Bibliography and Online Oral-Systemic References

Compiled by G. Lee Ostler DDS

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Antiseptics & Antimicrobial Periodontal Therapy, Volatile Sulfur Compounds

1. **[Subgingival irrigation combined with scaling and root planing. Results of a study with chlorhexidine and sodium hypochlorite]**. [Scaling and root planning is more and more associated with subgingival irrigation in chronics periodontal treatment. It is unreasonable to expect to control periodontal infections by mechanical treatment alone. Most patients do not achieve the necessary level of manual dexterity or motivation to control their plaque at home. It is rather better to deliver antimicrobial agents directly into the periodontal pocket. The aim of this study is to evaluate the action of subgingival irrigation associated to periodontal scaling on the clinical parameters and to compare the effects of chlorhexidine (Eludril) and sodium hypochlorite (Dakin Cooper) on adult's chronics periodontitis treatment. At the level of Plaque Index, Gingival Index and Bleeding on Probing, the results show that Eludril irrigation associated to scaling is lightly efficacious than Dakin cooper irrigation associated to scaling. And, the last one also is lightly efficacious than scaling alone. However, at the level of pocket depth, scaling alone has been also effective than scaling associated with subgingival irrigation.] Kamagate A, Kone D, et al. Odontostomatol Trop. 2005 Mar;28(109):28-32. http://www.ncbi.nlm.nih.gov/pubmed/16032944
2. **An in vitro comparative study determining bactericidal activity of stabilized chlorine dioxide and other oral rinses. [**OBJECTIVE: The study was conducted to determine the bactericidal activity of a stabilized chlorine dioxide oral rinse (ClōSYS Oral Rinse) compared to products currently available on the market. METHODS**:** Oral bacteria associated with gingivitis and periodontitis were exposed to rinses for one minute and five minutes. The numbers of colony forming units per milliliter (CFU/ml) were measured prior to and following exposure to determine the bactericidal activity. RESULTS: As expected, Listerine and Crest Pro-Health demonstrated complete kill on all bacteria exposed within one minute. Breath Rx exhibited the weakest levels of bactericidal effects overall. ClōSYS and chlorhexidine rinses proved identical 100% kills against the periodontal pathogens at five minutes; in some cases, ClōSYS oral rinse achieved a higher kill at the one-minute mark over the chlorhexidine rinse. CONCLUSION: The results demonstrated that ClōSYS Oral Rinse has potential for providing a therapeutic benefit, making it an attractive option to induce compliance in patients concerned about taste and tooth discoloration during oral health therapy.] Drake D, Villhauer AL. *J Clin Dent.* 2011;22(1):1-5. http://www.ncbi.nlm.nih.gov/pubmed/21290979
3. **Antibacterial agents in the control of supragingival plaque--a review.** [This review considers the main agents which have been used as antibacterial agents in mouthwashes and other vehicles to inhibit the growth of supragingival plaque. The agents discussed are bisguanide antiseptics, quaternary ammonium compounds, phenolic antiseptics, hexetidine, povidone iodine, triclosan, delmopinol, salifluor, metal ions, sanguinarine, propolis and oxygenating agents. The plaque inhibitory, anti-plaque and anti-gingivitis properties of these agents are considered along with their substantivity, safety and possible clinical usefulness. Clinical trials of these agents that have been published are also reported. The possible clinical uses of antiseptic mouthwashes are finally considered along with some advice about assessing manufacturers claims. Throughout this review the terms plaque inhibitory, anti-plaque and anti-gingivitis have been used according to the clarification of terminology suggested by the European Federation of Periodontology at its second workshop. This defines a plaque inhibitory effect as one reducing plaque to levels insufficient to prevent the development of gingivitis; an anti-plaque effect as one which produces a prolonged and profound reduction in plaque sufficient to prevent the development of gingivitis; and anti-gingivitis as an anti-inflammatory effect on the gingival health not necessarily mediated through an effect on plaque.] Eley BM. *Br Dent J.* 1999 Mar 27;186(6):286-96. http://www.ncbi.nlm.nih.gov/pubmed/10230103
4. **Antimicrobial mouthrinse as part of a comprehensive oral care regimen.** [Antimicrobial mouthrinses are safe and effective in reducing plaque and gingivitis, and they should be a part of a daily comprehensive oral health care regimen that includes brushing, flossing and rinsing to prevent or minimize periodontal disease.] Silverman S, Wilder R, *J Am Dent Assoc, Vol 137, No suppl_3, 22S-26S.* http://jada.ada.org/cgi/content/full/137/suppl_3/22S
5. **Antimicrobial peptides and periodontal disease.** [AIMS: The goal of this review is to identify the antimicrobial proteins in the oral fluids, saliva and gingival crevicular fluid and identify functional families and candidates for antibacterial treatment. RESULTS: Periodontal biofilms initiate a cascade of inflammatory and immune processes that lead to the destruction of gingival tissues and ultimately alveolar bone loss and tooth loss. Treatment of periodontal disease with conventional antibiotics does not appear to be effective in the absence of mechanical debridement. An alternative treatment may be found in antimicrobial peptides and proteins, which can be bactericidal and anti-inflammatory and block the inflammatory effects of bacterial toxins. The peptides have co-evolved with oral bacteria, which have not developed significant peptide resistance. Over 45 antibacterial proteins are found in human saliva and gingival crevicular fluid. The proteins and peptides belong to several different functional families and offer broad protection from invading microbes. Several antimicrobial peptides and proteins (AMPs) serve as templates for the development of therapeutic peptides and peptide mimetics, although to date none have demonstrated efficacy in human trials. CONCLUSIONS: Existing and newly identified AMPs may be developed for therapeutic use in periodontal disease or can serve as templates for peptide and peptide mimetics with improved therapeutic indices.] Gorr SU, Abdolhosseini M. *J Clin Periodontol.* 2011 Mar;38 Suppl 11:126-41. **http://www.ncbi.nlm.nih.gov/pubmed/21323710**.
6. **Bactericidal Activity of Stabilized Chlorine Dioxide Against Polymicrobial Biofilms.** [Objectives: CloSYSII is a novel antibacterial rinse that has a stabilized chlorine dioxide formulation. The purpose of this study was to determine bactericidal activity of a 0.5% rinse against polymicrobial biofilms containing both gram-positive and negative bacteria. Methods: The following bacteria were used in this study: Actinomyces viscosus, Streptococcus sanguinis, Fusobacterium nucleatum, Peptostreptococcus micros, and Porphyromonas gingivalis. Biofilms were cultured in enriched TSB-YE at 37° under

anaerobic conditions. Standardized, polymicrobial suspensions were used to establish the biofilms. Single and multiple one minute exposure regimens were done. The multiple exposure treatment regimens consisted of polymicrobial biofilms exposed for one minute 2-3x over 24 hours. Biofilms were maintained in artificial saliva supplemented with dilute tryptone and yeast extract and incubated anaerobically at 37° between exposures. After exposure, samples of the harvested biofilms were spiral-plated onto selective/differential media for isolation of each organism in the polymicrobial biofilms. Pilot studies were done to determine the ability for us to select and quant ify each organism from the harvested biofilms. Determination of numbers of viable bacteria was done following standard spiral-plating methodology. Data were analyzed via a 2-way ANOVA. Results: Single exposure did not result in statistically significant reductions in bacteria. However, multiple exposures of the polymicrobial biofilms resulted in significant decreases in numbers of viable cells. Reductions in 2-3 logs were observed with S. sanguinis ($p<0.05$). However, essentially no decreases were seen with A. viscosus. Stark differences were seen with the putative periodontal pathogens. P. gingivalis, P. micros, and F. nucleatum all were completely eliminated from the biofi lms ($p<0.001$). Conclusion: A stabilized chlorine dioxide rinse exhibited significant bactericidal activity against polymicrobial biofilms. Importantly, multiple exposures of polymicrobial biofilms by this formulation resulted in complete elimination of the periodontal pathogens with significantly less affect on bacteria more associated with oral health. Supported by Rowpar Pharmaceuticals, Inc.] Villhauer A, Olson B, et al. *IADR General Session*, Miami, FL, April 1-4, 2009. http://iadr.confex.com/iadr/2009miami/webprogram/Paper120614.html

7. **Bleach solution as adjunct to periodontal homecare. []** Microvision Dental Technologies, Inc. http://www.microvisiondental.com/phpBB3/viewtopic.php?f=1&t=297
8. **Effect of hydrogen sulfide and methyl mercaptan on the permeability of oral mucosa.** [Hydrogen sulfide (H2S) and methyl mercaptan (CH3SH) are the volatile sulfur compounds (VSC) that were investigated for a possible role in the etiology of periodontal disease. The results show that the permeability of porcine non-keratinized sublingual mucosa is increased by up to 75% or 103% following exposure to H2S and CH3SH, respectively. The effect may be attributed to VSC reaction with tissue components resulting in alteration in the integrity of the tissue barrier. Treatment of the mucosa with 0.22% ZnCl2, either prior to or after exposure to CH3SH, nullified the effect of CH3SH and restored the permeability to a state similar to that observed in control 95% air/5% CO2 systems.] Ng W., Tonzetich J., *Journal of Dental Research, Vol 63, 994-997***.** http://jdr.iadrjournals.org/cgi/content/abstract/63/7/994
9. **Effects of stabilized chlorine dioxide and chlorhexidene in vitro on cells involved in periodontal healing.** [Stabilized chlorine dioxide mouthrinse is less toxic than CHX to human gingival fibroblasts, periodontal ligament cells, and an osteoblast cell lines in vitro. In vitro tests on cell monolayers may not be fully applicable to therapy, so clinical significance of these findings remains to be explored.] Wirthlin MR, Ahn BJ, et al. *J West Soc - Periodontal Abstracts,Vol 54, Number 3, 2006.* http://www.ncbi.nlm.nih.gov/sites/entrez?cmd=Retrieve&db=PubMed&dopt=AbstractPlus&list_uids=17152122
10. **Efficacy of a Chlorine Dioxide-containing Mouthrinse in Oral Malodor.** [The objective of this study was to determine the efficacy of CloSYSII Oral Rinse in reducing oral malodor over a 96 hour period. This study employed serial organoleptic and Halimeter measurements to document the duration of action CloSYSII Oral Rinse (formerly Retardex) on oral malodor. The results show that a single 15-mL rinsing with the chlorine dioxide rinse, in its unflavored form, improves breath odor pleasantness, reduces breath malodor, and reduces VSC concentrations in the mouth through 8 hours after use.] Frascella J. et al, TKL Research, Inc., Paramus, NJ,. *Journal of Dental Research, , (IADR Abstracts) 1999, p. 356, Article 2004.* http://www.rowpar.com/professionals/oralhealth/research/5.html
11. **Efficient Antimicrobial treatment in periodontal maintenance care.** [Background. The goal of follow-up care after periodontal therapy is to preserve the function of individual teeth and the dentition, ameliorate symptoms and simplify future surgery or make it unnecessary. Effective follow-up periodontal care depends on early diagnosis and treatment, as well as patient education. Results. The main determinants of successful periodontal maintenance therapy are dental professionals' ability to combat periodontal infections and patients' compliance with prescribed follow-up care. Mechanical and chemical antimicrobial intervention is the mainstay of preventive periodontal therapy. Chemotherapeutics alone are unlikely to be effective in the presence of subgingival calculus, underscoring the importance of subgingival mechanical débridement. Also, because toothbrushing and rinsing alone do not reach pathogens residing in periodontal pockets of increased depths, oral hygiene procedures should include subgingival treatment with home irrigators or other appropriate self-care remedies. When considering possible preventive therapies, dental professionals must weigh the risk of patients' acquiring destructive periodontal disease against potentially adverse effects, financial costs and inconvenience of the preventive treatment. The authors discuss theoretical and practical aspects of follow-up care for patients with periodontal disease. In addition, because it can be both difficult and expensive to control periodontal disease via conventional preventive measures alone, they present a new, simple and more cost-effective antimicrobial protocol for supportive periodontal therapy. The initial course of periodontal therapy and follow-up care are essentially based on the premise of periodontal diseases being infectious disorders. Despite enhanced efficacy of newer antimicrobial treatments, therapeutic failure can occur and reinfection of periodontal sites is always a possibility. Also, long-term response to periodontal therapy is difficult to assess, and no definitive criteria exist for curing periodontitis. This makes optimal management of periodontitis unclear and underscores the need for clinicians to frequently monitor the patient's periodontal health with close clinical and, in some cases, microbiological follow-up. However, optimal follow-up care is poorly defined, and preventive periodontal programs are often designed presumptively. There is no uniformity of opinion in regard to the optimal periodontal health maintenance procedures and frequency of preventive care appointments. In this article, we outline current approaches to follow-up care after initial ("definitive") periodontal therapy and advance a suitable protocol for periodontal maintenance care. We assume the reader is familiar with

current concepts of antimicrobial therapy in the initial course of periodontal treatment.] Slots J, Jorgensen M. J Am Dent Assoc, Vol 131, No 9, 1293-1304. http://jada.ada.org/cgi/content/full/131/9/1293

12. **Formation of Methyl Mercaptan from L-Methionine by *Porphyromonas gingivalis.*** [Methyl mercaptan production by oral bacteria is thought to be one of the main causes of oral malodor. We examined the ability of periodontopathic *Porphyromonas gingivalis* to produce methyl mercaptan from L-methionine. These results suggest that methyl mercaptan not only is one of the sources of oral malodor, but may also play a role in the pathogenicity of *P. gingivalis.*] Yoshimura M., Nakano Y, et.al., Infection and Immunity, December 2000, p. 6912-6916, Vol. 68, No. 12. http://iai.asm.org/cgi/content/abstract/68/12/6912
13. **Management of Periodontitis with Oral Care Products.** [This study shows the effectiveness of the use of Rowpar's products, CloSYSII Toothpaste and CloSYSII Oral Rinse when used in a twice daily regimen as an effective aid for prevention of periodontitis and the maintenance of recall patients. 1,046 of the original 2,085 pockets were healed to normal probing depths. The relationship between reduction of VSC and the permeability of the epithelial barrier may be associated with the reduction in probing scores.] Chapek et al, *Compendium Vol. XV No 6, 740-746, 1994.* http://www.rowpar.com/professionals/oralhealth/research/6.html
14. **Managing the complexity of a dynamic biofilm.** [The pathogenic nature of the dental plaque biofilm can be diminished in the oral cavity by reducing the bioburden and effectively maintaining a normal oral flora via oral hygiene procedures that include daily toothbrushing, flossing and rinsing with an antimicrobial mouthrinse. An oral hygiene regimen that includes rinsing with an antimicrobial mouthrinse is a practical approach to the prevention and management of periodontal diseases. This strategy may have wider benefits when the link between periodontal disease and certain systemic diseases is considered.] Thomas JG, Nakaishi LA. *J Am Dent Assoc, Vol 137, Nov suppl_3, 10S-15S.* 2006. http://jada.ada.org/cgi/content/full/137/suppl_3/10S
15. **Periodontal antimicrobials--finding the right solutions**. [Strengthened by promising research data and commercial backing, interest in the field of anti-infective periodontal therapy is rapidly expanding. Management of the periodontal microbiota with antibiotic drugs and antiseptic agents in conjunction with mechanical debridement seems to be more effective than mechanical therapy alone, at least in the treatment of advanced periodontal disease. The choice of a periodontal chemotherapeutic regimen requires an understanding of the usual infecting flora, available antimicrobial agents, and pathogen susceptibility patterns. Systemic administration of combinations of metronidazole and either amoxicillin or ciprofloxacin has been widely used with great success; however the presence of subgingival yeasts and resistant bacteria can be a problem in some periodontitis patients. Valuable antiseptic agents for subgingival application include 10% povidone-iodine for professional use and 0.1-0.5% sodium hypochlorite for patient self-care. These antiseptics have significantly broader spectra of antimicrobial action, are less likely to induce development of resistant bacteria and adverse host reactions, and are considerably less expensive than commercially available antibiotics in controlled release devices. In practice, mechanical debridement combined with subgingival povidone-iodine application in the dental office and sodium hypochlorite irrigation for patient self-care are valuable antimicrobial remedies in the treatment of virtually all types of periodontal disease. Management of moderate to severe periodontitis may require additional systemic antibiotic and/or surgical treatment.] Jorgensen MG, et al. *Int Dent J.* 2005 Feb;55(1):3-12. http://www.ncbi.nlm.nih.gov/pubmed/15747646
16. **Plaque Removal from Less Accessible Sites by Baking Soda-Toothpastes** .[Most earlier studies have indicated that toothpastes have no material effect on the mechanical removal of plaque. However, recent studies have shown that, despite baking soda's remarkably low abrasivity, baking soda-dentifrices do promote the physical removal of plaque biofilm (J Clin Dent 19:120-126, 2008, J Clin Dent 19:111-119, 2008). Objectives: To determine if baking soda-toothpastes are relatively more effective than non-baking soda toothpastes in promoting plaque removal from harder to reach areas. Methods**:** A meta-analysis of three clinical studies using paired t-tests compared the relative plaque removal efficacy of baking soda-toothpastes and non-baking soda toothpastes from various areas of the dentition. … Baking soda-toothpastes were relatively more effective in promoting plaque removal from posterior than anterior, proximal than gingival and facial than lingual sites ($p<0.05$). Conclusion: Baking soda-toothpastes are relatively more effective in promoting plaque removal than non-baking soda-toothpastes from harder to reach areas of the dentition.] Hooper WJ, Winston AE, et al. *IADR General Session*, San Diego CA, March 2011. http://iadr.confex.com/iadr/2011sandiego/webprogram/Paper149786.html
17. **Povidone-iodine as a periodontal pocket disinfectant.** [OBJECTIVES AND BACKGROUND: Povidone-iodine [polyvinylpyrrolidone-iodine complex (PVP-iodine)] might constitute a valuable adjunct to current periodontal therapy because of its broad-spectrum antimicrobial activity, low potential for developing resistance and adverse reactions, wide availability, ease of use, and low financial cost. This investigation employed a randomized, split-mouth study design to determine the microbiological and clinical effects of 10% PVP-iodine subgingival irrigation in periodontitis lesions showing radiographic evidence of subgingival calculus. METHODS: Sixteen adults having at least one periodontal pocket of 6 mm or more in each quadrant of the dentition and harboring one or more periodontopathic bacteria participated in the study. In each subject, a study site in each quadrant was randomly chosen to receive either subgingival irrigation with 10% PVP-iodine together with scaling and root planing, scaling and root planing alone, subgingival irrigation with 10% PVP-iodine, or subgingival irrigation with sterile saline. Prior to therapy and at 5 weeks post-treatment, microbiological culture was carried out without knowledge of the clinical status or the type of treatment rendered. A blinded clinical examiner determined presence of dental plaque, probing pocket depth, and gingival bleeding on probing. Microbiological and clinical data were analyzed using a repeated measures analysis of variance and Kruskal-Wallis rank test with the Tukey and Mann-Whitney post hoc tests. RESULTS: At 5 weeks post-treatment, subgingival irrigation with PVP-iodine together with scaling and root

planing caused a 95% or greater reduction in total pathogen counts in 44% of pockets having >/= 6 mm depth whereas scaling and root planing alone, povidone-iodine irrigation alone and water irrigation alone caused 95% reduction of total pathogens only in 6-13% of similar study sites (P = 0.02). Reduction in mean pocket depth was 1.8 mm for the PVP-iodine/scaling and root planing group, 1.6 mm for the scaling and root planing group, and 0.9 mm for the PVP-iodine and the saline monotherapy groups, with statistical significance reached for the scaling and root planing group vs. the PVP-iodine group (P = 0.04) and for the scaling and root planing group vs. the saline group (P = 0.02). Reduction in visible dental plaque, which ranged from 38% to 62%, showed no significant differences among treatment groups. CONCLUSIONS: The addition of subgingival PVP-iodine irrigation to conventional mechanical therapy may be a cost-effective means of reducing total counts of periodontal pathogens and helping control periodontal disease. However, subgingival irrigation with PVP-iodine without concomitant mechanical debridement might not improve microbiological and clinical variables in comparison with saline irrigation, at least not in sites with radiographic evidence of subgingival calculus.*] hoang T, Jorgensen MG, et al. J Periodontal Res.* 2003 Jun;38(3):311-7. http://www.ncbi.nlm.nih.gov/pubmed/12753370

18. **Production and origin of oral malodor: a review of mechanisms and methods of analysis.** [Organoleptic studies indicate that the oral cavity is usually the principal source of physiologic malodor associated with the early morning halitosis. This results from normal metabolic activity in the oral cavity and is accentuated in cases with periodontal involvement. Proteolysis and reduction of disulphide bonds precedes the formation of odor. The odor intensity of putrescent saliva and plaque head-space vapor has been correlated with the concentration of volatile sulphur compounds consisting of hydrogen sulphide, methyl mercaptan, dimethyl sulphide and dimethyl disulphide.] Tonzetich J. *Periodontol. 1977 Jan;48(1):13-20.* http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=264535&dopt=Abstract
19. **Production of volatile sulphur compounds in diseased periodontal pockets is significantly increased in smokers.** [Increased production of volatile sulphur compounds may represent a further mechanism of increased susceptibility to periodontitis in smokers and also help to explain the reported association between smoking and halitosis.] Khaira N, Palmer, R.M., et.al., *Oral Dis. 2000 Nov;6(6):371-5.* http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11355269&dopt=Abstract
20. **Reduction of Bleeding on Probing by Oral Care Products**. [Bleeding can occur only with loss of integrity and continuity between epithelial cells. Penetration of bacterial antigens will not occur with an intact epithelial barrier. VSC have been associated with increased permeability of the epithelial barrier. The reduction of bleeding on probing with the use of CloSYSII Toothpaste and CloSYSII Oral Rinse when used twice daily between recall visits suggests that these patients had returned to a more healthy periodontal state.] Chapek et al, *Compendium, Vol. 16, No. 2, 1995, 188-196.* http://www.rowpar.com/professionals/oralhealth/research/7.html
21. **Selection of antimicrobial agents in periodontal therapy.** [BACKGROUND: The recognition over the past 3 decades of microbial specificity in periodontitis has afforded dental practitioners the ability to prevent and treat the disease with a variety of antimicrobial drugs. These include systemic antibiotics, topical antibiotics and topical antiseptics. RESULTS: Systemic antibiotic therapy can be essential in eliminating pathogenic bacteria that invade gingival tissue and in helping control periodontal pathogens residing in various domains of the mouth from where they may translocate to periodontal sites. Frequently used periodontal combination antibiotic therapies are metronidazole-amoxicillin (250-375 mg of each 3 x daily for 8 days) and metronidazole-ciprofloxacin (500 mg of each 2 x daily for 8 days). Microbiological analysis helps determine the optimal antibiotic therapy and effectiveness of treatment. Topical antibiotics that are commercially available as controlled release devices suffer from several potential problems, including insufficient spectrum of antimicrobial activity in some periodontal polymicrobial infections, risks of producing an antibiotic resistant microbiota, and high acquisition costs. Topical antiseptics of relevance in periodontal treatment include 10% povidone-iodine placed subgingivally by a syringe for 5 min, and 0.1% sodium hypochlorite solution applied subgingivally by patients using an irrigation device. CLINICAL IMPLICATIONS: The present paper recommends periodontal treatment that includes a battery of professionally and patient-administered antimicrobial agents (properly prescribed systemic antibiotics, povidone-iodine and sodium hypochlorite subgingival irrigants, and chlorhexidine mouthrinse). Available chemotherapeutics can provide effective, safe, practical and affordable means of controlling subgingival colonization of periodontal pathogens and various types of periodontal disease.] Slots J. *J Periodontal Res.* 2002 Oct;37(5):389-98. http://www.ncbi.nlm.nih.gov/pubmed/12366863
22. **Sulfur uptake by type I collagen from methyl mercaptan/dimethyl disulfide air mixtures.** [The results provide evidence that the reaction of collagen with H2S and CH3SH/(CH3S)2 mixture proceeded via the H2S and CH3SH thiol groups.] Johnson P.W. Tonzetich J., *Journal of Dental Research, Vol 64, 1361-1364.* http://jdr.iadrjournals.org/cgi/content/abstract/64/12/1361
23. **Sulphur By-Product: The Relationship between Volatile Sulphur Compounds and Dental Plaque-Induced Gingivitis.** [The purpose of this study was to evaluate the relationship between volatile sulphur compounds (VSC) and gingival health status, and to monitor the changes in VSC in early dental plaque-induced gingivitis. Sulfur levels were significantly higher on the non-brushing side at 4 of the 6 data collection intervals; therefore, sulfur levels may be associated with the initiation and progression of early plaque-induced gingivitis.] Zhou H, McCombs GB, Darby ML, et. al. *The Journal of Contemporary Dental Practice, Volume 5, No. 2, May 15, 2004.* http://72.14.253.104/search?q=cache:bRxqez1_m_kJ:www.thejcdp.com/issue018/zhou/zhou.pdf+Sulfur+uptake+by+type+I+collagen+from+methyl+mercaptan,+dimethyl+disulfide+air+mixtures&hl=en&gl=us&ct=clnk&cd=5
24. **Systematic review on the effect of rinsing with povidone-iodine during nonsurgical periodontal therapy.** [BACKGROUND AND OBJECTIVE: The existing literature is inconsistent regarding whether there is any additional effect

of povidone-iodine (PVP-iodine) as an adjunctive to scaling and root planing, and, if there is an effect, what its size is. Therefore, the aim of this study was to assess the additional effect of PVP-iodine as an adjunct to scaling and root planing compared with water, saline or no rinse in the treatment of chronic periodontitis. MATERIAL AND METHODS: An electronic literature search of the databases PubMed, EMBASE and the Cochrane Central Library, and a handsearch, were performed (up to November 2008). Two reviewers independently identified and selected screened abstracts for possible inclusion, and assessed randomized, controlled clinical trials comparing the additional benefit of PVP-iodine with water, saline rinsing or no rinsing in the nonsurgical periodontal therapy of patients with chronic periodontitis. A fixed-effects meta-analysis was conducted in the absence of statistically significant heterogeneity. RESULTS: A small, but statistically significant additional beneficial effect of the adjunctive use of PVP-iodine with enhanced probing pocket depth reductions of 0.28 mm (95% confidence interval: 0.08 to 0.48, p = 0.007) was found. There was no significant heterogeneity between studies (I(2) = 0%). However, most of the studies included in the meta-analysis were of low quality, and the treatment modalities showed various differences such as the use of PVP-iodine at different concentrations and application modalities. Nevertheless, single-rooted teeth, in particular, showed an additional benefit after scaling and root planing with PVP-iodine, particularly when the treatment was repeated during the healing stage. CONCLUSION: The adjunctive use of PVP-iodine during scaling and root planing may increase the clinical pocket depth reduction, although the clinical significance is small to moderate.] Sahrmann P, Puhan MA, et al. *J Periodontal Res.* 2010 Apr;45(2):153-64. http://www.ncbi.nlm.nih.gov/pubmed/19909406

25. **The capacity of subgingival microbiotas to produce volatile sulfur compounds in human serum.** [Hydrogen sulfide is formed by the subgingival microbiotas of periodontal pockets. The capacity of these microbiotas to form various volatile sulfur compounds in human serum was studied. Hydrogen sulfide was the predominant volatile sulfur compound, but also methyl mercaptan was formed in significant amounts.] Persson S, Claesson R. *Oral Microbiol Immunol. 1989 Sep;4(3):169-72. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2639302&dopt=Abstract*
26. **The rationale for the daily use of an antimicrobial mouthrinse.** [There is a twofold rationale for daily use of antimicrobial mouthrinses: first, given the inadequacy of mechanical plaque control by the majority of people, as a component added to oral hygiene regimens for the control and prevention of periodontal diseases; second, as a method of delivering antimicrobial agents to mucosal sites throughout the mouth that harbor pathogenic bacteria capable of recolonizing supragingival and subgingival tooth surfaces, thereby providing a complementary mechanism of plaque control.] Barnett ML, J Am Dent Assoc, Vol 137, No suppl_3, 16S-21S. http://jada.ada.org/cgi/content/full/137/suppl_3/16S
27. **The Relationship Between Oral Malodor, Gingivitis, and Periodontitis. A Review.** [Volatile sulfur compounds (VSC) are a family of gases which are primarily responsible for halitosis, a condition in which objectionable odors are present in mouth air. An increasing volume of evidence is demonstrating that extremely low concentrations of many of these compounds are highly toxic to tissues. VSC may, therefore, play a role in the pathogenesis of inflammatory conditions such as periodontitis. Two members of this family, hydrogen sulfide (H_2S) and methyl mercaptan (CH_3SH), are primarily responsible for mouth odor. Although many bacteria produce H_2S, the production of CH_3SH, especially at high levels, is primarily restricted to periodontal pathogens. Direct exposure to either of these metabolites adversely affects protein synthesis by human gingival fibroblasts in culture. However, methyl mercaptan has the greatest effect. Other in vitro experiments have demonstrated that cells exposed to methyl mercaptan synthesize less collagen, degrade more collagen, and accumulate collagen precursors which are poorly cross-linked and susceptible to proteolysis. CH_3SH also increases permeability of intact mucosa and stimulates production of cytokines which have been associated with periodontal disease. VSC, and in particular methyl mercaptan, are therefore capable of inducing deleterious changes in both the extracellular matrix and the local immune response of periodontal tissues to plaque antigens.] Ratcliff PA, Johnson PW., *J Periodontol. 1999 May;70(5):485-9* http://www.joponline.org/doi/abs/10.1902/jop.1999.70.5.485 Ratcliff PA, Johnson PW. J Periodontol. 1999 May;70(5):485-9. Review.
28. **Use of chlorine dioxide mouthrinse as the ultrasonic scaling lavage reduces the viable bacteria in the generated aerosols. [No abstract available]. Wirthlin MR, Choi JH, et al.** J West Soc Periodontol Periodontal Abstr. 2006;54(2):35-44. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17214015&itool=iconnoabstr&query_hl=15&itool=pubmed_docsum
29. **Volatile Sulfur Compounds and relation to Periodontal disease.** [Every mouth contains the components that produce volatile sulfur compounds (VSCs) bacterial, saliva, and proteins. VSCs are a major component in the development of periodontal diseases. There are three compounds that produce oral malodor: 1)- hydrogen sulphide, 2)-methyl mercaptan, & 3)-dimethyl sulphide. These compounds are the degradation end products from polypeptides. The maintenance of the tissue barrier is important, since toxic substances such as endotoxin and bacterial dextrans have been shown to be incapable of causing inflammation in healthy sulcular gingiva (Gaffar et al., 1981; Rizzo, 1968). VSCs have been shown to have a direct effect on protein synthesis by human gingival fibroblasts (Johnson and Tonzetich et al, 1980). VSCs play a major role in preparing tissues for the invasion of bacterial toxins. http://dentalimplants-usa.com/Conditions/breath.html
30. **What is Chlorine Dioxide?** http://www.lenntech.com/chlorine_dioxide.htm; http://www.epa.gov/pesticides/factsheets/chemicals/chlorinedioxidefactsheet.htm; http://www.clo2.com/**A study of the effects of antiseptic agents and a pulsating irrigating device on plaque and gingivitis.** [] Lobene RR, Soparkar PM, et al. *J Periodontol.* 1972 Sep;43(9):564-8. http://www.ncbi.nlm.nih.gov/pubmed/4506703

31. **Anti-inflammatory cytokines in gingival crevicular fluid in patients with periodontitis and rheumatoid arthritis: A preliminary report.** [Cytokines which are produced by host cells play an important role in pathogenesis both rheumatoid arthritis (RA) and chronic periodontitis (CP). In this study, we aim to investigate the levels of Interleukin (IL)-4 and IL-10 in gingival crevicular fluid (GCF). Seventeen patients with CP, 17 patients with RA and 17 healthy controls (HC) were included. The RA group was divided into two groups according to gingival sulcus depths (RA-a: PD $\leqslant$ 3 mm, (n = 12), RA-b: PD > 3 mm, (n = 5)). For each patient, clinical parameters were recorded. The GCF samples were evaluated by enzyme-linked immunosorbent assay (ELISA) for IL-4 and IL-10 levels. IL-4 levels in the RA-a, RA-b and CP subjects were significantly lower compared to the HC subjects ($p < 0.05$). The mean level of IL-4 in RA-b group was significantly higher than that in CP group ($p < 0.05$). IL-10 mean level in the HC group was higher than those in the other groups ($p < 0.05$). In the RA-a group, higher IL-10 level was found compared to the CP patients ($p < 0.05$). Within the limitations of this preliminary report, it can be concluded that the initiation and progression of periodontal inflammation may be due to a lack or inappropriate response of the anti-inflammatory cytokines in both CP and RA.] Bozkurt FY, Ay ZY, et al. *Cytokine, Volume 35, Issues 3-4, August 2006, Pages 180-185.* http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6WDF-4KXF2VS-1&_user=10&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_version=1&_urlVersion=0&_userid=10&md5=c2c0d4c52d4e9ae3f7e968023be1e09d
32. **Association Among Rheumatoid Arthritis, Oral Hygiene, and Periodontitis.** [Background: A limited number of studies suggest a higher prevalence of periodontal disease among individuals with rheumatoid arthritis (RA); however, results have been inconsistent. Further, it is unclear to what extent poor oral hygiene among patients with RA may account for this association. Methods: The association between RA and periodontitis was examined in 57 subjects with RA and 52 healthy controls, matched by age and gender. Oral examination included plaque index (PI), gingival index (GI), probing depth (PD), and clinical attachment loss (CAL). Potential risk factors for periodontal disease, such as smoking, education, alcohol consumption, and body mass index (BMI), as well as chronic diseases associated with RA and periodontal disease were assessed through questionnaires. Results: In a stepwise logistic regression, including RA status, age, gender, education, smoking, alcohol consumption, and BMI, only RA status and age remained significant predictors of periodontal disease. Subjects with RA had a significant 8.05-fold increased odds (95% confidence interval: 2.93 to 22.09) of periodontitis compared to controls. The strength of the association was attenuated but remained statistically significant after further adjustment for PI, GI, or both. PI alone accounted for 12.4%, GI alone accounted for 11.1%, and PI and GI combined accounted for 13.4% of the association between RA and periodontitis. Conclusions: Subjects with RA have significantly increased periodontal attachment loss compared to controls. Oral hygiene may only partially account for this association.] Pischon N, Pischon T, et al. Journal of Periodontology, 2008, Vol. 79, No. 6, Pages 979-986. http://www.joponline.org/doi/abs/10.1902/jop.2008.070501
33. **Association of periodontitis with rheumatoid arthritis: a pilot study.** [BACKGROUND: Similarities exist in the epidemiology and immunopathogenesis of periodontitis and rheumatoid arthritis (RA), but the associations between their respective disease activities and severities are less well documented. We evaluated the prevalence and severity of periodontitis in United States (U.S.) veterans with RA and their relationship to RA disease activity and severity. METHODS: Patients with RA from an outpatient rheumatology clinic were eligible, and patients with osteoarthritis (OA) served as controls. Dentists, masked to the rheumatologic diagnoses, performed periodontal probing and examined dental panoramic radiographs to assess the presence and severity of periodontitis. Associations of periodontitis with RA were examined using multivariate regression, whereas the association of periodontitis with disease-severity measures in RA was examined using the chi(2) test. RESULTS: Sixty-nine patients with RA (57 males and 12 females) and 35 patients with OA (30 males and five females) were studied. Moderate to severe periodontitis was more prevalent in patients with RA (51%) than controls (26%) (P = 0.03), an association independent of age, race, smoking, diabetes mellitus, and gender. Patients with RA who were seropositive for rheumatoid factor (RF) were more likely to have moderate to severe periodontitis (59%) than patients who were RF negative (15%) (P = 0.02). Likewise, patients with RA who were positive for the anti-cyclic citrullinated peptide (CCP) antibodies were more likely to have moderate to severe periodontitis (56%) than patients who were anti-CCP negative (22%) (P = 0.01). There were no associations of periodontitis status with other measures of RA disease activity or severity. CONCLUSIONS: In a cohort of U.S. veterans, periodontitis was more common and severe in patients with RA compared to patients with OA. Although unrelated to disease activity, the presence of periodontitis in patients with RA was associated with seropositivity for RF and the anti-CCP antibody, which was highly relevant given the associations of these autoantibodies with poor outcomes and disease pathogenesis in RA.] Dissick A, Redman RS, et al. J *Periodontol.* 2010 Feb;81(2):223-30 http://www.ncbi.nlm.nih.gov/pubmed/20151800
34. **Broad-range PCR, cloning and sequencing of the full 16S rRNA gene for detection of bacterial DNA in synovial fluid samples of Tunisian patients with reactive and undifferentiated arthritis. [**Introduction Broad-range rDNA PCR provides an alternative, cultivation-independent approach for identifying bacterial DNA in reactive and other form of arthritis. The aim of this study was to use broad-range rDNA PCR targeting the 16S rRNA gene in patients with reactive and other forms of arthritis and to screen for the presence of DNA from any given bacterial species in synovial fluid (SF) samples. Methods We examined the SF samples from a total of 27 patients consisting of patients with reactive arthritis (ReA) (n = 5),

undifferentiated arthritis (UA) (n = 9), rheumatoid arthritis (n = 7), and osteoarthritis (n = 6) of which the latter two were used as controls. Using broad-range bacterial PCR amplifying a 1400 bp fragment from the 16S rRNA gene, we identified and sequenced at least 24 clones from each SF sample. To identify the corresponding bacteria, DNA sequences were compared to the EMBL (European Molecular Biology Laboratory) database. Results Bacterial DNA was identified in 20 of the 27 SF samples (74, 10%). Analysis of a large number of sequences revealed the presence of DNA from more than one single bacterial species in the SF of all patients studied. The nearly complete sequences of the 1400 bp were obtained for most of the detected species. DNA of bacterial species including *Shigella* species, *Escherichia* species, and other coli-form bacteria as well as opportunistic pathogens such as *Stenotrophomonas maltophilia* and *Achromobacter xylosoxidans* were shared in all arthritis patients. Among pathogens described to trigger ReA, DNA from *Shigella sonnei* was found in ReA and UA patients. We also detected DNA from rarely occurring human pathogens such as *Aranicola* species and *Pantoea ananatis*. We also found DNA from bacteria so far not described in human infections such as *Bacillus niacini*, *Paenibacillus humicus*, *Diaphorobacter* species and uncultured bacterium genera incertae sedis OP10. Conclusions Broad-range PCR followed by cloning and sequencing the entire 16S rDNA, allowed the identification of the bacterial DNA environment in the SF samples of arthritic patients. We found a wide spectrum of bacteria including those known to be involved in ReA and others not previously associated with arthritis.] Siala M, Gdoura R, et al. *Arthritis Research & Therapy* 2009, 11**:**R102 http://arthritis-research.com/content/11/4/R102

35. **Clinical Significance of Cytokine Determination in Synovial Fluid.** [Cytokines are a complex family of small regulatory proteins able to mediate intercellular communication and play a crucial role in immunologic and inflammatory reactions. Many reports have demonstrated that some cytokines, in particular tumor necrosis factor α (TNFα) and interleukin (IL)-1β, IL-6, and IL-8, so-called proinflammatory, may have a major role in the pathogenesis of joint diseases. Thus, high levels of these substances have been found in inflammatory arthropathies, in particular in those characterized by a more aggressive and destructive outcome, such as rheumatoid arthritis, gout, and infectious arthritis. In keeping with their role, the determination of cytokines in synovial fluid may be proposed for clinical purposes, including diagnostic and prognostic assessments. Furthermore, as some of these cytokines may reflect disease activity, their determination may also be useful in the evaluation of therapy.] Punzi L, Calo L, et.al. Critical Reviews in Clinical Laboratory Sciences Volume 39, Number 1/January-February 2002. P 63-88. http://taylorandfrancis.metapress.com/content/xl7eupq0p2j9k8cq/
36. **Effects of tumor necrosis factor blockade on cardiovascular risk factors in psoriatic arthritis: A double-blind, placebo-controlled study. [Objective:** To conduct a robust, double-blind, placebo-controlled study examining the effects of tumor necrosis factor (TNF) modulation on concentrations of traditional and novel cardiovascular disease risk factors in patients with an inflammatory condition. This study is the first to demonstrate that targeting the TNF pathway can significantly decrease Lp(a) and homocysteine levels and elevate Apo A-I and SHBG concentrations. These data support an important precursor role for high-grade inflammation in modulating these putative risk parameters. However, TNF blockade-induced increases in triglyceride and Apo B levels were unexpected and suggest that it is not possible, on the basis of biochemical changes in isolation, to suggest that cardioprotection would necessarily follow; rather, direct measures of atherosclerotic progression with TNF blockade (e.g., using carotid ultrasound) would be better.] Sattar N, Crompton P, et.al. *Arthritis & Rheumatism, Vol 56, Issue 3, p 831-839.* http://www3.interscience.wiley.com/cgi-bin/abstract/114130672/ABSTRACT
37. **Generalized periodontal involvement in a young patient with systemic lupus erythematosus.** [Inflammation is considered to be a leading cause of morbidity in systemic lupus erythematosus (SLE), yet inflammatory periodontal involvement is rarely encountered. A young lady suffering from active SLE accompanied by severe periodontal loss, manifested by gingival recession of all her teeth, was referred to our clinic for treatment. The association between periodontal involvement and connective tissue diseases is unclear, and the literature dealing with periodontal involvement in patients suffering from Sjogren's syndrome and rheumatoid arthritis is comprised of studies showing both normal and pathological periodontal status. We discuss the possible underlying mechanisms] Nagler RM, Lorber M, et al. *Lupus, Vol. 8, No. 9, 770-772 (1999)* http://lup.sagepub.com/cgi/content/abstract/8/9/770
38. **Heightened immune response to autocitrullinated*Porphyromonas gingivalis* peptidylarginine deiminase: a potential mechanism for breaching immunologic tolerance in rheumatoid arthritis. [**Abstract **Background** Rheumatoid arthritis (RA) is characterised by autoimmunity to citrullinated proteins, and there is increasing epidemiologic evidence linking *Porphyromonas gingivalis* to RA. *P gingivalis* is apparently unique among periodontal pathogens in possessing a citrullinating enzyme, peptidylarginine deiminase (PPAD) with the potential to generate antigens driving the autoimmune response. **Objectives** To examine the immune response to PPAD in patients with RA, individuals with periodontitis (PD) and controls (without arthritis), confirm PPAD autocitrullination and identify the modified arginine residues. **Methods** PPAD and an inactivated mutant (C351A) were cloned and expressed and autocitrullination of both examined by immunoblotting and mass spectrometry. ELISAs using PPAD, C351A and another *P gingivalis* protein arginine gingipain (RgpB) were developed and antibody reactivities examined in patients with RA (n=80), individuals with PD (n=44) and controls (n=82). **Results** Recombinant PPAD was a potent citrullinating enzyme. Antibodies to PPAD, but not to Rgp, were elevated in the RA sera (median 122 U/ml) compared with controls (median 70 U/ml; $p<0.05$) and PD (median 60 U/ml; $p<0.01$). Specificity of the anti-peptidyl citrullinated PPAD response was confirmed by the reaction of RA sera with multiple epitopes tested with synthetic citrullinated peptides spanning the PPAD molecule. The elevated antibody response to PPAD was abolished in RA sera if the C351A mutant was used on ELISA. **Conclusions** The peptidyl citrulline-specific immune response to PPAD supports the hypothesis that, as a bacterial protein, it might break tolerance in RA, and could be a target

for therapy.] Quirke AM, Lugli EB, et al. *Ann Rheum Dis* doi:10.1136/annrheumdis-2012-202726**.** http://www.ncbi.nlm.nih.gov/pubmed/23463691

39. **Inflammatory cytokines activity in temporomandibular joint disorders: a review of literature. [**Cytokines are important polypeptides mediators of acute and chronic inflammation. These molecules act as a complex immunological network, in which there are pro-inflammatory cytokines, such as interleukin-1 (IL-1), IL-6 and tumor necrosis factor-a (TNF-a), and anti-inflammatory mediators like IL-10 and transforming growth factor-b. In spite of some controversial findings, in general high levels of pro-inflammatory cytokines have been correlated with signs and symptoms of temporomandibular disorders (TMD) such as internal derangement and osteoarthritis. These mediators promote degradation of cartilage and bone joint by inducing release of proteinases and other inflammatory molecules. Indeed, pro-inflammatory cytokines have been associated with temporomandibular joint (TMJ) tissue destruction. However, its mechanisms and pathophysiology have not been clearly delineated. In attempt to summarize the role of cytokines in TMD pathophysiology and its potential for medical intervention, the purpose of the current study was to review the literature concerning the analysis]. Campos MIG, Campos PSF, et.al. *Braz J Oral Sci. July-September 2006 - Vol. 5 - Number 18 http://www.fop.unicamp.br/brjorals/temp2/c18_Art1_inflammatory.pdf*
40. **Inter-relationships between rheumatoid arthritis and periodontal disease.** [This review considers the considerable similarities between periodontal disease and rheumatoid arthritis (RA). While the etiology of these two diseases may differ, the underlying pathogenic mechanisms are remarkably similar and it is possible that individuals manifesting both periodontitis and RA may suffer from a unifying underlying systemic dysregulation of the inflammatory response. In light of these findings, the implications for the use of disease-modifying medications in the management of these two chronic inflammatory conditions is apparent. Further longitudinal studies and medication-based intervention studies are required to determine just how closely these two conditions are allied.] Mercado FB, marshall RI, et al. *Clinical Periodontology*, Vol 30, Issue 9, pp 761-772. http://www3.interscience.wiley.com/journal/118839567/abstract
41. **Is there a relationship between rheumatoid arthritis and periodontal disease?** [Aim: The aim of this study was to determine whether there is a relationship between disease experience of rheumatoid arthritis and periodontal disease. Conclusions: Based on data derived from self-reported health conditions, and not withstanding the limitations of such a study, we conclude that there is good evidence to suggest that individuals with moderate to severe periodontal disease are at higher risk of suffering from rheumatoid arthritis and vice versa.] Mercado F, Marshall RI, et.al. *Journal of Clinical Periodontology Volume 27 Issue 4 Page 267 - April 2000.* http://www.blackwell-synergy.com/doi/abs/10.1034/j.1600-051x.2000.027004267.x?journalCode=cpe
42. **Peptidylarginine deiminase from Porphyromonas gingivalis citrullinates human fibrinogen and α-enolase: implications for autoimmunity in rheumatoid arthritis.** [OBJECTIVE: To investigate protein citrullination by the periodontal pathogen Porphyromonas gingivalis as a potential mechanism for breaking tolerance to citrullinated proteins in rheumatoid arthritis (RA). METHODS: The expression of endogenous citrullinated proteins was analyzed by immunoblotting of cell extracts from P gingivalis and 10 other oral bacteria. P gingivalis-knockout strains lacking the bacterial peptidylarginine deiminases (PADs) or gingipains were created to assess the role of these enzymes in citrullination. Citrullination of human fibrinogen and α-enolase by P gingivalis was studied by incubating live wild-type and knockout strains with the proteins and analyzing the products by immunoblotting and mass spectrometry. RESULTS: Endogenous protein citrullination was abundant in P gingivalis but lacking in the other oral bacteria. Deletion of the bacterial PAD gene resulted in complete abrogation of protein citrullination. Inactivation of arginine gingipains, but not lysine gingipains, led to decreased citrullination. Incubation of wild-type P gingivalis with fibrinogen or α-enolase caused degradation of the proteins and citrullination of the resulting peptides at carboxy-terminal arginine residues, which were identified by mass spectrometry. CONCLUSION: Our findings demonstrate that among the oral bacterial pathogens tested, P gingivalis is unique in its ability to citrullinate proteins. We further show that P gingivalis rapidly generates citrullinated host peptides by proteolytic cleavage at Arg-X peptide bonds by arginine gingipains, followed by citrullination of carboxy-terminal arginines by bacterial PAD. Our results suggest a novel model where P gingivalis-mediated citrullination of bacterial and host proteins provides a molecular mechanism for generating antigens that drive the autoimmune response in RA.] Wegner N, Wait R, et al. *Arthritis Rheum*. 2010 Sep;62(9):2662-72. doi: 10.1002/art.27552. http://www.ncbi.nlm.nih.gov/pubmed/20506214
43. **Periodontal condition in patients with rheumatoid arthritis.** [The purpose of this clinical study was to investigate if periodontal disease and rheumatoid arthritis (RA) are associated. The study included 39 RA patients (test group) and 22 age- and gender-matched healthy individuals (control group). Questionnaires on general and oral health were applied and a complete periodontal exam, including visible plaque, marginal bleeding, attachment loss (AL) and number of teeth present, was also performed by a single calibrated examiner. Diabetes *mellitus* patients and smokers were excluded. RA patients had fewer teeth, higher prevalence of sites presenting dental plaque and a higher frequency of sites with advanced attachment loss. Although the prevalence of dental plaque was higher in the test group (Chi-square test, $p = 0.0006$), the percentage of sites showing gingival bleeding was not different (Fishers exact test, $p > 0.05$). Based on our results, we suggest that there is an association between periodontal disease and RA.] Ishi ED, Bertolo MB, et al. *Braz. oral res. v.22 n.1 São Paulo ene./mar. 2008.* http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1806-83242008000100013&lng=es&nrm=iso&tlng=es http://www.scielo.br/pdf/bor/v22n1/a13v22n1.pdf
44. **Periodontal conditions in patients with juvenile idiopathic arthritis.** [Objective: Our aim was to compare the periodontal conditions in a group of juvenile idiopathic arthritis (JIA) patients with those in a control group of healthy subjects (CTR). Material and Methods: Thirty-two patients with JIA and 24 controls were selected. The measurements used to diagnose periodontal disease included plaque and bleeding scores, probing depths (PDs) and clinical attachment loss (CAL).

Laboratory indicators of JIA activity included the erythrocyte sedimentation rate (ESR) and capsule-reactive protein (CRP). The Mann–Whitney test was used to evaluate the data (α=0.05). Results: The mean ages were 15.9 (±2.7) years and 14.7 (±2.3) years for groups JIA and CTR, respectively. The median ESR was 42 mm/h in the JIA group and 13 mm/h in the CTR group (p=0.032) and the median CRP was 1.9 and 0.4 mg/l, respectively (p=0.001). The prevalence of patients with a proximal attachment loss of 2 mm or more in the JIA group was 25% and in controls it was 4.2%. The mean percentages of visible plaque and marginal bleeding were similar in the JIA (54±22 and 30±16, respectively) and CTR groups (44±18 and 29±11, respectively). The mean percentages of sites with PD⩾4 mm were significantly higher in the JIA group (3±4.7) than in the CTR group (0.4±1.7) (p=0.012). The mean percentages of sites with proximal CAL⩾2 mm were 0.7 (±1.4) in the JIA group and 0.001 (±0.2) in the CTR group (p=0.022). Conclusion: Adolescents with JIA present more periodontal attachment loss than healthy controls, in spite of similar plaque and marginal bleeding levels.] Miranda LA, Fischer RG, et al. Journal of Clinical Periodontology, *Volume 30 Issue 11*, *Pages 969 – 974*.
http://www3.interscience.wiley.com/journal/118839441/abstract

45. **Periodontal Disease and Rheumatoid Arthritis.** [Purpose of review This review was conducted to focus on the recent clinical and translational research related to the associations between periodontal disease and rheumatoid arthritis. Recent findings There is a growing interest in the associations between oral health and autoimmune and inflammatory diseases. A number of epidemiologic studies have described associations between rheumatoid arthritis and periodontal disease. Recent clinical studies continue to support these reports, and are increasingly linked with biological assessments to better understand the nature of these relationships. A number of recent studies have evaluated the periopathogenic roles of *Porphyromonas gingivalis*, the oral microbiome, and mechanisms of site-specific and substrate-specific citrullination. These are helping to further elucidate the interactions between these two inflammatory disease processes. Summary Studies of clinical oral health parameters, the gingival microenvironment, autoantibodies and biomarkers, and rheumatoid arthritis disease activity measures are providing a better understanding of the potential mechanisms responsible for rheumatoid arthritis and periodontal disease associations. The cumulative results and ongoing studies have the promise to identify novel mechanisms and interventional strategies to improve patient outcomes for both conditions.] Bingham III CO, Moni M. Curr Opin Rheumatol. 2013;25(3):345-353. http://www.ncbi.nlm.nih.gov/pubmed/23455329
46. **Periodontal Therapy Reduces the Severity of Active Rheumatoid Arthritis in Patients Treated With or Without Tumor Necrosis Factor Inhibitors** [Background: Rheumatoid arthritis (RA) and periodontitis are common chronic inflammatory conditions. Recent studies showed a beneficial effect of periodontal treatment on the severity of active RA. This study was undertaken to further examine the effect of non-surgical periodontal treatment on the signs and symptoms of RA in patients treated with or without anti-tumor necrosis factor-alpha (anti-TNF-α) medications. The effect of anti-TNF-α therapy on periodontitis also was assessed. Results: Patients receiving periodontal treatment showed a significant decrease in the mean DAS28, ESR (P <0.001), and serum TNF-α (P <0.05). There was no statistically significant decrease in these parameters in patients not receiving periodontal treatment. Anti-TNF-α therapy resulted in a significant improvement in CAL, PD, BOP, and GI. Conclusions: Non-surgical periodontal therapy had a beneficial effect on the signs and symptoms of RA, regardless of the medications used to treat this condition. Anti-TNF-α therapy without periodontal treatment had no significant effect on the periodontal condition.] Ortiz P, Bissada NF, et al. *Journal of Periodontology*, 2009, Vol. 80, No. 4, Pages 535-540.
http://www.joponline.org/doi/abs/10.1902/jop.2009.080447?prevSearch=allfield%3A%28bissada%29&searchHistoryKey=
47. **Periodontal disease and the oral microbiota in new-onset rheumatoid arthritis**. [OBJECTIVE.: To profile the subgingival oral microbiota abundance and diversity in never-treated, new-onset rheumatoid arthritis (NORA) patients. METHODS.: Periodontal disease (PD) status, clinical activity and sociodemographic factors were determined in patients with NORA, chronic RA (CRA) and healthy subjects. Massively parallel pyrosequencing was used to compare the composition of subgingival microbiota and establish correlations between presence/abundance of bacteria and disease phenotypes. Anti-P. gingivalis antibodies were tested to assess prior exposure. RESULTS.: The more advanced forms of periodontitis are already present at disease onset in NORA patients. The subgingival microbiota of NORA is distinct from controls. In most cases, however, these differences can be attributed to PD severity and are not inherent to RA. The presence and abundance of P. gingivalis is directly associated with PD severity as well, is not unique to RA, and does not correlate with anti-citrullinated peptide antibody (ACPA) titers. Overall exposure to P. gingivalis is similar in RA and controls, observed in 78.4% and 83.3%, respectively. Anaeroglobus geminatus correlated with ACPA/RF presence. Prevotella and Leptotrichia species are the only characteristic taxa in the NORA group irrespective of PD status. CONCLUSIONS.: NORA patients exhibit a high prevalence of PD at disease onset, despite their young age and paucity of smoking history. The subgingival microbiota of NORA patients is similar to CRA and healthy subjects of comparable PD severity. Although colonization with P. gingivalis correlates with PD severity, overall exposure is similar among groups. The role of A. geminatus and Prevotella/Leptotrichia species in this process merits further study.] Scher JU, Ubeda C, et al. *Arthritis Rheum*. 2012 May 10. doi: 10.1002/art.34539.
http://www.ncbi.nlm.nih.gov/pubmed/22576262
48. **Periodontal Treatment Decreases Levels of Antibodies to *Porphyromonas Gingivalis* and Citrulline in Patients With Rheumatoid Arthritis and Periodontitis**. [Background: *Porphyromonas gingivalis* has been implicated as an etiological agent of rheumatoid arthritis (RA) due to the expression of peptidylarginine deiminase. The present study was undertaken to evaluate whether periodontal treatment may affect serum antibodies to *P. gingivalis* and citrulline levels in relation to disease activity of RA. Methods: Fifty-five patients with RA were randomly assigned to receive oral hygiene instruction and supragingival scaling (treatment group, n = 26) or no periodontal treatment (control group, n = 29). Periodontal and

rheumatologic parameters and serum levels of cytokine and inflammatory markers, citrulline and immunoglobulin G (IgG) to *P. gingivalis* were examined at baseline and 8 weeks later. Results: Both groups did not differ statistically in all parameters except for % sites with probing depth and clinical attachment level ≥ 4 mm at baseline. The treatment group exhibited a significantly greater decrease in disease activity score including 28 joints using C-reactive protein (DAS28-CRP) ($P = 0.02$), serum levels of IgG to *P. gingivalis*hemin binding protein 35 (HBP35) ($P = 0.04$) and citrulline ($P = 0.02$) than the control group. Serum levels of IgG to *P. gingivalis* HBP35 were significantly correlated positively with those of anti-CCP antibodies ($P = 0.0002$). The same correlation was obtained between serum levels of IgG to *P. gingivalis* sonicated extracts and those of rheumatoid factor ($P = 0.02$). Conclusions: These results suggest that supragingival scaling decreases DAS28-CRP and serum levels of IgG to *P. gingivalis* HBP35 and citrulline in RA patients. These observations may reflect a role of *P. gingivalis* in the protein citrullination, which is related to the pathogenesis of RA.] Okada M, Kobayashi T, et al. *J Perio*, May 23, 2013 (doi:10.1902/jop.2013.130079). http://www.joponline.org/doi/abs/10.1902/jop.2013.130079

49. **Periodontitis and Rheumatoid Arthritis: Epidemiologic, Clinical, and Immunologic Associations. [**PURPOSE: Rheumatoid arthritis (RA) is a prevalent autoimmune-mediated, chronic inflammatory disorder that has been found in multiple epidemiologic studies to be associated with periodontal disease (PD). Despite the extensive epidemiologic evidence, the biologic basis of this association remains unclear. This article focuses on new insights into the potential mechanisms underlying the association between PD and RA. RECENT FINDINGS: Chronic periodontal and synovial inflammation share many common pathologic, cellular, and molecular features. In particular, the mechanisms involved in the destruction of the adjacent connective tissues are quite similar. Recent studies have shown anti-citrullinated protein antibodies (ACPA) that are highly specific for RA are detectable years before disease development. Emerging evidence suggests the oral pathogen porphymonas gingivalis may serve to break immune tolerance or amplify autoimmune responses to citrullinated antigens and, in turn, ultimately initiate RA in genetically susceptible persons. SUMMARY: Recognition of the association between RA and PD on both a clinical and biologic level may provide new opportunities for intervention that will modify the course of both of these prevalent chronic inflammatory disorders. Furthermore, an enhanced understanding of the early events that initiate RA may result in strategies that prevent disease-onset.] Smolik I, Robinson D, et al. *Compendium of Continuing Education*, May, 2009, 30(4):188-197. http://cde.dentalaegis.com/courses/16
50. ***Porphyromonas gingivalis* and the pathogenesis of rheumatoid arthritis: analysis of various compartments including the synovial tissue.** [Introduction We evaluated the presence of *Porphyromonas gingivalis* (Pg) DNA in the synovial tissue through synovial biopsy and in other compartments of rheumatoid arthritis (RA) patients in comparison with patients affected by other arthritides. Possible links with clinical, immunologic and genetic features were assessed. Methods Peripheral blood (PB), sub-gingival dental plaque, synovial fluid (SF) and synovial tissue samples were collected from 69 patients with active knee arthritis (32 with RA and 37 with other arthritides, of which 14 had undifferentiated peripheral inflammatory arthritis - UPIA). Demographic, clinical, laboratory and immunological data were recorded. The presence of Pg DNA was evaluated through PCR. The HLA-DR haplotype was assessed for 45 patients with RA and UPIA. Results No differences arose in the positivity for Pg DNA in the sub-gingival plaque, PB and SF samples between RA and the cohort of other arthritides. Full PB samples showed a higher positivity for Pg DNA than plasma samples (11.8% vs. 1.5%, $P = 0.04$). Patients with RA showed a higher positivity for Pg DNA in the synovial tissue compared to controls (33.3% vs. 5.9%, $P < 0.01$). UPIA and RA patients carrying the HLA DRB1*04 allele showed a higher positivity for Pg DNA in the synovial tissue compared to patients negative for the allele (57.1% vs. 16.7%, $P = 0.04$). RA patients positive for Pg DNA in the sub-gingival plaque had a lower disease duration and a higher peripheral blood leucocyte and neutrophil count. The presence of Pg DNA did not influence disease activity, disease disability or positivity for autoantibodies. Conclusions The presence of Pg DNA in the synovial tissue of RA patients suggests a pathogenic role of the bacterium. The higher positivity of Pg DNA in full peripheral blood and synovial tissue samples compared to plasma and synovial fluid suggests a possible intracellular localization of Pg, in particular in patients positive for HLA-DR4.] Totaro MC, Cattani P, et al. *Arthritis Research & Therapy* 2013, 15**:**R66, http://arthritis-research.com/content/15/3/R66
51. **Porphyromonas gingivalis may play an important role in the pathogenesis of periodontitis-associated rheumatoid arthritis. [**Rheumatoid arthritis (RA) is a common, systemic autoimmune disease which leads to destruction of the joint architecture and consequent disability. Although the aetiology of RA remains unknown, accumulating studies have established a strong association between RA and periodontitis (PD). Recently, anti-cyclic citrullinated peptide (anti-CCP) autoantibody and citrullinated peptide have been realized to be involved in the breaking of self-tolerance and development of autoimmune in RA. The citrullinated peptide is generated by post-translational modification (citrullination) of protein-bound arginine by peptidylarginine deiminase (PAD). Porphyromonas gingivalis(P. gingivalis), the major aetiological agent of PD and the only bacterium known to express a PAD enzyme, has been reported to be significantly associated with RA. The antibody titers to P. gingivalis are significantly increased in patients with RA and P. gingivalis antibody titers are significantly correlated with anti-CCP antibody isotypes that are specific to RA. Recent study indicates that the major synovial targets of the RA-specific anti-CCP autoantibodies are deiminated forms of the alpha- and beta- chains of fibrin. Meanwhile, it is also confirmed that bacterial PAD produced by P. gingivalis has the capacity of deiminating arginine in fibrin found in the periodontal lesion. What's more, it has been demonstrated that citrullination of HLA binding peptide causes a 100-fold increase in peptide-MHC affinity and leads to the activation CD4(+)T cells in HLA DRB1 0401 transgenic mice. Therefore, we postulate that P. gingivalis may play a crucial role in the pathogenesis of periodontitis-associated RA. P. gingivalis, which colonizes in the oral cavity, produces PAD enzyme continuously that leads to the citrullination of RA autoantigen such as fibrin in synovium joint. These PAD engendered antigens, presented in association with major

histocompatibility complex (MHC) molecules by antigen-presenting cells (APC), ultimately lead to production of the anti-CCP antibody. The anti-CCP antibodies form immune complexes with citrullinated proteins, which can be bound by inflammatory cells via their Fc receptors. The roles of these immune complexes and inflammatory cells are mediated by a complex cascade involving complement activation. These mechanisms result in a release of mediators of inflammation and joint destruction ultimately leading to the onset of RA. This hypothesis reveals that oral bacterial infection may play a role in peptide citrullination which might be involved in loss of self-tolerance and development of autoimmune in RA.] Liao F, Li Z, et al. *Med Hypotheses.* 2009 Jun;72(6):732-5. Epub 2009 Feb 25. http://www.ncbi.nlm.nih.gov/pubmed/19246161

52. **Relationship Between Rheumatoid Arthritis and Periodontitis.** [Background: Because of several similar features in the pathobiology of periodontitis and rheumatoid arthritis, in a previous study we proposed a possible relationship between the two diseases. Therefore, the aims of this study were to study a population of rheumatoid arthritis patients and determine the extent of their periodontal disease and correlate this with various indicators of rheumatoid arthritis. Methods: Sixty-five consecutive patients attending a rheumatology clinic were examined for their levels of periodontitis and rheumatoid arthritis. A control group consisted of age- and gender- matched individuals without rheumatoid arthritis. Specific measures for periodontitis included probing depths, attachment loss, bleeding scores, plaque scores, and radiographic bone loss scores. Measures of rheumatoid arthritis included tender joint analysis, swollen joint analysis, pain index, physician's global assessment on a visual analogue scale, health assessment questionnaire, levels of C-reactive protein, and erythrocyte sedimentation rate. The relationship between periodontal bone loss and rheumatological findings as well as the relationship between bone loss in the rheumatoid arthritis and control groups were analyzed. Results: No differences were noted for the plaque and bleeding indices between the control and rheumatoid arthritis groups. The rheumatoid arthritis group did, however, have more missing teeth than the control group and a higher percentage of these subjects had deeper pocketing. When the percentage of bone loss was compared with various indicators of rheumatoid arthritis disease activity, it was found that swollen joints, health assessment questionnaire scores, levels of C-reactive protein, and erythrocyte sedimentation rate were the principal parameters which could be associated with periodontal bone loss. Conclusions: The results of this study provide further evidence of a significant association between periodontitis and rheumatoid arthritis. This association may be a reflection of a common underlying disregulation of the inflammatory response in these individuals.] Mercado B, Marshall RI, et al. *J Periodontol 2001;72:779-787.* http://www.joponline.org/doi/abs/10.1902/jop.2001.72.6.779
53. **Rheumatoid arthritis and periodontal disease**. [The prevalence of periodontal disease has increased two-fold among patients with rheumatoid arthritis (RA) compared to the general population. This increased prevalence is unrelated to secondary Sjögren's syndrome but instead reflects shared pathogenic mechanisms, including an increased prevalence of the shared epitope HLA-DRB1-04; exacerbated T-cell responsiveness with high tissue levels of IL-17; exaggerated B-cell responses, with plasma cells being the predominant cell type found within gingival tissue affected with periodontitis and B cells being twice as numerous as T cells; RANK overexpression; and an increase in the ratio of RANK-L over osteoprotegerin with a high level of RANK-L expression on gingival B cells, most notably those capable of recognizing *Porphyromonas gingivalis*. Other factors conducive to periodontitis include smoking and infection with the Epstein-Barr virus or cytomegalovirus, which act by promoting the growth of organisms such as *P. gingivalis*, whose DNA is often found in synovial tissue from RA patients. *P. gingivalis* produces the enzyme peptidylarginine deiminase that induces citrullination of various autoantigens, and levels of anti-CCP antibodies are considerably higher in RA patients with than without periodontal disease, suggesting that periodontitis may contribute to the pathogenesis of RA. Further support for this hypothesis comes from evidence that other antigens involved in RA, such as HC-gp39, are also present in gingival tissue. TNFα antagonists slow alveolar resorption but may perpetuate infection of periodontal pockets. Therefore, rheumatology patients, including those taking biotherapies, are likely to benefit from increased referral to dental care (e.g., scaling, root planing and, if needed, dental surgery), particularly as periodontitis is also associated with an increased risk of premature atheroma.] Berthelot JM, Le Goff B. *Joint Bone Spine*, Volume 77, Issue 6, December 2010, Pages 537-541. http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6W90-50BKNDF-1&_user=10&_coverDate=12%2F31%2F2010&_rdoc=13&_fmt=high&_orig=browse&_origin=browse&_zone=rslt_list_item&_srch=doc-info(%23toc%236668%232010%23999229993%232759744%23FLA%23display%23Volume)&_cdi=6668&_sort=d&_docanchor=&_ct=41&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=a135eb1bf1e8ca2722b6d2fd7934ecac&searchtype=a
54. **Rheumatoid arthritis and the role of oral bacteria**. [Rheumatoid arthritis (RA) and periodontal disease (PD) have shown similar physiopathologic mechanisms such as chronic inflammation with adjacent bone resorption in an immunogenetically susceptible host; however, PD has a well-recognized bacterial etiology while the cause of RA is unclear. Some reports have indicated that an infectious agent in a susceptible host could be one possible trigger factor for RA, and it has been suggested that oral microorganisms, specialty periodontal bacteria could be the infectious agent (mainly *Porphyromonas gingivalis*). It has been reported that PD is more frequent and more severe in patients with RA, suggesting a positive association between both diseases. There have been reports regarding the detection of antibodies against periodontal bacteria while other studies have identified periodontal bacterial DNA in serum and synovial fluid of RA patients and have explored the possible pathways of transport of periodontal bacterial DNA. In conclusion, there is no question that RA and PD have pathologic features in common and there is strong evidence of an association between both diseases, but further studies, including experimental models, are needed to demonstrate the arthritogenicity of oral microorganisms.] Loyala-Rodriquez JP,

Martinez-Martinez RE, et al. J Oral Microbiol. 2010; 2: 10.3402/jom.v2i0.5784. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3084578/

55. **Rheumatoid arthritis is an autoimmune disease caused by periodontal pathogens**. [A statistically significant association between periodontal disease (PD) and systemic diseases has been identified. Rheumatoid arthritis (RA), which is a chronic inflammatory joint disease, exhibits similar characteristics and pathogenesis to PD. The association between RA and PD has been investigated, and numerous publications on this subject exist. Approximately 20 bacterial species have been identified as periodontal pathogens, and these organisms are linked to various types of PD. The most analyzed species of periodontopathic bacteria are *Porphyromonas gingivalis*, *Prevotella intermedia*, *Tannerella forsythia*, and *Aggregatibacter actinomycetemcomitans*. Antibodies and DNA from these oral pathogens have been isolated from the sera and synovial fluids of RA patients. This rapid communication describes the role of periodontal pathogens in the etiopathogenesis of RA.] Ogrendik M. *Int J Gen Med*, 2013; 6:383-386. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3668087/
56. **Rheumatoid arthritis is linked to oral bacteria: etiological association. [**The purpose of this review is to evaluate the association between rheumatoid arthritis (RA) and periodontopathic bacteria. Clinical studies of RA and periodontal disease have provided evidence for a significant association between the two disorders. Patients with long-standing active RA have a substantially increased frequency of periodontal disease compared with that among healthy subjects. High levels of oral anaerobic bacterial antibodies have been found in the serum and synovial fluid of RA patients. Porphyromonas gingivalis, Tannerella forsythensis, and Prevotella intermedia have been identified in RA synovial fluid. Ornidazole, levofloxacin, and clarithromycin are used in the treatment of infections caused by anaerobic bacteria. These antibiotics have been shown to be effective against RA. The evidence in this review indicates that oral bacteria directly associate with etiopathogenesis of RA.] Ogrendik M. *Mod Rheumatol.* 2009;19(5):453-6. http://www.ncbi.nlm.nih.gov/pubmed/19554393
57. **Rheumatoid arthritis, periodontal disease and coronary artery disease.** [Rheumatoid arthritis (RA), periodontal disease (PD), and coronary artery disease (CAD) are common chronic inflammatory diseases. RA is associated with accelerated vascular risk resulting in an increased prevalence of CAD with attendant early mortality and excess morbidity. RA and PD have a common pathobiology. Accordingly, the aim of this study was to evaluate the association between RA, PD, and CAD and the influence of systemic inflammatory factors. A total of 100 active RA patients of which 50 had established CAD and 50 had no CAD were assessed for PD. All subjects underwent a clinical, cardiac, dental, laboratory, and radiological evaluation. Blood samples were obtained, and the level of high sensitivity C-reactive protein (hs-CRP), total white blood counts (WBC), erythrocyte sedimentation rate (ESR), fibrinogen and tumor necrosis factor (TNF) alpha, total cholesterol (TC), and high density lipoprotein (HDL) were assayed. The findings of this study demonstrated an association between RA, PD, and CAD. The RA patients with CAD had significantly more PD than RA patients without CAD. The inflammatory markers, hsCRP, ESR, WBC, fibrinogen, and TNF-alpha, were raised in all patients but were significantly higher in RA patients with CAD who also had PD. HDL levels were lower in RA patients with CAD when compared to RA patients without CAD. Evidence from this study shows an association between RA, PD, CAD, and systemic levels of the inflammatory mediators. The implication is that inflammation may be the central link between the chronic inflammatory, autoimmune disorders, and atherosclerosis.] Abou-Raya S, Abou-Raya A, et al. *Clin Rheumatol*. 2008 Apr;27(4):421-7. Epub 2007 Aug 29. http://www.ncbi.nlm.nih.gov/pubmed/17763921
58. **Risk for periodontal disease in patients with longstanding rheumatoid arthritis.** [Objective. To quantify periodontal disease in rheumatoid arthritis (RA) patients and controls, and to correlate the degree of destruction from periodontal disease and from RA. Methods. Fifty RA patients were matched for age, sex, smoking status, and oral hygiene with 101 controls. Correlations between indices of chronic destruction in periodontal disease (gingival attachment loss) and in RA (Larsen radiographic score) were determined. Results. Patients with longstanding active RA (mean ± SD 13 ± 8 years) who were receiving treatment with disease-modifying antirheumatic drugs (n = 46), corticosteroids (n = 38), or nonsteroidal antiinflammatory drugs (n = 43) had a higher rate of gingival bleeding (increased by 50%), greater probing depth (increased by 26%), greater attachment loss (increased by 173%), and higher number of missing teeth (increased by 29%) compared with controls. No correlation was found between the Larsen radiographic score and gingival attachment. Conclusion. Patients with longstanding active RA have a substantially increased frequency of periodontal disease, including loss of teeth, compared with controls. Antiinflammatory treatment interferes with periodontal disease and might have masked a possible correlation between the indices of chronic destruction in RA and periodontal disease.] Kasser UR, Gleissner C, et al. Arthritis and Rheumatism, 1997, vol. 40, n°12, pp. 2248-2251. http://cat.inist.fr/?aModele=afficheN&cpsidt=2089082 http://www3.interscience.wiley.com/journal/112212854/abstract
59. **Soluble tumour necrosis factor receptors in synovial fluids from temporomandibular joints with painful anterior disc displacement without reduction and osteoarthritis.** [The objective of this study was to detect soluble-form tumour necrosis factor receptors (sTNFRs) in temporomandibular joint (TMJ) synovial fluid aspirates, and to compare the sTNFR concentrations between painful anterior disc displacement without reduction and osteoarthritis (ADDwoR/OA) and asymptomatic TMJs. Synovial fluid was sampled from the superior TMJ cavity of 11 painful ADDwoR/OA cases (mean age: 36.9 years) and 10 asymptomatic females (mean age: 24.7 years) by diluted aspiration. The concentrations of sTNFR-I and -II in the synovial fluid were measured using human sTNFR-I and -II enzyme-linked immunosorbent assays. The total protein concentrations in synovial fluids were measured using a bicinchoninic acid protein assay kit. All data were normalised to the total protein concentration of each sample. Two-way factorial analysis of variance and post hoc multiple comparison revealed that: (1) mean normalised sTNFR-I and -II concentrations were higher in TMJ synovial aspirates from ADDwoR/OA patients than from healthy controls; (2) in the ADDwoR/OA patients and the healthy controls, the sTNFR-I

concentration in TMJ synovial aspirates was higher than the sTNFR-II concentration; and (3) high TMJ synovial aspirate sTNFR-II seemed to be associated with less TMJ pain and a less restricted range of mouth opening in the ADDwoR/OA patients. The concentrations of sTNFRs in TMJ synovial fluid are higher in the presence of painful ADDwoR/OA, which could modulate intracapsular inflammation.] Uehara J, Kuboki T, et.al. *Arch of Oral biology vol 49, Issue 2, P 133-142.* http://www.aobjournal.com/article/PIIS0003996903002036/abstract

60. **The association between rheumatoid arthritis and periodontal disease. [**Chronic, plaque-associated inflammation of the gingiva and the periodontium are among the most common oral diseases. Periodontitis (PD) is characterized by the inflammatory destruction of the periodontal attachment and alveolar bone, and its clinical appearance can be influenced by congenital as well as acquired factors. The existence of a rheumatic or other inflammatory systemic disease may promote PD in both its emergence and progress. However, there is evidence that PD maintains systemic diseases. Nevertheless, many mechanisms in the pathogenesis have not yet been examined sufficiently, so that a final explanatory model is still under discussion, and we hereby present arguments in favor of this. In this review, we also discuss in detail the fact that oral bacterial infections and inflammation seem to be linked directly to the etiopathogenesis of rheumatoid arthritis (RA). There are findings that support the hypothesis that oral infections play a role in RA pathogenesis. Of special importance are the impact of periodontal pathogens, such as Porphyromonas gingivalis on citrullination, and the association of PD in RA patients with seropositivity toward rheumatoid factor and the anti-cyclic citrullinated peptide antibody.] Detert J, Pischon N, et al. *Arthritis Res Ther*. 2010;12(5):218. http://www.ncbi.nlm.nih.gov/pubmed/21062513
61. **The role of risk factors for periodontal disease in patients with rheumatoid arthritis.** [There are conflicting reports whether patients with rheumatoid arthritis (RA) are at a higher risk for periodontal disease (PD). Analogous mechanisms of tissue destruction have been reported for both diseases. This cross-sectional study should quantify PD in patients with longstanding RA and examine a possible association between the two diseases. It should also be investigated whether PD in RA patients could be the result of reduced functional capacity or be amplified by concomitant medical treatment. 50 RA patients were matched for age, sex, smoking and oral hygiene with 101 healthy controls. Data on the medication over the last three years was obtained by questionnaire. Among the rheumatological parameters recorded were a 28-joint-count, C-reactive protein (CRP), grip strength testing, upper extremity function (Keitel Index) and the Larsen-score of radiological joint destruction. The oral examination included the recording of individual oral hygiene measures and sicca symptoms, a modified Approximal Plaque- and Sulcus-Bleeding-Index (SBI), probing depths and clinical attachment loss and the Community Periodontal Index of Treatment Needs. The mean duration of RA was 13 (+/- 7.9) years. RA patients under treatment with disease modifying antirheumatic drugs (DMARDs, n = 46; 92%), corticosteroids (n = 38; 76%) and non steroidal antirheumatic drugs (NSAIDs, n = 43; 86%) had a higher rate of gingival bleeding (+ 50%), probing depth (+ 26%), clinical attachment loss (+ 173%) and number of missing teeth (+ 29%) compared with controls. While no correlation between the rheumatological variables (radiological destruction, functional capacity, grip strength) and the periodontal measurements (SBI, probing depth, clinical attachment loss) could be demonstrated, a positive correlation was observed between the CRP and the periodontal attachment loss ($r = 0.32$; $p < 0.05$). In spite of a strong correlation between the duration of DMARD- and cortisone-medication and the Larsen-score ($r = 0.48$ and 0.64; $p = 0.0005$ and 0.0001, rsp.), no correlation between the duration of pharmacotherapy and the periodontal parameters could be established. Patients with long-term active RA present a substantially higher degree of PD including loss of teeth compared with controls. Functional impairment of the upper extremity might amplify present PD. The longterm use of NSAIDs, corticosteroids and DMARDs shows no connection with the severe PD observed in these patients. Oral hygiene amplifies PD severity and treatment need. Intensive prophylactic measures are required to prevent or reduce the damage of the periodontal tissues in RA patients.] Gleissner C, Willershausen B, et al. Eur J Med Res. 1998 Aug 18;3(8):387-92. http://www.ncbi.nlm.nih.gov/pubmed/9707521

Brain and Neurological Disorders

62. **Cerebellar Brain Abscess Associated with Tongue Piercing.** [We describe a previously healthy adult who had a solitary cerebellar brain abscess diagnosed. This infection occurred 4 weeks after the patient underwent a tongue piercing procedure that was complicated by an apparent local infection. The clinical history, abscess culture results, and lack of an alternative explanation suggest that infection of the tongue piercing site was the source of the cerebellar abscess.] Martinello RA, Cooney EL. *Clinical Infectious Diseases*, 2003;36:e32-4. http://www.journals.uchicago.edu/doi/pdf/10.1086/345755
63. **Detection of a mixed infection in a culture-negative brain abscess by broad-spectrum bacterial 16S rRNA gene PCR. [**We describe the identification of two bacterial pathogens from a culture-negative brain abscess by the use of broad-spectrum 16S rRNA gene PCR. Simultaneous detection of Fusobacterium nucleatum and Porphyromonas endodontalis was possible due to a 24-bp length difference of their partially amplified 16S rRNA genes, which allowed separation by high-resolution polyacrylamide gel electrophoresis.] Keller PM, Rampini SK, et al. *J Clin Microbiol*. 2010 Jun;48(6):2250-2. Epub 2010 Apr 14. http://www.ncbi.nlm.nih.gov/pubmed/20392909
64. **Multiple Brain Abscesses Associated With Tongue Piercing.** [A previously healthy 22-year-old man was referred to our institution by another hospital because of high fever, drowsiness, and multiple ring-enhancing lesions on brain computed tomography (CT). Medical history was unremarkable, except for a tongue piercing the patient had gotten 2 weeks earlier. On hospital admission, global aphasia and right hemiplegia were found. His temperature was 39°C, and his white blood cell count showed leukocytosis with a left shift. The patient was given empirical antibiotic treatment. Magnetic resonance imaging of the brain revealed 13 ring enhancement lesions with surrounding edema, with focal bleeding in some of them (Figure).

Results of an extensive clinical and laboratory workup, including abdominal CT, transesophageal echocardiography, immunoelectrophoresis, complement levels, antinuclear antibody test, human immunodeficiency virus test, and sweat test for cystic fibrosis, were negative.] Herskovitz MY, Goldsher D, et al. *Archives of Neurology*, Vol. 66. No. 10, Oct 2009. http://archneur.ama-assn.org/cgi/content/extract/66/10/1292 http://rdouglasfields.wordpress.com/2010/05/03/festering-brain-infection-piercing-the-illusion-of-safety/

65. **Multiple brain abscesses caused by Fusobacterium nucleatum treated conservatively.** [BACKGROUND: Multiple brain abscesses are serious neurological problems with high mortality and disabling morbidity. The frequency is rising as a result of AIDS and the increasing number of immunocompromised patients. CASE STUDY: A 59-year-old woman developed signs and symptoms of diffuse brain dysfunction including fever and neck stiffness. A brain CT scan demonstrated nine contrast-enhancing ring-shaped lesions. Analysis of the cerebrospinal fluid using PCR-technique revealed DNA of Fusobacterium nucleatum. Conservative treatment with antibiotics was successful. The patient recovered with only mild cognitive deficits. RESULTS: The experience of our patient and the review of the literature indicate that multiple brain abscesses due to Fusobacterium nucleatum are rare. The most probable source is oral infection. CONCLUSION: Multiple brain abscesses may be caused by Fusobacterium nucleatum. Cerebrospinal fluid analysis using PCR technique is helpful with diagnosis. Conservative management can be successful.] Heckmann JG, Lang CJ, et al. *Can J Neurol Sci.* 2003 Aug;30(3):266-8. http://www.ncbi.nlm.nih.gov/pubmed/12945954
66. **Oral bacterial cultures in nontraumatic brain abscesses: results of a first-line study.** [OBJECTIVE: Bacterial cultures from nontraumatic brain abscesses (BAs) frequently contain oral bacteria. We assessed bacterial cultures from BAs and oral infective sources for a bacterial match. STUDY DESIGN: Bacterial samples from brain abscesses and oral abscesses, and at sites with probing depths >or=3.5 mm were taken from 11 nontraumatic BA patients and analyzed. RESULTS: Brain abscess bacterial cultures were obtained in 9 of the 11 cases, which revealed 5 cases of Streptococcus milleri group bacteria and 4 cases of subgingival flora. The bacteriologic results were interpreted taking all medical and bacteriologic findings into account, which made an oral origin of the BAs most likely in 6 of the 11 cases: from an oral abscess and from the subgingival flora in 3 cases each. CONCLUSIONS: Early collaboration between neurosurgeons, infectious disease specialists, and oral-maxillofacial surgeons will aid the identification and treatment of suspected oral sources of nontraumatic BAs.] Mueller AA, Saldamli B, et al. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2009 Apr;107(4):469-76. http://www.ncbi.nlm.nih.gov/pubmed/19121959

Alzheimer's Disease and Inflammation

67. **A Serum Protein–Based Algorithm for the Detection of Alzheimer Disease. [**Objective To develop an algorithm that separates patients with Alzheimer disease (AD) from controls. Design Longitudinal case-control study. Setting The Texas Alzheimer's Research Consortium project. Patients We analyzed serum protein–based multiplex biomarker data from 197 patients diagnosed with AD and 203 controls. Main Outcome Measure The total sample was randomized equally into training and test sets and random forest methods were applied to the training set to create a biomarker risk score. Results The biomarker risk score had a sensitivity and specificity of 0.80 and 0.91, respectively, and an area under the curve of 0.91 in detecting AD. When age, sex, education, and *APOE* status were added to the algorithm, the sensitivity, specificity, and area under the curve were 0.94, 0.84, and 0.95, respectively. Conclusions These initial data suggest that serum protein-based biomarkers can be combined with clinical information to accurately classify AD. A disproportionate number of inflammatory and vascular markers were weighted most heavily in the analyses. Additionally, these markers consistently distinguished cases from controls in significant analysis of microarray, logistic regression, and Wilcoxon analyses, suggesting the existence of an inflammatory-related endophenotype of AD that may provide targeted therapeutic opportunities for this subset of patients.] O'Bryant SE, Xiao G, et al. *Arch Neurol.* 2010;67(9):1077-1081. doi:10.1001/archneurol.2010.215. http://archneur.ama-assn.org/cgi/content/short/67/9/1077
68. **Alzheimer's disease - a neurospirochetosis. Analysis of the evidence following Koch's and Hill's criteria.** [It is established that chronic spirochetal infection can cause slowly progressive dementia, brain atrophy and amyloid deposition in late neurosyphilis. Recently it has been suggested that various types of spirochetes, in an analogous way to Treponema pallidum, could cause dementia and may be involved in the pathogenesis of Alzheimer's disease (AD). Here, we review all data available in the literature on the detection of spirochetes in AD and critically analyze the association and causal relationship between spirochetes and AD following established criteria of Koch and Hill. The results show a statistically significant association between spirochetes and AD (P = 1.5 x 10-17, OR = 20, 95% CI = 8-60, N = 247). When neutral techniques recognizing all types of spirochetes were used, or the highly prevalent periodontal pathogen Treponemas were analyzed, spirochetes were observed in the brain in more than 90% of AD cases. Borrelia burgdorferi was detected in the brain in 25.3% of AD cases analyzed and was 13 times more frequent in AD compared to controls. Periodontal pathogen Treponemas (T. pectinovorum, T. amylovorum, T. lecithinolyticum, T. maltophilum, T. medium, T. socranskii) and Borrelia burgdorferi were detected using species specific PCR and antibodies. Importantly, co-infection with several spirochetes occurs in AD. The pathological and biological hallmarks of AD were reproduced in vitro. The analysis of reviewed data following Koch's and Hill's postulates shows a probable causal relationship between neurospirochetosis and AD. Persisting inflammation and amyloid deposition initiated and sustained by chronic spirochetal infection form together with the various hypotheses suggested to play a role in the pathogenesis of AD a comprehensive entity. As suggested by Hill, once the

probability of a causal relationship is established prompt action is needed. Support and attention should be given to this field of AD research. Spirochetal infection occurs years or decades before the manifestation of dementia. As adequate antibiotic and anti-inflammatory therapies are available, as in syphilis, one might prevent and eradicate dementia.] Miklossy J. *Journal of Neuroinflammation* 2011, 8:90. http://www.jneuroinflammation.com/content/8/1/90/abstract http://www.jneuroinflammation.com/content/pdf/1742-2094-8-90.pdf

69. **Alzheimer's Disease and Periodontal Disease: The Inflammatory Link. [**This study is designed to obtain data exploring the role of periodontal disease in the pathogenesis of Alzheimer's disease. PD is a chronic infection resulting from the interaction of periodontopathic bacteria and a host response. This interaction leads to localized and systemic inflammation characterized by elevation of inflammatory molecules such as IL-1ß, IL-6, IL8, TNF-A, CRP; and high antibodies levels. PD through bacteria and/or inflammatory molecules may contribute to already elevated brain inflammatory molecules, therefore increasing risk of AD. We hypothesize that subjects with periodontal infections will be at an increased risk of developing AD. Objectives: We will determine whether a greater proportion of subjects developing AD had elevated levels of antibody titers to Aa, Pg, Td and Tf (markers of periodontopathic bacteria) and of systemic inflammatory markers (IL-1ß, Il-6, TNF-A, CRP and others) at baseline as compared control subjects. Methods: Stored plasma samples collected at baseline evaluation at the NYU ADCC and the affiliated CBH from cohorts of subjects are used in a nested case-control. Cases (AD) and Controls (NL, MCI) will be compared for the existence of exposures at baseline (antibodies to Aa, Pg, Td, Tf, CRP and cytokines). In this project we characterized the study population using several parameters, such as age, gender and race. Results: Since cytokine levels may differ based on the year of collection we characterized our study population by year. Our results showed that in 1998, 1999, 2000 and 2001 age was statistically greater in AD subjects compared to controls. In 1997 and 2004 age difference approached statistical significance. In contrast there was no significant difference in gender and race among groups. Conclusion: Our results showed that AD subjects are older than controls subjects suggesting that this parameter has to be considered in the final study analysis.] Akhtar S, Kamer AR. IADR General Session, Miami, FL April 2009. http://iadr.confex.com/iadr/2009miami/webprogram/Paper119192.html
70. **Association between cognitive function and periodontal disease in older adults.** [OBJECTIVES: To assess the association between cognitive function and periodontal disease in noninstitutionalized older adults. DESIGN: Population-based cross-sectional study. SETTING: National Health and Nutrition Examination Survey 2001 to 2002. PARTICIPANTS: Eight hundred three dentate participants aged 60 and older who completed the periodontal examination and cognitive function test. MEASUREMENTS: Periodontal examination, including assessment of probing depth and attachment loss, was performed. Periodontal disease was defined as at least 10% of sites with clinical attachment loss of more than 4 mm and at least 10% sites with probing depth greater than 3 mm. Cognitive function was measured using the 2-minute Digit Symbol Substitution Test (DSST). RESULTS: Higher cognitive function was associated with lower odds of periodontal disease. After controlling for demographics, educational level, body mass index, chronic diseases, health behaviors, bleeding on probing, and probing sites, the odds ratio for periodontal disease was 0.69 (95% confidence interval=0.51-0.94) for each standard deviation (SD) increase in the DSST score. Each SD increase in DSST score was associated with a 31% less likelihood of periodontal disease. Mean DSST scores for participants with and without periodontal disease were 42.2 and 45.5 (P=.02), respectively. CONCLUSION: Higher cognitive function was associated with lower odds of periodontal disease in noninstitutionalized older adults.] Yu YH, Kuo HK. *J Am Geriatr Soc*. 2008 Sep;56(9):1693-7 http://www.ncbi.nlm.nih.gov/pubmed/18691281
71. **Association between maternal periapical lesions and brain inflammation in rat pups. [**The objective of this study was to determine whether the presence of maternal tooth periapical lesions was associated with foetal brain inflammation in a pregnant rat model. METHODS: Sprague-Dawley rats were divided into two groups: pregnant rats with induced periapical abscesses (E, n=8) and sham-operated control pregnant rats (S, n=8). The pulps of the first and second maxillary right molars had been exposed and the tooth left open to the oral environment for two weeks prior to initiation of the pregnancy. Following delivery of the pups (E, n=99; S, n=101), each pup was decapitated and the brain was removed and immediately frozen in liquid nitrogen. The tissues were solubilized in PBS containing a protease inhibitor, and norepinephrine (NE), IL-6, IL-1-β, TNF-α, and myelin basic protein (MBP) were determined by ELISA. Group means were compared by factorial analysis of variance, a post hoc Tukey test, and Pearson's correlation test. $p<0.05$ was used to reject the null hypothesis. RESULTS: E pups were significantly heavier than S pups. Brain tissue concentrations of IL-6, IL-1-β, and TNF-α were significantly higher and MBP and norepinephrine concentrations significantly lower in E pups than S pups. Concentrations of IL-6, TNF-α and IL-1-β were significantly correlated between E serum, pup birthweight, and E pup brain tissue. MBP, NE and IL-6 were significantly correlated within the brain tissues of E pups. CONCLUSION: The data suggest that brain inflammation may be associated with maternal periapical inflammation. This association identifies a modifiable risk factor for adverse pregnancy outcomes.**]** Bain JL, Lester SR, et al. *Arch Oral Biol*. 2013 Mar;58(3):266-71. doi: 10.1016/j.archoralbio.2012.11.007. Epub 2012 Dec 12. http://www.ncbi.nlm.nih.gov/pubmed/23245577
72. **Association Between Self-Reported Dental Health Status and Onset of Dementia: A 4-Year Prospective Cohort Study of Older Japanese Adults from the Aichi Gerontological Evaluation Study (AGES) Project.** [Objectives Studies have shown that people with cognitive impairment have poor dental health. However, the direction of causality remains unknown. This prospective cohort study aimed to determine the association between four self-reported dental health variables and dementia onset in older Japanese people. Methods Analysis was conducted on 4425 residents 65 years or older. Four self-reported dental health variables included the number of teeth and/or use of dentures, ability to chew, presence/absence of a regular dentist, and taking care of dental health. Data were collected using self-administered questionnaires given in 2003.

Records of dementia onset during 2003 to 2007 were obtained from municipalities in charge of the public long-term care insurance system. Age, income, body mass index, present illness, alcohol consumption, exercise, and forgetfulness were used as covariates. Results Dementia onset was recorded in 220 participants. Univariate Cox proportional hazards models showed significant associations between the dental health variables and dementia onset. In models fully adjusted for all covariates, hazard ratios (95% confidence intervals) of dementia onset of respondents were as follows: 1.85 (1.04-3.31) for those with few teeth and without dentures; 1.25 (0.81-1.93) for those who could not chew very well; 1.44 (1.04-2.01) for those who did not have a regular dentist; and 1.76 (0.96-3.20) for those who did not take care of their dental health. Conclusions Few teeth without dentures and absence of a regular dentist, not poor mastication and poor attitudes toward dental health, were associated with higher risk of dementia onset in the older Japanese cohort even after adjustment for available covariates.] Yamamoto T, Kondo K, et al. *Psychosom Med*. 2012 Apr;74(3):241-8. Epub 2012 Mar 9. http://www.ncbi.nlm.nih.gov/pubmed/22408130

73. **Chronic inflammation and amyloidogenesis in Alzheimer's disease -- role of Spirochetes.** [Alzheimer's disease (AD) is associated with dementia, brain atrophy and the aggregation and accumulation of a cortical amyloid-beta peptide (Abeta). Chronic bacterial infections are frequently associated with amyloid deposition. It had been known from a century that the spirochete Treponema pallidum can cause dementia in the atrophic form of general paresis. It is noteworthy that the pathological hallmarks of this atrophic form are similar to those of AD. Recent observations showed that bacteria, including spirochetes contain amyloidogenic proteins and also that Abeta deposition and tau phosphorylation can be induced in or in vivo following exposure to bacteria or LPS. Bacteria or their poorly degradable debris are powerful inflammatory cytokine inducers, activate complement, affect vascular permeability, generate nitric oxide and free radicals, induce apoptosis and are amyloidogenic. All these processes are involved in the pathogenesis of AD. Old and new observations, reviewed here, indicate that to consider the possibility that bacteria, including several types of spirochetes highly prevalent in the population at large or their persisting debris may initiate cascade of events leading to chronic inflammation and amyloid deposition in AD is important, as appropriate antibacterial and antiinflammatory therapy would be available to prevent dementia.] Miklossy J. *J Alzheimers Dis*. 2008 May;13(4):381-91. http://www.ncbi.nlm.nih.gov/pubmed/18487847
74. **Could low dosage of doxycycline e considered for Alzheimer's disease treatment? [**Objectives: Alzheimer's disease (AD) is a neurodegenerative disease primarily of the elderly, and treatment modalities are limited. AD is characterized by the presence of senile plaques with its main component amyloid â , neurofibrillary tangles with phosphophorylated tau protein, and neuronal loss. These pathological components as well as inflammation are hypothesized to be involved in the pathogenesis of AD. When considering potential treatment modalities for AD, this pathogenesis should be considered. Periostat is a drug containing low dosages of Doxycycline and is used in long-term administration to treat periodontal disease without the side effects characterizing the anti-microbial doses of this medication. The objective of this study is to evaluate the possible use of Periostat for treating AD by critically analyzing the existing literature. Methods: a Medline search was undertaken using combinations of the following terms: doxycycline, tetracycline, minocycline, Alzheimer's disease, cognition, mild impairment cognition, metalloproteinase (MMP), amyloid, and inflammation. Then, the relevant papers were reviewed manually. Results: the database search resulted in a total 301 papers containing the search terms. Further evaluation resulted in 45 papers containing relevant data. The studies evaluated were based on in vitro, animal, and clinical data. Only one randomized control study was found. The review study found that tetracycline derivatives, including doxycycline: a) cross the brain blood barrier; b) have neuroprotective effects; c) destabilize the amyloid fibrils to make them susceptible to proteolysis; d) inhibit caspase-3 that has a role in tau protein neurotoxicity; e) inhibit the production of proinflammatory molecules; and f) slow cognitive decline. However, untoward effects have also been reported related to tetracyclines anti-MMPs activities. Conclusion: the available data suggest that in selective cases low dosage doxycycline may be effective in treating AD.] Kamer SA, Kamer AR. *IADR*, July 16, 2010. Barcelona Spain. http://iadr.confex.com/iadr/2010barce/webprogramcd/Paper140673.html
75. **Decreased C-Reactive Protein Levels in Alzheimer Disease.** [C-reactive protein (CRP) is an acute-phase reactant that has been found to be associated with Alzheimer disease (AD) in histopathological and longitudinal studies; however, little data exist regarding serum CRP levels in patients with established AD. The current study evaluated CRP levels in 192 patients diagnosed with probable AD (mean age = 75.8 ± 8.2 years; 50% female) as compared to 174 nondemented controls (mean age = 70.6 ± 8.2 years; 63% female). Mean CRP levels were found to be significantly decreased in AD (2.9 µg/mL) versus controls (4.9 µg/mL; P = .003). In adjusted models, elevated CRP significantly predicted poorer (elevated) Clinical Dementia Rating Scale sum of boxes (CDR SB) scores in patients with AD. In controls, CRP was negatively associated with Mini-Mental State Examination (MMSE) scores and positively associated with CDR SB scores. These findings, together with previously published results, are consistent with the hypothesis that midlife elevations in CRP are associated with increased risk of AD development though elevated CRP levels are not useful for prediction in the immediate prodrome years before AD becomes clinically manifest. However, for a subgroup of patients with AD, elevated CRP continues to predict increased dementia severity suggestive of a possible proinflammatory endophenotype in AD.] O'Bryant SE, Waring SC, et al. http://jgp.sagepub.com/content/23/1/49.short,
76. **Determining the Presence of Periodontopathic Virulence Factors in Short-Term Postmortem Alzheimer's Disease Brain Tissue**. [The aim of this study was to establish a link between periodontal disease and Alzheimer's disease (AD) with a view to identifying the major periodontal disease bacteria (Treponema denticola, Tannerella forsythia, and Porphyromonas gingivalis) and/or bacterial components in brain tissue from 12 h postmortem delay. Our request matched 10 AD cases for tissue from Brains for Dementia Research alongside 10 non-AD age-related controls with similar or greater postmortem

interval. We exposed SVGp12, an astrocyte cell line, to culture supernatant containing lipopolysaccharide (LPS) from the putative periodontal bacteria P. gingivalis. The challenged SVGp12 cells and cryosections from AD and control brains were immunolabeled and immunoblotted using a battery of antibodies including the anti-P. gingivalis-specific monoclonal antibody. Immunofluorescence labeling demonstrated the SVGp12 cell line was able to adsorb LPS from culture supernatant on its surface membrane; similar labeling was observed in four out of 10 AD cases. Immunoblotting demonstrated bands corresponding to LPS from P. gingivalis in the SVGp12 cell lysate and in the same four AD brain specimens which were positive when screened by immunofluorescence. All controls remained negative throughout while the same four cases were consistently positive for P. gingivalis LPS ($p = 0.029$). This study confirms that LPS from periodontal bacteria can access the AD brain during life as labeling in the corresponding controls, with equivalent/longer postmortem interval, was absent. Demonstration of a known chronic oral-pathogen-related virulence factor reaching the human brains suggests an inflammatory role in the existing AD pathology.] Poole S, Crean SJ, et al. J Alzheimers Dis. 2013 May 10. http://www.ncbi.nlm.nih.gov/m/pubmed/23666172/ ; http://iospress.metapress.com/content/b8475m589rp314j3/

77. **Dental health and cognitive impairment in an English national survey population.** [OBJECTIVES: To investigate the association between dental health and cognitive impairment and to examine the extent to which dental status accounts for the association between cognitive impairment and low body mass index (BMI) in a national survey sample. DESIGN: A secondary analysis of data from the Health Survey for England 2000. SETTING: A nationally representative cross-sectional population survey. PARTICIPANTS: Two thousand four hundred sixty-three adults aged 65 and older living in private households and 1,569 adults aged 65 and older living in care homes. MEASUREMENTS: Data collected by interview (self-reported or by proxy) included age, sex, level of education, disability, BMI, dental status, and cognitive function (Abbreviated Mental Test Score). RESULTS: Less than half of the community sample (40.4%) and 67.9% of the care home sample were edentulous; lack of teeth was significantly associated with cognitive impairment (odds ratio=3.59, 95% confidence interval=2.36-5.47). This association remained strong after adjustment for other covariates only in the community sample. Cognitive impairment was associated with lower BMI in both samples, but dental status did not explain this. CONCLUSION: Poor dentition is associated with cognitive impairment. Nutritional status in people with cognitive impairment is recognized to be at risk. Although dental health did not account for the association between cognitive impairment and low BMI in this sample, other possible nutritional consequences require further evaluation.] Stewart R, Hirani V. *J Am Geriatr Soc*. 2007 Sep;55(9):1410-4. http://www.ncbi.nlm.nih.gov/pubmed/17767683
78. **Determining the presence of periodontopathic virulence factors in short-term postmortem Alzheimer's disease brain tissue.** [The aim of this study was to establish a link between periodontal disease and Alzheimer's disease (AD) with a view to identifying the major periodontal disease bacteria (Treponema denticola, Tannerella forsythia, and Porphyromonas gingivalis) and/or bacterial components in brain tissue from 12 h postmortem delay. Our request matched 10 AD cases for tissue from Brains for Dementia Research alongside 10 non-AD age-related controls with similar or greater postmortem interval. We exposed SVGp12, an astrocyte cell line, to culture supernatant containing lipopolysaccharide (LPS) from the putative periodontal bacteria P. gingivalis. The challenged SVGp12 cells and cryosections from AD and control brains were immunolabeled and immunoblotted using a battery of antibodies including the anti-P. gingivalis-specific monoclonal antibody. Immunofluorescence labeling demonstrated the SVGp12 cell line was able to adsorb LPS from culture supernatant on its surface membrane; similar labeling was observed in four out of 10 AD cases. Immunoblotting demonstrated bands corresponding to LPS from P. gingivalis in the SVGp12 cell lysate and in the same four AD brain specimens which were positive when screened by immunofluorescence. All controls remained negative throughout while the same four cases were consistently positive for P. gingivalis LPS ($p = 0.029$). This study confirms that LPS from periodontal bacteria can access the AD brain during life as labeling in the corresponding controls, with equivalent/longer postmortem interval, was absent. Demonstration of a known chronic oral-pathogen-related virulence factor reaching the human brains suggests an inflammatory role in the existing AD pathology.] Poole S, Singhrao SK, et al. *J Alzheimers Dis*. 2013 Jan 1;36(4):665-77. doi: 10.3233/JAD-121918. **http://www.ncbi.nlm.nih.gov/pubmed/23666172**
79. **Emerging roles of pathogens in Alzheimer disease.** [Chronic spirochetal infection can cause slowly progressive dementia, cortical atrophy and amyloid deposition in the atrophic form of general paresis. There is a significant association between Alzheimer disease (AD) and various types of spirochete (including the periodontal pathogen Treponemas and Borrelia burgdorferi), and other pathogens such as Chlamydophyla pneumoniae and herpes simplex virus type-1 (HSV-1). Exposure of mammalian neuronal and glial cells and organotypic cultures to spirochetes reproduces the biological and pathological hallmarks of AD. Senile-plaque-like beta amyloid (Aβ) deposits are also observed in mice following inhalation of C. pneumoniae in vivo, and Aβ accumulation and phosphorylation of tau is induced in neurons by HSV-1 in vitro and in vivo. Specific bacterial ligands, and bacterial and viral DNA and RNA all increase the expression of proinflammatory molecules, which activates the innate and adaptive immune systems. Evasion of pathogens from destruction by the host immune reactions leads to persistent infection, chronic inflammation, neuronal destruction and Aβ deposition. Aβ has been shown to be a pore-forming antimicrobial peptide, indicating that Aβ accumulation might be a response to infection. Global attention and action is needed to support this emerging field of research because dementia might be prevented by combined antibiotic, antiviral and anti-inflammatory therapy.] Miklossy J., *Expert Rev Mol Med*. 2011 Sep 20;13:e30. doi: 10.1017/S1462399411002006, http://www.ncbi.nlm.nih.gov/pubmed/21933454
80. **Glucose tolerance status and risk of dementia in the community.** [Objective: We investigated the association between glucose tolerance status defined by a 75-g oral glucose tolerance test (OGTT) and the development of dementia. Methods**:** A total of 1,017 community-dwelling dementia-free subjects aged ≥60 years who underwent the OGTT were followed up for 15

years. Outcome measure was clinically diagnosed dementia. Results**:** The age- and sex-adjusted incidence of all-cause dementia, Alzheimer disease (AD), and vascular dementia (VaD) were significantly higher in subjects with diabetes than in those with normal glucose tolerance. These associations remained robust even after adjustment for confounding factors for all-cause dementia and AD, but not for VaD (all-cause dementia: adjusted hazard ratio [HR] = 1.74, 95% confidence interval [CI] = 1.19 to 2.53, $p = 0.004$; AD: adjusted HR = 2.05, 95% CI = 1.18 to 3.57, $p = 0.01$; VaD: adjusted HR = 1.82, 95% CI = 0.89 to 3.71, $p = 0.09$). Moreover, the risks of developing all-cause dementia, AD, and VaD significantly increased with elevated 2-hour postload glucose (PG) levels even after adjustment for covariates, but no such associations were observed for fasting plasma glucose (FPG) levels: compared with those with 2-hour PG levels of <6.7 mmol/L, the multivariable-adjusted HRs of all-cause dementia and AD significantly increased in subjects with 2-hour PG levels of 7.8 to 11.0 mmol/L or over, and the risk of VaD was significantly higher in subjects with levels of ≥11.1 mmol/L. Conclusions: Our findings suggest that diabetes is a significant risk factor for all-cause dementia, AD, and probably VaD. Moreover, 2-hour PG levels, but not FPG levels, are closely associated with increased risk of all-cause dementia, AD, and VaD.] Ohara T, Doi Y, et al. *Neurology* September 20, 2011 vol. 77 no. 12 1126-1134**.** http://www.neurology.org/content/77/12/1126.full

81. **Inflammation and Alzheimer's disease: Possible role of periodontal diseases.** [The molecular and cellular mechanisms responsible for the etiology and pathogenesis of Alzheimer's disease (AD) have not been defined; however, inflammation within the brain is thought to play a pivotal role. Studies suggest that peripheral infection/inflammation might affect the inflammatory state of the central nervous system. Chronic periodontitis is a prevalent peripheral infection that is associated with gram-negative anaerobic bacteria and the elevation of serum inflammatory markers including C-reactive protein. Recently, chronic periodontitis has been associated with several systemic diseases including AD. In this article we review the pathogenesis of chronic periodontitis and the role of inflammation in AD. In addition, we propose several potential mechanisms through which chronic periodontitis can possibly contribute to the clinical onset and progression of AD. Because chronic periodontitis is a treatable infection, it might be a readily modifiable risk factor for AD.] Kamer AR, Craig RG. et al. *Alzheimer's & Dementia*, Vol 4, Issue 4, pp242-250, July 2008. http://www.alzheimersanddementia.com/article/S1552-5260(07)00621-8/abstract
82. **Inflammation as a potential mediator for the association between periodontal disease and Alzheimer's disease**. [Periodontal disease (PDD) is associated with increased risk of cardiovascular disease, cerebrovascular disease, and mortality in many studies, while other studies have begun to suggest an association of PDD with Alzheimer's disease (AD). This paper discusses how infectious pathogens and systemic infection may play a role in AD. The roles of infection and inflammation are addressed specifically with regard to known AD pathologic lesions including senile plaques, neuron death, neurofibrillary tangles, and cerebrovascular changes. A testable model of proposed pathways between periodontal infection and AD is presented including three possible mechanisms: a) direct effects of infectious pathogens, b) inflammatory response to pathogens, and c) the effects on vascular integrity. The role of gene polymorphisms is discussed, including apolipoprotein (APOE) ε4 as a pro-inflammatory and pro-infection genotype.] Watts A, Crimmins EM, et al. Neuropsychiatr Dis Treat. 2008 October; 4(5): 865–876. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2626915/
83. **Inflammation Linked to Alzheimer's Disease.** [Exposure to inflammation early in life quadruples one's risk of developing Alzheimer's disease, said researchers in a presentation on June 19 at the first Alzheimer's Association International Conference on Prevention of Dementia in Washington. A research team led by Margaret Gatz, Ph.D. (a professor of psychology at the University of Southern California) and including researchers from the Karolinska Institute in Stockholm, Sweden, sifted through data on the 20,000 participants in the Swedish Twin Registry and found 109 "discordant" pairs of twins in which only one twin had been diagnosed with dementia. Previous studies by Dr. Gatz and colleagues have shown that Alzheimer's disease is strongly genetic; if one twin has the disease, his or her identical twin has a 60 percent chance of developing it. Information about participants' education, activities and health histories came from surveys they completed in the 1960s, when the registry was created, as well as from hospital discharge records. The surveys included questions about loose or missing teeth. Researchers used the answers to the dental-related questions to build a crude indicator of periodontal disease. They concluded that an inflammatory burden early in life, as represented by chronic periodontal disease, might have severe consequences later. "If what we're indexing with periodontal disease is some kind of inflammatory burden, then it is probably speaking to general health conditions," said Dr. Gatz. If the link between inflammation and periodontal disease is confirmed, researchers said it would add inflammatory burden to the short list of preventable risk factors for Alzheimer's disease.] News - *J Am Dent Assoc*, Vol 136, No 8, 1084. http://jada.ada.org/cgi/content/full/136/8/1084-a
84. **Inflammatory Markers and Cognition in well-functioning African-American and White Elders.** [Serum markers of inflammation, especially IL-6 and CRP, are prospectively associated with cognitive decline in well-functioning elders. These findings support the hypothesis that inflammation contributes to cognitive decline in the elderly.] Yaffe, K, Lindquist K, et al. *Neurology* 2003;61:76-80. http://www.neurology.org/cgi/content/abstract/61/1/76
85. **Inflammation Linked to Cognitive Decline.** [Inflammation is increasingly being implicated as a major factor contributing to several age-related diseases, including Alzheimer's and dementia. Now, researchers at the San Francisco VA Medical Center (SFVAMC) have found a link between inflammation and early cognitive decline in otherwise healthy individuals.] *J Neurology July 8, 2003* Yaffe, K, http://www.ncire.org/yaffe6.html
86. **Insulin resistance is associated with the pathology of Alzheimer disease.** [Objective: We examined the association between diabetes-related factors and pathology of Alzheimer disease (AD) to evaluate how diabetes affects the pathogenic process of AD. Methods: This study included specimens from a series of 135 autopsies of residents of the town of Hisayama in Fukuoka prefecture (74 men and 61 women) performed between 1998 and 2003, who underwent a 75-g oral glucose

tolerance test in clinical examinations in 1988. We measured diabetes-related factors including fasting glucose, 2-hour post-load plasma glucose, fasting insulin, and homeostasis model assessment of insulin resistance (HOMA-IR) in 1988. Neuritic plaques (NPs) were assessed according to the Consortium to Establish a Registry for Alzheimer's Disease guidelines and neurofibrillary tangles (NFTs) were assessed according to Braak stage. The associations between each factor and AD pathology were examined by analysis of covariance and logistic regression analyses. Results: Higher levels of 2-hour post-load plasma glucose, fasting insulin, and HOMA-IR were associated with increased risk for NPs after adjustment for age, sex, systolic blood pressure, total cholesterol, body mass index, habitual smoking, regular exercise, and cerebrovascular disease. However, there were no relationships between diabetes-related factors and NFTs. Regarding the effects of *APOE* genotype on the risk of AD pathology, the coexistence of hyperglycemia and *APOE* ε4 increased the risk for NP formation. A similar enhancement was observed for hyperinsulinemia and high HOMA-IR. Conclusion: The results of this study suggest that hyperinsulinemia and hyperglycemia caused by insulin resistance accelerate NP formation in combination with the effects of *APOE* ε4.] Matsuzaki T, Sasaki K, et al. *NEUROLOGY* 2010;75:764-770. http://www.neurology.org/cgi/content/abstract/75/9/764

