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Periodontal triggers of systemic disease: We are closer to causation than ever before

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Abstract

The first dental textbook pointing to oral bacterial colonies as the driving force behind systemic disease appeared in 1890.[1] In this seminal text more than 130 years ago, Willoughby Dayton Miller wrote the following: "It has been established beyond all question that myriads of micro-organisms are constantly present in the human mouth, and that these, under favorable circumstances, are capable of manifesting an action of the utmost significance upon the local as well as the general health of the patient."

Miller continued, "These various disturbances are produced partly by the direct action of the micro-organisms and their products upon the teeth and the mucous membrane of the mouth, partly by constant swallowing of large masses of bacteria, partly by carrying them into the lungs, particularly by violent inspiration, and, finally by their obtaining an entrance into the blood or lymph-vessels in the various ways described…"[1]

A critical look at the historical and contemporary data connecting periodontal disease to systemic disease proves Miller's writings to be nothing short of visionary at the very dawn of dental bacteriology. This review will link these data and trace the last 160 years of medical discovery in the peer-reviewed literature. It will also suggest modern diagnostic procedures to assist dentists in showing patients, with their own objective personal data, the long-term systemic health benefits of treating periodontal disease in the dental office.

Educational objectives

1. List the common risk factors for periodontal disease
2. Discuss the role of inflammation and infection in periodontal disease
3. Describe the relationship between periodontal disease and conditions, including diabetes, heart disease, and autoimmune disorders
4. Outline how the information in this course can be used to improve patient care outcomes

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Introduction

In the new National Institutes of Health (NIH) review of Oral Health in America (2021), the NIH states, "The relationship between oral and general health manifests in a variety of ways. The effects of periodontal disease—a chronic disease affecting the gums, bone, and other supporting tissues around teeth—has been studied in relation to nearly 60 other adverse health conditions, including diabetes, heart disease, and Alzheimer's disease."[2]

This confidence by the NIH in the connection between periodontal disease and systemic health conditions is not a new phenomenon in medicine. The initial declaration of such an epidemiologic connection was proclaimed by many of the early giants in microbiology, yet has been largely forgotten in history. To honestly examine the history of microbiology, one must begin by looking in the mouth.

The first human being to ever observe microorganisms was a Dutch scientist named Antonie van Leeuwenhoek, who wrote in his renowned paper, "Concerning animalcules found on the teeth" (1693), "I have often endeavored to discover Animalcules in Spittle, but in vain: But examining a kind of gritty Matter from between my Teeth, and mixing it sometimes with Rainwater, and sometimes with Spittle, both which before had no Animalcules, I discovered therein with admiration a great number of very small ones moving; they had a very strong and swift motion like Eeles."[3]

The gritty matter described by van Leeuwenhoek was his own dental calculus; the spittle, his saliva; and "animalcules" was the name he conceived for the observed microscopic organisms. Van Leeuwenhoek observed his oral bacteria (named by Ehrenberg in 1828)[4] with a handheld microscope that he fabricated in his drapery shop in the Netherlands. With this same microscope, van Leeuwenhoek was also the first human to observe spermatozoa and protozoa.[5]

In the period beginning 167 years later (from 1860–1940), dentists, physicians, and scientists ushered in an explosion of scientific data concerning the pathogenesis of oral bacteria and their relationship to human systemic disease. Highlights can be found in table 1.

As can be gleaned from Table 1, the dentists, physicians, and researchers of the late 19th and early 20th centuries were convinced of (a) the causation of periodontal disease as being bacterially generated; (b) the causation of systemic disease as related to periodontal disease; and (c) that a "slime" assisted bacterial growth. This slime (today known as biofilm) most likely was produced by the bacteria. These assertions are now thoroughly substantiated in the modern medical literature.[19]

Modern link of periodontal disease to the immune response

One hundred years after MacNevin and Vaughan's textbook connecting dental disease to the digestive system, nervous system, cardiovascular system, and the respiratory system, modern medicine now recognizes that it is the inflammatory response of the human immune system, chronically engaging periodontopathic bacteria, that is the material link to systemic disease.[20] There is now abundant data linking the immune system's chronic inflammatory response to: cardiovascular disease, rheumatoid arthritis, Parkinson's disease, kidney disease, metabolic disease, diabetes, fatty liver disease, gastrointestinal disease, cancer, macular degeneration, and preterm birth.[21]

