

The systemic theory of dental caries

Ken Southward, DDS, FAGD

There is growing awareness of oral/systemic links, especially with regard to periodontal disease, diabetes, and cardiovascular disease, among others. The process of dental caries has similar links. Bacterial and other acids in the oral environment can erode enamel and potentially initiate an inflammatory response in the dentin. The body's own matrix metalloproteinases, mostly from within the dentin, become activated, resulting in the caries process. A simplified explanation of the oxidative stress causing inflammation is developed from three equations, namely Health, Dis-ease, and Disease. The

healthy tooth is nourished by a centrifugal dental fluid flow. This flow is controlled by signals from the hypothalamus that are relayed to the endocrine portion of the parotid gland. The first step in the caries process is the reversal of the dental fluid flow, rather than the acid attack from the oral environment. A systemic understanding of the actual cause and progression of dental caries creates opportunities for more effective approaches to preventive care.

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Enamel erosion and dental caries are two different processes. The former is due to acids in the oral environment. There is evidence to demonstrate that dental caries occurs when the body can no longer control the inflammatory process within the tooth.¹ While acid may not be the direct cause of dental caries, it is the primary irritant initiating the inflammatory process in the dentin and the pulp. Acid usually is produced from sugars or refined carbohydrates by aerobic, Gram-positive pathogens like *Streptococcus mutans* and *Lactobacillus*.² While there can be other transient sources of acid, such as soft drinks, bacterial sources remain the most significant singular contributor to enamel erosion leading to dental caries because they can attach to the enamel surface.³

It is significant to note that not all acids have an equal effect on the tooth. Acids originating from bacteria and soft drinks can initiate a carious process. Alternately, acids originating from fruit, bulimia, or gastroesophageal reflux disorder (GERD) tend to erode only the enamel of the tooth in the oral environment.⁴⁻⁷ There are other systemic factors that can amplify the

acid-stimulated caries process, such as methamphetamines like crystal meth.⁸ These observations demonstrate that something more significant is happening internally beyond the oral or external acid attack. The same sugars and refined carbohydrates feeding the oral bacteria wreak havoc with the internal environment and are major factors in diabetes and obesity.⁹ Soft drinks have an insidious effect on the internal environment of the body in addition to their oral effects.¹⁰ It is because of their systemic effect that soft drinks are a contributor to not only enamel erosion but also dental caries.¹¹ *Meth mouth* is a dental symptom of system-wide devastation.¹²

In dental caries, the acidic environment primarily erodes the enamel and secondarily triggers an inflammatory response in the dentin layer of the tooth.¹³ Similar to the process of periodontal disease, where bacterial toxins initiate the body's own matrix metalloproteinases (MMPs) to break down the periodontium, the collagen matrix of the dentin also is lysed by endogenous MMPs such as collagenase.¹⁴ Essentially, both dental caries stimulated by acid and periodontal disease stimulated

by bacterial toxins share a common pathway of oral bacteria initiating a host inflammatory response. This is a significant departure from the concept of the oral bacteria's MMPs creating the dentinal breakdown recognized as caries.

A 2003 study by Larmas reviews the history and controversy regarding the debate in the 1940s between Miller's acid theory of dental caries and Schatz's proteolysis-chelation theory.^{15,16} The acid theory prevailed and has hampered dental research for over 60 years by creating a so-called "acid curtain." The Finnish group has continued its research and proven that acids are unable to destroy collagen in dentin and that it is the body's own MMPs rather than those of the oral bacteria that cause dentinal breakdown.^{17,18} Changing the model of dental caries from a bacterial acid-driven outside/in process to an inflammation-driven inside/out process creates many new preventive opportunities.

The significance of a correct caries theory

To many dentists, the caries theory controversy might seem irrelevant, because the solution to the problem

of dental caries is restorative dental care, regardless of the cause. The significance of a complete and correct theory can be better understood upon investigation of the preventive model propelled by the limited “acid theory.” Since acids demineralize enamel, fluoride is used to remineralize it and thus has become one of the pillars of preventive dentistry over the last several decades.

Based on this theory, Proctor & Gamble worked with the University of Indiana in the early 1950s to develop a toothpaste with stannous fluoride. In 1956, Crest went national in the United States.

