HOW GUM DISEASE AFFECTS THE WHOLE BODY
Paradigm Shift
Focal Infection Theory

• 1900, British physician William Hunter first developed the idea that oral microorganisms were responsible for a wide range of systemic conditions that were not easily recognized as being infectious in nature.
• Fell into disrepute during the 1940s and 1950s
Focal Infection Theory

Many of the precepts of the focal infection theory are being revived today in light of recent research demonstrating links between oral and systemic health.
Case report
• Provides relatively weak retrospective anecdotal evidence

Cross-sectional study +
• Compares groups of subjects at a single point in time

Longitudinal study ++
• Follows groups of subjects over time

Intervention trial +++
• Examines the effects of some intervention

Systematic review ++++
• Systematically evaluates evidence from multiple studies, especially randomized controlled trials

Adapted from Carranza's Clinical Periodontology, 12th edition
1970’s Model of Periodontitis

Occlusal Trauma

Bacterial Plaque → Calculus Formation → Periodontal Pocket Formation → Bone Loss
Current Model of Periodontitis

Environmental and Acquired Risk Factors

- Genetic Risk Factors
- Microbial Challenge
- Host Immuno-inflammatory response
  - Antibody
  - PMN’s
  - Antigens
  - Lipopolysaccharide
  - Other virulence factors
- Connective Tissue and Bone Metabolism
  - Cytokines & Prostanoids
  - Matrix Metalloproteinases
- Clinical signs of disease initiation and progression

Microbial Challenge

Genetic Risk Factors
Genetic Susceptibility to Periodontal Disease

Interleukin - 1β+3953 Allele 2: Association with Disease Status in Adult Periodontitis


Frequency of IL-1β genotypes including allele 2 of the IL-1β+3953 restriction fragment length biallelic polymorphism was significantly increased in patients with advanced periodontitis compared to those with early and moderate disease.
Figure 2—Percentage of subjects with greater than 10% bleeding on probing. Adapted from Kornman et al.7
Periodontal Disease: A Quick Overview

- Periodontal disease is a chronic inflammatory disease that destroys the bone and gum tissues that support the teeth.

- The American Academy of Periodontology (AAP) estimates that 3 out of 4 Americans are affected by periodontal disease, ranging from mild gingivitis to more severe periodontitis.

- If left untreated, mild cases of gingivitis can lead to periodontitis.
What is Inflammation?

- Inflammation is the body’s first response to an injury.
- The first phase (acute inflammation) includes redness, swelling, heat and altered function. It is self-perpetuating.
- Though inflammation can be helpful under certain conditions, uncontrolled inflammation, also called chronic inflammation, is harmful and causes tissue loss.
- Chronic inflammation can negatively affect all organs and tissues of the body.
- There are several biological markers of inflammation in your blood, including C-reactive protein.
Research has suggested that managing the inflammatory burden of one disease may help reduce the risk for the other.
Pathogenesis of Periodontal Disease: A Bacterial-Host Interaction

- Microbial Factors
  - LPS
  - Antigens

- Host Inflammatory Response

- Inflammatory mediators (e.g., IL-1β, TNFα, PGE₂)
Pathogenesis of Periodontal Disease: A Bacterial-Host Interaction

PMNs
Mediators (eg: IL-1β)

Osteoclasts

Host Enzymes

Connective Tissue
Bone
Pathogenesis of Periodontal Disease

Pro-inflammatory Mediators
- IL-1β
- IL-6
- TNFα
- PGE$_2$
- MMPs

Natural Inhibitors
- IL-1ra
- IL-10
- TGFβ
- IL-4
- TIMPS

Poor Oral Hygiene
High Susceptibility
Systemic Risk Factors
- Smoking
- Genetics
- Diabetes

Disease
Possible Mechanisms by Which Gingival Inflammation May Modulate Systemic Disease

Gingival Inflammation

- Periodontopathogens or their products (LPS)
- Bacteremia

Inflammatory mediators (IL-1, IL-6, TNF-α)

- Immune response
- (C-reactive protein, serum amyloid A, fibrinogen)

Liver

- Antibodies to bacteria, and to cross-reactive antigens such as heat-shock proteins; T-cells sensitized

Target Organ (eg, heart, brain, etc)

- Bacteria induce platelet aggregate, invade endothelium, digest matrix

From: Scannapieco, FA: Periodontal inflammation: from gingivitis to systemic disease?
C reactive protein

- acute-phase protein of hepatic origin
- increases following interleukin-6 secretion by macrophages and T cells
• Can the inflammatory response to bacterial infection of the periodontium have an effect that is remote from the oral cavity?

• Is periodontal infection a risk factor for systemic diseases or conditions that affect human health?
Bradford Hill Criteria for causation

**Strength** (effect size): A small association does not mean that there is not a causal effect, though the larger the association, the more likely that it is causal.

**Consistency** (reproducibility): Consistent findings observed by different persons in different places with different samples strengthens the likelihood of an effect.

