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Original Article

Periodontitis: A Dual Infection?

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Abstract:

Introduction: . Gingivitis always precedes developing periodontitis, but not all cases of gingivitis progress to periodontitis. Stagnating oral-biofilm over time causes decay and gum disease Different patterns of mild, moderate, and severe periodontitis manifest in younger people but not all old people develop periodontitis.

Aim: This study appraises established theoretical concepts and articulates them with recent discoveries on viral infections, into a coherent feasible hypothesis of the pathophysiology of periodontitis.

Discussion: Why periodontitis as rapidly progressive disease in juveniles and young adults, has been prevalent has been obscure for decades. Recent research implicates virus infection constrains, stresses and moderates immunology that allows strident progressive periodontal-ligament destruction deriving from climax ecosystems in stagnated biofilms. This explains why gum disease is prevalent when viruses are present and why unusually aggressive forms of gum disease occur.

Conclusion: Viral infection immobilizes immunity and susceptible individuals with gingivitis, when infected with a concomitant secondary viral infection, are prone to develop severe periodontitis.

Key words: Amoeba, biofilm, gums, disease, gingivitis, herpes, immunity, periodontitis, scurvy, virus.

Introduction

Tooth decay and gum disease are the two most commonly prevalent diseases afflicting humans. For centuries, right into the 20th Century, "pyorrhea" manifesting as "gum-boils" was an untreatable irreversible stigma that was not understood and frequently caused tooth loss. This resulted in partial or total edentulism, and all too often people resorted to voluntary total exodontia to avoid suffering the suffering emanating from their teeth. The human mouth functions as an organ in open contact with the external environment and acts as the initial location of the aero-digestive tract. Consequently, the mouth is populated with a vast array of microbiota in sessile and planktonic forms. While the sessile bacteria grow on the teeth and mucosal surfaces, the planktonic microbes float in saliva and this allows the bacteria to be ubiquitous in the oro-pharyngeal, upper digestive- and esophageal-tracts. The accumulated microbes on oral structures is called biofilm. The internal structure of oral biofilm produces multiple colonies of bacteria and grow nutrient channels which flow over and between the colonies. Metabolites are produced and exchanged as needed by the bacterial mix. Saliva provides and sustains moisture and nutrients which allow for continued growth. Floating planktonic clumps, continually and easily seed off the sessile colonies and are transported to new sites. [1]

Oral biofilms are typically white and camouflaged so that it cannot easily be recognized during a clinical examination. Accordingly, the term "*materia alba*" is used. Yet the biomass may be seen using disclosing solutions and colored dyes, many of which are safe when included as food colorings [2].

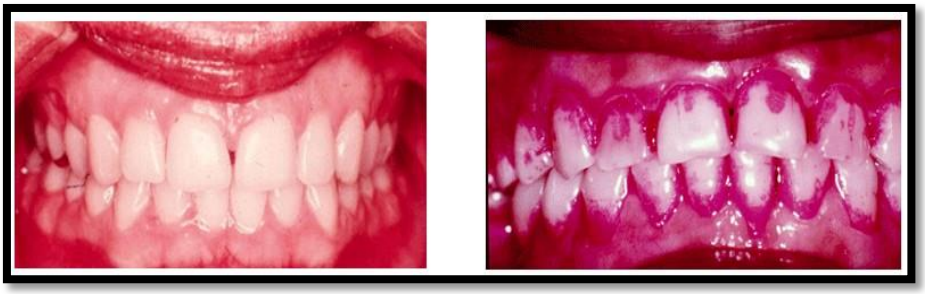

Figure 1: Biofilm cannot be seen, but with a disclosing solution the bacteria absorb the dye are visible. [1, 2]

A healthy clean mouth, when stained with a disclosing solution, does not show major color stains on teeth. But any dentate mouth not brushed clean will clearly reveal the dye on the teeth. A neglected mouth, not maintained in health and without oral hygiene techniques, will show up biofilm and possibly also disease of the teeth and gums. As undisturbed plaque stagnates, the conversion from early biofilm, into an invasive ecosystem, advances over weeks or months. The biofilm ecosystem transforms with major changes.

