A 10,000 YEAR OLD RIDDLE OF BREAD AND MILK: SOLVED

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FRUIT AND VEGETABLE WAXES

DERMAL DE-PIGMENTATION IN NORTHERN EUROPEANS

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A 10,000 YEAR OLD RIDDLE OF BREAD AND MILK SOLVED

Most nutrition students know that dietary proteins are not absorbed by the intestines because they are broken down into their component amino acids by enzymes in the gut during the digestive process. Even if dietary proteins escape proteolytic (protein shearing) degradation in the gut, they are normally denied entry into the bloodstream by various gut, liver and immune system barriers. For the past 20 years the pharmaceutical industry has been keenly interested in figuring out a way in which to get intact proteins past the gut barrier and into the bloodstream — and rightly so. A billion dollar market would be instantly opened up to any company that could develop a procedure to transport insulin (a large protein molecule) across the gut barrier without directly injecting it into the bloodstream. An insulin pill would be a diabetic patient’s dream come true. Well guess what? The day in which an insulin pill will become a reality is getting closer. As a Paleo Diet fan, you may be scratching your head and saying, “So-what – why should I be interested in an insulin pill. Shouldn't proper diet and exercise be the preferred approach for treating type 2 diabetics?” You are absolutely correct, but the relevance of the insulin pill for Paleo Diet devotees is not to be necessarily found in the clinical application, but rather in the pathway whereby intact proteins gain access to the bloodstream. This pathway and its nutritional ramifications represent one of the most fascinating and relevant evolutionary tales in all of human history.

LECTINS

Although cereal grains, legumes and dairy foods represent staples for most of the world’s people, these foods were infrequently or never consumed by humans living prior to the advent of agriculture 10,000 years ago. Both cereal grains and legumes are...
rich sources of proteins called lectins. In particular, whole wheat contains the lectin, wheat germ agglutinin (WGA), peanuts contain the lectin, peanut agglutinin (PNA), and kidney beans contain the lectin, phytohemagglutinin (PHA). Because of their sturdy molecular structure, lectins are resistant to the gut’s proteolytic enzymes and have been found fully intact in the guts of both humans and animals. Further, at least two animal studies have demonstrated that dietary WGA and PHA are rapidly transported across the gut wall into systemic circulation. Following consumption of tomato juice, tomato lectin (TL) has also been found in systemic circulation of both rats and humans. More recently, a single study in humans reported the presence of intact PNA in the bloodstream of healthy adults following ingestion of 200g of salted roasted peanuts.

Because of their resistance to digestive enzymes and their ability to rapidly cross the intestinal barrier, lectins have been intently studied by pharmaceutical scientists interested in creating a vehicle for delivering drugs into systemic circulation without the need to directly inject them with a hypodermic needle. Until 2003 it was unknown how lectins could so rapidly cross the gut barrier and enter the systemic circulation. However, recent studies using WGA as a drug delivery vehicle have identified the epidermal growth factor receptor (EGF-R) as the “back door” by which WGA gains entry into gut cells and then into circulation.

**HORMONES AND RECEPTORS**

A hormone is a chemical substance that is secreted into body fluids and transported to another organ or tissue, where it produces a specific effect upon metabolism. Hormones most frequently gain entry into organs and tissues by binding a receptor on the surface of the organ or tissue. You can think about the hormone as a key (referred to as a “ligand”) and the receptor as the lock. If the key fits the lock, then metabolic processes are put into place in organs and tissues which influence their metabolism.

The EGF-R is an unusual receptor in that it is expressed on the inside (luminal side) of the gut rather than on the blood (serosal) facing side. The reason for this anomaly is that saliva contains a hormone, epidermal growth factor (EGF), which binds to the EGF-R. So when you swallow saliva, you swallow a hormone (EGF) which may bind the EGF-R located on the luminal side of the gut. EGF found in saliva facilitates gut healing when it binds the EGF-R.

