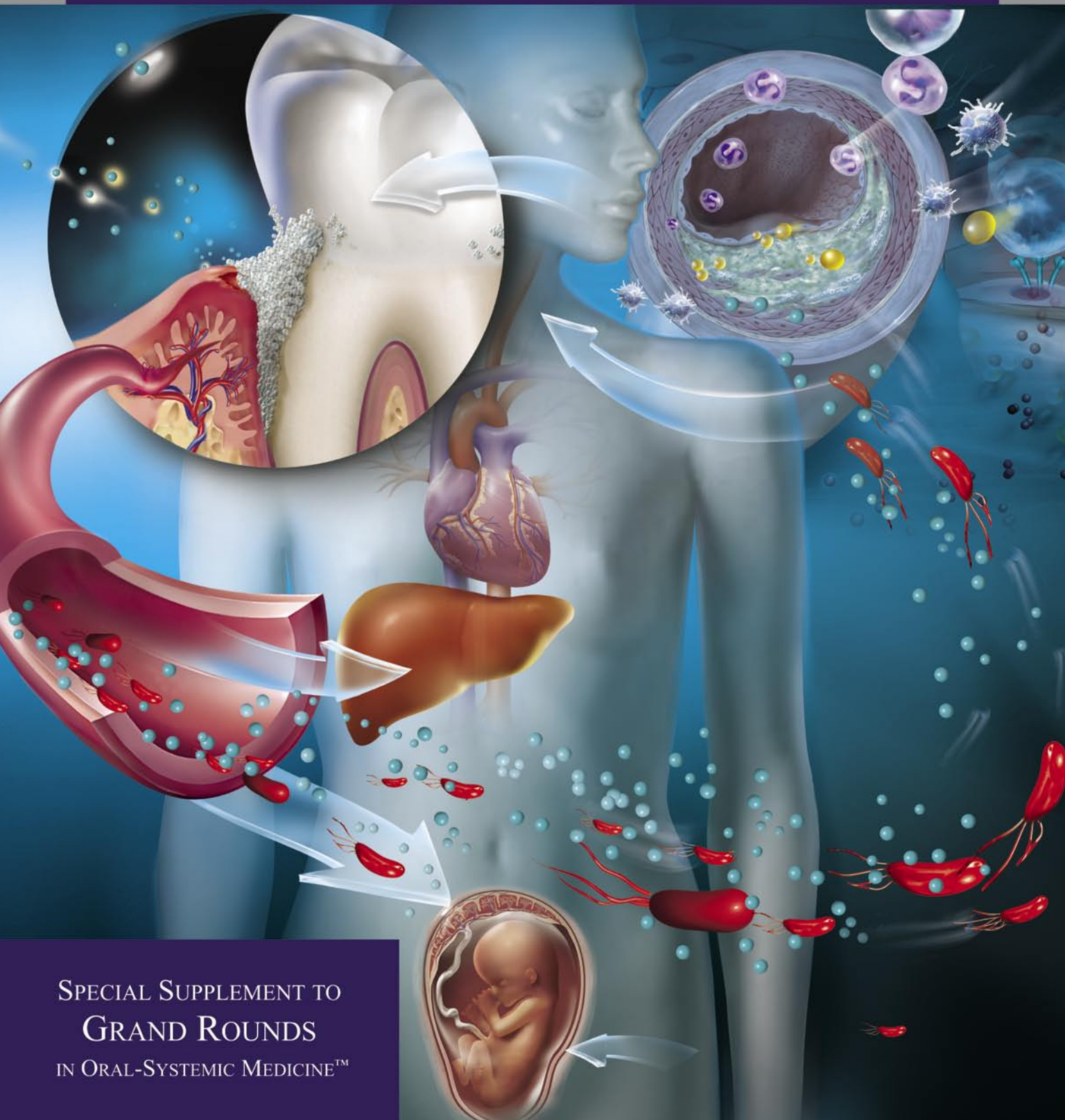


PROCEEDINGS AND CONSENSUS OPINION FROM THE GLOBAL ORAL AND SYSTEMIC HEALTH SUMMIT

Present Evidence and Future Directions



SPECIAL SUPPLEMENT TO
GRAND ROUNDS
IN ORAL-SYSTEMIC MEDICINE™

Continuing Education

SUPPLEMENT GOALS:

- ▶ *To explore the expert testimony that distinguished researchers presented at the Global Oral Health Summit relative to the strength of the present evidence supporting a relationship between periodontal disease and cardiovascular disease (CVD), cerebrovascular disease, and adverse pregnancy outcomes.*
- ▶ *By relying on the summit proceedings as the foundation for their conclusions, a postsummit Global Task Force developed a consensus opinion to provide clarity on 3 issues pertinent to the status of periodontal-systemic research, which includes the following:*
 - ❶ *What is the state of the research, specifically the strength of evidence to support the relationship between periodontal disease and increased risk for systemic diseases and disorders such as CVD, cerebrovascular disease, and adverse pregnancy outcomes?*
 - ❷ *What future direction should be taken to strengthen the body of evidence related to periodontal-systemic research?*
 - ❸ *What do we currently know about the suspected periodontal-systemic links that is reasonably certain and appropriate to share in the form of a published consensus statement that will be meaningful to dental professionals and the consumer public?*

Target Audience:

Dentists, dental hygienists, and other healthcare professionals

Learning Objectives:

After reading the scientific proceedings of the Global Oral and Systemic Health Summit, and the consensus opinion of the postsummit Global Task Force, readers should be able to:

- ❶ *Describe how orally derived bacteremia may be biologically linked to formation of atherosclerotic lesions.*
- ❷ *Identify the risk factors that increase a person's susceptibility to periodontal disease.*
- ❸ *Discuss the scientific evidence that satisfies several of the Bradford Hill criteria necessary to establish a cause-and-effect relationship between periodontal disease and CVD.*
- ❹ *Discuss the evidence that supports an association between periodontal disease and adverse pregnancy outcomes.*

Credit Designation:

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A Framework and Context for Moving Forward

Thoughts of the Proceedings and Consensus Opinion from the Global Oral and Systemic Health Summit

by Dominick P. DePaola, DDS, PhD

In the evolution of the health professions, certain seminal discoveries and observations engender quantum leaps from the status quo. In medicine, such an observation was made at the beginning of the twentieth century by Abraham Flexner, and it changed the course of medical education.¹ Similarly, the work of William Gies in the 1920s advocated a more scientific approach to dental education, and the result was a profound change in the characteristics of dentistry and subsequent clinical practice.²

Many scientific advancements — the discovery of penicillin, the development of vaccines for smallpox and other infectious diseases, the use of fluoride for the prevention of caries, and a host of others — have changed the course of medicine and public health. Recently, the sequencing of the human genome and the rapid expansion of the multiple “-omics” fields have enhanced our understanding of some of the most intricate aspects of life. These breakthroughs are promising advances in molecular medicine and the prevention of disease.

In 2000, the Surgeon General of the United States, Dr. David Satcher, issued the first *Surgeon General's Report on Oral Health in America*.³ In it, and in 2 subsequent calls to action, he called on the profession and on society to address the “silent epidemic of oral disease.” In my view, the Surgeon General's reports have had a profound effect on the will and leadership that are necessary to address oral health disparities and on the science necessary to move oral health to an even more prominent place in primary care.

A critical component of the surge in interest and broadened approaches to integrating dentistry with larger health-care issues has been the recognition that the 2 primary oral conditions, caries and periodontal disease, are global infections that have serious consequences. Just as important is the recognition that oral infections, particularly those associated with periodontal disease, can have profound effects on total body health, including cardiovascular disease (CVD), adverse pregnancy outcomes, diabetes, pulmonary disease, and stroke. Indeed, this recognition has propelled oral health research to the forefront of science and health-care.

The later observations, although not new, have led to a flurry of research to examine the linkages between oral infections and systemic diseases and disorders. In fact, a

recent special report published in *Scientific American*⁴ and a special supplement to the *Journal of the American Dental Association*⁵ recounted the possible linkages between those oral infections and their systemic sequelae.

In this same regard, in the summer of 2006, a unique conference was convened, the Global Oral and Systemic Health Summit, to survey the latest research on the mouth-body connection — specifically, the status of the evidence to support the relationship between periodontal disease and CVD and adverse pregnancy outcomes. The summit was designed to enable a global community made up of thought-leaders from around the world to assess the state of the science regarding these selected oral-systemic health linkages. The summit began with keynote presentations by Denis Kinane, BDS, PhD, of the University of Louisville School of Dentistry; Stephen Offenbacher, DDS, PhD, MMSC, of the University of North Carolina at Chapel Hill; and Maurizio Trevisan, MD, MS, of the University of Buffalo. The speakers focused on the bacteremia theory, which links oral infection and systemic disease; the inflammatory theory, which focuses on CVD and adverse pregnancy outcomes; and the public health implications of authentic oral-systemic linkages. The speakers also focused on the host response to these microbial challenges, which is at least as important as the microbial challenge itself.

