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Dietary Intake of AGEs and ALEs and Inflammation—Nutritional Aspects

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CONTENTS

KEY POINTS

- Chronic, silent, often low-grade, inflammation is associated with almost all lifestyle-associated chronic diseases.
- The degree of inflammation is enforced by postprandial inflammation induced by certain foods.

- Among factors documented to enhance chronic and postprandial inflammation are exposure to glycated, lipoxidated products; proteins such as gluten and casein; long-chain fatty acids, and lack of anti-inflammatory factors such as vitamin D and omega fatty acids.
- Chronic and postprandial inflammation is strongly associated with impaired and poorly functioning gut microbiota and impaired innate immune functions.
- Gut reconditioning—supply of bioactive lactic acid bacteria, bioactive plant fibers, and plant antioxidants by plant foods such as cloves, turmeric, Ceylon cinnamon, chili pepper, black pepper, wild caraway, and many other plants may have the ability to reduce chronic and postprandial inflammation.

26.1 Western Life Style and Food Habits—A Real Threat to Health

Most Western diseases are strongly associated with physical and mental stress, lack of exercise, and overconsumption of processed Western-type foods—often leading to metabolic syndrome and manifested in, what has been called the "deadly quartet": excessive body weight, hypertension, impaired glucose homeostasis, and atherogenic dyslipidemia (changes in serum cholesterol, increased triglycerides, decreased high density lipoprotein [HDL] cholesterol, and an increase of low-density lipoprotein [LDL] particles)—manifestations, which often lead to severe acute and chronic diseases such as diabetes mellitus type 2, cardiovascular disease (CVD), cancers (breast, colorectal, and pancreas), neurodegenerative diseases (e.g., Alzheimer's disease), pregnancy complications (gestational diabetes and preeclampsia), fertility problems (polycystic ovarian syndrome), and many more [1–4].

The development of metabolic syndrome with its components of abdominal obesity, high blood pressure, elevated blood sugar, elevated blood triglycerides, low HDL cholesterol, and high uric acid in blood is often, if not always, a result of malfunctioning gut flora (dysbiosis), induced endotoxemia, low-grade systemic inflammation, and malfunctioning immune system [1,2]—all constituting, what I call a "mother of disease" [3]. This chapter focuses only on the effects of Western food habits and its association to dysbiosis, in particular with the inflammation and immune dysfunctions induced by intake of glycated and lipoxidated molecules, often combined with lack of organ rest, recuperation, regeneration, and detoxification.

26.2 Inflammation—Early Warnings

Dysbiosis, which always induces a low-grade, often silent, inflammation and a malfunctioning immune system, leads early on to a series of various, seemingly benign manifestations in the body, for which the sufferers often seek medical advice at their local general practitioner, and often receive symptomatic treatment. However, these benign but irritating symptoms should nevertheless be taken seriously as they may be signs of ongoing low-grade inflammation, which with time might bring a series of consequences—severe diseases and eventually death. Such signals should be regarded as "early warnings" and encourage radical changes in lifestyle, especially in food habits.

Among these "early warnings" are manifestations such as acne, dandruff, unexplained fatigue, sleep problems, frequent headache, hair loss, gray hair, skin rashes, dry eyes, frail nails, dry mouth or increased salivation, reduced sex functions, irregular menstruations, obstipation or diarrhea, osteoporosis, overweight, frequent infections, mental depression, breathlessness, sweaty feet and palms, vaginal flour, and several more. If ignored—worse is to come. To treat these manifestations with lifestyle changes is more important than using drugs.

26.3 Without Lifestyle Changes—Worse Is to Come

A series of well-done published studies suggest that the incidence of most of the endemic chronic diseases from Attention Deficit/Hyperactivity Disorders (ADHD), Alzheimer, and diabetes, to prostatic and other cancers will in average triple by the year 2050. Incidence of diabetes will double [5] and that of ADHD, Alzheimer disease [6], and cancer [7] will triple or more. No health insurance system, governmental or private, will have a chance to survive under such conditions. Even in times of low inflation, health care costs seem to double in each 10-year period [8], and this has been happening for several decades. It is expected that in the United States, the country with the highest health care costs in the world, by the year 2020 the costs of health care will correspond to half (>$15,000) of the average family income (about $46,000) after tax (app 30,000)—sales taxes excluded.

A rather recent and most interesting study looked at the prospective landscape of health and disease up to the year 2030 in the United States and the United Kingdom [9], two countries already with the highest rates of obesity and chronic diseases in the world and representing approximately 5% of the world's population. The study suggests that these countries combined will by the year of 2030 have another 76 million obese adults, and have an additional 6–8.5 million cases of diabetes, 6–7 million cases of cardiovascular disease, 492,000–669,000 additional cases of cancer, which will result in another loss of between 26 and 55 million quality-adjusted life years and a dramatic increase in costs of care (the authors calculated to be $50–$68 billion per year) [9].

26.4 Easy Access of Food and High Consumption of Processed Foods Is the Problem

For some decades, the epidemic of obesity and chronic diseases has mainly been a problem for the Western world. Modern agricultural techniques, techniques for mass production, and easy access to cheap foods has led to a much too large consumption of agricultural foods, frequently and increasingly industrially manipulated and rich in processed and easy digestible products such as meat, dairy, and wheat, and foods that are often also rich in advanced glycation and lipoxidated end products—AGEs and ALEs (10–12). Similar developments are now observed in other parts of the world, largely in parallel to the adoption of "modern"/Western food habits.

Presently, the epidemic of obesity and associated diseases seems to have its epicenter in the Southern United States [13]; states like Alabama, Louisiana, and Mississippi having the highest incidence of obesity and chronic diseases in the United States and the world. These diseases are spreading around the world much like a tsunami; to the West to New Zeeland and Australia, to the North to Canada, to both Eastern and Western Europe, and now also to the Arab world and Asia, and to the South, particularly to Mexico and Brazil, most often in the footprints of the development of modern agriculture.

