

# WHY DO I STILL HAVE STOMACH PROBLEMS?

**THE REAL FACTS ON PROTON PUMP INHIBITORS,  
REFLUX AND STOMACH ACID**



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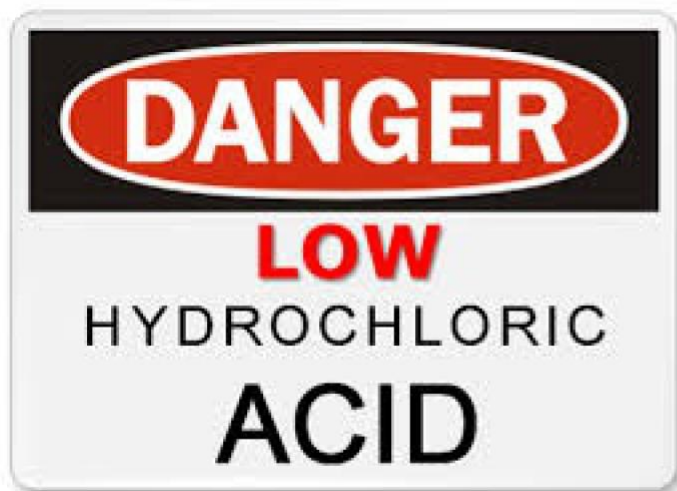
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## Summary

Low Stomach Acid or Long-Term Use of Proton Pump Inhibitors (PPI) May Cause or Contribute to:

- Osteoporosis*
- Cardiovascular Disease
- Barrett's Esophagitis
- Esophageal Cancer
- Atrophic Gastritis
- Hypochlorhydria
  - Poor Digestion
  - Small Intestinal Bacterial Overgrowth (SIBO)
  - Multiple GI Symptoms
  - GI Infection
  - Malabsorption
  - Toxicity
- Reduced gallbladder function
- Decreased endothelial Nitric Oxide (eNOS)
- Increased skin aging
- Elevated Chromogranin A disrupts normal signaling mechanisms



### Symptoms of Low Stomach Acid:

Epigastric pain & reflux  
Bad breath  
Decreased sense of taste & smell  
Anemia  
Excessive sense of fullness after meals  
Burping, belching, bloating or gas after eating  
Cannot digest protein  
History of ulcer  
Autoimmune disease  
Diarrhea or constipation  
Allergies  
Malabsorption

## Indications for Use

Proton Pump Inhibitors (PPI's) are among the most commonly prescribed drugs. They are also available over the counter. Doctors prescribe them like candy, apparently under the (incorrect) assumption that they are as safe as candy. Such is not the case. Prilosec (omeprazole) is the most commonly prescribed PPI with over 50 million prescriptions last year. It and other PPI drugs, acid reducers, and acid blockers (Axid, Nexium, Pepcid, Pepto-Bismol, Prevacid, Protonix, Tagamet, Tums, Zantac) are used to treat frequent heartburn. Other uses include: dyspepsia, stomach and duodenal ulcer, part of a program to eradicate H. pylori, Gastro-Esophageal Reflux Disease (GERD), Barrett's esophagitis, gastritis and gastrinomas. **Unfortunately, these drugs fail to address the underlying causes of heartburn and GERD. In fact, they make it worse, often creating a vicious cycle so that people who start taking PPI's end up taking them for the rest of their lives.**

Sixty million Americans have heartburn at least once a month, and twenty-five million experience symptoms daily. GERD, a more serious form of acid reflux, is the most common digestive problem in the USA.

Antacids, acid blockers and PPI's are cash cows for Big Pharma. Over 60 million prescriptions for GERD were filled in 2004. Americans spent \$13 billion on acid stopping medications in 2006. Nexium brings in \$5.1 billion; right behind Lipitor, the biggest money-making drug on the market. This is likely an underestimate due to the availability of many of these drugs over the counter. These people never see a doctor, so their GERD is not reported.

## **Proper Prescription**

The [Prilosec product insert](#) states that it is to be used daily for only 14 days, and that 14-day courses may be repeated only once every 4 months. **The product insert warns “Stop use and ask a doctor if your heartburn continues or worsens; if you need to take this product for more than 14 days; or if you need to take more than 1 course every 4 months.”** The FDA has advised that no more than three 14-day courses be used per year. Unfortunately, many doctors do not think there is anything wrong with patients using them for up to 20 years! If you have been taking PPI for more than 2 weeks and your doctor has told you that it is perfectly safe, then read on!

## **Efficacy**

How well do PPI's work? The Prilosec OTC product insert references two 14-day studies involving 3,120 people. At the end of 14 days, about 70% of the people taking 20 mg. of omeprazole reported complete heartburn relief. When no nighttime heartburn and no more than mild heartburn were added in, the percent reporting relief increased to about 81.4%. What is never stated in television commercials is that about 45% of people taking a placebo for 14 days reported complete relief and 71.2% had only mild heartburn! Also, **this study failed to follow those people after they stopped taking omeprazole, so there is no information on whether there was any significant long-term benefit.**

It is critical to note that the study referenced in the Prilosec OTC product insert, involving 3,120 people, only discussed symptomatic relief of heartburn. It did not address the root causes of the symptoms, **nor did it determine whether any of the patients were actually overproducing stomach acid!**

The significant question should be how well do PPI's work long term in refractory cases. A 2012 study was performed of 200 people with refractory GERD, which occurred at night while in bed. Half the patients took PPI twice daily and the other half took nothing. **The study concluded that those on PPI actually had more total episodes of reflux**, although fewer were of the acid type.

### **Method of Action**

PPI's are a class of drugs that cause prolonged reduction in the production of stomach acid. They work by binding to and blocking the hydrogen/potassium adenosine triphosphate enzyme in the parietal cells of the stomach, preventing the release of acid.

