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Evolutionary Medicine: New Avenues of Research on Sugar

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Abstract

This article may open new avenues of research on sugar (sucrose), because it challenges experts in clinical nutrition by questioning two deep-rooted medical tenets that stigmatize sugar in the media. The first entrenched medical tenet claims that the metabolic effects of sugar depend on its ingested quantity, regardless of its form of ingestion, which accordingly is omitted in many experimental studies on sugar. In sharp contrast, evolutionary medicine stresses that concentrated sugar is harmful because it is nonexistent in nature, but diluted sugar is harmless because it is the most abundant carbohydrate of fresh fruit, which was the main food of our prehistoric ancestors for tens of millions of years. Consequently, fruit shaped genetically their metabolic physiology. Thanks to evolutionarily conserved physiological traits adapted to fresh fruit, our absorption of diluted sugar is harmlessly "linear", i.e., slow and calorie-constant within the caloric range of fruit. Above this range, our absorption of concentrated sugar is harmfully "exponential", i.e., precipitous. The second ingrained medical tenet claims that the quantity of sugar in sugar-sweetened beverages explains the reported association between their intake and some diseases. By contrast, evolutionary medicine emphasizes that this association reflects primarily the neglected metabolic effects of dietary salt, which was unknown for the 99.99% of our evolutionary existence. Salt unnaturally accelerates the absorption of sugar-sweetened beverages when they are ingested together with salt-containing foods, as generally occurs. By passing partly into those beverages, salt abnormally turns the linear harmless absorption of diluted sugar into a virtually exponential harmful absorption.

Keywords: Absorption; Diabetes; Dietary salt; Evolutionary medicine; Fruit; Gastric emptying; Potassium; Sucrose; Sugar; Sugar-sweetened beverages

Introduction

In the book *The Origin of Species*, which "is the most radical reconfiguration of our place in the universe as individuals and as a single species" [1], Charles Darwin advanced his theory of evolution by natural selection, "the single best idea anyone has ever had" [2] (p. 289). Since 1859 when that book first appeared, "many tens of thousands of scientific research papers confirming the legitimacy of Darwinian natural selection have been published" [3]. Consequently, "Darwin's work on natural selection and the evolution of species is no longer a theory; rather it is a law of primary importance to contemporary biology and medicine" [3]. Indeed, "evolution is the unifying concept of biology and the basis for all modern biological research, including much research that affects our daily lives" [4]. Not only our daily lives, but also our daily meals may be affected by future research based on evolution, if an untested evolutionary hypothesis will prove right experimentally. This hypothesis was first advanced in 1997 [5], underpinned another evolutionary hypothesis [6,7], and was invoked in critiques [8-10]. Its complete version, including a proposed dietary trial to test it, appeared in 2004 [11]. This hypothesis argues that the impact of sugar on human health reflects its form of ingestion, not its ingested quantity. Ergo, this hypothesis (thereinafter: the "sugar form" hypothesis), contrasts strikingly with the inveterate medical tenet that resulted in the failure of tens of authors and coauthors to specify the forms of ingestion of sugar in their experimental studies on sugar [12-22].

Importantly, "evolutionary theorizing points to hypotheses that we otherwise might not even think of" [23] (p. 642). One of them is the "sugar form" hypothesis. Although 16 years have elapsed since its published extensive discussion [11], hitherto no researcher tested it, perhaps because "research funders are mainly concerned with practical factual research, not with research that develops theories … But theories are at the heart of practice, planning, and research … Because theories powerfully influence how evidence is collected, analyzed, understood, and used, it is practical and scientific to examine them" [24] (p. 1007). Moreover, a "new theory may lead to new experiments that herald the downfall of the old dogma" [25] (p. 845). This may greatly benefit humankind by fostering progress, because "sciencemoves forward when orthodoxy is challenged" [26] (p. 15) and "science is unique among all human activities unlike law, business, art, or religion in its identification with pro-

gress" [27].

This article aims primarily at emphasizing the scientific need to test experimentally the "sugar form" hypothesis, because "the issue of dietary sucrose must assume a prominent role in the discussion of the dietary treatment of diabetes" [28] (p. 62), which "is becoming the plague of the 21st century" [29]. This implies that the need to fund and perform the unprecedented study to test the "sugar form" hypothesis is urgent, because its potentially enlightening findings may revolutionize both the dietary treatment of diabetes and the prevention of this plague. As argued elsewhere [11], the "sugar form" hypothesis can easily be tested by an unprecedented dietary trial aimed at comparing the metabolic effects of, say, 100 g/day of concentrated sugar with the effects of 100 g/day of diluted sugar. All evolutionary considerations are omitted purposely in the first part of this article, because "current funding mechanisms reinforce a disjunction between evolutionary biology and medical science and make the development of research programs at their intersection problematic. The National Science Foundation and the National Institutes of Health each currently see this area as outside their respective domains" [30] (p. 1694). Thus, to make the funding of that urgent research less problematic, here the reasons for doing it are discussed in non-evolutionary terms. Only later will the physiological reasons be interpreted in evolutionary perspective.

