Go to: LINEAR MODEL (1960s) Studies in the 1960s gave experimental evidence stressing the critical role of bacteria in the etiology of periodontitis.[2] The linear model [Figure 1a] implicated that bacterial deposits are a primary and crucial factor in the pathogenesis of periodontal diseases.[1] The earlier concepts which involved nonbacterial factors (trauma from occlusion, systemic factors, etc.) were ruled out after the emergence of this model. An external file that holds a picture, illustration, etc. Object name is JISP-26-204-g001.jpg Figure 1 (a) 1960s Linear model; (b) Circa 1980s model; (c) Classical model (1997). PMNs – Polymorphonuclear leukocytes (Reprinted from Kornman.[1] With copyright permission from John Wiley and sons.) Go to: PAGE AND SCHROEDER'S MODEL (1976) Roy Page and Hubert Schroeder, for the first time, emphasized the histopathological events in the pathogenesis of human periodontitis in their article which became a citation classic.[3] This was the first systematic model to describe the temporal development of host response events leading to the development of periodontitis.[4] Four types of histopathologic lesions were described – initial, early, and established lesions showing distinct and sequential stages of gingivitis, and an advanced lesion, featuring bone loss and clinically manifested as periodontitis. A progression of cellular types from neutrophils in the initial lesion to macrophages and T-cells in the early lesion, and then to B and plasma cells in the established and advanced lesions, was clearly demonstrated in this model which, for the first time, gave a rational footing to the pathogenesis of human periodontitis.[3] Go to: CIRCA 1980s MODEL In the 1970s and 1980s, the role of specific Gram-negative bacteria was indicated as causative for periodontitis.[5,6] Besides, the protective and destructive nature of immune-inflammatory responses in periodontal health and disease was delineated.[7] The hallmark of this model[1] is that it illustrates the distinct roles of microbes and the interaction with host response in periodontal disease pathogenesis [Figure 1b]. Go to: CRITICAL PATHWAY MODEL (OFFENBACHER 1996) Owing to the fact that a linear model based on just a bacterial host response relationship does not answer a multitude of questions related to the variability and site specificity of periodontal disease among different individuals, nonlinear models of pathogenesis evolved which addressed the role of other factors/disease modifiers in altering the disease patterns, severity, and susceptibility. The critical pathway model[8] was the first nonlinear model to explain such an association. The term “critical path” refers to the steps along the cellular and molecular pathogenesis which is essential/indispensable for the disease process. The composite model included certain “critical regulatory nodes,” which determine the disease process. The “antibody-neutrophil axis” and the “monocyte–lymphocyte axis” were the key players in host response. The role of host-based risk factors/disease modifiers such as stress, genetic traits, diabetes, and smoking were introduced, for the first time, as major determinants in host response. Go to: THE CLASSICAL MODEL (PAGE AND KORNMAN 1997) Evidence accrued till 1995 increased our understanding of host-microbial interactions and the role of a myriad of factors attributing to the patient and site-level differences in periodontal disease expression.[9] The classical model incorporates the coaction of bacteria with host immune factors, along with an assortment of environmental, and acquired risk factors including genetics, in the pathogenesis of periodontitis [Figure 1c]. This nonlinear model justifies a range of clinical presentations of the disease, owing to the integrated effects of microbe-induced host responses and a specific combination of modifying factors.[10] Go to: BIOLOGICAL SYSTEMS MODELS With advances in