87. **Mercury Exposure from Dental Amalgam and Parkinson's and Alzheimer's Diseases**. [Exposure to mercury from dental amalgam has been related to changes in memory, motor-visual and neurobehavioral changes, renal and neurological disorders. Objective:The purpose of this case-control study is to explore the association between mercury exposure from dental amalgam and Parkinson's and Alzheimer's diseases in people 50 years and older. Methods: A sample of 108 male and female volunteers were selected and divided into cases (Parkinson's and Alzheimer's) and controls (without neurological disorders) selected from the same source. Participants signed consents approved by IRB and questionnaire was administered before oral examination. The questionnaire consists of four sections to eliminate confounders like other exposure sources to mercury different from dental amalgam. Trained examiners using the NIDCR diagnostic criteria performed oral examinations blinded for neurological disorders. Mean decayed, missing, and filled component of the DMFS Index were calculated by participant and group using ANOVA analysis of variance. Results: In the present study, no statistical association was observed between dental amalgams and neurological disorders (p=0.92). Statistically significant associations with neurological disorders were found for mean decayed surfaces, DMFS, and tooth loss due to periodontal disease (p<0.05). Significant association between periodontal disease and neurological disorders (OR=28.8) was observed; Alzheimer's (p=0.000) and a clinical tendency for Parkinson's (OR= 7.429 and p=0.10). Conclusion: Tooth loss findings from periodontal disease or caries agree with the reported leading causes of tooth loss in older adults. The association between periodontal disease and neurological disorders are relevant for the prevention and control of neurological disorders in the projected increase in population of older adults.]Gata G, Navarrete G, et al. *IADR, March 2005 Puerto Rico.* *http://iadr.confex.com/iadr/2005Balt/techprogram/abstract_52657.htm*
88. **Oral health and cognitive function in the Third National Health and Nutrition Examination Survey (NHANES III).** [OBJECTIVES: To investigate the association between oral health and cognitive function in early-, mid-, and late-adult life. METHODS: A secondary analysis was carried out of a large, well-characterized community sample (NHANES III). Analyzed variables included three measures of oral health (gingival bleeding, loss of periodontal attachment, loss of teeth) and three measures of cognitive function: the Symbol Digit Substitution Test (SDST), the Serial Digit Learning Test (SDLT) (both in 5138 participants aged 20-59 years), and a Story Recall test (in 1555 participants aged >or=70 years). Other covariates in linear regression models included age, gender, ethnicity, education and poverty, and cardiovascular risk factors. RESULTS: Worse scores on all three measures of oral health status were significantly associated with poorer performance on all three measures of cognitive function after adjustment for age. Education was an important confounding factor. However, after full adjustment for all other covariates, gingival bleeding (%) and loss of periodontal attachment (%) remained associated with relative impairment on SDST score (B coefficients both = 0.003), and gingival bleeding was associated with relative impairment on SDLT (B = 0.017). No effect modification by age was observed. CONCLUSIONS: Poor oral health is associated with worse cognitive function throughout adult life. This may, in part, be accounted for by early life education and social status. However, the possibility of direct causal pathways requires further investigation.] Stewart R, Sabbah W, et al. *Psychosom Med.* 2008 Oct;70(8):936-41. http://www.ncbi.nlm.nih.gov/pubmed/18842752
89. **Periodontal disease and impaired cognition.** Kaye E. http://www.dentistryiq.com/index/display/article-display/3992333948/articles/dentisryiq/clinical/oral-systemic_health/2010/06/Periodontal-disease-and-impaired-cognition.html
90. **Periodontitis is associated with cognitive impairment among older adults: analysis of NHANES-III.** [BACKGROUND: Periodontitis is ubiquitous and associated with serological evidence of exposure to periodontal organisms, systemic inflammation and vascular disease. Dementia is a major public health problem likely related to a complex interaction between genetics and diseases associated with systemic inflammation, including diabetes, smoking and stroke. METHODS: To assess relationships between systemic exposure to periodontal pathogens and cognitive test outcomes, data were analysed from the Third National Health and Nutrition Examination Survey (NHANES-III), a nationally representative cross sectional observational study among older adults. We included 2355 participants >or=60 years who completed measures of cognition and Poryphyromonas gingivalis IgG. Using SUDAAN, logistic regression models examined the association of P gingivalis IgG with cognitive test performance. RESULTS: Poor immediate verbal memory (<5/9 points) was prevalent in 5.7% of patients, and 6.5% overall had impaired delayed recall (<4/9); 22.1% had difficulty with serial subtractions (<5/5 trials correct). Individuals with the highest P gingivalis IgG (>119 ELISA Units (EU)) were more likely to have poor delayed verbal recall (OR 2.89, 95% CI 1.14 to 7.29) and impaired subtraction (OR 1.95, 95% CI 1.22 to 3.11) than those with the

lowest (<or=57 EU), with dose-response relationships for both (p trend, delayed memory = 0.045, subtraction = 0.04). After adjusting for socioeconomic and vascular variables, these relationships remained robust for the highest P gingivalis IgG group (delayed verbal memory OR 3.01 (95% CI 1.06 to 8.53); subtraction OR 2.00 (95% CI 1.19 to 3.36)). In contrast, immediate verbal memory was not significantly associated with P gingivalis. CONCLUSION: A serological marker of periodontitis is associated with impaired delayed memory and calculation. Further exploration of relationships between oral health and cognition is warranted.] Noble JM, Borrell LN, et al. *J Neurol Neurosurg Psychiatry*. 2009 Nov;80(11):1206-11 http://www.ncbi.nlm.nih.gov/pubmed/19419981

91. **Serum antibodies to periodontal pathogens are a risk factor for Alzheimer's disease.** [BACKGROUND: Chronic inflammation in periodontal disease has been suggested as a potential risk factor in Alzheimer's disease (AD). The purpose of this study was to examine serum antibody levels to bacteria of periodontal disease in participants who eventually converted to AD compared with the antibody levels in control subjects. METHODS: Serum samples from 158 participants in the Biologically Resilient Adults in Neurological Studies research program at the University of Kentucky were analyzed for immunoglobulin G antibody levels to seven oral bacteria associated with periodontitis, including Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Campylobacter rectus, Treponema denticola, Fusobacterium nucleatum, Tannerella forsythia, and Prevotella intermedia. All 158 participants were cognitively intact at baseline venous blood draw. In all, 81 of the participants developed either mild cognitive impairment (MCI) or AD or both, and 77 controls remained cognitively intact in the years of follow-up. Antibody levels were compared between controls and subjects with AD at baseline draw and after conversion and controls and subjects with MCI at baseline draw and after conversion using the Wilcoxon rank-sum test. AD and MCI participants were not directly compared. Linear regression models were used to adjust for potential confounding. RESULTS: Antibody levels to F nucleatum and P intermedia were significantly increased (α = 0.05) at baseline serum draw in the patients with AD compared with controls. These results remained significant when controlling for baseline age, Mini-Mental State Examination score, and apolipoprotein epsilon 4 status.CONCLUSIONS: This study provides initial data that demonstrate elevated antibodies to periodontal disease bacteria in subjects years before cognitive impairment and suggests that periodontal disease could potentially contribute to the risk of AD onset/progression. Additional cohort studies profiling oral clinical presentation with systemic response and AD and prospective studies to evaluate any cause-and-effect association are warranted.] Sparks SP, Steffen MJ, et al. *Alzheimers Dement.* 2012 May;8(3):196-203. **http://www.ncbi.nlm.nih.gov/pubmed/22546352**
92. **The Alzheimer's Disease-Associated Amyloid β-Protein Is an Antimicrobial Peptide.** [Background: The amyloid β-protein (Aβ) is believed to be the key mediator of Alzheimer's disease (AD) pathology. Aβ is most often characterized as an incidental catabolic byproduct that lacks a normal physiological role. However, Aβ has been shown to be a specific ligand for a number of different receptors and other molecules, transported by complex trafficking pathways, modulated in response to a variety of environmental stressors, and able to induce pro-inflammatory activities . Methodology/Principal Findings: Here, we provide data supporting an *in vivo* function for Aβ as an antimicrobial peptide (AMP). Experiments used established *in vitro* assays to compare antimicrobial activities of Aβ and LL-37, an archetypical human AMP. Findings reveal that Aβ exerts antimicrobial activity against eight common and clinically relevant microorganisms with a potency equivalent to, and in some cases greater than, LL-37. Furthermore, we show that AD whole brain homogenates have significantly higher antimicrobial activity than aged matched non-AD samples and that AMP action correlates with tissue Aβ levels. Consistent with Aβ-mediated activity, the increased antimicrobial action was ablated by immunodepletion of AD brain homogenates with anti-Aβ antibodies. Conclusions/Significance: Our findings suggest Aβ is a hitherto unrecognized AMP that may normally function in the innate immune system. This finding stands in stark contrast to current models of Aβ-mediated pathology and has important implications for ongoing and future AD treatment strategies.] Soscia SJ, Kirby JE, et al. *PLoS ONE* 5(3): e9505. http://www.plosone.org/article/info:doi%2F10.1371%2Fjournal.pone.0009505
93. **The Inflammatory Response in Alzheimer's Disease.** [Over the last 2 decades, numerous innate inflammatory mediators have been reported to be upregulated in pathologically vulnerable regions of the brain in Alzheimer's disease (AD). These data have led to a reexamination of the dogma of brain immunologic privilege and to new studies that examine the role of the innate inflammatory response in a number of other neurologic disorders, particularly Parkinson's disease and human immunodeficiency virus dementia. In addition, basic science discoveries about neuroinflammation are now beginning to move to the clinic. More than 20 epidemiologic surveys have consistently demonstrated that common non-steroidal anti-inflammatory drugs may protect against the development of AD. By contrast, anti-inflammatory treatment trials for existing AD have typically shown little to no effect on halting or reversing the disorder, although the agents tested have often been at odds with those suggested by the epidemiologic and basic science results. The extensive literature on innate inflammation and neurologic disease notwithstanding, three fundamental questions still remain to be answered fully. First, are innate inflammatory responses a cause of neurologic disease or merely a more sophisticated means than previously imagined for removing the detritus left by more primary pathogenic mechanisms? Second, can anti-inflammatory agents effectively treat existing neurologic disease, or is a protective strategy in high-risk patients the only reasonable option? Third, whether for protection or treatment, what is the best choice of anti-inflammatory agent given the basic science mechanisms and epidemiologic results that have been reported? …This article summarizes some of the key inflammatory mechanisms that have been elucidated in AD, their potential significance in causing neurodegeneration rather than simply removing it, and the generally problematic attempts that have been made to apply anti-inflammatory approaches to the treatment or prevention of AD.] Rogers J. *Journal of Periodontology, 2008, Vol. 79, No. 8s, Pages 1535-1543,* *http://www.joponline.org/doi/full/10.1902/jop.2008.080171*

94. **The role of TNF and its receptors in Alzheimer's disease. [**Tumor necrosis factor (TNF) is an important proinflammatory cytokine that is upregulated in Alzheimer disease (AD) patients and involved with AD genes. Several TNF promoter polymorphisms that increase expression are associated with inflammatory and infectious diseases. We previously reported results that detected a AD associated region near the TNF gene. Using family-based association tests we also reported an association between AD and a TNF haplotype in sibling-pair families, and a significant increase in the mean age of onset for a group of African-American AD patients carrying this same haplotype. Previous reports have shown that that the chromosome 1p and chromosome 12p regions are linked to late-onset AD. These two regions harbor TNF receptors (TNFR) 2 and 1, respectively, and binding to them mediates biological effects of TNF. We found a significant asssociation of a TNFR2 exon 6 polymorphism with late-onset AD in families with no individuals possessing the APOE E4E4 genotype under a dominant model. We found no significant association of three polymorphisms in the TNFR1 gene to AD. These results provide further evidence for the involvement of TNF in the pathogenesis of AD.] Perry RT, Collins JS, et al. *Neurobiol Aging.* 2001 Nov-Dec;22(6):873-83. http://www.ncbi.nlm.nih.gov/pubmed/11754994
95. **TNF-alpha and antibodies to periodontal bacteria discriminate between Alzheimer's disease patients and normal subjects. [**The associations of inflammation/immune responses with clinical presentations of Alzheimer's disease (AD) remain unclear. We hypothesized that TNF-alpha and elevated antibodies to periodontal bacteria would be greater in AD compared to normal controls (NL) and their combination would aid clinical diagnosis of AD. Plasma TNF-alpha and antibodies against periodontal bacteria were elevated in AD patients compared with NL and independently associated with AD. The number of positive IgG to periodontal bacteria incremented the TNF-alpha classification of clinical AD and NL. This study shows that TNF-alpha and elevated numbers of antibodies against periodontal bacteria associate with AD and contribute to the AD diagnosis.] Kamer AR, Craig RG, et al. *J Neuroimmunol*. 2009 Nov 30;216(1-2):92-7. http://www.ncbi.nlm.nih.gov/pubmed/19767111
96. **Tooth loss and cognitive impairment.** [OBJECTIVES: Chronic subclinical inflammation may elevate the risk of cognitive impairment. Periodontitis is associated with subclinical inflammation and accounts in part for tooth loss. The hypothesis was tested that periodontitis and tooth loss as a proxy of chronic periodontitis is associated with cognitive impairment in the elderly. SUBJECTS AND METHODS: The population-based Study of Health in Pomerania comprises 1336 subjects (60-79 years). Cognitive impairment was assessed with the Mini-Mental Status Examination (MMSE). Tobit regression analyses were adjusted for potential confounders. RESULTS: A decreased number of teeth was associated with lower MMSE scores in females ($p<0.001$) and males ($p=0.007$) in age-adjusted models. In the fully adjusted models, tooth loss was associated with cognitive impairment in females ($p=0.002$) but not in males ($p=0.825$). CONCLUSIONS: A significant association between tooth loss and cognitive impairment was found in females that was not accounted for by potential confounders. Former periodontitis may account for this association as periodontitis was frequently the cause for tooth extractions.] Grabe HJ, Schwahn C, et al. *J Clin Periodontol*. 2009 Jul;36(7):550-7. http://www.ncbi.nlm.nih.gov/pubmed/19538327
97. **Tooth Loss and Periodontal Disease Predict Poor Cognitive Function in Older Men**. [OBJECTIVES: To determine whether rates of tooth loss, periodontal disease progression, and caries incidence predict cognitive decline in men. DESIGN: Prospective study. SETTING: Community-dwelling men enrolled in the Veterans Affairs Dental Longitudinal Study. PARTICIPANTS: Five hundred ninety-seven dentate men aged 28 to 70 at study baseline who have been followed up to 32 years. MEASUREMENTS: Oral examinations were conducted approximately every 3 years. Periodontal disease measures included probing pocket depth and radiographic alveolar bone height. Participants underwent cognitive testing beginning in 1993. Low cognitive status was defined as less than 25 points or less than 90% of the age- and education-specific median on the Mini-Mental State Examination (MMSE) and less than 10 points on a spatial copying task. RESULTS: Each tooth lost per decade since the baseline dental examination increased the risks of low MMSE score (hazard ratio (HR)=1.09, 95% confidence interval (CI)=1.01–1.18) and low spatial copying score (HR=1.12, CI=1.05–1.18). Risks were greater per additional tooth with progression of alveolar bone loss (spatial copying: HR=1.03, CI=1.01–1.06), probing pocket depth (MMSE: HR=1.04, CI=1.01–1.09; spatial copying: HR=1.04, CI=1.01–1.06), and caries (spatial copying: HR=1.05, CI=1.01–1.08). Risks were consistently higher in men who were older than 45.5 at baseline than in younger men. CONCLUSION: Risk of cognitive decline in older men increases as more teeth are lost. Periodontal disease and caries, major reasons for tooth loss, are also related to cognitive decline.] Kaye EK, Valencia A, et al. *American Geriatrics Society*, Vol 58, Issue 4, pp 713-718, (April 2010). http://www3.interscience.wiley.com/journal/123339485/abstract
98. **Tooth loss, dementia and neuropathology in the Nun study.** [BACKGROUND: Numerous studies have linked dementia to the subsequent deterioration of oral health. Few investigators, however, have examined oral disease as a potential risk factor in the development of dementia. The authors conducted a study to investigate a potential association between a history of oral disease and the development of dementia. METHODS: Longitudinal dental records supplemented data collected from 10 annual cognitive assessments of 144 Milwaukee participants in the Nun Study, a longitudinal study of aging and Alzheimer disease, who were 75 to 98 years old. Neuropathologic findings at autopsy were available for 118 participants who died. RESULTS: A low number of teeth increased the risk of higher prevalence and incidence of dementia. CONCLUSION: Participants with the fewest teeth had the highest risk of prevalence and incidence of dementia. CLINICAL IMPLICATIONS: Edentulism or very few (one to nine) teeth may be predictors of dementia late in life.] Stein PS, Desrosiers M, et al. *J Am Dent Assoc*. 2007 Oct;138(10):1314-22. http://www.ncbi.nlm.nih.gov/pubmed/17908844

Cancer and Inflammation

99. **An exploration of the periodontitis-cancer association.** [PURPOSE: Periodontitis has been linked to the occurrence of various systemic diseases. The goal of this study was to explore the periodontitis-cancer association in the NHANES I Epidemiologic Follow-up Study. METHODS: Data were available on 11,328 adults, age 25 to 74 years, who were diagnosed as dentate individuals with either periodontitis (n = 2092), gingivitis (n = 2603), a healthy periodontium (n = 2,671), or as individuals without teeth (edentulous n = 3,962) at the beginning of the follow-up. The main outcome measure was fatal cancer, as ascertained from death certificates. RESULTS: Compared with individuals with a healthy periodontium, fatal cancer occurrence was positively associated with periodontitis at baseline (age and gender adjusted odds ratio = 1.55, 95% confidence interval: 1.25-1.92). Of the different cancer types, lung cancer demonstrated the strongest association. After adjustment for known risk factors for lung cancer, the magnitude of the association between periodontitis and lung cancer ranged between 1.48 (95% confidence interval: 0.88-2.50) and 1.73 (95% confidence interval: 1.01-2.97). CONCLUSIONS: Associations between periodontitis and lung cancer mortality can be identified above and beyond adjustment for known risk factors for lung cancer. Despite these apparent unconfounded associations, there are reasons to believe that the periodontitis-cancer associations may be spurious.] Hujoel PP, Drangsholt M, et al. *Ann Epidemiol*. 2003 May;13(5):312-6. http://www.ncbi.nlm.nih.gov/pubmed/12821269
100. **Extracellular deoxyribonuclease production by periodontal bacteria**. [Palmer LJ, Chapple ILC, Wright HJ, Roberts A, Cooper PR. Extracellular deoxyribonuclease production by periodontal bacteria. J Periodont Res 2011; doi: 10.1111/j.1600-0765.2011.01451.x © 2011 John Wiley & Sons A/S Background and Objective: Whilst certain bacteria have long been known to secrete extracellular deoxyribonuclease (DNase), the purpose in microbial physiology was unclear. Recently, however, this enzyme has been demonstrated to confer enhanced virulence, enabling bacteria to evade the host's immune defence of extruded DNA/chromatin filaments, termed neutrophil extracellular traps (NETs). As NETs have recently been identified in infected periodontal tissue, the aim of this study was to screen periodontal bacteria for extracellular DNase activity. Material and Methods: To determine whether DNase activity was membrane bound or secreted, 34 periodontal bacteria were cultured in broth and on agar plates. Pelleted bacteria and supernatants from broth cultures were analysed for their ability to degrade DNA, with relative activity levels determined using an agarose gel electrophoresis assay. Following culture on DNA-supplemented agar, expression was determined by the presence of a zone of hydrolysis and DNase activity related to colony size. Results: Twenty-seven bacteria, including red and orange complex members Porphyromonas gingivalis, Tannerella forsythia, Fusobacterium nucleatum, Parvimonas micra, Prevotella intermedia, Streptococcus constellatus, Campylobacter rectus and Prevotella nigrescens, were observed to express extracellular DNase activity. Differences in DNase activity were noted, however, when bacteria were assayed in different culture states. Analysis of the activity of secreted DNase from bacterial broth cultures confirmed their ability to degrade NETs. Conclusion: The present study demonstrates, for the first time, that DNase activity is a relatively common property of bacteria associated with advanced periodontal disease. Further work is required to determine the importance of this bacterial DNase activity in the pathogenesis of periodontitis.] Palmer LJ, Chapple IL, et al. *J Periodontal Res*. 2011 Dec 12. doi: 10.1111/j.1600-0765.2011.01451.x. http://www.ncbi.nlm.nih.gov/pubmed/22150619
101. **Metastatic breast carcinoma initially diagnosed as pulpal/periapical disease: a case report.** [INTRODUCTION: Metastatic tumors to oral cavity and jaws are rare, and mandible is the most commonly involved location. Because the most common jaw symptom is pain, these lesions could be misdiagnosed as pathologic entities with dental origin. In this article a case of metastatic breast carcinoma initially diagnosed as pulpal/periapical disease is presented and discussed.METHODS: A 40-year-old female patient was referred to our department with vague pain in right mandibular area. Clinical and radiographic examinations were performed, leading to the initial diagnosis. Patient's medical history was reevaluated, and an incisional biopsy was performed to confirm the final diagnosis.RESULTS: Regarding the initial signs and symptoms, a pulpal/periapical inflammatory process was considered in the differential diagnosis. Because lip paresthesia was also noted, a more aggressive process was suspected. Patient's medical records and histopathologic slides were requested and reviewed carefully. The diagnosis of metastatic breast carcinoma was confirmed by comparing the histopathologic findings of the jaw lesion with previous slides of the breast.CONCLUSIONS: Despite their rarity, metastatic tumors should be considered in the differential diagnosis of inflammatory and reactive lesions of the jaws. These lesions might be diagnosed first by the patient's dentist or by the maxillofacial surgeon. This case emphasized the importance of a complete and careful work-up with particular attention to detailed medical history as well as careful clinical and radiographic inspection for unusual signs and symptoms.] Khalili M, Mahboobi N, et al. *J Endod.*, 2010 May;36(5);922-5. http://www.ncbi.nlm.nih.gov/pubmed/20416447
102. **Metastasis of breast carcinoma to mandibular gingiva.** [Metastatic tumours to the oral region are rare but more often involve the jaws rather than the oral soft tissues. In this report, an infiltrative ductal carcinoma of the breast that metastasised to the mandibular gingiva is presented. The patient consulted her dentist for what she thought was a dental abscess in the bicuspid region of the lower left jaw. However, her dentist referred her for a specialist opinion of the lesion. The patient's medical history revealed that she had undergone a breast 'lumpectomy' 1 year previously. A provisional diagnosis of primary or metastatic malignancy was made, and a biopsy was performed. Microscopically, the lesion showed features of a poorly differentiated infiltrative ductal carcinoma. Subsequent microscopic review of the primary lesion also showed a poorly differentiated infiltrating ductal carcinoma of the breast identical to the features observed in the metastatic lesion.] Scipio JE, Murti PR, et al. *Oral Oncol.*, 2001 Jun'37(4);393-6. http://www.ncbi.nlm.nih.gov/pubmed/11337273

103. **Oral microbiota and cancer.** [Inflammation caused by infections may be the most important preventable cause of cancer in general. However, in the oral cavity the role of microbiota in carcinogenesis is not known. Microbial populations on mouth mucosa differ between healthy and malignant sites and certain oral bacterial species have been linked with malignancies but the evidence is still weak in this respect. Nevertheless, oral microorganisms inevitably up-regulate cytokines and other inflammatory mediators that affect the complex metabolic pathways and may thus be involved in carcinogenesis. Poor oral health associates statistically with prevalence of many types of cancer, such as pancreatic and gastrointestinal cancer. Furthermore, several oral micro-organisms are capable of converting alcohol to carcinogenic acetaldehyde which also may partly explain the known association between heavy drinking, smoking, poor oral health and the prevalence of oral and upper gastrointestinal cancer. A different problem is the cancer treatment-caused alterations in oral microbiota which may lead to the emergence of potential pathogens and subsequent other systemic health problems to the patients. Hence clinical guidelines and recommendations have been presented to control oral microbiota in patients with malignant disease, but also in this area the scientific evidence is weak. More controlled studies are needed for further conclusion.] Meurman JH. J Oral Microbiol. 2010; 2: 10.3402/jom.v2i0.5195. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3084564/
104. **Porphyromonas gingivalis promotes invasion of oral squamous cell carcinoma through induction of proMMP9 and its activation.** [Recent epidemiological studies have revealed a significant association between periodontitis and oral squamous cell carcinoma (OSCC). Furthermore, matrix metalloproteinase 9 (MMP9) is implicated in the invasion and metastasis of tumor cells. We examined the involvement of Porphyromonas gingivalis, a periodontal pathogen, in OSCC invasion through induced expression of proMMP and its activation. proMMP9 was continuously secreted from carcinoma SAS cells, while P. gingivalis infection increased proenzyme expression and subsequently processed it to active MMP9 in culture supernatant, which enhanced cellular invasion. In contrast, Fusobacterium nucleatum, another periodontal organism, failed to demonstrate such activities. The effects of P. gingivalis were observed with highly invasive cells, but not with the low invasive type. P. gingivalis also stimulated proteinase-activated receptor 2 (PAR2) and enhanced proMMP9 expression, which promoted cellular invasion. P. gingivalis mutants deficient in gingipain proteases failed to activate MMP9. Infected SAS cells exhibited activation of ERK1/2, p38, and NF-kB, and their inhibitors diminished both proMMP9-overexpression and cellular invasion. Together, our results show that P. gingivalis activates the ERK1/2-Ets1, p38/HSP27, and PAR2/NFκB pathways to induce proMMP9 expression, after which the proenzyme is activated by gingipains to promote cellular invasion of OSCC cell lines. These findings suggest a novel mechanism of progression and metastasis of OSCC associated with periodontitis.] Inaba H, Suqita H, et al. *Cell Microbiol*. 2013 Sep 2. doi: 10.1111/cmi.12211. http://www.ncbi.nlm.nih.gov/pubmed/23991831
105. **Recent advances in head and neck cancer.** [More than half a million patients receive the diagnosis of squamous-cell carcinoma of the head and neck worldwide each year. In this disease, which primarily affects the oropharynx, oral cavity, hypopharynx, and larynx, smoking and alcohol abuse are major risk factors. Symptoms vary, depending on the site of origin, and can include a sore throat, dysphagia, odynophagia, and hoarseness. On examination, patients often have an identifiable primary site and a palpable neck mass. A multidisciplinary approach is important in treating these patients, given the complexity of the treatment and the acute and long-term complications that result from chemotherapy, radiation therapy, . .] Haddad RI, Shin DM. *NEJM*, 2008 Sep 11;359(11):1143-43. http://www.ncbi.nlm.nih.gov/pubmed/18784104
106. **Risk Assessment of Tobacco Types and Oral Cancer. [**Abstract: Problem statement: Oral cancer is one of the most common life threatening cancers all over the world, in particular Asian countries and tobacco is considered to be the most potent risk factor for oral cancer. This study was conducted to investigate the risk factors for oral cancer among the subjects from the studied area. Approach: A case-control study of 350 cases and 350 controls over a period of 19 months during April 2005 and September 2006 was carried out. The self reported information about their tobacco, alcohol along with other associated habits was collected by structured questionnaires. The consumption of tobacco was classified into three types, active smoking, passive smoking and smokeless form of tobacco. Results: There was a significant association between consumption of tobacco and the development of oral cancer ($p<0.05$ for all). Active smoking, in particular bidi smoking showed strong association with oral cancer compared to the passive smoking. Of the smokeless tobacco type, gutkha and tobacco flakes consumption showed the strong association. However, betel leaf and paan parag chewing had no association. While, alcohol consumption was associated with oral cancer with strongest determinant being the consumption of hard liquor. Dietary habits, in particular the non-vegetarian diet was significantly associated with oral cancer. The entire associations were statistically adjusted for possible confounders like age, gender, alcohol, the use of other tobacco types, non-vegetarian diet, education, location and monthly household income as appropriate. Conclusion: Smokeless tobacco consumption emerged as the strongest risk factor for oral cancer.] Madani AH, jahromi AS, et al. *American Journal of Pharmacology and Toxicology* 5 (1): 9-13, 2010. http://www.scipub.org/fulltext/AJPT/AJPT519-13.pdf
107. **The antioxidant and pro-oxidant activities of green tea polyphenols: a role in cancer prevention.** [Green tea (Camellia sinensis) is rich in catechins, of which (-)-epigallocatechin-3-gallate (EGCG) is the most abundant. Studies in animal models of carcinogenesis have shown that green tea and EGCG can inhibit tumorigenesis during the initiation, promotion and progression stages. Many potential mechanisms have been proposed including both antioxidant and pro-oxidant effects, but questions remain regarding the relevance of these mechanisms to cancer prevention. In the present review, we will discuss the redox chemistry of the tea catechins and the current literature on the antioxidant and pro-oxidative effects of the green tea polyphenols as they relate to cancer prevention. We report that although the catechins are chemical antioxidants which can quench free radical species and chelate transition metals, there is evidence that some of the effects of these compounds may be related to induction of oxidative stress. Such pro-oxidant effects appear to be responsible for the induction of apoptosis in tumor cells. These pro-oxidant effects may also induce endogenous antioxidant systems in normal tissues that offer

protection against carcinogenic insult. This review is meant point out understudied areas and stimulate research on the topic with the hope that insights into the mechanisms of cancer preventive activity of tea polyphenols will result.] Lambert JD, Elias RJ. *Arch Biochem Biophys.* 2010 Sep 1;501(1):65-72. http://www.ncbi.nlm.nih.gov/pubmed/20558130

108. **The association between periodontal disease and cancer: a review of the literature. [**OBJECTIVES: Periodontal disease has long been linked to many systemic diseases, and recently a link between periodontal disease and cancer has been established. The purpose of this paper is to review the literature to explore the evidence to date of a relationship between periodontal disease and cancer. In addition, the main hypotheses for the association are discussed along with challenges in evaluating the evidence. DATA/SOURCES/STUDY SELECTION: In this review, English-language papers studying the relationship between periodontal disease or tooth loss in humans and increased risk of several types of cancers along with overall cancer risk between 1990 and April 2009 were reviewed. CONCLUSIONS: The most consistent increased risk was noted in studies of oral and esophageal cancers and periodontal disease. Gastric and pancreatic cancers had an association in most but not all studies. Lung, prostate, hematologic and other cancers were less consistently associated or did not have sufficient studies to determine a predictable pattern. Studies to date indicate a positive correlation between several forms of cancer and periodontal disease.] Fitzpatrick SG, Katz J. *J Dent.* 2010 Feb;38(2):83-95. http://www.ncbi.nlm.nih.gov/pubmed/19895866

Breast

109. **Periodontal disease may associate with breast cancer.** [The main purpose was to evaluate the association between periodontal disease and the incidence of breast cancer in a prospective study of 3273 randomly selected subjects aged 30-40 years at baseline. Breast cancer incidence was registered from 1985 to 2001 according to the WHO International Classification of Diseases criteria. At baseline, 1676 individuals also underwent a clinical oral examination (Group A) whereas 1597 subjects were not clinically examined but were registered (Group B). The associations between breast cancer, periodontal disease, and missing molars were determined using multiple logistic regression models with several background variables and known risk factors for cancer. In total 26 subjects in group A and 15 subjects in group B had breast cancer. The incidence of breast cancer was 1.75% in subjects who had periodontal disease and/or any missing molars, and 0 in subjects who had periodontal disease but had no missing molars. For periodontally healthy subjects with no missing teeth the breast cancer incidence was 1%. For group B the respective incidence was 0.94%. Female gender (odds ratio (OR) 13.08) and missing any molar in the mandible (OR 2.36) were explanatory variables for breast cancer. Of the subjects with periodontal disease and any missing molars in the mandible 5.5% had breast cancer in comparison to 0.5% of the subjects who had periodontal disease but no missing molars in the mandible ($P < 0.02$). Chronic periodontal disease indicated by missing molars seemed to associate statistically with breast cancer.] Soder B, Yakob M, et al. *Breast Cancer Res Treat.* 2011 Jun;127(2):497-502. http://www.ncbi.nlm.nih.gov/pubmed/20960226

Pancreatic

110. **A Prospective Study of Periodontal Disease and Pancreatic Cancer in US Male Health Professionals.** [Two previous cohort studies reported positive associations between tooth loss or periodontitis and pancreatic cancer risk. Data on periodontal disease were obtained at baseline and every other year thereafter in a cohort of 51 529 male health professionals aged 40–75 years. A total of 216 patients were diagnosed with incident pancreatic cancer during 16 years of follow-up. Multivariable relative risks (RRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models controlling for potential confounders, including detailed smoking history. All statistical tests were two-sided. Compared with no periodontal disease, history of periodontal disease was associated with increased pancreatic cancer risk (overall, multivariable RR = 1.64, 95% CI = 1.19 to 2.26; *P* = .002; crude incidence rates: 61 versus 25 per 100 000 person-years; among never smokers, multivariable RR = 2.09, 95% CI = 1.18 to 3.71; *P* = .01; crude incidence rates: 61 versus 19 per 100 000 person-years). In contrast, baseline number of natural teeth and cumulative tooth loss during follow-up were not strongly associated with pancreatic cancer. The association between periodontal disease and increased risk of pancreatic cancer may occur through plausible biologic mechanisms, but confirmation of this association is necessary.] Michaud DS, Joshipura K, et al. Journal of the National Cancer Institute 2007 99(2):171-175, http://jnci.oxfordjournals.org/cgi/content/abstract/99/2/171

111. **Plasma antibodies to oral bacteria and risk of pancreatic cancer in a large European prospective cohort study.** [OBJECTIVE: Examine the relationship between antibodies to 25 oral bacteria and pancreatic cancer risk in a prospective cohort study. DESIGN: We measured antibodies to oral bacteria in prediagnosis blood samples from 405 pancreatic cancer cases and 416 matched controls, nested within the European Prospective Investigation into Cancer and Nutrition study. Analyses were conducted using conditional logistic regression and additionally adjusted for smoking status and body mass index. RESULTS: Individuals with high levels of antibodies against Porphyromonas gingivalis ATTC 53978, a pathogenic periodontal bacteria, had a twofold higher risk of pancreatic cancer than individuals with lower levels of these antibodies (OR 2.14; 95% CI 1.05 to 4.36; >200 ng/ml vs ≤200 ng/ml). To explore the association with commensal (non-pathogenic) oral bacteria, we performed a cluster analysis and identified two groups of individuals, based on their antibody profiles. A cluster with overall higher levels of antibodies had a 45% lower risk of pancreatic cancer than a cluster with overall lower levels of antibodies (OR 0.55; 95% CI 0.36 to 0.83). CONCLUSIONS: Periodontal disease might increase the risk for pancreatic cancer. Moreover, increased levels of antibodies against specific commensal oral bacteria, which can inhibit growth of pathogenic bacteria, might reduce the risk of pancreatic cancer. Studies are needed to determine whether oral bacteria have

direct effects on pancreatic cancer pathogenesis or serve as markers of the immune response.] Michaud DS, Izard J, et al. *Gut*. 2012 Sep 18. [Epub ahead of print] **http://www.ncbi.nlm.nih.gov/pubmed/22990306**

112. **Role of bacterial infections in pancreatic cancer.** [Established risk factors for pancreatic cancer, including tobacco smoking, chronic pancreatitis, obesity, and type II diabetes, collectively account for less than half of all pancreatic cancer cases. Inflammation plays a key role in pancreatic carcinogenesis, but it is unclear what causes local inflammation, other than pancreatitis. Epidemiological data suggest that *Helicobacter pylori* may be a risk factor for pancreatic cancer, and more recently, data suggest that periodontal disease, and *Porphyromonas gingivalis*, a pathogen for periodontal disease, may also play a role in pancreatic carcinogenesis. Individuals with periodontal disease have elevated markers of systemic inflammation, and oral bacteria can disseminate into the blood, stomach, heart, and even reach the brain. These infections may contribute to the progression of pancreatic cancer by acting jointly with other pancreatic cancer risk factors that impact the inflammation and immune response, such as smoking and obesity, and the *ABO* genetic variant, recently linked to pancreatic cancer through genome-wide association studies. The complex interplay between bacteria, host immune response, and environmental factors has been examined closely in relation to gastric cancer, but new research suggests bacteria may be playing a role in other gastrointestinal cancers. This review will summarize the literature on epidemiological studies examining infections that have been linked to pancreatic cancer and propose mechanistic pathways that may tie infections to pancreatic cancer.] Michaud DS. *Carcinogenesis (2013) doi: 10.1093/carcin/bgt249* First published online: July 10, 2013 http://m.carcin.oxfordjournals.org/content/early/2013/07/10/carcin.bgt249.short

113. **Tooth loss, pancreatic cancer, and *Helicobacter pylori* .** [Background: Poor dental health has been associated with increased risks of oral, esophageal, and gastric cancer and may also be associated with pancreatic cancer. In addition, *Helicobacter pylori* has been found in dental plaque and has been associated with periodontal disease and pancreatic cancer. Objective: The objective was to investigate prospectively the relation between dentition history and pancreatic cancer in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort in Finland and the association between dentition history and *H. pylori* seropositivity in a cross-sectional sample of subjects without cancer (*n* = 475) from the same cohort. Design: Of the 29 104 male smokers aged 50–69 y in the cohort for whom there were complete data, 174 developed pancreatic cancer from 1985 to 1997. Cox proportional hazard models were used to estimate age-, smoking-, education-, urban living–, and height-adjusted hazard ratios and 95% CIs for pancreatic cancer, and logistic regression models were used to estimate age- and education-adjusted odds ratios for *H. pylori* carriage. Results: Tooth loss was positively associated with pancreatic cancer (edentulous compared with missing 0–10 teeth: hazard ratio = 1.63; 95% CI: 1.09, 2.46; *P* for trend = 0.02) but was not significantly associated with *H. pylori* seropositivity (edentulous compared with missing 0–10 teeth: odds ratio = 1.30; 95% CI: 0.73, 2.32; *P* for trend = 0.37). Conclusion: Additional studies are needed to evaluate the association between tooth loss and pancreatic cancer, as well as cancers at other gastrointestinal sites, particularly with respect to possible biological mechanisms.] Stolzenberg-Solomon RZ, Dodd KW, et al. *American Journal of Clinical Nutrition*, Vol. 78, No. 1, 176-181, July 2003. http://www.ajcn.org/cgi/content/full/78/1/176

114. **Variations of oral microbiota are associated with pancreatic diseases including pancreatic cancer**. [ObjectiveThe associations between oral diseases and increased risk of pancreatic cancer have been reported in several prospective cohort studies. In this study, we measured variations of salivary microbiota and evaluated their potential associations with pancreatic cancer and chronic pancreatitis.MethodsThis study was divided into three phases: (1) microbial profiling using the Human Oral Microbe Identification Microarray to investigate salivary microbiota variation between 10 resectable patients with pancreatic cancer and 10 matched healthy controls, (2) identification and verification of bacterial candidates by real-time quantitative PCR (qPCR) and (3) validation of bacterial candidates by qPCR on an independent cohort of 28 resectable pancreatic cancer, 28 matched healthy control and 27 chronic pancreatitis samples.ResultsComprehensive comparison of the salivary microbiota between patients with pancreatic cancer and healthy control subjects revealed a significant variation of salivary microflora. Thirty-one bacterial species/clusters were increased in the saliva of patients with pancreatic cancer (n=10) in comparison to those of the healthy controls (n=10), whereas 25 bacterial species/clusters were decreased. Two out of six bacterial candidates (Neisseria elongata and Streptococcus mitis) were validated using the independent samples, showing significant variation ($p<0.05$, qPCR) between patients with pancreatic cancer and controls (n=56). Additionally, two bacteria (Granulicatella adiacens and S mitis) showed significant variation ($p<0.05$, qPCR) between chronic pancreatitis samples and controls (n=55). The combination of two bacterial biomarkers (N elongata and S mitis) yielded a receiver operating characteristic plot area under the curve value of 0.90 (95% CI 0.78 to 0.96, $p<0.0001$) with a 96.4% sensitivity and 82.1% specificity in distinguishing patients with pancreatic cancer from healthy subjects.ConclusionsThe authors observed associations between variations of patients' salivary microbiota with pancreatic cancer and chronic pancreatitis. This report also provides proof of salivary microbiota as an informative source for discovering non-invasive biomarkers of systemic diseases.] Farrell JJ, Zhang L, et al. *Gut.* 2011 Oct 12. [Epub ahead of print] . http://www.ncbi.nlm.nih.gov/pubmed/21994333

Gastrointestinal

115. Association between oral health and gastric precancerous lesions. [Although recent studies have suggested that tooth loss is positively related to the risk of gastric non-cardia cancer, the underlying oral health conditions potentially responsible for the association remain unknown. We investigated whether clinical and behavioral measures of oral health are associated with the risk of gastric precancerous lesions. We conducted a cross-sectional study of 131 patients undergoing upper gastrointestinal

endoscopy. Cases were defined as those with gastric precancerous lesions including intestinal metaplasia or chronic atrophic gastritis on the basis of standard biopsy review. A validated structured questionnaire was administered to obtain information on oral health behaviors. A comprehensive clinical oral health examination was performed on a subset of 91 patients to evaluate for periodontal disease and dental caries experience. A total of 41 (31%) cases of gastric precancerous lesions were identified. Compared with non-cases, cases were significantly more likely to not floss their teeth [odds ratio (OR) = 2.89, 95% confidence interval (CI): 1.09-7.64], adjusting for age, sex, race, body mass index, smoking status, educational attainment and Helicobacter pylori status in serum. Among participants who completed the oral examination, cases (n = 28) were more likely to have a higher percentage of sites with gingival bleeding than non-cases [OR = 2.63, 95% CI: 1.37-5.05 for a standard deviation increase in bleeding sites (equivalent to 19.7%)], independent of potential confounders. Our findings demonstrate that specific oral health conditions and behaviors such as gingival bleeding and tooth flossing are associated with gastric precancerous lesions.] Salazar CR, Francois F, et al. *Carcinogenesis*. 2012 Feb;33(2):399-403. **http://www.ncbi.nlm.nih.gov/pubmed/22139442**

116. **Association between Selected Oral Pathogens and Gastric Precancerous Lesions**. [We examined whether colonization of selected oral pathogens is associated with gastric precancerous lesions in a cross-sectional study. A total of 119 participants were included, of which 37 were cases of chronic atrophic gastritis, intestinal metaplasia, or dysplasia. An oral examination was performed to measure periodontal indices. Plaque and saliva samples were tested with real-time quantitative PCR for DNA levels of pathogens related to periodontal disease (Porphyromonas gingivalis, Tannerella forsythensis, Treponema denticola, Actinobacillus actinomycetemcomitans) and dental caries (Streptococcus mutans and S. sobrinus). There were no consistent associations between DNA levels of selected bacterial species and gastric precancerous lesions, although an elevated but non-significant odds ratio (OR) for gastric precancerous lesions was observed in relation to increasing colonization of A. actinomycetemcomitans (OR=1.36 for one standard deviation increase, 95% Confidence Interval=0.87-2.12), P. gingivalis (OR=1.12, 0.67-1.88) and T. denticola (OR=1.34, 0.83-2.12) measured in plaque. To assess the influence of specific long-term infection, stratified analyses by levels of periodontal indices were conducted. A. actinomycetemcomitans was significantly associated with gastric precancerous lesions (OR=2.51, 1.13-5.56) among those with ≥ median of percent tooth sites with PD≥3 mm, compared with no association among those below the median (OR=0.86, 0.43-1.72). A significantly stronger relationship was observed between the cumulative bacterial burden score of periodontal disease-related pathogens and gastric precancerous lesions among those with higher versus lower levels of periodontal disease indices (p-values for interactions: 0.03-0.06). Among individuals with periodontal disease, high levels of colonization of periodontal pathogens are associated with an increased risk of gastric precancerous lesions.] Salazar CR, Sun J, et al. *PLoS One*. 2013;8(1):e51604. doi: 10.1371/journal.pone.0051604. Epub 2013 Jan 7. http://www.ncbi.nlm.nih.gov/pubmed/23308100

117. **C-reactive protein and the risk of incident colorectal cancer.** [Plasma CRP concentrations are elevated among persons who subsequently develop colon cancer. These data support the hypothesis that inflammation is a risk factor for the development of colon cancer in average-risk individuals.] Erlinger TP, Platz EA, et.al., *JAMA vol.291 No.5, Feb 4,2004.* http://jama.ama-assn.org/cgi/content/abstract/291/5/585

118. ***Fusobacterium nucleatum* infection is prevalent in human colorectal carcinoma** [An estimated 15% or more of the cancer burden worldwide is attributable to known infectious agents. We screened colorectal carcinoma and matched normal tissue specimens using RNA-seq followed by host sequence subtraction and found marked over-representation of *Fusobacterium nucleatum* sequences in tumors relative to control specimens. *F. nucleatum* is an invasive anaerobe that has been linked previously to periodontitis and appendicitis, but not to cancer. Fusobacteria are rare constituents of the fecal microbiota, but have been cultured previously from biopsies of inflamed gut mucosa. We obtained a *Fusobacterium* isolate from a frozen tumor specimen; this showed highest sequence similarity to a known gut mucosa isolate and was confirmed to be invasive. We verified overabundance of *Fusobacterium* sequences in tumor versus matched normal control tissue by quantitative PCR analysis from a total of 99 subjects ($p = 2.5 \times 10^{-6}$), and we observed a positive association with lymph node metastasis.] Castellarin M, Warren RL, et al. *Genome Research*, Published in Advance October 18, 2011, doi: 10.1101/gr.126516.111 http://genome.cshlp.org/content/early/2011/10/05/gr.126516.111.abstract

119. ***Fusobacterium nucleatum* Promotes Colorectal Carcinogenesis by Modulating E-Cadherin/β-Catenin Signaling via its FadA Adhesin.** [Highlights: *F. nucleatum* (*Fn*) adhesin FadA binds E-cadherin and promotes CRC cell proliferation; A peptide from the FadA-binding region of E-cadherin prevents *Fn*-mediated carcinogenesis; FadA promotes inflammation and E-cadherin-mediated CRC tumor growth in xenograft mice; Tissues from human adenomas and adenocarcinomas have elevated *fadA* gene levels; Summary:*Fusobacterium nucleatum* (*Fn*) has been associated with colorectal cancer (CRC), but causality and underlying mechanisms remain to be established. We demonstrate that *Fn* adheres to, invades, and induces oncogenic and inflammatory responses to stimulate growth of CRC cells through its unique FadA adhesin. FadA binds to E-cadherin, activates β-catenin signaling, and differentially regulates the inflammatory and oncogenic responses. The FadA-binding site on E-cadherin is mapped to an 11-amino-acid region. A synthetic peptide derived from this region of E-cadherin abolishes FadA-induced CRC cell growth and oncogenic and inflammatory responses. The *fadA* gene levels in the colon tissue from patients with adenomas and adenocarcinomas are >10–100 times higher compared to normal individuals. The increased FadA expression in CRC correlates with increased expression of oncogenic and inflammatory genes. This study unveils a mechanism by which *Fn* can drive CRC and identifies FadA as a potential diagnostic and therapeutic target for CRC.] Rubinstein MR, Wang X, et al. *Cell Host & Microbe,* Volume 14, Issue 2, 195-206, 14 August 2013. http://www.cell.com/cell-host-microbe/abstract/S1931-3128(13)00260-6

120. **Genomic analysis identifies association of *Fusobacterium* with colorectal carcinoma.** [The tumor microenvironment of colorectal carcinoma is a complex community of genomically altered cancer cells, nonneoplastic cells, and a diverse collection of microorganisms. Each of these components may contribute to carcinogenesis; however, the role of the microbiota is the least well understood. We have characterized the composition of the microbiota in colorectal carcinoma using whole genome sequences from nine tumor/normal pairs. *Fusobacterium* sequences were enriched in carcinomas, confirmed by quantitative PCR and 16S rDNA sequence analysis of 95 carcinoma/normal DNA pairs, while the Bacteroidetes and Firmicutes phyla were depleted in tumors. Fusobacteria were also visualized within colorectal tumors using FISH. These findings reveal alterations in the colorectal cancer microbiota; however, the precise role of Fusobacteria in colorectal carcinoma pathogenesis requires further investigation.]Kostic AD, Meyerson M, et al. *Genome Res. October 18, 2011 ; Published in Advance October 18, 2011.* http://genome.cshlp.org/content/early/2011/10/04/gr.126573.111.abstract
121. **Periodontal Disease, Porphyromonas Gingivalis (*P. gingivalis*) Serum Antibody Levels and Orodigestive Cancer Mortality**. [Periodontitis, the progressive loss of the alveolar bone around the teeth and the major cause of tooth loss in adults, is due to oral microorganisms, including *Porphyromonas gingivalis (*P gingivalis). Periodontitis is associated with a local overly aggressive immune response and a spectrum of systemic effects, but the role of this condition in orodigestive cancers is unclear. We prospectively examined clinically ascertained periodontitis (N=12,605) and serum IgG immune response to *P gingivalis* (N=7,852) in relation to orodigestive cancer mortality among men and women in the National Health and Nutrition Examination Survey (NHANES III). A detailed oral health exam was conducted from 1988-1994 in survey Phases I and II, while serum IgG for P gingivalis was measured from 1991-1994 in Phase II only. One-hundred and five orodigestive cancer deaths were ascertained through December 31, 2006. Periodontitis (moderate or severe) was associated with increased orodigestive cancer mortality (RR=2.28, 95%CI=1.17-4.45); mortality risks also increased with increasing severity of periodontal disease (p trend=0.01). Periodontitis-associated mortality was in excess for colorectal (RR=3.58; 95% CI=1.15-11.16) and possibly for pancreatic cancer (RR=4.56; 95%CI=0.93-22.29). Greater serum P gingivalis IgG tended to be associated overall with increased orodigestive cancer mortality (p trend=0.06); P gingivalis-associated excess orodigestive mortality was also found for healthy subjects not exhibiting overt periodontal disease (RR= 2.25; 95%CI=1.23-4.14). Orodigestive cancer mortality is related to periodontitis and to the periodontal pathogen, *P gingivalis*, independent of periodontal disease. P gingivalis is a biomarker for microbe-associated risk of death due to orodigestive cancer.] Ahn J, Segers S, et al. Carcinogenesis (2012) doi: 10.1093/carcin/bgs112. http://carcin.oxfordjournals.org/content/early/2012/02/25/carcin.bgs112.abstract
122. **Prospective study of tooth loss and incident esophageal and gastric cancers in China.** [OBJECTIVE: To determine the association between tooth loss and the risk of developing esophageal squamous cell carcinoma, gastric cardia adenocarcinoma, or gastric non-cardia adenocarcinoma in a prospective study. METHODS: Cox proportional hazards regression was used to examine these associations in a 28,868-person cohort followed prospectively for 5.25 years. The baseline questionnaire included questions regarding tooth loss, and individuals reporting lost teeth had their teeth counted by study personnel. The analytic cohort included 620 esophagus, 431 gastric cardia, and 102 gastric non-cardia cancer cases. RESULTS: Tooth loss was associated with a significantly elevated risk of developing all three cancers. When examined as median splits, tooth loss was associated with a relative risk (RR) (95% confidence interval, CI) of 1.3 (1.1-1.6) in the esophagus, 1.3 (1.0-1.6) in the gastric cardia, and 1.8 (1.1-3.0) in the gastric non-cardia. Further analysis demonstrated that this increased risk was most strongly associated with the loss of the first few teeth and was primarily confined to the younger members of our cohort. CONCLUSIONS: In this cohort tooth loss increased the risk of developing upper gastrointestinal cancer. We hypothesize that this may be related to alterations in oral bacterial flora and subsequent increases in the in-vivo production of carcinogens such as nitrosamines.] Abnet CC, Qiao YL, et al. *Cancer Causes Control*. 2001 Nov;12(9):847-54. http://www.ncbi.nlm.nih.gov/pubmed
123. **Tooth loss is associated with increased risk of gastric non-cardia adenocarcinoma in a cohort of Finnish smokers.** OBJECTIVE: Tooth loss has been associated with upper gastrointestinal cancer in several studies, but only one previous study used prospectively collected data. The importance of confounding by Helicobacter pylori has not previously been addressed. The objective was to determine the association between tooth loss and upper gastrointestinal cancer in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort and to determine the importance of potentially confounding dietary factors or H. pylori seropositivity. MATERIAL AND METHODS: A prospective cohort study with 29,124 subjects included 49 esophageal squamous cell carcinomas, 66 esophageal/gastric cardia adenocarcinomas, and 179 gastric non-cardia adenocarcinomas occurring between 1985 and 1999. Cox proportional hazards models adjusted for age and education were used to estimate hazard ratios (HRs) and 95% CIs. Odds ratios and 95% CIs were calculated with and without adjustment for H. pylori seropositivity in a nested case-control group to determine whether H. pylori confounded the association between tooth loss and gastric cancer. RESULTS: Tooth loss significantly increased the hazard ratio for gastric non-cardia cancer, the HR (95% CI) for edentulous subjects versus those with < 10 teeth lost was 1.65 (1.09, 2.49, respectively). No statistically significant associations were found between tooth loss and esophageal squamous cell carcinoma or esophageal/gastric cardia adenocarcinoma. Confounding by dietary factors, tobacco smoking, or H. pylori did not explain these results. CONCLUSIONS: Tooth loss was associated with increased risk of gastric non-cardia cancer, but not esophageal squamous cell carcinoma or esophageal/gastric cardia adenocarcinoma in this Finnish cohort.] Abnet CC, Kamangar F, et al. *Scand J Gastroenterol.* 2005 Jun;40(6):681-7. http://www.ncbi.nlm.nih.gov/pubmed/16036528
124. **Tooth loss is associated with increased risk of total death and death from upper gastrointestinal cancer, heart disease, and stroke in a Chinese population-based cohort.** [BACKGROUND: Tooth loss has previously been associated with a

higher risk of cancer, heart disease, and stroke, but the role of confounding by smoking remains an issue. METHODS: We conducted a cohort study including 29,584 healthy, rural Chinese adults who were participants in a chemoprevention trial from 1986 through 1991 and who have been followed-up through 2001. We categorized tooth loss for each subject as less than or equal to or greater than the median number of teeth lost for other subjects of the same age at baseline. Mortality outcomes were categorized as follows: total death (n = 9362), upper gastrointestinal (GI) cancer death (n = 2625), other cancer death (n = 514), heart disease death (n = 1932), and fatal stroke (n = 2866). RESULTS: Individuals with greater than the age-specific median number of teeth lost had statistically significant 13% increased risk of total death [95% confidence interval (CI) 9-18%], 35% increased risk of upper GI cancer death (95% CI 14-59%), 28% increased risk of heart disease death (95% CI 17-40%), and 12% increased risk of stroke death (95% CI 2-23%), but no significantly increased risk of death from cancer at other sites. These elevated risks were present in male smokers, male non-smokers, and females, nearly all never-smokers. CONCLUSIONS: In this Asian population, tooth loss significantly increased the risk of total death and death from upper GI cancer, heart disease, and stroke. These associations were not limited to tobacco smokers.] Abnet CC, Qiao YL, et al. *Int J Epidemiol.* 2005 Apr;34(2):467-74. http://www.ncbi.nlm.nih.gov/pubmed/15659476

Oral & Head-Neck

125. **Case-control study of squamous cell cancer of the oral cavity in Denmark.** [(After adjustment for smoking and alcohol, poor dentition as noted by missing teeth, is a high oral cancer risk factor, and those with lichen planus and leukoplakis showed elevated risk for oral cancer.) A population-based case-control study was designed to examine if the risk of developing intra-oral squamous-cell carcinoma in Denmark was associated with occupation, marital status, residence, dental status, and exposure to coffee, tea, tobacco, and alcohol. Cases consisted of 161 consecutively-admitted incident patients with histologically verified, primary, intra-oral squamous-cell carcinoma treated at the Aarhus University Hospital from January 1986 to November 1990. For each case, three controls of the same gender and age were selected randomly from among nonhospitalized residents in the hospital's catchment area (some 1.4 m inhabitants). Four hundred of the selected 483 controls participated in the study. Risk was associated significantly with marital status, residence, dental status, alcohol consumption, and exposure to tobacco. When correcting for tobacco and alcohol consumption, only marital status and dental status remained significant. The association between risk and marital status was particularly prominent among divorced compared with married persons (odds ratio [OR] = 2.3, 95 percent confidence interval [CI] = 1.1-4.6). Persons with less than five teeth had an OR of 2.4 (CI 1.3-4.1) compared with persons with 15 or more teeth. Tobacco and alcohol exposure were the strongest individual risk-indicators in both lifetime and current consumption estimates, and their composite effect was particularly strong. Compared with nonusers, OR for tobacco (> 20 g/d) adjusted for alcohol = 5.8 (CI = 3.1-10.9); OR for alcohol (> 5 drinks/d) adjusted for tobacco = 8.4 (CI = 4.0-17.6). The OR for heavy users of tobacco and alcohol (> 20 g tobacco/d and > 5 drinks/d) was 80.7 (CI = 21.8-298.8). These results confirm that tobacco and alcohol contribute significantly to the risk of developing oral cancer. There were no significant differences between the risk estimates for the two genders or young and old persons. Two simulation studies indicate that the observed risk associated with tobacco and alcohol consumption cannot be explained reasonably by a high consumption among the 83 nonrespondents.] Bundgaard T, Wildt J, et al. *Cancer Causes Control.* 1995 Jan;6(1):57-67. http://www.ncbi.nlm.nih.gov/pubmed/7718736
126. **Chronic Periodontitis and the Incidence of Head and Neck Squamous Cell Carcinoma.** [Substantial evidence supports an association between chronic infections/inflammation, and cancer. The aim of this study was to assess the effect of chronic periodontitis on head and neck squamous cell carcinoma (HNSCC). The study population consisted of new patients at the Department of Dentistry and Maxillofacial Prosthetics, Roswell Park Cancer Institute between 1999 and 2005. Cases were patients diagnosed with primary HNSCC. Controls were all patients seen during the same time period but negative for malignancy. Patients age <21 years, edentulous, immunocompromised, and those with history of cancer were excluded. Periodontitis was measured by alveolar bone loss (ABL) from panoramic radiographs by one examiner blind to cancer status. A total of 473 patients (266 cases and 207 controls) were included in the study. Each millimeter of ABL was associated with >4-fold increased risk of HNSCC (odds ratio, 4.36; 95% confidence interval, 3.16-6.01) after adjustment for age, gender, race/ethnicity, marital status, smoking status, alcohol use, and missing teeth. The strength of the association was greatest in the oral cavity, followed by oropharynx and larynx. The association persisted in subjects who never used tobacco and alcohol. There was a significant interaction between smoking and ABL ($P = 0.03$). Patients with periodontitis were more likely to have poorly differentiated oral cavity SCC than those without periodontitis (32.8% versus 11.5%; $P = 0.038$). This study suggests that chronic periodontitis is an independent risk factor for HNSCC and smoking modifies this association. These results have implications for practical and safe strategies for prevention, diagnosis, and treatment of HNSCC.] Tezal, M, *Cancer Epidemiol Biomarkers Prev*, 2009;18(9):2406–12. http://cebp.aacrjournals.org/content/18/9/2406.abstract
127. **Chronic Periodontitis and the Risk of Tongue Cancer. [**To assess the association between the history of chronic periodontitis and the risk of tongue cancer. …After adjusting for the effects of age at diagnosis, smoking status, and number of teeth, each millimeter of alveolar bone loss was associated with a 5.23-fold increase in the risk of tongue cancer (odds ratio, 5.23; 95% confidence interval, 2.64-10.35). Conclusions: This study suggests an association between chronic periodontitis and the risk of tongue cancer in men, independent of smoking status, age, race, ethnicity, and number of teeth. This association needs to be confirmed by larger studies using quantitative assessment of lifetime tobacco exposure. If this association is confirmed, it has a potential impact on understanding the etiology of oral cancer as well as on its prevention and

control.]Tezal Mine, Sullivan MA, et al. *Arch Otolaryngol Head Neck Surg.* 2007;133:450-454. http://archotol.ama-assn.org/cgi/content/abstract/133/5/450.

128. **Dentition, oral hygiene, and risk of oral cancer: a case-control study in Beijing, People's Republic of China.** [A case-control study of oral cancer was conducted in Beijing, People's Republic of China. The study was hospital-based and controls were hospital in-patients matched to the cases by age and gender. A total of 404 case/control pairs were interviewed. This paper provides data regarding oral conditions as risk factors for oral cancer, with every patient having an intact mouth examined (pre-operation among cases) using a standard examination completed by trained oral physicians. After adjustment for tobacco smoking and alcohol consumption, poor dentition--as reflected by missing teeth--emerged as a strong risk factor for oral cancer: the odds ratio (OR) for those who had lost 15-32 teeth compared to those who had lost none was 5.3 for men and 7.3 for women and the trend was significant (P less than 0.01) in both genders. Those who reported that they did not brush their teeth also had an elevated risk (OR = 6.9 for men, 2.5 for women). Compared to those who had no oral mucosal lesions on examination (OR = 1.0), persons with leukoplakia and lichen planus also showed an elevated risk of oral cancer among men and women. Denture wearing per se did not increase oral cancer risk (OR = 1.0 for men, 1.3 for women) although wearing metal dentures augmented risk (OR = 5.5 for men). These findings indicate that oral hygiene and several oral conditions are risk factors for oral cancer, independently of the known risks associated with smoking and drinking.] Zheng TZ, Boyle P, et al. *Cancer Causes Control.* 1990 Nov;1(3):235-41. http://www.ncbi.nlm.nih.gov/pubmed/2102296

129. **Examining the Association between Oral Health and Oral HPV Infection.** [Oral human papillomavirus (HPV) infection is the cause of 40% to 80% of oropharyngeal cancers; yet, no published study has examined the role of oral health in oral HPV infection, either independently or in conjunction with other risk factors. This study examined the relation between oral health and oral HPV infection and the interactive effects of oral health, smoking, and oral sex on oral HPV infection. Our analyses comprised 3,439 participants ages 30 to 69 years for whom data on oral HPV and oral health were available from the nationally representative 2009–2010 National Health and Nutrition Examination Survey. Results showed that higher unadjusted prevalence of oral HPV infection was associated with four measures of oral health, including self-rated oral health as poor-to-fair [prevalence ratio (PR) = 1.56; 95% confidence interval (CI), 1.25–1.95], indicated the possibility of gum disease (PR = 1.51; 95% CI, 1.13–2.01), reported use of mouthwash to treat dental problems in the past week (PR = 1.28; 95% CI, 1.07–1.52), and higher number of teeth lost (P_{trend} = 0.035). In multivariable logistic regression models, oral HPV infection had a statistically significant association with self-rated overall oral health (OR = 1.55; 95% CI, 1.15–2.09), independent of smoking and oral sex. In conclusion, poor oral health was an independent risk factor of oral HPV infection, irrespective of smoking and oral sex practices. Public health interventions may aim to promote oral hygiene and oral health as an additional measure to prevent HPV-related oral cancers.] Bui TC, Markham CM, et al. *Cancer Prev Res;* 6(9); 1–8. Aug 21, 2013. http://cancerpreventionresearch.aacrjournals.org/content/early/2013/08/20/1940-6207.CAPR-13-0081

130. **Immune activation and chronic inflammation as the cause of malignancy in oral lichen planus: is there any evidence?** **[**The association of chronic inflammation with a variety of epithelial malignancies has been recognised for centuries. Well established examples include, among many others, oesophageal adenocarcinoma associated with chronic oesophagitis and bowel cancer associated with chronic inflammatory bowel diseases. By now no data, other than clinical observation, have been available in understanding the pathogenesis of these inflammation-related tumours. However, recent molecular studies on the relationship between solid malignancies and the surrounding stroma have given new insights. There is now enough evidence to accept that the chronic inflammatory process per se is able to provide a cytokine-based microenvironment which is able to influence cell survival, growth, proliferation, differentiation and movement, hence contributing to cancer initiation, progression, invasion and metastasis. Here it is discussed whether also oral lichen planus (OLP), being a chronic inflammatory autoimmune disease which has been clinically associated with development of oral squamous cell carcinoma, might be categorised among these disorders. With this aim, we critically reviewed and detailed the presence, in OLP subepithelial infiltrate, of inflammatory cells and cytokine networks that might act to promote squamous tumorigenesis.**]** Mignogna M., *Oral Oncology , Volume 40 , Issue 2 , Pages 120 – 130,* http://linkinghub.elsevier.com/retrieve/pii/S1368837503001726

131. **Oral hygiene, dentition, sexual habits and risk of oral cancer.** [In an Italian case-control study of oral cancer, number of missing teeth and other aspects of dental care were similar, but the general condition of the mouth, as indicated by gum bleeding, tartar deposits and mucosal irritation, was worse among oral cancer cases than controls. No differences were detected in sexual practices (including oral sex) and (previous) sexually transmitted infections.] Talamini R, Vaccarella S, et al. *Br J Cancer.* 2000 Nov;83(9):1238-42. http://www.ncbi.nlm.nih.gov/pubmed/11027440

132. **Porphyromonas gingivalis promotes invasion of oral squamous cell carcinoma through induction of proMMP9 and its activation.** [Recent epidemiological studies have revealed a significant association between periodontitis and oral squamous cell carcinoma (OSCC). Furthermore, matrix metalloproteinase 9 (MMP9) is implicated in the invasion and metastasis of tumour cells. We examined the involvement of Porphyromonas gingivalis, a periodontal pathogen, in OSCC invasion through induced expression of proMMP and its activation. proMMP9 was continuously secreted from carcinoma SAS cells, while P. gingivalis infection increased proenzyme expression and subsequently processed it to active MMP9 in culture supernatant, which enhanced cellular invasion. In contrast, Fusobacterium nucleatum, another periodontal organism, failed to demonstrate such activities. The effects of P. gingivalis were observed with highly invasive cells, but not with the low invasivetype. P. gingivalis also stimulated proteinase-activated receptor 2 (PAR2) and enhanced proMMP9 expression, which promoted cellular invasion. P. gingivalis mutants deficient in gingipain proteases failed to activate MMP9. Infected SAS cells exhibited activation of ERK1/2, p38, and NF-kB, and their inhibitors diminished both proMMP9-overexpression and cellular invasion.

Together, our results show that P. gingivalis activates the ERK1/2-Ets1, p38/HSP27, and PAR2/NF-kB pathways to induce proMMP9 expression, after which the proenzyme is activated by gingipains to promote cellular invasion of OSCC cell lines. These findings suggest a novel mechanism of progression and metastasis of OSCC associated with periodontitis.] Inaba H, Sugita H, et al. *Cell Microbiol*. 2013 Sep 2. doi: 10.1111/cmi.12211. **http://www.ncbi.nlm.nih.gov/pubmed/23991831**

133. **Risk factors for cancer of the oral cavity and oro-pharynx in Cuba.** [In terms of worldwide levels, Cuba has an intermediate incidence of cancer of the oral cavity and oro-pharynx. We studied 200 cases of cancer of the oral cavity and pharynx, of whom 57 women (median age = 64) and 200 hospital controls, frequency matched with cases by age and sex, in relation to smoking and drinking history, intake of 25 foods or food groups, indicators of oral hygiene and sexual activity, and history of sexually transmitted diseases. Odds ratios (OR) and 95% confidence intervals (CI) were obtained from unconditional multiple logistic regressions and adjusted for age, sex, area of residence, education, and smoking and drinking habits. In the multivariate model, high educational level and white-collar occupation, but not white race, were associated with halving of oral cancer risk. Smoking > or =30 cigarettes per day showed an OR of 20.8 (95% CI: 8.9-48.3), similar to smoking > or =4 cigars daily (OR = 20.5). Drinking > or = 70 alcoholic drinks per week showed an OR of 5.7 (95% CI: 1.8-18.5). Hard liquors were by far the largest source of alcohol. Increased risk was associated with the highest tertile of intake for maize (OR = 1.9), meat (OR = 2.2) and ham and salami (OR = 2.0), whereas high fruit intake was associated with significantly decreased risk (OR = 0.4). Among indicators of dental care, number of missing teeth and poor general oral condition at oral inspection showed ORs of 2.7 and 2.6, respectively. Number of sexual partners, marriages or contacts with prostitutes, practice of oral sex and history of various sexually transmitted diseases, including genital warts, were not associated with oral cancer risk. 82% of oral cancer cases in Cuba were attributable to tobacco smoking, 19% to smoking cigars or pipe only. The fractions attributable to alcohol drinking (7%) and low fruit intake (11%) were more modest. Thus, decreases in cigarette and cigar smoking are at present the key to oral cancer prevention in Cuba.] Garrote LF, Herrero R, et al. *Br J Cancer.* 2001 Jul 6;85(1):46-54. http://www.ncbi.nlm.nih.gov/pubmed/11437401
134. **Risk factors in oral and oropharyngeal squamous cell carcinoma: a population-based case-control study in southern Sweden.** [In the year 2002, about 275,000 inhabitants around the world developed oral cancer and over half of them will die of their disease within 5 years. Oral and oropharyngeal squamous cell carcinoma (OOSCC) accounts for about 1% of all cancers in Sweden - which is low compared to the incidence on the Indian subcontinent and in other parts of Asia, where it is one of the most common forms of cancer. The incidence in Sweden is increasing, however. The study comprised 80% (132/165) of all consecutive cases living in the Southern Healthcare Region, born in Sweden and without previous cancer diagnosis (except skin cancer), who were diagnosed with OOSCC during the period September 2000 to January 2004. Using the Swedish Population Register, 396 cancer-free controls were identified and matched by age, gender and county. Of these individuals, 320 (81%) agreed to take part in the study. Cases and controls were subjected to a standardised interview, identical oral examinations including panoramic radiographs, and cell sampling for human papillomavirus (HPV) analysis. In total 128 patients with planned curative treatment were followed for a median time of 22 months (range 0 - 36). The aims were to assess different potential risk factors in OOSCC such as oral hygiene, dental status, oral mucosal lesions, alcohol and tobacco use, virus infection, and some related to lifestyle. A further aim was to assess the influence of these factors on recurrence or occurrence of a new second primary tumour (SPT) of squamous cell carcinoma. … In conclusion, the results in this study confirm that both smoking tobacco and alcohol consumption are risk factors for OOSCC. The use of Swedish moist snuff had no effect on the risk. Independent risk factors identified are poor oral hygiene, inadequate dental status and malfunctioning complete dentures. Regular dental check-ups are a preventive factor. Among other possible risk factors studied, high-risk HPV infection appears to be the strongest. High-risk HPV infection increases the cause-specific RR of recurrence or SPT. Tumour stage influences the rate] Rosenquist K. *Swed Dent J Suppl.* 2005;(179):1-66. http://www.ncbi.nlm.nih.gov/pubmed/16335030
135. **Smoking, alcohol, dentition and diet in the epidemiology of oral cancer.** [This matched case-control study was conducted in Western New York. The smoking, alcohol consumption, dental hygiene and diet of 290 cases were compared with those of 290 sex-, age-, and neighbourhood-matched controls. The results confirm earlier findings that cigarette smoking and alcohol consumption impart substantial risk of oral cancer. The results also confirm that poor oral hygiene increases the risk of oral cancer, although this effect is much smaller than those of cigarette smoking and alcohol consumption. The results suggest that, of macronutrients, intake of fat is more likely than those of protein or carbohydrate to be related to risk. Of micronutrients, calcium, sodium, riboflavin and retinol are associated with risk, while thiamin, niacin, and dietary fibre are associated with decreased risk. Although patterns of dietary effects are discernable, these effects are in general much weaker than are those of smoking and alcohol consumption.] Marshall JR, Graham S, et al. *Eur J Cancer B Oral Oncol.* 1992 Jul;28B(1):9-15. http://www.ncbi.nlm.nih.gov/pubmed/1422474

Prostate

136. **C-reactive protein is significantly associated with prostate-specific antigen and metastatic disease in prostate cancer.** [The strong association of CRP with PSA, independent of tumor stage, suggests that inflammation might be fundamental in prostate cancer, and that chronic inflammation may be a legitimate target for prostate cancer chemoprevention and treatment.] Lehrer S, Diamond EJ, et.al. *BJU Int.* 2005 May;95(7):961-2. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=15839913&dopt=Abstract

General- Other

137. **Cytokine-regulated expression of collagenase-2 (MMP-8) is involved in the progression of ovarian cancer. [**Matrix metalloproteinases (MMPs) have been implicated in ovarian cancer progression. Among them, MMP-8 that degrades type I collagen may play a crucial role. The aim of our study was to determine MMP-8 expression and regulation in ovarian cancer and its association with other MMPs and tissue inhibitors of metalloproteinases (TIMPs). Tissue microarrays (TMAs) containing tissue cylinders from 302 patients were used for immunohistochemical studies. In addition, MMP-8 expression in vitro was analysed by a specific immunoassay and PCR-analysis. MMP-7 (81%), MMP-8 (95%), MT3-MMP (100%), TIMP-2 (100%), and TIMP-3 (96%) were expressed in all the OVCAs, but the staining intensities varied. MMP-3 (6%), MMP-9 (57%) and TIMP-1 (43%) expressions were more rarely detected. Only MMP-8 expression levels correlated with tumour grade (P<0.01), tumour stage (P<0.01), and a poor prognosis (P<0.05). MMP-8 protein and gene expression in vitro was found to be significantly upregulated by interleukin-1beta (IL-1beta, P<0.01). The data indicate that MMP-8 overexpression in OVCAs is regulated by IL-1beta and that pro-inflammatory cytokines may promote the invasive potential of ovarian cancer**] Stadlmann S, Pollheimer J, et al. *Eur J Cancer* 2003 Nov;39(17):2499-505.** **http://www.ncbi.nlm.nih.gov/pubmed/14602136**
138. **Inflammation and Cancer.** [Recent data have expanded the concept that inflammation is a critical component of tumour progression. Many cancers arise from sites of infection, chronic irritation and inflammation. It is now becoming clear that the tumour microenvironment, which is largely orchestrated by inflammatory cells, is an indispensable participant in the neoplastic process, fostering proliferation, survival and migration. In addition, tumour cells have co-opted some of the signalling molecules of the innate immune system, such as selectins, chemokines and their receptors for invasion, migration and metastasis. These insights are fostering new anti-inflammatory therapeutic approaches to cancer development.] Coussens LM, Werb Z. *Nature, Vol 420, p 860-867, December 2002,* http://osteosarcomasupport.org/immunology/inflammation-cancer-nature-2002.pdf
139. **Inflammation and Cancer II. Role of chronic inflammation and cytokine gene polymorphisms in the pathogenesis of gastrointestinal malignancy.** [It is well established that cancer arises in chronically inflamed tissue, and this is particularly notable in the gastrointestinal tract. Classic examples include *Helicobacter pylori*-associated gastric cancer, hepatocellular carcinoma, and inflammatory bowel disease-associated colorectal cancer. There is growing evidence to suggest that this association is not coincidental but may indeed be causal. In this review, we discuss the role of chronic inflammation and cytokine gene polymorphisms in the pathogenesis of gastrointestinal malignancy and outline some of the possible mechanisms involved.] Maccarthur M, Hold, GL, El-Omar EE. *Am J Physiol Gastrointest Liver Physiol* 286: G515-G520, 2004, http://ajpgi.physiology.org/cgi/content/abstract/286/4/G515
140. **Inflammation Marker Predicts Colon Cancer.** [C-reactive protein, a marker of inflammation circulating in the blood already associated with increased risk of heart disease, can also be used to identify a person's risk of developing colon cancer, according to a Johns Hopkins study. People with higher levels of CRP in their blood were more likely to develop colorectal cancers than those with low levels of CRP. Higher levels of C-reactive protein are linked to an increased risk of several apparently distinct, chronic diseases: heart disease, stroke, diabetes, and now colon cancer. The odds of developing colorectal cancers increased progressively with higher concentrations of CRP.] Johns Hopkins Medicine
Office of Communications and Public Affairs. *Feb. 3, 2004 JAMA.*
http://www.hopkinsmedicine.org/Press_releases/2004/02_10_04.html
141. **Oral Cancer & Periodontal Disease.** [UB study links gum disease with oral cancer risk. Oral tumors were four times more prevalent and pre-cancerous lesions were twice as prevalent in people with periodontal disease (as assessed by clinical attachment loss) than in those without periodontal disease. These findings suggest strongly that infection is associated with oral cancer. Research shows an association between H. pylori and stomach cancer, human papillomavirus and cervical cancer, and cytomegalovirus and Kaposi's sarcoma.] Tezal Mine, Grossi SG., http://www.eurekalert.org/pub_releases/2003-03/uab-usl031303.php
142. **Periodontal disease, tooth loss, and cancer risk in male health professionals: a prospective cohort study.** [Summary: Background: Studies suggest that tooth loss and periodontal disease might increase the risk of developing various cancers; however, smoking might have confounded the reported associations. We aimed to assess whether periodontal disease or tooth loss is associated with cancer risk. …Interpretation: Periodontal disease was associated with a small, but significant, increase in overall cancer risk, which persisted in never-smokers. The associations recorded for lung cancer are probably because of residual confounding by smoking. The increased risks noted for haematological, kidney, and pancreatic cancers need confirmation, but suggest that periodontal disease might be a marker of a susceptible immune system or might directly affect cancer risk. …Dr. Michaud and colleagues found significant associations (P<0.05) between a history of periodontal disease and several cancers, including: 36% increase in risk of lung cancer; 49% increase in the risk of kidney cancer; 54% increase in the risk of pancreatic cancer; and a 30% increase in the risk of hematologic cancers, including non-Hodgkin's lymphoma, leukemia, and multiple myeloma.] Michaud DS, Giovannuci E, et al. *Lancet Oncology* 2008; 9:550-558.
http://www.thelancet.com/journals/lanonc/article/PIIS1470204508701062/abstract
143. **Vitamin D, periodontal disease, tooth loss, and cancer risk.** [(Suggestion is made that the underlying factor between the periodontal disease / tooth loss link with cancer is low serum 25-hydroxyvitamin D – calcidiol – levels.] Grant WB. *Lancet Oncol*. 2008 Jul;9(7):612-3. http://www.ncbi.nlm.nih.gov/pubmed/18598929

Caphosol – Calcium Phosphate

144. **A prospective, randomized trial for the prevention of mucositis in patients undergoing hematopoietic stem cell transplantation.** [Oral mucositis is a complication common to many cancer therapies and produces considerable pain and morbidity. The present study reports a double-blind, prospective, randomized clinical trial testing the efficacy of a calcium phosphate mouth rinse (Caphosol) with fluoride treatments vs a standard regimen of fluoride rinsing and placebo tray treatments in 95 patients undergoing hematopoietic stem cell transplantation (HSCT). The days and severity of mucositis were prospectively evaluated. There were statistically significant decreases in days of mucositis (3.72 vs 7.22 P=0.001), duration of pain (2.86 vs 7.67, P=0.0001), dose of morphine (34.54 mg vs 122.78 mg), days of morphine (1.26 vs 4.02, P=0.0001) and days to the onset of engraftment ANC (absolute neurotrophil count)>200 mm(3) (11.12 vs 12.56) in the Caphosol and fluoride treatment group vs fluoride-rinse group, respectively. Caphosol, a neutral, supersaturated, Ca(2+)/PO(4)(3-) mouth rinse, used in combination with topical fluoride treatments, is superior to fluoride rinse alone in reducing the frequency, intensity and duration of oral mucositis in patients undergoing HSCT.] Papas AS, Clark RE, et al. *Bone Marrow Transplant.* 2003 Apr;31(8):705-12. http://www.ncbi.nlm.nih.gov/pubmed/12692611
145. **Calcium phosphate mouth rinse for preventing oral mucositis**. [Caphosol artificial saliva is a topical oral agent that lubricates the mucosa dn helps maintain the integrity of the oral cavity. The agent is a neutral supersaturated calcium phosphate mouthrinse; it is believed that the ions exert a beneficial effect by diffusing into the intracellular spaces in the epithelium and permeating mucosal lesions in mucositis.] Abraham J. iCommunity Oncology, Volume 5, No. 4. April 2008, pp 171 – 172. http://www.communityoncology.net/journal/articles/0504171.pdf
146. **Caphosol reduces the severity of mucositis when started at the onset of cancer therapy.** [Caphosol (supersaturated calcium phosphate rinse) is a supersaturated electrolyte solution ressembling human saliva, designed in part to replace the normal ionic and pH balance in the oral cavity. Healthy functioning mouths naturally produce saliva, which includes calcium and phosphate that perform many important functions. Calcium ion plays an important role in the inflammatory process, the pathogenesis of pain and fever, leukocyte influx and adhesion, platelet aggregation, production of fibrin, and tissue repair in damaged mucosal surfaces.] Papas A. *Community Oncology*, Volume 5, No. 4. April 2008, pp 172.-173. http://www.communityoncology.net/journal/articles/0504171.pdf
147. **New frontiers in the management of chemotherapy-induced mucositis.** [About one-third of patients undergoing chemotherapy treatment suffer oral mucositis, an inflammatory-like change of the oral mucosa. Severe pseudomembranous/ulcerative mucositis can lead to secondary infection of lesions, sepsis and even cessation of treatment. Patients receiving curative head-neck irradiation are most susceptible and children undergoing chemotherapy are three times more likely to be affected. Mucositis is a costly side-effect of cancer therapy due to the extra time patients spend in hospital and currently there is no consistently effective treatment. Experimental studies with TGF-beta 3, a potent negative regulator of epithelial and haematopoietic stem cell growth, have shown that it is possible to temporarily arrest oral mucosal basal cell proliferation, and could therefore offer a new effective and safe form of preventative intervention for patients about to undergo aggressive regimens of cancer therapy.] Spijkervet FK, Sonis ST. *Curr Opin Oncol.* 1998 Aug;10 Suppl 1:S23-7. http://www.ncbi.nlm.nih.gov/pubmed/9801855

Cardiovascular Disease, Periodontitis and Inflammation

148. **16S rRNA-based detection of oral pathogens in coronary atherosclerotic plaque.** [Background: Atherosclerosis develops as a response of the vessel wall to injury. Chronic bacterial infections have been associated with an increased risk for atherosclerosis and coronary artery disease. The ability of oral pathogens to colonize in coronary atheromatous plaque is well known. Aim: The aim of this study was to detect the presence of *Treponema denticola, Porphyromonas gingivalis and Campylobacter rectus* in the subgingival and atherosclerotic plaques of patients with coronary artery disease. Materials and Methods: Fifty-one patients in the age group of 40-80 years with coronary artery disease were selected for the study. DNA was extracted from the plaque samples. The specific primers for *T. denticola, C. rectus and P. gingivalis* were used to amplify a part of the 16S rRNA gene by polymerase chain reaction. Statistical Analysis Used: Chi-square analysis, correlation coefficient and prevalence percentage of the microorganisms were carried out for the analysis. Results: Of the 51 patients, *T. denticola, C. rectus and P. gingivalis* were detected in 49.01%, 21.51% and 45.10% of the atherosclerotic plaque samples. Conclusions: Our study revealed the presence of bacterial DNA of the oral pathogenic microorganisms in coronary atherosclerotic plaques. The presence of the bacterial DNA in the coronary atherosclerotic plaques in significant proportion may suggest the possible relationship between periodontal bacterial infection and genesis of coronary atherosclerosis.] Mahendra J, Mahendra L, et al. *Indian Journal of Dental Research*, Vol. 21, Issue 2, p.248-252, 2010. http://www.ijdr.in/article.asp?issn=0970-9290;year=2010;volume=21;issue=2;spage=248;epage=252;aulast=Mahendra
149. **Acute Myocardial Infarction is Reflected in Salivary Matrix Metalloproteinase-8 Activation Level. [**Aim: To compare salivary and serum biomarker levels and degrees of MMP activation between subjects with acute myocardial infarction (AMI) and systemically healthy subjects (non-AMI) with similar periodontal conditions. Methods: A total of 92 subjects (47 AMI and 28 non-AMI subjects with gingivitis or periodontitis, and 17 systemically and periodontally healthy subjects as a control group) were recruited. Clinical periodontal measurements were recorded; stimulated whole saliva and serum samples were collected. AMI patients were clinically examined within three-four days after admission to the coronary care unit.

Saliva samples were analyzed for levels of matrix metalloproteinase (MMP) -8, MMP-7, tissue inhibitor of matrix metalloproteinase (TIMP) -1. Serums were tested for MMP-8, -9, and TIMP-1, -2 levels by immunofluorometric assay (IFMA) and ELISA. Molecular forms and degree of activation of salivary MMP-8, MMP-9 and MMP-13 were analyzed by computer-scanned immunoblots. Result: Total salivary MMP-8 assessed by IFMA method and immunoblot densitometric units was higher in non-AMI than in AMI subjects' saliva but a significantly higher percentage of AMI subjects' MMP-8 was activated PMN type ($p < 0.001$) regardless of periodontal diagnosis. Serum MMP-8, -9 and TIMP-1 levels were significantly higher in AMI (for all markers and all comparisons $p < 0.05$). Characteristic for AMI was dominance of active PMN type MMP-8 in saliva Conclusions: Enhanced MMP-8 activation in AMI subjects' saliva is evidently in part of systemic origin. Consequently, AMI is reflected in serum but also in saliva.] Buduneli E, Mantyla P, et al. *J Periodontol.* 2010 Nov 23. http://www.ncbi.nlm.nih.gov/pubmed/21091346

150. **Aggregatibacter Actinomycetemcomitans infection Accelerates Atherosclerosis through LDL Oxidation.** Objectives:Recent studies have shown that there is an association between periodontal disease and cardiovascular disease. In this study, we assessed the involvement of the periodontal pathogen *Aggregatibacter actinomycetemcomitans* (*A.a.*) in the development of atherosclerosis in apolipoprotein E-deficient spontaneously hyperlipidemic ($Apoe^{shl}$) mice. Methods:The mice were intravenously treated with live *A.a.* HK1651, heat–killed *A.a.*, *A.a.* LPS or vehicles. Histomorphometric features of atheromatous lesions, serum oxidized low–density lipoprotein (ox–LDL) levels, and gene expressions of oxidative stress as well as TLR and NLR were examined. Results:The areas of the aortic sinus that were covered with atherosclerosis plaque were larger in mice treated with live or heat–killed *A.a.* compared to other groups. The order of magnitude of atherosclerosis is live *A.a.*– > killed *A.a.*– >*A.a.* LPS– >PBS–treated group. TLR–9– and NOD–1–specific mRNA expressions in the aorta were significantly increased in live *A.a.*–treated group, whereas *A.a.* LPS–treated group showed increase in TLR–4– , NOD–1– and NOD–2–specific mRNAs. *A.a.* challenge markedly induced 4HNE positive areas in proximal aortic lesions and serum ox–LDL levels. The mRNA levels of oxidative stress-related genes, such as LOX–1, NOX–1 and NOX–2 was also greatly increased in the aorta. Conclusion:These results provide initial evidence that *A.a.* promotes the oxidation of LDL by activation of a signaling cascade involving LOX–1 and NAD(P)H oxidase expression, which suggest that *A.a.* may facilitate atheroma development.] Jia R. *IADR/AADR/CADR 89th General Session and Exhibition*, (March 2011). http://iadr.confex.com/iadr/2011sandiego/preliminaryprogram/abstract_145660.htm

151. **Angiographically Confirmed Coronary Heart Disease and Periodontal Disease in Middle-Aged Males.** [There was an association between coronary heart disease and poor periodontal status in the middle-aged males investigated. This association was independent of diabetes and all other cardiovascular risk factors investigated.] Briggs JE, McKeown PP, J Periodontol 2006.77.1.95. http://www.joponline.org/doi/abs/10.1902/jop.2006.77.1.95?prevSearch=keywordsfield%3AC-reactive_protein

152. **Arterial thrombosis after intravenous infusion of oral bacterium in a rat model.** [Oral bacteria have been detected at atherosclerotic plaque, aneurysms, and thrombosed arteries in Buerger disease. We explored a possible relationship between the oral bacterium Porphyromonas gingivalis and arterial thrombosis at proximal and distal sites in rats. Eighteen rats underwent subcutaneous placement of an infusion pump connected to the jugular vein. The Pg infusion group received a continuous infusion of P. gingivalis for 2 weeks, and the controls received normal saline. At 2 and 4 weeks, specimens were obtained from the iliac, superficial, and below-knee arteries, which were studied pathologically and by polymerase chain reaction (PCR) analysis to detect P. gingivalis-specific DNA. The Pg infusion group had thrombosis in 33.3% at 2 weeks and in 55.6% at 4 weeks, but normal arterial wall structure was preserved without any features of infection. Positive PCR findings were recognized in 73.3% and 22.2% at 2 and 4 weeks, respectively. At 4 weeks, thrombosis was observed in a higher proportion, with the below-knee specimens having an especially high thrombus rate (83.3%). No control specimen had thrombosis or positive PCR results. Bacteremia due to the oral pathogen P. gingivalis may lead to thrombus formation in the peripheral arteries, especially in small-sized arteries.] Kubota T, Inoue Y, et al. *Ann Vasc Surg.* 2008 May-Jun;22(3):412-6. doi: 10.1016 http://www.ncbi.nlm.nih.gov/pubmed/18411025

153. **Association between acute cerebrovascular ischemia and chronic and recurrent infection.** [BACKGROUND AND PURPOSE: We performed a case-control study to investigate whether chronic or recurrent respiratory, ear-nose-throat (ENT), and dental infections are risk factors for cerebrovascular ischemia. METHODS: Using a standardized questionnaire we investigated past infectious diseases in 166 consecutive patients with acute cerebrovascular ischemia and in 166 age- and sex-matched nonstroke neurological patient controls. In subgroups, we performed standardized ENT (69 patients, 66 control subjects) and dental examinations including orthopantomography (66 patients, 60 control subjects). Dental status was determined by a total dental index (TDI) that reflects caries, periapical lesions, periodontitis, and other dental lesions and by an orthopantomography index (OPGI) that was assessed blinded. RESULTS: Frequent (> or = 2 episodes in each of the 2 preceding years) or chronic bronchitis was associated with cerebrovascular ischemia in age-adjusted multiple logistic regression analysis (odds ratio, OR, 2.2; 95% confidence interval, CI, 1.04 to 4.6). Groups were not different in ENT examination. Patients tended to have a worse dental status (TDI: P = .070; OPGI: P = .062) and had more severe periodontitis (P = .047) and periapical lesions (P = .027) than control subjects. In age-adjusted multiple logistic regression analysis with social status and established vascular risk factors, poor dental status (TDI) was independently associated with cerebrovascular ischemia (OR, 2.6; 95% CI, 1.18 to 5.7). CONCLUSION: Recurrent or chronic bronchial infection and poor dental status, mainly resulting from chronic dental infection, may be associated with an increased risk for cerebrovascular ischemia.] Grau AJ, Buggle F, et al. *Stroke*. 1997 Sep;28(9):1724-9. http://www.ncbi.nlm.nih.gov/pubmed/9303015

154. **Association between dental health and acute myocardial infarction.** [Dental health was significantly worse in patients with acute myocardial infarction than in controls.] Mattila KJ, Nieminen MS, et.al., *Brit Med J 189; 298:779-81.* *http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2496855&dopt=Abstract*
155. **Association Between Nanobacteria and Periodontal disease.** [Because NB can be identified by using culture, monoclonal antibodies, and electron microscopy techniques, and because they were detected in both dental pulp stones and CA, NB should be considered a potential causative agent to be screened in related diseases. We propose that NB may provide a potential bridge between periodontal diseases and peripheral artery disease.] ÇiftçioÐlu N, McKay DS, *Circulation.* 2003;108:e58. http://circ.ahajournals.org/cgi/content/full/108/8/e58
156. **Associations between tooth loss and mortality patterns in the Glasgow Alumni Cohort.** [OBJECTIVE: To use data from the Glasgow Alumni Cohort to investigate whether oral health in young adulthood is independently associated with later life cardiovascular disease (CVD) and cancer mortality. METHODS AND RESULTS: Of the original cohort (n = 15 322), 12 631 subjects were traced through the National Health Service Central Register. Of these, 9569 men and 2654 women were 30 years or younger at baseline. During up to 57 years of follow-up, 1432 deaths occurred among subjects with complete data, including 509 deaths from CVD and 549 from cancer. After adjusting for potential confounders, no substantial association was found between the number of missing teeth (as a continuous variable) and all-cause mortality (hazard ratio (HR) for each extra missing tooth = 1.01; 95% confidence interval (CI) 1.00 to 1.02), CVD mortality (HR = 1.01; 95% CI 0.99 to 1.03) or cancer mortality (HR = 1.00; 95% CI 0.98 to 1.02). When the number of missing teeth was treated as a categorical variable, there was evidence that students with nine or more missing teeth at baseline had an increased risk of CVD (HR = 1.35; 95% CI 1.03 to 1.77) compared with those with fewer than five missing teeth. When the number of missing teeth was transformed using fractional polynomials, there seemed to be a non-linear relation between missing teeth and CVD mortality. CONCLUSIONS: Although some evidence was found to support the relation between tooth loss and CVD mortality, causal mechanisms underlying this association remain uncertain.] TU YK, Galobardes B, et al. *Heart.* 2007 Sep;93(9):1098-103. Epub 2006 Dec 12. http://www.ncbi.nlm.nih.gov/pubmed/17164486
157. **Association of the Metabolic Syndrome with Severe Periodontitis in a Large U.S. Population-Based Survey.** [Objective: The objective of the study was to assess the association between periodontitis and the metabolic syndrome in a cross-sectional survey of a nationally representative sample of the noninstitutionalized civilians in the United States. Design, Setting, and Participants: Data analysis from the Third National Health and Nutrition Examination Survey on 13,994 men and women aged 17 yr or older who received periodontal examination were studied. Main Outcome Measures: Association of diagnosis and extent of periodontitis (gingival bleeding, probing pocket depths) with the metabolic syndrome and its individual component conditions (central obesity, hypertriglyceridemia, low high-density lipoprotein-cholesterol, hypertension, and insulin resistance) were measured. Adjustment for age, sex, years of education, poverty to income ratio, ethnicity, general conditions, and smoking were considered. Results: The prevalence of the metabolic syndrome was 18% [95% confidence interval (CI) 16–19], 34% (95% CI 29–38), and 37% (95% CI 28–48) among individuals with no-mild, moderate, and severe periodontitis, respectively. After adjusting for confounders, participants aged older than 45 yr suffering from severe periodontitis were 2.31 times (95% CI 1.13–4.73) more likely to have the metabolic syndrome than unaffected individuals. Diagnosis of metabolic syndrome increased by 1.12 times (95% CI 1.07–1.18) per 10% increase in gingival bleeding and 1.13 times (95% CI 1.03–1.24) per 10% increase in the proportion of periodontal pockets. Conclusions: Severe periodontitis is associated with metabolic syndrome in middle-aged individuals. Further studies are required to test whether improvements in oral health lead to reductions in cardiometabolic traits and the risk of metabolic syndrome or vice versa.] D'Aiuto F, Sabbah W, et al., *Journal of Clinical Endocrinology & Metabolism*, Vol. 93, No.10, 3989-3994. http://jcem.endojournals.org/cgi/content/abstract/93/10/3989
158. **Atherogenesis in perspective: Hypercholesterolemia and inflammation as partners in crime.** [A historical perspective on atherosclerosis allows us to reflect on the once controversial hypotheses in the field. Plaque formation was once thought to be dependent upon hypercholesterolemia alone, or solely in response to injury. More recently, inflammatory cascades were thought to be at the root of lesion development. A more realistic view may be that atherosclerosis is neither exclusively an inflammatory disease nor solely a lipid disorder: it is both.] Daniel Steinberg, *Nature Medicine* 8, 1211 - 1217 (2002), http://www.nature.com/nm/journal/v8/n11/full/nm1102-1211.html
159. **Atherogenic lipoprotein parameters in patients with aggressive periodontitis.** [Background and Objective: Certain types of chronic infection increase the plasma level of very-low-density lipoprotein, leading to formation of the particularly atherogenic low-density lipoprotein subclass, small dense low-density lipoprotein. In the present study, we examined whether aggressive forms of periodontis are associated with these atherogenic lipoprotein parameters… Conclusion: These results indicate that periodontal infection is associated with elevated plasma levels of atherogenic lipoprotein species. This association may account for the increased risk of periodontitis patients for cardiovascular disease.] Rufail ML, Schenkein HA, et al., *Journal of Periodontal Research Volume 42 Issue 6 Page 495-502, December 2007.* http://www.blackwell-synergy.com/doi/abs/10.1111/j.1600-0765.2007.00973.x
160. **Atherosclerosis — An Inflammatory Disease.** [Atherosclerosis is an inflammatory disease. Because high plasma concentrations of cholesterol, in particular those of low-density lipoprotein (LDL) cholesterol, are one of the principal risk factors for atherosclerosis,[1] the process of atherogenesis has been considered by many to consist largely of the accumulation of lipids within the artery wall; however, it is much more than that. Despite changes in lifestyle and the use of new pharmacologic approaches to lower plasma cholesterol concentrations,[2,3] cardiovascular disease continues to be the principal cause of death in the United States, Europe, and much of Asia.(Inflammation and infection are factors that induce or promote

inflammation and artherogenesis.)] Ross R, *NEJM Vol.340:115-126 Jan 14, 1999*. http://content.nejm.org/cgi/content/short/340/2/115

161. **Atherosclerosis: The New View.** [Scientists now agree that inflammation fuels the development and progression of atherosclerosis. The old view – that fat builds up on passive arterial walls- does not fit recent evidence. Inflammation can also cause certain plaques to rupture. Blood clots tend to form over ruptured plaques and can then occlude arteries, leading to such atherosclerotic complications as heart attack and stroke. Excess LDL can trigger arterial inflammation. The presence of CRP in the blood signifies that inflammation is present somewhere in the body.] Peter Libby MD, *Scientific American, May 2002, p50-59*. http://www.ahs.uwaterloo.ca/~kh346/pdf/libby.pdf
162. **Bacteraemia due to dental flossing. [**AIMS: The aims of this study were to (1) investigate the incidence of bacteraemia following flossing in subjects with chronic periodontitis or periodontal health; (2) identify the micro-organisms in detected bacteraemias; and (3) identify any patient or clinical factors associated with such bacteraemia. MATERIAL AND METHODS: Baseline blood samples were obtained from 30 individuals with chronic periodontitis (17 M:13 F, 29-75 years) and 30 with periodontal health (17 M:13 F, 28-71 years) following a non-invasive examination. Each subject's teeth were then flossed in a standardized manner and blood samples obtained 30 s and 10 min. after flossing cessation. Blood samples were cultured in a BACTEC system and positive samples subcultured for identification. RESULTS: Forty per cent of periodontitis subjects and 41% of periodontally healthy subjects tested positive for bacteraemia following flossing. Viridans streptococci, which are commonly implicated in infective endocarditis (IE), were isolated from 19% of positive subjects and accounted for 35% of microbial isolates. Twenty per cent of subjects had a detectable bacteraemia at 10 min. post-flossing. No patient or clinical factors were significantly associated with post-flossing bacteraemia. CONCLUSIONS: Dental flossing can produce bacteraemia in periodontally healthy and periodontally diseased individuals at a rate comparable with that caused by some dental treatments for which antibiotic prophylaxis is given to prevent IE.] Crasta K, Daly CG, et al. *J Clin Periodontol*. 2009 Apr;36(4):323-32. Epub 2009 Mar 11. http://www.ncbi.nlm.nih.gov/pubmed/19426179
163. **Bacterial signatures in thrombus aspirates of patients with myocardial infarction.** [BACKGROUND: Infectious agents, especially bacteria and their components originating from the oral cavity or respiratory tract, have been suggested to contribute to inflammation in the coronary plaque, leading to rupture and the subsequent development of coronary thrombus. We aimed to measure bacterial DNA in thrombus aspirates of patients with ST-segment-elevation myocardial infarction and to check for a possible association between bacteria findings and oral pathology in the same cohort. METHODS AND RESULTS: Thrombus aspirates and arterial blood from patients with ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention (n=101; 76% male; mean age, 63.3 years) were analyzed with real-time quantitative polymerase chain reaction with specific primers and probes to detect bacterial DNA from several oral species and Chlamydia pneumoniae. The median value for the total amount of bacterial DNA in thrombi was 16 times higher than that found in their blood samples. Bacterial DNA typical for endodontic infection, mainly oral viridans streptococci, was measured in 78.2% of thrombi, and periodontal pathogens were measured in 34.7%. Bacteria-like structures were detected by transmission electron microscopy in all 9 thrombus samples analyzed; whole bacteria were detected in 3 of 9 cases. Monocyte/macrophage markers for bacteria recognition (CD14) and inflammation (CD68) were detected in thrombi (8 of 8) by immunohistochemistry. Among the subgroup of 30 patients with myocardial infarction examined by panoramic tomography, a significant association between the presence of periapical abscesses and oral viridans streptococci DNA-positive thrombi was found (odds ratio, 13.2; 95% confidence interval, 2.11-82.5; P=0.004). CONCLUSIONS: Dental infection and oral bacteria, especially viridans streptococci, may be associated with the development of acute coronary] Pessi T, Karhunen V, et al. *Circulation*. 2013 Mar 19;127(11):1219-28, e1-6. doi: 10.1161 **http://www.ncbi.nlm.nih.gov/pubmed/23418311**
164. **Bidirectional Relation Between Inflammation and Coagulation**. [Inflammation and coagulation play pivotal roles in the pathogenesis of vascular disease. Increasing evidence points to extensive cross-talk between these two systems, whereby inflammation leads not only to activation of coagulation, but coagulation also considerably affects inflammatory activity. Activation of coagulation and fibrin deposition as a consequence of inflammation is well known and can be viewed as an essential part of the host defense of the body against, for example, infectious agents or nonidentical cells, in an effort to contain the invading entity and the consequent inflammatory response to a limited area. An exaggerated or insufficiently controlled response may, however, lead to a situation in which coagulation and thrombosis contribute to disease, as illustrated by the fact that thrombus formation on a ruptured atherosclerotic plaque, containing abundant inflammatory cells, is the pathological basis of acute arterial thrombotic events such as myocardial infarction or unstable angina.[1] Expression of procoagulant material by inflammatory cells in the unstable plaque (in particular tissue factor) may initiate activation of coagulation, and the thrombin generated will both activate platelets and result in the formation of a platelet-fibrin thrombus (Figure 1). Another example is the occurrence of systemic coagulation activation in combination with microvascular failure that results from the systemic inflammatory response to severe infection or sepsis and that contributes to multiple organ dysfunction.[2] However, rather than this being a 1-way process with inflammation leading to coagulation, both systems closely interact, whereby coagulation can also substantially modulate inflammatory activity.] Levi, M, van der Poll, T, et al. *Circulation*. 2004;109:2698-2704. http://www.circ.ahajournals.org/cgi/content/extract/109/22/2698
165. **Blood Pressure, C-Reactive Protein, and Risk of Future Cardiovascular Events.** [CRP and blood pressure are independent determinants of cardiovascular risk, and their predictive value is additive. CRP showed a linear relationship with blood pressure across all categories of blood pressure. Both CRP and blood pressure were independent determinants of cardiovascular risk, and in combination, each parameter had additional predictive value. data suggest that increasing levels of

blood pressure may stimulate a proinflammatory response and that endothelial inflammation may also herald the changes in arterial wall that characterize the hypertensive state. Inflammatory processes are now recognized to play a fundamental role in atherogenesis. C-reactive protein (CRP) has been found to be a robust predictor of incident cardiovascular disease. In this regard, the American Heart Association and the Centers for Disease Control and Prevention have recently issued a class IIa recommendation for the measurement of CRP in primary prevention among those at intermediate risk.] Blake GJ, Rifai N. et. al., *Circulation.* 2003;108:2993. http://circ.ahajournals.org/cgi/content/full/108/24/2993

166. **Cardiovascular disease and the role of oral bacteria**. [In terms of the pathogenesis of cardiovascular disease (CVD) the focus has traditionally been on dyslipidemia. Over the decades our understanding of the pathogenesis of CVD has increased, and infections, including those caused by oral bacteria, are more likely involved in CVD progression than previously thought. While many studies have now shown an association between periodontal disease and CVD, the mechanisms underpinning this relationship remain unclear. This review gives a brief overview of the host-bacterial interactions in periodontal disease and virulence factors of oral bacteria before discussing the proposed mechanisms by which oral bacterial may facilitate the progression of CVD.] Leishman SJ, Do HL, et al. *J of Oral Microbiology*, Vol 2 (2010)5781 – DOI: 10.3402/jom.v2i0.5781. http://www.journaloforalmicrobiology.net/index.php/jom/article/view/5781/6549
167. **Changes in Clinical and Microbiological Periodontal Profiles Relate to Progression of Carotid Intima-Media Thickness: The Oral Infections and Vascular Disease Epidemiology Study**. [Background No prospective studies exist on the relationship between change in periodontal clinical and microbiological status and progression of carotid atherosclerosis. Methods and Results The Oral Infections and Vascular Disease Epidemiology Study examined 420 participants at baseline (68±8 years old) and follow-up. Over a 3-year median follow-up time, clinical probing depth (PD) measurements were made at 75 766 periodontal sites, and 5008 subgingival samples were collected from dentate participants (average of 7 samples/subject per visit over 2 visits) and quantitatively assessed for 11 known periodontal bacterial species by DNA-DNA checkerboard hybridization. Common carotid artery intima-medial thickness (CCA-IMT) was measured using high-resolution ultrasound. In 2 separate analyses, change in periodontal status (follow-up to baseline), defined as (1) longitudinal change in the extent of sites with a ≥3-mm probing depth (Δ%PD≥3) and (2) longitudinal change in the relative predominance of bacteria causative of periodontal disease over other bacteria in the subgingival plaque (Δetiologic dominance), was regressed on longitudinal CCA-IMT progression adjusting for age, sex, race/ethnicity, diabetes, smoking status, education, body mass index, systolic blood pressure, and low-density lipoprotein cholesterol and high-density lipoprotein cholesterol. Mean (SE) CCA-IMT increased during follow-up by 0.139±0.008 mm. Longitudinal IMT progression attenuated with improvement in clinical or microbial periodontal status. Mean CCA-IMT progression varied inversely across quartiles of longitudinal improvement in clinical periodontal status (Δ%PD≥3) by 0.18 (0.02), 0.16 (0.01), 0.14 (0.01), and 0.07 (0.01) mm (*P* for trend<0.0001). Likewise, mean CCA-IMT increased by 0.20 (0.02), 0.18 (0.02), 0.15 (0.02), and 0.12 (0.02) mm (*P*<0.0001) across quartiles of longitudinal improvement in periodontal microbial status (Δetiologic dominance). Conclusion Longitudinal improvement in clinical and microbial periodontal status is related to a decreased rate of carotid artery IMT progression at 3-year average follow-up]Desvarieux M, Demmer RT, et al. J Am Heart Assoc. 2013; 2: e000254 originally published October 28, 2013, doi: 10.1161/JAHA.113.000254 http://jaha.ahajournals.org/content/2/6/e000254.short?rss=1
168. **Chronic Periodontitis as a Risk Factor for Acute Myocardial Infarction**. [The relationship between periodontal disease and acute myocardial infarct has been investigated, but without conclusive results. Objective: To estimate the magnitude of the risk of acute myocardial infarct among patients with periodontal disease. Method: A case-control study was conducted in the city of Salvador, Brazil. A total of 621 subjects, 207 cases, 207 hospital controls and 207 community controls were selected. The cases with proven clinical and laboratory diagnoses of a first acute myocardial infarct event and controls without any history of acute myocardial infarct were matched according to sex and age. All the cases and controls underwent: a) complete periodontal examination; b) lipid and blood glucose profile tests; c) weight, height and hip and waist circumference measurements; d) questionnaire on sociodemographic and lifestyle habit conditions. The chi-square test was used in the descriptive analysis to compare proportions. To estimate the association, multivariate conditional logistic regression was used, and odds ratio measurements adjusted according to a series of potential confounders were obtained. Results: Among the individuals with periodontal disease, the chance of presenting acute myocardial infarct was greater than among those without periodontal disease, both for the community controls (ORcrude = 1.57; 95% CI [0.98-2.52]) and for the hospital controls (ORcrude = 1.73; 95% CI [1.11-2.72]). After adjustment for age, sex, smoking habit, schooling level and blood glucose level, this chance increased for both groups: community controls (ORadjusted = 1.89; 95% CI [1.11-3.28]) and hospital controls (ORadjusted = 1.92; 95% CI [1.14-3.23]). The fraction of the risk of acute myocardial infarct attributable to periodontal disease was around 12%. Conclusions: The findings from this study indicate that periodontal disease contributed independently to an important proportion of the occurrences of acute myocardial infarct in the study population.] Coelho J, Passos J, et al. *IADR General Session*, San Diego, CA March 2011. http://iadr.confex.com/iadr/2011sandiego/webprogram/Paper149200.html
169. **Clinical Periodontal and Microbiologic Parameters in Patients With Acute Myocardial Infarction.** [Background: The aim of this study was to evaluate the impact of clinical periodontal parameters and the presence of periodontal pathogens in patients with acute myocardial infarction (AMI). Methods: A total of 104 subjects (54 patients with AMI and 50 healthy controls) were included. Subgingival plaque samples were analyzed for periodontal pathogens *Aggregatibacter actinomycetemcomitans* (*Aa*; previously *Actinobacillus actinomycetemcomitans*), *Porphyromonas gingivalis* (*Pg*), *Tannerella*

forsythia (*Tf*; previously *T. forsythensis*), and *Prevotella intermedi*a (*Pi*) using dot-blot hybridization. Results: Patients with AMI had a significantly higher frequency of probing depths (PDs) ≥4 mm than controls (39.2% versus 14.9%; *P* <0.0001). Among different cutoff levels, the frequency of >50% sites with PDs ≥4 mm showed the highest discrepancy between both groups (33% versus 0%; *P* <0.001). All periodontal pathogens were overrepresented in patients with AMI and positively correlated with increased periodontal PD and clinical attachment level (CAL). After adjustment for age, gender, smoking, body mass index, hypertension, plaque index, statin intake, and ratio of cholesterol to high-density lipoprotein, *Pg* remained a significant predictor for AMI (odds ratio [OR]: 13.6; 95% confidence interval [CI]: 3.1 to 59.8; *P* = 0.0005). Furthermore, the simultaneous presence of *Aa* + *Pg* (*P* = 0.0005) and *Aa* + *Pg* + *Tf* (*P* = 0.0018) were found with significantly higher frequency in patients with AMI than controls. Conclusions: The results of our study confirm an association between periodontitis and AMI in which periodontal destruction was correlated with the presence of periodontal pathogens. In particular, *Pg* might be considered a potential risk indicator for AMI.] Stein JM, Kuch B, et al. *Journal of Periodontology*, October 2009, Vol. 80, No. 10, Pages 1581-1589 , DOI 10.1902/jop.2009.090170. http://www.joponline.org/doi/abs/10.1902/jop.2009.090170

170. **Cleveland Clinic researchers find link between dietary fat, gut bacteria and heart disease. [**A study by the researchers, published Wednesday, showed that people who eat high animal-fat diets are not predisposed to heart disease based on genetics alone but also on the composition of their gut bacteria and how these bacteria aid in the digestion of their food. The research group, led by Dr. Stanley Hazen, section head of preventive cardiology at the Clinic, found that a byproduct of the breakdown of a common dietary fat, lecithin, was a 10-fold stronger predictor of heart disease risk than cholesterol.] Zeltner B. http://www.cleveland.com/healthfit/index.ssf/2011/04/cleveland_clinic_researchers_f_2.html
171. **Coagulation and inflammation: Interrelated response to infection.** [Inflammation has long been known to be part of the body's response to infection. Evidence is accumulating that coagulation is part of that response as well….Aside from their usual role in hemostasis, platelets have other previously unrecognized abilities that closely link them to inflammation. … Platelets themselves release and display on their surfaces a variety of inflammatory mediators. Among those mediators are cytokines, such as interleukin 1b, and members of the CC and CXC chemokine family. Degranulation and secretion of preformed mediators is a critical and rapid innate hemostatic and inflammatory response.] *Pulmonary Reviews.com*, Vol.8, No.6. http://www.pulmonaryreviews.com/jun03/pr_jun03_coagulate.html
172. **Coagulation and Thrombosis in Cardiovascular Disease: Plausible Contributions of Infectious Agents.** [By initiating a procoagulant response, infectious agents can indirectly trigger a prothrombotic response. Alternatively, some microbes can directly trigger platelet aggregation in vitro and in animal models, suggesting direct prothrombotic potential in human cardiovascular disease. Activation of coagulation and thrombosis characterizes the pathological response to infectious agents in human disseminated intravascular coagulation and infective endocarditis. Given the underlying biological plausibility, the cumulative lifetime burden of chronic pathogens may be expected to create risk of atherosclerosis and thrombosis, and, indirectly, signs of cardiovascular disease.] Herzberg MC, Annals of Periodontology, 2001, Vol. 6, No. 1, Pages 16-19. http://www.joponline.org/doi/abs/10.1902/annals.2001.6.1.16
173. **Continuous Endothelial Cell Activation Increases Angiogenesis: Evidence for the Direct Role of Endothelium Linking Angiogenesis and Inflammation.** [There is increasing evidence that chronic inflammation is tightly linked to diseases associated with endothelial dysfunction, including the induction of aberrant angiogenesis. While leukocytes have been described as mediators of inflammation-associated angiogenesis, the effects of direct chronic endothelial activation have not been addressed in this context. Using an uncleavable mutant of the transmembrane form of tumor necrosis factor-α (TNF-α), we have established models of stable TNF-α expression in endothelial cells in vitro and in transgenic mice in vivo. In the in vitro model, continuous endothelial activation leads to increased leukocyte cellular adhesion molecule expression and intracellular reactive oxygen species, hallmarks of a proinflammatory and dysfunctional endothelium. In addition, stable expression of TNF-α in endothelial cells increased angiogenic sprout formation in the presence but also in the absence of angiogenic growth factors. The partial neutralization of this effect by TNF-α antibodies and the inability of conditioned media from stable TNF-α-expressing endothelial cells to induce angiogenic activities in control endothelial cells suggest that this effect does not require expression of additional autocrine factors, but is an autonomous effect of the transmembrane TNF on the endothelial cells. Furthermore, using the Matrigel plug assay in vivo, increased angiogenesis was observed in endothelial TNF-α-expressing transgenic versus control mice. In conclusion, chronic inflammatory changes mediated by TNF-α can induce angiogenesis in vitro and in vivo, suggesting endothelial cell activation as a direct link between inflammation and angiogenesis.] Rajashekhar G, Willuweit A, et al. *J Vasc Res* 2006;43:193-204. http://content.karger.com/ProdukteDB/produkte.asp?doi=10.1159/000090949
174. **C-Reactive Protein and the Risk of Developing Hypertension.** [C-reactive protein levels are associated with future development of hypertension, which suggests that hypertension is in part an inflammatory disorder.] Sesso HD, Buring JE, et. al., *JAMA*. 2003;290:2945-2951. http://jama.ama-assn.org/cgi/content/abstract/290/22/2945
175. **C-Reactive Protein Is Associated With Subclinical Epicardial Coronary Calcification in Men and Women.** [High C-reactive protein (CRP) levels are associated with an increased risk of cardiovascular events, even in apparently healthy individuals. It has not been established whether elevated CRP reflects an increased burden of subclinical coronary atherosclerosis. **…** *Conclusions***—** High CRP levels are associated with increased coronary calcification. Among individuals with elevated CRP, subclinical atherosclerosis may contribute to an increased risk for future cardiovascular events.] Wang TJ, Larson MG, et al. *Circulation*. 2002;106:1189. http://circ.ahajournals.org/cgi/content/abstract/106/10/1189

176. **C-reactive protein is increased in patients with degenerative aortic valvular stenosis.** [The goal of this study was to assess the presence of systemic inflammation in degenerative aortic valvular stenosis. Local inflammatory changes, resembling those observed in atherosclerosis, have been recently reported in degenerative aortic valvular stenosis. It is presently unknown whether systemic signs of inflammation, similar to those observed in atherosclerosis, may be present in this disorder. C-reactive protein (CRP) was measured by enzyme immunoassay in 141 subjects: 62 with trileaflet degenerative valvular aortic stenosis and 79 volunteers with similar demographic and clinical characteristics. IgG antibodies against *Helicobacter pylori* (enzyme-linked immunosorbant assay) and *Chlamydia pneumoniae* (microimmunofluorescence assay) were also measured. Systemic signs of inflammation, similar to those found in atherosclerosis, are present in patients with degenerative aortic valve stenosis. They do not seem to be linked to *C. pneumoniae* or *H. pylori* infection.] Galante A, Pietroiusti A, et.al. *J Am Coll Cardiol, 2001; 38:1078-1082.* http://content.onlinejacc.org/cgi/content/abstract/38/4/1078.