The summit assessed the state of the science against the Bradford Hill criteria, which are designed to test for a cause-and-effect relationship rather than an association based on epidemiologic evidence. In itself, this was unique, because, although the Bradford Hill criteria are used in medicine quite extensively, they have not been routinely applied to the oral-systemic disease connection. Note that the summit was quite selective by design and did not address some critical issues that are covered in other publications. Due to time constraints, the summit did not cover certain issues, including the link between oral infections and diabetes, respiratory disease, obesity, neurodegenerative diseases, immunocompromised disease states, and the lipoxin theory of inflammatory cessation.

After the summit, a Global Task Force was appointed to study both the expert testimony offered and the discussion that ensued, in order to formulate a consensus opinion on the state of research related to this evolving body of science.

A Framework and Context for Moving Forward

The Proceedings and Consensus Opinion that follow in this supplement are a summary of the presentation highlights and key points derived from discussions. The Global Task Force arrived at a true international consensus on the issues addressed at the summit. As such, it represents a broader approach, because the problems related to understanding the nature and possible causal linkage of oral infections to systemic health involve not only infection and the host response to the infectious agent(s), but also the socioeconomic-cultural dynamics that surround the clinical setting. The Global Task Force discovered, among other things, that oral-systemic relationships are unique to specific cultural mores and environments. As a result, the perspectives of individual members of the Global Task Force relative to these infections and linkages are quite different and revealing when compared with a purely American perspective.

An interesting example of the complexity associated with understanding the causal nature of the oral infectious-systemic health relationships was highlighted in a recent issue of the *New England Journal of Medicine*.⁶ The article reported on the results of a multicenter clinical trial in which the effects of nonsurgical periodontal treatment on preterm birth were assessed. The researchers concluded that although treatment of periodontitis in pregnant women is safe and improves periodontal health, it does not have material benefit on preterm birth, low birthweight, or fetal growth restriction.

Although the outcome of this study was disappointing, an accompanying editorial articulated the complexity of the risk factors associated with spontaneous preterm birth, including multiple gestation, a history of preterm birth, African-American race, low socioeconomic status, low maternal body-mass index, short cervical length, urogenital infections, and infections at other sites, including periodontal disease.⁷ In addition, the same editorial pointed out the need for refining the study design to consider other variables. Although the results of this particular study failed to provide evidence that treatment of periodontal disease decreased the incidence of adverse pregnancy outcomes, other recent studies indicate there may be a relationship.^{8,9} It is clear that much more work needs to be accomplished before the true nature of the relationship can be established.

The Global Task Force Consensus focused on 3 issues — an assessment of the biologic plausibility of bacteremia and inflammation as risk factors and contributors to adverse pregnancy outcomes and CVD; recommendations for strengthening the science base; and consensus

on data and information that could be provided to the professional dental and health communities, as well as to consumers and the media. It is anticipated that the following information, which captured the proceedings of the Global Oral and Systemic Health Summit and the subsequent consensus opinion of the Global Task Force, will add to the body of knowledge, stimulate worldwide effort for expanded research in this critical area of discovery, and provide credible background information for appropriate alignment of messages regarding the state of oral-systemic medicine for the public.

The 1 thing that is abundantly clear is that there is no downside to the prevention and treatment of periodontal disease. If aggressive prevention and treatment forestall 1 cardiovascular event or 1 adverse pregnancy outcome, the effort is worth every dollar invested in research.

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Proceedings and Consensus Opinion From the Global Oral and Systemic Health Summit:

Present Evidence and Future Directions

Preface

Evidence suggests that periodontal disease may be a modifiable risk factor for morbidity and mortality in a number of systemic diseases and conditions, including cardiovascular (CVD)^{1,2} and cerebrovascular diseases and adverse pregnancy outcomes.³ Periodontal disease is currently considered part of a continuum of the same chronic inflammatory condition that includes both gingivitis and chronic periodontitis.^{4,6} Collective epidemiologic data from various studies estimate that approximately 60 million adults in the United States have moderate to advanced chronic periodontitis.⁷

Inherent to the mounting evidence of the relationship between oral health and systemic disease are progressive prevention and treatment strategies for periodontal disease that may decrease the incidence and severity of chronic disease states and conditions such as heart disease, stroke, diabetes, adverse pregnancy outcomes, and respiratory ailments. The potential to make progress against these interrelated medical conditions underscores the importance of prevention and the diagnosis and treatment of periodontal disease. The public health ramifications of preventing and treating periodontal disease are significant. The possibility that periodontal disease is a modifiable risk factor for systemic inflammatory states or plays a role in exacerbating an already existing systemic condition has clearly redefined oral health as an essential component of overall health and emphasizes the necessity of proper oral care. The emerging relationship between periodontal disease and systemic disorders also offers unprecedented opportunities for medical and dental healthcare providers to collaborate on prevention and management of chronic disease.

Evidence to support periodontal-systemic correlations is strong, although cause-and-effect relationships have not yet been proven. The conclusions that scientists have drawn are based largely on animal model and *in vitro* data, as well as epidemiologic and selective clinical studies that have estimated positive associations without prov-

ing causality. Inconsistencies in how exposures (severity of periodontal disease) and outcomes (degree of systemic effect) are measured and the difficulty inherent to analyzing the substantial overlap in shared risk factors for many of the periodontal-systemic diseases are only a few of the obstacles that researchers have encountered in trying to determine the true nature of these associations.

Academicians, clinicians, and policy makers are awaiting further evidence that establishes a cause-and-effect relationship between oral infection and systemic disease and clarifies the biological pathways linking the two. Because of the evolving nature of this body of science and the absence of conclusive evidence to support a cause-and-effect relationship between periodontal infections and whole-body consequences, many questions remain unanswered. In the meantime, the dental and research communities are justifiably concerned about the lack of alignment between what the consumer public is hearing from the media about oral-systemic relationships and the present state of evidence to support such claims. Statements related to the risk that periodontal disease may pose for systemic consequences must be based on research that is validated by scientific evidence.

In an attempt to define these questions and assess the strength of the evidence supporting the relationship between periodontal disease and systemic health, a group of academicians, scientists, deans of dental schools, leaders of professional organizations, policy makers, healthcare insurers, and other opinion leaders from around the world met on July 24, 2006, in Basking Ridge, New Jersey, for the Global Oral and Systemic Health Summit.

The summit, which was moderated by Dr. Dominick DePaola, featured the expert testimony of three distinguished researchers (Drs. Denis Kinane, Maurizio Trevisan, and Steven Offenbacher), who presented scientific evidence that supports the role that oral infection, resultant bacteremia, and cumulative inflammatory burden play in linking periodontal disease to CVD and adverse pregnancy outcomes. The experts also discussed

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Criteria	Explanation of Criteria
1 Strength of association	A strong association is more likely to have a causal component than a modest association
2 Consistency	A relationship is observed consistently
3 Specificity	A factor influences a particular outcome or population
4 Temporality	A factor must precede the outcome it is assumed to affect
5 Biological gradient	The outcome increases monotonically with increasing dose of exposure or according to a function predicted by substantive theory
6 Plausibility	The observed association can be plausibly explained by substantive matter (eg, biological) explanations
7 Coherence	A causal conclusion should not fundamentally contradict present substantive knowledge
8 Experiment	Causation is more likely if evidence is based on randomized experiments
9 Analogy	For analogous exposures and outcomes, an effect has already been shown

Table 1. Bradford Hill Criteria

The Bradford Hill criteria are used to determine whether an association between 2 variables is purely an observed relationship or a cause-and-effect relationship. The 9 criteria are listed in the table above.

whether the application of the Bradford Hill criteria provides a threshold of evidence to support a cause-and-effect relationship between periodontal disease and these 2 systemic conditions (see Table 1).

The summit discussion also served as the foundation for a postsummit Global Task Force that drafted a consensus statement pertaining to 3 questions:

1. What is the state of the research, specifically the strength of evidence, to support the relationship between periodontal disease and increased risk for systemic diseases and disorders, specifically CVD and adverse pregnancy outcomes?
2. What future direction should be taken to strengthen the body of evidence related to periodontal-systemic research?
3. What do we currently know about the suspected periodontal-systemic links that is reasonably certain and appropriate to share in the form of a published consensus statement that will be meaningful to dental professionals and the consumer public?

The 6 key points that follow document the highlights of the Global Oral and Systemic Health Summit presentations and subsequent discussions.

Key Points and Discussion Highlights of Proceedings

Key Point #1: Orally derived transient bacteremia have been associated with an increased risk for systemic disease, including CVD.