mathematical modeling, computational biology, and the "–omics" technologies (genomic, metabolomic, and proteomic), the biologic systems approach has an integrated approach of converging them to investigate disease patterns from a genetic level to a tissue level. Many complex structures in the human body are recognized as integrated entities, in which diverse components have specific roles yet work together synergistically to achieve much greater tasks than what each component would accomplish on its own. This means that the overall biologic system has a distinct behavior that is more than the sum of its parts, i.e., it exhibits "emergent properties." Various systems biology models have tried to understand the nature of complex diseases including periodontal disease.[1,11] Multilevel hierarchical model (Kornman 2008) This model[1] is centered on multilevel hierarchical organization in the form of functional modules defined in terms of cellular and molecular inputs and outputs [Figure 2a]. The hierarchy progresses from subcellular and cellular biologic networks to tissue interactions represented in the top layer. Interaction of the factors within each module and among the modules governs the overall behavior of the system that translates into clinical outcomes. An external file that holds a picture, illustration, etc. Object name is JISP-26-204-g002.jpg Figure 2 (a) Multilevel hierarchical framework of biologic systems model; (b) A multilevel biologic systems model, representing pathogenesis of periodontitis (Reprinted from Kornman.[1] With copyright permission from John Wiley and sons.) When the constituents of periodontal disease progression are adapted to hierarchical models [Figure 2b], the lower levels are occupied by biologic mechanisms involved in immune–inflammatory mechanisms, bone and connective tissue metabolism. This is determined by microbial factors and modified by a blend of environmental and genetic factors. The upper levels denote the individual response, marked by specific patterns of gene, protein, and metabolite expression. The expressed proteins further regulate host response, bone and connective tissue metabolism, and control microbial challenge. Biologic systems model (Offenbacher 2008) The "biologic systems model"[11] incorporates all components that contribute to the final clinical phenotype (i.e., the clinical presentation of disease) into a stacked Venn diagram, which depicts the overlapping relationships and interactions among different factors. The clinical phenotype can be broken down into respective subclinical components [Figure 3]. The outermost component represents the unique exposures of the individual at a subject level, including the characteristics of the biofilm (e.g., the type of bacterial challenge) as well as the presence of other health conditions (e.g., diabetes) and environmental influences (e.g., smoking). The subject-level component interacts with the genetic background (gene polymorphisms that affect the host response), which potentially shapes the biologic phenotype (cellular and molecular processes including inflammatory biomarkers) which, in turn, determines the final clinical phenotype. An external file that holds a picture, illustration, etc. Object name is JISP-26-204-g003.jpg Figure 3 Biologic systems model (Reprinted from Offenbacher et al.[11] With copyright permission from John Wiley and sons.) Go to: GENERIC MULTICAUSALITY MODEL (HEATON AND DIETRICH 2012) Periodontal disease is a complex disease and its complexity involves multiple causal components which interplay with each other simultaneously.[12] The contribution of the five main causal components, i.e., genetic and epigenetic factors, lifestyle factors (smoking, stress, diet etc.), environmental factors (bacterial biofilms), systemic disease (diabetes), and some other unknown factors, is illustrated in a pie chart [Figure 4], showing their relative contribution.[13] It is proposed that

for each individual patient with periodontitis, the relative contribution of the causal factors varies. In younger patients with aggressive periodontitis, the contribution of genetics is relatively more than in adults with chronic periodontitis. Conversely, the contribution of lifestyle and environmental factors is more in patients with chronic periodontitis compared to those with aggressive periodontitis. An external file that holds a picture, illustration, etc. Object name is JISP-26-204-g004.jpg Figure 4 Generic multicausality model (Adapted from: Heaton and Dietrich[13]) Go to: KEYSTONE PATHOGENESIS MODEL (HAJISHENGALLIS 2012) This model elucidates the contribution of "Keystone pathogens," in the development of periodontal disease. These are a group of low abundance species of microbes, whose effects on the community are disproportionately large relative to their abundance. The quest to identify keystone pathogens in periodontal disease is still in progress. However, one potential candidate is Porphyromonas gingivalis, owing to its virtue of remodeling benign microbes to dysbiotic ones.