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Dietary Carbohydrates and Dental-Systemic Diseases

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ABSTRACT

Two contradictory hypotheses on the role of dietary carbohydrates in health and disease shape how dental-systemic associations are regarded. On one side, Cleave and Yudkin postulated that excessive dietary fermentable carbohydrate intake led—in the absence of dental interventions such as fluorides—*first* to dental diseases and *then* to systemic diseases. Under this hypothesis, dental and systemic diseases shared—as a common cause—a diet of excess fermentable carbohydrates. Dental diseases were regarded as an alarm bell for future systemic diseases, and restricting carbohydrate intake prevented both dental and systemic diseases. On the opposite side, Keys postulated the lipid hypothesis: that excessive dietary lipid intake caused systemic diseases. Keys advocated a diet high in fermentable carbohydrate for the benefit of general health, and dental diseases became regarded as local dietary side effects. Because general health takes precedence over dental health when it comes to dietary recommendations, dental diseases became viewed as local infections; interventions such as fluorides, sealants, oral hygiene, antimicrobials, and dental fillings became synonymous with maintaining dental health, and carbohydrates were no longer considered as a common cause for dental-systemic diseases. These opposing dietary hypotheses have increasingly been put to the test in clinical trials. The emerging trial results favor Cleave-Yudkin's hypothesis and may affect preventive approaches for dental and systemic diseases.

KEY WORDS: destructive periodontal disease, dental caries, chronic non-communicable diseases, carbohydrates, smoking.

Dietary Carbohydrates and Dental-Systemic Diseases

Around 60% of worldwide mortality is due to chronic non-communicable diseases (CNCDs) that are typified by affecting individuals for years, decades, or a lifetime, and for which there is no reliable evidence that transmission is readily possible from one individual to another (Daar *et al.*, 2007). Cardiovascular diseases, diabetes mellitus, certain cancers, and dementia are examples of *systemic* CNCDs. Dental caries, periodontal disease, certain oral cancers, and leukoplakia are examples of *dental* CNCDs. The associations between dental and systemic CNCDs have led to various hypotheses on etiology and prevention.

THE SAME OLD STORY: DENTAL AND SYSTEMIC DISEASES ARE ASSOCIATED

Many diseases characteristic of modern Western civilization are . . . frequently found associated with one another in individual patients.

—Burkitt, 1973

More than a dozen descriptors have been coined to reflect that dental and systemic CNCDs cluster across geography, genetics, and history, and that CNCD clustering occurs both within individuals and within populations. The evidence originates from paleopathology, medical explorer accounts, population migration studies, World Wars I and II evidence, and modern epidemiological studies.

Evidence from Paleopathology, Medical Explorer Accounts, and Population Migration Studies

Historically, clustering of CNCDs was first discussed within the context of nutrition transitions. Hunter-gatherers are typically characterized as being largely free from dental caries, periodontal disease, cardiovascular disease, diabetes, cancers, and obesity (Truswell, 1977). For instance, dental authorities report “never [having] seen paradontal [*sic*] disease in the Zulus living in their native reserves” (Cleave and Campbell, 1966), or Eskimos untouched by civilization with “magnificent dental development” and “so high an immunity to dental caries” (Price, 1945). The scarcity of dental CNCDs among hunter-gatherers coincides with an absence of systemic CNCDs. Prevalence of diabetes among Zulus living in tribal conditions was “extremely rare,” and for Eskimos it was reported to be less than 2 *per* 10,000 people (Price, 1945). Other diseases, such as coronary thrombosis, pulmonary embolism, gall stones, and rheumatoid arthritis, were similarly rare in populations with hunter-gatherer lifestyles such as reported in Africa, Australia, or other continents prior to the adoption of Western lifestyles (Trowell, 1960).

When individuals with a hunter-gatherer lifestyle transitioned to Western lifestyles as a result of agriculturization, migration, colonization, or other circumstances, CNCDs appeared. Within this context, CNCDs are referred to

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as diseases of civilization, degenerative diseases, Western diseases, diseases of modernization, or New World diseases. The change from native foods to modern foods in one Eskimo community was reportedly associated with a 144-fold increase in dental caries (Price, 1945). The prevalence of diabetes in this community is now considered “a major public health problem” (Acton *et al.*, 2002). Zulus transitioning to Western lifestyles experienced a quick deterioration of periodontal tissues and an increase in the prevalence of diabetes from rare to that observed in Westerners (Cleave, 1974). Ethiopian Jews migrating to Israel were afflicted by a six-fold increase in caries rates (Sarnat *et al.*, 1987) and “a rapid deterioration in periodontal status” that occurred hand-in-hand with the development of “early signs of risk factors for diabetes” (Trostler, 1997). Several other diseases typical of civilization have been documented in human migration studies: allergies (Geller-Bernstein and Kenett, 2004), cancers (Stemmermann *et al.*, 1979), and cardiovascular diseases (Robertson *et al.*, 1977). These nutrition transition reports are typically narrative—and consequently reflect a low level of evidence—but are convincing because of the consistency of the reports across investigators, populations, and scientific disciplines. Some reports suggested that the CNCDs associated with nutrition transitions were reversible (Price, 1945; O’Dea *et al.*, 1980; O’Keefe and Cordain, 2004), a finding which is consistent with World Wars I and II evidence.

World Wars I and II Evidence

CNCD patterns prior to, during, and after the World Wars have often been considered key evidence that systemic and dental CNCD incidences rise and fall in a synchronous fashion. In England, during World War II, the diabetes mortality among women dropped by 29% (Cleave and Campbell, 1966b), and caries in 5-year-old British schoolchildren dropped in a synchronous fashion by 28% (Sognaes, 1949). Subsequent to the Wars, diabetes and caries increased again. We report here similar findings from Japan on a synchronous fall and rise in diabetes and dental caries during World War II (Fig. 1). “Dramatic falls” in coronary deaths during World War II in several European countries were similarly used as an argument that dietary changes have profound impacts on health (Keys and Keys, 1975; Schettler, 1983) and suggest that the triad of diabetes, coronary heart disease, and dental caries incidence may have had similar temporal patterns during the World War eras.