Research provides strong and compelling evidence that oral bacteria presented either as short-term

recurrent bacteremias or chronic low-grade exposures may induce systemic consequences, including CVD.⁸ The loss of epithelial integrity within the periodontal pocket, as seen in periodontal disease, can lead to an ulcerated surface in contact with the dental plaque biofilm. Hujoel and colleagues⁹ calculated that among people with chronic periodontitis, the surface area of the dentogingival epithelium exposed to potential bacterial invasion or infiltration of antigenic microbial components ranges between 8 cm² and 20 cm². It is at this site that bacteria may penetrate and invade periodontal and vascular tissues. In periodontal disease, when tissue is more fragile, damage can occur during mastication, tooth brushing, and professional dental procedures, allowing a portal for bacteria and other cellular matter to enter the circulatory system.¹⁰ In fact, there is evidence that

orally derived bacteremia increases as periodontal disease progresses.¹¹ In light of these findings, it is not difficult to see how long-term collection of dental plaque biofilm originating from periodontal lesions can cause daily episodes of bacteremia, which may result in systemic effect,^{12,13} and which may explain in part the association between periodontal disease and CVD.¹⁴

CVD is among the leading causes of premature mortality and morbidity in the developed world. In the United States, 13.2 million men and women have coronary heart disease (CHD), and every year an estimated 5.5 million people have a stroke.¹⁵

The underlying pathology of CVD is atherosclerosis, the process in which deposits of fatty substances, cholesterol, cellular waste, calcium, and other products build up in the lining of the artery and may even result in thickening of the intima-media. Plaques, or atheromas, can grow large enough to reduce blood flow through an artery, but most cases of acute cardiovascular events occur when atherosclerotic plaques rupture and break off, potentially blocking blood flow or traveling to other parts of the body.¹⁵

Evidence suggests that dental plaque biofilm organisms, once in the bloodstream, may contribute to atheroma formation. Mastication, tooth brushing, and manipulative dental procedures, in the presence of periodontal disease, have been reported to initiate bacteremia and endotoxemia.¹⁰ The dental plaque biofilm in the subgingival space contains more than 700+ species of bacteria¹⁶ and provides a constant reservoir of organisms that can potentially enter into the circulation.

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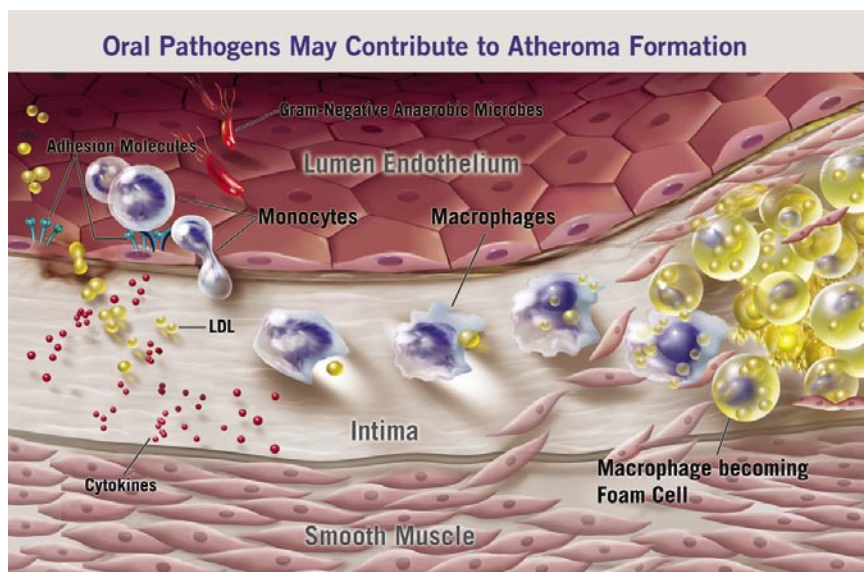


Figure 1. Oral Pathogens May Contribute to Atheroma Formation
When oral microbial pathogens enter the bloodstream, they elicit an inflammatory response that includes, among other things, monocyte infiltration of the vascular endothelium, where they differentiate into macrophages. The macrophages produce cytokines and stimulate production of other inflammatory mediators, while phagocytizing both the pathogenic bacteria and cellular debris, including oxidized low-density lipoprotein. When the macrophages die, they entomb the lipid in the subendothelial space, contributing to atheroma formation.

As oral pathogens enter the bloodstream, they may stimulate and activate endothelial cells, recruiting monocytes that potentially contribute to the formation of the atherosclerotic lesion (see Figure 1).^{17,18} In humans, oral microbes such as *Porphyromonas gingivalis* have been found in atheromas of major arteries.¹⁹ Different experimental models in mice, dogs, rabbits, pigs, and monkeys have all shown that exogenous oral infections are capable of inducing heart disease.²⁰⁻²²

The Oral Infections and Vascular Disease Epidemiology Study (INVEST)^{2,23} has investigated the relationship between periodontal bacterial load and early atherosclerosis, concluding that chronic infections, including periodontal infections, may predispose to CVD. After statistical adjustments and the appropriate assessments to measure carotid intima-media thickness (cIMT), a marker of early atherosclerosis, the researchers concluded that specific periodontal bacteria were correlated with cIMT and that there was a direct relationship between periodontal microbiology and subclinical atherosclerosis, independent of C-reactive protein (CRP), an independent marker and risk factor for CVD.

More recent research suggests that certain species of oral organisms may be risk factors in the development of acute coronary syndrome.²⁴ There is evidence that *P. gingivalis* can activate and multiply within blood vessel endothelial cells, and it has been discovered that viable *P. gingivalis* are present within the blood vessel wall.²⁵ However, researchers have also found that overall pathogen burden

may be more significant than any single bacterium in increasing the risk for CVD.^{24,26-29} Thus, the total oral burden of microbial exposure, expressed as either levels of bacteria within the subgingival plaque or as measured by systemic antibody response (e.g., IgG titers) to specific bacteria, appears to relate to more severe CVD.³⁰ Research has shown that orally derived bacteremia increases as periodontal disease progresses.¹¹ This may explain why recent studies have shown that periodontal treatment may decrease systemic inflammation and improve endothelial function.³¹

Discussion

The question was raised as to whether inflammation from periodontal disease had to be present to produce a bacteremia. Kinane responded that it was not just the bacteria, but the response to bacteria that was important. In this regard, Kinane was asked

whether there is enough evidence of the potential of periodontal disease to increase the systemic bacterial burden to begin to implement this science into clinical practice. He responded that although there is enough evidence, more studies are needed to determine appropriate strategies for implementing this science.

Kinane stated that there are specific microorganisms that are problematic. He noted the recent research that suggests that CRP-related pathology might not be as important as specific periodontal pathogens, such as *P. gingivalis*, which can cause endothelial damage.³² The specificity of bacteria was acknowledged as being important for intima-media thickness (IMT) to occur.

Dr. Daniel Fine noted the opportunity for bacteria within the dental plaque biofilm to enter the bloodstream with the subsequent ability to invade damaged or partially damaged blood vessels and induce local inflammation. The participants debated whether systemic inflammation or susceptibility at the local vascular site is primarily responsible for initiating CVD.

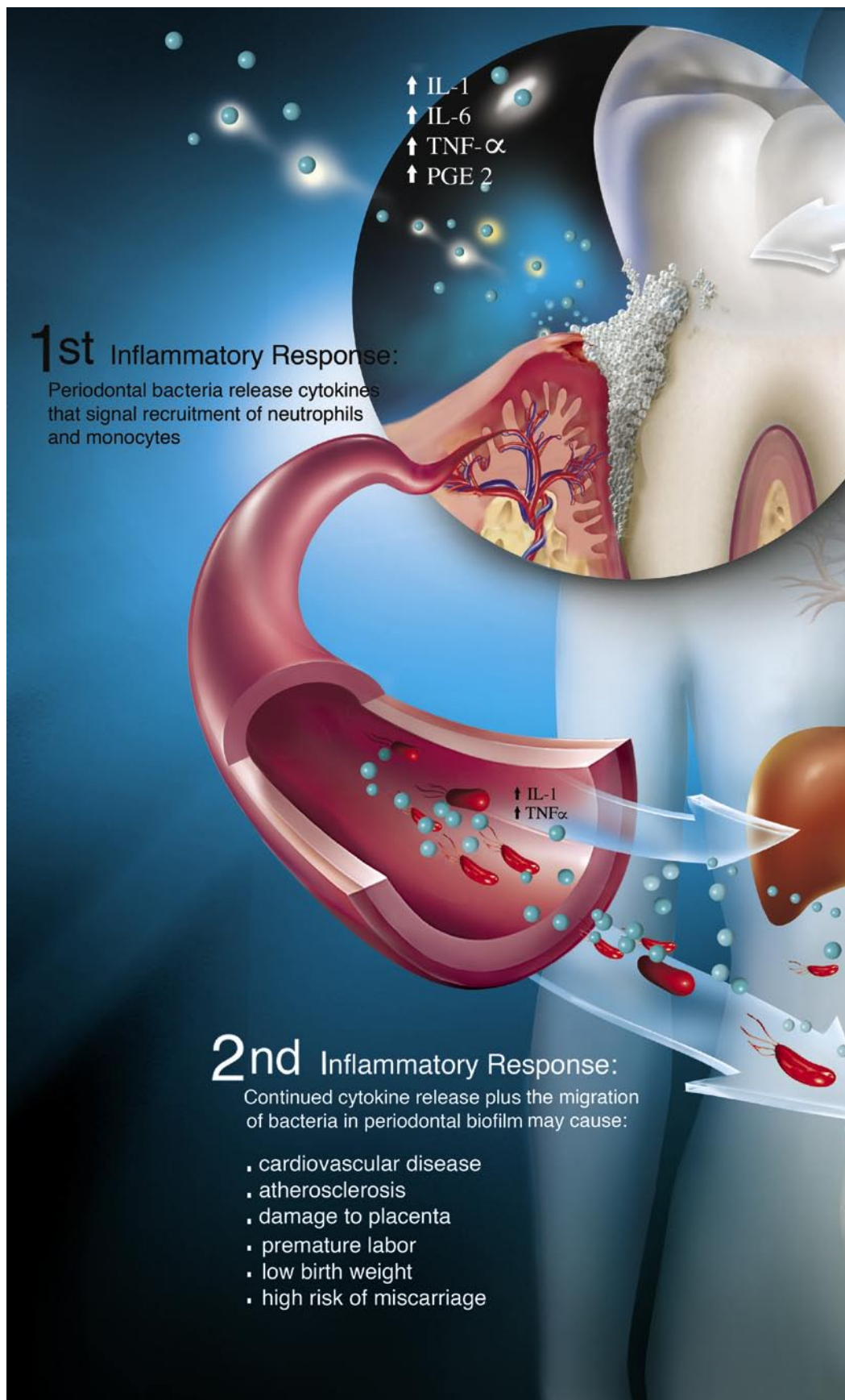
Summit participants noted that obstetricians, gynecologists, and other physicians may advise against dental treatment during pregnancy because of the bacteremia that occurs during dental prophylaxis. Kinane reported that these types of bacteremia usually are detectable for about 20 minutes and that bacteremias can also be induced by tooth brushing, flossing, and chewing. Furthermore, the longer a patient has oral problems, the more virulent the bacteremia becomes. Offenbacher cited

