These non-evolutionary food classes carry with them certain health risks with elevated intake, now being traced at the biochemical and genetic levels.

The Late Role of Grains and Legumes in the Human Diet, and Biochemical Evidence of their Evolutionary Discordance

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Introduction: The principle of evolutionary discordance

To set the context for this discussion, let's first briefly recap the basic evolutionary processes to which all species are subject. These principles are fundamental to understanding the repercussions of grains or any other food on the genetics that govern human biology.
• Mutations in genes cause variability in the population-wide genetic makeup of a species.
• Selective pressures due to environment (which includes diet) cause individuals with genetic makeups most suited to that environment to thrive the best under those selective pressures. These individuals achieve better rates of survival and differential reproductive success, thus leaving behind more descendants compared to those without the more advantageous traits.
• This process is iterative (repeats itself) with each generation.
• Thus with repeated generations, the characteristics of organisms in a population become more finely tuned to their environment, which again, includes the diet they habitually eat.
• After a point, assuming environmental factors are not themselves undergoing great change, the population(s) making up a species will tend to reach a point of relative genetic equilibrium. That is, the species' genetic makeup remains fairly stable with a genetic makeup as well-tuned to its environment as it is likely to be, though including some variability due to genetic mutations.
• When or if environmental conditions again change significantly, most individuals in the population experience what can be termed in plain language as "evolutionary discordance"—the negative results of having genes not as well-suited to the new environment (which again includes diet) as the former one. Such discordance results in poorer survival rates and less reproductive fitness for the majority of the population.
• Those individuals whose genetic variability is better suited to the new conditions survive and reproduce better, thus leading to another round of evolutionary/genetic adaptation.
• Such genetic adaptation, however, takes time, that is, many successive iterative generations to achieve. Evolution is conservative, and relatively permanent changes in the genetic makeup of a population do not take place without sustained changes in environment, which—once again, in the context of this paper—includes diet. The time span for relative genetic equilibrium to be reestablished can span many thousands of years for a species (i.e., humans) which reproduces a new generation approximately once each 20 to 25 years.

An appreciation of the above process of how evolutionary change occurs is fundamental to both the science of evolutionary biology itself and can help to elicit a deeper understanding of dietary fitness and health: it is the "how" and "why" that explains the reasons species come to have the nutritional requirements they do. The foods that humanity originally evolved to eat and those we now eat in modern civilization are in many cases significantly different—yet our basic underlying genetic inheritance remains basically the same as it was before, and has evolved only very slightly since then. Thus, many of the foods we now eat are discordant with our genetic inheritance. (This is not simply an idle or "just so" hypothesis. As we proceed, we will look at the considerable clinical evidence supporting this picture.) Such "evolutionary discordance" is a fundamental aspect of the evolutionary equation that governs fitness and survival (in which health plays a key role), which includes the question of the diet humans are evolved to handle best from the genetic standpoint.

To begin with, we will be examining evolutionary discordance from a general standpoint by looking at the mismatch between the characteristics of foods eaten since the "agricultural revolution" that began about 10,000 years ago compared with our genus’ prior two-million-year history as hunter-gatherers. As the article progresses, however, we'll be taking a look at some of the actual genetics involved so it can be seen that "evolutionary discordance" is not merely a theoretical concept but a very real issue with relevance in how diseases can be genetically expressed in response to dietary factors.

With this key concept in mind, let's now begin with a look at the history of grains and legumes in the human diet (quite recent in evolutionary time), after which we'll move on to some of the evolutionarily discordant effects of their consumption on human beings, as seen in modern clinical and genetic studies.

**Evidence for the late evolutionary role of grains in the human diet**

• **Timeframe for cereal grain domestication.** There are 8 major cereal grains which are consumed by modern man (wheat, rye, barley, oats, corn, rice, sorghum, and millet) [Harlan 1992]. Each of these grains were derived from wild precursors whose original ranges were quite localized [Harlan 1992]. Wheat and barley were domesticated only ~10,000 years ago in the Near East; rice was domesticated approximately 7,000 years ago in China, India, and southeast Asia; corn was
domesticated 7,000 years ago in Central and South America; millets were domesticated in Africa 5,000-6,000 years ago; sorghum was domesticated in East Africa 5,000-6,000 years ago; rye was domesticated ~5,000 years ago in southwest Asia; and oats were domesticated ~3,000 years ago in Europe. Consequently, the present-day edible grass seeds simply would have been unavailable to most of mankind until after their domestication because of their limited geographic distribution. Also, the wild version of these grains were much smaller than the domesticated versions and extremely difficult to harvest [Zohary 1969].

How recent in the human evolutionary experience is grain consumption in terms of our total dietary experience? The first member of the human genus, Homo, was Homo habilis who has now been dated to ~2.33 million years ago (MYA) [Kimbel et al. 1996]. Homo erectus, who had postcranial (the rest of the body below the skull) body proportions similar to modern humans, appeared in Africa by about 1.7 MYA and is thought to have left Africa and migrated to Asia by 1 MYA or perhaps even earlier [Larick and Ciochon 1996]. Archaic Homo sapiens (called by some, Homo heidelbergensis) has been dated to 600,000 years ago in Africa and to about 400,000 years ago in Europe or perhaps earlier [De Castro et al. 1997]. Anatomically modern Homo sapiens appear in the fossil record in Africa and the Mideast by about 90,000-110,000 years ago and behaviorally modern H. sapiens are known in the fossil record by ~50,000 years ago in Australia and by about ~40,000 yrs ago in Europe. The so-called "Agricultural Revolution" (primarily the domestication of animals, cereal grains, and legumes) occurred first in the Near East about 10,000 years ago and spread to northern Europe by about 5,000 years ago [Cavalli-Sforza et al. 1993]. The industrial revolution occurred roughly 200 years ago, and the technological revolution which brought us packaged, processed foods is primarily a development that has occurred in the past 100 years and has seen enormous growth in the last 50 years.