### **Short-Term Adverse Effects**

Common adverse effects on the product label include: headache, nausea, diarrhea, constipation, stomach pain, fatigue, dizziness, gas, allergic reaction, rash, itch anxiety, depression and myopathies, including rhabdomyolysis (which may be fatal). In addition, decreased absorption of Vitamin B12 and other essential minerals are known side effects, of which few prescribing

doctors advise their patients. Additional complications can include: increased rate of GI infection with *Clostridium difficile*, small intestinal bacterial overgrowth (SIBO), spontaneous bacterial peritonitis, fundus gland polyps and microscopic colitis. PPI's are contraindicated when used in combination with other drugs, including: warfarin, diazepam (Valium), digoxin, clopidogrel, cilostizol, prescription antifungal or anti-yeast medicines, tacroimus, mycophenolate mofetil, prescription antoretrovirals and methotrexate. In addition, there are a number of drugs whose absorption is decreased with reduced stomach acid, and therefore may not work as effectively.

The remainder of this eBook will deal with the potentially serious adverse effects of long-term use of PPI, which are not well known and certainly rarely, if ever, discussed by your doctor or pharmaceutical producers of the drugs, nor are they discussed on the product insert. The proper usage of PPI in certain situations that require acute relief of heartburn pain or for ulcer healing is not being questioned. Rather, **it is the potential grave harm caused by the all-too-common prescription of PPI that may go on for years, that forms this eBook.**

PPI's are the most common direct cause of low stomach acid (called [hypochlorhydria](#)) or total lack of stomach acid (called achlorhydria). As you will read, there are many other reasons one may have inadequate stomach acid production. Regardless of the cause, the consequences of low or no stomach acid are the same. Read on to learn the many adverse effects that PPI's cause.

## **Digestive Physiology**

To know why, in the vast majority of patients, long-term PPI use does not work and carries substantial health risks, you need to have an understanding of how the digestive system works.

The gastro-intestinal (GI) system extends from the brain to the rectum; it is one that is critical to health, but poorly appreciated. It communicates with the external environment, and actually has its own brain! The surface of the intestines, which is greater than that of a tennis court, is where most of the action occurs. This is where the body decides what to digest and absorb and what to excrete. It is where the outside world meets the inside of the body, so it is an area of battle between our body and other life forms that want to feed on it. The GI system contains the majority of immune cells in the body for good reason. As a result of its interaction with food, living organisms and toxins, the GI system is the major system where things go wrong. The main functions of the GI system are; digestion of fat, carbohydrate and protein; absorption of their constituent parts; excretion of waste and toxins; and to act as a barrier to keep out toxins, poisons, bacteria, viruses and parasites.

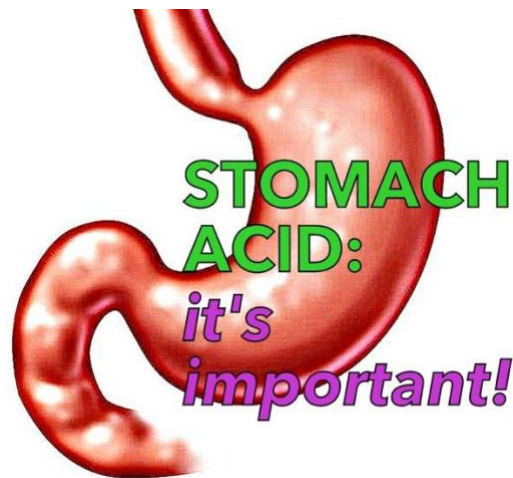
Digestion has components that include neurological, chemical, mechanical and hormonal influences. The GI tract may be broken down into distinct areas, which are: mouth (sensing toxins through taste, chewing, salivary digestive enzymes, swallowing); esophagus (transport from mouth to stomach); stomach (production of stomach acid for digestion and pepsin -- a digestive



enzyme, food storage and mechanical breakdown, and killing of microbes by stomach acid); small intestine (digestion by mechanical means, pancreatic enzymes and bile); hepato-biliary (bile formation and secretion, neutralization of toxins); and the large intestine (absorbs water and eliminates waste). Let's talk about each area in more detail.

Mucosal secretions protect the esophagus. Its major job is transporting food. The major problem with the esophagus is erosion from gastro-esophageal reflux (GERD).

**The stomach is the main area of protein digestion, which must occur in an acidic environment.** One of the truly amazing feats of the body, one that is little appreciated, is that, to go from the average body pH of about 7.2 to the harsh acidic environment of the stomach, pH of 1-2.5 requires that the body concentrate hydrogen ions (acid) over 3,000,000 times that of the rest of the body! To create a liter of stomach acid requires 1,500 calories!



Food digestion, (especially protein), which begins in the stomach, continues in the small intestine. The food bolus (chyme) passes into the duodenum as a result of smooth muscle contraction (peristaltic movement). This causes a reflex that decreases production of stomach acid (HCL) and also slows further emptying of the stomach. The reflex is triggered by: presence of acid and the mucosal irritation it causes in the small intestine, stretching of the upper duodenum and presence of protein breakdown products (peptides). The presence of HCL, fat and peptides also cause the release of two additional hormones: [secretin](#) and [cholecystokinin \(CCK\)](#). Therefore, one can see how important stomach acid is for the digestive process.

Secretin causes the release of very alkaline sodium and potassium bicarbonate from the pancreas. This neutralizes stomach acid and provides the required alkaline conditions in the small intestine necessary for the continuation of digestion. This also causes a reflex to slow stomach emptying so the proper pH can be maintained. PPI's and acid blockers reduce the secretion of secretin, which reduces the production of bicarbonate. Secretin promotes the growth and maintenance of the pancreas. It also increases the effect of CCK to induce digestive enzyme and bile secretions. Further, secretin triggers the release of

insulin to counteract spikes in blood sugar that occur during digestion. It also acts to inhibit release of the hormone gastrin from the G-cells of the stomach, while stimulating the release of the digestive enzyme pepsinogen from the stomach, so overall it is certainly a bad idea to artificially inhibit the production and release of this essential hormone on a long-term basis.

Fat and protein in the small intestine stimulate the release of the hormone CCK, which travels to the pancreas and causes the release of pancreatic enzymes that digest carbohydrate, protein and fat. Similar to the inactive pepsinogen in the stomach, the pancreatic digestive enzymes are also secreted in their inactive form. In the duodenum, however, they are activated by an alkaline environment, just the opposite of the stomach, where acid is required to activate pepsinogen.