Modern Epidemiological Evidence

The co-occurrence of systemic CNCNs within individuals has been documented in numerous studies and has been labeled as metabolic syndrome, the deadly quartet, or Syndrome X (Grundy *et al.*, 2004). The associations between the dental CNCNs on the one hand and systemic CNCNs on the other have become of renewed interest. Since the beginning of 1989, this field has burgeoned, with periodontal textbooks now including chapters on the topic (Newman *et al.*, 2006). While the dental-systemic disease associations have been consistently identified, the interpretations of these associations have been strongly influenced by the Zeitgeist, the dominant medical hypothesis on diet, health, and disease at their time of introduction.

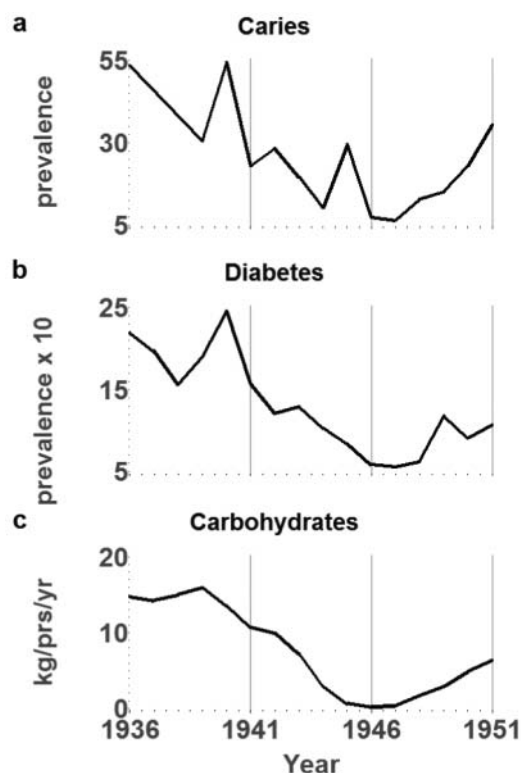


Figure 1. Sugar consumption, 1st molar caries incidence (ages 6 to 7), and diabetes prevalence in Japan between 1941 and 1956 (data abstracted from Goto *et al.*, 1958; Takahashi, 1961). In northern Europe, refined food imports were substituted with locally available natural products during the war, and caries rates dropped similarly (Sognaes, 1949), suggesting that the impact was not due to starvation. In Greece, reduced refined food imports could not be compensated for with local natural products, and calorie restriction with refined foods increased caries rates (Sognaes, 1949). The hypothesis that refined foods caused caries and diabetes explained these observations in *all* war-afflicted countries, and refined carbohydrates became regarded as causes for dental caries, diabetes, periodontal disease, myocardial infarction, and other chronic diseases (Cleave, 1974).

THE FORGOTTEN HYPOTHESIS: FERMENTABLE CARBOHYDRATES CAUSE FIRST DENTAL DISEASES, THEN SYSTEMIC DISEASES

Then, in the wink of an evolutionary eye, Western man changed his diet profoundly . . . and . . . became addicted to . . . refined carbohydrates. It is important to remember that it takes time for the consumption of refined carbohydrates to produce the various manifestations of the (diseases of civilization). The production of varicose veins, for example, takes longer than that of dental caries.

—Cleave and Campbell, 1966

Three hypotheses, or combinations thereof, may explain the co-occurrence of systemic and dental CNCNs within both individuals and populations. First, systemic CNCNs may cause dental CNCNs (*e.g.*, the presence of diabetes causes periodontal

disease). Second, dental CNCs may cause systemic CNCs (e.g., the presence of periodontal disease causes diabetes). Both these hypotheses have been expanded upon in numerous review articles and periodontal book chapters and will not be further discussed here (Newman *et al.*, 2006). A third hypothesis is that common causal factors are responsible for dental-systemic diseases.

There is little need to expand here on the generally accepted identity of tobacco smoking as an initial cause for destructive periodontal disease, oral cancer, and other systemic CNCs such as diabetes, lung cancer, and cardiovascular disease. Several reviews have expanded on the role of tobacco as a common cause of both dental and systemic CNCs (Hujoel *et al.*, 2002; Hyman *et al.*, 2002; Spiekerman *et al.*, 2003). There may now be a consensus that dental and medical professional organizations can work together in a synergistic fashion on tobacco cessation and prevention programs. Indeed, tobacco cessation programs initiated in the dental office increase the success rate of tobacco abstinence by 44% (Carr and Ebbert, 2007), suggesting that many lives could have been saved if dental professional organizations had recognized the periodontitis-smoking link earlier.

The goal of this report is to focus on dietary choices as a second common causal factor for dental and systemic diseases (Yellowlees, 1991; Campbell, 1996). Since the 1980s, medical and dental professionals often differed on how they perceive the role of diet in terms of disease prevention and management in their respective fields (much like in the past, when medical and dental professionals differed on the significance of smoking). Most medical organizations have identified unhealthy eating habits as a key behavioral risk factor responsible for the epidemic of systemic CNCs; such habits are considered an initial cause for the ongoing systemic CNC epidemic (*i.e.*, those causes which occur first in a sequential causal chain), and are considered to be responsible for a large proportion of the total mortality and morbidity in the world (Daar *et al.*, 2007). In contrast, in dentistry, since the 1980s, unhealthy eating habits have often been marginalized as an issue in the control of dental CNCs. As one illustration, a World Health Organization report suggested: "Dental health problems do not require any dietary recommendations" (Food and Agriculture Organization of the United Nations, 1998). Or, in 2006, "the majority of opinions" claimed "that there are no nutritional deficiencies that by themselves can cause gingivitis or periodontal pockets" (Newman *et al.*, 2006). The question raised in this review focuses on two contradictory dietary hypotheses regarding fermentable carbohydrates. In the next two sections, the potential role of fermentable carbohydrates as a cause of, *first*, dental CNCs, and *then* systemic CNCs is reviewed separately.

FERMENTABLE CARBOHYDRATES CAUSE FIRST DENTAL DISEASES: A TRUISM?

Caries of teeth is restricted to people and animals who eat liberally of carbohydrate containing foods. Carnivorous man and animals do not suffer from this disease.

—McCollum, 1941

A carbohydrate-free diet "prevents practically completely the initiation of periodontal lesions."

—Shaw and Griffith, 1961

Fermentable Carbohydrates and Dental Caries

Fermentable carbohydrates are recognized as a necessary cause of dental caries. The United States' National Research Council, while advocating increased fermentable carbohydrate consumption for systemic health, reported that 'dental caries does not develop in the absence of fermentable carbohydrates' (NRC, 1989). The deceptively simple rule 'no carbohydrates, no caries' appears to be strong not because of the presence of unequivocal randomized controlled trial evidence, but because of the inability to refute the hypothesis in a wide variety of research settings. For instance, in the Vipeholm study, it was reported that a "low carbohydrate, high fat diet depressed caries activity to practically nill" (Gustafsson *et al.*, 1954). The carbohydrate-caries connection has been documented in five continents, in humans and other animals, and as far back in time as archeology allows us to go.