To gauge how little geologic or evolutionary time humans have been exposed to foods wrought by the agricultural revolution, let's do a little paper experiment. Take a stack of computer paper (the kind in which each page is connected to one another) and count out 212 eleven-inch (28 cm) pages. The unravel the stack of paper and lay it out end to end--it will form a continuous 194-foot (59 meter) strip. Now, let's assume that 1 inch (2.54 cm) equals 1,000 years in our 194-foot strip of computer paper; thus, the first part of the first page represents the emergence of our genus 2.33 MYA and the last part of the last page represents the present day.

Now, take a slow walk down all 194 feet of the computer paper, and carefully look at each of the individual eleven-inch sections. When you get to the very last eleven-inch section (the 212th section), this represents approximately the beginning of agriculture in the Mideast 10,000 years ago; therefore, during the preceding 211 sheets humanity's foods were derived from wild plants and animals. This little experiment will allow you to fully grasp how recent in the human evolutionary experience are cereal grains (as well as dairy products, salt, and the fatty meats of domesticated animals).

Humans may have indeed eaten these foods for "millennia," but millennia (even 10 millennia) in the overall timeframe of human existence represents 0.4%. Because the estimated amount of genetic change (0.005%) which has occurred in the human genome over this time period is negligible, the genetic makeup of modern man has remained essentially unchanged from that of pre-agricultural man [Eaton et al. 1985]. Consequently, the human genome is most ideally adapted to those foods which were available to pre-agricultural man, namely lean muscle meats, limited fatty organ meats, and wild fruits and vegetables--but, significantly, not grains, legumes, dairy products, or the very high-fat carcasses of modern domesticated animals.

- **Processing technology required.** Clearly, grass seeds have a worldwide distribution and would have been found in most environments that early man would have inhabited. However because
almost all of these seeds are quite small, difficult to harvest, and require substantial processing before consumption (threshing, winnowing, grinding, and cooking), it would have been virtually impossible for pre-behaviorally modern humans (circa 35,000-40,000 years ago) to exploit this food source.

To harvest and process grains on a large scale, sickles, winnowing trays (baskets), threshing sticks, grinding stones, and cooking apparatus are required. There is no reliable evidence to indicate that this combination of technology was ever utilized by hominids until the late Pleistocene. The advent of grinding stones in the Mideast approximately 15,000 years ago heralds the first large-scale evidence of regular cereal grain consumption by our species [Eaton 1992]. There is substantial evidence that certain modern-day hunter-gatherers such as the Australian Aborigine and the American Great Basin Indians utilized grass seeds [Harlan 1992]; however, these grass seeds were not utilized as a staple and represented only a small percentage of the total caloric intake and were eaten for only a few weeks out of the year. For virtually all of the rest of the studied hunter-gatherer populations, cereal grains were not consumed.

• **Optimal foraging theory.** In view of the substantial amount of energy required (as just outlined) to harvest, process, and eat cereal grains, optimal foraging theory suggests that they generally would not be eaten except under conditions of dietary duress [Hawkes et al. 1985]. It seems likely that during the Late Paleolithic and before, when large mammals abounded, our ancestors would almost have never consumed the seeds of grass.

• **Comparison with other foraging primates.** Except for some species of baboons, no primate consumes gramineae (grass) seeds as a part of their regular natural diet. Primates in general evolved in the tropical rainforest in which dicotyledons predominate—consequently monocotyledons (gramineae) would not have been available to our primate ancestors.

• **Primate digestive physiology.** The primate gut is not equipped with the enzyme systems required to derive energy from the specific types of fiber which predominate in gramineae. Consequently, unless cereal grains are milled to break down the cell walls and cooked to crystallize the starch granules (and hence make them more digestible), the proteins and carbohydrates are largely unavailable for absorption and assimilation. Thus, until the advent of regular fire use and control (as evidenced by hearths ~125,000 years ago), it would have been almost virtually energetically impossible for our species to consume cereal grains to supply the bulk of our daily caloric requirements.

• **Repercussions of antinutrient load.** As has been suggested by John Yudkin almost 30 years ago, cereal grains are a relatively recent food for hominids and our physiologies are still adjusting and adapting to their presence. Clearly, no human can live on a diet composed entirely of cereal grains (for one thing they have no vitamin C). However, that is but one consideration, since eating raw cereal grains (as well as cooked cereal grains) wreaks havoc on the primate gut because of the high antinutrient content of grains. When cereal grain calories reach 50% or more of the daily caloric intake, humans suffer severe health consequences. One has to look no further than the severe pellagra epidemics of the late 19th century in America and the beri-beri scourges of southeast Asia to confirm this.

Additionally, in not only human beings, but in virtually every animal model studied (dog, rat, guinea pig, baboon, etc.), high cereal grain consumption promotes and induces rickets and osteomalacia [Robertson 1981; Ewer 1950; Sly 1984; Ford 1972, 1977; MacAuliffe 1976; Hidiroglou 1980; Dagnelie 1990]. Recent research has also implicated zinc deficiency due to the effects of excessive cereal grain consumption in retarding skeletal growth [Reinhold 1971; Halsted 1972; Sandstrom 1987; Golub 1996], including cases of hypogonadal dwarfism seen in modern-day Iran.
The pathologies introduced by higher levels of cereal grain consumption discussed above are due primarily to the effects of phytates in grains, which bind to minerals, preventing adequate uptake. To this point, we haven't even touched upon the other antinutrients which inflict damage on a wide variety of human physiological systems. These antinutrients include protease inhibitors, alkylrescorcinols, alpha-amylose inhibitors, molecular-mimicking proteins, etc. We will look further at these additional problems below. Clearly, however, cereal grains cannot contribute substantial calories to the diet of primates unless they are cooked and processed.