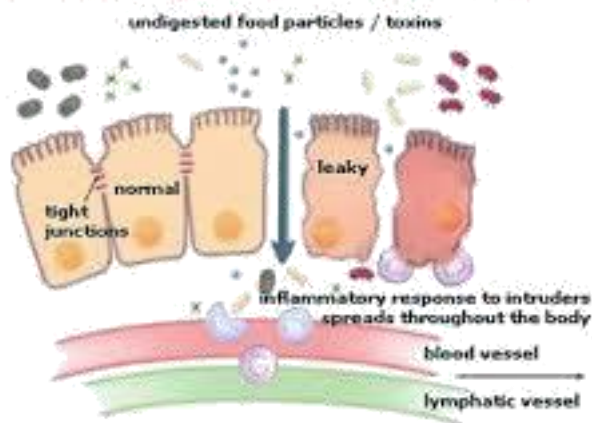
Fat digestion is a little more complicated. The liver produces 600-1200 ml. of [bile](#) each day. Bile contains acids that help emulsify fat and turn it into small particles (chylomicrons) that can be further digested by lipase enzymes. Bile acids also aid in transportation of the digested fat through the intestinal mucosal membranes in particles called micelles. Without bile acids, half of the fat is undigested and lost in the stool. Bile also aids in the excretion of excess cholesterol, bilirubin (the end product of red blood cell breakdown) and fat-soluble toxins. CCK stimulates release of bile from the gall bladder.

There are many things that can and do go wrong, and it often starts in the stomach. **Low stomach acid causes issues that continue into the small intestine. Lack of acid leads to poorly digested food that is dumped into the duodenum.** Since the conditions are not acidic but alkaline, this sets up a situation where secretin and CCK stimulation may be reduced. Any

bicarbonate released makes the conditions even more alkaline. Decreased amounts of digestive enzymes are released. Stimulation to the gall bladder is reduced.

**Low stomach acid causes failure of sterilization of food, which contains many microorganisms.** This, along with an overly alkaline condition, sets the stage for overgrowth of unfriendly bacteria in the small intestine, which is normally host to the friendly, protective lactobacillus bacteria. **This sets the stage for other pathological bacteria, parasites and yeast (Candida) to overproduce. This is called [Small Intestinal Bacterial Overgrowth \(SIBO\)](#), or **dysbiosis**,** and can: lead to inflammation and production of numerous toxins, reduce the production of short chain fatty acids by beneficial bacteria, thereby depriving the intestinal mucosal cells of their primary energy source; reduce production of Vitamin K and some B complex vitamins by friendly bacteria, cause irritable bowel syndrome, hydrogenate essential polyunsaturated fatty acids, block absorption of essential minerals, use essential amino acids leading to deficiencies, turn essential amino acids into toxic products that are absorbed and must be detoxified and excreted, increase the toxic burden of the body causing stress to the liver and kidneys, increase oxidative damage, interfere with the breakdown of bile acids and estrogens increasing the risk for certain cancers, increase the pH of the stool which increases the risk for colon cancer, cause toxic gasses methane and hydrogen sulfate to be produced, overstress the normal GI immune system and eventually reduce [Secretory IgA](#), and cause the GI mucosal tight cell junctions to become leaky, leading to [“Leaky Gut Syndrome”](#) which increases the risk for food allergies and autoimmune disorders.

# LEAKY GUT



Other common causes of dysbiosis include: repeat antibiotic therapy, toxic chemicals and heavy metals, exposure to pathogens and parasites, pancreatic insufficiency, slow bowel transit time (often caused by a low fiber diet), poor immune function, poor diet leading to multiple nutritional deficiencies, excess intake of sugar, refined carbohydrates, junk food, food allergies, (especially gluten and dairy products), sodas and alcohol. Add in hypochlorhydria and you have a recipe for disaster.

## **Treating Causes, Not Effects**

**Symptoms do not equal cause.** Unfortunately, this is the approach most doctors take in treating heartburn and GERD. Yes, it is true that any acid in the sensitive esophageal tissues, which are not protected like the stomach, causes symptoms. And yes, taking a drug to reduce or stop acid provides that ever-so-important temporary relief of symptoms. It is important to understand that **the amount of acid in the esophagus does not correlate with the amount of acid in the stomach!**

It should be apparent that **what goes wrong at the top of the system, in the stomach, carries through to the small and large intestines.** The logic used by a doctor who prescribes long-term use of PPI would imply that too much stomach acid (hyperchlorhydria) is the cause of your heartburn. On the surface, this makes sense, as acid from the stomach does irritate esophageal tissues. Unfortunately, your doctor makes an assumption that is a leap of faith; that, because acid causes esophageal irritation leading to “heartburn,” the *cause* of heartburn is too much stomach acid. Your doctor has now assumed that his/her assumption is correct and prescribes long-term use of PPI with little regard to the consequences. Let’s take a closer look at the faulty logic involved.

First, **without performing any testing, your doctor has made the assumption that you are overproducing stomach acid.** Of course, since PPI’s are top sellers, Big Pharma promotes this by inundating you with commercials of happy people who take their product to relieve excess stomach acid. So now, everyone is led to believe that too much acid is the obvious cause of heartburn and that you need to suppress its production. Does this make sense? No -- and here is why:

1) Virtually every animal has evolved to produce acid to aid in digestion, as well as to kill microbes that are on food and in water. **If production of stomach acid did not confer a significant evolutionary advantage, it would have long ago been selected against.** This is obviously not the case, but it is what your doctor is trying to do, when long-term PPI use is prescribed. This is in obvious contradiction to evolutionary facts.