[14] This task is accomplished by a combination of, host independent direct effects on gene expression, and by indirect effects on the community via host modulation.[14] P. gingivalis is labeled as "master of subversion" as it evolved ways to trick the components of innate immune system. In this regard, P. gingivalis operates by antagonizing toll-like receptor-4 (TLR-4) activation and instigating a subversive cross-talk between TLR-2 and complement system thus incapacitating the phagocytes.[15] It also induces TLR-2 inside-out signaling, transactivating CR-3-mediated ineffective phagocytosis, and inhibition of interleukin-12 (IL-12) expression.[16] In addition, P. gingivalis also causes chemokine paralysis of neutrophils by the inhibition of IL-8.[17] These major functions performed by this minor constituent of the microbial community give it the credentials of a keystone pathogen, as it triggers persistent but ineffective inflammation, enabling other pathogens to escape host defenses, and simultaneously secure essential nutrients for their survival.[18] The dysbiosis created by the keystone pathogen activates the destructive arm of immune responses, and lays foundations for the irreversible tissue damage in periodontitis. Go to: POLYMICROBIAL SYNERGY AND DYSBIOSIS MODEL (HAJISHENGALLIS 2012) The fundamental tenet of this model[19] is that periodontitis is caused by a group of synergistic and dysbiotic microbial communities of indigenous organisms working in concert [Figure 5]. The communities exhibit properties that are more than the sum of their constituent organism parts. Individual components fulfill distinct roles contributing to the overall pathogenic potential of the community.[20] The colonizing bacteria assemble and exhibit structural integrity, syntrophic nutritional relations, augmented by chemical signaling giving rise to a physically and physiologically integrated community.[21] An external file that holds a picture, illustration, etc. Object name is JISP-26-204-g005.jpg Figure 5 Polymicrobial synergy and dysbiosis model (Reprinted from Hajishengallis and Lamont.[20] With copyright permission from Elsevier.) The events leading to the development and progression of the disease are representative of a "driver-passenger model."[22] The introduction of "keystone pathogens" (bacterial drivers) shifts the circumstances in the microbial community toward dysbiosis. They drive the pathogenic process by disabling the immune surveillance, and targeted subversion of specific host responses. "Pathobionts" are bacterial passengers which exploit this altered host stability to their nutritional advantage to flourish and promote the disease.[21] At later stages, they outnumber the keystones and take over the mantle of disease progression. In periodontitis, pathobionts

comprise few previously underrated species such as Filifactor alocis, Selenomonas, and Desulfobulbus.[23] Furthermore, the synergistic interspecies interactions are enabled by “accessory pathogens” such as Streptococcus gordonii.[24] The communities involve in cooperative interactions which help them survive with limited resources, reminiscent of “Black queen hypothesis.”[25] However, not all interactions among periodontal bacteria are synergistic, few are antagonistic, which may result in the “Red queen effect,” where the organisms evolve and continually adapt to survive the competitive environment.[26] The collective synergy and antagonism determines the composition of the community and, ultimately, the disease-causing potential. This is termed nososymbiocity, which is the disease emerging from the co-existence of an assemblage of organisms in a susceptible host.[20] Therefore, the refined notions of periodontal disease pathogenesis dismiss the old-world concepts of disease caused by a single or few select pathogens, in favor of a group of organisms with hierarchical and temporally distinct communication systems, inducing dysregulated immune response, making periodontitis, a case of nososymbiocity par-excellence. The “Modified polymicrobial synergy and dysbiosis (PSD) model for peri implantitis”[27] is a modification of the PSD model to suit peri-implantitis, wherein the interactions between bacterial and host-related factors lead to homeostasis breakdown. Material-related factors (roughness, wettability, and chemical composition) also play a substantial role in this model. Go to: REVISED MODEL (BARTOLD AND VAN DYKE 2013) The concept of inflammation-driven shift in microbial composition was first acknowledged in the ecological plaque hypothesis.