Hypochlorhydria and Dementia

Part 1: Gastrointestinal pH, micronutrients and gut flora

This two-part article will highlight nutritional relationships between the aging gut and brain. Part one will briefly review gastrointestinal pH, micronutrients and gut flora. The sequel will extend these relationships to cognitive function and neurodegeneration.

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Natural history's aging studies of simple organisms have consistently described an ordinal pattern of organ system failure initiated by the gut. Aging in human studies manifests in numerous ways, but perhaps it adheres to this pattern. Naturopathic physicians are keen to this idea, and most might consider gut function as key to optimizing health in many disorders. For example, gastric acidity studies in humans have identified correlations with aging, atrophy of the oxyntic mucosa and commensurate decline of gastric acid secretion (Siurala et al., 1968). Depending on measures used, approximately 11% to 37% of the elderly have atrophic gastritis type B (*H. pylori* infection induced by definition), which results in elevated gastric pH (hypochlorhydria) (Krasinski et al., 1986; Selhub et al., 2000). I am unaware of studies reporting the prevalence or incidence of hypochlorhydria not associated with *H. pylori* infection. Characterization of hypochlorhydria in terms of what is biologically or clinically pertinent has likely hobbled work in this area. Nevertheless, there are ways to define hypochlorhydria, and some good studies of nutritional implications associated with it.

Hypochlorhydria and Micronutrients Associated with Dementia

Arguably, the most complex micronutrient in terms of absorption is cobalamin (vitamin B12). Bacteria synthesize B12 on animal organ meats, especially liver and kidney, but also on fish, mushrooms, eggs and milk products. The molecular and cellular processes of its digestion, absorption and assimilation are described elsewhere. Hypochlorhydria and the inability to release B12 from food or its binding protein were first described by Carmel in 1995 as Food Cobalamin Malabsorption Syndrome (FCMS) (Saltzman et al., 1994). This syndrome is accountable for the majority of B12 deficiencies in the elderly (Carmel, 1995). HCl is also required for catalyzing pepsinogen to pepsin, the dominant proteolytic enzyme in the stomach. The optimum pH for gastric pepsins varies between 1.0 and 2.0, and the enzymatic activity of pepsin declines with increasing pH to less than 5% at pH 5 (Koop, 1992). Entero-hepatic recirculation and hepatic stores may explain the observation of a multi-year delay in onset of clinical illness with insufficient intake of cobalamin (<2 micrograms/day) (Carmel, 2000).

Folate fortification of grains in the United States began as early as 1996, with companies anticipating policy change to fortify in 1998. This action has decreased the prevalence of folate deficiencies in the U.S. public. Nevertheless, its absorption is also dependent on optimal gastrointestinal pH. Small intestinal pH of about 6.3 is required for maximal absorption (Russell et al., 1979). In the elderly with hypochlorhydria secondary to atrophic gastritis, the pH at the ligament of Treitz is about a half-unit higher (7.1±0.1) than in those with normal acid production (6.6±0.1) (Russell et al., 1986). Russell et al. (1986) determined that this small rise in pH is enough to markedly reduce folate absorption compared to elderly controls with normal gastric acid production. Serum folate (5-methyl-FH4, the precursor to the functional form) levels are elevated in patients with atrophic gastritis secondary to B12 deficiency due to FCMS and the "methyl-folate trap" theory, or increased synthesis from bacterial overgrowth due to hypochlorhydria (Santarelli et al., 2004).

Carotenoids also prove dependent on gastrointestinal pH. Tang et al. (1996) conducted a randomized controlled trial, crossover design, inducing hypochlorhydria with proton pump inhibitors for seven days; they reported significant suppression of carotenoids blood response after dosage in subjects with hypochlorhydria. Observational analytic studies have provided evidence to support low gastric and plasma concentrations of vitamin C in subjects with atrophic gastritis type B (Jaskiewicz et al., 1990; Haenszel et al., 1985).

