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## Curbing Acid May Induce Dysbiosis

Dysbiosis, "acid stomach," and gastrointestinal erosions are complex conditions with numerous potential contributing factors, yet are relatively common among people with access to a plentiful and highly-processed food supply. But digestive juices have great influence over pH control in the lower reaches of the gastrointestinal tract as well as in and around the stomach, and recent research into stomach acid suppression shows that the composition of the oral/periodontal, esophageal, gastric, small intestinal, and colonic microbiomes can be strongly negatively impacted by it. Researchers found that, in some cases, growth of potentially pathogenic microbes was encouraged by this practice, while beneficial or commensal species (Bifidobacteria a striking example) were disadvantaged. While the significance of these changes is not yet completely known, the researchers discuss how dysbiosis and other gastrointestinal disorders may become an increasingly common finding in those undergoing acid suppression treatment.

Gastrointestinal pH plays a crucial role in setting up growth parameters for gut microbiota denizens, and gastric acid production influences other digestive factors (like bile, bicarbonate, nitrate/nitrite balance, mucus, etc.), functions (gastric emptying, intestinal transit) and environments. Furthermore, altering the composition of gastrointestinal microbiota also changes the profile of microbial metabolites introduced into these dynamic environments, changing overall exposure to ammonia, lactate, bacterial components, and other substances that can affect signaling processes, nutrient absorption, and the immune response. Other mediators of health such as perceived stress, toxic exposures, and others may also be involved, but establishing healthier eating windows, limiting snacking, and eliminating night-time eating may go a long way towards optimizing the stomach's scheduling of when it elaborates powerful digestive factors versus when it takes a break from that duty in order to prioritize crucial

housekeeping functions like metabolic detoxification, autophagy, mitophagy, and stem cell renewal.

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## An Aging Blood Stem Cell May Carry a CHIP

The growing fetus contains embryonic stem cells that differentiate into a broad variety of more specialized cells and tissues during fetal growth, but the adult body also harbors stem cells in the blood, intestines, bone marrow, breast, and possibly also the brain. Adult stem cells contribute to tissue repair and cell replacement despite possessing narrower developmental potential than those of embryos, but they also accumulate mutations throughout their longer lives. Genome sequencing studies have recently noted mutations in hematopoietic stem cells (cells that differentiate into the wide spectrum of white and red blood cells) that have been found in up to 28 percent of older people and confer extra cardiovascular and cancer risks to these carriers.

While increases in specific subpopulations of blood cells have long been seen in blood cancers and pre-cancers, they were not considered significant in broader populations in the absence of these conditions. The recent genome studies discovered that, with aging, particular mutations can expand certain blood cell lineages at the expense of others, and that this was associated not only with risk for cancers of these blood cell "clone" populations but also for all-cause mortality and cardiometabolic disease. The presence of such "clonal" mutant cell populations has been called CHIP, or Clonal Hematopoiesis of Indeterminate Potential. It is not considered to constitute a malignant condition, but rather a preclinical manifestation of aging worthy of noting and tracking, especially in those showing cytopenia not explained by current diagnoses. CHIPs are not often seen in those under 40 years of age but become more common in those over 65. A study measuring the accumulation of mutations in hematopoietic stem cells in healthy volunteers estimated that around 0.13 such mutations normally occur each year.

A striking characteristic of CHIP is that associated mutations often affect the very epigenetic mechanisms by which blood cell replication is controlled—DNA methylation, transcription and transduction, and histone modification, to name a few. Changes in these functions confer advantage to particular cell populations and can alter balance between, as one example, lymphoid and myeloid stem cells. Studies including this 2015 study describing CHIP found variants in the *DNMT3A*, *TET2*, and *ASXL1* genes (all key regulators of epigenetic modification) to be the most common in CHIP, and these three were also widely identified in blood stem cells in those with type 2 diabetes. Later research published in the New England Journal of Medicine found these three mutations and another in the *JAK2* gene associated with coronary heart disease and progression of coronary calcification, with greater blood proportion of mutated cells correlating to atherosclerosis and coronary events. Significantly increased risks for myocardial infarction (four-fold), coronary heart disease (doubled), ischemic stroke, all-cause mortality, and hematologic cancer (about ten-fold) were also reported among CHIP carriers.