2) By now, you should understand that humans produce stomach acid because it is important in digestion. If this were not the case, then we would have no need for a highly evolved organ -- the stomach. This organ is extremely specialized to do one thing; it concentrates acid by up to 3,000,000 (yes, that is 3 million) times more than in the blood. It requires a significant amount of energy and biological machinery to do so. Not only does it produce acid, the stomach has to protect itself from acid that can reach a pH of 0.5 (basically pool acid). Try putting pool acid on your skin to see what happens- actually don't -- that was rhetorical. So the stomach has specialized cells that produce mucus which lines the stomach, creating a barrier against acid that would erode the stomach lining. This requires specialized cells and also takes energy. Then the stomach also produces a protein-digesting enzyme, called **pepsinogen**. This enzyme is also made in specialized stomach cells called chief cells. Of course, it cannot be active in the cells or it

would digest them. So the enzyme is secreted in an inactive form that requires stomach acid to activate it to pepsin. **The optimal environment for pepsin is pH 2.0. Activity is reduced as the pH increases (acid decreases), so at pH 6.5 it is inactive.** Pepsin is one of three protein digesting enzymes in the GI tract and it specializes in breaking apart bonds between specific amino acids, called aromatic

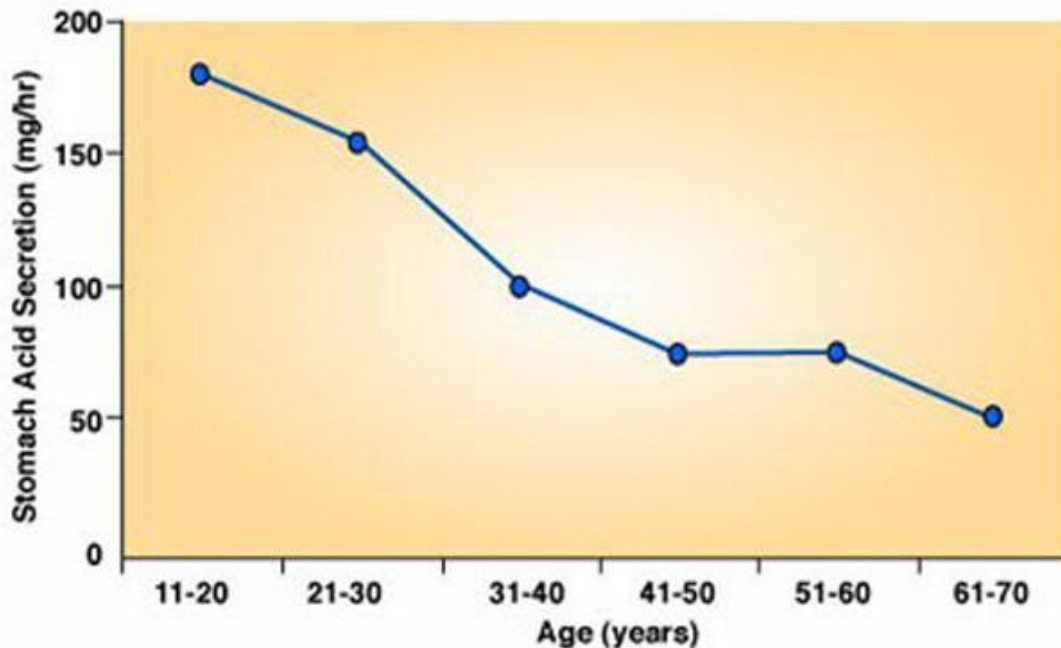
amino acids (phenylalanine, tryptophan and tyrosine). No pepsin= decreased protein digestion.

- 3) **If excess stomach acid were the problem, then you would expect to see much more heartburn and GERD in a younger population, who can produce more stomach acid.** It is estimated that 50% of people over the age of 60 have hypochlorhydria, yet it is the older population with the most symptoms. Approximately 27% of Medicare patients used GERD medications. 50% of all GERD diagnoses are in the elderly. GERD is most often diagnosed in people over 40, with about 50% of all GERD diagnosis occurring between 45-64 years of age. Add the 27% of Medicare aged patients (over 65) and about 77% of GERD diagnoses occur after age 40.
- 4) Long-term use of PPI fails the majority of the time. In a 2007 study of 5,672 people who had used PPI for more than 22 days, 1,741 had persistent and intense symptoms, 2,126 had intermediate symptoms and only 1,805 had low symptoms. The researchers concluded, “The 2007 NHWS gives support to the hypothesis that persistent and intense GORD (GERD) symptoms, despite PPI therapy, have a significant and negative impact on both HR-QOL (Health Related Quality of Life), and healthcare resource utilization. **These findings outline the need for new treatment options for symptomatic GERD patients taking PPI therapy.**” This should have been the nail in the coffin for PPI, yet they remain among the most popular drugs.
- 5) A recent study of 89 patients clearly showed that gastric hypochlorhydria in female patients with dyspepsia was clearly associated with higher pain-related symptom scores.
- 6) Multiple studies show the association between age and hypochlorhydria:



- a. 80% of the elderly (average age 84) in one study were hypochlorhydric.
- b. Over 30% of people over age 60 suffer from [atrophic gastritis](#), characterized by low stomach acid production, in another study.
- c. Up to 40% of postmenopausal women have low to no basal gastric acid secretion.
- d. In a huge study of 3,484 people, 27% had no stomach acid (achlorhydria), with a higher incidence in the elderly.**
- e. There is a link between atrophic gastritis, stomach infection with the bacteria [Helicobacter pylori](#), and low to no stomach acid production. In general, the incidence of H. pylori infections increases with age, so that by age 50, 50% of people are infected. This correlates with the increasing rate of atrophic gastritis and reduced acid output.

From Nutrition Review and Why Stomach Acid is Good For You.



**Fig. 1.** Contrary to popular belief, stomach acid secretions drop with advancing age. This graph shows average decline in stomach acid secretion in humans between age 20 to age 80. (From "Why Stomach Acid is Good For You.")

It should now be obvious that **the correlation between excess stomach acid production and heartburn/GERD is poor.** The fact is that low stomach acid has a closer association with the incidence of these symptoms than does high acid. **It is not over-acidity of the stomach that is the problem; rather it is that the Lower Esophageal Sphincter (LES) does not close properly, allowing for acid to reflux into the esophagus.** Let's explore why this occurs.

## **Stomach Acid, Gastrin and the Lower Esophageal Sphincter**

The LES is the circular muscle between the esophagus and the stomach. It relaxes for entry of food and is normally supposed to close to prevent reflux of food and acid into the esophagus. **When you experience symptoms of GERD is when it does not work properly.** Thinking about food, smelling it, stretching of the stomach by food, and partially digested proteins stimulate the production of the hormone [gastrin](#). Gastrin causes the release of stomach acid and pepsinogen, which is an inactive protein-digesting enzyme. Stomach acid then activates pepsinogen to create the active enzyme pepsin, which further assists with the digestion of protein. There is a feedback mechanism that regulates the secretion of gastrin and the subsequent production of stomach acid, when enough has been produced to digest the food.