**Digestive considerations and technology required**

**Question:** Granted that grains would not have made up a large portion of the diet. Nevertheless, if people could in some way have comfortably eaten some amount of wild grains without technology, then given the opportunistic nature of human beings, there's not much reason to think they wouldn't have, is there?

**Commentary:** People can put many plant items as well as non-edible items (stones, bones, feathers, cartilage, etc.) into their gastrointestinal tracts by way of putting them into their mouths. The key here is the ability of the GI tract to extract the nutrients (calories, protein, carbohydrate, fat, vitamins, and minerals). Bi-gastric herbivores (those having second stomachs) have evolved an efficient second gut with bacteria that can ferment the fiber found in leaves, shrubs, grasses, and forbs (broad-leaved herbs other than grass) and thereby extract nutrients in an energetically efficient manner. (That is, there is more energy in the food than in the energy required to digest it.) Humans can clearly put grasses and grass seeds into our mouths; however, we do not have a GI tract which can efficiently extract the energy and nutrients.

The starch and hence carbohydrate and protein calories in cereal grains occur inside the cell walls of the grain. Because the cell walls of cereal grains are almost completely resistant to the mechanical and chemical action of the human GI tract, cereal grains have been shown to pass through the entire GI tract and appear intact in the feces [Stephen 1994]. In order to make the nutrients in cereal grains available for digestion, the cell walls must first be broken (by milling) to liberate their contents and then the resultant flour must be cooked. Cooking causes the starch granules in the flour to swell and be disrupted by a process called gelatinization which renders the starch much more accessible to digestion by pancreatic amylase [Stephen 1994]. It has been shown that the protein digestibility of raw rice is only 25% whereas cooking increases it to 65% [Bradbury 1984].

The main cereal grains that humans now eat (wheat, rice, corn, barley, rye, oats, millet, and sorghum) are quite different from their wild, ancestral counterparts from which all were derived in the past 10,000 years. We have deliberately selected for large grains, with minimal chaff, and which are easily harvestable. The wild counterparts of these grains were smaller and difficult to harvest. Further, separation of the chaff from the grain was time-consuming and required fine baskets for the winnowing process. Once the chaff is separated from the grain, the grains have to be milled and the resultant flour cooked. This process is time-consuming and obviously could have only come about in very recent geologic times. Further, the 8 cereal grains now commonly eaten are endemic to very narrow geographic locations and consequently by their geographic isolation would have been unavailable to all but a selected few populations of hominids.

As touched upon previously, the issue of antinutrients in raw cereal grains is a very real issue. There are components in raw cereal grains which wreak absolute havoc with human health and well-being. The primary storage form of phosphorous in cereal grains is phytate, and phytates bind virtually all divalent ions, i.e., minerals for our purposes. Excessive consumption of whole-grain unleavened breads (50-60% of total calories) commonly results in rickets [Robertson 1981; Ewer 1950; Sly 1984; Ford 1972, 1977; MacAuliffe 1976; Hidiroglou 1980; Dagnelie 1990], retarded skeletal growth [Reinhold 1971; Halsted 1972; Sandstrom 1987; Golub 1996] including hypogonadal dwarfism, and iron-deficiency anemia (will provide the references upon request). The main lectin in wheat (wheat germ agglutinin) has catastrophic effects upon the gastrointestinal tract [Pusztai 1993a]. Additionally, the alkylrescorcinols of cereals influence prostanoid tone and induce a more inflammatory profile [Hengtrakul 1991], as well as depressing growth [Sedlet 1984].
Given the barriers to grain consumption that primitive hominids would have faced, who did not possess the more sophisticated technology only seen since about 15,000 years ago, optimal foraging theory, again, strongly suggests any consumption would have been at extremely minimal levels. Given also the lack of adaptation of the human gut to prevent the negative effects of their consumption which are only mitigated (and only partially) by such technology, it is extremely unlikely cereal grains were ever more than a very minute fraction of the human diet until very recent times.

**Genetic changes to the human gut in evolutionary perspective**

**Question:** What evidence is there for the speed at which genetic changes that govern the way the gastrointestinal tract functions can occur? Isn’t there evidence showing that, for example, the genes governing lactose intolerance can be quite rapid in evolutionary terms? What basis is there for believing that the human gut is really the same as that of our hominid ancestors during Paleolithic times?

**Commentary:** There are calculations which estimate how long it took to increase the gene for adult lactase persistence (ALP) in northern Europeans from a pre-agricultural incidence rate of 5% to its present rate of approximately 70% [Aoki 1991]. (Note: The enzyme lactase is required to digest the sugar lactose in milk, and normally is not produced in significant quantity in human beings after weaning.) In order for the gene frequency to increase from 0.05 to 0.70 within the 250 generations which have occurred since the advent of dairying, a selective advantage in excess of 5% may have been required [Aoki 1991].

Therefore, some genetic changes can occur quite rapidly, particularly in polymorphic genes (those with more than one variant of the gene already in existence) with wide variability in their phenotypic expression. ("Phenotypic expression" means the physical characteristic(s) which a gene produces.) Because humans normally maintain lactase activity in their guts until weaning (approximately 4 years of age in modern-day hunter-gatherers), the type of genetic change (neoteny) required for adult lactase maintenance can occur quite rapidly if there is sufficient selective pressure. Maintenance of childlike genetic characteristics (neoteny) is what occurred with the geologically rapid domestication of the dog during the late Pleistocene and Mesolithic [Budiansky 1992].