The immune system comprises two interconnected and constantly communicating parts—the innate and the adaptive immune systems.[22] The innate immune system is the first defense against microorganisms entering the human body.[23] It is nonspecific and responds with the same inflammatory reaction to all invading microorganisms and foreign substances. When periodontopathic bacteria such as *Porphyromonas gingivalis* take up residence in the ecological niche that is a periodontal pocket (i.e., ≥4 mm), polymorphonuclear (PMN) leukocytes and macrophages will migrate into the tissues of the periodontal pocket and become activated.[24-27] Lipopolysaccharide (LPS) and biofilm from periodontopathic bacteria act as antigens and quickly stimulate PMN leukocytes.[28,29] The activated PMN leukocytes then secrete multiple inflammatory cytokines and chemokines into the tissues and periodontal pocket area that include tumor necrosis factor-alpha (TNF-α), interleukin-6 (Il-6), interleukin-17 (Il-17), and matrix metalloproteinases (MMPs). The presence of PMN leukocytes in inflamed periodontal tissues was first codified in dentistry at least 100 years ago.[30]

Periodontopathic bacteria such as *P. gingivalis* and *Actinobacillus actinomycetemcomitans* are also considered leukoaggressive. The pathogens are genetically capable of producing cellular toxins that kill or reduce neutrophil function, causing neutrophil dysregulation, and thereby furthering chronic inflammation.[26] When the innate immune system does not clear periodontal pathogens and the inflammation becomes chronic, the adaptive immune system then engages in the continued immune response, directed by cytokines and chemokines. There is also a phenomenon described as chemokine paralysis that causes resistance in the bacteria to oxidative death by PMN leukocytes. As a result of the aberrant innate immune response, the number of periodontal pathogens increases significantly, and the inflammation becomes a chronic manifestation of the persistent infection.[31] From the inception of the innate immune response to the periodontopathic bacteria, all elements of the immune system begin to cooperate in an effort to protect periodontal tissues.[32] A partial list of immune cytokines and chemokines is listed here.[33]

Pro-inflammatory cytokines:

- Interleukin-1-alpha (IL-1α)
- Interleukin-1-beta (IL-1β)
- Interleukin-6 (IL-6)
- Interleukin-12 (IL-12)
- Tumor necrosis factor-alpha (TNF-α)

Regulatory cytokines:

- Interleukin-4 (IL-4)
- Interleukin-1 (IL-1(RA) receptor antagonist)
- Interleukin-10 (IL-10)
- Induced protein (IP-10)

Innate immunity is now known to be far more than nonspecific immunity. The neutrophils and macrophages that phagocytose microorganisms also have surface proteins that recognize and bind to the surface of periodontopathic bacteria and coordinate with the adaptive immune response.[34,35] The adaptive immune system begins its attack if the innate immune system cannot eradicate the pathogens. It first identifies and then targets the periodontal pathogens with far greater accuracy than the innate immune system. It also has a memory function to remember pathogens and respond almost immediately the next time the same pathogen is encountered.

The adaptive immune system is composed of T and B lymphocytes and antibodies. The modern definition of periodontal disease describes an inflammatory response to bacteria and biofilm buildup in the periodontal pocket. The host inflammatory response is facilitated by both the innate and adaptive immune responses, consisting primarily of neutrophils, macrophages, and T and B lymphocytes. The etiology of periodontal disease is a concentrated inflammatory infiltrate populating the periodontal tissues with copious innate and adaptive immune cells that do not resolve the infection. The chronic immune cell infiltrate and the corresponding cytokines, chemokines, and antibodies influence chronic systemic inflammation and systemic disease.[36]

Over time, low-grade chronic systemic inflammation will lead to systemic diseases such as cardiovascular disease (CVD), diabetes, and neurodegenerative disease. The longer that inflammation is present, the higher the probability of the incidence of systemic disease.[37,38]

The systemic disease connection

Periodontal disease influences atherogenic plaques in the vascular wall by chronically subjecting the endothelium to LPS and proinflammatory cytokines. Ulceration of the periodontal pocket produces a bacterial infiltration (bacteremia) into the systemic circulation, which is evidenced by *P. gingivalis* in atherosclerotic plaque.[39] All periodontopathic bacteria that reside in a periodontal pocket can enter the circulation and travel to distal areas in the body. As bleeding upon simple mastication is a common aspect of periodontal disease, each time there is bleeding within a periodontal pocket, multiple different species of pathogenic bacteria and biofilm will enter the systemic circulation and further stimulate the immune response.[40]

Table 2 highlights research from the last 12 years. This research corroborates the vast majority of the early observations from physicians and scientists in the 19th and 20th centuries, which are listed in Table 1.