26.5 Developing Countries Soon to Take Over the "Yellow Jersey"

Japan was the first country outside the Western hemisphere to adapt a Western lifestyle and it suffers now the burden of Western diseases— to an extent not seen before. The island of Okinawa, once said to have the healthiest populace and the greatest numbers of centenarians in the world, has lost its leading position of having the lowest incidence of obesity and chronic diseases, and the highest number of centenarians in the world. This occurred after the United States built military bases on the island, thereby westernizing the island—today, the island ranks among the lowest from the perspective of health when the 50 Japanese states (prefectures) are studied.

The mortality rate of prostatic cancer increased 25-fold and almost linearly between the years 1948 and 1998, when Japan after the Second Word War, at least to some extent, adopted its food habits to

Western agriculture-based foods, which happened in parallel to the increase in the consumption of eggs (7-fold), meat (9-fold), and milk products (20-fold) [14,15]. Now, the same development is seen not only in China, India, and other Asian countries but also to a great extent in African countries. China, for example, once known for its extremely good lifestyle and food habits, especially in rural areas, and low incidence of obesity as well as chronic diseases with high numbers of centenarians [16] is today badly affected by obesity and chronic diseases, much in parallel to the introduction of western-type agriculture and especially in parallel to the increased production and consumption of dairy products. I have had difficulties in accessing official information, but my colleagues in China tell me that the incidence of chronic diseases such as coronary heart diseases, diabetes, and cancers such as breast cancer and prostatic cancer seem to double every 10 years, especially in the large cities.

26.6 Incidence of Obesity and Chronic Disease Increases with Unprecedented Speed

It has been recently reported that the incidence of metabolic syndrome and cardiovascular risk rose dramatically in the Chinese population in the 8 years between 2002 and 2010 [17]. A 4-fold increase in the incidence of metabolic syndrome was observed, affecting only 5.4% of the population in 2002 and rising to as much as 21.3% in 2010. The situation seems even more worrisome considering that the rate of hyperglycemia rose five times from 9.1% in 2002 to 53.1% in 2010. Furthermore, the age-standardized prevalence of obesity did double during the same period, from 13.5% to 25.4%, much in parallel to the increased incidence in hypertension (from 23.6% to 40.8%), hypertriglyceridemia (from 12.1% to 17.4%), and an alarming rise of low-density cholesterol LDL (from 32.1% to 71.1%).

It is also reported that the gap in the incidence of metabolic syndrome and its serious consequences, previously much in favor of rural compared to urban populations, decreased significantly during the 8 years, from 2002 to 2010 [17]. A just published study reports much similar development in cancer disease in Southeast Asia—exemplified by fast increasing instances of prostatic cancer, already high in Japan, Taiwan, Hong Kong, and Korea, with Shanghai and most likely also Beijing—and the whole of urban China—fast following in the footprints of the most affected large cities [18]. Furthermore, Western food habits are increasingly being adopted by the Chinese youth, which is even more worrisome. Metabolic syndrome and obesity are increasing faster in younger age groups and the prevalence of juvenile type 2 diabetes is reported to have doubled within the recent 5-year period.

26.7 The Interval between Change of Lifestyle and Signs of Ill Health Is Shorter than Ever Before

It is of great interest to observe that the interval between change of lifestyle and altered pattern of disease is much shorter than previously ever believed. What took about 100 years to occur in the Western world is happening in Southeast Asia in less than 10 years. The large increase in dairy production and consumption, which exploded after the shift of the millennium, was seemingly followed almost immediately by a typhoon of obesity and chronic diseases.

Feeding large populations with cheap, calorie-condensed foods are seemingly one of the greatest political priorities, and a favored political task in almost all countries. Western politicians know well the negative health consequences of such policies and have done so for decades, but they seem unwilling to make any serious attempt to stop the epidemic of obesity and chronic diseases that follows. Both in Europe and in the United States, governments continue to subsidize mass agriculture with large sums of money in order to produce even more of such disease-promoting foods and are obviously prepared to pay for subsequent attempts to try to cure those who have been affected by disease due to overconsumption of cheap, calorie-condensed agricultural foods.

Consumption of refined sugar, strongly associated with obesity and Western diseases, has sky-rocketed in the last 150 years from a decent half a kg in 1,850 to presently about 50 kg/person/year in Western

and even more in South American countries. The consumption of sugar is still comparatively low in Asian countries—usually below 10 kg/person/year, but is growing fast. Asian countries, in addition to having a considerable internal and fast-growing production, are big importers of sugar. For example, India and China are the largest importers of sugar in the world—China is expected to be by far the largest importer in the year 2020. One can only speculate about the damaging effects on public health that such a development will lead to. Africa is now following in the same path—a recent study reports a fast increasing public health problem with obesity in Tanzanian women with damaging physical and social consequences—the prevalence of overweight reported as considerable for the continent: 16% overweight and 6% obese [19].

Behind dysbiosis, the 10 most important factors contributing to chronic inflammation and subsequent chronic diseases are the following:

- Very high intake of insulinogenic foods such as refined carbohydrates; cereals, bread, sweets, cookies, rice, pasta, cooked tubers, including potatoes, and foods that are highly absorbed in the small intestine and are of no or minimal benefit to microbiota.
- Too high intake of fructose, above 25 g a day, particularly of high fructose corn syrup.
- High intake of dairy products, especially butter, cheese, and milk powder, rich in long-chain fatty acids, absorbed via the thoracic duct and remaining for hours in general circulation, contributing to postprandial endotoxemia and postprandial inflammation.
- High intake of foods rich in hormones and growth factors such as IGF1.
- High intake of meat, especially inflammation-inducing processed and cured meat, such as bacon and sausages, meatballs, which also are detrimental to microbiota and induce dysbiosis.
- High intake of foods exposed to industrial processes and heated in temperatures above 80°C/175F° known to induce synthesis of molecules such as AGEs and ALEs.
- Exposure to microbe-derived highly inflammation-inducing endotoxin, especially rich in meat hung for several days, hard cheeses, pork, and ice creams.
- Intake of foods rich in proteotoxin pesticides such as casein, gluten, and zein (maize).
- Intake of chemicals of all kinds, also including alcohol, nicotine, most pharmaceutical drugs, even pain relievers, sedatives, sleeping pills, proton pump inhibitors, all detrimental to microbiota.
- Too small intake of plant fibers, fresh and raw greens, fresh spices, and vegetables, and too little intake of antioxidants, minerals (especially magnesium-rich), and other anti-inflammatory nutrients.