The plaque alters its character and properties when left undisturbed and renders the biofilm dysfunctional. Consequently, not all biofilms are the same, and the various biofilms have differing properties. The biomass microflora multiply into an adherent, glue-like, interdependent biomass with transport and transfer channels in plaques of flat biologically combined sessile sticky growths on hard surfaces, as well as freely floating planktonic ecosystems. Each type of colony growth (sessile or planktonic) can easily seed each other, and the enveloping extra-cellular polysaccharide matrix acts as a barrier to deeper layers of organisms. [1-7].

Oral biofilms cause gum disease by colonizing loci in the gingival sulcus. All the ecosystems yield biochemical destruction with molecules including: - Gram negative bacterial endotoxin, combined with acids, extracellular toxins, antigens and a vast array of enzymes which induce inflammation and subsequent facilitate tissue destruction. The enzymes include enzymes like proteases, lipases, collagenase [Metallo Matrix Proteases MMP's] from (Porphyromonas gingivalis, A. actinomycetes comitans), Trypsin-like enzyme (P. gingivalis, Aggregatibacter actinomycetemcomitans Aa, Treponema denticola), keratinase & sulfatase (P. Gingivalis, T. denticola), Arylsulfatas (C. rectus), Neuraminidase (P. gingivalis, Treponema forsythia, Bacillus melaninogenicus), Fibronectin degrading enzyme (protease from Prevotella intermedia), and Black Pigmented Bacteroides. These all combine to collectively induce tissue necrosis. [3-5]

The biofilm destruction prevents renewal of periodontal and gingival cells from reattachment to the tooth surface and stops any junctional hemi-desmosomes attaching to the tooth. The biofilm also releases dystrophic biochemical signaling molecules; substances like toxins and cytokines that include endotoxin, and Interleukin 1, 6, & 8, and TNF (Tumor Necrosis Factor-α) which exert direct cytotoxicity on epithelial, connective-tissue, and alveolar bone cells.[6-9]

Gingivitis and Periodontitis

This produces gingivitis initially (**Figure 2-A and 2-B**) and that may progress to periodontal disease (**Figure 3-A and 3-B**), alveolar bone resorption, and finally teeth loss. The destruction of the epithelial attachment to the dental root, with disruption of the pocket lining, facilitates entrance of the biofilm microbes and their metabolites into the general circulation of the body, and contributes to endotoxemia and bacteremia. This may be directly cause-related to systemic disease or have effects in remote sites of the body, like the heart-valves (infective endocarditis), stomach (ulcers), or lungs (bronchitis, pneumonia).

Gingivitis has no probing depths greater than 3.5mm (A Periodontal Score Recording or PSR-1) Greater recorded depths than 3.5mm indicate periodontitis is present.

Periodontitis may be *mild* (with recording depths ranging between 3.5mm and 5.5mm; A Periodontal Score Recording or PSR-2) *moderate*

(with probing depths between 5.5 and 7.5mm; PSR-3) or *severe* (with probing depths greater than 7.5mm; PSR-4). Different depths may be localised or generalized in the mouth, with or without bleeding and pus may be present on probing. Oral malodor as *fetor-ex-oris* is common. The diagnosis is made clinically from a full oral examination which could include a direct visual examination, and probing, mobility, radiographic, vitality and microbiological assessment, of the teeth, the gums and all surrounding soft tissues. [10-12]

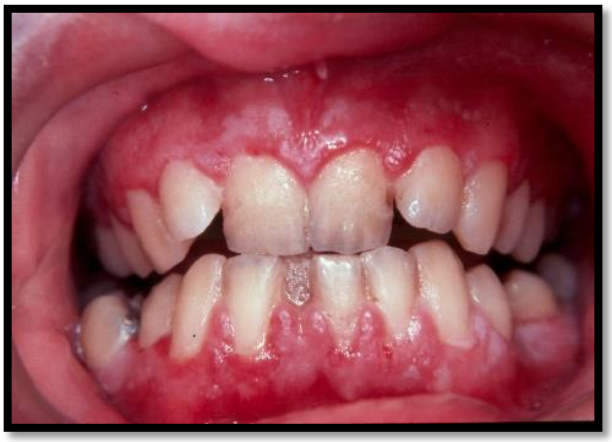

Figure 2-A: Gingivitis: note the gingival marginal erythema, swelling, bacterial plaque.