[28] The revised model[29] underscores the paradigm shift, from the primary role of bacteria in periodontal disease to bacterial colonization as a secondary event to inflammation. Host response is deemed as the principal driving force for uncontrolled inflammation and subsequent tissue destruction. According to this model, gingivitis develops as a nonspecific inflammatory response, leading to altered environment and overgrowth of specific periodontal pathogens. An effective host response accompanied by favorable genetic and environmental factors will contain the pathogenic process. An alternative scenario will lead to disease progression and clinical evidence of periodontitis.[29] Go to: IMMUNOMICROBIAL PATHOGENESIS MODEL (HAJISHENGALLIS 2014) This model[30] is based on the conceptual framework that periodontitis is a result of disruption of host-microbiome homeostasis. It underlines the mechanisms that steer the dysbiotic microbiota to induce a dysregulated immune response, which ultimately leads to periodontal disease [Figure 6]. An external file that holds a picture, illustration, etc. Object name is JISP-26-204-g006.jpg Figure 6 Immunomicrobial pathogenesis model. (Reprinted from Hajishengallis[30] With copyright permission from Elsevier.) M□ – Macrophage; DC – Dendritic cell; TNF – Tumor necrosis factor; IL-1 □ – Interleukin-1 □; IL-17 – Interleukin-17; CXC chemokine–Cysteine-X-Cysteine chemokine; Th-1 – T helper-1; Th-17 – T helper-17; ROS – Reactive oxygen species; MMP – Matrix metalloproteinases; RANKL – Receptor activator of nuclear factor kappa beta ligand; OPG – Osteoprotegerin; IL-10 – Interleukin-10; B – Bursa of Fabricius cell; T reg – T Regulatory cells; IFN □ – Interferon □; IL-4 – Interleukin 4; IL-13 – Interleukin-13; OCP – Osteoclast precursor; OCL – Osteoclast; T cell – Thymus derived cell The collective role of synergistic microbiome is featured, wherein the keystone pathogens orchestrate the shift from symbiosis. This kindles the inflammatory process, which paves the way for selective blooming of inflammophilic bacteria, which have evolved not only to endure

inflammation but also take advantage of it, thus culminating in a community-level microbial dysbiosis.[31] In a susceptible host, this ensues a disturbance in the armed peace between host and microbes which further establishes an imbalanced and uncontrolled inflammatory dialogue, causing collateral tissue damage. Besides, this model[30] highlights the explicit roles of innate and adaptive immune elements in the pathogenesis of periodontal diseases. Emphasis is given to the renewed roles of neutrophils, and functions of newer T helper cell subsets (Th-17, Treg), parallel to Th-1, Th-2, supported by B-cells in osteoclastogenesis. This complex interplay of host immunity and microbial components propels a self-perpetuating cycle, which accelerates dysbiosis and tissue destruction.[30] Go to: CONTEMPORARY MODEL (MEYLE AND CHAPPLE 2015) A healthy periodontal state is characterized by a symbiotic biofilm which triggers a proportionate and resolving host response. If this biofilm is allowed to accumulate, conditions favor the evolution of certain bacterial species which operate with their quorum sensing mechanisms to elicit a stronger host response and inflammation. This gingival inflammation which is rich in certain nutrients like heme and peptides encourages the proliferation of a certain group of bacteria leading to a state of "incipient dysbiosis."[32] There is a proportionate host response and a chronic resolution of inflammation. In a susceptible host, the incipient dysbiosis can lead to an excessive and inappropriate host response paving the way to a state of "frank dysbiosis" resulting in tissue destruction and a chronic nonresolving inflammatory condition. The pathogenic role of viruses was also acknowledged in this model. The contemporary model[32] showcases a transition from a health-promoting biofilm to one of the incipient and then to frank dysbiosis. The host inflammatory response shows an evolution of being proportionate and proresolving to proportionate/nonresolving and then to disproportionate/nonresolving. Go to: POLYMICROBIAL GENETIC DYSBIOSIS MODEL (STEIN AND KARYDIS, 2015) The evolution of the periodontal disease pathogenesis paradigm