Current Status of Knowledge

Many "discrepancies between studies" [31] (p. 251S) characterize the research on sugar. For example, "several authors have reported no change in plasma cholesterol in response to sucrose, even when sucrose was given as a very high proportion of the diet (11%-65% of energy) … In contrast, in other studies, plasma cholesterol concentrations were observed to rise in response to sucrose consumption within a broad range (18%-52% of energy)" [31] (p. 251S). Moreover, some authors wrote "there is evidence from several well-controlled prospective studies demonstrating that the consumption of moderate amounts of sucrose may result in hyperglycemia, hyperinsulinemia, hypertriglyceridemia, hypercholesterolemia, and reduced high-density lipoprotein cholesterol concentrations. The fact that not all studies demonstrate these deleterious effects does not negate the positive data" [28] (p. 62). These conflicting results originated "considerable debate concerning the effects of sucrose on plasma lipids and in particular triglyceride levels" [32] (p. 498). Discrepancies between studies also regard the effects of sugar on glycemic control. Indeed, "studies that have examined the addition of sucrose to the diet of noninsulin-dependent diabetes mellitus (NIDDM) subjects for periods of 2-6 wk have produced conflicting results" [33] (p. 474). These originated discrepant medical guidelines. Indeed, their recommended ingestion of sugar ranges conflictingly from 5% to 25% of energy requirement [34].

Comparative Reasons for Testing the "Sugar Form" Hypothesis

The abovementioned experimental inconsistencies are explainable by comparing the findings of the few studies that administered sugar in a single form and chose to specify it. This comparison reveals that diluted sugar is harmless and concentrated sugar is harmful. Here the terms "diluted" and "concentrated", for physiological reasons discussed below, refer to sugar within 1.08 kcal/ml and to sugar above this density, respectively. After administering sugar solely in a liquid diet [35], some researchers wrote "the feeding of 80% of calories as sucrose did not lead to an impairment of the GTT [glucose tolerance test] in any subject" [35] (p. 600). Conversely, after administering only 30% of calories as sucrose patties [36], other researchers wrote "sucrose feeding produces undesirable changes in several of the parameters associated with glucose tolerance" [36] (p. 2206). The virtually opposite effects of diluted sugar [35] and concentrated sugar [36] are in keeping with the observation that "diabetes was absent in cane cutters who atelarge amounts of sugar by chewing cane, but common in their employers who ate large amounts as refined sugar" [37] (p. 62). However, sugar contained in cane is always in a naturally diluted form, whereas refined sugar often is ingested in concentrated forms.

Another comparative example emerges from the results of two studies [38,39] that used different forms for administering an almost identical quantity of sugar. After administering 220 g/day of sugar mainly in "a specially prepared sweetened beverage" [38] (p. 194), some researchers concluded that sugar "did not affect glycemic or triglyceridemic control in type II diabetic patients" [38] (p. 193). Conversely, after administering 210 g/day of sugar as "a sucrose patty" [39] (p. 1661), other researchers wrote "total serum lipids, triglycerides, and total cholesterol levels were significantly higher when the subjects consumed the sucrose diet" [39] (p. 1659).

Physiological Reasons for Testing the "Sugar Form" Hypothesis

Physiologically, "gastric emptying is a major factor in blood glucose homeostasis, in normal subjects and in patients with diabetes" [40] (p. 857). Indeed, "the rate of gastric emptying is an important determinant of carbohydrate absorption" [41] (p. 79). Actually, "it is the rate of absorption of nutrients by the small intestine that is the most important factor in controlling gastric emptying" [42] (p. 2025). The following physiological data explain why diluted sugar is harmless and concentrated sugar is harmful:

1. Diluted glucose and diluted sucrose, which is a mixture of glucose and fructose [43], empty identically from the stomach [43]. Indeed, "the effects of sucrose and a glucose and fructose mixture … are indistinguishable … in slowing gastric emptying" [43] (p. 323-4). This identical gastric emptying reflects the identical caloric density of diluted sugar and diluted glucose, because "the rate of gastric emptying is a function of the caloric density of the ingested meal" [44] (p. 553).

2. In humans and in monkeys, the gastric emptying

of diluted glucose is "linear", i.e., it is "a slow and calorie-constant emptying pattern" [45] (p. 76), which proceeds "progressively more slowly with increasing concentrations" [46] (p. R254), thereby determining the absorption of a constant quantity of calories per unit time [45,46]. Indeed, "glucose empties so as to maintain a constant rate of delivery of calories to the small intestine over a range of energy densities of 0.2-1.0 kcal/ml" [46] (p. R256). Consequently, "although gastric emptying slowed as glucose concentration increased, when gastric emptying was expressedas the rate of calories delivered to the intestine, all three glucose solutions emptied at indistinguishable rates" [45] (p. 78).