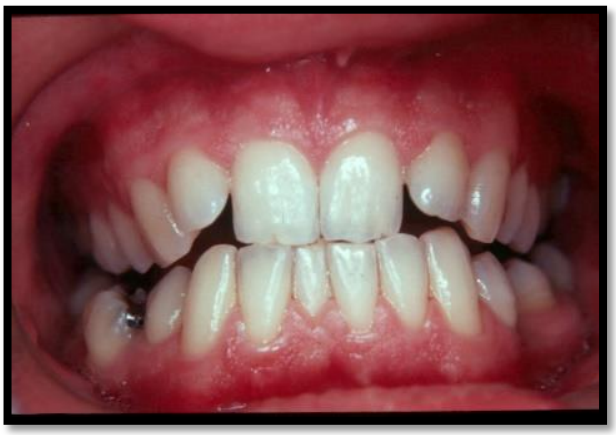

Figure 2-B: After treatment with prophylactic Scaling and Polishing. Scaling is the removal of extrinsic tooth material, namely calculus, stain and debris. No probing- depths exceeding 3 mm.

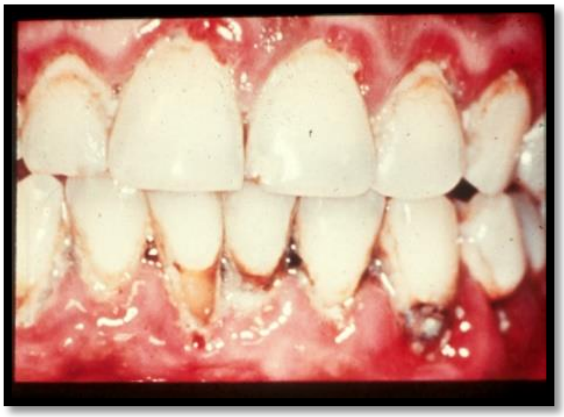

Figure 3-A: Mild Periodontitis. Note gingivitis with calculus, and plaque; Periodontal Score Record (PSR-2) with probing-depths between 3.5mm and 5.5mm with the loss of periodontal attachment.

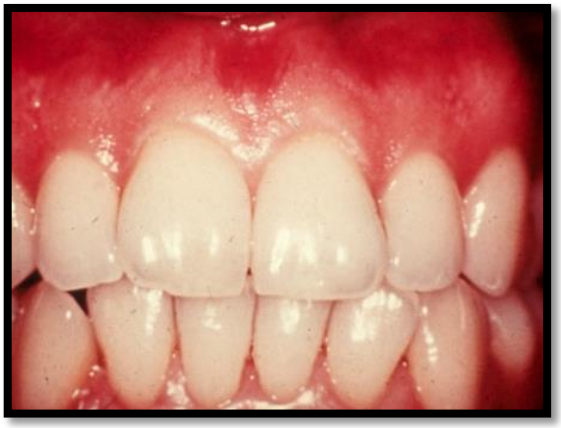

Figure 3-B: After treatment. Same case as in Figure 3A: with Scaling-and-Polishing (S&P), and also Root-Plaining. *Scaling-and-Polishing* is removal of extrinsic tooth material, calculus stain and debris. *Root-plaining* is removal of intrinsic tooth material infected or affected by biofilm.

While accepting that stagnating oral-biofilm over time causes decay and gum disease, and that gingivitis always precedes developing periodontitis ….. not all cases of gingivitis progress to periodontitis. [10-12] This is because natural resistance as immunity manages to sustain various protective, reactive and immune mechanisms, that don't allow the dystrophic biomass elements to multiply and invade the infected areas.

Gingivitis, swollen edematous gums, gingival recession, tooth mobility, deep *probing depths that exceed 3.5mm*, poor oral hygiene and various stages of bone loss are all prevalent when mild and severe periodontitis manifest. **(See Figures 4 and Figure 5).**

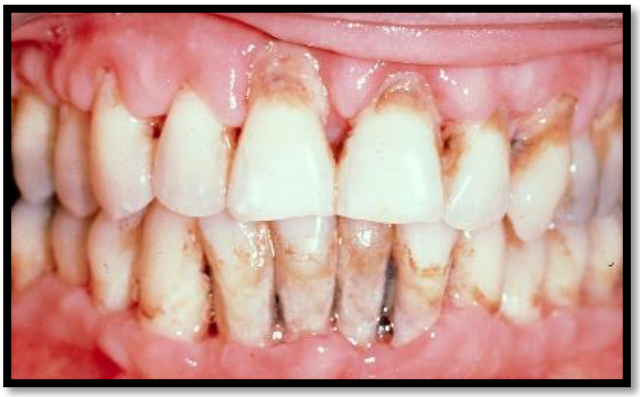

Figure 4: Severe Periodontitis in an adult male. Periodontal Score Record (PSR-3) with probing depths between 5.5mm and 7.5mm