Tribes who lived on an almost exclusively carnivorous diet rarely developed caries. The advent of agriculture and the development of staple crops that are high in carbohydrates increased caries prevalence (Hillson, 1996). For instance, around the Arabian Gulf, tribes living on an exclusively marine diet had virtually no caries, much like the Eskimos, whereas tribes consuming a mixture of the marine diet with carbohydrates had increased caries rates (Littleton and Frohlich, 1993). In another striking example, unprecedented high caries rates were observed in ancient Chileans upon the introduction of sticky fruit into the diet (Kelley and Larsen, 1991). The "no carbohydrates, no caries" dictum applies equally to animals. Gorillas eat less fruit than chimpanzees and also have less caries (Hillson, 1996).

Fermentable Carbohydrates and Periodontal Disease

The question could be asked: 'No carbohydrates or tobacco, no periodontal disease?' Tobacco is now recognized as one of the primary causes of periodontal disease (Bergström, 2004), yet during most of the 20th century it remained largely unrecognized. Is it possible that fermentable carbohydrate is *another* primary cause of periodontal disease which remained largely unrecognized during the latter half of the 20th century? The evidence is suggestive.

Like dental caries, periodontal disease is rare among animals living in the wild, but common among captive and domesticated animals (Colyer, 1947). Page and Schroeder considered the hypothesis that the diet is responsible for this difference "extremely farsighted and, in fact, corroborated by later detailed studies" (Page and Schroeder, 1982). While they did not report what aspect of the diet caused periodontal disease to occur in domesticated animals, circumstantial evidence implicates dietary carbohydrates; wild canids and felids live on a diet scarce in carbohydrates, and their domesticated counterparts consume a diet containing 30% to 50% carbohydrates (Logan, 2006).

Evidence from controlled animal experiments is consistent with such an interpretation. Experiments in mice indicated that consuming a partially restricted carbohydrate diet for 90 days reduced the score for alveolar bone loss by 38% (Baer and White, 1961). More dramatic results were reported in rice rats (Auskaps *et al.*, 1957; Shaw and Griffiths, 1961). When sucrose was replaced by lard in the diet, the periodontal soft tissue lesions of these rice rats were reduced by 90% and the calcified periodontal tissue lesions by 75%. The findings led the investigators to report that a no-carbohydrate diet “prevents practically completely the initiation of periodontal lesions in the soft tissues for at least 20 weeks” (Shaw and Griffiths, 1961).

Controlled human experiments suggest that these experimental animal findings may have relevance to humans. Six clinical trials provided evidence that moderate reduction in carbohydrate intake reduced gingivitis scores on average by one-third (Fig. 2). Additional studies on other periodontal parameters pointed in a similar direction. As little as two 50-gram sucrose drinks *per* day increased the probing pocket depth by 0.4 mm (Cheraskin *et al.*, 1965), and self-reports of gingival tenderness were related to glucose tolerance test results (Cheraskin and Ringsdorf, 1963). This evidence is consistent with the narrative accounts of rapid periodontal disease onset in hunter-gatherers who switched to a Western diet. Stringent restriction of carbohydrates—which animal models suggested was necessary to prevent destructive periodontal disease—was reported to be “completely impractical” (Gaengler *et al.*, 1986). As a result, we do not know the extent to which the beneficial impact of a no-carbohydrate diet in animal results can be extrapolated to humans.

The most recent evidence stems from epidemiological studies that relate markers of fermentable carbohydrate metabolism to markers of periodontal disease. Diabetes, a marker of abnormal blood glucose metabolism, has been associated with markers of periodontal disease in both children and adults (Tsai *et al.*, 2002; Lalla *et al.*, 2006). Physical activity, which decreases blood glucose levels, has been related to a reduced risk of destructive periodontal disease in adults (Merchant *et al.*, 2003). Obesity, a marker of excessive fermentable carbohydrate intake, is associated with an increased risk of periodontal disease (Perlstein and Bissada, 1977; Saito *et al.*, 1998, 2005; Alabdulkarim *et al.*, 2005; Dalla Vecchia *et al.*, 2005; Reeves *et al.*, 2006).

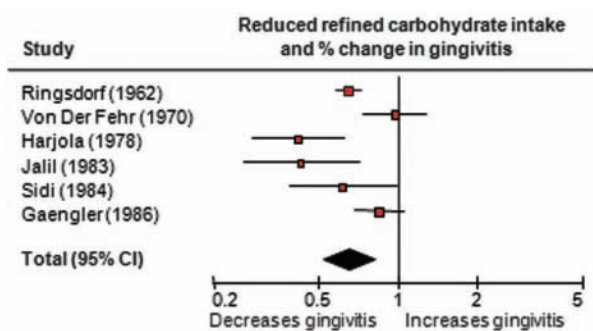
FERMENTABLE CARBOHYDRATES THEN CAUSE SYSTEMIC DISEASES: A CONTENTIOUS HYPOTHESIS

My research on coronary heart disease has convinced me beyond doubt that sugar plays a considerable part in this terrifying modern epidemic.

—Yudkin, 1972b

From an evolutionary point of view, the refined carbohydrates, both on account of the magnitude and the recentness of the alterations, are always the foods most likely to be at fault (for the diseases of civilization), and not the fats.

—Cleave, 1975



Square black box reflects point estimate of percent reduction in gingivitis score for individual studies and whiskers on box reflect the 95% confidence intervals. The diamond-shaped symbol at the bottom of the graph reflects the summary estimate and 95% confidence interval.

Figure 2. A summary of six clinical trials on the effects of small intake changes in fermentable carbohydrate intake on gingivitis (Ringsdorf and Cheraskin, 1962; Von der Fehr *et al.*, 1970; Harjola and Liesmaa, 1978; Jalil *et al.*, 1983; Sidi and Ashley, 1984; Gaengler *et al.*, 1986). Reducing sugar intake for 4 to 21 days lowered gingivitis scores by approximately one-third.

The evidence for sucrose as the “greatest killer” in Western societies is “utter nonsense” and “would never pass an acceptable term paper in an undergraduate course in home economics.”

