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Foreword

The field of evolutionary health is relatively new, and over the last two decades, has come to signify the interest in the extent of mismatch between factors common in our modern day world, and our evolutionary milieu, which is a combination of genetic and environmental interactions that occurred over the course of many thousands if not hundreds of thousand years.

At each conference, we have had discussants explain about brain function, sleep and light, various components of the diet, aging, cardiovascular disease, exercise, bone health, obesity, vitamin levels, hormonal regulation, inflammation and cancer, with the emphasis on the degree of mismatch between what our hominid ancestors did, and modern humans today.

We'd like to thank the Journal of Evolutionary Health for allowing us to publish some of the abstracts of our last conference. A playlist of some of the recorded talks from our conferences is also available on Youtube, at https://www.youtube.com/playlist?list=PL8YBjoaaAb9OcJI5TDgE-xK0S76HRSORr.

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THE ANTI-AGING POTENTIAL OF A LOW ACID DIET

Lynda A. Frassetto, MD

In many people with increasing age, renal function declines. And with declining renal function, the kidney's ability to excrete excess metabolic acids (such as phosphates, sulfates, chlorides and organic acids) also decreases.

However, it has recently been demonstrated that high acid levels themselves cause the kidneys to fail more quickly. [1] Bicarbonate supplementation has been shown to increase the interval of time before dialysis needs to be initiated. As such, many nephrologists now give bicarbonate supplements to subjects with low levels of kidney function and low serum bicarbonate levels.

One of the sources of metabolic acids is the diet. Diets high in phosphate have been shown to raise FGF-23 production, and FGF-23 lowers both 1,25 vitamin D and klotho levels. [2] Klotho is an important factor in increasing renal tubular excretion of phosphate, helping to maintain phosphate homeostasis.

But klotho has another interesting property; rats and mice that overexpress the klotho gene live 20-30% longer than wild type animals, while those that are klotho knockouts die rapidly of organ failure similar to rapid aging, including more rapid damage to the kidneys. [3] In animals that are klotho deficient, treatment with bicarbonate lets them live longer.

Another factor associated with aging are telomeres; TTAGGG tandom repeats at the ends of the chromosomes that help control DNA replication. Longer lifespans are associated with longer telomeres and increased activity of the enzyme telomerase, which adds the TTAGGG units to the chromosomes. Diets high in metabolic acids such as phosphate are associated with both lower GFR and shorter telomere length. [4] Diets that low in metabolic acids are associated with longer telomere length. [5]

Thus, we hypothesize that perhaps eating a low acid (and particularly a low phosphate) diet and/or supplementing the diet with base precursors such as bicarbonate could 1) slow damage to the kidneys which would help preserve the kidneys ability to excrete acid, 2) avoid the downregulation of klotho that occurs with constant high dietary phosphate intake and FGF-23 production, and 3) could potentially improve telomerase activity to help maintain telomere length. And potentially, allow one to live longer and remain healthier?

Link to internet talk: https://www.youtube.com/watch?v=yzrIB4jZKos&list=PL8YBjoaaAb9OcJI5TDgE-xK0S76HRSORr&index=25

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MODERN EXPOSOME AND LOW-GRADE CHRONIC INFLAMMATION

Pedro Bastos, MS, PhD candidate

Although inflammation is often viewed as an adverse reaction, its goal is to actually protect the host from infectious agents, toxins and other environmental aggressions, and to initiate the repairing process after a surgery or an injury. [1-3]

Inflammation is thus a normal and crucial response characterized by the recruitment of various immune and non-immune cells. [1-3] Since these activated cells will have increased energy requirements, as well as specific nutrient needs, there will be a competition for those resources between the immune system and many other organs and systems (such as the muscle, the adipose tissue and the brain, among others). [4-6] Therefore, various metabolic, neurological and hormonal changes must occur to supply more nutrients to the activated immune system and less so to the other organs, while at the same time limiting nutrient (such as iron, zinc and manganese) access to infectious organisms. [4-7]

Those alterations include insulin resistance in liver, muscle and adipose tissue [5,8] various hormonal changes, [5] anabolic resistance leading to decreased muscle protein synthesis and loss of muscle mass, [5,9] increased coagulation and dyslipidemia, [5,10] increased water retention,[4] decreased circulating concentrations of various micronutrients (e.g. iron, zinc, vitamin A [retinol], vitamin B2, vitamin B6 [pyridoxal phosphate], vitamin C and 25-hydroxyvitamin D), [5,7,11-14] bone mineral loss, [15] and depressive-like symptoms (the so called *sickness behavior* [6] which also includes anorexia, fatigue, sleep changes, and decreased libido [4-6]). If they remain uncontrolled, all of these inflammation-induced perturbations can compromise survival and reproduction. [4-6,15].