In addition to stimulating the release of stomach acid, gastrin also stimulates the stomach muscles to contract, assisting in the digestion process. Simultaneously it triggers the pyloric sphincter, located between the stomach and first part of the small intestine (duodenum), to contract to reduce the rate of stomach emptying, so food can continue the digestion process properly as it passes through the GI tract. Gastrin, in normal physiological quantities as reached after a normal meal, causes the LES pressure to reduce! This may occur to allow food to more easily pass through the esophagus and into the stomach. This does not mean that the normal reduction of LES pressure causes GERD. It is what is called [Transient Lower Esophageal Sphincter Relaxations \(TLESR\)](#) which are a major cause of GERD. From GERD in the 21<sup>st</sup> Century, Series #5 “Transient LES relaxations are a physiologic response to gastric distention that lead to gastric-gas venting and avoidance of gastrointestinal bloating, and may occur with belching, vomiting, or rumination. Not surprisingly, **transient LES relaxations are the primary**

**cause of post-prandial reflux.”** Gastrin, while lowering LES pressure, did not increase the number of TLESR.

OK. This is where things get spooky! **PPI’s actually cause the LES to relax in a dose-dependent manner! In addition, they reduce normal contraction of the LES.** The difference is that normal gastrin release at physiological levels occurs during a meal, while the effect of gastrin stimulation by PPI is constant. **PPI therapy significantly increases gastrin levels. One study showed that PPI patients had gastrin levels more than 16 times higher than normal** patients not on PPI. Gastrin is a hormone. Just like any other hormone, it is important to maintain levels within a narrow range for optimal health. High or low levels of hormones carry consequences. Let’s see what are the penalties for long-term PPI use and elevated gastrin levels.

**So you have been on PPI for years. The odds are low that your doctor has ever checked your Gastrin levels. It is a simple blood test I perform on all patients taking PPI’s.**

## **Barrett's Esophagitis and Gastrin**

Do you have [Barrett's esophagitis](#)? Have you been warned that it is a consequence of long-term GERD? Then you will love this! The standard of care for patients with Barrett's is PPI. We know that PPI use elevates gastrin levels. What you didn't know is that serum gastrin levels are significantly associated with cellular proliferation. Specifically, it has been found that gastrin induces a receptor, called the CCK-2 receptor, increasing its levels in patients with Barrett's by two levels of magnitude, or 100 times that of non-Barrett's controls. This is the cause of overgrowth of abnormal tissue. There is a significant association between Barrett's and esophageal cancer, hence **PPI may increase the risk for developing esophageal cancer and promote Barrett's!**

## **GI Infection Risk**

So you have learned that the stomach produces acid, and a protein-digesting enzyme called pepsin. It also stores food while it is being digested and moves it along to the duodenum when it is ready for further digestion. It also does one more critical thing that is related to acid production. Acid kills bugs (bacteria, viruses, mold, fungus, yeast and parasites) that enter the body on food and water. PPI's stop acid production, which also stops the bug killing. This then significantly affects your [microbiome](#) (the bugs that live in you). This can lead to dysbiosis (bad bugs), SIBO and outright infections. One of the chief roles of stomach acid is to inhibit bacterial overgrowth. The normal pH (acidity) of the fasting stomach is between 0.5-1.3, according to information obtained from Heidelberg Gastric pH Analysis testing for stomach acid. My personal experience is that, even in patients with hypochlorhydria, 98% have a fasting pH of 0.5. The fasting pH does not tell you how much acid you can produce in response to food in your stomach. Most bacteria cannot survive for more than

a few minutes with that much acid. But when the pH rises above 5, bacteria can start to survive. Prilosec reduces the secretion of stomach acid (HCL) to almost nothing, which is what it was designed to do. **A study of 30 people with GERD treated with Prilosec for at least 3 months showed that about 33% developed significant bacterial overgrowth**, compared to only 10% in the control group.

Patients with low stomach acid have excessive growth of bacteria in the digestive tract and a much higher incidence of gastrointestinal infections. Modern treatment of GERD with acid secretion inhibitors creates a similar low acid state. Suppression of gastric acid secretion causes a dose-dependent increased risk of a wide variety of intestinal infections especially for people over 65, immune compromised persons, sick patients with a reduced resistance, and travelers to tropical areas. Studies and reviews of multiple studies have shown an increased risk of community acquired pneumonia associated with gastric acid inhibitor treatments. A study of 186 children, 91 of whom were being treated with PPI and H2 blockers, clearly showed a significant increase in both GI infections (gastroenteritis) and pneumonia. The researches stated that the effects of therapy on increased infections remained after treatment was stopped! A recent article in the prestigious journal JAMA about the serious GI bacterial infection with [Clostridium difficile](#) concluded **“PPI use is surely associated with the development of *C difficile*-associated diarrhea, and less PPI use should lead to less disease.”**

## **Small Intestinal Bacterial Overgrowth (SIBO)**

Normally, few bacteria live in the upper part of the small intestine. Their numbers normally increase the further along the intestine you go. Small intestinal bacterial overgrowth is a condition where there are increased numbers of bacteria living in the small intestine. This leads to major GI problems, including gas, bloating, altered motility, pain, poor digestion, etc. The bacteria produce gasses including carbon dioxide, methane and hydrogen. This can be measured with a hydrogen breath test. A positive test is indicative of SIBO. **In a study of 450 people, SIBO was found in 50% of patients using PPI. The rate of SIBO increased after 1 year of PPI use. The rate of SIBO in PPI users was over 800% that of a normal population.**

Now you've got to love this -- **SIBO is a potential cause of GERD! Why? The gasses produced increase abdominal pressure, which naturally increases reflux.** They also cause the LES to relax, making reflux easier. So Big Pharma sells a product that gives temporary relief of reflux symptoms while, at the same time, increasing the underlying causes of those symptoms, essentially guaranteeing that the patient will use PPI forever. What a great business!