177. **C-Reactive Protein Stimulates MMP-1 Expression in U937 Histiocytes Through FcγRII and Extracellular Signal-Regulated Kinase Pathway: An Implication of CRP Involvement in Plaque Destabilization.** [These findings suggest that CRP may promote matrix degradation and thus contribute to plaque vulnerability.] Williams TN, et.al., Arteriosclerosis, Thrombosis, and Vascular Biology. 2004;24:61. http://atvb.ahajournals.org/cgi/content/abstract/24/1/61

178. **Cultivation of Enterobacter Hormaechei from Human Atherosclerotic Tissue.** [Aim: To determine whether culturable bacterial strains are present in human atheromatous tissue and to investigate their properties using culture, quantitative PCR, metagenomic screening, genomic and biochemical methods. Methods: We analyzed femoral atherosclerotic plaque and five pairs of diseased and healthy arterial tissue for the presence of culturable bacteria using cell cultures and genomic analysis. Results: Gram negative aerobic bacilli were cultivated from the plaque tissue. Ribosomal 16S DNA amplification and sequencing identified the isolates as Enterobacter hormaechei. The isolate was resistant to ampicillin, cefazolin, and erythromycin. A circular 10kb plasmid was isolated from the strain. Antibiotic protection assays of the isolate demonstrated invasive ability in a human monocytic cell line. To extend the study, five matched pairs of diseased and healthy aortic tissue were analyzed via quantitative PCR. Eubacterial 16S rDNA was detected in all specimens, however, E. hormaechei DNA was detected in surprisingly high numbers in two of the diseased tissues only. Conclusions: While it is well documented that inflammation is an important risk factor for vascular pathophysiology, the association of bacteria with atherosclerosis has not been clearly established, in large part due to the inability to isolate live bacteria from atheromatous tissue. This is the first study providing direct evidence of Enterobacter spp. associated with atheromatous tissues. The data suggest that chronic infection with bacteria may be an under-reported etiologic factor in vascular pathogenesis. Importantly, characterization of the clinical isolate supports a model of atherogenesis where systemic dissemination of bacteria to atherosclerotic sites may occur via internalization in phagocytic cells.] Rafferty B, Dolgilevich S, et al. *Journal of Atherosclerosis and Thrombosis,* Advanced Publication, Sept 2010. http://www.jstage.jst.go.jp/article/jat/advpub/0/advpub_1010190295/_article http://jat.umin.jp/jat/jat_18_1.html http://www.sciencedaily.com/releases/2011/01/110105131753.htm

179. **Current Concepts of the Pathogenesis of the Acute Coronary Syndromes.** [These various findings all highlight the central role of inflammation as a determinant of the biology underlying the acute thrombotic complications of atherosclerosis. Inflammation has emerged as a leading pathophysiologic mechanism (for thrombosis and acute myocardial infarction). In addition to local effects of inflammation at the level of the atherosclerotic lesion itself, systemic aspects of the inflammatory response may alter thrombotic risk. Inflammation upsets the prevailing homeostatic balance. Increased fibrinogen and plasminogen activator inhibitor circulate at higher concentrations in inflammatory states. A given plaque disruption could have a greater chance to produce an occlusive thrombus under such conditions.] Libby P. *Circulation.* 2001;104:365. http://circ.ahajournals.org/cgi/content/full/104/3/365

180. **Deep periodontal pockets linked with ECG abnormalities.** [Patients with deep periodontal pockets have an increased risk for electrocardiographic abnormalities, suggesting a heightened risk of cardiovascular disease. Elevated levels of the inflammatory compounds C-reactive protein, interleukin-6 and neutrophils associated with periodontitis may cause inflammatory changes to atherosclerotic lesions, increasing the risk of cardiac events, the researchers concluded.] ADA News Release. http://www.ada.org/prof/resources/pubs/adanews/adanewsarticle.asp?articleid=956

181. **Dental and Periodontal Status and Risk for Progression of Carotid Atherosclerosis, The Inflammation and Carotid Artery Risk for Atherosclerosis Study Dental Substudy. [**Background and Purpose— Dental and periodontal disease are potentially involved in the pathogenesis of atherosclerosis. We investigated whether dental and periodontal status is associated with the presence and future progression of carotid stenosis. *Methods*— We randomly selected 411 of 1268 participants from the prospective Inflammation and Carotid Artery Risk for Atherosclerosis Study and evaluated dental and periodontal status and oral hygiene at baseline measuring three World Health Organization-validated indices: DMFT (decayed, missing, filled teeth), SLI (Silness-Löe Index), and CPITN (community periodontal index for treatment needs), respectively. The degree of carotid stenosis was measured by duplex ultrasound at baseline and after median 7.5 months (range=6 to 9 months) to identify patients with progressive carotid stenosis. *Results*— DMFT (P<0.01), SLI (P=0.048), CPITN (P=0.007), and edentulousness (P=0.007) were associated with the baseline degree of carotid stenosis. Atherosclerosis progression was observed in 48 of 411 patients (11.7%). DMFT (adjusted odds ratio [OR]=1.11, 95% CI=1.01 to 1.22, P=0.032) and SLI (adjusted OR=1.77, 95% CI=1.09 to 2.79, P=0.021), but not CPITN (adjusted OR=1.51, 95% CI=0.89 to 2.45, P=0.16) were significant predictors of disease progression, irrespective of traditional cardiovascular risk factors and the baseline degree of stenosis. Edentulous patients had a significantly increased risk for disease progression as compared with patients with teeth (adjusted OR=2.10, 95% CI=1.06 to 4.16, P=0.33). Dental status, oral hygiene, and particularly tooth loss

are associated with the degree of carotid stenosis and predict future progression of the disease.] Schillinger T, Kluger W, et al. *Stroke.* 2006;37:2271.) http://stroke.ahajournals.org/cgi/content/full/strokeaha;37/9/2271

182. **Dental disease and risk of coronary heart disease and mortality.** [OBJECTIVE: To investigate a reported association between dental disease and risk of coronary heart disease. SETTING: National sample of American adults who participated in a health examination survey in the early 1970s. DESIGN: Prospective cohort study in which participants underwent a standard dental examination at baseline and were followed up to 1987. Proportional hazards analysis was used to estimate relative risks adjusted for several covariates. MAIN OUTCOME MEASURES: Incidence of mortality or admission to hospital because of coronary heart disease; total mortality. RESULTS: Among all 9760 subjects included in the analysis those with periodontitis had a 25% increased risk of coronary heart disease relative to those with minimal periodontal disease. Poor oral hygiene, determined by the extent of dental debris and calculus, was also associated with an increased incidence of coronary heart disease. In men younger than 50 years at baseline periodontal disease was a stronger risk factor for coronary heart disease; men with periodontitis had a relative risk of 1.72. Both periodontal disease and poor oral hygiene showed stronger associations with total mortality than with coronary heart disease. CONCLUSION: Dental disease is associated with an increased risk of coronary heart disease, particularly in young men. Whether this is a causal association is unclear. Dental health may be a more general indicator of personal hygiene and possibly health care practices.] DeStefano f, Anda RF, et al. *BMJ.* 1993 Mar 13;306(6879):688-91. http://www.ncbi.nlm.nih.gov/pubmed/8471920
183. **Dental Disease, Coronary Heart Disease and Stroke, and Inflammatory Markers.** [In addition to "classical" risk factors for coronary heart disease (CHD) and stroke, "emerging" risk predictors (which may also play roles in pathogenesis) include measures of chronic infections and of chronic, low-grade activation of inflammation and of hemostasis. As all dental healthcare professionals know (but probably fewer medical practitioners and their patients), the oral cavity is a major site of chronic infection and inflammation, particularly periodontal disease. In recent years there has been increasing interest in the "periodontal-systemic connection" between dental health parameters and the risks of cardiovascular disease, respiratory disease, diabetes mellitus, osteoporosis, and adverse pregnancy outcomes.] Lowe G, *Circulation 2004;109:1076-1078.* http://circ.ahajournals.org/cgi/content/full/109/9/1076 .
184. **Dental disease, fibrinogen and white cell count; links with myocardial infarction?** [Inflammatory dental disease may be a determinant of fibrinogen level and white cell count in the general population, and that fibrinogen and white cell count may be two mediators of the link between dental disease and myocardial infarction.] Kweider M, Lowe GD, et. al, *Scott med J. 1993 Jun;38(3):73-4.* Department of Oral Surgery, Dental Hospital & School, Glasgow. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8356427&dopt=Abstract
185. **Dental infection and vascular disease. [**Periodontitis is a chronic inflammatory response to bacterial plaque in which the anchoring bone and soft tissues supporting teeth are destroyed, resulting in tooth mobility and loss. Dental caries involves the spread of infection from the dentine to the vascular dental pulp and periapical bony tissues, before involvement of adjacent soft tissues and spreading sepsis. Several case-controlled, cross-sectional, and cohort studies report correlation between periodontitis and increased cardiovascular, cerebrovascular, and peripheral artery disease, as determined by clinical disease, angiography, ultrasonography, and reduced flow-mediated dilation. Some studies report a similar relationship of atherosclerosis with periapical infection and potentially also with coronal caries, and this review identifies the need to investigate these associations further. Smoking and cadmium exposure are epidemiologically confounding environmental risk factors shared by atherosclerosis and periodontitis. Further complicating epidemiological studies are the risk factors for both atherosclerosis and periodontitis, with which periodontitis appears to have separate positive feedback relationships. These include diabetes, increased plasma lipid levels, hypertension, and white blood cell count. Animal and human intervention studies provide some direct support of a causal role for periodontitis in atherosclerosis, and possible mechanisms include bacterial invasion of arteries, specific atherogenic properties of oral bacteria, the acute phase response, and cytokine polymorphisms.] Zoellner H. *Semin Thromb Hemost.* 2011 Apr;37(3):181-92. Epub 2011 Mar 31. http://www.ncbi.nlm.nih.gov/pubmed/21455852
186. **Detection of Periodontal Bacteria in Atheromatous Plaques by Nested Polymerase Chain Reaction**. [Background. In recent years, increasing evidence regarding the potential association between periodontal diseases and cardiovascular diseases has been elicited. The available evidence underlines the importance of detecting periodontal pathogens on atheromatous plaques as the first step in demonstrating the causal relationship between both entities. It is the main aim of this investigation to detect periodontitis-associated bacteria from carotid artery atheromatous plaques recovered from patients who received an endarterectomy, using strict sample procurement and laboratory procedures. Methods. Atheromatous plaques from endarterectomies from carotid arteries were scraped, homogenized and bacterial DNA was extracted. In order to obtain a representative concentration of amplicons, two amplifications of the bacterial 16S ribosomal-RNA gen were carried out for each sample with universal eubacteria primers by polymerase chain reaction (PCR). Nested-PCR with specific primers for the target bacteria was performed next. Statistical tests included $\chi(2)$ test. Results. Forty-two atheromatous plaques were analyzed. All of them were positive for at least one target bacterial species. The bacterial species most commonly found in atheromatous plaques was Porphyromonas gingivalis (78.57%, 33/42), followed by Aggregatibacter actinomycetemcomitans (66.67%, 28/42), Tannerella forsythia (61.90%, 26/42), Eikenella corrodens (54.76%, 23/42), Fusobacterium nucleatum (50.00%, 21/42) and Campylobacter rectus (9.52%, 4/42). The simultaneous presence of various bacterial species within the same specimen was a common observation. Conclusion. Within the limitations of this study, the presence of DNA from periodontitis-associated bacteria in carotid artery atheromatous plaques retrieved by endarterectomy

was confirmed.] Fiquero E, Sanchez-Beltran M, et al. *J Periodontol.* 2011 Mar 29. http://www.ncbi.nlm.nih.gov/pubmed/21453047

187. **Detection of periodontal bacteria in thrombi of patients with acute myocardial infarction by polymerase chain reaction.** [BACKGROUNDS: Numerous reports have demonstrated that periodontal bacteria are present in plaques from atherosclerotic arteries. Although periodontitis has recently been recognized as a risk factor for coronary artery disease, the direct relationship between periodontal bacteria and coronary artery disease has not yet been clarified. It has been suggested that these bacteria might contribute to inflammation and plaque instability. We assumed that if periodontal bacteria induce inflammation of plaque, the bacteria would be released into the bloodstream when vulnerable plaque ruptures. To determine whether periodontal bacteria are present in thrombi at the site of acute myocardial infarction, we tried to detect periodontal bacteria in thrombi of patients with acute myocardial infarction by polymerase chain reaction (PCR). METHODS: We studied 81 consecutive adults with ST-segment elevation acute myocardial infarction who underwent primary percutaneous coronary intervention (PCI). All patients underwent removal of thrombus with aspiration catheters at the beginning of percutaneous coronary intervention, and a small sample of thrombus was obtained for PCR.RESULTS: The detection rates of periodontal bacteria by PCR were 19.7% for Aggregatibacter actinomycetemcomitans, 3.4% Porphyromonas gingivalis, and 2.3% for Treponema denticola. CONCLUSIONS: Three species of periodontal bacteria were detected in the thrombi of patients with acute myocardial infarction. This raises the possibility that such bacteria are latently present in plaque and also suggests that these bacteria might have a role in plaque inflammation and instability.] Ohki T, Itabashi Y, et al. *Am Heart J.* 2012 Feb;163(2):164-7. **http://www.ncbi.nlm.nih.gov/pubmed/22305832**

188. **Detection of *Porphyromonas gingivalis* DNA in Aortic Tissue by PCR.** [Background: Periodontopathogens may play a role in the etiology of cardiovascular disease. The aim of the present study was to investigate biopsies of aortic tissue for the presence of periodontopathogens. Methods: Samples taken from the aortas of 26 patients connected to a heart-lung machine during open-heart surgery were analyzed in a gene-diagnostics laboratory by polymerase chain reaction. Immediately after biopsy, the samples were transferred into liquid nitrogen and stored at −80°C. 16S rRNA gene-directed primers were used for general detection of bacterial cells, and specific primers for detection of *Porphyromonas gingivalis* and *Actinobacillus actinomycetemcomitans.* Questionable amplificons were verified by Southern hybridization using DNA probes. Results: Bacterial DNA was found in 23 of 26 (88.5%) samples, in most cases only in concentrations around the detection limit. Four samples were clearly positive for *P. gingivalis; A. actinomycetemcomitans* was not detected. Conclusion: These results might indicate a link between periodontopathogens entering the cardiovascular system and cardiovascular disease.] *Journal of Periodontology, 2002, Vol. 73, No. 8, Pages 868-870.* Stelzel M, Conrads G, et al. http://www.joponline.org/doi/abs/10.1902/jop.2002.73.8.868

189. **Early Carotid Atherosclerosis in Subjects With Periodontal Diseases.** [*Background and Purpose*— There is growing experimental evidence implicating chronic inflammation/infection as an atherosclerotic risk factor. In this study, the involvement of periodontal disease in the development of early atherosclerotic vascular lesions has been evaluated. *Methods*— In randomly chosen 82 patients with periodontal disease and 31 periodontally healthy individuals subjected to a clinical oral examination in 1985, atherosclerotic risk factor analysis and carotid ultrasonography was performed during reexamination 16 years later. Common carotid artery intima-media thickness (IMT) and lumen diameter were measured and intima-media area (cIMA) was calculated. The relationship between IMT and cIMA as dependent variables and periodontal disease, age, gender, body mass index, heredity for atherosclerosis, diabetes mellitus, hypertension, plasma cholesterol, smoking, and education as independent variables was evaluated in a multiple logistic regression model. … *Conclusions*— The present results indicate that periodontal disease is associated with the development of early atherosclerotic carotid lesions.] Soder P, Soder B. *Stroke.* 2005;36:1195. http://stroke.ahajournals.org/cgi/content/full/36/6/1195

190. **Effect of aortic valve replacement on c-reactive protein in nonrheumatic aortic stenosis.** [Plasma levels of C-reactive protein were higher in 20 patients with bicuspid or trileaflet degenerative aortic stenosis than in 31 normal controls and in 19 patients with pure aortic regurgitation. C-reactive protein decreased from before to 6 months after aortic valve replacement for aortic stenosis. These observations suggest that aortic stenosis is an inflammatory disease.] Gerber IL, Stewart RA, et.al. *Am J Cardiol. 2003 Nov 1;92(9):1129-32.* http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14583374&dopt=Abstract.

191. **Endotoxemia, Immune Response to Periodontal Pathogens, and Systemic Inflammation Associate With Incident Cardiovascular Disease Events.** [*Objective*— In periodontitis, overgrowth of Gram-negative bacteria may cause endotoxemia and systemic inflammation leading to cardiovascular diseases (CVD). We investigated in a prospective study the associations of serum endotoxin, antibodies to periodontal pathogens, and inflammation markers with the risk of incident CVD. *Methods and Results*— The FINRISK 1992 cohort of 6051 individuals was followed up for 10 years. We examined 185 incident CVD events and a control cohort of 320 individuals using a prospective case–cohort design. High antibody response to periodontal pathogens independently predicted incident CVD events with hazard ratios (HR, quartile 4 versus quartiles 1 to 3, 95% CI) of 1.87 (1.13 to 3.08). The subjects with a high antibody response and high CRP or interleukin (IL)-6 had multivariate-adjusted HRs of 3.01 (1.27 to 7.09) and 3.11 (1.42 to 6.83) compared with low-responders, respectively. The corresponding HRs for high endotoxin concentration were 1.82 (1.22 to 2.73, alone), 3.92 (1.99 to 7.74, with CRP), 3.54 (1.78 to 7.03, with IL-6), and 2.26 (1.13 to 4.52, with tumor necrosis factor (TNF)-α) after adjusting for age and gender. These associations were abolished after adjusting for serum lipids. High endotoxin/HDL ratio, however, had a multivariate-adjusted HR of 1.92 (1.19 to 3.08) for CVD events. *Conclusions*— Our results suggest that the exposure to periodontal

pathogens or endotoxin induces systemic inflammation leading to increased risk for CVD.] Pussinen PJ, Tuomisto K, et al. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 2007;27:1433. http://atvb.ahajournals.org/cgi/content/abstract/27/6/1433

192. **Evaluation of the Incidence of Periodontitis-Associated Bacteria in the Atherosclerotic Plaque of Coronary Blood Vessels.** Unstable atherosclerotic plaque is a dangerous clinical condition, possibly leading to acute coronary deficiency resulting in cardiac infarction. Questions about the role of inflammatory factors in the formation of pathological lesions in the endothelium of coronary vessels have often been raised. This condition may be caused by bacteria that are able to initiate clot formation in a blood vessel, destabilizing an atherosclerotic plaque that is already present. The sources of these pathogens are chronic inflammatory processes occurring in the host, including periodontal disease, which is one of the most frequent conditions. The aim of this study was to evaluate the incidence of selected anaerobic bacteria in subgingival and atherosclerotic plaque in patients treated surgically because of coronary vessel obliteration. …In patients with the severe form of chronic periodontitis, it seems that clinical attachment loss is not associated with bacterial permeability into coronary vessels. What is important is the presence of an active inflammatory process expressed by a significantly higher bleeding index in those patients in whom the examined bacterial species were found in atherosclerotic plaque.] Zaremba M, Górska R, et.al. *Journal of Periodontology 2007, Vol. 78, No. 2, Pages 322-327.* http://www.joponline.org/doi/abs/10.1902/jop.2006.060081

193. **Evidence supporting a key role of Lp-PLA2 generated lysophosphatidylcholine in human atherosclerotic plaque inflammation.** [Objective: To determine whether the level of lysophosphatidylcholine (lysoPC) generated by lipoprotein-associated phospholipase A2 (Lp-PLA2) is associated with severity of inflammation in human atherosclerotic plaques. Elevated plasma Lp-PLA2 is associated with increased cardiovascular risk. Lp-PLA2 inhibition reduces atherosclerosis. Lp-PLA2 hydrolyzes low-density lipoprotein-oxidized phospholipids generating lysoPCs. According to in vitro studies, lysoPCs are proinflammatory but the association between their generation and plaque inflammation remains unknown. METHODS AND RESULTS: Inflammatory activity in carotid plaques (162 patients) was determined immunohistochemically and by analyzing cytokines in homogenates (multiplex immunoassay). LysoPCs were quantified using mass spectrometry and Lp-PLA2 and the lysoPC metabolite lysophosphatidic acid (LPA) by ELISA. There was a strong correlation among lysoPC 16:0, 18:0, 18:1, LPA, and Lp-PLA2 in plaques. LysoPC 16:0, 18:0, 18:1, LPA, and Lp-PLA2 correlated with interleukin-1β, interleukin-6, monocyte chemoattractant protein-1, macrophage inflammatory protein-1β, regulated on activation normal T-cell expressed and secreted, and tumor necrosis factor-α in plaques. High lysoPC and Lp-PLA2 correlated with increased plaque macrophages and lipids and with low content of smooth muscle cells, whereas LPA only correlated with plaque macrophages. Lp-PLA2, lysoPC 16:0, 18:0, and 18:1, but not LPA were higher in symptomatic than in asymptomatic plaques. CONCLUSIONS: The associations among Lp-PLA2, lysoPCs, LPA, and proinflammatory cytokines in human plaques suggest that lysoPCs play a key role in plaque inflammation and vulnerability. Our findings support Lp-PLA2 inhibition as a possible strategy for the prevention of cardiovascular disease.] Goncalves I, Edsfeldt A, et al. *Arterioscler Thromb Vasc Biol*. 2012 Jun;32(6):1505-12. http://www.ncbi.nlm.nih.gov/pubmed/22499993

194. **Heart disease and stroke.** [Researchers have found that people with periodontal disease are almost twice as likely to suffer from coronary artery disease as those without periodontal disease. Additional studies have pointed to a relationship between periodontal disease and stroke. In one study that looked at the causal relationship of oral infection as a risk factor for stroke, people diagnosed with acute cerebrovascular ischemia were found more likely to have an oral infection when compared to those in the control group.] http://www.perio.org/consumer/mbc.heart.htm

195. **High-density lipoproteins inhibit cytokine-induced expression of endothelial cell adhesion molecules.** [While an elevated plasma concentration of HDLs is protective against the development of atherosclerosis and ensuing coronary heart disease (CHD), the mechanism of this protection is unknown. One early cellular event in atherogenesis is the adhesion of mononuclear leukocytes to the endothelium. This event is mediated principally by vascular cell adhesion molecule-1 (VCAM-1) but also involves other molecules, such as intercellular adhesion molecule-1 (ICAM-1) and E-selectin. We have investigated the effect of isolated plasma HDLs and reconstituted HDLs on the expression of these molecules by endothelial cells. We show that physiological concentrations of HDLs inhibit tumor necrosis factor-α (TNF-α) or interleukin-1 (IL-1) induction of these leukocyte adhesion molecules in a concentration-dependent manner. Steady state mRNA levels of TNF-α-induced VCAM-1 and E-selectin are significantly reduced by physiological concentrations of HDLs. At an HDL concentration of 1 mg/mL apolipoprotein A-I, the protein expressions of VCAM-1, ICAM-1, and E-selectin were inhibited by 89.6±0.4% (mean ± SD, n=4), 64.8±1.0%, and 79.2±0.4%, respectively. In contrast, HDLs have no effect on the expression of platelet endothelial cell adhesion molecule (PECAM) or on the expression of the p55 and p75 subunits of the TNF-α receptor. HDLs were effective when added from 16 hours before to 5 minutes after cytokine stimulation. HDLs had no effect on TNF-α-induced expression of ICAM-1 by human foreskin fibroblasts, suggesting that the effect is cell-type restricted. This study provides the first evidence that HDLs may protect against CHD by inhibiting the expression of adhesion molecules, which are required for the interaction between leukocytes and the endothelium.] Cockerill GW, Rye KA, et al. Arteriosclerosis, thrombosis, and vascular biology 1995, vol. 15, n°11, pp. 1987-1994. http://cat.inist.fr/?aModele=afficheN&cpsidt=2905502

196. **High incidence of actinobacillus actinomycetemcomitans infection in acute coronary syndrome.** [Recent epidemiological studies suggest that periodontitis is an important risk factor for coronary heart disease (CHD). The aim of this study was to evaluate the association between periodontitis and CHD, particularly acute coronary syndrome (ACS), focusing on microbiological and immunological features. Twenty-eight CHD patients, 15 with ACS and 13 with chronic CHD, were included in this study. Coronary angiography, periodontal examination, and dental radiography were performed

in all patients. Subgingival plaque, saliva, and blood samples were analyzed for the periodontopathogens Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Tannerella forsythensis, Treponema denticola, and Prevotella intermedia using polymerase chain reaction. Specific serum antibody titers to the 5 periodontal pathogens were determined by enzyme-linked immunosorbent assay. It was found that 33% of the ACS patients (5/15) harbored A. actinomycetemcomitans in oral samples, whereas no A. actinomycetemcomitans (0/13) was found in the chronic CHD patients ($P < 0.05$). Furthermore, ACS patients showed significantly higher serum IgG titers to A. actinomycetemcomitans ($P < 0.05$) compared with chronic CHD. More tooth loss and alveolar bone loss were noted in ACS patients than in chronic CHD patients, although the differences were not statistically significant. Periodontal pathogens, particularly A. actinomycetemcomitans, may play a role in the development of ACS.] Sakurai K, Wang D, et al.*Int Heart J*. 2007 Nov;48(6):663-75.
http://www.ncbi.nlm.nih.gov/pubmed/18160759

197. **High serum antibody levels to *Porphyromonas gingivalis* predict myocardial infarction.** [Background An association between coronary heart disease (CHD) and clinically diagnosed periodontitis has been found in several epidemiological studies. However, seroepidemiologic evidence based on prospective data on this association is totally lacking. Design The aim of the study was to investigate serum antibodies to major periodontal pathogens for their prediction of myocardial infarction (MI) in men free of CHD at baseline. Methods Cases and controls were ascertained from a random population sample of 4255 men aged 30 to 59 years at baseline. The study cases included 63 men with nonfatal MI or coronary death within the follow-up time of 10 years. Age-matched control subjects ($n = 63$) were randomly chosen from the same cohort. Serum antibody levels to two major periodontopathogenic bacteria, *Actinobacillus actinomycetemcomitans* and *Porphyromonas gingivalis*, were determined. *Results* There was no significant association between the risk for MI and IgG- or IgA-class antibody levels to *A. actinomycetemcomitans* or IgG-class antibody levels to *P. gingivalis.* However, a high *P. gingivalis* IgA-class antibody level predicted MI independently of classical cardiovascular risk factors. The risk for MI increased by increasing quartiles of antibody levels (*P* for the trend 0.021). Compared with the first quartile, the multivariate odds ratios of MI in the second, third and fourth quartiles were 2.47 (95% CI 0.75-8.11), 3.30 (1.03-10.58) and 3.99 (1.22-13.10), respectively. Conclusion The study provides serological evidence that an infection caused by the periodontal pathogen, *P. gingivalis*, increases the risk for MI.] Pussinen PJ, Alfthan G, et al. *European Journal of Cardiovascular Prevention & Rehabilitation*, October 2004 vol. 11 no. 5 408-411. http://cpr.sagepub.com/content/11/5/408.abstract

198. **Homocysteine and pro-inflammatory cytokine concentrations in acute heart disease**. [Inflammation is involved in development and progression of atherosclerosis. Interleukin-2 (IL-2) and interleukin-6 (IL-6) have been correlated with various cardiovascular diseases. Hyperhomocysteinemia is an important risk factor for atherosclerosis and thrombotic disease. Recent studies have demonstrated that homocysteine (Hcy) enhances productions of several pro-inflammatory cytokines. In the light of these findings, we decided to determine if any relationship exists between IL-2 and IL-6, the pro-inflammatory cytokines, and total homocysteine (tHcy) in acute coronary syndrome (ACS). A total of 102 patients with ACS and 90 healthy subjects were included in the study. The levels of tHcy, IL-2 and IL-6 were higher and folic acid was lower in patients as compared with those of controls. Furthermore, data of the area under ROC plot for IL-2 demonstrated that IL-2 had higher sensitivity. These data suggest that enhanced inflammation may be associated with tHcy-related cardiovascular disease.] Gokkusu C, Tulubas F, et al. *Cytokine*, Volume 50, Issue 1, April 2010, Pages 15-18 .
http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6WDF-4Y9C18M-1&_user=10&_coverDate=04%2F30%2F2010&_rdoc=1&_fmt=high&_orig=search&_sort=d&_docanchor=&view=c&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=4931a469428b3599fba8869ab10f9d7e

199. **Human atherosclerotic plaque contains viable invasive *actinobacillus actinomycetemcomitans* and *porphyromonas gingivalis*, Arteriosclerosis.** [Detection of periodontal pathogens in atherosclerotic plaques by PCR does not provide evidence as to the bacteria's viability within the plaque. This is the first report to provide evidence for the presence of invasive periodontal pathogens at the sites of atherosclerotic disease. In addition, their presence was demonstrated at the DNA levels. The intracellular bacteria must have been viable because only viable *P gingivalis* and *A actinomycetemcomitans* can invade host cells.8,9 Notably, the images presented here are all from the same patient. The patient apparently harbors periodontal organisms, judging from his oral health (partial dentition only). Further investigative work needs to be performed to determine whether periodontal pathogens truly have a role in the pathogenesis of atherosclerotic disease and, if so, how the bacteria contribute to the progression of this disease. Nevertheless, establishing such an unequivocal physical link between these two prevalent conditions will certainly support the notion of periodontitis as an exacerbating factor in cardiovascular pathologies. Identifying the inflammatory bacteria associated with vascular pathogenesis will be beneficial to understanding the epidemiological link between periodontal disease and CVD as well as in developing novel therapies for CVD..] Kozarov et al. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2005;25:e17.
http://atvb.ahajournals.org/cgi/reprint/25/3/e17?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=1&author1=kozarov&andorexacttitle=and&andorexacttitleabs=and&andorexactfulltext=and&searchid=1&FIRSTINDEX=0&sortspec=relevance&volume=25&resourcetype=HWCIT

200. **Human oral, gut, and plaque microbiota in patients with atherosclerosis**. [Periodontal disease has been associated with atherosclerosis, suggesting that bacteria from the oral cavity may contribute to the development of atherosclerosis and cardiovascular disease. Furthermore, the gut microbiota may affect obesity, which is associated with atherosclerosis. Using qPCR, we show that bacterial DNA was present in the atherosclerotic plaque and that the amount of DNA correlated with the amount of leukocytes in the atherosclerotic plaque. To investigate the microbial composition of atherosclerotic plaques and test the hypothesis that the oral or gut microbiota may contribute to atherosclerosis in humans, we used 454 pyrosequencing

of 16S rRNA genes to survey the bacterial diversity of atherosclerotic plaque, oral, and gut samples of 15 patients with atherosclerosis, and oral and gut samples of healthy controls. We identified *Chryseomonas* in all atherosclerotic plaque samples, and *Veillonella* and *Streptococcus* in the majority. Interestingly, the combined abundances of *Veillonella* and *Streptococcus* in atherosclerotic plaques correlated with their abundance in the oral cavity. Moreover, several additional bacterial phylotypes were common to the atherosclerotic plaque and oral or gut samples within the same individual. Interestingly, several bacterial taxa in the oral cavity and the gut correlated with plasma cholesterol levels. Taken together, our findings suggest that bacteria from the oral cavity, and perhaps even the gut, may correlate with disease markers of atherosclerosis.] Koren O, Spor A, et al. Published online before print October 11, 2010, doi: 10.1073/pnas.1011383107.
http://www.pnas.org/content/early/2010/10/04/1011383107.abstract
http://www.pnas.org/content/108/suppl.1/4592.full.pdf+html

201. **Hyperhomocysteinemia is Associated With Human Coronary Atherosclerosis Through the Reduction of the Ratio of Endothelium-Bound to Basal Extracellular Superoxide Dismutase** [Background Homocysteine is involved in coronary atherosclerosis through oxidative stress, so the present study investigated the association between plasma concentrations of homocysteine and extracellular superoxide dismutase (EC-SOD) in coronary artery disease (CAD). Methods and Results The study group comprised 154 consecutive male patients with suspected CAD who had undergone angiography. Plasma concentrations of homocysteine and EC-SOD, which was determined before (basal) and after heparin therapy, were measured and the difference was designated as endothelium-bound EC-SOD. The EC-SOD ratio (endothelium-bound/basal EC-SOD) was also evaluated as an index of binding capacity. The plasma homocysteine concentration in the stenosis (+) group (n=97, 12.0±4.6μmol/L) was significantly higher than that of the stenosis (-) group (n=57, 10.2±3.0μmol/L, p=0.004). Plasma homocysteine correlated positively with the basal EC-SOD (r=0.377, p<0.001) and negatively with the EC-SOD ratio (r=-0.199, p=0.014). When the group was subdivided according to either homocysteine or the EC-SOD ratio, there were 2 groups with high homocysteine concentration and of these atherosclerosis was reduced in the group with a high EC-SOD ratio. Conclusions In CAD patients, homocysteine is involved in the significant release of EC-SOD from the endothelium. Furthermore, the higher EC-SOD binding capacity, even at high concentrations of homocysteine, suggested that homocysteine-induced atherosclerosis was suppressed.] Shunn-ichi N, Hiromi T, et al. Circ J 2004 ; 68 : 822-828.
http://ci.nii.ac.jp/Detail/detail.do?LOCALID=ART0002937051&lang=en

202. **Identification of periodontal pathogens in atheromatous plaques.** [BACKGROUND: Recent studies suggest that chronic infections including those associated with periodontitis increase the risk for coronary vascular disease (CVD) and stroke. We hypothesize that oral microorganisms including periodontal bacterial pathogens enter the blood stream during transient bacteremias where they may play a role in the development and progression of atherosclerosis leading to CVD. METHODS: To test this hypothesis, 50 human specimens obtained during carotid endarterectomy were examined for the presence of Chlamydia pneumoniae, human cytomegalovirus, and bacterial 16S ribosomal RNA using specific oligonucleotide primers in polymerase chain reaction (PCR) assays. Approximately 100 ng of chromosomal DNA was extracted from each specimen and then amplified using standard conditions (30 cycles of 30 seconds at 95 degrees C, 30 seconds at 55 degrees C, and 30 seconds at 72 degrees C). Bacterial 16S rDNA was amplified using 2 synthetic oligonucleotide primers specific for eubacteria. The PCR product generated with the eubacterial primers was transferred to a charged nylon membrane and probed with digoxigenin-labeled synthetic oligonucleotides specific for Actinobacillus actinomycetemcomitans, Bacteroides forsythus, Porphyromonas gingivalis, and Prevotella intermedia. RESULTS: Eighty percent of the 50 endarterectomy specimens were positive in 1 or more of the PCR assays. Thirty-eight percent were positive for HCMV and 18% percent were positive for C. pneumoniae. PCR assays for bacterial 16S rDNA also indicated the presence of bacteria in 72% of the surgical specimens. Subsequent hybridization of the bacterial 16S rDNA positive specimens with species-specific oligonucleotide probes revealed that 44% of the 50 atheromas were positive for at least one of the target periodontal pathogens. Thirty percent of the surgical specimens were positive for B. forsythus, 26% were positive for P. gingivalis, 18% were positive for A. actinomycetemcomitans, and 14% were positive for P. intermedia. In the surgical specimens positive for periodontal pathogens, more than 1 species was most often detected. Thirteen (59%) of the 22 periodontal pathogen-positive surgical specimens were positive for 2 or more of the target species. CONCLUSIONS: Periodontal pathogens are present in atherosclerotic plaques where, like other infectious microorganisms such as C. pneumoniae, they may play a role in the development and progression of atherosclerosis leading to coronary vascular disease and other clinical sequelae.] Haraszthy V.I., Zambon J.J., et al. *J Periodontol. 2000 Oct;71(10):1554-60*
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed&cmd=Retrieve&list_uids=11063387&dopt=Abstract

203. **Impact of Infectious Burden on Extent and Long-Term Prognosis of Atherosclerosis**. [BACKGROUND: Recent findings suggest a causative role of infections in the pathogenesis of atherosclerosis. In hypothesizing an association between infectious agents and the development of atherosclerosis, we would expect a correlation to the extent of atherosclerosis. Moreover, this effect could be multiplied by the number of pathogens to which an individual had been exposed. METHODS AND RESULTS: In 572 patients, IgG or IgA antibodies to herpes simplex virus 1 and 2, cytomegalovirus, Epstein-Barr virus, Hemophilus influenzae, Chlamydia pneumoniae, Mycoplasma pneumoniae, and Helicobacter pylori were measured. The extent of atherosclerosis was determined by coronary angiography, carotid duplex sonography, and evaluation of the ankle-arm index. Elevated IgA antibodies against C pneumoniae (P<0.04) and IgG antibodies against H pylori (P<0.02), cytomegalovirus (P<0.05), and herpes simplex virus 2 (P<0.01) were associated with advanced atherosclerosis (> or =2 vascular regions), adjusted for age, sex, cardiovascular risk factors, and highly sensitive C-reactive protein. Infectious burden divided into 0 to 3, 4 to 5, and 6 to 8 seropositivities was significantly associated with advanced atherosclerosis, with an odds

ratio (95% CI) of 1.8 (1.2 to 2.6) for 4 to 5 (P<0.01) and 2.5 (1.2 to 5.1) for 6 to 8 seropositivities (P<0.02) (adjusted). After a mean follow-up of 3.2 years, cardiovascular mortality rate was 7.0% in patients with advanced atherosclerosis and seropositive for 0 to 3 pathogens compared with 20.0% in those seropositive for 6 to 8 pathogens. CONCLUSIONS: Our results support the hypothesis that infectious agents are involved in the development of atherosclerosis. We showed a significant association between infectious burden and the extent of atherosclerosis. Moreover, the risk for future death was increased by the number of infectious pathogens, especially in patients with advanced atherosclerosis.] Espinola-Klein C, Rupprecht HJ, et al. Circulation. 2002 Jan 1;105(1):15-21. http://www.ncbi.nlm.nih.gov/pubmed/11772870

204. **Improved periodontal health and cardiovascular risk**. [Background: Previous studies have demonstrated variable effects on systemic inflammatory and immune responses following improved periodontal health. This study examined changes in serum levels of the inflammatory mediators IL-1b, IL-6, TNF-a and sICAM-1, and antibodies to Porphyromonas gingivalis, human heat shock protein (hHSP) 60 and P. gingivalis GroEL following improvement in periodontal health in high cardiovascular (CV) risk and low CV-risk patients. Methods: Patients retrospectively selected from a longitudinal study, had undergone yearly periodontal examinations and peripheral blood collections. They had demonstrated a quantifiable improvement in periodontal health (>60% reduction in number of sites with probing depth ‡4 mm from the baseline visit) and could be classified as either high CV-risk (‡6 classical risk factors, n = 13) or low CV-risk (£ 1 classical risk factor, n = 14). Serum levels of the cytokines and antibodies were measured using ELISA. Results: For sICAM-1 and anti-P. gingivalis GroEL and anti-hHSP60 antibodies, most patients recorded decreased levels. Reductions in serum sICAM-1 levels were more notable in low CV-risk patients (p = 0.006); and reductions in levels of anti- P. gingivalis GroEL and anti-hHSP60 antibodies (p = 0.001 and 0.009 respectively) were more notable in high CV-risk patients. Conclusions: This study found that subsequent to improved periodontal health, the anti-HSP (HSP60 and GroEL) antibody response was reduced, particularly for high CV-risk patients. sICAM-1 levels were also lowered, more so for low CV-risk patients.] Rose-Hill S, Ford PJ, et al. *Australian Dental Journal 2011; 56: 352-357;* doi: 10.1111/j.1834-7819.2011.01363.x http://www.ada.org.au/app_cmslib/media/lib/1112/m346898_v1_rose-hill.pdf

205. **Infections and their role in atherosclerotic vascular disease.** [Infectious agents may play a role in the pathogenesis of atherosclerosis by several mechanisms of action and at different stages. Microorganisms could infect vascular endothelial cells directly, initiating the inflammatory response needed for the initial process of inducing atherosclerosis. Furthermore, even if the induction or initial injury to the endothelium was caused by another inciting agent or factor (for example, hypercholesterolemia or hypertension), infectious agents could accelerate or enhance the process through several mechanisms of action. They include further recruitment and stimulation of proinflammatory cytokines and tissue growth factors in the arterial wall, as well as enhancement of lipid (low-density lipoprotein, or LDL) accumulation through stimulation of macrophage scavenger or LDL-receptors. Microbes could indirectly influence the development and progression of atherosclerosis by a systemic effect without directly invading the arterial endothelium. Release of endotoxin or lipopolysaccharide into the circulation could indirectly damage vascular endothelium or the immune response, and systemic cytokine release could result in lipid profile predisposing to atherosclerosis or could predispose the arterial environment to a procoagulant state, resulting in acute thrombus on a pre-existent unstable or critical plaque, thus causing an acute ischemic event. Infectious agents may play an important role in atherogenesis, but the jury is not in. Further studies are needed to prove causality of atherogenesis from *C. pneumoniae* and to establish an association between cardiovascular disease and periodontitis. There is, however, sufficient evidence from biological mechanisms and animal models to warrant interventional studies on periodontitis and development of cardiovascular events.] Fong IW, J Am Dent Assoc, Vol 133, No suppl_1, 7S-13S. http://jada.ada.org/cgi/content/full/133/suppl_1/7S

206. **Infections as a stimulus for coronary occlusion, obstruction, or acute coronary syndromes.** [Background: Atherosclerosis is considered to be an inflammatory disease. Infections are a significant cause of inflammation. Acute infections might precipitate acute coronary syndromes (ACS) whereas chronic infections might be stimuli for the development of atherosclerosis. Methods: Coronary angiograms were done on 211 of 335 patients with ACS and the percentage of coronary obstruction was determined. Serum antibody levels to Chlamydia pneumoniae, C. pneumoniae heat shock protein 60 (CpnHSP60), human heat shock protein 60 (hHSP60), enterovirus (EV), herpes simplex virus (HSV), cytomegalovirus (CMV), and two major periodontal pathogens, Aggregatibacter actinomycetemcomitans and Porphyromonas gingivalis, were measured in healthy controls (n = 355) and all patients. Results: Serum antibody levels to periodontal pathogens did not correlate with ACS. However, IgA-class antibody levels to Aggregatibacter actinomycetemcomitans (p = 0.021), CpnHSP60 (p = 0.048) an hHSP60 (p = 0.038) were higher in patients with coronary occlusion or obstruction compared to those without any obstruction. Odds ratios for coronary changes in the highest quartile as compared to the lower quartiles were for A. actinomycetemcomitans IgA 7.84 (95% CI 1.02—60.39, p = 0.048), for CpnHSP60 IgA 8.61 (1.12—65.89, p = 0.038), and for human HSP60 IgA 3.51 (0.79—15.69, p = 0.100). Conclusions: We have previously reported that EV and HSV titres correlated significantly to acute coronary events. They do not correlate to the degree of coronary obstruction as shown here. However, infection by A. actinomycetemcomitans or C. pneumoniae or host response against them associated with coronary obstruction. Clinical coronary events may arise by the effect of acute infections and obstructing lesions by a chronic inflammatory stimulus.] Pesonen E, El-Segaier M, et al. Therapeutic Advances in Cardiovascular Disease, Vol. 3, No. 6, 447-454 (2009). http://tak.sagepub.com/cgi/content/short/3/6/447

207. **Inflammation, C-Reactive Protein, and Atherothrombosis.** [Atherothrombosis of the coronary and cerebral vessels is understood to be a disorder of inflammation and innate immunity, as well as a disorder of lipid accumulation. From a vascular biology perspective, the processes of cellular adhesion, monocyte and macrophage attachment, and transmigration of

immune cells across the endothelium are crucial steps in early atherogenesis and in the later stages of mature plaque rupture, particularly the transition of unstable plaque at the time of acute thrombosis. There is abundant clinical evidence demonstrating that many biomarkers of inflammation are elevated years in advance of first ever myocardial infarction (MI) or thrombotic stroke and that these same biomarkers are highly predictive of recurrent MI, recurrent stroke, diabetes, and cardiovascular death. In daily practice, the inflammatory biomarker in widest use is high-sensitivity C-reactive protein (hsCRP); when interpreted within the context of usual risk factors, levels of hsCRP <1, 1 to 3, and >3 mg/l denote lower, average, and higher relative risk for future vascular events. Risk-prediction models that incorporate hsCRP, such as the Reynolds Risk Score, have been developed that improve risk classification and the accuracy for global risk prediction, particularly for those deemed at "intermediate risk" by usual algorithms, such as the Framingham Risk Score. With regard to cerebral vessels, increased biomarkers of inflammation, including hsCRP, have been associated with increased stroke risk as well as an increased rate of atherosclerosis progression in the carotid vessels. Although the proportion of variation in hsCRP explained by genetic factors may be as large as 20% to 40%, diet, exercise, and smoking cessation remain critical tools for risk reduction and CRP reduction. Statin therapy reduces hsCRP in a largely low-density lipoprotein (LDL)-independent manner, and the "anti-inflammatory" properties of these agents have been suggested as a potential mechanism beyond LDL reduction for the efficacy of these agents. The ongoing multinational Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial of 17,802 initially healthy men and women with low levels of LDL cholesterol but increased levels of hsCRP will help to define whether vascular protection can be achieved with statin therapy, even in the absence of hyperlipidemia. Targeted anti-inflammatory therapies are being developed that may provide a direct method of translating the biology of inflammation into new clinical treatments across multiple vascular beds. This article summarizes data supporting a role for inflammation in cardiovascular disease and offers the possibility that other disorders characterized by inflammation, such as periodontal disease, may have an indirect role by influencing the risk, manifestation, and progression of vascular events.] Ridker PM, Silvertown JD. *Journal of Periodontology, 2008, Vol. 79, No. 8s, Pages 1544-1551.* http://www.joponline.org/doi/full/10.1902/jop.2008.080249

208. **Inflammation and cardiovascular disease mechanisms.** [The traditional view of atherosclerosis as a lipid storage disease crumbles in the face of extensive and growing evidence that inflammation participates centrally in all stages of this disease, from the initial lesion to the end-stage thrombotic complications. Investigators now appreciate that narrowing arteries do not necessarily presage myocardial infarction and that simply treating narrowed blood vessels does not prolong life. Although invasive approaches such as angioplasty and coronary artery bypass will remain necessary in some cases, we now understand that at least some of the cardiovascular benefits attributable to medical treatment and lifestyle modification (diet and physical activity) may result from reductions in inflammatory processes.] Libby P, American Journal of Clinical Nutrition, Vol. 83, No. 2, 456S-460S, February 2006. http://www.ajcn.org/cgi/content/abstract/83/2/456S
209. **Inflammation, heat shock proteins and periodontal pathogens in atherosclerosis: an immunohistologic study.** **[**Background: Inflammation is a significant component of atherosclerosis lesions. Bacteria, including periodontopathogens, have been demonstrated in atherosclerotic plaques and cross-reactivity of the immune response to bacterial GroEL with human heat shock protein 60 has been suggested as a link between infections and atherosclerosis. Methods: In this study, the nature of the inflammatory infiltrate and the presence of human heat shock protein 60 and GroEL were examined in 31 carotid endarterectomy specimens. Additionally, monoclonal antibodies were used to detect the presence of six bacteria, including those implicated in periodontal disease. Results: The inflammatory cell infiltrate of the lesions was dominated by $CD14^+$ macrophages and $CD4^+$ T cells. Most cells of the infiltrate as well as the endothelium were HLA-DR^+, indicating activation; however, there was an absence of CD25 expression, demonstrating that the activated T cells were not proliferating. Few $CD1a^+$ and $CD83^+$ cells were noted. Human heat shock protein 60 expression was evident on endothelial cells and cells with the appearance of smooth muscle cells and lymphocytes. GroEL and bacteria were detected within intimal cells. *Chlamydia pneumoniae, Porphyromonas gingivalis, Fusobacterium nucleatum, Tannerella forsythia, Prevotella intermedia*, and *Actinobacillus actinomycetemcomitans* were found in 21%, 52%, 34%, 34%, 41%, and 17% of arteries, respectively. Conclusion: These results give evidence for a specific immune response associated with atherosclerosis. Whether bacteria initiate the observed inflammation in atherosclerotic lesions is not clear; however, the present study shows that maintenance of inflammation may be enhanced by the presence of periodontopathic bacteria.] Ford PJ, Gemmell E, et al. *Oral Microbiology and Immunology, Volume 21 Issue 4 Page 206-211, August 2006.* http://www.blackwell-synergy.com/doi/abs/10.1111/j.1399-302X.2006.00276.x
210. **Inflammation in Atherosclerosis.** [Experimental work has elucidated molecular and cellular pathways of inflammation that promote atherosclerosis. Unraveling the roles of cytokines as inflammatory messengers provided a mechanism whereby risk factors for atherosclerosis can alter arterial biology, and produce a systemic milieu that favors atherothrombotic events. The discovery of the immune basis of allograft arteriosclerosis demonstrated that inflammation per se can drive arterial hyperplasia, even in the absence of traditional risk factors. Inflammation regulates aspects of plaque biology that trigger the thrombotic complications of atherosclerosis. Translation of these discoveries to humans has enabled both novel mechanistic insights and practical clinical advances.] Libby P. Arteriosclerosis, Thrombosis, and Vascular Biology. 2012**;** 32: 2045-2051 doi: 10.1161/ATVBAHA.108.179705. http://atvb.ahajournals.org/content/32/9/2045.abstract
211. **Interaction between periodontal disease and systemic secondary amyloidosis: from inflammation to amyloidosis.** **[**markers. We have previously shown that the prevalence of moderate to severe periodontitis was significantly higher in patients with familial Mediterranean fever (FMF) with amyloidosis than in patients with FMF without amyloidosis. Thus, the aim of this study is to investigate if chronic periodontitis is associated with secondary amyloidosis in the Black Sea region of

Turkey. Methods: A total of 112 patients with biopsy-proven secondary amyloidosis (59 patients with FMF, 40 patients who were either chronically infected or had malignant disease, 13 patients with periodontitis) and 22 healthy subjects, were included in this study. Periodontal health and disease were evaluated using gingival index (GI), papillary bleeding index (PBI), plaque index (PI), and periodontal disease index (PDI). The concentrations of serum acute phase reactants (APRs) were measured at baseline and at 4 to 6 weeks after completion of the non-surgical periodontal therapy. Results: The prevalence of moderate to severe periodontitis was 47.5% in patients with FMF, 72.5% in patients who were either chronically infected or had malignant disease, and 84.6% in patients with periodontitis. Serum levels of APRs in patients with amyloidosis were reduced significantly after non-surgical periodontal therapy (P <0.01). Conclusions: Periodontitis can increase the levels of APRs and potentiate the development of amyloidosis either by themselves or association with traditional factors, such as FMF and other chronic inflammatory diseases. Thus, preventing or treating periodontitis might prevent or at least alleviate the progression of amyloidosis. Periodontal evaluation should be performed as part of a medical assessment and considered as an etiologic factor for secondary amyloidosis.] Cenqiz MI, Yala N, et al. J *Periodontol.* 2011 Apr;82(4):566-74. http://www.ncbi.nlm.nih.gov/pubmed/21043797

212. **Invasion of Aortic and Heart Endothelial Cells by *Porphyromonas gingivalis.*** [Invasion of host cells is believed to be an important strategy utilized by a number of pathogens, which affords them protection from the host immune system. The connective tissues of the periodontium are extremely well vascularized, which allows invading microorganisms, such as the periodontal pathogen Porphyromonas gingivalis, to readily enter the bloodstream. However, the ability of P. gingivalis to actively invade endothelial cells has not been previously examined. In this study, we demonstrate that P. gingivalis can invade bovine and human endothelial cells as assessed by an antibiotic protection assay and by transmission and scanning electron microscopy. P. gingivalis A7436 was demonstrated to adhere to and to invade fetal bovine heart endothelial cells (FBHEC), bovine aortic endothelial cells (BAEC), and human umbilical vein endothelial cells (HUVEC). Invasion efficiencies of 0.1, 0.2, and 0. 3% were obtained with BAEC, HUVEC, and FBHEC, respectively. Invasion of FBHEC and BAEC by P. gingivalis A7436 assessed by electron microscopy revealed the formation of microvillus-like extensions around adherent bacteria followed by the engulfment of the pathogen within vacuoles. Invasion of BAEC by P. gingivalis A7436 was inhibited by cytochalasin D, nocodazole, staurosporine, protease inhibitors, and sodium azide, indicating that cytoskeletal rearrangements, protein phosphorylation, energy metabolism, and P. gingivalis proteases are essential for invasion. In contrast, addition of rifampin, nalidixic acid, and chloramphenicol had little effect on invasion, indicating that bacterial RNA, DNA, and de novo protein synthesis are not required for P. gingivalis invasion of endothelial cells. Likewise de novo protein synthesis by endothelial cells was not required for invasion by P. gingivalis. P. gingivalis 381 was demonstrated to adhere to and to invade BAEC (0.11 and 0.1% efficiency, respectively). However, adherence and invasion of the corresponding fimA mutant DPG3, which lacks the major fimbriae, was not detected. These results indicate that P. gingivalis can actively invade endothelial cells and that fimbriae are required for this process. P. gingivalis invasion of endothelial cells may represent another strategy utilized by this pathogen to thwart the host immune response.] Deshpande RG, Khan MB, et al. *Infect Immun.* 1998 Nov;66(11):5337-43. *http://intl-iai.asm.org/cgi/content/abstract/66/11/5337*

213. **Invasion of human aortic endothelial cells by oral viridans group streptococci and induction of inflammatory cytokine production.** [Oral viridans group streptococci are the major commensal bacteria of the supragingival oral biofilm and have been detected in human atheromatous plaque. Atherosclerosis involves an ongoing inflammatory response, reportedly involving chronic infection caused by multiple pathogens. The aim of this study was to examine the invasion of human aortic endothelial cells (HAECs) by oral viridans group streptococci and the subsequent cytokine production by viable invaded HAECs. The invasion of HAECs by bacteria was examined using antibiotic protection assays and was visualized by confocal scanning laser microscopy. The inhibitory effects of catalase and cytochalasin D on the invasion of HAECs were also examined. The production of cytokines by invaded or infected HAECs was determined using enzyme-linked immunosorbent assays, and a real-time polymerase chain reaction method was used to evaluate the expression of cytokine messenger RNA. The oral streptococci tested were capable of invading HAECs. The number of invasive bacteria increased with the length of the co-culture period. After a certain co-culture period, some organisms were cytotoxic to the HAECs. Catalase and cytochalasin D inhibited the invasion of HAECs by the organism. HAECs invaded by Streptococcus mutans Xc, Streptococcus gordonii DL1 (Challis), Streptococcus gordonii ATCC 10558 and Streptococcus salivarius ATCC 13419 produced more cytokine(s) (interleukin-6, interleukin-8, monocyte chemoattractant protein-1) than non-invaded HAECs. The HAECs invaded by S. mutans Xc produced the largest amounts of cytokines, and the messenger RNA expression of cytokines by invaded HAECs increased markedly compared with that by non-invaded HAECs. These results suggest that oral streptococci may participate in the pathogenesis of atherosclerosis.] Nagata E, de Toledo A, et al. *Mol Oral Microbiol.* 2011 Feb;26(1):78-88. doi: 10.1111/j.2041-1014.2010.00597.x. Epub 2010 Dec 3. http://www.ncbi.nlm.nih.gov/pubmed/21214874

214. **Invasion of human coronary artery endothelial cells by Streptococcus mutans OMZ175.** [Introduction: Dissemination of oral bacteria into the bloodstream has been associated with eating, oral hygiene, and dental procedures; including tooth extraction, endodontic treatment, and periodontal surgery. Recently, studies identified Streptococcus mutans, the primary etiological agent of dental caries, as the most prevalent bacterial species found in clinical samples from patients who underwent heart valve and atheromatous plaque surgery. METHODS: By using antibiotic protection assays, we tested the capacity of 14 strains of S. mutans to invade primary human coronary artery endothelial cells (HCAEC). RESULTS: Serotype e strain B14 and serotype f strain OMZ175 of S. mutans were able to efficiently invade HCAEC. Among the tested strains, serotype f S. mutans OMZ175 was the most invasive, whereas strains of serotype c S. mutans, the most prevalent serotype in dental plaque, were not invasive. Based on its high invasion rate, we further investigated the invasive properties

of serotype f OMZ175. Using transmission electron microscopy and antibiotic protection assays we demonstrate that S. mutans OMZ175 is capable of attaching to the HCAEC surface, entering the cells and surviving in HCAEC for at least 29 h. DISCUSSION: Our findings highlight a potential role for S. mutans in the pathogenesis of certain cardiovascular diseases.]. Abranches J, Zeng L, et al. Oral *Microbiol Immunol*. 2009 Apr;24(2):141-5. doi: 10.1111/j.1399-302X.2008.00487.x. http://www.ncbi.nlm.nih.gov/pubmed/19239641

215. **Invasive Dental Treatment and Risk for Vascular Events; A Self-Controlled Case Series**. [Background: Treatment of periodontal disease may reduce cardiovascular risk in the longer term, but studies have suggested a link among dental procedures, acute inflammation, and endothelial dysfunction. However, whether such acute inflammatory effects translate into a short-lived increased risk for vascular events is not known. Objective: To investigate whether invasive dental treatment transiently increases the risk for vascular events. Design: Self-controlled case series. Setting: Data came from the U.S. Medicaid claims database. Patients: All persons exposed to invasive dental treatment with a primary hospital discharge diagnosis of ischemic stroke (n = 650) or myocardial infarction (n = 525) from 2002 to 2006. Measurements: The incidence of ischemic stroke and myocardial infarction in periods immediately after invasive dental treatment was compared with the incidence in all other observed time periods. Incidence ratios and 95% CIs were calculated. Results: The rate of vascular events significantly increased in the first 4 weeks after invasive dental treatment (incidence ratio, 1.50 [95% CI, 1.09 to 2.06]) and gradually returned to the baseline rate within 6 months. The positive association remained after exclusion of persons with diabetes, hypertension, or coronary artery disease or persons with prescriptions for antiplatelet or salicylate drugs before treatment. Limitations: Power to examine the effects of invasive dental treatment on stroke and myocardial infarction separately was limited because of the low frequency of invasive dental procedures. Lack of information about use of over-the-counter drugs limited the ability to assess confounding by possible withholding of antiplatelet or salicylate drugs before invasive dental treatment or by the use of nonsteroidal anti-inflammatory drugs after treatment. Conclusion: Invasive dental treatment may be associated with a transient increase in the risk for vascular events. However, the absolute risks are minimal, and the long-term benefits on vascular health will probably outweigh the short-lived adverse effects.] Minassian C, D'Aiuto F, et al. *Annals of Int Med*, oct 19, 2010, Vol. 153, no. 8, pp 499-506. http://www.annals.org/content/153/8/499.abstract

216. **'Jailbreak' Bacteria Can Trigger Heart Disease. [**Plaque-causing bacteria can jailbreak from the mouth into the bloodstream and increase your risk of heart attack.] Jenkinson H. Reported in: *ScienceDaily* 6 September 2010. Society for General Microbiology (2010, Sept 6). http://www.sciencedaily.com/releases/2010/09/100905231231.htm

217. **Level of serum antibody against a periodontal pathogen is associated with atherosclerosis and hypertension**. [Inflammation has a role in the pathogenesis of atherosclerosis, which causes hypertension. Results from some studies have suggested links between periodontal disease and atherosclerosis, but links between periodontal disease and hypertension have been seldom studied. We investigated whether periodontal disease and serum antibody level were associated with hypertension. We studied 127 patients (93 men and 34 women, mean age 68±9 years) who were admitted with ischemic heart disease to our institution. A composite periodontal risk score was calculated from five periodontal vector scores. The levels of serum antibody against Porphyromonas gingivalis (Pg) were measured. Pulse pressure, mean blood pressure (BP) and pulse wave velocity were used as indices of atherosclerosis. We divided patients into two groups according to the levels of serum antibody against Pg: higher or equal to the median (high Pg antibody group) and lower than the median (low Pg antibody group).There was no difference in the use of antihypertensive agents between the two groups. The composite periodontal risk score (P=0.0003), systolic BP (P=0.030), diastolic BP (P=0.038), pulse pressure (P=0.050) and mean BP (P=0.055) were higher in the high Pg antibody group than in the low Pg antibody group. The composite periodontal risk score (r=0.320, P=0.0003), systolic BP (r=0.212, P=0.017), diastolic BP (r=0.188, P=0.035) and mean BP (r=0.225, P=0.011) correlated with the level of serum antibody against Pg, even after adjustment for age. An elevated antibody level against Pg indicates advanced periodontal disease and suggests advancement of atherosclerosis and hypertension.Hypertension Research advance online publication, 16 May 2013; doi:10.1038/hr.2013.46.] Hanaoka Y, Soejima H. et al. *Hypertens Res.* 2013 May 16. doi: 10.1038/hr.2013.46. *http://www.ncbi.nlm.nih.gov/pubmed/23676848*

218. **Lipopolysaccharide associates with pro-atherogenic lipoproteins in periodontitis patient**s [INTRODUCTION: Periodontitis patients are known to suffer from endotoxemia, which may be among the major risk factors for atherosclerosis. In health, lipopolysaccharide (LPS) is mainly carried with high density lipoprotein (HDL) particles. Shift of LPS toward lipoproteins with lower densities may result in less effective endotoxin scavenging. Our aim was to determine plasma LPS activity and lipoprotein-distribution before and after treatment in periodontitis patients. PATIENTS AND METHODS: Very low and intermediate density (VLDL-IDL), low density (LDL), HDL 2, HDL3, and lipoprotein-deficient plasma (LPDP) were isolated by sequential ultracentrifugation. Patients included 34 subjects aged 53.5 +/- 8.3 years, before and 6 months after periodontal treatment. RESULTS: The mean LPS distribution decreased among lipoprotein classes as follows: VLDL-IDL 41.3 +/- 12.1%, LPDP 25.0 +/- 7.0%, HDL3 13.1 +/- 5.2%, LDL 11.5 +/- 3.7%, and HDL2 9.2 +/- 2.8%. Plasma and VLDL-IDL-associated LPS correlated positively, and LDL- and HDL-associated LPS negatively with clinical periodontal parameters and plasma cytokine concentrations. Mean plasma LPS activity increased after periodontal treatment from 44.0 +/- 17.0 to 55.7 +/- 24.2 EU/ml (P = 0.006). No significant changes were found in LPS lipoprotein distribution and lipoprotein compositions after the treatment. CONCLUSIONS: Endotoxemia increases with severity of periodontitis. In periodontitis, LPS associates preferentially with the pro-atherogenic VLDL-IDL fraction. Periodontal treatment has only minor effects on plasma LPS activity or distribution, which reflects persistence of the disease**.]** Kallio KA, Buhlin K, et al. Innate Immun. 2008 Aug;14(4):247-53. http://www.ncbi.nlm.nih.gov/pubmed/18669610

219. **Lipoprotein-associated phospholipase A_2 and plasma lipids in patients with destructive periodontal disease.** [OBJECTIVES: Periodontitis is believed to be an independent risk factor of cardiovascular disease (CVD) and to be associated with a moderate systemic inflammatory reaction and hyperlipidaemia. Lipoprotein-associated phospholipase A(2) (Lp-PLA(2)) is an enzyme that has been shown to be a risk factor of CVD and that is involved in the degradation of the phospholipid mediator platelet-activating factor (PAF), a potent mediator of inflammation. MATERIAL AND METHODS: In the present study, we measured concentrations of plasma lipids and plasma activity of Lp-PLA(2) in 32 patients (mean age 43+/-11 years) with moderate-to-severe periodontitis before and 3 months after local treatment. RESULTS: Periodontal therapy resulted in a significant reduction of local inflammation and tissue destruction as reflected in reduced pocket depths and reduced bleeding indices. Pre- and post-treatment plasma lipid levels were (median and range, mmol/l): total cholesterol (C) 5.01 (3.94-7.15) and 4.91 (3.32-8.01); low-density lipoprotein-cholesterol (LDL-C) 3.14 (2.40-4.84) and 2.96 (1.39-5.04); HDL-C 1.27 (0.73-2.17) and 1.25 (0.74-2.55); triglycerides 1.37 (0.48-5.11) and 1.14 (0.38-792). Using the Wilcoxon's rank test, neither parameter showed a significant change. In contrast to the lacking response of plasma lipids, we observed a significant reduction in the activity of Lp-PLA(2). Local treatment lowered the enzyme activity by about 10% from 3.61+/-0.99 to 3.29+/-0.94 micromol/ml/h (mean+/-SD; $p<0.001$). The pre-treatment values of Lp-PLA(2) and LDL-C significantly correlated with clinical parameters of inflammation and periodontal destruction. CONCLUSION: This study indicates that treatment of periodontitis significantly reduces the serum activity of Lp-PLA(2), which is believed to be an independent cardiovascular risk factor.] Losche W, Marshal GJ, et al. *J Cln Periodontol.* 2005 Jun;32(6)640-4. **http://www.ncbi.nlm.nih.gov/pubmed/15882224**

220. **Lipoproteins and lipoprotein metabolism in periodontal disease.** [A growing body of evidence indicates that the incidence of atherosclerosis is increased in subjects with periodontitis – a chronic infection of the oral cavity. This article summarizes the evidence that suggests periodontitis shifts the lipoprotein profile to be more proatherogenic. LDL-C is elevated in periodontitis and most studies indicate that triglyceride levels are also increased. By contrast, antiatherogenic HDL tends to be low in periodontitis. Periodontal therapy tends to shift lipoprotein levels to a healthier profile and also reduces subclinical indices of atherosclerosis. In summary, periodontal disease alters lipoprotein metabolism in ways that could promote atherosclerosis and cardiovascular disease.] Griffiths R, Barbour S. Clin Lipidol. 2010 June; 5(3): 397–411. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2933935/

221. **Live Oral Bacteria Found in Arterial Plaque.** [There are live periodontal bacteria in human atherosclerotic tissue.] March 22, 2005 Ann Progulske-Fox, chief investigator, U of FL College of Dentistry. http://www.research.ufl.edu/publications/explore/v10n2/extract5.html

222. **Long-Term Effects of Inflammation-Sensitive Plasma Proteins and Systolic Blood Pressure on Incidence of Stroke.** [*Background and Purpose*— The present study investigated the relationships between inflammation-sensitive plasma proteins (ISPs) and systolic blood pressure (SBP), as well as the joint long-term effects of ISP and SBP on incidence of stroke. *Methods*— BP and 5 ISPs (fibrinogen, α1-antitrypsin, haptoglobin, ceruloplasmin, orosomucoid) were assessed in 6071 healthy men 28 to 61 years of age. All-cause mortality and incidence of stroke were monitored over a mean follow-up of 18.7 years in men defined by SBP (<120, 120 to 139, ≥140 mm Hg) and ISP (0 to 1 or 2 to 5 ISPs in the top quartile). *Results*— SBP and diastolic BP were significantly and positively associated with the number of ISPs in the top quartile. As expected, elevated SBP was associated with an increased incidence of stroke. Among men with SBP ≥140 mm Hg, there were, however, significant differences between those with high and low ISP levels. After risk factor adjustment, men with SBP ≥ 140 mm Hg and high ISP levels had a relative risk of stroke of 4.3 (95% CI, 2.3 to 7.8) compared with men with SBP <120 mm Hg and low ISP levels. In the absence of high ISP levels, the risk associated with SBP ≥140 was 2.5 (95% CI,1.4 to 4.6). Men with high ISP levels had a significantly increased risk of stroke also after exclusion of the events from the first 10 years of follow-up. *Conclusions*— High ISP levels are associated with elevated BP. These proteins are associated with an increased risk of stroke among men with high BP and provide information on stroke risk even after many years of follow-up.] Engstrom G, Lind P, et al. *Stroke.* 2002;33:2744. http://stroke.ahajournals.org/cgi/content/abstract/33/12/2744.

223. **Markers of Systemic Bacterial Exposure in Periodontal Disease and Cardiovascular Disease Risk: A Systematic Review and Meta-Analysis.** [Recent meta-analyses reported a weak association between periodontal disease (PD) on clinical examination and cardiovascular disease (CVD). Systemic bacterial exposure from periodontitis, which correlates poorly with the clinical examination, has been proposed as the more biologically pertinent risk factor. The purpose of this study was to review and analyze the association between PD with elevated systemic bacterial exposure and CVD… Periodontal disease with elevated bacterial exposure is associated with CHD events and early atherogenesis (CIMT), suggesting that the level of systemic bacterial exposure from periodontitis is the biologically pertinent exposure with regard to atherosclerotic risk.] Mustapha IZ, Debrey S, et al. *Journal of Periodontology, 2007, Vol. 78, No. 12, Pages 2289-2302* http://www.joponline.org/doi/abs/10.1902/jop.2007.070140.

224. **Markers of Periodontal Disease Predict Myocardial Infarction, Stroke and Heart Failure Differently in a Cohort of 7999 Subjects.** [Objective: Oral health has been associated with an increased risk for different cardiovascular disorders. So far, however, no study has investigated oral health in relation to the three most common cardiovascular diseases in the same cohort. The aim of the study was to investigate if different markers of periodontal disease relate to the three most common cardiovascular disorders, myocardial infarction, and stroke in different ways. Material and method: Seven thousand nine hundred and ninety nine subjects, referred to a specialist clinic for periodontal treatment between 1976 and 2008, received a full mouth dental investigation including x-ray. Number of remaining teeth (NT), periodontal severity index (PDSI), number of deepened periodontal pockets (NDP), and bleeding on probing (BOP) were evaluated in relation to fatal/non fatal

myocardial infarction (MI), heart failure (HF), and stroke. Results: During a median follow up time of 13.6 years, 414 events involved fatal/non fatal MI; 204 involved HF; and 438 involved a stroke. Possible associations to above mentioned oral parameters as independent variables were investigated using three multivariate models with three cardiovascular endpoints as dependent variables. When comparing the highest quartile with the lowest one, and adjusting for age, gender, smoking as well as education level, both NT and NDP related significantly to MI (HR 1.69, 95% CI 1.02-2.81, and HR 1.53, 95%CI 1.03-2.27, respectively). NT was also related to HF (HR 2.52, 95% CI 1.20-5.28), while fatal/non fatal stroke was only predicted by BOP (HR 2.13, 95%CI 1.48-3.05). Conclusion: Markers of periodontal disease predict future common cardiovascular events in different ways, suggesting that they are risk indicators for different cardiovascular disorders.] Holmlund A, Lind L. Circulation. 2011;124:A10576. http://circ.ahajournals.org/cgi/content/meeting_abstract/124/21_MeetingAbstracts/A10576

225. **Microbiological Effects of Scaling and Root Planing.** [The endpoint of clinical therapy is the elimination of inflammation. To achieve this, open debridement may be required in addition to scaling and root planing, and treatment may be aided by chemotherapeutic agents. Scaling and root planing results in systemic effects (including bacteremia) and local effects which include decreases in the levels of calculus, pathogenic microorganisms and clinical inflammation. Additional therapy may be required to achieve clinical health.] Haake SK, Isaacs D. (Note: http://www.dent.ucla.edu/pic/members/microscaling/
226. **Molecular detection of Treponema denticola and Porphyromonas gingivalis in carotid and aortic atheromatous plaques by FISH: report of two cases. [**Treponema denticola and Porphyromonas gingivalis have been identified in atheromatous plaques of two patients suffering from atherosclerosis by PCR and fluorescence in situ hybridization (FISH). The use of the FISH technique suggested that these periodontopathic micro-organisms might be metabolically active within the wall of arteries, under the atherosclerotic lesion.] Cavrini Fm, SAmbri V, et al. *J Med Microbiol.* 2005 Jan;54(Pt 1):93-6. http://www.ncbi.nlm.nih.gov/pubmed/15591262
227. **Multiple infections in carotid atherosclerotic plaques**. [Background *Chlamydia pneumoniae* , cytomegalovirus, herpes simplex virus, and recently, periodontal disease, have been associated with human atherosclerosis. *Porphyromonas gingivalis* and *Streptococcus sanguis* are major pathogens associated with periodontitis, a common chronic inflammatory condition in adults. Investigators have found that these infectious agents may influence vascular cell functions by inducing thrombus formation, vascular cell proliferation, apoptosis, and cell death. Methods and Results The main purpose of our study was to investigate the relation between the presence of multiple infectious agents in human carotid endarterectomy specimens and pathoanatomic features of the corresponding carotid plaques. Histologically, plaque rupture of the fibrous cap and communication of the luminal thrombus with the central necrotic lipid core was seen in or at proximity to the macrophage-rich shoulder (unstable plaque region). Thrombus within the lipid core without plaque rupture was occasionally found near the internal elastic lamina, associated with increased vascularity and lymphocytic infiltrate. Apoptosis, as detected by both the immunohistochemical staining of apoptosis-related proteins and in situ labeling of internucleosomally degraded DNA, was common in atherosclerotic plaques. Immunostainings for *C pneumoniae* , cytomegalovirus, herpes simplex virus-1, *P gingivalis*, and *S sanguis* were positive in the carotid plaques. From 1 to 4 organisms were found in the same specimen. The micro-organisms were immunolocalized in plaque shoulders and lymphohistiocytic infiltrate, associated with ulcer and thrombus formation, and adjacent to areas of strong labeling for apoptotic bodies. Conclusions Our data provide evidence that multiple infectious agents may be found in atherosclerotic plaques, and sometimes in the same specimen. The current study is the first to report the detection of 2 major odontopathogens, *P gingivalis* and *S sanguis*, in atherosclerotic plaques. The immunolocalization of these micro-organisms within unstable plaque regions and their association with plaque ulceration, thrombosis, and apoptosis in vascular cells are intriguing. Multiple infectious agents may alter vascular cell function and provide a “trigger” for acute ischemic stroke events. Further evidence from human studies and animal models will be needed.] Chiu B. *Am Heart J* 1999;138:S534-S536. http://www.ahjonline.com/article/S0002-8703(99)70294-2/abstract http://www.ncbi.nlm.nih.gov/pubmed/10539867
228. **New research finds link between gum disease, acute heart attacks.** [Heart attack survivors who suffer advanced gum disease show significantly higher levels of C-reactive protein in their blood than patients without gum disease, new University of North Carolina at Chapel Hill research indicates.] UNC News Services, http://www.unc.edu/news/archives/nov00/deliar111300.htm ; http://www.sciencedaily.com/releases/2000/11/001113071724.htm
229. **Oral Bacteria are a Possible Risk Factor for Valvular Incompetence in Primary Varicose Veins.** [Objectives: To investigate a possible link between valvular incompetence in primary varicose veins and chronic infection of periodontal disease by assessing the presence of oral bacteria in the great saphenous vein from patients with varicose veins and control subjects. Material and methods: Forty-four primary varicose vein patients were enrolled in the study. 12 control saphenous veins were obtained from patients undergoing peripheral arterial bypass without clinical evidence of venous reflux. In total, 56 saphenous vein specimen (44 varicose veins and 12 control veins) were examined for 7 periodontal bacteria using a polymerase chain reaction (PCR) method. Results: Of the 44 primary varicose vein patients, 31 patients were women and mean age was 59 years (range, 39–79 years). PCR examination of the diseased vein specimens showed that 48% were positive for at least one of 7 periodontal bacterial DNA. No bacteria were detected in the control specimens. Conclusion: Bacterial colonisation or infection of varicose veins is a frequent event although we were not able to establish whether this is a cause or consequence of the development of varices but this could be considered a risk factor for the development of

varices.] Kurihara N, Inoue Y, et al. European Journal of Vascular and Endovascular Surgery , Volume 34 , Issue 1 , Pages 102 – 106. http://linkinghub.elsevier.com/retrieve/pii/S1078588407001499

230. **Oral care for patients with cardiovascular disease and stroke.** [Many systemic diseases and conditions have oral manifestations that may be the initial signs of clinical disease. The mouth is a portal of entry as well as the site of disease for microbial infections that affect general health status. Sufficient evidence exists to conclude that oral lesions, especially advanced periodontic pathogies, place certain patients at increased risk of developing cardiovascular disease and stroke.] Rose LF, Mealey B**.** *J Am Dent Assoc*, Vol 133, No suppl_1, 37S-44S. *http://jada.ada.org/cgi/content/full/133/suppl_1/37S*

231. **Oral infection-inflammatory pathway, periodontitis, is a risk factor for endothelial dysfunction in patients with coronary artery disease.** [Objective: Several studies have shown that periodontitis is a risk factor for cardiovascular diseases. There is an association between inflammation and endothelial dysfunction. The purpose of this study was to evaluate endothelial function in patients with coronary artery disease (CAD) who had periodontitis. Methods and results: We evaluated forearm blood flow (FBF) responses to acetylcholine (ACh), an endothelium-dependent vasodilator, and to sodium nitroprusside (SNP), an endothelium-independent vasodilator, in 101 CAD patients with periodontitis (37 men and 11 women, 63 ± 12 yr) and without periodontitis (36 men and 17 women, 62 ± 13 yr). FBF was measured by using strain-gauge plethysmography. Circulating levels of C-reactive protein and interleukin-6 were significantly higher in the periodontitis group than in the non-periodontitis group. FBF response to ACh was significantly smaller in the periodontitis group than in the non-periodontitis group. SNP-stimulated vasodilation was similar in the two groups. Periodontal therapy reduced serum concentrations of C-reactive protein from 2.7 ± 1.9 to 1.8 ± 0.9 mg/L ($P < 0.05$) and interleukin-6 from 2.6 ± 3.4 to 1.6 ± 2.6 ng/L ($P < 0.05$) and augmented ACh-induced vasodilation from 14.7 ± 5.2 to 20.1 ± 6.1 mL/(min 100 mL) tissue ($P < 0.05$) in patients with periodontitis. The SNP-stimulated vasodilation was similar before and after treatment. After administration of NG-monomethyl-L-arginine, a nitric oxide synthase inhibitor, FBF response to ACh was similar before and after treatment. Conclusion: These findings suggest that periodontitis is associated with endothelial dysfunction in patients with CAD through a decrease in nitric oxide bioavailability. Systemic inflammation may be, at least in part, a cause and predictor of progression of endothelial dysfunction.] Higashi Y, Goto C, et al. *Atherosclerosis*, Vol 206, Issue 2, Pp 604-910. http://www.atherosclerosis-journal.com/article/S0021-9150(09)00248-2/abstract

232. **Pathogen-related oral spirochetes from dental plaque are invasive.** [These findings indicate that gingival tissues may be a port of entry for previously unrecognized invasive spirochetes in humans.] *Infect Immuno* 59:3377-80, 1991. Riviere GR et al. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1894352&dopt=Abstract

233. **Periodontal disease and cardiovascular disease.** [It is our central hypothesis that periodontal diseases, which are chronic Gram-negative infections, represent a previously unrecognized risk factor for atherosclerosis and thromboembolic events. Previous studies have demonstrated an association between periodontal disease severity and risk of coronary heart disease and stroke. We hypothesize that this association may be due to an underlying inflammatory response trait, which places an individual at high risk for developing both periodontal disease and atherosclerosis. We further suggest that periodontal disease, once established, provides a biological burden of endotoxin (lipopolysaccharide) and inflammatory cytokines (especially TxA2, IL-1 beta, PGE2, and TNF-alpha) which serve to initiate and exacerbate atherogenesis and thromboembolic events. A cohort study was conducted using combined data from the Normative Aging Study and the Dental Longitudinal Study sponsored by the United States Department of Veterans Affairs. Mean bone loss scores and worst probing pocket depth scores per tooth were measured on 1,147 men during 1968 to 1971. Information gathered during follow-up examinations showed that 207 men developed coronary heart disease (CHD), 59 died of CHD, and 40 had strokes. Incidence odds ratios adjusted for established cardiovascular risk factors were 1.5, 1.9, and 2.8 for bone loss and total CHD, fatal CHD, and stroke, respectively. Levels of bone loss and cumulative incidence of total CHD and fatal CHD indicated a biologic gradient between severity of exposure and occurrence of disease.] Beck J, Garcia G, et al. *J Periodontol.* 1996 Oct;67(10 Suppl):1123-37. http://www.ncbi.nlm.nih.gov/pubmed/8910831

234. **Periodontal Disease and Coronary Heart Disease; A reappraisal of the exposure. [**BACKGROUND: Results from studies relating periodontal disease to cardiovascular disease have been mixed. Residual confounding by smoking and use of clinical measures of periodontal disease rather than measures of infection have been 2 major criticisms. The aims of this study were to investigate relationships between prevalent coronary heart disease (CHD) and 2 exposures, (1) clinical periodontal disease and (2) IgG antibodies to 17 oral organisms, and to evaluate the role of smoking in these relationships. METHODS AND RESULTS: Our study is based on a subset of participants in the Atherosclerosis Risk in Communities (ARIC) Study, who received a complete periodontal examination during visit 4 (1996-1998). The exposures were periodontal status and serum IgG antibody levels against 17 periodontal organisms, and the outcome was prevalent CHD at visit 4. Multivariable analyses indicate that periodontal status is not significantly associated with CHD in either ever smokers or never smokers. Similar analyses evaluating antibodies indicate that high antibodies (above the median) to Treponema denticola (odds ratio [OR]=1.7; 95% CI, 1.2 to 2.3), Prevotella intermedia (OR=1.5; 95% CI, 1.1 to 2.0), Capnocytophaga ochracea (OR=1.5; 95% CI, 1.1 to 2.1), and Veillonella parvula (OR=1.7; 95% CI, 1.2 to 2.3) are significantly associated with CHD among ever smokers, whereas Prevotella nigrescens (OR=1.7; 95% CI, 1.1 to 2.6), Actinobacillus actinomycetemcomitans (OR=1.7; 95% CI, 1.2 to 2.7), and Capnocytophaga ochracea (OR=2.0; 95% CI, 1.3 to 3.0) were associated with CHD among never smokers. CONCLUSIONS: Clinical signs of periodontal disease were not associated with CHD, whereas systemic antibody response was associated with CHD in ever smokers and never smokers. These findings indicate that the quality and quantity of the host response to oral bacteria may be an exposure more relevant to systemic

atherothrombotic coronary events than clinical measures.] Beck JD, Eke P, et al. *Circulation.* 2005 Jul 5;112(1):19-24. Epub 2005 Jun 27. http://www.ncbi.nlm.nih.gov/pubmed/15983248

235. **Periodontal disease and cardiovascular disease - Epidemiology and possible mechanisms.** [Mild forms of periodontal disease affect 75 percent of adults in the United States, and more severe forms affect 20 to 30 percent of adults. Because periodontal disease is common in the population, it may account for a significant portion of the proposed infection-associated risk of cardiovascular disease.] Genco R, Offenbacher S. *J Am Dent Assoc*, Vol 133, No suppl_1, 14S-22S. http://jada.ada.org/cgi/content/full/133/suppl_1/14S
236. **Periodontal Disease and Heart Health.** [According to the American Academy of Periodontology, people with periodontal disease are almost twice as likely to have coronary artery disease (also called heart disease). And one study found that the presence of common problems in the mouth, including gum disease (gingivitis), cavities, and missing teeth, were as good at predicting heart disease as cholesterol levels.] April, 2005, WebMD. http://www.webmd.com/content/Article/104/107270.htm?printing=true
237. **Periodontal Disease and Ischemic Stroke in Women**. [Background: Previous studies have suggested an association between periodontitis and ischemic stroke, but very few have been conducted among women. Objective: To evaluate the relation between radiographically measured periodontal bone loss and the risk of ischemic stroke. Methods: We conducted a nested case-control study within the ongoing prospective cohort of U.S. female nurses (Nurses' Health Study). Among women who provided blood samples in 1989-1990, after excluding those who had myocardial infarction prior to the stroke diagnosis, we included all 483 confirmed incident ischemic stroke cases that occurred between 1989 and 2006. Each case was individually matched with one eligible control by age, smoking, race, date of blood draw, fasting, menopause status, post-menopausal hormone use at blood collection, and availability of second blood sample from 2000. We requested pre-existing dental radiographs from all eligible 335 live cases and 393 controls, and evaluated periodontal bone loss on posterior teeth. Logistic regression models were used to evaluate the association between periodontal disease and incident ischemic stroke. Results: 186 participants (82 cases and 104 controls) provided dental radiographs dated prior to the stroke case diagnosis and the corresponding date for the controls. After adjusting for the matching factors, baseline diabetes, hypertension, BMI, alcohol and physical activity, being in the upper tertile of percent of sites with bone loss ≥2 mm was associated with a RR of 3.05 for ischemic stroke (95%CI: 1.29-7.22). There was no significant association between percentage of sites with bone loss ≥3mm (RR for 10% increment=0.96, 95%CI: 0.84-1.10), or severe periodontitis (≥1 site of ≥5mm) and ischemic stroke (RR=0.49, 95%CI: 0.24-1.01). Conclusions: Generalized periodontal bone loss seems to be associated with increased risk of ischemic stroke in this cohort. However, we did not observe a dose-response between periodontal bone loss severity and ischemic stroke risk.] Rexrode K, Lugo F, et al. *IADR General Session*, San Diego CA, March 2011. http://iadr.confex.com/iadr/2011sandiego/webprogram/Paper148475.html
238. **Periodontal Disease and Risk of Cerebrovascular Disease** [Periodontal disease is an important risk factor for total CVA and, in particular, nonhemorrhagic stroke.] Wu T, Trevisan M, et al. *Arch Intern Med.* 2000;160:2749-2755. http://archinte.ama-assn.org/cgi/content/abstract/160/18/2749
239. **Periodontal disease and recurrent cardiovascular events in survivors of myocardial infarction (MI): the Western New York Acute MI Study.** [BACKGROUND: Periodontal disease and cardiovascular disease (CVD) have been the focus of much research, but little is known about their roles in the recurrent event risk in patients with CVD. This study investigates whether periodontal disease is related to recurrent CVD events and mortality in survivors of incident myocardial infarction (MI). METHODS: Participants (668 males and 216 females; mean age: 54 + or - 8.5 years) were recruited (1997 through 2004) from two western New York county hospitals and completed an interviewer-administered questionnaire regarding lifestyle habits, clinical measurements, and a comprehensive dental examination. The periodontal disease status was measured by the mean clinical attachment loss (AL). Follow-up surveys assessed hospitalizations or medical procedures; cardiovascular events were validated by medical records. A National Death Index (NDI) Plus search was conducted. The outcome was recurrent fatal and non-fatal cardiovascular events (International Classification of Diseases codes 390 to 450). RESULTS: After an average follow-up of 2.9 years, 154 events were reported. Among never-smokers, the adjusted hazard ratio (95% confidence interval) for the mean clinical AL (millimeters) was 1.43 (1.09 to 1.89). No associations were found in ever-smokers (clinical AL by smoking interaction: P <0.05). CONCLUSION: These findings indicate that periodontal disease may be an important factor in determining recurrent cardiovascular events in MI patients and not merely a marker for the effects of cigarette smoking.] Dorn JM, Genco RJ, et al. *J Periodontol.* 2010 Apr;81(4):502-11. http://www.ncbi.nlm.nih.gov/pubmed/20367093
240. **Periodontal Disease May Increase Risk of Stroke.** [People with periodontal disease are more likely to have thickened carotid arteries, which can lead to stroke, according to a study released at the American Academy of Neurology's 51st annual meeting in Toronto.] American Academy of Neurology 51st annual meeting Toronto CA, 4/21/1999, Mitchell Elkind, MD, Columbia Univ, New York. http://www.pslgroup.com/dg/f896a.htm
241. **Periodontal diseases: A risk factor to cardiovascular disease.** [Periodontitis is a destructive inflammatory disease of the supporting tissues of the teeth and is caused by specific microorganisms or group of specific microorganisms resulting in progressive destruction of periodontal ligament and alveolar bone with periodontal pocket formation, gingival recession or both. The host responds to the periodontal infections with an array of events involving both innate and adaptive immunity. Atherosclerosis and its consequent cardiovascular diseases represent one of the leading causes of death in the industrialized world and its etiological pathway is one of the chronic inflammatory diseases. Periodontitis has been proposed as having an etiological or modulating role in cardiovascular and cerebrovascular disease, diabetes, respiratory disease and adverse

pregnancy outcome and several mechanisms have been proposed to explain or support such theories and oral lesions are indicators of disease progression and oral cavity can be a window to overall health and body systems. One of these is based around the potential for the inflammatory phenomenon of periodontitis to have effects by the systemic dissemination of locally produced mediators such as C-reactive protein (CRP), interleukins -1 beta (IL-1b) and -6 (IL-6) and tumor necrosis factor alpha (TNF-a). This concept has been supported by work suggesting that elevated levels of a number of inflammatory molecules (together with sialic acid (SA) may be accurate indicators of cardiovascular risk. Oral disease, periodontitis has, for many years, been considered a disease confined to the oral cavity. It is only in the past several years that substantial scientific data have emerged that indicate that the localized infections characteristic of periodontitis can have a significant effect on the systemic health of both humans and animals. There is strong relationship between the periodontal and cardiovascular diseases and two directions have been the focus of delineating the relationship: (I) bacteria from the oral cavity directly exacerbating the cardiovascular disease or altering systemic risk factors for cardiovascular disease; and, (II) the chronic periodontal inflammation at the focus of infection increasing circulating levels of host inflammatory macromolecules, and/or bacteria translocated to the circulation eliciting elevations in systemic host inflammatory macromolecules that exacerbate cardiovascular disease directly or alter other systemic risk factors for cardiovascular disease.] Saini R, Saini S, et al. *Annals of Cardiac Anaesthesia*, Vol. 13, Issue 2, pp 159-161, 2010. http://www.annals.in/article.asp?issn=0971-9784;year=2010;volume=13;issue=2;spage=159;epage=161;aulast=Saini

242. **Periodontal disease severity and urinary albumin excretion in middle-aged hypertensive patients**. [To address whether periodontal disease indexes are associated with urinary albumin-to-creatinine ratio (UACR) in conditions of high and low systemic inflammation as reflected by levels of high-sensitivity C-reactive protein (hs-CRP) in untreated hypertensive patients, we studied 242 hypertensive patients 51 ± 9 years old (24-hour systolic/diastolic blood pressure [BP] 132 ± 10/83 ± 8 mm Hg) with varying severity of periodontal disease evaluated by 3 periodontal disease indexes (PDIs) (i.e., mean clinical loss of attachment, maximum probe depth, and gingival bleeding index). Patients underwent BP measurements, echocardiography, and periodontal examination, and from fasting blood samples we assessed metabolic profile and hs-CRP. From 2 nonconsecutive overnight spot urine samples we evaluated UACR. With respect to median hs-CRP and UACR levels (1.67 mg/L and 10 mg/g, respectively), the total population was divided into patients with low-UACR/low-hs-CRP (n = 65), low-UACR/high-hs-CRP (n = 63), high-UACR/low-hs-CRP (n = 51), and high-UACR/high-hs-CRP (n = 63). PDIs differed among the 4 groups, and those with high UACR had significantly higher 24-hour systolic BP compared to those with low UACR. UACR was determined by all periodontal disease indexes, hs-CRP, and the interaction of each periodontal disease index with hs-CRP. In addition, mean clinical loss of attachment was the strongest determinant of the high-UACR/high-hs-CRP pattern among all studied periodontal disease indexes. In conclusion, in untreated middle-aged hypertensive patients, periodontal disease indexes and hs-CRP have a synergistic effect on UACR levels independently of the underlying hemodynamic load.] Tsioufis C, Thomopoulos C, et al. *Am J Cardiol.* 2011 Jan;107(1):52-8. **http://www.ncbi.nlm.nih.gov/pubmed/21146686**

243. **Periodontal infections and atherosclerosis: mere associations?** [The influence of periodontitis on lipoprotein metabolism has emerged as a new, important factor. Recent studies provide experimental proof that periodontitis may predispose to atherosclerosis.] Pussien PJ et al. *Current Opinion in Lipidology*. 15(5):583-588, Oct 2004. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=15361795&dopt=Abstract

244. **Periodontal infections and cardiovascular disease – the heart of the matter.** [Evidence continues to support an association among periodontal infections, atherosclerosis and vascular disease. Most studies reported positive associations between periodontal disease and cardiovascular disease after accounting for the effects of multiple risk factors such as age, sex, diabetes, cholesterol levels, blood pressure, obesity, smoking status, dietary patterns, race/ethnicity, education and socioeconomic status. Carotid atherosclerosis as measured by intima-media thickening increased with higher levels of the periodontal bacteria. The mounting evidence points to an association of periodontal disease at th eibological, clinical, radiographic and microbiological levels in relation to clinical and subclinical vascular disease. The emergence of periodontal infections as a potential risk factor for CVD is leading to a convergence in oral and medical care that can only benefit the patients and public health.] Demmer RT, Desvarlieux M., *JADA, Vol.137, Oct 2006 Supplement, pp.15s-20s. http://jada.ada.org/content/vol137/suppl_2/index.dtl*

245. **Periodontal Infections and Coronary Heart Disease.** [Chronic inflammation from any source is associated with increased cardiovascular risk. Periodontitis is a possible trigger of chronic inflammation. We investigated the possible association between periodontitis and coronary heart disease (CHD), focusing on microbiological aspects. Our findings suggest an association between periodontitis and presence of CHD. Periodontal pathogen burden, and particularly infection with A actinomycetemcomitans, may be of special importance.] Spahr A, Klein E, et. al., Arch Intern Med. 2006;166:554-559. http://archinte.ama-assn.org/cgi/content/short/166/5/554

246. **Periodontal microbiota in patients with coronary artery disease measured by real-time polymerase chain reaction: a case-control study**. [Recent data have shown that periodontal disease may increase the risk of occurrence of coronary heart disease in which inflammation initiated by bacteria and their compounds might be a common causal factor. This case-control study aimed at studying the relationship between periodontal disease and coronary artery disease (CAD) based on clinical and periodontal microbiologic parameters. METHODS: A total of 90 male subjects, 48 to 80 years of age, were included in this study. Forty-five men had CAD (CAD+), which was confirmed by coronary angiography. Forty-five age-matched controls showed no history or symptoms of CAD (CAD-). All subjects underwent a clinical periodontal examination including assessment of tooth loss, probing depth, clinical attachment level, and bleeding on probing. In the CAD+ group,

this examination took place 1 day before coronary angiography. Subgingival microbial samples were taken and evaluated by means of real-time polymerase chain reaction (RT-PCR) for the total amount of bacteria and the following periodontopathogens: Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Parvimonas micra (formerly Micromonas micros), Dialister pneumosintes, and Campylobacter rectus. RESULTS: Compared to control subjects, CAD+ subjects had significantly deeper pockets (2.28 mm versus 2.96 mm; P <0.001) and greater attachment loss (2.85 mm versus 3.65 mm; P <0.001), and this difference remained statistically significant after adjusting for smoking. No significant differences were observed between cases and controls with regard to the number of teeth present. P. intermedia was the only periodontal pathogen that showed significantly higher mean counts in CAD+ subjects compared to CAD- subjects. Higher counts of total bacteria, P. micra, D. pneumosintes, and C. rectus were found in the CAD- group. CONCLUSION: The results suggest that a relationship between periodontal disease and coronary heart disease exists, although P. intermedia was the only periodontopathogen related to CAD]. Nonnenmacher C, Stelzel M, et al. *J Periodontol*. 2007 Sep;78(9):1724-30. http://www.ncbi.nlm.nih.gov/pubmed/17760542

247. **Periodontitis: a risk factor for coronary heart disease?** [New findings are presented which indicate that the extent of the periodontal infection, a measure reflecting microbial burden, also is related to onset of new CHD events. Our previously published model describing the potential biological mechanisms underlying the associations found is reviewed. This model places the associations into a context of an intrinsic or acquired hyperinflammatory monocyte trait that results in a more intense inflammatory response to lipopolysaccharide (LPS) challenges, such as periodontal infections. This hyperinflammatory response may promote atheroma formation and thromboembolic events. finally, new findings from ongoing animal studies are presented, indicating that high fat diets in atherosclerotic-susceptible mice induce greater inflammatory responses to Porphyromonas gingivalis challenges. We conclude that the available evidence does allow an interpretation of periodontitis being a risk factor for atherosclerosis/CHD. Current findings regarding the associations between oral conditions and atherosclerosis/CHD imply that the criteria for causality may be met in the not-too-distant future.] Beck JD, Offenbacher S. *Ann Periodontol. 1998 Jul;3(1):127-41.* http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9722697&dopt=Citation

248. **Periodontitis and atherogenesis: causal association or simple coincidence?** [OBJECTIVES: The aim of this study was to assess the systemic effects of treating severe widespread periodontitis in a population of otherwise healthy individuals by examining treatment associated changes in markers of inflammation that are also implicated in cardiovascular atherosclerotic diseases. The potential impact of specific polymorphisms in cytokine genes known to influence both periodontitis and cardiovascular diseases was also examined. MATERIALS AND METHODS: A convenience sample of patients affected with severe generalised periodontitis was enrolled into a prospective single blind longitudinal intervention trial with a 6 months follow-up. Serum C-reactive protein (CRP) and interleukin-6 (IL-6) levels were assessed by high-sensitivity assays. Serological and clinical periodontal parameters were evaluated at baseline, 2 and 6 months after completion of non-surgical periodontal therapy. Results: In the 94 subjects that completed this pilot trial improvements in all clinical periodontal parameters were achieved. These were accompanied with significant reductions in serum IL-6 and CRP concentrations. In a multivariate model, serum CRP levels were significantly associated with the outcome of periodontal treatment after correcting for potential covariates (age, body mass index, gender, smoking) and polymorphisms in the IL-6 (-174 C/G) and IL-1A (-889) genes. A median decrease in serum CRP of 0.5 mg/l (95% CI 0.4-0.7 mg/l) was observed 6 months after completion of periodontal therapy in this population. Subjects with above average response to periodontal therapy (<30 residual pockets and <30% of sites bleeding on probing) accounted for the observed improvement in serum CRP. CONCLUSIONS: Control of periodontitis, achieved with non-surgical periodontal therapy, significantly decreased serum mediators and markers of acute phase response. The significance of the serum response was associated with the half of the population that responded better to non-surgical periodontal therapy. The results of this pilot study indicate that severe generalised periodontitis causes systemic inflammation. This is consistent with a causative role of periodontitis in atherogenesis.] D'Aiuto F, Parkar M, et al. *J Clin Periodontol.* 2004 May;31(5):402-11. http://www.ncbi.nlm.nih.gov/pubmed/15086624

249. **Periodontitis decreases the antiatherogenic potency of high density lipoprotein.** [Periodontitis, a consequence of persistent bacterial infection and chronic inflammation, has been suggested to predict coronary heart disease (CHD). The aim of this study was to investigate the impact of periodontitis on HDL structure and antiatherogenic function in cholesterol efflux in vitro. HDL was isolated from 30 patients (age 43.6 ± 6.1 years, mean ± SD) with periodontitis before and after (3.2 ± 1.4 months) periodontal treatment. The capacity of HDL for cholesterol efflux from macrophages (RAW 264.7), HDL composition, and key proteins of HDL metabolism were determined. After periodontal treatment, phospholipid transfer protein (PLTP) activity was 6.2% ($P < 0.05$) lower, and serum HDL cholesterol concentration, PLTP mass, and cholesteryl ester transfer protein activity were 10.7% ($P < 0.001$), 7.1% ($P = 0.078$), and 19.4% ($P < 0.001$) higher, respectively. The mean HDL_2/HDL_3 ratio increased from 2.16 ± 0.87 to 3.56 ± 0.48 ($P < 0.05$). HDL total phospholipid mass and sphingomyelin-phosphatidylcholine ratio were 7.4% ($P < 0.05$) and 36.8% ($P < 0.001$) higher, respectively. The HDL-mediated cholesterol efflux tended to be higher after periodontal treatment; interestingly, this increase was significant ($P < 0.05$) among patients whose C-reactive protein decreased (53.7% reduction, $P = 0.015$) and who were positive by PCR for *Actinobacillus actinomycetemcomitans*. These results suggest that periodontitis causes similar, but milder, changes in HDL metabolism than those that occur during the acute-phase response and that periodontitis may diminish the antiatherogenic potency of HDL, thus increasing the risk for CHD.] Pussinen PJ, Jauhiainen M, et al. *J of Lipid Research,* 45. 139-147. http://www.jlr.org/content/45/1/139.full

250. **Periodontitis is associated with altered plasma fatty acids and cardiovascular risk markers**. [BACKGROUND AND AIMS: In periodontitis it has been found that some perturbation exists in lipid biomarkers, such as increased serum total cholesterol and low-density lipoprotein cholesterol. Nevertheless, the relationship between fatty acids and periodontitis has been demonstrated only in a few studies and remains controversial. The aim of this investigation was to explore the effects of periodontitis on a cluster of traditional and novel cardiovascular risk factors such as plasma-lipids profile, types of plasma fatty acids, adhesion molecules and systemic inflammatory markers. METHODS AND RESULTS: At a university dental school, 56 patients all over 35 years old were enrolled and invited to participate in the study. Total plasma fatty acids, saturated, n-6 polyunsaturated and monounsaturated fatty acids, peroxidability index, soluble VCAM, TNF-alpha, cholesterol, triacylglycerols, and VLDL-c were significantly higher in the periodontitis group compared to the non-periodontitis group. CONCLUSIONS: This close association found between plasma triacylglycerols, LDL-c, saturated fatty acids, polyunsaturated fatty acids, total amount of fatty acids and coenzyme Q(10) with some periodontal data such as periodontal probing depth, recession of the gingival margin and clinical attachment level (Pearson correlation between 0.3 and 0.6), leads to the conclusion that there is an inter-relationship between periodontitis, plasma fatty acids profile and the increase in metabolic risk factors for cardiovascular **diseases**.] Ramirez-Tortosa MC, Quiles JL, et al. *Nutr Metab Cardiovasc Dis.* 2010 Feb;20(2):133-9 **http://www.ncbi.nlm.nih.gov/pubmed/19500957**

251. **Periodontitis in Patients With Coronary Artery Disease: An 8-year Follow-up**. [**Aim:** To study if preceding assessment of periodontal status in patients with established coronary artery disease (CAD) can predict future CAD endpoints (myocardial infarction, new revascularization procedure or CAD-related death) during 8-year follow-up, and if the changes in periodontal status over time differ in patients with CAD compared to healthy controls. **Methods:** In 2003, periodontal status was examined in 161 CAD patients who underwent percutaneous coronary intervention or coronary artery by-pass graft due to significant stenosis in the coronary arteries, and in 162 controls without CAD history. Eight years later, 126 CAD patients (mean age 68± 8.9, 102 men) and 121 controls (mean age 69± 9.0, 101 men) were periodontally re-examined. A standard classification of periodontal disease in three groups (mild, moderate and severe) was used. CAD endpoints during follow-up were obtained by review of medical records. Cause of death due to CAD was confirmed from the Swedish Cause of Death Register. **Results:** No significant differences were found among CAD patients with or without CAD related endpoints at 8 year follow-up and severity of periodontitis at baseline (P =0.7). CAD did not influence the incidence or severity of periodontitis over time. Significant differences were found at the final examination in periodontitis prevalence and severity (P =0.001), number of teeth (P =0.006), probing pocket depth 4-6 mm (P =0.016), bleeding on probing (P =0.001) and radiographic bone level (P =0.042) between CAD-patients and controls, all in favour of controls. **Conclusion:** The study results did not show a significant association between CAD endpoints during 8 years and periodontal status at baseline. The progression of periodontitis was low in booth groups although the higher proportion of individuals with severe periodontitis among CAD patients compared to controls remained unchanged over the 8 year follow up. Further long-term prospective studies are needed to show whether periodontitis can be considered a risk or prognostic factor for CAD, in terms of endpoints including myocardial infarction, new revascularization procedure or CAD-related death.] Johansson CS, Ravald N, et al. *Journal of Periodontology*, Posted online on May 31, 2013. (doi:10.1902/jop.2013.120730) http://www.joponline.org/doi/abs/10.1902/jop.2013.120730

252. **Porphyromonas gingivalis accelerates neointimal formation after arterial injury. [**Inflammation plays a key role in neointimal hyperplasia after an arterial injury. Chronic infectious disorders, such as periodontitis, are associated with an increased risk of cardiovascular diseases. However, the effects of a periodontal infection on vascular remodeling have not been examined. We assess the hypothesis that periodontal infection could promote neointimal formation after an arterial injury. METHODS: Mice were implanted with subcutaneous chambers (n = 41). Two weeks after implantation, the femoral arteries were injured, and Porphyromonas gingivalis (n = 21) or phosphate-buffered saline (n = 20) was injected into the chamber. The murine femoral arteries were obtained for the histopathological analysis. The expression level of mRNA in the femoral arteries was analyzed using quantitative reverse transcriptase polymerase chain reaction (n = 19-20). RESULTS: The intima/media thickness ratio in the P. gingivalis infected group was found to be significantly increased in comparison to the non-infected group. The expression of matrix metalloproteinase-2 mRNA was significantly increased in the P. gingivalis infected group compared to the non-infected group. CONCLUSION: These findings demonstrate that P. gingivalis injection can promote neointimal formation after an arterial injury. Periodontitis may be a critical factor in the development of restenosis after arterial intervention.**]** Kobayashi N, Suzuki J, et al. *J Vasc Res.* 2012;49(5):417-24. http://www.ncbi.nlm.nih.gov/pubmed/22739347

253. **Porphyromonas gingivalis-dendritic cell interactions: consequences for coronary artery disease.** [An estimated 80 million US adults have one or more types of cardiovascular diseases. Atherosclerosis is the single most important contributor to cardiovascular diseases; however, only 50% of atherosclerosis patients have currently identified risk factors. Chronic periodontitis, a common inflammatory disease, is linked to an increased cardiovascular risk. Dendritic cells (DCs) are potent antigen presenting cells that infiltrate arterial walls and may destabilize atherosclerotic plaques in cardiovascular disease. While the source of these DCs in atherosclerotic plaques is presently unclear, we propose that dermal DCs from peripheral inflamed sites such as CP tissues are a potential source. This review will examine the role of the opportunistic oral pathogen Porphyromonas gingivalis in invading DCs and stimulating their mobilization and misdirection through the bloodstream. Based on our published observations, combined with some new data, as well as a focused review of the literature we will propose a model for how P. gingivalis may exploit DCs to gain access to systemic circulation and contribute to coronary artery disease. Our published evidence supports a significant role for P. gingivalis in subverting normal DC function,

promoting a semimature, highly migratory, and immunosuppressive DC phenotype that contributes to the inflammatory development of atherosclerosis and, eventually, plaque rupture.] Zeituni AE, Carrion J, et al. *J Oral Microbiol.* 2010 Dec 21;2. doi: 10.3402/jom.v2i0.5782. http://www.ncbi.nlm.nih.gov/pubmed/21523219. http://www.journaloforalmicrobiology.net/index.php/jom/article/view/5782/6563

254. **Porphyromonas gingivalis induces murine macrophage foam cell formation**. [Atherosclerosis is a complex pathologic process initialed by the formation of cholesterol-rich plaque. Macrophages play a central role in the development of atherosclerosis, specifically in the initial accumulation of cholesterol in the arterial wall. It has been suggested that infection and chronic inflammatory conditions such as periodontitis may influence the atherosclerosis process. Porphyromonas gingivalis, one of the major pathogens involved in periodontitis, has been detected in human atheromas, suggesting that P. gingivalis infection may be associated with atherosclerosis. However, a causal relationship between this pathogen and the disease process has not yet been established. The purpose of the present investigation was to determine whether P. gingivalis could induce macrophages to form foam cells using the murine macrophage cell line (J774) as a model system. For inocula smaller than one bacterium per ten cells, P. gingivalis 381, as well as its lipopolysaccharide (LPS), induced foam cell formation of macrophages when cultured in the presence of human low-density lipoprotein (LDL). Infection of macrophages with increasing doses of P. gingivalis resulted in higher levels of foam cell formation. More than 70% of the cultured macrophages form cholesterol ester droplet-rich cells in the presence of 100 mug/ml of LDL when the inocula was more than 10 bacteria per cell. Low concentrations of P. gingivalis outer membrane vesicles also induced foam cell formation in the presence of LDL. In addition, it was demonstrated that P. gingivalis LPS alone was able to induce macrophage foam cell formation. P. gingivalis and its vesicles not only promoted LDL binding to macrophages but also induced macrophages to modify native LDL, which plays an important role in foam cell formation and the pathogenesis of atherosclerosis. Therefore, P. gingivalis cells or its vesicles released from periodontal lesions into the circulation may deliver virulence factor(s) such as LPS to the arterial wall to initiate or promote foam cell formation in macrophages and contribute to atheroma development.] QiM, Miyakawa H, et al. *Microb Pathog*. 2003 Dec;35(6):259-67. http://www.ncbi.nlm.nih.gov/pubmed/14580389

255. **Porphyromonas gingivalis induces myocarditis and/or myocardial infarction in mice and IL-17A is involved in pathogenesis of these diseases.** [OBJECTIVES: Although an association between periodontitis and cardiovascular diseases has been suggested, the role of Porphyromonas gingivalis in cardiovascular diseases is not clear. In this study, we examined whether experimental bacteremia of P. gingivalis causes cardiovascular diseases and investigated the mechanism of pathogenesis of cardiovascular diseases induced by P. gingivalis. DESIGN: C57BL/6 mice were intravenously inoculated with 2.0×10(8)CFU of P. gingivalis A7436 strain. Mice were sacrificed at specified days and their hearts were collected. The collected organs were divided into two halves and used for histological evaluation and cytokine analysis. IL-17A(-/-), IFN-γ(-/-) and TNF-α(-/-) mice were also intravenously inoculated and the histological changes of hearts in mice were examined. RESULTS: Myocarditis and/or myocardial infarction were observed in mice injected with P. gingivalis. The levels of IL1-β, IL-6, IL-17A, IL-18, TNF-α and IFN-γ mRNA increased significantly after P. gingivalis injection. In particular, high levels of IL-17A and IFN-γ mRNA expression were observed in hearts of mice after P. gingivalis injection in comparison with these levels before injection. Furthermore, the production of IL-17A was detected in hearts of wild-type mice after P. gingivalis injection. In wild-type, TNF-α(-/-) and IFN-γ(-/-) mice, moderate infiltration of neutrophils and monocytes was observed in hearts at 5 days after injection. In contrast, no inflammatory findings were observed in hearts of IL-17A(-/-) mice. CONCLUSION: We have demonstrated that an experimental bacteremia of P. gingivalis could induce myocarditis and/or myocardial infarction in mice, and IL-17A plays an important role in the pathogenesis of these diseases.] Akamatsu Y, Yamamoto T, et al.*Arch Oral Biol*, 2011 Jun 15. http://www.ncbi.nlm.nih.gov/pubmed/21683342

256. ***Porphyromonas gingivalis* lipopolysaccharide alters atherosclerotic-related gene expression in oxidized low-density-lipoprotein-induced macrophages and foam cells.** [Background and Objective: The molecular mechanism linking atherosclerosis formation and periodontal pathogens is not clear, although a positive correlation between periodontal infections and cardiovascular diseases has been reported. The aim of this study was to determine whether stimulation with *Porphyromonas gingivalis* lipopolysaccharide (LPS) affected the expression of atherosclerosis-related genes, during and after the formation of foam cells. Material and Methods: Macrophages from human THP-1 monocytes were treated with oxidized low-density lipoprotein (oxLDL) to induce the formation of foam cells. *P. gingivalis* LPS was added to cultures of either oxLDL-induced macrophages or foam cells. The expression of atherosclerosis-related genes was assayed by quantitative real-time PCR, and the production of granulocyte–macrophage colony-stimulating factor, monocyte chemotactic protein-1, interleukin (IL)-1β, IL-10 and IL-12 proteins was determined using ELISA. Nuclear translocation of nuclear factor-kappaB (NF-κB) P_{65} was detected by immunocytochemistry, and western blotting was used to evaluate inhibitory kappa B-α (IκB-α) degradation to confirm activation of the NF-κB pathway. Results: *P. gingivalis* LPS stimulated atherosclerosis-related gene expression in foam cells and increased the oxLDL-induced expression of chemokines, adhesion molecules, growth factors, apoptotic genes and nuclear receptors in macrophages. Transcription of the proinflammatory cytokines *IL1β* and *IL12* was elevated in response to LPS in both macrophages and foam cells, whereas transcription of the anti-inflammatory cytokine, *IL10*, was not affected. Increased activation of the NF-κB pathway was also observed in macrophages costimulated with LPS + oxLDL. Conclusion: *P. gingivalis* LPS appears to be an important factor in the development of atherosclerosis by stimulation of atherosclerosis-related gene expression in both macrophages and foam cells via activation of the NF-κB pathway.] Lei L, Li H, et al. *J Periodontal Research*, 21 March 2011 DOI: 10.1111/j.1600-0765.2011.01356.x. http://onlinelibrary.wiley.com/doi/10.1111/j.1600-0765.2011.01356.x/abstract

257. **Porphyromonas gingivalis mediated periodontal disease and atherosclerosis: disparate diseases with commonalities in pathogenesis through TLRs.** [Toll-like receptors (TLRs) are a group of pathogen-associated molecular pattern receptors, which play an important role in innate immune signaling in response to microbial infection. It has been demonstrated that TLRs are differentially up regulated in response to microbial infection and chronic inflammatory diseases such as atherosclerosis. Furthermore hyperlipidemic mice deficient in TLR2, TLR4, and MyD88 signaling exhibit diminished inflammatory responses and decreased atherosclerosis. Accumulating evidence has implicated specific infectious agents including the periodontal disease pathogen Porphyromonas gingivalis in the progression of atherosclerosis. Evidence in humans suggesting that periodontal infection predisposes to atherosclerosis is derived from studies demonstrating that the periodontal pathogen P. gingivalis resides in the wall of atherosclerotic vessels and seroepidemiological studies demonstrating an association between pathogen-specific IgG antibodies and atherosclerosis. We have established that the inflammatory signaling pathways that P. gingivalis utilizes is dependent on the cell type and this specificity clearly influences innate immune signaling in the context of local and distant chronic inflammation induced by this pathogen. We have demonstrated that P. gingivalis requires TLR2 to induce oral inflammatory bone lose in mice. Furthermore, we have demonstrated that P. gingivalis infection accelerates atherosclerosis in hyperlipidemic mice with an associated increase in expression of TLR2 and TLR4 in atherosclerotic lesions. Our recent work with P. gingivalis has demonstrated the effectiveness of specific intervention strategies (immunization) in the prevention of pathogen-accelerated atherosclerosis. Improved understanding of the mechanisms driving infection, and chronic inflammation during atherosclerosis may ultimately provide new targets for therapy.] Gibson FC, Genco CA. Curr Pharm Des. 2007;13(36):3665-75. http://www.ncbi.nlm.nih.gov/pubmed/18220804