A normal and healthy inflammatory response normally ceases in a matter of days or, at the most, weeks, once the trigger ceases and the healing process has occurred. [2-5] Nevertheless, the modern exposome (i.e., the lifelong exposure to a variety of novel environmental factors, [16] including the typical western diet,[16-20] various xenobiotics, [16,21,22] chronic psychological stress, [22,23] physical inactivity,[24] and light at atypical times, [25,26] leading to disturbed sleep and circadian rhythms [26-28]), coupled with visceral obesity, [29] increased intestinal permeability, [29] and a reduction in microbiota diversity [30] (as a result of increased sanitation, overuse of antibiotics, less time spent in natural spaces and adoption of western-like diets [16,31,32]) can persistently activate numerous inflammatory pathways, leading to a state of low-grade chronic inflammation, [16-24,27-30] which in turn could trigger the mechanisms described above. In the long-run, this can cause, promote or exacerbate various chronic degenerative conditions, such as numerous types of cancer, [33], type 2 diabetes, [34] non-alcoholic fatty liver disease, [35] hypertension, [36] cardiovascular disease, [36,37] osteopenia/osteoporosis, [15,38] sarcopenia, [9] depression, [39] and neurodegenerative diseases.[40]

Link to internet talk:

https://www.youtube.com/watch?v=xyJ_2IlGZQo&list=PL8YBjoaaAb9OcJI5TDgE-xK0S76HRSORr&index=27&t=0s

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VARIATION IN CALORIC INTAKE IN WEIGHT, WAIST CIRCUMFERENCE AND COMPLIANCE

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(4) Professor at Collective Health Program at University of Ceará State

Obesity is an increasingly present disease, being complex and multifactorial, associated with the current lifestyle. [1] Nutritional intervention is one of the main forms of treatment of obesity and, in recent years, the Paleolithic diet (PD) has been gaining great proportions due to its supposed benefits, one of them, the weight loss. [2] However, there is a difficulty present in many patients who are in the process of losing weight: compliance to the proposed treatment. [3 4] The aim of this study was verify the weight loss of patients in different levels of compliance to a Paleolithic Diet.

The study is a subanalysis, carried out *a posteriori* from the controlled clinical trial for the treatment of obesity, developed with overweight or obese patients recruited from the Medical Attention Center Integrated University of Fortaleza (NAMI-UNIFOR). The PD interaction (n=76) was for 30 days. Subjects were advised to follow an *ad libitum* consumption of natural foods, excluding legumes, cereals, dairy products, salt, sugar and industrialized foods. Weight, waist circumference and 24-hour diet recall were measured at baseline and after the 30 days. The nutritional composition of the diets was evaluated using DietWin® software. Compliance based on the percentage of calories provided by allowed foods versus total calories consumed. The groups were divided into compliance quartiles. Compliance to the Paleolithic diet (CPD), caloric intake (CI), percentage weight variation (% WV) and waist circumference (% WC) SD) were analyzed as means (±SD) using the One Way ANOVA test, with Bonferroni correction and $p < 0.05$ as significant. The project was approved by the Research Ethics Committee of the related institution CAAE 58415016.0.0000.5534.

The results for the study are summarized below:

The first quartile: CPD=22.77% (SD =16.77), CI=1.166 kcal (SD =671), %WV=-1.17 (SD =1.79), %WC=-2.21 (SD =3.78).

The second quartile: CPD=64.51% (SD =7.68), CI=1.285 kcal (SD =739), %WV=-1.85 (SD =2.32), %WC=-3.59 (SD =4.09).

The third quartile: CPD=88.67% (SD =5.12), CI=1.292 kcal (SD =450), %WV=-4.81 (SD =2.57), %WC=-2.90 (SD =4.56).