Hypochlorhydria and Microbial Infection in Dementia

Gastric acid secretion maintains the optimal milieu for pH-dependent enzymatic processes and the gut flora. As the oxyntic mucosa becomes more atrophic with increasing age, and acid secretion commensurately declines, the ubiquity and role of *H. pylori* is unclear and hotly debated. Histological and serological confirmed *H. pylori* infection is associated with lower B12 levels; hyperhomocysteinemia and eradication of *H. pylori* lowers HCy and raises B12 (Kutluanam, 2005). Serum folate levels are elevated in patients with atrophic gastritis secondary to either cobalamin deficiency or to increased synthesis from bacterial overgrowth due to hypochlorhydria (Santarelli et al., 2004). It is not uncommon to find *H. pylori* associated with Alzheimer's disease compared against similar age controls (Malaguarnera et al., 2004). In fact, a recently published study confirmed histologically increased prevalence of *H. pylori* infection in Alzheimer's compared to anemic controls with an odds ratio of 8.4 (2.4-28.7, $p<0.001$) (Kountouras et al., 2006). *H. pylori* have also been associated with peripheral neuropathies, where autoantibodies to specific targets may impair native neural function (Kountouras et al., 2005). Gastric acid suppression with either H-2 receptor antagonists or proton pump inhibitors has been shown to cause bacterial overgrowth in a significant number of both the healthy and subjects with peptic ulcer disease (Theisen et al., 2000). Profound and prolonged gastric acid suppression is associated with higher incidence of non-*H. pylori* bacterial infection in upper intestinal aspirates (Fried, 1994), damaging the intestinal mucosa and causing inflammation (Kirsch, 1990). This damaged intestinal mucosa may allow the passage of larger maldigested protein particles into circulation, evoking a pro-inflammatory cytokine reaction. To accompany a history and physical exam, an ideal panel illustrating this naturopathic suspicion might include measures of gut pH, IL-6, high sensitivity CRP, *H. pylori* test (IgG Abs or urea breath test), gastrin and pepsinogen I to II ratio.

Characterizing Hypochlorhydria

The gold standard technique for assessment of hypo/hyperchlorhydria is a formal gastric acid secretory test (GAST). This is performed by nasogastric tube placement into the stomach and subsequent challenge with pentagastrin injection while collecting several samples (Schubert, 2003). This method is invasive and complex; therefore, I propose using an alternative technique incorporating a swallowed telemetry pH capsule. This less invasive, direct measure is an FDA-approved technology and requires the fasting subject to swallow a small vitamin-size capsule; it is commonly referred to in the naturopathic community as the Heidelberg technique. This preferred method measures fasting gastric acidity and functional capacity of the parietal cells. The Heidelberg pH capsule system has been validated in several studies as an accurate, noninvasive and direct measurement of basal pH and gastric acidifying rate in the elderly (Russell et al., 1993; Connell, 1973; Dressman et al., 1990). Determining the appropriate treatment to optimize gut pH improves gut flora and digestion, absorption and assimilation of macro- and micro-nutrients.

Heidelberg pH Capsule System

A 15.5- x 7.1-mm single-use tethered capsule has a filament attached to one end to retrieve the capsule after measurement and to assure the capsule remains in the stomach during the test. The non-radioactive capsule is made of polyacrylate plastic designed for swallowing. It has a high-frequency transmitter with an average frequency of 1.9 MHz. Retrieval of the capsule is accomplished while the patient drinks some water to maintain an open upper esophageal sphincter. After swallowing the capsule, a fasting gastric pH is quantified. Once fasting basal pH is established, a challenge is administered to assess functional gastric acidification rate. Categories of gastric acid sub-functionality may be determined and appropriate intervention administered during the test. Understanding the underlying physiology here and its response to trial treatments is key to providing an individualized naturopathic prescription.

This measure is sensitive to underlying mechanisms by which the autonomic nervous system engages the gastric mucosal cells. In *NDNR*'s December issue (which focuses on neurology), I will underscore this point, discussing neurocognitive testing for neurodegenerative disease and naturopathic research underway.

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Hypochlorhydria and Homocysteine in Mild Cognitive Impairment

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In the October issue of NDNR, *we reviewed relationships between hypochlorhydria, micronutrients and gut flora pertinent to dementia. This article will extend these ideas to Alzheimer's disease, neurocognitive testing and rationale for clinical investigations.*

Alzheimer's: Public Health Impact

Alzheimer's disease (AD), the most common form of dementia, is a devastating neurodegenerative condition that, once identified, is largely irreversible. In the next 50 years, its prevalence is predicted to quadruple as the "baby boomer" generation enters elderly status. The characteristic pathology involves neurofibrillary tangles and Beta pleated amyloid plaques that pepper areas of the brain responsible for memory and other executive cognitive functions. This "amyloid hypothesis" is laboriously described elsewhere, but more insights into etiologic factors and potential preventive strategies are needed. Early stages of the disease need to be identified so therapies can be initiated prior to severe cognitive loss.

Identifying Early Stages

Ninety percent of the time, the pathology report at an autopsy confirms the diagnosis of probable AD made by a neurologist. We are now able to identify earlier stages of AD, called Mild Cognitive Impairment (MCI). Patients with MCI and Parkinson's disease are at high risk for progression to AD. Diagnosis is primarily through neurocognitive testing and other studies to rule out reversible causes (hypothyroidism, vitamin B12 deficiency, neurosyphilis) and other causes of cognitive deficits (stroke, tumor, normal pressure hydrocephalus).