—Keys and Keys, 1975

Up until now, public health policies on the role of fermentable carbohydrates have not been guided by pivotal randomized trial results (Taubes, 2007). In the absence of pivotal evidence, opposing *medical* hypotheses on the role of fermentable carbohydrates in health and disease have affected all aspects of *dentistry* (Fig. 3). When diets high in fermentable carbohydrate diets were deemed to prevent systemic CNCs, then the dental profession had to tell patients “to enjoy foods traditionally considered ‘bad’ from a dental viewpoint, as long as they brush their teeth with a fluoride containing dentifrice” (Duggal and van Loveren, 2001). Under the opposite medical hypothesis, a diet restricted in fermentable carbohydrate was deemed to prevent systemic CNCs, and dental professionals could tell their patients to restrict “bad foods” to achieve “the larger and more important goal” of preventing both dental and systemic CNCs (Cleave, 1974). Because these contradictory *medical* hypotheses on fermentable carbohydrates drive many aspects of *dentistry*, the evidence on both hypotheses is briefly reviewed.

Two protagonists for the hypothesis that fermentable carbohydrates are harmful for health were Thomas Cleave and John Yudkin. Cleave hypothesized that refined carbohydrates such as white flour and white or brown sugar were the cause of many Western diseases, including dental diseases (Cleave and Campbell, 1966). Yudkin hypothesized that sugar was causative of both dental and systemic CNCs (Yudkin, 1972a). While both Cleave and Yudkin had distinct hypotheses regarding which dietary carbohydrates caused CNCs, they were unified regarding the significance of high-glycemic dietary carbohydrates and dental

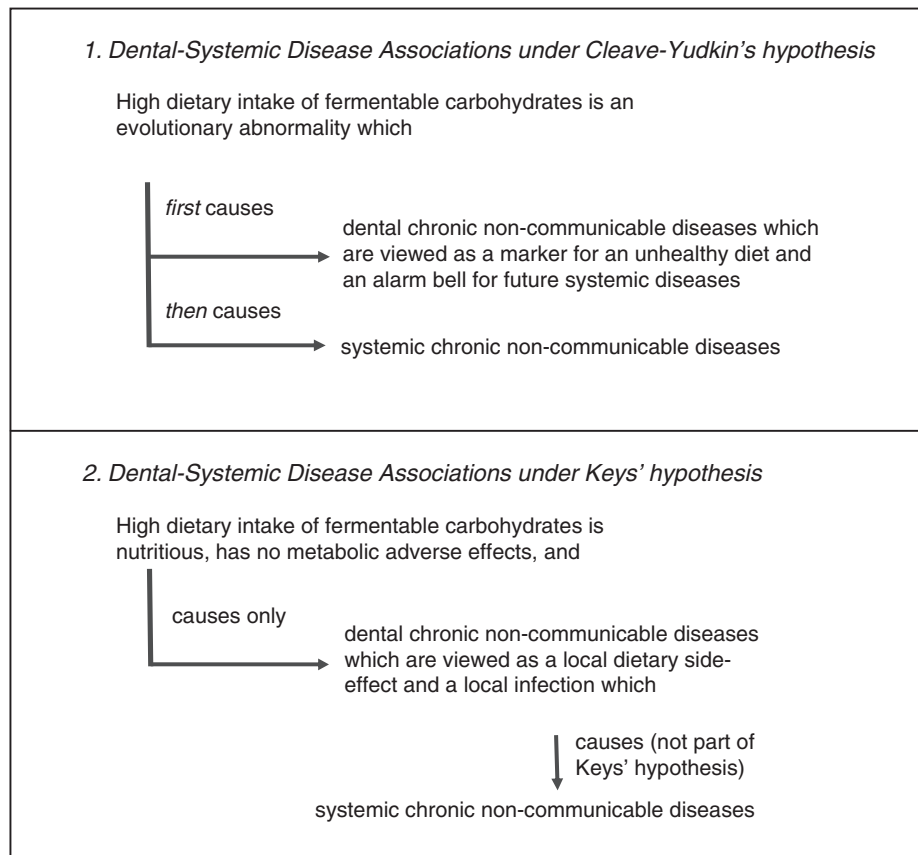


Figure 3. A causal diagram of two contradictory hypotheses on fermentable carbohydrates and dental-systemic disease associations. The size or shape of the causal arrows does not reflect the level of evidence in support of the hypothesis.

CNCDs. According to their hypothesis—which is henceforth referred to as Cleave-Yudkin's hypothesis—both dental and systemic CNCDs were due to an excess intake of fermentable carbohydrates, dental CNCDs were the early marker for systemic CNCDs, and dental CNCDs should be primarily prevented by restriction of fermentable carbohydrates, and only secondarily with interventions such as fluorides.

On the opposite side of this medical scientific fence was Ancel Keys. He was the protagonist of the lipid hypothesis and focused on excess fat intake as the primary cause of systemic CNCDs; a healthy diet consisted of *increasing* intake of fermentable carbohydrates—hence in apparent opposition to Cleave-Yudkin's hypothesis—while decreasing fat intake (Keys and Keys, 1959). Health recommendations based on Keys' hypothesis asserted that a diet high in fermentable carbohydrates and low in fat reduced systemic CNCDs, with dental diseases as a “local dietary side-effect” (König, 2000). Keys' hypothesis pitted dietary prevention for dental diseases and dietary prevention for systemic diseases against one another (NRC, 1989).

In the United States, the first national dietary guidelines released in 1980 largely endorsed Keys' hypothesis (Mottern, 1977). Specific recommendations were to increase the consumption of carbohydrates and to decrease the consumption of fat. The scientific bases for these recommendations in the 1980s were

predominantly ecological associations, not randomized trials (Keys, 1980). Between 1980 and 2009, these dietary guidelines have become increasingly scrutinized as cohort studies and randomized trials—higher levels of evidence than ecological studies—have been conducted. Emerging evidence is bringing Cleave-Yudkin's hypothesis, albeit under different names, such as dietary glycemic load, back to the forefront of medical research.

A first line of evidence against Keys is that the few trials on the effectiveness of low-fat diets failed to support his hypothesis. In a pivotal trial with about 13,000 male participants, a low-fat diet combined with smoking cessation and blood pressure medication resulted in a slight increase in mortality, the opposite of what was expected (Multiple risk factor intervention trial risk group, 1982). In the Women's Health Initiative study, with about 50,000 participants, a low-fat diet failed to reduce cardiovascular disease (Howard *et al.*, 2006), breast cancer, or colon cancer (Beresford *et al.*, 2006; Prentice *et al.*, 2006). A systemic review of

randomized controlled trials on low-fat diets failed to show an impact on obesity (Pirozzo *et al.*, 2002) or survival (Hooper *et al.*, 2000).

