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The Gut-Immune Interface

We ingest approximately 30-40 tons of food in a lifetime. The food passes through a dynamic selection process. During this process, food is digested, nutrients are extracted and absorbed, and waste is excreted. Digestion is regulated in part by the Gut Associated Lymphoid Tissue (GALT) which comprises >60% of total immune activity with 10¹⁰ lymphocytes per meter of bowel. The GALT, along with the bowel microflora and mucous barrier, comprise a defense system, that if not functioning well can have a significant impact on the body's health.¹

INTERESTING FACT

The human body has more prokaryotic cells (foreign DNA) than eukaryotic cells (of our own DNA) mainly due to the number of bacteria living in our bowels.

FACTORS THAT CAN HAVE A NEGATIVE IMPACT ON THE GUT-IMMUNE BARRIER: (SEE FIGURE 1)

Birth method

- Vaginal birth exposes the infant GI tract to bacterial flora which begins a healthy inoculation for bacterial growth. Abdominal birth (Cesarean section) is a sterile birth where this early exposure does not take place.^{2,3}

Feeding in infancy

- Breast feeding results in exposure to more beneficial bacteria from the *Bifidobacteria* and *Lactobacilli* families, which result in more mucosal IgA secretion, and a balance of Th1 and Th2 immunity.
- Bottle feeding is associated with a greater growth of enterococci and enterobacteria which has been associated with more atopy by stimulating the Th2 (humoral) response.⁴

Chronic stress

- In animal models, chronic stress (separation of animals from their mothers) has resulted in increased intestinal permeability and a reduction in mucin production (mucous layer) and IgA secretion.⁵

Chronic acid suppression

- Long-term use of acid suppressing medications can lead to an increased risk of pneumonia⁶ due to higher levels of bacteria in the upper GI tract that can be aspirated. In addition, B-vitamins, calcium, and iron are malabsorbed;⁷ and there is a higher prevalence of *C. difficile colitis*.⁸

Chronic use of NSAIDs and antibiotics

- Non-steroidal anti-inflammatory drugs have a direct toxic effect on the integrity of the GI mucosa.⁹ Antibiotics can create an imbalance of bacteria (dysbiosis) that has a negative effect on the gut-immune interface and increases intestinal permeability.¹⁰

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WHAT IS INTESTINAL PERMEABILITY?

Intestinal permeability (commonly called leaky gut) has been most studied in animals and patients in the intensive care unit. Intestinal permeability results in the breakdown of the normal gut-immune barrier. Gaps in the enterocytes and dysfunction of the microvilli result in antigen exposure that triggers a systemic inflammatory response. This inflammatory response results in the release of nitric oxide and the production of inflammatory cytokines.¹¹ Atopic dermatitis, asthma, auto-immune disease, food allergy, irritable bowel, and inflammatory bowel disease are among some of the conditions that are exacerbated. The enterocytes are one of the most rapidly reproducing cells in the body (3-4 day turnover) and the nutritional reserves of the critically ill do not allow for healthy cell regeneration. This has been found to aggravate the inflammation associated with sepsis and acute respiratory distress syndrome (ARDS).¹²

L-Glutamine, a non-essential amino acid is critical for enterocyte production. Supplementation attenuates the inflammation stimulated by intestinal cytokines and reduces the risk of gut-derived septicemia.¹³⁻¹⁵ It should be noted that L-Glutamine supplementation has not been adequately studied in non-critically ill humans with increased intestinal permeability.

WHAT CAN BE DONE TO REDUCE INTESTINAL PERMEABILITY AND IMPROVE THE GUT-IMMUNE BARRIER?

The "Four R" approach was originated by our naturopathic colleagues and has been used clinically for many years. The "Four Rs" are defined as:

• **Remove:**

- o Foods that one may be intolerant to (elimination diet: start with wheat and dairy).
- o Medications that may negatively influence the optimal GI environment¹⁶ (such as PPIs, H2 blockers, NSAIDs, antibiotics, steroids).
- o Infectious agents (*C. difficile* colitis, *H. pylori*, parasites, etc.)
- o Stress.

• **Replace:** Proper acidity of the stomach by removing inhibitors. Some practitioners suggest using betaine hydrochloride 650 mg 1-3 with each meal. Start at a low dose and increase as tolerated. Reduce the dosage, if a warm sensation is felt in the stomach. Use only for one month to help with digestion and the stimulation of pancreatic enzymes. (Removal of acid suppressing agents, if able, is often adequate and hydrochloric acid may not be necessary.)