26.8 Postprandial Inflammation: A "Deadly" Threat to Long-Term Health

The factors mentioned above do, more or less all, contribute to severe postprandial inflammation, especially when consuming a meal rich in long-chain fatty acids, sugars, and AGEs and ALEs. Frequent episodes of postprandial inflammation has for years been recognized as a key factor behind the development of arteriosclerosis [20] and various other chronic diseases, especially metabolic syndrome [21], diabetes [22], and hepatosteatosis [23]. Every meal rich in fat is associated with significant derangement of microbiota [24], cascades of markers of inflammatory and oxidative stress [25], particularly tumor necrosis factor-α (TNF-α) [26] and significant endothelial dysfunction [27].

Plasma endotoxin levels were studied in 12 healthy men (20–58 years, mean age: 32 years) after exposure to no meal, three cigarettes, and a high-fat meal, or a high-fat meal with three cigarettes [26]. The high-fat meal with or without cigarettes, but not the no meal or smoking alone, reduced significantly ($P < 0.05$) endotoxin neutralization capacity of plasma, an indirect measure of endotoxin exposure. The levels of endotoxin/plasma increased with a mean of 50% ($P < 0.05$) and remained significantly elevated for about 1.5 hours, while the triacylglycerol concentrations remained statistically significantly elevated as long as 4 hours after the meal [26]. This study provides strong support to the hypothesis of

food/dysbiosis/endotoxemia-induced postprandial inflammation as a major contributor to endothelial activation and development of atherosclerosis. It is also observed that simultaneous intake of sugars significantly potentiates the postprandial inflammation induced by a high-fat meal [27]. The inflammatory response in vascular endothelial cells varies directly with the subject's postprandial serum triglyceride level and waist circumference [28].

26.9 Abdominal/Visceral Obesity Enhances Postprandial Inflammation

Visceral obesity was extremely rare among our forefathers and remained so until only a few decades ago. A recent study that measured anthropometric parameters using nuclear magnetic resonance was performed in 54 otherwise healthy volunteers with BMI ranging from 19 to 57 kg/m^2 and demonstrated that visceral obesity can vary from only a few milliliters in lean individuals to over 6 L in morbidly obese individuals [24]. Furthermore, a strong correlation was observed between visceral amount of fat, waist circumference, and waist-to-hip ratio [29]. It is of the greatest interest that visceral adipocytes exposed to stress secrete significantly more free fatty acids and also approximately three times as much proinflammatory factors such as IL-6 and PAI-1 per gram tissue compared with subcutaneous fat cells. These observations might well explain the high risk of acute and also chronic diseases in individuals with visceral obesity [29]. As a matter of fact, the stress-induced load on the vascular endothelium and particularly those of the brain, the heart, and the lungs can be extreme as the proinflammatory and procoagulant molecules can vary up to 1,000 times. These observations provide strong support to what has been called the "portal theory", which proposes that the liver when exposed to larger amounts of free fatty acids and proinflammatory factors, released from visceral depots of fat into the portal vein, especially in obese individuals, will promote development of liver steatosis and hepatic insulin resistance, and enhance the development of metabolic syndrome, particularly type 2 diabetes [30]. Dysbiosis with metabolic endotoxemia is strongly associated with general obesity and insulin resistance both in mice and humans, supporting a strong linkage between gut microbes, gut barrier function, acute and chronic inflammation, adipose tissue inflammation, endothelial inflammation and dysfunction, obesity, chronic inflammation and insulin resistance, and various chronic diseases.

26.10 Postprandial Inflammation Induced by Long-Chain but Not Medium-Chain Fatty Acids

The metabolism of consumed medium-chain fatty acids (MCFAs, C6-C12) in the body is fundamentally different from long-chain fatty acids (C12 – C21). This is an observation which is receiving increasing interest. Medium-chain triglycerides (MCT) are among the most readily hydrolyzed nutritional fats, much in contrast to long-chain triglycerides (LCT). MCFAs are known to be absorbed from the small intestine by a pathway, which is more direct and much more rapid than that of long-chain fatty acids (LCFAs), for example, via the portal vein to the liver. Since several decades ago, it is known that MCTs undergo a rapid hydrolysis by the gastric, salivary, or pancreatic lipases, most likely due to much better solubility and motility of the MCT lipid droplet. MCFAs are rapidly transported as nonesterified fatty acids into the portal blood stream to reach the liver, while LCFAs are transported as chylomicrons into the thoracic duct and after remaining up to several hours in the general circulation are redistributed as LCTs by hepatic lipoproteins to nonhepatic tissues [31,32].

The effects of fatty acid chain length were tested on male Wistar rats which were fed iso-caloric high-fat diets containing triacylglycerols composed of either MCFAs or LCFA. After 4 weeks, insulin sensitivity was reduced by 30% in the LCFA group, while it remained nonaffected in the MCFA group [33]. Triacylglycerol concentrations in muscle were higher in both high-fat groups compared to controls. No diet-induced changes were found in acyl-CoA oxidase (ACO) activity (liver and muscle) in the MCFA group, while feeding significantly raised carnitine palmitoyltransferase activity in the LCFA group. It was concluded that the chain length of saturated fatty acids clearly affects whole-body insulin

sensitivity and mitochondrial fatty acid uptake, even in the absence of obesity. It was also observed that MCT compared to LCT feeding resulted in significantly lowered fasted and postprandial triglyceride concentrations [33]. Feeding sows with diets containing 15% MCTs resulted in a significantly lower mortality of newborns and promoted development, particularly of underweight piglets [33,34].