3. Within the range 0.2-1.0 kcal/ml, "doubling the volume of a glucose meal does not significantly alter the rate of emptying" [46] (p. R256), so that "the number of glucose calories passed per unit time (2.13 kcal/min) remained the same over a fivefold concentration range" [45] (p. 78). Within this range (0.2-1.0 kcal/ml), "such constancy suggests in humans, as in the monkey, that glucose emptying differs from the emptying of physiological saline in being subject to tight regulation" [45] (p. 80).

4. In sharp contrast with the calorie-constant emptying pattern of diluted glucose, the gastric emptying of concentrated glucose is "exponential", i.e., precipitous and massive. Indeed, "when glucose concentration exceeds 1.0 kcal/ml, gastric emptying does not slow further. As a result with each increment in concentration above 1.0 kcal/ml, there is more rapid delivery of calories to the small bowel, i.e., a loss of regulation to caloric concentration" [46] (p. R256). More precisely, this loss of regulation occurs at a currently indefinite concentration between 1.08 kcal/ml and 1.33 kcal/ml. Indeed, although "extremely prolonged" [47] (p. 379), the gastric emptying of glucose solutions is still linear "after ingestion of the 400-kcal glucose (100 g in 300 cc H_2O) solution" [47] (p. 378), which contains 1.08 kcal/ml, but their gastric emptying is exponential when their density is 1.33 kcal/ml [46].

The abovementioned physiological data show that diluted sugar proved harmless [35,38] because its absorption was linearly slow and calorie-constant, thereby preserving blood glucose homeostasis. Conversely, concentrated sugar proved harmful [36,39] because its absorption was exponentially precipitous and massive, thereby compromising blood glucose homeostasis and enhancing abnormally the endogenous production of blood lipids. Remarkably, those data corroborate the central notion of the "sugar form" hypothesis, namely, the concept that the form of ingestion of sugar is metabolically more important than its ingested quantity [11]. Indeed, the absorption of diluted glucose, which empties identically to diluted sucrose [43], remains linear even doubling its ingested quantity [46] but becomes exponential when its density increases even moderately from 1.08 kcal/ml [47] to 1.33 kcal/ml [46].

Should the "sugar form" hypothesis prove right experimentally, its practical and clinical implications will be far-reaching. For instance, the failure to disentangle the effects of diluted sugar from those of concentrated sugar will presumably originate a reanalysis of a recent investigation [48] that raised several comments [49-54]. Its conclusion that there is "a significant relationship between added sugar consumption and increased risk for CVD [cardiovascular disease] mortality" [48] (p. 516) will sound misleading should future studies demonstrate that the metabolic effects of sugar depend on its form of ingestion, not on its ingested quantity.

Heuristic Ability of Evolutionary Medicine

Some authors wondered: "why do meals of high caloric concentrations empty more slowly in volume but just slowly enough as to deliver the same number of calories over time as more dilute meals?" [55] (p. R413). This question can be answered thanks to the heuristic ability of Evolutionary Medicine (thereinafter: EvolMed) [56-58], which is a relatively "new, interdisciplinary field that brings together physicians, biologists, anthropologists, psychologists, and others to address questions about the evolutionary origins of many medical problems facing modern humans" [58] (p. 99). EvolMed "is supplanting its predecessor synonym "Darwinian medicine"" [59] (p. 1), which was preferred previously [60-64]. The fundamental concept of EvolMed is that "medicine needs evolution" [65], because "nothing in medicine makes sense except in the light of evolution" [66,67].

Thanks to its heuristic ability and explanatory capacity, "evolutionary thinking on medical issues can sometimes illuminate features quite unexpected by nonevolutionary approaches" [30] (p. 1691). For example, "evolution does offer a way to ground the otherwise faddish area of nutrition research in a solid general understanding of the diets of our ancestors" [68] (p. 40). EvolMed argues that their diets represent "the nutrition for which human beings are in essence genetically programmed" [69] (p. 283).

Indeed, "the introduction of agriculture and animal husbandry ~10000 y ago occurred too recently on an evolutionary time scale for the human genome to adjust" [70] (p. 341). Therefore, "genetically speaking, humans today live in a nutritional environment that differs from that for which our genetic constitution was selected" [71] (p. S10). Consequently, "from a genetic standpoint, humans living today are Stone Age hunter-gatherers" [72] (p. 739), whose dietary requirements "were met exclusively by uncultivated vegetables and wild game" [73] (p. 591). Of note, "wild animals hunted for prey as food do not accumulate the high percentage of fat seen in domesticated pigs, sheep, or cattle" [74] (p. 914). Also, "since they had no domesticated animals, Stone Age people had no dairy products whatsoever after they were weaned" [75] (p. 816). Ergo, "the genetically ordered physiology of contemporary humans was selected over eons of evolutionary experience for a nutritional pattern affording much less fat" [75] (p. 814). Indeed, "the fat intake in late Paleolithic diets was estimated to be ~10%-20% of calories" [76] (p. 202).