• **Re-inoculate:** Administer probiotics from the following three families that have been found to be beneficial for GI function: *Bifidobacteria*, *Lactobacilli*, and *Saccharomyces*. Administer prebiotics (food that promotes beneficial bacterial growth) such as bananas, Jerusalem artichoke, onions, asparagus and garlic.

• **Repair:** The following recommendations are important for optimal bowel function and enterocyte repair.

- o **Fiber:** Consider psyllium or guar gum, 1 tsp in 8-10 oz of water before each meal.^{17, 18}
- o **Fluids:** 2 liters of water daily.
- o **Whole Food Nutrition:** Incorporate a hypoallergenic, nutrient rich diet.
- o **Regular Exercise.**¹⁹
- o **A multi-vitamin containing vitamins C, E, carotenoids, and selenium.**
- o **Zinc:** 25-30 mg a day for one month.²⁰
- o **Omega-3 fatty acids (EPA/DHA) and/or Gamma Linolenic Acid (Evening primrose Oil, Borage Oil or Black Currant Oil):** Total of 2 gms daily for one month.^{21, 22}
- o **L-Glutamine Powder:** 5 gms twice daily for one month.²³

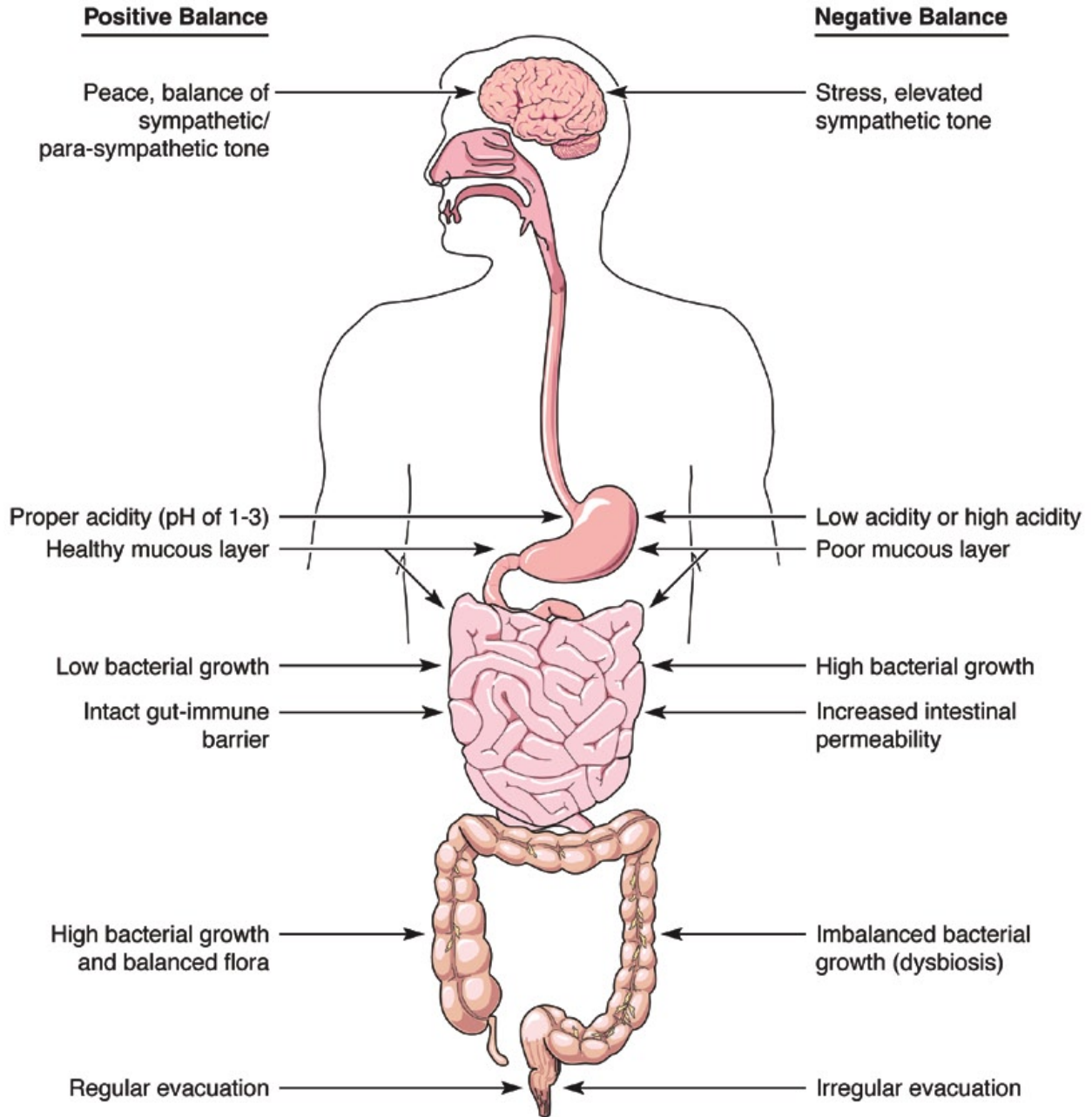
– DR

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OPTIMAL HEALING ENVIRONMENT FOR THE GI TRACT



Mind-Gut Interface

On a personal level, most of us have had experience with the way the mind can affect the gut. When we prepare for a high stress presentation or performance, our GI system may function differently, such as with diarrhea.

How is it that the mind can affect cellular and molecular structure of the GI epithelium? Located in sheaths of tissue lining the esophagus, stomach, small intestine and colon is a network of neurons, neurotransmitters, neuropeptides and hormones called the enteric nervous system (ENS). The ENS transmits messages between neurons and is a complex circuit with the ability to act independently, as well as communicate, with the brain and the central nervous system (CNS). Nearly every substance that helps run and control the brain has turned up in the gut including serotonin, dopamine, and benzodiazepines.^{1,2}

Symptoms can occur for many reasons. When the central brain experiences something fearful, for example, the vagus nerve can increase activity on serotonin circuits in the gut resulting in over stimulation and diarrhea.