258. **Porphyromonas gingivalis promotes neointimal formation after arterial injury through toll-like receptor 2 signaling.** [We previously demonstrated that Porphyromonas gingivalis infection induces neointimal hyperplasia with an increase in monocyte chemoattractant protein (MCP)-1 after arterial injury in wild-type mice. Toll-like receptor (TLR) 2 is a key receptor for the virulence factors of P. gingivalis. The aim of this study was to assess whether TLR2 plays a role in periodontopathic bacteria-induced neointimal formation after an arterial injury. Wild-type and TLR2-deficient mice were used in this study. The femoral arteries were injured, and P. gingivalis or vehicle was injected subcutaneously once per week. Fourteen days after arterial injury, the murine femoral arteries were obtained for histopathologic and immunohistochemical analyses. The immunoglobulin-G levels of the P. gingivalis-infected groups were significantly increased in comparison with the level in the corresponding noninfected groups in both wild-type and TLR2-deficient mice. TLR2 deficiency negated the P. gingivalis-induced neointimal formation in comparison with the wild-type mice, and reduced the number of positive monocyte chemoattractant protein-1 cells in the neointimal area. These findings demonstrate that P. gingivalis infection can promote neointimal formation after an arterial injury through TLR2 signaling.] Kobayashi N, Suzuki JI, et al. Heart Vessels. 2013 Sep 4 http://www.ncbi.nlm.nih.gov/pubmed/24002697

259. ***Porphyromonas gingivalis* Participates in Pathogenesis of Human Abdominal Aortic Aneurysm by Neutrophil Activation. Proof of Concept in Rats.** [BACKGROUND: Abdominal Aortic Aneurysms (AAAs) represent a particular form of atherothrombosis where neutrophil proteolytic activity plays a major role. We postulated that neutrophil recruitment and activation participating in AAA growth may originate in part from repeated episodes of periodontal bacteremia. METHODS AND FINDINGS: Our results show that neutrophil activation in human AAA was associated with Neutrophil Extracellular Trap (NET) formation in the IntraLuminal Thrombus, leading to the release of cell-free DNA. Human AAA samples were shown to contain bacterial DNA with high frequency (11/16), and in particular that of Porphyromonas gingivalis (Pg), the most prevalent pathogen involved in chronic periodontitis, a common form of periodontal disease. Both DNA reflecting the presence of NETs and antibodies to Pg were found to be increased in plasma of patients with AAA. Using a rat model of AAA, we demonstrated that repeated injection of Pg fostered aneurysm development, associated with pathological characteristics similar to those observed in humans, such as the persistence of a neutrophil-rich luminal thrombus, not observed in saline-injected rats in which a healing process was observed. CONCLUSIONS: Thus, the control of periodontal disease may represent a therapeutic target to limit human AAA progression.] Delbosc S, Alsac JM**, et al. *PLoS One*. 2011 Apr 13;6(4):e18679. http://www.ncbi.nlm.nih.gov/pubmed/21533243**

260. **Positron Emission Tomography Measurement of Periodontal ^{18}F-Fluorodeoxyglucose Uptake Is Associated With Histologically Determined Carotid Plaque Inflammation. [**Objectives: This study aimed to test the hypothesis that metabolic activity within periodontal tissue (a possible surrogate for periodontal inflammation) predicts inflammation in a remote atherosclerotic vessel, utilizing ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging. Background: Several lines of evidence establish periodontal disease as an important risk factor for atherosclerosis. FDG-PET imaging is an established method for measuring metabolic activity in human tissues and blood vessels. Methods: One hundred twelve patients underwent FDG-PET imaging 92 ± 5 min after FDG administration (13 to 25 mCi). Periodontal FDG uptake was measured by obtaining standardized uptake values from the periodontal tissue of each patient, and the ratio of periodontal to background (blood) activity was determined (TBR). Standardized uptake value measurements were obtained in the carotid and aorta as well as in a venous structure. Localization of periodontal, carotid, and aortic activity was facilitated by PET coregistration with computed tomography or magnetic resonance imaging. A subset of 16 patients underwent carotid endarterectomy within 1 month of PET imaging, during which atherosclerotic plaques were removed and subsequently stained with anti-CD68 antibodies to quantify macrophage infiltration. Periodontal FDG uptake was compared with carotid plaque macrophage infiltration. Results: Periodontal FDG uptake (TBR) is associated with carotid TBR ($R = 0.64$, $p < 0.0001$), as well as aortic TBR ($R = 0.38$; $p = 0.029$). Moreover, a strong relationship was observed between periodontal TBR

and histologically assessed inflammation within excised carotid artery plaques (R = 0.81, p < 0.001). Conclusions: FDG-PET measurements of metabolic activity within periodontal tissue correlate with macrophage infiltration within carotid plaques. These findings provide direct evidence for an association between periodontal disease and atherosclerotic inflammation.**]** Fifer KM, Qadir S, et al. *J Am Coll Cardiol*, 2011; 57:971-976, doi:10.1016/j.jacc.2010.09.056. http://content.onlinejacc.org/cgi/content/short/57/8/971

261. **Prevalence of Nonstenosing, Complicated Atherosclerotic Plaques in Cryptogenic Stroke. [**Background. In up to 40% of ischemic stroke patients, no definite cause can be established despite extensive workup (i.e., cryptogenic stroke). To test the hypothesis if nonstenosing complicated carotid plaques may be the underlying etiology in some of these patients, we used high-resolution black-blood carotid magnetic resonance imaging (MRI), which can quantitatively assess plaque composition and morphology with good correlation to histopathology. Specifically, we focused on AHA type VI plaques, which are characterized by hemorrhage, thrombus, or fibrous cap rupture. Methods. Thirty-two consecutive patients (22 male; mean age 71.7 ± 11.9 years) with cryptogenic stroke and nonstenosing (<50%) eccentric carotid plaques were recruited from a single stroke unit. All patients underwent extensive clinical workup (brain MRI, duplex sonography, electrocardiography and Holter monitoring, transthoracic and transesophageal echocardiography, and laboratory investigations) to exclude other causes of stroke. All patients received a black-blood carotid MRI at 3-T with fat-saturated pre- and post-contrast T-1–, proton density–, and T-2–weighted and time-of-flight images using surface coils and parallel imaging techniques. Prevalence of AHA type VI plaque was determined in both carotid arteries on the basis of previously published MRI criteria. Results. AHA type VI plaques were found in 12 of 32 arteries (37.5%) ipsilateral to the stroke, whereas there were no AHA type VI plaques contralateral to the stroke (p = 0.001). The most common diagnostic feature of AHA type VI plaques was intraplaque hemorrhage (75%), followed by fibrous plaque rupture (50%) and luminal thrombus (33%). Conclusions. This pilot study suggests that arterio-arterial embolism from complicated, nonstenosing carotid atherosclerotic plaques may play a role in a subgroup of patients previously diagnosed with cryptogenic stroke. To further evaluate the significance of AHA type VI plaques in cryptogenic stroke, future studies will have to analyze both clinical and imaging follow-up data, including event rates for secondary strokes.] Freilinger TM, Schindler A, et al. *JCC: Cardiovascular Imaging*, Vol 5 issue 4, April 2012, P 397-405. http://www.sciencedirect.com/science/article/pii/S1936878X12000939

262. **Presence of periodontopathic bacteria in coronary arteries from patients with chronic periodontitis. [**In this study the presence of periodontopathic pathogens in atheromatous plaques removed from coronary arteries of patients with chronic periodontitis and periodontally healthy subjects by PCR was detected. Our results indicate a significant association between the presence of Porphyromonas gingivalis and atheromas, and the periodontal bacteria in oral biofilm may find a way to reach arteries.] Marcelino SL, Gaetti-Jardim E Jr, et al. *Anaerobe*. 2010 Dec;16(6):629-32. http://www.ncbi.nlm.nih.gov/pubmed/20816998

263. **Prevalence of periodontal pathogens in coronary atherosclerotic plaque of patients undergoing coronary artery bypass graft surgery**. [Background Chronic bacterial infections have been associated with an increased risk for atherosclerosis and coronary artery disease. The ability of oral pathogens to colonize in coronary atheromatous plaque is well known. The aim of our study was to detect the presence of four common periodontal pathogens in coronary plaques. We detected the presence of 16S rRNA of *Treponema denticola, Eikenella Corrodens, Porphyromonas gingivalis* and *Campylobacter rectus* in subgingival and atherosclerotic plaques of CABG surgery by using Polymerase Chain Reaction. Methods 51 patients in the age group of 40 to 80 years with chronic periodontitis were recruited for the study. These patients were suffering from Coronary Artery Disease (CAD) and underwent Coronary Artery Bypass Grafting (CABG). DNA was extracted from the subgingival plaque and coronary atheromatous plaque samples. Universal Primer for the general detection of bacterial DNA and the primers for *T.denticola, E. Corrodens, C.rectus* and *P.gingivalis* were used to amplify part of 16SrRNA gene by Polymerase Chain Reaction. Results *T.denticola, E.corrodens, C.rectus* and *P.gingivalis* were detected in 49.01 %, 27.45 %, 21.51% and 45.10% of atherosclerotic plaque samples. In both subgingival and coronary plaque samples, *T. denticola* was detected in 39.21% of the cases, *E.corrodens* in 19.60%, *C.rectus* in 11.76% and *P.gingivalis* in 39.22% of the cases respectively. Conclusion Our study revealed the presence of significant bacterial DNA of oral pathogens in coronary plaques. This suggests possible relationship between periodontal infection and atherosclerosis and can help devise preventive treatment strategies.] Mahendra J, Mahendra L, et al. *Journal of Maxillofacial and Oral Surgery* , Volume 8, Number 2, 108-113, DOI: 10.1007/s12663-009-0028-5. http://www.springerlink.com/content/d77x1w5470144441/

264. **Professional dental cleanings may reduce risk of heart attack, stroke.** [] American heart Association, Nov 13, 2011. http://newsroom.heart.org/pr/aha/_prv-professional-dental-cleanings-217760.aspx

265. **Quantitative detection of periodontopathic bacteria in atherosclerotic plaques from coronary arteries.** [Oral pathogens, including periodontopathic bacteria, are thought to be aetiological factors in the development of cardiovascular disease. In this study, the presence of *Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum–periodonticum–simiae* group, *Porphyromonas gingivalis, Prevotella intermedia, Prevotella nigrescens* and *Tannerella forsythia* in atheromatous plaques from coronary arteries was determined by real-time PCR. Forty-four patients displaying cardiovascular disease were submitted to periodontal examination and endarterectomy of coronary arteries. Approximately 60–100 mg atherosclerotic tissue was removed surgically and DNA was obtained. Quantitative detection of periodontopathic bacteria was performed using universal and species-specific TaqMan probe/primer sets. Total bacterial and periodontopathic bacterial DNA were found in 94.9 and 92.3%, respectively, of the atheromatous plaques from periodontitis patients, and in 80.0 and 20.0%, respectively, of atherosclerotic tissues from periodontally healthy subjects. All periodontal bacteria except for the *F. nucleatum–periodonticum–simiae* group were detected, and their DNA represented 47.3% of the total bacterial DNA

obtained from periodontitis patients. *Porphyromonas gingivalis*, *A. actinomycetemcomitans* and *Prevotella intermedia* were detected most often. The presence of two or more periodontal species could be observed in 64.1% of the samples. In addition, even in samples in which a single periodontal species was detected, additional unidentified microbial DNA could be observed. The significant number of periodontopathic bacterial DNA species in atherosclerotic tissue samples from patients with periodontitis suggests that the presence of these micro-organisms in coronary lesions is not coincidental and that they may in fact contribute to the development of vascular diseases.] Gaetti-Jardim Jr E, Marcelino SL, et al. *Journal of Medical Microbiology*, Dec 2009, Vol. 58, No. 12 p 1568-1575. http://jmm.sgmjournals.org/content/58/12/1568.abstract

266. **Receptor for advanced glycation endproducts mediates pro-atherogenic responses to periodontal infection in vascular endothelial cells.** [OBJECTIVE: A link between periodontal infections and an increased risk for vascular disease has been demonstrated. Porphyromonas gingivalis, a major periodontal pathogen, localizes in human atherosclerotic plaques, accelerates atherosclerosis in animal models and modulates vascular cell function. The receptor for advanced glycation endproducts (RAGE) regulates vascular inflammation and atherogenesis. We hypothesized that RAGE is involved in P. gingivalis's contribution to pro-atherogenic responses in vascular endothelial cells. METHODS AND RESULTS: Murine aortic endothelial cells (MAEC) were isolated from wild-type C57BL/6 or RAGE-/- mice and were infected with P. gingivalis strain 381. P. gingivalis 381 infection significantly enhanced expression of RAGE in wild-type MAEC. Levels of pro-atherogenic advanced glycation endproducts (AGEs) and monocyte chemoattractant protein 1 (MCP-1) were significantly increased in wild-type MAEC following P. gingivalis 381 infection, but were unaffected in MAEC from RAGE-/- mice or in MAEC infected with DPG3, a fimbriae-deficient mutant of P. gingivalis 381. Consistent with a role for oxidative stress and an AGE-dependent activation of RAGE in this setting, both antioxidant treatment and AGE blockade significantly suppressed RAGE gene expression and RAGE and MCP-1 protein levels in P. gingivalis 381-infected human aortic endothelial cells (HAEC). CONCLUSION: The present findings implicate for the first time the AGE-RAGE axis in the amplification of pro-atherogenic responses triggered by P. gingivalis in vascular endothelial cells.] Pollreisz A, Hudson BI, et al. *Atherosclerosis*. 2010 Jul 21 http://www.ncbi.nlm.nih.gov/pubmed/20701913

267. **Relation of circulating C-reactive protein to progression of aortic valve stenosis.** [C-reactive protein (CRP) is a marker of inflammation and predicts outcome in apparently healthy subjects and patients with coronary artery disease. Systemic inflammation is present in patients with aortic valve stenosis (AS). The aim of this prospective study was to assess whether CRP levels predict the progression of AS severity. Blood samples for high-sensitivity CRP measurements and echocardiographic data were obtained in 43 patients (70% men; mean age 73 +/- 8 years) with asymptomatic degenerative AS at study entry. On the basis of repeat echocardiographic assessment at 6 months, patients were grouped as (1) slow progressors (a decrease in aortic valve area [AVA] <0.05 cm2 and/or an increase in aortic peak velocity <0.15 m/s) and (2) rapid progressors (a decrease in AVA > or =0.05 cm2 and/or an increase in aortic peak velocity > or =0.15 m/s). Plasma CRP levels were significantly higher in rapid progressors than slow progressors (median 5.1 [range 2.3 to 11.3] vs 2.1 [range 1.0 to 3.1] mg/L, p = 0.007). In multivariate analysis, CRP levels >3 mg/L were independently associated with rapid AS progression (odds ratio 9.1, 95% confidence interval 2.2 to 37.3). In conclusion, CRP levels are higher in patients with degenerative AS who show rapid valve disease progression. These findings suggest that inflammation may have a pathogenic role in degenerative AS.] Sanchez Pl, Santos JL, et.al. *Am J Cardiol. 2006 Jan 1;97(1):90-3. Epub 2005 Nov 10.* http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=16377290&dopt=Abstract

268. **Relationship of Periodontal Disease to Carotid Artery Intima-Media Wall Thickness.** [Periodontitis has been linked to clinical cardiovascular disease but not to subclinical atherosclerosis. The purpose of this study was to determine whether periodontitis is associated with carotid artery intima-media wall thickness. These results provide the first indication that periodontitis may play a role in the pathogenesis of atheroma formation, as well as in cardiovascular events.] http://atvb.ahajournals.org/cgi/content/abstract/atvbaha;21/11/1816

269. **Researchers link periodontal bacteria to atherosclerosis.** [Patients with periodontal disease are more likely to suffer from atherosclerosis than their counterparts with healthy gums, researchers from Columbia University Medical Center report. Bacteria that cause periodontal disease can migrate throughout the body via the bloodstream and stimulate the immune system, causing inflammation that results in the build up of deposits in the arteries.] ADA News Release. http://www.ada.org/prof/resources/pubs/adanews/adanewsarticle.asp?articleid=1267

270. **Role for Periodontal Bacteria in Cardiovascular Diseases.** [*P. gingivalis* exhibits several properties which could play a role in CVD as mediators of LDL oxidation, foam cell formation, and rupture of atherosclerotic plaque.] Kuramitsu HK, Annals of Periodontology, 2001, Vol. 6, No. 1, Pages 41-47. http://www.joponline.org/doi/abs/10.1902/annals.2001.6.1.41

271. **Roles of oral bacteria in cardiovascular diseases--from molecular mechanisms to clinical cases: Implication of periodontal diseases in development of systemic diseases. [**Periodontal diseases, some of the most common infectious diseases seen in humans, are characterized by gingival inflammation, as well as loss of connective tissue and bone from around the roots of the teeth, which leads to eventual tooth exfoliation. In the past decade, the association of periodontal diseases with the development of systemic diseases has received increasing attention. Although a number of studies have presented evidence of close relationships between periodontal and systemic diseases, the majority of findings are limited to epidemiological studies, while the etiological details remain unclear. Nevertheless, a variety of recent hypothesis driven investigations have compiled various results showing that periodontal infection and subsequent direct oral-hematogenous spread of bacteria are implicated in the development of various systemic diseases. Herein, we present current understanding in regard to the relationship between periodontal and systemic diseases, including cardiovascular diseases, preterm delivery

of low birth weight, diabetes mellitus, respiratory diseases, and osteoporosis.] Inaba H, Amano A. *J Pharmacol Sci*. 2010 Jun;113(2):103-9. http://www.ncbi.nlm.nih.gov/pubmed/20501966

272. **Roles of oral bacteria in cardiovascular diseases--from molecular mechanisms to clinical cases: Porphyromonas gingivalis is the important role of intimal hyperplasia in the aorta.** [It has been reported that DNA of oral bacterial species, such as Porphyromonas gingivalis and Streptococcus mutans, was detected frequently in specimens of arteriosclerotic vessels. However, the source of DNA, whether from live intact bacteria or a part of the bacteria, has not been identified yet. Moreover, there was no precise evidence concerning involvement of oral bacteria in the progression of arteriosclerosis. We tried to clarify the involvement of P. gingivalis on the mechanisms of development of aortic intimal hyperplasia. Intravenous administration of P. gingivalis dramatically induced intimal hyperplasia in the mouse model with photochemical impairment of the femoral artery. However there were no changes identified in the mice without aortic impairment, even with the P. gingivalis infection. Concomitantly, S100 calcium-binding protein A9 (S100A9) and the embryonic isoform of myosin heavy chain (SMemb), a proliferative phenotypic marker of smooth muscle cells, were significantly overexpressed on the surfaces of smooth muscle cells present in the injured blood vessels. Similarly, increased expressions of S100A9 and SMemb proteins were observed in aneurismal specimens obtained from P. gingivalis-infected patients. We found that bacteremia induced by P. gingivalis leads to intimal hyperplasia associated with overexpressions of S100A9 and SMemb. Our results strongly suggest that oral-hematogenous spreading of P. gingivalis is a causative event in the development of aortic hyperplasia in periodontitis patients.] Hokamura K, Umemura K. *J Pharmacol Sci.* 2010;113(2):110-4**. http://www.ncbi.nlm.nih.gov/pubmed/20501963**

273. **Specific protein may increase risk of blood-vessel constriction linked to gum disease**. [A protein involved in cellular inflammation may increase the risk of plaque containing blood vessels associated with inflammatory gum disease, according to research presented at the American Heart Association's Arteriosclerosis, Thrombosis and Vascular Biology 2012 Scientific Sessions in Chicago. The protein, CD36, is found in blood cells, as well as many other cell types. Research has shown that CD36 may increase the harmful effects of "bad cholesterol," or low-density lipoprotein (LDL). Investigators "knocked out," or deleted, the gene responsible for CD36 production, then induced plaque in blood vessels by feeding mice a high fat diet. Some animals were also infected with the bacteria associated with gum disease. More fatty plaque accumulation occurred in the blood vessels of the animals that were infected with gum disease. In the animals with the deleted CD36 gene, however, vessels remained free of new plaque even when oral inflammation occurred.] Febbraio M. http://newsroom.heart.org/pr/aha/specific-protein-may-increase-231926.aspx http://www.medscape.com/viewarticle/762746?src=emailthis

274. **Study links gum disease, heart attack risk independent of smoking.** [Subjects under 55 with markers for periodontal disease showed a two- to four-times greater risk of having a heart attack, regardless of tobacco use.] ADA News Release. http://www.ada.org/prof/resources/pubs/adanews/adanewsarticle.asp?articleid=939

275. **The Association Between Cumulative Periodontal Disease and Stroke History in Older Adults.** [Based on the results of this study, there is evidence of an association between cumulative periodontal disease, based on PHS, and a history of stroke. However, it is unclear whether cumulative periodontal disease is an independent risk factor for stroke or a risk marker for the disease.] Lee HJ, Garcia RI, Journal of Periodontology, 2006, Vol. 77, No. 10, Pages 1744-1754. http://www.joponline.org/doi/abs/10.1902/jop.2006.050339?journalCode=jop

276. **The association of gingivitis and periodontitis with ischemic stroke**. [OBJECTIVES: The aim of this study was to assess the associations of different periodontal parameters with cerebral ischemia. METHODS: In a case-control study, 303 consecutive patients with ischemic stroke or transient ischemic attack, and 300 representative population controls received a complete clinical and radiographic dental examination. Patients were examined on average 3 days after ischemia. The individual mean clinical attachment loss measured at four sites per tooth was used as indicator variable for periodontitis. RESULTS: Patients had higher clinical attachment loss than population ($p<0.001$). After adjustment for age, gender, number of teeth, vascular risk factors and diseases, childhood and adult socioeconomic conditions and lifestyle factors, a mean clinical attachment loss >6 mm had a 7.4 times (95% confidence interval 1.55-15.3) a gingival index >1.2 a 18.3 times (5.84-57.26) and a radiographic bone loss a 3.6 times (1.58-8.28) higher risk of cerebral ischemia than subjects without periodontitis or gingivitis, respectively. CONCLUSION: Periodontitis is an independent risk factor for cerebral ischemia and acute exacerbation of inflammatory processes in the periodontium might be a trigger for the event of cerebral ischemia.] Dorger CE, Becher H, et al. *J Clin Periodontol*. 2004 May;31(5):396-401. **http://www.ncbi.nlm.nih.gov/pubmed/15086623**

277. **The Association of Tooth Scaling and Decreased Cardiovascular Disease -A Nationwide Population-Based Study.** [Background: Poor oral hygiene has been associated with increased risk for cardiovascular disease frequent tooth brushing has been reported to decrease the risk for CVD recently. However, the association between preventive dentistry and cardiovascular risk reduction remained undetermined. The aim of this study is investigate the effect of mouth scaling on cardiovascular disease and stroke risk, using a nationwide, population-based study and a retrospective cohort design. Methods: 51108 adult subjects without previous history of stroke or myocardial infarction (MI) who had received full or partial mouth scaling at least once were rerolled from the Taiwan National Health insurance. Another 51512 age-, gender-, and cormobidities-matched subjects without history of stroke or MI and did not receive mouth scaling comprised the comparison control. Cox proportional hazard regressions were performed as a means of comparing the cardiovascular events rate between these two cohorts. Results: During an average follow-up period of 7 years, a total of 102,620 patients were enrolled, of which 51,108 patients who had ever received tooth mouth scaling had lower incidence of acute MI and stroke

when compared to the control group (0.55% vs. 0.44%, p=0,013 and 2.57% vs. 2.27%, p=0.002, respectively). The log-rank test and Kaplan-Meier survival analysis showed that patients with tooth scaling have significantly higher AMI- free and higher stroke-free survival rates (*p*=0.027 and p= 0.04 respectively). Cox proportional hazard regression model analysis showed that tooth scaling was the independent factor associated with less risk of developing future MI (Hazard Ratio, HR, 0.76, 95% CI, 0.60-0.96; *p*=0.021) and stroke (HR 0.87, 95% CI, 0.78-0.96; *p*=0.007). Furthermore, the frequency of tooth scaling correlated with the risk reduction of MI with HR of 0.76 (95% CI, 0.60-0.96; *p*=0.021) and HR of 0.87 (95% CI, 0.71-1.07; *p*=0.188), comparing often and occasional with never tooth scaling, respectively; stroke with HR 0.87, (95% CI, 0.78-0.96; *p*=0.007) and HR of 0.91 (95% CI, 0.83-1.00; *p*=0.045), comparing often and occasional with never tooth scaling, respectively. Conclusions: Tooth scaling was associated with decreased risk for cardiovascular risk and stroke. *] Chen Z, Leu H. Circulation*. 2011; 124:A17704http://circ.ahajournals.org/cgi/content/meeting_abstract/124/21_MeetingAbstracts/A17704

278. **The autoimmune concept of atherosclerosis**. [This review summarizes the recent data on the 'Autoimmune Concept of Atherosclerosis', according to which the first stage of this disease is due to an autoimmune reaction against arterial endothelial cells expressing heat shock protein 60 (HSP60) and adhesion molecules when stressed by classical atherosclerosis risk factors. Special emphasis is put on oxidized low-density lipoproteins as early endothelial stressors. Recent findings: Plasma cholesterol and LDL levels considered 'normal' by the medical community are possibly too high from an evolutionary viewpoint. The proinflammatory milieu at sites of early atherosclerotic lesions could be conducive to oxidation of LDL *in situ*. LDL oxidation can also take place at nonvascular sites or in the circulation under general proinflammatory conditions explaining its proatherosclerotic role in 'normocholesterolemic' individuals. Summary: We hypothesize that the plasma cholesterol and LDL levels currently considered normal are evolutionarily too high. Cholesterol and/or oxidized low-density lipoprotein, even as a mild HSP60-inducing endothelial stressor, function as a ubiquitous risk factor. If this hypothesis is true, most members of developed societies might be at risk to develop atherosclerotic plaques at anti-HSP60-immunity-triggered intimal inflammatory foci, irrespective of the primary risk-factor(s).] Grundtman C, Wick G. *Curr Opin Lipidol.* 2011 October; 22(5): 327–334. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3216126/

279. **The collagen-binding protein Cnm is required for Streptococcus mutans adherence to and intracellular invasion of Human Coronary Artery Endothelial Cells.** [Treptococcus mutans is considered the primary etiologic agent of dental caries, a global health problem that affects 60 - 90% of the population, and a leading causative agent of infective endocarditis. It can be divided into four different serotypes (c, e, f, and k), with serotype c strains being the most common in the oral cavity. Here, we demonstrate that in addition to OMZ175 and B14, three other strains (NCTC11060, LM7 and OM50E) of the less prevalent serotypes e and f could invade primary human coronary artery endothelial cells (HCAEC). Invasive strains were also significantly more virulent than non-invasive strains in the Galleria mellonella (greater wax worm) model for systemic disease. Interestingly, the invasive strains carry an additional gene, cnm, previously shown to bind to collagen and laminin in vitro. Inactivation of cnm rendered the organisms unable to invade HCAEC and attenuated their virulence in G. mellonella. Notably, the cnm-knockout strains did not adhere to HCAEC cells as efficiently as the parental strains, indicating that loss of the invasion phenotype observed for the mutants is linked to an adhesion defect. Comparisons of the invasive strains and their respective cnm mutants did not support a correlation between biofilm formation and invasion. Thus, Cnm is required for S. mutans invasion of endothelial cells and possibly represents an important virulence factor of S. mutans that could contribute to cardiovascular infections and pathologies.] Abranches J, Miller JH, et al. *Infect Immun*. 2011 Mar 21. http://www.ncbi.nlm.nih.gov/pubmed/21422186

280. **The connection between ruptured cerebral aneurysms and odontogenic bacteria**. [BACKGROUND: Patients with ruptured saccular intracranial aneurysms have excess long-term mortality due to cerebrovascular and cardiovascular diseases compared with general population. Chronic inflammation is detected in ruptured intracranial aneurysms, abdominal aortic aneurysms and coronary artery plaques. Bacterial infections have been suggested to have a role in the aetiology of atherosclerosis. Bacteria have been detected both in abdominal and coronary arteries but their presence in intracranial aneurysms has not yet been properly studied.OBJECTIVE: The aim of this preliminary study was to assess the presence of oral and pharyngeal bacterial genome in ruptured intracranial aneurysms and to ascertain if dental infection is a previously unknown risk factor for subarachnoid haemorrhage. METHODS: A total of 36 ruptured aneurysm specimens were obtained perioperatively in aneurysm clipping operations (n=29) and by autopsy (n=7). Aneurysmal sac tissue was analysed by real time quantitative PCR with specific primers and probes to detect bacterial DNA from several oral species. Immunohistochemical staining for bacterial receptors (CD14 and toll-like receptor-2 (TLR-2)) was performed from four autopsy cases. RESULTS: Bacterial DNA was detected in 21/36 (58%) of specimens. A third of the positive samples contained DNA from both endodontic and periodontal bacteria. DNA from endodontic bacteria were detected in 20/36 (56%) and from periodontal bacteria in 17/36 (47%) of samples. Bacterial DNA of the Streptococcus mitis group was found to be most common. Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum and Treponema denticola were the three most common periodontal pathogens. The highly intensive staining of CD14 and TLR-2 in ruptured aneurysms was observed. CONCLUSIONS: This is the first report showing evidence that dental infection could be a part of pathophysiology in intracranial aneurysm disease.] Pyysalo MJ, Pyysalo LM, et al. *J Neurol Neurosurg Psychiatry*, 2013 Nov;84(11):1214-1218. doi: 10.1136/jnnp-2012-304635. Epub 2013 Jun 12. http://www.ncbi.nlm.nih.gov/pubmed/23761916

281. **The metabolic syndrome and inflammation: association or causation?** [The aim of this editorial was to discuss evidence indicating a role for low-grade inflammation as a pathogenetic event of the metabolic syndrome. The metabolic syndrome has emerged as an important cluster of risk factors for atherosclerotic disease. Common features are central (abdominal) obesity, insulin resistance, hypertension, and dyslipidemia, namely high triglycerides and low high-density lipoprotein cholesterol.

According to the clinical criteria developed by ATP III, it has been estimated that 1 out of 4 adults living in the United States merits the diagnosis. The presence of the metabolic syndrome is highly prognostic of future cardiovascular events. Chronic inflammation may represent a triggering factor in the origin of the metabolic syndrome: stimuli such as overnutrition, physical inactivity, and ageing would result in cytokine hypersecretion and eventually lead to insulin resistance and diabetes in genetically or metabolically predisposed individuals. Alternatively, resistance to the anti-inflammatory actions of insulin would result in enhanced circulating levels of proinflammatory cytokines resulting in persistent low-grade inflammation. A generally enhanced adipose tissue derived cytokine expression may be another plausible mechanism for the inflammation/metabolic syndrome relationship. The role of adipose tissue as an endocrine organ capable of secreting a number of adipose tissue-specific or enriched hormones, known as adipokines, is gaining appreciation. Although the precise role of adipokines in the metabolic syndrome is still debated, an imbalance between increased inflammatory stimuli and decreased anti-inflammatory mechanisms may be an intriguing working hypothesis. The proinflammatory state that accompanies the metabolic syndrome associates with both insulin resistance and endothelial dysfunction, providing a connection between inflammation and metabolic processes which is highly deleterious for vascular functions.] Esposito K, Giugliano D. *Nutr Metab Cardiovasc Dis*. 2004 Oct;14(5):228-32. http://www.ncbi.nlm.nih.gov/pubmed/15673055

282. **The relationship between oral conditions and ischemic stroke and peripheral vascular disease.** [Studies to date suggest that oral conditions may be associated with increased risk of ischemic stroke and peripheral vascular disease.] Joshipura K. J Am Dent Assoc, Vol 133, No suppl_1, 23S-30S. *http://jada.ada.org/cgi/content/full/133/suppl_1/23S*
283. **The Role of Inflammatory and Immunological Mediators in Periodontitis and Cardiovascular Disease.** [Oral pathogens and inflammatory mediators (such as interleukin [IL]-1 and tumor necrosis factor [TNF]-α) from periodontal lesions intermittently reach the bloodstream inducing systemic inflammatory reactants such as acute-phase proteins, and immune effectors including systemic antibodies to periodontal bacteria.] DeNardin E, Annals of Periodontology, 2001, Vol. 6, No. 1, Pages 30-40. http://www.joponline.org/doi/abs/10.1902/annals.2001.6.1.30
284. **The Role of Periodontal Disease and other Infections in the Pathogenesis of Atherosclerosis and Systemic Diseases.** [Introduction: Cardiovascular disease is predicted to be the most common cause of death worldwide by the year 2020. Half of heart disease patients lack established risk factors such as elevated lipids, hypertension, tobacco abuse, and positive family history. Additionally, these risk factors are generally associated with the disease, and the exact mechanism by which they may contribute to the development of atherosclerosis is not clear. However, previous and recent studies point to a linkage between infection with different bacteria and heart disease in the other 50% of observed incidences. Moreover, pathogenesis of the disease induced by infectious agents is described by three different mechanisms of action: induction of inflammation, release of toxins or superantigens, and molecular mimicry or cross-reactivity. This may result in plaque formation or antimyosin cellular and humoral immunity and subsequently, to myocarditis or other autoimmune diseases. Infectious Agents: Through the years many reports have incriminated various infectious agents in the pathogenesis of autoimmune disease. Beta-hemolytic streptococcus has been implicated in rheumatic fever, Epstein-Barr virus in rheumatoid arthritis, Coxsackie virus B_4 in diabetes, Herpes type-6 and measles virus in multiple sclerosis, cytomegalovirus, chlamydia pneumoniae and many other infectious agents in coronary artery disease. In addition, evidence has accumulated to suggest that chronic dental infection may be another factor for the development of atherosclerotic heart disease. Patients with poor dentition, especially those with periodontal disease are noted to have frequent recurrent episodes of bacteremia. The infectious agents involved are usually anaerobic proteolytic bacteria. These studies indicate that the most common strain of bacteria in dental plaque may cause blood clots. When blood clots escape into the bloodstream, they may increase the risk of heart attack and other heart illnesses. The plausible cause was further strengthened by the study of Dr. Beck and his associates published in The Journal of Periodontology, October 1996. In this study, the severity of periodontal disease during a three-year period in the 1970's was determined in 1147 men who were followed for 20 years. For those men with significant periodontal disease, the odds ratios for fatal coronary disease or stroke were 1.9 and 2.8, respectively. An association between periodontal disease and atherosclerotic or thrombotic events could arise from underlying inflammatory response or prothrombotic traits that place some people at high risk for both periodontal disease and atherosclerosis or thrombosis. It may also be that the chronic inflammation induced by the periodontal disease contributes to the pathogenesis of atherosclerosis.] Vojdani A. *Immunosciences Lab, Inc.* http://www.immuno-sci-lab.com/theroleofperiodontal.html
285. **Toothbrushing, inflammation, and risk of cardiovascular disease: results from Scottish Health Survey.** [Main outcome measures: Oral hygiene assessed from self reported frequency of toothbrushing. Surveys were linked prospectively to clinical hospital records, and Cox proportional hazards models were used to estimate the risk of cardiovascular disease events or death according to oral hygiene. The association between oral hygiene and inflammatory markers and coagulation was examined in a subsample of participants (n=4830) by using general linear models with adjustments. Results: There were a total of 555 cardiovascular disease events over an average of 8.1 (SD 3.4) years of follow-up, of which 170 were fatal. In about 74% (411) of cardiovascular disease events the principal diagnosis was coronary heart disease. Participants who reported poor oral hygiene (never/rarely brushed their teeth) had an increased risk of a cardiovascular disease event (hazard ratio 1.7, 95% confidence interval 1.3 to 2.3; P<0.001) in a fully adjusted model. They also had increased concentrations of both C reactive protein (β 0.04, 0.01 to 0.08) and fibrinogen (0.08, −0.01 to 0.18). Conclusions: Poor oral hygiene is associated with higher levels of risk of cardiovascular disease and low grade inflammation, though the causal nature of the association is yet to be determined.] de Oliveira C. *BMJ* 2010; 340:c2451 doi: 10.1136/bmj.c2451 (Published 27 May 2010). http://www.bmj.com/content/340/bmj.c2451.full . http://www.ncbi.nlm.nih.gov/pubmed/20508025

286. **Treatment of Periodontitis and Endothelial Function. [***Background* Systemic inflammation may impair vascular function, and epidemiologic data suggest a possible link between periodontitis and cardiovascular disease. *Methods* We randomly assigned 120 patients with severe periodontitis to community-based periodontal care (59 patients) or intensive periodontal treatment (61). Endothelial function, as assessed by measurement of the diameter of the brachial artery during flow (flow-mediated dilatation), and inflammatory biomarkers and markers of coagulation and endothelial activation were evaluated before treatment and 1, 7, 30, 60, and 180 days after treatment. *Conclusions* Intensive periodontal treatment resulted in acute, short-term systemic inflammation and endothelial dysfunction. However, 6 months after therapy, the benefits in oral health were associated with improvement in endothelial function.] Tonetti MS, D'Aiuto F, et.al. *New England Journal of Medicine Vol 356:911-920, March 1, 2007, No.9. http://content.nejm.org/cgi/content/abstract/356/9/911*
287. **Treatment of periodontal disease results in improvements in endothelial dysfunction and reduction of the carotid intima-media thickness.** [Several cohort studies reported a relation of cardiovascular events and periodontal disease. In particular, Porphyromonas gingivalis is associated with the development of atherosclerotic plaques. We verified in a longitudinal study whether inflammation biomarkers, endothelial adhesion molecules, leukocyte activation markers, and intima-media thickness could be beneficially modified by periodontal treatment alone. Thirty-five otherwise healthy individuals affected by mild to moderate parodontopathy were enrolled in the study. Echo-Doppler cardiography of the carotid artery, fluorescence-activated cell sorting analyses on lymphocytes and monocytes, and plasma inflammatory indices were evaluated at baseline and at multiple time points after the periodontal treatment. Results showed that inflammation biomarkers were abnormally increased at baseline. Periodontal treatment resulted in a significant reduction of the total oral bacterial load that was associated with a significant amelioration of inflammation biomarkers and of adhesion and activation proteins. Notably, intima-media thickness was significantly diminished after treatment. Inflammatory alterations associated with the genesis of atherosclerotic plaques are detected in otherwise healthy individuals affected by parodontopathy and are positively influenced by periodontal treatment. Reduction of oral bacterial load results in a modification of an anatomical parameter directly responsible for atherosclerosis. These results shed light on the pathogenesis of atherosclerosis and could have practical implications for public health.] Piconi S, Trabattoni D, et al. FASEB J. 2009 Apr;23(4):1196-204. http://www.ncbi.nlm.nih.gov/pubmed/19074511
288. U**sefulness of self-reported periodontal disease to identify individuals with elevated inflammatory markers at risk of cardiovascular disease.** [Periodontal disease has been associated with cardiovascular disease (CVD), and inflammation may represent a common pathophysiology. Oral health screening in the context of CVD risk assessment represents a potential opportunity to identify individuals at risk for CVD. The purposes of this study were to determine if self-reported oral health status is independently associated with inflammatory markers and if oral health assessment as part of CVD risk screening can identify at-risk individuals without traditional CVD risk factors. A baseline analysis was conducted among participants in the National Heart, Lung, and Blood Institute's Family Intervention Trial for Heart Health (FIT Heart; n = 421, mean age 48 +/- 13.5 years, 36% nonwhite) without CVD or diabetes who underwent standardized assessment of oral health, lifestyle, CVD risk factors, and the inflammatory markers high-sensitivity C-reactive protein and lipoprotein-associated phospholipase A(2). Statistical associations between oral health, risk factors, and inflammatory markers were assessed, and logistic regression was used to adjust for effects of lifestyle and potential confounders. Periodontal disease was independently associated with being in the top quartile of lipoprotein-associated phospholipase A(2) Lp-PLA2 compared with the lower 3 quartiles (odds ratio 1.9, 95% confidence interval 1.1 to 3.2) after adjustment for lifestyle and risk factors. Histories of periodontal disease were reported by 24% of non-overweight, non-hypertensive, non-hypercholesterolemic participants, and of these participants, 37% had elevated high-sensitivity C-reactive protein (> or =3 mg/L) or lipoprotein-associated phospholipase A(2) (> or =215 ng/ml) levels. In conclusion, self-reported periodontal disease is independently associated with inflammation and common in individuals without traditional CVD risk factors.] Mochari H, Grbic JT, et al. *Am J Cardiol.* 2008 Dec 1;102(11):1509-13. **http://www.ncbi.nlm.nih.gov/pubmed/19026305**
289. **UC Davis researchers discover receptor pathway for C reactive protein and its effects.** [Scientists have discovered how C-reactive protein, or CRP, is able to access endothelial cells. CRP is a known risk marker for heart disease. This is the first time that anyone has shown how CRP is able to get into the human aortic endothelial cells.] http://www.eurekalert.org/pub_releases/2005-06/uocd-udr062105.php
290. **UC Davis Study Identifies C-reactive Protein as Cause of Blood Clot Formation.** [A new study by UC Davis physicians is the first to conclusively link C-reactive proteins (CRP) to formation of blood clots, a major cause of heart attacks, strokes and other vascular disease. Until now, CRP had been recognized mainly as a risk marker of heart disease. CRP causes cells in the arteries, endothelial cells, to produce higher levels of an enzyme that inhibits the breakdown of clots. The enzyme, plasminogen activator inhibitor-1 (PAI-1) is also a strong risk marker for heart disease, especially in diabetics.] http://www.ucdmc.ucdavis.edu/news/CRP_study.html
291. **Usefulness of Self-Reported Periodontal Disease to Identify Individuals With Elevated Inflammatory Markers at Risk of Cardiovascular Disease.** [Periodontal disease has been associated with cardiovascular disease (CVD), and inflammation may represent a common pathophysiology. Oral health screening in the context of CVD risk assessment represents a potential opportunity to identify individuals at risk for CVD. The purposes of this study were to determine if self-reported oral health status is independently associated with inflammatory markers and if oral health assessment as part of CVD risk screening can identify at-risk individuals without traditional CVD risk factors. A baseline analysis was conducted among participants in the National Heart, Lung, and Blood Institute's Family Intervention Trial for Heart Health (FIT Heart; n = 421, mean age 48 ± 13.5 years, 36% nonwhite) without CVD or diabetes who underwent standardized assessment of oral health, lifestyle, CVD

risk factors, and the inflammatory markers high-sensitivity C-reactive protein and lipoprotein-associated phospholipase A**2**. Statistical associations between oral health, risk factors, and inflammatory markers were assessed, and logistic regression was used to adjust for effects of lifestyle and potential confounders. Periodontal disease was independently associated with being in the top quartile of lipoprotein-associated phospholipase A**2** compared with the lower 3 quartiles (odds ratio 1.9, 95% confidence interval 1.1 to 3.2) after adjustment for lifestyle and risk factors. Histories of periodontal disease were reported by 24% of nonoverweight, nonhypertensive, nonhypercholesterolemic participants, and of these participants, 37% had elevated high-sensitivity C-reactive protein (≥3 mg/L) or lipoprotein-associated phospholipase A**2** (≥215 ng/ml) levels. In conclusion, self-reported periodontal disease is independently associated with inflammation and common in individuals without traditional CVD risk factors.] Mochari H, Frbic JT, et al. *The American Journal of Cardiology* vol 102, Issue 11, Pp 1509-1513 December 2008. http://www.ajconline.org/article/S0002-9149(08)01272-1/abstract

292. **Valsartan, Blood Pressure Reduction, and C-Reactive Protein.** [Increased levels of high-sensitivity C-reactive Protein (hsCRP) are associated with incident hypertension as well as cardiovascular events, and angiotensionII is a potent proinflammatory mediator.] Ridker PM, Danielson E, et. al., *Hypertension*. 2006;48:1-7. http://hyper.ahajournals.org/cgi/content/abstract/01.HYP.0000226046.58883.32v1?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=valsartan&searchid=1&FIRSTINDEX=0&resourcetype=HWCIT
293. **VCU Study Suggests New Link Between Severe Periodontitis and Cardiovascular – Disease**. [Virginia Commonwealth University researchers have found that changes in the plasma lipoprotein profile of patients with severe periodontitis – a condition characterized by chronic infection and inflammation of the gums - may contribute to these patients' elevated risk for heart disease and stroke. Patients with periodontitis had elevated plasma levels of a particularly bad subclass of the low density lipoprotein (LDL) called small-dense LDL. Also the decrease of LDL associated PAF-AH activity in patients with severe periodontitis may increase cardiovascular risk in these patients.] RICHMOND, Va. (Dec. 1, 2005) http://www.vcu.edu/uns/Releases/2005/dec/120105.html

Carotid Ultrasound

294. **Carotid intima-media thickness testing by non-sonographer clinicians: the office practice assessment of carotid atherosclerosis study.** [BACKGROUND: The purpose of this study was to determine whether a non-sonographer clinician (NSC) could obtain ultrasound images of the carotid artery, measure carotid intima-media thickness (CIMT), and identify findings indicating increased cardiovascular risk in an office setting. METHODS: Eight NSCs from five sites were trained to use a handheld ultrasound device to screen the carotid arteries for plaques and to measure CIMT. RESULTS: NSCs scanned 150 subjects who provided 900 images, of which 873 (97%) were interpretable. Differences between NSCs and the core laboratory were small (0.002 +/- 0.004 mm) and bioequivalent (P(TOST) < 0.05) with a low coefficient of variation (3.9% +/- 0.5%). There was > or = 90% agreement on the presence of CIMT > or = 75th percentile and > or = 80% agreement on plaque presence. CONCLUSIONS: This is the first multicenter study to show that NSCs can obtain images of the carotid arteries using a handheld ultrasound device, accurately measure CIMT, and identify findings indicating increased cardiovascular risk.] Korcarz CE, Hirsch AT, et al. *J Am Soc Echocardiogr*. 2008 Feb;21(2):117-22 http://www.ncbi.nlm.nih.gov/pubmed/17904806
295. **Changes in Clinical and Microbiological Periodontal Profiles Relate to Progression of Carotid Intima-Media Thickness: The Oral Infections and Vascular Disease Epidemiology Study.** [**Background** No prospective studies exist on the relationship between change in periodontal clinical and microbiological status and progression of carotid atherosclerosis. **Methods and Results** The Oral Infections and Vascular Disease Epidemiology Study examined 420 participants at baseline (68±8 years old) and follow-up. Over a 3-year median follow-up time, clinical probing depth (PD) measurements were made at 75 766 periodontal sites, and 5008 subgingival samples were collected from dentate participants (average of 7 samples/subject per visit over 2 visits) and quantitatively assessed for 11 known periodontal bacterial species by DNA-DNA checkerboard hybridization. Common carotid artery intima-medial thickness (CCA-IMT) was measured using high-resolution ultrasound. In 2 separate analyses, change in periodontal status (follow-up to baseline), defined as (1) longitudinal change in the extent of sites with a ≥3-mm probing depth (Δ%PD≥3) and (2) longitudinal change in the relative predominance of bacteria causative of periodontal disease over other bacteria in the subgingival plaque (Δetiologic dominance), was regressed on longitudinal CCA-IMT progression adjusting for age, sex, race/ethnicity, diabetes, smoking status, education, body mass index, systolic blood pressure, and low-density lipoprotein cholesterol and high-density lipoprotein cholesterol. Mean (SE) CCA-IMT increased during follow-up by 0.139±0.008 mm. Longitudinal IMT progression attenuated with improvement in clinical or microbial periodontal status. Mean CCA-IMT progression varied inversely across quartiles of longitudinal improvement in clinical periodontal status (Δ%PD≥3) by 0.18 (0.02), 0.16 (0.01), 0.14 (0.01), and 0.07 (0.01) mm (*P* for trend<0.0001). Likewise, mean CCA-IMT increased by 0.20 (0.02), 0.18 (0.02), 0.15 (0.02), and 0.12 (0.02) mm (*P*<0.0001) across quartiles of longitudinal improvement in periodontal microbial status (Δetiologic dominance). **Conclusion** Longitudinal improvement in clinical and microbial periodontal status is related to a decreased rate of carotid artery IMT progression at 3-year average follow-up.] Desvarieux M, Demmer RT, et al. J Am Heart Assoc. 2013; 2: e000254 originally published October 28, 2013, doi: 10.1161/JAHA.113.000254. http://jaha.ahajournals.org/content/2/6/e000254.short
296. **Does detection of carotid plaque affect physician behavior or motivate patients?** [BACKGROUND: Imaging techniques to identify subclinical atherosclerosis are becoming more widespread, but few data exist regarding their influence on patient

or physician behavior. We evaluated the impact of ultrasound screening to identify carotid artery plaques on physician treatment plans and patient motivation. METHODS: Subjects included asymptomatic patients without known vascular disease who had 2 or more cardiac risk factors. Circumferential scanning of the right and left carotid arteries to identify carotid plaques was performed using a handheld ultrasound device in an office setting. The physician's initial treatment recommendations were assessed before and after the results of the carotid scan were reported. Subjects completed a survey to assess motivation to make lifestyle changes before and after the results of the scan were provided. RESULTS: Fifty subjects were enrolled over 9 months. Their mean (SD) age was 54.0 (10.4) years and their mean Framingham 10-year cardiovascular risk was 7.8% (7.9%). More than half (58%) of the subjects had at least one carotid plaque. When carotid plaque was identified, physicians were more likely to prescribe aspirin (P = .031) and lipid-lowering therapy (P = .004). Although subjects with carotid plaque reported an increase in their perceived likelihood of developing heart disease (P = .013), they did not report increased motivation to make lifestyle changes. CONCLUSIONS: Ultrasound screening for carotid plaque in an office setting can alter physician treatment plans. Although the presence of plaque increased patient perception of cardiovascular risk, it did not motivate patients to make lifestyle changes.] Wyman RA, Gimelli G, et al. *Am Heart J*. 2007 Dec;154(6):1072-7. **http://www.ncbi.nlm.nih.gov/pubmed/18035077**

297. **Ultrasound detection of increased carotid intima-media thickness and carotid plaque in an office practice setting: does it affect physician behavior or patient motivation.** [BACKGROUND: The aim of this multicenter study was to determine if identifying increased carotid intima-media thickness (CIMT) or carotid plaque during office-based ultrasound screening examinations could alter physicians' treatment plans and patients' motivation regarding health-related behaviors. METHODS: Carotid ultrasound studies were performed by a nonsonographer clinician using a handheld system. Changes in physicians' treatment plans and patients' motivation on the basis of scan results were analyzed using multivariate regression. RESULTS: There were 253 subjects (mean age, 58.1 +/- 6.6 years). When increased CIMT or carotid plaque was detected, physicians were more likely to prescribe aspirin and lipid-lowering therapy (P < .001). Subjects were more likely to report increases in plans to take cholesterol-lowering medication (P = .002) and the perceived likelihood of having or developing heart disease (P = .004). CONCLUSIONS: Findings from office-based carotid ultrasound studies can influence physicians' prescriptions of evidence-based interventions. Patients with abnormal ultrasound findings recognize their increased cardiovascular risk and plan to take cholesterol-lowering medication.] Korcarz CE, DeCara JM, et al. *J Am Soc Echocardiogr*. 2008 Oct;21(10):1156-62. Epub 2008 Jun 16. http://www.ncbi.nlm.nih.gov/pubmed/18558473

298. **Use of hand-held ultrasound by a nonsonographer clinician to measure carotid intima-media thickness**. [OBJECTIVE: We sought to evaluate the accuracy of carotid intima-media thickness (CIMT) measurements by a nonsonographer clinician using hand-held ultrasound (HHU). BACKGROUND: Use of a HHU for point-of-care CIMT measurement has not been tested previously. METHODS: Participants underwent reference ultrasound and HHU studies. HHU validity was tested by an expert sonographer. Nonsonographer clinician accuracy using the HHU was tested against the expert sonographer. CIMT bioequivalence was tested with .5 pixel limits. RESULTS: The 75 participants were (mean [SD]) 55 [7] years old. CIMT values were bioequivalent (0.714 [0.029] vs 0.685 [0.029] mm, phase I; 0.697 [0.015] vs 0.687 [0.015] mm, phase II; P(two 1-sided t test) < .05). Agreement was 80% for CIMT classifications (intraclass correlation coefficient = 0.451, P < .001) and 90% for plaque presence (intraclass correlation coefficient = 0.797, P < .001). CONCLUSIONS: CIMT measured by HHU was bioequivalent to a reference ultrasound system, when used by an expert sonographer or nonsonographer clinician. Clinical classifications by CIMT quartile and plaque presence were similar. HHU may be suitable for office-based atherosclerosis screening.] Tzou WS, Korcarz CE, et al. *J Am Soc Echocardiogr*. 2006 Oct;19(10):1286-92. **http://www.ncbi.nlm.nih.gov/pubmed/17000369**

Hypertension and Inflammation

299. **Acute Systemic Inflammation Increases Arterial Stiffness and Decreases Wave Reflections in Healthy Individuals.** [This is the first study to show through a cause-and-effect relationship that acute systemic inflammation leads to deterioration of large-artery stiffness and to a decrease in wave reflections. These findings have important implications, given the importance of aortic stiffness for cardiovascular function and risk and the potential of therapeutic interventions with anti-inflammatory properties.] Vlachopoulos C et.al., *Circulation 2005 112: 2193 – 2200* http://circ.ahajournals.org/cgi/content/abstract/112/14/2193

300. **Arterial Stiffness in Chronic Inflammatory Diseases.** [Arterial stiffness is increased in chronic inflammatory disorders independent of the presence of atherosclerosis and is related to disease duration, cholesterol, and the inflammatory mediator C-reactive protein and the cytokine that stimulates its production, IL-6.] Roman M, Devereux RB, et.al., *Hypertension. 2005;46:194.* http://hyper.ahajournals.org/cgi/content/abstract/46/1/194

301. **Arterial Stiffness Is Related to Systemic Inflammation in Essential Hypertension.** [The acute phase–reactant high-sensitivity C-reactive protein, a marker of vascular inflammation and an atherosclerotic risk factor, is related to arterial stiffness in healthy subjects and in systemic vasculitis.] Mahmud A, et.al., Hypertension. *2005;46:1118.* http://hyper.ahajournals.org/cgi/content/abstract/46/5/1118

302. **Blood Pressure, C-Reactive Protein, and Risk of Future Cardiovascular Events.** [CRP and blood pressure are independent determinants of cardiovascular risk, and their predictive value is additive. CRP showed a linear relationship with

blood pressure across all categories of blood pressure. Both CRP and blood pressure were independent determinants of cardiovascular risk, and in combination, each parameter had additional predictive value. data suggest that increasing levels of blood pressure may stimulate a proinflammatory response and that endothelial inflammation may also herald the changes in arterial wall that characterize the hypertensive state. Inflammatory processes are now recognized to play a fundamental role in atherogenesis. C-reactive protein (CRP) has been found to be a robust predictor of incident cardiovascular disease. In this regard, the American Heart Association and the Centers for Disease Control and Prevention have recently issued a class IIa recommendation for the measurement of CRP in primary prevention among those at intermediate risk.] Blake GJ, Rifai N. et. al., *Circulation.* 2003;108:2993. http://circ.ahajournals.org/cgi/content/full/108/24/2993

303. **C-Reactive Protein and the Risk of Developing Hypertension.** [C-reactive protein levels are associated with future development of hypertension, which suggests that hypertension is in part an inflammatory disorder.] Sesso HD, Buring JE, et.al., *JAMA. 2003;290:2945-2951. http://jama.ama-assn.org/cgi/content/abstract/290/22/2945*

304. **C-Reactive Protein Is Related to Arterial Wave Reflection and Stiffness in Asymptomatic Subjects From the Community.** [Systemic inflammation leads to Endothelial dysfunction which leads to arterial stiffness and wave reflection. CRP, a marker of systemic inflammation, is associated with measures of arterial stiffness and wave reflection in asymptomatic subjects drawn from the community. Changes in arterial stiffness and wave reflection are seen in both acute inflammation and chronic inflammation. CRP levels are predictive of future development of hypertension. Subclinical systemic inflammation is linked to functional alterations of the arterial bed. Arterial stiffness is increased in people with chronic systemic inflammation.] Kullo IJ et.al., *American Journal of Hypertension Volume 18, Issue 8 , August 2005, Pages 1123-1129. http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6T0Y-4GWPPSS-K&_user=10&_handle=V-WA-A-W-WB-MsSAYWA-UUW-U-AACBEWZDDU-AACACUDCDU-EZAUYYBAE-WB-U&_fmt=summary&_coverDate=08%2F31%2F2005&_rdoc=17&_orig=browse&_srch=%23toc%234875%232005%23999819991%23604286!&_cdi=4875&view=c&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=40bdb7a0738f7c972a6417738de5aff7*

305. **High-sensitivity C-reactive protein affects central haemodynamics and augmentation index in apparently healthy persons.** [This study shows that plasma levels of hsCRP are positively correlated with AIx, central pulse pressure and central systolic blood pressure. Apparently healthy subjects with increased inflammatory markers have increased systemic arterial stiffness, which might reflect early atherosclerotic changes. Our results suggest that hsCRP and non-invasively measured arterial stiffness could serve as additional tools, beside conventional cardiovascular risk factors, for assessment of global arterial risk and preclinical atherosclerotic changes in arteries.] Kampus, Priit, *Journal of Hypertension. 22(6):1133-1139, June 2004.* http://www.jhypertension.com/pt/re/jhypertension/abstract.00004872-200406000-00014.htm;jsessionid=GgKHTLvGHmcM3LHQ20mrl0dJCl8RcxQ79gZJLzSQgb0sv1hW8LDZ!-1734750035!-949856144!8091!-1

306. **Oscillatory Shear Stress Stimulates Adhesion Molecule Expression in Cultured Human Endothelium.** [Altered arterial flow patterns increase expression of adhesion molecules. Surface intercellular adhesion molecule-1 induction by pro-inflammatory cytokine stimulation for 24 hours was found to be approximately five times the level detected after 24 hours of oscillatory shear stress. These results further indicate that atherosclerotic lesion initiation is likely related, at least in part, to unique signals generated by oscillatory shear stress and that the mechanism of upregulation is, to some extent, reduction/oxidation sensitive.] Chappell DC, Varner SE, et.al., *Circulation Research. 1998;82:532-539.* http://circres.ahajournals.org/cgi/content/abstract/82/5/532

307. **Periodontal bacteria and hypertension: the oral infections and vascular disease epidemiology study (INVEST).** [OBJECTIVE: Chronic infections, including periodontal infections, may predispose to cardiovascular disease. We investigated the relationship between periodontal microbiota and hypertension. METHODS AND RESULTS: Six hundred and fifty-three dentate men and women with no history of stroke or myocardial infarction were enrolled in INVEST. We collected 4533 subgingival plaque samples (average of seven samples per participant). These were quantitatively assessed for 11 periodontal bacteria using DNA-DNA checkerboard hybridization. Cardiovascular risk factor measurements were obtained. Blood pressure and hypertension (SBP > or =140 mmHg, DBP > or =90 mmHg or taking antihypertensive medication, or self-reported history) were each regressed on the level of bacteria: considered causative of periodontal disease (etiologic bacterial burden); associated with periodontal disease (putative bacterial burden); and associated with periodontal health (health-associated bacterial burden). All analyses were adjusted for age, race/ethnicity, sex, education, BMI, smoking, diabetes, low-density lipoprotein and high-density lipoprotein cholesterol. Etiologic bacterial burden was positively associated with both blood pressure and prevalent hypertension. Comparing the highest and lowest tertiles of etiologic bacterial burden, SBP was 9 mmHg higher, DBP was 5 mmHg higher (P for linear trend was less than 0.001 in each case), and the odds ratio for prevalent hypertension was 3.05 (95% confidence interval 1.60-5.82) after multivariable adjustment. CONCLUSION: Our data provide evidence of a direct relationship between the levels of subgingival periodontal bacteria and both SBP and DBP as well as hypertension prevalence.] Desvarieux M, Demmer RT, et al. *J Hypertens.* 2010 Jul;28(7):1413-21. http://www.ncbi.nlm.nih.gov/pubmed/20453665

308. **Plasma Hydrogen Peroxide Production in Human Essential Hypertension.** [Increased pulse pressure is associated with generation of pro-inflammatory reactive oxygen species.] Lacy F; Kailasam MT, et.al., *Hypertension. 2000;36:878.)* http://hyper.ahajournals.org/cgi/content/abstract/36/5/878 .

309. **Progression of Carotid Plaque Volume Predicts Cardiovascular Events.** [***Background and Purpose***—Carotid ultrasound evaluation of intima-media thickness (IMT) and plaque burden has been used for risk stratification and for evaluation of

antiatherosclerotic therapies. Increasing evidence indicates that measuring plaque burden is superior to measuring IMT for both purposes. We compared progression/regression of IMT, total plaque area (TPA), and total plaque volume (TPV) as predictors of cardiovascular outcomes. ***Methods***—IMT, TPA, and TPV were measured at baseline in 349 patients attending vascular prevention clinics; they had TPA of 40 to 600 mm2 at baseline to qualify for enrollment. Participants were followed up for ≤5 years (median, 3.17 years) to ascertain vascular death, myocardial infarction, stroke, and transient ischemic attacks. Follow-up measurements 1 year later were available in 323 cases for IMT and TPA, and in 306 for TPV. ***Results***—Progression of TPV predicted stroke, death or TIA (Kaplan-Meier logrank *P*=0.001), stroke/death/MI (*P*=0.008) and Stroke/Death/TIA/Myocardial infarction (any Cardiovascular event) (*P*=0.001). Progression of TPA weakly predicted Stroke/Death/TIA (*P*=0.097) but not stroke/death/MI (*P*=0.59) or any CV event (*P*=0.143); likewise change in IMT did not predict Stroke/Death/MI (*P*=0.13) or any CV event (*P*=0.455). In Cox regression, TPV progression remained a significant predictor of events after adjustment for coronary risk factors (*P*=0.001) but change in TPA did not. IMT change predicted events in an inverse manner; regression of IMT predicted events (*P*=0.004). ***Conclusions***—For assessment of response to antiatherosclerotic therapy, measurement of TPV is superior to both IMT and TPA.] Wannarong T, Parraga G, et al. Stroke. 2013;44:00-00. http://stroke.ahajournals.org/content/early/2013/06/04/STROKEAHA.113.001461.abstract?cited-by=yes&legid=strokeaha;STROKEAHA.113.001461v1

310. **Significant association of C-reactive protein with arterial stiffness in treated non-diabetic hypertensive patients.** [C-reactive protein (CRP) has been known to be associated with vascular inflammation and hypertension. Pulse wave velocity may be correlated with CRP levels in treated hypertensive patients. hsCRP was associated with arterial stiffness, independent of age, systolic BP, gender, heart rate, glucose, lipid profiles and medications in treated hypertension. Therefore, hsCRP could be a useful marker of arterial stiffness in treated hypertension patients and a possible target for arterial inflammation in hypertension.] Jung-Sun Kim, Tae Soo Kang et al., *Journal of Atherosclerosis, 2006.05.025*, http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6T12-4K716DT-2&_coverDate=06%2F19%2F2006&_alid=457204692&_rdoc=1&_fmt=&_orig=search&_qd=1&_cdi=4878&_sort=d&view=c&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=12ad92736d996f1da97c2e9c5aed8356
311. **The connection between ruptured cerebral aneurysms and odontogenic bacteria**. [Background Patients with ruptured saccular intracranial aneurysms have excess long-term mortality due to cerebrovascular and cardiovascular diseases compared with general population. Chronic inflammation is detected in ruptured intracranial aneurysms, abdominal aortic aneurysms and coronary artery plaques. Bacterial infections have been suggested to have a role in the aetiology of atherosclerosis. Bacteria have been detected both in abdominal and coronary arteries but their presence in intracranial aneurysms has not yet been properly studied. Objective The aim of this preliminary study was to assess the presence of oral and pharyngeal bacterial genome in ruptured intracranial aneurysms and to ascertain if dental infection is a previously unknown risk factor for subarachnoid haemorrhage. Methods A total of 36 ruptured aneurysm specimens were obtained perioperatively in aneurysm clipping operations (n=29) and by autopsy (n=7). Aneurysmal sac tissue was analysed by real time quantitative PCR with specific primers and probes to detect bacterial DNA from several oral species. Immunohistochemical staining for bacterial receptors (CD14 and toll-like receptor-2 (TLR-2)) was performed from four autopsy cases. Results Bacterial DNA was detected in 21/36 (58%) of specimens. A third of the positive samples contained DNA from both endodontic and periodontal bacteria. DNA from endodontic bacteria were detected in 20/36 (56%) and from periodontal bacteria in 17/36 (47%) of samples. Bacterial DNA of the *Streptococcus mitis* group was found to be most common. *Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum* and *Treponema denticola* were the three most common periodontal pathogens. The highly intensive staining of CD14 and TLR-2 in ruptured aneurysms was observed. Conclusions This is the first report showing evidence that dental infection could be a part of pathophysiology in intracranial aneurysm disease.] Pyysalo MJ, Pyysalo LM, et al. *J Neurol Neurosurg Psychiatry* 2013;84:1214-1218. http://jnnp.bmj.com/content/84/11/1214.abstract
312. **The Relationship Between Blood Pressure and C-Reactive Protein in the Multi-Ethnic Study of Atherosclerosis (MESA).** [This study confirms the existence of an independent association between hypertension and inflammation in both men and women.] Susan G. Lakoski MD, Mary Cushman MD, Journal of the American College of Cardiology Volume 46, Issue 10 , 15 November 2005, pp 1869-1874. http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6T18-4HD8B8W-9&_coverDate=11%2F15%2F2005&_alid=457161432&_rdoc=1&_fmt=&_orig=search&_qd=1&_cdi=4884&_sort=d&view=c&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=41ee28feacb6799762011cc40fceb428

Cytokines, C-reactive Protein, Inflammatory Mediators, Oxidative Stress, Immunity

313. **A formal analysis of cytokine networks in Chronic Fatigue Syndrome.** [Chronic Fatigue Syndrome (CFS) is a complex illness affecting 4 million Americans for which no characteristic lesion has been identified. Instead of searching for a deficiency in any single marker, we propose that CFS is associated with a profound imbalance in the regulation of immune function forcing a departure from standard pre-programmed responses. To identify these imbalances we apply network analysis to the co-expression of 16 cytokines in CFS subjects and healthy controls. Concentrations of IL-1a, 1b, 2, 4, 5, 6, 8,

10, 12, 13, 15, 17 and 23, IFN-gamma, lymphotoxin-alpha (LT-alpha) and TNF-alpha were measured in the plasma of 40 female CFS and 59 case-matched controls. Cytokine co-expression networks were constructed from the pair-wise mutual information (MI) patterns found within each subject group. These networks differed in topology significantly more than expected by chance with the CFS network being more hub-like in design. Analysis of local modularity isolated statistically distinct cytokine communities recognizable as pre-programmed immune functional components. These showed highly attenuated Th1 and Th17 immune responses in CFS. High Th2 marker expression but weak interaction patterns pointed to an established Th2 inflammatory milieu. Similarly, altered associations in CFS provided indirect evidence of diminished NK cell responsiveness to IL-12 and LT-alpha stimulus. These observations are consistent with several processes active in latent viral infection and would not have been uncovered by assessing marker expression alone. Furthermore this analysis identifies key sub-networks such as IL-2:IFN-gamma:TNF-alpha that might be targeted in restoring normal immune function.] Broderick G, Fuite J, et al. *Brain Behav Immun.* 2010 May 4 http://www.ncbi.nlm.nih.gov/sites/entrez

314. **Additive Value of Immunoassay-Measured Fibrinogen and High-Sensitivity C-Reactive Protein Levels for Predicting Incident Cardiovascular Events.** [Current guidelines suggest measuring high-sensitivity C-reactive protein (hs-CRP) as an aid to coronary risk assessment in adults without cardiovascular disease (CVD). Whether other inflammatory biomarkers, such as fibrinogen, add further prognostic information is uncertain. In this cohort of initially healthy women, baseline levels of fibrinogen measured with a high-quality immunoassay provided additive value to hs-CRP and traditional risk factors in predicting incident CVD.] Mora S, Rifai N, et.al. *Circulation. 2006;114:381-387.* http://circ.ahajournals.org/cgi/content/abstract/114/5/381?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=1&andorexacttitle=and&andorexacttitleabs=and&andorexactfulltext=and&searchid=1&FIRSTINDEX=0&sortspec=relevance&volume=114&firstpage=381&resourcetype=HWCIT

315. **Age and Duration of Follow-up as Modulators of the Risk for Ischemic Heart Disease Associated With High Plasma C-Reactive Protein Levels in Men.** [Background Plasma C-reactive protein (CRP) levels recently have been identified as an emerging risk factor for ischemic heart disease (IHD). However, whether plasma CRP levels predict an increased risk for future IHD beyond traditional risk factors has yet to be evaluated in a large prospective, population-based study. Methods The association between elevated plasma CRP levels and the risk for future IHD was investigated in the prospective, population-based cohort of 2037 IHD-free middle-aged men from the Quebec Cardiovascular Study. During a 5-year follow-up, 105 first IHD events were recorded. Baseline plasma CRP levels were measured using a highly sensitive assay. Results High plasma CRP concentrations (equal to or above vs below the median level of 1.77 mg/L) were associated with a significant 1.8-fold increase in IHD risk (95% confidence interval [CI], 1.2-2.7). This association remained significant after adjustment for lipid risk factors but not when the simultaneous contribution of nonlipid traditional risk factors was taken into account. Multivariate analyses indicated that CRP level predicted short-term risk for IHD (events that occurred ≤2 years after the baseline evaluation), but not long-term risk (>2 years). Moreover, high plasma CRP levels predicted an increased risk for IHD, independent of any other confounder, in younger (≤55 years) but not in older (>55 years) individuals. Plasma CRP levels may provide independent information on IHD risk only in younger middle-aged men and in the case of IHD events that may occur relatively soon after the baseline evaluation.] Pirro M, Bergeron J, Lamarche B, et al. *Arch Intern Med.* 2001;161:2474-2480. http://archinte.ama-assn.org/cgi/content/abstract/161/20/2474

316. **Anti-inflammatory cytokines in gingival crevicular fluid in patients with periodontitis and rheumatoid arthritis: A preliminary report.** [Cytokines which are produced by host cells play an important role in pathogenesis both rheumatoid arthritis (RA) and chronic periodontitis (CP). In this study, we aim to investigate the levels of Interleukin (IL)-4 and IL-10 in gingival crevicular fluid (GCF). Seventeen patients with CP, 17 patients with RA and 17 healthy controls (HC) were included. The RA group was divided into two groups according to gingival sulcus depths (RA-a: PD ⩽ 3 mm, (n = 12), RA-b: PD > 3 mm, (n = 5)). For each patient, clinical parameters were recorded. The GCF samples were evaluated by enzyme-linked immunosorbent assay (ELISA) for IL-4 and IL-10 levels. IL-4 levels in the RA-a, RA-b and CP subjects were significantly lower compared to the HC subjects ($p < 0.05$). The mean level of IL-4 in RA-b group was significantly higher than that in CP group ($p < 0.05$). IL-10 mean level in the HC group was higher than those in the other groups ($p < 0.05$). In the RA-a group, higher IL-10 level was found compared to the CP patients ($p < 0.05$). Within the limitations of this preliminary report, it can be concluded that the initiation and progression of periodontal inflammation may be due to a lack or inappropriate response of the anti-inflammatory cytokines in both CP and RA.] Bozkurt FY, Ay ZY, et al. *Cytokine, Volume 35, Issues 3-4, August 2006, Pages 180-185.* http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6WDF-4KXF2VS-1&_user=10&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_version=1&_urlVersion=0&_userid=10&md5=c2c0d4c52d4e9ae3f7e968023be1e09d

317. **Antimicrobial Periodontal Treatment Decreases Serum C-Reactive Protein, Tumor Necrosis Factor-Alpha, But Not Adiponectin Levels in Patients with Chronic Periodontitis.** [Background: Elevated levels of C-reactive protein (CRP) and decreased plasma adiponectin are associated with increased risk of atherosclerosis. Furthermore, recent observations suggested that adiponectin and tumor necrosis factor-α(TNF-α) suppressed each other's production. Since periodontal disease has been suggested to act as a risk factor for atherosclerosis, we examined the effects of antimicrobial periodontal treatment on CRP, adiponectin, and TNF-α levels. Methods: Fifteen chronic periodontitis patients with various systemic conditions at high risk for atherosclerosis were enrolled in the study. Patients were non-surgically treated with topical application of antibiotics and mechanical debridement of calculus once a week for 1 month. Before and after therapy, CRP, adiponectin, and TNF-α levels were measured. Results: Both CRP and TNF-α levels were signifi- cantly decreased after treatment (P

<0.01 and P <0.03, respectively), while adiponectin levels did not change significantly. Conclusions: Periodontal treatment is effective in reducing CRP and TNF-α, while adiponectin does not appear to be influenced by periodontal treatment. Elevated levels of CRP and TNF-α may be associated with increased risk for future development of atherosclerosis in periodontitis patients Iwamoto Y, Nishimura F, et al. .] *J Periodontol 2003; 74:1231-1236.*
http://www.joponline.org/doi/abs/10.1902/jop.2003.74.8.1231

318. **Assessment of Hemostatic Risk Factors in Predicting Arterial Thrombotic Events.** [Arterial thrombosis results from endovascular injury and, to a lesser extent, alterations in hemostatic equilibrium. Endothelial cell injury with the elaboration of proinflammatory mediators stimulates the process of arterial thrombosis. Although this is most often the result of endovascular injury attributable to atherosclerotic disease, other disease states can elicit a similar response as well. Epidemiological studies have identified several acquired or inherited states that may result in endothelial damage or altered hemostatic equilibrium, thereby predisposing patients to arterial thrombosis. These include hyperhomocysteinemia, elevated C-reactive protein, antiphospholipid antibodies, elevated fibrinogen, Factor VII, plasminogen activator inhibitor-1 (PAI-1), hereditary thrombophilias, and platelet hyper-reactivity. At present, the literature supports a role for hyperhomocysteinemia, elevated C-reactive protein, and elevated fibrinogen as risk factors for arterial thrombosis.] David Feinbloom; Kenneth A. Bauer. *Arteriosclerosis, Thrombosis, and Vascular Biology.* 2005;25:2043.
http://atvb.ahajournals.org/cgi/content/abstract/25/10/2043

319. **Association Between Alveolar Bone Loss and Elevated Serum C-Reactive Protein in Japanese Men**. [Background: Moderate elevation of C-reactive protein (CRP) is thought to predict type 2 diabetes and cardiovascular disease (CVD), both of which are associated with periodontitis. Recent studies indicate that periodontal disease is associated with moderate elevation of CRP; however, the relationship between alveolar bone loss (ABL) and CRP elevation is unclear. Methods: A total of 179 Japanese men aged 50 to 54 years old, with at least 10 teeth, were examined as part of a comprehensive health examination before retirement from the Japan Self-Defense Force. ABL was measured at proximal sites of posterior teeth on a panoramic x-ray film. The relationship between the mean ratio of ABL to root length and serum CRP level and other variables was analyzed. Results: ABL was significantly correlated with serum CRP level (P = 0.008), alkaline phosphatase (P = 0.008), high-density lipoprotein (HDL) cholesterol (P = 0.04, inversely), white blood cell count (P <0.001), erythrocyte sedimentation rate (P = 0.002), age (P = 0.03), and smoking history (P <0.001). In a multiple logistic regression model adjusted for age, smoking history, systolic blood pressure, body-mass index, triglyceride, and HDL cholesterol, subjects in the highest tertile of ABL had an increased risk for CRP elevation ≥1.3 mg/l (odds ratio [OR] = 8.20; 95% confidence interval [CI], 1.6 to 40.7; P = 0.01) when compared to the lowest tertile of ABL. Conclusion: ABL around posterior teeth was associated with elevated CRP in Japanese men, suggesting an association between periodontal disease and increased risk of type 2 diabetes and CVD.] Saito T, Murakami M, et al. *J Periodontol 2003;74:1741-1746.*
http://www.joponline.org/doi/abs/10.1902/jop.2003.74.12.1741

320. **Biomarkers of Vascular Disease Linking Inflammation to Endothelial Activation.** [Atherosclerosis is regarded as a dynamic and progressive disease arising from the combination of endothelial dysfunction and inflammation. This article is the second in a 2-part series examining emerging markers of inflammation and endothelial cell activation. The first article provided a brief overview of the link between inflammation, endothelial dysfunction, and atherosclerosis and began the examination of emerging inflammatory mediators. This second article continues with an exploration of more novel markers for cardiovascular disease. Conclusion: Atherosclerosis is no longer considered a pure lipid disorder.It has become increasingly clear that inflammation is at the root of atherosclerosis and its complications. In addition to playing a causal role in lesion formation, inflammation can yield predictive and prognostic information of considerable clinical utility. A number of mechanisms and mediators of inflammation have been identified, of which high-sensitivity CRP has emerged as one of the most important. In addition to serving as biomarkers of atherosclerotic events, inflammatory mediators directly participate in lesion formation, propagation, and eventual rupture and in this fashion may represent a powerful tool to assess endothelial cell activation. Clearly, understanding the mechanisms and mediators of endothelial dysregulation and inflammation may yield new targets to predict, prevent, and treat cardiovascular disease.] Szmitko PE, Wang CH, et al. *Circulation.* 2003;108:2041
http://circ.ahajournals.org/cgi/content/full/108/17/2041?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=wang&searchid=1&FIRSTINDEX=0&resourcetype=HWCIT

321. **Blood Test Values and Community Periodontal Index Scores in Medical Checkup Recipients.** [Background: We examined the blood test values of people who received general medical checkups and their Community Periodontal Index (CPI) score. Methods: A total of 7,452 persons (5,742 males and 1,710 females), who had general medical and dental checkups, were the subjects of the study. Many were people who worked for companies in and around Nagoya and their family members, ranging in age from 16 to 80 years. The blood test in our study consisted of 37 items used in general blood tests. Partial-mouth recordings were used to measure CPI scores. The highest CPI score for each subject was used for analysis. Odds ratios and confidence interval values were obtained using the Mantel-Haenszel method to analyze the results. Results: CPI scores of 3 and 4 were related to the test values of high-density-lipoprotein cholesterol, serum iron, white blood cell count, fasting blood sugar, glycosylated hemoglobin A_1, glycosylated hemoglobin A_{1c}, and C-reactive protein. Conclusion: Blood test values tended to show correlations with CPI scores, more clearly seen in males than in females.] Takami Y, Nakagaki H, et al. *J Periodontol 2003;74:1778-1784.*
http://www.joponline.org/doi/abs/10.1902/jop.2003.74.12.1778

322. **C-Reactive protein and its relation to cardiovascular risk factors: a population based cross sectional study.** [The body's response to inflammation may play an important part in influencing the progression of atherosclerosis.] Mendall MA, Patel P, et. al. *BMJ* 1996;312:1061-1065 (27 April). http://bmj.bmjjournals.com/cgi/content/abstract/312/7038/1061
323. **Cholesterol, C-reactive protein, and cerebrovascular events following intensive and moderate statin therapy.** [achieved LDL levels did not appear to independently impact the rate of CVE. In contrast, patients with elevated CRP levels were at higher risk of stroke or transient ischemic attack, reinforcing the link between inflammation and CVE. **Condensed abstract :** The goal of this PROVE IT-TIMI 22 sub-study was to examine the relationship between cholesterol, CRP, and CVE in patients on intensive and moderate statin therapy. The achieved lipid levels were similar in patients with and without a CVE; however, the achieved levels of CRP were higher in patients who subsequently developed a stroke or TIA. These findings further support the relationship between inflammation and CVE.] Mega JL, Morrow DA, et al. *Journal of Thrombosis and Thrombolysis, Volume 22, Number 1 / August, 2006,* http://www.springerlink.com/content/741j686630768782/?p=074be5c62cac44ab980715597fe3dc41&pi=9.
324. **Chronic fatigue syndrome: identification of distinct subgroups on the basis of allergy and psychologic variables.** [BACKGROUND: We investigated a role for allergic inflammation and psychologic parameters in the development of chronic fatigue syndrome (CFS). METHODS: The design was a comparison between subjects with CFS and age- and sex-matched control cohorts. Studies were performed on CFS subjects (n = 18) and control cohorts consisting of normal subjects (n = 11), allergic subjects (n = 14), and individuals with primary depression (n = 12). We quantified cytokines at baseline as cell-associated immunoreactive peptides and as transcripts evaluated by means of semiquantitative RNA-based polymerase chain reactions. Psychologic evaluations included administration of the Diagnostic Interview Schedule, the Structured Clinical Interview, and the Symptom Checklist 90-Revised. RESULTS: Increases in tumor necrosis factor (TNF)-alpha were identified in individual subjects with CFS (50.1 +/- 14.4 pg TNF-alpha per 10(7) peripheral blood mononuclear cells [PBMCs]; mean +/- SEM) and allergic subjects (41.6 +/- 7.6) in comparison with normal subjects (13.1 +/- 8.8) ($P < .01$ and $P < .05$, respectively). Similar trends were observed for interferon (IFN)-alpha in allergic subjects (3.0 +/- 1.7 pg/10(7) PBMCs) and subjects with CFS (6.4 +/- 3.4) compared with normal subjects (1.9 +/- 1.4). A significant increase ($P < .05$) in TNF-alpha transcripts was demonstrated between subjects with CFS and depressed subjects. In contrast to these proinflammatory cytokines, both subjects with CFS (2.6 +/- 1.8 pg/10(7) PBMCs) and allergic subjects (3.4 +/- 2.8) were associated with a statistically significant ($P < .01$) decrease in IL-10 concentrations compared with normal subjects (60.2 +/- 18.2). As shown in other studies, most of our subjects with CFS were allergic (15 of 18) and therefore presumably demonstrated cytokine gene activation on that basis. The seasonal exacerbation of allergy was associated with a further increase in cellular IFN-alpha (from 2.1 +/- 1.2 to 14.2 +/- 4.5 pg/107 PBMCs; $P < .05$) but no further modulation of TNF-alpha or IL-10. Similarly, self-reported exacerbations of CFS were associated with a further increase in IFN-alpha (from 2.5 +/- 1.0 to 21.9 +/- 7.8; $P < .05$) and occurred at times of seasonal exposures to allergens. This linkage does not permit making any definitive conclusions regarding a causative influence of either seasonal allergies or the increase in cellular IFN-alpha with the increase in CFS symptoms. The close association between atopy and CFS led us to speculate that CFS may arise from an abnormal psychologic response to the disordered expression of these proinflammatory and antiinflammatory cytokines. Psychologic variables were predictive of immune status within the CFS sample (65.9% of the variance in immune status; $F(3,10) = 6.44$, $P < .05$). Specifically, the absence of a personality disorder but greater endorsement of global psychiatric symptoms was predictive of immune activation. CONCLUSIONS: Most of our subjects with CFS were allergic, and the CFS and allergy cohorts were similar in terms of their immune status. However, the CFS subjects could be discriminated by the distinct psychologic profiles among subjects with and without immune activation. We propose that in at least a large subgroup of subjects with CFS who had allergies, the concomitant influences of immune activation brought on by allergic inflammation in an individual with the appropriate psychologic profile may interact to produce the symptoms of CFS. In a psychologically predisposed individual, symptoms associated with allergic inflammation are recognized as illness.] Borish L, Schmaling K, et al. *J Allergy Clin Immunol.* 1998 Aug;102(2):222-30. http://www.ncbi.nlm.nih.gov/pubmed/9723665
325. **Clinical Application of C-Reactive Protein Across the Spectrum of Acute Coronary Syndromes**. [High-sensitivity C-reactive protein (hsCRP) is associated with adverse cardiovascular outcomes in acute coronary syndromes (ACS). The ability to formulate recommendations regarding clinical use of hsCRP is limited by a paucity of data regarding several key issues. The purpose of this study was to evaluate hsCRP across the spectrum of ACS…. Increased baseline concentrations of hsCRP are strongly associated with mortality and heart failure across the ACS spectrum. hsCRP measurement should be performed early after presentation and index diagnosis-specific cutpoints should be used. Lower CRP in patients on prior aspirin or statin therapy, is a finding which supports the hypothesis that these agents may affect the inflammatory processes in acute coronary syndrome.] Scirica BM, Morrow, DA, et al. *Clinical Chemistry 53:1800-1807, Oct 2007.* http://www.clinchem.org/cgi/content/abstract/53/10/1800
326. **Clinical Application of C-Reactive Protein for Cardiovascular Disease Detection and Prevention.** [C-reactive protein (CRP), a marker of inflammation that has been shown in multiple prospective epidemiological studies to predict incident myocardial infarction, stroke, peripheral arterial disease, and sudden cardiac death. CRP levels have also been shown to predict risk of both recurrent ischemia and death among those with stable and unstable angina, those undergoing percutaneous angioplasty, and those presenting to emergency rooms with acute coronary syndromes. CRP is an independent predictor of future cardiovascular events that adds prognostic information to lipid screening, to the metabolic syndrome, and to the Framingham Risk Score.] Ridker PM, *Circulation: Journal of the American Heart Association: Volume 107(3) 28*

January 2003 pp 363-369, http://pt.wkhealth.com/pt/re/circ/fulltext.00003017-200301280-00017.htm;jsessionid=GdsbRvFtQ8wg71bkQySLXZ1GXT5pcLhGS5mJTfPnvMWsJL5Zvm3m!869285401!-949856145!8091!-1

327. **Coming of Age of C-Reactive Protein. Using Inflammation Markers in Cardiology.** [a recently published prospective study comprising 28 000 women, Ridker et al showed that C-reactive protein (CRP) is a better predictor of the risk of cardiovascular events than low-density lipoprotein (LDL) cholesterol. The implication of this and many other supporting studies is profound and will change the way we screen and manage our patients with atherosclerosis and its associated clinical syndromes. CRP is one of the acute phase proteins that increase during systemic inflammation.[2,3] Individuals without inflammation usually have CRP levels below 1 µg/mL; however, patients with bacterial infections, autoimmune diseases, and cancer frequently have CRP level as high as 100 µg/mL or even higher. It is clear that a high CRP level has no specificity in differentiating disease entities from one another. Despite its lack of specificity, CRP has now emerged as one of the most powerful predictors of cardiovascular risk. Even more remarkable, CRP's predictive power resides in the range between 1 to 5 µg/mL, which was previously regarded to be normal in the era preceding the high-sensitivity CRP test. In fact, tests showing serum CRP levels greater than 10 µg/mL in apparently healthy men or women should be repeated to exclude occult infection or other systemic inflammatory process (see Figure). To understand CRP's transition from an acute phase protein to a most useful inflammatory biomarker for predicting future cardiovascular events, we must know more about the role of the immune system in the pathogenesis of atherosclerosis.] Yeh ETH, Willerson JT. *Circulation* 2003;107:370. http://circ.ahajournals.org/cgi/content/extract/107/3/370?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=ridker&searchid=1&FIRSTINDEX=0&resourcetype=HWCIT

328. **Comparison of C-Reactive Protein and Low-Density Lipoprotein Cholesterol Levels in the Prediction of First Cardiovascular Events.** […because C-reactive protein and LDL cholesterol measurements tended to identify different high-risk groups, screening for both biologic markers provided better prognostic information than screening for either alone. Independent effects were also observed for C-reactive protein in analyses adjusted for all components of the Framingham risk score. These data suggest that the C-reactive protein level is a stronger predictor of cardiovascular events than the LDL cholesterol level and that it adds prognostic information to that conveyed by the Framingham risk score.] Ridker PM, Rifai N, et.al., *NEJM*, Nov 14, 2002 Vol. 347:1557-1565 No 20. http://content.nejm.org/cgi/content/abstract/347/20/1557

329. **C-Reactive Protein Accelerates the Progression of Atherosclerosis in Apolipoprotein E–Deficient Mice. ("C-reactive Protein – More Than A Heart Disease Marker" [**Plasma C-reactive protein (CRP) concentration is a strong predictor of atherosclerosis. However, to date, there is no in vivo evidence that CRP is proatherogenic. *Conclusions*— Human CRP transgene expression causes accelerated aortic atherosclerosis in apoE$^{-/-}$ mice. CRP was detected in the lesion, which was associated with increased C3 deposition and increased AT1-R, vascular cell adhesion molecule-1, and collagen expression. These data document a proatherogenic role for CRP in vivo. Paul A, Ko KWS, Chan L, et al *Circulation.* 2004;109:647-655 http://circ.ahajournals.org/cgi/content/abstract/109/5/647?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=lawrence+chan&searchid=1&FIRSTINDEX=0&resourcetype=HWCIT

330. **C-reactive protein adversely alters the protein-protein interaction of the endothelial isoform of nitric oxide synthase.** [BACKGROUND: C-reactive protein (CRP) inhibits the activity of the endothelial isoform of nitric oxide synthase (eNOS) via uncoupling of the enzyme both in vitro and in vivo. eNOS activity appears to be related in part to its interaction with other cellular proteins, including heat shock protein 90 (Hsp90), caveolin-1, and porin. In this study, we examined the effect of CRP treatment of human aortic endothelial cells (HAECs) on eNOS interaction with caveolin-1, Hsp90, and porin. METHODS: We incubated HAECs with CRP (0, 12.5, and 25 mg/L) for 1, 6, or 24 h and assessed the interaction of these proteins with eNOS by immunoprecipitation and western blotting. RESULTS: CRP treatment (12.5 and 25 mg/L) of HAECs for 24 h significantly increased eNOS binding to caveolin-1 (40% and 54% increase, respectively; *P* _ 0.05) and decreased binding to Hsp90 (33% and 66% decrease, respectively; *P* _ 0.05). CRP (25 mg/L) also significantly decreased the binding of porin to eNOS (11% decrease, *P* _ 0.05). Similar results were seen when HAECs were treated with CRP for 6 h. CONCLUSIONS: These negative protein–protein interactions of eNOS were able to partly explain the CRPinduced decreases in the activity of this critical enzyme, which caused endothelial dysfunction.]Valleggi S, Devaral S, et al. *Clinical Chemistry*, 56:8, pp 1345-1348 (2010). http://www.clinchem.org/cgi/content/abstract/56/8/1345

331. **C-reactive protein and atherogenesis: From fatty streak to clinical event**. [In recent years, it has become increasingly clear that arterial inflammation represents a key feature determining the course of atherogenesis. The consecutive stages in the evolution of atherosclerotic lesions are respectively, plaque buildup and growth, and destabilization, predisposing to plaque rupture and intravascular thrombosis. This chain of events leading from lesion formation to clinical events has been carefully elucidated during the last three decades. C-reactive protein (CRP) has been directly implicated in the pathogenesis of atherosclerosis. In the present review, we will focus on a potentially causal role of CRP during the various stages of atherogenesis.] Bisoendial RJ, Kastelein JJ, et al. *Atherosclerosis*, Vol 195, Issue 2, P e10-e18 (Dec 2007). http://www.atherosclerosis-journal.com/article/S0021-9150(07)00290-0/abstract

332. **C-Reactive Protein and Coronary Heart Disease: Predictive Test or Therapeutic Target?** [Background: The hepatocyte-derived acute-phase reactant C-reactive protein (CRP) has been the subject of intense research over the last 2 decades for its possible role in the pathogenesis of cardiovascular diseases. This research has spawned interest in the use of the blood concentration of CRP for predicting a first coronary heart disease (CHD) event, which has been made possible with the development of high-sensitivity CRP (hsCRP) assays that can measure the typically low concentrations of CRP that circulate in the absence of an overt infective or inflammatory episode, and as a potential causal factor that might be targeted

therapeutically. The research has encompassed observational and genetic epidemiology, basic science studies with cells and tissues, experiments with animal models and humans, and randomized trials (although not of specific CRP-lowering therapies as yet). Content: We focus on investigations of the potential role of small differences in basal hsCRP concentration seen in healthy individuals and the relationship of such differences to the long-term risk of a first CHD event, rather than on research devoted to the high acute-phase CRP concentrations, which occur after acute atherothrombotic events and can influence the severity of ischemic tissue damage and the subsequent prognosis. We concentrate mainly on research findings at the translational interface and draw on evidence from human observational and genetic epidemiology, as well as from randomized trials. Conclusions: As the field matures from one of discovery to an evaluative science, the development of possible clinical applications requires a sharpening of focus on and a critical appraisal of the strengths and deficiencies of the accumulated evidence. Such assessments require attention to both the current state of affairs and the design of future research, so that the existing uncertainties about the utility of CRP in predicting CHD and its role in causing this disease can be resolved.] Hingorani AD, Shah T, et al. *Clinical Chemistry*. 2009;55:239-255. http://www.clinchem.org/cgi/content/abstract/55/2/239

333. **C-Reactive Protein and Incident Cardiovascular Events Among Men With Diabetes**. [Several large prospective studies have shown that baseline levels of C-reactive protein (CRP) are an independent predictor of cardiovascular events among apparently healthy individuals. However, prospective data on whether CRP predicts cardiovascular events in diabetic patients are limited so far. High plasma levels of CRP were associated with an increased risk of incident cardiovascular events among diabetic men, independent of currently established lifestyle risk factors, blood lipids, and glycemic control.] Schulze M, Rimm EB, et.al. *Diabetes Care* 27:889-894, 2004. http://care.diabetesjournals.org/cgi/content/abstract/27/4/889?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&author1=Schulze&searchid=1081215809897_10507&stored_search=&FIRSTINDEX=0&sortspec=relevance&volume=27&firstpage=889&journalcode=diacare
334. **C-Reactive Protein and LDL Cholesterol Levels in Women.** [The authors concluded that increasing levels of C-reactive protein are an independent predictor of cardiovascular events and are even more strongly associated with cardiovascular risk than increased LDL cholesterol levels.] http://www.aafp.org/afp/20030315/tips/27.html
335. **C-Reactive Protein and Other Circulating Markers of Inflammation in the Prediction of Coronary Heart Disease**. [*Background* C-reactive protein is an inflammatory marker believed to be of value in the prediction of coronary events. We report data from a large study of C-reactive protein and other circulating inflammatory markers, as well as updated meta-analyses, to evaluate their relevance to the prediction of coronary heart disease. *Methods* Measurements were made in samples obtained at base line from up to 2459 patients who had a nonfatal myocardial infarction or died of coronary heart disease during the study and from up to 3969 controls without a coronary heart disease event in the Reykjavik prospective study of 18,569 participants. Measurements were made in paired samples obtained an average of 12 years apart from 379 of these participants in order to quantify within-person fluctuations in inflammatory marker levels. *Results* The long-term stability of C-reactive protein values (within-person correlation coefficient, 0.59; 95 percent confidence interval, 0.52 to 0.66) was similar to that of both blood pressure and total serum cholesterol. After adjustment for base-line values for established risk factors, the odds ratio for coronary heart disease was 1.45 (95 percent confidence interval, 1.25 to 1.68) in a comparison of participants in the top third of the group with respect to base-line C-reactive protein values with those in the bottom third, and similar overall findings were observed in an updated meta-analysis involving a total of 7068 patients with coronary heart disease. By comparison, the odds ratios in the Reykjavik Study for coronary heart disease were somewhat weaker for the erythrocyte sedimentation rate (1.30; 95 percent confidence interval, 1.13 to 1.51) and the von Willebrand factor concentration (1.11; 95 percent confidence interval, 0.97 to 1.27) but generally stronger for established risk factors, such as an increased total cholesterol concentration (2.35; 95 percent confidence interval, 2.03 to 2.74) and cigarette smoking (1.87; 95 percent confidence interval, 1.62 to 2.16). *Conclusions* C-reactive protein is a relatively moderate predictor of coronary heart disease. Recommendations regarding its use in predicting the likelihood of coronary heart disease may need to be reviewed.]Danesh J, Wheeler JG, et al. *NEJM*, Volume 350:1387-1397, April 1, 2004 Number 14. **http://content.nejm.org/cgi/content/abstract/350/14/1387**
336. **C-Reactive Protein and the 10-Year Incidence of Coronary Heart Disease in Older Men and Women: The Cardiovascular Health Study.** [High C-reactive protein (CRP) is associated with increased coronary heart disease risk. Few long-term data in the elderly are available. In older men and women, elevated CRP was associated with increased 10-year risk of CHD, regardless of the presence or absence of cardiac risk factors. A single CRP measurement provided information beyond conventional risk assessment, especially in intermediate-Framingham-risk men and high-Framingham-risk women.] Cushman M, Arnold A, et.al. *Circulation.* 2005;112:25-31. http://circ.ahajournals.org/cgi/content/abstract/112/1/25
337. **C-Reactive Protein as a Risk Factor for Coronary Heart Disease: A Systematic Review and Meta-analyses for the U.S. Preventive Services Task Force.** [Background: C-reactive protein (CRP) may help to refine global risk assessment for coronary heart disease (CHD), particularly among persons who are at intermediate risk on the basis of traditional risk factors alone. Purpose: To assist the U.S. Preventive Services Task Force (USPSTF) in determining whether CRP should be incorporated into guidelines for CHD risk assessment. Data Sources: MEDLINE search of English-language articles (1966 to November 2007), supplemented by reference lists of reviews, pertinent studies, editorials, and Web sites and by expert suggestions. Study Selection: Prospective cohort, case–cohort, and nested case–control studies relevant to the independent predictive ability of CRP when used in intermediate-risk persons. Data Extraction: Included studies were reviewed according to predefined criteria, and the quality of each study was rated. Data Synthesis: The validity of the body of evidence and the

net benefit or harm of using CRP for CHD risk assessment were evaluated. The combined magnitude of effect was determined by meta-analysis. The body of evidence is of good quality, consistency, and applicability. For good studies that adjusted for all Framingham risk variables, the summary estimate of relative risk for incident CHD was 1.58 (95% CI, 1.37 to 1.83) for CRP levels greater than 3.0 mg/L compared with levels less than 1.0 mg/L. Analyses from 4 large cohorts were consistent in finding evidence that including CRP improves risk stratification among initially intermediate-risk persons. C-reactive protein has desirable test characteristics, and good data exist on the prevalence of elevated CRP levels in intermediate-risk persons. Limited evidence links changes in CRP level to primary prevention of CHD events. Limitations: Study methods for measuring Framingham risk variables and other covariates varied. Ethnic and racial minority populations were poorly represented in most studies, limiting generalizability. Few studies directly assessed the effect of CRP on risk reclassification in intermediate-risk persons. Conclusion: Strong evidence indicates that CRP is associated with CHD events. Moderate, consistent evidence suggests that adding CRP to risk prediction models among initially intermediate-risk persons improves risk stratification. However, sufficient evidence that reducing CRP levels prevents CHD events is lacking.] Buckley DI, Rongwei F, et al. *Annls of Int Med*, October 6, 2009 vol. 151 no. 7 483-495. http://www.annals.org/content/151/7/483.abstract

338. **C-reactive protein, depressed mood, and the prediction of coronary heart disease in initially healthy men: results from the MONICA–KORA Augsburg Cohort Study 1984–1998.** [Aims C-reactive protein and depressive mood (DM) are novel risk factors for coronary heart disease (CHD). The goal of the present study was to assess possible combined effects of these factors on the prediction of a future fatal and non-fatal coronary event. Methods and results Baseline highly sensitive (hs) C-reactive protein and DM were analysed in 3021 apparently healthy male subjects aged 45–74 from three subsequent population based surveys (1984–95) of the MONICA–KORA Augsburg Cohort Study. During a median follow-up period of 7.7 years (IQR=6.9 years), 165 CHD events occurred. Risks of CHD were estimated from Cox proportional hazard models adjusted for age and survey and multiple risk factors. The age and survey adjusted interaction term of continuous hs-C-reactive protein by DM disclosed a significant effect (HR 1.03; 95% CI 1.00–1.06; *P*=0.037). A stratified analysis of subpopulations with (*n*=986) and without (*n*=2035) DM revealed that high hs-C-reactive protein (>3 mg/L) was predictive in the group with DM (HR 2.69; 95% CI 1.32–5.47) but was not significant in the low-level depression group (HR 1.55; 95% CI 0.89–2.69). Relative to the low C-reactive protein/no depression subgroup (*n*=712), high C-reactive protein/no depression (*n*=565) did not significantly predict a future CHD event. However, combined high C-reactive protein and DM (*n*=282) significantly predicted future CHD events (HR 2.91; 95% CI 1.25–2.18; *P*>0.0001). Conclusion In apparently healthy men, a DM substantially increases the power of elevated C-reactive protein to predict a subsequent myocardial infarction. Both conditions may share a common underlying mechanism.] Ladwig KH, Marten-Mittag B,e t al. European Heart Journal 2005 26(23):2537-2542 http://eurheartj.oxfordjournals.org/cgi/content/abstract/26/23/2537

339. **C-reactive protein in gingival crevicular fluid may be indicative of systemic inflammation.** [C-reactive protein in gingival crevicular fluid may be indicative of systemic inflammation. J Clin Periodontol 2010; doi: 10.1111/j.1600-051X.2010.01603.x. Abstract Background and Aim: Periodontitis is associated with elevated C-reactive protein (CRP) in both serum and gingival crevicular fluid (GCF). Although the liver is the primary source of CRP, extra-hepatic production of CRP has been reported. This study aimed to determine whether CRP in GCF is produced locally in the gingivae. Materials and Methods: Gingivae and GCF were collected from non-periodontitis and periodontitis sites. Presence of CRP in gingivae was assessed by immunohistochemistry. CRP in GCF was measured using ELISA. Gene expression for CRP in gingivae was determined using real-time polymerase chain reaction. Results: CRP was found in both the gingivae and GCF. No gingivae had detectable amounts of CRP mRNA. Not all patients with periodontitis had detectable levels of CRP in the GCF. Some non-periodontitis patients had detectable levels of CRP in the GCF. Conclusion: CRP in the GCF appears to be of systemic origin, and therefore may be indicative of systemic inflammation from either a periodontal infection or inflammatory disease elsewhere. The correlation between levels of CRP in GCF and serum requires validation in future studies.] Megson E, Fitzsimmons T, et al. *J Clin Periodontol*. 2010 Jul 4 http://www.ncbi.nlm.nih.gov/pubmed/20618548

340. **C-Reactive Protein Increases Plasminogen Activator Inhibitor-1 Expression and Activity in Human Aortic Endothelial. Cells. [**Inflammation plays a pivotal role in atherosclerosis. In addition to being a risk marker for cardiovascular disease, much recent data suggest that C-reactive protein (CRP) promotes atherogenesis via effects on monocytes and endothelial cells. The metabolic syndrome is associated with significantly elevated levels of CRP. Plasminogen activator inhibitor-1 (PAI-1), a marker of atherothrombosis, is also elevated in the metabolic syndrome and in diabetes, and endothelial cells are the major source of PAI-1. This study makes the novel observation that CRP induces PAI-1 expression and activity in HAECs and thus has implications for both the metabolic syndrome and atherothrombosis.] *American Heart Assoc Journal Circulation, 2003;107:398-404*. Devaraj S et.al, Univ of California, Davis Medical Center. *http://circ.ahajournals.org/cgi/content/abstract/107/3/398*

341. **C-Reactive Protein Inhibits Insulin Activation of Endothelial Nitric Oxide Synthase via the Immunoreceptor Tyrosine-Based Inhibition Motif of FcγRIIB and SHIP-1**. [Insulin promotes the cardiovascular protective functions of the endothelium including NO production by endothelial NO synthase (eNOS), which it stimulates via Akt kinase which phosphorylates eNOS Ser1179. C-reactive protein (CRP) is an acute-phase reactant that is positively correlated with cardiovascular disease risk in patients with type 2 diabetes. We previously showed that CRP inhibits eNOS activation by insulin by blunting Ser1179 phosphorylation. We now elucidate the underlying molecular mechanisms. We first show in mice that CRP inhibits insulin-induced eNOS phosphorylation, indicating that these processes are operative in vivo. In endothelial cells we find that CRP attenuates insulin-induced Akt phosphorylation, and CRP antagonism of eNOS is negated

by expression of constitutively active Akt; the inhibitory effect of CRP on Akt is also observed in vivo. A requirement for the IgG receptor FcγRIIB was demonstrated in vitro using blocking antibody, and reconstitution experiments with wild-type and mutant FcγRIIB in NIH3T3^{IR} cells revealed that these processes require the ITIM (immunoreceptor tyrosine-based inhibition motif) of the receptor. Furthermore, we find that endothelium express SHIP-1 (Src homology 2 domain–containing inositol 5′-phosphatase 1), that CRP induces SHIP-1 stimulatory phosphorylation in endothelium in culture and in vivo, and that SHIP-1 knockdown by small interfering RNA prevents CRP antagonism of insulin-induced eNOS activation. Thus, CRP inhibits eNOS stimulation by insulin via FcγRIIB and its ITIM, SHIP-1 activation, and resulting blunted activation of Akt. These findings provide mechanistic linkage among CRP, impaired insulin signaling in endothelium, and greater cardiovascular disease risk in type 2 diabetes.] Tanigaki K, Mineo C, et al. *Circ Res*, 2009 June 5; 104(11):1275-1282. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2733870/

342. **C-reactive Protein Level and Risk of Aging Macula Disorder The Rotterdam Study** [Objective: To examine whether C-reactive protein (CRP) level is a risk factor for aging macula disorder (AMD) in a general population. …Conclusion: Elevated baseline levels of HsCRP were associated with the development of early and late AMD in this large population-based cohort.] Boekhoorn SS, Vingerling JR, Witteman JCM, Hofman A, et al. *Arch Ophthalmol.* 2007;125:1396-1401. http://archopht.ama-assn.org/cgi/content/short/125/10/1396
343. **C-Reactive Protein Modulates Risk Prediction Based on the Framingham Score. [**The Framingham Coronary Heart Disease (CHD) prediction score is recommended for global risk assessment in subjects prone to CHD. Recently, C-reactive protein (CRP) has emerged as an independent predictor of CHD. We sought to assess the potential of CRP measurements to enhance risk prediction based on the Framingham Risk Score (FRS) in a large cohort of middle-aged men from the general population. Our results suggest that CRP enhances global coronary risk as assessed by the FRS, especially in intermediate risk groups. This might have implications for future risk assessment.] Koenig W, Löwel H, et.al. *Circulation.* 2004;109:1349-1353. http://circ.ahajournals.org/cgi/content/abstract/109/11/1349
344. **C-Reactive Protein, a Sensitive Marker of Inflammation, Predicts Future Risk of Coronary Heart Disease in Initially Healthy Middle-Aged Men**. [Inflammatory reactions in coronary plaques play an important role in the pathogenesis of acute atherothrombotic events; inflammation elsewhere is also associated with both atherogenesis generally and its thrombotic complications. Recent studies indicate that systemic markers of inflammation can identify subjects at high risk of coronary events. These results confirm the prognostic relevance of CRP, a sensitive systemic marker of inflammation, to the risk of CHD in a large, randomly selected cohort of initially healthy middle-aged men. They suggest that low-grade inflammation is involved in pathogenesis of atherosclerosis, especially its thrombo-occlusive complications.] Koenig et al, *Circulation.* 1999;99:237-242. http://circ.ahajournals.org/cgi/content/abstract/circulationaha;99/2/237
345. **C-Reactive Protein, Subclinical Atherosclerosis, and Risk of Cardiovascular Events.** [C-reactive protein (CRP) is an independent determinant of risk of stroke among both men and women. Emerging data suggest that CRP may be a mediator as well as a marker of atherosclerosis. CRP induces expression of cellular adhesion molecules, interleukin-6, and endothelin-1 by endothelial cells. CRP also mediates monocyte chemoattractant protein-1 induction, and it has been shown to mediate uptake of LDL by macrophages. Furthermore, smooth muscle cells and macrophages in arterial tissue have been shown to produce CRP, a process that is substantially upregulated in atherosclerotic plaque.] Gavin J. Blake; Paul M. Ridker, *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2002;22:1512. http://atvb.ahajournals.org/cgi/content/full/22/10/1512
346. **C-Reactive Protein, the Metabolic Syndrome, and Risk of Incident Cardiovascular Events.** [Prospective data suggest that measurement of CRP adds clinically important prognostic information to the metabolic syndrome.] Ridker PM, Buring JE, et al. *Circulation.* 2003;107:391. http://circ.ahajournals.org/cgi/content/abstract/107/3/391
347. **Circulating Levels of Oxidative Stress Markers and Endothelial Adhesion Molecules in Men with Abdominal Obesity.** [Context: It has been suggested that oxidative stress and endothelial dysfunction could play a role in the higher cardiovascular disease risk noted in the abdominally obese population. Objective: The objective of this study was to describe the associations between abdominal fat accumulation, oxidative stress, and endothelial dysfunction in men. Design: A complete physical and metabolic profile was assessed in a group of 56 men covering a wide range of adiposity and plasma oxidized low-density lipoprotein (OxLDL), and soluble intercellular adhesion molecule-1, soluble vascular cell adhesion molecule-1, E-selectin, and C-reactive protein concentrations were determined. Results: We found that abdominal visceral adipose tissue was positively associated with plasma OxLDL ($r = 0.52$; $P < 0.0001$) and C-reactive protein ($r = 0.60$; $P < 0.0001$) concentrations. We also found significant associations between plasma E-selectin levels and hyperinsulinemia ($r = 0.39$; $P < 0.005$) as well as with the homeostasis model assessment index of insulin resistance ($r = 0.42$; $P < 0.005$). Conclusions: Our study showed that plasma OxLDL levels and low-grade systemic inflammation are increased in men with a high visceral adipose tissue accumulation. Furthermore, our results support the notion that insulin resistance is associated with endothelial activation. Overall, our observations give us further insights on the increased cardiovascular disease risk frequently noted among viscerally obese, insulin-resistant individuals.] Couillard C, Ruel G, et al. The Journal of Clinical Endocrinology & Metabolism Vol. 90, No. 12 6454-6459. http://jcem.endojournals.org/cgi/content/abstract/90/12/6454
348. **CRP—Marker or Maker of Cardiovascular Disease?** [C-reactive protein (CRP) has emerged as an interesting novel and potentially clinically useful marker for increased cardiovascular risk. This is an attractive concept because atherosclerosis is a disease characterized by chronic arterial inflammation and suggests the possibility that subclinical states of atherosclerosis can be identified by an increase in circulating markers of inflammation before acute events occur. Based on data obtained primarily from in vitro studies it has also been proposed that CRP in itself is actively contributing to disease progression and that it should be considered as true risk factor and consequently as a target for intervention. The association between

moderately elevated CRP levels and an increased risk for development of cardiovascular disease is well established.] Jan Nilsson. *Arteriosclerosis, Thrombosis, and Vascular Biology.* 2005;25:1527. http://atvb.ahajournals.org/cgi/content/full/25/8/1527

349. **Cytokine profile in synovial fluid from patients with internal derangement of the temporomandibular joint: a preliminary study. [**Temporomandibular joint disorders (TMD) comprise a group of chronic painful conditions of mastication in the temporomandibular joint (TMJ). Although the association between TMD and internal derangement of the TMJ is well documented, the functional relevance is still unclear. Increased concentrations of inflammatory mediators have been identified in the synovial fluid of affected patients with TMD, suggesting an underlying degenerative or inflammatory process. The aim of this study was to generate a comprehensive cytokine expression profile in TMD. **Conclusions:** This study confirmed previous reports of elevated cytokine levels in TMD. Additionally, we identified previously undescribed cytokines that were upregulated and correlated significantly with the presence of JE. We were able to identify novel cytokines that have hitherto not been described in TMD. Strategies targeting the identified cytokines may represent a novel therapy option in TMD.] Matsumoto K, Honda K, et.al. *Dentomaxillofacial Radiology (2006) 35, 432-441.* http://dmfr.birjournals.org/cgi/content/abstract/35/6/432

350. **Cytokines That Promote Periodontal Tissue Destruction,** [Although periodontal diseases are initiated by bacteria that colonize the tooth surface and gingival sulcus, the host response is believed to play an essential role in the breakdown of connective tissue and bone, key features of the disease process. An intermediate mechanism that lies between bacterial stimulation and tissue destruction is the production of cytokines, which stimulates inflammatory events that activate effector mechanisms. These cytokines can be organized as chemokines, innate immune cytokines, and acquired immune cytokines. Although they were historically identified as leukocyte products, many are also produced by a number of cell types, including keratinocytes, resident mesenchymal cells (such as fibroblasts and osteoblasts) or their precursors, dendritic cells, and endothelial cells. Chemokines are chemotactic cytokines that play an important role in leukocyte recruitment and may directly or indirectly modulate osteoclast formation. This article focuses on aspects of osteoimmunology that affect periodontal diseases by examining the role of cytokines, chemokines, and immune cell mediators. It summarizes some of the key findings that attempt to delineate the mechanisms by which immune factors can lead to the loss of connective tissue attachment and alveolar bone. In addition, a discussion is presented on the importance of clarifying the process of uncoupling, a process whereby insufficient bone formation occurs following resorption, which is likely to contribute to net bone loss in periodontal disease.] Graves D. *Journal of Periodontology, 2008, Vol. 79, No. 8s, Pages 1585-1591.* http://www.joponline.org/doi/full/10.1902/jop.2008.080183

351. **Definition of Tumor necrosis factor.** [Tumor necrosis factor: A member of a superfamily of proteins, each with 157 amino acids, which induce necrosis (death) of tumor cells and possess a wide range of proinflammatory actions. Tumor necrosis factor is a multifunctional cytokine with effects on lipid metabolism, coagulation, insulin resistance, and the function of endothelial cells lining blood vessels. Blocking the action of TNF has been shown to be beneficial in reducing the inflammation in inflammatory diseases.] http://www.medterms.com/script/main/art.asp?articlekey=25458

352. **Effect of treating Periodontitis on C-reactive protein levels: a pilot study.** [Periodontitis is associated with elevated levels of C-reactive protein and fibrinogen and it may be a coronary heart disease risk factor. Periodontitis seems to increase C-reactive protein only in some individuals, presumably the ones reacting to it with a systemic inflammatory reaction. Periodontal treatment decreases C-reactive protein levels in these individuals and it may thus decrease their risk of coronary heart disease.] Mattila K, Vesanen M, et al, *BMC Infectious Diseases* 2002, 2:30. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=138813&rendertype=abstract

353. **Effects of Inflammatory Cytokines on Production of MMPs and Extracellular Matrix Proteins in Cultured Human Periodontal Ligament Fibroblasts.** [Interleukin-1.BETA.(IL-1.BETA.) and tumor necrosis factor-.ALPHA.(TNF-.ALPHA.), two potent inflammatory cytokines in periodontitis, were believed to play a significant role in production of matrix metalloproteinases(MMPs), which might be involved in bone loss and connective tissue breakdown. On the other hand, IL-1.BETA. had been shown to induce expression of decorin which was a major small proteoglycan participating in the maintenance of periodontal tissue integrity. These cytokines appeared to have a divergent biochemical function in either tissue degradation or regeneration process. To elucidate the molecular mechanisms involved in periodontitis, we examined the effects of IL-1.BETA. and TNF-.ALPHA. on expression of MMPs, tissue inhibitors of matrix metalloproteinases(TIMPs), type I collagen and decorin in cultured human periodontal ligament fibroblasts(HPLF). Northern blot analyses showed that each cytokine alone increased the expression of MMP-1 and MMP-2 mRNA and no synergistic effect of these cytokines were detected. Furthermore, Western blot analyses showed that each cytokine increased the production of partially activated MMP-1, while only TNF-.ALPHA. participated in the formation of fully activated MMP-1. Since MMP-3 and plasmin were reported to be important activators of MMP-1, we have examined the effects of inflammatory cytokines on the expression of MMP-3 and urokinase type plasminogen activator(uPA), an activator of plasminogen to plasmin. Neither IL-1.BETA. nor TNF-.ALPHA. participated in the induction of active form of MMP-3 or uPA, suggesting that the enzyme and the activator were not involved in the cascade of MMP-1 activation. Whereas IL-1.BETA. or TNF-.ALPHA. alone increased the expression of decorin mRNA, the addition of both cytokines resulted in suppression of the decorin gene expression. The production of type I collagen mRNA was markedly decreased by either cytokine and the synergistic suppressive effect of these cytokines was detected] Hasegawa Eli, Sasaguri Ken'ichi, et al. *Journal of the Kanagawa Odontological Society, V*ol. 35; No. 1; Pp 27-28(2000). http://sciencelinks.jp/j-east/article/200103/000020010300A1036009.php

354. **Elevation of Systemic Markers Related to Cardiovascular Diseases in the Peripheral Blood of Periodontitis Patients.** [Periodontitis is a common, often undiagnosed, chronic infection of the supporting tissues of the teeth, epidemiologically associated with cardiovascular diseases. Since Creactive protein (CRP) and other systemic markers of inflammation have been identified as risk factors for cardiovascular diseases, we investigated whether these factors were elevated in periodontitis. Periodontitis results in higher systemic levels of CRP, IL-6, and neutrophils. These elevated inflammatory factors may increase inflammatory activity in atherosclerotic lesions, potentially increasing the risk for cardiac or cerebrovascular events. Loos BG, Craandijk J, et al. *Journal of Periodontology, October 2000, Vol. 71, No. 10, Pages 1528-1534*. http://www.joponline.org/doi/abs/10.1902/jop.2000.71.10.1528

355. **Established and Emerging Plasma Biomarkers in the Prediction of First Atherothrombotic Events.** [In the current Adult Treatment Panel guidelines for cardiovascular risk detection, the plasma-based markers recommended for use in global risk assessment or in the definition of the metabolic syndrome are low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, and triglycerides. It is widely recognized, however, that more than half of all future vascular events occur in individuals without overt hyperlipidemia. … Although risk-scoring systems that additionally evaluate traditional risk factors such as smoking, hypertension, and diabetes greatly improve risk prediction, multiple studies demonstrate that 20% to 25% of all future events occur in individuals with only 1 of these factors. Moreover, the prevalence of traditional risk factors is almost as high in those without disease as in affected individuals. As our understanding of the pathobiology of atherothrombosis has improved, researchers have attempted to evaluate the activities of these biological processes by measuring markers in plasma or urine (ie, biomarkers). Indeed, a series of candidate biomarkers reflecting inflammation, hemostasis, thrombosis, and oxidative stress have been evaluated as potential clinical tools in an effort to improve risk prediction. To be useful in a clinical setting, the biomarker of interest must be shown in multiple prospective studies to predict future cardiovascular events. Retrospective studies are of limited value because they are prone to bias and cannot exclude the possibility that the particular biomarker is elevated as a result of, rather than a cause of, disease. To be used widely, the proposed biomarker should provide independent information on risk or prognosis beyond that available from global assessment algorithms such as the Framingham Risk Score. The biomarker additionally should be easy to measure in a cost-effective manner in outpatient settings. This typically requires an inexpensive and standardized commercial assay with low variability that does not require specialized plasma collection or assay techniques. Although not a critical issue for risk prediction, the biomarker will have broader acceptance if reduction of the biomarker leads to reduced vascular risk. Several established and emerging novel biomarkers for vascular risk meet these criteria, although few are ready for clinical practice. With the exception of high-sensitivity C-reactive protein (hsCRP), none has demonstrated additive value over and above Framingham risk scoring, and few are supported by commercial assays that achieve appropriate levels of standardization and accuracy for clinical use. Additionally, no clear evidence exists that lowering plasma levels of any of these biomarkers, including hsCRP, lowers vascular risk. However, many of these novel biomarkers provide important insights into the pathophysiology of atherothrombosis and serve as important research tools. This overview focuses on established and emerging biomarkers in the prediction of atherothrombotic events in apparently healthy individuals and thus includes discussion of markers of inflammation, fibrinolysis, oxidative stress, and altered lipids. It is important to recognize that other emerging vascular biomarkers, including brain natriuretic peptide and myeloperoxidase, have shown initial promise in the setting of acute myocardial ischemia but have yet to be evaluated in outpatient screening of healthy individuals. Other novel markers emerging in primary prevention include those related to adipocyte function, including adiponectin.…There is considerable pathophysiologic and clinical interest in the development of novel biomarkers for inflammation, hemostasis, thrombosis, and oxidative stress that may help in the detection of individuals at high risk for future vascular events. However, ··· few of these markers have demonstrated an ability to predict risk over and above information available from global assessment tools such as the Framingham Risk Score, and no evidence is available demonstrating that specific reductions in any of these novel markers will lower vascular risk. Although this overview has focused on the role of biomarkers for prognosis in primary prevention, it remains possible that several biomarkers will prove useful for demonstrating efficacy of therapy or in predicting specific patient groups more or less likely to benefit from targeted interventions. It also remains probable that no single biomarker will emerge that provides appropriate information for all clinical settings; thus, multimarker approaches also need evaluation. Ongoing efforts in plasma-based biomarker research will simultaneously need to address novel pathways of disease and carefully evaluate clinical applications and clinical efficacy.] Ridker PM, Brown NJ, et al. *Circulation* 2004;109:IV-6-IV-19). http://circ.ahajournals.org/cgi/content/full/109/25_suppl_1/IV-6?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=ridker&searchid=1&FIRSTINDEX=0&resourcetype=HWCIT

356. **Evaluation of Gingival Crevicular Fluid and Serum Levels of High-Sensitivity C-Reactive Protein in Chronic Periodontitis Patients With or Without Coronary Artery Disease.** [Most studies have evaluated serum C-reactive protein (CRP) levels in chronic periodontitis (CP) patients, and a few investigations have examined gingival crevicular fluid (GCF) CRP levels. The aims of this study were to determine GCF and serum levels of high-sensitivity CRP (HsCRP) in CP patients with or without coronary artery disease (CAD) and to investigate the relationship between the GCF and serum HsCRP levels in CP patients with and without CAD. … Patients with CP and CP + CAD had statistically significant elevations in serum HsCRP levels compared to healthy subjects. However, HsCRP levels of GCF did not differ from those of the control and CP groups or the control and CP + CAD groups. Further studies are needed to clarify the relationship between GCF CRP levels and periodontal diseases.] Tuter G, Kurtis B, Serdar M. *Journal of Periodontology 2007, Vol. 78, No. 12, Pages 2319-2324* , http://www.joponline.org/doi/abs/10.1902/jop.2007.070150 .