There is "evidence that men with familial hypercholester-

olemia can avoid early coronary death" [77], simply "by strictly adhering to a low-fat diet without drugs" [77] (p. 224). This indirectly explains why "migration studies have clearly shown that the change from a low-fat diet (15% of energy as fat) to a diet similar to that usually consumed in the United States (37% of energy as fat) is associated with 20% higher body weight, 20% higher plasma cholesterol levels, and a three-fold higher incidence of coronary heart disease mortality" [78] (p. 1454). This disease is one of the undesirable conditions that "are virtually unknown among the few surviving hunter gatherer populations whose way of life and eating habits most closely resemble those of preagricultural human beings" [69] (p. 283).

The first 10 experimental studies on the Paleolithic diet were published between 2007 and 2015 [79-88]. All of them demonstrate its beneficial effects, as many papers based on EvolMed had heuristically predicted before 2007 [69,72,89-112]. A recent systematic review and meta-analysis [113] concluded that "the Paleolithic diet resulted in greater short-term improvements in metabolic syndrome components than did guideline-based control diets" [113] (p. 922).

Evolutionarily Conserved Physiological Traits

EvolMed recalls that "humans are not self-made creations dietarily, but rather have an evolutionary history as anthropoid primates stretching back more than 25 million years, a history that shaped their nutrient requirements and digestive physiology well before they were humans or even protohumans. In hominoids, features such as nutrient requirements and digestive physiology appear to be genetically conservative and probably were little affected by the hunter-gatherer phase of human existence" [114] (p. 665). Accordingly, EvolMed argues that the linear absorption of diluted sugars is an evolutionarily conserved physiological trait that was selected well before the existence of Paleolithic humans. EvolMed can explain that linear absorption because its "evolutionary perspective fundamentally challenges the prevalent but fundamentally incorrect metaphor of the body as a machine designed by an engineer" [68] (p. 28). Indeed, "bodies are not designed; they are shaped by natural selection" [68] (p. 42). The evolutionary genetic molding of bodies occurs because "natural selection tends to increase the frequencies of alleles of individuals that survive and reproduce better than others in specific environments" [115] (p. 1800). Hence, these individuals are selectively "better adapted to their environments" [115] (p. 1800).

We should bear in mind that "one of the most important influences affecting genetic selection and adaptation is the interaction between a species and its food supply" [75] (p. 814). Consequently, "available food shapes all species, and we were shaped by the fruit of the tree" [116] (p. 737), because "during the Miocene era (from about 24 to about 5 million years ago) fruits appear to have been the main dietary constituent for hominids" [69] (p. 284). Indeed, "early hominids ate fleshy fruits" [117] (p. 368), and "the known early Miocene hominoids … probably had diets consisting largely of fruit" [118] (p. 630). We should also remember that "modern humans and chimpanzees diverged from a common ancestor who was chimp-like, forest-dwelling, and predominantly arboreal and fruit-eating between 5 and 8 Myr [million years] ago" [119] (p. 219). Anthropoids is "the group of higher primates that includes humans as well as monkeys and apes" [120] (p. 1516). These latter species of nonhuman primates still live on fruits. Notably, "the anthropoid lineage may have emerged as many as 50 million or even 60 million years ago" [120] (p. 1516). Evolutionarily, "inside we're all primate, equipped with the instinctive and anatomical arrangements for eating mainly fruit" [116](p. 737). Indeed, "our eating instincts, and our bodies that receive the food, were unalterably moulded during those 50 million years in the trees" [116] (p. 738). This corroborates the suggestion that "scenarists of hominid evolution wouldbe wise to pay more attention to arboreal lodging behavior in nonhuman primates because the reliance on trees was part of the hominid adaptive complex during much of our ancestry" [121].

Regarding the physiological data discussed above, "physiologists are interested in how organisms work. A subset of physiologists also wants to know why organisms are designed to work in particular ways. Unless one assumes special creation of all organisms, an understanding of such why questions requires an evolutionary perspective" [122] (p. 581). Accordingly, EvolMed explains that the linearly slow and calorie-constant absorption of diluted sugars constitutes an optimal adaptation to fresh fruits. This adaptation is really optimal because it preserves the blood glucose homeostasis of primates living on fresh fruits, which precisely contain mainly diluted sugars [123-125]. Fresh fruits are virtually "solid juices", because their solidity is due only to their tiny quantity of fiber. For instance, "the total fiber (unavailable carbohydrate and lignin) content of apples is only about 1.5% by weight, but this fiber is wholly responsible for the solidity of apples" [126] (p. 679). Moreover, "as the time after ingestion of a solid meal increases it becomes a suspension of solid particles mixed with gastric secretions and thus comes to resemble a viscous liquid mixture rather than a solid meal" [127] (p. S11).