26.11 Reduced Intake of LCFAs and Increased Intake of MCFAs Are Good for Microbiota and Health

Numerous studies have demonstrated significant beneficial impacts of feeding MCFAs on both composition of the intestinal microbiota and inhibitory effects on bacterial concentrations in the digesta, mainly on Salmonella and coliforms. Apart from the specific nutritional and metabolic effects of MCTs and MCFA, especially their rapid digestion, passive absorption, and obligatory oxidation, they also possess immunomodulatory effects. While LCTs and LCFAs have meat and dairy as their dominating food source, MCTs and MCFAs typically come from plant fats. The MCT content is especially high in coconut oil: caprylic acid (C8), 3.2%–15% of capric acid (C1), and 41%–56% of lauric acid (C12). High contents of caprylic (2.4%–6.2%), capric (2.6%–7.0%), and lauric acid (41%–55%) can also be found in palm kernel oil. Cuphea seeds (family of loosestrife) have a broad species-dependent diversity in MCFA. Oil from Cuphea seeds has an extraordinarily high content of MCFA; Cuphea lanceolata and Cuphea ignea oils containing over 80 % capric acid have been used particularly as sources of MCTs in piglets [35].

Too few studies have been performed in humans. Some studies, however, report positive clinical effects of increased consumption of MCTs or MCFAs. One study reported that plasma triglycerides decreased from a mean of 1,601 to 554 mg/dL ($p < 0.05$), total cholesterol levels were reduced from 417 to 287 mg/dL ($p < 0.001$), and slight decreases in fasting glucose (–8%) and uric acid levels (–12%) when patients with severe hypertriglyceridemia were treated for 7 days with a formula diet rich in omega-3 fatty acids and MCT [36]. Positive effects of supplementation with MCFAs are also reported in conditions such as obesity (reduced body weight, waist line, and insulin resistance) [37,38], mild-to-moderate dementia in Alzheimer (improved cognition) [39], in type 1 diabetic subjects [40], on aging and arteriosclerosis [41], inherited cardiomyopathy [42,43], and chronic pancreatitis [44].

26.12 Intake of Animal-Based Foods Induces Dysbiosis and Inflammation within 24 Hours

As discussed above, the gut microbiota over the years has decreased in size and diversity. As a matter of fact, recent studies suggest a decrease of up to 40% [45] when compared to the Paleolithic microbiota, and evidence suggests that it will continue to do so [46]. Furthermore, recent studies demonstrate that such changes occur within 24 hours as immediate reaction to the content of our daily food [47]. Consumption of a diet high in saturated (milk- or meat-derived) fats (MF), but not consumption of polyunsaturated (safflower oil) fat (PUFA), changes the conditions for microbial assemblage and promotes expansion of the sulfite-reducing pathobiont, *Bilophila wadsworthia*, which induces a shift in hepatic conjugation of bile acids, from glycocholic to taurocholic acid that is especially important for solubilizing a hydrophobic diet such as milk. These changes are strongly associated with a strong proinflammatory TH1 immune response and increased incidence of inflammatory conditions such as colitis [48,49].

Numerous environmental and other toxins have AGE- ALE-like effects on the microbiota, immune system, and disease development, including uremic toxins. About 100 such toxins have been identified today, but most likely there exists many more, yet unidentified, with profound negative effects on health [50]. Several identified and unidentified uremic toxins are badly removed by renal dialysis, particularly those, which much like AGEs, are bound to proteins, such as p-cresyl sulfate (PCS) [50].

High intake, especially of meat, but also to some extent milk, and to a large extent powdered milk and a large majority of processed foods [51], is strongly associated with high intake of AGEs and ALEs, factors that in turn further support the development of inflammatory conditions. A recent review addressed the

role of saturated fatty acid, sodium, advanced glycation end products (AGEs), nitrates/nitrites, heme iron, trimethylamine N-oxide (TMAO), branched amino acids (BCAAs), and endocrine disruptor chemicals (EDCs)—all more or less strong inducers of inflammation—in the development of type 2 diabetes [52].

26.13 No AGE-Preventing Drug Available—But Lifestyle Changes Are Very Effective

There are currently no drugs available that are effective and nontoxic at preventing AGE formation, and/or target preformed AGEs. Both aminoguanidine (AG) and the thiazolium-derived compound algebrium showed potential, but studies with both were discontinued due to safety and/or efficacy concerns. The fact that several second-generation compounds in experimental studies exhibit increased AGE inhibition and ability to breaking activity compared to the first-generation compounds including aminoguanidine gives some hope [53], but it will most likely take many years, if ever to happen, for such a "magic pill" to be available. It is, however, clear that significant benefits will be obtained by reducing the intake of cheese, meats, powdered milk, and other processed foods such as heated oils, and also of bread, and instead increase the consumption of vegetables and fruits, especially when raw. These recommendations are in line with the policy of various expert organizations with the aim to reduce chronic diseases such as cancer, heart diseases, and hypertension: American Cancer Society [54], American Heart Association Nutrition Committee [55], and the US Department of Health and Human Services [56].

26.14 AGE-Reducing Eating Habits

Eating foods preferably raw or at least prepared at a low temperature (below 80°C), steam-cooked or boiled, with minimal cooking time are much healthier than eating foods prepared by frying, grilling, microwaving, and roasting but also salting. Recent information warns against microwaving food that may dramatically accelerate the rate of AGE formation [57]. A randomized cross-over trial compared the metabolic effects of two different diets, one based on mild steam cooking while the other was based on high-temperature cooking in 62 volunteers (university students) during a period of 4 weeks [58]. Consuming the steamed-cooked food for 1 month induced significantly improved insulin sensitivity and increased plasma levels of omega-3 fatty acids (217%, $p = 0.002$), vitamin C (213%, $p = 0.0001$), and vitamin E (28%, $p = 0.01$) in comparison to the high temperature–exposed diet. Furthermore, significant reductions in concentrations of plasma cholesterol (5%, $p = 0.01$) and triglycerides (9%, $p = 0.01$) were also reported in the steamed-cooked foods group.

A great challenge for the future, and especially for the Western world, is to find techniques to produce bread at or below 100°C/215°F as the Chinese have done for centuries and continue to do. The synthesis of the toxic/inflammation-inducing substance acrylamide, normally not detected in unheated control or boiled foods (<5 μg/kg), increases when temperatures exceed 120°C/250°F and is found to be increased manifold at temperatures usually used for baking bread in Western Societies, often as high as 275°C/530° F [59,60]. High levels of acrylamide (up to 4,000 μg/kg) are observed in conventionally baked bread, being the highest in crispbreads, and also high in high temperature oven–baked or grilled vegetables, especially when vegetables are rich in carbohydrates, such as potatoes, carrots, beetroots, parsnips, and even more so in most commercially heated products such as potato chips, French fries, and toasted bread [61,62].

