Objectives
1. Recognize the mechanism and role of inflammation in the body
2. Identify key inflammatory mediators and their systemic action
3. Understand periodontal disease as a chronic inflammatory disease, affecting multiple systemic conditions
4. Discover new connections between periodontitis, the prostate and colon cancer

Inflammation
- Latin – “to set on fire”
- Normal response to harmful stimuli and injury

Purpose of Inflammation
- Destroys, dilutes or walls off
- Disposes cell debris and pathogens
- Prevents spread of damaging agents
- Sets stage for repair

Acute Inflammation Process
- Injured area signals liver to “send in the troops”
- Inflammatory mediators infiltrate injured site
- Characterized by Cardinal Signs

Four Cardinal Signs of Inflammation
- Redness – dilation of blood vessels
- Heat - ↑ localized tissue metabolism
- Swelling - ↑ vascular fluid and cells
- Pain – compression of nerve endings + chemicals

The 5th Cardinal Sign
- Rudolf Virchow – 19th century
  - Redness – rubor
  - Heat – calor
  - Swelling – tumor
  - Pain – dolor
  - Loss of function – functio laesa
Chronic Inflammation Characteristics
- Active inflammation
- Tissue destruction
- Attempts repair

**Inflammatory Phases Review**

1. Injury
   - Bacterial
   - Viral
   - Physical
   - Auto-immune

2. Vascular
   - Increased blood volume
   - Vessel permeability
   - Fluid leakage in surrounding tissues

3. Cellular
   - Cell migration
   - Tissue destruction
   - Debridement

4. Healing
   - Vascular proliferation (new capillaries formed)
   - Proliferation of fibroblasts = new connective tissue

5. Maturation
   - Collagen formation

*Periodontal disease named #1 chronic inflammatory disease!*

**Periodontal Disease**
- Chronic low-grade infection
  - Active inflammation
  - Tissue destruction
  - Attempts at repair
- What do we know?
  - Bacterial
    - Specific pathogens
  - Host inflammatory response
    - Genetic factor
    - Systemic susceptibility
- Silent Epidemic, over 100M infected today
- Casual: Specific Pathogens

**Inflammatory Mediators in Periodontal Disease**
- Macrophages
- PMNs (neutrophils)
- Cytokines
- Interleukins 1, 6 (IL)
- Tumor necrosis factor alpha (TNF-a)
- Fibrinogen
- C-Reactive protein (C-RP)

**White Blood Cells**
- Leukocytes (leuko – white)
  - Granular
    - Basophil – .5%
    - Eosinophil – 3%
    - Neutrophil – 65%
  - Agranular
    - Lymphocytes – 25%
    - Monocytes – 5%

**IL – 1**
- Associated with increased risk of periodontal disease and within atherosclerotic plaques
- Stimulates osteoclasts to remove bone matrix

**IL – 6**
- High in chronic periodontitis
- Elevated levels predict development of Type II diabetes

**Fibrinogen**
- Clotting factor
- Helps and harms = thrombi in vessels

**TNF-alpha**
- Found in chronic periodontal disease
- Causes synthesis of triglycerides = elevated triglycerides
- Lowers “good” cholesterol (HDL) = increased coronary disease

**C-RP**
- Found in chronic periodontal disease
- Increased levels in blood cause damage to smooth muscles of blood vessels
- C-RP Assay test for heart disease risk

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**The News about Periodontal Disease and Total Health**
- Pregnancy
- Diabetes
- Alzheimer’s
- Heart Disease
- Colon Cancer
**Periodontal Disease/Diabetes**
- Diabetes - #1 systemic factor for periodontal disease
- The connection is bi-directional; both diseases increase inflammatory response and stress the immune system
- Periodontal disease – a predictor of Type II diabetes later in life
- Impaired resistance, abnormal collagen metabolism, abnormal host response disallows healing and accelerates periodontal disease effects
- Periodontal inflammatory mediators exacerbate insulin resistance

**Periodontal Disease/Heart Disease**
- Elevated levels of LDL and fibrinogen are associated with 3 to 6-fold increased risk for heart disease and stroke Periodontal bacterial pathogens (PBP) can invade coronary arteries, weakening walls and increasing thrombosis formation
- Those with periodontal disease have 30% higher risk of heart disease Inflammation foundation for all stages of arterial thombus formation: plaque development, progression, and final stages of infarction
- *Porphyromonas gingivalis* found residing in heart tissues and plaque build-ups within vessels *Actinobacillus actinomycetemcomitans (AA)* has also been detected in cardiac tissues
- Shared genetic link between periodontitis and coronary heart disease (European Society of Human Genetics, annual conference May 25, 2009)
  - Genetic risk variant – identical for both diseases
  - Ground breaking!!