According to an article in the *Harvard Business Review*, sales languished until the early 1960s:

The breakthrough that resulted in Crest’s dominating the U.S. market came four years after its national launch (and eight years after its “invention”), when, in 1960, it became the first brand of toothpaste to receive an endorsement from the American Dental Association (ADA).¹⁹

The real innovation that Proctor & Gamble used to dominate the toothpaste market for over 30 years was getting the ADA to endorse its product. This endorsement was granted with a limited understanding of the caries process based on the acid theory. Acid is now understood to be only an initiator of enamel erosion and stimulator of an uncontrolled inflammatory response in the dentin.²⁰

Emerging evidence now demonstrates that antioxidants in green tea (epigallocatechin gallate, or EGCG) acting as MMP inhibitors are significantly more effective than sodium fluoride at preventing acid erosion.²¹ Organized dentistry must recognize that its endorsement of the

$$\textit{endogenous oxidation} = \textit{endogenous antioxidation}$$

Fig. 1. The Health Equation.

$$\textit{endogenous oxidation} = \textit{endogenous antioxidation} + \textit{controlled inflammation}$$

Fig. 2. The Endogenous Dis-ease Equation.

$$\textit{endogenous} + \textit{exogenous oxidation} = \textit{endogenous} + \textit{exogenous antioxidation}$$

Fig. 3. The Expanded Health Equation.

limited acid theory has contributed significantly to the marginal success of preventive dentistry. In fact, childhood caries is increasing rather than declining.²² Where would clinical dentists be today in terms of preventive dentistry if Shatz’s proteolysis-chelation theory had prevailed? More importantly, what can dentists do with this evidence?

Mapping inflammation

The biochemical reactions provided by the immune system to defend the body from insults and foreign bodies exhibit themselves as inflammation; clinically, it is recognized as heat, redness, swelling, and pain. A road map is a simplified visual to aid understanding of where one is now and to assist one in reaching a destination. To create a visual map or simplified explanation to understand inflammation, the author has developed three equations known as the Health, Dis-ease, and Disease equations.

Biochemical reactions essentially involve the transfer of electrons. Oxidation involves the loss of an electron. Conversely, reduction (antioxidation) involves the gain of an electron. These electron transfers are known as *redox reactions*. Many

of these reactions occur in the mitochondria of the cell as it produces energy.²³ In this simplified explanation, this can be understood as an equation where oxidation produced within the cell (endogenous) would equal reduction or antioxidation within the cell. This is the Health Equation (Fig. 1)—in short, when oxidation equals antioxidation, health exists.

No reaction is perfect, so there is an exhaust produced. In the mitochondria, some molecules such as oxygen are oxidizing (losing an electron) but do not get reduced properly (regain the electron). Oxygen is involved in these energy-producing reactions, so the name given to charged or “oxidized” oxygen molecules is *reactive oxygen species* (ROS). The broader term “free radicals” also is used to describe positively charged molecules, but that can include other charged molecules, such as nitrogen. Energy production, however, mostly involves oxygen, so ROS is more appropriate for most of this simplified explanation.

In basic terms, positively charged ROS will steal an electron from anywhere they can to neutralize themselves. Potential targets can be

$$\text{endogenous} + \text{exogenous oxidation} = \text{endogenous} + \text{exogenous antioxidation} + \text{controlled inflammation}$$

Fig. 4. The Expanded Dis-ease Equation.

$$\text{endogenous} + \text{exogenous oxidation} = \text{endogenous} + \text{exogenous antioxidation} + \text{uncontrolled inflammation}$$

Fig. 5. The Disease Equation.

the proteins or fats in the cell wall or even the DNA in the nucleus.²⁴ ROS from cellular energy production are known as *endogenous free radicals*. To defend cells from damage, bodies produce endogenous antioxidants like glutathione. An antioxidant essentially is a substance that can donate one or more electrons without the cell becoming damaged or toxic. In the previous equation, when endogenous oxidation producing ROS equals endogenous antioxidants (like glutathione), health exists.

When oxidation is greater than antioxidation, oxidative stress is created, and the body is forced to balance the equation.²⁵ It does so through inflammation.^{26,27} This “Dis-ease Equation” (Fig. 2) created by oxidative stress can be stated as oxidation equals antioxidation plus controlled inflammation; this tends to be acute, and tissue integrity is restored after the need for inflammation is eliminated.