26.15 Reduction in Intake of Protein, Especially Sulfur-Containing, Is also of Importance for Health

Some prevention is offered by marinating the foods for some hours at room temperature with ingredients such as antioxidant-rich herbs, garlic, tea, red wine, onions, olive oil, and beers, which significantly, but not totally, reduces the development of AGEs/ALEs [63]. Reduction in total intake of proteins [64],

and most likely a particular reduction in methionine and other sulfur-containing amino acids, is an additional issue of relevance [65]. Significant reduction in body content of AGEs/ALEs in comparison to controls (eating standard Western food) is observed in individuals, who for >2 years practiced what is called caloric restriction (CR)—eating only two-thirds of what they would like to. This practice was accompanied by significant health advantages compared to the matched controls: lower blood pressure (102/61 ± 7 vs. 131/83 mm Hg) and lower levels of markers of inflammation such as CRP (0.3 vs. 1.9 mg /L), TNF-α (0.8 vs. 1.5 pg/ mL^{-1}), and TGF-β (29.4 vs. 35.4 ng/mL^{-1}) [66].

Elevated RAGE and low sRAGE is frequently seen in patients with active rheumatoid arthritis [67]. Thirty-seven obese individuals (mean BMI 28.3 ± 3.2) with rheumatoid arthritis were treated with calorie restriction, and after 8 weeks demonstrated not only significantly lower levels of pentosidine (an often-measured AGE) in urine, and reduction in BMI (6.3%, $p < 0.001$), waist circumference (5.7%, $p < 0.002$), triglycerides (11.9 % $p < 0.002$), and AGEs (7.21%, $p < 0.001$) but also much lower disease activity [68]. As an example, forced expiratory volume (FEV1), an expression of lung function, almost doubled.

26.16 Antioxidants and Vitamins

Provision of vitamins such as A, various B (especially B6 and B12), C, D, E, and K, as well as glutathione and folic acid, is often recommended for the prevention of accumulation in the body of AGEs/ALEs. Many plant antioxidants, particularly those collectively defined as polyphenols, are claimed to have oxidation-quenching properties, some say up to 10 times more powerful than conventional vitamins. They are also claimed to have great chemo-preventive properties, marked ability to prevent accumulation of AGEs/ALEs in the body, and significant capacity to reduce inflammation and to prevent impaired organ function and premature aging [69–72]. It is regrettable, as emphasized in a recent systematic review of the literature regarding antioxidant intake and protein glycation in normoglycemic individuals, that human trials with polyphenol-rich supplements are not only few but also characterized by high heterogeneity, poor design, and small sample size [73]. During the last 20 years, only 14 trials have tried polyphenols as a means to reduce glycation in nondiabetic individuals [73,74].

Plant antioxidants exist in nature in many thousands—most probably hundreds of thousands of different compounds. More than 4,000 have been identified only among flavonoids, and almost 1,000 among carotenoids. Most investigated antioxidants have been isothiocyanates in cruciferous vegetables; anthocyanins and hydroxycinnamic acids in cherries; epigallo-catechin-3-gallate (EGCG) in green tea; chlorogenic acid and caffeic acid in fresh coffee beans and also in fresh tobacco leaves; capsaicin in hot chili peppers; chalcones in apples; eugenol in cloves; gallic acid in rhubarb; hesperidin and naringin in citrus fruits; kaempferol in white cabbage; myricetin in berries; rutin and quercetin in apples and onions; resveratrol and other procyanidin dimers in red wine and virgin peanuts; various curcumenoids, the main yellow pigments in turmeric curry foods; and daidzein and genistein from the soy bean [10–12]. Most of these substances/foods are not yet tried in experimental or clinical studies, which is discouraging. It is clear that antioxidant molecules in food have a wide range of functions, but many of these seem unrelated to the ability to absorb free radicals.

A recent study looked at the anti-AGE effects of nine different plants. Three spices, namely seeds from Coriandrum sativum (cilantro or Chinese parsley), bark from Cinnamomum zeylanicum (Ceylon cinnamon) bark, and flower buds from Syzygium aromaticum (clove tree)—all well-known and common spices among the 20 spices with the highest antioxidant capacity, demonstrated a high ability to inhibit *in vitro* cross-linking [75].

26.17 Turmeric with Its Curcumenoids: Strong Inhibitors of Inflammatory Genes Such as COX-2—"The World's Healthiest Food"

Central to inflammation is the expression of numerous inflammation-inducing genes such as COX-2, matrix metalloproteinase-9 (MMP-9), inducible nitric oxide synthase (iNOS), TNF, IL-8, eotaxin, various cell surface adhesion molecules, and antiapoptotic proteins, regulated by NF-κB. COX-2 is inducible

and barely detectable under normal physiological conditions, but is rapidly, but transiently, induced as an early response to proinflammatory mediators and mitogenic stimuli.

Curcuminoids, important bioactive ingredient of turmeric, are not only inexpensive atoxic and potent inflammation inhibitors (COX-2 and iNOS) but also potent inducers of heat shock proteins (HSPs) and other cytoprotecting factors. The most important chemical components of turmeric are a family of compounds called curcuminoids, which include several important anti-inflammatory substances, which seemingly interact, and should be used in combination, among them curcumin (diferuloylmethane), demethoxycurcumin, and bisdemethoxycurcumin. At least 5% of turmeric consists in curcumenoids of which curcumin is about 3% of the powdered turmeric. In addition, other important health-promoting ingredients are volatile oils such as turmerone, atlantone, and zingiberene. Half of the turmeric contains important fibers in addition to the several important vitamins as well as some well-defined sugars, proteins, and resins—all good reasons why this food often has been called "the world's healthiest food" (76–78). The curcumenoids inhibit not only COX-2 but also LOXs and leukotrienes, such as LBT4 and 5HETE, especially when bound to phosphatidylcholine micelles and are suggested to be especially effective in Th1-mediated immune conditions [79]. A recent publication suggests, based on *in vitro* studies, that curcuminoid effect reducing AGEs is achieved by interrupting leptin signaling [80].