Some authors "postulated that, with fiber-depleted foods, there is abnormally rapid absorption of carbohydrate and hence excessive stimulation of insulin secretion, which could lead eventually to diabetes" [126] (p. 679). However, "with grapes, the insulin response to the whole fruit was, paradoxically, more than that to the juice" [128] (p. 211). Nonetheless, it is true that the juices of other fruits, such as apples [126] and oranges [128,129], are slightly more insulinogenic than the whole fruits [126,128,129]. However, this difference, which may well reflect a somewhat slower absorption of the sugars from the whole fruits, cannot be of clinical importance in the prevention of diabetes. Indeed, the linearly slow and calorie-constant absorption of such fiber-free foods as glucose solutions [45-47] is already regulatory enough to prevent any diabetogenic disruption of

blood glucose homeostasis.

The range 0.2-1.08 kcal/ml [45-47] within which our absorption of sugars is linear virtually overlaps the caloric range of the solutions of sugars present in fresh fruits [123-125]. This further confirms that fresh fruits shaped our metabolic physiology of sugars. The "loss of regulation to caloric concentration" [46] (p. R256) of glucose solutions exceeding the caloric range of sugars present in fresh fruits suggests that concentrated sugars are "genetically unknown foods" [6,7]. One might object that our prehistoric ancestors also ingested such concentrated sugars as honey and dried fruits. Before apiculture, however, honey was rare and guarded by bees. Dried fruits were virtually nonexistent in the "relatively heavily wooded habitats" [117] (p. 368) of early African hominids, because of the frequent tropical-equatorial rains and the shade of those tick forests. Ergo, the ingestion of dense sugars was not frequent and abundant enough to produce a genetic adaptation similar to that originated by the daily and large ingestions of fresh fruits. This ancestral adaptation also explains why a diet rich in fresh fruits is beneficial to contemporary humans [130-137].

Sugar Sweetened Beverages (SSBs)

The intake of SSBs has frequently been associated with diabetes [138-142], metabolic syndrome [143-146], and cardiovascular disease [147-154]. Besides being linked to these diseases, the intake of SSBs is also associated with weight gain [155-162] and obesity [163-168]. Obesityin itself is not a disease but "is a risk factor for chronic diseases and premature mortality" [169] (p. 89), because it "is an independent predictor of clinical CVD" [170] (p. 1156), and "predisposes to non-insulin dependent diabetes mellitus, hypertension, dyslipidemia, cholelithiasis, some malignancies and osteoarthritis" [171] (p. 360). The association of SSBs intake with those diseases and unwanted conditions is currently attributed to the "large quantities of easily absorbable sugars" [141] (p. 1325) present in SSBs. Indeed, this attribution, although paraphrased with substantially similar words, has been expressed by others, who wrote that SSBs are harmful because they "contain large amounts of rapidly resorbed carbohydrates" [142] (p. 6), and because of their "high content of rapidly absorbable carbohydrates" [146] (p. 2477). Notably, the adverb "rapidly" betrays the failure to realize that the absorption of diluted sugars, such as those of SSBs, is actually "slow and calorie constant" [45] (p. 76).

The deep-seated medical tenet attributing the harmfulness of SSBs to their quantity of sugar stigmatizes sugar and implicitly blames their heavy consumers. That settled tenet seems to disprove the "sugar form" hypothesis. Indeed, "the sugar content of colas, soft drinks, fruit punches, 100% fruit juices, and liquid shakes is ~10–12 g/100 g" [172] (p. 658). Since sugar provides 4 kcal/g, one can easily calculate that all of those beverages are far from exceeding 1.08 kcal/ml, which is the safety limit of sugar, according to the "sugar form" hypothesis. EvolMed once again demonstrates its heuristic ability by enabling us to realize that the quantity of sugar contained in SSBs is not responsible for their harmful effects. These damages are due to two neglected nutritional factors. We can detect them only thanks to the "maieutic" art that allows EvolMed to display its heuristic ability. This art derives its metaphorical meaning from the Greek words "μαιευτική τέχνη" (maieutiké téchne, i.e., obstetric art). The Greek philosopher Socrates used this art "to stimulate critical thinking and expose faulty reasoning through a series of questions and responses" [173] (p. 538), which eventually delivered philosophical "truths". Likewise, EvolMed raises three questions to identify the real culprits of the harmful effects misattributed to the quantity of sugar present in SSBs.