TABLE 1: The pathogenesis of oral bacteria and their relationship to human systemic disease

1860	Louis Pasteur	Pasteur's research showed that the growth of microorganisms was responsible for spoiling beverages, such as beer, wine, and milk.[6]
1864	Dr. J. Smith	"I have no hesitation in stating the existence of dental disease to be a most prolific source of constitutional disturbance, quite apart from mere local irritation; that the removal of such a morbid cause is equivalent to the cure of many obscure and chronic constitutional derangements."[7]
1867	Joseph Lister	Joseph Lister describes the application of carbolic acid as an antiseptic in wounds, treating compound fractures, and preventing infection with bacteria.[8]
1870	George B. Harrimore, DDS	"The dentist is to remember that not only are infusoria or bioplasms destructive to the gums, teeth, and alveolar processes of the patient, but that they engender a foetid breath of extreme unpleasantness to all coming in contact with it, and of great power in the production of bodily disease."[9] *This is the first written record of using Lister's carbolic acid in treating periodontal disease.*
1880	Robert Koch	Koch's Postulates of Infective Disease with Microorganisms10
1884	William Grove and Robert Kippax	*These are the reported first instances of "slime" or early biofilm (most likely dental plaque) in the literature accompanying bacterial growth on teeth.* "Mixed with the micrococci in the white slime of teeth, on the epithelium of the mouth, and in hollow teeth; probably the cause of dental caries."[11] "A great part of the whitish slime that collects on the teeth is composed of vibrios."[12]
1887	R. J. Porre, DDS	"Physicians are awakening to the importance of exploring the mouth in all cases of pyaemic and neuralgic symptoms of obscure origin, and, having long regarded all diseases of the teeth as the special province of the dentist, are now bringing ten such cases to him for diagnosis and consultation where one was brought before."[13]
1890	Willoughby Miller, DDS	"It has been established beyond all question that myriads of microorganisms are constantly present in the human mouth, and that these, under favorable circumstances, are capable of manifesting an action of the utmost significance upon the local as well as the general health of the patient. These various disturbances are produced partly by the direct action of the micro-organisms and their products upon the teeth and the mucous membrane of the mouth, partly by constant swallowing of large masses of bacteria, partly by carrying them into the lungs, particularly by violent inspiration, and, finally by their obtaining an entrance into the blood or lymph-vessels in the various ways described…"[14]
1895	Lambert Pharmaceutical Company	Listerine Antiseptic was first promoted to dentists for oral care.[15]
1899	Eugene Talbot	Pyorrhea alveolaris may act in three different ways in the causation of systemic disease. 1) Bacteria and pus are swallowed, causing stomach distress; 2) Toxins generated in the mouth may be absorbed by the mucus membrane in the mouth and stomach and passed into the general circulation; 3) Local mouth conditions may favor the growth of pathogenic organisms, making a patient more liable to certain infectious disorders.[16]
1922	MacNevin and Vaughan	This dental textbook from 100 years ago contains chapter headings connecting dental disease to the digestive system, nervous system, cardiovascular system, respiratory system, and blood.[17]
1940	Heukelekian and Heller	*This is the reported first instance of "slime" or early biofilm in the literature related to accelerated bacterial growth.* "Surfaces enable bacteria to develop in substrates otherwise too dilute for growth. Development takes place either as bacterial slime or colonial growth attached to the surfaces. Once a biologically active slime is established on surfaces, the rate of biological reaction is greatly accelerated."[18]

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TABLE 2: Research from the last 12 years