26.18 Curcuminoid Treatment—Strong Clinical Effects

Although no human studies, known to me, have dealt with the specific effects of curcuminoids on AGE/ALE-induced chronic inflammation, numerous clinical studies support strong positive effects induced by numerous other similar lifestyle-associated factors. Here are some recent examples:

To prevent release of proinflammatory cytokines. Thirty obese individuals were randomized to receive pure curcumin 1 g/day or matched placebo for 4 weeks. Following a 2-week washout period, each group was assigned to the alternate treatment regimen for another 4 weeks. Serum samples were collected at the start and end of each study period. Serum levels of IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, VEGF, IFNγ, EGF, MCP-1, and TNF α were measured using a multiplex Biochip Array Technology–based method. Only, but importantly, mean serum IL-1β ($P = 0.042$), IL-4 ($P = 0.008$), and VEGF ($P = 0.01$) were significantly reduced by 4 weeks of curcumin therapy [81].

*To reduce metabolic syndrom*e. A total of 50 patients diagnosed with metabolic syndrome (MS) according to the NCEP-ATPIII criteria, who were receiving standard of care, were assigned for 8 weeks to curcuminoids (1,000 mg/day) while another 50 MS patients received placebo. In order to improve the oral bioavailability, curcuminoids were coadministered with piperine in a ratio of 100:1 [82]. Significant positive impacts of curcuminoid supplementation were observed on triglycerides ($p = 0.003$), total cholesterol ($p = 0.042$), Lp(a) ($p < 0.001$), and non-HDL-C ($p = 0.009$), but not HDL-C ($p = 0.235$) or LDL-C ($p = 0.833$); all changes remained statistically significant after adjustment for baseline BMI [82]. In another study, overweight/obese type 2 diabetic patients (BMI ≥ 24.0; fasting blood glucose ≥7.0 mmol/L or postprandial blood glucose ≥11.1 mmol/L) were randomly assigned to curcuminoids (300 mg/day) or placebo for 3 months [83]. A total of 100 patients (curcuminoids, $n = 50$; placebo, $n = 50$) completed the trial. Curcuminoid supplementation significantly decreased fasting blood glucose ($p < 0.01$), HbA1c ($p = 0.031$), and insulin resistance index (HOMA-IR) ($p < 0.01$). In addition, curcuminoids also induced a significant decrease in serum total FFAs ($p < 0.01$), triglycerides ($P = 0.018$), and an increase in LPL activity ($p < 0.01$) [83].

To improve lung function, especially in smokers. Curry intake (at least once monthly) was significantly associated with better forced expiratory volume (FEV1) ($b = 0.045 \pm 0.018$, $p = 0.011$) and FEV1/FVC ($b = 1.14 \pm 0.52$, $p = 0.029$) in multivariate analyses that controlled simultaneously for gender, age, height, height-squared, smoking, occupational exposure and asthma/COPD history, and other dietary or supplementary intakes. Increasing levels of curry intake ("never or rarely," "occasional," "often," and "very often") were associated with higher mean adjusted FEV1 (p for linear trend = 0.001) and FEV1/FVC% (p for linear trend = 0.048). Significant effect modifications were

observed for FEV1 (curry* smoking interaction, $p = 0.028$) and FEV1/FVC ($p = 0.05$). There were significantly larger differences in FEV1 and FEV1/FVC% between curry intake and noncurry intake among current and past smokers—the mean adjusted FEV1 associated with curry intake being 9.2% higher among current smokers, 10.3% higher among past smokers, and 1.5% higher among nonsmokers [84].

To reduce risk of arteriosclerosis in diabetes. The effects of curcumin on risk factors for atherosclerosis in individuals with diabetes were investigated during a 6-month period in a randomized, double-blinded, and placebo-controlled clinical trial, in which 107 individuals were treated with 1.5 g curcumin and 106 with placebo. Curcumin intervention significantly reduced pulse wave velocity ($P < 0.001$) and decreased level of leptin ($P < 0.001$) but increased level of serum adiponectin ($P < 0.001$). These results were associated with reduced levels of homeostasis model assessment-insulin resistance (HOMA) ($P < 0.001$), triglycerides ($P < 0.001$), uric acid ($P < 0.001$), visceral fat ($P < 0.001$), and total body fat ($P < 0.001$) [85].

To improve mood in mental depression. A total of 56 individuals with a major depressive disorder were treated with curcumin (500 mg twice daily) or placebo for 8 weeks. From Weeks 4 to 8, curcumin was significantly more effective than placebo in improving several mood-related symptoms, demonstrated by significant differences in both IDS-SR30 total score ($p = 0.045$) and IDS-SR30 mood score ($p = 0.014$), in addition to a nonsignificant trend for STAI trait score ($p = 0.097$). Greater efficacy from curcumin treatment was identified in a subgroup of individuals with atypical depression [86].

To reduce osteoarthritis. A total of 185 and 182 patients with knee osteoarthritis were randomly assigned into curcumin (C. domestica) extracts and ibuprofen groups, respectively. All WOMAC showed significant improvement scores at Weeks 0, 2, and 4 when compared to the baseline in both groups. All scores, WOMAC total, WOMAC pain, and WOMAC function scores showed no difference between the groups at Week 4. The number of patients complaining of abdominal pain/discomfort was significantly higher in the ibuprofen group ($P = 0.046$). Most subjects (96%–97%) were satisfied with the treatment, and two-thirds rated themselves as improved in a global assessment [87]. Others have observed similar effects [88].

To reduce disease activity in rheumatoid arthritis. Forty-five patients diagnosed with rheumatoid arthritis were randomized into three groups to receive daily curcumin (500 mg), and diclofenac sodium (50 mg) alone or in combination for 8 weeks [89]. The primary endpoints were reduction in Disease Activity Score (DAS). The secondary endpoints included American College of Rheumatology (ACR) criteria for reduction in tenderness and swelling of joint scores. Patients in all three treatment groups showed statistically significant changes in their DAS scores. It is of special interest that the curcumin group showed the highest percentage of improvement in overall DAS and ACR scores (ACR 20, 50, and 70) and these scores were significantly better than the patients in the diclofenac sodium group. It is important to note that curcumin treatment was found to be safe and no adverse events were reported [89].