Lack of Potassium Makes SSBs Harmful

EvolMed poses this first maieutic question "Can we attribute the harmfulness of SSBs to their quantity of sucrose? Reason forces us to answer negatively. In fresh fruits, sucrose is generally the most abundant carbohydrate and its quantity often exceeds that of the other sugars combined [123-125]. Examples: 100 g of ripe banana contain 9.64 g of sucrose, 2.26 g of glucose, and 0.02 g of fructose [124]; 538 g of oranges contain 26.3 g of sucrose, 11.8 g of glucose, and 12.4 g of fructose [123]. Ergo, it is clear that our prehistoric ancestors living on fresh fruits ate sucrose in quantities exceeding those ingested by heavy consumers of SSBs. If we attribute the harmfulness of SSBs to their quantity of sucrose, then the untenable implication is that our remote ancestors were severely harmed by their main foods. Many nutritionists could object that SSBs are harmful because they contain added sugar, whereas fresh fruits are harmless because they contain naturally-occurring sugar. However, "there is often no difference in responses between foods containing added sugars and those containing naturally-occurring sugars" [174] (p. 613). This reflects the fact that "the classification of natural and added sugars is not very instructive because they are indistinguishable in metabolism or chemical composition" [175] (p. 1486).

Other nutritionists discriminate "intrinsic" sugars from "extrinsic" sugars [176]. However, "such a classification of sugars was not based on scientific research and it remains impossible to distinguish between intrinsic and extrinsic sugars using any form of chemical analysis" [176] (p. 503).

A physical analysis, however, reveals that naturally-occurring and intrinsic sugars are always ingested in naturally diluted forms. Conversely, added and extrinsic sugars can be ingested in concentrated forms, too. Therefore, only the evolutionary discrimination between diluted sugars and concentrated sugars is clinically useful.

Both the absorption of diluted sugar of SSBs and the absorption of solutions of sugar present in fruits are linearly slow and calorie-constant. However, SSBs are harmful, whereas those solutions are harmless. Hence, EvolMed poses this second maieutic question: What differentiates metabolically SSBs from the sugar solutions of fruits? Lack of potassium (K) is the answer. K has been defined "a non-celebrity cation" [177], because its medical importance is generally neglected. SSBs, being solutions of re-

fined sugar, do not contain K, whereas fresh fruits are rich in K [178]. This abundance of K in their main foods explains why early humans "became exceedingly well adapted to this very high-K diet. Such a diet could be considered the "natural" diet of humans" [179] (p. 273). In view of the various benefits of K [180-187], it is arguable that K largely explains the benefits of fresh fruits [130-137]. Indeed, "fruits and vegetables have been associated with a benefit to bone health. Potassium levels in fruits and vegetables have been a leading candidate for this benefit" [180] (p. 371S). Furthermore, "higher dietary potassium intake is associated with lower rates of stroke and might also reduce the risk of CHD [coronary heart disease] and total CVD" [181] (p. 1210). Unsurprisingly, "cardiovascular as well as total mortality was significantly lower among men with high fruit consumption" [137] (p. 337). Moreover, many independent studies show that potassium protects against cancer [185]. K may well explain why "a diet that includes four or five fruits or vegetables per day substantially reduces the incidence of many types of cancers" [186]. The view that K largely explains the benefits of fresh fruits is further strengthened by the conclusion that "a low daily dietary supplement of K, equivalent to the content of five portions of fresh fruits and vegetables, induced a substantial reduction in MAP [mean arterial pressure], similar in effect to single-drug therapy for hypertension" [187] (p. 53).

EvolMed argues that the high content of K dissolved in fresh fruits played a central role in their ancestral shaping effects on our metabolic physiology of sugars. Hence, EvolMed predicts that a lack of K may compromise our metabolic responses to sugars. As an additional confirmation that EvolMed possesses remarkable heuristic abilities, "a large body of experimental evidence indicates that potassium deficiency leads to deterioration of carbohydrate tolerance" [188] (p. 1138). Indeed, "potassium depletion causes glucose intolerance, which is associated with impaired insulin secretion" [189] (p. 498). Predictably, "potassium supplementation during a 2-week fast was associated with a statistically significant improvement in GTT" [190] (p. 1592). Thus, EvolMed surmises that the enormous quantities of diluted sucrose (80% of calories) that produced a "significant improvement in the oral GTT" [35] (p. 604) were supplemented with K. Indeed, those large amounts of diluted sugar were ingested in a liquid diet "supplemented with vitamins and minerals" [35] (p. 600), which were unspecified but intuitively included K.

Many foods contain adequate K, thereby making glucose intolerance caused by K depletion improbable in moderate consumers of SSBs. However, to prevent glucose intolerance in persons whose caloric intake derives mainly from SSBs, EvolMed recommends supplementing SSBs with at least ~90 mg/100 ml of K, because 83 mg/100 g is the lowest content of K found in 23 varieties of fresh fruits [178]. That supplementation should be in the form of K citrate, not K chloride, to mimic as much as possible fresh fruits, which contain K in non-chloride salts [191]. Chloride concurs to produce hypertensive effects [192]. This may explain why K citrate proved more beneficial than K chloride in reducing blood pressure [193]. Other studies [194,195] found that the effects of K citrate and K chloride "did not differ significantly" [194] (p. 1284). Nonetheless, leaving aside possible economic reasons, there is no scientific reason to supplement SSBs with K chloride instead of non-chloride salts.