to a polymicrobial genetic dysbiosis model[33] includes the polymicrobial synergy in a specific environment, the microbial dysbiotic gene expression, and the host genetic susceptibility to encompass the complexity of the periodontal diseases. Polymicrobial synergy involves interbacterial growth facilitation and complex interbacterial signaling, where variable dysbiotic microorganism communities contribute as a group the genes necessary for periodontal disease progression. Go to: REVISED PAGE AND SCHROEDER MODEL (HAJISHENGALLIS 2017) The Page and Schroeder model proposed in 1976 provided a histopathologic roadmap to the pathologic events leading to clinical outcomes.[3] Although this model gives a bird's eye view of the histologic events underlying the pathogenesis of periodontal disease, there is a need to reperceive the stages in the light of advances in our understanding of immune-inflammatory mechanisms.[34] To begin with, the Page and Schroeder model confined the role of neutrophils to the initial stages of periodontal lesion, with restricted functions. On the contrary, with the recent developments, their structural heterogeneity and functional versatility emerged, explaining their hitherto untold functions in innate and adaptive immunity.[35] It is also fascinating that neutrophils regulate other lymphocytes and also play a crucial role in RANKL-mediated bone destruction, pointing to their contribution not only in initiation but also in disease progression.[36] In stark contrast to the Page and Schroeder model, the presence of macrophage cell plasticity, with both pro-inflammatory and anti-inflammatory actions, has also been unveiled.[37] Moreover, the precise roles of newer T helper cell

subsets became cognizant, and the shift of concepts from defective surveillance to disruptive homeostasis is witnessed.[34] Forging ahead, B-cells are predominant in the advanced lesion of Page and Schroeder model. Owing to the then limited information, they were unaware of the fact that the role of B-cells goes well beyond antibody production and extends to bone and tissue destruction.[38] Enhanced knowledge on osteoimmunology proves that B-cells are involved in RANKL-dependent and independent osteoclastic activity. Furthermore, since the Page and Schroeder model, we also acknowledge the importance of innate immune components in instructing and determining the nature of adaptive immune responses.[34] The fine line between the tasks of innate and adaptive immune elements is becoming increasingly blurred due to the complex functions of individual elements and their complicated interactions. Go to: INVERTED MODEL (BARTOLD AND VAN DYKE 2019) Although most models discussed so far have focused on the role of specific bacteria in the initiation and progression of periodontitis, they fail to fully explain the host-microbe interactions in health and disease. Studies have shown that putative pathogens are also present in health but are not pathogenic.[39] The inverted model[40] proposes that periodontitis is a continuum of inflammation, tissue destruction, and microbial dysbiosis modified by factors such as smoking, systemic diseases, and genetics. The initial inflammatory response in periodontal disease always precedes the emergence of periodontal pathogens.[29,41] This increasing inflammation results in the production of "inflammatory spoils"[4] which act as nutrients to fuel the selective expansion of a specific subset of bacteria (proteolytic and assacharolytic). Against the conventional paradigm where a dysbiotic community leads to inflammation, the inverted model stresses that it is inflammation that drives development of dysbiosis. Go to: INFLAMMATION-MEDIATED POLYMICROBIAL-EMERGENCE AND DYSBIOTIC-EXACERBATION (IMPEDE) MODEL (VAN DYKE ET AL. 2020) As a sequel to the previous work on inflammation-mediated dysbiosis,[29,40] the "Inflammation-Mediated Polymicrobial-Emergence and Dysbiotic-Exacerbation" model [Figure 7a] gives us a holistic understanding of how inflammation is a principal driver of plaque-associated periodontitis. This unifying model is designed to integrate into and complement the 2017 World Workshop Classification of Periodontitis,[42] and recognizes five stages (0–IV) [Figure 7b]. With health representing Stage 0, there are four subsequent disease development phases: (1) gingivitis (inflammation associated with an overgrowth of commensal plaque bacteria); (2) initiation/early periodontitis (inflammation-induced polymicrobial diversity increases and dysbiosis triggered); (3) inflammation-mediated exacerbation of dysbiosis by a self-sustained feedforward loop, and (4) late-stage periodontitis characterized by a decrease in polymicrobial diversity associated with the emergence of a polymicrobial infection. An external file that holds a picture, illustration, etc. Object name is JISP-26-204-g007.jpg Figure 7 (a) IMPEDE model; (b) IMPEDE model and periodontal disease stages (Reprinted from Van Dyke et al.