

# Small Intestinal Bacterial Overgrowth

GI dysbiosis is described as any imbalance within the gut microbiota that leads to negative health consequences for the host (see also page 103). One particular form of dysbiosis is referred to as small intestinal bacterial overgrowth (SIBO), or alternatively, small bowel bacterial overgrowth (SBBO) or bacterial overgrowth of the small intestines (BOSI). This phenomenon has been described for decades and was classically associated with signs and symptoms of maldigestion/malabsorption (e.g., steatorrhea, B12 deficiency).[1] Today, SIBO is mostly defined by characteristic symptoms such as diarrhea, abdominal pain and bloating, symptoms that overlap significantly with the diagnostic criteria for IBS (see page 197 for discussion of IBS and SIBO). A similar, though much less studied phenomena called SIFO, or small intestinal fungal overgrowth (mostly linked to *Candida spp*), is likely co-incident with SIBO in many subjects and is especially linked with immunocompromised individuals.[2,3]

As the name implies, its most basic definition is fundamentally a quantitative overgrowth of bacteria within the small bowel. More specifically, it has been defined as 1 x$10^5$ or more colony-forming units per milliliter (CFU/ml) of bacteria from small intestinal aspirate (duodenum/jejunum). This is roughly two-to-three orders of magnitude higher than the amount thought to be normal in these areas of the gut (see Figure 18, page 93). While this quantitative characterization is considered by some to be the "gold standard" definition of SIBO, there is still much debate about this.[4] Since this definition relies upon bacterial plate counts rather than metagenomics, it is highly skewed toward the minority of bacterial species that can be cultivated; and assumes the area of the aspirate collection is uniform in concentration with the entire small bowel. Others speculate that specific, unidentified species are the real culprit related to symptoms coincident with overgrowth, or that symptoms only exist when specific species of bacteria from the colon migrate into the small intestines. Furthermore, since this test is difficult, invasive and expensive to perform routinely in a clinical setting, simpler breath tests have become more popular in defining SIBO, creating a surrogate definition of SIBO (i.e., breath test positive).

## Breath Tests for SIBO: Are They Diagnostic?

Since aspirating the small intestines for a bacterial plate count is not a routine procedure, a variety of breath tests using carbohydrate ingestion have been employed. The idea is based on the fact that when various carbohydrates (lactulose, glucose, xylose, etc.) are available to specific species of bacteria, hydrogen or methane gas will be produced during the fermentation of those carbohydrates (methane is actually produced by methanogenic bacteria using hydrogen formed by other bacteria). The measure (timing and quantity) of these gases in the patient's breath after consuming the test carbohydrate helps determine the location of the fermenting bacteria (small bowel or colon). Ghoshal et al., in their comparison of both breath tests with aspirate plating, describe the testing procedures as follows[5] (different labs may have slight variations on these procedures):

> *Basal breath specimens were obtained after a 12 h fast; the patients avoided slowly absorbed carbohydrates (lentils, bread, potato, corn) and fiber the previous evening to avoid delayed excretion of hydrogen in the breath. Cigarette smoking and physical exercise were not permitted for 2 h before and during the test to prevent hyperventilation and consequent changes in breath hydrogen content. The patients then brushed their teeth, and rinsed their mouth with an antiseptic wash, followed by tap water, to eliminate an early hydrogen peak because of the action of oral bacteria on test sugars. An*

*average of three values was considered as the basal breath hydrogen and methane levels. The patients were then asked to ingest 100 g glucose dissolved in 200 ml water or a 15 ml solution containing 10 g lactulose. Thereafter, breath hydrogen and methane were estimated every 15 min for 3 and 4 h during GHBT*[glucose hydrogen breath test] *and LHBT* [laculose hydrogen breath test], *respectively. An increase in hydrogen excretion, in ppm, following glucose or lactulose administration was calculated by subtracting the fasting value from the highest value of hydrogen obtained. A sustained increase in breath hydrogen (at least two consecutive readings) by 12 ppm above basal level following the administration of glucose was considered evidence of SIBO. A characteristic double peak or an early peak (increase in breath hydrogen 20 ppm above basal levels within 90 min) in breath hydrogen was considered SIBO. Fasting breath methane level of at least 10 ppm or increase by at least 10 ppm above basal after substrate ingestion was considered as a positive methane breath test.*

