meal. This dietary pathway for generation of NO is dependent upon select bacteria in the mouth and sufficient acid production in the stomach. Research groups at the Karolinska Institute have convincingly shown that use of antiseptic mouthwash or abolishing gastrointestinal bacteria affect endogenous NO production.[48–50] Patients on broad-spectrum antibiotics are at increased risk of opportunistic gastrointestinal tract infections from species such as *Clostridium albicans* and *Clostridium difficile*. The overuse of antibiotics might be responsible for killing off the commensal bacteria responsible for salivary nitrate reduction, and thus reducing salivary nitrite that allows for the same bacteria to be established in the GI tract.

The salivary reduction mechanism might also play a role in the innate immune response and wound healing. Both humans and animals will lick their wounds upon sustaining injury, an action that promotes wound healing.[51] Although numerous innate immune defense mechanisms and immunoglobulins are present in saliva, part of the mechanism may in fact be through an NO pathway by salivary nitrite.[52] Licking of human skin results in production of NO as salivary nitrite is reduced on the acidic skin surface.[53] A number of common skin pathogens are effectively killed by acidified nitrite.[54] The acidification of nitrite from dietary nitrate likely plays a role in the wound healing aspect of saliva.

Processes that kill or disrupt commensal bacterial function in the mouth, GI tract, and skin are likely to disrupt NO production. Everyday actions such as the use of antibacterial soaps, antiseptic mouthwash, overuse of antibiotics, and even seemingly beneficial activities, such as bathing twice a day, affect fundamental pathways for NO production. It is critical to remember that not all bacteria are bad and that the numbers of commensal bacteria that reside in our body outnumber our own human cells 10 to 1. The majority of the commensal bacterial in the human body play incredibly vital roles, and maintaining communities of these while combating infectious or pathogenic bacteria should be a balanced effort and the goal of hygiene and antibiotic use.

**Proton Pump Inhibitors**

Stomach acid levels directly correlate to the nitrate reduction cycle in the mouth. Nitrite produced on the dorsal surface of the tongue by bacterial reduction is further reduced to NO under acidic conditions and result in the destruction of acid-producing organisms.[39] NO from acidic reduction of nitrite, along with other reactive nitrogen species, is produced in the stomach following a nitrate-rich meal in quantities far greater than that required to produce vasodilatation, suggesting a role other than modulation of gastric blood flow.[55] A number of important human pathogens (*C. albicans*, *E. coli* 0157, *Salmonella*, *Shigella*) are resistant to a low pH found in the stomach, which enables them to survive passage through the stomach.[56] The addition of nitrite in concentrations found in human saliva results in much more effective killing of these pathogens than in acid alone.[47,57] Indeed even *H. pylori*, a bacterium well adapted to colonize the human stomach, is susceptible to acidified nitrite.[58] Acidified nitrite plays a pivotal role in protection against ingested pathogens. Further support for this can be found in the reduced levels of postprandial salivary nitrite found in subjects treated with the broad-spectrum antibiotic amoxicillin.[59] Since the pKa of nitrite is approximately 3.3, in order to effectively generate NO disproportionation, the stomach must be acidic. A reduction of acid production, and the resulting pH spike, leads to a disruption of this pathway. Achlorhydria has been defined by multiple separate systems in reference to gastric acid secretion. First, achlorhydria has been defined by a peak acid output in response to a maximally effective stimulus that results in an intragastric pH of greater than 5.09 in men and greater than 6.81 in women. Second, achlorhydria has been defined by a maximal acid output of less than 6.9 m/mole/h in men and less than 5.0 m/mole/h in women. Third, achlorhydria has been defined as a ratio of serum pepsinogen I/pepsinogen II of less than 2.9. It is estimated that approximately 30% of the population over 65 years are hypochlorhydric. Several medical conditions and specific gastric surgery can lead to achlorhydria. Several conditions associated with achlorhydria lead to increased mortality and morbidity. Specifically, achlorhydria has been associated with gastric cancer, hip fracture, and bacterial overgrowth, all of which may be partly due to disruption of NO production from nitrite.

Proton pump inhibitors (PPIs) are the third-highest selling class of drugs in the US, with $13.9 billion in annual sales and a staggering 113.4 million prescriptions filled each year. The drugs are used for gastroesophogeal reflux disease (GERD) and bleeding peptic ulcers. Yet a study found that high-dose PPIs, when compared with low-dose PPIs, do not further reduce the rates of rebleeding, need for surgical intervention, or mortality after endoscopic treatment in patients with bleeding peptic ulcers.[60] There is emerging evidence that chronic use of PPIs is associated with a number of other health problems that appear to be related to NO biology. Postmenopausal women who used PPIs had a 26% increased risk for forearm and wrist fractures, a 47% increased risk for spine fractures, and a 25% increased risk for total fractures.[61] Long-term PPI therapy, particularly at high doses, is associated with an increased risk of hip fracture.[62] The mortality rate during the first year after a hip fracture is 20%. Among those who survive, 1 in 5 patients require nursing home care. Several potential mechanisms may explain this association. Significant hypochlorhydria, particularly among the elderly, who may have a higher prevalence of *H. pylori* infection, could result in calcium malabsorption secondary to small bowel bacterial overgrowth. Limited animal and human studies have shown that PPI therapy may decrease insoluble calcium absorption or bone density.[63] NO, in addition to its known cardioprotective effects, appears to also play a role in osteoblast function and bone turnover.[64] Supporting this notion, in a small randomized controlled trial, nitroglycerine (an NO donor) was found to be as effective as estrogen in preventing bone loss in women with surgical menopause.[65] Disruption of the acid disproportionation of nitrite to nitric oxide through PPI use may also affect the NO biology of bone metabolism.

Achlorhydria is an important cause of hypergastrinemia, which can subsequently lead to the development of GI carcinoid tumors. There are now enough data from patients who have been taking PPIs for sufficient periods to begin to assess the consequences of long term therapy and it appears that chronic use of these is associated with gastric carcinoid