Dietary Salt Makes SSBs More Harmful

EvolMed poses this third maieutic question: Which dietary factor absent in prehistoric nutrition can alter the metabolic response to SSBs? Dietary salt (sodium chloride, NaCl) is the answer. As rightly stressed, "the diet of early humans was unsalted, and the Na content of breast milk (6 mmol/kg) shows how little NaCl is needed even during the most rapid period of growth" [196] (p. S35). EvolMed argues that the tiny content of Na of breast milk is an evolutionarily conserved result of the ancestral diets based on fruits, in which the disproportion between K and Na is impressive. For instance, "a single serving (150 g) of raw, sliced bananas contains 594 mg (15.2 mmol) of K,..., and 1 mg (0.043 mmol) of Na" [197] (p. 649). However, "humans began to use large amounts of salt for the main purpose of food preservation approximately 5,000 years ago" [198] (p. 83). This period is 10,000 times shorter than the 50 million years of our evolutionary lineage as anthropoids [120] living on unsalted diets based on fresh fruits, which abound in K but contain little Na [178,197]. So, "in response to these dietary habits, evolutionary forces (acting over millions of years) fostered the development of physiological systems (primarily renal) that conserved sodium and excreted potassium" [199] (p. 45E). That period of 5,000 years is "brief, by evolutionary standards … and thus, there has been little time for the physiologic systems that promote sodium retention and potassium excretion to adapt" [199] (p. 45E). Even an incomplete adaptation to salt would have rendered it almost harmless. In fact, a complete evolutionary adaptation of a given species to any environmental dietary component entails that this component became not only harmless, but also beneficial to that species. For example, the evolutionary adaptation of early humans to fresh fruits was so perfectly complete that these foods are beneficial to modern humans [130-137]. By implication, the various harmful effects of salt [200] show that we are far from being adapted to salt, which was nutritionally unknown for the 99.99% of our evolutionary history.

Virtually all the harmful effects of salt are opposite to the beneficial effects of fruits or K. Salt favors hypertension [201-205]; fruits or K prevent it [206-209]. Salt favors cardiovascular disease [210-214]; fruits or K prevent it [214-216]. Salt favors stroke [217-219]; fruits or K prevent it [220-222]. Salt favors osteoporosis [223-225]; fruits or K prevent it [180,226]. Salt favors cancer [227-230]; fruits or K prevent it [231-234]. Salt favors asthma [235-237]; fruits prevent it [238-240]. Salt favors kidney stone formation [241-243]; fruits or K prevent it [244-246]. Salt favors heart failure [247-249]; K prevents it [250,251]. Revealingly, the authors who found "a low sodium, high water, high potassium regimen" [251] to be very

beneficial "even in refractory cardiac failure" [251] (p. 243) unknowingly used a regimen mimicking the composition of fresh fruits. Finally, salt restriction benefits also patients with chronic kidney disease [252-255]. Hence, "substantial health benefits might be achieved when added salt is removed from processed foods" [256] (p. 446).

Because of the "multiorgan targets" of Na [257], salt has been defined "the neglected silent killer" [258]. Indeed, "higher sodium intake is associated with increased total mortality in the general US population" [259] (p. 1183). This association also reflects the neglected harmful effects of salt on the absorption of SSBs. Many consumers of SSBs ingest them jointly with salt-containing foods. For example, afterschool programs served SSBs and "salty snacks" [260] (p. 118). In the stomach, at least a tiny part of their salt unavoidably passes into SSBs, thereby unhealthily compromising their normal physiological absorption. Indeed, "at low concentrations the addition of sodium chloride and sodium sulphate to test meals increased the rate of gastric emptying" [261] (p. 268). As additional evidence that Na and K almost invariably produce opposite effects, "potassium chloride was … effective in slowing gastric emptying" [261] (p. 256). The accelerating effect of Na on absorption occurs because Na "greatly facilitates glucose uptake" [262] (p. 1228). Consequently, "sodium ion … increases the rate of absorption of glucose" [43] (p. 318). This confirms the importance of "the role of sodium in intestinal glucose absorption in man" [263]. Indeed, "a small amount of NaCl in the solutions can potentiate intestinal absorption of sugars" [44] (p. 558). As a metabolic consequence, "the addition of sodium chloride enhances the glycemic response to glucose ingestion through facilitation of intestinal absorption" [264] (p. 458). Therefore, dietary salt unnaturally accelerates the absorption of diluted glucose, thereby abnormally turning its typically linear and harmless absorption into a virtually exponential harmful absorption. Remembering that the absorption of diluted glucose and diluted sucrose are physiologically identical [43], it is evident that the salt-induced hastened absorption of SSBs largely accounts for their observed harmfulness [138-154].