Irritable bowel syndrome (IBS) is an excellent example of a disorder that has been shown to have such a mind-gut connection. As a group, it is well known that IBS patients report more anxiety and depression,^{3,4} a higher rate of childhood abuse,^{5,6} and may experience more major life stressors than non-IBS individuals. Although we can not say that stress “causes” the symptoms, research shows a strong concurrent relationship, whether the period of time is a day or 3 months.⁷ Irritable Bowel Syndrome sufferers, appear to be aware of this connection with the vast majority acknowledging

the role of stress in contributing to their symptoms.⁸

Psychological interventions that have been explored to effect change in functional symptoms are many. To date, formal research reports the highest success rates in IBS for cognitive therapy and hypnosis. Both methods demonstrated an extra bonus by improving measures of mood and quality of life.^{9,10}

Cognitive therapy works with the mind to identify dysfunctional thinking patterns and building skills for more balanced self talk. For example, an individual with IBS may feel less mental and physical stress if she can consistently replace the maladaptive thought of “I must do everything perfectly” with “I need only do the best I can.” Studies showed that between 75-83% of research participants demonstrated significant improvement and maintained these gains during short-term follow-up.¹¹⁻¹³

Using gut-focused imagery and suggestions, hypnosis has also been shown to be a viable treatment for IBS. Hypnosis is a state of inner absorption, concentration, and focused attention typically associated with deep relaxation. Since the first published research in 1984, 80-95% of IBS patients significantly improved and were able to maintain these gains in long-term follow-up.¹⁴⁻¹⁸

Information on the self-hypnosis technique for IBS can be found in the Health Professionals Section of our website at uwhealth.org/integrativemed.



Clinical Wisdom

Certain interventions have been shown to not only improve the symptoms of IBS, but also mood and quality of life. Although gut-focused hypnosis or cognitive therapy exhibit the best results, general stress management and psychotherapy may prove beneficial.

Most IBS patients recognize the role of stress in their symptoms and may be open to relevant mind-body treatments.

– JS

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Yogurt and GI Health

YOGURT, A FERMENTED FOOD, HELICOBACTER PYLORI, AND GI HEALTH

Objective: To test whether prior treatment with AB-yogurt improved the efficacy of quadruple therapy in eradicating *H. pylori* after failed triple therapy.