2010	Diabetes Care	Periodontal treatment leads to improvement of glycemic control in type 2 diabetic patients. This improvement lasts for a minimum of three months.[41]
2010 2015	Genomics BMC Neuroscience	*Treponema denticola* and *Chlamydia pneumoniae* have been detected in postmortem Alzheimer's disease brains. This implies that periodontopathic bacteria and inflammatory cytokines can enter the brain by crossing the blood-brain barrier.[42,43]
2011	Journal of Oral Microbiology	Pathogens from the lungs isolated from dental plaque and bronchoalveolar lavage fluid in the intensive care unit (from the same patients) were genetically identical. This strengthens the argument that dental plaque is a reservoir for respiratory pathogens.[44]
2013	Journal of Alzheimer's Disease	Interestingly, lipopolysaccharide from periodontal pathogens such as *P. gingivalis* and *T. denticola* was isolated from short-term postmortem Alzheimer's disease human brains, suggesting that virulence factors from these pathogens could play a role in development of brain inflammation and Alzheimer's disease.[45]
2017	Journal of Oral Microbiology	There is significant detection of *P. gingivalis* in the arteries of patients with periodontal disease.[46]
2018	Postgraduate Medicine	The concomitant presence of periodontitis and diabetes impairs glycemic control in people with diabetes, thereby increasing the risk of other complications in diabetes. Proinflammatory mediators such as TNF-α, IL-1, and IL-6 that are increased in both diseases represent a fundamental linkage.[47]
2019	Biomedical Journal	The association between oral inflammation and systemic inflammation is fundamental to understanding the detrimental effects of oral inflammation on several organ systems and the ability of oral disease to increase the risk of developing nonoral disease. Several oral pathogens are associated with a higher risk of cardiovascular disease in humans.[48]
2019	Mediators of Inflammation	The literature demonstrates that inflammatory mediators in periodontal disease or periodontal bacteria can affect transforming cells.[49]
2020	High Blood Pressure & Cardiovascular Prevention	Periodontitis can act as a source of inflammation and oxidative stress, and it might contribute to functional and anatomic vascular changes in the long term, leading to arterial stiffness, increased vascular resistance, and volume overload, with an ultimate rise in blood pressure.[50]
2020	Biochemical and Cellular Archives	Lipopolysaccharide from *Porphyromonas gingivalis* and other periodontopathic bacteria stimulates C-reactive protein release from the liver as part of the chronic innate immune response. C-reactive protein increases plaque deposition in blood vessels by stimulating the healing and repair phase of damaged endothelium and simultaneously activates the chemotaxis of neutrophils. The elevated C-reactive protein is a systemic marker of cardiovascular disease.[51]
2020	Frontiers in Immunology	Much of the dysbiosis theory in periodontitis is an extension of gut microbiome research. The transition in the polymicrobial community from largely gram-positive commensal to a gram-negative enriched inflammogenic community is well established. Taken together, the data suggests that the inflammatory response and the resident microbiome are linked in a bidirectional balance in health and a bidirectional imbalance in disease.[52]
2020	Medicina	Systemic low-grade inflammation is influenced by the composition of the oral microbiome, and specifically by periodontitis.[53]
2021	Diagnostics	The balance of oral microbiota plays a major role in an individual's general homeostasis. Increases in gram-negative bacteria maintain chronic low-grade inflammation.[54]
2021	Nature Reviews Immunology	Inflammation in extraoral sites such as the lungs and digestive tract can be induced to inflammatory progression by translocating periodontopathic bacteria.[55]
2021	BMC Oral Health	The systemic markers of C-reactive protein, erythrocyte sedimentation rate, and leukocytes were significantly elevated in periodontal disease patients vs. control. Periodontitis is a risk factor for myocardial infarction and also affects the degree of postinfarction left ventricular damage, which means that there is an inflammatory link between these two pathogenetically inflammatory diseases.[56]
2021	Biomolecules	There's a confirmed relationship between *Porphyromonas gingivalis* abundance in the oral cavity and neurodegenerative diseases. Patients suffering from a neurodegenerative disease showed a higher abundance of *Porphyromonas gingivalis* in the oral cavity than patients affected by a neurological, nondegenerative disease and healthy controls.[57]
2022	Science	*Porphyromonas gingivalis* is considered a "keystone pathogen" because it plays a critical role in maintaining the structure of an inflammatory biofilm by subverting host immune and inflammatory responses, and its impact on the community is greater than would be expected on the basis of its relative abundance.[58]

Given the abundance of data pointing to chronic and constant inflammation from untreated periodontal disease, three different simple blood tests can be performed to measure a patient's systemic inflammatory burden before and after periodontal therapy. These tests will assist the treating dentist and the patients in measuring their systemic health before and after periodontal therapy.