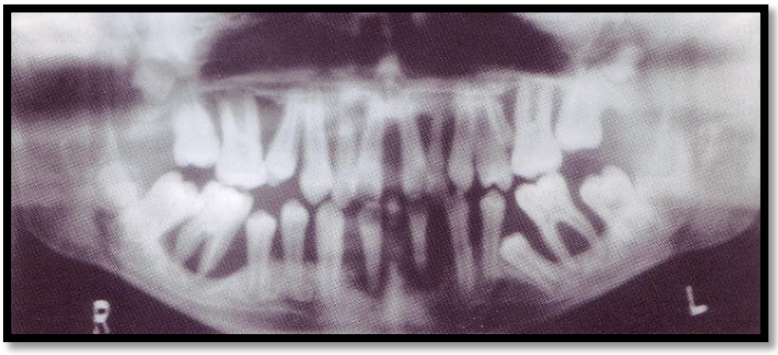

Figure 5: Severe Rapidly Progressive Periodontitis in a young adult (20 years old), with a PSR-4 with probing depths over 7.5mm. Note loss of lower incisors with generalized severe bone loss around the molars and incisors. There are unerupted wisdom teeth, and minimal signs of tooth decay.

ANUG and NUG

Another common form of gum disease is **Acute Necrotizing Ulcero-membranous Gingivitis (ANUG)**, and a low-grade chronic form **Necrotizing Ulcero-membranous Gingivitis (NUG).** The cause of the infection is endogenous and it's source is from within the patient's own mouth. The disease can affect the oro-pharynx (called Vincent's angina") and may overcome all local resistance and develop spreading necrosis as Cancrum-Oris, or Noma. This is a serious severe condition and carries a high morbidity and mortality rate. Ludwig's Angina is a rare complication with uncontrolled cellulitis from spreading infection into the pharyngeal spaces and is usually fatal. ANUG and NUG occur in people under physical and psychological stress; the distress reaction causes lowered resistance and reduced immune reactions; combined with poor oral hygiene, and a stagnation of biofilm, ANUG develops. (Figure 7 & 8)

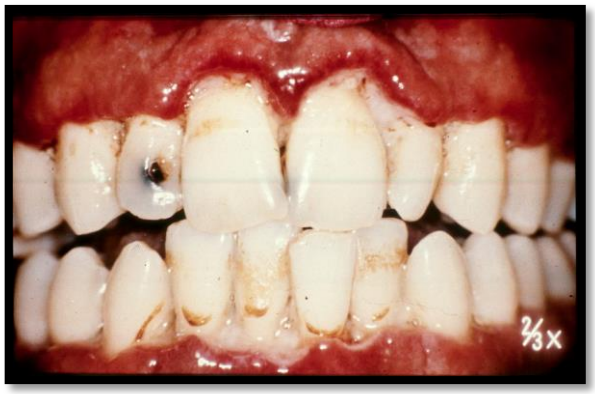

Figure 7: Acute Necrotic Ulcero-membranous Gingivitis (ANUG): Note the gingival marginal erythema and necrosis on both upper and lower gingivae.

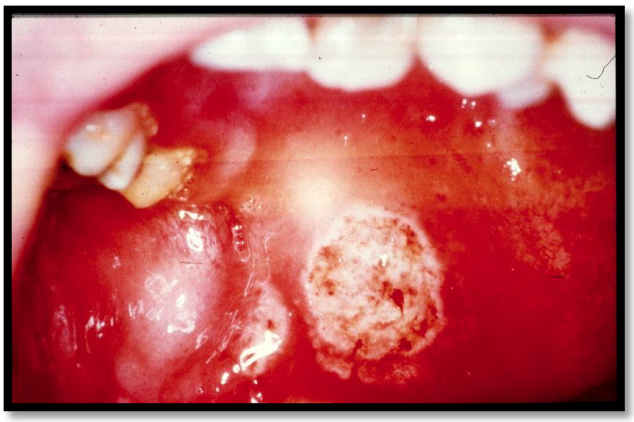

Figure 8: A case Vincent's angina with NUG, and complicated by localized ulcero-membranous lesion on the anterior fauces of the pharynx.

