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Oral microbiota and systemic disease

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ABSTRACT

It is well known that bacteria are the primary cause of infectious diseases, however, evidence is emerging that these organisms are also indirectly responsible for several diseases including cancer and rheumatoid arthritis. The oral cavity is home to several million bacteria that can cause two major diseases-periodontitis and caries. The relationship between periodontopathic bacteria and systemic diseases has been explored for several years. The concept of the oral cavity as a source of distant infection has been debated for at least a century. This review will discuss the historic aspects of the development of the focal infection theory, the reasons for its demise, its re-emergence and current status.

1. Introduction

During the Anaerobe 2012 meeting, a session entitled "Oral Microbiota and Systemic Disease " reviewed current knowledge about the inter-relationships between oral bacteria and susceptibility to systemic diseases. This article will discuss the historic aspects of the development of the focal infection theory, the reasons for its demise, its re-emergence and current status.

2. Rise, fall and rise of the focal infection theory

A focus of infection is best described as a circumscribed lesion that is clinically asymptomatic and contains pathogenic bacteria. According to the theory of focal infection, bacteria and/or bacterial products are disseminated from this nidus to distant parts, leading to disease in these organ systems. Several foci of infection have been described in the literature, including tonsils, sinuses, prostate, appendix, bladder, gall bladder, and kidney. Several diseases have been attributed to focal infections, including arthritis, neuritis, myalgia, nephritis, osteomyelitis, endocarditis, pneumonia, asthma, emphysema, gastritis, pancreatitis, colitis, diabetes, goiter, thyroiditis and Hodgkin's disease.

The tooth as a focus of infection: The theory of the oral cavity as a focus of infection is not new; Hippocrates reported arthritis being cured following extraction of a tooth [1]. The term oral focal sepsis was introduced by W.D. Miller in his 1890 article "*The Micro-Organisms of the Human Mouth: The Local and General Diseases Which Are Caused by Them*" and recommended removing decayed parts of a tooth and replacing them with fillings or root canal fillings [2]. However, in 1900, British physician William Hunter ascribed a plethora of systemic diseases to the preservation of a carious tooth by building 'a veritable mausoleum of gold fillings, crowns and bridges over a mass of sepsis' [3]. In 1940, Fish published an article on teeth as a source of systemic infections [4]. He described a state where teeth affected by periodontitis (a bacterially-induced disease that affects the structures that support the tooth and anchor it to the jawbone) "shower bacteria into the blood stream" even during the simple process of chewing or tooth brushing. He cited evidence from his own and other studies where dental bacteria could be detected in proximal and distant blood vessels (median basilic and peri-apical veins) following tooth extraction or chewing on hard candy. He proposed that the bacteria or their toxins stagnate in areas where tissues of mesenchymal origin predominate, namely joints, muscle and nerve sheaths. The purported susceptibility of these tissues was due to their 'unique functions of repair, regeneration and scavenging of waste products'. Thus, he hypothesized that dissemination of bacteria of oral origin to tissues of mesenchymal origin led to the pathogenesis of diverse diseases like osteomyelitis, fasciitis of the sciatic nerve, fibromyalgia and endocarditis.

Therapeutic impact of the oral focal sepsis theory: The focal sepsis theory gained momentum in the 19th century and the early 20th century based on the recommendations of prominent

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physicians like William Hunter, Russell Cecil and Charles Mayo [5]. Physicians recommended prophylactic or therapeutic removal of all teeth (and thus earned the moniker 'one hundred percenters') or just nonvital teeth, for the treatment of diverse conditions ranging from allergy to schizophrenia [6]. It was recommended as one of the most predictable treatment options for arthritis deformans, and for the treatment of blindness [7,8]. Soon, therapeutic edentulation became the norm. These treatment modalities were bolstered by Rosenow's theory of 'elective dissemination', which stated that certain pathogens demonstrated affinities for colonizing specific sites [9]. However, it was soon apparent that the routine removal of teeth did not provide a cure for diverse maladies. Vaizey and Clark-Kennedy [10] in 1939 and Cecil and Angevine in 1940 [11] demonstrated a worsening of arthritic symptoms and development of digestive complications following therapeutic edentulation. Thus, focal infection was disregarded as a scientific theory for several decades.

Reemergence of focal infection theory: Developments of new techniques to identify and classify microorganisms, for example polymerase chain reaction, *in situ* hybridization, as well as open-ended molecular approaches such as 16S sequencing revealed the presence of previously unknown and unsuspected organisms in the oral cavity [12,13]. The subgingival sulcus (the space between the tooth and the gingiva) was revealed as a reservoir for several systemic pathogens including *Hemophilus influenzae, Pseudomonas aeruginosa* and *Trophyrema whipplei* [14–17]. Advances in surgical techniques allowed access to deep tissues with minimal morbidity and revealed the presence of periodontal pathogens, for example, *Porphyromonas gingivalis, Treponema denticola* and *Campylobacter rectus* in atheromatous plaques, valvular vegetations, the tracheobronchial tree, joint cavities and the pancreas [18]. Thus, it soon became apparent that the oral cavity does indeed act as a reservoir of bacteria that metastasize to distant regions and cause disease in susceptible individuals. The World Workshop in Periodontics introduced the term 'Periodontal Medicine' in 1996 to describe the relationship between periodontitis and systemic diseases [19]. Thus, the last decade has seen a reemergence of the focal infection theory, albeit with a healthy dose of caution.