Carcinogenic Bacteria and Heart Disease
- Strep mutans most frequently detected species in cardiovascular specimens
- Those patients who had strep mutans in dental plaque, 78% of those positive s. mutans in heart tissue

**New Guidelines for Doctors and Dentists – American Journal of Cardiology and Journal of Periodontology**
1. Patients with perio with CVD with another risk factor – medical evaluation warranted every 12 months
2. Newly diagnosed perio with known CVD – closely collaborate with doctor
3. Patients with CVD exhibiting signs and/or symptoms of oral disease or high levels of C-RP = referral
4. What the perio evaluation should consist of
   *(J of Perio, June 2009, online; Am J Cardiol, Nov 2008, online)*
**Periodontal Disease/Rheumatoid Arthritis**

Significant association between extent and severity of the two diseases…

- Both result from an imbalance of pro and anti-inflammatory cytokines
- As early as 1999 some researchers suggest the two are part of the same disease
- Shared features:
  - Local destruction of connective tissue/bone
  - Bacteria combined with inflammatory response = disease progression
  - Some experience disease progression irrespective of treatment provided
- Helped with NSAIDs

New Research, Case Western Reserve University School of Dental Medicine and Research Reports

- Study of subjects with moderate to severe periodontitis and severe rheumatoid arthritis results
  - Group 1 – Anti-inflammatory drugs
  - Group 2 – Dental treatment
  - Group 3 – Both
- Groups treated with anti-inflammatory drugs and receiving appropriate dental treatment found substantial easing of arthritic symptoms

**Periodontal Disease/Impacts Pregnancy**

- Adverse pregnancy outcomes: pre-term and low birth weight babies
- Periodontal disease triggers a chronic inflammatory state, releasing mediators, C-RP being primary
- C-RP levels in general are found to be 65% higher in pregnant women than in non-pregnant women (Pitipat et al., *J of Perio*, 2006)
- This heightened state of naturally occurring inflammatory response in pregnant women is the mechanism by which labor occurs
- Periodontal disease = increased inflammation + existing systemic inflammatory state… an overload is created, often sending the body into premature labor
- Gram-negative anaerobic bacteria of periodontal disease have been found in the amniotic fluid, placenta, and amniotic membranes of the uterus
  - Result – direct transmission of oral bacteria to fetus (Han et al., 2004, *Infection & Immunity*; Offenbacher, 2006)
- A new inflammatory response is activated by the fetus due to the presence of oral bacteria
  - The mediators of the inflammatory response can cause the cervix to dilate and trigger uterine contractions, prompting premature labor

- Term stillbirth caused by *fusobacterium nucleatum*
  - First case of oral bacteria causing stillbirth
  - 39 weeks
  - Mother had pregnancy gingivitis, under control

- Upper respiratory infection before birth
- Allowed bacteria to cross placenta resulting in an overwhelming bacterial infection which was the cause of death (*Ob & Gyn*, Feb 2010)
**Periodontal Disease/Prostate**

The **prostate** is a walnut-sized gland located between the bladder and the penis. The **prostate** secretes fluid that nourishes and protects sperm. Urethra runs through the center of the **prostate**, from the bladder to the penis.

What is PSA? Prostate-specific antigen (PSA) is an enzyme created in the prostate that is normally found in the blood in very small amounts.

PSA testing is not currently automatic, Discuss with Health Care provider.

Prostate concerns; Prostatitis, Impotence, Cancer

Chronic inflammation is connection between P. disease and Prostatitis

Research shows:
- Subjects having comorbidity of CAL > or = 2.7 mm and moderate/severe prostatitis have higher PSA levels than those with either condition alone. *J.Periodontology 2012*

- Treatment of periodontal disease significantly improved clinical symptoms of prostatitis as well as reduced PSA levels in patients having high PSA levels (>4 ng/ml), in chronic prostatitis and periodontitis *Case Western Reserve U. 2015*

**Periodontal Disease/Colorectal Cancer**

**Epidemiology**
- Affects 5% of the population
- Accounts for 21% of all cancers
- 3rd most frequently diagnosed cancer
- 2nd leading cancer killer in the US
- 150,000 new cases/year
• 57,000 deaths/year
• Cost estimated at 6 billion dollars/year
• Both men & women are at risk
• Increases with age
• One of the most potentially curable
• > 1/3 of the deaths could be avoided if everyone above age 50 had a screening
• More lives saved with high risk screening

Periodontal Connection:
Fusobacterium Nucleatum FN– August 2013—Yiping Han (Case Western) Identified FanA that is on the surface of FN and provides an Adhesion to the Colon cell inducing changes that lead to Cancer Cells

• Association Strong
• Mechanism nearly outlined
• BLOCKING Agent Found
• ORAL HEALTH—The ULTIMATE Blocking Agent

Colon Health: Prevention – Diet
• Decrease fat and calories
• Increase fiber
• Anti-oxidants – at least 5 servings of fruit and vegetables/day
• Folic acid, calcium and Vitamin D
• Phytochemicals – tomatoes, citrus, berries, peppers, carrots, broccoli, cabbage and soy beans
• Eat less red meat

A complete list of resources available upon request.

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