Although ANUG usually occurs in adults, ANUG may appear in malnourished children. ANUG was frequently encountered in World War I (1914-1918) in the trenches, where soldiers were extremely stressed with poor oral hygiene. Subsequently it was known as 'Trench Mouth'. The biofilm dysbiosis is caused by an over-growth of commensals in the mouth; when the local conditions develop into the right modified environment, a spirillum *Borrelia Vincenti* combines with a large fusiform bacillus, *Fusobacterium fusiformis*, combine to form a pathogenic symbiosis, and together they attack the gingivae. Numbers increase when local resistance is reduced and infection takes hold with necrotic destruction of the gingival margins, especially inter-dentally and under gingival flaps over partly erupted teeth (pericoronitis). Low grade pain is felt with regional lymphadenopathy and there is mild pyrexia. A typical sign and symptom is the distinctive foul oral mal-odor emanating from these volatile-sulfur-gas producing microbes. Other factors that facilitate ANUG developing as a complication are:- Deficiencies of vitamins (like Vit-C and niacin); infection with viruses like

Herpes and mononucleosis; HIV, agranulocytosis and leukemia. Occasionally infective emboli with *B. Vincenti and F. fusiformis* are discharged into the blood circulation, that are conveyed to the lungs where they initiate formation of pulmonary abscesses. Therapy involves local debridement with systemic antibiotic cover with either bactericidal (penicillin) or bacteriostatic (tetracyclines); frequent (every two hours) oral lavages with 2% hydrogen peroxide or a saline-solution helps. Topical application of chromic acid and stringent oral hygiene, arrests the progress of the condition, and rapid relief and recovery follows within ten days. [15-21]

Advanced rapidly progressive periodontitis manifests in younger people and in older individuals; yet not all cases with gingivitis progress to periodontitis …. or grow old and develop periodontitis. The reasons, as to *how and why* these variations of periodontitis manifest, have been prevalent for years, only partially understood and remained obscure for decades.

Aim: This study appraises established empirical concepts of the pathology of periodontitis, articulates and clarifies them with recent discoveries on viral infections into a coherent feasible, understandable and rational hypothesis of the pathophysiology of periodontitis.

Besides bacteria, **viral infections** have been implicated in periodontitis**.**

Herpes Virus.

Herpesviridae are structurally various complex viruses conspiring of double stranded DNA genomes. Eight types of human Herpes Viruses are known: Herpes simplex types 1 and 2 (HHSV-1 and HHSV-2); Varicella zoster (HHVZ, or HHSV-3); Epstein-Barr Virus (EBV or HHSV-4); Human cytomegalovirus HCVM, or HSV-5); Human herpes virus 6 (HHSV-6); Human herpes virus 7 (HHSV-7); and Human herpes virus 8 (HHSV-8). These eight groups are divided into three subfamilies, namely the ***alpha-herpesviruses*** that include HHSV-1, HHSV-2 and HHSV-3 (HHVZ). These are neurotropic viruses that invade rapidly, reproduce and establish themselves in sensory ganglia as dormant viruses. The ***beta- and gamma-herpesviruses*** are lymphotropic. These three groups **(Alpha and Beta-with-Gamma groups)** are identified and differentiated on the basis of their genomes-organization and replication- patterns. [22].

Human Herpes Varicella-zoster virus (HHVZ) among the Human alpha-herpesvirus group, is globally prevalent, and causes the exanthemata H. zoster disease Chickenpox (Varicella) in children, and Shingles (Herpes zoster) later in life. Chickenpox is common childhood disease (mainly before puberty but may occur up to age 25), is globally ubiquitous, and manifests with vesicular lesions of the skin following patterns of neural innovation, accompanied by pyrexia, viremia, and malaise. [22-25]

Atypical behavior of the alpha Herpes viruses, (Human Herpes Simplex Virus type 1 and Human-Herpes Simplex Virus Type 2: HHVS-1 & HHVS-2) is to be dormant in sensory dorsal root ganglia cells, after a primary HHSV-1 and HHSV-2 infection and are responsible for Herpes labialis and/or facial Herpes, and genital Herpes respectively. [26-29]. Herpes virus infections have been consistently associated with aggressive forms of periodontitis. [31-45] Herpes remains dormant in sensory ganglions and can be reactivated with physical trauma, as what happens with *Herpes gladiatorum* manifesting in physical sports, (25) or post operatively when Herpes infection occurs post-operatively after periodontal surgery. [46]