357. **Gingival inflammation, increased periodontal pocket depth and elevated interleukin-6 in gingival crevicular fluid of depressed women on long-term sick leave.** [Background and Objective: The aim of this work was to investigate periodontal status, in relation to inflammatory markers and cortisol, in the gingival crevicular fluid and saliva of a homogenous group of women on long-term sick leave for job-stress related depression in comparison to nondepressed women… Conclusion: Women on long-term sick-leave for depression had more severe periodontitis and higher concentrations of interleukin-6 in gingival crevicular fluid than healthy controls. An alteration of the immune system in these patients might be interpreted as reflecting the consequences of long-term stress exposure and might contribute to worse periodontal conditions in these particular patients.] Johannsen A, Rydmark I, et al., *Journal of Periodontal Research Volume 42 Issue 6 Page 546-552, December 2007,* http://www.blackwell-synergy.com/doi/abs/10.1111/j.1600-0765.2007.00980.x
358. **Gram-negative periodontal bacteria induce the activation of Toll-like receptors 2 and 4, and cytokine production in human periodontal ligament cells.** [BACKGROUND: Periodontitis is a bacterially induced chronic inflammatory disease. Toll-like receptors (TLRs), which could recognize microbial pathogens, are important components in the innate and adaptive immune systems. Both qualitatively and quantitatively distinct immune responses might result from different bacteria stimulation and the triggering of different TLRs. This study explores the interaction of Porphyromonas gingivalis, Prevotella intermedia, Fusobacterium nucleatum, and Aggregatibacter actinomycetemcomitans (previously Actinobacillus actinomycetemcomitans) with TLR2 and TLR4 .METHODS: We studied the gene expression changes of TLR2 and TLR4 and cytokine production (interleukin-1β, -6, -8, -10, and tumor necrosis factor-alpha) in human periodontal ligament cells (HPDLCs) stimulated with heat-killed bacteria or P. gingivalis lipopolysaccharide (LPS) in the presence or absence of monoclonal antibodies to TLR2 or TLR4 (anti-TLR2/4 mAb). RESULTS: Both test bacteria and 10 microg/ml P. gingivalis LPS treatment increased the gene expression of TLR2 and TLR4 and cytokine production in HPDLCs. In addition, these upregulations could be blocked by anti-TLR2/4 mAb. However, the expression of TLR4 mRNA in HPDLCs stimulated with 1 microg/ml P. gingivalis LPS was not increased. No differences were found in the cytokine production caused by 1 microg/ml P. gingivalis LPS treatment in the presence or absence of anti-TLR4 mAb. CONCLUSION: These patterns of gene expression and cytokine production indicate that Gram-negative periodontal bacteria or their LPS might play a role in triggering TLR2 and/or TLR4, and be of importance for the immune responses in periodontitis.] Sun Y, Shu R, et al. J *Periodontol.* 2010 Oct;81(10):1488-96. http://www.ncbi.nlm.nih.gov/pubmed/20528699
359. **High-Sensitivity C-Reactive Protein Potential Adjunct for Global Risk Assessment in the Primary Prevention of Cardiovascular Disease**. [Inflammation plays a major role in atherothrombosis, and measurement of inflammatory markers such as high-sensitivity C-reactive protein (HSCRP) may provide a novel method for detecting individuals at high risk of plaque rupture. Several large-scale prospective studies demonstrate that HSCRP is a strong independent predictor of future myocardial infarction and stroke among apparently healthy men and women and that the addition of HSCRP to standard lipid screening may improve global risk prediction among those with high as well as low cholesterol levels. Because agents such as aspirin and statins seem to attenuate inflammatory risk, HSCRP may also have utility in targeting proven therapies for primary prevention. Inexpensive commercial assays for HSCRP are now available; they have shown variability and classification accuracy similar to that of cholesterol screening. Risk prediction algorithms using a simple quintile approach to HSCRP evaluation have been developed for outpatient use. Thus, although limitations inherent to inflammatory screening remain, available data suggest that HSCRP has the potential to play an important role as an adjunct for global risk assessment in the primary prevention of cardiovascular disease.] Ridker PM *Circulation.* 2001;103:1813. http://circ.ahajournals.org/cgi/content/full/103/13/1813#F4
360. **High-Sensitivity Serum C-Reactive Protein Levels in Subjects With or Without Myocardial Infarction or Periodontitis.** [As expected, elevated serum hsC-rp concentration and serum WBC counts are associated with acute coronary heart disease. (2) Elevated serum hsC-rp values are associated with radiographically defined periodontitis in subjects with no evidence of CVD.] Persson G., Pettersson T., et al,*J Clin Perio 32: 219–224, 2005.* *http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=15766362&dopt=Abstract*
361. **How the Blood Talks to the Brain Parenchyma and the Paraventricular Nucleus of the Hypothalamus During Systemic Inflammatory and Infectious Stimuli.** [There are exciting new developments regarding the molecular mechanisms involved in the influence of circulating proinflammatory molecules within cells of the blood-brain barrier (BBB) during systemic immune challenges. These molecules, when present in the circulation, have the ability to trigger a series of events in cascade, leading to either the mitogen-activated protein (MAP) kinases/nuclear factor kappa B (NF-κB) or the janus kinase (JAK)/signal transducer and activator of transcription (STAT) transduction pathways in vascular-associated cells of the central nervous system (CNS). The brain blood vessels exhibit both constitutive and induced expression of receptors for different proinflammatory ligands that have the ability to stimulate these signaling molecules. Depending on the challenges and the cytokines involved, the transduction signal(s) solicited in cells of the BBB may orient the neuronal activity in a very specific manner in activating the transcription and production of soluble factors, such as prostaglandins (PGs). It is interesting to note that cytokines as well as systemic localized inflammation stimulate the cells of the BBB in a nonselective manner (i.e., within both large blood vessels and small capillaries across the brain). This nonselectivity raises several questions with regard to the localized neuronal activation induced by different experimental models of inflammation and cytokines. It is possible that the selectivity of the neuronal response is a consequence of the fine interaction between nonparenchymal synthesis of soluble mediators and expression of specific receptors for these ligands within parenchymal elements of different brain nuclei. This review will present the recent developments on this concept and the mechanisms that take place in cells of the BBB, which lead to the neuronal circuits involved in restoring the body's homeostasis during

systemic immunogenic challenges. The induction of fever, the hypothalamic-pituitary adrenal (HPA) axis, and other autonomic functions are among the physiological outcomes necessary for the protection of the mammalian organism in the presence of foreign material.] Rivest S, Lacroix S, et.al. *Proceedings of the Society for Experimental Biology and Medicine* 223:22-38 (2000). http://www.ebmonline.org/cgi/content/abstract/223/1/22

362. **Humoral immune responses in gingival crevice fluid: local and systemic implications. [ ]** Ebersole, JL. *Periodontology 2000. Volume 31 Issue 1 Page 135 - February 2003.* http://www.blackwell-synergy.com/doi/abs/10.1034/j.1600-0757.2003.03109.x?journalCode=prd
363. **Increased TLR2 and TLR4 Expression in Monocytes from Patients with Type 1 Diabetes: Further Evidence of a Pro-inflammatory state.** [Type 1 diabetes (T1DM) is associated with increased cardiovascular mortality. It is a pro-inflammatory state as evidenced by increased circulating biomarkers and monocyte activity. The toll-like receptors (TLRs) are pattern recognition receptors, expressed abundantly on monocytes. TLR2 and TLR4 are important in atherosclerosis. However, there is a paucity of data examining TLR2 and TLR4 expression in T1DM and examining its contribution to the pro-inflammatory state. Objective: Thus, we examined TLR2 and TLR4 expression in monocytes from T1DM patients compared to controls (n=31/group)….Conclusion: Thus, we make the novel observation that TLR2 and TLR4 expression and signaling are increased in T1DM and contribute to the pro-inflammatory state.] Devaraj S, Dasu MR, Jialal I, et al. *Online Journal of Clinical Endocrinology & Metabolism, Nov 20, 2007.* http://jcem.endojournals.org/cgi/content/abstract/jc.2007-2185v1?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=1&author1=Jialal&andorexacttitle=and&andorexacttitleabs=and&andorexactfulltext=and&searchid=1&FIRSTINDEX=0&sortspec=relevance&resourcetype=HWCIT
364. **Inflammation and C-reactive protein in cardiovascular disease.** (Article in Norwegian).[BACKGROUND: This article reviews the role of inflammation in development of atherosclerosis and associated complications and discusses use of the inflammatory marker - high-sensitivity C-reactive protein (hs-CRP) - in risk stratification. MATERIAL AND METHODS: The article is based on selected publications retrieved from a non-systematic search of PubMed and the authors' experience within the field. RESULTS: Both chronic inflammatory disease and acute infections are associated with an increased risk of cardiovascular events. Influenza vaccination reduces the risk of coronary ischaemic events in patients with coronary artery disease, but the effect on cardiovascular mortality is not documented. Hs-CRP is an independent predictor of cardiovascular events in populations with and without established cardiovascular disease. Treatment with Rosuvastatin led to decreased hs-CRP-levels and a reduced risk for cardiovascular events in subjects without known cardiovascular disease, with normal serum cholesterol and hs-CRP-levels above 2 mg/l. INTERPRETATION: Individuals with chronic inflammatory disease and those with high risk and acute infection are at risk for cardiovascular events and should be evaluated for primary prevention. In patient groups at moderate risk for cardiovascular disease, hs-CRP can be a valuable supplement to established factors for risk stratification. Despite numerous studies confirming hs-CRP's role as an independent risk marker, hs-CRP has not found its place in international guidelines. This should be reconsidered on the background of new study results.] Munk PS, Larsen AL. *Tidsskr Nor Laegeforen.* 2009 Jun 11;129(12):1221-4. http://www.ncbi.nlm.nih.gov/pubmed/19521445
365. **Inflammation and Factors That May Regulate Inflammatory Response.** [The concept of inflammation has a long history. Although an inflammatory response to injury or another trigger is necessary, chronic diseases, such as coronary heart disease and diabetes, may develop because of unchecked inflammatory responses that have maladapted over decades. For example, the earliest changes in atherosclerosis occur in the endothelium, leading to a cascade of inflammatory responses, such as accumulation of monocytes and T cells, migration of leukocytes into the intima, monocyte differentiation and proliferation, and lesion and fibrous cap development. Inflammatory markers, such as C-reactive protein, may allow clinical insight into these decades-long processes, adding value to predictive measures of disease outcomes. Anti-inflammatory factors, such as adiponectin, may provide further understanding of the inflammatory pathways involved. Greater understanding of the complex pathways involved in inflammation may provide alternative therapeutic strategies to combat inflammation and chronic diseases potentially arising from it.] Van Dyke TE, Kornman KS. *J Periodontol 2008;79:1503-1507.* http://www.joponline.org/doi/pdf/10.1902/jop.2008.080239
366. **Inflammation and Periodontal Diseases: A Reappraisal.** [A recent search (Google News) for media articles published on inflammation identified more than 9,000 stories in a 4-week period in 2008. … This interest by the media and public is being fueled by an explosion of scientific knowledge on inflammation and chronic diseases of aging. For example, a recent PubMed search for scientific publications on “inflammation” published within a 12-month period prior to May 1, 2008 returned >16,500 papers. During the same period, 161 papers were published on “periodontal disease” and “inflammation.” Recognition of the research advances and importance of inflammatory mechanisms in essentially all of the chronic diseases of aging, including periodontal diseases, led the American Academy of Periodontology to convene a conference on January 29 and 30, 2008 in Boston titled, “Inflammation and Periodontal Diseases: A Reappraisal.” This conference brought together opinion leaders in several major diseases and in the inflammatory mechanisms that seem to underlie and unify all of these diseases. Inflammation is now known to play a critical role in diseases that are not usually classified as inflammatory diseases, such as cardiovascular disease and Alzheimer's disease. Although this conclusion is the result of many years of research, much of the knowledge has crystallized into coherent concepts only very recently. The Boston conference brought together many of the people who have lead the new thinking relative to inflammation. Much of this new knowledge and the new concepts are captured in outstanding short overview papers in this supplement to the *Journal of Periodontology*.] Van Dyke TE. *Journal of Periodontology 2008, Vol. 79, No. 8s, Pages 1501-1502,* http://www.joponline.org/doi/full/10.1902/jop.2008.080279

367. **Inflammation Biomarkers and Near-Term Death in Older Men.** [Associations of C-reactive protein (CRP) and fibrinogen with death may weaken over time. Combining both markers may improve prediction of death in older adults. In 5,828 Cardiovascular Health Study participants (United States, 1989–2000), 383 deaths (183 cardiovascular disease (CVD)) in years 1–3 (early) and 914 deaths (396 CVD) in years 4–8 (late) occurred. For men, when comparing highest to lowest quartiles, hazard ratios for early death were 4.1 (95% confidence interval (CI): 2.7, 6.3) for CRP and 4.1 (95% CI: 2.7, 6.4) for fibrinogen in models adjusted for CVD risk. For early CVD death, hazard ratios were 4.3 (95% CI: 2.2, 8.4) and 3.4 (95% CI: 1.8, 6.3), respectively. When comparing men in the highest quartiles of both biomarkers with those in the lowest, hazard ratios were 9.6 (95% CI: 4.3, 21.1) for early death and 13.5 (95% CI: 3.2, 56.5) for early CVD death. Associations were weaker for late deaths. For women, CRP (hazard ratio = 2.3, 95% CI: 1.4, 3.9), but not fibrinogen (hazard ratio = 1.3, 95% CI: 0.8, 2.2), was associated with early death. Results were similar for CVD death. Neither was associated with late deaths. CRP and fibrinogen were more strongly associated with death in older men than women and more strongly associated with early than late death. Combining both markers may identify older men at greatest risk of near-term death.]. Jenny NS, Yanez ND, et al. American Journal of Epidemiology 2007 165(6):684-695.
http://aje.oxfordjournals.org/cgi/content/abstract/165/6/684

368. **Inflammation, Heart Disease and Stroke: The Role of C-Reactive Protein.** American Heart Association Review.
http://www.americanheart.org/presenter.jhtml?identifier=4648

369. **Inflammation: the link between insulin resistance, obesity and diabetes**. [Recent data have revealed that the plasma concentration of inflammatory mediators, such as tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6), is increased in the insulin resistant states of obesity and type 2 diabetes, raising questions about the mechanisms underlying inflammation in these two conditions. It is also intriguing that an increase in inflammatory mediators or indices predicts the future development of obesity and diabetes. Two mechanisms might be involved in the pathogenesis of inflammation. Firstly, glucose and macronutrient intake causes oxidative stress and inflammatory changes. Chronic overnutrition (obesity) might thus be a proinflammatory state with oxidative stress. Secondly, the increased concentrations of TNF-α and IL-6, associated with obesity and type 2 diabetes, might interfere with insulin action by suppressing insulin signal transduction. This might interfere with the anti-inflammatory effect of insulin, which in turn might promote inflammation.] Dandona P, Aljada A, Bandyopadhyay A. *Trends in Immunology*, Vol. 25, Issue 1, Jan 2004, P 4-7.
http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6W7H-49YH899-1&_user=10&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=f92755b6c587b8b7a67701c6d0579e0c

370. **Inflammatory biomarkers and risks of myocardial infarction, stroke, diabetes, and total mortality: implications for longevity.** [Inflammation is recognized as a major etiologic determinant of multiple disease states including myocardial infarction, stroke, diabetes, and metabolic syndrome, and individuals with elevated levels of the inflammatory biomarker high-sensitivity C-reactive protein (hsCRP) are at increased risk of mortality and morbidity from these conditions. Novel screening algorithms, such as the Reynolds Risk Score, that incorporate inflammation can greatly improve risk detection in primary prevention. In high-risk secondary prevention settings such as acute coronary syndrome patients being treated with statin therapy, achieving low levels of plasma hsCRP concentration appears to be of similar importance as achieving low levels of LDL cholesterol. Whether inflammation in general or CRP in particular are appropriate targets for therapy remains controversial and is under investigation. Several novel methods to reduce CRP have been proposed, including direct inhibitors as well as antisense technologies.] Ridker PM, *Nutr Rev*. 2007 Dec;65(12 Pt 2):S253-9.
http://www.ncbi.nlm.nih.gov/pubmed/18240558

371. **Inflammatory Protein CD36 the Link Between Gum and Heart Disease?** [Atherosclerosis associated with periodontal disease might be mediated by cellular inflammatory responses that involve the inflammatory protein CD36 and Toll-like receptors.] Febbraio M, et al. Arteriosclerosis, Thrombosis and Vascular Biology 2012 Scientific Sessions.
http://www.medscape.com/viewarticle/762746?src=emailthis

372. **Immunogenetic Susceptibility of Atherosclerotic Stroke; Implications on Current and Future Treatment of Vascular Inflammation.** [The understanding of the pathophysiology governing atherosclerosis supports a prominent role for inflammation pathways in plaque initiation and progression that result in stroke and myocardial infarction. Elevated levels of inflammatory markers in the blood, such as C-reactive protein and CD40 ligand/CD40, in concert with increased expression of adhesion molecules, chemokines, cytokines, matrix metalloproteinases (MMP), and inflammatory cells in the plaque, characterize the symptomatic atherothrombotic state.] Thomas J. DeGraba, MD *Stroke.* 2004;35:2712.
http://stroke.ahajournals.org/cgi/content/full/35/11_suppl_1/2712

373. **Inflammation Marker Predicts Colon Cancer. Feb. 4, 2004 *JAMA.*** [C-reactive protein, a marker of inflammation circulating in the blood already associated with increased risk of heart disease, can also be used to identify a person's risk of developing colon cancer, according to a Johns Hopkins study.]
http://www.hopkinsmedicine.org/Press_releases/2004/02_10_04.html

374. **Inflammatory markers and cardiovascular health in older adults.** [In the past decade inflammatory markers have emerged as strong independent risk indicators for cardiovascular disease. Even though adults over the age of 65 experience a high proportion of such events, most epidemiologic data are from middle-aged populations. In this review we examine the role that inflammatory markers play in the prediction of incident cardiovascular disease specifically in older adults. In studies of adults < 65 years, IL-6, TNFα and IL-10 levels have been shown to predict cardiovascular outcomes. The data on C-reactive protein are inconsistent, but CRP levels appear to be less useful in old-age than in middle-age. Fibrinogen levels

predict mortality but in a non-specific manner. In the elderly inflammatory markers are non-specific measures of health and predict both disability and mortality even in the absence of clinical cardiovascular disease. Thus it is possible that, in older age-groups, interventions designed to prevent cardiovascular disease through the modulation of inflamation would also be helpful in reducing disability and mortality.] Kritchevsky SB, Cesari M, et al. Cardiovascular Research 2005 66(2):265-275 http://cardiovascres.oxfordjournals.org/cgi/content/abstract/66/2/265

375. **Inhibition of activator protein-1 transcription factor activation by [omega]-3 fatty acid modulation of mitogen-activated protein kinase signaling kinases.** [Background: Lipopolysaccharide (LPS)-stimulated macrophages (M[Phi]) produce excess tumor necrosis factor (TNF), and the direct inhibition of I[kappa]B phosphorylation and its subsequent separation from the nuclear factor [kappa]B (NF[kappa]B)-I[kappa]B complex has been experimentally supported as a mechanism for [omega]-3 fatty acid (FA) inhibition of this TNF response. However, TNF production is a "late" event in the LPS-mduced M[Phi] inflammatory cascade, and in addition to NF[kappa]B-associated pathways, a separate transcription factor, activator protein-1 (AP-1) is an important pathway for M[Phi] proinflammatory cytokine production. The mitogen-activated protein kinase (MAPK) cascade regulates both NF[kappa]B-I[kappa]B-and AP-1-associated gene transcription through several cross-amplifying phosphorylation kinases, specifically p44/42 [ie, extracellular signal-regulated kinase (ERK) 1/2], p38, and c/jun N-terminal kinase (JNK)/stress-activated protein kinase (SAPK). The activation of these kinases occurs in the proximal MAPK cascade and activation modulates AP-1 activation. In this set of experiments, it was hypothesized that inhibition of MAPK signaling phosphorylation kinases by [omega]-3 fatty acids in a model of LPS-stimulated M[Phi]s would alter the activation of the proinflammatory cytokine transcription factor AP-1. …Conclusions: [omega]-3 FA inhibited p44/42 and JNK/SAPK phosphorylation; however, p38 remained unchanged. Phosphorylation of p44/42 and JNK/SAPK are the immediate prior steps in AP-1 activation. Attenuated AP-1 activation and subsequent attenuated gene-level proinflammatory cytokine elaboration is anticipated after inhibition of these MAPK intermediates and is confirmed by the reduction in AP-1 activity. These results provide further evidence for the transcriptional level regulation in the elaboration of proinflammatory cytokines by [omega]-3 FA in this M[Phi] model.] Babcock TA, Kurland A, et.al. *Journal of Parenteral and Enteral Nutrition 27:176-181, 2003.* *http://findarticles.com/p/articles/mi_qa3762/is_200305/ai_n9216984*

376. **Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies. IL6R Genetics Consortium Emerging Risk Factors Collaboration. [**Persistent inflammation has been proposed to contribute to various stages in the pathogenesis of cardiovascular disease. Interleukin-6 receptor (IL6R) signalling propagates downstream inflammation cascades. To assess whether this pathway is causally relevant to coronary heart disease, we studied a functional genetic variant known to affect IL6R signalling. METHODS: In a collaborative meta-analysis, we studied Asp358Ala (rs2228145) in IL6R in relation to a panel of conventional risk factors and inflammation biomarkers in 125,222 participants. We also compared the frequency of Asp358Ala in 51,441 patients with coronary heart disease and in 136,226 controls. To gain insight into possible mechanisms, we assessed Asp358Ala in relation to localised gene expression and to postlipopolysaccharide stimulation of interleukin 6. FINDINGS: The minor allele frequency of Asp358Ala was 39%. Asp358Ala was not associated with lipid concentrations, blood pressure, adiposity, dysglycaemia, or smoking (p value for association per minor allele ≥0·04 for each). By contrast, for every copy of 358Ala inherited, mean concentration of IL6R increased by 34·3% (95% CI 30·4-38·2) and of interleukin 6 by 14·6% (10·7-18·4), and mean concentration of C-reactive protein was reduced by 7·5% (5·9-9·1) and of fibrinogen by 1·0% (0·7-1·3). For every copy of 358Ala inherited, risk of coronary heart disease was reduced by 3·4% (1·8-5·0). Asp358Ala was not related to IL6R mRNA levels or interleukin-6 production in monocytes. INTERPRETATION: Large-scale human genetic and biomarker data are consistent with a causal association between IL6R-related pathways and coronary heart disease.**]** Sarwar N, Butterworth AS, et al. http://www.ncbi.nlm.nih.gov/pubmed/22421339

377. **Interleukin-6, C-Reactive Protein, and Mortality Risk.** [There is an increased risk of death associated with elevated levels of IL-6 and CRP in nondisabled older persons. These findings may broaden our understanding of the health correlates and consequences of low-level inflammation, as well as providing a new way to identify high-risk subgroups for anti-inflammatory interventions.] Harris TB, Ferrucci Luigi, et al., *Am J Med. 1999;106:506-512.* http://dceg.cancer.gov/pdfs/harris1065061999.pdf

378. **Interleukin-12 and interleukin-16 in periodontal disease.** [The immune system plays an important role in the pathological process of periodontitis. Interleukin-12 (IL-12) is produced by monocytes, macrophages and neutrophils. These cells are proinflammatory infiltrates in periodontitis tissues. High IL-12 will contribute to the immune reaction to Th1 type. IL-12 is an inducer of INF-r production. IFN-gamma itself can also activate IL-12 production. Lipopolysaccharides (LPS) of periodontopathogens are also activators of IL-12. Interleukin-16 (IL-16) can cause the high affinity of IL-2 receptors on CD4+ cells and is chemotaxis to Th1 cells and CD4+ T cells. IL-16 can stimulate monocytes to produce proinflammatory cytokines and is highly associated with inflammation including arthritis, enteritis and allergic rhinitis. However, the information on IL-12 and IL-16 in periodontitis is not clear. In this study, 105 GCF samples were collected from 19 periodontal disease patients and 6 healthy ones. The clinical periodontal indices, the habits of cigarette smoking and alcohol drinking were recorded. ELISA was used to determine the levels of IL-12 and IL16 in the GCF. In the non-smoking/non-alcohol-drinking individuals: (1) the total amount of IL-12 (but not IL-16) was significantly higher in chronic periodontitis (CP) sites than gingivitis (G) or healthy (H) sites; (2) the diseased sites (CP + G) had a significantly higher total amount of IL-12 (but not IL-16) than the H sites. Among CP sites, both the concentration and total amount of IL-16 (but not IL-12) were significantly higher in alcohol drinkers/cigarette smokers as compared to the non-drinkers/non-smokers. CP sites of the

drinkers/smokers also had significantly deeper probing pocket depth than sites of those without these two habits. IL-12 and IL-16 may be related to the pathogenesis of periodontal disease, but within the periodontitis sites, IL-16 may be related to disease severity in alcohol drinkers/smokers.] Tsai IS, Tsai CC, et al. *Cytokine*. 2005 Jul 7;31(1):34-40. http://www.ncbi.nlm.nih.gov/pubmed/15886011

379. **Intracytoplasmic enzymes in gingival crevicular fluid of patients with aggressive periodontitis. [**Biochemical parameters of crevicular fluid could provide evidence of periodontal tissue disease. The aim of this study was to analyze enzymes in crevicular fluid in aggressive localized and generalized periodontitis. MATERIAL AND METHODS: One hundred and twenty-four subjects were classified as having localized (n = 36) or generalized aggressive periodontitis (n = 38) and subclassified into moderate and severe groups. Controls were 50 periodontitis-free subjects. Activities of the enzymes lactate dehydrogenase, neutrophil elastase, alkaline phosphatase and aspartate aminotransferase were determined. Data were analyzed using one-way ANOVA and Tukey's test. RESULTS: Among the subjects with localized aggressive periodontitis, values of lactate dehydrogenase and alkaline phosphatase increased notably in moderate and severe periodontitis compared with control subjects. Values for aspartate aminotransferase increased with the severity of the disease, and neutrophil elastase was increased in the moderate and severe states. In generalized aggressive periodontitis, lactate dehydrogenase showed higher values than in control subjects in both periodontal subgroups. Alkaline phosphatase and neutrophil elastase showed higher significant differences between moderate and severe periodontitis compared with the control group. Aspartate aminotransferase showed differences between the severe and moderate periodontitis groups compared with the control group. Of all the enzymes analyzed, only lactate dehydrogenase showed higher values in localized than in generalized aggressive periodontitis. CONCLUSION: Lactate dehydrogenase may distinguish localized and generalized aggressive periodontitis. Alkaline phosphatase increases from moderate to severe states in both types of periodontitis. Aspartate aminotransferase and neutrophil elastase only increase with strong evidence of periodontal destruction.] Castro CE, Koss MA, et al. *J Periodontal Res*. 2011 Oct;46(5):522-7. doi: 10.1111/j.1600-0765.2011.01367.x. Epub 2011 Apr 13. http://www.ncbi.nlm.nih.gov/pubmed/21488876

380. **Joint Effects of C-Reactive Protein and Glycated Hemoglobin in Predicting Future Cardiovascular Events of Patients With Advanced Atherosclerosis.** [C-reactive protein (CRP) and glycohemoglobin (HbA1c) are established risk factors for the development of cardiovascular disease. Inflammation, indicated by hs-CRP, and hyperglycemia, indicated by HbA1c, jointly contribute to the cardiovascular risk of patients with advanced atherosclerosis. Patients with both hs-CRP and HbA1c in the upper quartiles (>0.44 mg/dL and >6.2%, respectively) are at particularly high risk for poor cardiovascular outcome.] Schillinger et al, *Circulation*. 2003;108:2323. http://circ.ahajournals.org/cgi/content/abstract/108/19/2323

381. **Levels of soluble cytokine factors in temporomandibular joint effusions seen on magnetic resonance images.** [OBJECTIVE: To elucidate the correlations between joint effusion (JE) on T2-weighted magnetic resonance images (MRI) of the temporomandibular joint (TMJ) and the levels of various cytokine receptors, cytokine antagonists, and protein in the synovial fluid of patients with temporomandibular joint disorders (TMD). STUDY DESIGN: Fifty-five TMJs of 55 patients with TMD were scanned by MRI, and synovial fluid samples were obtained on the same day. The grade of JE was evaluated on a scale of 0 to 3: Grades 0 and 1 indicated absence, and grades 2 and 3 indicated the presence of JE. Correlations were evaluated between JE and the concentrations of soluble tumor necrosis factor receptors I and II (sTNFR-I and sTNFR-II, respectively), IL-6 soluble receptor (IL-6sR), IL-1 soluble receptor type II, and IL-1 receptor antagonist and protein in the synovial fluid of patients with TMD. RESULTS: The concentrations of sTNFR-I and protein in the group with JE (18 joints) were significantly higher than in the group without JE (37 joints). In addition, there were significant positive correlations between the grade of JE and the levels of sTNFR-I, sTNFR-II, and protein. CONCLUSIONS: sTNFRs and protein may play important roles in the pathogenesis of TMD. These mediators seem to influence the expression of JE, which may reflect synovial inflammation of the TMJ.] Kaneyama K, Segami N, et.al. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005 Apr;99(4):411-8.* http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=15772591&dopt=Citation

382. **Lipopolysaccharide and interleukin 1 augment the effects of hypoxia and inflammation in human pulmonary arterial tissue. [**The combined effects of hypoxia and interleukin 1, lipopolysaccharide, or tumor necrosis factor alpha on the expression of genes encoding endothelial constitutive and inducible nitric oxide synthases, endothelin 1, interleukin 6, and interleukin 8 were investigated in human primary pulmonary endothelial cells and whole pulmonary artery organoid cultures. Hypoxia decreased the expression of constitutive endothelial nitric oxide synthase (NOS-3) mRNA and NOS-3 protein as compared with normoxic conditions. The inhibition of expression of NOS-3 corresponded with a reduced production of NO. A combination of hypoxia with bacterial lipopolysaccharide, interleukin 1 beta, or tumor necrosis factor alpha augmented both effects. In contrast, the combination of hypoxia and the inflammatory mediators superinduced the expression of endothelin 1, interleukin 6, and interleukin 8. Here, we have shown that inflammatory mediators aggravate the effect of hypoxia on the down-regulation of NOS-3 and increase the expression of proinflammatory cytokines in human pulmonary endothelial cells and whole pulmonary artery organoid cultures.] Ziesche R, Petkov V, et al. *Proc Natl Acad Sci U S A. 1996 Oct 29;93(22):12478-83.* http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8901607&dopt=Abstract

383. **Lipoprotein-associated phospholipase A2 and serum lipid levels in subjects with chronic periodontitis and hyperlipidemia.** [OBJECTIVE: To evaluate the relationships between clinical periodontal parameters and levels of lipoprotein-associated phospholipase A2 (Lp-PLA2) and lipid profile markers in subjects with or without hyperlipidaemia. METHODS: Forty chronic periodontitis (CP) subjects with hyperlipidaemia (CP/HPL group), 40 systemically healthy CP

subjects (CP group) and 20 systemically and periodontally healthy subjects (control group) were enrolled. The clinical periodontal parameters, the serum concentrations of Lp-PLA2, lipid profiles including total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c) and white blood cell (WBC) counts were determined and compared between different groups. Linear regression analysis was performed to identify the contributing factors of Lp-PLA2. RESULTS: Serum Lp-PLA2 level in the CP/HPL group and the CP group was significantly higher than in the healthy group. TC and TG levels in the CP/HPL group were higher than in the CP and control groups. No difference was observed for levels HDL-c and LDL-c and WBC counts among the groups. Linear regression analysis showed that the serum level of Lp-PLA2 was positively associated with bleeding on probing and WBC counts. CONCLUSION: Elevated level of Lp-PLA2 is associated with periodontal inflammation, indicating that periodontal treatment could reduce the risk of cardiovascular disease in CP subjects with hyperlipidaemia.] Zhou SY, Xiao Wm, et al. Chin J Dent Res. 2012;15(1):25-9. **http://www.ncbi.nlm.nih.gov/pubmed/22866279**

384. **Local Complement-Targeted Intervention in Periodontitis: Proof-of-Concept Using a C5a Receptor (CD88) Antagonist.** [When excessively activated or deregulated, complement becomes a major link between infection and inflammatory pathology including periodontitis. This oral inflammatory disease is associated with a dysbiotic microbiota, leads to the destruction of bone and other tooth-supporting structures, and exerts an adverse impact on systemic health. We have previously shown that mice deficient either in complement C5a receptor (C5aR; CD88) or TLR2 are highly and similarly resistant to periodontitis, suggesting that a cross-talk between the two receptors may be involved in the disease process. In this paper, we show that C5aR and TLR2 indeed synergize for maximal inflammatory responses in the periodontal tissue and uncover a novel pharmacological target to abrogate periodontitis. Using two different mouse models of periodontitis, we show that local treatments with a C5aR antagonist inhibited periodontal inflammation through downregulation of TNF, IL-1β, IL-6, and IL-17 and further protected against bone loss, regardless of the presence of TLR2. These findings not only reveal a crucial cooperation between C5aR and TLR2 in periodontal inflammation but also provide proof-of-concept for local targeting of C5aR as a powerful candidate for the treatment of human periodontitis.] Abe T, Hosur KB, et al. The Journal of Immunology, December 1, 2012vol. 189 no. 11 5442-5448. **http://www.jimmunol.org/content/189/11/5442.abstract?sid=05a73e77-e07a-4df1-b08f-0c3df56911f2**

385. **Low-Grade Inflammation, Obesity, and Insulin Resistance in Adolescents.** [Low-grade inflammation is associated with insulin resistance and precedes the onset of type 2 diabetes mellitus in adults, but there are no comparable data in youth. The objective of the study was to characterize the pattern of subclinical immune activation that is associated with indices of obesity and insulin resistance in youth and analyze whether this association is explained by obesity. Conclusions: We found that a differential low-grade immune activation is associated with parameters of obesity in adolescents. Moreover, there is evidence that IL-6, IL-18, IP-10, and adiponectin (inversely) are associated with insulin resistance and that these associations can mainly be attributed to obesity.] Herder C, Schneitler S, et al. Journal of Clinical Endocrinology & Metabolism, Vol. 92, No. 12 4569-4574. http://jcem.endojournals.org/cgi/content/abstract/92/12/4569

386. **Low-Grade Systemic Inflammation and the Development of Type 2 Diabetes.** [To examine the association of low-grade systemic inflammation with diabetes, as well as its heterogeneity across subgroups, we designed a case-cohort study representing the ~9-year experience of 10,275 Atherosclerosis Risk in Communities Study participants. … In conclusion, a low-grade inflammation predicts incident type 2 diabetes.] Duncan BB, Schmidt MI, et al. *Diabetes* 52:1799-1805, 2003. http://diabetes.diabetesjournals.org/cgi/content/full/52/7/1799

387. **Major surface protein complex of Treponema denticola induces the production of tumor necrosis factor alpha, interleukin-1beta, interleukin-6 and matrix metalloproteinase 9 by primary human peripheral blood monocytes.** [Gaibani P, Caroli F, Nucci C, Sambri V. Major surface protein complex of Treponema denticola induces the production of tumor necrosis factor alpha, interleukin-1beta, interleukin-6 and matrix metalloproteinase 9by primary human peripheral blood monocytes. Background and Objective: Treponema denticola is a micro-organism that is involved in the pathogenesis of periodontitis. Major surface protein complex (MSPc), which is expressed on the envelope of this treponeme, plays a key role in the interaction between T. denticola and gingival cells. The peptidoglycan extracted from T. denticola induces the production of a large variety of inflammatory mediators by macrophage-like cells, suggesting that individual components of T. denticola cells induce the inflammatory response during periodontal disease. This study was designed to demonstrate that MSPc of T. denticola stimulates release of proinflammatory mediators in primary human monocytes. Material and Methods: Primary human monocytes were separated from the blood of healthy donors and incubated for up to 24 h with varying concentrations of MSPc. The production of tumor necrosis factor alpha (TNF-alpha), interleukin-1beta (IL-1beta), interleukin-6 (IL-6) and matrix metalloproteinase 9 (MMP-9) was measured at different time points with commercially available enzyme-linked immunosorbent assays. Results: T. denticola MSPc induced the synthesis of TNF-alpha, IL-1beta, IL-6 and MMP-9 in a dose- and time-dependent manner. Similar patterns of TNF-alpha, IL-1beta and IL-6 release were observed when cells were stimulated with 100 and 1000 ng/mL of MSPc. The production of MMP-9 was significant only when cells were treated with 1000 ng/mL of MSPc. Conclusion: These results indicate that T. denticola MSPc, at concentrations ranging from 100 ng/mL to 1.0 mug/mL, activates a proinflammatory response in primary human monocytes.] Gaibani P, Caroli F, et al. *J Periodontal Res*. 2010 Mar 9. http://www.ncbi.nlm.nih.gov/pubmed/20337896

388. **Matrix Metalloproteinases.** [The timely breakdown of extracellular matrix (ECM)[1] is essential for embryonic development, morphogenesis, reproduction, and tissue resorption and remodeling. The matrix metalloproteinases (MMPs), also called matrixins, are thought to play a central role in these processes. The expression of most matrixins is transcriptionally regulated by growth factors, hormones, cytokines, and cellular transformation. The proteolytic activities of MMPs are precisely

controlled during activation from their precursors and inhibition by endogenous inhibitors, α-macroglobulins, and tissue inhibitors of metalloproteinases (TIMPs)…. Matrixins participate in many normal biological processes (*e.g.* embryonic development, blastocyst implantation, organ morphogenesis, nerve growth, ovulation, cervical dilatation, postpartum uterine involution, endometrial cycling, hair follicle cycling, bone remodeling, wound healing, angiogenesis, apoptosis, etc.) and pathological processes (*e.g.* arthritis, cancer, cardiovascular disease, nephritis, neurological disease, breakdown of blood brain barrier, periodontal disease, skin ulceration, gastric ulcer, corneal ulceration, liver fibrosis, emphysema, fibrotic lung disease, etc.)]Nagase H, Woessner Jr, JF. *J Biol Chem*, vol. 274, Issue 31, 21491-21494, July 20, 1999. http://www.jbc.org/cgi/content/short/274/31/21491

389. **Markers of Inflammation and Cardiovascular Disease. Application to Clinical and Public Health Practice: A Statement for Healthcare Professionals From the Centers for Disease Control and Prevention and the American Heart Association** [This working group sought to translate the rapidly growing body of evidence for inflammation as a key process in atherosclerosis into clinical and public health practice. Basic science and epidemiological studies have developed an impressive case that atherogenesis is essentially an inflammatory response to a variety of risk factors and the consequences of this response lead to the development of acute coronary and cerebrovascular syndromes. Although several cytokines, acute-phase reactants, and cellular responses to inflammatory stimuli potentially might be predictive of clinical disease, the laboratory tests to assess inflammation are limited to those that are employable in clinical settings, have commercially available assays that can be standardized, and have adequate precision. On the basis of these considerations, it is most reasonable to limit current assays of inflammatory markers to hs-CRP, measured twice, either fasting or nonfasting, with the average expressed in mg/L, in metabolically stable patients….In patients with stable coronary disease or acute coronary syndromes, hs-CRP measurement may be useful as an independent marker for assessing likelihood of recurrent events, including death, myocardial infarction, or restenosis after percutaneous coronary intervention.] Pearson TA, Mensah GA, et al. Circulation 2003;107:409) http://circ.ahajournals.org/cgi/content/full/107/3/499
390. **Microbial Hijacking of Complement–Toll-Like Receptor Crosstalk**. [Crosstalk between complement and Toll-like receptors (TLRs) coordinates innate immunity. We report a previously unknown immune subversion mechanism involving microbial exploitation of communication between complement and TLRs. *Porphyromonas gingivalis*, a major oral and systemic pathogen with complement C5 convertase–like activity, synergizes with C5a (fragment of complement protein C5) to increase cyclic adenosine monophosphate (cAMP) concentrations, resulting in suppression of macrophage immune function and enhanced pathogen survival in vitro and in vivo. This synergy required TLR2 signaling, a pertussis toxin– and thapsigargin-sensitive C5a receptor pathway, with protein kinase A and glycogen synthase kinase-3β as downstream effectors. Antagonistic blockade of the C5a receptor abrogated this evasive strategy and may thus have important therapeutic implications for periodontitis and atherosclerosis, diseases in which *P. gingivalis* is implicated. This first demonstration of complement-TLR crosstalk for immunosuppressive cAMP signaling indicates that pathogens may not simply undermine complement or TLRs (or both) as separate entities, but may also exploit their crosstalk pathways.] Wang M, Krauss JL, et al. *Sci. Signal.*, 16 February 2010 Vol. **3**, Issue 109, p. ra11 http://stke.sciencemag.org/cgi/content/abstract/sigtrans;3/109/ra11
391. **National Academy of** Clinical **Bio**chemistry **Laboratory Medicine Practice Guidelines: Emerging Biomarkers for Primary Prevention of Cardiovascular Disease.** [Background: Heart disease and stroke continue to be the leading causes of death in the US. As a result, investigators continue to look for new and emerging biomarkers of disease risk. Because many of these emerging biomarkers are not as well documented as those of conventional lipid and lipoprotein risk factors, their value in clinical practice needs to be critically appraised and appropriate guidelines developed for their proposed use. Content: The National Academy of Clinical Biochemistry (NACB) convened a multidisciplinary expert panel to develop laboratory medicine practice guidelines for a selected subset of these emerging risk factors as applied in a primary prevention setting of heart disease and stroke. The NACB expert panel selected lipoprotein subclasses and particle concentration, lipoprotein(a), apolipoproteins A-I and B, high sensitivity C-reactive protein (hsCRP), fibrinogen, white blood cell count, homocysteine, B-type natriuretic peptide (BNP), N-terminal proBNP (NT-proBNP), and markers of renal function as biomarkers that fell within the scope of these guidelines. Conclusions: Based on a thorough review of the published literature, only hsCRP met all of the stated criteria required for acceptance as a biomarker for risk assessment in primary prevention.] Myers GL, Christenson RHM, et al. *Clinical Chemistry* 55:378-384, 2009. http://www.clinchem.org/cgi/content/abstract/55/2/378.
392. **New Markers of Inflammation and Endothelial Cell Activation.** [Current views regard atherosclerosis as a dynamic and progressive disease arising from the combination of endothelial dysfunction and inflammation.[1–6] The vascular endothelium, located at the interface of blood and tissue, is able to sense changes in hemodynamic forces and bloodborne signals and react by synthesizing and releasing vasoactive substances. Vascular homeostasis is maintained by a balance between endothelium-derived relaxing and contracting factors. With disruption of this balance, mediated by inflammatory and traditional cardiovascular risk factors, the vasculature becomes susceptible to atheroma formation. Inflammatory mediators appear to play a fundamental role in the initiation, progression, and eventual rupture of atherosclerotic plaques. As evidence accumulates linking inflammatory processes to atherogenesis, markers of inflammation and endothelial activation may become useful by providing additional information about a patient's risk of developing cardiovascular disease, as well as providing new targets for treatment.[7,8] This review article is the first part of a two-article series examining emerging markers of inflammation and cardiovascular disease. Part 1 will provide a brief overview of the link between inflammation, endothelial dysfunction, and atherosclerosis and will begin highlighting emerging inflammatory mediators of endothelial cell (EC) activation, a discussion that will be continued in Part 2.] Szmitko PE, Wang CH, et al. *Circulation.* 2003;108:1917

http://circ.ahajournals.org/cgi/content/full/108/16/1917?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=wang&searchid=1&FIRSTINDEX=0&resourcetype=HWCIT

393. **New research finds link between gum disease, acute heart attacks.** [Heart attack survivors who suffer advanced gum disease show significantly higher levels of a protein in their blood called C-reactive protein (CRP) than such patients without gum disease, new University of North Carolina at Chapel Hill research indicates.] UNC News Service. http://www.unc.edu/news/archives/nov00/deliar111300.htm
394. **Neutrophil migration during endotoxemia.** [Endotoxemia is marked by a global activation of inflammatory responses, which can lead to shock, multiple organ failure, and the suppression of immune and wound healing processes. Neutrophils (PMNs) play a central role in some of these responses by accumulating in tissues and releasing reactive oxygen species and proteases that injure host structures. This review focuses on altered PMN migratory responses that occur during endotoxemia and their consequences in the development of pulmonary infection. The inflammatory mediators that might be responsible for these altered responses are discussed. The oxidant potential of PMNs is increased after exposure to endotoxin both in vitro and during clinical and experimental endotoxemia. However, other functions such as chemotaxis and phagocytosis are often depressed in these same cells. Endotoxin exposure renders PMNs hyperadhesive to endothelium. The sum of these effects produces activated inflammatory cells that are incapable of leaving the vasculature. As such, the endotoxic PMN is more likely to promote tissue injury from within microvascular beds than to clear pathogens from extravascular sites. Moreover, the functional characteristics of endotoxic PMNs are similar to those observed during trauma, burn injury, sepsis, surgery, and other inflammatory conditions. Accordingly, several clinical conditions might have a common effector in the activated, yet migratorially dysfunctional, PMN. Direct effects of endotoxin on PMNs as well as effects of endogenous mediators released during endotoxemia are discussed. Understanding PMN behavior during endotoxemia may provide basic and critical insights that can be applied to a number of inflammatory scenarios.] Wagner JG, Roth RA. *J Leukoc Biol.* 1999 Jul;66(1):10-24 http://www.ncbi.nlm.nih.gov/pubmed/10410985
395. **Nitric oxide and oxidative stress in vascular disease. [**Endothelium-derived nitric oxide (NO) is a paracrine factor that controls vascular tone, inhibits platelet function, prevents adhesion of leukocytes, and reduces proliferation of the intima. An enhanced inactivation and/or reduced synthesis of NO is seen in conjunction with risk factors for cardiovascular disease. This condition, referred to as endothelial dysfunction, can promote vasospasm, thrombosis, vascular inflammation, and proliferation of vascular smooth muscle cells. Vascular oxidative stress with an increased production of reactive oxygen species (ROS) contributes to mechanisms of vascular dysfunction. Oxidative stress is mainly caused by an imbalance between the activity of endogenous pro-oxidative enzymes (such as NADPH oxidase, xanthine oxidase, or the mitochondrial respiratory chain) and anti-oxidative enzymes (such as superoxide dismutase, glutathione peroxidase, heme oxygenase, thioredoxin peroxidase/peroxiredoxin, catalase, and paraoxonase) in favor of the former. Also, small molecular weight antioxidants may play a role in the defense against oxidative stress. Increased ROS concentrations reduce the amount of bioactive NO by chemical inactivation to form toxic peroxynitrite. Peroxynitrite-in turn-can "uncouple" endothelial NO synthase to become a dysfunctional superoxide-generating enzyme that contributes to vascular oxidative stress. Oxidative stress and endothelial dysfunction can promote atherogenesis. Therapeutically, drugs in clinical use such as ACE inhibitors, AT(1) receptor blockers, and statins have pleiotropic actions that can improve endothelial function. Also, dietary polyphenolic antioxidants can reduce oxidative stress, whereas clinical trials with antioxidant vitamins C and E failed to show an improved cardiovascular outcome.] Forstermann U. *Pflugers Arch.* 2010 May;459(6):923-39. Epub 2010 Mar 21. http://www.ncbi.nlm.nih.gov/pubmed/20306272
396. **Non–HDL Cholesterol, Apolipoproteins A-I and B_{100}, Standard Lipid Measures, Lipid Ratios, and CRP as Risk Factors for Cardiovascular Disease in Women. [**Current guidelines for cardiovascular risk detection are controversial with regard to the clinical utility of different lipid measures, non–high-density lipoprotein cholesterol (non–HDL-C), lipid ratios, apolipoproteins, and C-reactive protein (CRP). Non–HDL-C and the ratio of total cholesterol to HDL-C were as good as or better than apolipoprotein fractions in the prediction of future cardiovascular events. After adjustment for age, blood pressure, smoking, diabetes, and obesity, high-sensitivity CRP added prognostic information beyond that conveyed by all lipid measures.] Ridker P, Rafai N, et.al. *JAMA.* 2005;294:326-333. http://jama.ama-assn.org/cgi/content/abstract/294/3/326
397. **Oral treatment with complement factor C5a receptor (CD88) antagonists inhibits experimental periodontitis in rats**. **[**The complement activation product 5a (C5a) is a potent mediator of the innate immune response to infection, and may thus also importantly determine the development of periodontitis. The present study was designed to explore the effect of several novel, potent and orally active C5a receptor (CD88) antagonists (C5aRAs) on the development of ligature-induced periodontitis in an animal model. MATERIAL AND METHODS: Three different cyclic peptide C5aRAs, termed PMX205, PMX218 and PMX273, were investigated. Four groups of Wistar rats (n = 10 in each group) were used. Starting 3 d before induction of experimental periodontitis, rats either received one of the C5aRas (1-2 mg/kg) in the drinking water or received drinking water only. Periodontitis was assessed when the ligatures had been in place for 14 d. RESULTS: Compared with control rats, PMX205- and PMX218-treated rats had significantly reduced periodontal bone loss. CONCLUSION: The findings suggest that complement activation, and particularly C5a generation, may play a significant role in the development and progression of periodontitis. Blockade of the major C5a receptor, CD88, with specific inhibitors such as PMX205, may offer novel treatment options for periodontitis.] Breivik T, Gundersen Y, et al. *J Periodontal Res.* 2011 Dec;46(6):643-7. doi: 10.1111/j.1600-0765.2011.01383.x. Epub 2011 Jul 3. http://www.ncbi.nlm.nih.gov/pubmed/21722134
398. **Pathogen Recognition and Inflammatory Signaling in Innate Immune Defenses.** [Summary: The innate immune system constitutes the first line of defense against invading microbial pathogens and relies on a large family of pattern recognition

receptors (PRRs), which detect distinct evolutionarily conserved structures on pathogens, termed pathogen-associated molecular patterns (PAMPs). Among the PRRs, the Toll-like receptors have been studied most extensively. Upon PAMP engagement, PRRs trigger intracellular signaling cascades ultimately culminating in the expression of a variety of proinflammatory molecules, which together orchestrate the early host response to infection, and also is a prerequisite for the subsequent activation and shaping of adaptive immunity. In order to avoid immunopathology, this system is tightly regulated by a number of endogenous molecules that limit the magnitude and duration of the inflammatory response. Moreover, pathogenic microbes have developed sophisticated molecular strategies to subvert host defenses by interfering with molecules involved in inflammatory signaling. This review presents current knowledge on pathogen recognition through different families of PRRs and the increasingly complex signaling pathways responsible for activation of an inflammatory and antimicrobial response. Moreover, medical implications are discussed, including the role of PRRs in primary immunodeficiencies and in the pathogenesis of infectious and autoimmune diseases, as well as the possibilities for translation into clinical and therapeutic applications.] Mogensen TH. Clin Microbiol Rev. 2009 April; 22(2): 240–273. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2668232/

399. **Patterns of chemokines and chemokine receptors expression in different forms of human periodontal disease.** [Current knowledge states that periodontal diseases are chronic inflammatory reactions raised in response to periodontopathogens. Many cell types and mediators, including Th1 and Th2 lymphocytes, cytokines and chemokines, appear to be involved in the immunopathogenesis of periodontal diseases. Chemokines, a family of chemotactic cytokines, bind to specific receptors and selectively attract different cell subsets to the inflammatory site. They can also interact with classical cytokines and modulate the local immune response. Chronic periodontitis patients exhibited a more frequent and higher expression of monocyte chemoattractant protein-1 (MCP-1) and its receptor CCR4, and higher expression of IL-10. It is possible that chemokines, in addition to the classical cytokines, are involved in the immunopathogenesis of periodontal disease, driving the migration and the maintenance of several inflammatory cell types such as polymorphonuclear leukocytes, dendritic cells (DCs) , natural killer cells, macrophages, and subsets of lymphocytes in the gingival tissues. These cells are thought to participate in the inflammatory and immune reaction that takes place in periodontal disease, killing pathogens, presenting antigens, and producing cytokines. The selective recruitment of polarized lymphocyte subsets could result in differential cytokine production at the site of response, which is supposed to determine the stable or progressive nature of the lesion. Besides, the role of chemokines as activators and chemoattracts of osteclasts may be involved in the determination of disease severity.] Garlet G.P, Martins W. et al., *Journal of Periodontal Research, Volume 38, Number 2, April 2003, pp. 210-217(8).* http://www.ingentaconnect.com/content/mksg/per/2003/00000038/00000002/art00015
400. **Periodontal Disease, C-Reactive Protein and Overall Health.** [CRP levels are predictive of heart disease, and as a predictor for heart disease, is superior to and independent of cholesterol.] http://www.perio.org/consumer/happy-heart.htm
401. **Periodontal therapy lowers levels of heart disease inflammation markers.** [Treating periodontal disease with scaling and root planing combined with a topical antibiotic gel can significantly lower the levels of two inflammatory proteins associated with a heightened risk of heart disease.] Grossi S. ADA News Release. http://www.ada.org/prof/resources/pubs/adanews/adanewsarticle.asp?articleid=841
402. **Periodontal Treatment Reduces CRP and TNF-a**. [Periodontal treatment is effective in reducing CRP and TNF-α value, mechanisms independent of adiponectin. Thus, the results indicate that periodontal inflammation up-regulate CRP and TNF-α, although still for the most part in the healty reference range. Elevated level of CRP and TNF-α might be associated with increased risk for future development of atherosclerosis in periodontal patients.] Iwamoto Y, Nishimura, F, et al., Okayama University Graduate School of Medicine and Dentistry, Japan. http://iadr.confex.com/iadr/2003Goteborg/techprogram/abstract_30513.htm
403. **Population Distributions of C-reactive Protein in Apparently Healthy Men and Women in the United States: Implication for Clinical Interpretation**. [Measurement of the acute-phase reactant C-reactive protein (CRP) has been used historically in the diagnosis and monitoring of active infection or inflammation. Recent prospective epidemiologic studies have demonstrated that CRP, at concentrations within the reference interval, is a strong predictor of myocardial infarction stroke, sudden cardiac death, and peripheral arterial disease in apparently healthy adults.] Nader Rifai1,2,a and Paul M. Ridker2,3. *Clinical Chemistry*. 2003;49:666-669.) http://www.clinchem.org/cgi/content/full/49/4/666
404. **Porphyromonas gingivalis mediated periodontal disease and atherosclerosis: disparate diseases with commonalities in pathogenesis through TLRs.** [ll-like receptors (TLRs) are a group of pathogen-associated molecular pattern receptors, which play an important role in innate immune signaling in response to microbial infection. It has been demonstrated that TLRs are differentially up regulated in response to microbial infection and chronic inflammatory diseases such as atherosclerosis. Furthermore hyperlipidemic mice deficient in TLR2, TLR4, and MyD88 signaling exhibit diminished inflammatory responses and decreased atherosclerosis. Accumulating evidence has implicated specific infectious agents including the periodontal disease pathogen Porphyromonas gingivalis in the progression of atherosclerosis. Evidence in humans suggesting that periodontal infection predisposes to atherosclerosis is derived from studies demonstrating that the periodontal pathogen P. gingivalis resides in the wall of atherosclerotic vessels and seroepidemiological studies demonstrating an association between pathogen-specific IgG antibodies and atherosclerosis. We have established that the inflammatory signaling pathways that P. gingivalis utilizes is dependent on the cell type and this specificity clearly influences innate immune signaling in the context of local and distant chronic inflammation induced by this pathogen. We have demonstrated that P. gingivalis requires TLR2 to induce oral inflammatory bone lose in mice. Furthermore, we have demonstrated that P. gingivalis infection accelerates atherosclerosis in hyperlipidemic mice with an associated increase in

expression of TLR2 and TLR4 in atherosclerotic lesions. Our recent work with P. gingivalis has demonstrated the effectiveness of specific intervention strategies (immunization) in the prevention of pathogen-accelerated atherosclerosis. Improved understanding of the mechanisms driving infection, and chronic inflammation during atherosclerosis may ultimately provide new targets for therapy.] Gibson FC, et al. *Curr Pharm Des.* 2007;13(36):3665-75. http://www.ncbi.nlm.nih.gov/pubmed/18220804

405. **Production of interleukin-1 and tumor necrosis factor by human peripheral monocytes activated by periodontal bacteria and extracted lipopolysaccharides.** [Whole Gram-negative bacteria associated with juvenile and adult periodontitis, and their respective extracted lipopolysaccharides (LPS), were tested for the ability to activate quiescent human peripheral blood monocytes. Results indicate that monocytes are activated by free LPS or LPS bound to Gram-negative pathogenic periodontal bacteria to produce monokines which may contribute to the destruction of periodontal bone.] R. A. Lindemann, J. S. Economou., Journal of Dental Research, Vol 67, 1131-1135. http://jdr.iadrjournals.org/cgi/content/abstract/67/8/1131
406. **Profiling the Cytokines in Gingival Crevicular Fluid Using a Cytokine Antibody Array.** [In this study, we detected several cytokines in GCF using a cytokine antibody array system, including both inflammatory cytokines and various growth factors. Therefore, periodontal disease may participate in the wound healing process and in tissue destruction via the inflammatory process.] Sakai A, Ohshima M, et. al., Journal of Periodontology 2006.050340. http://www.joponline.org/doi/abs/10.1902/jop.2006.050340
407. **Proinflammatory cytokines detectable in synovial fluids from patients with temporomandibular disorders.** [OBJECTIVE: To measure the levels of the proinflammatory cytokines, interleukin (IL)-1 beta, IL-6, tumor necrosis factor- (TNF) alpha, IL-8, and interferon- (IFN) gamma in synovial fluid samples taken from patients with temporomandibular disorders (TMD). STUDY DESIGN: We studied 6 asymptomatic volunteers and 51 patients with TMD. The IL-1 beta, IL-6, TNF-alpha, IL-8, and IFN-gamma levels in temporomandibular joint synovial fluid were measured using enzyme-linked immunosorbent assay. RESULTS: Measurable level of at least one cytokine in the synovial fluid was found in 40 (64.5%) of 62 joints in the patients: IL-1 beta and IFN-gamma were each detected in 18 (29.0%) of 62 joints; IL-6 in 13 (21.0%) of 62 joints; IL-8 in 11 (19.3%) of 57 joints; and TNF-alpha in only 5 (8.1%) of 62 joints. None of these cytokines was detectable in the synovial fluid in the control group. Furthermore, there was a strong correlation between the detection of IL-1 beta and pain in the joint area. CONCLUSIONS: These data clearly demonstrate increased levels of several proinflammatory cytokines in certain patients with TMD and suggest that these cytokines may play a role in the pathogenesis of synovitis and degenerative changes of the cartilaginous tissue and bone of the temporomandibular joint.] Takahashi T, Kondoh T, et.al. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1998 Feb;85(2):135-41.* http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9503445&dopt=Citation
408. **Prospective Study of C-Reactive Protein, Homocystine, and Plasma Lipid Levels as Predictors of Sudden Cardiac Death.** [These results confirm the prognostic relevance of CRP, a sensitive systemic marker of inflammation, to the risk of CHD in a large, randomly selected cohort of initially healthy middle-aged men. They suggest that low-grade inflammation is involved in pathogenesis of atherosclerosis, especially its thrombo-occlusive complications.] http://circ.ahajournals.org/cgi/content/abstract/99/2/237
409. **Prospective study of high-sensitivity C-reactive protein as a determinant of mortality: results from the MONICA/KORA Augsburg Cohort Study, 1984-1998. [**BACKGROUND: C-reactive protein (CRP), an exquisitely sensitive systemic marker of inflammation, has emerged as an independent predictor of cardiovascular diseases (CVD). Because other chronic diseases are also associated with an inflammatory response, we sought to assess the association of high-sensitivity CRP (hsCRP) with total and cause-specific mortality in a large cohort of middle-aged men. METHODS: We measured hsCRP at baseline in 3620 middle-aged men, randomly drawn from 3 samples of the general population in the Augsburg area (Southern 0Germany) in 1984-85, 1989-90, and 1994-95. Outcome was defined as all deaths, fatal CVD, fatal coronary heart disease (CHD) including sudden cardiac deaths, and cancer deaths. … CONCLUSIONS: Our results suggest that increased circulating hsCRP concentrations are associated with an increased risk of death from several widespread chronic diseases. Persistently increased hsCRP is a sensitive and valuable nonspecific indicator of an ongoing disease process that deserves serious and careful medical attention.] Koenig W, Khuseyinova N, et al. *Clin Chem. 2008 Feb;54(2):335-42.* http://www.ncbi.nlm.nih.gov/pubmed/18156284?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVAbstract
410. **Psychosocial Factors and Inflammation in the Multi-Ethnic Study of Atherosclerosis.** [Psychosocial factors are associated with the development and progress of cardiovascular disease, but the pathological mechanisms remain unclear. Psychosocial risk factors for cardiovascular disease with concentrations of inflammatory markers, were examined. The extent to which these associations are mediated by behaviors, body mass index (BMI), and diabetes mellitus, was examined. Higher levels of cynical distrust were associated with higher levels of inflammatory markers. Higher levels of chronic stress were associated with higher concentrations of IL-6 and C-reactive protein. Depression was positively associated with the level of IL-6. Psychosocial factors are associated with higher levels of inflammatory markers, most consistently for cynical distrust. Results are compatible with a mediating role of BMI, behaviors, and diabetes.] Ranjit N, Diez-Roux A, et.al. *Arch Intern Med.* 2007;167:174-181. http://archinte.ama-assn.org/cgi/content/abstract/167/2/174.
411. **Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial.** [BACKGROUND: Statins lower high-sensitivity C-reactive protein (hsCRP) and cholesterol concentrations, and hypothesis generating analyses suggest that clinical outcomes improve in patients given

statins who achieve hsCRP concentrations less than 2 mg/L in addition to LDL cholesterol less than 1.8 mmol/L (<70 mg/dL). However, the benefit of lowering both LDL cholesterol and hsCRP after the start of statin therapy is controversial. We prospectively tested this hypothesis. METHODS: In an analysis of 15 548 initially healthy men and women participating in the JUPITER trial (87% of full cohort), we prospectively assessed the effects of rosuvastatin 20 mg versus placebo on rates of non-fatal myocardial infarction, non-fatal stroke, admission for unstable angina, arterial revascularisation, or cardiovascular death (prespecified endpoints) during a maximum follow-up of 5 years (median 1.9 years), according to on-treatment concentrations of LDL cholesterol (>/=1.8 mmol/L or <1.8 mmol/L) and hsCRP (>/=2 mg/L or <2 mg/L). We included all events occurring after randomisation. This trial is registered with ClinicalTrials.gov, number NCT00239681. FINDINGS: Compared with placebo, participants allocated to rosuvastatin who achieved LDL cholesterol less than 1.8 mmol/L had a 55% reduction in vascular events (event rate 1.11 vs 0.51 per 100 person-years; hazard ratio [HR] 0.45, 95% CI 0.34-0.60, p<0.0001), and those achieving hsCRP less than 2 mg/L a 62% reduction (event rate 0.42 per 100 person-years; HR 0.38, 95% CI 0.26-0.56, p<0.0001). Although LDL cholesterol and hsCRP reductions were only weakly correlated in individual patients (r values <0.15), we recorded a 65% reduction in vascular events in participants allocated to rosuvastatin who achieved both LDL cholesterol less than 1.8 mmol/L and hsCRP less than 2 mg/L (event rate 0.38 per 100 person-years; adjusted HR 0.35, 95% CI 0.23-0.54), versus a 33% reduction in those who achieved one or neither target (event rate 0.74 per 100 person-years; HR 0.67, 95% CI 0.52-0.87) (p across treatment groups <0.0001). In participants who achieved LDL cholesterol less than 1.8 mmol/L and hsCRP less than 1 mg/L, we noted a 79% reduction (event rate 0.24 per 100 person-years; HR 0.21, 95% CI 0.09-0.52). Achieved hsCRP concentrations were predictive of event rates irrespective of the lipid endpoint used, including the apolipoprotein B to apolipoprotein AI ratio. INTERPRETATION: For people choosing to start pharmacological prophylaxis, reduction in both LDL cholesterol and hsCRP are indicators of successful treatment with rosuvastatin.] Ridker PM, Danielson E, et al. *Lancet* 2009 April 4;373(9670):1175-82. http://www.ncbi.nlm.nih.gov/pubmed/19329177?dopt=Abstract

412. **Regulation of matrix metalloproteinase production by cytokines, pharmacological agents and periodontal pathogens in human periodontal ligament fibroblast cultures.** [Matrix metalloproteinases (MMPs), produced by both infiltrating and resident cells of the periodontium, play a role in physiologic and pathologic events. It is recognized that an imbalance between activated MMPs and their endogenous inhibitors leads to pathologic breakdown of the extracellular matrix during periodontitis. To date, little is known about the regulation of MMP synthesis and secretion in human periodontal ligament fibroblasts (PDLFs). The purpose of this study was to examine the effects of cytokines, pharmacological agents (protein synthesis inhibitor and protein kinase C inhibitors) and predominant periodontal pathogens (*Actinobacillus actinomycetemcomitans* and *Porphyromonas gingivalis*) on MMP production in human PDLFs using gelatin zymography. The gelatin zymograms revealed that the main gelatinase secreted by human PDLFs migrated at 72 kDa and represents MMP-2. Minor gelatinolytic bands were also observed at 92 kDa regions that correspond to MMP-9. We found that *A. actinomycetemcomitans*, *P. gingivalis* and IL-1α can elevate MMP-2 secretion in human PDLFs. These results indicate that periodontal pathogens and inflammatory cytokines play an important role in tissue destruction and disintegration of extracellular matrix in periodontal diseases. Thus, activation of MMPs may be one of the distinct host degradative pathways in the pathogenesis of periodontitis. In addition, H7, staurosporine, cycloheximide and TGF-β could suppress MMP-2 production. Agents that target protein synthesis or the protein kinase C pathway in human PDLFs inhibit MMP-2 production, and such inhibition may contribute to the pathogenesis of periodontal inflammation. Taken together, these findings suggest a possible new therapeutic approach, involving the use of drugs that modify host-response mechanisms to suppress or inhibit MMP-mediated tissue destruction.] Chang YC, Yang SF, et al. *Journal of Periodontal Research*, Vol 37, Issue 3, Pp 196-203, Jun 28, 2008. http://www3.interscience.wiley.com/journal/118943882/abstract?CRETRY=1&SRETRY=0

413. **Relationship of Destructive Periodontal Disease to the Acute-Phase Response.** [Destructive periodontal diseases have been associated with an increased risk of atherosclerotic complications; however, the potential mechanisms are yet to be defined. Inflammation plays a central role in atherosclerosis since CRP, an acute-phase protein monitored as a marker of inflammatory status, has been identified as a major risk factor for atherosclerotic complications. Recent reports that destructive periodontal diseases can increase CRP values present the possibility that the acute-phase response may link these 2 disease processes. These results suggest that destructive periodontal disease and disease progression are associated with changes in serum components consistent with an acute-phase response.] Craig RG, Yip JK., et. al., *J Periodontol 2003;74:1007-1016. http://www.joponline.org/doi/abs/10.1902/jop.2003.74.7.1007?prevSearch=keywordsfield%3AC-reactive_protein*

414. **Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein.** [BACKGROUND: Increased levels of the inflammatory biomarker high-sensitivity C-reactive protein predict cardiovascular events. Since statins lower levels of high-sensitivity C-reactive protein as well as cholesterol, we hypothesized that people with elevated high-sensitivity C-reactive protein levels but without hyperlipidemia might benefit from statin treatment. METHODS: We randomly assigned 17,802 apparently healthy men and women with low-density lipoprotein (LDL) cholesterol levels of less than 130 mg per deciliter (3.4 mmol per liter) and high-sensitivity C-reactive protein levels of 2.0 mg per liter or higher to rosuvastatin, 20 mg daily, or placebo and followed them for the occurrence of the combined primary end point of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes. RESULTS: The trial was stopped after a median follow-up of 1.9 years (maximum, 5.0). Rosuvastatin reduced LDL cholesterol levels by 50% and high-sensitivity C-reactive protein levels by 37%. The rates of the primary end point were 0.77 and 1.36 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio for rosuvastatin,

0.56; 95% confidence interval [CI], 0.46 to 0.69; P<0.00001), with corresponding rates of 0.17 and 0.37 for myocardial infarction (hazard ratio, 0.46; 95% CI, 0.30 to 0.70; P=0.0002), 0.18 and 0.34 for stroke (hazard ratio, 0.52; 95% CI, 0.34 to 0.79; P=0.002), 0.41 and 0.77 for revascularization or unstable angina (hazard ratio, 0.53; 95% CI, 0.40 to 0.70; P<0.00001), 0.45 and 0.85 for the combined end point of myocardial infarction, stroke, or death from cardiovascular causes (hazard ratio, 0.53; 95% CI, 0.40 to 0.69; P<0.00001), and 1.00 and 1.25 for death from any cause (hazard ratio, 0.80; 95% CI, 0.67 to 0.97; P=0.02). Consistent effects were observed in all subgroups evaluated. The rosuvastatin group did not have a significant increase in myopathy or cancer but did have a higher incidence of physician-reported diabetes. CONCLUSIONS: In this trial of apparently healthy persons without hyperlipidemia but with elevated high-sensitivity C-reactive protein levels, rosuvastatin significantly reduced the incidence of major cardiovascular events] Ridker PM, Danielson E, et al. *N Engl J Med* 2008 Nov 20;359(21)"2195-207. http://www.ncbi.nlm.nih.gov/pubmed/18997196?dopt=Abstract

415. **Salivary nitric oxide levels in inflammatory periodontal disease - a case-control and interventional study.** **[**BACKGROUND: Biochemical markers of inflammatory periodontal disease present in saliva can partially determine the extent of periodontal disease. Furthermore, collection of salivary constituents is a simple and non-invasive procedure. Nitric oxide (NO) has been linked to etiopathogenesis of inflammatory periodontal disease and is expressed in saliva. This study was conducted with the objective of estimating salivary NO levels in inflammatory periodontal diseases (gingivitis and periodontitis) and comparing these levels with control subjects. A re-assessment of these levels was also made after providing appropriate treatment with a view to ascertain its diagnostic and prognostic values. METHODS: This was a case-control as well as an interventional study including a total of 90 (30 control, 30 gingivitis and 30 periodontitis) subjects. Saliva samples were collected from each subject, and NO levels were assayed by Griess reaction. RESULTS: NO levels were increased significantly in gingivitis and periodontitis subjects as compared with controls. There was a statistically significant decrease in the NO levels in each study group after the healing period (corresponding to the reduced clinical signs of inflammation). Our study also correlated probing pocket depths with salivary NO levels in periodontitis group where we found a positive correlation between the two. CONCLUSION: Salivary NO levels can be utilized as a good indicator of the inflammatory status of the periodontium, and evaluating its levels in saliva by Griess reaction on a photoelectric colorimeter is a reliable, accurate and faster method to estimate the level of inflammation in periodontal tissues.] Parwani SR, Chitnis PJ, et al. *Int J Dent Hyg.* 2012 Feb;10(1):67-73. doi: 10.1111/j.1601-5037.2011.00508.x. Epub 2011 May 12. http://www.ncbi.nlm.nih.gov/pubmed/21564536

416. **Serum C-Reactive Protein and Risk of Cardiovascular Events in Middle-Aged and Older Chinese Population**. [The purpose of the present study was to investigate the effect of high-sensitivity C-reactive protein (hs-CRP) on the risk of cardiovascular disease (CVD) in a Chinese population. A total of 2,656 participants (aged 30 to 95 years) with baseline hs-CRP levels available were monitored for the incidence of a composite of CVD events (stroke and coronary heart disease) during a 5.5-year period. With increasing quartiles of hs-CRP (<0.47, 0.47 to 0.97, 0.97 to 2.09, and ≥2.09 mg/L), the incidence of CVD increased progressively (11.7, 16.4, 24.7, and 36.5 per 1,000 person-years, respectively). In a Cox model adjusted for other traditional risk factors (e.g., age, blood pressure, diabetes mellitus, lipids, body mass index, smoking status), elevated hs-CRP (≥2.0 mg/L) independently predicted the risk of CVD (hazard ratio 1.39; 95% confidence interval 1.04 to 1.87). The effect was especially significant for stroke (hazard ratio 1.58; confidence interval 1.08 to 2.31). In conclusion, the results of our study suggest that elevated hs-CRP (≥2.0 mg/L) is an effective predictor of CVD in a Chinese population.] Jiang S, Bao Y, et al. *The American journal of Cardiology*, vo. 103, Issue 12, pp 1727-1731, June 2009. http://www.ajconline.org/article/S0002-9149(09)00609-2/abstract

417. **Soluble Interleukin**-6 receptor. [Interleukin-6 (IL-6) is a multifunctional cytokine that regulates pleiotropic roles in immune regulation, inflammation, hematopoiesis, and oncogenesis. Its biological activities are shared by IL-6-family of cytokines such as leukemia inhibitory factor and oncostatin M. IL-6 exerts its biological activities through interaction with specific receptors expressed on the surface of target cells.] SBH Sciences. http://www.sbhsciences.com/SIL6R_info.asp

418. **Statin Therapy, LDL Cholesterol, C-Reactive Protein, and Coronary Artery Disease.** [Recent trials have demonstrated better outcomes with intensive than with moderate statin treatment. Intensive treatment produced greater reductions in both low-density lipoprotein (LDL) cholesterol and C-reactive protein (CRP), suggesting a relationship between these two biomarkers and disease progression.] Nissen SE, et al *NEJM 352:29-38 January 6, 2005 Number* 1 http://content.nejm.org/cgi/content/abstract/352/1/29?hits=20&andorexactfulltext=and&where=fulltext&searchterm=statin+C+Reactive+nissen&search_tab=articles&sortspec=Score%2Bdesc%2BPUBDATE_SORTDATE%2Bdesc&sendit=GO&excludeflag=TWEEK_element&searchid=1&FIRSTINDEX=0&resourcetype=HWCIT

419. **Strategies to reduce oxidative stress in cardiovascular disease.** [A multitude of studies in experimental animals, together with clinical data, provide evidence that increased production of ROS (reactive oxygen species) are involved in the development and progression of cardiovascular disease. As ROS appear to have a critical role in atherosclerosis, there has been considerable interest in identifying the enzyme systems involved and in developing strategies to reduce oxidative stress. Prospective clinical trials with vitamins and hormone replacement therapy have not fulfilled earlier promises, although there is still interest in other dietary supplements. Superoxide dismutase mimetics, thiols, xanthine oxidase and NAD(P)H oxidase inhibitors are currently receiving much interest, while animal studies using gene therapy show promise, but are still at an early stage. Of the drugs in common clinical use, there is evidence that ACE (angiotensin-converting enzyme) inhibitors and AT1 (angiotensin II type 1) receptor blockers have beneficial effects on oxidative stress above their antihypertensive properties, whereas statins, in addition to improving lipid profiles, may also lower oxidative stress.] Hamilton CA, Miller

WH, et al. *Clin Sci (Lond).* 2004 Mar;106(3):219-34. http://www.ncbi.nlm.nih.gov/pubmed/14733610 http://www.clinsci.org/cs/106/0219/cs1060219.htm

420. **Targeting C-reactive protein for the treatment of cardiovascular disease.** [Complement-mediated inflammation exacerbates the tissue injury of ischemic necrosis in heart attacks and strokes, the most common causes of death in developed countries. Large infarct size increases immediate morbidity and mortality and, in survivors of the acute event, larger non-functional scars adversely affect long-term prognosis. There is thus an important unmet medical need for new cardioprotective and neuroprotective treatments. We have previously shown that human C-reactive protein (CRP), the classical acute-phase protein that binds to ligands exposed in damaged tissue and then activates complement[1], increases myocardial and cerebral infarct size. …Therapeutic inhibition of CRP is a promising new approach to cardioprotection in acute myocardial infarction, and may also provide neuroprotection in stroke. Potential wider applications include other inflammatory, infective and tissue-damaging conditions characterized by increased CRP production, in which binding of CRP to exposed ligands in damaged cells may lead to complement-mediated exacerbation of tissue injury.] Pepys MB, Hirschfield GM et.al,. *Nature 440, 1217-1221 (27 April 2006).* *http://www.nature.com/nature/journal/v440/n7088/abs/nature04672.html*

421. **The Cholinergic Anti-inflammatory Pathway: A Missing Link in Neuroimmunomodulation.** [This review outlines the mechanisms underlying the interaction between the nervous and immune systems of the host in response to an immune challenge. The main focus is the cholinergic anti-inflammatory pathway, which we recently described as a novel function of the efferent vagus nerve. This pathway plays a critical role in controlling the inflammatory response through interaction with peripheral α7 subunit–containing nicotinic acetylcholine receptors expressed on macrophages. We describe the modulation of systemic and local inflammation by the cholinergic anti-inflammatory pathway and its function as an interface between the brain and the immune system. The clinical implications of this novel mechanism also are discussed… Introduction: Inflammation is a normal response to disturbed homeostasis caused by infection, injury, and trauma. The host responds with a complex series of immune reactions to neutralize invading pathogens, repair injured tissues, and promote wound healing. The onset of inflammation is characterized by release of pro-inflammatory mediators including tumor necrosis factor (TNF), interleukin (IL)-1, adhesion molecules, vasoactive mediators, and reactive oxygen species. The early release of pro-inflammatory cytokines by activated macrophages has a pivotal role in triggering the local inflammatory response. Excessive production of cytokines, such as TNF, IL-1β, and high mobility group B1 (HMGB1), however, can be more injurious than the inciting event, initiating diffuse coagulation, tissue injury, hypotension, and death. The inflammatory response is balanced by anti-inflammatory factors including the cytokines IL-10 and IL-4, soluble TNF receptors, IL-1 receptor antagonists, and transforming growth factor (TGF)β. Although simplistic the pro-/anti- terminology is widely used in the discussion of the complex cytokine network. Apart from their involvement in local inflammation, TNF and IL-1β are signal molecules for activation of brain-derived neuroendocrine immunomodulatory responses. Neuroendocrine pathways, such as the hypothalamo-pituitary-adrenal (HPA) axis and the sympathetic division of the autonomic nervous system (SNS), control inflammation as an anti-inflammatory balancing mechanism. The host thereby mobilizes the immunomodulatory resources of the nervous and endocrine systems to regulate inflammation. Restoration of homeostasis as a logical resolution of inflammation does not always occur. Insufficient inflammatory responses may result in increased susceptibility to infections and cancer. On the other hand, excessive responses are associated with autoimmune diseases, diabetes, sepsis, and other debilitating conditions. When control of local inflammatory responses is lost, pro-inflammatory mediators can spill into the circulation, resulting in systemic inflammation that may progress to shock, multiple organ failure, and death. Effective therapies for diseases of excessive inflammation are needed.] Pavlov VA, Wang H, et.al. *Mol Med. 2003 May–Aug; 9(5-8): 125–134.* http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1430829

422. **The Effect of Including C-Reactive Protein in Cardiovascular Risk Prediction Models for Women.** [A global risk prediction model that includes hsCRP improves cardiovascular risk classification in women, particularly among those with a 10-year risk of 5% to 20%. In models that include age, blood pressure, and smoking status, hsCRP improves prediction at least as much as do lipid measures.] Cook NR, Buring JE, et.al. *Annals of Internal Medicine, Vol.145 Issue 1, P 21-29, 4 July 2006,* http://www.annals.org/cgi/content/abstract/145/1/21

423. **The Fire That Burns Within; C-Reactive Protein.** [A complex interplay between proinflammatory stimuli and endogenous heritable-genetic vascular reparative processes has been proposed as a determinant of vascular disease activity. The validity of this premise is supported by the presence and prospective predictive value of cytokine and cellular "markers" of inflammation, including interleukins 6 and 18 and C-reactive protein (CRP). Furthermore, the fact that physiologically occurring concentrations of CRP exert proinflammatory, proatherogenic, and prothrombotic effects provides impetus to define antiinflammatory treatments capable of suppressing this incestuous marker-mediator cycle.] Kereiakes DJ. *Circulation 2003;107;373-374.* http://circ.ahajournals.org/cgi/reprint/107/3/373?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=ridker&searchid=1&FIRSTINDEX=0&resourcetype=HWCIT

424. **The I kappa B kinase (IKK) and NF-kappa B: key elements of proinflammatory signalling. [**NF-kappa B is a heterodimeric transcription factor that plays a key role in inflammatory and immune responses. In nonstimulated cells, NF-kappa B dimers are maintained in the cytoplasm through interaction with inhibitory proteins, the I kappa Bs. In response to cell stimulation, mainly by proinflammatory cytokines, a multisubunit protein kinase, the I kappa B kinase (IKK), is rapidly activated and phosphorylates two critical serines in the N-terminal regulatory domain of the I kappa Bs. Phosphorylated I kappa Bs are recognized by a specific E3 ubiquitin ligase complex and undergo polyubiquitination which targets them for

rapid degradation by the 26S proteasome. NF-kappa B dimers, which are spared from degradation, translocate to the nucleus to activate gene transcription. There is strong biochemical and genetic evidence that the IKK complex, which consists of two catalytic subunits, IKK alpha and IKK beta, and a regulatory subunit, IKK gamma, is the master regulator of NF-kappa B-mediated innate immune and inflammatory responses. In the absence of IKK gamma, which normally connects IKK to upstream activators, no IKK or NF-kappa B activation can occur. Surprisingly, however of the two catalytic subunits, only IKK beta is essential for NF-kappa B activation in response to proinflammatory stimuli. The second catalytic subunit, IKK alpha, plays a critical role in developmental processes, in particular formation and differentiation of the epidermis.] Karin M, Delhase M. *Semin Immunol.* 2000 Feb;12(1):85-98. http://www.ncbi.nlm.nih.gov/pubmed/10723801

425. **The link between inflammation and diabetes. [**Inflammation is typically the way the body responds to injury. However, if the immune system malfunctions, this inflammatory process can damage healthy tissue. Recent research shows inflammation may play a role in diseases that are not typically considered inflammatory diseases, such as heart disease. In much the same way doctors have found a link between inflammation and heart disease, they have now found a link between inflammation and diabetes. Researchers say there are several markers of inflammation that are increased in people who have diabetes. … Researchers say the finding that inflammation is linked to the onset of type 2 diabetes may open new avenues for the prevention and treatment of the disease.] Duncan, Bruce MD. American Diabetes Assoc Meeting, San Francisco, June 2002. http://www.defeatdiabetes.org/Articles/inflam020617.htm
426. **The role of brain insulin in the neurophysiology of serious mental disorders: review.** [The purpose of this review is to indicate the role insulin plays in normal brain neurophysiology, together with the role insulin may play in the regulation of regional cerebral blood flow (rCBF). The relationship between sustained elevation of the inflammatory cytokines and brain insulin dysregulation, with respect to the serious mental disorders, is also discussed. It has been observed that, as the inflammatory cytokines increase, they exert a synergistic influence on insulin and somatostatin, by initially increasing and then decreasing insulin secretion. In the brain, increased levels of insulin result in increased glucose utilization and over-stimulation of the autonomic nervous system (ANS), while the inhibition of insulin secretion results in decreased glucose utilization and dysregulation of the hypothalamo-pituitary-adrenal (HPA) axis. It will further be argued that these alterations in brain insulin influence rCBF in the serious mental disorders such as schizophrenia and the affective disorders. It is hypothesized that insulin regulates rCBF either directly, or indirectly via GLUT4 in the hypothalamus now considered the glucose-sensing, insulin-sensing mechanism of the brain and the body. Thus, we shall propose that insulin plays an important role in normal neurophysiology and that sustained elevation of the inflammatory cytokines dysregulates insulin secretion, rCBF, ANS and the HPA-axis in serious mental disorders.] Holden RJ. *Med Hypotheses. 1999 Mar;52(3):193-200.* http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10362277&dopt=Citation
427. **Toll-Like Receptors: Sensors that Detect Infection.** [A diverse range of microbes, including viruses, bacteria, fungi, and protists, stand ready to attack the human body and thrive in the nutrient-richenvironment it provides. Fortunately, the immune response functions as a defense mechanism and counterattacks by recognizing and destroying foreign invaders. But what alerts the body to danger? How are foreign organisms detected? The discovery of microbial-sensing proteins called Toll-like receptors is helping to answer these questions and transform our understanding of the response to infection.] Christmas P, (2010) Toll-Like Receptors: Sensors that Detect Infection. *Nature Education* 3(9):85. http://www.nature.com/scitable/topicpage/toll-like-receptors-sensors-that-detect-infection-14396559 .
428. **Toll-like Receptor Signaling**. [The innate immune response in vertebrates is the first line of defense against invading microorganisms. The main players in innate immunity are phagocytes such as neutrophils, macrophages, and dendritic cells. These cells can discriminate between pathogens and self by utilizing signals from the Toll-like receptors (TLRs)1 (1–4). TLRs recognize conserved motifs predominantly found in microorganisms but not in vertebrates. Stimulation of TLRs causes an immediate defensive response, including the production of an array of antimicrobial peptides and cytokines. Accumulating evidence has shown that individual TLRs can activate overlapping as well as distinct signaling pathways, ultimately giving rise to distinct biological effects.] Akira S. October 3, 2003 The Journal of Biological Chemistry, 278, 38105-38108. http://www.jbc.org/content/278/40/38105
429. **Too old to fight? Aging and its toll on innate immunity**. [Elderly individuals display increased susceptibility to chronic inflammatory diseases and microbial infections, such as periodontitis and oral aspiration pneumonia. The resurgent interest in innate immunity in the 2000s has been accompanied by parallel studies to understand the impact of aging on the function of the innate immune system, which not only provides first-line defense but is essential for the development of adaptive immunity. This review summarizes and discusses our current understanding of age-associated molecular alterations in neutrophils and macrophages, key inflammatory phagocytes implicated in both protective and destructive host responses. The analysis of recent literature suggests that, in advanced age, phagocytes undergo significant changes in signal transduction pathways that may affect their ability to perform antimicrobial functions or regulate the inflammatory response. These abnormalities are expected to contribute to the pathology of oral infection-driven inflammatory diseases in the elderly. Moreover, the elucidation of age-associated defects in the innate immune system will facilitate the development of intervention therapeutic strategies to promote or restore innate immune function and improve the quality of health in old age.] Hajishengallis G. *Molecular Oral Microbiology*, Vol 25, Issue 1, pp. 25-37. http://www3.interscience.wiley.com/journal/123261441/abstract?CRETRY=1&SRETRY=0
430. **Transcription factor NF-kappaB: a sensor for smoke and stress signals.** [Nuclear factor-kappa B (NF-kappaB) is a transcription factor that resides in the cytoplasm of every cell and translocates to the nucleus when activated. Its activation is induced by a wide variety of agents including stress, cigarette smoke, viruses, bacteria, inflammatory stimuli, cytokines, free

radicals, carcinogens, tumor promoters, and endotoxins. On activation, NF-kappaB regulates the expression of almost 400 different genes, which include enzymes (e.g., COX-2, 5-LOX, and iNOS), cytokines (such as TNF, IL-1, IL-6, IL-8, and chemokines), adhesion molecules, cell cycle regulatory molecules, viral proteins, and angiogenic factors. The constitutive activation of NF-kappaB has been linked with a wide variety of human diseases, including asthma, atherosclerosis, AIDS, rheumatoid arthritis, diabetes, osteoporosis, Alzheimer's disease, and cancer. Several agents are known to suppress NF-kappaB activation, including Th2 cytokines (IL-4, IL-13, and IL-10), interferons, endocrine hormones (LH, HCG, MSH, and GH), phytochemicals, corticosteroids, and immunosuppressive agents. Because of the strong link of NF-kappaB with different stress signals, it has been called a "smoke-sensor" of the body.] Ahn Ks, Aggarwal BB. Ann N Y Acad Sci. 2005 Nov;1056:218-33. http://www.ncbi.nlm.nih.gov/pubmed/16387690

431. **Tumor necrosis factor.** [Tumor necrosis factor alpha is a cytokine produced primarily by monocytes and macrophages. It is found in synovial cells and macrophages in the tissues.
It shares many properties with another cytokine - interleukin 1. It is not unique to RA, but occurs in many inflammatory diseases, and also as a response to endotoxins from bacteria for example.] Drdoc on-line. http://www.arthritis.co.za/tnf.htm
432. **Tumor necrosis factor.** [TNFα is released by white blood cells, endothelium and several other tissues in the course of damage, e.g. by infection. Its release is stimulated by several other mediators, such as interleukin 1 and bacterial endotoxin. It has a number of actions on various organ systems, generally together with interleukins 1 and 6. On the liver: stimulating the acute phase response, leading to an increase in C-reactive protein and a number of other mediators. It attracts neutrophils very potently, and helps them to stick to the endothelial cells for migration. On macrophages: stimulates phagocytosis, and production of IL-1 oxidants and the inflammatory lipid prostaglandin E2 (PGE2). On other tissues: increasing insulin resistance.] http://en.wikipedia.org/wiki/Tumor_necrosis_factor
433. **Tumor Necrosis Factor.** [Tumor necrosis factor is a multifunctional proinflammatory cytokine, with effects on lipid metabolism, coagulation, insulin resistance, and endothelial function.]
http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?cmd=entry&id=191160
434. **Vitamin C reduces level of C-reactive protein, finds UC Berkeley-led study.** [Vitamin C supplements can reduce levels of C-reactive protein, a marker of inflammation and chronic disease risk in humans, according to a new study led by researchers at the University of California, Berkeley. Participants who took about 500 milligrams of vitamin C supplements per day saw a 24 percent drop in plasma C-reactive protein (CRP) levels after two months. The study, published in the April issue of the Journal of the American College of Nutrition, is the first time vitamin C has been shown to decrease levels of CRP, a biomarker that has garnered increasing attention among health researchers in recent years. C-reactive protein is a marker of inflammation, and there is a growing body of evidence that chronic inflammation is linked to an increased risk of heart disease, diabetes and even Alzheimer's disease, said Gladys Block, UC Berkeley professor of epidemiology and public health nutrition and lead author of the study. If our finding of vitamin C's ability to lower CRP is confirmed through other trials, vitamin C could become an important public health intervention. Inflammation occurs as part of the body's defense against infection or injury. The body triggers the production of inflammatory cytokines, such as interleukin-6, that then set off the production of CRP by the liver.] Apr-2004, http://www.eurekalert.org/pub_releases/2004-04/uoc--vcr041204.php
435. **What Is Nuclear Factor-Kappa Beta?** [NFkB is a protein that acts as a switch to turn inflammation on and off in the body. Scientists describe NFkB as a “smoke sensor” that detects dangerous threats like free radicals and infectious agents. In response to these threats, NFkB “turns on” the genes that produce inflammation. As we age, NFkB expression in the body increases, provoking widespread chronic inflammation and setting the stage for diseases ranging from atherosclerosis and diabetes to Alzheimer’s. The knowledge of this simple fact should motivate us to counteract NFkB’s deleterious effects and thus guard against many of the diseases commonly associated with aging. As we have reported over the last several years, inflammation is the key initiating factor in major degenerative diseases. In fact, some scientists estimate that inflammation underlies up to 98% of the diseases afflicting humans, including a vast array of seemingly different conditions such as cancer, heart disease, diabetes, and neurodegenerative disorders] Goepp JG, *Life Extension Magazine*,
http://www.lef.org/magazine/mag2006/jul2006_report_nuclear_01.htm

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436. **Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance.** [Tumor necrosis factor-alpha (TNF-alpha) has been shown to have certain catabolic effects on fat cells and whole animals. An induction of TNF-alpha messenger RNA expression was observed in adipose tissue from four different rodent models of obesity and diabetes. TNF-alpha protein was also elevated locally and systemically. Neutralization of TNF-alpha in obese fa/fa rats caused a significant increase in the peripheral uptake of glucose in response to insulin. These results indicate a role for TNF-alpha in obesity and particularly in the insulin resistance and diabetes that often accompany obesity.] Hotamisligil GS, Shargill NS, et al., Science. 1993 Jan 1;259(5091):87-91., http://www.ncbi.nlm.nih.gov/pubmed/7678183?dopt=Abstract
437. **Association of periodontal parameters with metabolic level, systemic inflammatory markers in type 2 diabetes patients**. [**Backgrounds:** While world-wide evidence tends to prove that diabetes adversely affects periodontal health, there is insufficient clue that periodontitis may aggravate metabolic controlling and systemic inflammation. This study, as a preliminary part of an ongoing research project, aims to clarify the relationship of periodontal parameters with metabolic level as well as systemic inflammatory markers in diabetes patients.Methods: 140 qualified adult patients with type 2 diabetes

and periodontitis were recruited in this study. Periodontal examinations including full-mouth assessment of probing depths (PD), bleeding on probing (BOP), gingival recession (GR) and clinical attachment level (AL) were applied. Blood analyses were carried out for glycated hemoglobin (HbA1c), fasting glucose, high-sensitivity C reactive protein (hsCRP), tumor necrosis factor-a (TNF-a) and lipid profiles. Then subjects were divided into 3 groups according to tertile of mean PD and compared.Results: Upon ANCOVA, subjects with increased mean PD had significantly higher HbA1c and hsCRP (P <0.05). No significant difference was found among different groups in serum TNF-α, fasting glucose and lipid profiles levels (P >0.05). After controlling for age, gender, body mass index (BMI), duration of diabetes mellitus, smoking, regular physical exercise and alcohol drinking, positive correlations were found between mean PD with HbA1c (r = 0.2272, P = 0.009) and mean PD with hsCRP (r = 0.2336, P = 0.007). After adjustment for possible confounders, the mean PD emerged as a significant predictor variable for elevated HbA1c and hsCRP (P <0.05).Conclusion: The chronic periodontitis is associated with glycaemic metabolic and serum hsCRP levels in type 2 diabetes patients.] Chen L, Wei B, et al. *Journal of Periodontology*, Posted online on November 25, 2009. http://www.joponline.org/doi/abs/10.1902/jop.2009.090544?journalCode=jop

438. **Attitudes, awareness and oral health-related quality of life in patients with diabetes. [**The purpose of this study was to assess the knowledge diabetic patients have of their risk for periodontal disease, their attitude towards oral health and their oral health-related quality of life (OHRQL). One hundred and one consecutive patients (age range 31-79 years) recruited from a diabetic outpatient clinic participated in the study. Twenty-seven per cent of participants had type 1 diabetes, 66% type 2 and 7% did not know what type of diabetes they had. The length of time since participants were diagnosed as diabetic ranged from 1 to 48 years. Metabolic control of diabetes as determined by HbA1c levels ranged from 6.2% to 12.0% compared with the normal range of 4.5-6.0%. Thirty-three per cent of participants were aware of their increased risk for periodontal disease, 84% of their increased risk for heart disease, 98% for eye disease, 99% for circulatory problems and 94% for kidney disease. Half of the participants who were aware of their increased risk for periodontal disease had received this information from a dentist. Dental attendance was sporadic, with 43% reporting attendance within the last year. OHRQL was not significantly affected by the presence of diabetes in the group surveyed, in comparison with a previous survey of non-diabetic patients. A significant association was found between metabolic control and dentate status. Awareness of the potential associations between diabetes, oral health and general health needs to be increased in diabetic patients.] Allen EM, Ziada HM, et al. *J Oral Rehab*, 2008 March;35(3):218-23. http://www.ncbi.nlm.nih.gov/pubmed/18254800
439. **Bidirectional Interrelationships Between Diabetes and Periodontal Diseases: An Epidemiologic Perspective.** [The evidence reviewed supports viewing the relationship between diabetes and periodontal diseases as bidirectional.] Taylor G. *Annals of Periodontology, 2001, Vol. 6, No. 1, Pages 99-112.* http://www.joponline.org/doi/abs/10.1902/annals.2001.6.1.99
440. **Chronic Subclinical Inflammation as Part of the Insulin Resistance Syndrome**. [*Background*—Inflammation has been suggested as a risk factor for the development of atherosclerosis. Recently, some components of the insulin resistance syndrome (IRS) have been related to inflammatory markers. We hypothesized that insulin insensitivity, as directly measured, may be associated with inflammation in nondiabetic subjects. *Methods and Results*—We studied the relation of C-reactive protein (CRP), fibrinogen, and white cell count to components of IRS in the nondiabetic population of the Insulin Resistance Atherosclerosis Study (IRAS) (n=1008; age, 40 to 69 years; 33% with impaired glucose tolerance), a multicenter, population-based study. None of the subjects had clinical coronary artery disease. Insulin sensitivity (S_I) was measured by a frequently sampled intravenous glucose tolerance test, and CRP was measured by a highly sensitive competitive immunoassay. All 3 inflammatory markers were correlated with several components of the IRS. Strong associations were found between CRP and measures of body fat (body mass index, waist circumference), S_I, and fasting insulin and proinsulin (all correlation coefficients >0.3, P<0.0001). The associations were consistent among the 3 ethnic groups of the IRAS. There was a linear increase in CRP levels with an increase in the number of metabolic disorders. Body mass index, systolic blood pressure, and S_I were related to CRP levels in a multivariate linear regression model. *Conclusions*—We suggest that chronic subclinical inflammation is part of IRS. CRP, a predictor of cardiovascular events in previous reports, was independently related to S_I. These findings suggest potential benefits of anti-inflammatory or insulin-sensitizing treatment strategies in healthy individuals with features of IRS.] Festa A, D'Agostino R, et al. *Circulation* 2000;102:42. http://www.circ.ahajournals.org/cgi/content/abstract/102/1/42
441. **Clinical and Metabolic Changes After Conventional Treatment of Type 2 Diabetic Patients With Chronic Periodontitis**. [The aim of this study was to compare the response to conventional periodontal treatment between patients with or without type 2 diabetes mellitus from a clinical and metabolic standpoint. Both groups of patients showed a clinical improvement after basic non-surgical periodontal treatment. The diabetic patients showed improved metabolic control (lower HbA1c) at 3 and 6 months after periodontal treatment.] Faria-Almeida R, Navarro A, et. al, *Journal of Periodontology 2006.050084.* http://www.joponline.org/doi/abs/10.1902/jop.2006.050084
442. **Collagenases in Gingival Crevicular Fluid in Type 1 Diabetes Mellitus.** [Background: Studies have demonstrated that high levels of collagenase activity in gingival crevicular fluid (GCF) are associated with degradation of periodontal tissues in progressive periodontitis compared to periodontally healthy tissues. Because the activation of collagenases is an important issue in periodontitis, we have studied the activation of collagenase in gingival crevicular fluid samples of diabetic patients. Methods: Collagenase activity was studied in human gingival crevicular fluids. Twenty-two poorly controlled diabetic patients (e.g., blood glucose: 11.0 ± 0.7 mmol/l; hemoglobin A_{1c} [HbA_{1c}]: 9.6% ± 0.3%) and five well-controlled diabetic patients were compared to six chronic periodontitis subjects and five healthy controls. Collagenase activity against type I collagen was measured using sodium dodecyl sulfate-polyacrylamide gel electrophoresis analysis quantitated by laser

densitometry. Results: The poorly controlled diabetic patients had more alveolar bone loss than the well-controlled diabetic subjects and controls (P <0.001; t test). The activity of collagenases in GCF in poorly controlled diabetic patients was similar to that seen in chronic periodontitis subjects (P >0.05) but higher than in healthy controls (P <0.01; t test), whereas there was no difference between the well-controlled diabetic subjects and systemically healthy controls (P >0.05; t test). Conclusion: Poorly controlled diabetes is strongly related to periodontal tissue destruction, and collagenases in GCF may mediate and reflect this effect. Safkan-Seppala B, Sorsa T, et al. *Journal of Periodontology*, 2006, Vol. 77, No. 2, Pages 189-194. http://www.joponline.org/doi/abs/10.1902/jop.2006.040322?prevSearch=allfield%253A%2528collagenases%252C%2Bdiabetes%2529&searchHistoryKey=

443. **C-Reactive Protein and Incident Cardiovascular Events Among Men With Diabetes**. [Several large prospective studies have shown that baseline levels of C-reactive protein (CRP) are an independent predictor of cardiovascular events among apparently healthy individuals. However, prospective data on whether CRP predicts cardiovascular events in diabetic patients are limited so far. High plasma levels of CRP were associated with an increased risk of incident cardiovascular events among diabetic men, independent of currently established lifestyle risk factors, blood lipids, and glycemic control.] Schulze M, Rimm EB, et.al. *Diabetes Care* 27:889-894, 2004. http://care.diabetesjournals.org/cgi/content/abstract/27/4/889?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&author1=Schulze&searchid=1081215809897_10507&stored_search=&FIRSTINDEX=0&sortspec=relevance&volume=27&firstpage=889&journalcode=diacare
444. **Dental considerations for the treatment of patients with diabetes mellitus**. [The susceptibility to periodontal disease—often called the "sixth complication of diabetes mellitus"—is the most common oral complication of diabetes. The patient with poorly controlled diabetes is at greater risk of developing periodontal disease. The dental team can improve the metabolic control of a patient's diabetes by maintaining optimal oral health.] Vernillo AT, J Am Dent Assoc, Vol 134, No suppl_1, 24S-33S. **http://jada.ada.org/cgi/content/full/134/suppl_1/24S**
445. **Detection and prevention of periodontal disease in diabetes.** [Recent studies in which the age relationship of periodontal disease is accounted for show that in type 2 diabetics, periodontal disease is more severe and more prevalent than in non-diabetics.] Diabetes Monitor. http://www.diabetesmonitor.com/b116.htm
446. **Diabetes and Oral Health. An Overview.** [Diabetes mellitus affects people of all ages, and its prevalence has been increasing. Providing safe and effective oral medical care for patients with diabetes requires an understanding of the disease and familiarity with its oral manifestations. The goal of therapy is to promote oral health in patients with diabetes, to help prevent and diagnose diabetes in dental patients receiving routine stomatological care and to enhance the quality of life for patients with this incurable disease. Diabetes is a common disease with concomitant oral manifestations that impact dental care. Safely managing the patients with diabetes requires effective communication among multiple health care providers. Dentists must be familiar with techniques to diagnose, treat and prevent stomatological disorders in patients with diabetes.] Ship, JA. JADA, vol. 134, October 2003. http://www.ada.org/prof/resources/pubs/jada/reports/suppl_diabetes_02.pdf
447. **Diabetes in the dental office: using NHANES III to estimate the probability of undiagnosed disease.** [Background and Objective: Recent data have suggested that in the past 15 years there has been a dramatic increase in the incidence of diabetes mellitus in the USA. However, evidence suggests that approximately one-third of diabetes cases remain undiagnosed. Because 60% of Americans see a dentist at least once per year for routine, nonemergent, care, it is reasonable to propose that the dental office can be a healthcare location actively involved in screening for unidentified diabetes. Material and Methods: This study used NHANES III to develop a predictive equation that can form the basis of a tool to help dentists determine the probability of undiagnosed diabetes by using self-reported data and periodontal clinical parameters routinely assessed in the dental office. Results: Our analyses reveal that individuals with a self-reported family history of diabetes, hypertension, high cholesterol levels and clinical evidence of periodontal disease bear a probability of 27–53% of having undiagnosed diabetes, with Mexican–American men exhibiting the highest probability and white women the lowest. Conclusion: These findings suggest that the dental office could provide an important opportunity to identify individuals unaware of their diabetic status.] Borrell LN, Kunzel C, et al. *Journal of Periodontal Research Volume 42 Issue 6 Page 559-565, December 2007,* **http://www.blackwell-synergy.com/doi/abs/10.1111/j.1600-0765.2007.00983.x**
448. **Diabetes mellitus and periodontal diseases.** [The purpose of this review is to provide the reader with practical knowledge concerning the relationship between diabetes mellitus and periodontal diseases. Over 200 articles have been published in the English literature over the past 50 years examining the relationship between these two chronic diseases. Data interpretation is often confounded by varying definitions of diabetes and periodontitis and different clinical criteria applied to prevalence, extent, and severity of periodontal diseases, levels of glycemic control, and complications associated with diabetes. METHODS: This article provides a broad overview of the predominant findings from research published in English over the past 20 years, with reference to certain "classic" articles published prior to that time. RESULTS: This article describes current diagnostic and classification criteria for diabetes and answers the following questions: 1) Does diabetes affect the risk of periodontitis, and does the level of metabolic control of diabetes have an impact on this relationship? 2) Do periodontal diseases affect the pathophysiology of diabetes mellitus or the metabolic control of diabetes? 3) What are the mechanisms by which these two diseases interrelate? and 4) How do people with diabetes and periodontal disease respond to periodontal treatment? CONCLUSIONS: Diabetes increases the risk of periodontal diseases, and biologically plausible mechanisms have been demonstrated in abundance. Less clear is the impact of periodontal diseases on glycemic control of diabetes and the mechanisms through which this occurs. Inflammatory periodontal diseases may increase insulin resistance in a way similar to obesity, thereby aggravating glycemic control. Further research is needed to clarify this aspect of the relationship between

periodontal diseases and diabetes.] Mealey BL, Oates TW. *J Periodontol. 2006 Aug;77(8):1289-303.* http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=16881798&ordinalpos=12&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