Ghoshal et al. performed a comparison of each breath test and various interpretations (single peak, double peak; hydrogen and/or methane) with the "gold standard" microbial quantification of upper gut aspirates in 80 subjects with irritable bowel syndrome.[5] In this cohort of IBS subjects, 15 (19%) had SIBO as defined by an upper gut aspirate above $10^5$ CFU/ml (18/80 had levels between $10^3$ to$10^5$). Compared to this standard test (deemed to be 100% sensitive and 100% specific), each of the other breath tests were analyzed for their relative sensitivity (ability to correctly identify SIBO when present) and specificity (ability to accurately identify a SIBO-negative subject). They found that using the glucose hydrogen breath test (GBT), that only four of the 15 SIBO subjects had a positive breath test (27% sensitive), while none of the SIBO-negative subjects had a positive breath test (100% specific). The lactulose breath test (LBT) included two diagnostic categories; an early hydrogen peak detected one more SIBO patient than the GBT (5/15 or 33% sensitive), but incorrectly identified 23/65 non-SIBO subjects with a positive breath test (only 35% sensitive), while a double-peak was positive for only one (non-SIBO) subject (0% sensitivity, 98% specific). Using methane (alone) measures in the lactulose group also had limited sensitivity (13.3%) and specificity (41.3%).

These results clearly show what many have suggested: Breath tests are prone to misinterpretation or over-interpretation.[6,7,8] A Rome consensus conference, published some five years prior to the data described above, suggests the sensitivity and specificity of the lactulose and glucose breath tests are: for LBT, 52.4% and 85.7%, respectively; and for GBT, 62.5% and 81.8%, respectively.[9] The Rome Consensus statements related to SIBO are 1) *The jejunal aspirate culture is traditionally considered the gold standard diagnostic test for SIBO, despite some serious methodological limitations and lack of accessibility to clinical practice,* and 2) *Glucose Breath Test is the most accurate hydrogen breath test for non-invasive diagnosis of SIBO.* The addition of methane to hydrogen is helpful in capturing the overgrowth of methanogenic organisms common in about one in five subjects (i.e., improving sensitivity), though this may not increase the poor specificity of these tests.[10] Elevated methane-producing organisms increase the likelihood of constipation fivefold.[11]

The interpretation of these breath tests are dependent on the cut-offs used to define normal transit time and average fermentation in normal subjects. Since the average transit time is shorter in some populations, this is considered the main cause of frequent misinterpretation of an early hydrogen peak after lactulose ingestion, (see Figure 40).[12,13] In one study performed in India, comparing the LBT and the GBT in 175 IBS-D and 150 apparently healthy controls, the LBT was unable to differentiate between these two groups (34.3% and 30% positive breath test, respectively), while the GBT

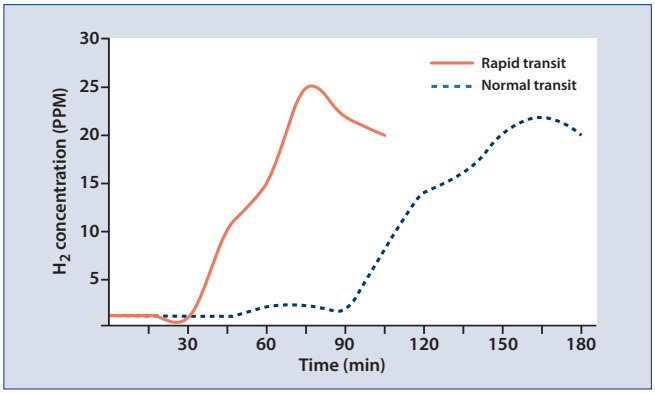



**Figure 40: Bowel Transit Time Affects Interpretation of Lactulose Breath Test.** The timing of lactulose fermentation is assumed to be early only if certain types of quantities of bacteria are in the small intestines (i.e., SIBO). However this assumes that the consumed lactulose would not reach the large intestines until at least 90 minutes after ingestion. A short bowel transit time will permit lactulose to reach the large intestines earlier, which many clinicians could inadvertently interpret as SIBO.

showed a statistical difference between these groups (6.2% and 0.66% positive breath test, respectively).[14] These differences also highlight the wide variability of the association between SIBO and IBS reported in the literature (see IBS and SIBO on page 197).

**Breath Testing, Our Recommendation**

Whether a positive breath test is diagnostic for SIBO or merely the evidence of elevated and early production of gas due to the fermentation of undigested carbohydrates may be an unimportant distinction, since both scenarios may contribute equally to the patient's signs and symptoms (gas, bloating, diarrhea, abdominal pain). And, with the exception of the use of antibiotics, which some clinicians may consider appropriate for a diagnosis of SIBO, the therapies for these are similar (see below). Clinicians should consider testing for SIBO when such a diagnosis is likely to alter their therapeutic strategy. Check with existing labs for their available test methods, substrates and cut-off points. One final note: Since breath testing is highly dependent on proper test methods, including pre-testing dietary restrictions, clinicians should be careful to ensure the patient understands these restrictions and is capable of performing the test as instructed.