Since WGA, PHA and PNA, as well as high wheat diets in normal, healthy humans, may cause extensive damage and disruption to the epithelial cells lining the gut, it is likely that these lectins induce gut cells to up regulate (increase) the numbers of EGF-R to facilitate healing. However, the down side of increasing gut EGF-R in the continued presence of dietary lectins in the gut is that it creates a vicious cycle for enhanced lectin entry into these cells, and thence into the systemic circulation.

**WHOLE GRAIN CEREALS AND VITAMIN D METABOLISM**

Nutritional scientists have known forever and a day that excessive consumption of whole grain cereals severely impairs vitamin D metabolism and can lead to the bone disease, rickets. In fact, as far back as 1918, before vitamin D was discovered, a scientist in England by the name of Mellanby routinely induced experimental rickets in puppies by feeding them an oat diet. Epidemiological studies of human populations consuming high levels of unleavened whole grain breads show vitamin D deficiency and rickets to be widespread. A study of radio-labeled vitamin D in humans consuming 60 g of wheat bran daily for 30 days clearly demonstrated an enhanced elimination of vitamin D in the intestines.

**THE EGF-R, WGA AND RICKETS**

Mechanistically, scientists have never really understood why excessive consumption of whole grains, particularly wheat, could cause rickets. However, with the recent discovery that WGA gains access to the systemic circulation by binding the EGF-R in the gut, it became increasingly clear that
WGA and similar whole grain lectins could impair vitamin D metabolism.

Because of its affinity to the EGF-R, WGA circulating in the bloodstream has the capacity to gain entry into any cell expressing the EGF-R. It should be noted that epithelial cells located in skin tissue express the EGF-R. Consequently the keratinocytes within the epidermis, because of their expression of the EGF-R will internalize WGA if it is present in peripheral blood. Keratinocytes are also the site of vitamin D synthesis upon ultraviolet (sunlight) irradiation of 7-dehydrocholesterol in the cell. Once within skin keratinocytes, WGA blocks the nuclear pore,22,23 a structure that normally allows passage of certain cellular hormones and large molecules into the nucleus which then cause gene transcription. In particular, WGA blocks the cellular transport of the vitamin D receptor and its endogenous ligand (vitamin D) to the nucleus24,25 which may result in impaired vitamin D utilization, and systemically increases the risk for rickets.

**NEOLITHIC FOOD INTRODUCTIONS AND RICKETS: EVOLUTIONARY IMPLICATIONS**

The Neolithic (new Stone Age) was the period between 6,000 and 10,000 years ago when Agriculture first began in the Near East and then gradually spread to Northern Europe and elsewhere. As former hunter gatherers adopted a farming way of life, their diets changed rather dramatically. Whereas cereal grains were rarely or never consumed by hunter-gatherers, whole grain emmer wheat and barley became staples as hunter gatherers transitioned into early farmers.4,16 Because whole wheat flour contains sizeable amounts of WGA (30-50 mg/ kg),26 a typical Neolithic farmer could easily have consumed 15-25 mg of WGA per day on a regular basis. High intakes of WGA like these have the potential to severely impair vitamin D metabolism and thereby increase the risk for developing rickets. Although rickets is rarely fatal in children and adolescents, it can cause flattening of the pelvic bones in females which may permanently narrow the birth canal. A rickets-induced, narrowed birth canal would have greatly increased mortality for mother and child during childbirth (27).

In England between the 16th and 18th centuries, the maternal mortality rate was estimated to be 24 to 29 deaths per 1000 births, and many of these deaths were directly attributed to maternal rickets.27 It is likely that maternal mortality would have been higher still under the more primitive birthing conditions during the Neolithic. Hence, the reliance upon whole wheat as a staple food in Neolithic people would have represented a powerful negative evolutionary selective pressure that surely was responsible for millions of deaths over the course of thousands of years.