The fourth quartile presented CPD=99.87% (SD =0.08), CI=999 kcal (SD =484), %WV=-4.23 (SD =2.37), %WC=-3.47 (SD =2.54).

Compliance showed a significant difference between all quartiles (p <0.05). The %WV demonstrated no statistical difference between quartiles 1 and 2, and quartiles 3 and 4. However, quartiles 1 and 2 were significantly difference when compared to 3 and 4 (p<0.05). The IC and the %WC didn't present a significant difference between the quartiles.

In conclusion, the compliance with the PD with a minimum percentage of 88% for 30 days demonstrated significant weight reduction, despite there being no difference in caloric intake between the groups. This level of compliance during the same period did not however significantly change %WC.

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EVOLUTIONARY PSYCHIATRY: FOOD AND MOOD

Emily Deans, MD

Diet is as important to psychiatry as it is to endocrinology, cardiology, and gastroenterology. [1] The brain is 60% fat with the highest concentration of cholesterol in the body, and processes in the brain are highly energetic requiting many micronutrients for optimal function. Based on the recent literature, including two randomized controls of dietary interventions for depression, specific vitamins, minerals, fermented foods along with global dietary patterns are linked to mental illness. [2] Vegetables, tubers, grains, fruit, meat, eggs, dairy, and nuts contribute varying nutrition to the diet, whereas processed foods in general fall far short of what humans require for a healthy brain. A healthy diet seems to reduce overall body inflammation as well as markers of neuroinflammation.

Gut and mental health are linked as increasing evidence links microbiome changes to mental illness and cognitive function. [3] Humans have co-evolved over the entire history of our species and beyond with our microbiome and parasitic infections. Recently, massive changes in hygiene and diet have led to remarkable differences in the population and diversity of our microbiomes. Copious animal evidence and an exponentially increasing number of human trials show us that eukaryotic and prokaryotic guests in our guts influence our mental health via immunomodulatory and hormonal mechanisms.

Changes to most important specific brain nutrients can have psychiatric implications. Every few years a new dietary practice (fad) comes into vogue, such as gluten-free diets. Others, such as ketogenic diets, which fell out of fashion, make comebacks into common practice. While the nutrition literature is often contradictory, controversial, and constantly changing, there is now an evidence base to navigate these murky waters.

Link to internet talk:
https://www.youtube.com/watch?v=UO6IcJ4um18&list=PL8YBjoaaAb9OcJI5TDgE-xK0S76HRSORr&index=24&t=26s

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THE ORIGINS OF SLEEP AND MODERN DAY MISMATCHES

Dan Pardi, PhD

Sleep is a mysterious behavior. Its origins, however, may have evolved from a fundamental need of increasingly complex life forms to thrive in their environmental niche: the ability to learn and maximize self-directed fitness based on life experience. Neuron plasticity is an energetically costly process. Sleep provides a stable environment for plasticity to occur, and learning is the result of such dynamic plasticity. [1] Sleep cycles are controlled by genetic, biochemical and light/dark (circadian) signals. [2]

Sleep across primates, including humans, share many similarities. But there are differences, too. For instance, baboons sleep upright and huddle in a group. Their sleep is light and they all scatter with the slightest of disturbance. Orangutans, on the other hand, create “sleeping platforms, which allows for deeper sleep. This deeper sleep in orangutans affects their performance on cognitive performance tasks. Interestingly, when controlling for phylogenetic relatedness between species, humans sleep fewer hours than other primate species, and spend the greatest proportion of sleep in REM sleep. [3]

In hunter-gatherer groups, not everyone sleeps at the same times. [4] The older people tend to be awake during the early morning hours, while the younger people are awake later into the night and sleep later into the morning. Thus, teenagers may be genetically programmed to stay up late and it has been hypothesized that the first adult responsibility for a teenager was to be up at night to watch for dangers to the tribe.