Design: One hundred thirty-eight patients in whom triple therapy failed were enrolled for a culture study of *H. pylori*. Patients were then randomized in equal numbers to either a yogurt-plus-quadruple therapy group or a quadruple therapy-only group. The patients received 1 wk of quadruple therapy with or without a 4 wk pre-treatment with AB-yogurt (400mL/d). In the yogurt-plus-quadruple group, excessive $8^{13}\text{CO}_2/\text{mL}$ values of the ^{13}C -urea breath test were collected before and every 2 wks during the 4-wk ingestion of yogurt. For both groups, a ^{13}C -urea breath test was conducted ≥ 6 wk after the quadruple therapy to assess the outcome of residual *H. pylori* eradication.

Results: For the patients in the yogurt-plus-quadruple therapy group infected with either antibiotic-sensitive or-resistant *H. pylori*, the excessive $^{13}\text{CO}_2/\text{mL}$ values of the ^{13}C -urea breath test were significantly decreased after the 4-wk ingestion of AB-yogurt ($P < 0.0001$). The yogurt-plus-quadruple therapy group had a higher *H. pylori* eradication rate than did the quadruple therapy-only group.

Conclusion: A 4-wk pretreatment with AB-yogurt can decrease *H. pylori* loads despite antimicrobial resistance, thus improving the efficacy of quadruple therapy in eradicating residual *H. pylori*.³

Quadruple therapy = 1 g amoxicillin twice daily, 500 mg metronidazole twice daily, 20 mg omeprazole twice daily, and 120 mg bismuth subcitrate three times daily.

Triple therapy = 1 g amoxicillin, 500 mg clarithromycin, and 20 mg omeprazole twice daily.

AB-yogurt: Fermented milk with sugar, high-fructose corn syrup, pectin, galactooligosaccharide, and an approximately equal mixture of *L. acidophilus La5*, *Bifidobacterium lactis Bb12*, *Lactobacillus bulgaricus*, and *Streptococcus thermophilus* at a concentration of $\geq 10^9$ bacteria/mL. 200mL AB-yogurt twice daily for 4 wks.

– SKK

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Prebiotics:

A non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon.¹

Probiotics:

A preparation of or a product containing viable, defined microorganisms in sufficient numbers, which alter the microflora (by implantation or colonization) in a compartment of the host and by that exert beneficial health effects in this host.²

Foodways Focus: Fermented Food

Fermentation is a miracle of transformative dimensions, a process by which microscopic organisms—our ancestors and allies—modify our biological terrain to extend the usefulness of our foods.⁵



In the Integrative Medicine Updates, we highlight foodways and focus on food history, recipes, food and/or spice mixtures unique to different cuisines, and food preparation techniques that result in tastier, more complex, less toxic or just better food. In short, we will celebrate the richness and diversity of food and foodways as well as some of the wisdom associated with these creative and finely-honed recipes and techniques. We begin this section with one of the simplest and oldest methods of food preservation and flavor enhancement: fermentation.

But why learn about the multiple bacterial and yeast strains used in producing distinctive regional tastes? Why are these techniques even important? Often modern researchers disregard the knowledge passed down from one generation to another (i.e., wives tales or folklore often carry negative connotations); we often discount the techniques as uninformed, not scientific, too simplistic to be of value, or assume that the technique evolved by accident, certainly not derived from astute observation and/or experimentation. Is this the case with fermented foods? Let's take a closer look.

FOOD PRESERVATION

Historically food preservation included three main forms: drying, salting, and fermentation. Fermented foods are defined as those foods that have been subjected to the action of micro-organisms or enzymes so that desirable biochemical changes cause significant modification to the food.² Fermentation required no particular climate, no cooking, and no expenditure of fuel, just a container.

Fermentation prolonged the shelf life, increased the digestibility, increased the nutritive value providing nutrients and co-factors, enhanced or altered smell and taste, provided beneficial bacteria to compete with pathogens, and stimulated the hosts immune response by producing specific polysaccharides.

NATURE OF FERMENTATION

McGee concisely summarized how plants and animal foods are preserved by fermentation. Plants are the natural home of certain benign microbes. Under the right conditions, primarily the absence of air, these microbes flourish and suppress the growth of other microbes that cause spoilage and disease. The microbes accomplish this suppression by being the first to consume the plant's readily metabolized sugars, and by producing a variety of antimicrobial substances, including lactic and other acids, carbon dioxide, and alcohol.⁶

CLASSIFICATION OF FERMENTED FOODS²

1. Beverages
2. Cereal products
3. Dairy products
4. Fish products
5. Fruit and vegetable products
6. Legumes
7. Meat products
8. Starch crop products
9. Miscellaneous products