The complete re-arrangement of gut morphology or evolution of new enzyme systems capable of handling novel food types is quite unlikely to have occurred in humans in the short time period since the advent of agriculture. Some populations have had 500 generations to adapt to the new staple foods of agriculture (cereals, legumes, and dairy) whereas others have had only 1-3 (i.e., Inuit, Amerindians, etc). Because anatomical and physiological studies among and between various racial groups indicate few differences in the basic structure and function of the gut, it is reasonable to assume that there has been insufficient evolutionary experience (500 generations) since the advent of agriculture to create large genetic differences among human populations in their ability to digest and assimilate various foods.

Of the population differences in gastrointestinal function which have been identified, they generally are associated with an increased ability to digest disaccharides (lactose and sucrose) via varying disaccharidase activity. Although insulin metabolism is not a direct component of the gastrointestinal tract, there is substantial evidence to indicate that recently acculturated populations are more prone to hyperinsulinemia and its various clinical manifestations, including non-insulin-dependent diabetes mellitus (NIDDM), obesity, hypertension, coronary heart disease and hyperlipidemia [Brand-Miller and Colagiuri 1994]. It is thought that these abnormalities, collectively referred to as "syndrome X" [Reaven 1994], are the result of a so-called "thrifty gene" [Neel 1962] which some groups have suggested codes for glycogen synthase [Schalin-Jantti 1996]. Consequently, the ability to consume increasing levels of carbohydrate without developing symptoms of syndrome X is likely genetically based and a function of relative time exposure of populations to the higher carbohydrate contents of agriculture [Brand-Miller and Colagiuri 1994].

There are no generally recognized differences in the enzymes required to digest fats or proteins among human populations. Additionally, all human groups regardless of their genetic background have not been
able to overcome the deleterious effects of phytates and other antinutrients in cereal grains and legumes. Iranian populations, Inuit populations, European populations, and Asian populations all suffer from divalent ion (calcium, iron, zinc, etc.) sequestration with excessive (>50% total calories) cereal or legume consumption. All racial groups also have not evolved gut characteristics which allow them to digest the food energy which is potentially available in the major type of fiber contained in cereal grains. Further, most of the antinutrients in cereal grains and legumes (alkylrescorcinols, amylase inhibitors, lectins, protease inhibitors, etc.) wreak their havoc upon human physiologies irrespective of differing genetic backgrounds.

Thus, most of the available evidence supports the notion that except for the evolution of certain disaccharidases and perhaps changes in some genes involving insulin sensitivity, the human gut remains relatively unchanged from paleolithic times.

**Celiac disease as evidence of genetic and evolutionary discordance**

Simoons classic work on the incidence of celiac disease [Simoons 1981] shows that the distribution of the HLA B8 haplotype of the human major histocompatibility complex (MHC) nicely follows the spread of farming from the Mideast to northern Europe. Because there is strong linkage disequilibrium between HLA B8 and the HLA genotypes that are associated with celiac disease, it indicates that those populations who have had the least evolutionary exposure to cereal grains (wheat primarily) have the highest incidence of celiac disease. This genetic argument is perhaps the strongest evidence to support Yudkin's observation that humans are incompletely adapted to the consumption of cereal grains.

Thus, the genetic evidence for human disease (in this case, I have used celiac disease; however, other models of autoimmune disease could have been used) is supported by the archeological evidence which in turn supports the clinical evidence. Thus, the extrapolation of paleodiets has provided important clues to human disease--clues which may have gone unnoticed without the conglomeration of data from many diverse fields (archaeology, nutrition, immunology, genetics, anthropology, and geography).

For a celiac, a healthy diet is definitely cereal-free--why is this so? Perhaps now the evolutionary data is finally helping to solve this conundrum.

**Biotin deficiency and the case of Lindow Man**

Lindow Man, whose preserved body was found in a peat bog in Cheshire, England in 1984, is one of the more extensively studied of the so-called "bog mummies" [Stead, Bourke, and Brothwell 1986]. The principal last meal of Lindow Man likely consisted of a non-leavened whole-meal bread probably made of emmer wheat, spelt wheat, and barley. Unleavened whole-grain breads such as this represented a dietary staple for most of the less-affluent classes during this time. Excessive consumption of unleavened cereal grains negatively impacts a wide variety of physiological functions which ultimately present themselves phenotypically (i.e., via changes in physical form or growth). The well-documented phytates of cereal grains sequester many divalent ions including calcium, zinc, iron, and magnesium, which can impair bone growth and metabolism. Further, there are antinutrients in cereal grains which directly impair vitamin D metabolism [Batchelor 1983; Clement 1987]; and rickets are routinely induced in animal models via consumption of high levels of cereal grains [Sly 1984].

Less well-appreciated are the ability of whole grains to impair biotin metabolism. My colleague, Bruce Watkins [Watkins 1990], as well as others [Blair 1989; Kopinksi 1989], have shown that biotin deficiencies can be induced in animal models by feeding them high levels of wheat, sorghum, and other cereal grains. Biotin-dependent carboxylases are important metabolic pathways of fatty-acid synthesis, and deficiencies severely inhibit the chain-elongation and desaturation of 18:2n6 (linoleate) to 20:4n6 (arachidonic acid). Human dietary supplementation trials with biotin have shown this vitamin to reduce fingernail brittleness and ridging that are associated with deficiencies of this vitamin [Hochman 1993].