It must be briefly noted here that the dietary hypotheses on lack of dietary fiber and nutritional deficiencies as causes of diseases of civilization were similarly refuted in pivotal trials. Five randomized trials on over 4000 individuals failed to provide evidence that fiber supplementation reduced colon cancer risk (Asano and McLeod, 2002). Similarly, the hypothesis that nutritional deficiencies were the cause of the diseases of civilization, and that this needed to be remedied by micronutrient supplementation, was forcefully refuted. Micronutrient supplementation trials with anti-oxidants were almost consistently associated with an increased mortality risk (Bjelakovic *et al.*, 2007). Most recently, the “largest individually randomized cancer prevention trial ever conducted” ended by refuting the hypothesis that Vitamin E or selenium supplementation could reduce prostate cancer risk (Lippman *et al.*, 2008). With Keys' hypothesis, the fiber hypothesis, and the nutritional deficiency hypothesis refuted, Cleave-Yudkin's hypothesis is the only one left untested in a definitive randomized trial.

The second line of evidence is the positive results in support of Cleave-Yudkin's hypothesis. A systematic review of the adverse effects of foods with a high glycemic index suggests an

increased risk for type 2 diabetes, coronary heart disease, gall bladder disease, and breast cancer, as well as for all of these diseases combined (Barclay *et al.*, 2008). Consistent with the epidemiological evidence, systematic reviews of randomized controlled trials have suggested low-carbohydrate diets as being most effective in achieving weight loss and improving cardiovascular disease markers (Thomas *et al.*, 2007). The recent series of randomized controlled trials on restricted fermentable carbohydrate diets have largely reported consistent beneficial results on weight loss and improvements in surrogate markers of diabetes and cardiovascular diseases (Ebbeling *et al.*, 2007; Gardner *et al.*, 2007; Jenkins *et al.*, 2008; Salas-Salvado *et al.*, 2008; Shai *et al.*, 2008).

Nonetheless, there are currently no definitive trials to indicate that restriction of dietary carbohydrates will reduce morbidity and mortality, an essential step to ending the controversy. The best available current evidence is in favor of Cleave-Yudkin's hypothesis and may be causing a glacial shift toward recognition of the harmful effects of fermentable carbohydrates. One organization has advised restriction of the fermentable carbohydrates that used to be considered the staples of the food pyramid (World Cancer Research Fund, 2008). Similarly, the adverse impact of sweet soft drinks on obesity is becoming increasingly well-documented (Schulze *et al.*, 2004). If changes in public health policy or public perception on fermentable carbohydrates were to occur as a result of this emerging evidence, it may affect dental CNCND incidence, perspectives on dental-systemic CNCND associations, and, consequently, the dental profession.

DENTAL DISEASES: A MARKER OF AN UNHEALTHY DIET OR A LOCAL DIETARY SIDE-EFFECT?

Eliminating symptoms is like responding to a car's oil light by clipping the wires rather than addressing the underlying causes.

—Nesse, 2007

Dental Diseases as the Marker of an Unhealthy Diet

Cleave considered dental and general health to be the evolutionary normality, "the perfect adaptation of all species to their natural environment," and dental and systemic CNCNDs a reflection of "an unnatural feature in the environment" (Cleave, 1975). Teeth, being critical to survival, have been subjected to strong selective pressures, and some dental tissue genes, such as amelogenin, have been conserved nearly unchanged for 400 million years without microbiological plaque control (Delgado *et al.*, 2008). Under Cleave-Yudkin's hypothesis, the natural diet for men is "rich in protein, moderately rich in fat, and usually poor in carbohydrate" (Yudkin, 1972b). Dental diseases appeared *en force*, according to Cleave and Yudkin, because of the nutrition transitions with their gradual increase in fermentable carbohydrate consumption. Oral hygiene and fluoride abruptly became necessary to maintain oral health to cope with the emerging unnatural diet.

There are at least three dental consequences to these evolutionary arguments. First, prevention of dental diseases through fermentable carbohydrate restriction helps 'the larger and more important goal' (Cleave, 1974) of reducing the burden of diabetes and other systemic CNCNDs. Second, a primary focus on preventing dental diseases with non-dietary approaches becomes questionable, since "it is into educative channels (on refined carbohydrates) that fluoridation costs would seem better directed" (Cleave, 1975). Yudkin's point, that if "dental decay can be preventable; why not prevented?" (Yudkin, 1969), drove home the message that successful prevention through fermentable carbohydrate restriction was, at least in theory, possible. And finally, non-dietary prevention of dental diseases may come with side-effects or unintended consequences that can be avoided with a dietary approach.

With respect to the last point, in favor of Cleave-Yudkin's hypothesis is that dietary prevention of dental diseases is not associated with side effects. Side effects of dental interventions can be an issue, because common approaches such as fluorides and dental materials can lead to the exposure of billions of individuals, sometimes from conception to grave. Even rare side effects can become a concern under such circumstances, and yet such reliable evidence is often missing. Side effects with even potentially common outcomes often remain unstudied. One example is the commercial promotion and professional endorsement to chew sugar-free gums to promote oral health. Yudkin hypothesized that "people are laying the foundations for serious disease in later life by encouraging the development of a sweet tooth in children" (Yudkin, 1972a). Is it possible that daily exposure to sugar-free gums contributes to obesity (Stellman and Garfinkel, 1986; Bellisle and Drewnowski, 2007; Swithers and Davidson, 2008)? Recommending a one-hour-a-day habit without an answer to this question may be surprising, considering how simply and inexpensively weight changes could have been measured in the clinical trials that were conducted.

A second consideration in favor of Cleave-Yudkin's hypothesis is that dental symptoms such as pain or hypersensitivity to sweets may represent evolutionary defense mechanisms which, when eliminated, may in and of themselves cause harm. Pain features prominently among the important evolutionary defense mechanisms. Those rare individuals born with an absence of pain sensitivity typically die young (Cox *et al.*, 2006). Pain due to bodily injury limits movement and allows healing to occur. Animals may self-medicate with dietary choices (Engel, 2002), suggesting that dental pain could be considered an evolutionary mechanism intended to minimize the over-consumption of fermentable carbohydrates. Studies exploring such evolutionary hypotheses may be warranted, given the global scale on which organizations are attempting to prevent dental diseases with non-dietary approaches.