Exogenous or outside-source free radicals (not only ROS) also bombard the body. While cigarette smoking is one of the worst culprits, bacterial acids on the teeth initiating dental caries and bacterial toxins in gingival pockets initiating gingivitis both create a storm of free radicals that must be neutralized.^{28,29} Outside source or exogenous antioxidants, as found in brightly colored fruits and vegetables, are

necessary to help balance the new equation, and the Health Equation can be expanded (Fig. 3).

Once again, in simplified terms, inflammation is used to balance the equation if oxidation overwhelms antioxidation, creating oxidative stress. The clinical symptoms of inflammation exhibit the increased energy production on behalf of cells in the body to defend themselves from the free radical stressors.³⁰ The equation can be balanced or oxidative stress eliminated either by decreasing oxidation, increasing antioxidation, or a combination of the two. Smoking cessation and teeth cleaning are examples of decreasing oxidation. Eating 8–10 servings of fresh fruits and vegetables each day or taking high-quality nutritional supplements that include antioxidants are ways to increase the antioxidant side.

The Dis-Ease Equation can be expanded (Fig. 4): The more the oxidation side overwhelms the antioxidation side, or the greater the oxidative stress, the more inflammation is required to balance the equation. The most important concept, and the one most critical to understanding tissue breakdown, is that inflammation is a double-edged sword. Controlled inflammation is the body’s natural defense system. Without it, as in AIDS, the body is significantly compromised. Uncontrolled inflammation can

turn on the body and cause tissue breakdown. Chronic, excessive oxidation can exhaust the antioxidant reserves that control the inflammatory response. At that point, tissue destruction moves from acute (reversible) to chronic (irreversible). For example, gingivitis becomes periodontitis, or a demineralized white spot enamel lesion progresses to dental caries. It is at this critical point that the equation changes from the Dis-ease Equation to the Disease Equation (Fig. 5).

The number of free radicals, specifically ROS, is one way to measure the amount of oxidation on the left of the Health Equation. Conversely, the Oxygen Radical Absorption Capacity (ORAC) scale, developed by scientists at the National Institutes of Health, measures the antioxidant potential of different exogenous substances. The Health Equation can be balanced by decreasing ROS or increasing the ORAC. Extensive dental caries, to the point of causing a toothache, is a situation where generous amounts of painful inflammation in the dentin and the pulp are required to balance the equation. Dentistry’s goal is to balance the equation as quickly as possible so that inflammation is no longer required to balance it and the pain subsides.

ORAC values of many natural foods can be found at www.oracvalues.com. Some

examples of commonly recognized antioxidants, in ascending order, are lemon juice (1,225), green tea (1,253), pomegranate (2,341), blueberries (6,552), raw cranberries (9,584), and dark chocolate (20,823). All of these examples pale in comparison to cloves and their essential oil, known as eugenol (314,446). Whether knowingly or not, early dentistry recognized that increasing the antioxidant side of the equation with a topical application of a substance with a high ORAC value would minimize the oftentimes painful inflammation required to cope with oxidative stress in the tooth. For this reason, zinc oxide and eugenol were the materials of choice.

Tissue inhibitors of metalloproteinases (TIMPs) are physiological inhibitors of MMPs such as collagenase. They are secreted proteins that combine with the MMPs to return them to their dormant state. Antioxidants can mimic the TIMP effect by reducing the free radical excess so that MMPs do not have to be activated.³¹ The TIMP effect of some antioxidant-rich foods has been reported.³²⁻³⁴ Pharmacokinetically, host modulators such as bisphosphonates and low-dose doxycycline actually handicap the body's immune system to reduce the MMPs produced.³⁵ Essentially, the equation never gets balanced. While these therapies might have positive short-term results, one should wonder about their side effects and long-term usage, especially if the lifestyle or oxidative imbalance is never altered.