Careful examination of the photograph of Lindow's man fingernail (still attached to a phalange of the right hand [Stead 1986, p. 66]) shows the characteristic "ridging" of biotin deficiency. It is likely that regular
daily consumption of high levels (>50% daily calories) of unleavened cereal-grain breads, which Lindow man may have consumed, caused a biotin deficiency, which in turn caused nail ridging.

**Antinutritional properties of legumes**

**Question:** So far we have been discussing grains. What about legumes? Could they have been realistically eaten as a staple by primitive groups without cooking, and if they are natural to the human evolutionary experience, why do they cause gas which indicates fermentation of indigestible products in the gut? If they are not natural for us, how do we account for the !Kung and other primitive groups who eat them?

**Commentary:** As with grain consumption, there are hunter-gatherers who have been documented eating legumes. However, under most cases, the legumes are cooked or the tender, early sprouts eaten raw rather than the mature pod. Some legumes in their raw state are less toxic than others. However, most legumes in their mature state are non-digestible and/or toxic to most mammals when eaten in even moderate quantities. I refer interested readers to:

- Noah ND et al. (1980) "Food poisoning from raw red kidney beans." *Brit Med J*, vol. 2, pp. 236-237; and

These references summarize the basics about legume indigestibility/toxicity; however, there are hundreds if not thousands of citations documenting the antinutritional properties of legumes. Legumes contain a wide variety of antinutrient compounds which influence multiple tissues and systems, and normal cooking procedures do not always eliminate these [Grant 1982]. There are a variety of compounds in beans which cause gas. Mainly, these are the non-digested carbohydrates raffinose, stachyose, and sometimes verbascose, which provide substrate for intestinal microflora to produce flatus [Calloway 1971].

*(The Evolutionary Discordance of Grains and Legumes in the Human Diet--continued, Part B)*

**Starch digestion and alpha-amylase**

**Question:** If it's true that starches such as grains and legumes are a relatively recent addition to the human diet, why then do humans have such an extraordinary ability to secrete the starch-digesting enzyme alpha-amylase, which is present in both saliva and pancreatic secretions? Some biochemists have characterized the level of secretion as "alpha-amylase overkill."

**Commentary:** The highest levels of alpha-amylase occur in the human pancreas followed by the parotid (salivary) glands. The amylase isoenzyme levels in parotid glands are of an order of magnitude less than those in pancreas [Sobiech 1983]. Because starch boluses do not remain in the mouth for more than a few seconds, parotid-derived alpha-amylase has little influence upon immediate starch digestion. Additionally, if the starch is wheat-based, there are endogenous alpha-amylase inhibitors in wheat (also in legumes) which effectively inhibit salivary amylase [O'Donnell 1976]. Further, wheat alpha-amylase inhibitors also influence pancreatic amylase secretion [Buonocore 1977] and have been shown to result in pancreatic hypertrophy in animal models [Macri 1977]. Legume starch contains trypsin inhibitors which inactivate native pancreatic trypsin so as to abnormally increase pancreatic cholecystokinin levels and also cause pancreatic enlargement in animal models [Liener 1994].

The point here is that humans obviously have adequate salivary and pancreatic amylase levels to digest moderate amounts of certain kinds of starch. However, antinutrients in our main starch sources (grains and beans) when consumed in excessive quantities may negatively impact endocrine function.
**Question:** Isn't it true, though, that amylase inhibitors are very heat-labile and denatured by cooking so that they then present little problems in digestion?

**Comment:** Both alpha-amylase inhibitors (in cereals and legumes) and trypsin inhibitors (primarily in legumes) are not fully denatured by normal cooking processes. It is reported, "Protein alpha-amylase inhibitors may represent as much as 1% of wheat flour and, because of their thermostability, they persist through bread-baking, being found in large amounts in the center of loaves." [Buonocore 1977] Further in his treatise on antinutrients, Liener states, "However, because of the necessity of achieving a balance between the amount of heat necessary to destroy the trypsin inhibitors and that which may result in damage to the nutritional or functional properties of the protein, most commercially available edible-grade soybean products retain 5 to 20% of the trypsin inhibitor activity originally present in the raw soybeans from which they were prepared." [Liener 1994]

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**Genetic changes in human populations due to agriculture**

**Question:** What exactly are some of the known genetic differences among populations as a result of the spread of agriculture; what is the timescale for any changes; and what is the evidence?

**Commentary:** It took roughly 5,000 years for agriculture to spread from the Mideast to the far reaches of northern Europe. In this part of the world, agrarian diets were characterized by a cereal staple (wheat or barley early on; later rye and oats), legumes, dairy products, salt, and the flesh of domesticated animals (sheep, goats, cows, and swine). There is strong evidence to suggest that the retention of lactase (the enzyme required to digest lactose in milk) into adulthood is related to the spread of dairying [Simoons 1978]. Most of the world's populations which were not exposed to dairying did not evolve the gene coding for adult lactase retention.

Favism is an acute hemolytic anemia triggered by ingestion of fava beans in genetically susceptible subjects with severe deficiency of glucose-6-phosphate dehydrogenase (G6PD). G6PD deficiency is thought to confer protection against malaria only in those geographic areas where favism exists [Golenser 1983]. A substance in fava beans called isouramil (IU) triggers the hemolytic anemia in G6PD-deficient individuals, and it is this interaction of IU with G6PD erythrocytes which renders these red blood cells incapable of supporting the growth of the malarial pathogen (Plasmodium falciparum). Thus, the spread of agriculture (fava beans in this case) to geographic locations surrounding the Mediterranean was responsible for the selection of G6PD in early farmers.