Discussion

Rationale of Periodontitis as a dual infection

Besides bacteria, viral infections have been implicated in aggravating periodontitis as a necessary co-factor. Combinations of HHSV's viruses collectively seem to make predisposing susceptibility of systemic and local conditions to promote aggressive forms of periodontitis. Co-infection with (especially) HHSV, or EBV-I, and / or HCMV all correlate with increased BOP, PD and CAL. Yet association is not necessarily proof of cause-and-effect. However, viruses are consistently found and demonstrated with aggressive forms of periodontitis, and consequently experimental and clinical findings become plausible and coherent. Infection of Periodontium with biofilm-plaque alone may negatively influence the local immune system, but with a virus as a co-factor in immune suppression, bacterial virulence is increased with rapidly

destructive necrosis becoming prevalent, and periodontitis then may be regarded as a dual infection. Many cases of rapidly aggressive cases of periodontitis seem to selectively affect the permanent incisors and first molars; this may simply be correlated with times-of-eruption and when the viruses first infect the susceptible individual to potentiate biofilm invasion of the gingivae. When full immunity is established again the viral and bacterial activity is moderated. With therapy, the process can be stopped completely. This not only explains why many cases of gingivitis do not progress to periodontitis, but also why periodontitis affects young people who harbor common hebephrenic viruses like Herpes HHV1, EBV, and later in young adults HPV, or HIV.

Periodontitis remains mainly a bacterially mediated disease, but co-infection with any virus that suppresses the resistance by reducing natural immunity, will allow the oral biofilm to become invasive. Coinfection of HSV and HCMV is consistently associated with aggressive periodontal destruction. Simultaneous co-infection with any two herpesviruses is also associated with greater clinical attachment loss and probing depths ≥ 4 .5mm.

Periodontal disease once established, is a slow but progressive disease and left unchecked, will destroy the periodontal attachment apparatus until the affected teeth are lost. Periodontitis as a painless progressive disease needs early detection and treatment to arrest the breakdown and re-establish a healthy dentition. Treatment involves disrupting the pathogenic biofilm, restoring a healthy oral biome, and restraining any further active viral activity. This includes a course of antibiotics and antivirals, supplemented with surgical physical interference. Periodontal surgery is preceded by closed root-plaining. Persistent pocketing is managed by invasive open-flap curettage and bone enhancement with osseous-grafts or bone-forming material, and introducing, and maintaining and sustaining stringent oral hygiene home and professional regime. In healthy non-virally infected, or with intact immunity, both gingivitis and periodontitis respond well to treatment. The recent research implicates virus infection diminishing immunology allows strident progressive periodontal-ligament destruction from climax ecosystems in stagnated biofilms. The associated viral infections, become dormant, and can be reactivated after trauma, like from surgery or from trauma experienced during physical-contact sports like rugby. This also explains why these abstruse forms of gum disease occur.

Chemotherapy as an adjunct to ensure successful outcomes when treating periodontitis includes use of anti biotics, antimicrobials, and antivirals. The selection of orally administered antibiotics and antimicrobials used to moderate the oral biome and biofilms include penicillins, metronidazole and macrolides. The penicillins (like Amoxil) and macrolides must not be administered together in combination, as penicillins are bacteriocidal (relies on disrupting membranes of bacterial multiplication) while the macrolides like tetracyclines and erythromycin are bacteriostatic (disrupts microbial protein synthesis). Each may be administered separately. [46-51] Also the anti-microbial metronidazole is very effective against gram negative microbes.[51] The use of antibiotic cover for invasive periodontal open flap surgeries should be used with circumspection and is not usually required. [53] These chemotherapies may be used in combination with orally administered anti-viral medications that include anti-virals such as Acyclovir, Valacyclovir or Famciclovir. [25, 46]

Other notions about the Pathogenesis of Gum Disease.

Vitamin C

For centuries gum disease was thought to result from lack of Vit-C. Avitaminosis -C results in scurvy with inadequate collagen formation.