3. The periodontal pocket as a source of infection

Bacteria colonize the oral cavity soon after birth and form organized, co-operating communities called biofilms within specific ecological niches, for example, the tongue, tooth, subgingival sulcus, tonsil and buccal mucosa [20]. These biofilms allow the bacteria to live in a nutrient-rich environment that is protected from environmental insults, antimicrobial agents and frictional forces. These biofilms perform two important functions – (i) they prevent pathogenic colonization and (ii) they educate the immune system to recognize 'friend and foe'. In a state of health, equilibrium exists between biofilm antigens and toxins and the host immune response. Under certain circumstances, for example, a change in pH, oxygen tension, nutrient availability or a change in immune status, a shift occurs in the resident microflora, transforming this community from a commensal population to a pathogen enriched one [20]. The host responds to this pathogenic colonization by a florid immune response, leading to a breakdown of the attachment between the tooth, the gingiva and the alveolar socket, loss of bone that supports the tooth and a deepening of the space between the tooth and the gingiva (the sulcus) [21]. This deepened sulcus, now called a pocket, provides a protected anaerobic, reducing environment that is rich in blood and blood-derived nutrients and thus acts as a reservoir for pathogens. It has been estimated that 1 mg of dental plaque contains more than ten billion bacteria [22]. Recent molecular investigations have indicated that over 1000 bacterial species reside in the oral cavity and that each individual carries over 200 species in their oral microbiome [13,23]. The proximity of these bacteria to the vascular supply of the periodontium and the breakdown of epithelial integrity during disease progression predisposes to states of bacteremia when the biofilm is disrupted.

Oral bacteria, bacterial products, toxins and inflammatory products can metastasize to non-oral sites both during simple oral hygiene procedures and dental procedures [24,25]. These episodes of bacteremia are higher in individuals with oral infections. The incidence of bacteremia following tooth brushing in children with extensive dental decay ranges from 17 to 40% [26]. Bacteremia has been reported in 100% of cases following dental extraction [27], 70% after routine professional dental cleaning [28], 97% following administration of dental anesthesia by needle and 20% following root canal therapy [29]. In most cases, this bacteremia is transient and the organisms are eliminated from the circulation. However, in certain cases, especially in individuals with a compromised immune system, for example diabetics and those with upper respiratory disease, the oral organisms may colonize certain non-oral sites and lead to disease. Bacterial products, for example, lipopolysaccharide (LPS) and endotoxin are also released into the systemic circulation, and may trigger inflammatory responses in the target organs. The diseased periodontium also acts as a reservoir for inflammatory molecules, especially those that mediate chronic inflammation. Tumor necrosis factor (TNFα), Interleukin-1 (IL-1), Interleukin-2 (IL-2), Interleukin-8 (IL-8) and prostaglandins are produced in significant quantities by the diseased periodontium [30,31], and may contribute to systemic inflammation.

4. Periodontal disease and bacterial pneumonia

Pneumonia is an inflammation of the lungs caused by infection with a bacterium, virus, fungus or parasite; and the most common type is bacterial pneumonia. Typically, the lower respiratory tract is protected from microorganisms by several mechanisms, including a powerful cough reflex, ciliary movement and secretion of innate immune mediators [32]. Small amounts of bacteria normally aspirated during sleep or accidental swallowing are cleared by these mechanisms. However, these defenses can be impaired in smokers, diabetics, those with chronic obstructive pulmonary disease, and those who are intubated, immunosuppressed or have a prolonged post-operative hospital stay, resulting in community-acquired or hospital acquired (nosocomial) pneumonia [33,34]. Cross-sectional studies have demonstrated that dentate patients, those with poor oral hygiene, and those who do not regularly visit their dentist are more likely to develop pneumonia, suggesting a potential link between poor oral health and lung disease [35]. Further, treatment of periodontal disease and improving the oral hygiene decreased the incidence of pneumonia in children and hospitalized adults [36]. Dental plaque of hospitalized subjects with pneumonia has been shown to be a reservoir for *P. aeruginosa* [37,38], a respiratory pathogen, while periodontal pathogens, for example, *P. gingivalis*, *Fusobacterium nucleatum*, *Prevotella oralis*, *Campylobacter gracilis*, *Fusobacterium necrophorum* and *Aggregatibacter actinomycetemcomitans* have been cultured from lung fluids of subjects diagnosed with pneumonia [39–42].

Several mechanisms have been proposed to explain the role of periodontal infections in the etiopathogenesis of respiratory diseases: (i) aspiration of oral pathogens into the lungs, (ii) modification of respiratory mucosa by salivary enzymes released in the pathogenesis of periodontal disease, (iii) modification of respiratory mucosa by circulating pro-inflammatory cytokines [43].

5. Periodontal disease and cardiovascular diseases

A potential link between infections and atherosclerosis dates back to the early 19th century, when Gilbert and Lion described the