Do current-day hunter-gatherer’s have “better” sleep than humans living in modernized cultures? It’s a challenging question to asses directly from sleep and wake data. The clearest signal from the research available today is that these people living in natural environments have greater circadian amplitude than do many modern humans. Living outside, exposure to natural light across the day, and zero artificial light at night, is likely the strongest mediating influencing in this observation. Perhaps surprisingly, these people living in natural environments don’t actually sleep more than humans living in modern environments. In fact, they sleep on the lower end of the spectrum for what the Natural Sleep Foundations has determined to be a normal range for sleep duration within a 24-hour period. Does this lower end range of natural sleep times mean that they are sleeping in an environment that is less suited for longer sleep or does the totality of their lifestyles somehow confer a reduced sleep need? Are both options simultaneously true? The answers to these questions are not yet known.

Modern sleep patterns are affected by the expanded use of artificial lighting, including digital screens and the work and entertainment delivered through them, shift work, social jetlag, and novel environmental stimuli that can disrupt and influence sleep and it’s timing, such as noise in urban areas. Sleep is challenged in modern life and gleaning a greater understanding of various sleep patterns

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expressed in natural living communities can play a useful role in informing future scientific investigations into how to optimize sleep today.

Link to internet talk:
https://www.youtube.com/watch?v=P4P7IYdby9k&list=PL8YBjoaaAb9OcJI5TDgE-xK0S76HRSORr&index=31

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CIRCADIAN RHYTHM DISRUPTION AS AN EVOLUTIONARY MISMATCH. HEALTH CONSEQUENCES

Angelo Rossiello, Alessio Angeleri, Ethel Cogilani

The Nobel Prize for Medicine and Physiology of 2017 was rewarded to three researchers for their discoveries of molecular mechanisms controlling the circadian clock. Since circadian rhythms regulate a huge variety of physiological processes, a lack of a proper synchronization of internal clocks may be at the root of all modern diseases, from cancer to autoimmune diseases, diabetes, and cardiovascular diseases.

Circadian rhythms appear to be entrained via a central pacemaker in the suprachiasmic nuclei (SCN) in the brainstem. The SCN receives light input from the retina. Light, especially blue light, appears to most strongly stimulate the photoreceptors called intrinsically photosensitive retinal ganglion cells, which then leads to suppression of melatonin production. [1] Human eyes are very sensitive to light, and even small amounts can suppress melatonin production. [2] Melatonin, an endogenous neurohormone derived from tryptophan, thus serves as a molecular “sleep messenger” for the body.

Light pollution is one of the causes of circadian phase shift, and the exposure to light patterns that differ from sunlight in terms of irradiance, spectrum and timing, leads to a reduced and delayed melatonin production. [3] Melatonin is also a powerful antioxidant, and its reduced production and depletion may result in oxidative stress, leading to peroxidation of polyunsaturated fatty acids in the cell membrane, ultimately resulting in tissue damage. Antioxidant depletion can pose a serious threat, especially in modern society, laden with pro-inflammatory and oxidative triggers.

The SCN sends both biochemical and neural signals to tracts in the brain, as well as to other parts of the body. Circadian disruptions may be accompanied by changes to the hypothalamic-pituitary-adrenal axis. The adrenal glands regulate glucocorticoid secretion, with the highest levels being in the early morning hours. Glucocorticoids directly affect both the brain, the immune system and at high levels can lead to hyperglycemia. [4] Additionally, light exposure at night is associated with increases in plasma glucose and insulin. [5] Alterations in glucose and insulin are precursors to diabetes and a key factor in the progression of cardiovascular disease.

Artificial lighting can affect mood and behavior. [6] Inadequate sleep affect both learning abilities and emotional balance. Circadian rhythms disruption can also trigger alterations in intestinal permeability. A protein encoded by the clock gene is a transcriptional regulator of a number of upstream protein complexes that help regulate the circadian clock. Alterations in the complex system can lead to a number of abnormalities. In mice with mutations in this gene exhibit increased intestinal permeability. Light phase shifts in these animals lead to increased lipoprotein saccharide (LPS) production, and LPS

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is widely recognized as an inflammatory marker. LPS can also affect the gut-brain axis. [7] Increased intestinal permeability has been implicated in many of the so-called “diseases of civilization”.

Finally, it is clear that some people are more prone to interruptions in the light/dark cycle. These include some professional categories such as shift workers, nurses, and other medical personnel, intercontinental travellers, children and the elderly. Protocols for managing light exposure, and especially exposure to blue light, may be useful in helping to prevent some of the problems related to chronic circadian rhythm disruption.

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