Dental Diseases as a Local Dietary Side-effect

While Keys did not disagree that sugar "strongly promotes tooth decay" (Keys and Keys, 1975), he failed to explain why a diet *bad* for dental health would be *good* for systemic health, why caries and periodontal disease were not diseases of civilization, or how his lipid hypotheses could be explained in terms of evolutionary principles. This lack of an explanation

did not hinder the rise of Keys' hypothesis to dominance. Consequently, dental diseases became regarded as a local dietary side effect, the biological normality associated with a diet high in fermentable carbohydrates. Keys' hypothesis became squarely in the center of mainstream dental philosophy and literature: 'Dietary counseling places an emphasis of the reduction of fat intake and promotes the consumption of starch-rich foods . . . ' (Van Loveren, 2000). "The potential of lipids as anticarcinogenic food additives" became forgotten, maybe because of "the dietary goal of limiting consumption of saturated fats" (Newbrun, 1989).

Instead of recommendations restricting fermentable carbohydrates, the opposite recommendations were made. The high-glycemic index carbohydrates, such as certain fruits, cereals, bread, corn, and potatoes, became considered food staples that improved systemic health. It was reported to be "irrational to advise against fruit consumption based on its cariogenicity" (Food and Agriculture Organization of the United Nations, 1998). Even candy appeared to be acceptable for dental health. A World Health Organization publication in 1998 reported on the evidence that "frequent consumption of candy did not seem to be a significant determinant of caries" (Food and Agriculture Organization of the United Nations, 1998).

Because of the dominant nature of Keys' hypothesis in the 20th century, the dental profession may have been forced to focus on non-dietary preventive approaches for dental CNCDs. A carbohydrate world needed to become fluoridated, teeth needed to become sealed with plastics, and dental diseases became labeled as infectious diseases to be treated with antimicrobials. Dental health became dependent, as a first line of defense, on a \$25 billion market of oral hygiene devices, rinses, fluoride delivery devices, and antimicrobials (Research and Markets, 2008).

While such approaches helped turn a pandemic into an epidemic for certain populations, the approach remained a failure globally: Oral diseases remain a major public health problem that is growing in low- and middle-income countries (Petersen, 2008). Even in most industrialized countries, dental caries still affects 60% to 90% of school-aged children and the vast majority of adults (Petersen, 2008). If nothing else, these statistics suggest that neutralizing the harmful dental effects of fermentable carbohydrates is challenging. Given such disappointing statistics, ever more aggressive use of fluorides and oral hygiene was advocated.

Dental congresses under the auspices of the World Health Organization were devoted to means of promoting more effective use of fluorides for large fractions of the global population (Petersen *et al.*, 2008). Dietary guidelines in 2005 indicated that "there is concern that Americans may not be getting enough fluoride for maintenance of oral health" (US Department of Health and Human Services and US Department of Agriculture, 2005). This statement was made even though 1 in 5 people between the ages of 6 and 39 years have fluorosis (Beltran-Aguilar *et al.*, 2005). A "personal prevention package of oral hygiene habits" was advocated which allegedly could reduce caries prevalence to 25% in adolescents (Food and Agriculture Organization of the United Nations, 1998). This latter implied that even under what

appear to be unrealistic hopes on the effectiveness of non-dietary prevention, tertiary prevention such as fillings, implants, and dentures remained an accepted trade-off for a large proportion of the population living in a high-glycemic carbohydrate world.

DENTAL DISEASES: AN ALARM BELL OR A CAUSE FOR SYSTEMIC DISEASES?

The value of a scientific hypothesis lies less in the number of observations that it can explain than in the number that it can successfully predict.

—Sir Richard Doll (Cleave and Campbell, 1966)

Dental CNCDs, an Alarm Bell Warning for Systemic CNCDs

Cleave and Yudkin considered both dental caries *and* periodontal disease to be early warning lights for the development of diabetes, obesity, and coronary heart disease. Because the onset of "(dental) decay (occurred) in matter of months" and the onset of "diabetes maybe 20 years, coronary heart disease 30 years" (Cleave and Campbell, 1966), dental caries and pyorrhea were considered an alarm bell for future systemic diseases.

Evidence from subsequent clinical studies supported the Cleave-Yudkin view of dental diseases as both an early and sensitive alarm bell for dietary fermentable carbohydrate exposure. The addition of two 50-gram sucrose drinks a day increased pocket depth in four *days* (Cheraskin *et al.*, 1965). Conversely, eliminating refined carbohydrates reduced gingival bleeding in *weeks*, possibly independent of oral hygiene (Fig. 2). The addition of 50 grams *per* day of carbohydrates to a low-carbohydrate diet produced significantly increased caries activity within a *year* (Gustafsson *et al.*, 1954). It is now becoming apparent that even destructive periodontal disease is a sensitive marker for adverse lifestyles. Obesity and diabetes—both diet-related diseases—have been associated with periodontal attachment destruction at a young age and decades before systemic morbidity and mortality become apparent (Hujoel, 2008). Clearly, the dental alarm bell has an extremely low threshold for activation; the response occurs in days, weeks, or, at most, years, as opposed to the decades it takes for systemic CNCDs to become clinically apparent.

Of significance to the dental profession, dental diseases are not silent sentinels such as retinopathy for diabetes (Klein *et al.*, 2006), but are more like five-alarm fire bells, difficult to ignore by the affected individuals or society. The shrill dental alarm bell in Alaskan Natives could not be ignored and led to political controversy and a new dental "specialty" (Bolin, 2008). The tooth loss among potential military recruits for World War II could not be ignored and was in part responsible for creating the National Institute of Dental Research (Slavkin, 1998). At an individual level, dental pain is notorious for its severity and thus may very well be one of the loudest alarm bells in the body. Silencing such an alarm bell with "antidotes" may not be without risks.

Cleave and Yudkin, with their central focus on fermentable carbohydrate intake and metabolism, provided a simple, consistent, and predictive hypothesis on dental-systemic disease associations. The hypothesis specified that both dental caries and destructive periodontal disease can predict systemic CNCs (Cleave and Campbell, 1966), it predicts that those systemic CNCs caused by fermentable carbohydrates will be associated with dental CNCs, and it rests on the biological plausibility of fermentable carbohydrate metabolism as the driving mechanism.