The accelerating effect of salt on the absorption of diluted sugar is also responsible for the weight gain and obesity linked to SSBs consumption [155-168]. Some authors did realize that dietary salt concurs to explain the association between SSBs and obesity [265-267]. However, they failed to mention the accelerating effect of salt on the absorption of sugar. Those authors merely suggest that salt, by causing thirst, "may drive greater consumption of SSBs and contribute to obesity risk" [266] (p. 189). Without salt, SSBs are unlikely to favor obesity, because EvolMed suggests that the linear absorption of diluted sugar is a function of exogenous glucose oxidation [268,269]. This entails that the rate of absorption of SSBs is regulated by the personal caloric needs of their individual consumer, thereby making his/her weight gain virtually impossible. Tellingly, the Yanomamo Indians, who live mainly on bananas [270], the most caloric fruits [123-125], "are seldom obese and rarely demonstrate weight gain with advance in age" [270] (p. 150), thanks to their "no-salt" diet [270] and to the linear absorption of diluted sugars of bananas. Of note, those Indians "are physically a highly active people" [270] (p. 150). Thus, as was appropriately remarked, "these observations on an unacculturated people provide further support for Dahl's conclusion that in civilized societies "salt *appetite* is not to be equated with salt *requirement*""[270] (p. 151).

Fructose

Although "both controversy and confusion exist concerning fructose, sucrose, and high-fructose corn syrup (HFCS) with respect to their metabolism and health effects" [271] (p. 236), this article so far focused only on sucrose. However, for the sake of completeness, now it is opportune to add a brief discussion about fructose and HFCS in evolutionary perspective. Once again, the explanatory capacities of EvolMed enable us to shed a clarifying light on another otherwise obscure medical issue, namely, the controversial and confuse topic regarding fructose and HFCS.

EvolMed explains that pure fructose proved harmful [272-276] because it represents one of the "genetically unknown foods" [6,7] that were unavailable to our prehistoric ancestors. Indeed, pure fructose is inexistent in nature. They ingested fructose only by eating fresh fruits, in which fructose is always diluted and indivisibly commingled with diluted glucose [123-125]. Consequently, the linear absorption of diluted glucose [45-47] prevents fructose from displaying its typically exponential absorption, which conversely is evident when fructose is investigated isolatedly [277]. In fact, "fructose empties exponentially and more rapidly than the other sugars" [277] (p. R25). Considering that "the rate of delivery of fructose is twice that seen with glucose" [277] (p. R26), it is clear why pure fructose proved harmful [272-276].

As to fructose contained in HFCS, "some would like to continue to demonize HFCS" [278] (p. 1715S) by claiming that "the large amounts of fructose now consumed from sugar or HFCS are hazardous to our health" [279] (p. 1004). HFCS "has replaced sucrose as the predominant sweetener used in soft drinks" [280] (p. 1195). EvolMed argues that diluted HFCS cannot be harmful because "HFCS is very similar to sucrose, being about 55% fructose and 45% glucose" [278] (p. 1715S). Indeed, sucrose "is composed of 50% glucose and 50% fructose" [280] (p. 1195). Therefore, "not surprisingly, few metabolic differences were found comparing HFCS and sucrose" [278] (p. 1715S). The overlapping effects of sucrose and HFCS have been confirmed by a study entitled "Consumption of honey, sucrose, and high-fructose corn syrup produces similar metabolic effects in glucose-tolerant and intolerant individuals" [281]. Notably, honey is metabolically similar to sucrose and HFCS because it shares their composition, i.e., fructose and glucose. Indeed, "the principal carbohydrate constituents of honey are fructose (32.56% to 38.2%) and glucose (28.54% to 31.3%), which represents 85%–95% of total sugars" [282] (p. 732).

Conclusion

In fresh fruits, fructose is always present, often abundantly. Some fruits contain more fructose than the other sugars combined. For instance, 100 g of apples contain 6.08 g of fructose, 3.62 g of sucrose, and 1.72 g of glucose [125] (p. 94). Hence, it is intuitive that our prehistoric ancestors living on fresh fruits for tens of millions of years ate fructose in daily quantities exceeding those ingested today by consumers of SSBs containing mainly HFCS. Therefore, it is absurd to define "fructose as a weapon of mass destruction" [283]. These evolutionarily nonsensical words, written in the title of a medical article aimed at demonizing unjustly HFCS, constitute a sad and disheartening proof that "the canyon between evolutionary biology and medicine is wide" [68] (p. 28). Indeed, "evolutionary biology is an essential basic science for medicine, but few doctors and medical researchers are familiar with its most relevant principles" [68] (p. 28). Therefore, it is appropriate to conclude this article by emphasizing that "teaching medical students about our evolutionary legacy and the biological forces that shaped our past will help them to be better prepared for our future" [284] (p. 8).

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