Celiac disease is an autoimmune disease in which the body's white blood cells (T-lymphocytes) destroy intestinal cells causing malabsorption of many nutrients. The disease is caused by consumption of gliadin (a peptide found in wheat, rye, barley, and possibly oats). Withdrawal of gliadin-containing cereals causes complete remission of the disease symptoms. Only genetically susceptible individuals (certain HLA haplotypes) develop the disease upon consumption of gliadin-containing cereals. There is a geographic gradient of susceptible HLA haplotypes in Europe, with the lowest incidence of susceptible HLA haplotypes in the Mideast and the highest frequency in northern Europe that parallels the spread of agriculture from the Mideast 10,000 years ago. This information is interpreted as showing that agriculture (via wheat, rye, and barley) genetically altered portions of the human immune system [Simoons 1981].

Diseases of insulin resistance, particularly non-insulin-dependent diabetes mellitus (NIDDM) occur in greater frequency in populations that are recently acculturated compared to those with long histories of agriculturally based (high-carbohydrate) diets. It has been hypothesized that insulin resistance in hunter-gatherer populations perhaps is an asset, as it may facilitate consumption of high-animal-based diets [Miller and Colagiuri 1994]; whereas when high-carbohydrate, agrarian-based diets replace traditional hunter-gatherer diets, it (insulin resistance) becomes a liability [Miller and Colagiuri 1994] and promotes NIDDM.

**Question:** What about D'Adamo's ideas that the ABO blood groups correlate with adaptation to different dietary patterns? Type O is said to be the original hunter-gatherer blood type, with Types A
and B having originated more recently in response to agriculture and supposedly being blood types that are more adapted to vegetarian diets.

Commentary: In regard to D'Adamo's ideas concerning ABO blood groups, diet, and disease susceptibility, I suspect that the relationship is significantly more complex than what he has proposed. There are numerous examples in the literature showing an association with blood types and diet-related disease [Hein 1992; Dickey 1994]; however, it is unclear whether a causal relationship is present. It is generally conceded that human blood types have evolved in response to infectious disease [Berger 1989]. Because there are 30 common blood cell surface antigens (groups) in addition to the ABO group, it seems improbable that if blood typing is associated with certain dietary-induced maladies that they would be exclusively a function of only ABO groups. The two references I have cited demonstrate a relationship with Lewis blood types, not ABO.

Consequently, it is more probable that a complex relationship exists between blood cell surface antigens, diet, and disease that likely involves multiple blood-group types. Further, because of the confounding effect of genetic disequilibrium (the associated inheritance of genotypes that do not follow Hardy-Weinberg equilibrium patterns), the relationship may only be serendipitous in nature and not causal as proposed by D'Adamo.

Evidence of genetic discordance as seen in autoimmune diseases

Up to this point, we have only briefly touched upon the role cereal grains have in inducing autoimmune disease (except for a brief look at celiac disease). There is substantial evidence (both epidemiological and clinical) showing the role cereal grains may play in the etiology of such diverse autoimmune diseases as multiple sclerosis (MS), insulin-dependent diabetes mellitus (IDDM), rheumatoid arthritis, sjogrens syndrome, dermatitis herpetiformis, and IgA nephropathy.

Although this proposal may at first seem preposterous, there is strong data to suggest that cereal grains may be involved in all of these diseases through a process of molecular mimicry whereby certain amino acid sequences within specific polypeptides of the gramineae family are homologous to (have the same structural form as) a variety of amino acid sequences in mammalian tissue. These homologous amino-acid (AA) sequences can ultimately confuse our immune systems so that it becomes difficult to recognize "self" from "non-self." When this happens, T-cells, among other immune-system components, launch an autoimmune attack upon a body tissue with AA sequences similar to that of the dietary antigen.

It seems that grass seeds (gramineae) have evolved these proteins with similarity to mammalian tissue to protect themselves from predation by mammals, vertebrates, and even insects. This evolutionary strategy of molecular mimicry to deter predation or to exploit another organism has apparently been with us for hundreds of millions of years and is a quite common evolutionary strategy for viruses and bacteria. It has only been realized since about the mid-1980s [Oldstone 1987] that viruses and bacteria are quite likely to be involved in autoimmune diseases through the process of molecular mimicry. Our research group has put together a review paper compiling the evidence (and the evidence is extensive) implicating cereal grains in the autoimmune process, and with a little bit of luck it should be published during 1998. [Editorial note as of June 1999: The paper has now been published; the citation is: Cordain L (1999) "Cereal grains: humanity's double-edged sword." World Review of Nutrition and Dietetics, vol. 84, pp. 19-73.]

Without the evolutionary template and without the evidence provided us by the anthropological community showing that cereal grains were not part of the human dietary experience, the idea that cereal grains had anything to do with autoimmune disease would probably have never occurred to us. This new electronic medium has allowed instant cross-fertilization of disciplines which probably would have rarely occurred as recently as five years ago.

How peptides in cereal grains may lead to molecular mimicry and autoimmune disease
In the human immune system, there are a number of individual mechanisms which allow the body the ability to determine self from non-self so that foreign proteins (i.e., bacteria, viruses, etc.) can be recognized, destroyed, and eliminated. Perhaps the most complex system which nature and evolution have engineered to accomplish this is the human leucocyte antigen (HLA) system. This system was discovered when early physicians found out that tissue from one human could not be grafted to another without rejection. The physiological function of this system was not to foil the efforts of transplant surgeons, but to initiate an immune response to parasites (viruses, bacteria).