Figure 2. The Systemic Inflammatory Impact of Periodontal Disease

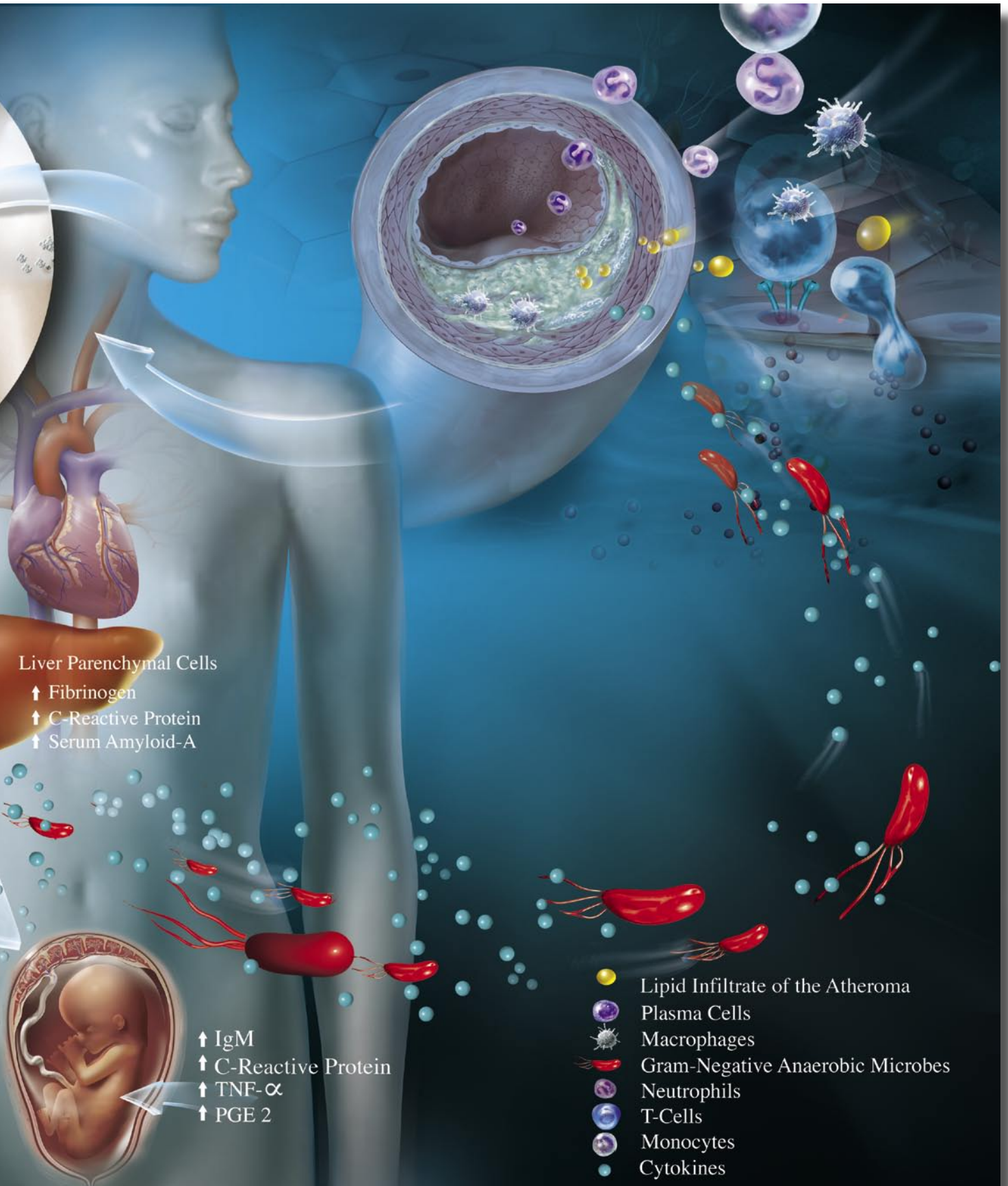
As subgingival biofilms grow, there is a concomitant increase in the proportions of gram-negative anaerobic microbes. The endotoxins, enzymes, and metabolic by-products produced by gram-negative microflora cause ulceration and cellular necrosis in the epithelial lining of the periodontal pocket. The epithelial ulceration presents a pathway of invasion for bacteria and endotoxins to the underlying connective tissues and blood vessels. The host immune response to these invading microbes and their by-products results in accumulation of an inflammatory cell infiltrate, characterized initially by neutrophils, and eventually includes lymphocytes, plasma cells, monocytes, and macrophages. Locally, the inflammatory cells and other host cells produce inflammatory cytokines and chemical mediators of inflammation, such as interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and prostaglandins E₂ (PGE₂).

The locally produced inflammatory cytokines gain access to dilated capillaries at the site of inflammation and are transported to the liver. The liver parenchymal cells are stimulated to produce acute-phase proteins, i.e., C-reactive protein, fibrinogen, serum amyloid-A. In addition, bacteria and endotoxins may also gain access to the dilated capillaries, resulting in bacteremia and endotoxemia.

The combined effect of circulating inflammatory cytokines, bacteremia, endotoxemia, and acute-phase proteins results in damage to the endothelial lining of coronary, cerebral, and other arteries, the first step in atheroma formation. Furthermore, certain bacteria may promote aggregation of platelets and thereby promote thrombus formation. Lastly, specific bacteria, inflammatory cytokines, and chemical mediators of inflammation can penetrate the placental barrier and, in turn, increase the risk for adverse pregnancy outcomes.



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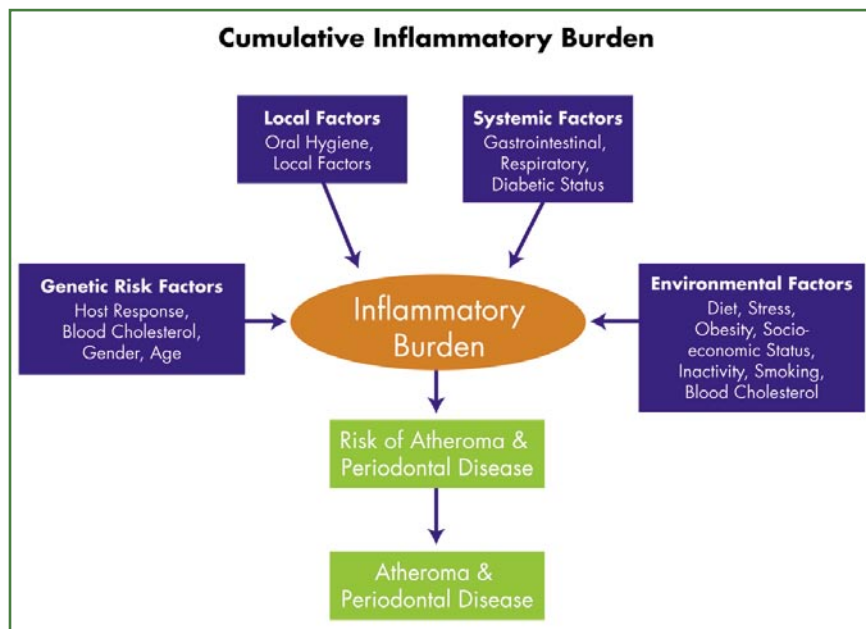


Figure 3. Cumulative Inflammatory Burden

There are several factors that contribute to the cumulative inflammatory burden, including genetic, local, systemic and environmental risk factors. Evidence suggests the greater the total systemic inflammatory burden, the greater the risk and incidence of atheroma formation and periodontal disease.

a number of intervention trials that suggest that treating periodontal disease during pregnancy is safe and does not cause significant risk to the mother or the fetus.³³⁻³⁶

Regarding the strength of the correlation between the severity of systemic disease and bacteremia, Kinane responded that the longer a periodontal lesion is present, the larger it is, and the longer it has existed, the higher the levels of bacteremia. Whether and how this contributes to the severity of systemic disease still needs to be determined.