Early screening is necessary to identify mild cognitive deficits, which are thought to be most responsive to treatment. Neurocognitive screening challenges multiple domains, including attention and orientation, language (comprehension, repetition, naming), memory, executive function (volition, planning, purposive action, effective performance), abstract thinking and calculations. The Mini Mental Status Examination (MMSE) is the most common screen employed in primary care. Complementing this test with the Neurobehavioral Cognitive Status Examination, Wechsler Memory Scale, Clock Drawing Task and Trail Making Tests A and B is encouraged as a more comprehensive evaluation critical to early detection. In other words, by the time deficits are recognized on the MMSE, the neurodegeneration may be well on its way. These tests also provide a baseline for the patient and data comparable to reference norms by age and education.

AD and Homocysteinemia: Cause or Association?

Epidemiologic studies support the notion that homocysteinemia precedes sporadic AD, increases the risk in a continuous dose-dependent manner, and correlates with neurocognitive test scores and brain atrophy rates over time. High levels of homocysteine (HCy) are toxic to vascular endothelial cells and may be directly neurotoxic. Cell and animal models describe mechanisms of neurotoxicity, including:

1) stimulating glutamatergic N-*methyl* D-*aspartate* receptors, leading to neuron death
2) changes in hippocampal plasticity and a slow-onset disruption in synaptic transmission
3) promotion of *tau* hyperphosphorylation by inhibiting protein phosphatase 2
4) inducing endoplasmic reticulum stress protein (Herp), which interacts with presenilin 1 and 2 to increase beta amyloid generation.

AD and Hypochlorhydria

Inability to acidify one's stomach can lead to elevated homocysteine, and both are common in the elderly. Another implication of hypochlorhydria is a micro flora shift. In the absence of the anti-microbial effect of normal stomach pH, exogenous and endogenous bacteria modify bile metabolism. Bacterial species identified in gastrum and jejunum of patients with hypochlorhydria include *Escherichia coli, Candida albicans, enteroccocus, Lactobacillus bifidis, Bacteroides vulgatus, B. uniformis, Eubacterium lentum, E. parvum* and *Cornybacterium granulosum*. With the exception of *E. coli* and *C. albicans*, all are associated with bile acid deconjugation. Micro flora shift secondary to hypochlorhydria is associated with fat-soluble nutrition imbalances. This remains true even though lipase is most active at pH of 3.5-4.0.

Allopaths treat mild-moderate AD with acetylcholine esterase inhibitors, and add NMDA receptor antagonists for more severe stages of probable AD. The rationale for acetylcholine esterase inhibitors is based on pathology findings of attenuated acetylcholine in AD brain tissue and that increasing levels may slow memory loss. Quantifying acetylcholine after administration of ACEI has eluded scientists thus far, and some patients have GI side effects. Maybe these ACEIs are good for hypochlorhydria. I mention acetylcholine here because it is theoretically possible that *rate* of reacidification of gastric contents after a bicarbonate challenge is essentially quantifying the functional capacity of the autonomic nervous system and this neurotransmitter. Acetylcholine derived from postganglion cholinergic muscarine branches of the vagus nerve directly stimulates the gastric mucosal parietal cell.

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HCy-lowering strategies in vascular disease have been largely disappointing, and it is likely that trials of B vitamins alone for AD will follow suit. These studies reduced HCy levels by roughly 12%-25% over a two-year period. The most recent trial measured cognition by neurocognitive testing and found no cognitive benefit of reducing HCy levels by about 25%; however, neither the treatment nor the placebo group showed cognitive deficits during the trial. An HCy-lowering trial in AD is underway, although to see benefit in a two-year period may require a more robust reduction in HCy, basically using B vitamins as drugs.

Lowering HCy by about 50% has improved blood-brain barrier integrity in patients with MCI over a nine-month period. CSF/plasma ratio of vitamin C is >1 in healthy elderly and >3 in cognitively impaired, favoring downward diffusion from the CSF to the plasma. This high antioxidant concentration in the CSF may be an adaptive physiologic response to the burden of oxidation in the AD brain. The "leaky" blood-brain barrier in AD appears to handicap one's ability to concentrate antioxidants in the brain, and this significantly correlates with rate of disease progression over one year. Contribution of homocysteinemia in AD pathogenesis may be mediated partially through aggravation of the blood-brain barrier and subsequent vitamin C loss.

But what is the *underlying cause* here? An alternative hypothesis is that hypochlorhydria is an unidentified factor that contributes to homocysteinemia and AD.

My ongoing clinical research will get at some of these relationships using pH capsule, blood and genetic testing, food and exercise questionnaires, neurocognitive testing and neurologic exams. Two studies are recruiting men and women age 55 or older with and without mild memory problems and Parkinson's disease. If you or someone you know is interested in participating in these studies, please contact the Aging and Alzheimer's Disease Center of Portland, 503-494-6976.

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