All cells of the body manufacture HLA proteins, whose function is to bind short peptides (protein fragments) and display them on the cell surface. Most of the peptides are derived from the body's own proteins (self-peptides). However, when the body is infected by a virus or bacteria, the HLA molecules pick up peptides derived from broken-down proteins of the virus or bacteria and present them to T-lymphocytes. The purpose of T-lymphocytes is to continually scan the surfaces of other cells to recognize foreign peptides while ignoring self-peptides.

Once a T-cell receptor "recognizes" a foreign peptide, a complex series of steps is set into play which ultimately destroys the cell presenting the foreign peptide as well as living viruses or bacteria in the body which also have peptide sequences similar to those which were presented. When the HLA system loses the ability to recognize self (self-peptides) from non-self (foreign peptides), T-lymphocytes attack self-tissue, resulting in what is known as an autoimmune disease (i.e., celiac disease, IDDM, multiple sclerosis, dermatitis herpetiformis, ankylosing spondylitis, etc.).

The HLA proteins which present foreign peptides to circulating T-lymphocytes are coded by DNA sequences on chromosome 6. The entire HLA system includes more than 100 genes, and occupies a region more than four million base pairs in length which represents 1/3,000 of the total human genome. On chromosome 6, the HLA is sub-divided into Class I (HLA-A, HLA-B, HLA-C) and Class II segments (HLA-DR, HLA-DQ, HLA-DP). Individuals with autoimmune disease inherit characteristic HLA combinations which identify their disease. People with celiac disease have genetic markers (HLA-DR3, HLA-B8, and HLA-DQ2) which are associated with the disease; people with insulin-dependent diabetes mellitus (IDDM) almost always have DQ and DR genotypes. Thus, the manner in which foreign proteins are presented to circulating T-cells by HLA proteins tends to be different for individuals with autoimmune diseases compared to those without these maladies.

As mentioned previously, the incidence of a variety of autoimmune diseases follows a southeasterly gradient from northern Europe (highest incidence) to the Mideast (lowest incidence). This gradient occurs because the incidence of susceptible HLA haplotypes increases as one moves northwesterly from the Mideast. This gradient—which occurs for both the incidence of autoimmune diseases and HLA haplotypes—is not a serendipitous relationship, but occurred as a result of the spread of agriculture from the Mideast to northern Europe [Simoons 1981]. Consequently, as agriculture spread into Europe there were environmental elements associated with this demic expansion ("demic" means the spread of genes through either the migration or interbreeding of populations) which progressively selected against HLA haplotypes (combinations of HLA genes inherited from the two chromosomes in each cell) that were originally present in the pre-agrarian peoples of Europe.

Now, the question is, what were those environmental selective elements? In the case of celiac disease, it doesn't take a rocket scientist to determine that it was wheat. Increasing consumption of wheat caused increased mortality from celiac disease—thus, the incidence of celiac disease and its susceptible HLA haplotypes (HLA-B8, HLA-DQ, HLA-DR) are lowest in those populations with the most chronologic exposure to wheat (Mideasterners and southern Europeans) and greatest in those populations with the least exposure (northern Europeans). Similar arguments can be made for IDDM and a host of other autoimmune diseases. There are a substantial number of animal studies showing that consumption of wheat by rats increases the incidence of IDDM [Scott 1988a; Scott 1988b; Scott 1991; Elliott 1984; Hoofar 1993; Storlien 1996; Am J Physiol 1980;238:E267-E275; Schechter 1983].

How is it that wheat can wreak such havoc with the autoimmune system? Our research group believes that wheat contains peptide sequences which remain undigested and which can enter into systemic circulation.
These peptide sequences are homologous to a wide variety of the body's tissue peptide sequences and hence induce autoimmune disease via the process of molecular mimicry. E.g., macrophages ingest the circulating wheat peptides. HLA molecules within the macrophage then present amino-acid sequences of the fragmented peptide to circulating T-lymphocytes, which through clonal expansion create other T-cells to "attack" the offending dietary antigen and any other self-antigen which has a similar peptide sequence--i.e., the body's own tissues.

The original non-agricultural HLA haplotypes conferred selective advantage in earlier evolutionary times because these genotypes provided enhanced immunity from certain types of infectious diseases. However, with the advent of cereals in the diet they represented a liability. Thus, the genetic data clearly shows that a recently introduced food type has resulted in genetic discordance between our species and those from the gramineae family.

**Possible autoimmune connection between dietary peptides and some forms of autism**

Autism in children is a neuro-developmental disorder characterized by few or no language and imaginative skills, repetitive rocking and self-injurious behavior, and abnormal responses to sensations, people, events, and objects. The cause of the syndrome is unknown, but there is increasing evidence that it may be autoimmune in nature.

Reed Warren's group [Singh 1993] found that 58% of autistic children maintained antibodies to myelin basic protein (a protein found in the myelin sheaths of nerves and suspected of being the target protein [self-antigen] for T-lymphocytes in the autoimmune disease multiple sclerosis). Additional support for the concept that autism may be autoimmune in nature comes from work showing that 46% of autistic children maintain major histocompatibility complex (MHC) alleles associated with the disease [Warren 1996]. The function of the MHC is to present self- and foreign peptides to circulating T-lymphocytes at the surface of all cells throughout the body. Thus, if foreign peptides are presented by the MHC, circulating T-lymphocytes can mount an immune response on the cell or cells that present, via the MHC, those foreign peptides, and destroy them.