**PREVALENCE OF LACTASE IN NORTHERN EUROPEANS**

Northern Europeans and their descendants are unusual amongst the world’s peoples in that they maintain the ability to consume cow’s milk without digestive discomfort because their guts produce lactase, the enzyme necessary to digest lactose, the sugar found in milk. Between 70 to 90 % of Northern Europeans maintain the adult lactase persistence (ALP) gene, whereas the presence of ALP in most of the world’s people is much lower, ranging from approximately 3 to 25 % (Figure 1.)28

The standard evolutionary explanation for the presence
of ALP in Northern Europeans is that once they had adopted dairying, selection for the ALP genes allowed lactose in milk to be digested without gastrointestinal disturbances and diarrhea. Consequently, ALP enabled calcium and other nutrients in milk to be readily digested, thereby enhancing nutrition and increasing survival. One of the problems with this explanation is that many of the world’s societies with long histories of dairying, such as the Mongols, the Herero, the Nuer, the Dinka, the Zulu and the Xhosa have low levels of the ALP gene and are generally lactase deficient. These people have taken a behavioral approach to reduce the lactose in milk by consuming it as fermented products (sour milk, kumis, and yogurt) or as cheese. Certainly, Northern Europeans could have taken this approach. So the evidence suggests that the selection for ALP in Northern Europeans must have occurred for reasons other than the additional calcium and food calories found in fermented milk products.

**EXTREME DERMAL DE-PIGMENTATION IN NORTHERN EUROPEANS**

In addition to maintaining a high frequency of ALP, Northern Europeans are unique amongst the world’s people in that they exhibit extreme dermal de-pigmentation. Blond or red hair, very light skin and blue or gray irises are external characteristics that rarely occur together in any other people of the world. The standard evolutionary explanation for extreme dermal de-pigmentation is that Northern Europeans resided at high latitudes where sunlight was seasonally restricted causing impaired vitamin D metabolism. Accordingly, the selection for light skin enhanced vitamin D synthesis during brief periods of sunlight exposure in these high latitude, sunlight compromised people. The problem with this explanation, as has been previously pointed out, is that other world’s people living at similar or higher latitudes have not evolved extreme dermal depigmentation as depicted from the Biasutti map below (Figure 2.)

**PUTTING IT ALL TOGETHER: THE BIGGER PICTURE**

The reason why Northern Europeans evolved extreme dermal de-pigmentation was two fold. First vitamin D metabolism was slightly compromised in these people from reduced sunlight exposure by living at higher latitudes. But more importantly, regular consumption of whole wheat, because of its high WGA content, pushed vitamin D metabolism to the breaking point, likely causing an epidemic of rickets during the Neolithic. Remember that WGA gets into the bloodstream by binding the EGF-R, and then impairs vitamin D metabolism by blocking the nuclear pore, thereby preventing vitamin D from doing its job. So, one evolutionary strategy employed to overcome WGA’s deleterious effect upon vitamin D metabolism was to select genes coding for lighter skin so that more vitamin D could be synthesized during intermittent sunlight exposure.

The second evolutionary strategy taken by natural selection was to reduce or impair the uptake of any WGA that was ingested from wheat. This is where the selection for the adult lactase persistence (ALP) gene comes in. Raw cow’s milk is a rich source of epidermal growth factor (EGF) and contains 325 ng per ml. In contrast, the processing of milk to make fermented milk products will greatly reduce or destroy EGF as it is unstable when exposed to heat, light and acidity. By ingesting raw cow’s milk Neolithic people would be directly dosing themselves with EGF which then could compete with and displace WGA for the EGF-R. Further, EGF from cow’s milk would facilitate gut healing to reduce the number of EGF receptors elicited by the destructive effect of WGA on the gut lining. The net effect of additional EGF from cow’s milk would be to impede entry of WGA into the bloodstream thereby improving vitamin D metabolism, which in turn would reduce the incidence of rickets.