## **Irritable Bowel Syndrome**

[Irritable Bowel Syndrome](#) (IBS) is the most common diagnosis made by gastroenterologists. This is often a “wastebasket” diagnosis by your doctor which means, let us give your symptoms a name so you can be blessed with my diagnosis. What is not said is “I have no clue what is wrong with you, or what to do about it.” It is a collection of ill-defined symptoms for which, until very recently, seem to have no pathological findings. You have learned that PPI’s increase bacterial overgrowth and infection in the GI tract, which, of course, causes a host of symptoms. There seems to be a correlation between PPI use, SIBO and IBS. Recent findings indicate that the majority of IBS cases are preceded by infection (gastroenteritis) by various bacteria that produce a toxin called [Cytotoxic Distending Toxin B \(CdtB\)](#). Antibodies are produced against this toxin to fight the infection. Unfortunately, these antibodies cross react with a molecule, called vinculin found in the endings of nerves in the GI tract and elsewhere. Vinculin is associated with cell adhesion and cell movement structure and function. Binding of antibodies to vinculin negatively affects its functions. This, and the inflammatory cascade of events associated with an immune response, is an underlying cause of IBS symptoms.



## **Helicobacter pylori (H. pylori)**

H. pylori is present in the stomachs of approximately 50% of Americans, and up to 90% of people living in third world countries, such as India. Infection rates increase with age by about 1% per year. Contrary to the popularly held belief that stress causes ulcers, H. pylori is the direct cause of the vast majority of stomach and duodenal ulcers, as well as stomach inflammation and gastritis. Barry Marshall, M.D., won the Nobel Prize in 2005 for proving the relationship between H. pylori and ulcers. In addition, H. pylori infection is associated with a higher incidence of [stomach cancer \(gastric carcinoma\)](#).

I previously noted that stomach acid decreases with age. A **chronic H. pylori infection suppresses stomach acid secretion**, which is how it survives in an acidic environment of the stomach. Since stomach acid decreases with age and H. pylori increases, **it may be the increased rate of H. pylori infection that is a cause for lower stomach acid levels with advancing age.**

Not only does H. pylori suppress acid production, it appears that the initial infection with H. pylori can only occur under conditions of low stomach acid. In a research study, people given an acid blocking drug were inoculated with H. pylori. A control group did not get the acid blockers, but was also inoculated. Only those on acid blockers became infected.

Up to 80% of people with H. pylori do not have any symptoms. In these people, H. pylori may be commensal bacteria, just like most of the several thousand other species that live in the digestive tract. A trigger may be necessary to turn it into a symptomatic infection. So what happens if you already have H. pylori and start taking PPI's? The already low stomach acid becomes even lower. This makes the infection worse. A study in the prestigious New England Journal of Medicine showed that **people taking**

**long-term Prilosec for 5 years who had a documented H. pylori infection had a huge increase and rate of *atrophic gastritis*.** At the end of the study, 81% of the people with pre-existing H. pylori who took PPI had atrophic gastritis, versus only 4% of the control group. One of the primary problems with atrophic gastritis is that it causes hypochlorhydria or achlorhydria (complete lack of stomach acid), making the vicious cycle even worse.

### Symptoms of H.pylori infection

- Abdominal pain with burning or gnawing sensation.
- Pain is often made worse with empty stomach; night time pain is common.
- Poor appetite.
- Weight loss.
- Heart burn.
- Indigestion (dyspepsia)
- Belching.
- Nausea.
- Vomiting.
- Blood in stool.



## **Leaky Gut Syndrome**

A recent study examined whether the PPI, esomeprazole (Nexium), affects the barrier function of the upper GI tract. A compromised GI barrier (Leaky Gut Syndrome), has many adverse consequences, including being a cause of GERD. Perhaps the worst concern is that Leaky Gut is a primary cause of many [autoimmune conditions](#), which are rampant in the USA, having increased dramatically in the past 50 years (interestingly, along with a huge increase in PPI use). Thirty-seven patients with GERD and 25 healthy controls were tested. Nexium caused significant leak across the upper GI tract mucosal barrier of patients taking the drug for the first time. The leak occurred quickly, within days of first taking the drug. The leak was also reversed within days of stopping the medication. They concluded, “This is the first patient-based study showing that a PPI compromises upper GI barrier function. There are potential implications for transmucosal leak of other medications that a patient on a PPI may be taking, as well as possible leak of endogenous peptides/proteins. The clinical consequences of this phenomenon are currently unknown, but are potentially important.” In other words, **Nexium caused Leaky Gut Syndrome within days of starting its usage. Imagine what damage long-term usage of PPI may do to the GI barrier system!**

## **Hip Fractures**

PPI's reduce calcium (and other essential nutrient) absorption due to a reduction of HCL. Minerals and vitamins are usually found tightly bound to protein molecules, which must first be digested for the nutrient to be available for absorption. As we know, stomach acid is needed for proper protein digestion. PPI may also act to increase the rate of bone breakdown. A huge study on patients with hip fractures concluded that **use of PPI for more than one year significantly increased the risk of hip fracture**; that the longer

the usage past one year, the greater the frequency of fracture; and that the higher the dose of PPI, the higher the risk. What they did not say, but which is obvious, is that long-term PPI use increases the risk for osteoporosis.

## **Gallbladder Function**

PPI's reduce the normal motor (muscular contraction) function of the gallbladder. After discontinuation of PPI, normal function returns in the majority of patients studied. In a study performed on normal subjects given PPI for only 30 days, reduced gallbladder function was seen in 15/19 subjects. In addition, 27% of the subjects began having gallbladder-related symptoms. The authors concluded, "Short-term PPI therapy reduces gallbladder motility in healthy volunteers. **Chronic PPI therapy may pose a risk for long-term gallbladder dysfunction and biliary complications.**"

## **Malabsorption**

It would be a safe bet to say that if you have no stomach acid, if you cannot activate the protein-digesting enzyme pepsin, if your gallbladder is not functioning, and you get SIBO because you don't have any acid to kill the bugs, that you probably are not going to be able to obtain essential nutrients from your food. This, in turn, will cause a whole host of problems, such as osteoporosis. I would be willing to bet that, if tested, virtually all of the essential nutrients will be absorbed at lower levels. Research shows that the following are affected:

- a) Carbohydrates -- Stomach acid begins the digestive process of breaking the bonds between polysaccharides (complex carbohydrates such as vegetables and starches). Without appropriate stomach acid, the pH of the small intestines is not optimal and the

secretion of necessary digestive enzymes from the pancreas does not properly occur. The carbohydrates are not digested to individual molecules, which can then be absorbed and used. Instead, bacteria use these sugars as food. Fermentation of carbohydrates produces various gasses, including: carbon dioxide, hydrogen, methane, and hydrogen sulfide. A small amount of carbohydrate is capable of producing a huge amount of gas.