Diagnostic procedures to assist in a patient's objective assessment of the success of periodontal therapy

Three blood analytes that have shown consistent elevation in patients with periodontal disease and are markers of systemic inflammation are C-reactive protein (CRP), erythrocyte sedimentation rate (ERS), and elevated leukocyte counts.[59-65]

The three analyte levels of inflammation can act as objective markers to measure the systemic benefits to the patient undergoing periodontal therapy. As will occur in most cases, if the periodontal treatment is successful, the CRP, ERS, and leukocyte counts should all be lower three to four months after therapy than they were when assessed at baseline. This lowering of the systemic inflammatory markers will herald a lower burden of systemic inflammation over time and thereby slow down or inhibit the development of inflammaging and inflammatory-based systemic diseases.[66]

Additional clinical and diagnostic testing for specific periodontopathic bacteria (such as ***P. gingivalis*** and ***Actinobacillus actinomycetemcomitans***) can also be accomplished with commercial qPCR-based genetic analysis. Commercial qPCR microbiology tests can be completed simply by inserting sterile paper points to the depth of the periodontal pocket and left in situ for 10 seconds. Once removed, the paper points are then placed in sterile vials for delivery to the DNA/microbiology labs.[67-70] These new microbiological diagnostic tools can identify inflammatory periodontal pathogens and bacterial load before and after periodontal procedures. Oral microbiology laboratory testing services can also aid in antimicrobial treatment selection and clinical decision-making for periodontal therapy.[71,72]

It should become the standard practice of dentists who treat periodontal disease to discuss the systemic and inflammatory issues surrounding untreated periodontal disease with their patients.

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ERIC S. BORNSTEIN, DMD, is a biochemist, dentist, and medical lecturer. He has served as an expert witness and consultant in many medical/dental malpractice cases and criminal opioid and opioid malpractice cases. For the last four years, Dr. Bornstein has been a senior lecturer for INR (inrseminars.com), conferring CE credits to medical and dental professionals in the subjects of pharmacology, periodontal/systemic disease, opioids, medical and recreational marijuana, psychedelics, and hallucinogens. His first novel, *The Goliath Pathogen*, is forthcoming from Adir Press in 2023. Dr. Bornstein can be reached at drericdmd@mindspring.com.

Notes

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QUESTIONS

1. The first person to visualize bacteria in dental plaque was:
   A. Anton van Leeuwenhoek
   B. Joseph Lister
   C. Alexander Fleming
   D. Louis Pasteur

2. The first person to utilize carbolic acid as a disinfectant was:
   A. Anton van Leeuwenhoek
   B. Joseph Lister
   C. Alexander Fleming
   D. Louis Pasteur

3. The first person to put forth the postulates of infectious disease was:
   A. Anton van Leeuwenhoek
   B. Joseph Lister
   C. Robert Koch
   D. Louis Pasteur

4. The main pathogenic bacteria that causes periodontal disease is:
   A. Staphylococcus aureus
   B. Escherichia coli
   C. Porphyromonas gingivalis
   D. Lactobacillus acidophilus

5. Dentists, physicians, and researchers of the late 19th and early 20th centuries were convinced of:
   A. The causation of periodontal disease as being bacterially generated
   B. The causation of systemic disease as related to periodontal disease
   C. A "slime"–assisted bacterial growth, today known as biofilm
   D. All of the above

6. The immune system comprises ___ interconnected and constantly communicating parts.
   A. 2
   B. 3
   C. 4
   D. 5

7. The innate immune system is:
   A. The first defense against microorganisms entering the human body
   B. The second defense against microorganisms entering the human body
   C. A fictitious entity
   D. Part of the nervous system

8. Polymorphonuclear leukocytes and macrophages:
   A. Stay away from the periodontal pocket.
   B. Migrate to the periodontal pocket with the assistance of antibiotics.
   C. Are generated in the periodontal pocket.
   D. Migrate into the tissues of the periodontal pocket and become activated.

9. It is thought that some of the main diseases caused by untreated periodontal disease are:
   A. Insomnia and headaches
   B. Alzheimer's disease, atherosclerosis, and diabetes
   C. Toenail fungus and athlete's foot
   D. Acne and rosacea

10. The chief antigenic factor of *Porphyromonas gingivalis* is:
    A. DNA
    B. RNA
    C. Biofilm
    D. Lipopolysaccharide

11. When the innate immune system does not clear periodontal pathogens, and the inflammation becomes chronic:
    A. The adaptive immune system turns off.
    B. The innate immune system turn off.
    C. The adaptive immune system then engages in the continued immune response.
    D. None of the above

12. The main cause of periodontal disease is:
    A. Eating too much fat
    B. Not enough exercise
    C. Poor oral hygiene
    D. Bad posture

13. Antibodies are formed in response to what?
    A. Food particles
    B. Tartar
    C. Plaque
    D. Porphyromonas gingivalis