FERMENTATION CONDITION AND RESULTS

The diverse molecules generated from fermentation, such as alcohols and acids, contribute to both complex flavors and odors. Modifying and regulating the conditions, such as salt or sugar content, temperature, humidity, or oxygen level alter the

flavors. Most fermentations stop when the food source is depleted (i.e., the sugars in grape must) or when conditions inhibit the fermenting organisms (i.e., acid accumulation in yogurt).¹⁰ At the same time, the microbes leave most of the plant material intact, including its vitamin C (protected from oxidation by the carbon dioxide they generate). These benign microbes often add significant amounts of B vitamins and generate new volatile substances that enrich the food's aroma. Additionally, various strains of lactic acid bacteria show beneficial effect by increasing the gut microflora.^{1, 3, 8, 9} These benign lactic acid bacteria apparently evolved eons ago in oxygen-poor piles of decaying vegetation, and now transform the carefully gathered harvest into dozens of different foods across the globe (see Table: A Few Fermented Foods of the World), as well as turning milk into yogurt and cheese, and chopped meat into tangy sausages.⁶

McDonalds is an ethnic food. In fact, every food preparation has its ethnic roots whether it is German bratwursts in Native American areas of Wisconsin, Southern Chinese food in Hong Kong, Gujarati cuisine in East Africa, Scandinavian food in Canada, North Indian food in the lower east side of Manhattan, or foods and foodways introduced by enslaved Africans in southern USA.

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ANCIENT TECHNIQUES

The conversion of lactose to lactic acid in yogurt; the breakdown of toxic glucoside linamarin in cassava production (during fermentation, hydrolysis linamarin takes place, rendering bitter cassava safe to eat); and the breakdown of anti-nutrients and improved digestibility in fermented legume products are illustrations of the nutritive importance of fermented foods.²

These few examples also reflect the creativity, experience, and observational skills required to develop these ancient techniques without the aid of modern science. Perhaps we are misguided if we assume that these techniques evolved merely as a result of accident or did not require a sophisticated and intimate understanding of their natural surroundings.

In fact, these fermentation techniques represent the master chef's acumen and observational skills required to develop an array of flavors. And they symbolize a culture's innovative ability to nourish and sustain itself.

Gary P. Nabhan notes that each distinctive food tradition around the world does not simply consist of random ingredients brought together through some serendipitous experimentation by a master cook. Instead, each cuisine reflects the evolutionary history of a particular human population as it responded to the edible plants and animals available through local foraging and through trade, and to the prevailing frequencies of diseases, droughts, and plagues within each population's homeland.⁷

– SKK

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A Few Fermented Foods of the World