Nourishing the tooth

All body tissues need continual nourishment. A healthy tooth is nourished by a blood supply to the pulp. The dentin portion of the tooth, being nonvascular living

tissue, is nourished by a centrifugal (outward) fluid flow through the dentin and enamel. Leonora *et al* proved this concept in rats and pigs many years ago at Loma Linda University Dental School.³⁶

Through many years of diligent research, they were able to prove the existence of a fluid flow through the dentin and enamel of the healthy tooth. Furthermore, they discovered that a high-sucrose diet could halt the fluid flow and might even reverse it! This was significant because instead of a healthy tooth continually cleansing itself from the inside, plaque now was able to adhere to the surface of the dis-eased tooth with a stagnant or reversed fluid flow, allowing acid production to be concentrated and absorbed.³⁷ Step one in the caries process is not the acid production of bacteria, but instead the tooth dis-easing and becoming susceptible to bacterial acids accumulating on its surface by the reversal of the dentinal fluid flow.³⁸

Leonora *et al* went on to demonstrate that the parotid gland is a dual-function gland, like the pancreas. It has both a well-known exocrine function (to secrete saliva) and a little-known endocrine function (to secrete a parotid hormone to control dentinal fluid flow).³⁹ This is similar to the pancreas' endocrine function of secreting insulin and its exocrine function of secreting pancreatic enzymes into the digestive tract. The submandibular gland does not have this dual function and possesses only an exocrine function to secrete saliva.

Leonora *et al* reasoned and proved that there must be a signal mechanism or stimulating hormone controlling the parotid gland and that it is controlled by the hypothalamus portion of the brain. The Loma Linda researchers demonstrated

that a high-sucrose diet would stop the hypothalamus signals within minutes.⁴⁰ Further, they could overcome the high-sucrose effect with carbamyl phosphate. Sucrose down-regulates the parotid-stimulating hormone from the hypothalamus; this diminishes the parotid hormone and ultimately reverses or halts dentinal fluid flow.

Working with Steinman and Leonora, Tjaderhane discovered that high-sucrose diets also interfered with primary dentinogenesis, or the formation of dentin.^{41,42} He proved that the dentinal fluid flow affected not only the rate of caries in teeth but also the actual formation of the tooth. How could restorative dentistry cope with teeth already compromised by high-sucrose diets at the age of 3? This discovery could explain the current increase in early childhood caries rates. Essentially, not all teeth are created equal, and diet is the determining factor. This also explains why early teens have higher caries rates, due to more active dentinogenesis and susceptible fluid flows. Junk food diets have a leveraged effect in teens with developing teeth, while the same poor diet has less of an effect in later years.

Building on the research of Steinman and Leonora, the team at Loma Linda identified and synthesized the complete 30 amino acid parotid hormone in 2005.⁴³ Compare this to insulin, which was discovered and produced commercially for decades before amino acid sequencing was available: Since the amino acid sequence of insulin was discovered, specific amino acids and bonds have been altered to enhance absorption, distribution, metabolism, and excretion. If dentistry had followed the medical model of care, Steinman and Leonora's research might have triggered much greater interest in dental caries

management through manipulation of the parotid hormone, similar to diabetes management with insulin. Unlike medicine, however, dentistry has been limited by its focus on the “acid theory” of dental caries.

Steinman and Leonora were able to override the signals from the hypothalamus to the parotid gland with carbamyl phosphate, thus maintaining the flow of parotid hormone and dentinal fluid transport. Their dilemma was that they were never able to explain how hypothalamic signaling worked. In fact, ground-up egg shells and some trace minerals such as zinc also seemed to work well.⁴⁴ Modern research provides the evidence to develop a hypothesis.

Applied research solves the dilemma

The inflammatory response is similar throughout the body. This understanding encourages medical professionals to tap different areas of research to help determine what is really going on in the body relative to the disease processes most relevant to them. Recent diabetic research has provided some breakthrough insights. It is reported that an increase in ROS in the mitochondria of the hypothalamus alters regulation of insulin production.⁴⁵ Basically, increased blood sugar after a high sucrose intake increased metabolism in the mitochondria, in turn increasing the ROS exhaust. This trigger mechanism in the hypothalamus up-regulated insulin production in the pancreas to deal with the elevated blood glucose level. This same high-sucrose diet simultaneously down-regulated the parotid hormone.

This breakthrough research completely inverts the current understanding of ROS. What was thought to be the useless exhaust of an energy-producing cycle that needs only to be neutralized or reduced

(electrons added) now takes center stage. They are the critical triggers of hypothalamic hormones to regulate different parts of the body.

Carbamyl phosphate is actually an anion carrying two uncoupled electrons so that it can act as a mitochondrial antioxidant.⁴⁶ It is an intermediate metabolite in the energy production process. Enhancing the efficiency of this process minimizes the ROS exhaust and diminishes the strength of the signaling process.⁴⁷ Steinman and Leonora did not have this understanding. It is the evasive answer to their dilemma.