The periodontal ligament is mainly collagen, is in a state of continual renewal and with a lack of Vit-C in the diet, the periodontal attachment apparatus is prone to infection from the oral biome and breaks down. Consequently, the teeth become loose and in scurvy the teeth tend to exfoliate and `fall out`. Scurvy is not the same as bacterially mediated periodontitis. Scurvy was common among sailors who prior to the 19th Century would spend months at sea with a diet of fish and salted meat, had an inadequate Vit-C intake. Vit-C is found in most fresh fruits and vegetables with broccoli, parsley and citrus being among the better rich sources of Vit-C. Although reported cases in

the 21s Century of scurvy are rare, scurvy may still be encountered in situations when diets are deficient, like in poorly run institutions, or impoverished and isolated communities. Smoking tobacco makes extra demands on Vit-C and aggravates gingival breakdown. Scurvy is totally reversible with adequate intake of Vit-C. One gram immediately, followed by 100 mg daily for two weeks restores health. The subsequent RDA for Vit-C is 15mg Vit-C per day which will satisfy demands for sustained health. [51,52,53]

Amoebiasis

Entamoeba histolytica is a unicellular protozoan parasite. The seven species of concern are: *Ent. Gingivalis, Ent. Coli, Ent Hartmann, Ent Histolytica, Endolimax nana, Iodamoeba butschlii, and Dientamoeba fragilis*. *E. histolytica* is regarded as the most important pathogen as it infects humans and is labeled *amebiasis (A).* Amebae, or Amebic cysts, trophozoites or spores are ingested and can settle, infect and cause abscesses in the intestine (amebic dysentery,) in the liver (hepatic amebiasis) or lungs (pulmonary amebiasis). Amebiasis necrosis macroscopically resembles a characteristic pinkish paste (fish-paste necrosis), and microscopically reflects cell debris with many large uni-cellular amoebic cells or clumps of amebic organisms. Active disease may produce distinct skin lesions (amebic cutis) with ulcers and undermining borders surrounded by erythematous rims. *[54] Entamoeba gingivalis* as a microbe may be involved in the inflammatory process during periodontitis [55,56] . The typical Amoebic pasty necrosis is not seen with periodontitis, and the cytology from periodontal pockets show many unicellular epithelial cells, some of which may be designated as Entamoeba organisms. The presence of *E. gingivalis* is purported to be associated only with diseased gingival pocket sites and is not found in healthy mouths. [56, 57] To date *Entamoeba gingivalis* has not been proven to be causally associated as an initiator of periodontitis, but when present, is considered only as a harmless commensal species. Culturing E. gingivalis from deep periodontal pockets is challenging and consequently direct evidence for cause-and-effect is weak. Amoeba are sensitive to metronidazole and if this antimicrobial is used to arrest biofilm destruction, metronidazole not only affects the putative gram-negative biofilm bacteria but also any Entamoeba. This *Entamoeba gingivalis* etiology of periodontitis remains controversial.

Concluding remarks

Gingivitis affects most people, and gingivitis precedes the development of all periodontitis. But not every case of gingivitis will inexorably progress to periodontitis. Consistent intact immunity keeps gingivitis in check. Not all oral biofilms are the same. Periodontitis develops when stagnated oral biofilms become opportunistic infections and invade susceptible immune deficient hosts. Viral infections immobilize immunity and susceptible infected individuals with gingivitis, and a concomitant secondary viral infection are prone to developing severe periodontitis.

Conclusion: Periodontitis may be regarded as a dual infection. Gum disease is bacterially mediated and gingivitis that is aggravated with a predisposing viral infection that reduces host immunity, precipitates formation of periodontitis.

Authors statement: The author has no conflicts of interest to declare.

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Abbreviations used:

AIDS = Acquired immunodeficiency syndrome

ANUG = Acute necrotizing ulcero-membranous Gingivitis

NUG = Necrotizing Ulcero-Membranous Gingivitis

BOP = Bleeding-On-Probing

PD = Probing Depths

CAL = Clinical Attachment loss (Recession and PD measure)

HHSV = Human Herpes Simplex Virus

HHSV-1 and HHSV-2 = Human Herpes simplex types 1 and 2

HHVZ, or HHSV-3 = Varicella zoster

EBV= Epstein-Barr or **HHSV-4**

HCVM, **or HHSV-5**= Human cytomegalovirus)

HHSV-6 = Human herpes virus 6
HHSV-7 = Human herpes virus 7

HHSV-8 = Human herpes virus 8

HIV = Human Immuno-Deficiency Virus

HPV = Human Papilloma Virus

MMP's = Metallo-Matrix Proteases

PSR = Periodontal Score Record

RDA = Recommended Daily Allowance

S&P = Scaling-and Polishing

TNF = Tumor Necrosis Factor

Vit-C = Vitamin C