449. **Does Inflammation Trigger Insulin Resistance and Diabetes?** [Several decades ago scientists noticed that people with type 2 diabetes have overly active immune responses, leaving their bodies rife with inflammatory chemicals. In the early 1990s researchers at Harvard University pinpointed one major immune player as TNF-alpha, a chemical secreted by immune cells; such compounds are generally referred to as cytokines. They found high levels of the cytokine in the fat tissue of rats with type 2 diabetes, and when they bred obese rats that could not make the cytokine, diabetes did not develop in the animals. Researchers have since shown that TNF-alpha—and, more generally, inflammation—activates and increases the expression of several proteins that suppress insulin-signaling pathways, making the human body less responsive to insulin and increasing the risk for insulin resistance.] Wenner M. *Scientific American*, December 2009. http://www.scientificamerican.com/article.cfm?id=inflammatory-clues
450. **Educational resources on diabetes mellitus.** [Multiple resources available on managing diabetes.] Eisenberg ES, *J Am Dent Assoc, Vol 134, No suppl_1, 59S-60S.* http://jada.ada.org/cgi/content/full/134/suppl_1/59S
451. **Effect of Periodontitis on Insulin Resistance and the Onset of Type 2 Diabetes Mellitus in Zucker Diabetic Fatty Rats. [Background:** Studies indicate that an association exists between periodontitis and type 2 diabetes mellitus (T2DM) and/or obesity, with chronic inflammation hypothesized as the common denominator. The purpose of this study was to determine the causal effect of periodontitis and the concomitant impact of diet on the onset of insulin resistance (IR) and T2DM using a rat model system that simulates human obesity and T2DM. **Methods:** Twenty-eight, 5-week-old female Zucker diabetic fatty (ZDF, *fa/fa*) rats were divided into four groups of seven animals: high-fat fed–periodontitis (HF/P), high-fat fed–no periodontitis (HF/C), low-fat fed–periodontitis (LF/P), and low-fat fed–no periodontitis (LF/C). Periodontitis was induced by ligature placement. Fasting plasma insulin and glucose levels were measured, and glucose tolerance tests were performed to assess glucose homeostasis, IR, and the onset of T2DM. The level of tumor necrosis factor-alpha (TNF-α), leptin, triglycerides, and free fatty acids were determined in week 13 at sacrifice. **Results:** HF/P rats developed more severe IR compared to HF/C rats (P <0.01) and LF/P or LF/C rats (P <0.001) as measured by fasting insulin levels and homeostasis model assessment analysis. The onset of severe IR occurred ~3 weeks earlier in HF/P rats compared to HF/C rats. HF/P rats developed impaired (110 to 125 mg/dl) and frank fasting hyperglycemia (>125 mg/dl) 2 weeks earlier than HF/C rats. There was no difference in the severity and onset of IR and T2DM between LF/P and LF/C rats. The level of TNF-α was significantly higher in HF/P rats compared to HF/C rats (P <0.01). **Conclusion:** Periodontitis accelerated the onset of severe IR and impaired glucose homeostasis in high-fat fed ZDF rats.**] Watanabe K, Petro B, et al.** Journal of Periodontology, 2008, Vol. 79, No. 7, Pages 1208-1216. http://www.joponline.org/doi/abs/10.1902/jop.2008.070605?cookieSet=1&journalCode=jop
452. **Effect of Periodontitis on Overt Nephropathy and End-Stage Renal Disease in Type 2 Diabetes. [**The purpose of this study was to investigate the effect of Periodontitis on development of overt nephropathy, defined as macroalbuminuria, and end-stage renal disease (ESRD) in type 2 diabetes. Periodontitis predicts development of overt nephropathy and ESRD in individuals with type 2 diabetes. Whether treatment of Periodontitis will reduce the risk of diabetic kidney disease remains to be determined.] Shultis, WA, Weil EJ, et.al. *Diabetes Care 30:306-311, 2007.* http://care.diabetesjournals.org/cgi/content/abstract/30/2/306
453. **Glucose tolerance status and risk of dementia in the community.** [Objective: We investigated the association between glucose tolerance status defined by a 75-g oral glucose tolerance test (OGTT) and the development of dementia. Methods**:** A total of 1,017 community-dwelling dementia-free subjects aged ≥60 years who underwent the OGTT were followed up for 15 years. Outcome measure was clinically diagnosed dementia. Results**:** The age- and sex-adjusted incidence of all-cause dementia, Alzheimer disease (AD), and vascular dementia (VaD) were significantly higher in subjects with diabetes than in those with normal glucose tolerance. These associations remained robust even after adjustment for confounding factors for all-cause dementia and AD, but not for VaD (all-cause dementia: adjusted hazard ratio [HR] = 1.74, 95% confidence interval [CI] = 1.19 to 2.53, p = 0.004; AD: adjusted HR = 2.05, 95% CI = 1.18 to 3.57, p = 0.01; VaD: adjusted HR = 1.82, 95% CI = 0.89 to 3.71, p = 0.09). Moreover, the risks of developing all-cause dementia, AD, and VaD significantly increased with elevated 2-hour postload glucose (PG) levels even after adjustment for covariates, but no such associations were observed for fasting plasma glucose (FPG) levels: compared with those with 2-hour PG levels of <6.7 mmol/L, the multivariable-adjusted HRs of all-cause dementia and AD significantly increased in subjects with 2-hour PG levels of 7.8 to 11.0 mmol/L or over, and the risk of VaD was significantly higher in subjects with levels of ≥11.1 mmol/L. Conclusions: Our findings suggest that diabetes is a significant risk factor for all-cause dementia, AD, and probably VaD. Moreover, 2-hour PG levels, but not FPG levels, are closely associated with increased risk of all-cause dementia, AD, and VaD.] Ohara T, Doi Y, et al. *Neurology* September 20, 2011 vol. 77 no. 12 1126-1134**.** http://www.neurology.org/content/77/12/1126.full
454. **Glycated Hemoglobin Level Is Strongly Related to the Prevalence of Carotid Artery Plaques With High Echogenicity in Nondiabetic Individuals.** [*Background***—** High levels of HbA_{1c} have been associated with increased mortality and an increased risk of atherosclerosis assessed as carotid intima-media thickness or plaque prevalence. In the present population-based study, we examined the association between HbA_{1c} and plaque prevalence with emphasis on plaque echogenicity in subjects not diagnosed with diabetes. *Conclusions***—** Metabolic changes reflected by HbA_{1c} levels may contribute to the development of hard carotid artery plaques, even at modestly elevated levels.] Jorgensen Lone, Jenssen Trond, et.al. *Circulation. 2004;110:466-47.* http://www.circ.ahajournals.org/cgi/content/full/110/4/466

455. **Glycated Hemoglobin, Diabetes, and Cardiovascular Risk in Nondiabetic Adults.** [*Background* Fasting glucose is the standard measure used to diagnose diabetes in the United States. Recently, glycated hemoglobin was also recommended for this purpose. *Methods* We compared the prognostic value of glycated hemoglobin and fasting glucose for identifying adults at risk for diabetes or cardiovascular disease. We measured glycated hemoglobin in whole-blood samples from 11,092 black or white adults who did not have a history of diabetes or cardiovascular disease and who attended the second visit (occurring in the 1990–1992 period) of the Atherosclerosis Risk in Communities (ARIC) study. *Results* The glycated hemoglobin value at baseline was associated with newly diagnosed diabetes and cardiovascular outcomes. For glycated hemoglobin values of less than 5.0%, 5.0 to less than 5.5%, 5.5 to less than 6.0%, 6.0 to less than 6.5%, and 6.5% or greater, the multivariable-adjusted hazard ratios (with 95% confidence intervals) for diagnosed diabetes were 0.52 (0.40 to 0.69), 1.00 (reference), 1.86 (1.67 to 2.08), 4.48 (3.92 to 5.13), and 16.47 (14.22 to 19.08), respectively. For coronary heart disease, the hazard ratios were 0.96 (0.74 to 1.24), 1.00 (reference), 1.23 (1.07 to 1.41), 1.78 (1.48 to 2.15), and 1.95 (1.53 to 2.48), respectively. The hazard ratios for stroke were similar. In contrast, glycated hemoglobin and death from any cause were found to have a J-shaped association curve. All these associations remained significant after adjustment for the baseline fasting glucose level. The association between the fasting glucose levels and the risk of cardiovascular disease or death from any cause was not significant in models with adjustment for all covariates as well as glycated hemoglobin. For coronary heart disease, measures of risk discrimination showed significant improvement when glycated hemoglobin was added to models including fasting glucose. *Conclusions* In this community-based population of nondiabetic adults, glycated hemoglobin was similarly associated with a risk of diabetes and more strongly associated with risks of cardiovascular disease and death from any cause as compared with fasting glucose. These data add to the evidence supporting the use of glycated hemoglobin as a diagnostic test for diabetes.] Selvin E, Steffes MW, et al. *NEJM*, Vol 362:800-811, March 4, 2010, No. 9. http://content.nejm.org/cgi/content/short/362/9/800?rss=1&query=current

456. **Heightened Gingival Inflammation and Attachment Loss in Type 2 Diabetics With Hyperlipidemia**. [This confirms our earlier work in the diabetic rat model. These studies indicate that decreased metabolic control in type 2 diabetics results in increased serum triglycerides and has a negative influence on all clinical measures of periodontal health, particularly in patients without preexisting periodontitis. Levels of the cytokine IL-1β showed a trend for increasing as diabetic control diminished. In contrast, levels of the growth factor PDGF, which normally increase in periodontitis, decreased in poorly controlled diabetics with periodontitis. These studies suggest a possible dysregulation of the normal cytokine/growth factor signaling axis in poorly controlled type 2 diabetics that may contribute to periodontal breakdown/diminished repair.] Cutler CW, Machen RL, et al. *J Periodontol 1999;70:1313-1321*. http://www.joponline.org/doi/abs/10.1902/jop.1999.70.11.1313

457. **Identification of Unrecognized Diabetes and Pre-diabetes in a Dental Setting**. [Many diabetic patients remain undiagnosed, and oral findings may offer an unrealized opportunity for the identification of affected individuals unaware of their condition. We recruited 601 individuals who presented for care at a dental clinic, were ≥ 40 years old, if non-Hispanic white, and ≥ 30 years old, if Hispanic or non-white, and had never been told they have pre-diabetes or diabetes. Those with at least one self-reported diabetes risk factor (N = 535) received a periodontal examination and a point-of-care hemoglobin A1c (HbA1c) test. A fasting plasma glucose (FPG) test was used as the study outcome, signifying potential diabetes or pre-diabetes. Performance characteristics of simple models of dysglycemia (FPG ≥ 100 mg/dL) identification were evaluated and optimal cut-offs identified. A model including only two dental variables had an estimated area under the receiver operating characteristic curve (AUC) of 0.65. The addition of a point-of-care HbA1c test improved the AUC to 0.79 ($p < 0.001$). The presence of ≥ 26% deep pockets or ≥ 4 missing teeth correctly identified 73% of true cases; the addition of an HbA1c ≥ 5.7% increased correct identification to 92%. Analysis of our data suggests that oral healthcare professionals have the opportunity to identify unrecognized diabetes and pre-diabetes in dental patients and refer them to a physician for further evaluation and care.] Lalla E, Kunzel C, et al. *JDR* July 2011 vol. 90 no. 7 855-860 http://jdr.sagepub.com/content/90/7/855.abstract

458. **Impact of advances in diabetes care on dental treatment of the diabetic patient.** [In medicine and dentistry, studies are published periodically that have a potentially wide-ranging impact on patient health and management. One such study is the Diabetes Control and Complications Trial (DCCT), which offers new hope for millions of individuals with diabetes and has begun to significantly alter medical management of these patients. Advances in the medical treatment of diabetes require a heightened awareness by dental practitioners of the various treatment regimens of their patients with diabetes, especially because of potential complications associated with diabetes care. Intensive medical treatment with oral agents and exogenous insulin injection promises to decrease the long-term risks of major complications of diabetes, but these treatments increase the risk of medical emergencies, especially hypoglycemia. This article reviews the findings of the DCCT, diabetes treatment regimens that might be encountered in a dental practice, and potential alterations to dental treatment protocols.]Mealey BL. *Compend Contin Educ Dent*. 1998 Jan;19(1):41-4, 46-8. http://www.ncbi.nlm.nih.gov/pubmed/9533351

459. **Increased serum levels of lipoprotein(a) in diabetes mellitus and their reduction with glycemic control.** [It has been sad that serum levels of lipoprotein(a) are genetically determined and are poorly influenced either by dietary measures or by hypolipidemic drugs. Substantial epidemiologic data support a potential relationship between serum levels of Lp(a) and atherosclerotic disease. Atherosclerotic disease is the most common complication of diabetes, especially in case of poor glycemic control; however, the mechanism whereby such complication arises is not well understood. We have found high serum levels of Lp(a) in 10 poorly controlled insulin-dependent diabetics when compared with nondiabetic control subjects. Twenty-one days after control of blood glucose levels, Lp(a) levels were dramatically decreased and a significant correlation was found between the percentage reduction in serum Lp(a) level and the percentage decrease in the concentration of both fasting glood glucose and glycosylated hemoglobin. The relationship between diabetes and Lp(a) levels has not yet been

described and may constitute an important risk factor in poorly controlled diabetes.] Bruckert E, Davidoff P, et al. *JAMA.* 1990 Jan 5;263(1):35-6. http://www.ncbi.nlm.nih.gov/pubmed/2136711?dopt=Abstract

460. **Inflammation and insulin resistance.** [Over a hundred years ago, high doses of salicylates were shown to lower glucose levels in diabetic patients. This should have been an important clue to link inflammation to the pathogenesis of type 2 diabetes (T2D), but the antihyperglycemic and antiinflammatory effects of salicylates were not connected to the pathogenesis of insulin resistance until recently. Together with the discovery of an important role for tissue macrophages, these new findings are helping to reshape thinking about how obesity increases the risk for developing T2D and the metabolic syndrome. The evolving concept of insulin resistance and T2D as having immunological components and an improving picture of how inflammation modulates metabolism provide new opportunities for using antiinflammatory strategies to correct the metabolic consequences of excess adiposity…. TNF-α, IL-6, resistin, and undoubtedly other pro- or antiinflammatory cytokines appear to participate in the induction and maintenance of the subacute inflammatory state associated with obesity. MCP-1 and other chemokines have essential roles in the recruitment of macrophages to adipose tissue. These cytokines and chemokines activate intracellular pathways that promote the development of insulin resistance and T2D.] Shoelson SE, Lee J, Goldfine AB. *J. Clin. Invest.* 116(7):1793-1801(2006). http://www.jci.org/articles/view/29069
461. **Inflammation and Progressive Nephropathy in Type 1 Diabetes Mellitus in the Diabetes Control and Complications Trial (DCCT). [**Objective: Progressive nephropathy represents a substantial source of morbidity and mortality in type 1 diabetes. Increasing albuminuria is a strong predictor of progressive renal dysfunction and heightened cardiovascular risk. Early albuminuria likely reflects vascular endothelial dysfunction, which may be mediated in part by chronic inflammation. Research Design and Methods: We measured baseline levels of four inflammatory biomarkers (high sensitivity C-reactive protein [hsCRP], soluble intercellular adhesion molecule-1 [sICAM-1], soluble vascular cell adhesion molecule-1 [sVCAM-1], and soluble tumor necrosis factor alpha receptor-1 [sTNF-R1]) in stored blood samples from the 1441 participants of the Diabetes Control and Complication Trial (DCCT). We used mixed effects regression models to determine the average change in urinary albumin excretion (AER) by tertiles of each biomarker. We also used Cox proportional hazards models to estimate the relative risk of incident sustained microalbuminuria (MA) according to levels of each biomarker. Results: After adjustment for baseline age, sex, duration of diabetes, hemoglobin A1c%, and randomized treatment assignment, we observed a significantly higher 5.9 mcg/min/year increase in AER among those in the highest compared to the lowest tertile of baseline sICAM-1 (p=0.04). Those in the highest tertile of sICAM-1 had an adjusted relative risk of 1.67 (95% CI, 0.96 to 2.92) of developing incident sustained MA (p-for-trend=0.03). Conclusions: Higher baseline sICAM-1 levels predicted an increased risk of progressive nephropathy in type 1 diabetes and may represent an early risk marker that reflects the important role of vascular endothelial dysfunction in this long-term complication.] Lin J, Glynn Rj, Ridker PM, et al. *Diabetes Care, 2008 Sep 16.*
http://www.ncbi.nlm.nih.gov/pubmed/18796620?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum
462. **Inflammation and Type 2 Diabetes. [**The link between heart disease and inflammation was made, in part, when doctors found higher levels of markers of inflammation in the blood of people with heart disease and then found that such markers also predicted risk for a heart attack. Higher levels of those same markers have now been found in people with diabetes and those at high risk for diabetes. One of those markers is CRP (C-reactive protein), which appears to be elevated in the presence of heart disease, diabetes, and obesity.] American Diabetes Association 62nd Annual Scientific Session.
http://www.scienceblog.com/community/older/archives/K/2/pub2830.html
463. **Inflammation, Stress and Diabetes**. [Over the last decade, an abundance of evidence has emerged demonstrating a close link between metabolism and immunity. It is now clear that obesity is associated with a state of chronic low-level inflammation. In this article, we discuss the molecular and cellular underpinnings of obesity-induced inflammation and the signaling pathways at the intersection of metabolism and inflammation that contribute to diabetes. We also consider mechanisms through which the inflammatory response may be initiated and discuss the reasons for the inflammatory response in obesity. We put forth for consideration some hypotheses regarding important unanswered questions in the field and suggest a model for the integration of inflammatory and metabolic pathways in metabolic disease.] Wellen KE< Hotamisligil GS. *J. Clin. Invest.* **115**(5): 1111-1119 (2005). http://www.jci.org/115/5/1111?content_type=full
464. **Inflammation.** [Research has uncovered a link between inflammation and diabetes as well. In the Cardiovascular Health Study, the quartile of people with the highest CRP levels were three to four times more likely to develop diabetes within three to four years of the study than the quartile of people with the lowest levels of CRP. Some researchers speculate that Type 2 diabetes and atherosclerosis may be caused by some of the same underlying mechanisms—and that one of these mechanisms may be inflammation.] Diabetes Self-Management.
http://www.diabetesselfmanagement.com/articles/Diabetes_Definitions/Inflammation
465. **Insulin resistance, inflammation, and the prediabetic state.** [Type 2 diabetes is associated with a marked increase in the incidence of coronary artery disease (CAD); however, the correlation between glycemia and CAD in patients with type 2 diabetes is only modestly positive. This relatively weak association between glycemia and CAD in subjects with diabetes may be caused by the existence of an atherogenic prediabetic state. In the San Antonio Heart Study, subjects who start with normal glucose tolerance and later develop type 2 diabetes have increased triglyceride levels, increased systolic blood pressure, and decreased levels of high-density lipoprotein cholesterol before the onset of type 2 diabetes. The basis for these atherogenic prediabetic changes may be related to insulin resistance rather than reduced insulin secretion. Recently, interest has focused on a possible role of fibrinolysis and increased subclinical inflammation, as determined by high-sensitivity C-

reactive protein (CRP) levels. The Insulin Resistance Atherosclerosis Study found that insulin resistance, as determined by a frequently sampled glucose tolerance test, is significantly related to higher CRP levels, higher fibrinogen, and higher plasminogen activator inhibitor-1 (PAI-1) levels. The investigators also have shown that high PAI-1 and CRP levels are predictors of the development of type 2 diabetes. In addition, the Women's Health Study has shown that high CRP levels predict type 2 diabetes. Insulin-sensitizing interventions have been demonstrated to reduce these nontraditional risk factors. Rosiglitazone, an agent with insulin-sensitizing properties, decreases PAI-1 and CRP levels. Some of the adverse cardiovascular effects seen in patients with type 2 diabetes may be reversed by insulin-sensitizing agents.] Haffner SM. *Am J Cardiol*, 2003 Aug 18;92(4A):18J-26J. http://www.ncbi.nlm.nih.gov/pubmed/12957323

466. **Links between periodontal disease and general health. Preterm birth, diabetes and autoimmune diseases.** [The condition of the periodontium may effect people's general health. There is evidence of a correlation between periodontal disease and preterm birth or low birth weight. In pregnant women with periodontal disease, scaling and root planing seems to reduce the risk of preterm birth or low birth weight. Furthermore, periodontal disease appears to have an adverse effect on glycemic control in diabetics. However, periodontal treatment as a means to glycemic control is restricted unless it includes the use of systemic antibiotics. Slowly, a possible correlation between periodontal disease and autoimmune diseases is emerging. Further research into the correlations between periodontal disease and systemic health is desirable and might well result in new therapeutic options.] Neese W, Spijkervat FK, et al. *Ned Tijdschr Tandheelkd. 2006 May;113(5):191-6.* http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=16729564&ordinalpos=16&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

467. **Lipopolysaccharide activates an innate immune system response in human adipose tissue in obesity and type 2 diabetes.** [Type 2 diabetes (T2DM) is associated with chronic low-grade inflammation. Adipose tissue (AT) may represent an important site of inflammation. 3T3-L1 studies have demonstrated that lipopolysaccharide (LPS) activates toll-like receptors (TLRs) to cause inflammation. For this study, we *1*) examined activation of TLRs and adipocytokines by LPS in human abdominal subcutaneous (AbdSc) adipocytes, *2*) examined blockade of NF-κB in human AbdSc adipocytes, *3*) examined the innate immune pathway in AbdSc AT from lean, obese, and T2DM subjects, and *4*) examined the association of circulating LPS in T2DM subjects. The findings showed that LPS increased TLR-2 protein expression twofold ($P < 0.05$). Treatment of AbdSc adipocytes with LPS caused a significant increase in TNF-α and IL-6 secretion (IL-6, Control: 2.7 ± 0.5 vs. LPS: 4.8 ± 0.3 ng/ml; $P < 0.001$; TNF-α, Control: 1.0 ± 0.83 vs. LPS: 32.8 ± 6.23 pg/ml; $P < 0.001$). NF-κB inhibitor reduced IL-6 in AbdSc adipocytes (Control: 2.7 ± 0.5 vs. NF-κB inhibitor: 2.1 ± 0.4 ng/ml; $P < 0.001$). AbdSc AT protein expression for TLR-2, MyD88, TRAF6, and NF-κB was increased in T2DM patients ($P < 0.05$), and TLR-2, TRAF-6, and NF-κB were increased in LPS-treated adipocytes ($P < 0.05$). Circulating LPS was 76% higher in T2DM subjects compared with matched controls. LPS correlated with insulin in controls ($r = 0.678$, $P < 0.0001$). Rosiglitazone (RSG) significantly reduced both fasting serum insulin levels (reduced by 51%, $P = 0.0395$) and serum LPS (reduced by 35%, $P = 0.0139$) in a subgroup of previously untreated T2DM patients. In summary, our results suggest that T2DM is associated with increased endotoxemia, with AT able to initiate an innate immune response. Thus, increased adiposity may increase proinflammatory cytokines and therefore contribute to the pathogenic risk of T2DM.] Creely SJ, McTernan PG, et al. *Am J Physiol Endocrinol Metab* 292: E740-E747, 2007 . http://ajpendo.physiology.org/cgi/content/abstract/292/3/E740

468. **Low-Grade Inflammation, Obesity, and Insulin Resistance in Adolescents.** [Low-grade inflammation is associated with insulin resistance and precedes the onset of type 2 diabetes mellitus in adults, but there are no comparable data in youth. The objective of the study was to characterize the pattern of subclinical immune activation that is associated with indices of obesity and insulin resistance in youth and analyze whether this association is explained by obesity. Conclusions: We found that a differential low-grade immune activation is associated with parameters of obesity in adolescents. Moreover, there is evidence that IL-6, IL-18, IP-10, and adiponectin (inversely) are associated with insulin resistance and that these associations can mainly be attributed to obesity.] Herder C, Schneitler S, et al. Journal of Clinical Endocrinology & Metabolism, Vol. 92, No. 12 4569-4574. http://jcem.endojournals.org/cgi/content/abstract/92/12/4569

469. **Low-Grade Systemic Inflammation and the Development of Type 2 Diabetes.** [To examine the association of low-grade systemic inflammation with diabetes, as well as its heterogeneity across subgroups, we designed a case-cohort study representing the ~9-year experience of 10,275 Atherosclerosis Risk in Communities Study participants. Analytes were measured on stored plasma of 581 incident cases of diabetes and 572 noncases. Statistically significant hazard ratios of developing diabetes for those in the fourth (versus first) quartile of inflammation markers, adjusted for age, sex, ethnicity, study center, parental history of diabetes, and hypertension, ranged from 1.9 to 2.8 for sialic acid, orosomucoid, interleukin-6, and C-reactive protein. After additional adjustment for BMI, waist-to-hip ratio, and fasting glucose and insulin, only the interleukin-6 association remained statistically significant (HR = 1.6, 1.01–2.7). Exclusion of GAD antibody-positive individuals changed associations minimally. An overall inflammation score based on these four markers plus white cell count and fibrinogen predicted diabetes in whites but not African Americans (interaction $P = 0.005$) and in nonsmokers but not smokers (interaction $P = 0.13$). The fully adjusted hazard ratio comparing white nonsmokers with score extremes was 3.7 (P for linear trend = 0.008). In conclusion, a low-grade inflammation predicts incident type 2 diabetes. The association is absent in smokers and African-Americans.] Duncan BB, Schmidt MI, et al. *Diabetes* 52:1799-1805, 2003 http://diabetes.diabetesjournals.org/cgi/content/abstract/52/7/1799

470. **Oral Complications in Diabetes.** [Periodontal disease is more severe and occurs with higher frequency in diabetic patients. http://diabetes.niddk.nih.gov/dm/pubs/america/pdf/chapter23.pdf

471. **Oral Health in Diabetes Care Gaining Traction at the American Diabetes Association.** ["As long as [diabetic patients] have ongoing infections in their mouths, their diabetes is very difficult to manage often leading to the need for more and more insulin."] Casey Hein, quoting Nathaniel G. Clark, V.P. of American Diabetic Assoc. *Grand Rounds in Oral-Systemic Medicine*, p. 48 http://www.grandrounds-digital.com/grandrounds/200605/
472. **Periodontitis and diabetes associations with measures of atherosclerosis and CHD.** [OBJECTIVE: Diabetes has been linked with more severe periodontal disease and with coronary heart disease (CHD). The purpose of this study was to determine if periodontal infection was a significant modifier in the risk that diabetes poses for increased carotid artery intimal-medial wall thickness (IMT) and more advanced atheroma lesions as reflected in atherosclerotic plaque calcification measured by acoustic shadowing. METHODS AND RESULTS: Comparisons for analyses of cardiovascular outcomes were performed based upon periodontitis and diabetes status. Periodontitis was measured using pocket depth and attachment loss at six sites per tooth. Cross-sectional data on 6048 persons aged 52-74 years were obtained from the Dental Atherosclerosis Risk in Communities Study. Participants without diabetes (n=5257) were compared to those with diabetes (n=791). Dependent variables were thick IMT (>1mm), presence of acoustic shadowing, and prevalent CHD. All models were adjusted for the following covariates: gender, age, race/center, LDL and HDL cholesterol, BMI, triglycerides, hypertension, smoking, income and education. For multivariate model building, all non-normally distributed variables were transformed and multivariable logistic regression analyses were performed to evaluate the relationship between periodontal infection, diabetes, and cardiovascular outcomes. Individuals with diabetes and with severe periodontitis were found to be significantly more likely to have IMT>1mm [OR=2.2, (1.4-3.5)], acoustic shadowing [OR=2.5, (1.3-4.6)], and CHD [OR=2.6, (1.6-4.2)] compared to those without diabetes or periodontal disease. CONCLUSION: Results from this study suggest that among people with diabetes, periodontal disease may increase the likelihood of subclinical atherosclerotic heart disease and CHD.] Southerland JH, Moss K, et al. *Atherosclerosis*. 2012 May;222(1):196-201. Epub 2012 Jan 30. http://www.ncbi.nlm.nih.gov/pubmed/22440543
473. **Periodontal Disease – Its Impact on Diabetes and Glycemic Control**. [There is a bidirectional link between diabetes mellitus and periodontal disease. It is important to note that evidence is accumulating that supports the role of periodontal treatment in the improvement of poor glycemic control. Therefore, both dental professionals and primary care practitioners should understand the significance of this link, as it can impact treatment and progression of both diabetes and periodontal disease.] Cheung S, Hsu WC, et al.Joslin Diabetes Center, Harvard University. http://jpec.joslin.org/JPECWeb/CareKitFiles/SunStar%20Diabetes%20and%20Dental%20Health%20Provider%20Handout.pdf
474. **Periodontal disease and control of diabetes mellitus.** [Data from the Centers for Disease Control and Prevention indicate that more than 20 million people (approximately 7% of the population) in the United States have diabetes mellitus. Physicians often fail to examine the mouths and teeth of their patients, even though the condition of the mouth and teeth have clinical relevance for the treatment of patients with diabetes mellitus. The authors examine the current state of knowledge regarding periodontal disease and the effect of periodontal disease on worsening of glycemic control. They review several studies investigating how the management of periodontal disease affects the ability of patients to control symptoms of diabetes mellitus. The authors conclude with several recommendations for the treatment of patients with periodontal disease to improve glycemic control.] Herring ME, Shah SK. *J Am Osteopath Assoc. 2006 Jul;106(7):416-21.* http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=16912341&ordinalpos=43&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum
475. **Periodontal disease and diabetes – A two way street.** [A large evidence base suggests that diabetes is associated with an increased prevalence, extent and severity of gingivitis and periodontitis. Furthermore, numerous mechanisms have been elucidated to explain the impact of diabetes on the periodontium. While inflammation plays an obvious role in periodontal diseases, evidence in the medical literature also supports the role of inflammation as a major component in the pathogenesis of diabetes and diabetic complications. Research suggests that, as an infectious process with a prominent inflammatory component, periodontal disease can adversely affect the metabolic control of diabetes. Conversely, treatment of periodontal disease and reduction of oral inflammation may have a positive effect on the diabetic condition, although evidence for this remains somewhat equivocal.] Mealey BL, *JADA, Vol.137, Oct.2006 Supplement, pp.26s-31s.* http://jada.ada.org/content/vol137/suppl_2/index.dtl
476. **Periodontal disease and diabetes mellitus.** [Infections of the tissue surrounding the teeth (periodontitis) are usually caused by anaerobic gram-negative microorganisms. This infection causes destruction of the supporting alveolar bone and can lead to tooth loss. Removal of these microorganisms can slow or arrest the progression of periodontitis. Diabetes patients are at greater risk of developing periodontitis, may not respond as well to periodontal therapy as nondiabetic patients, and may require more aggressive treatment to manage periodontitis. Microorganisms that cause periodontitis and the host response to these may increase insulin resistance in diabetic patients. Treatment of periodontitis could improve glycemic control. A model is presented in which periodontal pathogens may cause increases in proinflammatory cytokines that mediate increases in insulin resistance, resulting in an increase in blood glucose. Following periodontal therapy, this process may be reversed.] Pucher J, Stewart J. *Current Diabetes Reports*, Vol 4, No. 1, pp46-50, Feb 2004. http://www.springerlink.com/content/rj40r60044t24735/
477. **Periodontal disease and diabetes mellitus: a two-way relationship.** [Severe periodontal disease often coexists with severe diabetes mellitus. Diabetes is a risk factor for severe periodontal disease. A model is presented whereby severe periodontal disease increases the severity of diabetes mellitus and complicates metabolic control. We propose that an infection-mediated

upregulation cycle of cytokine synthesis and secretion by chronic stimulus from lipopolysaccharide (LPS) and products of periodontopathic organisms may amplify the magnitude of the advanced glycation end product (AGE)-mediated cytokine response operative in diabetes mellitus. In this model, the combination of these 2 pathways, infection and AGE-mediated cytokine upregulation, helps explain the increase in tissue destruction seen in diabetic periodontitis, and how periodontal infection may complicate the severity of diabetes and the degree of metabolic control, resulting in a 2-way relationship between diabetes mellitus and periodontal disease/infection. This proposed dual pathway of tissue destruction suggests that control of chronic periodontal infection is essential for achieving long-term control of diabetes mellitus. Evidence is presented to support the hypothesis that elimination of periodontal infection by using systemic antibiotics improves metabolic control of diabetes, defined by reduction in glycated hemoglobin or reduction in insulin requirements.] Grossi SG, Genco RJ. *Ann Periodontol. 1998 Jul;3(1):51-61*.
http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed&uid=9722690&cmd=showdetailview&indexed=google

478. **Periodontal Disease and Mortality in Type 2 Diabetes.** [Periodontal disease may contribute to the increased mortality associated with diabetes. Methods: In a prospective longitudinal study of 628 subjects aged 35 years, we examined the effect of periodontal disease on overall and cardiovascular disease mortality in Pima Indians with type 2 diabetes. Periodontal abnormality was classified as no or mild, moderate, and severe, based on panoramic radiographs and clinical dental examinations. Results: During a median follow-up of 11 years (range 0.3–16), 204 subjects died. The age- and sex-adjusted death rates for all natural causes expressed as the number of deaths per 1,000 person-years of follow-up were 3.7 (95% CI 0.7– 6.6) for no or mild periodontal disease, 19.6 (10.7–28.5) for moderate periodontal disease, and 28.4 (22.3–34.6) for severe periodontal disease. Periodontal disease predicted deaths from ischemic heart disease (IHD) (*P* trend_0.04) and diabetic nephropathy (*P* trend _ 0.01). Death rates from other causes were not associated with periodontal disease. After adjustment for age, sex, duration of diabetes, HbA1c, macroalbuminuria, BMI, serum cholesterol concentration, hypertension, electrocardiographic abnormalities, and current smoking in a proportional hazards model, subjects with severe periodontal disease had 3.2 times the risk (95% CI 1.1–9.3) of cardiorenal mortality (IHD and diabetic nephropathy combined) compared with the reference group (no or mild periodontal disease and moderate periodontal disease combined). Conclusions: Periodontal disease is a strong predictor of mortality from IHD and diabetic nephropathy in Pima Indians with type 2 diabetes. The affect of periodontal disease is in addition to the effects of traditional risk factors for these diseases.] Harold Loe, Robert J. Genco. *Diabetes Care 28L27-32, 2005*.
http://care.diabetesjournals.org/cgi/reprint/28/1/27?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=periodontal+disease&searchid=1&FIRSTINDEX=0&sortspec=relevance&resourcetype=HWCIT

479. **Periodontal Disease and Systemic Health – Diabetes**. [This article discusses the biologic basis of periodontal disease and diabetes mellitus. Following is a consideration of the possibility of a link between diabetes and periodontal disease. Mounting evidence suggests that there is, indeed, a connection between periodontal disease and diabetes.] Pucher JJ, Otomo-Corgel J. *Journal of CA Dent Assoc. April 2002*. http://www.cda.org/library/cda_member/pubs/journal/jour0402/diabetes.html

480. **Periodontal disease is associated with gestational diabetes mellitus: a case-control study**. [BACKGROUND: Few studies have specifically examined the relationship between periodontal disease and gestational diabetes mellitus (GDM). The objective of this study was to examine whether maternal periodontal disease is associated with GDM. METHODS: A case-control study was conducted of 53 pregnant women with GDM and 106 pregnant women without GDM at Woman's Hospital, Baton Rouge, Louisiana. The periodontal examinations were performed by a calibrated dentist who was masked to the diabetic status of the pregnant women. Periodontitis was defined as the presence of any site with a probing depth (PD) >or=4 mm or a clinical attachment loss (AL) >or=4 mm. The severity of periodontal disease was measured in quartiles of PD and clinical AL. Univariable analysis and multivariable logistic regression were used to examine the relationships between periodontal disease and GDM. RESULTS: The percentage of periodontitis was 77.4% in women with GDM and 57.5% in women without GDM, with an odds ratio (OR) of 2.5 and a 95% confidence interval (CI) of 1.2 to 5.3. After adjusting for confounding variables of maternal age, parity, race, marital status, education, family income, smoking, alcohol consumption, systemic antibiotics during pregnancy, family history of diabetes, income, dental insurance coverage, and body mass index, the adjusted OR (95% CI) was 2.6 (1.1 to 6.1). The adjusted ORs (95% CIs) of GDM comparing the highest-to-lowest quartiles of PD and clinical AL were 3.8 (1.0 to 14.0) and 4.5 (1.2 to 16.9). CONCLUSION: This study supports the hypothesis of an association between periodontal disease and GDM.] Xiong X, Elkind-Hirsch KE, et al. *J Periodontol*. 2009 Nov;80(11):1742-9. http://www.ncbi.nlm.nih.gov/pubmed/19905944

481. **Periodontal disease linked to mortality in diabetes patients: study.** [Investigators from the National Institute of Diabetes and Kidney Disease found a positive association between severity of periodontal disease and mortality in diabetes patients. The investigators found that periodontal disease was a positive predictor for deaths from ischemic heart disease and diabetic nephropathy. After adjusting for factors such as duration of diabetes, hypertension, tobacco use and other factors, they noted that "subjects with severe periodontal disease had 3.2 times the risk of cardiorenal mortality" compared with the groups with no or mild to moderate periodontal disease combined.] ADA News Release.
http://www.ada.org/prof/resources/pubs/adanews/adanewsarticle.asp?articleid=1219

482. **Periodontal Disease Predicts Mortality in Diabetics.** [Those with severe periodontal disease had a 28.4 % death rate and those with no or little periodontal disease had a 3.7% death rate.]
http://www.defeatdiabetes.org/Articles/periodontal050124.htm

483. **Periodontal Disease Predicts Mortality in Diabetics.** www.DiabetesinControl.com *Diabetes Care 2005;28:27-32* National Institute of Diabetes and Digestive and Kidney Disease, Phoenix, AZ. http://www.diabetesincontrol.com/modules.php?name=News&file=print&sid=2402

484. **Periodontal disease, diabetes, and immune response: a review of current concepts.** [A reasonable interpretation of the present evidence indicates that diabetes, when a complication of periodontitis, acts as a modifying and aggravating factor in the severity of periodontal infection. Diabetics with periodontitis who were young and poorly controlled, those who were long-duration diabetics, especially those over 30 years old, demonstrated more attachment loss, bone loss, and deeper probing pocket depths than their nondiabetic controls. It seems that the earlier the onset of diabetes and the longer the duration, especially without consistent control, the more susceptible the individual will be to periodontal disease. Consequently, once a diabetic contracts periodontal disease, it is usually more destructive. Although plaque scores of diabetics may be comparable to or even less than those of nondiabetics, diabetics often exhibit higher gingival index scores. The elevation of this particular clinical parameter is indicative of the microangiopathy associated with diabetes. Diabetic microangiopathy contributes to compromised delivery of nutrients to surrounding tissues and poor elimination of metabolic waste products. The complications associated with diabetes such as macroangiopathy, microangiopathy (i.e., retinopathy), ketoacidosis, and hyperglycemia result in impaired wound healing, immunosuppression, and susceptibility to bacterial infection. Individuals ages 30 to 40 suffering from diabetic retinopathy had significantly more gingival inflammation than controls or diabetics without complications. Collagen metabolism is defective in diabetics and is one component underlying delayed wound healing. Animal studies have been instrumental in elucidating the details of delayed wound healing. Hyperglycemia was associated with increased collagenase and protease activity in the gingiva of rats. Vascular wound healing in rats, particularly new re-endothelialization across vascular anastomoses, was significantly impaired. Diabetic abnormalities in immune response include impaired neutrophil chemotaxis, phagocytosis, and adhesion. Decreased neutrophilic chemotactic response seems to be attributable to protein factors in diabetic serum that competitively bind neutrophil receptors, thereby preventing complement-mediated phagocytosis. Because diabetics are not able to eliminate circulating immune complexes (CIC) effectively, serum CIC levels are elevated. There are microbiological differences in the characteristic flora of NIDDM patients and IDDM patients with periodontitis. These differences are not associated with diabetic impaired immune response. Ultimately, bacterial plaque is the primary etiology of periodontal diseases. Evidently, the host's response to bacterial plaque and ability to heal following surgery is altered by diabetic disease. Therefore, a thorough history regarding onset of diabetes, duration, and diabetic control would prove useful in the clinical management of diabetics presenting for treatment of periodontal disease.] Grant-Theule DA. *J West Soc Periodontol Periodontal Abstr. 1996;44(3):69-77.* http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9477864&dopt=Abstract

485. **Periodontal disease. The sixth complication of diabetes mellitus.** [ ] *Diabetes Care. 1993 Jan;16(1):329-34.* http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed&uid=8422804&cmd=showdetailview&indexed=google

486. **Periodontal Pathogens and Gestational Diabetes Mellitus.** [In previous cross-sectional or case-control studies, clinical periodontal disease has been associated with gestational diabetes mellitus. To test the hypothesis that, in comparison with women who do not develop gestational diabetes mellitus, those who do develop it will have had a greater exposure to clinical and other periodontal parameters, we measured clinical, bacteriological (in plaque and cervico-vaginal samples), immunological, and inflammatory mediator parameters 7 weeks before the diagnosis of gestational diabetes mellitus in 265 predominantly Hispanic (83%) women in New York. Twenty-two cases of gestational diabetes mellitus emerged from the cohort (8.3%). When the cases were compared with healthy control individuals, higher pre-pregnancy body mass index ($p = 0.004$), vaginal levels of *Tannerella forsythia* ($p = 0.01$), serum C-reactive protein ($p = 0.01$), and prior gestational diabetes mellitus ($p = 0.006$) emerged as risk factors, even though the clinical periodontal disease failed to reach statistical significance (50% in those with gestational diabetes mellitus *vs.* 37.3% in the healthy group; $p = 0.38$).] Dasanayake AP, Chhun N, et al. *J Dent Res* 87(4):328-333, 2008 http://jdr.iadrjournals.org/cgi/content/abstract/87/4/328 http://www.sciencedaily.com/releases/2008/03/080324122301.htm

487. **Periodontal problems can complicate the management of diabetes**, and uncontrolled diabetes may aggravate periodontal disease. Recent studies indicate that the majority of the U.S. population has some periodontal disease including the most common form, chronic adult periodontitis, formerly known as pyorrhea. http://www.diabetesmonitor.com/b285.htm

488. **Periodontal therapy reduces the cost of medical care in diabetics.** [Objectives: The aim of this study was to determine if periodontal treatment affected the cost of medical care in diabetics. Methods: A longitudinal study compared medical costs for diabetic subjects receiving periodontal treatment versus control diabetic subjects during a three year study period (2006-2008, N=3449). Subjects were enrolled in CIGNA's medical and dental plans, aged 18-62, and received medical services, and dental services. The periodontal treatment group had periodontal disease at baseline, was treated in the first year, and maintained thereafter. The control group had received periodontal therapy prior to baseline, and did not receive regular maintenance during the study. Descriptive statistics were calculated. A multi-variant analysis of the variance was used with the following variables sex, age and periodontal treatment. The primary outcome was the medical cost in 2008. Results: The mean cost for medical care in diabetics was $9697.40 in 2008. The medical costs for all diabetic subjects categorized by periodontal treatment group are shown in the table below … Significantly lower medical costs were associated with periodontal treatment (effect $F(1,3447)$-5.3444,$p=0.021$). Thus a mean savings of $2483.51 was realized per patient in a single year independent of age. In males, there was a $3212.36 mean difference in medical costs in 2008 per patient per year favoring the periodontal treatment group. ($p<0.03$) In females, this result was also significant, but the mean difference between treatment and controls was smaller ($735.27 per patient per year)($p<0.05$). Conclusions: In this data set periodontal

treatment was associated with a significant decrease in the cost of medical care in diabetics. These savings averaged $2483.51 per patient in a single year independent of age.] Jeffcoat M, Tanna N, et al. *IADR General Session,* San Diego CA, March 2011. http://iadr.confex.com/iadr/2011sandiego/webprogram/Paper143286.html

489. **Periodontitis as a component of hyperinflammation: treating periodontitis in obese diabetic patients.** [Increasing evidence points to periodontal disease as a significant risk factor in the etiology of other diseases with inflammatory components, such as cardiovascular disease and type 2 diabetes mellitus. Thus, it may be possible to reduce the risk for other diseases with an inflammatory component by maintaining a healthy periodontium. In addition to plaque and calculus, other factors such as diet, body weight, lifestyle, and environmental stress complicate the maintenance of a healthy periodontium. It is becoming more important for the general dentist to address these additional risk factors in addition to providing conventional treatment for periodontal disease. This review addresses a multifactorial approach to the treatment of periodontal disease and suggests that the "focal theory" of infection may still be relevant for oral inflammation.] Johnson RB. *Compend Contin Educ Dent*. 2007 Sep;28(9):500-4. http://www.ncbi.nlm.nih.gov/pubmed/17907373
490. **Periodontitis Is Associated With Aggravation of Prediabetes in Zucker Fatty Rats.** [Prediabetes is part of the natural history of type 2 diabetes. Few human studies have addressed the relationship between periodontitis and prediabetes. The Zucker fatty rat (ZFR) is a known model of prediabetes, characterized by hyperinsulinemia, dyslipidemia, and moderate hypertension. The aim of the present study was to investigate whether periodontitis affects the prediabetic state of ZFRs. Prediabetes worsened periodontitis, and periodontitis, in turn, was associated with deterioration of glucose metabolism in ZFRs, suggesting a progress toward diabetes. Furthermore, periodontitis also affected glucose regulation in lean rats.] Andersen CCP, Flyvbjerg Allan, et al. *Journal of Periodontology, 2007, Vol. 78, No. 3, Pages 559-565.* http://www.joponline.org/doi/abs/10.1902/jop.2007.060358
491. **Poor Oral Health Puts Patients with Diabetes at Higher Risk of Death**. [Severe gum disease in patients with diabetes makes them twice as likely to die from kidney failure or heart disease. When the gums pull far away from the teeth due to severe gum disease, harmful bacteria from the mouth are allowed to enter the bloodstream, affecting these organs.] ADA news release, http://www.ada.org/public/media/releases/0310_release07.asp
492. **Poorly controlled Type 2 diabetics twice as likely to develop periodontal disease.** [People with diabetes are more likely to have periodontal disease than people without diabetes, probably because diabetics are more susceptible to contracting infections. In fact, periodontal disease is often considered the sixth complication of diabetes. Those people who don't have their diabetes under control are especially at risk. Research has emerged that suggests that the relationship between periodontal disease and diabetes goes both ways - periodontal disease may make it more difficult for people who have diabetes to control their blood sugar.] American Academy of Periodontology. http://www.perio.org/consumer/mbc.diabetes.htm
493. **Relationship between metabolic syndrome and diagnoses of periodontal diseases among participants in a large Taiwanese cohort.** [OBJECTIVE: Epidemiological studies suggested that individuals suffering from periodontitis present with greater prevalence of metabolic syndrome (MetS) and diabetes. We used a large health check-up data set in Taiwan to investigate this association. DESIGN AND METHODS: Data from 33,740 individuals, who undertook comprehensive health check-up at a university hospital in Taipei, Taiwan, were analysed. The dental examinations were undertaken by experienced dentists, and the diagnosis of MetS was made according to the criteria defined by the Third Adult Treatment Panel of the National Cholesterol Education Program. RESULTS: After adjusting for potential confounders, females and males in the periodontitis group had higher levels of blood pressure, blood glucose, triglyceride and body mass index, but lower high-density lipoprotein compared to controls. Females in the gingivitis and periodontitis group showed greater odds ratios [1.42 (95% CI: 1.30-1.56) and 1.52 (1.41-1.63) respectively] of being diagnosed with MetS, whereas males in the gingivitis and periodontitis group presented with odds ratios of being diagnosed with MetS of 1.06 (0.94-1.18) and 1.04 (0.96-1.12) respectively. CONCLUSIONS: A small but statistically significant association between MetS and the diagnosis of periodontal diseases was found in Taiwanese women and a weaker association in Taiwanese men.] Ru YK, D'Aiuto F, et al. *J Clin Periodontol*. 2013 Nov;40(11):994-1000. http://www.ncbi.nlm.nih.gov/pubmed/24007401
494. **Relationship between periodontal disease and diabetes mellitus: an Asian perspective**. [Physicians and dentists have restricted themselves to their own respective fields in the past, only treating diseases that are relevant to their own fields of specialization. However, recent findings indicate that oral health may influence systemic health, and that this may influence systemic health, and that this maybe a bi-directional relationship in some conditions. This is particularly true for the relationship betweenperiodontal disease and diabetes mellitus. The inter-relationship between periodontal disease and diabetes mellitus provides an example of a cyclical association, whereby a systemic disease predisposes the individual to oral infections, and, once the oral infection is established, it exacerbates the systemic disease. There are also associations between periodontal disease and systemic conditions such as cardiovascular problems, pulmonary conditions, osteoporosis, obesity, pancreatic cancer and Alzherimer's diseas. Hence, emphasis should now be placed on treating periodontal and other chronic dental diseases as a means of ameliorating systemic diseases.] Taiyeb-Ali, TB, Renukanth P, et al. *Periodontology 2000,* vol 56, issue 1 pp 258-268, June 2011. **http://www.ncbi.nlm.nih.gov/pubmed/21501247**; **http://onlinelibrary.wiley.com/doi/10.1111/j.1600-0757.2010.00370.x/abstract**
495. **Relationship of Porphyromonas gingivalis with glycemic level in patients with type 2 diabetes following periodontal treatment.** [INTRODUCTION: The aim of this study was to assess the relationship between serum glycemic levels and subgingival microbial profile alteration following periodontal treatment in patients with type 2 diabetes mellitus. METHODS: We studied 30 periodontitis patients with type 2 diabetes mellitus who received full-mouth subgingival

debridement by analyzing their subgingival microbial profiles using a polymerase chain reaction method at baseline and various time-points for 12 months following treatment. Concurrently, probing pocket depth, bleeding on probing, and metabolic parameters, including glycated hemoglobin A1c (HbA1c), blood sugar level, C-reactive proteins, total cholesterol, triglyceride, and high-density and low-density lipoprotein cholesterol, were recorded. RESULTS: Periodontal conditions were significantly improved after treatment, and the occurrence rates of periodontal bacterial species, including Porphyromonas gingivalis, Tannerella forsythensis, Treponema denticola, and Prevotella intermedia, were also reduced. Interestingly, P. gingivalis was detected more frequently in subjects with increased HbA1c values after periodontal treatment than in those patients with decreased HbA1c values. Furthermore, P. gingivalis with type II fimbriae was detected only in HbA1c-increased subjects, while improvements in HbA1c values were observed only in subjects without type II clones. CONCLUSIONS: These results suggest that glycemic level in diabetes is affected by the persistence of P. gingivalis, especially clones with type II fimbriae, in periodontal pockets.] Makiura N, Ojima M, et al. Oral Microbiol Immunol. 2008 Aug;23(4):348-51. http://www.ncbi.nlm.nih.gov/pubmed/18582336

496. **Skeletal muscle insulin resistance: role of inflammatory cytokines and reactive oxygen species.** [The cardiometabolic syndrome (CMS), with its increased risk for cardiovascular disease (CVD), nonalcoholic fatty liver disease (NAFLD), and chronic kidney disease (CKD), has become a growing worldwide health problem. Insulin resistance is a key factor for the development of the CMS and is strongly related to obesity, hyperlipidemia, hypertension, type 2 diabetes mellitus (T2DM), CKD, and NAFLD. Insulin resistance in skeletal muscle is particularly important since it is normally responsible for more than 75% of all insulin-mediated glucose disposal. However, the molecular mechanisms responsible for skeletal muscle insulin resistance remain poorly defined. Accumulating evidence indicates that low-grade chronic inflammation and oxidative stress play fundamental roles in the development of insulin resistance, and inflammatory cytokines likely contribute to the link between inflammation, oxidative stress, and skeletal muscle insulin resistance. Understanding the mechanisms by which skeletal muscle tissue develops resistance to insulin will provide attractive targets for interventions, which may ultimately curb this serious problem. This review is focused on the effects of inflammatory cytokines and oxidative stress on insulin signaling in skeletal muscle and consequent development of insulin resistance.] Wei Y, Chen K, et al. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology*, Published 1 March 2008Vol. 294no. R673-R680DOI: 10.1152/ajpregu.00561.2007. http://ajpregu.physiology.org/content/294/3/R673

497. **Standards of Medical Care in Diabetes—2009.** [Diabetes is a chronic illness that requires continuing medical care and patient self-management education to prevent acute complications and to reduce the risk of long-term complications. Diabetes care is complex and requires that many issues, beyond glycemic control, be addressed. A large body of evidence exists that supports a range of interventions to improve diabetes outcomes. Joint committee of ADA, the European Association for the Study of Diabetes, and the International Diabetes Federation will likely recommend that the A1C become the preferred diagnostic test for diabetes.] American Diabetes Association. http://care.diabetesjournals.org/content/32/Supplement_1/S13.full.

498. **Study Links Good Oral Care to Lower Diabetes Care Costs** [University of Michigan researchers studied claims of an unprecedented 21,000 adults with diabetes who had Blue Cross Blue Shield of Michigan medical, pharmacy and Blue Dental coverage. Time in a dentist's chair may save medical dollars; 10 to 40 percent for individuals with diabetes and other chronic health conditions. A University of Michigan study, commissioned by the Blue Cross Blue Shield of Michigan Foundation, suggests a link between good oral health and lower medical costs for people with diabetes. The recently completed U-M study is the largest known of its kind to examine the link between dental care and diabetes. Researchers found that regular, non-surgical periodontal — or gum — care is linked to lower diabetes-related medical care costs, possibly more than 10 percent per year. The same care was associated with up to 20 percent lower annual medical costs for treatment related to cardiovascular disease in individuals with both diabetes and heart disease. For individuals receiving periodontal treatment, medical costs were more than 30 percent lower for kidney disease treatment for individuals with diabetes and kidney disease. Periodontal treatment for patients with diabetes and congestive heart failure was associated with 40 percent lower medical care costs for treatment related to congestive heart failure. "Our results are consistent with an emerging body of evidence that periodontal diseases adversely impact diabetes," said Taylor. "Treating periodontal infection may improve control of high levels of sugar in the blood. Other evidence also suggests that individuals with periodontal infections may be more likely to develop diabetes, and those with diabetes have a greater likelihood of having diabetes complications. At the minimum, physicians and dentists should be aware of these potentially important linkages and incorporate this knowledge into their practice decisions and patient communication."] George Taylor, et al. University of Michigan, blue Cross Blue Shield of Michigan Foundation. http://www.bcbsm.com/pr/pr_08-27-2009_71090.shtml

499. **Study to Explore the Link Between Periodontal Treatment and Medical Costs for People with Diabetes [**Researchers from the Delta Dental Research and Data Institute and the University of Michigan School of Dentistry are studying the impact that periodontal (gum) treatment may have on the medical costs of people with diabetes. … The study, titled "Periodontal Therapy: Dental Insurance Claims and Medical Care Costs in Diabetes," will analyze dental and medical claims data from 2000 to 2007 for approximately 3,300 Chrysler employees and their dependents with diabetes.] Delta Dental News Room. Sept 3, 2008. http://www.deltadentalin.com/PublicWeb/appmanager/portal/desktop?_nfpb=true&portlet_TopNews_1_actionOverride=%2Fportlets%2FepContentEditor%2FonExpand&_windowLabel=portlet_TopNews_1&portlet_TopNews_1year=&portlet_TopNews_1title=Top+News&portlet_TopNews_1path=%2FBEA+Repository%2FDeltaDental%2FNewsroom%2FNewsReleases%2Fnews_releases_09102008104337_4&_pageLabel=bDD_bNR_pNRHome

500. **The dental office visit as a potential opportunity for diabetes screening: an analysis using NHANES 2003-2004 data.** [Objectives: The bidirectional relationship between periodontitis and diabetes suggests that the dental visit may offer a largely untapped opportunity to screen for undiagnosed diabetes. To better examine this potential opportunity, data from the National Health and Nutrition Examination Survey (NHANES) 2003-2004 were used to determine if a larger proportion of patients with periodontal disease as compared with those without periodontitis would be recommended for screening according to American Diabetes Association (ADA) guidelines. The data were also used to determine whether at-risk individuals with periodontitis visited a dental professional recently, so that they could avail themselves of this opportunity for screening, if offered.Methods: Data to perform these analyses were collected from 2,923 subjects aged 20 and older who reported that they were never told that they had diabetes, had a periodontal examination, and had sufficient data to compute body mass index. Descriptive statistics, *t*-tests, and chi-square analyses that compared those with and without periodontitis were extrapolated to the US population. Results: A total of 62.9 percent of those without periodontitis and 93.4 percent of those with periodontal disease met ADA guidelines for diabetes screening. Of those at-risk with periodontal disease, 33.9 percent had seen a dentist in the past 6 months, 50 percent in the past year, and 60.4 percent in the past 2 years. Conclusions: As almost all individuals with periodontitis would have been recommended for diabetes screening, and many at-risk persons with periodontal disease recently visited a dentist, our data suggest that the dental visit provides an important potential venue for this screening.] Strauss SM, Russell S, et al. *Journal of Public Health Dentistry*, Published Online 11 Dec 2009. http://www3.interscience.wiley.com/journal/123210997/abstract?CRETRY=1&SRETRY=0
501. **The Effect of Antimicrobial Periodontal Treatment on Circulating Tumor Necrosis Factor-Alpha and Glycated Hemoglobin Level in Patients With Type 2 Diabetes.** [Tumor necrosis factor-α (TNF-α) may play an important role in insulin resistance. Antimicrobial therapy significantly reduced the number of microorganisms in periodontal pockets. The results indicate that anti-infectious treatment is effective in improving metabolic control in diabetics, possibly through reduced serum TNF-α and improved insulin resistance.] *J Periodontol 2001;72:774-778.* http://www.joponline.org/doi/abs/10.1902/jop.2001.72.6.774?journalCode=jop
502. **The effects of glucose on ascorbic acid uptake in heart endothelial cells: possible pathogenesis of diabetic angiopathies.** [Glucose in concentrations of 20 mg% (or greater) significantly inhibited 14C-labelled ascorbic acid (1.25 mg%) uptake in endothelial cells in the presence of insulin (1600 microU/ml). The absence of insulin also significantly reduced ascorbic acid uptake. Furthermore, this reduction could be exacerbated by glucose (40, 160 mg%) but not equimolar concentrations of fructose. Increased ascorbic acid concentrations (two-fold) in the absence of insulin (1) significantly enhanced uptake, and (2) reversed the inhibition of glucose. These findings support earlier reports that ascorbic acid uptake into the cell may be compromised by decreased insulin and/or increased extracellular glucose levels. Since previous animal studies have correlated experimental ascorbic acid deficiencies with atherogenic processes (presumably by altering glycosaminoglycan metabolism), the postulation that the "diabetic condition" (low insulin, hyperglycemia) accelerates the cellular changes leading to atherosclerosis by impairing ascorbic acid uptake into the vascular endothelium, may now be supported.] Kapeghian JC, Verlangieri AJ. *Life Sci*. 1984 Feb 6;34(6):577-84.. http://www.ncbi.nlm.nih.gov/pubmed/6363863
503. **The hyperglycemia-induced inflammatory response in adipocytes: the role of reactive oxygen species.** [Hyperglycemia is a major independent risk factor for diabetic macrovascular disease. The consequences of exposure of endothelial cells to hyperglycemia are well established. However, little is known about how adipocytes respond to both acute as well as chronic exposure to physiological levels of hyperglycemia. Here, we analyze adipocytes exposed to hyperglycemia both in vitro as well as in vivo. Comparing cells differentiated at 4 mm to cells differentiated at 25 mm glucose (the standard differentiation protocol) reveals severe insulin resistance in cells exposed to 25 mm glucose. A global assessment of transcriptional changes shows an up-regulation of a number of mitochondrial proteins. Exposure to hyperglycemia is associated with a significant induction of reactive oxygen species (ROS), both in vitro as well as in vivo in adipocytes isolated from streptozotocin-treated hyperglycemic mice. Furthermore, hyperglycemia for a few hours in a clamped setting will trigger the induction of a pro-inflammatory response in adipose tissue from rats that can effectively be reduced by co-infusion of N-acetylcysteine (NAC). ROS levels in 3T3-L1 adipocytes can be reduced significantly with pharmacological agents that lower the mitochondrial membrane potential, or by overexpression of uncoupling protein 1 or superoxide dismutase. In parallel with ROS, interleukin-6 secretion from adipocytes is significantly reduced. On the other hand, treatments that lead to a hyperpolarization of the mitochondrial membrane, such as overexpression of the mitochondrial dicarboxylate carrier result in increased ROS formation and decreased insulin sensitivity, even under normoglycemic conditions. Combined, these results highlight the importance ROS production in adipocytes and the associated insulin resistance and inflammatory response.] Lin Y, Berg AH, et al. *J Biol Chem. 2005 Feb 11;280(6):4617-26.* http://www.ncbi.nlm.nih.gov/pubmed/15536073?dopt=Abstract
504. **The Link Between Inflammation and Diabetes.** […eating induces an inflammatory state in everyone. Normally, inflammation occurs for three or four hours after eating but will then taper off. Though people can't avoid eating, Dr. Dandona says they can avoid what and how much they eat. He says, "If people eat McDonald's-type meals every three or four hours, and many do, they spend most of their time in a pro-inflammatory state." Researchers say the finding that inflammation is linked to the onset of type 2 diabetes may open new avenues for the prevention and treatment of the disease.] American diabetes Association Meeting, San Francisco June 2002. http://www.defeatdiabetes.org/Articles/inflam020617.htm
505. **The Pathobiology of Diabetic Complications – A Unifying Mechanism**. Brownlee M. Banting Lecture 2004, Diabetes, Vol. 54, june 2005. http://diabetes.diabetesjournals.org/content/54/6/1615.full.pdf+html
506. **The Prevalence of Calcified Carotid Artery Atheromas on the Panoramic Radiographs of Patients with Type 2 Diabetes Mellitus.** [Type 2 diabetes mellitus, which affects 15 Million Americans, is assocated with accelerated cervical

carotid artery atherosclerosis and a heightened risk of stroke.] Friedlander AH, Maeder LA, Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2000:89:420-4.
http://www.journals.elsevierhealth.com/periodicals/ymoe/article/PIIS1079210400701223/abstract?source=aemf

507. **The Relationship Between Periodontal Diseases and Diabetes: An Overview.** [This overview looks at the bidirectional relationship between periodontitis and diabetes.] Soskolne WA, Klinger A, et. al., *Annals of Periodontology* 2001.6.1.91.
http://www.joponline.org/doi/abs/10.1902/annals.2001.6.1.91?prevSearch=keywordsfield%3Adiabetes_mellitus

508. **The Role of Inflammatory Cytokines in Diabetes and Its Complications.** [The prevalence of diabetes worldwide is increasing rapidly in association with the increase in obesity. Complications are a major fear of patients with diabetes. Complications of diabetes affect many tissues and organs, causing retinopathy, nephropathy, neuropathy, cardiovascular diseases, peripheral vascular diseases, stroke, and periodontal pathologies. Immunologic abnormalities are associated with type 1 and type 2 diabetes and diabetic complications. T cell abnormalities are believed to be the major cause of autoimmune disease in type 1 diabetes, leading to the destruction of pancreatic islets. In type 2 diabetes, inflammation and activation of monocytes are postulated to be important for enhancing insulin resistance and may contribute to the loss of insulin secretory function by islet cells. Many factors can enhance insulin resistance, including genetics, a sedentary lifestyle, obesity, and other conditions, such as chronic inflammation or infection. Increases in inflammation, such as activation of monocytes and increased levels of inflammatory markers, e.g., C-reactive protein, plasminogen activator inhibitor-1, and other cytokines, were reported in insulin-resistant states without diabetes. One possible mechanism is that abnormal levels of metabolites, such as lipids, fatty acids, and various cytokines from the adipose tissue, activate monocytes and increase the secretion of inflammatory cytokines, enhancing insulin resistance. According to this model, obesity activates monocytes and enhances insulin resistance, increasing the risk for type 2 diabetes. Abnormalities in innate immunity might also participate in the development of diabetic complications. In general, hyperglycemia is the main initiator of diabetic retinopathy, nephropathy, and neuropathy, and it participates in the development of diabetic cardiovascular diseases. Although the precise role of inflammation in the development of diabetic microvascular diseases is still unclear, it is likely that inflammation induced by diabetes and insulin resistance can accelerate atherosclerosis in patients with diabetes. Also, it was shown that conditions with an inflammatory basis, such as obesity and type 2 diabetes, can contribute to periodontal disease, suggesting that periodontal abnormalities may be partly influenced by inflammatory changes. Further research is required to confirm the role of inflammation and the onset of diabetes, microvascular diseases, and periodontal pathologies.] King GL. *Journal of Periodontology, 2008, Vol. 79, No. 8s, Pages 1527-1534.* http://www.joponline.org/doi/full/10.1902/jop.2008.080246

509. **The Severity of Periodontal Disease is Associated with the Development of Glucose Intolerance in Non-diabetics: The Hisayama Study.** [Inflammation is hypothesized to play a significant role in the development of type 2 diabetes. In the subgroup with normal glucose tolerance 10 years previously, subjects who subsequently developed impaired glucose tolerance were significantly more likely to have deep pockets. Deep pockets were closely related to current glucose tolerance status and the development of glucose intolerance.] *Dent Res* 83(6):485-490,2004.
http://jdr.iadrjournals.org/cgi/content/abstract/83/6/485?etoc

510. **Treatment of Periodontal Disease and Control of Diabetes: An Assessment of the Evidence and Need for Future Research.** [Evidence points to an increased cytokine response in type 2 diabetes, especially the proinflammatory cytokines interleukin (IL)-1 beta, IL-6, and tumor necrosis factor (TNF)-alpha. Porphyromonas gingivalis, one of the microorganisms responsible for this infection, is able to invade endothelial cells and is a potent signal for monocyte and macrophage activation. Thus, once established in the diabetic host, this chronic infection complicates diabetes control and increases the occurrence and severity of microvascular and macrovascular complications. The evidence supports the notion that treatment of chronic periodontal infection is essential in the diabetic patient. Assessment of infection status in diabetic patients is fundamental for appropriate treatment decisions.] Grossi SG. *Annals of Periodontology* 2001, Vol. 6, No. 1, Pages 138-145.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11887456&dopt=Citation ;
http://www.joponline.org/doi/abs/10.1902/annals.2001.6.1.138

511. **Treatment of Periodontal Disease in Diabetics Reduces Glycated Hemoglobin.** [Periodontal disease is a common infection-induced inflammatory disease among individuals suffering from diabetes mellitus. Effective treatment of periodontal infection and reduction of periodontal inflammation are associated with a reduction in level of glycated hemoglobin. Control of periodontal infections should thus be an important part of the overall management of diabetes mellitus patients.] *J Periodontaol 1997;68:713-719,* Sara Grossi, et.al, SUNY Buffalo
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9287060&dopt=Citation
http://www.electronicipc.com/JournalEZ/detail.cfm?code=02250010680801

512. **Treatment of periodontitis in the diabetic patient. A critical review.** [Both type 1 and type 2 diabetes mellitus are associated with increased periodontal disease susceptibility. Conventional periodontal therapy appears to be effective in diabetic patients. It has not been demonstrated that chemotherapeutics are necessary for successful periodontal therapy in most diabetic patients. The effect of periodontal therapy on metabolic control of diabetes may not be clinically significant.] Gustke CJ. *J Clin Periodontol. 1999 Mar;26(3):133-7.*
http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=10100037&ordinalpos=11&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

513. **Type 2 Diabetes: Local Inflammation and Direct Effect of Bacterial Toxic Components** [Abstract: *Objectives*: It has been known for almost a century that amyloidosis is frequently associated with chronic bacterial infection. Islet amyloid deposit is characteristic of type 2 diabetes. Periodontal disease, which is predominantly caused by several Gram negative

bacteria, is a risk factor for type 2 diabetes. The goal of the study was to explore whether bacteria or their toxic components may play a role in type 2 diabetes. *Material & Methods*: The pancreas in 22 autopsy cases was analyzed for the presence of lipopolysaccharide (LPS), bacterial peptidoglycan (BPG) and local inflammatory processes. Ten of the cases had clinically diagnosed type 2 diabetes, and 12 were age matched controls.*Results*: The results of an immunohistochemical analysis showed the presence of LPS and BPG in association with islet amyloid deposits in all the 10 diabetic cases as well as in 3 controls with clinically silent amyloid deposits. *Chlamydia pneumoniae* and *Helicobacter pylori* specific antigens were detected in the affected islets in a subset of diabetic patients. Clumps of HLA-DR positive activated macrophages, abundant immunoreactivity to the activated complement components C3d, C4d and C5b-9, the terminal attack complex, and a moderate numbers of T4 and particularly of T8 lymphocytes were present in the pancreas of all diabetic cases. *Conclusions:* These results suggest that bacteria or their slowly degradable remnants may initiate and sustain chronic inflammation in the pancreas and therefore play a role in the pathogenesis of type 2 diabetes. They also indicate that local immune responses, including activation of the classical complement pathway are important in the pathogenesis of type 2 diabetes. There may also be some involvement of the adaptive immune system. Further investigations are essential since a parallel use of antibacterial and anti-inflammatory drugs may prevent or slow down the disease progression.] Miklossy J, Martins R, et al *The Open Pathology Journal*, 2008, 2, 86-95. http://www.miklossy.ch/media/Miklossy_OPATJ.pdf

514. **Type 2 diabetes mellitus and periodontal disease.** [The relationship between type 2 diabetes mellitus and periodontal disease was evaluated in 2,878 Pima Indians of the southwestern United States. Two independent measures of periodontal disease, probing attachment loss and radiographic bone loss, were used to compare prevalence and severity of periodontal disease in diabetic and nondiabetic subjects. In all age groups studied, subjects with diabetes had a higher prevalence of periodontal disease, indicating that diabetes may be a risk factor for periodontal disease.] Shlossman M, Knowler WC et al. *J Am Dent Assoc. 1990 Oct;121(4):532-6.* http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=2212346&ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVAbstractPlus
515. **University of Michigan, Blue Care Network Study Quantifies Health Care Savings of Regular Dental Care for Patients with Diabetes** [Overall medical and pharmacy costs in people with diabetes can be lower by more than 10 percent per year in individuals receiving regular, non-surgical periodontal services, according to a recent University of Michigan study. The study also showed the same procedures were linked to as much as 19 percent lower diabetes-related medical costs. The research findings further underscore the importance of the link between medical and dental health.] Blue Cross Network of Michigan, News Room. http://www.mibcn.com/newsroom/2008/pr_12-09-2008_11079.shtml

Endodontics and Inflammation

516. **Comparative evaluation of endodontic irrigants against Enterococcus faecalis biofilms.** [The aim of this study was to compare the efficacy of root canal irrigants against E. faecalis biofilms using a novel in vitro testing system. Biofilms grown in a flow cell system were submerged in test irrigants for either 1 or 5 minutes. Statistical analysis revealed a significant relationship between test agent and percentage kill of the biofilm bacteria ($P < 0.05$). No statistically significant relationship between time and percentage kill was found. The percentage kill of the biofilm bacteria was: 6% NaOCl (>99.99%), 1% NaOCl (99.78%), Smear Clear (78.06%), 2% chlorhexidine (60.49%), REDTA (26.99%), and BioPure MTAD (16.08%). Post-hoc analysis showed a significant difference between 1% and 6% NaOCl, and all other agents including Smear Clear, 2% chlorhexidine, REDTA, and BioPure MTAD ($P < 0.05$). Within the parameters of this study, both 1% NaOCl and 6% NaOCl were more efficient in eliminating E. faecalis biofilm than the other solutions tested.] Dunavant TR, Regan JD, et.al. *J Endod. 2006 Jun;32(6):527-31.* http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=retrieve&db=pubmed&list_uids=16728243&dopt=abstract ; http://www.aae.org/joe/abstracts/abst0606.htm
517. **Comparison of profiles of key periodontal pathogens in periodontium and endodontium.** [Despite the established anatomical relationship between the periodontal and pulpal tissues, bacterial migration between endodontium and periodontium is still under discussion. The objective of this study was an investigation of profiles of periodontal pathogens in pulpal and periodontal diseases affecting the same tooth by means of 16S rRNA gene directed polymerase chain reaction (PCR). 31 intact teeth with both pulp and marginal infections were investigated. The diagnosis was based on clinical and radiological examination. Samples were taken from the gingival sulcus or periodontal pocket, respectively, with sterile paper points before trepanation of the teeth. After trepanation sterile paper points and Hedstroem files were used for taking samples from the root canal. Specific PCR methods were used to detect the presence of the following pathogens: Actinobacillus actinomycetemcomitans, Bacteroides forsythus, Eikenella corrodens, Fusobacterium nucleatum, Porphyromonas gingivalis, Prevotella intermedia and Treponema denticola. In addition, quantitative competitive PCR was used to determine the total bacterial count of the samples. The investigated pathogens were proven to be present in the endondontium in all disease categories. Particularly in endodontic samples of "chronic apical periodontitis" and "chronic adult periodontitis" profiles of the periodontal pathogens were found. The results confirmed that periodontal pathogens often accompany endodontic infections and supported the idea that the periodontic-endodontic interrelationships should be considered as critical pathways which might contribute to refractory courses of endodontic or periodontal diseases.] Rupf S, Kannengiesser S, et al. *Endod Dent Traumatol*. 2000 Dec;16(6):269-75. http://www.ncbi.nlm.nih.gov/pubmed/11202893

518. **Eradication of Enterococcus faecalis biofilms by cetrimide and chlorhexidine.** [INTRODUCTION: Enterococcus faecalis is the most commonly isolated bacteria from root canals of teeth with persistent periapical periodontitis. Its ability to grow as a biofilm impedes the elimination of E. faecalis by using irrigating solutions. The purpose of this study was to assess the efficacy of cetrimide and chlorhexidine (CHX), alone and in association, in combined and alternating form, in eradicating biofilms of E. faecalis. METHODS: Biofilms grown in the MBEC-high-throughput device for 24 hours were exposed to irrigating solutions for 30 seconds and 1 and 2 minutes. Eradication was defined as 100% kill of biofilm bacteria. The Student t test was used to compare the efficacy of the associations of the 2 irrigants. RESULTS: Cetrimide eradicated E. faecalis biofilms at concentrations of 0.5%, 0.0312%, and 0.0078% at 30 seconds and 1 and 2 minutes of contact time, respectively. CHX did not eradicate the biofilms at any of the concentrations (4% initial concentration) or times assayed. The association of 0.1% and 0.05% cetrimide with any concentration of CHX, whether in combined or alternating application, effectively eradicated E. faecalis biofilms at all the contact times tested. Eradication was also achieved with 0.02% and 0.01% cetrimide at 2 minutes. Statistical analysis revealed significantly better results with alternating rather than combined use of cetrimide and CHX ($P < .05$). CONCLUSIONS: The associated use of cetrimide and CHX provided better results than their applications as single agents against E. faecalis biofilms, and the alternating application was significantly more effective than the combined mode of application.] Arias-Moliz MT, Ferrer-Luque CM, et al. *J Endod.* 2010 Jan;36(1):87-90. http://www.ncbi.nlm.nih.gov/pubmed/20003941

519. **Lesions of Endodontic Origin and Risk of Coronary Heart Disease.** [A paucity of epidemiologic research exists regarding systemic health consequences of endodontic disease. This study evaluated whether incident radiographically evident lesions of endodontic origin were related to development of coronary heart disease (CHD) among 708 male participants in the VA Dental Longitudinal Study. At baseline and every three years for up to 32 years, participants (who were not VA patients) received complete medical and dental examinations, including full-mouth radiographs. Cox regression models estimated the relationship between incident lesions of endodontic origin and time to CHD diagnosis. Among those ≤40 years old, incident lesions of endodontic origin were significantly associated with time to CHD diagnosis ($p < 0.05$), after adjustment for covariates of interest, with hazard ratios decreasing as age increased. Among those > 40 years old, no statistically significant association was observed. These findings are consistent with research that suggests relationships between chronic periodontal inflammation and the development of CHD, especially among younger men.] Caplan DJ, Chasen JB, et.al. *Dent Res* 85(11):996-1000, 2006. http://jdr.iadrjournals.org/cgi/content/abstract/85/11/996.

520. **Oral inflammatory process and general health Part 1: The focal infection and the oral inflammatory lesion.** [Abstract. – A focal infection is a localized or generalized infection caused by the dissemination of microorganisms or toxic products from a focus of infection in various organic districts, including the oral district. In the Part 1 of this two-part review article, after historical signs, the Authors describe the current pathogenic concepts like the “immuno-allergic theory” and the formation of auto-antibodies in human body, contributing to the genesis of autoimmune illnesses sustained by individual reactivity linked to eredo-constitutionality. Some theories suppose a focal origin even for general pathology such as cancer, sarcoidosis, multiple sclerosis, amyotrophic lateral sclerosis, autism, Guillain-Barré syndrome, Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS), Tourette’s syndrome, myasthenia gravis, polycystic kidney disease, obesity, Alzheimer’s disease and diabetes mellitus. Laboratory analyses (leucocytic formula, protein electrophoresis, C-reactive protein, REUMA test VES, TAS, etc.) are suggestive of the presence of an inflammatory process or of the presence of an aspecific answer to an inflammatory situation. The DNA-Polymerase Chain Reaction method (PCR) is fundamental for the diagnosis of bacterial and viral infections, particularly for those that have non-culturable microorganisms or in cases where are present but in extremely small number in the sample to be analyzed. A positive result confirms the diagnosis, but negative result is not indicator of the absence of illness. Even for oral inflammatory lesions, different basic mechanisms concerning the possible association with systemic diseases exist. They concern local spread, metastatic spread or immunologic cross-reactivity. In this case we assume that most of the ailments come from dental or periodontal foci, as in the bacterial endocarditis, but instead of considering them as possible pathogenetic mechanism of an immune nature, we consider them as originated by the body’s response to the presence of bacterial antigens through the formation of specific antibodies. Much researche, sometimes contrasting, has evaluated periodontal pathogens in atheromatous plaques isolated from patients with chronic periodontitis. Oral inflammatory lesions have been shown unequivocally to contribute to elevated systemic inflammatory responses. In some researches intensive periodontal therapy showed a significant reduction of lymphocyte formula, of CRP levels, of interleukin-6 (IL-6) and of LDL cholesterol after two months.] Somma F, Castagnola R, et al. *Eur Rev Med Pharmacol Sci* 2010; 14 (12): 1085-1095. http://www.europeanreview.org/article/861

521. **Oral inflammatory process and general health. Part 2: How does the periapical inflammatory process compromise general health?** [At present, the focal infection theory still has very controversial aspects. In spite of the great number of studies, there is no evidence that focal infections or even antigenic mimicry are responsible for anything other than sporadic abscesses/infections and possibly rare autoimmune disorders. linflammation of endodontic origin (i.e., apical periodontitis--AP) has not received the same attention as inflammation originating from the periodontium. Endodontics is a microbiological problem, since the bacterial infection is the "prime mover" of pulp (before) and periapical (later) disease. The aims of endodontic treatment have to be considered from a microbiological viewpoint. Considering these problems in this second part of their study, the Authors, after close examination of the virulence of microorganisms and of the host defense, analyze the endodontic infection and microbiological species. They emphasize the possibility of a relationship between periapical inflammatory lesions and bacterial endocarditis in preventing metafocal disease. Bacterial endocarditis deserves special

mention because despite involving specialists of two scientific fields, its prophylaxis is almost always assigned to medical practice, and especially, to dentistry. Given the dangers of the disease, antibiotic prophylaxis is both absolutely necessary and can be very effective, and it should be used especially in clinical situations with high risk individuals. However, the ability of antibiotic therapy to prevent or reduce the frequency, magnitude or duration of bacteremia associated with a dental procedure is controversial. Studies should also be undertaken to determine to compare the efficacy of endodontic treatment with alternative therapy such as implants, prosthetic replacements or no treatment other than extraction. To date, these studies have not been carried out, and there is no evidence to support the theory that modern endodontic therapy is not safe and effective.] Somma F, Castagnola R, et al. *Eur Rev Med Pharmacol Sci*. 2011 Jan;15(1):35-51. http://www.ncbi.nlm.nih.gov/pubmed/21381498

522. **Pathogenesis of apical periodontitis and the causes of endodontic failures.** [Apical periodontitis is a sequel to endodontic infection and manifests itself as the host defense response to microbial challenge emanating from the root canal system. It is viewed as a dynamic encounter between microbial factors and host defenses at the interface between infected radicular pulp and periodontal ligament that results in local inflammation, resorption of hard tissues, destruction of other periapical tissues, and eventual formation of various histopathological categories of apical periodontitis, commonly referred to as periapical lesions. The treatment of apical periodontitis, as a disease of root canal infection, consists of eradicating microbes or substantially reducing the microbial load from the root canal and preventing re-infection by orthograde root filling. The treatment has a remarkably high degree of success. Nevertheless, endodontic treatment can fail. Most failures occur when treatment procedures, mostly of a technical nature, have not reached a satisfactory standard for the control and elimination of infection. Even when the highest standards and the most careful procedures are followed, failures still occur. This is because there are root canal regions that cannot be cleaned and obturated with existing equipments, materials, and techniques, and thus, infection can persist. In very rare cases, there are also factors located within the inflamed periapical tissue that can interfere with post-treatment healing of the lesion. The data on the biological causes of endodontic failures are recent and scattered in various journals. This communication is meant to provide a comprehensive overview of the etio-pathogenesis of apical periodontitis and the causes of failed endodontic treatments that can be visualized in radiographs as asymptomatic post-treatment periapical radiolucencies.] Nair PN. *Crit Rev Oral Biol Med. 2004 Nov 1;15(6):348-81.* http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=15574679&dopt=Abstract

523. **The Relationship Between Self-Reported History of Endodontic Therapy and Coronary Heart Disease in the Atherosclerosis Risk in Communities Study.** [Background. Results from numerous studies have suggested links between periodontal disease and coronary heart disease (CHD), but endodontic disease has not been studied extensively in this regard. Methods. The authors evaluated the relationship between self-reported history of endodontic therapy (ET) and prevalent CHD in the Atherosclerosis Risk in Communities (ARIC) Study, aprospective epidemiologic study sponsored by the National Heart, Lung, and Blood Institute. The authors used multivariable logistic regressionto analyze data obtained from oral health questionnaires, medical evaluations and clinical dental examinations. Results. Of 6,651 participants analyzed, 50.4 percent reported never having had ET; 21.5 percent reported having had ET one time; and 28.0 percent reported having had ET two or more times. Final multivariable regression models indicated that among participants with 25 or more teeth, those reporting having had ET two or more times had 1.62 (95 percent confidence interval [CI], 1.04–2.53) times the odds of prevalent CHD compared with those reporting never having had ET. Among participants with 24 or fewer teeth, no significant differences in CHD prevalence were observed among groups regardless of their history of ET. Conclusions. Among participants with 25 or more teeth, those with a greater self-reported history of ET were more likely to have CHD than were those reporting no history of ET.**]** Caplan DJ, Pankow JS, et al. *J Am Dent Assoc*, Vol 140, No 8, 1004-1012. http://jada.ada.org/cgi/content/short/140/8/1004

524. **Spinal abscess and mitral valve endocarditis secondary to asymptomatic fusobacterium-induced dental abscess.** [*Fusobacterium nucleatum* is an anaerobic bacillus of oropharyngeal origin. We describe a case of two manifestations of fusobacterium-induced sepsis originating from an asymptomatic dental root abscess.] Goolamali SI, Carulli MT< et al. J R Soc Med. 2006 July; 99(7): 368–369. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1484547/

525. **Treponema species detected in infected root canals and acute apical abscess exudates.** [INTRODUCTION: Different microbial communities have been associated with acute endodontic infections. The majority of the microorganisms are as yet uncultivable or difficult to grow under current laboratory conditions. Treponema species are strict anaerobic bacteria that are involved in several oral diseases. The aim of this study was to detect the presence of Treponema species in infected root canals (RCs) and exudates related to acute apical abscesses (AAAs) as well as to determine positive association between targeted species and clinical signs/symptoms. METHODS: Paired samples of infected RCs and AAAs were collected from 20 subjects. Nested polymerase chain reaction assay with species-specific primers for 16S rDNA and downstream intergenic spacer region was used for microbial detection. The frequency of species and statistical associations between species and signs/symptoms of endodontic origin as well as their simultaneous detection in both milieus were investigated. RESULTS: The most frequently detected species were T. socranskii (RC, 17/20; AAA, 15/20), T. denticola (RC, 8/20; AAA, 11/20); T. medium (RC, 6/20; AAA, 9/20); and T. amylovorum (RC, 5/20; AAA, 9/20). Positive correlation was found for simultaneous presence of T. denticola in both RCs and AAAs ($p = 0.01$). Positive association was observed between T. medium and T. vincentii ($p = .037$). No positive statistical association was observed between the targeted species and signs/symptoms. CONCLUSIONS: The high incidence of Treponema species in RC and AAA samples from the same tooth indicated that they are important pathogens in acute endodontic infections.] Montagner F, Jacinto RC, et al. *J Endod.* 2010 Nov;36(11):1796-9. http://www.ncbi.nlm.nih.gov/pubmed/20951290

Erectile Dysfunction

526. **Association Between Chronic Periodontitis and Vasculogenic Erectile Dysfunction**. [BACKGROUND & OBJECTIVES: Erectile dysfunction (ED) and chronic periodontitis (CP) shares the common risk factors. There is only a single report on the association between ED and CP Thus the aim of this study is to find the association between vasculogenic ED and CP. METHODS: Total of 70 male subjects (Mean age 35.3 ± 3.64 years), clinically diagnosed with erectile dysfunction was included in the study. They were given Sexual Health Inventory for Men Questionnaire and subjected to colored penile Doppler ultrasound. Periodontal parameters like probing pocket depth and clinical attachment level were recorded. 5 subjects with erectile dysfunction and chronic periodontitis were selected randomly for cardiac color Doppler to assess the integrity. RESULTS: Among the all selected vasculogenic ED subjects, mild to moderate vasculogenic ED showed the highest prevalence. While prevalence for CP among all vasculogenic ED subjects was highest among severe ED (81.8%). Association of CP and vasculogenic ED was found to be correlated positively but it showed no statistically significance. 2 subjects out of 5 subjects were found for vascular insufficiency. CONCLUSION: It can be hypothesized that an association exists between vasculogenic ED in young men and CP. However, a large-scale study with confounder analysis and a longitudinal follow-up is warranted.] Pradeep AR, Sharma A, et al. *J Perio*, Posted online on April 5, 2011. http://www.joponline.org/doi/abs/10.1902/jop.2011.110049 ; http://www.ncbi.nlm.nih.gov/pubmed/21513476
527. **Endothelial Dysfunction, Erectile Dysfunction, and Coronary Heart Disease: The Pathophysiologic and Clinical Linkage.** [Our rapidly expanding knowledge regarding the biology of the endothelial cell and the pathophysiology of coronary heart disease (CHD) and endothelial dysfunction indicates important common factors and overlapping clinical presentations. We are, in effect, presented with a new paradigm-that of varying vascular manifestations of disease linked to the functioning of endothelial cell lining. This article reviews these areas of advancement and addresses their clinical implications regarding erectile dysfunction and CHD, as well as the role of the phosphodiesterase-5 inhibitor sildenafil.] Stein RA. *Reb Urol*. 2003;5(Suppl 7): S21-27. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1502382/
528. **Linking erectile dysfunction and coronary artery disease.** [Coronary artery disease (CAD) and erectile dysfunction (ED) are both highly prevalent conditions that frequently coexist. Additionally, they share mutual vascular risk factors, suggesting that they are both manifestations of systemic vascular disease. The role of endothelial dysfunction in CAD is well established. Normal erectile function is primarily a vascular event that relies heavily on endothelially derived, nitric oxide-induced vasodilation. Accordingly, endothelial dysfunction appears to be a common pathological etiology and mechanism of disease progression between CAD and ED. The risk factors of diabetes mellitus, hypertension, hyperlipidemia, obesity and tobacco abuse contribute to endothelial dysfunction. This article reviews the role of vascular endothelium in health, the abnormalities resulting from vascular risk factors, and clinical trials evaluating the role of endothelial dysfunction in ED.]Rodriguez JJ, Al Dashti R, et al. *Int J Impot Res*. 2005 Dec;17 Suppl 1:S12-8. http://www.ncbi.nlm.nih.gov/pubmed/16391538
529. **Metabolic risk factors, endothelial dysfunction, and erectile dysfunction in men with diabetes.** [BACKGROUND: The prevalence of men with erectile dysfunction (ED) and concomitant diabetes mellitus continues to increase. ED, diabetes, hypertension, and dyslipidemia (components of the metabolic syndrome) are associated with endothelial dysfunction. ED has been reported to be a marker for cardiovascular arterial disease. Effective treatment of ED requires recognition of the condition and its associated comorbidities, including endothelial dysfunction. METHODS: An electronic search of the literature was conducted to review information concerning the prevalence of ED, diabetes, metabolic syndrome, endothelial dysfunction, and treatment of ED. RESULTS: Phosphodiesterase type 5 (PDE5) inhibitors are effective vasodilating agents with a predominant effect on penile vasculature and are therefore first-line treatment for men with ED. These agents have also been demonstrated to have a beneficial effect in other vascular beds. PDE5 inhibitors have not been shown to have an adverse effect on cardiovascular morbidity or mortality or on glycemic control in men with diabetes. In addition, no causal association has been established between nonarteritic ischemic optic neuropathy and PDE5 inhibitors. CONCLUSIONS: PDE5 inhibitors have a beneficial effect on endothelial dysfunction and ED in men with diabetes and metabolic risk factors.] Palumbo PJ. *Am J Med Sci*. 2007 Dec;334(6):466-80. http://www.ncbi.nlm.nih.gov/pubmed/18091369
530. **Relation of endothelial cell function to erectile dysfunction: implications for treatment.** [The prevalence of both cardiovascular disease (CVD) and erectile dysfunction (ED) increases with advancing age. These conditions share the common risk factors of diabetes mellitus, hypertension, hyperlipidemia, smoking, and obesity. They also share a pathophysiologic mechanism of decreased vascular blood flow via endothelial dysfunction. There are several lines of evidence that endothelial dysfunction in men with ED can be detected well before overt manifestations of vascular damage, including atherosclerotic effects. Some evidence shows that ED can be improved not only with phosphodiesterase 5 inhibitors but also by treating the risk factors directly. This includes cessation of smoking, correction of hyperlipidemia, and amelioration of obesity through weight loss. Conversely, ED may be prevented through maintenance of lean body mass, consistency of physical activity, and smoking abstinence, similar to other risk factors for CVD.] Guay AT. *Am J Cardiol*. 2005 Dec 26;96(12B):52M-56M. Epub 2005 Dec 7. http://www.ncbi.nlm.nih.gov/pubmed/16387568

General Interest, Financial – Misc

531. **ADA, AMA collaborate on oral and systemic health. February 2006- First Joint ADA-AMA Conference.** [Oral health conditions and other health conditions are more closely related than many may once have thought, and viewing them as separate matters no longer makes sense. “This kind of research is life and death," said Dr. Louis F. Rose, a periodontist and physician. "We can't overstate it, but we must inform the public."] http://www.ada.org/prof/resources/pubs/adanews/adanewsarticle.asp?articleid=1815
532. **ADA/Colgate Begin “Oral Systemic Education Campaign”.** [Many in the oral health community have long recognized the relationship of oral health to general health. There are a number of articles that have recently been published in the scientific literature that add to the existing body of peer-reviewed published information on the association of periodontal disease and systemic conditions including heart disease, stroke, diabetes and the birth of pre-term and low birth-weight babies. To help spread the word among dental and medical professionals and the public, the ADA and Colgate are developing a new campaign that demonstrates why the mouth is an integral part of the body.] January 2006. http://www.ada.org/prof/resources/pubs/adanews/adanewsarticle.asp?articleid=1611
533. **Aetna And Columbia Announce Results From Study Showing Relationship Between Periodontal Treatment And A Reduction In The Overall Cost Of Care For Three Chronic Conditions.** [Periodontal care appears to have a positive effect on the cost of medical care, with earlier treatment resulting in lower medical costs for members with diabetes, coronary artery disease (CAD), and stroke.] March 2006- Aetna-Columbia U. Research- http://www.aetna.com/news/2006/pr_20060317.htm
534. **An examination of periodontal treatment and per member per month (PMPM) medical costs in an insusred population.** [Background: Chronic medical conditions have been associated with periodontal disease. This study examined if periodontal treatment can contribute to changes in overall risk and medical expenditures for three chronic conditions [Diabetes Mellitus (DM), Coronary Artery Disease (CAD), and Cerebrovascular Disease (CVD)]. Methods: 116,306 enrollees participating in a preferred provider organization (PPO) insurance plan with continuous dental and medical coverage between January 1, 2001 and December 30, 2002, exhibiting one of three chronic conditions (DM, CAD, or CVD) were examined. This study was a population-based retrospective cohort study. Aggregate costs for medical services were used as a proxy for overall disease burden. The cost for medical care was measured in Per Member Per Month (PMPM) dollars by aggregating all medical expenditures by diagnoses that corresponded to the International Classification of Diseases, 9th Edition, (ICD-9) codebook. To control for differences in the overall disease burden of each group, a previously calculated retrospective risk score utilizing Symmetry Health Data Systems, Inc. Episode Risk Groups™ (ERGs) were utilized for DM, CAD or CVD diagnosis groups within distinct dental services groups including; periodontal treatment (periodontitis or gingivitis), dental maintenance services (DMS), other dental services, or to a no dental services group. The differences between group means were tested for statistical significance using log-transformed values of the individual total paid amounts. Results: The DM, CAD and CVD condition groups who received periodontitis treatment incurred significantly higher PMPM medical costs than enrollees who received gingivitis treatment, DMS, other dental services, or no dental services ($p < .001$). DM, CAD, and CVD condition groups who received periodontitis treatment had significantly lower retrospective risk scores (ERGs) than enrollees who received gingivitis treatment, DMS, other dental services, or no dental services ($p < .001$). Conclusion: This two-year retrospective examination of a large insurance company database revealed a possible association between periodontal treatment and PMPM medical costs. The findings suggest that periodontitis treatment (a proxy for the presence of periodontitis) has an impact on the PMPM medical costs for the three chronic conditions (DM, CAD, and CVD). Additional studies are indicated to examine if this relationship is maintained after adjusting for confounding factors such as smoking and SES.] Albert DA, Sadowsky D , et al. *BMC Health Services Research* 2006;6:103 http://www.biomedcentral.com/content/pdf/1472-6963-6-103.pdf
535. **Can the relation between tooth loss and chronic disease be explained by socio-economic status? A 24-year follow-up from the population study of women in Gothenburg, Sweden.** [The objective of this study was to evaluate the association between number of missing teeth and all cause, cardiovascular, and cancer mortality as well as morbidity and to explore whether socio-economic factors mediate this association. An ongoing prospective cohort study of 1462 Swedish women included a dental survey in 1968/69 with follow-up until 1992/93. The dental examination included a panoramic radiographic survey and a questionnaire. Number of missing teeth at baseline was analysed in a Cox proportional hazards model to estimate time to mortality and morbidity. Number of missing teeth, independently of socio-economic status variables (the husband's occupational category, combined income, and education) was associated with increased all cause mortality and cardiovascular disease mortality respectively (relative risk (RR): 1.36; 95% confidence interval (95% CI): 1.18-1.58) and (RR: 1.46; 95% CI: 1.15-1.85 per 10 missing teeth), but no associations were found for cancer mortality (RR: 1.18; 95% CI: 0.91-1.52). The relation between poor oral health and future cardiovascular disease could not be explained by measures of socio-economic status in this study.] Cabrera C, Hakeberg M, et al. *Eur J Epidemiol.* 2005;20(3):229-36. http://www.ncbi.nlm.nih.gov/pubmed/15921040
536. **Does Treatment of Oral Disease Reduce the Costs of Medical Care?** [*The* following analysis, although not a randomized controlled trial, tests a potential, and important, association between oral and systemic health. Data are derived from a convenience sample of insured persons with both diabetes and periodontal disease. Although the generalizability of these results to other populations (such as the uninsured) is not known, we believe that these findings could serve as a springboard

for further research exploring this association. This compelling preliminary analysis may be of interest to researchers in many arenas, including dentistry, chronic disease, and healthcare costs.] Jeffcoat M, Tanna NK, et al. *Medscape Family Medicine News*, http://www.medscape.com/viewarticle/751609

537. **How your dentist can save your life: The dentist may be the most important doctor you see this year.** [The immune system fights gum infections to keep oral bacteria from spreading to other parts of the body. It usually succeeds, but not always. Gum-disease bacteria can enter the bloodstream and move to the heart, creating life-threatening infections in previously damaged heart valves. What's more, scientists believe the resulting inflammation releases infection-fighting compounds that can inadvertently damage other tissues.] December 2005 – Readers Digest. http://www.rd.com/content/openContent.do?contentId=19084
538. **Inclusion of oral-systemic health in predoctoral/undergraduate curricula of pharmacy, nursing, and medical schools around the world: a preliminary study**. [There is increasing evidence that oral health is a critical component of overall health and that poor oral health may lead to initiation or exacerbation of chronic inflammatory diseases/conditions and adverse pregnancy outcomes. Added to this is an increasing awareness that among non-dental health care professions curricula (e.g., medicine, nursing, pharmacy, and allied health) there is an apparent lack of information regarding the interrelationships between oral health and overall health or recognition of the significance of oral health in achieving and sustaining general health outcomes. This study explored the amount of information related to oral-systemic science currently being taught in the predoctoral/undergraduate professional curricula of pharmacy, nursing, and medical schools in English-speaking universities around the world. The Oral-Systemic Health Educational Curriculum Survey was circulated online to associate or academic deans at medical, nursing, and pharmacy schools in universities across Canada, the United States, Europe, Asia, Australia, and New Zealand. The survey found that 53.7 percent of the respondents ranked the inclusion of oral-systemic science as somewhat important, 51.2 percent reported no or limited requirements to incorporate oral health education within their curricula, and 59.6 percent rated their current curricula in oral-systemic health as inadequate. The majority of students in these programs are not being instructed to examine the mouth, nor are they being taught how to perform an oral examination. Despite growing awareness of emerging evidence of oral-systemic relationships and recommendations that all health care providers should contribute to enhancing oral health, this knowledge base appears to be substantially deficient in the curricula of pharmacy, nursing, and medical students in many universities. This study provides the first formal documentation that the curricula of non-dental health care professions, specifically in medicine, nursing, and pharmacy, do not contain adequate content related to oral-systemic health.] Hein C, Schonwetter DJ, et al. *J Dent Educ.* 2011 Sep;75(9):1187-99. http://www.ncbi.nlm.nih.gov/pubmed/21890848
539. **January 2006- CIGNA begins "Dental Oral Health Maternity Program"**. [CIGNA Dental has followed the research that shows women with periodontal (gum) disease may be at increased risk for pre-term babies. That's why we are launching our new CIGNA Dental Oral Health Maternity Program, which enhances benefits for pregnant members with CIGNA medical and fully-insured dental coverage.] http://www.cigna.com/health/consumer/dental/oral_health_maternity_program.html
540. **March 2006- Consumer Articles increase- Save Your Smile and Health.** [Teeming with bacteria from rotting food, it's a gateway to infection, inflammation and systemic disease. It's your mouth. Ignore it at your own risk. That risk may be greater than you realize. Skipping basic oral hygiene and dental checkups not only can lead to a dingy smile but to serious health problems. Over the past few years, researchers have been focusing on the connections between periodontal disease and cardiovascular disease, stroke, diabetes and problems in pregnancy. Diabetes and periodontal disease appear to be a two-way street, with each disorder exacerbating the other. Studies have shown that treating gum disease can make diabetes easier to manage. Chronic gum disease in pregnant women is also linked to preeclampsia, a serious disorder characterized by high blood pressure, as well as to low-birth-weight babies.] Mary Beth Faller, The Arizona Republic Mar. 21, 2006. http://www.azcentral.com/health/news/articles/0321dentalsins0321.html

Mouth Body Connection. [In July of 1998, the American Academy of Periodontology launched an effort to educate the public about new findings which support what dental professionals had long suspected: Infections in the mouth can play havoc elsewhere in the body. Periodontal bacteria can enter the blood stream and travel to major organs and begin new infections. Research is suggesting that this may: Contribute to the development of heart disease, the nation's leading cause of death, Increase the risk of stroke, Increase a woman's risk of having a preterm, low birth weight baby, or Pose a serious threat to people whose health is compromised by diabetes, respiratory diseases, or osteoporosis.] American Academy of Periodontology http://www.perio.org/consumer/mbc.top2.htm

542. **Oral biofiom-associated diseases: trends and implications for quality of life, systemic health and expenditures.** [Biofilms are surface-associated communities of microorganisms embedded in an extracellular polymeric substance, which upon contact with the host may affect tissue hemostasis and result in disease. It is estimated that approximately 80% of the world's microbial biomass resides in a biofilm state and that microbial biofilms cause more than 75% of all microbial infections found in humans. The oral cavity is replete with biofilms colonizing mucous membranes, dental materials and teeth. Oral biofilms are strongly associated with the etiology of periodontal diseases, dental caries, pulpal diseases, apical periodontitis, peri-implant diseases and candidosis.] Beikler T, Flemmig TF. *Periodontology 2000*, Vol 55, Issue 1 Pages 87-103, Feb 2011. http://onlinelibrary.wiley.com/doi/10.1111/j.1600-0757.2010.00360.x/abstract
543. **Perio Treatments Found to Save $2500 a Year for Diabetics**. [Patients with diabetes cost insurance companies $2484 more per year if they don't receive routine dental care and get immediate treatment for periodontitis, according to researchers here at the International Association of Dental Research 89th General Session and Exhibition.] Harrison L. *Medscape Family*

Medicine News, International Association of Dental Research (IADR) 89th General Session and Exhibition: Abstract 892. Presented March 17, 2011, http://www.medscape.com/viewarticle/739665

544. **US Department of Health and Human Services: Oral Health in America: A Report of the Surgeon General – Executive Summary** [The terms oral health and general health should not be interpreted as separate entities. Oral health is integral to general health; this report provides important reminders that oral health means more than healthy teeth and that you cannot be healthy without oral health.] Rockville, MD: National Institute of Dental and Craniofacial Research, National Institutes of Health, 2000 http://www2.nidcr.nih.gov/sgr/execsumm.htm#message

Genetics and Periodontal Disease

545. **A TaqI polymorphism in the human interleukin-1β (IL-1β) gene correlates with IL-1β secretion *in vitro***. [Abstract. In the present study we searched for restriction fragment length polymorphisms (RFLP) in the human interleukin-1β (IL-lβ) gene and for correlations to monocyte (Mo) function in non-related healthy donors and insulin-dependent diabetic patients. We demonstrated a diallelic polymorphism with the restriction enzyme TaqI consisting of fragments of 9.4 kb and 13.4 kb. No differences in allele or genotype frequencies of this RFLP were observed between randomly selected controls and randomly selected patients with insulin-dependent diabetes mel-litus (IDDM). However, when analysing IDDM patients negative for HLA-DR3 and -DR4, our data demonstrate that the 13.4 kb allele is more frequent in this group compared to a matched control group. The functional impact of this RFLP was studied by analysing *in vitro* stimulated Mo IL-1β response. An IL-lβ allele dosage effect on secretory capacity was observed after LPS-stimulation: 13.4/13.4 kb homo-zygous individuals secreted significantly more IL-lβ than 9.4/13.4 kb heterozygous individuals, who secreted significantly more than 9.4/9.4 kb homozygous individuals. Analyses of supernatants from LPS-sti-mulated Mo cultures from individuals with each TaqI IL-lβ genotype revealed no differences in the mouse thymocyte co-stimulatory assay when compared on a molar basis, indicating that the TaqI polymorphism gave rise only to quantitative differences in expression levels and probably not to a mutant IL-lβ. We conclude that the 13.4 kb allele represents an IL-1β'high-secretor' phenotype, that the observed RFLP may be a genetic susceptibility marker for IDDM in non-DR3 and non-DR4 individuals and that high IL-1β secretory capacity may be a pathogenic factor for IDDM in these patients.] Pociot F, Molvig J, et al. *European Journal of Clinical Investigation*, Volume 22 Issue 6, Pages 396 - 402 http://www3.interscience.wiley.com/journal/119318083/abstract

546. **Adenovirus Encoding Human Platelet-Derived Growth Factor-B Delivered to Alveolar Bone Defects Exhibits Safety and Biodistribution Profiles Favorable for Clinical Use. [**Platelet-derived growth factor (PDGF) gene therapy offers promise for tissue engineering of tooth-supporting alveolar bone defects. To date, limited information exists regarding the safety profile and systemic biodistribution of PDGF gene therapy vectors when delivered locally to periodontal osseous defects. The aim of this preclinical study was to determine the safety profile of adenovirus encoding the PDGF-B gene (AdPDGF-B) delivered in a collagen matrix to periodontal lesions. Standardized alveolar bone defects were created in rats, followed by delivery of matrix alone or containing 5.5x108 or 5.5x109 pfu/ml AdPDGF-B. The regenerative response was confirmed histologically. Gross clinical observations, hematology and blood chemistries were monitored to evaluate systemic involvement. Bioluminescence and QPCR were utilized for assessing vector biodistribution. No significant histopathological changes were noted during the investigation. Minor alterations in specific hematological and blood chemistries were seen, however, most parameters were within the normal range for all groups. Bioluminescence analysis revealed vector distribution at the axillary lymph nodes during the first 2 weeks with subsequent return to baseline levels. AdPDGF-B was well-contained within the localized osseous defect area without viremia or distant organ involvement. These results indicate that AdPDGF-B delivered in a collagen matrix exhibits acceptable safety profiles for consideration of human clinical studies.] Chang PC, Cirelli JA et al. *Hum Gene Ther.* 2009 Feb 6 (online ahead of print). http://www.ncbi.nlm.nih.gov/pubmed/19199824?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

547. **An Interleukin-1β (IL-1β) Single-Nucleotide Polymorphism at Position 3954 and Red Complex Periodontopathogens Independently and Additively Modulate the Levels of IL-1β in Diseased Periodontal Tissues.** [Inflammatory cytokines such as interleukin-1β (IL-1β) are involved in the pathogenesis of periodontal diseases. A high individual variation in the levels of IL-1β mRNA has been verified, which is possibly determined by genetic polymorphisms and/or by the presence of periodontopathogens such as *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola*, and *Aggregatibacter actinomycetemcomitans*. In this study, we investigated the role of an IL-1β promoter single-nucleotide polymorphism at position 3954 [IL-1β(3954) SNP] and the presence of the periodontopathogens in the determination of the IL-1β levels in the periodontal tissues of nonsmoking chronic periodontitis (CP) patients (n = 117) and control (C) subjects (n = 175) and the possible correlations with the clinical parameters of the disease. IL-1β(3954) SNP was investigated by restriction fragment length polymorphism, while the IL-1β levels and the presence of the periodontopathogens were determined by real-time PCR. Similar frequencies of IL-1β(3954) SNP were found in the C and CP groups, in spite of a trend toward a higher incidence of T alleles in the CP group. The IL-1β(3954) SNP CT and TT genotypes, as well as *P. gingivalis*, *T. forsythia*, and *T. denticola*, were associated with higher IL-1β levels and with higher values of the clinical parameters of disease severity. Concomitant analyses demonstrate that IL-1β(3954) and the red complex periodontopathogens were found to independently and additively modulate the levels of IL-1β in periodontal tissues. Similarly, the concurrent presence of both factors was associated with increased scores of disease severity. IL-1β(3954) genotypes and red complex periodontopathogens, individually and additively, modulate the levels of IL-1β in the diseased tissues of nonsmoking CP patients and, consequently, are potentially

involved in the determination of the disease outcome.] Ferreira SB, Trombone APF, et al. *Infection and Immunity*, August 2008, p. 3725-3734, Vol. 76, No. 8. http://iai.asm.org/cgi/content/abstract/76/8/3725

548. **Assessment of Single Nucleotide Polymorphism at IL-1A+4845 and IL-1B+3954 as Genetic Susceptibility Test for Chronic Periodontitis in Maharashtrian Ethnicity**. [Background: The inflammatory response that is directed in large part by proinflammatory cytokine interleukin (IL)-1 is genetically determined, with some people having a more vigorous response than others to the same stimulus. The reason for this is speculated that the dysregulated production of IL-1 in some individuals overrides the feedback mechanisms that normally master the dose of inflammation to a level sufficient to fight microbial invasion without long-lasting damage to the tissues involved. The aims of the present study were to determine the distribution of IL-1 gene polymorphism (IL-1A+4845 and IL-1B+3954) and their association with periodontal disease severity and to determine the significance of detecting the composite genotype (IL-1A allele2 + IL-1B allele2) versus detecting either of them alone. Methods: A total of 120 subjects were included and divided into four groups of 30 subjects each, namely, healthy, mild, moderate, and severe periodontitis groups. After a complete clinical examination, DNA was isolated from 0.5 ml blood. Specific primers were used to detect the presence of IL-1 gene polymorphism with the help of polymerase chain reaction (PCR) and subsequent allele detection with restriction fragment length polymorphism (RFLP) and separation by gel electrophoresis. Results: The distribution of the allele1 homozygous genotype was 3% in the severe periodontitis group, and the distribution for the allele2 genotype was 30%. A higly significant difference (Wilcoxon signed-rank test; P <0.001) was seen between subjects positive and negative for the composite genotype. Conclusions: Results of the present study reinforced the association of the IL-1 genotype as a risk factor for severe chronic periodontitis. Positivity for the composite genotype was found to be significantly associated with severe chronic periodontitis (odds ratio [OR] = 12.42).] Agrawal AA, Kapley A, et al. *Journal of Periodontology*, 2006, Vol. 77, No. 9, Pages 1515-1521. http://www.joponline.org/doi/abs/10.1902/jop.2006.050427?journalCode=jop

549. **Association of interleukin-1 polymorphisms with periodontal disease. [**BACKGROUND: Several studies have investigated genetic polymorphisms for cytokines as potential genetic markers for periodontitis. Some studies have found that interleukin (IL)-1A and IL-1B polymorphisms are associated with a higher severity of periodontitis, while others found no association. The aims of this study were to determine the prevalence of the IL-1A-889 and IL-1B+3954 (previously described as +3953) polymorphisms in Chileans and their association with periodontitis. METHODS: Subjects aged 20 to 48 were selected from people requesting dental treatment at a public health center in Santiago, Chile. A case-control study of 330 cases of periodontitis patients and 101 healthy controls was performed. A full-mouth periodontal examination was performed on each subject and a structured questionnaire was conducted to determine smoking habits. Cases were categorized as having initial, moderate, or severe periodontitis according to the percentage of sites with clinical attachment loss > or =3 mm. Genomic DNA was analyzed for polymorphism in the IL-1A gene at site -889 and IL-1B gene at site +3954 by polymerase chain reaction (PCR) amplification followed by restriction enzyme digestion and gel electrophoresis. Data were analyzed by chi square test, analysis of variance (ANOVA), and by calculating odds ratio (OR) and 95% confidence intervals (CI). RESULTS: Demographic and socio-economic characteristics of subjects were similar in cases and in controls. A higher frequency of heterozygous of the IL-1A-889 was found in cases than in controls, but the difference was not significant. The heterozygous of the IL-1B+3954 was significantly higher in cases than in controls and was associated with periodontitis (OR 3.12, 95% CI 1.59 to 6.09, P = 0.001). The homozygous for allele 1 of the IL-1B+3954 was a protective factor for periodontitis (OR 0.35, 95% CI 0.19 to 0.66, P = 0.001). The prevalence of positive genotype (at least one allele 2 present at each locus) was significantly higher in cases (26.06%) than in controls (9.9%) and was significantly associated with periodontitis (OR 3.21, 95% CI 1.60 to 6.44, P = 0.001), irrespective of the smoking status and periodontitis severity. Sensitivity of positive genotype was 26%, the specificity 90%, and the positive predictive value 89%. CONCLUSION: Within the limits of this study, the results show that individuals carrying the positive genotype have significantly greater risk for developing periodontitis.] Lopez NJ, Jara L, et al. *J Periodontol.* 2005 Feb;76(2):234-43. http://www.ncbi.nlm.nih.gov/pubmed/15974847

550. **C-reactive protein levels are influenced by common IL-1 gene variations.** [Elevated markers of systemic inflammation are associated with the development of acute coronary syndromes, but there is no current explanation for increased inflammation in overtly healthy individuals. The influence of genetic control of the inflammatory response on the observed variability is unknown. We studied the frequency of four polymorphisms in interleukin (IL) 1 genes, known to modulate inflammation, in 454 individuals undergoing coronary angiography and analysed their influence on plasma C-reactive protein (CRP) and fibrinogen levels. Females and smokers had higher levels of CRP than males (Π=0.001) and non-smokers (Π=0.001). Patients with genotype 2.2 for the IL-1B(+3954) polymorphism had twice the median CRP levels of patients who were genotype 1.1 (4.33 vs 2.01 mg/l; ***P***=0.001). Patients with genotype 1.2 or 2.2 at the IL-1A(+4845) polymorphism also had higher median CRP (2.92 vs 2.05 mg/l, Π=0.023). In multivariate analyses, CRP levels remained significantly associated with IL-1 polymorphisms after adjustment for smoking, gender and age. Fibrinogen levels had similar associations with the IL-1 genotypes. These data indicate that IL-1 gene polymorphisms known to affect the inflammatory response are highly related to plasma levels of CRP and fibrinogen in patients referred for coronary angiography.] Berger P, McConnel JP, et al. *Cytokine*, Vol 17, Issue 4, Feb 2002, pp171-174. http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6WDF-45S4NW9-1&_user=10&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=ef46c5870ba746b49c6ff6848add064e

551. **Clinical state of the patients with periodontitis, IL-1 polymorphism and pathogens in periodontal pocket--is there a link? (An introductory report).** [PURPOSE: According to last years' research, polymorphism of IL-1 has an influence on the progression of periodontal disease. Oral mouth microflora can also have an effect on the disease process. The aim of the work was to evaluate the amount of microbacterial pathogens in the periodontal pockets of patients with positive and negative genotype. MATERIAL AND METHODS: Study group comprised of 16 patients, aged 25-50 years. Only patients with severe generalized form of chronic periodontititis were included into the study. After clinical examination patients were subjected to the IL-1 genotype evaluation (Genotype PST, Hain Lifescience GmbH, Germany) and PCR examination of selected bacteria pathological for periodontium (Perio-Analyse, Pierre Fabre Medicament, France). RESULTS: 7 out of 16 individuals were diagnosed as genotype positive (alleles 2 for genes IL-1A and IL-1B). Genetically positive individuals had greater mean pocket depth, clinical attachment loss and percentage of pockets deeper than 4 mm. Although in both groups similar bacterial pathogens have been identified, greater amounts of bacteria have been counted in group with positive genotype. Total count of bacteria from so-called "red complex" (P. gingivalis, T. forsythensis, T. denticola), and "orange complex" (F. nucleatum, P. micros, P. intermedia, C. rectus) were respectively 3-fold and 2-fold higher in group with positive genotype, despite the fact that group was smaller (7 vs 9 persons with negative genotype). Number and species of bacteria seems to correlate with pocket depth, clinical attachment loss, and percentage of pockets deeper than 4 mm. CONCLUSION: Observed association may have an influence on increased severity of periodontal disease in patients with positive genotype.] Kowalski J, Gorska R, et al. *Adv Med Sci*. 2006;51 Suppl 1:9-12. http://www.ncbi.nlm.nih.gov/pubmed/17458052

552. **Comparison of microbial cultivation and a commercial PCR based method for detection of periodontopathogenic species in subgingival plaque samples.** [OBJECTIVES: Microbiological laboratory procedures are involved in diagnosis and therapy control of progressive and refractory forms of periodontitis. In recent years techniques have been developed based on the detection of nucleic acids. The purpose of this study was to validate the commercially available micro-Dent(R) test which employs probes for A. actinomycetemcomitans, P. gingivalis, P. intermedia, B. forsythus and T. denticola. METHODS: 122 plaque samples obtained from periodontal pockets with various depths from 33 early onset periodontitis (EOP) patients and 15 periodontally healthy subjects were analysed by cultivation and the microDent(R) kit. RESULTS: Both cultivation and the nucleic acid based assay showed a positive correlation of pocket depth with the frequency and quantity of periodontopathogenic species. T. denticola was found only in pockets > 4 mm in EOP patients. Comparison of the two methods revealed that the microDent(R) kit identified both P. gingivalis and B. forsythus more often than did the cultivation method. Conclusions: Nucleic acid techniques should replace cultivation methods as gold standard in microbiological diagnosis of progressive periodontitis. The micro-Dent(R) kit can be recommended for microbiological laboratories analysing subgingival plaque samples.] Eick S, Pfister W. *J Clin Periodontol*. 2002 Jul;29(7):638-44. http://www.ncbi.nlm.nih.gov/pubmed/12354089