To reduce inflammation in dialysis patients and reduce pruritus. A total of 100 HD patients with end-stage renal disease (ESRD) and suffering from severe pruritus were randomized into two groups: turmeric and placebo. The pruritus score and biochemical determinants including high-sensitivity C-reactive protein (hs-CRP) were compared before and at the end of the study between the two groups. A significant reduction of pruritus scores accompanied by a significant decrease in inflammation (hs-CRP) was observed in the turmeric group ($p = 0.012$) compared to the placebo group ($p = 0.001$) [90]. Other authors have observed similar effects [91].

To maintain remission in ulcerative colitis. A total of 45 patients were randomized for 6 months to curcumin treatment (2 g/day) and 44 patients to placebo. All patients received in parallel treatment with sulfasalazine or mesalamine. Four percent of patients in the curcumin group relapsed at 6 months compared to 18% of patients in the placebo group ($P = 0.06$). Twenty-two percent of the curcumin-treated patients had relapsed at 12 months compared to 32% of placebo patients ($P = 0.31$). A total of nine adverse events were reported in seven patients. Both clinical activity index (CAI) and endoscopic index were significantly lower in the curcumin-treated group than in the placebo group after 6 months [92]. Others have also obtained similar results [93].

26.19 Probiotics, Especially When Combined with Plant Fibers (Synbiotics), Are Effective to Eliminate Poisonous Substances

Some specific lactobacilli might well have the ability to eliminate AGEs/ALEs from foods, in a way that is very similar to that demonstrated for gluten [94] and also for heterocyclic amines [95]. *In vitro* studies have shown that fructoselysine, the dominating AGE in heated milk, can be effectively eliminated when incubated with fresh intestinal flora [96]. It is a weakness that no study up to this point seems to have investigated the possibilities to eliminate AGEs and ALEs through gut reconditioning, for example, achieved by supplementation of live lactobacilli with or without simultaneous supply of plant fibers. Significant detoxification and clinical improvements are, however, reported when applied to reduce other noxious substances—here follows some examples, which gives strong support to the assumption that supply of probiotics or better synbiotics might have strong positive clinical effects in individuals exposed to larger amounts of AGEs and ALEs.

To prevent effects of local toxic metal exposure. A study in Mwanza, Tanzania, investigated the efficacy of probiotic foods, nutritious and affordable means to prevent consequences of high local toxic metal exposures. A group of 44 school-aged children was followed over 25 days, and 60 pregnant women were followed over their last two trimesters until birth [97]. A yogurt containing 10^{10} colony-forming units (CFU) *Lactobacillus rhamnosus* GR-1 per 250 g was administered, while control groups received either whole milk or no intervention. Changes in blood metal levels were assessed, and the gut microbiomes of the children were profiled by analyzing 16S rRNA sequencing via the Ion Torrent platform. The children and pregnant women in the study were found to have elevated blood levels of lead and mercury compared to age- and sex-matched Canadians. Consumption of probiotic yogurt had a statistically significant protective effect against further increases in mercury (3.2 nmol/L; $p = 0.035$) and arsenic (2.3 nmol/L; $p = 0.011$) blood levels in the pregnant women, but this trend was not statistically significant in the children [97].

To improve intestinal barrier function and prevent leakage. Twenty-five healthy subjects were randomized into two groups: Group A (13 subjects) was given an active formulation containing 250 mg of tara gum, a plant fiber, and 1 billion viable cells of a potential probiotic, *Streptococcus thermophilus* ST10, whereas 12 subjects were given a placebo formulation, one dose per day for 30 consecutive days [98]. The presence and concentration of exopolysaccharides (EPSs) in the feces was determined at Time 0, after 30 days of treatment, and at the end of a 2-week follow-up period. The monosaccharide composition of EPSs was used to quantify the possible contribution of tara gum (a substance similar to guar gum) to the amount of polysaccharides detected in the fecal material. Intestinal permeability was evaluated at the same time by means of the lactitol/mannitol ratio (LM ration expresses small intestine permeability) and sucralose concentration (expression of colonic permeability) in urine specimens sampled after specified times. Supplementation with *S. thermophilus* ST10 and tara gum increased significantly the fecal EPSs concentration compared with placebo ($P < 0.001$) in parallel to induce significant decreases in intestinal permeability, both of the small bowel and colon. The L/M ratio diminished from 0.021 in the active group to 0.014 and 0.015 after 30 and 45 days, respectively ($P = 0.045$ and $P = 0.033$ compared with placebo). The sucralose concentration decreased from 35.8 to 27.9 mg and 29.1 mg ($P = 0.038$ and $P = 0.026$ compared with placebo) at the end of the supplementation period and after the follow-up, respectively. No significant differences were recorded in the placebo after 30 days or at the end of the follow-up [98].

To reduce exposure to hepatotoxins and carcinogens. Both *in vitro* and *in vivo* studies suggest that selected strains of probiotic bacteria can form tight complexes with aflatoxin B1 and other carcinogens and eliminate them. Ninety healthy young men from Guangzhou, China, were enrolled in a study aimed to determine whether administration of probiotic bacteria could block the intestinal absorption of aflatoxin B1 and thereby lead to reduced urinary excretion of aflatoxin B1-N(7)-guanine (AFB-N(7)-guanine), a marker for a biologically effective dose of aflatoxin exposure [99]. They were randomly assigned into two groups; one group received a mixture of *Lactobacillus rhamnosus* LC705 and *Propionibacterium freudenreichii* subsp. shermanii strains two times per day for 5 weeks, and the other group received a placebo preparation. The percentage of samples with negative AFB-N(7)-guanine values were higher in

the probiotic group than in the placebo group after the 5-week intervention period ($p = 0.052$), and the decrease in urinary AFB-N(7)-guanine was statistically significant in the probiotic group ($p < 0.05$). The observed reduction was 36% after 3 weeks and 55% after 5 weeks. The geometric means for the probiotic and placebo groups during the intervention period were 0.24 and 0.49 ng AFB-N(7)-guanine/mL, respectively ($p = 0.005$) [99].