In favor of Cleave-Yudkin's hypothesis is the ability to predict and explain dental-systemic disease associations that were unknown when the hypothesis was formulated. It is now known, for instance, that markers of abnormal glucose metabolism, such as high levels of advanced glycation end-products or post-load plasma glucose concentration, have been related to diverse systemic outcomes such as Alzheimer's (Takeuchi and Yamagishi, 2008), chronic kidney disease (Thomas *et al.*, 2005), pancreatic cancer (Gapstur *et al.*, 2000), adverse pregnancy outcomes (Metzger *et al.*, 2008), and cardiovascular disease (Jandeleit-Dahm and Cooper, 2008). Cleave-Yudkin's hypothesis is therefore consistent with the findings that dental disease markers can be associated with these same systemic CNCs (Kshirsagar *et al.*, 2005; Michaud *et al.*, 2007; Stein *et al.*, 2007; Heimonen *et al.*, 2008).

Similarly, the more a diet drops dental plaque pH, the more it spikes blood glucose levels, providing an elegant biological plausibility model for Cleave-Yudkin's hypothesis that dental caries is an alarm bell for systemic CNCs (Lingström *et al.*, 1993). This close correlation suggests that advising a person to avoid high-glycemic foods will be of benefit both in terms of caries prevention and in terms of avoiding steep rises in blood glucose that complicate diabetes control, and all of its associated morbidities. This close correlation also suggests that advising a person to avoid frequent snacking on fermentable carbohydrates will avoid the frequent pH drops that have been linked to caries risk (Gustafsson *et al.*, 1954) and to the increases in glycated hemoglobin levels (Morse *et al.*, 2006; Overby *et al.*, 2008) that have been linked to microvascular complications. The dental plaque pH-glycemic index correlation provides a compelling biological argument that dietary habits bad for dental health really may be bad for general health, the opposite of Keys' assertion.

The Cleave-Yudkin's hypothesis may also predict when caries or periodontal disease will be associated with systemic diseases. Animal experiments suggested that fermentable carbohydrates can induce destructive periodontal disease at *any* point during a lifespan (Shaw and Griffiths, 1961). In contrast, dental caries is induced most easily when dietary carbohydrates are provided prior to and during tooth eruption, *not* after tooth eruption. These findings suggest that the associations between dental diseases and systemic diseases depend on when carbohydrate exposure is initiated. If carbohydrate exposure is initiated after tooth eruption, systemic CNCs will be associated more strongly with periodontal diseases than with caries. In contrast, if carbohydrate exposure is initiated prior to tooth eruption, both periodontal disease and caries can be expected to be associated with systemic CNCs. The ability to test such predictions of a global hypothesis against observations is what makes Cleave-Yudkin's hypothesis powerful.

Dental CNCs as a Cause for Systemic CNCs

For Keys, dental diseases had no significance in dietary considerations. They became described as the opposite of an alarm bell, a mere local dietary side-effect. Maybe in part because of the dominance of Keys' hypothesis, both caries and periodontal disease became regarded as local infections, not lifestyle diseases. At the same time, medical infections were found to be associated with adverse systemic effects. Vaginal infections were associated with adverse pregnancy outcomes (Minkoff *et al.*, 1984), and acute respiratory infections with stroke (Grau *et al.*, 1995). For a Finnish investigative team, it became a logical step to implicate dental infection as just another example of a medical infection that could cause systemic diseases. Indeed, it is some of these same Finnish investigators who were the first to suggest that chronic *Chlamydia pneumoniae* infections "could be a factor in the pathogenesis of cardiovascular diseases" (Saikku *et al.*, 1988), and who suggested a year later that chronic dental infections also played a causal role in myocardial infarction (Mattila *et al.*, 1989). It is within this medical infection Zeitgeist of the early 1990s that the excitement of considering dental diseases as a cause for systemic diseases flourished. The hypothesis driving pivotal dental clinical trials became, according to one of its primary investigators: "If periodontal infection is suppressed by an anti-infective intervention" (Baker, 2001), systemic outcomes will improve.

A first setback was that dental CNCs are no longer regarded as "medical infections" (Marsh, 2003), thereby bringing into question the very premise on which clinical trials were initiated. In the early 1990s, when dental CNCs were first suggested to cause systemic CNCs, both caries and periodontal disease were hypothesized to be local infectious diseases (Tanzer, 1995; Lindhe *et al.*, 1997). Neither tobacco nor diet was cited as a potential cause for periodontal disease in authoritative reviews or textbooks of that era (Williams, 1990; Lindhe *et al.*, 1997). These beliefs changed dramatically after dental infections were postulated to cause systemic diseases. Tobacco is now described as a "major risk factor" for destructive periodontal disease (Newman *et al.*, 2002). Increasing evidence links obesity, and therefore diet, to destructive periodontal disease (Saito *et al.*, 1998). At the same time, evidence in favor of the infection hypothesis became increasingly refuted. "(T)he widely held belief that caries is an infectious disease is mainly based on coprophagous rodents, and attempts to control caries using this approach have been unsuccessful this far" (Zero, 2004). Similar comments can be made about periodontal disease.

A second setback was the strong evidence in the medical literature that treating infections worsened the systemic outcomes, the opposite of what was expected under the infection hypothesis. A meta-analysis of trials concluded that macrolides against *Chlamydia pneumoniae* increased mortality risk, mostly from coronary heart disease (2006). For low birthweight, which was similarly hypothesized to be the result of infections, metronidazole increased the risk of preterm birth (Okun *et al.*, 2005). In 2008, the United States Preventive Services Task Force recommended *against* screening for bacterial vaginosis in pregnant women considered to have low risk for preterm delivery

(2008). Two pivotal dental trials similarly failed to show an impact of treating periodontal infections (Michalowicz *et al.*, 2006; Beck *et al.*, 2008). The “medical infection” Zeitgeist which was the basis for the hypothesis that dental diseases were infections and that infections caused systemic diseases became largely refuted.