The MHC not only presents foreign peptides, but it also presents peptides derived from the proteins of genes comprising the MHC itself. The susceptibility genes for autism are: DRB1*0404, DRB1*0401, and DRB1*0101 [Warren 1996]. In a particular portion of these genes (the third hypervariable region [HVR-3]), there is a common amino-acid sequence shared by all three genes. This amino-acid sequence is either QKRAA (glutamine-lysine-arginine-arginine-alanine-alanine) or QRRAA. Thus, either the QKRAA amino-acid motif or the QRRAA amino-acid motif can be presented to circulating T-lymphocytes. This particular shared epitope increases the susceptibility to a number of autoimmune diseases, including rheumatoid arthritis [Auger 1997]. (An epitope is the part of an antigen recognized by an antigen receptor, i.e., a specific amino acid sequence of a protein.)

The QKRAA or QRRAA amino-acid motif also occurs quite frequently in pathogens which reside in the human gastrointestinal tract including *Escherichia coli*, *Proteus mirabilis*, *Lactobacillus lactis*, *Brucella ovis*, and many other anaerobic gut bacteria [Auger 1997]. The QKRAA or QRRAA sequences are found specifically in a particular type of protein contained in gut bacteria, called DnaJ proteins. DnaJ proteins normally have a bacterial partner/ligand protein called heat-shock proteins (HSP70). It is the QKRAA or QRRAA amino-acid sequence of DnaJ which allows it to bind HSP70.

When the MHC presents endogenously derived DRB1 alleles which contain the QKRAA or QRRAA amino-acid motif, then circulating HSP70 proteins (which normally bind DnaJ proteins) can bind the body's own MHC-presented QKRAA or QRRAA sequences. Circulating CD4+ T-lymphocytes recognize this HSP70/QRRAA sequence as foreign, and mount an immune response on all cells presenting this (HSP70) amino-acid motif.
We believe that myelin basic protein contains an amino-acid sequence that is homologous to an amino-acid sequence found in HSP70, and it is this three-way mimicry between DRB1 peptides, bacterial peptides, and self-peptides which causes self-tolerance to be broken.

So, how does a paleodiet have anything to do with this process? Paleodiets are characterized by their lack of cereal grains, legumes, dairy products, and yeast-containing foods. Both cereal grains and legumes contain glycoproteins (conjugated proteins that have a carbohydrate as the non-protein component) called lectins which bind intestinal epithelial cells and change the permeability characteristics of these intestinal cells [Liener 1986; Puszta1993b]. Not only do these lectins cause an increase of the translocation of gut bacteria to the periphery, they cause an increased overgrowth of gut bacteria as well as a change in the gut flora [Liener 1986; Puszta1993b]. Further, cereal and legume-derived lectins (WGA and PHA respectively) cause increased expression of intracellular adhesion molecules (ICAM) in lymphocytes [Koch 1994] which allows bacterial/immune complexes to move from gut to the affected tissue. Additionally, cereal and legume lectins increase lymphocytic expression of common inflammatory cytokines such as tumor necrosis factor alpha (TNFa), interleukin 1 (IL-1) and IL-6 which are known promoters of autoimmune disease.

The cell walls of cereals and legumes contain a storage protein, GRP 180, which also can act as a ligand to self-presented MHC peptides [Dybwad 1996]. Further, peptides contained in dairy proteins (bovine serum albumins--BSA, among many) also may contain peptide sequences which can interact with endogenously presented peptides [Perez-Maceda 1991]. Cereal, legume, dairy, and yeast-free diets potentially have therapeutic benefit in many autoimmune related disorders via their ability to reduce gut permeability and decrease the exogenous antigenic load both from pathogenic bacteria and from potentially self-mimicking dietary peptides.

**Conclusion**

The study of the evolutionary relationship of diet to health and the repercussions of evolutionary discordance on human biology is still in its infancy. As an interdisciplinary study that depends on the correlation of insights from numerous scientific fields such as archaeology, anthropology, ethnobotany, evolution, biology, genetics, autoimmunity, and clinical nutritional research, its insights have to this point been appreciated only by a relative few.

However, the case of cereal grains and legumes in the diet presents one of the clearest examples where data from these various disciplines is beginning to come together in a way that can be tested and verified by controlled clinical studies. As such it represents an example of the power of the evolutionary approach to provide new directions for research that can give us insights into human diet that may not have been heretofore possible.

Cereal grains are a particularly good example of both the promise and the perils of the evolutionary process--in both its physiological and cultural guises. Without cereal grains as the agricultural base for modern civilizations, it is exceedingly doubtful whether humanity would have developed the culture or the technologies that have led to the accomplishments and scientific insight we now enjoy. Obviously, modest amounts of cereal grains can be a part of the diets of most people with effects that, at least given our current state of knowledge, can be considered negligible.

At the same time, however, to rely on cereals as more than a supplemental part of the diet increases the likelihood they will lead to problems due to their evolutionary discordance. For some people with the "wrong" genetic heritage (even though it may be a very normal aspect of the inherent variability of the human genome), any cereal grains at all are destructive enough--as in the case of celiac disease--that they are simply not an option if such individuals wish to avoid health problems due to their consumption.

As well, with the advent of the young and newly expanding field of autoimmune research, there is increasing recognition of the role that autoimmunity may play in more disease conditions than has perhaps heretofore been thought. Given the potential that peptides in cereal grains have shown for precipitating
autoimmune dysfunction, it may be that linkages with further disease conditions will be discovered as time goes on, which is cause for concern and points to the need for more intensive research in this area.

I hope you have enjoyed our look at this example of the power of the interdisciplinary approach employed in the field of paleolithic diet to bring new insights to the study of human diet and uncover compelling new areas for nutritional research.

--Loren Cordain, Ph.D.

For further Paleodiet research from Dr. Cordain, you can download printable PDFs of his research group's peer-reviewed papers (more than 20 at last count) at his website, plus get information about his 2002 book, The Paleo Diet.

REFERENCES


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