Key Point #2: Whether a person develops periodontal disease is dictated largely by that person's susceptibility, which is determined by genetics, host response, and environmental, behavioral, and acquired risk factors.

The shift in host response during the transition from gingivitis to periodontitis occurs as plaque biofilm bacteria cause the recruitment of inflammatory cell infiltrate within the gingival tissue (see Figure 2). In gingivitis, the alveolar bone and the periodontal ligament remain intact and undisturbed. When gingivitis progresses, there is a shift in the biochemistry of the lesion as neutrophils and eventually macrophages, lymphocytes and other cells infiltrate the connective tissue adjacent to the sulcular epithelium. These cells produce cytokines and inflammatory mediators such as prostaglandin E₂, interleukin-1 beta (IL-1 β), tumor necrosis factor-alpha (TNF- α), and interleukin-6 (IL-6) that are associated with the local tissue and bone destruction seen in periodontal disease. The host response is complex, because other biochemi-

cal mediators apart from cytokines and inflammatory mediators also intervene in local tissue destruction, such as matrix metalloproteinases. This local inflammatory cascade is also associated with other inflammatory conditions that occur throughout the body and can be elicited at distant organs and tissues targeted by oral organisms (see Figure 2).

In periodontitis, the host response to specific microorganisms, coupled with the virulence and pathogenesis of *P. gingivalis* and *A. actinomycetemcomitans* may collectively determine the extent of inflammation and the magnitude of the disease.³⁶ The host response may also be a significant risk factor for other systemic conditions (see Figure 3).

Key Point #3: Research examining the association between periodontal disease and systemic diseases, particularly CVD, satisfies many, but not all, of the Bradford Hill criteria necessary to establish a causal relationship.

The observed association between periodontal disease and CVD satisfies many of the 9 Bradford Hill criteria for causality, including consistency, specificity, temporality, and a dose-response relationship (see Table 1).

A study published in 1989 in the *British Medical Journal* by Mattila and colleagues³⁷ was among the first to demonstrate consistency in the association between dental health and CHD. Mattila found that people with CHD were more likely than their healthy counterparts to have missing teeth. Danesh's 4 meta-analyses³⁸ demonstrated a relationship between different infections and CHD. The association between CHD and infectious agents such as *Helicobacter pylori*, *Chlamydia pneumoniae*, cytomegalovirus, and periodontal infection was relatively small; however, compared with the other infections, periodontitis was the only one that withstood the scrutiny of the meta-analysis.³⁸

In spite of significant positive associations, there are problems inherent to controlling for residual confounding factors in determining whether there is a cause-and-effect relationship between periodontal disease and CVD. Some experts have argued that socioeconomic status is a major determinant of periodontal disease, CVD, and health in general, and that even after adjusting for socioeconomic status and years of education, these variables cannot be completely accounted for in the data set. However, the First National Health and Nutrition Examination Survey (NHANES I) epidemiologic follow-up study (NHEFS)³⁹ demonstrated a clear association between periodontal disease and stroke with sufficient specificity in the asso-

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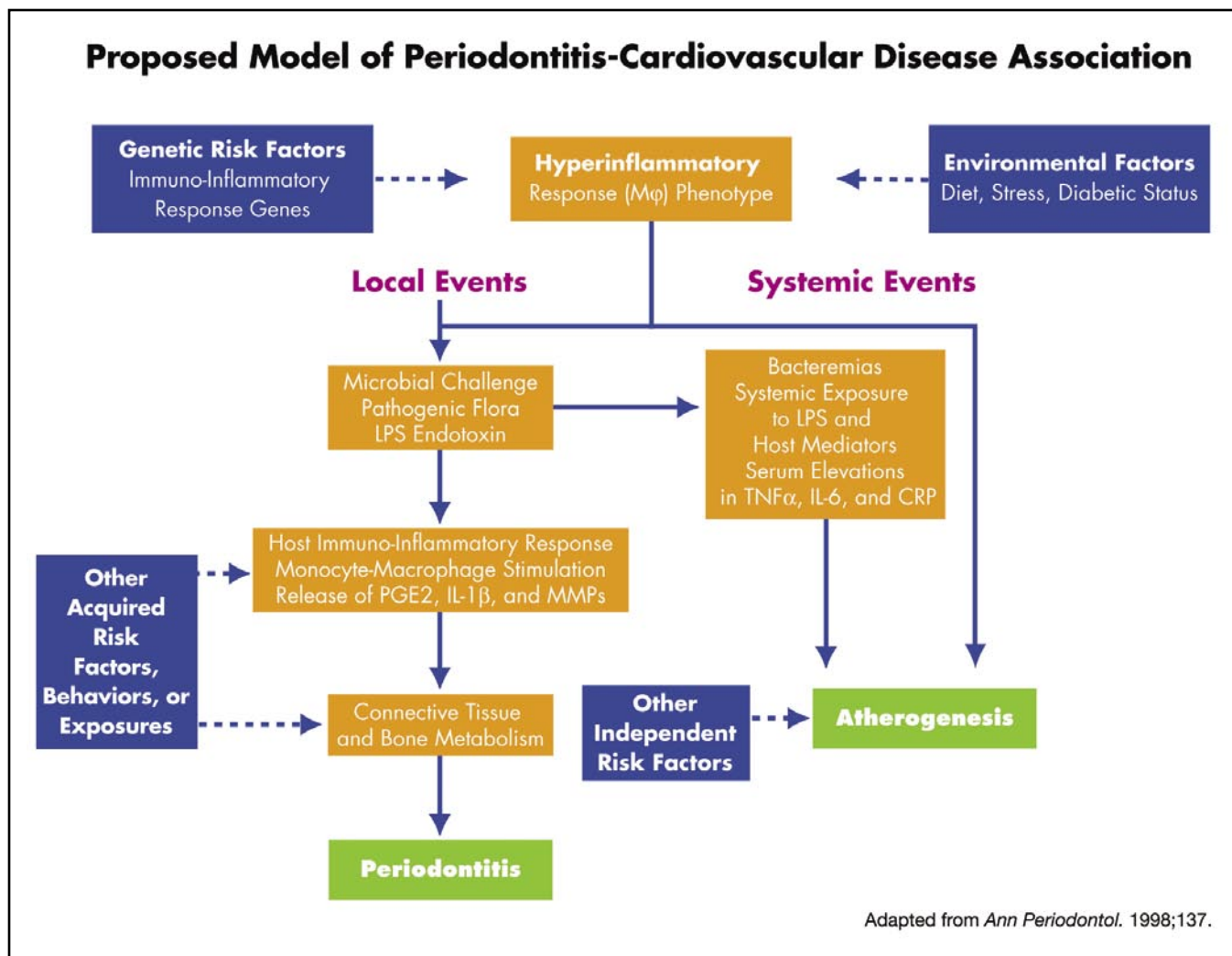


Figure 4. Proposed Model of Periodontitis-Cardiovascular Disease Association

ciation to attribute the occurrence to a cause-and-effect relationship. Trevisan explained that investigators found periodontal disease to be more significantly linked to thrombotic stroke and not hemorrhagic stroke.⁴⁰⁻⁴³ This is what had been hypothesized.

In 1996, Beck and colleagues⁴⁴ demonstrated an association between periodontal bone loss and the incidence of CVD across time, which suggests not only a temporal association (the exposure preceded the event), but also a clear dose-response relationship.

Similarly, the MYLIFE Study,⁴⁵ a population case-controlled study that included patients who had experienced a myocardial infarction (MI) and were evaluated for periodontal disease, showed that the association between periodontal disease and the incidence of MI was found in both men and women, with a stronger association in women. Patients diagnosed with MI were compared with healthy controls to determine the incidence of periodontal disease between the 2 groups. Among the 3 measure-

ments of periodontal disease — clinical attachment loss, pocket depth, and missing teeth — the one that was most strongly associated with MI was pocket depth. Of these measures, pocket depth is most closely related to the gingival component of inflammation.

Although some researchers would argue that smoking is a confounding factor in studying the association between periodontal disease and CVD, findings from the MYLIFE study indicated that the association between pocket depth and MI was found in both smokers and nonsmokers. In another longitudinal study that followed 884 patients with MI for 6 years, Dorn and colleagues⁴⁶ found that the association between periodontal disease and recurrent CVD events was seen only in patients who never smoked.⁴⁶ Other studies have also reported that smoking is not a confounding factor in the association between periodontal disease and CVD.^{47,48} In contrast, it is possible that smoking is such a powerful predictor of secondary events in people with a history of MI that peri-

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odontal disease does not have much of an impact. When smoking is present, periodontal disease may contribute to the risk for developing CVD events.