**Specificity**: Causation is likely if there is a very specific population at a specific site and disease with no other likely explanation. The more specific an association between a factor and an effect is, the bigger the probability of a causal relationship.
Bradford Hill Criteria

**Temporality**: The effect has to occur after the cause (and if there is an expected delay between the cause and expected effect, then the effect must occur after that delay).

**Biological gradient**: Greater exposure should generally lead to greater incidence of the effect. However, in some cases, the mere presence of the factor can trigger the effect. In other cases, an inverse proportion is observed: greater exposure leads to lower incidence.

**Plausibility** A plausible mechanism between cause and effect is helpful (but Hill noted that knowledge of the mechanism is limited by current knowledge).
Bradford Hill Criteria

**Coherence:** Coherence between epidemiological and laboratory findings increases the likelihood of an effect. However, Hill noted that "... lack of such [laboratory] evidence cannot nullify the epidemiological effect on associations".

**Experiment:** "Occasionally it is possible to appeal to experimental evidence".

**Analogy:** The effect of similar factors may be considered
Organ Systems and Conditions Possibly Influenced by Periodontal Infection

Endocrine System
• Diabetes mellitus

Cardiovascular/Cerebrovascular System
• Atherosclerosis, Coronary heart disease, Angina, Myocardial infarction, Cerebrovascular accident (stroke)
• Erectile Dysfunction

Reproductive System
• Preterm low-birth-weight infants
• Preeclampsia
• COPD, acute bacterial pneumonia
• Cancer
• Cognitive impairment, chronic kidney disease, rheumatoid arthritis,
Periodontal Disease

- Periodontal Pathogen
  - Endotoxin, toxins, cell membrane products
    - Proinflammatory cascade
      - Secretion TNF-α + IL-1β
        - Connective Tissue Destruction
          - Bone resorption

Diabetes Mellitus

- AGE-protein
  - Hyperglycemia
  - Macrophage AGE-receptor
    - Synthesis + Secretion TNF-α + IL-1β
      - Degradative Cascade
        - Hydrolase, MMP, Collagenase secretion
          - Connective tissue degradation
Mechanism of Diabetic Complications

- Glucose / Protein interaction leads to formation of glycated proteins – AGEs
- AGEs have negative effects on cell and tissue function
  - Interaction with receptors on monocytes and other cells – RAGEs – leads to inflammation
  - Incorporation of AGEs in membranes and connective tissue leads to defects in function
    - Cardiovascular disease
    - Nephropathy
    - Retinopathy
Diabetes and Periodontitis

AGE - enriched gingival tissues

Activation of RAGE

Endothelial RAGE
- permeability & adhesion molecules

Fibroblast RAGE
- MMPs
- Collagen

Macrophage RAGE
- macrophage migration & immobilization at AGE rich sites,
- Cytokines (IL-1,6, TNF-α)
- MMPs

Neutrophil RAGE
- protein kinase C
- ROS

Exaggerated response to periodontal pathogens

Accelerated destruction of non-mineralized connective tissue and bone in diabetes
GUM DISEASE AND HEART DISEASE

Several studies have shown that periodontal disease is associated with heart disease. While a cause-and-effect relationship has not yet been proven, research has indicated that periodontal disease increases the risk of heart disease. Scientists believe that inflammation caused by periodontal disease may be responsible for the association. Periodontal disease can also exacerbate existing heart conditions.
Low-birth-weight (LBW) infants

- Endotoxins (LPSs) and bioactive enzymes produced by many organisms associated with vaginosis may directly injure tissue and induce the release of proinflammatory cytokines and prostaglandins.

- In addition to prostaglandins, various proinflammatory cytokines (e.g., IL-1, IL-6, TNF) have been found in the amniotic fluid of women with preterm labor.
Arthritis

- Arthritis (Rheumatoid arthritis and osteoarthritis) is an inflammation of the joints.

- Patients with arthritis have a higher incidence of periodontal disease compared to healthy controls.*

- Periodontal treatment decreases arthritis parameters:**
  - Patients’ number of swollen and tender joints decreased following periodontal treatment.
  - Patients’ assessment of pain also decreased following periodontal treatment.


Erectile Dysfunction

- Elevated levels of oxidative stress and systemic inflammation are common to both periodontal diseases and ED.
Cancers

- Pancreatic cancer
  - Men with a history of gum disease are 54% more likely to develop pancreatic cancer than men with healthy gums.*

- Head and neck cancers
  - Chronic periodontitis is independently associated with the incidence of head and neck cancers.**
  - Smoking increases this association.

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Alzheimer’s Disease

- Alzheimer’s disease is an inflammation of the brain.
- Antibodies and immune cells cross the blood brain barrier.
- Exposure to chronic periodontal disease quadruples an individual's risk of developing Alzheimer's disease.*

Research has found that bacteria that grow in the oral cavity can be aspirated into the lungs to cause respiratory diseases such as pneumonia, especially in people with periodontal disease.
• Insufficient evidence to date to infer causal relationships with the exception that organisms originating in the oral microbiome can cause lung infections.

• Associations do not imply causality

• Establishment of causality will require new studies that fulfill the Bradford Hill or equivalent criteria.