Though it is not yet fully understood why certain individuals "collect more CHIPs" during aging, early research suggests potential contributions from stress and inflammation. Upon finding that cardiovascular risk may be predicted by metabolic activity in the brain and bone marrow, a "neural-hematopoietic" axis between these locations has been posited. Much like the hypothalamic-pituitary-adrenal axis of distress signaling that mediates the effects of chronic stress on long-term health, altered communications between brain and bone marrow (where blood cell progenitors develop) is hypothesized to influence balance among proliferating stem cells and thereby impact coronary events. Animal models of social stress show that it can trigger an inflammatory response, priming circulating myeloid cells (such as neutrophils and macrophages) and recruiting battle-ready macrophages to brain regions (including the amygdala, hypothalamus, and hippocampus, associated with the fear response) while chronically stimulating defensive responses—a pattern that in humans may relate to some mood disorders. Unhealthy

lifestyles, repeated stressors, and aging are likewise known to activate pro-inflammatory cytokines like tumor necrosis factor-alpha (TNFα). The *TET2* gene codes for an enzyme that influences DNA methylation and macrophage Th1/Th2 polarization, and *TET2* mutations can impair resolution of inflammation by hampering macrophage clearance of cellular debris and heightening genetic expression of the pro-inflammatory cytokines interleukin-1β and IL-6. Aging increases the appearance of *TET2* mutations that drive proliferation of myeloid blood cell clones, and macrophages carrying these *TET2* mutations express hyperinflammatory potential and thrive in the presence of TNFα compared to macrophages without the mutation, further accentuating the pro-inflammatory response (and atherosclerosis) in *TET2* carriers.

Genomic science has only recently discovered CHIP, but this emerging avenue of research suggests that CHIP carriers experience more immunometabolic stress during aging. Though no mitigating strategies have been developed for CHIP as a preclinical condition, studies in more advanced conditions have noted that *DNMT* and *TET* mutations seem to respond well to hypomethylating agents. Addressing the chronic stress response, encouraging inflammation resolution, and supporting metabolic detoxification function through personalized diet and lifestyle recommendations may be worthy of consideration.

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## Sunnier Outlooks for Mothers and Newbies

The broad applicability of the Mediterranean Diet towards maintaining comfort and function in health and in inflammatory and age-related conditions makes it a natural for consideration during pregnancy—after all, it's worked out well for generations of Mediterraneans, hasn't it? Several recent studies (including two controlled trials of around 1000 participants) have looked into this question, and while not all outcomes are in complete agreement, they found consensus on a couple of extremely important points: observing some form of the Mediterranean Diet appears to relate to reduced risk for gestational diabetes and excessive weight gain during pregnancy.

One clinical trial was conducted in Madrid, Spain—a Mediterranean region where there is likely some degree of underlying influence from traditional dietary patterns. Starting at 8-12 weeks' gestation, pregnant women (most of whom were of normal weight) were instructed to observe a fairly basic, conservative Mediterranean Diet eating pattern focusing on olive oil, pistachio nuts, vegetables, fish, fruit, legumes, and whole grains, with the addition of low-fat dairy products allowed. At term, the rate of gestational diabetes was significantly reduced compared to controls and comparable to women undergoing specific intervention for the condition, percentage of large-for-gestational-age babies was reduced, and percentage of diabetic mothers with excessive weight gain was reduced without significant increase in those with insufficient weight gain. The researchers concluded that early adherence to Mediterranean Diet may constitute firstline therapy for gestational diabetes.

Another was conducted in England, where the average diet is comparatively divergent from the Mediterranean eating pattern and the population is considerably more diverse; a significant proportion of subjects were obese. In this investigation, participants were given individualized instruction on following the Mediterranean diet and provided walnuts, hazelnuts, almonds, and olive oil. As in the Madrid study, researchers found a significant reduction in risk for gestational diabetes and significantly less gestational weight gain in this distinctive population at higher risk due to the higher prevalence of obesity. Finally, a systematic review of published literature examined the potential benefits of the Mediterranean Diet for newborns as well as their mothers, and concluded that adherence to it was associated with reduced risk for gestational diabetes and congenital defects and later reduced weight circumference in offspring, and may also be protective against later cardiometabolic disease and symptoms of atopy in offspring.

Thus, the Mediterranean Diet appears to blunt risks for as well as effects of gestational diabetes, and may have some later immunometabolic benefits in children whose mothers adhered to it during pregnancy. Makes one wonder: what if couples were made aware of potential advantages presented by a personalized Mediterranean Diet and began to observe it prior to conception, enjoy its effects through pregnancy and lactation, and raise a family with it?

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