Regions	Fermented Product	Consumption	Yeast/bacteria/mold
North Africa	Injera	Thin soft bread, with numerous holes, baked in Ethiopia from the cereal teff.	<i>Candida guilliermondii</i> , <i>Torulopsis</i> species isolated, and lactic acid bacteria
Europe, Middle East, North Africa, S.E. Asia	Tarama	Dried, salted fish roe, often from grey mullet.	Probably a combination of enzymes from the roe, and salt tolerant bacteria such as <i>Micrococcus</i> and <i>Staphylococcus</i> .
S. Africa, N. Africa, Middle East, Europe, Indian subcontinent, E. Asia, S.E. Asia	Bantu beer	Thick, sour alcoholic beverage made from sorghum or millet, or sometimes maize, occasionally with banana. Important source of nutrients, particularly B vitamins in people on marginal diets.	<i>Mucor</i> , <i>Rhizopus</i> , <i>Aspergillus</i> and <i>Penicillium</i> species have been isolated from malting stage. Main fermentation by yeasts of <i>Saccharomyces cerevisiae</i> and other species, <i>Candida</i> species and <i>Geotrichum candidum</i> . Lactic acid bacteria of <i>Leuconostoc</i> and <i>Lactobacillus</i> species also play a role in souring.
North America, South America, South Africa	Corn bread	Flat bread, usually circular, made from maize flour, occasionally with some added wheat flour. Usually baked over a hot griddle and eaten hot.	After the alkaline precook, there is likely to be some limited growth of lactic acid bacteria during the soaking period. <i>Saccharomyces cerevisiae</i> , is occasionally added.
South America	Cocoa	Fermented beans of the cocoa trees, <i>Theobroma cacao</i> are roasted and ground. The fat, cocoa butter can be extracted, and used for making chocolate, and the remaining cocoa powder is used for making beverage by extraction with boiling water, or as a major ingredient in chocolate.	<i>Kloeckera</i> , <i>Hansenula</i> and <i>Saccharomyces</i> species are present. Acetic acid bacteria of <i>Gluconobacter</i> , and later <i>Acetobacteria</i> species persistent. Yeasts are replaced by lactic acid bacteria, particularly <i>Lactobacillus plantarum</i> and <i>L. collinoides</i> . Cocoa bean proteolysis during fermentation leads to production of peptides/amino acids, which contribute to desired final roasting cocoa flavor by Maillard reaction non-enzymatic browning during roasting.
S.E. Asia, East Asia, Europe	Fish sauce	Brown, salty liquid produced from breakdown of fish by fish enzymes	Process is autolytic breakdown of fish protein by proteases from fish muscle and gut. Because of the high salt concentration, and anaerobic conditions, microbial activity is limited, but salt tolerant <i>Micrococcus</i> , <i>Staphylococcus</i> and <i>Bacillus</i> bacteria can play a minor role in flavor development.
Indian subcontinent	Idli	Steamed acidic whitish or yellowish bread made from rice and legume flour, eaten with coconut, pickles, or lentils for breakfast, or as a snack.	Lactic acid bacterial fermentation, with most of carbon dioxide gas production, which acts as an aerating agent, by <i>Leuconostoc mesenteroides</i> .
Worldwide	Pickled fruits and vegetables	General term used for pickled fruits and vegetables to preserve food from harvest time into seasons of shortage.	Gram-negative bacteria of <i>Enterobacteriaceae</i> grow, but Gram-positive bacteria lactic acid bacteria of <i>Leuconostoc</i> , <i>Streptococcus</i> , <i>Pediococcus</i> and <i>Lactobacillus</i> tend to dominate, producing lactic acid, and some acetic acid, ethanol and carbon dioxide.
Europe, Middle East, North America, South America, S.E. Asia	Salt meat	Semi-dry uncooked beef, but may be lamb, mutton, goat, or other meat, which has been cured, during which mild fermentation takes place, then smoked and dried. Long maturation period of several months allows development of full characteristic flavors.	Meat cut up and heavily salted with dry curing salts with small amounts of sugar, spices, and seasonings added. Chemical curing process with nitrates aided by <i>Micrococcus</i> and <i>Staphylococcus</i> bacteria reducing nitrate to nitrite, and some growth of fermentative lactic acid bacteria.
Oceania	Poi	Starchy fruit or tubers of breadfruit, unripe banana, or cocoyam or taro, made into sour dough, and then baked into bread-like food. Staple food in Hawaii and some Pacific Islands.	<i>Lactobacillus delbrueckii</i> and <i>Streptococcus lactis</i> , with other lactic acid bacteria. In acidic dough, yeasts of <i>Candida</i> species and the mould <i>Geotrichum candidum</i> become active if fermentation prolonged, producing flavor compounds.

Compiled from: Campbell-Platt, G., *Fermented Foods of the World: A Dictionary and Guide*. 1987, Cambridge: Butterworths, University Press.

Outside the Box

Match the Metaphor

1. "This job is tying me up in knots"
2. "Eating me up inside"
3. "Gut wrenching"
4. "Pain in the rear"
5. "I'm all choked up." or
"I have a lump in my throat."

- A. "Proctalgia fugax"
- B. IBS (Irritable Bowel Syndrome)
- C. Globus Syndrome
- D. GERD (Gastro Esophageal Reflux Disease)
- E. PUD (Peptic Ulcer Disease)

1. B 2. E 3. D 4. A 5. C

Metaphor can be an excellent tool to understand how events in our lives, influence symptoms in our body. Lord Chesterfield said, "I find by experience, that the mind and the body are more than married, for they are most intimately united; and when one suffers, the other sympathizes."

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621 Science Drive, Madison, WI 53711
(608) 262-WELL (9355)
uwhealth.org/integrativemed

Editor

Sarah K. Khan
MS Clinical Nutrition, MPH, PhD Botany
Clinical Assistant Professor
UW Department of Family Medicine

Associate Editor

David Rakel, MD
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UW Department of Family Medicine

Contributing Writer

Janice Singles, PhD
Senior Psychologist/Assistant Professor
Department of Orthopedics and
Rehabilitation UW Madison

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