- b) Vitamin B12 -- Prolonged PPI use reduces levels. Giving RDA replacement levels does not increase this decline.
- c) PPI use can inhibit magnesium transport in the intestine. Long-term PPI users can totally deplete their magnesium stores, with severe consequences.
- d) Iron-deficiency can lead to anemia. In addition, iron is required for the production of energy that occurs in the mitochondria of every cell. A study showed 35/40 people with anemia to have hypochlorhydria, so obviously PPI can contribute to iron deficiency.
- e) Calcium.
- f) Vitamin C.
- g) Zinc.
- h) Folate.

## **Cardiovascular Disease**

Just when you thought it could not get any worse! Long-term use of PPI's is associated with an increased risk for heart attack and vascular disease. A June, 2015 study reviewed over 16 million (that's a lot!) clinical documents on 2.9 million individuals to see if PPI increased the risk of heart attack (MI) in the

general population. Their conclusions were that PPI use led to a 116% increase in MI and a whopping 200% increase in mortality!

There may be multiple mechanisms at work here. PPI's reduce levels of essential nutrients critical to normal function of the heart and vascular endothelium. Decreased Vitamin B12 levels are associated with increased [homocysteine](#), a known risk marker for cardiovascular disease. In addition, PPI increase the levels of another chemical that is highly detrimental to cardiovascular health. [Asymmetric dimethyl arginine \(ADMA\)](#) appreciably increases in PPI treated individuals due to inhibition of the enzyme DDAH. Increased ADMA reduces a critical regulator of normal function of the lining of blood vessels (vascular endothelium) called [endothelial nitric oxide \(eNOS\)](#), which causes dilation of the blood vessels due to relaxation of the smooth muscles lining the vessels.

But it gets even worse. Not only do PPI increase ADMA, which directly competes with eNOS, but also eNOS is further reduced by a second mechanism.

Nitric oxide (NO) is a regulator of many cellular functions whose discovery led to it being named the "Molecule of the Year" in 1992 and Nobel prizes for the discoverers in 1998. A family of enzymes catalyzes its production from the amino acid arginine. Recently a second mechanism for the creation of NO was discovered that involves stomach acid. The levels of NO in air expelled directly from the stomach are 100 times higher than from the lungs. **When pre-treated with PPI, the amount of NO produced by the stomach was decreased a remarkable 95%! NO created by stomach acid may be**

important for maintaining the integrity of the normal stomach lining, so PPI may impair this function.

Not only is eNOS involved with maintaining normal smooth muscle tone of the vascular endothelium, it is also involved with many other regulatory functions, including: insulin secretion, airway tone, growth of new blood vessels, embryonic heart and coronary artery and valve development, reducing platelet adhesion and aggregation to the lining of blood vessels (reducing plaque formation), increasing the antioxidant enzyme Superoxide Dismutase (SOD), regulating DNA methylation and transcription, and a host of other critical functions.

## **Asthma**

Numerous studies show the correlation between low stomach acid and asthma. There is a close association between asthma and GERD. Up to 80% of people with asthma have GERD, according to an article in “Nature.” Acid can reflux into the trachea, causing difficulty breathing, wheezing and vocal changes.

## **Skin Aging**

In a 2010 paper, two researchers suggest that PPI can promote skin aging by two distinct mechanisms. They state that the lowered acidity of the stomach in turn causes an increased alkalinity of lysosomes (intracellular organelles which contain a variety of enzymes that function in an acidic environment). This, in turn, suppresses [transforming growth factor beta \(TGF-B\)](#), a protein that controls proliferation and differentiation of many cell types. They also state

that PPI inhibits an enzyme called lysyl oxidase by reducing copper transport. This enzyme cross-links new collagen to make new skin.

## **What the Heck is Chromogranin A?**

The adrenal medulla, and heart secrete [Chromogranin A \(CgA\)](#). It is used as a marker in the diagnosis of neuroendocrine tumors, meaning that, in many tumors, its level increases significantly above the normal range. Well, guess what? PPI also increases CgA levels. A study of GERD patients on PPI showed that only 5 days of PPI therapy was enough to start increasing CgA levels, and that the higher the PPI dose, the greater the increase. **After 6 months of PPI therapy, both CgA and gastrin levels were markedly elevated.** The good news is that levels significantly decreased after 5 days of PPI cessation.

A 10-year study of 470 elderly patients with heart failure concluded that CgA could identify those who were at increased risk for mortality. CgA is not just a marker for neuroendocrine tumors and heart failure. It is a protein that is released with [catecholamines](#) (epinephrine and nor-epinephrine) in response to appropriate stimuli. It is a pro-hormone that is split into several peptides that have biological activity. A thorough review of relevant literature between 1985 and 2013 showed 209 references. This review article concluded that **CgA had broad-spectrum regulatory activity of the endocrine, cardiovascular, immune systems; glucose and calcium homeostasis.** Some of the active peptides had opposite effects and unbalanced production of peptides can play a role in several diseases. Chronic PPI use disrupts normal CgA signaling mechanisms through prolonged elevation.



## **Increased Risk of Liver Cancer**

Primary liver cancer has increased dramatically and is now among the leading types of cancer. It has a very poor 5-year survival rate. Recent animal studies using PPI's have shown increased risks of stomach and liver cancer. In human case studies comparing a group of people with primary liver cancer to a control group, PPI use was associated with an 80% increased risk of developing liver cancer. In a second prospective cohort study looking at almost 500,000 people, people who used PPI's almost doubled their risk of developing liver cancer. Rat studies using PPI's show they promote liver cancer. We know that PPI's elevate the hormone gastrin, which has known cancer inducing effects. Reduced nutrient absorption leading to nutritional deficiencies, and bacterial overgrowth in the intestines may contribute to increasing the risk as well.