Key Point #4: *Current evidence suggests that a number of biologically plausible mechanisms may be implicated in the association between periodontal disease and CVD.*

In addition to direct vascular/endothelial invasion of periodontal microorganisms reviewed in Key Point #1, other biological mechanisms have been reported in linking periodontal disease to the development of atherosclerotic lesions. These include a) the cumulative inflammatory burden contributed by risk factors common to both periodontal disease and atheroma formation, and b) the possible role of antibody response and autoimmunity and the potential for a hyperinflammatory response as contributing to atheroma formation.

Cumulative inflammatory burden may be an important aspect of the relationship between periodontal disease and atheroma formation. The total periodontal bacterial burden appears to be more significant in increasing risk for CVD than most single bacterial exposures,²⁸ although a recent investigation has demonstrated that specific bacterial profiles may be concomitant risk factors in the development of acute coronary syndrome.²⁴

The theories regarding the formation of atheromas are changing, suggesting more systemic causes of vascular disease. Smoking, stress, obesity, respiratory diseases, and periodontal disease can all contribute to the cumulative inflammatory burden, which in turn can result in CVD.⁴⁹ While older theories suggested that lipids or blood clots caused atheromas, newer theories focus on the reaction to injury from infection and inflammation.⁵⁰ These ideas support the notion that there are a variety of mechanisms that cause injury or inflammation to the blood vessel wall (see Figure 4).

Risk factors for vascular atheromas include increased blood levels of fibrinogen, white blood cells, and lipids, all of which have been related to periodontitis.⁵¹ Studies show that patients with periodontal disease have higher levels of fibrinogen and white blood cells than what is observed in controls.¹⁴ More recently, an association was seen between periodontitis, hyperlipidemia, and hyperglycemia, which are major risk factors for CVD.^{52,53} Patients most susceptible to periodontitis are equally or similarly susceptible to heart disease.⁵⁴

Antibody response may also play a role in the relationship between periodontal disease and atheroma formation. Some researchers theorize that there is a potential interaction between antibodies directed against orally derived bacteria and their proteins, which cross-react with host proteins. This cross-reaction triggers a localized autoimmune response within the endothelium, that results in an inflammatory response that may lead to endothe-

lial damage.⁵⁵⁻⁵⁷ A strong antibody response to periodontal pathogens further demonstrates that the response to these microorganisms is systemic and not confined to the oral cavity.⁵⁸ The mechanism of cross-reactive antibodies is controversial and needs considerable research before it can be accepted as a plausible mechanism.

Discussion

The question was raised as to whether dentists receive referrals from cardiologists or other physicians. Offenbacher said he is aware of this happening, but that there needs to be greater awareness of the association between periodontal disease and CVD among medical practitioners. This can be done through public awareness campaigns, scientific literature, and scientific meetings. Trevisan commented that less than one third of the papers published about periodontal disease and CVD appear in medical journals. He also noted that many of these studies are weak in design, with small patient populations. Trevisan also pointed out that the infectious etiology of CVD seems not to be widely accepted among cardiologists.

Key Point #5: *Research on the relationship between periodontal disease and systemic inflammation, together with its effect on systemic diseases and disorders, has yielded conflicting data.*

Systemic inflammation can increase the risk for several diseases and disorders, including CVD, cerebrovascular disease, adverse pregnancy outcomes, and insulin resistance.

CRP is a well-known marker of systemic inflammation produced by the liver as part of the acute-phase response.^{59,60} More specifically, CRP is synthesized in response to TNF- α , IL-1, and IL-6, which are released in association with inflammation.

CRP is measured by the high-sensitivity CRP test (hsCRP). Generally, CRP levels are <3 mg/L in the blood of healthy people, but can increase more than 100-fold when severe acute inflammation is triggered.⁶⁰ In chronic inflammation, such as CVD, CRP levels increase to a "high normal" range of 3 to 10 mg/L. In fact, CRP is recognized as a marker in determining the relative risk for CVD. Multiple case-controlled studies have shown that CRP levels are elevated in subjects with periodontal disease compared with healthy controls.⁶¹ Daily episodes of bacteremia originating from periodontal lesions may be the cause of increased CRP levels, which may explain the association between periodontal disease and CVD.^{14,62} Slade and colleagues⁶³ reported that the effects of periodontal disease on CRP could be as important in contributing to heart disease as other risk factors such as smoking or diabetes. As such, CRP may be a useful marker in determining the relative risk for CVD. However, a recently published review on the subject of CRP as a risk

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Figure 5. Fetal Exposure to Oral Bacteria

An estimated 1 in 5 preterm births may be attributable to maternal periodontal infections. It is hypothesized that maternal infection, whether from oral bacteria or other sources, induces an inflammatory response first in the placenta and placental membranes, then in the fetal circulation via the umbilical cord. The inflammatory response may affect the exchange of nutrients between the mother and fetus, and may cause premature rupture and preterm delivery.

indicator is more conservative and suggests the evidence is not strong enough to warrant inclusion into a risk prediction algorithm or recommending inclusion of CRP in universal screening.⁶⁴

CRP has been shown to be significantly higher in patients with periodontal disease.⁶⁵ However, as noted earlier, the INVEST study found a link between periodontal bacterial burden and vascular dysfunction, independent of CRP. This means that there are inconsistencies in the link between periodontal disease, CRP and CVD, and other markers, as yet unidentified, are needed. It is possible that other confounding factors such as obesity play an important role in determining marker formation.

Periodontal intervention, antimicrobial periodontal treatment, and tooth extraction have been shown to lower CRP.⁶⁶ Recent studies have shown that periodontal therapy may decrease systemic inflammation, lower CRP, and improve endothelial function.³¹

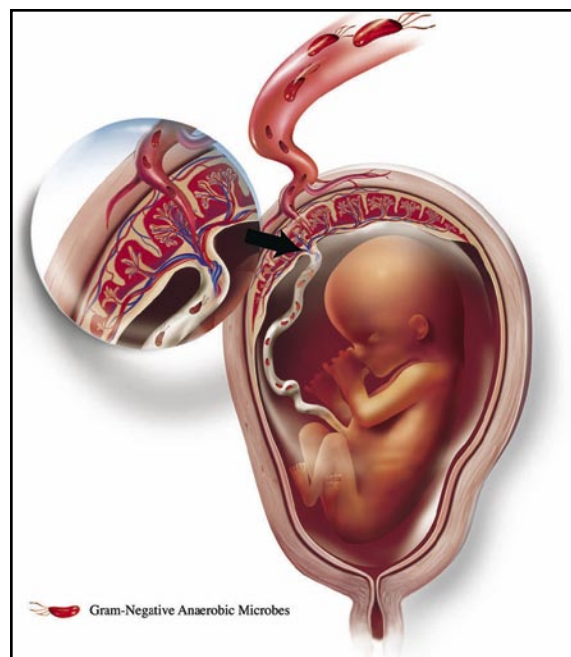
Discussion

The expert panel was asked whether it was possible that CVD is worsened not by inflammation, but by higher levels of CRP. Trevisan responded that inflammation plays a role in CVD, but there is disagreement on what that role is, and that inflammation may be a triggering factor for CVD. He said it is clear that CRP is not the whole story, and that more research is needed to understand the mechanisms linking pathogen burden to CVD.

Another question was whether using intermediate biomarkers to study the relationship between periodontal disease and CVD would be useful. Trevisan responded that cIMT is the most commonly used measurement, but there may be other markers that are useful.