To reduce the accumulation of urea in chronic kidney disease. Patients with chronic kidney disease (CKD) show an increase in bowel aerobic bacteria that produce uremic toxins and decreased anaerobic bacteria as bifidobacteria and lactobacillus [100]. Different strains of *Lactobacillus casei* Shirota (LcS) were tried for 8 weeks in CKD patients in a randomized, controlled clinical trial in two doses: Group A: 8×10^9 CFU and Group B: 16×10^9 CFU. The larger dose induced a statistically significant reduction in blood urea concentrations [100].

To reduce inflammation in dialysis patients. Peritoneal dialysis patients received one capsule of a probiotic containing 10^9 cfu *Bi-fidobacterium bifidum* A218, 10^9 cfu *Bifidobacterium catenulatum* A302, 10^9 cfu *Bifidobacterium longum* A101, and 10^9 cfu *Lactobacillus plantarum* A87 daily for 6 months, and a placebo group received maltodextrin for the same duration [101]. A total of 39 patients completed the study (21 in the probiotics group and 18 in the placebo group). The serum levels of proinflammatory cytokines TNF-α, IL-5, IL-6, and endotoxin were significantly decreased after 6 months of treatment, while serum levels of anti-inflammatory cytokine IL-10 were significantly increased in the active group. In contrast, no significant changes in levels of serum cytokines and endotoxin occur in the placebo group after 6 months. Importantly, the residual renal function was well preserved in patients receiving probiotics [101].

To reduce uremic waste products in patients with CKD. In a 6-month cross-over trial, 46 outpatients were supplemented with a probiotic formulation consisting of a gel capsule containing a mix of *Lactobacillus acidophilus* KB27, *B. longum* KB31, and *S. thermophilus* KB19, totalling 1.5×1010 CFU/day [102]. Significant improvements were observed in terms of enhanced well-being (quality of life—QLT), absence of serious adverse effects, and impressive reductions in blood urea nitrogen (BUN)—the improvement in QOL as well as in BUN being statistically significant ($P < 0.05$). BUN levels decreased by 63% ($P < 0.05$), serum creatinine levels by 43%, and uric acid levels by 33%. The improvement in QOL was estimated to be 86% ($p < 0.05$) [102].

26.20 First Ever Trial with Synbiotic Treatment in Chronic Renal Disease Published in 2011

The first study ever undertaken to investigate the effects of combined fiber/probiotic (synbiotic treatment) was recently published [103]. This study demonstrated that fecal flora before supplementation with probiotics contained not only a significantly greater proportion of aerobic bacteria (specifically *Escherichia coli*)—100 times higher than that in healthy matched controls—but also significantly lower levels of the beneficial bifidobacteria. A significant decrease in both pathogenic Enterobacteria and in serum indoxyl sulfate levels was observed in dialysis patients receiving a supplement with a combination of 10^8 *Lactobacillus casei* strain Shirota, 10^8 *Bifidobacterium breve* (Yakult), and 4 g of the plant fibregalacto-oligosaccharides, three times a day for 2 weeks—a well-known prebiotic. The serum p-cresol level, poorly removed by dialysis, was significantly decreased during the treatment. Patients with a high serum p-cresol level tend to have often hard, but sometimes muddy, stools, and difficulty with defecation—a problem, which was eliminated by synbiotic treatment—replaced by normal ones [103]. However, the effects are not long-lasting, both protein-bound uremic toxins, PCS and IS, do return to pre-intervention levels 2 weeks after conclusion of the studies [104]. Most likely future should aim to, in addition to radical diet changes, supply pre-, pro-, and synbiotics on a regular basis as the disease remains, and most likely also provide both pre- and probiotics (synbiotics) in significantly larger doses.

A recent meta-analysis at the effectiveness of pre-, pro-, and synbiotics on reducing two protein-bound uremic toxins, PCS and IS, summarizes all studies published before 2012 [104]. Eight studies were found

to have investigated prebiotics, six probiotics, one synbiotics, one both pre- and probiotics. The quality of the studies ranged from *moderate* to *very low*. Twelve studies were included in the meta-analyses, which reported statistically significant reductions in both IS and PCS. Their conclusion was that "there is a limited but supportive evidence for the effectiveness of pre- and probiotics on reducing PCS and IS in the CKD population," but that "further studies are needed to provide more definitive findings before routine clinical use can be recommended" [104].

26.21 Rest, Recuperation, Cleansing, Detoxification—Important to Reduce Poisonous Substances and Maintain Health

Daily nocturnal fasting is important in order to reduce/eliminate poisonous substances from blood and tissues, particularly from the liver, kidneys, skeletal muscles, and brain. Disturbed function of the diurnal clocks is strongly associated with impaired glucose tolerance in diseases such as Alzheimer's disease, type 2 diabetes, Parkinson's disease, multiple sclerosis, epilepsy, other seizure disorders, amyotrophic lateral sclerosis, Huntington's disease, restless legs, obstructive sleep apnea, and other chronic disorders [1]. Significant positive physiological consequences of time-restricted feeding are observed in experimental animals (mice). In an experimental study, two groups of animals receive exactly the same food and the same amounts of calories; the only difference was that one group was allowed to consume freely day and night, while the other had its food intake restricted to only half of the 24-hour day. Dramatic positive differences in body weight, glucose intolerance (insulin resistance), leptin resistance, liver pathology (fatty infiltration), degree of inflammation, and motor coordination were observed in the group with time-restricted food intake [105].

26.22 Paleolithic Lifestyle Stimulates a Robust Circadian Rhythm and a Healthy and Long-Lasting Life

Observations that our forefathers might have eaten only twice a day are supported by studies in people with similar lifestyle. One such group is the Hunzas in Northern Pakistan, today known for their good health and high number of centenarians. The adult Hunzas are reported to live on a daily 1,800-calorie 99% plant-based diet, consisting of 73% of mostly unrefined/unprocessed carbohydrates, 17% fat, and 10% protein (http://thepdi.com/hunza_health_secrets.htm). They go out to work in the fields around 5 o'clock in the morning on an empty stomach, and eat their main meal of the day at noon, and a lighter meal just before going to bed around dusk (http://projectavalon.net/forum4/showthread.php?48210HUNZAS-a-people-who-live-to-age-145-)— allowing the organs 15–18 hours daily for rest, cleansing, and detoxification.

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