14. Chemokine paralysis causes:
    A. Resistance in the bacteria to oxidative death by PMN leukocytes
    B. Aggressive PMN leukocyte activity against bacteria
    C. Aggressive PMN leukocyte activity against periodontal tissues
    D. Resistance to the adaptive immune system

15. Inflammatory factors that can be measured in response to untreated periodontal disease are:
    A. CRP, ESR, and leukocytes
    B. A1C protein
    C. Eosinophils
    D. Blood glucose

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QUESTIONS

16. As a result of the aberrant innate immune response in periodontal disease:
    A. Patients become susceptible to autoimmune disease
    B. Periodontal disease is cured
    C. The number of periodontal pathogens increases significantly
    D. None of the above

17. Other areas that present with bacterial dysbiosis in untreated periodontal disease are:
    A. Skin colonization
    B. Intestinal microbiome
    C. Neither A nor B
    D. Both A and B

18. Dental treatment for periodontal disease should begin with:
    A. Dental hygiene instruction and dental scaling
    B. Laser therapy
    C. Periodontal surgery and systemic antibiotics
    D. Testing for systemic inflammation

19. Pro-inflammatory cytokines include:
    A. Interleukin-1-alpha and -beta
    B. Interleukin-6
    C. Interleukin-12
    D. All of the above

20. Regulatory cytokines include:
    A. Interleukin-4
    B. Interleukin-10
    C. Induced protein-10
    D. All of the above

21. The adaptive immune system begins its attack if:
    A. The innate immune system eradicates the pathogens
    B. The innate immune system fails to eradicate the pathogens
    C. Both A and B
    D. Neither A nor B

22. The adaptive immune system is composed of:
    A. Follicles
    B. Vessels
    C. Nerves
    D. T and B lymphocytes and antibodies

23. Over time, low-grade chronic systemic inflammation will lead to:
    A. Healthy bones and muscles
    B. Weight loss
    C. Systemic diseases such as cardiovascular disease, diabetes, and neurodegenerative disease
    D. Looking and feeling younger

24. Periodontal treatment leads to improvement of:
    A. Glycemic control in type 2 diabetic patients
    B. Increased appetite
    C. Both A and B
    D. Neither A nor B

25. The association between oral inflammation and systemic inflammation is:
    A. Proven false
    B. New information
    C. Fundamental to understanding the detrimental effects on several organ systems
    D. Against the tenets of science and medicine

26. Lipopolysaccharide from *Porphyromonas gingivalis* and other periodontopathic bacteria stimulates:
    A. Myostatin release from the muscles
    B. C-reactive protein release from the liver as part of the chronic innate immune response
    C. Glucose release from the liver
    D. Free fatty acid release from adipocytes

27. The systemic markers of C-reactive protein, erythrocyte sedimentation rate, and leukocytes are ___ in periodontal disease patients vs. control.
    A. Significantly decreased
    B. Significantly elevated
    C. The same
    D. Not relevent

28. Patients suffering from a neurodegenerative disease show a higher abundance of ___ in the oral cavity.
    A. Staphylococcus aureus
    B. Escherichia coli
    C. Porphyromonas gingivalis
    D. Candida albicans

29. C-reactive protein increases plaque deposition in the:
    A. Eyes
    B. Muscles
    C. Liver
    D. Blood vessels

30. With successful periodontal therapy, a lower burden of systemic inflammation over time will:
    A. Slow down or inhibit the development of inflammaging
    B. Slow down or inhibit inflammatory-based systemic diseases
    C. Both A and B
    D. Neither A nor B

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ANSWER SHEET

Periodontal triggers of systemic disease: We are closer to causation than ever before

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1. List the common risk factors for periodontal disease
2. Discuss the role of inflammation and infection in periodontal disease
3. Describe the relationship between periodontal disease and conditions, including diabetes, heart disease, and autoimmune disorders
4. Outline how the information in this course can be used to improve patient care outcomes

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9.	Ⓐ	Ⓑ	Ⓒ	Ⓓ		24.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
10.	Ⓐ	Ⓑ	Ⓒ	Ⓓ		25.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
11.	Ⓐ	Ⓑ	Ⓒ	Ⓓ		26.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
12.	Ⓐ	Ⓑ	Ⓒ	Ⓓ		27.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
13.	Ⓐ	Ⓑ	Ⓒ	Ⓓ		28.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
14.	Ⓐ	Ⓑ	Ⓒ	Ⓓ		29.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
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