553. **DNA methylation profiles of gingival tissues in periodontal disease.** [Objective: We have recently reported that periodontal pathogens can alter DNA methylation patterns of host genomic DNA. DNA methylation is an epigenetic phenomenon that controls gene expression without a change in DNA sequence. Changes in DNA methylation generally remain stable following cell division to permanently alter the tissue gene expression and response to challenge. The goal of this study was to determine whether the biofilm was inducing local alterations in host DNA methylation patterns that could potentially modulate gene expression. Material and Methods: Genome-wide alterations in DNA methylation patterns were performed by analyses using CpG island microarrays. Diseased gingival tissues collected from patients with severe periodontal disease were compared with healthy gingival tissues from either healthy or diseased patients. Genomic DNA was isolated and restrictively digested with MseI, ligated to linkers and subjected to restrictive digestion by two methylation-sensitive restrictive enzymes, BstUI and HpaII. Following PCR amplification, products were labeled by Cy5 for test samples and Cy3 for control samples, hybridized to a 12K Human CpG-island microarray and analyzed for differences in CpG methylation patterns comparing health to disease. Results: Altered DNA methylation patterns were found in samples from patients with periodontal disease suggesting a local epigenetic modulation of host DNA structure. Preliminary results suggest that many genes are differentially methylated at sites of periodontal disease compared to health. Hypermethylation, which is usually associated with gene silencing, was observed for many genes including SOCS3, VDR, MMP25 and BMP4. Conclusion: Chronic infection and underlying inflammation in gingival tissue is associated with altered DNA methylation of multiple genes. Such modification may significantly contribute to permanent alteration of the local environment to further enhance the inflammatory tissue phenotype.] Barros S, Zhang S, et al. IADR 86th General Session & Exhibition. http://iadr.confex.com/iadr/2008Toronto/techprogram/abstract_108338.htm

554. **Effect of periodontal treatment on IL-1beta, IL-1ra, and IL-10 levels in gingival crevicular fluid in patients with aggressive periodontitis.** [AIM: The aim of this study was to examine the effect of phase I periodontal treatment on the levels of interleukin (IL)-1beta, IL-1ra, and IL-10 in gingival crevicular fluid (GCF) in patients with generalized aggressive periodontitis (G-AgP). MATERIAL AND METHODS: Data were obtained from 15 patients with aggressive periodontitis and 15 healthy controls. GCF was collected from at least four pre-selected sites (one shallow, at least two moderate, or at least one deep pockets) in patients with G-AgP. In the healthy group, GCF samples were collected from one site. The cytokine levels were determined by an enzyme-linked immunosorbent assay. Probing depth, clinical attachment level (CAL), gingival and plaque indices, and bleeding on probing were measured. The GCF sampling and clinical measurements were recorded at baseline and 6 weeks later after periodontal treatment. RESULTS: IL-1beta levels were significantly higher at the moderate and deep pocket sites compared with the shallow sites ($p<0.05$). After periodontal therapy, IL-1beta levels were significantly reduced in the moderate and deep pocket sites ($p<0.05$). IL-1ra levels at baseline of the moderate and deep

pocket sites were significantly lower than the control sites ($p<0.05$). IL-10 levels were similar in all pockets and did not change after periodontal therapy. CONCLUSIONS: The periodontal treatment improves the clinical parameters in G-AgP, and this improvement is evident in deep pocket sites for pocket depth and CAL values. These results confirm that IL-1beta is effective for evaluating the periodontal inflammation and can thus be used as a laboratory tool for assessing the activity of periodontal disease.] Toker H, Poyraz O. et al. *J Clin Periodontol*. 2008 Jun;35(6):507-13 http://www.ncbi.nlm.nih.gov/pubmed/18371054

555. **Epigenetic Regulation of Gene Expression in the Inflammatory Response and Relevance to Common Diseases.** [Epigenetics can be defined as all the meiotically and mitotically inherited changes in gene expression that are not encoded in the DNA sequence itself. Epigenetic modifications of chromatin and DNA have been recognized as important permissive and suppressive factors in controlling the expressed genome via gene transcription. Two major epigenetic mechanisms are the posttranslational modification of histone proteins in chromatin and the methylation of DNA itself, which are regulated by distinct, but coupled, pathways. It is clear that the epigenetic state is a central regulator of cellular development and activation. Emerging evidence suggests a key role for epigenetics in human pathologies, including in inflammatory and neoplastic disorders. The epigenome is influenced by environmental factors throughout life. Nutritional factors can have profound effects on the expression of specific genes by epigenetic modification, and these may be passed on to subsequent generations with potentially detrimental effects. Many cancers are associated with altered epigenetic profiles, leading to altered expression of the genes involved in cell growth or differentiation. Autoimmune and neoplastic diseases increase in frequency with increasing age, with epigenetic dys-regulation proposed as a potential explanation. In support of this hypothesis, studies in monozygotic twins revealed increasing epigenetic differences with age. Differences in methylation status of CpG sites, monoallelic silencing, and other epigenetic regulatory mechanisms have been observed in key inflammatory response genes. The importance of the epigenome in the pathogenesis of common human diseases is likely to be as significant as that of traditional genetic mutations. With advances in technology, our understanding of this area of biology is likely to increase rapidly in the near future.] Wilson AG. *J Perio* Vol. 79, No 8, Sup (115 p.) 2008. http://cat.inist.fr/?aModele=afficheN&cpsidt=20604912

556. **Epithelial cell TLRs in disease susceptibility. [Abstract:** Humans develop gingivitis and periodontitis in response to the challenges produced by microbial dental plaque. Individuals vary in their susceptibility to both gingivitis (superficial inflammation) and periodontitis (extensive inflammation causing bone and tooth loss). The etiology of periodontal disease is not fully understood; however, it is accepted that variance in the human host response to microbial plaque will relate to the host´s innate, inflammatory or immune defense systems. Single nucleotide polymorphisms (SNPs) exist in the human genes encoding many molecules pertinent to the host-microbe interaction. Periodontal inflammation (gingivitis and periodontitis) begins with the perturbation of the epithelial cells by bacteria via receptors, including Toll-like Receptors (TLRs). Our preliminary data indicates that the pro-inflammatory cytokines and chemokines produced in response to bacterial and cytokine perturbations differ between individuals and these differences may relate to carriage of a specific TLR4 polymorphism. Our general hypothesis is that individual response characteristics of gingival epithelial cells to foreign challenges, relate to their cellular TLR genotype which influences susceptibility to gingivitis and periodontitis. Thus we will address the following aims utilizing multiple primary human gingival epithelial cells (HGECs), clinical studies and genotype and phenotype analyses. The first aim is to characterize molecularly the inter-patient differences in TLR expression in HGECs using qPCR, gene expression profiling, protein assays and immunoreactivity and to correlate this to the TLR genotype. Secondly, functional analysis of genetically- modified HGECs (using siRNA knock-downs and over-expression) will elucidate the role of TLR4 and the Asp299Gly and other SNPs in epithelial LPS hypo-responsiveness. Thirdly, we aim to translate this work by determining clinically if TLR4 polymorphisms and hypo-responsiveness correlate with the severity of experimental gingivitis and if they can differentiate periodontitis cases and controls. Finally, we aim to challenge HGECs and other cell types, monocytes, gut epithelia and endothelial cells to assess LPS responsiveness relevant to the etiopathology of TLR4 associated diseases such as inflammatory bowel disease, atheroma and asthma. Characterization of response differences and determination of related SNPs may lead to new therapeutics or diagnostics in a range of infectious and inflammatory diseases.] Kinane DF. Periodontics, Endodontics And Dental Hygieneuniversity Of Louisville. Grant 5R01DE017384-03 from National Institute Of Dental & Craniofacial Research IRG: ODCS. http://www.researchgrantdatabase.com/g/5R01DE017384-03/Epithelial-Cell-TLRs-in-Disease-Susceptibility/

557. **Engineering of Tooth-Supporting Structures by Delivery of PDGF Gene Therapy Vectors**. [Platelet-derived growth factor (PDGF) exerts potent effects on wound healing including the regeneration of tooth-supporting structures. Limitations of topical protein delivery to periodontal osseous defects include transient biological activity and the bioavailability of PDGF at the wound site. The objective of this investigation was to determine the feasibility of *in vivo* PDGF-B gene transfer to stimulate periodontal tissue regeneration in large tooth-associated alveolar bone defects in rats. Periodontal lesions (0.3×0.2 cm in size) were treated with a 2.6% collagen matrix alone or a matrix containing adenoviruses encoding luciferase (control), a dominant negative mutant of PDGF-A (PDGF-1308), or PDGF-B. Block biopsies were harvested at 3, 7, and 14 days post-gene delivery and descriptive histology and histomorphometric analyses were performed. The defects treated with Ad-PDGF-B demonstrated greater proliferating cell nuclear antigen positively stained cells and strong evidence of bone and cementum regeneration beyond that of Ad-luciferase and Ad-PDGF-1308 groups. Quantitative image analysis showed a nearly fourfold increase in bridging bone and sixfold increase in tooth-lining cemental repair in the Ad-PDGF-B-treated sites compared to lesions treated with Ad-luciferase or collagen matrix alone, which showed limited hard tissue neogenesis. In addition, the Xenogen *In Vivo* Imaging System revealed sustained and localized gene expression of the luciferase reporter at the

periodontal lesions for up to 21 days after gene transfer. These results indicate that *in vivo* direct gene transfer of PDGF-B stimulates alveolar bone and cementum regeneration in large periodontal defects. Gene therapy utilizing PDGF-B may offer the potential for periodontal tissue engineering applications.] Aiming J, Anausaksathien O, et al. *Molecular Ther*. 2004 April;9(4):519-526. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2572773

558. ***FAM5C* Contributes to Aggressive Periodontitis.** [Aggressive periodontitis is characterized by a rapid and severe periodontal destruction in young systemically healthy subjects. A greater prevalence is reported in Africans and African descendent groups than in Caucasians and Hispanics. We first fine mapped the interval 1q24.2 to 1q31.3 suggested as containing an aggressive periodontitis locus. Three hundred and eighty-nine subjects from 55 pedigrees were studied. Saliva samples were collected from all subjects, and DNA was extracted. Twenty-one single nucleotide polymorphisms were selected and analyzed by standard polymerase chain reaction using TaqMan chemistry. Non-parametric linkage and transmission distortion analyses were performed. Although linkage results were negative, statistically significant association between two markers, rs1935881 and rs1342913, in the *FAM5C* gene and aggressive periodontitis ($p = 0.03$) was found. Haplotype analysis showed an association between aggressive periodontitis and the haplotype A-G (rs1935881-rs1342913; $p = 0.009$). Sequence analysis of *FAM5C* coding regions did not disclose any mutations, but two variants in conserved intronic regions of *FAM5C*, rs57694932 and rs10494634, were found. However, these two variants are not associated with aggressive periodontitis. Secondly, we investigated the pattern of *FAM5C* expression in aggressive periodontitis lesions and its possible correlations with inflammatory/immunological factors and pathogens commonly associated with periodontal diseases. *FAM5C* mRNA expression was significantly higher in diseased versus healthy sites, and was found to be correlated to the *IL-1β*, *IL-17A*, *IL-4* and *RANKL* mRNA levels. No correlations were found between *FAM5C* levels and the presence and load of red complex periodontopathogens or *Aggregatibacter actinomycetemcomitans*. This study provides evidence that *FAM5C* contributes to aggressive periodontitis.] Carvalho FM, Tinoco EMB, et al. (2010) *FAM5C* Contributes to Aggressive Periodontitis. PLoS ONE 5(4): e10053. doi:10.1371/journal.pone.0010053. http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0010053

559. **Gene–Environment Interactions and Susceptibility to Metabolic Syndrome and Other Chronic Diseases** [There is an intrinsic complexity in the pathogenesis of common diseases. The concept of gene–environment interaction is receiving support from emerging evidence coming primarily from studies involving diet and cardiovascular disease (CVD) and its various risk factors. The accumulating evidence shows that common variants at candidate genes for lipid metabolism, inflammation, and obesity are associated with altered plasma levels of classic and new biomarkers of metabolic syndrome and CVD risk. Major contributors to this knowledge have been a series of large population studies containing phenotype-rich databases and dietary information to which genetic data have been added. Although this approach has provided strong evidence supporting the concept of gene–diet interactions modulating CVD risk factors, the strength of the individual effect is very small, and the replication among studies is rather disappointing. Current population studies are starting to incorporate experimental and analytical approaches that could provide more solid and comprehensive results. However, other limitations, such as the size of the populations required to examine higher-level interactions, are still major obstacles to translating this knowledge into practical public health applications. Nevertheless, data from numerous molecular and genetic epidemiological studies provide tantalizing evidence suggesting that gene–environment interactions, i.e., the modulation by a genetic polymorphism of a dietary component effect on a specific phenotype (e.g., cholesterol levels and obesity), can interact in ways that increase the risk for developing chronic disease, including susceptibility to developing the metabolic syndrome. Once further experience is gained from patients and/or individuals at high risk, more personalized genetic-based approaches may be applied toward the primary prevention and treatment of CVDs and other complex inflammatory diseases.] Ordovas JM, Shen J. *Journal of Periodontology*, Vol. 79, No. 8s, pp1508-1513, Aug 2008. http://www.joponline.org/doi/abs/10.1902/jop.2008.080232

560. **Gene Therapy Effective Treatment Against Gum Disease.** [Univ of Michigan scientists demonstrate effective gene therapy for periodontal disease. Using NIH funding, Seattle based company Targeted Genetics tested 127 human subjects and showed 30% improvement in pain relief and function using gene treatment for rheumatoid arthritis using a gene therapy approach used to stop periodontal disease. People with RA are four times more likely to have periodontitis. Researchers were successful in getting inactivated virus' to produce the naturally produced molecule soluble TNF receptor, a biochemical that is under-produced in people with periodontal disease. This molecule delived by gene therapy soaks up excessive levels of TNF which is involved in inflammatory processes such as periodontal disease. The gene is delivered once into the host target cells which produces the receptor molecule for a very long time.] Giannobile W. U of Michigan. Science News – Science Daily. http://www.sciencedaily.com/releases/2008/12/081211081448.htm ; http://www.dentaleconomics.com/display_article/358587/54/none/none/IndNw/Gene-therapy-appears-safe-to-regenerate-gum-tissue

561. **Gene Therapy in Periodontics: A Review and Future Implications.** [New advancements in gene therapy continue to have a significant impact on dentistry since 1995. At the same time, periodontal disease has attracted the attention of scholars and research scientists as a global concern. With a better understanding of disease progression and new advancement in biological science, gene therapy has emerged to enhance existing therapy and has radically recast approaches to the management of periodontal disease. Since the advent of gene therapy in dentistry, significant progress has been made to control periodontal disease and reconstruct the dentoalveolar apparatus. However, to date, gene therapy methods have not been developed to control periodontal disease due to its multifactorial origin, complex genetic predisposition, and risk associated with it. This review article provides a brief insight into the ever-expanding field of gene therapy and its possible

future implication in the field of periodontics. Most of the modalities described in this article are more theoretical and still in infancy stage except for genetically fabricated materials used for regenerative purposes.] Karthikeyan BV, Pradeep AR. *J Contemp Dent Pract* 2006 July;(7)3:083-091. http://www.thejcdp.com/issue027/karthideyan/01karthikeyan.htm

562. **Genetic Links to Periodontal Disease and Dental Caries Formation. [**According to research published in the Journal of Dental Research and the online PloS One online research journal, researchers confirm genetic links associated with periodontal disease and dental caries. The gene "defense, beta 1" (DEFB1) is responsible for producing proteins which destroy viruses, bacteria and for triggering human immune response. These proteins are created in the mouths of otherwise healthy people to help control oral bacteria. Researchers found a link between DEF1 variations and the chance of having mising teeth, dental decay or fililngs (DMF), and that the rate was five times higher than those with no genetic variations. Parents in the study all had extreme gum disease, and a linnke was found between periodontal disease and variations in the FAM5C gene – a genetic variation also found in people with heart problems. http://worldental.org/dental-news/genetic-links-to-periodontal-disease-and-dental-caries-formation/1286/
563. **Gingival crevicular fluid levels of RANKL and OPG in periodontal diseases: implications of their relative ratio.** [AIM: Receptor activator of NF-kappaB ligand (RANKL) and osteoprotegerin (OPG) are a system of molecules that regulate bone resorption. This study aims to compare the levels of RANKL, OPG and their relative ratio in gingival crevicular fluid (GCF) of healthy and periodontal disease subjects. MATERIAL AND METHODS: GCF was obtained from healthy (n=21), gingivitis (n=22), chronic periodontitis (n=28), generalized aggressive periodontitis (n=25) and chronic periodontitis subjects under immunosuppressant therapy (n=11). RANKL and OPG concentrations in GCF were measured by enzyme-linked immunosorbent assays. RESULTS: RANKL levels were low in health and gingivitis groups, but increased in all three forms of periodontitis. OPG levels were higher in health than all three periodontitis, or gingivitis groups. There were no differences in RANKL and OPG levels between chronic and generalized aggressive periodontitis groups, whereas these were lower in the immunosuppressed chronic periodontitis group. The RANKL/OPG ratio was significantly elevated in all three periodontitis forms, compared with health or gingivitis, and positively correlated to probing pocket depth and clinical attachment level. CONCLUSION: GCF RANKL and OPG levels were oppositely regulated in periodontitis, but not gingivitis, resulting in an enhanced RANKL/OPG ratio. This ratio was similar in all three periodontitis groups and may therefore predict disease occurrence.] Bostanci N, Ilgenli T, et al. *J Clin Periodontol.* 2007 May;34(5):370-6. http://www.ncbi.nlm.nih.gov/pubmed/17355365
564. **Gum Disease, Heart Disease Share Genetic Link.** [TUESDAY, May 26 (HealthDay News) -- A genetic link between gum disease (periodontitis) and heart disease has been discovered by German scientists. The association between periodontitis and coronary heart disease (CHD) has been known for years, but a genetic link between the conditions hadn't been confirmed. The University of Kiel team found that the two diseases share a genetic variant on chromosome 9.] http://health.usnews.com/articles/health/healthday/2009/05/26/gum-disease-heart-disease-share-genetic-link.html
565. **Identification of a Shared Genetic Susceptibility Locus for Coronary Heart Disease and Periodontitis**. [Recent studies indicate a mutual epidemiological relationship between coronary heart disease (CHD) and periodontitis. Both diseases are associated with similar risk factors and are characterized by a chronic inflammatory process. In a candidate-gene association study, we identify an association of a genetic susceptibility locus shared by both diseases. We confirm the known association of two neighboring linkage disequilibrium regions on human chromosome *9p21.3* with CHD and show the additional strong association of these loci with the risk of aggressive periodontitis. For the lead SNP of the main associated linkage disequilibrium region, rs1333048, the odds ratio of the autosomal-recessive mode of inheritance is 1.99 (95% confidence interval 1.33–2.94; $P = 6.9\times10^{-4}$) for generalized aggressive periodontitis, and 1.72 (1.06–2.76; $P = 2.6\times10^{-2}$) for localized aggressive periodontitis. The two associated linkage disequilibrium regions map to the sequence of the large antisense noncoding RNA *ANRIL*, which partly overlaps regulatory and coding sequences of *CDKN2A/CDKN2B*. A closely located diabetes-associated variant was independent of the CHD and periodontitis risk haplotypes. Our study demonstrates that CHD and periodontitis are genetically related by at least one susceptibility locus, which is possibly involved in *ANRIL* activity and independent of diabetes associated risk variants within this region. Elucidation of the interplay of *ANRIL* transcript variants and their involvement in increased susceptibility to the interactive diseases CHD and periodontitis promises new insight into the underlying shared pathogenic mechanisms of these complex common diseases.] Schaefer AS, Richter GM, et al. PLoS Genet 5(2): e1000378. http://www.plosgenetics.org/article/info%3Adoi%2F10.1371%2Fjournal.pgen.1000378
566. **Interleukin-1 genetic association with periodontitis in clinical practice.** [BACKGROUND: Periodontitis is a bacterial disease modified by multiple risk factors. The pro-inflammatory cytokine interleukin- (IL-1) is a key regulator of the host responses to microbial infection and a major modulator of extracellular matrix catabolism and bone resorption. It has been reported that variations in the IL-1 gene cluster on chromosome 2 are associated with increased susceptibility to severe adult periodontitis. METHODS: The present study evaluated the association between a composite IL-1 genotype, including allele 2 at each of two loci (IL-1A +4845 plus IL- B +3954), and a broad spectrum of periodontally healthy to diseased patients in a population that is typically encountered in a dental practice setting. Ninety patients, non-smokers or former smokers with less than 10 pack-year (pk/yr) history, were recruited from a private dental practice. The major outcome variable was bone loss determined by computerized linear measurements of radiographs. Genotypes were analyzed from finger-stick blood samples using previously reported methods. RESULTS: Multivariate logistic regression models demonstrated that patient age, former smoking history, and the IL-1 genotype were significantly associated with severity of adult periodontitis. For non-smokers or former light smokers (<5 pk/yr), IL-1 genotype positives were at increased odds ratio of having moderate to severe periodontal disease of 3.75 (95% CI: 1.04-13.50) to 5.27 (95% CI: 1.23-22.70), depending on ethnicity, compared to IL-1

genotype negatives. Former moderate smokers (>5 pk/yr and <10 pk/yr) who were IL-1 genotype negative were at increased odds ratio of having moderate to severe periodontal disease of 7.43 (95% CI: 1.20-46.20) compared to non-smokers or former light smokers who were IL-1 genotype negative. In addition, past smoking history was also a significant effect modifier as demonstrated by the statistically significant interaction between past smoking history status and IL-1 genotype status. CONCLUSIONS: This study demonstrates that the composite IL-1 genotype is significantly associated with the severity of adult periodontitis. It also confirmed that both IL-1 genotyping and smoking history provide objective risk factors for periodontal disease in a private practice environment.] McDevitt MJ, Wang HY, et al. *J Periodontol*. 2000 Feb;71(2):156-63. **http://www.ncbi.nlm.nih.gov/pubmed/10711605**

567. **IL-1 Gene Variants Determine Increased Risk for Coronary Artery Disease.** [Oxidized phospholipids play a critical role in the initiation and progression of cardiovascular disease. These new data suggest a novel and clinically relevant biological link between pro-inflammatory IL-1 genotypes, oxidation of phospholipids and predisposition to CAD in younger individuals.]Tsimikas S, et al. & Interleukin Genetics Inc, *American College of Cardiology Meeting Abstract*, http://www.ilgenetics.com/content/news-events/newsDetail.jsp/q/news-id/105

568. **IL1B gene promoter haplotype pairs predict clinical levels of interleukin-1β and C-reactive protein.** [Interleukin-1β 1β (IL-1β activâtes inflammatory mediator cascades and has been implicated in the pathogenesis of several diseases. Single nucleotide polymorphisms (SNPs) of the IL1B promoter have been associated with various inflammatory diseases. We recently reported that IL1B gene transcription was influenced by four promoter SNPs, and that individual SNP function in vitro was governed by haplotype context. In the present study we tested the in vivo relevance of this observation by comparing IL1B promoter haplotype-pairs with IL-1β protein levels in 900 gingival tissue fluid samples. Three SNPs (-511, -1464, -3737) defined four IL1B promoter haplotypes that occurred in the study population and could be assigned unambiguously to each chromosome. The four haplotypes defined ten haplotype-pairs of which four pairs, representing 57% of the population, were associated with 28-52% higher IL-1β protein levels in vivo. Two of these pairs, characterized by homozygosity for the common allele at -3737, were also associated with raised serum levels of C-reactive protein (p = 0.02). We validated these findings in stimulated peripheral blood mononuclear cells (PBMCs) from a separate population (N=70). PBMCs with IL1B haplotype-pairs associated with higher in vivo levels of IL-1/β produced 86-287% more IL-1β in vitro than the reference group. We believe that this is the first demonstration of a relationship between in vivo levels of an inflammatory mediator and gene promoter haplotypes on both chromosomes. These findings may apply to other inducible genes and could provide a logical framework for exploring disease risk related to genetic variability in pathogenic mediators.] Rogus J, Offenbacher S, et al. *Human Genetics*, Vol. 123, No 4, pp 387-398, 2008. http://cat.inist.fr/?aModele=afficheN&cpsidt=20282581

569. **Interleukin-1 gene polymorphism, diabetes, and periodontitis: results from the Study of Health in Pomerania (SHIP).** [BACKGROUND: Periodontitis is a bacterial inflammatory disease leading to attachment loss with the consequence of tooth loss. There exists a multifactorial risk pattern including bacterial challenge, age, smoking, diabetes mellitus, as well as socioeconomic and genetic factors. An interleukin (IL)-1 haplotype is associated with periodontitis. We report the relationship between type 2 diabetes, the IL-1A/1B haplotype, and periodontitis in a population-based study. METHODS: In a cross-sectional health survey in northeast Germany, we genotyped 1,515 subjects aged 40 to 60 years for the IL-1 genotype, examined their periodontal status, and assessed diabetes, including the history of diagnosed diabetes, the use of antidiabetic medications, and hemoglobin A(1c) (HbA(1c)) measures. RESULTS: Subjects with increased levels of HbA(1c) had more widespread and severe periodontal disease than normoglycemic subjects. There is a gene-environmental interaction because diabetic subjects bearing a variant IL-1 genotype C/T or T/T had an enhanced risk for periodontal disease in comparison with their IL-1 wild-type counterparts. Bleeding on probing (P = 0.007), attachment loss (P = 0.009), and number of teeth (P <0.001) were associated significantly with diabetes and the IL-1 genotype. Logistic regression and a matched-pair analysis confirmed these results. CONCLUSION: Subjects with type 2 diabetes have an increased risk for periodontitis, which is aggravated further if combined with the variant IL-1A/1B genotype.] Struch F, Dau M, et al. *J Periodontol*. 2008 Mar;79(3):501-7. **http://www.ncbi.nlm.nih.gov/pubmed/18315433**

570. **Interleukin 1 genetics, inflammatory mechanisms, and nutrigenetic opportunities to modulate diseases of aging.** [Inflammation plays a central role in many diseases of aging, and genetic differences in the inflammatory response appear to influence different disease courses among individuals. Variations in the genes for the family of interleukin 1 (IL-1) proteins are inherited together in a small set of patterns and provide an example of the role of inflammatory genetics as a modifier of diseases of aging. The IL-1 genetic variations are associated with variation in both the inflammatory response and the clinical presentation of a range of diseases, including coronary artery disease, Alzheimer disease, gastric cancer, and periodontitis. This growing understanding of the role of genetic variation in inflammation and chronic disease presents opportunities to identify healthy persons who are at increased risk of disease and to potentially modify the trajectory of disease to prolong healthy aging. Nutrition represents one of the promising approaches to modulation of the risk of diseases of aging because of the effects of certain nutrients on gene expression. One of the most practical applications of nutritional modulation of chronic disease may be nutrients that regulate the expression of key inflammatory genes.] Kornman KS. *American Journal of Clinical Nutrition*, Vol 83, NO.2,475S-483S, Feb 2006. http://www.ajcn.org/cgi/content/abstract/83/2/475S http://www.ncbi.nlm.nih.gov/pubmed/16470016

571. **Interleukin-1 Gene Polymorphism and Periodontitis in Subjects from Indian Subcontinent. [**IL-1 is a specific pro-inflammatory cytokine and is one of the key mediators of the inflammatory process. The association between IL-1 gene polymorphisms and periodontal disease has been shown to be variable in different populations. Objective: to investigate the

association of IL-1 polymorphisms and periodontitis in a population from the Indian subcontinent. Methods: Clinical examinations including dental radiographs were carried out to determine the periodontal status (mild, moderate, severe), including pocket depth (PD), clinical attachment level (CAL), plaque index and gingival index, and smoking history. In addition, IL-1 gene polymorphisms of IL-1A (+4845), IL-1B (+3954), IL-1B (-511), and IL-1RA (+2018) were evaluated using PCR. Results: The frequencies of IL-1 genotype of the subjects with mild, moderate and severe periodontitis were compared with healthy and gingivitis groups using a chi-square test and one-way analysis of variance. In assessing periodontitis with clinical parameters, no significant differences were found in allele frequencies or combined allotypes between subjects with periodontitis (all three categories combined) versus subjects with no periodontitis (healthy and gingivitis combined). However, mean probing depth was found to be significantly associated with IL-1A (+4845) among genotype positive (1,2 and 2,2) subjects. In addition, IL-1A (+4845) and the IL-1 composite genotype were found to be significantly associated with periodontitis in this population, while the association between IL-1B (+3954) and periodontitis was close to significance. Smoking and age were found to be the major risk determinants to increase the association. Conclusions: There is a significant association between IL-1A (+4845) and periodontitis in a population of Indian subcontinent origin. These data confirm that both IL-1 genotyping and smoking history are objective risk factors for periodontal disease. Supported by GCRC Grant MO1 RR00533.] Hasturk H, Serrenho AC, et al. ADEA/AADR/CADR Meeting & Exhibition, March 2006. http://iadr.confex.com/iadr/2006Orld/techprogram/abstract_76499.htm

572. **Interleukin-1 genotype-selective inhibition of inflammatory mediators by a botanical: a nutrigenetics proof of concept.** [Objective: Although observational studies have shown that genotype may influence nutritional effects on target outcomes, there are few reported studies that stratified subjects by genotype before a nutritional intervention. This proof-of-concept trial determined whether specifically formulated botanical mixtures reduced inflammation in individuals with genetic variations that predispose to overexpression of interleukin-1β (IL-1β) and early heart disease. Methods: Healthy adults with elevated C-reactive protein (CRP) were stratified into genetic groups based on being positive (IL1Pos) or negative (IL1Neg) for the at-risk IL-1 gene variations. IL1Pos (n = 39) and IL1Neg (n = 40) subjects were then randomized to the candidate botanical formulation or placebo. The botanical formulation included rose hips, a blueberry and blackberry mixture, and a grapevine extract. Results: At 12 wk of dosing with the botanical formulation, IL-1β gene expression by stimulated peripheral blood mononuclear cells was significantly lower than at baseline and significantly lower than placebo in IL1Pos and IL1Neg subjects. Mean IL-1β gene expression treatment effect over the 12-wk period was greater in IL1Pos than in IL1Neg subjects. At 12 wk of dosing the botanical mixture produced no mean change in serum CRP levels. However, in IL1Pos subjects, significantly more subjects achieved a reduction in CRP with the botanical mixture than with placebo. No CRP effect was observed in the IL1Neg subjects. Conclusion: This study represents one of a few prospective clinical trials in which genetic variations were shown to differentially influence nutrient effects on outcomes.] Kornman Ken, Rogus J, et al. Nutrition, Vol 23, Issue 11, pp 844-852, Nov 2007. http://www.nutritionjrnl.com/article/S0899-9007(07)00246-8/abstract

573. **Microbiological parameters associated with IL-1 gene polymorphisms in periodontitis patients.** [BACKGROUND, AIMS: Polymorphisms in the cluster of IL-1 genes have been significantly associated with the severity of adult periodontitis. The purpose of this study was to compare microbiological parameters in IL-1 genotype negative and positive adult subjects with a range of periodontitis severities. METHOD: The study included 108 subjects in good general health. Clinical parameters were recorded at 6 sites/tooth excluding 3rd molars and included: plaque accumulation, gingival erythema, bleeding on probing, suppuration, pocket depth and attachment level. Subgingival plaque samples were collected from the mesiobuccal surface of up to 28 teeth in each subject (mean 25.3) providing a total of 2736 samples. The levels of 40 subgingival taxa were determined in each sample using checkerboard DNA-DNA hybridization. Fingerstick blood samples were collected for IL-1A (+4845) and IL-1B (+3954) genotyping using PCR-based methods. RESULTS: The proportion of IL-1 genotype positive subjects that exhibited mean counts of specific subgingival species above selected thresholds was significantly higher than the proportion of genotype negative subjects. Prominent among species that were detected at higher levels in genotype positive subjects were members of the "red" and "orange" complexes and included: Bacteroides forsythus, Treponema denticola, the Fusobacterium nucleatum subspecies, Fusobacterium periodonticum, Campylobacter gracilis, Campylobacter showae and Streptococcus constellatus. Streptococcus intermedius, Streptococcus gordonii and 3 Capnocytophaga species were also detected more frequently at high numbers in genotype positive subjects. Significantly higher mean counts of B. forsythus, Porphyromonas gingivalis, T. denticola, the F. nucleatum subspecies, F. periodonticum, Campylobacter rectus, C. showae, Eubacterium nodatum, S. constellatus, S. gordonii, and S. intermedius were detected at periodontal pockets >6 mm in subjects who were genotype positive when compared with genotype negative subjects. The increase was due to increased numbers of cells of these species rather than a major shift in proportion. CONCLUSION: The data suggest that genotype positive subjects more frequently had higher levels of "red" and "orange" complex species that are known to be strongly associated with measures of periodontal inflammation.] Socransky SS, haffajee AD, et al. *J Clin Periodontol.* 2000 Nov;27(11):810-8. http://www.ncbi.nlm.nih.gov/pubmed/11073323

574. **Periodontitis Associated With Development of Type 2 Diabetes and Its Complications.** ["The inflammation from the oral cavity may be contributing to the insulin resistance in this patient population," said Dr. Ryan. Also measured in this group were levels of cytokines, such as IL-1 beta, which are pro-inflammatory mediators involved in the long-term diabetes complications. "Genetic testing revealed that 50% of the insulin resistant patients had an IL-1 polymorphism -- in contrast to 20% in the overall population, meaning that they are genetically susceptible to an excessive inflammatory response, and this 50% was the group that had high levels of insulin resistance and more severe periodontal disease," she said. The presence of the IL-1 polymorphism fits with one theory of how periodontitis worsens glycemic control in type 2 diabetes. "We think

periodontitis may adversely affect glycemic control because the pro-inflammatory chemicals produced by the infection -- such as IL-1-beta, IL-6, and TNF-alpha -- could transfer from the gum tissue into the bloodstream and stimulate cells to become resistant to insulin," said Dr. Taylor. "Then insulin resistance prevents cells in the body from removing glucose from the bloodstream for energy production."] Am Diabetes Assoc, Ryan ME, Taylor GW. http://www.marketwire.com/press-release/American-Diabetes-Association-865852.html

575. **Polymorphisms of the Interleukin-1ß Gene Affect the Risk of Myocardial Infarction and Ischemic Stroke at Young Age and the Response of Mononuclear Cells to Stimulation In Vitro.** [Methods: The study looked at IL-1 gene variations in 406 patients with a heart attack at a young age, compared to 419 healthy controls matched for age and sex, and 134 patients experiencing a stroke at a young age compared to 134 controls and matched accordingly. Results: Certain IL-1 gene variations were associated with a protective effect, or lower risk of early heart attack or stroke in this population (heart attack odds ratio [OR], 0.36; 95% CI, 0.20-0.64; stroke OR, 0.32 95% CI, 0.13-0.81). These 'protective' IL-1 gene variations are associated with decreased expression of inflammatory mediators; immune (mononuclear) cells sampled from these individuals expressed lower levels of IL-1β and tissue factor (TF). Such findings suggest a muted inflammatory response, and particularly reduced inflammation-activated coagulation. Further analysis identified a two-fold higher risk of heart attack in people with IL-1 gene variations consistent with IL-1 Risk Patterns. For one gene variation, the heart attack odds ratio [OR] was 2.1; (P = 0.003); for another; it was 1.8 (P = 0.02) Our data support a primary role of inflammation-activated coagulation in the development of MI and ischemic stroke at a young age and give the first evidence that the association between IL-1β and ischemic disease at young age is genetically modulated." "The evidence for an association between IL-1β genetics and the risk of myocardial infarction and ischemic stroke suggests a primary pathogenic role of inflammation in such diseases.] Iacoviello L, DiCastelnuovo A, et al. *Arteriosclerosis, Thrombosis, and Vascular Biology.* 2005;25:222. http://atvb.ahajournals.org/cgi/content/full/25/1/222

576. P**revalence of OPG and IL-1 gene polymorphisms in chronic periodontitis.** [AIM: To investigate the association of polymorphisms in the osteoprotegerin (OPG) and interleukin 1 (IL-1) genes with chronic periodontitis (CP). MATERIAL AND METHODS: One hundred and ninety-four individuals (97 CP patients, 97 controls) were genotyped for the OPG polymorphisms Lys3Asn and Met256Val and for the IL-1 polymorphisms IL-1A (-889C/T) and IL-1B (+3953C/T). RESULTS: The homozygous variants coding for Lys3 were present at a higher frequency, whereas Asn3 and Met256 were present at a lower frequency in CP patients/controls (Lys3: 31%/25%, Asn3: 23%/32% and Met256: 66%/73%). Heterozygosity for Lys3Asn was observed at a higher frequency in CP patients/controls (46%/43%). Homozygosity for the Val256 genotype was observed in two CP patients (one in controls). Met256Val heterozygosity was more prevalent in CP patients/controls (32%/20%). All differences were statistically not significant between CP patients and controls. In contrast, both IL-1 polymorphisms were statistically significant. The heterozygous variant for IL-1A was present in 32% of the CP patients and in 20% of the controls (homozygosity (patients/controls) CC: 10%/21% and TT: 55%/33%). Heterozygosity for IL-1B was observed in 37% of the CP patients versus 34% in the controls (homozygosity (patients/controls) CC: 26%/57% and TT: 37%/9%). CONCLUSION: While the association between the IL-1 polymorphisms and CP was confirmed, no association between the OPG polymorphisms and CP could be found.] Wagner J, Kaminski WE, et al. *J Clin Periodontol.* 2007 Oct;34(10):823-7. http://www.ncbi.nlm.nih.gov/pubmed/17711477

577. **Prognosis versus actual outcome. IV. The effectiveness of clinical parameters and IL-1 genotype in accurately predicting prognoses and tooth survival**. [Background: Recently, a genetic marker (IL-1 genotype) that identifies individuals at higher risk for developing severe periodontal disease was discovered. A subgroup of the population reported on earlier was evaluated to determine if knowledge of the patient's IL-1 genotype would improve accuracy in assignment of prognoses and prediction of tooth loss. METHODS: This subgroup consisted of 42 patients (1,044 teeth) in maintenance care for 14 years; 16 tested IL-1 genotype-positive (IL-1GP). Nine were smokers, and 30 had a history of smoking, with an average of 29.44 pack years. A multiple Cox regression model and Kaplan-Meier survival plots were fit to the subset of patients to evaluate tooth loss. RESULTS: Both IL-1GP and heavy smoking were significantly related to tooth loss. A positive IL-1 genotype increased the risk of tooth loss by 2.7 times, and heavy smoking by 2.9 times. The combined effect of IL-1GP and heavy smoking increased the risk of tooth loss by 7.7 times. The value of clinical parameters traditionally used to assign prognosis was found to be dependent on IL-genotype and smoking status. In the model that included IL-1 genotype and heavy smoking, none of the clinical parameters added significantly to the model for tooth loss while mobility, probing depth, crown-to-root ratio, and percent bone loss added significantly to the model, which included IL-1 genotype in non-smokers. IL-1GP patients and patients who smoked heavily demonstrated a much worse tooth survival rate when compared to IL-1 genotype-negative patients and non-smokers, respectively. CONCLUSIONS: Knowledge of the patient's IL-1 genotype and smoking status will improve the clinician's ability to accurately assign prognosis and predict tooth survival. Clinical implications are as follows. Investigators were unable to judge which patients would be IL-GP or negative based on their clinical presentation or family history of tooth loss due to periodontal disease. Since periodontal diseases are multifactorial, knowledge of the patient's genotype is more important in predicting future risk than explaining past disease. Knowledge of IL-1 genotype status would be important in developing a treatment plan and predicting tooth survival for a new patient who smokes and presents with periodontal disease, especially if restorative care is needed. Knowledge of a maintenance patient's IL-1 status would help target therapy for non-responding areas; one would be less likely to take a "wait and see approach" with IL-1GP patients. IL-1 positive non-smokers can be successfully treated and maintained over long periods of time.] McGire MK, Nunn ME *J Periodontol.* 1999 Jan;70(1):49-56. . http://www.ncbi.nlm.nih.gov/pubmed/10052770

578. **Scientists find shared genetic link between the dental disease periodontitis and heart Attack**. [The relationship between the dental disease periodontitis and coronary heart disease (CHD) has been known for several years. Although a genetic link seemed likely, until now its existence was uncertain. Now, for the first time, scientists have discovered a genetic relationship between the two conditions, a researcher told the annual conference of the European Society of Human Genetics today (Monday 25 May). Dr. Arne Schaefer, of the Institute for Clinical Molecular Biology, University of Kiel, Germany, said that his team had discovered a genetic variant situated on chromosome 9 which was shared between the two diseases. “We studied a genetic locus on chromosome 9p21.3 that had previously been identified to be associated with myocardial infarction, in a group of 151 patients suffering from the most aggressive, early-onset forms of periodontitis, and a group of 1097 CHD patients who had already had a heart attack. The genetic variation associated with the clinical pictures of both diseases was identical," he said. The scientists went on to verify the association in further groups of 1100 CHD patients and 180 periodontitis patients. “These factors already indicated a possible mutual genetic basis underlying the two diseases”, said Dr. Schaefer. Now we know for sure that there is a strong genetic link, patients with periodontitis should try to reduce their risk factors and take preventive measures at an early stage”, he said. “We hope that our findings will make it easier to diagnose the disease at an early stage, and that in future a greater insight into the specific pathophsyiology might open the way to effective treatment before the disease can take hold.”] Schaefer A, European Society of Human Genetics, May 25, 2009. https://www.eshg.org/fileadmin/www.eshg.org/press/2009/Schaefer.pdf https://www.eshg.org/13.0.html

579. **The cost-effectiveness of interleukin-1 genetic testing for periodontal disease**. [BACKGROUND: A genetic test for a composite interleukin-1 (IL-1) genotype is being marketed to predict risk for progression of periodontal disease. The objective of this study was to determine the clinical scenario required to produce cost-effective results with the use of IL-1 testing to identify high-risk patients. METHODS: A disease simulation model was developed using decision-analytic techniques and a 30-year time frame. RESULTS: Using different modeling scenarios, the genetic test produced results ranging from cost savings of $830,140 and 52.8 fewer cases of severe periodontitis to increased costs of $300,430 and 3.6 additional cases of severe periodontitis (per 1,000 patients). Three parameters in the analysis were highly influential: 1) the compliance rate for maintenance therapy in test positive versus non-tested patients; 2) the effectiveness of non-surgical therapy; and 3) the relative risk of disease progression for test positive patients. CONCLUSION: The model produced a wide range of outcomes reflecting our incomplete understanding of the biology, optimal treatment, and genetic susceptibility of periodontal diseases. However, the model demonstrates that three clinical parameters are highly influential in determining if IL-1 testing can be implemented in a primary care setting in a cost-effective manner.] Higashi MK, Veenstra DL, et al. *J Periodontol*. 2002 Dec;73(12):1474-84. **http://www.ncbi.nlm.nih.gov/pubmed/12546098**

580. **The effect of interleukin-1 allele 2 genotype (IL-1a(-889) and IL-1b(+3954)) on the individual's susceptibility to peri-implantitis: case-control study**. [Individuals bearing the combination of interleukin (IL)-1 allele 2 at IL-1A(-889) and IL-1B(+3954) are referred to as being genotype positive and are susceptible to increased periodontal tissue destruction. The aim of this study was to assess the possible association of IL-1 allele 2 (IL-1A(-889) and IL-B(+3954)) genotypes with the severity of peri-implantitis progression and the effect of this combination on treatment outcomes. Fifty patients with International Team for Implantology implants were studied; patients ranged in age from 35-55 years, and each patient had 1 implant. According to peri-implant tissue status, patients were divided into 2 groups: group I consisted of 25 patients with peri-implantitis, and group II comprised 25 patients with healthy peri-implant tissue. Clinical parameters were assessed at baseline and after 3 and 6 months. Epithelial cells were collected from the oral mucosa by plastic spatula and were used for IL-1 genotyping by the polymerase chain reaction technique. Group I patients were subjected to a peri-implantitis treatment and maintenance program. In all, 17 patients from group I and 5 patients from group II were genotype positive, with a statistically significant difference noted between the 2 groups. Group I genotype-positive patients presented with higher scores and measurements of clinical parameters with increased suppuration from peri-implant tissues compared with group II; differences were statistically significant ($P < .05$). In terms of response to treatment, genotype-negative patients demonstrated better response than genotype-positive patients. The combination of IL-1 allele 2 (IL-1A(-889) and IL-1B(+3954)) in patients with inflamed periodontal or peri-implant tissues acts as a risk factor that leads to greater tissue destruction. IL-1 gene polymorphism at IL-1A(-889) and IL-1B(+3954) may affect outcomes of treatment for peri-implantitis in genotype-positive individuals.] Hamdy AA, Ebrahem MA. *J Oral Implantol*. 2011 Jun;37(3):325-34. http://www.ncbi.nlm.nih.gov/pubmed/20594066

581. **The interleukin-1 genotype as a severity factor in adult periodontal disease.** [Although specific bacteria, dental plaque, and age are associated with periodontal disease, there are currently no reliable predictors of periodontitis severity. Studies in twins have suggested a genetic contribution to the pathogenesis of periodontitis, but previous attempts to identify genetic markers have been unsuccessful. The pro-inflammatory cytokines interleukin-1 (IL-1) and tumor necrosis factor alpha (TNFα) are key regulators of the host responses to microbial infection. IL-1 is also a major modulator of extracellular matrix catabolism and bone resorption. We report a specific genotype of the polymorphic IL-1 gene cluster that was associated with severity of periodontitis in non-smokers, and distinguished individuals with severe periodontitis from those with mild disease (odds ratio 18.9 for ages 40–60 years). Functionally, the specific periodontitis-associated IL-1 genotype comprises a variant in the IL-1B gene that is associated with high levels of IL-1 production. In smokers severe disease was not correlated with genotype. In this study, 86.0% of the severe periodontitis patients were accounted for by either smoking or the IL-1 genotype. This study demonstrates that specific genetic markers, that have been associated with increased IL-1 production, are a strong indicator of susceptibility to severe periodontitis in adults.] Kornman KS, Crane A, et al. *Journal of Clinical Periodontology*, Vol 24, Issue 1, pp 72-77. http://www3.interscience.wiley.com/journal/119171812/abstract?CRETRY=1&SRETRY=0

582. **The Interleukin-1 Polymorphism, Smoking, and the Risk of Periodontal Disease in the Population-based SHIP Study.** [Several studies have shown a role for interleukin-1 gene cluster polymorphisms in the risk assessment for periodontal diseases. In the Study of Health in Pomerania (SHIP), 3148 subjects were randomly selected from the population and assessed for a broad range of diseases and environmental/behavioral risk factors. From the complete study group in the age 40 to 60 years, N = 1085 subjects were genotyped for the interleukin-1 genotype composite polymorphism in relation to periodontal parameters. The study objective was to elucidate the gene-environment interaction between the risk factors smoking and IL-1 polymorphism. An increased risk of periodontal disease was found for IL-1 genotype-positive smokers: odds ratio adjusted for age, sex, education, and plaque OR = 2.50 (95% C.I. 1.21 to 5.13; p = 0.013). This was not the case with subjects who never smoked: OR = 1.09 (0.73-1.62; p = 0.676). These results support the hypothesis of gene-environmental interaction in periodontitis.] Meisel P, Siegemund A, et al. Journal of Dental Research, Vol. 82, No. 3, 189-193 (2003). http://jdr.sagepub.com/cgi/content/full/82/3/189
583. **The intriguing biology of the tumour necrosis factor/tumour necrosis factor receptor superfamily: players, rules and the games.** [The members of the tumour necrosis factor (TNF)/tumour necrosis factor receptor (TNFR) superfamily are critically involved in the maintenance of homeostasis of the immune system. The biological functions of this system encompass beneficial and protective effects in inflammation and host defence as well as a crucial role in organogenesis. At the same time, members of this superfamily are responsible for host damaging effects in sepsis, cachexia, and autoimmune diseases. This review summarizes recent progress in the immunbiology of the TNF/TNFR superfamily focusing on results obtained from animal studies using gene targeted mice. The different modes of signalling pathways affecting cell proliferation, survival, differentiation, apoptosis, and immune organ development as well as host defence are reviewed. Molecular and cellular mechanisms that demonstrate a therapeutic potential by targeting individual receptors or ligands for the treatment of chronic inflammatory or autoimmune diseases are discussed.] Hehlgans T, PfefferK. *Immunology* Vol 115 Issue 1, Pp1-20. http://www3.interscience.wiley.com/journal/118685566/abstract

MTHFR-Polymorphism, Homocystein

584. **Association of Methylenetetrahydrofolate reductase (MTHFR) polymorphism and the risk of Squamous Cell Carcinoma in renal transplant patients.** [The relative risk of developing cutaneous squamous cell carcinoma (SCC) is significantly increased after organ transplantation. We investigated the genetic association of SCC in two pathways associated with cancer risks, with the potential for modification by vitamin supplementation. A total of 367 renal transplant recipients (117 with SCC and 250 without any skin cancer) were genotyped for key polymorphisms in the folate pathway (methylene tetrahydrofolate reductase; MTHFR:C677T), and the vitamin D pathway (vitamin D receptor: Intron8G/T;). Individuals carrying the MTHFR 677T allele had a marked increase in risk of SCC (adjusted odds ratio=2.54, P=0.002, after adjustment for age, ender, skin type, sun exposure score, and immunosuppression duration; lower 95% confidence boundary odds ratio of 1.41). In contrast, vitamin D receptor polymorphisms were not significantly associated. Folate-sensitive pathways may play a critical role in the elevated rate of SCC in renal transplant recipients.]Laing ME, Dicker P, et *Transplantation*. 2007 Jul 15;84(1):113-6. http://www.ncbi.nlm.nih.gov/pubmed/17627246
585. **Association of MTHFR Gene Variants with Autism.** [Autism is a complex neurodevelopment disorder with numerous possible genetic and environmental influences. We retrospectively examined the laboratory data of 168 children sequentially referred to our facility with a confirmed diagnosis of autism or pervasive developmental disabilities (PDD). Since folate and methylation (single carbon metabolism) are vital in neurological development, we routinely screened children for the common mutations of the methylenetetrahydrofolate reductase gene (MTHFR), which regulates this pathway. All children had polymerase chain reaction (PCR) DNA evaluation to determine the frequency of the 677 and 1298 common polymorphisms in the MTHFRgene. We observed a significantly increased frequency of the homozygous mutation 677CT allele (TT): 23% in the autistic children compared to 11% in the control population (<0.0001). Additionally, the heterozygous 677CT allele (CT) was present in 56% of the autistic children compared to 41% in the control population (<0.0001). Somewhat paradoxically, the normal 1298AA allele was significantly higher in the autistic group, 55%, compared to the controls, 44% (<0.05). Despite the increased frequency of normal 1298AA alleles, the compound 677CT/1298AC heterozygous mutations were more prevalent in the autistic population, 25%, than in controls, 15% (=0.01). Overall, the data show an increased risk of autism spectrum disorder (ASD) associated with common mutations affecting the folate/methylation cycle. These associations by themselves may provide a partial explanation for a subgroup of children genomically at risk for ASD disorders. Increased folinic acid during pregnancy and early development may offset the genomic risk factors, and this deserves further study. Further, since folate-dependent methylation provides, in part, the methyl group for inactivation of monoamine neurotransmitters via the catecholamine-O-methyltransferase (COMT) system, this observation may help to further differentiate subtypes within the broad phenotype of ASD. A search for additional genomic and environmental risk factors should be undertaken. In particular, the methylation/transsulfation and COMT pathways should be investigated.] Boris M, Goldblatt A, et al. *J of American Physicians and Surgeons*, vol. 9, No. 4, pp 106-108. http://www.autismny.com/uploads/3/3/9/1/3391982/mthfr_-_boris_james_etal.pdf
586. **Common Mutation in Methylenetetrahydrofolate Reductase.** [*Background* Increased homocysteine levels are a risk factor for atherosclerosis and its sequelae. A common genetic mutation in methylenetetrahydrofolate reductase (MTHFR), an enzyme required for efficient homocysteine metabolism, creates a thermolabile enzyme with reduced activity. We determined the prevalence of this mutation in many subjects with and without vascular disease and related it to homocysteine and folate

levels. *Methods and Results* DNA from 247 older subjects with vascular disease and 594 healthy subjects without vascular disease (in three different control groups) was screened for the MTHFR 677 C-to-T mutation. Within each group, 9% to 17% of the subjects were homozygous for this mutation, and the mutant allele frequency was 31% to 39%. The genotype distributions, homozygote frequencies, and allele frequencies did not differ significantly between the study groups. In the vascular disease subjects, despite significantly lower folate levels in MTHFR homozygotes, there was no significant difference in homocysteine levels among the MTHFR genotype groups. The negative slope of the regression line relating homocysteine and folate was significantly steeper for those with a homozygous MTHFR mutation compared with those without this mutation. *Conclusions* Although the thermolabile MTHFR mutation is very common, it does not appear to be a significant genetic risk factor for typical late-onset vascular disease. Because MTHFR homozygotes have increased homocysteine with low folate levels, this mutation may contribute to early-onset or familial vascular disease. The genotype dependence of the folate-homocysteine correlation further suggests that homozygotes for this mutation may have both an exaggerated hyperhomocysteinemic response to folic acid depletion and a better response to folic acid therapy.] Deloughery TG, Evans A, et al. *Circulation.* 1996;94:3074-3078. http://www.circ.ahajournals.org/cgi/content/abstract/94/12/3074

587. **Comparison of the effect of low-dose supplementation with L-5-methyltetrahydrofolate or folic acid on plasma homocysteine: a randomized placebo-controlled study.** [Background: Food fortification with folic acid has been introduced in several countries for the prevention of neural tube defects. Fortification has lowered total homocysteine (tHcy) concentrations in the US population, a consequence that may have health benefits. However, folic acid fortification could mask vitamin B-12 deficiency. Synthetic L-5-methyltetrahydrofolate (L-MTHF) may be more appropriate than folic acid as a fortificant because it is unlikely to mask the hematologic indicators of vitamin B-12 deficiency. Objective: The objective of the study was to compare the effectiveness of 100 µg folic acid/d with that of equimolar L-MTHF in lowering tHcy in healthy volunteers. Design: The study was designed as a 24-wk, randomized, placebo-controlled intervention. Free-living healthy volunteers (n = 167) were randomly assigned to receive a daily supplement containing folic acid (100 µg), L-MTHF (113 µg), or placebo. Blood collected at baseline and at 8, 16, and 24 wk was analyzed for tHcy, plasma folate, and red blood cell folate (RCF) concentrations. Results: At 24 wk, after adjustment for baseline values, mean (95% CI) tHcy was 14.6% (9.3, 19.5%) and 9.3% (3.7, 14.6%) lower, mean plasma folate was 34% (14, 56%) and 52% (30, 78%) higher, and mean RCF was 23% (12, 35%) and 31% (19, 44%) higher in the L-MTHF and folic acid groups, respectively, than in the placebo group. L-MTHF was more effective than was folic acid in lowering tHcy ($P < 0.05$). At 24 wk, the increases in plasma folate and RCF concentrations did not differ significantly between the 2 supplemented groups. Conclusion: Low-dose L-MTHF is at least as effective as is folic acid in reducing tHcy concentrations in healthy persons.] Venn BJ, Green TJ, et al. *American Journal of Clinical Nutrition*, Vol. 77, No. 3, 658-662, March 2003, http://www.ajcn.org/cgi/content/abstract/77/3/658

588. **Contribution of methylenetetrahydrofolate reductase (MTHFR) polymorphisms to negative symptoms in schizophrenia.** [BACKGROUND: Folate deficiency may contribute to negative symptoms in schizophrenia, but the underlying mechanism remains uncertain. We examined whether the methylenetetrahydrofolate reductase (MTHFR) C677T and A1298C functional polymorphisms contribute to negative symptoms. METHODS: Outpatients with schizophrenia (n = 200) were evaluated with the Positive and Negative Syndrome Scale (PANSS). Subjects also provided a blood sample for MTHFR genotype and serum chemistries. Comparisons of PANSS symptoms, folate, and homocysteine status were conducted based on genotype. RESULTS: The 677T allele load was associated with negative symptom severity. Contrary to our expectations, the T allele was also found to be protective against positive symptoms. The A1298C polymorphism did not contribute to negative symptoms, and only weakly to positive symptoms. The specific effects of the C677T polymorphism were confirmed with haplotype analysis. Among patients homozygous for the 667T allele, serum folate levels correlated with negative symptom severity. CONCLUSIONS: Increased MTHFR 677T allele load confers risk for negative symptoms in schizophrenia, while reducing severity of positive symptoms. Further, the biochemical interaction of low serum folate with 677T-variant MTHFR may induce downstream effects salient to the expression of negative symptoms.] Roffman JL, Weiss AP, et al. *Biol Psychiatry*. 2008 Jan 1;63(1):42-8. http://www.ncbi.nlm.nih.gov/pubmed/17543893

589. **Detection *of MTHFR C677T and A1298C* Gene Polymorphism in Congenital Heart Disease**. [Specific objectives of the study were to analyze in children with and without congenital heart disease and their mother. The prevalence of Single Nucleotide Polymorphisms (SNPs) of *MTHFR* gene (677C-T and 1298A-C) and its relation to CHD. Estimate the risk of combined genotype among cases and controls. To correlate the prevalence of the SNPs among children with maternal *MTHFR* genotype.] Deeparani T, Pillai MR, et al. *Middle-East journal of Scientific Research* 4(2):127-132, 2009. http://www.idosi.org/mejsr/mejsr4(2)/15.pdf

590. **Effects of the C677T and A1296C polymorphisms of the MTHFR gene on the genetic predisposition for diabetic nephropathy.** [B**a**ckground. Methylenetetrahydrofolate reductase (MTHFR) is a regulatory enzyme of homocysteine metabolism. The C677T polymorphism of the MTHFR gene has been reported to be a**s**sociated with elevated plasma homocysteine in patients with low folic acid intake**.** A recently reported second common polymorphism**,** A1298C, ma**y** **i**ncrea**s**e homocysteine, but only in individuals carrying the T677 allele. This study aimed to investigate the influence of the C677T and A1298C polymorphism**s** of the MTHFR gene on the development of diabetic nephropathy in Caucasian patients with type 2 diabetes**.** Conclusions. These findings indicate that the C677T polymorphism is a risk factor for diabetic nephropathy in male pa**t**ients with type 2 di**a**betes.] Moczulski D, Fojcik H, et al. *Nephrol dial Transplant*, 2003) 18:1535-1540. http://ndt.oxfordjournals.org/cgi/content/full/18/8/1535

591. **Effects of homocysteine on endothelial nitric oxide production.** [Hyperhomocysteinemia (HHCy) is an independent and graded cardiovascular risk factor. HHCy is prevalent in patients with chronic renal failure, contributing to the increased

mortality rate. Controversy exists as to the effects of HHCy on nitric oxide (NO) production: it has been shown that HHCy both increases and suppresses it. We addressed this problem by using amperometric electrochemical NO detection with a porphyrinic microelectrode to study responses of endothelial cells incubated with homocysteine (Hcy) to the stimulation with bradykinin, calcium ionophore, or L-arginine. Twenty-four-hour preincubation with Hcy (10, 20, and 50 microM) resulted in a gradual decline in responsiveness of endothelial cells to the above stimuli. Hcy did not affect the expression of endothelial nitric oxide synthase (eNOS), but it stimulated formation of superoxide anions, as judged by fluorescence of dichlorofluorescein, and peroxynitrite, as detected by using immunoprecipitation and immunoblotting of proteins modified by tyrosine nitration. Hcy did not directly affect the ability of recombinant eNOS to generate NO, but oxidation of sulfhydryl groups in eNOS reduced its NO-generating activity. Addition of 5-methyltetrahydrofolate restored NO responses to all agonists tested but affected neither the expression of the enzyme nor formation of nitrotyrosine-modified proteins. In addition, a scavenger of peroxynitrite or a cell-permeant superoxide dismutase mimetic reversed the Hcy-induced suppression of NO production by endothelial cells. In conclusion, electrochemical detection of NO release from cultured endothelial cells demonstrated that concentrations of Hcy >20 microM produce a significant indirect suppression of eNOS activity without any discernible effects on its expression. Folates, superoxide ions, and peroxynitrite scavengers restore the NO-generating activity to eNOS, collectively suggesting that cellular redox state plays an important role in HCy-suppressed NO-generating function of this enzyme.] Zhang X, Li H, et al. *Am J Physiol Renal Physiol*. 2000 Oct;279(4):F671-8. http://www.ncbi.nlm.nih.gov/pubmed/10997917

592. **Elevation in *S*-Adenosylhomocysteine and DNA Hypomethylation: Potential Epigenetic Mechanism for Homocysteine-Related Pathology.** [Chronic nutritional deficiencies in folate, choline, methionine, vitamin B-6 and/or vitamin B-12 can perturb the complex regulatory network that maintains normal one-carbon metabolism and homocysteine homeostasis. Genetic polymorphisms in these pathways can act synergistically with nutritional deficiencies to accelerate metabolic pathology associated with occlusive heart disease, birth defects and dementia. A major unanswered question is whether homocysteine is causally involved in disease pathogenesis or whether homocysteinemia is simply a passive and indirect indicator of a more complex mechanism. *S*-Adenosylmethionine and *S*-adenosylhomocysteine (SAH), as the substrate and product of methyltransferase reactions, are important metabolic indicators of cellular methylation status. Chronic elevation in homocysteine levels results in parallel increases in intracellular SAH and potent product inhibition of DNA methyltransferases. SAH-mediated DNA hypomethylation and associated alterations in gene expression and chromatin structure may provide new hypotheses for pathogenesis of diseases related to homocysteinemia. … Genetic polymorphisms in genes coding for enzymes involved in these pathways interact with nutritional deficiencies to magnify imbalances in one-carbon metabolism that may promote several chronic disease states in humans. Gene-nutrient interactions that elevate Hcy levels have been associated with increased risk of cardiovascular disease, colon cancers, birth defects, recurrent early pregnancy loss, central nervous system (CNS) demyelinization and neuropsychiatric disease. Most recently, an increment of 5 μM plasma Hcy was associated with a 49% increase in all-cause mortality among individuals 65–72 y of age. Although numerous hypotheses have been proposed linking plasma Hcy to mechanisms underlying increased risk of occlusive heart disease, dementia and certain birth defects, none have been conclusive. Whether elevated Hcy is directly and causally involved in these pathologic processes or is a passive and indirect indicator of a more complex mechanism remains an open question] James, SJ, Melnyk S, et al. *Journal of Nutrition*, J. Nutr. 132:2361S-2366S, 2002 http://jn.nutrition.org/cgi/content/full/132/8/2361S

593. **Folate Augmentation of Treatment – Evaluation for Depression (FolATED): protocol of a randomised controlled trial**. [Clinical depression is common, debilitating and treatable; one in four people experience it during their lives. The majority of sufferers are treated in primary care and only half respond well to active treatment. Evidence suggests that folate may be a useful adjunct to antidepressant treatment: 1) patients with depression often have a functional folate deficiency; 2) the severity of such deficiency, indicated by elevated homocysteine, correlates with depression severity, 3) low folate is associated with poor antidepressant response, and 4) folate is required for the synthesis of neurotransmitters implicated in the pathogenesis and treatment of depression. The primary objective of this trial is to estimate the effect of folate augmentation in new or continuing treatment of depressive disorder in primary and secondary care. Secondary objectives are to evaluate the cost-effectiveness of folate augmentation of antidepressant treatment, investigate how the response to antidepressant treatment depends on genetic polymorphisms relevant to folate metabolism and antidepressant response, and explore whether baseline folate status can predict response to antidepressant treatment. Seven hundred and thirty patients will be recruited from North East Wales, North West Wales and Swansea. Patients with moderate to severe depression will be referred to the trial by their GP or Psychiatrist. If patients consent they will be assessed for eligibility and baseline measures will be undertaken. Blood samples will be taken to exclude patients with folate and B12 deficiency. Some of the blood taken will be used to measure homocysteine levels and for genetic analysis (with additional consent). Eligible participants will be randomised to receive 5 mg of folic acid or placebo. Patients with B12 deficiency or folate deficiency will be given appropriate treatment and will be monitored in the 'comprehensive cohort study'. Assessments will be at screening, randomisation and 3 subsequent follow-ups. If folic acid is shown to improve the efficacy of antidepressants, then it will provide a safe, simple and cheap way of improving the treatment of depression in primary and secondary care.] Roberts SH, Bedson D, et al. *BMC Psychiatry*. 2007; 7: 65. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2238748/

594. **Genetic polymorphism of methylenetetrahydrofolate reductase as a risk factor for diabetic nephropathy in Chinese type 2 diabetic patients**. [*Objective:* Genetic predisposition has been implicated in diabetic nephropathy (DN). The C677T variant of the methylenetetrahydrofolate reductase (MTHFR) gene, one of the key enzymes catalyzing remethylation of

homocysteine, may play a role in the development of not only vascular disease but also diabetic microangiopathies. In this study, we examined the distribution of the MTHFR genotypes in the Chinese population and the association between the C677T variant and diabetic nephropathy. *Methods:* 220 unrelated patients with type 2 diabetes mellitus and 130 controls were recruited. The MTHFR genotype was analyzed by PCR followed by *Hin*fI digestion. Plasma total homocysteine levels were measured using high-performance liquid chromatography (HPLC) with fluorescence detection. *Results:* In 130 healthy control subjects, the frequency of the mutant *T* allele was 30.0%, comparable to that of a Hong Kong (Chinese) population. The distribution of the three genotypes was as follows: *TT* genotype, 16.9%; *CT* genotype, 26.2%; and *CC* genotype, 56.9%. This genotype distribution did not differ between control subjects and type 2 diabetic patients in which 19.1% were TT, 34.5% were CT and 46.4% were CC (χ2=3.85, *P*>0.05). The frequency of the mutant T allele was 42.3% in diabetic patients with nephropathy (*n*=124) versus 28.6% in those without nephropathy (*n*=96). The genotype frequencies were TT, 21.0%; CT, 42.7%; CC, 36.3% in diabetic patients with nephropathy versus TT, 16.7%; CT, 23.9%; CC, 59.4% in those without nephropathy. The MTHFR genotype and allele frequencies were different between diabetic patients with and without nephropathy (χ2=12.27, *P*<0.005; χ2=8.77, *P*<0.005, respectively). Moreover, plasma homocysteine levels were markedly higher in individuals with TT genotype than those with CC or CT genotype. *Conclusions:* The *C677T mutation* of MTHFR gene is common in the Chinese population. MTHFR C677T gene polymorphism associated with a predisposition to increased plasma homocysteine levels may represent a genetic risk factor for diabetic nephropathy in Chinese type 2 diabetic patients.] Sun J, Zu Y, et al. *Diabetes Research and Clniical Practice*, Vol 64, Issue 3, pp 185-190 (June 2004). http://www.journals.elsevierhealth.com/periodicals/diab/article/PIIS0168822703002936/abstract

595. **Homocysteine and cardiovascular disease: interactions between nutrition, genetics and lifestyle**. [Homocysteine is a sulfur-containing amino acid that arises during methionine metabolism. Although its concentration in plasma is only about 10 micromolar, even moderate hyperhomocysteinemia is associated with increased incidence of cardiovascular disease and Alzheimer's disease. Elevations in plasma homocysteine are commonly found as a result of vitamin deficiencies, polymorphisms of enzymes of methionine metabolism, and renal disease. Pyridoxal, folic acid, riboflavin, and Vitamin B(12) are all required for methionine metabolism, and deficiency of each of these vitamins result in elevated plasma homocysteine. A polymorphism of methylenetetrahydrofolate reductase (C677T), which is quite common in most populations with a homozygosity rate of 10-15 %, is associated with moderate hyperhomocysteinemia, especially in the context of marginal folate intake. Plasma homocysteine is inversely related to plasma creatinine in patients with renal disease. This is due to an impairment in homocysteine removal in renal disease. The role of these factors, and of modifiable lifestyle factors, in affecting methionone metabolism and in determining plasma homocysteine levels is discussed.] Brosnan JT. Can J Appl Physiol. 2004 Dec;29(6):773-80. http://www.ncbi.nlm.nih.gov/pubmed/15630149
596. **Homocysteine and Impaired Wound Heal: Discussion.** [The results of this preliminary clinical study suggest a correlation exists between elevated serum Hcy and impaired chronic wound healing with patients receiving dermal substitute therapy. Furthermore, the preliminary data indicate that elevated serum Hcy may also be correlated with significantly decreased wound NO bioactivity as determined by wound fluid NOx assay, and left untreated, elevated Hcy may become common among patients with chronic wounds (50% incidence). Additionally, the observations of a single case report suggest that successful treatment of elevated Hcy in a patient with impaired wound healing may promote the restoration of normal wound healing…. Multivitamin therapy, including folic acid, vitamin B6, and vitamin B12 in elevated doses, has been referenced as an acceptable treatment for elevated Hcy. Folic acid normally requires 4 separate biochemical reactions for its conversion into L-methylfolate, the bioavailable form of folate directly involved in Hcy metabolism. These steps include the conversion of folic acid to dihydrofolate (DHF) by dihydrofolate reductase enzyme (DHFR); the metabolism of DHF into tetrahydrofolate (THF) by DHFR; the metabolism of THF into 5,10-methylene-THF; and finally the conversion of 5,10-methylene-THF into L-methylfolate by the methyltetrahydrofolate reductase enzyme (MTHFR). A polymorphism of MTHFR (C677T) is common in most populations with a homozygosity rate of 10%-15% that is associated with moderate hyperhomocysteinemia, especially in the context of marginal folate intake. Overall, 40%-50% of the population exhibit a genetic polymorphism in which folic acid is incompletely converted to the active isomer of folate for homocysteine metabolism] Boykin, JV, Baylis C. Medscape Today / WebMD. http://www.medscape.com/viewarticle/531998_5
597. **Homocysteine and reactive oxygen species in metabolic syndrome, type 2 diabetes mellitus, and atherosclerosis: the pleiotropic effects of folate supplementation.** [Homocysteine has emerged as a novel independent marker of risk for the development of cardiovascular disease over the past three decades. Additionally, there is a graded mortality risk associated with an elevated fasting plasma total homocysteine (tHcy). Metabolic syndrome (MS) and type 2 diabetes mellitus (T2DM) are now considered to be a strong coronary heart disease (CHD) risk enhancer and a CHD risk equivalent respectively. Hyperhomocysteinemia (HHcy) in patients with MS and T2DM would be expected to share a similar prevalence to the general population of five to seven percent and of even greater importance is: Declining glomerular filtration and overt diabetic nephropathy is a major determinant of tHcy elevation in MS and T2DM. There are multiple metabolic toxicities resulting in an excess of reactive oxygen species associated with MS, T2DM, and the accelerated atherosclerosis (atherosclerosis). HHcy is associated with an increased risk of cardiovascular disease, and its individual role and how it interacts with the other multiple toxicities are presented.The water-soluble B vitamins (especially folate and cobalamin-vitamin B12) have been shown to lower HHcy. The absence of the cystathionine beta synthase enzyme in human vascular cells contributes to the importance of a dual role of folic acid in lowering tHcy through remethylation, as well as, its action of being an electron and hydrogen donor to the essential cofactor tetrahydrobiopterin. This folate shuttle facilitates the important recoupling of the uncoupled endothelial nitric oxide synthase enzyme reaction and may restore the synthesis of the

omnipotent endothelial nitric oxide to the vasculature.] Hayden MR, Tyagi SC *Nutr J*. 2004 May 10;3:4. http://www.ncbi.nlm.nih.gov/pubmed/15134582

598. **Methionine Synthase Reductase 66A→G Polymorphism Is Associated with Increased Plasma Homocysteine Concentration When Combined with the Homozygous Methylenetetrahydrofolate Reductase 677C→T Variant.** [Methylenetetrahydrofolate reductase (MTHFR) and methionine synthase reductase (MTRR) are important for homocysteine remethylation. This study was designed to determine the influence of genetic variants (MTHFR 677C→T, MTHFR 1298A→C, and MTRR 66A→G), folate, and vitamin B-12 status on plasma homocysteine in women (20–30 y; n = 362). Plasma homocysteine was inversely ($P < 0.0001$) associated with serum folate and plasma vitamin B-12 regardless of genotype. Plasma homocysteine was higher ($P < 0.05$) for women with the MTHFR 677 TT/1298 AA genotype combination compared with the CC/AA, CC/AC, and CT/AA genotypes. Women with the MTHFR 677 TT/MTRR 66 AG genotype had higher ($P < 0.05$) plasma homocysteine than all other genotype combinations except the TT/AA and TT/GG genotypes. There were 5.4-, 4.3-, and 3.8-fold increases ($P < 0.001$) in risk for plasma homocysteine in the top 5, 10, and 20%, respectively, of the homocysteine distribution for subjects with the MTHFR 677 TT compared with the CC and CT genotypes. Predicted plasma homocysteine was inversely associated with serum folate ($P = 0.003$) and plasma vitamin B-12 ($P = 0.002$), with the degree of correlation dependent on MTHFR 677C→T genotype. These data suggest that coexistence of the MTHFR 677 TT genotype with the MTRR 66A→G polymorphism may exacerbate the effect of the MTHFR variant alone. The potential negative effect of combined polymorphisms of the MTHFR and MTRR genes on plasma homocysteine in at-risk population groups with low folate and/or vitamin B-12 status, such as women of reproductive potential, deserves further investigation.] Vaughn JD, Bailey LB, et al. *The American Society for Nutritional Sciences J. Nutr.* 134:2985-2990, November 2004. http://jn.nutrition.org/cgi/content/abstract/134/11/2985

599. **Methylenetetrahydrofolate reductase polymorphism 677C>T is associated with peripheral arterial disease in type 2 diabetes.** [Background: Individuals with diabetes are twice as likely to develop peripheral arterial disease (PAD), the manifestation of extensive atherosclerosis throughout the lower extremities. One putative determinant of PAD is the 677C>T polymorphism in the gene encoding methylenetetrahydrofolate reductase (*MTHFR*), which has previously been found to associate with various diabetic complications including retinopathy, nephropathy, atherosclerosis and coronary heart disease. The objective of this study was to investigate a possible role for the MTHFR 677C>T gene polymorphism with PAD in subjects with type 2 diabetes from an isolated aboriginal Canadian population. Methods: The 677C>T MTHFR gene polymorphism was genotyped in 138 subjects of Oji-Cree descent. Participants were selected from a community-wide survey that included PAD assessment by ankle-brachial index (ABI) measurement, and also intermittent claudication assessment by the Rose questionnaire. Results: *MTHFR* 677T allele carriers had an increased risk of PAD with an odds ratio of 3.54 (95% CI 1.01, 12.4), $P = 0.049$, after adjustment for age, sex, duration of diabetes, hypertension, current smoking habits, and use of insulin or oral treatment for diabetes. None of these additional co-variables was significantly associated with PAD. No association was found between *MTHFR* genotype and intermittent claudication. Conclusion: The genetic influence of the *MTHFR* 677C>T genotype on diabetic PAD is modest, yet for the Oji-Cree it is a major risk factor in comparison to other traditional risk factors.] Pollex RL, Mamakeesick M, et al. *Cardiovascular Diabetology* 2005, 4**:**17. http://www.cardiab.com/content/4/1/17

600. **MTHFR (ALA 222 VAL) Polymorphism and ami in patients with type II diabetes mellitus.** [The prevalent Ala222Val single nucleotide polymorphism of the MTHFR gene has been shown to be associated with type II diabetes. The objective of the present study was to find out whether there is genetic predisposition for development of acute myocardial infarction in type II diabetes mellitus among South Indian Tamil population. PCR-based restriction enzyme analysis was performed in DNA isolated from 120 acute myocardial infarction patients with diabetes mellitus and 100 non diabetic healthy individuals with no documented cardiovascular diseases. The results indicate that the MTHFR 677TT genotype is absent in both case and controls. The MTHFR 677CT genotype was observed among 32 (26.7 %) cases and 20 (20%) controls and the MTHFR 677CC genotype among 88 (73.3%) cases and 80 (80%) controls. The allelic frequencies were in accordance to Hardy Weinberg equilibrium. There was no statistical difference in genotype distribution between cases and controls. In conclusion, we suggest that the analysis of MTHFR genotyping for C677T polymorphism alone need not be considered to find out whether there is genetic predisposition for development of acute myocardial infarction in type II diabetes mellitus among South Indian Tamil population.] Angeline T, Thiruvarutselvi G, et al. *Indian Journal of Clinical Biochemistry*, 2009 / 24 (2) 137-141. http://medind.nic.in/iaf/t09/i2/iaft09i2p137.pdf

601. **MTHFR 677C-->T polymorphism and risk of coronary heart disease: a meta-analysis.** [CONTEXT: In observational studies, individuals with elevated levels of plasma homocysteine tend to have moderately increased risk of coronary heart disease (CHD). The MTHFR 677C-->T polymorphism is a genetic alteration in an enzyme involved in folate metabolism that causes elevated homocysteine concentrations, but its relevance to risk of CHD is uncertain. OBJECTIVE: To assess the relation of MTHFR 677C-->T polymorphism and risk of CHD by conducting a meta-analysis of individual participant data from all case-control observational studies with data on this polymorphism and risk of CHD. DATA SOURCES: Studies were identified by searches of the electronic literature (MEDLINE and Current Contents) for relevant reports published before June 2001 (using the search terms MTHFR and coronary heart disease), hand searches of reference lists of original studies and review articles (including meta-analyses) on this topic, and contact with investigators in the field. STUDY SELECTION: Studies were included if they had data on the MTHFR 677C-->T genotype and a case-control design (retrospective or nested case-control) and involved CHD as an end point. Data were obtained from 40 (34 published and 6 unpublished) observational studies involving a total of 11 162 cases and 12 758 controls. DATA EXTRACTION: Data were

collected on MTHFR 677C-->T genotype, case-control status, and plasma levels of homocysteine, folate, and other cardiovascular risk factors. Data were checked for consistency with the published article or with information provided by the investigators and converted into a standard format for incorporation into a central database. Combined odds ratios (ORs) for the association between the MTHFR 677C-->T polymorphism and CHD were assessed by logistic regression. DATA SYNTHESIS: Individuals with the MTHFR 677 TT genotype had a 16% (OR, 1.16; 95% confidence interval [CI], 1.05-1.28) higher odds of CHD compared with individuals with the CC genotype. There was significant heterogeneity between the results obtained in European populations (OR, 1.14; 95% CI, 1.01-1.28) compared with North American populations (OR, 0.87; 95% CI, 0.73-1.05), which might largely be explained by interaction between the MTHFR 677C-->T polymorphism and folate status. CONCLUSIONS: Individuals with the MTHFR 677 TT genotype had a significantly higher risk of CHD, particularly in the setting of low folate status. These results support the hypothesis that impaired folate metabolism, resulting in high homocysteine levels, is causally related to increased risk of CHD.] Klerk M, Verhoef P. et al. J*AMA*. 2002 Oct 23-30;288(16):2023-31. http://www.ncbi.nlm.nih.gov/pubmed/12387655

602. **Pharmacokinetic study on the utilisation of 5-methyltetrahydrofolate and folic acid in patients with coronary artery disease**. [Methylenetetrahydrofolate reductase (MTHFR) is a regulating enzyme in folate-dependant homocysteine remethylation, because it catalyses the reduction of 5,10 methylenetetrahydrofolate to 5-methyltetrahydrofolate (5-MTHF). Subjects homozygous for the 677C → T mutation in the MTHFR enzyme suffer from an increased cardiovascular risk. It can be speculated that the direct administration of 5-MTHF instead of folic acid can facilitate the remethylation of homocysteine in methionine. The aim of this study was to determine the pharmacokinetic properties of orally administered 6[*R*,*S*] 5-MTHF *versus* folic acid in cardiovascular patients with homozygosity for 677C → T MTHFR. This is an open-controlled, two-way, two-period randomised crossover study. Patients received a single oral dose of either 5 mg folic acid or 5 mg 5-MTHF in each period. The concentrations of the 6[*S*] 5-MTHF and 6[*R*] 5-MTHF diastereoisomers were determined in venous blood samples. All pharmacokinetic parameters demonstrate that the bioavailability of 5-MTHF is higher compared to folic acid. The peak concentration of both isomers following the administration of 6[*R*,*S*] 5-MTHF is almost seven times higher compared to folic acid, irrespective of the patient's genotype. However, at 1 week after the administration of a single dosage 6[*R*,*S*] 5-MTHF, we detected 6[*R*] 5-MTHF following the administration of folic acid, indicating storage of this isomer in the body. Our results demonstrate that oral 5-MTHF has a different pharmacokinetic profile with a higher bioavailability compared to folic acid, irrespective of the patient's genotype. Detrimental effects of the storage of high levels of the non-natural isomer 6[*R*] 5-MTHF cannot be excluded.] Willems FF, Boers GHJ, et al. *Br J Pharmacol*. 2004 March; 141(5): 825–830. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1574248/

603. **Plasma Total Homocysteine Levels and Methylenetetrahydrofolate Reductase Gene Polymorphism in Patients with Type 2 Diabetes Mellitus**. [*Background:* Thrombotic episodes account for approximately 80% of deaths in type 2 diabetic patients. Hyperhomocysteinaemia is a well recognized independent risk factor for atherosclerosis and thromboembolism. Increased homocysteine levels may occur due to a number of factors including inherited gene polymorphism of methylenetetrahydrofolate reductase (MTHFR) C677T. Here, we evaluate plas- ma total homocysteine (tHcy) levels and frequency of the MTHFR C677T gene polymorphism in asymptomatic healthy volunteers and type 2 diabetic patients with hypertension but without nephropathy. We have also investigated the relationship between tHcy levels and the presence of MTHFR C677T gene polymorphism. *Methods:* Plasma tHcy levels and MTHFR C677T genotype were investigated in a total of 53 subjects. These included asymptomatic healthy volunteers (n = 16), patients with type 2 diabetes (n = 7), subjects with hypertension (n = 12) and patients with both type 2 diabetes and hypertension (n = 18). Renal function, serum lipids and other metabolites were also assessed. *Results:* There was no significant difference in tHcy levels between the groups studied. The frequency of MTHFR C677T gene polymorphism observed was similar to that obtained for the general Brazilian population. In patients with type 2 diabetes and hypertension but without impaired renal function, we observed no meaningful correlation between increased tHcy levels and the presence of MTHFR C677T gene polymorphism. *Conclusions:* Type 2 diabetics who are homozygous or heterozygous for the MTHFR C677T gene polymorphism showed normal tHcy levels. Our results further suggest that diabetes without an associated adverse risk profile is not an independent correlate of increased tHcy levels.] soares AL, Fernandes AP, et al. *Pathophysiology of Haemostasis and Thrombosis*, vol 36, No. 5, 2007.2008.
http://content.karger.com/ProdukteDB/produkte.asp?Aktion=ShowFulltext&ArtikelNr=252825&Ausgabe=253635&ProduktNr=224034

604. **Polymorphism of the methylenetetrahydrofolate reductase gene association with homocysteine and ischemic stroke in type 2 diabetes.** [Background : Ischemic stroke is a frequent heterogeneous multifactorial disease. A number of genetic mutations and environmental factors have been implicated. A polymorphism in the gene for methylenetetrahydrofolate reductase (MTHFR) has been reported to be associated with hyperhomocysteinemia a risk for atherosclerotic vascular diseases. **Aim** : A cross-sectional study was performed to determine the relationship between the gene polymorphism for MTHFR and ischemic stroke in type 2 diabetes mellitus. Materials and Methods : Of the 215 unrelated patients with type 2 diabetes mellitus recruited, 119 patients had ischemic stroke, Control group included 142 healthy subjects. The genotype of the subjects for the C677T polymorphism of MTHFR was analyzed by using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) followed by HinfI digestion. Plasma total homocysteine (Hcy) levels were measured using high-performance liquid chromatography (HPLC) with fluorescence detection. Results : The genotype distribution did not differ between the control subjects and type 2 diabetic patients ($P > 0.05$). Plasma homocysteine levels were markedly higher in diabetic patients with TT genotype than those with CC or CT genotype ($P > 0.05$). Ischemic stroke was more

frequently observed in type 2 diabetic patients with the TT genotype than in those with the CT and CC genotype (odds ratio=4.04, 95% CI=1.95-8.34, P=0.0036). Logistic regression analysis revealed that the C677T mutation of MTHFR gene was independently associated with ischemic stroke in type 2 diabetes. Conclusion : MTHFR C677T gene polymorphism associated with a predisposition to hyperhomocysteinemia could constitute a useful predictive marker for ischemic stroke in type 2 diabetic Chinese patients.] Sun J, Xu Y, et al. *Neurology India*, Vol 57, issue 5, pp 589-593, 2009. http://www.neurologyindia.com/article.asp?issn=0028-3886;year=2009;volume=57;issue=5;spage=589;epage=593;aulast=Sun

605. **Prevalence of MTHFR gene polymorphisms (C677T and A1298C) among Tamilians.** [We have investigated the incidence of the C677T and A1298C methylene tetrahydrofolate reductase (MTHFR) gene single nucleotide polymorphisms (SNPs) in the South Indian Tamil Nadu population with a total number of 72 individuals. The MTHFR genotyping was performed using the polymerase chain reaction followed by restriction enzyme analysis. Homozygosity for the MTHFR A1298C SNP was detected in 15.3% (11/72) of the individuals tested, and 47.2% (34/72) were heterozygous for this SNP. Homozygosity for the C677T MTHFR SNP was detected in 1.38%(1/72), and the frequency of the C677T heterozygotes was 18.1%(13/72). When we analyzed the combined frequency of the two SNPs, the frequency of double heterozygosity was19.6%, and the frequency of double homozygosity was completely absent among the study group. The 'C' allele frequency for MTHFR A1298C was 0.389, and the 'T' allele frequency for C677T mutation was 0.104. Out of the 72 individuals included in the study, 52 were acute myocardial infarction (AMI) patients and 20 were healthy individuals with no documented history of heart disease. The results of this study indicate that the MTHFR A1298C SNP is more prevalent among the Tamilians when compared to the MTHFR C677T SNP, suggesting a possible role of MTHFR A1298C in the pathogenesis of heart diseases.] Angeline T, Jeraraj N, et al. *Exp Mol Pathol*. 2004 Oct;77(2):85-8. http://www.ncbi.nlm.nih.gov/pubmed/15351230
606. **The 677 C/T MTHFR polymorphism is associated with essential hypertension, coronary artery disease, and higher homocysteine levels.** [BACKGROUND: Essential hypertension (EH) and cardiovascular disease are common, multifactorial disorders likely to be influenced by multiple genes of modest effect. The C677T methylenetetrahydrofolate reductase (MTHFR) gene polymorphism is related to MTHFR enzyme activity and to plasma homocysteine (Hcy) concentration. This study was designed to investigate an association of this polymorphism with coronary artery disease (CAD), EH, and healthy subjects. METHODS: In this study, we measured serum folate, serum vitamin B12, and plasma homocysteine and determined the MTHFR C677T genotype of 78 patients with essential hypertension, 100 patients with coronary artery disease, and 100 healthy subjects. MTHFR genotypes were assessed by real-time polymerase chain reaction. RESULTS: CC, CT, and TT genotype frequencies were 52, 44.0, and 4.0% in patients with CAD, respectively. In patients with essential hypertension, the CC, CT, and TT genotype frequencies were 46.2, 41.0, and 12.8%, respectively. In control subjects, the CC, CT, and TT genotype frequencies were 72.0, 26.0, and 2.0%, respectively. The C allele was significantly more frequent in controls compared with patients with EH ($p<0.05$), and CC genotypes were more frequent in controls compared to patients with EH and CAD. Homocysteine level was higher in TT genotypes in CAD patients compared with CC and CT genotypes ($p<0.01$). MTHFR gene polymorphism is an independent risk factor for EH but not for CAD. CONCLUSIONS: The TT genotype of the 677C/T MTHFR polymorphism is associated with EH and CAD. In addition, TT genotypes had higher plasma Hcy levels in CAD patients compared with CC and CT genotypes. MTHFR gene polymorphism is an independent risk factor for EH but not for CAD.] Ilhan N, Kucuksu M, et al. *Arch Med Res.* 2008 Jan;39(1):125-30 http://www.ncbi.nlm.nih.gov/pubmed/18068006
607. **The relationship between MTHFR gene polymorphisms, plasma homocystein levels and diabetic retinopathy in type 2 diabetes mellitus.** [Objective: To evaluate the role of methylenetetrahydrofolate reductase (MTHFR) gene polymorphisms and plasma homocysteine levels in patients with type 2 diabetes mellitus and diabetic retinopathy (DR). Conclusions: MTHFR gene C577T mutation associated with a predisposition to increased plasma homocysteine levels may be considered as a genetic risk factor for diabetic microangiopathy (such as (DR) in Chinese patients with type 2 diabetes mellitus.] Sun J, Xy Y, et al. *Chin Med J*, 2003l 11(1):145-147. http://www.cmj.org/Periodical/PDF/2003/20031145.pdf

Epigenetic Modification

608. **Alteration of *PTGS2* Promoter Methylation in Chronic Periodontitis.** [Levels of prostaglandin E_2 and the prostaglandin-endoperoxide synthase-2 (*PTGS2*, or COX-2) increase in actively progressing periodontal lesions, but decrease in chronic disease. We hypothesized that chronic inflammation is associated with altered DNA methylation levels within the *PTGS2* promoter, with effects on COX-2 mRNA expression. *PTGS2* promoter methylation levels from periodontally inflamed gingival biopsies showed a 5.06-fold increase as compared with non-inflamed samples ($p = 0.03$), and the odds of methylation in a CpG site in the inflamed gingival group is 4.46 times higher than in the same site in the non-inflamed group ($p = 0.016$). The level of methylation at –458 bp was inversely associated with transcriptional levels of *PTGS2* (RT-PCR) ($p = 0.01$). Analysis of the data suggests that, in chronically inflamed tissues, there is a hypermethylation pattern of the *PTGS2* promoter in association with a lower level of *PTGS2* transcription, consistent with a dampening of COX-2 expression in chronic periodontitis. These findings suggest that the chronic persistence of the biofilm and inflammation may be associated with epigenetic changes in local tissues at the biofilm-gingival interface.] Zhang S, Barros SP, et al. Journal of Dental Research, Vol. 89, No. 2, 133-137 (2010) v http://jdr.sagepub.com/cgi/content/abstract/89/2/133

609. **Bacterial Infection Promotes DNA Hypermethylation.** [Maternal oral infection, caused by bacteria such as *C. rectus* or *P. gingivalis*, has been implicated as a potential source of placental and fetal infection and inflammatory challenge, which increases the relative risk for pre-term delivery and growth restriction. Intra-uterine growth restriction has also been reported in various animal models infected with oral organisms. Analyzing placental tissues of infected growth-restricted mice, we found down-regulation of the imprinted *Igf2* gene. Epigenetic modification of imprinted genes *via* changes in DNA methylation plays a critical role in fetal growth and development programming. Here, we assessed whether *C. rectus* infection mediates changes in the murine placenta *Igf2* methylation patterns. We found that infection induced hypermethylation in the promoter region-P0 of the *Igf2* gene. This novel finding, correlating infection with epigenetic alterations, provides a mechanism linking environmental signals to placental phenotype, with consequences for development.] Bobetsis YA, Barros SP, et al. Journal of Dental Research, Vol. 86, No. 2, 169-174 (2007). http://jdr.sagepub.com/cgi/content/abstract/86/2/169

610. **Clinical innovations in managing inflammation and periodontal diseases:** "The workshop on inflammation and periodontal diseases". [Determinationof genetic risk profiles for periodontal disease based upon: a) genome-wide association studies of genetic changes encoded in DNA (SNPs, insertion, deletion, and inversions); and/or b) epigenetics (changes inmeiotic or mitotic inherited change in gene expressionnot included inDNAitself).Theseepigenetic changes involve posttranslational methylation of DNA or modification of histone proteins in the chromatin. They are influenced by environmental factors including diet, infection and inflammation, aging, and other factors; and/or c) based on micro-RNAs, the small non-coding RNAs that regulate expression of many genes (Wilson, p. 1514). … It is possible that inflammatory changes alter susceptibility of the periodontium to reinfection. That is, changes do not lead to persistence of an inflammatory response in the periodontium after removing the infectious insult but do alter susceptibility to reinfection. The inflammation resulting from periodontal infection changes the tissue in some way so that it is more susceptible to another bout of infection with oral biofilm. The possibility raised in this symposiumis that this occurs through epigenetic changes in DNA or histones by methylation. It is hypothesized that these changes then persist in the tissue and increase the susceptibility to reinfection (Offenbacher et al., p. 1577); in this instance, long-term tissue changes that might increase susceptibility to reinfection but directly do not cause inflammation. If this were the case, an approach to therapy would be to not only remove the infection but also to treat the tissue somehow to mitigate, modulate, or eliminate the posttranscriptionally altered DNA and histones resulting from epigenetic changes."] Genco RJ. *J Periodontol*, Aug 2008, p 1609-1611. http://www.joponline.org/doi/pdf/10.1902/jop.2008.080305

611. **DNA methylation profiles of gingival tissues in periodontal disease.** [Objective: We have recently reported that periodontal pathogens can alter DNA methylation patterns of host genomic DNA. DNA methylation is an epigenetic phenomenon that controls gene expression without a change in DNA sequence. Changes in DNA methylation generally remain stable following cell division to permanently alter the tissue gene expression and response to challenge. The goal of this study was to determine whether the biofilm was inducing local alterations in host DNA methylation patterns that could potentially modulate gene expression. Material and Methods: Genome-wide alterations in DNA methylation patterns were performed by analyses using CpG island microarrays. Diseased gingival tissues collected from patients with severe periodontal disease were compared with healthy gingival tissues from either healthy or diseased patients. Genomic DNA was isolated and restrictively digested with MseI, ligated to linkers and subjected to restrictive digestion by two methylation-sensitive restrictive enzymes, BstUI and HpaII. Following PCR amplification, products were labeled by Cy5 for test samples and Cy3 for control samples, hybridized to a 12K Human CpG-island microarray and analyzed for differences in CpG methylation patterns comparing health to disease. Results: Altered DNA methylation patterns were found in samples from patients with periodontal disease suggesting a local epigenetic modulation of host DNA structure. Preliminary results suggest that many genes are differentially methylated at sites of periodontal disease compared to health. Hypermethylation, which is usually associated with gene silencing, was observed for many genes including SOCS3, VDR, MMP25 and BMP4. Conclusion: Chronic infection and underlying inflammation in gingival tissue is associated with altered DNA methylation of multiple genes. Such modification may significantly contribute to permanent alteration of the local environment to further enhance the inflammatory tissue phenotype.] Barros S, Zhang S, et al. IADR 86th General Session & Exhibition. http://iadr.confex.com/iadr/2008Toronto/techprogram/abstract_108338.htm

612. **Epigenetics and periodontal disease: future perspectives.** [Periodontitis is a multifactorial infection characterized by inflammation and destruction of tooth supporting tissues, as a result of the response of a susceptible host to bacterial challenge. Studies have demonstrated that epigenetic events are able to influence the production of cytokines, contributing to the development of inflammatory diseases. Epigenetic events act through the remodeling of chromatin and can selectively activate or inactivate genes, determining their expression. The epigenetic process, by inducing a change in cytokine profile, may subsequently influence the pathogenesis and determine the outcome of many infectious diseases. These findings may have relevance for inflammatory diseases in which the expression of cytokines is unregulated. The purpose of this review is to show evidence that supports the hypothesis that epigenetic alterations, such as hyper and hypomethylation, of cytokine genes, could help to understand the mechanisms related to periodontal disease activity. Therefore, epigenetics may have future impact on diagnosis and/or therapeutics of periodontal disease.]GomezRS, Dutra WO, et al. Inflamm Res. 2009 Oct;58(10):625-9. Epub 2009 May 8. http://www.ncbi.nlm.nih.gov/pubmed/19440658

613. **Epigenetics: New Explanations for Old Problems?** [Epigenetics refers to changes in gene expression that are not mediated by alterations of the genetic code itself (mutations). Epigenetic changes are caused by biochemical modifications of the nucleotide bases that alter the 3-dimensional structure of DNA, thereby preventing the genetic code from being read (silencing or reducing gene expression). Thus, epigenetic changes cause some genes that were previously expressed to

become hidden or less accessible to the transcription system that converts the genetic code into functional proteins. Epigenetic changes in periodontal tissues may facilitate the rapid reestablishment of a virulent biofilm and may help to explain refractory cases of periodontitis. In such cases, periodontal surgery might be justified if it is deemed beneficial to remove epigenetically modified tissues that may serve to maintain active disease.] Lacopino AM. *JCDA*, June 17, 2010. *http://www.jcda.ca/article/a76*

614. **Epigenetic Regulation of Gene Expression in the Inflammatory Response and Relevance to Common Diseases.** [Epigenetics can be defined as all the meiotically and mitotically inherited changes in gene expression that are not encoded in the DNA sequence itself. Epigenetic modifications of chromatin and DNA have been recognized as important permissive and suppressive factors in controlling the expressed genome via gene transcription. Two major epigenetic mechanisms are the posttranslational modification of histone proteins in chromatin and the methylation of DNA itself, which are regulated by distinct, but coupled, pathways. It is clear that the epigenetic state is a central regulator of cellular development and activation. Emerging evidence suggests a key role for epigenetics in human pathologies, including in inflammatory and neoplastic disorders. The epigenome is influenced by environmental factors throughout life. Nutritional factors can have profound effects on the expression of specific genes by epigenetic modification, and these may be passed on to subsequent generations with potentially detrimental effects. Many cancers are associated with altered epigenetic profiles, leading to altered expression of the genes involved in cell growth or differentiation. Autoimmune and neoplastic diseases increase in frequency with increasing age, with epigenetic dys-regulation proposed as a potential explanation. In support of this hypothesis, studies in monozygotic twins revealed increasing epigenetic differences with age. Differences in methylation status of CpG sites, monoallelic silencing, and other epigenetic regulatory mechanisms have been observed in key inflammatory response genes. The importance of the epigenome in the pathogenesis of common human diseases is likely to be as significant as that of traditional genetic mutations. With advances in technology, our understanding of this area of biology is likely to increase rapidly in the near future.] Wilson AG. *J Perio* Vol. 79, No 8, Sup (115 p.) 2008. http://cat.inist.fr/?aModele=afficheN&cpsidt=20604912

615. **Horizontal Transfer, Not Duplication, Drives the Expansion of Protein Families in Prokaryotes**. [Gene duplication followed by neo- or sub-functionalization deeply impacts the evolution of protein families and is regarded as the main source of adaptive functional novelty in eukaryotes. While there is ample evidence of adaptive gene duplication in prokaryotes, it is not clear whether duplication outweighs the contribution of horizontal gene transfer in the expansion of protein families. We analyzed closely related prokaryote strains or species with small genomes (Helicobacter, Neisseria, Streptococcus, Sulfolobus), average-sized genomes (Bacillus, Enterobacteriaceae), and large genomes (Pseudomonas, Bradyrhizobiaceae) to untangle the effects of duplication and horizontal transfer. After removing the effects of transposable elements and phages, we show that the vast majority of expansions of protein families are due to transfer, even among large genomes. Transferred genes--xenologs--persist longer in prokaryotic lineages possibly due to a higher/longer adaptive role. On the other hand, duplicated genes--paralogs--are expressed more, and, when persistent, they evolve slower. This suggests that gene transfer and gene duplication have very different roles in shaping the evolution of biological systems: transfer allows the acquisition of new functions and duplication leads to higher gene dosage. Accordingly, we show that paralogs share most protein-protein interactions and genetic regulators, whereas xenologs share very few of them. Prokaryotes invented most of life's biochemical diversity. Therefore, the study of the evolution of biology systems should explicitly account for the predominant role of horizontal gene transfer in the diversification of protein families.] Treangen TJ, Roch EP. *PLoS Genet.* 2011 Jan 27;7(1):e1001284. http://www.ncbi.nlm.nih.gov/pubmed/21298028 ; http://www.plosgenetics.org/article/info%3Adoi%2F10.1371%2Fjournal.pgen.1001284

616. **Metabolic Shifts in Immunity and Inflammation.** [Sites of ongoing inflammation and triggered immune responses are characterized by significant changes in metabolic activity. Recent studies have indicated that such shifts in tissue metabolism result from a combination of profound recruitment of inflammatory cells (neutrophils and monocytes) and high proliferation rates among lymphocyte populations. The resultant shifts in energy supply and demand can result in metabolic acidosis and diminished delivery and/or availability of oxygen, leading to hypoxia extensive enough to trigger transcriptional and translation changes in tissue phenotype. Such phenotypic shifts can imprint fundamental changes to tissue metabolism. In this study, we review recent work addressing metabolic changes and metabolic control of inflammation and immunity.] Kominsky DJ, Campbell EL, et al. *The Journal of Immunology*, 2010, 184, 4062 -4068. http://www.jimmunol.org/cgi/content/abstract/184/8/4062

617. **Methylation Status of IL-1B Promoter Region In Chronic Periondontitis Patients**. [Objectives: Chronic periodontitis has been associated with persistent elevated levels of PGE2 and IL-1b. In previous studies we have found altered COX-2 promoter methylation levels in disease suggesting the biofilm induces local epigenetic changes in inflammatory pathways. This pilot study sought to determine the DNA methylation status of the promoter region of interleukin-1 beta (IL-1B) genes in human gingival tissue biopsies from patients with periodontitis in comparison to those subjects free of periodontitis. Methods: Genomic DNA was isolated from 23 surgically removed gingival tissues: 12 with chronic periodontitis and 11 free of periodontitis. After bisulfite conversion, a promoter region of IL-1B promoter region (-3757 to -2508bp) was amplified by PCR with the primers that are specific to modified DNA template. Methylation level of 6 potential methylation sites (CpG sites) within the promoter region in the PCR products was then analyzed by Pyrosequencing technology (Biotage). Differences between CpG site specific methylation levels at all 6 CpG sites between health and disease were tested using Student's T-test. Results: Of the 6 potential methylation sites studied there was no significant difference in methylation levels comparing health to disease (62.5+4.2% vs 67.6+5.9%), respectively. Thus, in contrast to the epigenetic modifications of the

COX-2 promoter, the increases in tissue levels of IL-1b may not be attributable to differential methylation of the IL1B promoter. Conclusions: These findings suggest that chronic periodontal disease is not associated with alteration in the DNA methylation of the IL1B promoter. This suggests that epigenetic changes are not uniformly associated with regulating inflammatory molecules, but rather suggests a selective process targeting specific genes.] Zhang S, Barros S, et al. *IADR General Session*, Miami, FL, April 1-4, 2009. http://iadr.confex.com/iadr/2009miami/webprogram/Paper120733.html

618. **Rethinking Periodontal Inflammation.** [Clinical signs and symptoms, as well as medical and dental history, are all considered in the clinical determination of gingival inflammation and periodontal disease severity. However, the "biologic systems model" highlights that the clinical presentation of periodontal disease is closely tied to the underlying biologic phenotype. We propose that the determination and integration of subject-level factors, microbial composition, systemic immune response, and gingival tissue inflammatory mediator responses will better reflect the biology of the biofilm–gingival interface in a specific patient and may provide insights on clinical management. Disease classifications and multivariable models further refine the biologic basis for the increasing severity of periodontal disease expression. As such, new classifications may better identify disease-susceptible and treatment–non-responsive individuals than current classifications that are heavily influenced by probing and attachment level measurements alone. New data also suggest that the clinical characteristics of some complex diseases, such as periodontal disease, are influenced by the genetic and epigenetic contributions to clinical phenotype. Although the genetic basis for periodontal disease is considered imperative for setting an inflammatory capacity for an individual and, thus, a threshold for severity, there is evidence to suggest an epigenetic component is involved as well. Many factors long associated with periodontitis, including bacterial accumulations, smoking, and diabetes, are known to produce strong epigenetic changes in tissue behavior. We propose that we are now able to rethink periodontal disease in terms of a biologic systems model that may help to establish more homogeneous diagnostic categories and can provide insight into the expected response to treatment.] Offenbacher S, Barros SP, Beck JD. Journal of Periodontology, 2008, Vol. 79, No. 8s, Pages 1577-1584. http://www.joponline.org/doi/full/10.1902/jop.2008.080220

619. **The Biology, Prevention, Diagnosis and Treatment of Periodontal Diseases Scientific Advances in the United States.** [Background. Major scientific advances in periodontology in the past 150 years have fundamentally changed how clinicians detect and treat periodontal diseases. These advances include the demonstration that gingivitis and periodontitis are biofilm-induced infections caused by components of the indigenous oral microbiota, and that host inflammatory-immunologic responses to these microbial challenges are responsible for most of the observed tissue damage. Types of Studies Reviewed. In this brief overview, the authors focus on the discovery of the relationships between dental plaque and the host periodontal tissues. They highlight some of the pioneers in the United States who shaped new approaches to prevention and treatment of periodontal disease. Results. Biofilms that cause gingivitis and periodontitis are complex polymicrobial communities that are resistant to antimicrobial agents and host defense mechanisms. An increased understanding of natural inflammation-resolving mechanisms suggests that control of inflammation is at least as important as is antimicrobial therapy in the treatment of periodontal infections. Data from randomized controlled clinical trials have shown that most conventional forms of periodontal therapy are effective as long as patients comply with posttreatment maintenance programs. Many mechanisms involved in the repair and regeneration of periodontal tissues have been identified. Results of laboratory studies of factors that enhance prevention and treatment of periodontal disease have made the transition to clinical practice. Advances in the fields of molecular biology, human genetics and stem cell biology have set the stage for significant discoveries that will pave the way for the development of procedures needed for the predictable regeneration of periodontal tissues. As a result, new generations of people in the United States can expect to retain a healthy and functional dentition for a lifetime.] Armitage GC, Robertson PB. J Am Dent Assoc, Vol 140, No suppl_1, 36S-43S. http://jada.highwire.org/cgi/content/full/140/suppl_1/36S

HIV – Periodontal Disease

620. **Association Of Neutrophil Counts With Periodontitis Among HIV Positive Patients**. [BACKGROUND: Periodontal disease has been associated with several systemic conditions such as cardiovascular diseases. Some studies have linked periodontal disease with high leukocyte counts which has also associated with ischemic heart disease (IHD). This association of leukocyte counts with periodontal disease needs to be investigated in HIV positive patients. OBJECTIVE: The aim of this study was to investigate the relationship between periodontal disease and neutrophil counts in HIV positive patients. METHODS: A cross-sectional study of 132 consecutive HIV positive patients. The CPITN index was used to assess periodontal disease, while blood samples were taken to determine Total White blood cell (WBC) counts and absolute neutrophil counts. Data entry and analysis were done with Epi info 2007 statistical software. RESULTS: A total of 45 patients (34.1%) had gingivitis (CPITN maximum scores 1 and 2) while 84 patients (63.6%) had periodontitis (CPITN maximum scores 3 and 4). The total WBC count was not significantly associated with periodontal disease. However, mean neutrophil counts were significantly higher ($p= 0.0384$) in patients with periodontitis (3.01 ± 0.98) compared with patients who had gingivitis (1.37 ± 0.38). CONCLUSION: The findings from this study support the growing evidence from other studies linking severe forms of periodontal disease with higher neutrophil counts. This may account for the greater periodontal destruction seen in HIV positive patients by enzymes released from hyperactive neutrophils. Thus, neutrophil counts can be used to determine the risk of developing periodontitis in HIV positive patients.] Umeizukike K, Savage KO, et al. The Preliminary Program for IADR 2nd African and Middle East Regional Conference (23rd-25th September 2009). http://iadr.confex.com/iadr/amer09/preliminaryprogram/abstract_123061.htm

621. **Association of T CD4 lymphocyte levels and subgingival microbiota of chronic periodontitis in HIV-infected Brazilians under HAART.** [Objective The aim of this study was to determine the subgingival microbiota of HIV-infected patients with chronic periodontitis and different T CD4 lymphocyte levels under HAART. Study design 64 HIV+ patients (mean age 34.5 ± 7.3; 75% males) were distributed into Group I: chronic periodontitis (≥ 3 sites with probing pocket depth (PPD) and/or clinical attachment level (CAL) ≥ 5 mm); and Group II: periodontal health (no sites with PPD > 3 mm and/or CAL > 4 mm). All subjects received conventional periodontal therapy. Periodontal clinical parameters were evaluated at 6 sites/tooth in all teeth at baseline and 4 months after therapy. The levels of T CD4 were obtained from the patient's medical record. Subgingival plaque samples were taken from the 6 sites with the largest pocket depth in each subject of Group I, and 6 randomly selected sites in subjects of Group II. The presence of 22 subgingival species was determined using the checkerboard DNA-DNA hybridization method. Significant microbiological differences within and among groups were sought using Wilcoxon signed-rank and Mann-Whitney tests, respectively. Relationships between T CD4 levels and microbiological parameters were determined using Kruskal-Wallis test. Results Sixty-one percent of the HIV-infected patients represented AIDS cases, although 69% of them were periodontally healthy. The T CD4 lymphocyte mean level was 333 cells/mm^3 and viral load was 12,815 ± 24,607 copies/mm3. Yet, the prevalence of chronic periodontitis was relatively low (36%). Several periodontal pathogens, in particular T. forsythensis ($P < .05$), were more prevalent in HIV-positive patients with periodontitis than in HIV-positive subjects with periodontal health. Most of the species decreased in frequency after therapy, particularly P. gingivalis ($P < .05$). E. faecalis and F. nucleatum were significantly more prevalent in the subgingival microbiota of patients with chronic periodontitis and lower levels of T CD4 ($P < .05$), while beneficial species tended to be more frequently detected in individuals with T CD4 counts over 500 cells/mm3.Conclusion The subgingival microbiota of HIV-infected patients with chronic periodontitis include a high prevalence of classical periodontal pathogens observed in non-infected individuals. Furthermore, the severe immunosuppression seems to favor the colonization by these species, as well as by species not commonly found in the subgingival microbiota.] Goncalves L, Ferreira S, et al. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology & Endodontics*, Volume 97, Issue 2, Pages 196-203. http://linkinghub.elsevier.com/retrieve/pii/S1079210403005316

622. **Clinical Manifestations and Management of HIV-Related Periodontal Disease.** [The most important components in the management of HIV-associated gingival and periodontal disease should be the removal of local irritants from the root surfaces, débridement of necrotic tissues, and appropriate use of antibiotics. Two types of gingival/periodontal disease associated with HIV infection have been widely reported in the literature. In the past, these have been called HIV-associated gingivitis (HIV-G) and HIV-associated periodontitis (HIV-P). There is now evidence that these diseases also occur in HIV-negative immunocompromised individuals and are not specific to HIV infection, thus making the original terms inappropriate. Therefore, HIV-associated gingivitis has been renamed linear gingival erythema (LGE) and HIV-associated periodontitis has been renamed necrotizing ulcerative periodontitis (NUP).] Office of the Medical Director, New York State Dept of Health AIDS Insitute / John Hopkins University Division of Infectious Diseases. http://www.hivguidelines.org/GuideLine.aspx?GuideLineID=56

623. **HIV-associated periodontal disease: new oral spirochete found.** [This study examines plaque for the presence of a recently described oral spirochete, tentatively called pathogen-related oral spirochete. This investigation found PROS in plaque of patients with HIV-associated periodontal disease.] Rosenstein DI, Riviere GR, et al. J Am Dent Assoc, Vol 124, No 7, 76-80. http://jada.ada.org/cgi/content/abstract/124/7/76

624. **HIV Infection and Bone Loss Due to Periodontal Disease** [**Purpose:** The goal of this study was to determine whether HIV infection and/or high-risk behaviors associated with HIV infection are related to alveolar bone loss in a sample of subjects screened at a dental school clinic. Methods: Subjects were included in this study (N = 355) if they were HIV positive (HIV +) or had high risk behaviors associated with HIV infection as identified by health risk behavior screening questionnaire . Bone loss measurements were obtained from radiographs. Both bivariate relationships and multi-variate relationships between alveolar bone loss and three sets of variables were evaluated: high-risk behavior questions, demographic variables and HIV infection. Results: The following variables were found related to alveolar bone loss in bivariate relationships: 1) age ($P \leq 0.0001$), 2) smoking (pack years) ($P \leq 0.0001$), 3) race ($P \leq 0.002$), 4) gender ($P \leq 0.032$), 5) male-male sex ($P < 0.001$), 6) diabetes ($P \leq 0.015$), 7) sharing of needles ($P \leq 0.02$), and 8) hepatitis C positive ($P \leq 0.05$). In the multiple regression model, age, smoking, race, gender and male-male sex remained significant. In both analyses, HIV positive individuals had similar bone loss compared to those that were HIV negative. Conclusion: These results suggest that HIV infection is not related to alveolar bone loss in individuals with high risk behaviors for HIV infection. These results also suggest that previously reported relationships between HIV infection and increased alveolar bone loss may be explained by other factors, such as smoking. Individuals in this study population with risk behaviors associated with HIV infection, smoked at a high rate, and due to the smoking behavior have a high rate of periodontal disease.] Aichelmann-Reidy ME, Wrigley D, et al. J*ournal of Periodontology*, Posted online on February 22, 2010. http://www.joponline.org/doi/abs/10.1902/jop.2010.070675

625. **HIV-periodontal disease, epidemiology, aetiology and significance.** [Earlier reports of high incidence of acute gingival lesions and rapidly progressing periodontal disease among the HIV+ve patients raised the question that immunosuppression could have attributed to the progression of periodontal disease as characterised by the rapid loss of periodontal attachment. However, subsequent cross-sectional clinical studies failed to demonstrate a significant difference in the prevalence of gingivitis and periodontal disease in HIV+ve patients compared to that of the general population. There is some evidence to suggest that the progression of periodontal disease is greater in HIV+ve patients compared to that of HIV-ve patients in a study conducted by the author. The reason for this difference is unclear. A modified host response to periodontopathic

organisms is the likely hypothesis that awaits definitive proof. For HIV+ve patients, persistent gingival inflammation and preventable tooth loss could added misery to an already horrific illness. Constant bleeding from gingival and periodontal lesions could also contribute to the transmission of HIV through salivary contact alone. The need to treat and resolve all gingivitis and periodontitis is obvious. Periodontal care should be an integral part of the protocol in the comprehensive care of HIV+ve patients.] Stephen Y. *Annu Conf Australas Soc HIV Med.* 1997 Nov 13-16; 9: 62.
http://gateway.nlm.nih.gov/MeetingAbstracts/ma?f=102226215.html