## **Decreased Production of Antimicrobial Peptides**

Earlier in this monograph, you learned that the stomach normally produces acid, which initiates the direct breakdown of protein by breaking bonds between amino acids. Acid also turns the inactive protein-digesting enzyme pepsinogen into active pepsin, further assisting protein breakdown. The acidic environment itself acts as an antimicrobial in that it kills microbes that enter the stomach with food and water.

Just published research in 2018 tells us that pepsinogen itself is broken down into several smaller peptides that show significant anti-bacterial action *in an acidic environment*. The authors stated “for relevant foodborne pathogens, suggesting that this new class of previously unexplored AMPs may contribute to microbial surveillance within the human stomach.

The peptides showed no toxicity toward human cells and exhibited anti-infective activity in vivo, reducing by up to 4 orders of magnitude the bacterial load in a mouse skin infection model”.

What this means is that the digestive enzyme pepsinogen is broken down by stomach acid into various fragments that possess significant bactericidal properties. ( 4 orders of magnitude means 10,000 times as much anti-bacterial action). This may therefore play a major role in preventing SIBO, a condition discussed previously in which there is bacterial overgrowth in the small intestine.

### **PPI and Early Death Risk**

Just when you think it can't get worse! A 2016 study of medical records of 275,000 people showed that compared to people who took PPI's for 1-2 years had a 50% higher risk of dying over the subsequent 5 years. Not exactly the safe candy you and your doctor thought you were gobbling down. Given that millions of Americans take PPI's on a routine, long-term basis, this means that PPI's may be responsible for thousands of deaths each year. Oh- and the longer people took PPI's the greater the death risk. If none of the other reasons for stopping chronic PPI use rattled your cage- this study should.

## Solutions, Not Assumptions

It does little to tell you the dangers of PPI unless there is a solution to your problem. If you are a long-term user and still have problems, then it should be obvious that the root causes of your condition have not been addressed. Fortunately, finding the root causes of your GERD can successfully resolve the condition. If you have used PPI for a prolonged period of time, there probably is no single, magic pill to take. By chronically blocking the production of stomach acid, a chain of events has occurred, much like knocking over a line of dominoes. One problem leads to another, so in the end there is a whole host of potential problems created. To successfully treat the underlying reasons why you have GERD, you need to know what those reasons are as well.

Fortunately, there are Functional Diagnostic Medicine lab tests that will help identify the reasons you have GERD. The following tests are recommended:

- 1) [Heidelberg Gastric pH Analysis](#): This test checks for your ability to produce stomach acid. Since hypochlorhydria is a primary reason for the development of GERD, one must start by correcting problems at the top of the GI tract so that the effects carry all the way through.
- 2) [Comprehensive Digestive Stool Analysis \(CDSA\)](#): This test can help determine the species of bacteria living in you and whether you have bacterial overgrowth or pathogenic bacteria, such as *H. pylori* or *C. difficile*. Included in this test are a number of parameters of GI function, such as immune function, inflammation, levels of beneficial short-chain fatty acids, pancreatic digestive enzyme secretion, and more.
- 3) [SIBO Breath Test](#): This test determines if you have overgrowth of bacteria contributing to your problems by measuring the levels of hydrogen and methane gasses.

- 4) [Food Allergy Testing](#): Sensitivities to foods contribute to gastritis, intestinal inflammation, a chronic immune response and possibly Leaky Gut Syndrome.
- 5) [GI Permeability \(Leaky Gut Syndrome\) Test](#): The root cause for many abnormal immune reactions originates in the gastrointestinal tract. GI tract abnormality can compromise the integrity of the gut barrier and increases the entry of undigested antigens into the circulation, activating the immune system, resulting in the production of pro-inflammatory cytokines and an array of antibodies, which further contributes to increased intestinal barrier permeability (leaky gut syndrome)
- 6) Irritable Bowel Syndrome: IBS is a real diagnosis, with real reasons why you may have it. A simple blood test, called [IBSchek](#), is 90% accurate in diagnosing this condition, which actually has an autoimmune component.

Once the underlying causes are identified, specific, natural treatments may be used to address each issue. The basic program is called “The 4-R GI Restoration Protocol.” It consists of the following:

- 1) Remove: Eliminate all identified food allergens to reduce a major source of inflammation. Even if not identified on your food allergy testing, remove all gluten, dairy and yeast sources. Remove all alcohol and refined sugars and processed foods. The Paleo diet is an excellent choice as it removes the major food allergens and irritants.
- 2) Replace: If your testing has shown low stomach acid, replace with Betaine HCL and Pepsin. Pancreatic enzymes should be used to supplement digestive function. A hypoallergenic medical meal replacement powder that contains a full array of essential nutrients is needed to replace protein and essential nutrients that have been lost due to malabsorption.

- 3) Repopulate: Based on the results of your CDSA, the appropriate probiotics and prebiotics can be recommended. In general, a broad-based, high potency probiotic containing multiple species and strains should be used. If dysbiotic bacteria are present, there are a variety of natural products that will kill or significantly reduce their numbers. Prebiotics may be used to help feed the friendly bacteria you have reintroduced.
- 4) Repair: The GI tract cells must be repaired and regenerated. In addition to making sure that an optimal supply of essential vitamins and minerals is given, there are a number of Nutraceuticals that can accelerate healing, including: Glutamine, Butyrate, Zinc Carnosine and DGL. Inflammation can be reduced with Curcumin, Resveratrol, Vitamin D and Omega-3 EFA's. Aloe Vera, Slippery Elm Bark, Marshmallow Root can all sooth the GI tract. Perilla leaf extract can help normalize GI motility and relieve discomfort. Reflux can be treated with Alginic Acid. When mixed with stomach contents, Alginic Acid expands and creates a "raft" that floats on top of the stomach, blocking contents from refluxing into the esophagus. Peppermint oil and Limonene can sooth inflamed GI tissue.

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