Key Point #6: *Cumulative evidence suggests that periodontal disease is linked to adverse pregnancy outcomes. Some studies indicate that treating mothers before and throughout pregnancy may result in full-term, larger, and healthier babies.*

Current research supports an association, which may vary by patient population, between periodontal disease and adverse pregnancy outcomes, and demonstrates that birth weight, gestational age, and infant health are correlated to the periodontal health of the mother. Approximately 10% of all births are preterm births (PTBs) (<37 weeks gestation). It is estimated that PTBs account for two thirds of all infant mortality and generate



more than \$17.2 billion each year in neonatal intensive care unit costs. PTB is the major cause of infant and long-term disability, particularly in very preterm deliveries. It has been suggested that up to 50% of neurologic defects in children are associated with PTB, while extreme low birth weight is associated with asthma, low IQ, cerebral palsy, poor motor skills, and other functional abnormalities.⁶⁷

Periodontal infections have been found to be more prevalent in pregnant women than all other obstetric and sexually transmitted infections combined. It has been estimated that 1 in 5 PTBs may be attributable to periodontal infections,³ and periodontal pathogens have been found in amniotic fluid.⁶⁸

The current theory regarding periodontitis-associated adverse pregnancy outcomes is based on both animal and human studies. Evidence suggests that intrauterine fetal exposure to oral microorganisms can occur⁶⁹ (see Figure 5). As a result of placental exposure to oral bacteria, inflammation is induced, which may adversely impact the normal exchange of nutrients between the mother and fetus.⁶⁹ In one study, the presence of inflammatory markers such as CRP, prostaglandin E₂, and TNF- α in umbilical cord blood raised the odds ratio of PTB.⁷⁰ Researchers theorize that the same inflammatory process that occurs during periodontal disease can occur in the placental membrane, inducing premature rupture and preterm delivery.⁷⁰

The Fetal Inflammatory Response Syndrome hypothesizes that maternal infection from any cause, including periodontal disease, induces an inflammatory response in the fetal compartments. First the placenta and placental membranes respond, then the fetal circulation via the

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umbilical cord. At this point, the fetal brain is exposed to inflammatory proteins, whether or not infection is present. Animal model data have shown brain damage in fetal animals when this occurs.⁷¹

Another important finding is the impact of periodontal disease progression on pregnancy outcomes. Although the risk of PTB is greater among pregnant women who begin their pregnancy with periodontal disease, recent evidence suggests that there is also risk for women who develop gingival inflammation during pregnancy. In one study, pregnant women who experienced periodontal disease progression were at 2-to-3-fold greater risk for delivering at less than 32 weeks.⁷² Disease progression was also related to birth weight. Research shows that moderate to severe periodontal disease increases the odds ratio for having a small baby by about 2.3 ($P=0.02$).⁷²

Treating periodontal disease to improve oral health in pregnant women may reduce the risk of PTB.^{34,35} A landmark study by Lopez and colleagues³⁴ in Santiago, Chile, enrolled and randomly assigned 870 pregnant women, all of whom had gingivitis, into 2 groups: one group received periodontal treatment before 28 weeks of gestation; the other group did not receive treatment until after delivery. The pregnant women who received periodontal treatment had a 2.1% incidence of PTB compared with 6.7% in the untreated group, a more than 3-fold reduction.

Still, other studies have yielded conflicting results. One such study that recently came to the forefront was published in November 2006 in the *New England Journal of Medicine* by Michalowicz and colleagues.³⁶ This recent multi-centered clinical trial, called the Obstetrics and Periodontal Therapy (OPT) study of 823 women with periodontal disease, failed to demonstrate a difference in the rates of preterm birth, low birth weight, or fetal growth restriction following treatment for periodontal disease. This study did demonstrate that treatment of periodontal disease in pregnant women is safe.³⁶

In response to these research findings, Goldenberg and Culhane wrote a compelling editorial in the same issue of the *New England Journal of Medicine* which suggested that “once the inflammatory cascade is activated during pregnancy, interventions targeting this pathway may be ineffective in reducing the rate of PTB. Treatment during pregnancy may be too late; it is possible that treatment either before pregnancy (in nulliparous women) or in the period between pregnancies (for multiparous women, especially those with a history of PTB) may yield more promising results.”⁷³ Most researchers agree that it will be many years before definitive conclusions can be drawn relative to the impact that prevention or treatment of periodontal disease may have on pregnancy outcomes. If periodontal therapy is proven to reduce the rate of PTB, both healthcare costs and the rate of infant mortality could be significantly reduced.

Discussion

Offenbacher said he believed that obstetricians are beginning to accept the link between periodontal disease and adverse pregnancy outcomes and noted that some of the data from his presentations have appeared in obstetrics journals. He suggested that the literature is being well received by the obstetrics community and theorized that this acceptance level is a result in part of obstetricians’ understanding of infectious etiologies to explain adverse pregnancy outcomes.

Recent research suggesting a relationship between periodontal disease and increased risk for preeclampsia was discussed. Offenbacher said that periodontal disease in the mother seems to be an independent contributor to preeclampsia.

One attendee asked whether pregnant women with periodontal disease should be treated with a combination of antibiotics or surgery. Offenbacher responded that there is no optimum therapy to recommend; however, he said that he would use antibiotics only if the disease could not be treated by conventional means. Offenbacher advised that practitioners consult with obstetricians before using antibiotics. He said he would not perform quadrant-based periodontal surgery, but rather employ conservative local instrumentation and patient education about oral self-care whenever possible. Dr. Panos Papapanou agreed that using antibiotics as a routine precaution for treatment of periodontal disease in pregnant women is contraindicated and pointed out that his own study using scaling without antiseptics or antibiotics was proven to be effective. The participants pointed out that there are some data suggesting that the use of antibiotics may actually increase adverse pregnancy outcomes. It was also noted that systemic antibiotics do not necessarily control the dental plaque biofilm infection.

Panel Discussion Subsequent to Presentations

DePaola began the panel discussion by addressing Dr. Ira Lamster’s concern that medical practitioners do not communicate sufficiently with dentists. DePaola noted that pediatricians are beginning to embrace the notion of oral health in their practices and that the American Academy of Pediatrics has developed new policy statements on oral care. He suggested that there was no reason not to share this communication on periodontal disease and systemic health with medical practitioners.

It was suggested that periodontal disease be considered an open, septic wound, and as such, if it were anywhere else in the body, it would receive significantly greater attention. Trevisan commented that there is not enough convincing evidence for the medical community to recognize the causal relationship between periodontal disease and systemic injury. He went on to say that the addition of periodontal disease as a risk factor in ongoing and new clinical trials or observational studies would add credibility to the oral-

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systemic link. It was noted that usually there are no dentists on the study teams to advocate for including periodontal disease as a risk factor. Trevisan said that future National Institutes of Health (NIH) initiatives should include more interdisciplinary approaches, which he hoped would result in dentists being routinely included on study teams. He also said that diagnostic tools, including biomarkers, will make it easier to identify the presence and severity of systemic and oral disease and strengthen the findings of research. New health delivery models are being implemented and evaluated, including the NIH Clinical and Translational Science Awards (CTSA), a national consortium designed to transform how clinical and translational research is conducted. These CTSA are required to include dental components.

Trevisan noted that although a fair amount is known about major risk factors for CVD, there is still room to add other risk factors, including periodontal infection.

Lamster pointed out that the National Institute of Diabetes and Digestive and Kidney Diseases and the National Institute of Dental and Craniofacial Research (NIDCR) cosponsored a conference that examined the relationship between diabetes mellitus and periodontal disease. This raised the question of the role the NIDCR could have in bringing together interested groups of clinicians and researchers to discuss the association between periodontal disease and CVD, where the evidence for an association between periodontal disease and CVD is gaining strength.

Dr. Moise Desvarieux said that the dental profession should be careful about how the association between periodontal disease and systemic health is presented to the public. Trevisan agreed that deciding when and where to intervene required full understanding of the mechanism linking periodontal disease to systemic disease(s). He said the public should be informed that periodontal disease is a major public health problem that can be prevented and treated. He stated that although dentists cannot tell patients that treating periodontal disease will prevent heart attacks, they can promote the message that there is a strong link between oral health and systemic health. Kinane concluded that the message needs to include emphasis on gingivitis, periodontitis, and other oral inflammatory conditions and emphasize the importance of the overall body inflammatory burden on systemic health. Offenbacher pointed out that the public needs to be educated about the role of oral organisms and the benefits of self-care on reducing bacteremia, which in turn can reduce the inflammatory burden.

It was suggested that given the body of evidence surrounding periodontal-systemic relationships, there should be discussion among dental and medical professionals about transdisciplinary models of care. Dental hygienists and nurses should increasingly work together to bilaterally screen for oral and systemic conditions, i.e., hygienists should screen for systemic diseases and nurses should screen

for oral diseases. Offenbacher commented that although the notion of interdisciplinary care is a wise suggestion, the challenge lies in funding pilot trials to demonstrate the potential benefit of this type of collaboration.

Kinane stated that there should be some sort of standard of care for everyone in the healthcare profession — dentists and physicians alike. He emphasized that to overlook a disease because it is not in an area of expertise is ethically wrong. Kinane suggested that perhaps the problem lies in how medical and dental students are educated and trained and concluded that more work needs to be done in the area of education. Once additional evidence is established linking periodontal disease to systemic disease, the idea of transdisciplinary models of care will become widely accepted.

The issue of universal access to periodontal care was brought up. It was suggested that in countries where access to periodontal care is universal, it may be easier to form relationships between the medical and dental communities. Scandinavia was cited as an example where physicians and dentists create joint protocols for the purposes of scientific studies and the development of standards of practice. It was pointed out that access to care may be as important as any of the scientific issues that have been discussed.

Kinane, Offenbacher, and Trevisan were asked to identify 3 things that should be done to change the practice of dentistry so as to promote better health outcomes. Kinane responded that the 3 things to focus on relating to inflammatory burden are obesity, diabetes, and smoking. He suggested that dentists could start taking blood pressure, test urine, discuss smoking cessation, and evaluate body mass index. If problems were detected, patients could be referred back to their physician thus enhancing the dentist's role as a primary care provider.