Neolithic individuals bearing the ALP genes would gain selective advantage over those who didn’t have this gene because they could drink EGF containing cow’s milk without gastrointestinal discomfort. Consequently, over...
the course of hundred of generations, there would have been a rapid selection for the ALP genes, not because the calcium and food calories in milk provided crucial nutrition, but rather because the EGF in milk countered the rickets producing effects of WGA from whole wheat consumption. Thus, the extreme dermal depigmentation and high prevalence of the lactase enzyme in Northern Europeans were caused by the same negative selective pressure: high consumption of WGA containing whole wheat. Perhaps there are additional lessons to be learned by us all from this 10,000 year evolutionary experiment in eating whole grains.

FRUIT AND VEGETABLE WAXES: ARE THEY SAFE?

When you visit the produce section of your local supermarket, have you ever noticed the glossy wax that is frequently present on cucumbers and apples, and sometimes on bell peppers and other fruits and vegetables? Have you wondered why these waxes were applied and if they are safe or if they may have any deleterious health effects?

The purpose of fruit and vegetable waxes are fourfold: 1) to reduce shrinkage from water loss, 2) to provide a barrier to gas exchange which prolongs shelf life by simultaneously reducing the oxygen content and increasing the carbon dioxide content of the fruit or vegetable, 3) to improve appearance by

[Figure 2.] THE BIASUTTI MAP DEPICTING SKIN PIGMENTATION IN THE WORLD’S PEOPLES

Figure 2. Variation in human skin color is associated with levels of UV irradiation, which are higher near the equator.

Figure 2., modified from Barsh G.S., PLoS Biol. 1: 019, © 2003 Public Library of Science
adding a shiny film, and 4) to sometimes provide a carrier for fungicides or other chemical agents to prevent microbial decay.\textsuperscript{36-38}

The waxes applied to fruits and vegetables can take on many different formulations incorporating a variety of waxes and other substances. Listed below are five common waxing formulas:\textsuperscript{37}

1) 18.6\% oxidized polyethylene, 3.4\% oleic acid, 2.8\% morpholine, 0.01\% polydimethylsiloxane antifoam  
2) 18.3\% candelilla wax, 2.1\% oleic acid, 2.4\% morpholine, 0.02\% polydimethylsiloxane antifoam  
3) 9.5 \% shellac, 8.3\% carnauba wax, 3.3\% morpholine, 1.7\% oleic acid, 0.17\% ammonia, 0.01\% polydimethylsiloxane antifoam  
4) 19\% shellac, 1.0\% oleic acid, 4.4\% morpholine, 0.3\% ammonia, and 0.01 \% polydimethylsiloxane antifoam  
5) 13.3 \% shellac, 3.0\% whey protein isolate, 3.1\% morpholine, 0.7 \% oleic acid, 0.2\% ammonia, 0.01 \% polydimethylsiloxane antifoam

Note that morpholine is a common element in almost all waxing formulas and is permitted for use in the U.S., Australia, Canada and other countries, but not in Germany. Morpholine’s function is to serve as a solvent and fungicide.\textsuperscript{39,40} Morpholine, by itself, in the doses that are present in fruits and vegetables probably does not constitute a health risk.\textsuperscript{39,40} However, during the digestive process, if there are nitrites simultaneously present, morpholine is chemically changed into N-nitrosomorpholine (NMOR), a potent carcinogen in rodents. The estimated safe lower limit for NMOR is 4.3 \text{ng/kg body weight per day}. It has been estimated that for adults, consuming waxed apples and a mixed diet, NMOR ingestion can approach (3.6 \text{ng/kg body weight}) the lower limit of safety. However, these estimates did not actually measure NMOR formation in humans.\textsuperscript{40} Additionally, nitrite ingestion is quite variable in humans.\textsuperscript{41} Hence, it is entirely possible that chronic consumption of waxed fruit and vegetables containing morpholine could present a slight risk for cancer in certain individuals. Shellac is a common ingredient in many waxes and is derived from the hardened secretion of the lac insect, Laccifer lacca. It has been reported to elicit allergies in some susceptible people, as has carnauba wax.\textsuperscript{36} Waxes generally cannot be removed by regular washing. So if you prefer not to consume waxes, you must buy un-waxed produce or peel the fruit or vegetable.