Steinman and Leonora did have success altering dentinal fluid flow with zinc and egg shells. Zinc is used as an antioxidant on galvanized nails to prevent them from the oxidative process of rusting. As for egg shells, nature would not let its most prized possession of new life go without antioxidant protection; these antioxidants are found in the membrane of the egg shell.⁴⁸ This explains why egg shells would maintain dentinal fluid flow while calcium would not.

Conversely, there should be evidence of other sources of excessive free radicals beyond diet, which can cause an increase in dental caries. Smoking is regarded as one of the most significant producers of free radicals, whether it is first- or secondhand smoke. Many of these free radicals are not ROS but are still positively charged molecules that need to be neutralized. It has been demonstrated that secondhand smoke increases the rate of dental caries in children, regardless of diet.⁴⁹ Essentially, excessive free radicals in the bloodstream from inhaling secondhand smoke will down-regulate the hypothalamic stimulus to the parotid gland, decreasing the parotid hormone and stopping or reversing the dentinal

fluid flow. Both dentinogenesis and caries rates are affected by the free radicals in secondhand smoke. Similarly, methamphetamine consumption can lead to oxidative stress and mitochondrial injury.⁵⁰ The associated rampant dental caries is commonly called *meth mouth*.

The systemic theory of dental caries

All body parts constantly move between states of health, dis-ease, and disease, based on oxidative stress and the corresponding inflammatory response. Controlled inflammation often is an acute phase, whereas uncontrolled inflammation usually is more chronic. A similar reaction takes place throughout the body, including in the periodontal tissues and teeth. The balance can be explained by utilizing the Health, Dis-ease, and Disease equations.

Nourishment, by either blood supply or fluid flow, replenishes nutrients and antioxidant reserves in cells. The body has sensing and control mechanisms to up- or down-regulate hormones and fluid flows. Dentinal fluid flow is regulated by the endocrine portion of the parotid gland, which receives signals from the hypothalamus. Free radicals, specifically ROS, produced in the mitochondria of the hypothalamus increase with elevated blood glucose, which in turn down-regulates the parotid hormone. Minimizing the effect of free radicals on the hypothalamus with antioxidants can avoid down-regulation of the parotid hormone, maintaining centrifugal dentinal fluid flow. This effectively self-cleanses the tooth and controls inflammation by replenishing antioxidant stores. Excessive MMP (collagenase) release causing carious breakdown is prevented, and dentinogenesis is enhanced.

The tooth is designed to withstand the harsh oral environment, provided it is properly nourished. A high-sucrose diet affects the tooth from the outside by enabling oral bacteria to produce acid and from the inside by reducing the dentinal fluid flow and the body's ability to control the inflammatory process in the dentin. Antioxidants can shield the dentition by decreasing the effects of acid erosion, by minimizing the effect of ROS in the hypothalamus, and by replenishing TIMPs in the dentin. Minimizing sucrose as well as increasing fruit and vegetable intake and nutritional supplementation are modifiable lifestyle decisions with significant measurable benefits.

Summary

In the age of evidence-based dentistry, it is important to reflect on the limiting effect of the 1940s debate of the outside/in acid theory and inside/out proteolysis/chelation theory of dental caries. Organized dentistry then amplified the problem by endorsing one brand of toothpaste to remineralize enamel with fluoride, propelling it to new marketing heights. The economic model of restorative dentistry thrived when preventive efforts continually failed or were minimally successful, due mostly to the fact that clinical dentistry was looking at a faulty or at least limited model of dental caries for guidance. Dentistry now has the opportunity to take existing research and review it in a different light. Similarly, new research can be undertaken to optimize preventive efforts with a more systemic focus.

Managing inflammation is the key to both dentinogenesis and the caries process. Antioxidant nourishment to help manage inflammation in the tooth and control hypothalamic signaling will be areas of new therapeutic approaches.

Diabetes management has long focused on insulin management and supplementation when necessary. Dental caries management gives little recognition to the parotid hormone even years after its amino acid sequencing has been identified.

Public health dentistry could stand to gain the most from this new understanding of dental caries and the preventive opportunities it will create. The pharmaceutical industry also could play a significant role, just as it has in diabetes. The question is whether general dentistry, with its economic base in restorative care, will lead or be led.

Author information

Dr. Southward has always practiced general dentistry in Beamsville, Ontario, Canada.

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