Conclusions

Cumulative evidence suggests that apart from its local destructive effects, chronic inflammatory periodontal disease may be a modifiable risk factor for morbidity and mortality in a number of serious systemic diseases and conditions. Clinically, this means that treatment for gingivitis and periodontitis may help improve general health outcomes and reduce the risk of systemic disorders such as CVD and adverse pregnancy outcomes.

The biologic pathways through which periodontal disease and chronic systemic disease are related are not entirely understood. However, bacteria in the oral cavity may contribute directly or indirectly to CVD and adverse pregnancy outcomes by entering the circulatory system, increasing the inflammatory burden, forming atherosclerotic plaques, and/or invading the placenta. Additional work needs to be done to understand the precise mechanisms linking periodontal disease with systemic diseases. Multicenter trials must continue to be conducted to prove

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a cause-and-effect relationship between periodontal disease and systemic health and to understand the impact of periodontal disease on public health.

The possibility that periodontal disease may be a modifiable risk factor associated with systemic inflammatory states has clearly redefined oral health as an essential component of overall health. Although little is known conclusively about periodontal disease and its relation to systemic disease, by actively working to control pathological species of oral bacteria, clinicians can take steps to modulate the inflammatory burden, which will likely have health benefits that extend beyond the oral cavity.

Consensus Opinion Derived From Postsummit Global Task Force Meeting

Based on the summit proceedings, it became apparent that there was a need to clarify the state of the science linking periodontal disease with systemic disease and to decide what research is needed for the future, as well as to address what changes are necessary for the implementation of periodontal-systemic medicine in clinical practice. In addition, consumer messaging must be aligned with current research. In view of these needs, a postsummit Global Task Force was appointed to develop a consensus opinion pertaining to the 3 specific questions iterated in the Preface. These questions and the Global Task Force's consensus opinions follow.

1. *What is the state of the research, specifically the strength of evidence to support the relationship between periodontal disease and systemic diseases and disorders, specifically CVD, cerebrovascular disease, and adverse pregnancy outcomes?*

- ❑ As to whether the association between periodontal disease and CVD is purely observed or causal in nature, various studies have provided evidence that the association satisfies a number of the Bradford Hill criteria that establish cause and effect. Specifically, current evidence suggests that many of the Bradford Hill criteria, including consistency, specificity, temporality, and a dose-response relationship, have been demonstrated in studies investigating the association between periodontal disease and CVD.
- ❑ Current evidence supports the theory that dental plaque biofilm, with its potential for increased risk of bacteremia (infectious burden) and resulting inflammatory response, may adversely affect distant sites and various organ systems. As such, periodontally derived bacteremias have a role in increasing the risk for systemic diseases and disorders.
- ❑ Periodontal disease is a major public health problem that can be prevented and treated.
- ❑ Periodontal disease can be an important modifiable risk factor for morbidity and mortality of various systemic diseases and disorders.
- ❑ Pilot intervention studies have shown promising results

The association between periodontal disease and CVD has important potential public health implications.

in decreasing the risk for systemic diseases by treating periodontal disease; however, they have been conducted in limited cohorts of the global population. Large multicenter trials currently underway for pregnancy outcomes must provide more consistent results.

- ❑ The potential public health impact of this research is significant enough to warrant funding for future intervention trials that study the impact of periodontal disease treatment on systemic diseases, in particular, CVD and adverse pregnancy outcomes.
 - ❑ The public must be educated about the role of dental plaque biofilm in systemic inflammatory burden. The public should be made aware that effective daily oral self-care can improve oral health and minimize the risk for oral pathogens to enter in the bloodstream.
 - ❑ Although there is growing recognition that periodontal disease is an important modifiable risk factor for systemic diseases or conditions, to date this concept has not been widely recognized by the broader medical community.
2. *What future direction should be taken to strengthen the body of evidence related to periodontal-systemic research?*
- ❑ Ongoing observational and additional pilot intervention studies that focus on periodontal disease and systemic outcomes are needed to provide the information necessary for the design of large-scale clinical intervention studies.
 - ❑ Studies must be conducted in a variety of populations around the world to reflect specific socioeconomic, biologic, and environmental determinants in each population.
 - ❑ More mechanistic studies are needed to define the role of periodontal disease relative to systemic modifications. These studies should investigate the role periodontal microorganisms, inflammatory markers, and genetic markers play in systemic diseases and disorders.
 - ❑ The role of genetics in a person's susceptibility to periodontal disease and its systemic sequelae needs more study.
 - ❑ Funding must be made available through public and private partnerships to conduct large, multicentered, appropriately designed trials. These studies must have strong methodology to minimize disputed or ambiguous research findings.
 - ❑ Adding dental professionals to peer-review teams for clinical trials of certain systemic diseases may increase the understanding of why periodontal disease should be considered a risk factor for systemic sequelae.

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- ❑ New biomarkers and diagnostic tools for periodontal disease must be identified and developed to make it easier to identify the presence and severity of periodontal disease.
- ❑ All healthcare professionals must be made aware of the oral-systemic link. Research should be conducted on how best to educate other oral health professionals on oral systemic linkages.
- ❑ Future education initiatives in dental and medical schools should include:
 - Educational programming that focuses on risk assessment and risk modification for the prevention or management of chronic diseases
 - An emphasis on periodontitis as being connected to the rest of the body, with a focus on the cumulative effect of the bacterial burden of periodontal disease and resultant inflammatory burden on systemic health
 - Awareness of the full spectrum of health issues related to periodontal disease and emphasis on transdisciplinary models of care
 - Integration of basic biologic information into the dental and medical healthcare delivery system

3. *What do we currently know about the suspected periodontal-systemic links that is reasonably certain and appropriate to share in the form of a published consensus statement that will be meaningful to dental professionals and the consumer public?*

- ❑ Periodontal disease can be an important risk factor for morbidity and mortality of various systemic diseases.
- ❑ Gingivitis and, more importantly, chronic periodontitis are now considered part of a continuum of a chronic inflammatory condition termed periodontal disease. Clinically, this means that the treatment for gingivitis as well as periodontitis may reduce the risk for systemic diseases such as CVD and adverse pregnancy outcomes.
- ❑ Periodontal disease constitutes a chronic exposure to a complex of pathogenic bacteria that trigger a host inflammatory response.
- ❑ Oral bacteria have been found systemically and are associated with systemic outcomes, e.g., bacteria in atheromas.
- ❑ Inflammation anywhere in the body can adversely affect other sites as well as the system as a whole.
- ❑ The association between periodontal disease and CVD has important potential public health implications.
- ❑ Although there is no conclusive evidence that treating periodontal disease will prevent heart attacks and adverse pregnancy outcomes, dental professionals can promote the message that there is a strong link between oral health and systemic health. In any case, treatment of periodontal disease will improve oral health.
- ❑ It is estimated that oral infections are more prevalent in pregnant women than all other obstetric and sexually transmitted infections combined.

- ❑ Periodontal therapy performed on pregnant women during their second trimester is a safe and effective means to improve maternal oral health.
- ❑ In the near future, if periodontal therapy is proven to reduce the rate of premature births, new healthcare practices may potentially result in significant reductions in maternal and infant healthcare costs, as well as reduced rates of infant morbidity.

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Continuing Education Test Questions for:

Proceedings and Consensus Opinions From the Global Oral and Systemic Health Summit

4 CEUs

Circle the letter that corresponds to your answer for each question.

- Collective epidemiologic data from various studies estimate how many adults in the United States have some form of periodontal disease?
 - 28 million
 - 35 million
 - 60 million
 - 70 million
- Which of the following is believed to be a biologically plausible mechanism linking periodontal disease and cardiovascular disease?
 - The cumulative inflammatory burden contributed by risk factors common to both periodontal disease and atheroma formation
 - Direct invasion of endothelium by periodontal microorganisms
 - Antibody response and autoimmunity and the potential for a hyperinflammatory response to certain bacteria
 - All of the above
- Which of the following is the only cardiovascular disease biomarker shown to be significantly higher in patients with periodontal disease?
 - C-reactive protein (CRP)
 - Fibrinogen
 - White blood cells
 - Interleukin-6
- CRP is synthesized by the:
 - Liver
 - Kidney
 - Pancreas
 - None of the above
- The observed association between periodontal disease and cardiovascular disease satisfies which of the following Bradford Hill criteria for causality?
 - Consistency
 - Specificity
 - Dose-response relationship
 - All of the above
- Among individuals with chronic periodontitis, the surface area of the dentogingival epithelium exposed to potential bacterial invasion and/or infiltration of antigenic microbial components ranges between:
 - 8 cm² to 20 cm²
 - 40 cm² to 62 cm²
 - 50 cm² to 72 cm²
 - 60 cm² to 82 cm²
- How many preterm births are estimated to be attributable to periodontal infections?
 - 1 in 3
 - 1 in 4
 - 1 in 5
 - 1 in 6
- Which of the following cytokines and inflammatory mediators are produced as a result of the host inflammatory response to oral bacteria?
 - Prostaglandin E₂
 - Interleukin-1 β
 - Tumor necrosis factor- α
 - All of the above

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After completing the test, fill in the requested personal information below and return the form and test answers via either of two options:

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