These setbacks to the dental infection hypothesis have led to alternative and often inconsistent causal explanations for dental-systemic diseases. For instance, some investigators have suggested that dental-systemic disease associations are more likely to reflect causality if the associations are positive for the periodontitis markers (that were viewed as medical systemic infections), and negative for dental caries markers (which were viewed, by some, as infections not in contact with the systemic environment) (Demmer *et al.*, 2008). Several dental-systemic reports failed to support this specificity hypothesis. For instance, pulpal inflammation and root canals have been associated with coronary heart disease (Joshupura *et al.*, 2006). Students—*i.e.*, young individuals—with 9 or more missing teeth—think caries—exhibit increased incidence of cardiovascular disease (Tu *et al.*, 2007). The first tooth lost, confined to the younger cohort members, is associated with increased cancer and cardiovascular diseases (Abnet *et al.*, 2001, 2005). Such incongruent findings led to mutually exclusive hypotheses on whether caries or periodontal disease should be causally associated with systemic diseases. In contrast, the finding that both caries and periodontal disease markers are associated with systemic CNCDS is exactly what Cleave and Yudkin observed and predicted.

Similarly, there are conflicting causal explanations about how eradicated dental infections can still cause systemic CNCDS decades later. Edentulism has the ability to ‘cause’ diabetes 20 years later (Demmer *et al.*, 2008). Extractions at a young age have the ability to ‘cause’ a heart attack 3 decades later (Tu *et al.*, 2007). These associations between long-gone infections and systemic events were paradoxically interpreted to “bolster the periodontal infection hypothesis” (Demmer *et al.*, 2008) and to have “greater implication for the cardiovascular health of the public . . . in view of the continuing decline in the number of dentists” (Tu *et al.*, 2007). Yet, such a causal interpretation is inconsistent with the original infection hypothesis, which stated that infections needed to be present to do harm. Pivotal randomized controlled trials were initiated on the very premise that the “real association should be with infection” that is present (Karow, 2001). Providing *post hoc* causal interpretations to such unanticipated findings is difficult without resorting to conflicting explanations. In contrast, the finding that dental CNCDS occur decades before systemic CNCDS is what Cleave observed and explained as the incubation times required for fermentable carbohydrates to lead to clinically apparent diseases (Cleave and Campbell, 1966).

The conflicts in causal hypotheses on dental-systemic disease associations do not end there. There is no agreement as to whether gingivitis, destructive periodontal disease, denture sores, pulpal inflammation, or other dental markers cause systemic disease. There is no agreement on which of the numerous ‘causal’ dental-systemic disease associations are to be expected as opposed to observed and fitted with *post hoc* causal explanations. Neither

is there an agreement on which biological mechanisms cause systemic CNCDS. Cleave-Yudkin’s hypothesis currently has the edge when it comes to satisfying the Occam’s razor principle: It provides the simplest, most consistent hypothesis for explaining and—more importantly—predicting dental-systemic disease associations.

CAN THE DENTAL AND MEDICAL PROFESSIONS WORK TOGETHER ON DIETARY PREVENTION, AGAIN?

The topic is critical to the oral and systemic health . . .

—Meskin, 2001 (*JADA* editor)

Both the emerging randomized trial evidence and the ongoing obesity and diabetes epidemic may cause shifts in public health policies on dietary advice. In the United States, morbid obesity is increasing rapidly (Freedman *et al.*, 2002), one-third of the children born in 2000 are anticipated to develop diabetes in their lifetime (Narayan *et al.*, 2003), the life-expectancy in large segments of the population is decreasing (Ezzati *et al.*, 2008), and dental caries may be on the rise again in children (Dye *et al.*, 2007). Some dietary guidelines published by augur institutions are focusing specifically on dietary fermentable carbohydrates in an effort to stem the epidemic of systemic CNCDS. For instance, the 2008 guidelines from the World Cancer Research Fund to prevent cancer recommended limiting starchy foods and sugary drinks, all high-glycemic fermentable carbohydrates (World Cancer Research Fund, 2008).

Similarly, some dental investigators are providing clues that fermentable carbohydrates are once again considered as a common cause of both dental and systemic CNCDS. In one series of studies linking tooth loss to cancer, it was reported that a “high reliance on corn and wheat as dietary staples increased the risk for esophageal cancer. Unfortunately, we did not have information on corn or wheat intake” (Abnet *et al.*, 2001). Such specific acknowledgment that gastrointestinal cancer may be due to what were once considered dietary food staples illustrates the shift in thinking that is occurring. The evidence on fermentable carbohydrates is changing from a description as “a valuable source of energy” to a suspected cause of dental-systemic disease associations which remains to be addressed.

Given that the food industry is a multi-billion-dollar industry, it can be expected that changes in public health policy or research priorities will be challenging. The tactics used by the tobacco lobby (Kessler, 2001) have allegedly been adopted by the food industry lobby (Apovian, 2004). First, the absence of definitive randomized trial evidence allows the industry to create doubt by advocating that the associations between fermentable carbohydrate and CNCDS are ‘not proven’ (Kessler, 2001). For instance, a report by authors associated with one trade association suggested that when it comes to caries, “studies challenge the assumption that sugar should be kept to mealtimes” or “the value of using reduction in average sugar consumption as a public health measure” (Ruxton *et al.*, 1999).

Second, the pleasures associated with fermentable carbohydrates such as sucrose (and tobacco) may actually reflect addictions which make it challenging to modify deleterious lifestyles (Corsica and Spring, 2008; Spring *et al.*, 2008). The addictiveness may already have been observed approximately a thousand years ago, when it was reported that people “seem unable to sate themselves with this pleasure” (Mintz, 1985). Finally, “hook them while they’re young” was an important aim of cigarette companies and may be similarly important for the food industry. The high concentration of sugars in some infant formulas (Moskin, 2008), the “outrageous” marketing strategies to increase sales of soft drinks at schools (Meskin, 2001), and an unrestricted donation by a soft drink company to a dental pediatric professional organization (Shenkin, 2003) may suggest the food industry’s interest in the young.

Nonetheless, the evidence door may have opened wide enough to allow dental and medical research to synergistically explore an important question: Are dietary habits that are good for oral health also good for systemic health? An unequivocally positive answer to this question—obtained from a pivotal trial—could have a substantial impact on the dental profession. Dental diseases could become increasingly regarded as the early marker of adverse lifestyle choices. Associations between dental and systemic CNCDS could provide independent verification of suspected etiologies of systemic diseases such as Alzheimer’s disease. And, secular trends in dental CNCDS and carbohydrate and tobacco consumption could lead to novel insights into dental disease etiology and prevention. Possibly, when it comes to fermentable carbohydrates, teeth would then become to the medical and dental professionals what they have always been for paleoanthropologists: “extremely informative about age, sex, diet, health” (Johanson and Edgar, 2006).

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