Fruits and vegetables which are waxed include: apples, avocados, bell peppers, cantaloupes, cucumbers, eggplants, grapefruits, lemons, limes, melons, oranges, parsnips, passion fruit, peaches, pineapples, pumpkins, rutabagas, squash, sweet potatoes, tomatoes, turnips and yucca. Since many of these fruits and vegetables are typically peeled and the peel is not consumed, only a few common fruits and vegetables present a problem.

Until only very recent times, fruits and vegetables were generally harvested when ripe and brought to market without wax coatings. Even today, fruit and vegetables can be harvested, packed, and stored without the use of waxes, and storage life can be extended through careful handling (36).

The relative cancer risk of not eating fresh fruits and vegetables is much greater than the small risk posed by consuming waxed fruits and vegetables. Personally, I prefer my produce wax-free, and as fresh as possible.
**BROILED PORK TENDERLOIN ZESTY RUB**

1 minced garlic clove  
1 Tb. paprika  
1 Tb. dry mustard  
1 Tb. ground coriander  
1 Tb. canola oil  
1 Tb. olive oil  
1 Tb. red wine  
1 pound of very lean pork tenderloin, trimmed of all visible fat

Mix dry spices and garlic in a mortar and pestle – add in the oils and wine to make into a paste. Rub the paste onto the pork one hour before broiling. Broil pork 2 to 3 inches from heat source for about six minutes per side or until it is cooked to desired condition.
SUCCESS STORY

Dr. Cordain,

My name is Jonathon Edward, I’ve corresponded with you via e-mail on many occasions. I just want to let you know how incredibly grateful I am for your research. I own both of your books and have read through all of the research on your site. I’ve been following the plan for well over a year now and have never looked or felt better. Headaches, allergies, and skin problems that used to constantly plague me have vanished and people constantly comment on my “radiant appearance.” The Paleo diet combined with an excellent exercise program (CrossFit) has allowed me to effortlessly optimize my body composition. I’ve stabilized at a lean (single digit body fat)/muscular 160 lb (I’m 5’6). My workout performance continues to increase as well. The benefits have extended to my family as well. In the past couple of months I’ve managed to get my mom and dad on the wagon and they have both experienced enhanced health and vitality. The plan has helped to alleviate aches and pains and is providing a route for my mother to get back to her ideal weight. Both of them are also experiencing higher levels of energy and greater resistance to fatigue. Needless to say, the plan has been a panacea for all involved.

The intention of this e-mail was not to write a testimonial, but I figured you ought to know the impact your research has had on the lives of my family and myself. I am an undergraduate student majoring in Biochemistry and I am seriously considering graduate level work geared toward research in evolutionary diet and medicine. I was wondering if you offer any type of summer internship to bright students interested in Paleo nutrition oriented research? If not, do you have any suggestions? I genuinely would like to start contributing to the field while still an undergraduate.

Last but not least, I am a personal trainer and have been, with great success, implementing the Paleo Diet with all of my clients. Their first homework assignment is to pick up your book and read it cover to cover. After that, I like for them to go to your site, among others, and familiarize themselves with the vast amount of science backing up the plan. The individuals who fully commit themselves to the regimen + the training program I develop, progress toward and reach their goals with unbelievable rapidity. Along the way to reaching their aesthetic and performance goals, they optimize their health and well-being without trying. Your research lends itself to optimized body composition, performance, health, and longevity. Truly amazing! If you care to know, my newly established web site is www.primal-movement.com. The nutrition section of the site is dedicated to the Paleo diet and major kudos are given to you and your work. In the future I’ll be writing various articles outlining how to integrate intermittent fasting into the plan and how to tweak the plan for muscle/strength gain, performance enhancement, and fat loss.

I know that one of your main goals is to disseminate scientifically validated information that will change people’s lives for the better. I want to let you know that you’re accomplishing that goal in the lives of my family, clients, friends, and in my own life. Thanks again.

Regards,

Jonathon
REFERENCES


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