[42] With copyright permission from Creative Commons Attribution License). IMPEDE – Inflammation-Mediated Polymicrobial-Emergence and Dysbiotic-Exacerbation Thus, a continuum of health, gingivitis, and periodontitis is depicted, where the central role of inflammation is prioritized. An inflammation-mediated microbial succession leads to the emergence of disease-associated pathogens resulting in a dysbiotic state to initiate periodontitis. As the disease progresses, the transitional microbiota is temporally and spatially replaced predominantly by pathogenic

species. This dysbiotic signature of subgingival plaque, especially at the base of the pocket, results in an opportunistic polymicrobial synergistic infection, and will have more influence on the immune subversion and inflammatory process leading to tissue destruction.[43] Go to: MODELS OF PERIODONTAL DISEASE PROGRESSION Disease progression can be considered as an indispensable part of periodontal disease pathogenesis. Therefore, the knowledge of models of periodontal disease progression becomes paramount to ensure opportune diagnosis and treatment. 1. CONTINUOUS MODEL The continuous model[44] describes chronic destructive periodontal disease as slow, continual, and progressive in nature. Certain sites are depicted as not changing throughout an individual's life, and other sites demonstrate the initiation of attachment loss at different times in an individual's life. 2. RANDOM BURST MODEL The random burst model[44] incorporates the concept of bursts of activity, where the attachment loss is considered as a measure of the cumulative effect of multiple disease episodes. Disease activity is depicted as occurring at random, at any site, where some sites show no activity, while others show one or several bursts of activity. 3. ASYNCHRONOUS MULTIPLE BURST MODEL This model[44] is an extension to random burst model where the major difference from the preceding one is that multiple sites show breakdown within a reasonably short period of an individual's life with prolonged periods of remission. 4. STOCHASTIC MODEL (MANJI 1989) In this model,[45] the disease process is expected to be in periods of sharp bursts and remission, even though the underlying disease activity is stationary. Furthermore, the disease process is postulated to behave similar to Brownian motion, taking into consideration the multifactorial and cumulative nature of the disease. 5. FRACTAL MODEL (LANDINI 1991) The fractal model[46] describes time-dependent events as noise and provides a theoretical context for relations between the causes and effects in periodontal breakdown. This model explains the multifactorial nature of periodontal disease, and also provides a basis for the large changes resulting due to small variations in specific attributes. 6. UNIFICATION OF BURST AND LINEAR THEORIES (GILTHORPE 2003) In this model,[47] the concepts attributing both the linear and burst models are satisfied, as periodontal disease is examined in a multilevel context. A multilevel model is a new approach, employed for the data that form a hierarchy. The variations at each level are determined separately, thus providing an insight into the dynamic system of periodontal breakdown. 7. MATHEMATICAL MODEL (PAPANTONOPOULOS 2013) The mathematical model[48] identifies periodontitis as a nonlinear chaotic process and presents a quantitative assessment of the disease rate. The host response to bacterial challenge is compared to that of a pendulum of a clock. There are two zones of host response that overlap, an aberrant zone resulting in relatively fast periodontal progression rate and resolving zone with minimal progression. The overlap between the zones is the settlement or the accommodation zone. It is suggested that in cases of aggressive periodontitis, the host response swings to the aberrant zone, and in cases of chronic periodontitis, there is a swing into the settlement or the resolving zone.