## PPI Use and SIBO

Low stomach acid (hypochlorhydria or achlorhydria) is thought to create an environment that allows for increase overgrowth of bacteria in the small intestines, especially when this condition is induced by drugs.[15,16] Therefore, the relationship between the use (or overuse) of proton-pump inhibitors (PPIs) as a contributing risk factor for SIBO is of concern to many. A recent systematic review and meta-analysis was conducted to evaluate the association between PPI use and SIBO, and found when SIBO was defined by duodenal or jujunal aspirate overgrowth, there was a strong association showing PPI users had a sevenfold higher incidence of SIBO.[17] However, while the risk for a positive breath test as a measure of SIBO in PPI users was nearly double (OR 1.93), this association did not reach statistical significance.

While some studies show no difference in the incidence of SIBO in those who use PPIs compared to subjects who do not, on balance, the majority of studies confirm this association, as does the physiology of an altered gastric and duodenal pH. In a study of 70 children (mean age 13.5 years) given 20 mg of omeprazole for four weeks who were glucose breath-test negative for SIBO at baseline, 21 of the 70 (30%) became breath-test positive after PPI use and an additional five more developed symptoms of SIBO while remaining breath-test negative.[18] The use of a probiotic (2 billion CFU/day of *L. rhamnosus* and *L. acidophilus*) in these children was not able to mitigate the PPI-induced SIBO. Therefore, unless their use is strongly indicated, there are many reasons to limit the use of PPIs in patients; the increased risk of small intestinal dysbiosis is merely one more. When possible, clinicians should help patients taper the use of PPIs and use therapies addressing the root cause of the condition for which the PPI was prescribed in the first place (see the negative consequences of PPI use and ways to taper patients off PPIs on page 219).

## Prevention and Intervention Strategies for SIBO

Since the difference between a "normal" small intestinal microbiome and one defined as "SIBO" is difficult to define, it is not surprising that the majority of prevention and intervention strategies are also difficult to assess. The primary goal of most therapies is to eradicate the overgrowth (or at least the harmful and out-of-place organisms) while allowing the appropriate growth of the commensal organisms to thrive. This is typically attempted by limiting the environmental conditions for SIBO (avoiding PPIs and certain carbohydrates), directly altering the microbiota (antibiotics, probiotics) or by stimulating changes in bowel transit (laxatives, prokinetics, fiber supplementation).

**Dietary Restriction**

Since SIBO is characterized by altered fermentation of carbohydrates, many clinicians, nutritionists and dietitians recommend restriction of certain carbohydrates (fructose, lactose, FODMAPs, etc.). Surprisingly, we are not aware of any studies looking into the efficacy of these dietary approaches for non-IBS, SIBO-specific outcomes. One retrospective study suggests that in obese subjects, carbohydrate intake may influence their risk for SIBO.[19] Comparing 60 obese subjects with normal lean controls, 23.3% of the obese subjects had a positive glucose breath test, while only 6.6% of lean subjects had a positive breath test. Using diet recall, obese subjects with SIBO consumed statistically higher amounts of carbohydrates, refined sugars and less total and insoluble

# A Balanced and Evidence-Based Approach

While the foundational role of a healthy gastrointestinal tract is undisputed, there is often a fundamental gap between therapies that are commonly used to treat GI dysfunctions and the underlying root causes of those dysfunctions. The unfortunate result is an ever-increasing burden of chronic gastrointestinal complaints, for which a growing list of approved pharmaceuticals are struggling to alleviate. Thankfully, new approaches to chronic gastrointestinal health and disease management have emerged; approaches specifically designed to assess and support the core functions of the GI tract, rather than mask the symptoms of dysfunction. At the same time, scientific research into the role of nutrition, nutrigenomics, the gut microbiome, gut barrier functions and so-called "gut/brain" interactions has confirmed the importance of supporting core GI functions in the management of complex GI disorders.

*Functional Strategies for the Management of Gastrointestinal Disorders* is designed to help clinicians and other healthcare professionals understand the important relationships between core GI functions and common GI disorders. In addition, this Road map provides an updated summary of the best-researched lifestyle and nutrient approaches for supporting these core GI functions, allowing the clinician to form effective, evidence-based strategies to prevent and treat chronic gastrointestinal disorders.

**This guide is intended to be an indispensable resource for anyone making lifestyle, nutritional or dietary supplement recommendations within a healthcare setting:**

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- **Pharmacists**
- **Nutritionists**
- **Dietitians**
- **Nurses/Nurse Practitioners**
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