626. **Is Periodontal Disease A Risk Factor For HIV-1?** [The investigators demonstrated the effects of such periodontopathic bacteria on HIV-1 replication. They found that P. gingivalis could strongly facilitate HIV-1 reactivation via chromatin modification. The bacteria produced high concentrations of butyric acid, a potent inhibitor of HDACs, and induced acetylation of histones, leading to reactivation of HIV-1 in latently infected cells. These results suggest that periodontal disease could act as a risk-factor for HIV-1 reactivation in latently infected individuals, and might contribute to the systemic dissemination of the virus causing clinical progression of acquired immunodeficiency syndrome (AIDS). The findings emphasize the essential role of maintaining oral hygiene and controlling oral diseases for the prevention of AIDS.]
http://www.medicalnewstoday.com/articles/145158.php

627. **New concepts regarding the pathogenesis of periodontal disease in HIV infection.** [known as linear gingival erythema [LGE]) and HIV-associated periodontitis (now known as necrotizing ulcerative periodontitis [NUP]). The true prevalence of LGE was difficult to determine due to variable diagnostic criteria. Recently, LGE has been associated with intraoral Candida infection. The prevalence of NUP is low (< or = 5%), and this lesion is associated with pronounced immunosuppression. Current focus on the periodontal manifestations of HIV infection centers on rapid progression of chronic adult periodontitis in HIV+ patients. Attempts to identify the pathogenesis of the increased progression of periodontitis have not proven successful. For example, analysis of subgingival plaque for the presence of bacterial pathogens has failed to detect differences between HIV+ and HIV- patients. Recently our laboratory has identified alterations in the host response in the gingival crevice of HIV+ patients. Comparing HIV+ and HIV- injecting drug users (IDU), levels of the proinflammatory cytokine interleukin-1 beta (IL-1 beta) in gingival crevicular fluid (GCF) were slightly elevated at sites with a probing depth of 1 to 3 mm. At deeper sites (> or = 4 mm), total IL-1 beta in GCF was significantly greater in HIV+ individuals. Using the lysosomal acid glycohydrolase beta-glucuronidase (beta G) as a measure of the influx of polymorphonuclear leukocytes (PMN) into the gingival crevice, our data indicated a significant correlation of total beta G in GCF and probing depth in the HIV-IDU (r = 76; P = .02). This result was similar to what we have observed in other studies. In contrast, for HIV+ subjects, total beta G was not associated with probing depth (r = .20; NS). These data suggest that HIV+ patients have altered regulation of PMN recruitment into the gingival crevice. We have begun to investigate the conditions under which subgingival Candida may contribute total periodontal lesions in HIV+ individuals. Candida from subgingival sites has been cultured in HIV+ individuals. Subgingival Candida was distinct from Candida isolated from tongue and buccal mucosal surfaces (as indicated by genomic fingerprinting). We hypothesize the absence of adequate priming of PMN by HIV+ patients. This may be due to a reduced Th1 lymphocyte response. The inability of HIV+ individuals to adequately prime PMN may allow Candida to colonize the subgingival environment. In that milieu, it may act directly or in concert with subgingival bacterial pathogens, or as a cofactor (by inducing production of proinflammatory cytokines) to increase the occurrence of periodontal attachment loss.] Lamster IB, Brbic JT, et al. *Ann Periodontol*. 1998 Jul;3(1):62-75.
http://www.ncbi.nlm.nih.gov/pubmed/9722691

628. **Periodontal diseases and HIV infection.** [The workshop considered six related questions about periodontal changes seen in HIV infection. 1) To what extent are specific periodontal changes associated with HIV? 2) Are conventional periodontal diseases modified by HIV infection? The changes associated with HIV appear to be modified presentations of conventional diseases. Research should identify initiation and progression factors for necrotizing diseases. 3) What is the role of geography and transmission groups? These questions cannot be answered without greater standardisation of research methods. 4) Has the epidemiology of these changes changed with the advent of new therapies? The data required to answer this question should be available soon but this question is irrelevant to the vast majority of people with HIV. 5) What pathogens are involved in periodontal changes seen in HIV infection? The role of Candida spp. and other potential pathogens requires further investigation. 6) What management protocols are suitable for the periodontal diseases? The significance of periodontal diseases among people with HIV in developing countries is not known. Further research is needed of the effectiveness of interventions especially necrotizing disease in developing countries. The quality of research of these diseases would be enhanced by standardized approaches. A list of relevant variables might prevent their omission from studies.] Robinson PG, Adegboye A, et al. Oral Diseases Volume 8 Issue s2, Pages 144 – 150.
http://www3.interscience.wiley.com/journal/118931261/abstract?CRETRY=1&SRETRY=0

629. **Periodontal Pathogens Enhance HIV-1 Promoter Activation In T cells.** [Although oral co-infections (e.g. periodontal disease) are highly prevalent in HIV-1 patients and appear to positively correlate with viral load levels, the potential for oral bacteria to induce HIV-1 reactivation in latently infected cells has received little attention. The researchers involved in this study have proved that periodontal pathogens enhanced HIV-1 promoter activation in T-cells, monocytes/macrophages and dendritic cells; however the mechanisms involved in this response remain undetermined.]
http://www.redorbit.com/news/health/1832517/periodontal_pathogens_enhance_hiv1_promoter_activation_in_t_cells/

630. **Reactivation of latent HIV-1 by *Porphyromonas gingivalis* involves histone modification**. [Objectives:Latently infected cells harbor the HIV-1 proviral DNA integrated in heterochromatins allowing the persistence of transcriptionally-silent proviruses. Hypoacetylation of histone proteins by histone deacetylases (HDACs) is involved in the maintenance of HIV-1

latency by repressing transcription from HIV-1 proviral DNA. Progression of AIDS is associated with development of severe periodontitis. Although it is known that a bacterial metabolite, butyric acid, is involved in reactivation of the "repressed" chromatin, it is not known whether periodontitis is involved in progression of HIV-infection. Thus, we examined whether *P. gingivalis* infection could facilitate progression of AIDS by reactivating the latent HIV provirus. Methods: ACH-2 and U1 cells, latently infected with HIV-1, were incubated with various components of *P. gingivalis*. HIV-1 proteins were detected by immunoblot and ELISA. Luciferase and chromatin immunoprecipitation assays were employed to analyze the HIV transcription. Butyric acid and other short chain fatty acids were measured by gas chromatography. Results: We found that the culture supernatant of *P. gingivalis* strongly induced HIV-1 replication via chromatin modification and these effects could be ascribed to butyric acid. No such activity was found with neither the fimbriae nor LPS components of *P. gingivalis*. In summary, we found that *P. gingivalis* produces high concentrations of butyric acid that acts as a potent inhibitor of HDACs and appears to induce acetylation of histone, thus eventually leading to reactivation of HIV-1 in latently infected cells. Conclusion: Our observations indicate that periodontal diseases could act as a significant risk-factor for HIV-1 reactivation and might contribute to the systemic dissemination of the virus. Because this could result in the clinical progression of AIDS, the essential role of maintaining oral hygiene and controlling oral diseases is warranted in prevention of AIDS progression.] Ochiai K, Imai K, et al. *IADR General Session*, Miami, GL, April 1-4, 2009. http://iadr.confex.com/iadr/2009miami/webprogram/Paper117893.html

631. **TLR2 and TLR9 Activation by Periodontal Pathogens induce HIV-1 Reactivation.** [Background: Although oral co-infections (e.g. periodontal disease) are highly prevalent in HIV-1^+ patients and appear to positively correlate with viral load levels, the potential for oral bacteria to induce HIV-1 reactivation in latently infected cells has received little attention. We showed that periodontal pathogens enhanced HIV-1 promoter activation in T-cells, monocytes/macrophages and dendritic cells; however the mechanisms involved in this response remain undetermined. Objective: To determine the role of Toll-like receptors (TLR) in HIV-1 reactivation induced by periodontal pathogens. Methods: BF24 monocytes/macrophages stably transfected with the HIV-1LTR promoter driving CAT expression, and THP89GFP cells, a model of HIV-1 latency, were exposed to oral bacteria, including *P. gingivalis* and *F. nucleatum*, *S. gordonii* and *S. sanguinis*. HIV-1 reactivation was determined by CAT-ELISA, fluorescence microscopy, flow cytometry and fluorometry. Levels of p24 and pro-inflammatory cytokines in supernatants were determined by ELISA. Antagonists and neutralizing antibodies against TLRs and cytokines were also used. Results: The oral Gram-negative but not Gram-positive bacteria enhanced HIV-1LTR activation in BF24 cells. TLR9 activation by *F. nucleatum* and TLR2 by both Gram-negative bacteria were involved in this response, however TLR4 activation had no effect. Use of NFkB or Sp1 specific chemical inhibitors suggested that these transcription factors are positive and negative regulators of bacterially-induced HIV-1LTR activation, respectively. HIV-1LTR activation and viral replication were similarly induced in THP89GFP cells. Finally, production of TNFa was enhanced by Gram-negative bacteria and its neutralization reduced HIV-1 reactivation. Conclusions: These results suggest that TLR2 and TLR9 activation by *P. gingivalis* and *F. nucleatum*, as well as TNFa produced in response to challenge enhance HIV-1 reactivation in monocytes/macrophages. Increased bacterial growth and emergence of periodontopathogens or their products accompanying chronic oral inflammatory diseases could be risk modifiers for viral replication and transmission, systemic immune activation and AIDS progression in HIV-1^+ patients.]Gonzalez OA, Ebersole JL, et al. AADR Annual Meeting, March 3-6, 2010, Wash DC. http://iadr.confex.com/iadr/2010dc/webprogram/Paper128186.html

Implants – Periimplantitis

632. **Peri-implant diseases: Consensus Report of the Sixth European Workshop on Periodontology.** [Issues related to peri-implant disease were discussed. It was observed that the most common lesions that occur, i.e. peri-implant mucositis and peri-implantitis are caused by bacteria. While the lesion of peri-implant mucositis resides in the soft tissues, peri-implantitis also affects the supporting bone. Peri-implant mucositis occurs in about 80% of subjects (50% of sites) restored with implants, and peri-implantitis in between 28% and 56% of subjects (12–40% of sites). A number of risk indicators were identified including (i) poor oral hygiene, (ii) a history of periodontitis, (iii) diabetes and (iv) smoking. It was concluded that the treatment of peri-implant disease must include anti-infective measures. With respect to peri-implant mucositis, it appeared that non-surgical mechanical therapy caused the reduction in inflammation (bleeding on probing) but also that the adjunctive use of antimicrobial mouthrinses had a positive effect. It was agreed that the outcome of non-surgical treatment of peri-implantitis was unpredictable. The primary objective of surgical treatment in peri-implantitis is to get access to the implant surface for debridement and decontamination in order to achieve resolution of the inflammatory lesion. There was limited evidence that such treatment with the adjunctive use of systemic antibiotics could resolve a number of peri-implantitis lesions. There was no evidence that so-called regenerative procedures had additional beneficial effects on treatment outcome.] Lindhe J, Meyle J, et al. *Journal of Clinical Periodontology*, Vol 35, pp 282-285, Sept 2008. http://onlinelibrary.wiley.com/doi/10.1111/j.1600-051X.2008.01283.x/abstract

633. **The effect of interleukin-1 allele 2 genotype (IL-1a(-889) and IL-1b(+3954)) on the individual's susceptibility to peri-implantitis: case-control study**. [Individuals bearing the combination of interleukin (IL)-1 allele 2 at IL-1A(-889) and IL-1B(+3954) are referred to as being genotype positive and are susceptible to increased periodontal tissue destruction. The aim of this study was to assess the possible association of IL-1 allele 2 (IL-1A(-889) and IL-B(+3954)) genotypes with the severity of peri-implantitis progression and the effect of this combination on treatment outcomes. Fifty patients with International Team for Implantology implants were studied; patients ranged in age from 35-55 years, and each patient had 1

implant. According to peri-implant tissue status, patients were divided into 2 groups: group I consisted of 25 patients with peri-implantitis, and group II comprised 25 patients with healthy peri-implant tissue. Clinical parameters were assessed at baseline and after 3 and 6 months. Epithelial cells were collected from the oral mucosa by plastic spatula and were used for IL-1 genotyping by the polymerase chain reaction technique. Group I patients were subjected to a peri-implantitis treatment and maintenance program. In all, 17 patients from group I and 5 patients from group II were genotype positive, with a statistically significant difference noted between the 2 groups. Group I genotype-positive patients presented with higher scores and measurements of clinical parameters with increased suppuration from peri-implant tissues compared with group II; differences were statistically significant ($P < .05$). In terms of response to treatment, genotype-negative patients demonstrated better response than genotype-positive patients. The combination of IL-1 allele 2 (IL-1A(-889) and IL-1B(+3954)) in patients with inflamed periodontal or peri-implant tissues acts as a risk factor that leads to greater tissue destruction. IL-1 gene polymorphism at IL-1A(-889) and IL-1B(+3954) may affect outcomes of treatment for peri-implantitis in genotype-positive individuals.] Hamdy AA, Ebrahem MA. *J Oral Implantol*. 2011 Jun;37(3):325-34. http://www.ncbi.nlm.nih.gov/pubmed/20594066

Interdisciplinary Care

634. **Curriculum and Clinical Training in Oral Health for Physicians and Dentists, Report of Panel 2 of the Macy Study**. [Across health professions, there is a growing appreciation of the need to address patient care systemically and holistically. The development of two separate health professions—one medical and one dental—has its origins in the early nineteenth century,[1] but advances in biomedical science have blurred this distinction from both diagnostic and therapeutic standpoints. The knowledge and skills physicians need related to clinical dentistry and the knowledge and skills dentists need related to clinical medicine are progressively overlapping. The two professions hold common biomedical science foundations, which include growing evidence of the relationship of oral to systemic health. A goal of this report is to identify learning objectives in oral and systemic health that will enhance each profession's capacity to improve and maintain the oral and overall health of individuals and populations.] Mouradian W, Bertolami CN, et al. Journal of Dental Education**February 1, 2008 vol. 72no. 2 suppl 73-85. http://www.jdentaled.org/content/72/2_suppl/73.full.pdf+html**
635. **Identifying Unaddressed Systemic Health Conditions at Dental Visits: Patients Who Visited Dental Practices But Not General Health Care Providers in 2008**. [We assessed the proportion and characteristics of patients who do not regularly visit general health care providers but do visit dentists and whose unaddressed systemic health care conditions could therefore be identified by their dentist. Of the 26.0% of children and 24.1% of adults that did not access general outpatient health care in 2008, 34.7% and 23.1%, respectively, visited a dentist. They varied by census region, family income, and sociodemographics. Dental practices can serve as alternate sites of opportunity to identify concerns among diverse groups of US patients.] Strauss SM, Alfano MC, et al. *Am J Public Health*. Published online ahead of print December 15, 2011: e1-e3. doi:10.2105/AJPH.2011.300420.
http://ajph.aphapublications.org/doi/abs/10.2105/AJPH.2011.300420?prevSearch=%5BContrib%3A+Shiela+Strauss%5D&searchHistoryKey= http://www.kaiserhealthnews.org/Daily-Reports/2011/December/16/dentsts-and-health-check-ups.aspx
http://www.foxnews.com/health/2011/12/16/dentists-chair-good-place-for-medical-checkup-study-says/
636. ***The American Journal of Cardiology* and *Journal of Periodontology* Editors' Consensus: Periodontitis and Atherosclerotic Cardiovascular Disease.** [The organization of the health professions into specialties and subspecialties according to body organs and systems is often more pragmatic than scientific. The human organism is a single unit composed of a seemingly infinite number of biologic processes so intertwined that abnormalities of almost any of its parts or processes have profound effects on multiple other body areas, exemplified in this document by the common and complex theme of *inflammation*. In recent years, the immune system, once believed to be only a vital defense against infection and a promoter of healing—except in the instances of a few uncommon connective tissue disorders—is now recognized as a significant active participant in many chronic diseases, including hypertension, diabetes mellitus, arthritis, inflammatory bowel disease, psoriasis, and the 2 diseases addressed in this Editors' Consensus: atherosclerotic cardiovascular disease (CVD) and periodontitis. This aim of this document is to provide health professionals, especially cardiologists and periodontists, a better understanding of the link between atherosclerotic CVD and periodontitis and, on the basis of current information, an approach to reducing the risk for primary and secondary atherosclerotic CVD events in patients with periodontitis.] Friedewald VE, Kornman KS, Beck JD, Genco R, Goldfine A, Libby P, Offenbacher S, Ridker, PM, Van dyke TE, Roberts W. *J Perio*, June 1 2009 1-10. http://www.joponline.org/doi/pdf/10.1902/jop.2009.097001

Kidney Disease, Inflammation and Periodontal Disease

637. **Bidirectional Relationship between Chronic Kidney Disease and Periodontal Disease: Structural Equation Modeling.** [Periodontal disease is associated with diabetes, heart disease, and chronic kidney disease (CKD), an effect postulated to be due in part to endovascular inflammation. While a bidirectional relationship between CKD and periodontal disease is plausible, it has not been previously reported in the literature. Over 11 200 adults 18 years or older were identified in the Third National Health and Nutrition Examination Survey. Analyses were conducted in two stages. First, multivariable logistic regression models were fitted to test the hypothesis that periodontal disease was independently associated with CKD.

Given the potential that the periodontal disease and CKD relationship may be bidirectional, a two-step analytic approach was used that involved 1) tests for mediation, and 2) structural equation models to examine more complex direct and indirect effects of periodontal disease on CKD, and vice versa. In two separate models periodontal disease (OR_{Adi} =1.62 (95% CI: 1.17-2.26) and edentulism (OR_{Adi} = 1.83 (1.31-2.55) and periodontal disease score (OR_{Adi} = 1.01 (1.01-1.02) were associated with CKD, when simultaneously adjusting for 14 other factors. Three of four structural equation models were most plausible suggesting bidirectional relationships. Collectively, these analyses provide for the first time empirical support for a bidirectional relationship between CKD and periodontal disease, and mediation of that relationship by diabetes duration and hypertension.*Kidney Int*.2011 February; 79(3): 347–355. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3045269/

639. **Biochemistry and Biomarkers of Inflamed Patients: Why Look, What to Assess.** [Specific laboratory tests and physical findings are available to the practicing clinician that should raise the suspicion of inflammation. Inflammation is related to specific clinical outcomes. Once identified, changes in clinical practice may affect the level of inflammation in individual and or groups of dialysis patients with the hope that these changes may in turn affect outcome in a positive manner. Standard clinical tests and observations associated with inflammation are hypoalbuminemia, erythropoietin resistance, decreased iron saturation accompanied by high ferritin, frailty, low serum creatinine, reduced total and LDL-cholesterol, and increased C reactive protein (CRP). Inflammation is strongly associated with loss of physical function, dyslipidemia (low LDL- and HDL-cholesterol, increased triglycerides), and anemia that is unresponsive to erythropoietin. Inflammation is associated with cardiovascular events, increased hospitalization, and death. Correctible causes of inflammation are tunneled dialysis catheters, arteriovenous grafts, catheter infection, periodontal disease, poor water quality, and dialyzer incompatibility. Obesity also is a source of cytokines but may be less amenable to treatment. Inflammation is multifactorial in dialysis patients. Some sources are recognizable and correctable, such as vascular access type, clinical infection, and water quality, and some are not. Inflammation is strongly associated with outcome.] Kaysen GA. *Clin J Am Soc Nephrol* 4: S56-S63, 2009. http://cjasn.asnjournals.org/cgi/content/abstract/4/Supplement_1/S56

640. **Clinical and Serologic Markers of Periodontal Infection and Chronic Kidney Disease**. [Background: Chronic kidney disease and its concomitant sequelae represent a major public health problem. Recent data suggest periodontal infection contributes to chronic kidney disease. Methods: This United States population–based study of 4,053 adults ≥40 years of age investigated the association between chronic kidney disease and clinical measures and serologic markers of periodontal infection. Chronic kidney disease was defined as moderate-to-severe reduction of kidney function with glomerular filtration rate of 15 to 59 ml/minute/1.73 m^2 based on stages 3 and 4 of the Kidney Disease Outcome Quality Initiative. Chronic oral inflammatory burden was measured as 1) clinical periodontal infection categorized as no periodontal disease, periodontal disease (at least one tooth with ≥4 mm loss of attachment and bleeding on probing as an indicator of inflammation), or edentulism and 2) serum immunoglobulin G antibody response to *Aggregatibacter actinomycetemcomitans* (previously *Actinobacillus actinomycetemcomitans*) and *Porphyromonas gingivalis*. Multiple logistic regression modeling quantified the association between chronic kidney disease and chronic inflammatory burden and other risk factors. Results: Nine percent of the study population had chronic kidney disease, 22% had high *A. actinomycetemcomitans* antibody titer, 24% had high *P. gingivalis* antibody titer, 9% had periodontal disease, and 17% were edentulous. After simultaneously adjusting for recognized risk factors, adults with a high *A. actinomycetemcomitans* titer were less likely to have chronic kidney disease (adjusted odds ratio [OR_{Adj}] = 0.67; 95% confidence interval [CI]: 0.46 to 0.98), and adults with edentulism were more likely to have chronic kidney disease (OR_{Adj} = 1.64; 95% CI: 1.11 to 2.44). Conclusion: These results support considering edentulism and low serum titer to *A. actinomycetemcomitans* as risk indicators for chronic kidney disease.] Fisher MA, Taylor GW, et al. *J Perio 2008, Vol 79, No. 9, pg 1670-1678.* http://www.joponline.org/doi/abs/10.1902/jop.2008.070569

641. **Does periodontitis reflect inflammation and malnutrition status in hemodialysis patients?** [BACKGROUND: Chronic infection and inflammation, including periodontitis, is linked to an increased risk for atherosclerosis. To investigate the possible adverse effects of periodontitis in maintenance hemodialysis patients, we compared periodontal severity with malnutrition and inflammation, which are associated with poor atherosclerotic outcome in hemodialysis patients. METHODS: Two hundred fifty-three hemodialysis patients were included in this study to evaluate clinical periodontal status by using the Plaque Index, Gingival Index, and Periodontal Disease Index. Geographic, hematologic, biochemical, and dialysis-related data also were collected. Values for nutritional and inflammatory markers, such as albumin, blood urea nitrogen, creatinine, transferrin, absolute lymphocyte count, normalized protein catabolic rate, high-sensitivity C-reactive protein, and ferritin, were included for analysis with the Periodontal Index. RESULTS: Poor oral health status was shown by 80.6% of hemodialysis patients with periodontal disease. In an analysis of geographic and disease-related parameters, we found that aging, smoking, diabetes, and longer dialysis duration were associated with severity of periodontitis. Parameters of malnutrition and inflammation also were associated with poor periodontal status. We next conducted multiple regression analysis and found that age, diabetes, smoking, albumin level, and dialysis duration were associated independently with periodontitis severity in hemodialysis patients. According to the severity of periodontitis, there were higher percentiles of patients with malnutrition (chi-square = 13.055; P = 0.005) and inflammation (chi-square = 10.046; P = 0.018) in the severe group. CONCLUSION: Periodontal health is poor in hemodialysis patients and correlates with markers of malnutrition and inflammation. Its diagnosis and treatment deserve better awareness.] Chen LP, Chiang CK, et al. *American Journal of Kidney Disease*, 2006-May; Vol. 47 (issue 5) pp 815-22. http://www.ncbi.nlm.nih.gov/sites/entrez

642. **Effect of Periodontitis on Overt Nephropathy and End-Stage Renal Disease in Type 2 Diabetes. [**The purpose of this study was to investigate the effect of periodontitis on development of overt nephropathy, defined as macroalbuminuria, and end-stage renal disease (ESRD) in type 2 diabetes. Periodontitis predicts development of overt nephropathy and ESRD in

individuals with type 2 diabetes. Whether treatment of periodontitis will reduce the risk of diabetic kidney disease remains to be determined.] Schultis WA, Weil EJ, et.al. ***Diabetes Care*** *30:306-311, 2007.* http://care.diabetesjournals.org/cgi/content/abstract/30/2/306

643. **Importance of periodontal disease in the kidney patient.** [C-reactive protein (CRP), the major acute phase protein in man, has been found to predict all-cause and cardiovascular mortality in ESRD patients on hemodialysis maintenance therapy. Hepatic CRP synthesis is upregulated by proinflammatory cytokines released locally at sites of infection or inflammation, although many patients experience elevated CRP values in the absence of overt infection or inflammation. Destructive periodontal diseases in the general population have been associated with both an increased prevalence of atherosclerotic complications and an elevation in serum CRP values. In view of the prevalence of destructive periodontal diseases in the general population, and since periodontal evaluations are normally not performed as part of a medical assessment, destructive periodontal diseases may be an over looked source of inflammation in ESRD patients on hemodialysis therapy.] Craig R.G., Spittle M.A., *Blood Purif. 2002;20(1):113-9.* http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11803168&dopt=Abstract
644. **Periodontal disease: a covert source of inflammation in chronic kidney disease patients.** [The prevalence of atherosclerotic complications (myocardial infarction, stroke, and sudden death) is increased in end-stage renal disease (ESRD) patients, especially in haemodialysis patients. Increasing evidence suggests that both in general population and in dialysis patients, systemic inflammation plays a dominant role in the pathogenesis of atherosclerotic complications. In general population, also, evidence shows that moderate to severe periodontitis can contribute to inflammatory burden by increasing serum CRP levels and may increase the prevalence of atherosclerotic events. Moreover, the results of some new interventional studies reveal that effective phase I periodontal therapy may decrease serum CRP levels, the most important acute phase protein, monitored as a systemic marker of inflammation and endothelial dysfunction as well, used as an initial predictor of atherosclerotic events. Considering that moderate to severe periodontal diseases have a higher prevalence in CKD and in dialysis population and that periodontal examination is not part of the standard medical assessment, destructive periodontitis might be an ignored source of systemic inflammation in end-stage renal disease patients and may add to the chronic inflammatory status in CKD.] Ismail G, Dumitriu HT, et al. *Int J Nephrol.* 2013;2013:515796. **http://www.ncbi.nlm.nih.gov/pubmed/23840952**
645. **Periodontal disease adversely affects the survival of patients with end-stage renal disease.** [Periodontal disease is associated with cardiovascular disease and is thought to accelerate systemic atherosclerosis. Here we examined the relationship between periodontitis and cardiovascular disease mortality in outpatients on hemodialysis using a retrospective analysis of 168 adult patients in New York City and North Carolina. During 18 months of follow-up, cardiovascular disease and all-cause mortality were determined from a centralized dialysis registry. One hundred patients had mild or no periodontal disease but the remaining 68 had moderate-to-severe disease defined as 2 or more teeth with at least 6 mm of inter-proximal attachment loss. At baseline, the proportion of males was significantly lower in the moderate-to-severe group. Compared with mild or no periodontal disease, moderate-to-severe disease was significantly associated with death from cardiovascular causes. Adjustment for age, gender, center and dialysis vintage, smoking status, and history of diabetes mellitus or hypertension did not diminish the strength of this association. Our findings suggest a need for larger studies to confirm this connection, along with intervention trials to determine if treating periodontitis reduces cardiovascular disease mortality in dialysis patients.] Kshirsagar AV, Craig RG, et al. Kidney Int. 2009 Apr;75(7):746-51. http://www.ncbi.nlm.nih.gov/pubmed/19165177
646. **Periodontal Disease in Chronic Kidney Disease and End-Stage Renal Disease Patients: A Review.** [Periodontal disease is a chronic inflammatory disorder and being so it has been associated with accelerated atherosclerosis and malnutrition. Cardiovascular diseases are the leading cause of mortality in chronic kidney disease (CKD) and end-stage renal disease (ESRD) patients [National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: Annual Data Report, 2010]. A recent scientific statement released by the American Heart Association [Lockhart et al.: Circulation 2012;125:2520-2544] claims that, even though evidence exists to believe that periodontal interventions result in a reduction in systemic inflammation and endothelial dysfunction, there is little evidence that those interventions prevent atherosclerotic vascular disease or modify the outcomes. In this review, we discuss the periodontal findings and their association with an increased prevalence of inflammatory markers and cardiovascular mortality in ESRD patients and CKD.] Ariyamuthu VK, Nolph KD, et al. Cardiorenal Med. 2013 April; 3(1): 71–78. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3678148/
647. **Periodontal Disease in Chronic Kidney Disease and End-Stage Renal Disease Patients: A Review** [Periodontal disease is a chronic inflammatory disorder and being so it has been associated with accelerated atherosclerosis and malnutrition. Cardiovascular diseases are the leading cause of mortality in chronic kidney disease (CKD) and end-stage renal disease (ESRD) patients [National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: Annual Data Report, 2010]. A recent scientific statement released by the American Heart Association [Lockhart et al.: Circulation 2012;125:2520-2544] claims that, even though evidence exists to believe that periodontal interventions result in a reduction in systemic inflammation and endothelial dysfunction, there is little evidence that those interventions prevent atherosclerotic vascular disease or modify the outcomes. In this review, we discuss the periodontal findings and their association with an increased prevalence of inflammatory markers and cardiovascular mortality in ESRD patients and CKD.Cardiorenal Med. 2013 April; 3(1): 71–78. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3678148/ **Periodontal disease is associated with renal insufficiency in the Atherosclerosis Risk In Communities (ARIC) study.** [Periodontitis, a chronic bacterial infection of the oral cavity, is a novel risk factor for atherosclerotic cardiovascular disease (CVD). Given the numerous

shared risk factors for CVD and chronic kidney disease (CKD), we hypothesized that periodontitis also is associated with renal insufficiency in the Dental Atherosclerosis Risk in Communities study. This is the first study to show an association of periodontal disease with prevalent renal insufficiency. A prospective study is necessary to determine the exact nature of the observed relationship.] Kshirsagar, A.V., Moss K.L.., et.al., *Am J Kidney Dis. 2005 Apr;45(4):650-7* .http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=15806467&dopt=Abstract

649. **Periodontitis and the end-stage renal disease patient receiving hemodialysis maintenance therapy.** [Atherosclerotic complications, including myocardial infarction and stroke, are highly prevalent and associated with increased systemic inflammation in patients who have end-stage renal disease (ESRD) and are receiving renal hemodialysis maintenance therapy. In the general population, an increasing body of evidence suggests periodontitis can contribute to systemic inflammation and may contribute to atherosclerotic complications. In addition, results of recent interventional trials suggest effective periodontal therapy may decrease systemic inflammation as well as endothelial dysfunction, an early predictor of atherosclerotic complications. Because moderate-to-severe periodontitis appears to be highly prevalent in the renal hemodialysis population, effective periodontal therapy may reduce systemic inflammation and thereby become a treatment consideration for this population. This article will acquaint dental practitioners with ESRD and the association between systemic inflammation and mortality. Also discussed are the possible contributions of destructive periodontal diseases to systemic inflammation and the dental management of patients receiving renal replacement therapies.] Craig RG, Kotanko P. *Compend Contin Educ Dent.* 2009 Oct;30(8):544, 546-52. **http://www.ncbi.nlm.nih.gov/pubmed/19824568**

650. **Periodontitis Is an Important and Occult Source of Inflammation in Hemodialysis Patients. [***Aim:* To evaluate the association between C-reactive protein (CRP) levels and the periodontal status of hemodialysis (HD) patients. *Methods:* 41 HD patients on rHuEPO therapy were enrolled in the study. Hematologic and biochemical parameters and CRP levels were recorded. The plaque index, gingival index, probing pocket depth and periodontal disease index were used to identify periodontal disease. The patients were divided into 2 groups: group 1 (n = 21), high CRP, and group 2 (n = 20), normal CRP. *Results:* After periodontal therapy, while the mean CRP level and erythrocyte sedimentation rate declined from 30.46 to 10.36 (p = 0.001) and from 93.4 to 35.8 mg/l (p = 0.001), respectively, the hemoglobin level increased from 9.4 to 10.6 g/dl (p = 0.009) and hematocrit level from 28.2 to 32.0% (p = 0.008) in group 1. *Conclusion:* Periodontitis is an important and occult source of chronic inflammation and increases the CRP levels in HD patients. Periodontitis can cause hyporesponsiveness to rHuEPO treatment and decrease the hemoglobin levels. **]** Kadiroglu AK, Kadiroglu ET, et al. *Blood Purif 2006;24:400-404.* http://content.karger.com/produktedb/produkte.asp?typ=fulltext&file=BPU2006024004400

651. **Poor Nutritional Status and Inflammation: Linknig Oxidative Stress and Inflammation in Kidney Disease.** [For end-stage renal disease (ESRD) patients, cardiovascular disease remains the single most common cause of excess morbidity and mortality. Furthermore, although the prevalence of traditional cardiovascular risk factors is high in the dialysis population, the extent and severity of associated cardiovascular morbidity and mortality remain disproportionate to traditional risk factor profiles. Consequently, considerable effort has been focused on "nontraditional" risk factors for cardiovascular events in this patient population. Among the examined nontraditional risk factors, increased oxidative stress as well as increased acute phase inflammation are postulated to be important contributors to uremic cardiovascular risk. Additional important uremic cardiovascular risk factors include malnutrition and endothelial dysfunction, both of which may be directly linked to the processes that cause increased oxidative stress and inflammation in uremia. In this context I review available data linking the pathogenesis of oxidative stress to acute phase inflammation and uremia. I also review data suggesting that oxidative stress in uremia directly contributes to the development of acute phase inflammation and that patients with higher levels of inflammation have higher levels of oxidative stress biomarkers. Similarly I review emerging data on the potential effects of antioxidant therapy on inflammatory biomarkers, as well as data suggesting that strategies to lower acute phase inflammation may also improve biomarkers of oxidative stress. Theoretical constructs evaluating the linkage of oxidative stress and inflammation in uremia and their contribution to the pathogenesis of atherosclerosis are suggested.] Himmelfarb J. *Seminars In Dialysis, Volume 17 Issue 6 Page 449 - November 2004. http://www.blackwell-synergy.com/doi/abs/10.1111/j.0894-0959.2004.17605.x?journalCode=sdi*

Laser Assisted Periodontal Therapy

652. **Advantages of a pulsed CO2 laser in direct pulp capping: a long-term in vivo study.** [The CO2 laser seems to be a valuable aid in direct pulp capping; the efficiency of laser treatment can be increased by using a pulsed CO2 laser.] Moritz A, Schoop U, et al. *Lasers Surg Med* 1998;22(5):288-93. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&list_uids=9671995&cmd=Retrieve&dopt=Citation&indexed=google

653. **Bactericidal effect of erbium YAG laser on periodontopathic bacteria.** [Recently Erbium (Er) YAG laser has been developed for dentistry. It may be suitable for periodontal therapy. This study examined the bactericidal effect of the Er: YAG laser on periodontopathic bacteria in vitro. Results: Growth inhibitory zones were found at the irradiated sites at the energy of about 0.3 J/cm^2 and higher. The survival ratios of the viable bacteria in the lased *P. gingivalis* colonies decreased significantly at the energy of 7.1 and 10.6 J/cm^2, as compared with that of the control. Conclusion: These findings suggest that the Er:YAG laser has a high bactericidal potential at a low energy level.] Ando Y, Aoki A, et al. *Lasers in Surgery and Medicine, Vol 19, Issue 2, P.190-200.* http://www3.interscience.wiley.com/cgi-bin/abstract/66371/ABSTRACT

654. **Bacterial reduction in periodontal pockets through irradiation with a diode laser: a pilot study. [**This study examines the application of a diode laser with a wavelength of 805 nm for periodontal treatment. While the use of the diode laser in this field has not been investigated so far, several authors have reported on the use of neodymium:yttrium-aluminum-garnet (Nd:YAG) laser for such applications. The aim of this study was to examine the immediate effect of the diode laser in reducing the bacterial concentration in periodontal pockets. Important periodontal indices (PBI, CPITN) were assessed in 50 patients to obtain initial values for a planned long-term study and to select appropriate periodontal pockets for this study. The periodontal pockets were required to have a minimum depth of 4 mm. Only proximal pockets were included in this study. The patients were subdivided into two groups. After microbiological samples had been collected with sterile paper tips, the group selected for laser treatment was subjected to scaling. One week after scaling, the patients underwent laser treatment. One week later, a second series of microbiological samples were obtained and the patients were subjected again to scaling; this time, however, they did not undergo laser treatment after 1 week. Two weeks after scaling, another series of microbiological samples was collected. The microbiological samples were evaluated to verify bacterial elimination from the periodontal pockets. A comparison between the initial and the final bacterial counts revealed that irradiation with the diode laser facilitates considerable bacterial elimination, especially of Actinobacillus actinomycetemcomitans, from periodontal pockets.] Moritz A, Butknecht N, et al. *J Clin Laser Med Surg*. 1997 Feb;15(1):33-7. http://www.ncbi.nlm.nih.gov/pubmed/9467340

655. **Advantages of a pulsed CO2 laser in direct pulp capping: a long-term in vivo study.** [The CO2 laser seems to be a valuable aid in direct pulp capping; the efficiency of laser treatment can be increased by using a pulsed CO2 laser.] Moritz A, Schoop U, et al. *Lasers Surg Med* 1998;22(5):288-93. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&list_uids=9671995&cmd=Retrieve&dopt=Citation&indexed=google

656. **Bactericidal effect of erbium YAG laser on periodontopathic bacteria.** [Recently Erbium (Er) YAG laser has been developed for dentistry. It may be suitable for periodontal therapy. This study examined the bactericidal effect of the Er: YAG laser on periodontopathic bacteria in vitro. Results: Growth inhibitory zones were found at the irradiated sites at the energy of about 0.3 J/cm^2 and higher. The survival ratios of the viable bacteria in the lased *P. gingivalis* colonies decreased significantly at the energy of 7.1 and 10.6 J/cm^2, as compared with that of the control. Conclusion: These findings suggest that the Er:YAG laser has a high bactericidal potential at a low energy level.] Ando Y, Aoki A, et al. *Lasers in Surgery and Medicine, Vol 19, Issue 2, P.190-200.* http://www3.interscience.wiley.com/cgi-bin/abstract/66371/ABSTRACT

657. **Bactericidal effect of malachite green and red laser on Actinobacillus actinomycetemcomitans.** [The aim of this study was to investigate the ability of malachite green (MG) combined with a low-power red laser to kill Actinobacillus actinomycetemcomitans and to investigate MG photodegradation after photodynamic therapy (PDT) by optical absorption spectroscopy. The etiology of periodontal disease is that microorganisms form a bacterial biofilm on the surface of the teeth. It is an infectious disease and A. actinomycetemcomitans is considered an important agent in biofilm ecology. Instead of using antibiotics, PDT is an alternative approach to eradicate bacteria. Cultures of A. actinomycetemcomitans were exposed to a 30 mW diode red laser, in the presence or absence of MG. A group of cultures was treated in dark conditions in the presence of MG (0.01% w/v) for 5 min. In the presence of MG, two exposure times for laser irradiation were used: t=3 min (energy dose=5.4 J/cm(2)), and t=5 min (energy dose=9 J/cm(2)). The samples were diluted and bacterial colonies were counted and converted into colony forming units. Absorption spectra of the bacterial suspensions, MG, MG-stained bacterial suspensions, and photosensitized bacterial suspensions were obtained. A. actinomycetemcomitans can be photoinactivated by a red laser in the presence of MG. Significant differences were observed between the two energy doses used ($p<0.05$). Red laser alone and MG alone were not able to kill bacteria. Optical absorption showed that MG is photobleached after irradiation. These results indicate that A. actinomycetemcomitans can be photosensitized by red laser combined with MG and that the dye is photodegraded following irradiation.] Prates RA, Yamada AM, et al. *J Photochem Photobiol B, 2007 Jan 3;86((1):70-6.* http://www.ncbi.nlm.nih.gov/sites/entrez?cmd=Retrieve&db=PubMed&list_uids=16979345&dopt=Abstract

658. **Bactericidal effect of the Nd:YAG lasers in laser-supported curettage.** [In this study, the efficacy of laser-supported curettage was examined with relation to the periodontitis-reference germs. Initially, a manual subgingival curettage followed by irradiation using the Nd:YAG-laser was carried out on 18 diseased periodontia. At two further appointments with weekly intervals, only laser irradiation was performed. Prior to and upon completion of therapy, subgingival plaque samples were taken at each appointment from all the treated periodontia. These were then examined microbiologically to establish the number of prevotella intermedia. A distinct bacterial reduction as well as a decrease in recolonization was shown. In conclusion the application of the Nd:YAG laser with a 400 micron fiber and an energy setting of 2 watts, 20 pps is beneficial when used in conjunction with manual periodontal treatment because of its disinfecting effect.] Gutknecht N, Fisher, J, et al. Lasers in Dentistry III, Harvey A. Wigdor; John D. Featherstone; Peter Rechmann; Eds http://adsabs.harvard.edu/abs/1997SPIE.2973..221G

659. **Bactericidal effects of the neodymium:YAG laser: in vitro study. [**The effects of laser energy on three bacterial strains, Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa were studied utilizing the neodymium:YAG laser. Cell suspensions of each strain were divided into four groups. In group I, suspensions from each strain were exposed to laser energy densities of 555-3,333 J/cm2. In groups II and III, two artificial dyes, congo red or methylene blue, were added to the suspensions prior to lasing. In group IVa, no laser energy was used, and group IVb was used to measure the bactericidal thermal effects of the laser. It was concluded that: Low dosages of laser energy exceeding 1,667 J/cm2 resulted in a 2 to 8 log decline in the number of viable bacterial colonies in vitro. Compared to the other two bacterial strains, P aeruginosa was the

most sensitive to YAG laser irradiation. Addition of methylene blue, a dark-colored dye, enhanced the bactericidal effects of the YAG laser as indicated by the significantly reduced viability of P aeruginosa after irradiation with 2,222 J/cm2.] Schultz RJ, Harvey GP, et.al. *Lasers Surg Med. 1986;6(5):445-8.*
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=3100891&dopt=Abstract

660. **Bacterial reduction in periodontal pockets through irradiation with a diode laser: a pilot study. [**This study examines the application of a diode laser with a wavelength of 805 nm for periodontal treatment. A comparison between the initial and the final bacterial counts revealed that irradiation with the diode laser facilitates considerable bacterial elimination, especially of Actinobacillus actinomycetemcomitans, from periodontal pockets.] Moritz a, Gutknecht N, et al. J Clin Laser Med Surg. 1997 Feb;15(1):33-7.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&list_uids=9467340&dopt=Citation
661. **Clinical advances of the pulsed Nd:YAG laser in periodontal therapy.** [Since the Nd:YAG laser was first developed in the 1960s, its spectrum of capabilities has continued to expand in the medical field. In dentistry, treatment of both hard and soft tissue has been affected, with the most noticeable change occurring in the management of periodontal disease. The learning objective of this article is to review the utilization of the pulsed Nd:YAG laser (American Dental Technologies, Southfield, MI) in the management of periodontal disease. Cases are presented to document the clinical aspects, and directions of future research are indicated.] Bader HI, Epstein SR. Pract Periodontics Aesthet Dent. 1997 Aug;9(6 Suppl):6-9.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9573832&dopt=Abstract
662. **Clinical and microbiological follow-up evaluations after non-surgical periodontal treatment with Er:YAG laser and scaling and root planing**. [Background: This study compared Er:YAG laser irradiation (100 mJ/pulse, 10 Hz, 12.9 J/cm^2) with or without conventional scaling and root planing (SRP) versus SRP only for treatment of periodontal pockets. Methods: Nineteen patients, with pockets from 5 to 9 mm, were included. In a split-mouth design, each site was allocated to a treatment group: 1) SRPL - SRP and laser; 2) L - laser ; 3) SRP - SRP only; 4) C - no treatment. Clinical parameters of probing depth (PD), gingival recession (GR), and clinical attachment level (CAL) were evaluated at baseline and 1, 3, 6 and 12 months after treatment. Visible plaque index (PI), gingival bleeding index (GI), bleeding on probing (BOP) and subgingival plaque samples were also measured 12 days postoperatively, in addition to the above mentioned months. Inter and intragroup statistical analyses were performed (P <0.05). Results: GI decreased for SRPL and increased for L, SRP and C (P <0.05) 12 days postoperatively and decreased for SRPL and SRP (P <0.05) 3, 6 and 12 months after baseline; BOP and PD decreased for all treated groups (P <0.01) 3, 6 and 12 months after treatment. CAL gain was significant for SRPL, L and SRP (P <0.05) 3, 6 and 12 months postoperatively. SRPL and L presented a significant reduction in the percentage of sites with bacteria, 6 and 12 month after treatment (P <0.05). Conclusions: Non-surgical periodontal treatment with Er:YAG laser may be an alternative treatment for reduction and control of the proliferation of microorganisms in persistent periodontitis.] Lopes BMV, Theodoro LH, et al. *J Perio*, Online Jan 27, 2010. http://www.joponline.org/doi/abs/10.1902/jop.2010.090300
663. **Clinical applications of the Nd:YAG laser in oral soft tissue surgery and periodontology.** [Different clinical applications of the Nd:YAG laser in periodontology are discussed in this study. Several clinical cases are presented showing the application spectrum of the Nd:YAG laser in oral soft tissue surgery. Literature reports are discussed to present to the clinical practitioner the advantages and disadvantages of laser surgery. Lasers have a useful place in the periodontal and oral surgical techniques, if manufacturer's guidelines are strictly followed.] Romanos GE. *J Clin Laser Med Surg. 1994 Apr;12(2):103-8.*
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10147186&dopt=Citation
664. **Clinical Effects of Diode Laser Treatment on Wound Healing.** [To clinically evaluate the effect of a laser (Odyssey Soft Tissue Diode Laser, Ivoclar) on healing of periodontal pockets treated by scaling and root planing (SRP) and on patient comfort. …Conclusions: Diode laser therapy in conjunction with SRP showed no adverse effects on wound healing associated with scaling and root planing and improved patient soft tissue comfort and reduced tooth sensitivity in 70% of the patients. Also, improvements in gingival health were more stable in the SRPL group.] Ciancio SG, Kazmierczak M, et al. Int. Assoc for Dent Res. http://iadr.confex.com/iadr/2006Orld/techprogram/abstract_72866.htm
665. **Clinical efficacy of the Nd:YAG laser for combination periodontitis therapy.** [Recent results of a limited clinical trial suggest that mechanical root scaling and root planing therapy alone may not be the most effective mode of treatment for patients affected by moderate to severe adult periodontitis. However, scaling and planing combined with laser therapy utilizing a low-powered pulsed Nd:YAG laser have been shown to be successful in the elimination of the bacteria commonly associated with the development of this oral condition. The double-blind, split mouth design study involved 10 human subjects randomly assigned to one of three treatments: 1) scaling and root planing alone, 2) dental laser plus scaling and root planing, and 3) control only. This article presents the clinical results of the trial, which suggest that laser therapy is a viable adjunct to local, nonsurgical therapy such as scaling and planing.] Neill ME, Mellonig JT. Pract Periodontics Aesthet Dent. 1997 Aug;9(6 Suppl):1-5.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9573831&dopt=Citation
666. **Clinical efficacy of semiconductor laser application as an adjunct to conventional scaling and root planning [**The aim of the in vitro study was to examine the clinical efficacy of semiconductor laser periodontal pocket irradiation as an adjunct to conventional scaling and root planing. Conclusions:The higher reduction in tooth mobility and probing depths is probably not predominantly related to bacterial reduction in the periodontal pockets but to the de-epithelization of the periodontal pockets leading to an enhanced connective tissue attachment. The application of the diode laser in the treatment of inflammatory periodontitis at the irradiation parameters described above is a safe clinical procedure and can be recommended

as an adjunct to conventional scaling and root planing.] Kreisler M, Al Haj. *Lasers in Surgery and Medicine Volume 37, Issue 5 , Pages 350 – 355.* *http://www3.interscience.wiley.com/cgi-bin/abstract/112219184/ABSTRACT?CRETRY=1&SRETRY=0*

667. **Clinical evaluation of an Er:YAG laser combined with scaling and root planing for non-surgical periodontal treatment. A controlled, prospective clinical study.** [OBJECTIVES: The purpose of the present controlled clinical trial was to compare the treatment of advanced periodontal disease with a combination of an Er:YAG laser (KEY II, KaVo, Germany) and scaling and root planing with hand instruments (SRP) to laser alone. MATERIAL AND METHODS: Twenty healthy patients with moderate to advanced periodontal destruction were randomly treated in a split-mouth design with a combination of an Er:YAG laser and SRP (test) or with laser (control) alone. The used energy setting for laser treatment was 160 mJ/pulse at a repetition rate of 10 Hz. Prior to treatment and 3, 6 and 12 months later the following parameters were evaluated by a blinded examiner: Plaque index (PI), gingival index (GI), bleeding on probing (BOP), probing depth (PD), gingival recession (GR) and clinical attachment level (CAL). Subgingival plaque samples were taken at each appointment and analysed using darkfield microscopy for the presence of cocci,-non-motile rods, motile rods and spirochetes. No statistical significant differences in any of the investigated parameters between both groups were observed at baseline. RESULTS: Initially, the plaque index was 1.0 +/- 0.6 in both groups. At the 3-month examination the plaque scores were markedly reduced and remained low throughout the study. A significant reduction of the GI and BOP occurred in both groups after 3, 6 and 12 months ($P < 0.05$, $P < 0.05$, respectively). The mean PD decreased in the test group from 5.2 +/- 0.8 mm at baseline to 3.2 +/- 0.8 mm after 12 months ($P < 0.05$) and in the control group from 5.0 +/- 0.7 mm at baseline to 3.3 +/- 0.7 mm after 12 months ($P < 0.05$). The mean CAL decreased in the test group from 6.9 +/- 1.0 mm at baseline to 5.3 +/- 1.0 mm after 12 months ($P < 0.05$) and in the control group from 6.6 +/- 1.1 mm at baseline to 5.0 +/- 0.7 after 12 months ($P < 0.05$). Both groups showed a significant increase of cocci and-non-motile rods and a decrease in the amount of motile rods and spirochetes. Conclusion: In conclusion, the present results have indicated that: (i) non-surgical periodontal therapy with both an Er:YAG laser + SRP and an Er:YAG laser alone may lead to significant improvements in all clinical parameters investigated, and (ii) the combined treatment Er:YAG laser + SRP did not seem to additionally improve the outcome of the therapy compared to Er:YAG laser alone.]SchwarzF, Sculean A, et al. *J Clin Periodontol*. 2003 Jan;30(1):26-34. http://www.ncbi.nlm.nih.gov/pubmed/12702108

668. **Comparison of the effectiveness of the conservative treatment of the periodontal pockets with or without the use of laser biostimulation. [**The use of laser therapy as the agent reinforcing conventional treatment of the periodontal diseases becomes more and more common. In the physiotherapy of the periodontal diseases the biostimulating, laser is eagerly used because of its action which accelerates the healing of wounds and also because of its antioedematous, anti-inflammatory and analgesic action. The aim of work was the evaluation of the influence of laser biostimulation on the change of the periodontological pockets depth after the routine conservative periodontological treatment with additional use of laser biostimulation and without it for two groups of pockets: above and below 5 mm. …In both studied groups statistically essential decrease of the evaluated parameters was obtained. Reinforcing the conventional treatment with laser biostimulation shortens its duration and leads to the elimination of pain faster than with the use of conservative treatment only. The changes of the PPD index among the successive examinations were statistically essentially higher in the therapy with the use of laser, especially in relation to deep pockets.] Kiernicka M, Owczarek B, et al. Ann Univ Mariae Curie Sklodowska [Med]. 2004;59(1):488-94.
http://www.unboundmedicine.com/medline/ebm/record/16146036/abstract/Comparison_of_the_effectiveness_of_the_conservative_treatment_of_the_periodontal_pockets_with_or_without_the_use_of_laser_biostimulation

669. **Conventional versus laser-assisted therapy of periimplantitis: a five-year comparative study.** [Between 1994 and 1999, 50 patients were treated with either profound parodontopathy (30) or periimplantitis (20). Half of each of the two groups of patients was treated conventionally, and the other half was treated with laser support. Before the operation, microbiological examinations were carried out, in addition to registering the clinical findings and taking x-rays. These procedures were repeated after the operation, and again after 6, 12, 24, 36, 48, and 60 months. The surgical part of therapy for each half of the patient groups included surface decontamination with diode laser light (1-watt output, maximum of 20 seconds) in addition to conventional procedures. The values of the laser-supported therapy were lower than those specified in the relevant literature. The relapse rate of the two diseases (13% for the periimplantitis and 23% for the parodontopathy group) after 5 years was lower than the comparative values of researched literature where decontamination was not included in the therapy. We think that integrating diode laser light decontamination in the approved treatment schemes for periimplantitis and parodontitis contributes considerably to the success of this therapy.] Bach G, Neckel C, et al. Implant Dent. 2000;9(3):247-51. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11307411&dopt=Abstract

670. **Diode Laser (980 nm) as Adjunct to Scaling and Root Planing.** [The aim of this study was to evaluate clinical efficacy of InGaAsP diode laser as adjunct to traditional scaling and root planing. *Conclusions:* Scaling and root planing in combination with laser produce moderate clinical improvement over traditional treatment.] Borrajo JLL, Varela LG, et al. *Photomedicine and Laser Surgery Vol. 22, No. 6 : 509 -512.*
http://www.liebertonline.com/doi/abs/10.1089/pho.2004.22.509?journalCode=pho

671. **Effects of CO2 Laser Treatment on Fibroblast Attachment to Root Surfaces. A Scanning Electron Microscopy Analysis.** [The group of specimens treated by laser and scaling showed the highest number of fibroblastic cells and a prevalence of well attached fibroblasts higher than control group and scaling/root planing group. The SEM observation didn't show any damages such as cracks and fissures of root surfaces treated by laser and scaling. These findings could suggest that CO_2 laser treatment could be considered as an adjunctive tool to detoxify and to condition the root surfaces in periodontal

treatment. CO_2 laser treatment in defocused, pulsed mode with a low power of 2W combined with mechanical instrumentation constitutes a useful tool to condition the root surface and increase fibroblast attachment to root surfaces.] Crespi, R, Barone, A, et al, Journal of Periodontology 2002; 73, No.11 pp 1308-1312. http://www.joponline.org/doi/abs/10.1902/jop.2002.73.11.1308?journalCode=jop

672. **Effects of Nd:YAG and CO2 laser treatment and ultrasonic scaling on periodontal pockets of chronic periodontitis patients.** [Our data suggest that Nd:YAG laser and ultrasonic scaling treatments showed significant improvements regarding the clinical parameters and subgingival microflora compared to the baseline, but no significant difference was observed between the 3 groups.] Miyazaki A, Yamaguchi T, et al. *J Periodontol. 2003 Feb;74(2):175-80.* http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12666705&dopt=Abstract

673. **Effects on oral soft tissue produced by a diode laser in vitro. [**This investigation determined incision characteristics and soft-tissue damage resulting from standardized incisions using a wide range of laser modes and parameters of a diode laser at 810 nm.The remarkable cutting ability and the tolerable damage zone clearly show that the diode laser is a very effective and, because of its excellent coagulation ability, useful alternative in soft-tissue surgery of the oral cavity.] Goharkhay K, Moritz A, et al. *Lasers in Surgery and Medicine*

674. **Five-year comparative study on conventional and laser-assisted therapy of periimplantitis and Periodontitis.** [Numerous groups have recommended the use of the diode laser to decontaminate infected root and implant surfaces. The aim of this study was to show the outcome after laser assisted and conventional therapy of periimplantitis and periodontitis administering approved treatment protocols. Between 1994 and 1999 a total of 50 patients with periimplantitis (20) and periodontitis (30) were treated in two groups each. Clinical, microbiological and radiographic evaluation was performed before and 6, 12, 24, 36, 48 and 60 months after treatment. In addition to the conventional treatment protocol, flap surgery, the tooth or implant surface was decontaminated with a 810 nm diode laser using 1 Watt output for 20 sec (CW mode). All accessible surfaces were decontaminated at the follow up dates. In the periimplantitis group recurrence of the marker bacteria was higher and faster over time for the conventionally operated patients. Also the clinical and radiographic reevaluation showed significantly better results. The laser group of the periodontitis patients also showed significantly better outcome in terms of clinical evaluation, microbiological counts, radiographic evaluation and tooth loss. In comparison to other long term studies our results for the conventional therapy were adequate, the laser assisted therapy brought up significantly better and reproducible results.] Bach G, Neckel CP. Lasers in Dentistry VI, John D. Featherstone; Peter Rechmann; Daniel Fried; Eds http://adsabs.harvard.edu/abs/2000SPIE.3910...12B

675. **Histoligic Evaluation of an Nd:YAG laser-assisted new attachment procedure in humans**. [There was no evidence of any adverse histologic changes around the LANAP specimens. These cases support the concept that LANAP can be associated with cementum-mediated new connective tissue attachment and apparent periodontal regerneration of diseased root surfaces in humans.] Yukna RA, Carr RL, et al. *The Int. journal of Periodontics and Restorative Dentistry*, Vol. 27, no. 6, 2007, p 576-587. http://www.lanap.com/pdf/YuknaArticle.pdf http://www.ncbi.nlm.nih.gov/pubmed/18092452

676. **Histological Evaluation of the Use of Diode Laser as an Adjunct to Traditional Periodontal Treatment. [**The present *in vivo* study showed that associated therapy was suitable for non-surgical periodontal treatment. The results suggest that the diode laser may be routinely used as an adjunct to scaling and root planing without damage to the cementum tissue.] Castro GL, Gallas M, et al. *Photomedicine and Laser Surgery, Vol. 24, No. 1 : 64 -68* http://www.liebertonline.com/doi/abs/10.1089/pho.2006.24.64?journalCode=pho

677. **In vivo and in vitro effects of an Er:YAG laser, a GaAlAs diode laser, and scaling and root planing on periodontally diseased root surfaces: A comparative histologic study.** [The present in vivo results showed that (i) ERL, combined with a fluorescent calculus detection system, provided a selective subgingival calculus removal on a level equivalent to that provided by SRP, and (ii) DL, using this power output, was unsuitable for calculus removal and altered the root surface in an undesirable manner. Lasers Surg. Med. 32:359-366, 2003. © 2003 Wiley-Liss, Inc.] Schwarz F, Sculean A, et al. Lasers in Surgery and Medicine Volume 32, Issue 5 , Pages 359 – 366. http://www3.interscience.wiley.com/cgi-bin/abstract/104532827/ABSTRACT

678. ***In vivo* killing of *Staphylococcus aureus* using a light-activated antimicrobial agent**. [Background: The widespread problem of antibiotic resistance in pathogens such as *Staphylococcus aureus* has prompted the search for new antimicrobial approaches. In this study we report for the first time the use of a light-activated antimicrobial agent, methylene blue, to kill an epidemic methicillin-resistant *Staphylococcus aureus* (EMRSA-16) strain in two mouse wound models. Results: Following irradiation of wounds with 360 J/cm^2 of laser light (670 nm) in the presence of 100 μg/ml of methylene blue, a 25-fold reduction in the number of viable EMRSA was seen. This was independent of the increase in temperature of the wounds associated with the treatment. Histological examination of the wounds revealed no difference between the photodynamic therapy (PDT)-treated wounds and the untreated wounds, all of which showed the same degree of inflammatory infiltration at 24 hours. Conclusion: The results of this study demonstrate that PDT is effective at reducing the total number of viable EMRSA in a wound. This approach has promise as a means of treating wound infections caused by antibiotic-resistant microbes as well as for the elimination of such organisms from carriage sites.] Zolfaghari PS, Packer S, et al. *BMC Microbiol.* 2009; 9: 27. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2642833/

679. **Killing of cariogenic bacteria by light from a gallium aluminium arsenide diode laser. [**Suspensions of *Streptococcus mutans, S. sobrinus, Lactobacillus casei* and *Actinomyces viscosus* were exposed to light from a gallium aluminium arsenide ‹**laser**› in the presence of aluminium disulphonated phthalocyanine and the numbers of survivors determined. Exposure to the ‹**laser**› light in the absence of the dye, or the dye in the absence of the ‹**laser**› light, had no significant effect on the

viability of the organisms. However, a light-dose-related decrease in the viable count of all four target organisms was found on exposure to the **laser** light in the presence of the dye. The kills attributable to lethal photosensitization amounted to approximately 10^6 CFU in the case of each organism. As appreciable kills were achieved within clinically convenient exposure times (30–90 s), these results imply that lethal photosensitization may be a useful technique for eliminating bacteria from carious lesions prior to restoration.] Burns T, Wilson, et al. *Journal of Dentistry Volume 22, Issue 5, October 1994, Pages 273-278.* http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6T86-4C06C37-66&_user=10&_coverDate=10%2F31%2F1994&_alid=569662287&_rdoc=1&_fmt=summary&_orig=search&_cdi=5078&_sort=d&_docanchor=&view=c&_ct=1&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=a9850ab28022bb43a40f8420124f5e93

680. **Laser-assisted new attachment procedure in private practice.** [Three private dental practices conducted a retrospective analysis of patients receiving the laser-assisted new attachment procedure (LANAP). Retrospective results were compared to clinical trail data from the Univeristy of Texas Health Sciences Center in San Antonio to determine if outcomes from a controlled clinical trial can be duplicated in private practice. Results also are compared with published results of other surgical and non surgical therapies for inflammatory periodontal disease.] Harris DM, Gregg RH, et al. *General Dentistry*, September-October 2004, Vol 52, no. 5, http://www.lanap.com/pdf/MDT-GD-Sept-Oct-2004.pdf
681. **Laser Curretage when combined with SRP gives Superior results to SRP alone when measured by probing scores.** [Laser assisted periodontal treatment when combined with SRP gives better healing and less patient discomfort than with SRP alone]. Sulcular Debridement with Pulsed Nd: YAG *Lasers in Dentistry* January 2002. http://www.millenniumdental.com/research/jan-02.html
682. **Lasers Demonstrate the Power to Heal Without Scarring.** ScientificAmerican.com, May 5, 2010. http://www.scientificamerican.com/article.cfm?id=photochemical-tissue-bond&sc=CAT_TECH_20100505
683. **Effects on oral soft tissue produced by a diode laser in vitro.** [This investigation determined incision characteristics and soft-tissue damage resulting from standardized incisions using a wide range of laser modes and parameters of a diode laser at 810 nm. Histologic examinations were performed to verify vertical and horizontal tissue damage as well as incision depth and width. Incision depth and width correlated strongly with average powers, but not with laser parameters or the used tips. No laser damage was visible to the naked eye in the bone underlying the incisions in the range between 0.5-4.5 W. The remarkable cutting ability and the tolerable damage zone clearly show that the diode laser is a very effective and, because of its excellent coagulation ability, useful alternative in soft-tissue surgery of the oral cavity.] Koharkhay K, Moritz A, et al. *Lasers Surg. Med.* 25:401-406, 1999. http://www3.interscience.wiley.com/cgi-bin/abstract/68502094/ABSTRACT
684. **Microbial reduction in periodontal pockets under exposition of a medium power diode laser: an experimental study in rats.** [This work evaluates the application of a 810 nm diode laser operating in the range of 400-1,200 mW for bacterial reduction at periodontal treatment. The aim of this study is to examine the immediate effect of the diode medium power laser in reducing the bacterial concentration at periodontal pockets induced in Wistar rats. …CONCLUSIONS: Our results indicate that this laser can constitute an alternative device to traditional infrared systems for bacterial reduction, with some advantage when economical and practical standpoints are considered.] Fontana CR, Kurachi C, et al. Lasers Surg Med. 2004;35(4):263-8. http://www.ncbi.nlm.nih.gov/sites/entrez?cmd=Retrieve&db=PubMed&list_uids=15493030&dopt=Abstract
685. **Nd:YAG Assisted Periodontal Curettage to Prevent Bacteremia Before Cardiovascular Surgery.** [Laser decontamination is more effective for reducing the occurrence of bacteremia than alternative methods.] Dentistry Today, March 1998. Nd: YAG - Assisted Periodontal Curettage to Prevent Bacteremia Before Cardiovascular Surgery".
686. **Laser de-epithelialization for enhanced guided tissue regeneration. A paradigm shift?** Rossmann JA; Israel M. (Department of Periodontics, Baylor College of Dentistry, Texas A&M University System Health Science Center at Dallas. *Dent Clin North Am 2000 Oct;44(4):793-809* http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11048272&dopt=Abstract
687. **Periodontal tissue regeneration in beagle dogs after laser therapy.** [CO2 laser treatment of class III furcation induced formation of new periodontal ligament, cementum and bone.] Crespi R, Covani U, et al. Hospital S. Raffaele, Milan, Italy. *Lasers Surg Med* 1997;21(4):395-402. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9328987&dopt=Abstract
688. **The antibacterial effect of photodynamic therapy in dental plaque-derived biofilms.** [BACKGROUND AND OBJECTIVE: Photodynamic therapy has been advocated as an alternative to antimicrobial agents to suppress subgingival species and to treat periodontitis. Bacteria located within dense biofilms, such as those encountered in dental plaque, have been found to be relatively resistant to antimicrobial therapy. In the present study, we investigated the ability of photodynamic therapy to reduce the number of bacteria in biofilms by comparing the photodynamic effects of methylene blue on human dental plaque microorganisms in the planktonic phase and in biofilms. MATERIAL AND METHODS: Dental plaque samples were obtained from 10 subjects with chronic periodontitis. Suspensions of plaque microorganisms from five subjects were sensitized with methylene blue (25 microg/mL) for 5 min then exposed to red light. Multispecies microbial biofilms developed from the same plaque samples were also exposed to methylene blue (25 microg/mL) and the same light conditions as their planktonic counterparts. In a second set of experiments, biofilms were developed with plaque bacteria from five subjects, sensitized with 25 or 50 microg/mL of methylene blue and then exposed to red light. After photodynamic therapy, survival fractions were calculated by counting the number of colony-forming units. RESULTS: Photodynamic therapy killed approximately 63% of bacteria present in suspension. By contrast, in biofilms, photodynamic therapy had much less of an effect on the viability of bacteria (32% maximal killing). CONCLUSION: Oral bacteria in

biofilms are affected less by photodynamic therapy than bacteria in the planktonic phase. The antibacterial effect of photodynamic therapy is reduced in biofilm bacteria but not to the same degree as has been reported for treatment with antibiotics under similar conditions.] Fontana CR, Abernethy AD, et al. *J Periodontal Res.* 2009 Dec;44(6):751-9. http://www.ncbi.nlm.nih.gov/pubmed/19602126

689. **The carbon dioxide laser as an aid in apicoectomy: an in vitro study.** [CO2 laser treatment optimally prepares the tooth for final intraoperative filling because of sealing of the dentinal tubules, the resultant elimination of niches for bacteria and the sterilizing effect of the laser.] Moritz A, Gutknecht N, et al. *J Clin Laser Med Surg* 1997;15(4):185-8.
690. **The effects of a pulsed Nd:YAG laser on subgingival bacterial flora and on cementum: an in vivo study. [**The effects of laser on root surfaces were assessed by SEM examination and the sample consisted of 13 teeth from 5 different patients. Four sets of 3 teeth each were treated with Nd:YAG laser using 0.8, 1.0, 1.2, and 1.5 W, respectively. One tooth was just scaled and not treated with laser to serve as a control. Microbiological analysis of Group A samples indicated posttreatment reduction in levels of all 4 bacterial types tested compared to pretreatment levels and Group B controls. SEM examination of the specimens treated with Nd:YAG laser at different levels exhibited different features of root surface alterations.] Ben Hatit Y, Blum R, et al. *J Clin Laser Med Surg. 1996 Jun;14(3):137-43.* http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9484091&dopt=Citation
691. **The Ins and Outs of Periodontal Antimicrobial Therapy. [**A multifaceted antimicrobial approach is necessary for the successful management of destructive periodontal disease. Effective antimicrobial periodontal therapy aims to overwhelm periodontal pathogens with aggressive initial therapy and prevent previously suppressed pathogens from rising up anew through daily oral hygiene measures and frequent professional cleaning. Current antimicrobial periodontal therapy employs mechanical debridement performed with and without surgery, antibiotics, and antiseptics. Subgingival irrigation with povidone-iodine at the dentist's office and subgingival irrigation with dilute sodium hypochlorite for home-care constitute effective, safe, and affordable periodontal antimicrobial therapy. This article describes theoretical and practical guidelines for implementing rational and cost-effective antimicrobial principles in the management of periodontal disease.] Jorgensen MG,Slots J. *Journal of CA Dental Assoc, April 2002.* http://www.cda.org/library/cda_member/pubs/journal/jour0402/antimicrobials.html
692. **The CO2 laser as an aid in direct pulp capping.** [The CO2 laser seems to be a valuable aid in direct pulp capping.] Moritz A, Schoop U, et al. *J Endod* 1998 Apr;24(4):248-51. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9641128&dopt=Abstract
693. **Treatment of periodontal pockets with a diode laser. [**The aim of this study is to examine the long-term effect of diode laser therapy on periodontal pockets with regard to its bactericidal abilities and the improvement of periodontal condition. RESULTS: The bacterial reduction with diode laser therapy was significantly better than in the control group. The index of bleeding on probing improved in 96.9% in the laser-group, whereas only 66.7% in the control group. Pocket depths could be more reduced in the laser group than in the control group. CONCLUSION: The diode laser reveals a bactericidal effect and helps to reduce inflammation in the periodontal pockets in addition to scaling. The diode laser therapy, in combination with scaling, supports healing of the periodontal pockets through eliminating bacteria.] Moritz A, Schoop U, et al. *Lasers Surg Med. 1998;22(5):302-11.* *http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9671997&dopt=Abstract*

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694. **An unusual autopsy case of pyogenic liver abscess caused by periodontal bacteria.** [yogenic liver abscess (PLA) formation is thought to originate from the transmission of infection via three major routes including the biliary tract, portal vein and hepatic artery. However, about 50% of PLA cases are considered to be cryptogenic. Here we report an unusual autopsy case of PLA associated with periodontopathic bacterial infection. A 59-year-old female suddenly developed cardiopulmonary arrest and died. Despite macroscopic and microscopic examinations, the infectious routes and source of infection were unidentified, and the case appeared to be cryptogenic. Since this patient had suffered severe periodontitis for a long period of time, we investigated the involvement of periodontal infection in PLA formation by performing immunohistochemical analyses. We identified several periodontopathic bacterial species in the PLA of this patient, including Fusobacterium nucleatum, Treponema denticola, Prevotella intermedia and Porphyromonas gingivalis. Thus, we demonstrate here that periodontal infection is a potential source of infection in the formation of PLA.] Ohyama H, Nakasho K, et al. *Jpn J Infect Dis.* 2009 Sep;62(5):381-3. http://www.ncbi.nlm.nih.gov/pubmed/19762989
695. **An unrecognized etiology for pyogenic hepatic abscesses in normal hosts: dental disease**. [Cryptogenic pyogenic hepatic abscesses are a diagnosis of exclusion. We have identified two patients with severe dental disease at the time of the diagnosis of their liver abscess. In both cases, oral flora was cultured from the abscess. Unlike a previous report, both patients were immunocompetent. When compared with a group of patients with liver abscesses and diverticulitis, two differences were found. In contrast to the single abscesses seen in 10 of 10 patients with diverticulitis, the patients with dental disease had multiple abscesses ($p < 0.02$). In addition, Fusobacterium nucleatum was cultured from both dental disease associated abscesses but only one of the diverticulitis associated liver abscesses ($p < 0.05$). If a liver abscess is thought to be cryptogenic, a thorough dental exam is recommended.] Crippin JS, Wang KK. *Am J Gastroenterol.* 1992 Dec;87(12):1740-3. http://www.ncbi.nlm.nih.gov/pubmed/1449134

696. **Colonization of Dental Plaques A Reservoir of Respiratory Pathogens for Hospital-Acquired Pneumonia in Institutionalized Elders.** [*Study objectives:* Poor dental hygiene has been linked to respiratory pathogen colonization in residents of long-term care facilities. We sought to investigate the association between dental plaque (DP) colonization and lower respiratory tract infection in hospitalized institutionalized elders using molecular genotyping. *Methods:* We assessed the dental status of 49 critically ill residents of long-term care facilities requiring intensive care treatment. Plaque index scores and quantitative cultures of DPs were obtained on ICU admission. Protected BAL (PBAL) was performed on 14 patients who developed hospital-acquired pneumonia (HAP). Respiratory pathogens recovered from the PBAL fluid were compared genetically to those isolated from DPs by pulsed-field gel electrophoresis. *Measurements and results:* Twenty-eight subjects (57%) had colonization of their DPs with aerobic pathogens. *Staphylococcus aureus* (45%) accounted for the majority of the isolates, followed by enteric Gram-negative bacilli (42%) and *Pseudomonas aeruginosa* (13%). The etiology of HAP was documented in 10 patients. Of the 13 isolates recovered from PBAL fluid, nine respiratory pathogens matched genetically those recovered from the corresponding DPs of eight patients. *Conclusions:* These findings suggest that aerobic respiratory pathogens colonizing DPs may be an important reservoir for HAP in institutionalized elders. Future studies are needed to delineate whether daily oral hygiene in hospitalized elderly would reduce the risk of nosocomial pneumonia in this frail population.] El-Solh AA, Pietrantoni C, et al. *Chest*, vol. 126, no 5, pp 1575-1582, nov 2004. http://chestjournal.chestpubs.org/content/126/5/1575.full

697. **Divergent Profiles of Oral Microbiota are Associated with Risk of Healthcare-Associated Pneumonia in Humans.** [Background: Healthcare associated pneumonia (HCAP) is a growing public health problem. Strategies to identify high risk patients for HCAP remain problematic, hampering effective prevention efforts. Impaired oral hygiene is a known modifiable risk factor for HCAP, but the precise alterations in oral microbiota associated with pneumonia risk are unknown. Our goal was to determine if there was an association between the oral microbial profile and subsequent development of pneumonia. Methods:We used 16S rRNA gene pyrosequencing to compare the oral microbial profiles of healthy community dwelling adults with those at risk for HCAP (i.e., nursing home residents, and mechanically ventilated ICU patients). A total of 37 subjects were prospectively followed for 1 month for pneumonia development. Results: Streptococcaceae represented the dominant taxa within the oral cavity, but the average proportion differed across the three clinical settings: community dwellers (0.65), nursing home residents (0.43), and mechanically ventilated ICU patients (0.33; p=0.02 compared to community dwellers). Furthermore, ICU subjects who subsequently developed pneumonia had a significantly smaller average proportion of oral Streptococcaceae (0.07) at baseline compared to the ICU subjects who did not develop pneumonia (0.49; p=0.02). The mean weighted UniFrac distance, a measure of bacterial community composition, among ICU subjects who developed pneumonia (0.36) was significantly different than the mean weighted UniFrac distance among ICU subjects who did not develop pneumonia (0.24, p=0.005). Principal Coordinate Analysis of the weighted UniFrac distances confirmed a distinct divergence of the ICU subjects who developed pneumonia from the cluster of ICU subjects who did not develop pneumonia. Conclusion: Oral microbial profiles differ in community dwelling adults compared to those in healthcare settings at high risk for pneumonia. Mechanically ventilated ICU subjects who subsequently developed pneumonia had a distinct divergence of their oral microbial profiles compared to ICU subjects who did not develop pneumonia. Pyrosequencing of oral microbiota may identify patients at high risk of HCAP, and suggest innovative ways for targeted prevention.] Joshi S, Bruce C, et al. IDSA Annual Meeting Boston, *Oct 20-23, 2011*. **Session**: Oral Abstract Session: Microbiome and Susceptibility to Infection http://idsa.confex.com/idsa/2011/webprogram/Paper31577.html

698. **Involvement of Periodontopathic Anaerobes in Aspiration Pneumonia.** [Increasing evidence has linked the anaerobic bacteria forming periodontopathic biofilms with aspiration pneumonia in elderly persons.] Okuda K et al, *J Periodontology* 2005, Vol. 76, No. 11-s, pp2154-2160. http://www.joponline.org/doi/abs/10.1902/jop.2005.76.11-S.2154

699. **Respiratory Diseases.** [Scientists believe that through the aspiration process, bacteria can cause frequent bouts of infection in patients with COPD.] http://www.perio.org/consumer/mbc.respiratory.htm

700. **Oral Decontamination with Chlorhexidine Reduces the Incidence of Ventilator-associated Pneumonia. *[Rationale:*** Ventilator-associated pneumonia (VAP) is the most frequently occurring nosocomial infection associated with increased morbidity and mortality. Although oral decontamination with antibiotics reduces incidences of VAP, it is not recommended because of potential selection of antibiotic-resistant pathogens. We hypothesized that oral decontamination with either chlorhexidine (CHX, 2%) or CHX/colistin (CHX/COL, 2%/2%) would reduce and postpone development of VAP, and oral and endotracheal colonization. *Conclusions:* Topical oral decontamination with CHX or CHX/COL reduces the incidence of VAP.] Koeman M, van der Ven, AJAM, et al. *American Journal of Respiratory and Critical Care Medicine*, Volume 173. pp. 1348-1355, (2006) *http://ajrccm.atsjournals.org/cgi/content/abstract/173/12/1348*

701. **Oral health and mortality risk from pneumonia in the elderly. [**Although poor oral health influences the occurrence of pulmonary infection in elderly people, it is unclear how the degree of oral health is linked to mortality from pulmonary infection. Therefore, we evaluated the relationship between oral health and four-year mortality from pneumonia in an elderly Japanese population. The study population consisted of 697 (277 males, 420 females) of the 1282 individuals who were 80 years old in 1997. Data on oral and systemic health were obtained by means of questionnaires, physical examinations, and laboratory blood tests. One hundred eight of the study persons died between 1998 and 2002. Of these, 22 deaths were due to pneumonia. The adjusted mortality due to pneumonia was 3.9 times higher in persons with 10 or more teeth with a probing

depth exceeding 4 mm (periodontal pocket) than in those without periodontal pockets. Therefore, the increase in teeth with periodontal pockets in the elderly may be associated with increased mortality from pneumonia.[Awano S, Ansai T, et al. *J Dent Res.* 2008;87(4):334-339. http://www.ncbi.nlm.nih.gov/pubmed/18362314

702. **Pneumonia in nonambulatory patients, The role of oral bacteria and oral hygiene. [**Considerable evidence exists to support a relationship between poor oral health, the oral microflora and bacterial pneumonia, especially ventilator-associated pneumonia in institutionalized patients. Teeth or dentures have nonshedding surfaces on which oral biofilms (that is, dental plaque) form that are susceptible to colonization by respiratory pathogens. Subsequent aspiration of respiratory pathogens shed from oral biofilms into the lower airway increases the risk of developing a lung infection. In addition, patients may aspirate inflammatory products from inflamed periodontal tissues into the lower airway, contributing to lung insult. A number of studies have shown that the mouth can be colonized by respiratory pathogens and serve as a reservoir for these organisms. Other studies have demonstrated that oral interventions aimed at controlling or reducing oral biofilms can reduce the risk of pneumonia in high-risk populations. Taken together, the evidence is substantial that improved oral hygiene may prevent pneumonia in vulnerable patients.] Scannapieco FA. J Am Dent Assoc, Vol 137, No suppl_2, 21S-25S, http://jada.ada.org/cgi/content/abstract/137/suppl_2/21S

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703. **Cyclosporin-induced gingival overgrowth: correlation with dental plaque scores, gingivitis scores, and cyclosporin levels in serum and saliva.** [Gingival overgrowth, dental plaque, and gingivitis were assessed by means of standardized semiquantitative indices in thirty renal transplant patients undergoing immunosuppression with cyclosporin-A (Cy-A). Radioimmunoassay techniques were used to determine Cy-A in serum samples and in parotid, submandibular, and whole saliva samples from each patient. A significant positive correlation was found between gingival overgrowth scores and both dental plaque and gingivitis scores. A significant positive correlation was found between whole-saliva Cy-A and both plaque and gingival overgrowth scores. No such correlation was found when parotid Cy-A or submandibular Cy-A was considered. This was attributed to differences in saliva-collection methods, and a possible role of dental plaque as a local reservoir of Cy-A is proposed.] McGaw T, Lam S, et al. *Oral Surg Oral Med Oral Pathol*. 1987 Sep;64(3):293-7. http://www.ncbi.nlm.nih.gov/pubmed/3477745

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704. **“Red complex" (Bacteroides forsythus, Porphyromonas gingivalis, and Treponema denticola) in endodontic infections: A molecular approach1.** [Objective: The red complex, composed of Bacteroides forsythus, Porphyromonas gingivalis, and Treponema denticola, is implicated in severe forms of periodontal diseases. The purpose of this study was to assess the occurrence of the red complex in root canal infections through the use of a sensitive technique the 16S rDNA directed polymerase chain reaction (PCR). Study Design: Samples were obtained from 50 necrotic pulps with periradicular pathosis. Ten cases were diagnosed as acute periradicular abscesses. DNA was extracted from the samples and analyzed with a PCR-based identification assay. Results: At least 1 member of the red complex was found in 33 of 50 cases. T denticola, P gingivalis, and B forsythus were detected in 44%, 30%, and 26% of the cases, respectively. The red complex was found in 4 of 50 cases. No particular signs or symptoms were associated with the presence of these bacterial species. Conclusions: Despite what is indicated in reports with respect to marginal periodontitis, red complex bacteria[mdash]either singularly or collectively[mdash]was not associated with any particular pattern of clinical symptoms. However, because the bacterial species from the red complex are recognized oral pathogens, their occurrence in root canal infections suggests that they may play a role in the pathogenesis of periradicular diseases.] Rocas I, Siqueira J, et al. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology & Endodontics*, Volume 91, Issue 4, Pages 468-471. http://linkinghub.elsevier.com/retrieve/pii/S107921040159887X

705. “**Red complex" (Bacteroides forsythus, Porphyromonas gingivalis, and Treponema denticola) in endodontic infections: a molecular approach.** [OBJECTIVE: The "red complex," composed of Bacteroides forsythus, Porphyromonas gingivalis, and Treponema denticola, is implicated in severe forms of periodontal diseases. The purpose of this study was to assess the occurrence of the red complex in root canal infections through the use of a sensitive technique-the 16S rDNA-directed polymerase chain reaction (PCR). STUDY DESIGN: Samples were obtained from 50 necrotic pulps with periradicular pathosis. Ten cases were diagnosed as acute periradicular abscesses. DNA was extracted from the samples and analyzed with a PCR-based identification assay. RESULTS: At least 1 member of the red complex was found in 33 of 50 cases. T denticola, P gingivalis, and B forsythus were detected in 44%, 30%, and 26% of the cases, respectively. The red complex was found in 4 of 50 cases. No particular signs or symptoms were associated with the presence of these bacterial species. CONCLUSIONS: Despite what is indicated in reports with respect to marginal periodontitis, red complex bacteria-either singularly or collectively-was not associated with any particular pattern of clinical symptoms. However, because the bacterial species from the red complex are recognized oral pathogens, their occurrence in root canal infections suggests that they may play a role in the pathogenesis of periradicular diseases.] Rocas IN, Sigueira JF Jr, et.al. *Oral Surg Oral Med Oral*

Pathol Oral Radiol Endod. 2001 Apr;91(4):468-71.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11312465&dopt=Abstract

706. **A 52-kDa leucyl aminopeptidase from treponema denticola is a cysteinylglycinase that mediates the second step of glutathione metabolism. [**The metabolism of glutathione by the periodontal pathogen Treponema denticola produces hydrogen sulfide, which may play a role in the host tissue destruction seen in periodontitis. H2S production in this organism has been proposed to occur via a three enzyme pathway, gamma-glutamyltransferase, cysteinylglycinase (CGase), and cystalysin. In this study, we describe the purification and characterization of T. denticola CGase. Standard approaches were used to purify a 52-kDa CGase activity from T. denticola, and high pressure liquid chromatography electrospray ionization tandem mass spectrometry analysis of this molecule showed that it matches the amino acid sequence of a predicted 52-kDa protein in the T. denticola genome data base. A recombinant version of this protein was overexpressed in and purified from Escherichia coli and shown to catalyze the hydrolysis of cysteinylglycine (Cys-Gly) with the same kinetics as the native protein. Surprisingly, because sequence homology indicates that this protein is a member of a family of metalloproteases called M17 leucine aminopeptidases, the preferred substrate for the T. denticola protein is Cys-Gly (k cat/Km of 8.2 microm(-1) min(-1)) not l-Leu-p-NA (k cat/Km of 1.1 microm(-1) min(-1)). The activity of CGase for Cys-Gly is optimum at pH 7.3 and is enhanced by Mn2+, Co2+, or Mg2+ but not by Zn2+ or Ca2+. Importantly, in combination with the two other previously purified T. denticola enzymes, gamma-glutamyltransferase and cystalysin, CGase mediates the in vitro degradation of glutathione into the expected end products, including H2S. These results prove that T. denticola contains the entire three-step pathway to produce H2S from glutathione, which may be important for pathogenesis.] Chu L, Lai Y, et al. *J Biol Chem.* 2008 Jul 11;283(28):19351-8. Epub 2008 May 15. http://www.ncbi.nlm.nih.gov/pubmed/18482986

707. **A new understanding of these microbial communities is driving a revolution that may transform the science of microbiology.** [The Centers for Disease Control and Prevention estimates that up to 70 percent of the human bacterial infections in the Western world are caused by biofilms. This includes diseases such as prostatitis and kidney infections, as well as illnesses associated with implanted medical devices such as artificial joints and catheters and the dental diseases—both tooth decay and gum disease—that arise from dental plaque, a biofilm. In the lungs of cystic fibrosis patients, *Pseudomonas aeruginosa* frequently forms biofilms that cause potentially lethal pneumonias. There is a long list of biofilm-related ailments, and many scientists believe the list will continue to grow as we learn more about the function of these microbial structures.] Harrison J, Turner R, et al. American Scientist. Nov-Dec, 2005.
http://www.americanscientist.org/issues/feature/biofilms/3

708. **A zymographic assay for detection of hyaluronidase activity on polyacrylamide gels and its application to enzymatic activity found in bacteria**. [A zymographic assay for the determination of hyaluronidase activity in cell-free extracts on native polyacrylamide gels has been developed. In this assay an agarose replica of the polyacrylamide gel which contains hyaluronic acid and bovine serum albumin (BSA) was used. After an incubation at 37°C to allow transfer and development of enzymatic activity, the hyaluronic acid and BSA were precipitated in the agarose gel with 2 **M**acetic acid. Areas of enzymatic activity appeared as clear zones in the agarose replica. The assay was sensitive and was used to demonstrate hyaluronidase activity in cell-free extracts from a number of bacterial and mammalian species.] Steiner B, Cruce D. *Analytical Biochemistry* Volume 200, Issue 2, 1 February 1992, Pages 405-410 .
http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6W9V-4DP5KH8-15&_user=10&_rdoc=1&_fmt=&_orig=search&_sort=d&_docanchor=&view=c&_searchStrId=1116551817&_rerunOrigin=google&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=8f11e3618282a89557f98ab45069a498

709. **Aggregation of group A streptococci by human saliva and effect of saliva on streptococcal adherence to host cells.** [The aggregation of group A streptococci by whole, stimulated human saliva (WHS) and the effect of saliva on streptococcal adherence to host cells was investigated. WHS samples from 11 individuals were found to aggregate both M+ and M- group A streptococci to various degrees. The aggregating activity was sensitive to heat, EDTA, EGTA [ethylene glycol-bis(beta-aminoethyl ether)-N,N,N',N'-tetraacetic acid], sodium dodecyl sulfate, and lipoteichoic acid. None of the simple sugars tested, mercaptoethanol, albumin, or nonionic detergents had any effect on aggregation. The aggregating activity of EDTA-treated saliva was restored by 0.1 mM Ca2+ and 1.0 mM Mn2+ but not by up to 5 mM Mg2+. Only streptococci from the stationary phase were aggregated. Hyaluronidase treatment of streptococci from the exponential phase of growth restored their ability to be aggregated, suggesting that the hyaluronic acid capsule interferes with agglutination. Adsorption of WHS by one strain of Streptococcus pyogenes removed aggregating activity for other strains of S. pyogenes and Streptococcus sanguis but not agglutinins for Escherichia coli, suggesting that the agglutinin is specific for certain gram-positive bacteria. Molecular sieve chromatography of WHS and identification of streptococcus-binding components of saliva suggest that either a glycoprotein of approximately 360 kDa or a mucin of saliva of greater than 1,000 kDa mediates aggregation of streptococci. WHS also inhibited adherence of S. pyogenes to buccal epithelial cells.] Courtney HS, Hasty DL. *Infect Immun*. 1991 May; 59(5): 1661-1666. http://iai.asm.org/cgi/content/abstract/59/5/1661

710. **Anaerobic periodontal infections as risk factors for medical diseases.** [Advanced forms of periodontal disease are associated with the overgrowth of a limited number of gram-negative anaerobic species in plaques found in periodontal pockets. Double-blind clinical trials of metronidazole and doxycycline, combined with debriding of the tooth surfaces, have significantly reduced the need for periodontal surgery. Epidemiologic studies have indicated that untreated periodontal disease could be a risk factor for preterm delivery of low birth weight infants, coronary heart disease, and cerebral vascular accidents. This is because gram-negative anaerobic species implicated in periodontal disease, *eg*, *Bacteroides forsythus, Porphyromonas gingivalis*, and *Treponema denticola*, could introduce lipopolysaccharides, heat-shock proteins, and

proinflammatory cytokines into the blood stream. If periodontal disease is a risk factor for cardiovascular disease, then it is a modifiable risk factor, as periodontal disease is treatable.] Loesche WJ. *Current Infectious Disease Reports, Vol1, Number 1 pp 33-38, Feb, 1999.* *http://www.springerlink.com/content/e34377m011177524/*

711. **Antibiotic resistance of bacteria in biofilms.** [Bacteria that adhere to implanted medical devices or damaged tissue can encase themselves in a hydrated matrix of polysaccharide and protein, and form a slimy layer known as a biofilm. Antibiotic resistance of bacteria in the biofilm mode of growth contributes to the chronicity of infections such as those associated with implanted medical devices. The mechanisms of resistance in biofilms are different from the now familiar plasmids, transposons, and mutations that confer innate resistance to individual bacterial cells. In biofilms, resistance seems to depend on multicellular strategies. We summarise the features of biofilm infections, review emerging mechanisms of resistance, and discuss potential therapies.] Stewart PS, Costerton JW. *Lancet.* 2001 Jul 14;358(9276):135-8. http://www.ncbi.nlm.nih.gov/pubmed/11463434
712. **Antimicrobial and antibiofilm activity of quorum sensing peptides and Peptide analogues against oral biofilm bacteria**. [Widespread antibiotic resistance is a major incentive for the investigation of novel ways to treat or prevent infections. Much effort has been put into the discovery of peptides in nature accompanied by manipulation of natural peptides to improve activity and decrease toxicity. The ever increasing knowledge about bacteria and the discovery of quorum sensing have presented itself as another mechanism to disrupt the infection process. We have shown that the natural quorum sensing (QS) peptide, competence-stimulating peptide (CSP), used by the caries causing bacteria Streptococcus mutans when used in higher than normally present concentrations can actually contribute to cell death in S. mutans. Using an analogue of this quorum sensing peptide (KBI-3221), we have shown it to be beneficial at decreasing biofilm of various Streptococcus species. This chapter looks at a number of assay methods to test the inhibitory effects of quorum sensing peptides and their analogues on the growth and biofilm formation of oral bacteria.] LoVetri K, Madhyastha S. Methods Mol Biol. 2010;618:383-92.h http://www.ncbi.nlm.nih.gov/pubmed/20094877
713. **Atherogenic Responses in Endothelial Cells Following Infection with Porphyromonas gingivalis.** [Objectives: Recent studies have suggested that chronic infections increase athrogenesis. Systemic responses to periodontitis have been linked to interspecies differences in bacterial virulence factors. Specifically, the presence of fimbriae on *Porphyromonas gingivalis* has been suggested to alter the organism's ability to adhere, invade, and activate host cells. This study defines the atherogenic ability of invasive *P. gingivalis* infection mediated by fimbriae. Methods: The *P. gingivalis* gene encoding the minor fimbriae (*mfa1*) was cloned and disrupted by *tetQ* gene insertion. The recombinant plasmids were transferred into *P.gingivalis* strains, 381 and DPG3 (*fimA*-) to generate 381MF1 (*mfa1*-) and DPGMFB (double fimbrial knock out), respectively. Primary human aortic endothelial cells (HAEC) were infected with wild-type bacteria, fimbrial-deficient mutants and purified native fimbrial proteins. Pro-inflammatory molecules previously shown to correlate with the formation of atherosclerosis were determined by RT-PCR, ELISA and/or FACS. Results: Invasive *P. gingivalis* strains, 381 and 381MF1, elicited strong induction of IL-8 and MCP-1 at 1 and 6 hours post-infection, respectively. These chemokines were not induced by the non-invasive strains DPG3 and DPGMFB at 6 hours, but minor responses were observed at 24 hours. IL-8 and MCP-1 were also induced by native preparations of major and minor fimbriae. Competition assays with mutant strains and purified fimbriae resulted in an attenuated chemokine response by HAEC. The two invasive strains additionaly induced production of adhesion molecules, ICAM-1, VCAM-1, and P-/E-selectins at 6 hours. Moreover, inhibition of invasion by cytochalasin D resulted in decreased expression of chemokines and adhesion molecules. Conclusions: These results demonstrate that the active, major fimbriae-mediated process of *P. gingivalis* invasion of endothelial cells induces inflammatory gene expression and protein production. This data suggests a novel and differential role of major and minor fimbriae as virulence factors in this pathogenic process which induce potentially pro-atherosclerotic changes in HAEC.] c http://iadr.confex.com/iadr/2004Hawaii/techprogram/abstract_47376.htm
714. **Bacterial Small-Molecule Signaling Pathways.** [Bacteria use diverse small molecules for extra- and intracellular signaling. They scan small-molecule mixtures to access information about both their extracellular environment and their intracellular physiological status, and based on this information, they continuously interpret their circumstances and react rapidly to changes. Bacteria must integrate extra- and intracellular signaling information to mount appropriate responses to changes in their environment. We review recent research into two fundamental bacterial small-molecule signaling pathways: extracellular quorum-sensing signaling and intracellular cyclic dinucleotide signaling. We suggest how these two pathways may converge to control complex processes including multicellularity, biofilm formation, and virulence. We also outline new questions that have arisen from recent studies in these fields.] Camilli A, Bassler BL. *Science* 24, Feb. 2006:Vol 311. No. 5764, pp. 1113-1116. http://www.sciencemag.org/cgi/content/abstract/311/5764/1113
715. **Biofilm Basics** [The road to understanding dental biofilms has been so long and winding because bacteria behave differently when examined in a laboratory setting than they do in nature. The advancement of certain experimental tools and methods has further opened the study of biofilms in their natural environment. For example, digital imaging devices, such as confocal scanning laser microscopy and the use of various nontoxic fluorescent probes, allow us to observe fully hydrated and viable bacterial biofilms in their native state.[4] Identifying individual species or molecules that form a biofilm community is now possible.[5] In the future, we will be able to obtain a detailed microbial or molecular anatomy of naturally occurring biofilms.] Casey C, Sandra R. I*Dimensions of Dental Hygiene*, http://www.dimensionsofdentalhygiene.com/ddhright.aspx?id=59
716. **Biofilm Removal with a Dental Water Jet.** [Objective:The objective of this study was to evaluate the effect of a dental water jet on plaque biofilm removal using scanning electron microscopy (SEM). Methodology: Eight periodontally involved teeth were extracted. Ten slices were cut from four teeth and were inoculated with saliva and left for four days to further

grow plaque biofilm (ex vivo). Four slices were treated with the standard jet tip, four slices were treated with the orthodontic jet tip, and two slices were used as controls. The remaining 4 teeth were treated with the orthodontic jet tip to evaluate the removal of calcified plaque biofilm (in vivo). All teeth were treated using medium pressure for three seconds and evaluated by SEM. Results: The standard jet tip removed 99.9% and the orthodontic jet tip removed 99.8% of the salivary biofilm after 3-second treatment on the 8 teeth slices as viewed by SEM. Observation of the remaining four teeth by the naked eye indicated that the orthodontic jet tip removed significant amounts of calcified (in vivo) plaque biofilm. This was confirmed by SEM evaluations. Conclusion: The Waterpik dental water jet can remove both ex vivo and in vivo plaque biofilm significantly.] Gorur A, Lyle DM, et al. *Compendium of Continuing Education in Dentistry – Supplement*, March 2009, Vol 30, p 1-6. http://www.waterpik.com/oral-health/whitepapers/WP_BiofilmStudyAbstract_0209_v2.pdf

717. **Biofilm, City of Microbes.** [We liken the multispecies bacterial biofilm to a city where bacteria settle selectively, limit settlements of new bacteria, store energy in exopolysaccharide, and transfer genetic material horizontally all for the good of the many. A genetic and biochemical understanding of the interactions between species in a biofilm, complex though they may be, is critical to our understanding of how the biofilm city functions and survives. We predict that in multiple-species biofilms many different types of soluble biofilm-specific signals will be discovered whose influence on dissimilar bacterial neighbors will be sometimes helpful and sometimes detrimental or even fatal. When conditions in the biofilm change, such interactions may determine which cells survive, which perish, and which move on. An understanding of the relationships among species in the biofilm city is essential to our appreciation of the benefits of biofilm-associated living.] Watnick P, Kolter R. *Journal of Bacteriology*, May 2000, p.2675-2679, Vol. 182,No.10. http://jb.asm.org/cgi/content/full/182/10/2675

718. **Biofilms as complex differentiated communities.** [Prokaryotic biofilms that predominate in a diverse range of ecosystems are often composed of highly structured multispecies communities. Within these communities metabolic activities are integrated, and developmental sequences, not unlike those of multicellular organisms, can be detected. These structural adaptations and interrelationships are made possible by the expression of sets of genes that result in phenotypes that differ profoundly from those of planktonically grown cells of the same species. Molecular and microscopic evidence suggest the existence of a succession of de facto biofilm phenotypes. We submit that complex cell-cell interactions within prokaryotic communities are an ancient characteristic, the development of which was facilitated by the localization of cells at surfaces. In addition to spatial localization, surfaces may have provided the protective niche in which attached cells could create a localized homeostatic environment. In a holistic sense both biofilm and planktonic phenotypes may be viewed as integrated components of prokaryote life.] Stoodley P, sauer K, et al. *Annu Rev Microbiol.* 2002;56:187-209. Epub 2002 Jan 30. http://www.ncbi.nlm.nih.gov/pubmed/12142477

719. **Correlation between the CPITN Score and Anaerobic Periodontal Infections Assessed by BANA Assay**. [The present results show that 136 of the 281 sites analyzed had a CPITN of 2, with a highly significant BANA-positive test (107 sites). A CPITN equal to 3 was also significantly BANA positive (Tables 1 and 2). These findings clearly demonstrate the relationship between the CPITN and the BANA test indicating the presence of periodontal infection with anaerobic microorganisms (BANA positive).
Individual analysis of the results obtained showed that 83.2% of the 281 sites examined presented scores of 2 and 3, whereas only 36 sites (12.8%) with a score of 4 required a complex treatment involving a surgical approach. These observations agree with those reported by Caldas and Bervique (1992) and Campos Jr. et al. (1992). Although formation of moderate pockets (3.5 to 5.5 mm) was present in approximately 30% of the adult population, the need for complex treatment (pockets deeper than 5.5 mm) was observed in only 1.3% of the individuals (Beck et al., 1984).
With respect to BANA hydrolysis, the present results demonstrate a significant correlation between increased pocket depth and positive results (Figure 1), in agreement with data reported by Syed et al. (1984), Loesche et al. (1987), Bretz and Loesche (1987), Schmidt et al. (1988), and Grisi et al. (1996).] Grisi MFM, Salvador SL, et al. *Braz Dent J (1999) 10(2):93-97*, http://www.forp.usp.br/bdj/bdj10(2)/t05102/t05102.html

720. **Correlation of Red-complex Bacteria in Active Periodontal Disease Sites**. [Objectives: *Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia*, which exist as a consortium in subgingival biofilms, belong to the principal periodontopathogenic bacteria known as red complex. We aimed to examine the relationships between the quantity and prevalence of *P. gingivalis*, *T. denticola*, and *T. forsythia* in subgingival biofilms and local periodontal health. Methods: The subjects in this study were 35 adult patients who visited the Kyusyu Dental College Hospital. Plaque samples were collected from 105 periodontal pocket sites. Quantitative analyses of each of the three periodontopathogenic bacteria were performed using the real-time polymerase chain reaction (PCR) with species-specific primers and hybridization probes. Conclusions: This study suggested that *P. gingivalis*, *T. denticola*, and *T. forsythia* might exist coordinately in subgingival biofilms, and that symbiotic effects of them might influence periodontal disease activity.] Nimeoka T, Awano S, et al. IADR 86th General Session, Toronto CA, July 5, 2008. Abstract 3403.
http://iadr.confex.com/iadr/2008Toronto/techprogram/abstract_106302.htm

721. **Correlation of Red-complex Bacteria in Active Periodontal Disease Sites**. [Objectives: *Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia*, which exist as a consortium in subgingival biofilms, belong to the principal periodontopathogenic bacteria known as red complex. We aimed to examine the relationships between the quantity and prevalence of *P. gingivalis*, *T. denticola*, and *T. forsythia* in subgingival biofilms and local periodontal health. Methods: The subjects in this study were 35 adult patients who visited the Kyusyu Dental College Hospital. Plaque samples were collected from 105 periodontal pocket sites. Quantitative analyses of each of the three periodontopathogenic bacteria were performed using the real-time polymerase chain reaction (PCR) with species-specific primers and hybridization probes. Conclusions:

This study suggested that *P. gingivalis*, *T. denticola*, and *T. forsythia* might exist coordinately in subgingival biofilms, and that symbiotic effects of them might influence periodontal disease activity.] Nimeoka T, Awano S, et al. IADR 86th General Session, Toronto CA, July 5, 2008. Abstract 3403. http://www3.interscience.wiley.com/journal/118653261/abstract

722. **Cross-reactivity of GroEL antibodies with human heat shock protein 60 and quantification of pathogens in atherosclerosis.** [BACKGROUND/AIMS:Chronic infections such as those caused by Chlamydia pneumoniae and periodontopathic bacteria such as Porphyromonas gingivalis have been associated with atherosclerosis, possibly due to cross-reactivity of the immune response to bacterial GroEL with human heat shock protein (hHSP) 60. METHODS: We examined the cross-reactivity of anti-GroEL and anti-P. gingivalis antibodies with hHSP60 in atherosclerosis patients and quantified a panel of six pathogens in atheromas. RESULTS: After absorption of plasma samples with hHSP60, there were variable reductions in the levels of anti-GroEL and anti-P. gingivalis antibodies, suggesting that these antibodies cross-reacted with hHSP60. All of the artery specimens were positive for P. gingivalis. Fusobacterium nucleatum, Tannerella forsythia, C. pneumoniae, Helicobacter pylori, and Haemophilus influenzae were found in 84%, 48%, 28%, 4%, and 4% of arteries, respectively. The prevalence of the three periodontopathic microorganisms, P. gingivalis, F. nucleatum and T. forsythia, was significantly higher than that of the remaining three microorganisms. CONCLUSIONS: These results support the hypothesis that in some patients, cross-reactivity of the immune response to bacterial HSPs including those of periodontal pathogens, with arterial endothelial cells expressing hHSP60 may be a possible mechanism for the association between atherosclerosis and periodontal infection.] Ford PJ, Gemmell E, et al. *Oral Microbiol Immunol.* 2005 Oct;20(5):296-302. **http://www.ncbi.nlm.nih.gov/pubmed/16101965**

723. **Defining the Normal Bacterial Flora of the Oral Cavity.** [More than 700 bacterial species or phylotypes, of which over 50% have not been cultivated, have been detected in the oral cavity. Our purposes were (i) to utilize culture-independent molecular techniques to extend our knowledge on the breadth of bacterial diversity in the healthy human oral cavity, including not-yet-cultivated bacteria species, and (ii) to determine the site and subject specificity of bacterial colonization. Nine sites from five clinically healthy subjects were analyzed. Sites included tongue dorsum, lateral sides of tongue, buccal epithelium, hard palate, soft palate, supragingival plaque of tooth surfaces, subgingival plaque, maxillary anterior vestibule, and tonsils. 16S rRNA genes from sample DNA were amplified, cloned, and transformed into *Escherichia coli*. Sequences of 16S rRNA genes were used to determine species identity or closest relatives. In 2,589 clones, 141 predominant species were detected, of which over 60% have not been cultivated. Thirteen new phylotypes were identified. Species common to all sites belonged to the genera *Gemella*, *Granulicatella*, *Streptococcus*, and *Veillonella*. While some species were subject specific and detected in most sites, other species were site specific. Most sites possessed 20 to 30 different predominant species, and the number of predominant species from all nine sites per individual ranged from 34 to 72. Species typically associated with periodontitis and caries were not detected. There is a distinctive predominant bacterial flora of the healthy oral cavity that is highly diverse and site and subject specific. It is important to fully define the human microflora of the healthy oral cavity before we can understand the role of bacteria in oral disease.] Aas, JA, Paster BJ, et al. *Journal of Clinical Microbiology*, Nov. 2005, p.5721-5732, vol. 43, No.11. http://jcm.asm.org/cgi/content/abstract/43/11/5721

724. **Detection of enterococcus faecalis in subgingival biofilm of patients with chronic refractory periodontitis.** [OBJECTIVES: Refractory periodontitis is the occurrence of additional clinical attachment loss after repeated attempts to control the infection with conventional periodontal therapy. Some microorganisms seem to be involved in the pathogenesis of chronic refractory periodontitis. The prevalence of Enterococcus faecalis in the oral cavity seems to be higher in individuals with periodontitis. Therefore, the present study investigated the presence of E. faecalis in subgingival biofilm of patients with chronic refractory periodontal disease. STUDY DESIGN: Periodontal treatment was instituted for 100 patients suffering from chronic periodontitis. Then samples were obtained from 27 successfully treated and 27 chronic refractory periodontitis subjects and then cultured. Statistical evaluation was performed for descriptive purposes. RESULTS: 27% of the patients had chronic refractory periodontitis. The difference in the presence of E. faecalis in the pockets between the successfully treated (11.1%) and chronic refractory (51.8%) groups by culture methods was statistically significant ($p<0.05$). CONCLUSION: Data showed that E. faecalis is probably involved in the pathogenesis of refractory periodontitis. Accurate knowledge about the pathogen and its role in the pathogenesis of refractory infections helps develop effective treating strategies.] Balaei-Gajan E, Shirmohammadi A, et al. *Med Oral Patol Oral Cir Bucal.* 2010 Jul 1;15(4):e667-70. http://www.ncbi.nlm.nih.gov/pubmed/20173722

725. **Disruption of epithelial barrier and impairment of cellular function by Porphyromonas gingivalis.** [Porphyromonas gingivalis is a predominant periodontal pathogen that expresses a number of potential virulence factors involved in the pathogenesis of periodontitis. Gingival epithelial cells are spontaneously exposed to bacterial attacks and function to prevent invasion by bacteria into deeper tissues. P. gingivalis fimbriae are a critical factor for mediation of interaction of the organism with host tissues, as they promote both bacterial adhesion to and invasion of targeted sites. Fimbriae are capable of binding to human salivary components, extracellular matrix proteins, and commensal bacteria, while they also strongly adhere to cellular alpha5beta1-integrin. Following adhesion to alpha5beta1-integrin, P. gingivalis is captured by cellular pseudopodia, which enables invagination through an actin-mediated pathway. The invasive event has been reported to require host cellular dynamin, actin fibers, microtubules, and lipid rafts. Following passage through the epithelial barrier, the intracellular pathogen impairs cellular function. Fimbriae are classified into 6 genotypes (types I to V and Ib) based on the diversity of the fimA genes encoding each fimbria subunit, and intracellular P. gingivalis with type II fimbriae has been found to clearly degrade integrin-related signaling molecules, paxillin, and focal adhesion kinase, which disables cellular migration and

proliferation. These events are considered to integrate the bacterial strategy for persistence in periodontal tissues.] Amano A. *Front Biosci.* 2007 May 1;12:3965-74. http://www.ncbi.nlm.nih.gov/pubmed/17485350

726. **Elective Localization in the eye of bacteria from infected teeth.** [An etiologic relationship between chronic foci of infection and systemic disease is accepted by most clinicians. The cure or marked improvement in some systemic disorder which may follow the removal of a septic focus seems conclusive proof of a causal relation. The clinical manifestations of focal infection depend primarily on the site of localization of the bacteria which are fed into the blood stream. The extent of clumping of the organism, the nature of the blood supply, the food supply and local tissue resistance must play important parts in determining the localization and resulting infection. Rosenow[1] has emphasized also the individual variation in bacteria and has advanced the theory that bacteria have a specific tendency to localize in certain tissues of the body, dependent on some peculiar inherent property. The theory is a most attractive one and has evoked a great deal of discussion.] Haden RL. *Arch Intern Med.* 1923;32(6):828-849. http://archinte.ama-assn.org/cgi/content/summary/32/6/828

727. **Focal Infection. [] Newman HN, *J Dent Res* 1996; 75; 1912.**

728. **Fusobacterium nucleatum adhesin FadA binds vascular endothelial cadherin and alters endothelial integrity**. [Fusobacterium nucleatum is a Gram-negative oral anaerobe, capable of systemic dissemination causing infections and abscesses, often in mixed-species, at different body sites. We have shown previously that F. nucleatum adheres to and invades host epithelial and endothelial cells via a novel FadA adhesin. In this study, vascular endothelial (VE)-cadherin, a member of the cadherin family and a cell-cell junction molecule, was identified as the endothelial receptor for FadA, required for F. nucleatum binding to the cells. FadA colocalized with VE-cadherin on endothelial cells, causing relocation of VE-cadherin away from the cell-cell junctions. As a result, the endothelial permeability was increased, allowing the bacteria to cross the endothelium through loosened junctions. This crossing mechanism may explain why the organism is able to disseminate systemically to colonize in different body sites and even overcome the placental and blood-brain barriers. Co-incubation of F. nucleatum and Escherichia coli enhanced penetration of the endothelial cells by the latter in the transwell assays, suggesting F. nucleatum may serve as an 'enabler' for other microorganisms to spread systemically. This may explain why F. nucleatum is often found in mixed infections. This study reveals a possible novel dissemination mechanism utilized by pathogens.] Fardini Y, Wang X, Han YW, et al. http://www.ncbi.nlm.nih.gov/pubmed/22040113 http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2958.2011.07905.x/abstract

729. **Helicobacter pylori in dental plaque and stomach of patients from Northern Brazil.** [AIM: To establish whether virulence factor genes vacA and cagA are present in Helicobacter pylori (H. pylori) retrieved from gastric mucosa and dental plaque in patients with dyspepsia. METHODS: Cumulative dental plaque specimens and gastric biopsies were submitted to histological examination, rapid urease test and polymerase chain reaction (PCR) assays to detect the presence of cagA and vacA polymorphisms. RESULTS: Detection of H. pylori from dental plaque and gastric biopsy samples was greater by PCR compared to histological examination and the rapid urease test. DNA from H. pylori was detected in 96% of gastric mucosa samples and in 72% of dental plaque samples. Sixty-three (89%) of 71 dental plaque samples that were H. pylori-positive also exhibited identical vacA and cagA genotypes in gastric mucosa. The most common genotype was vacAs1bm1 and cagA positive, either in dental plaque or gastric mucosa. These virulent H. pylori isolates were involved in the severity of clinical outcome. CONCLUSION: These pathogenic strains were found simultaneously in dental plaque and gastric mucosa, which suggests that gastric infection is correlated with the presence of H. pylori in the mouth.] Assumpcao MB, Martins LC, et al. *World J Gastroenterol*. 2010 Jun 28;16(24):3033-9. http://www.ncbi.nlm.nih.gov/pubmed/20572307

730. ***Helicobacter pylori* in the oral cavity is associated with gastroesophageal disease.** [In Mexico, more than 80% of the population is infected with *Helicobacter pylori*. The frequency of *H. pylori* detection in the oral cavity is unknown, as its relationship with gastroesophageal pathology. Aim: To detect the presence of *H. pylori* in the oral cavity in Mexican population by PCR and to determine its association with gastroesophageal disease. Methods: Patients were divided into two groups with different clinic conditions from whom gastric biopsy, dental plaque, and saliva samples were taken and analyzed. The first group comprised of hospitalized patients, the majority of whom were diagnosed with gastroesophageal disease, while the second group was selected from a dental clinic (ambulatory population) the majority of whom appeared to be healthy subjects. Results: *H. pylori* was detected in gastric biopsy, dental plaque and saliva samples by PCR using a set of specific primers for the signal sequence of the vacuolating cytotoxin gene; detection of *H. pylori* in general was higher in gastric biopsy and dental plaque samples than in saliva samples. Detection of *H. pylori* in the oral cavity is significantly ($P = 0.0001$) associated with patients presenting gastroesophageal disease, while healthy subjects and those with other non-gastric disease do not present with *H. pylori* in their oral cavity. Conclusions: *H. pylori* detection in the oral cavity is associated to gastroesophageal disease. In addition, it is suggested that all patients presenting gastric symptoms and *H. pylori* detection in the oral cavity would begin bacterial treatment immediately.] Morales-Espinosa R, Fernandez-Presas A, et al. *Oral Microbiol Immunol 2009: 24: 464-468* http://www.ingentaconnect.com/content/mksg/omi/2009/00000024/00000006/art00004

731. **Human viruses in periodontitis.** [] Slots J. *Periodontol* 2000. 2010 Jun;53:89-110. http://www.ncbi.nlm.nih.gov/pubmed/20403107

732. **Increased levels of *Porphyromonas gingivalis* are associated with ischemic and hemorrhagic cerebrovascular disease in humans: an *in vivo* study.** [OBJECTIVE: This study investigated the role of periodontal disease in the development of stroke or cerebral infarction in patients by evaluating the clinical periodontal conditions and the subgingival levels of periodontopathogens. MATERIAL AND METHODS: Twenty patients with ischemic (I-CVA) or hemorrhagic (H-CVA) cerebrovascular episodes (test group) and 60 systemically healthy patients (control group) were evaluated for: probing depth,

clinical attachment level, bleeding on probing and plaque index. *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* were both identified and quantified in subgingival plaque samples by conventional and real-time PCR, respectively. RESULTS: The test group showed a significant increase in each of the following parameters: pocket depth, clinical attachment loss, bleeding on probing, plaque index and number of missing teeth when compared to control values ($p<0.05$, unpaired t-test). Likewise, the test group had increased numbers of sites that were contaminated with*P. gingivalis* (60%x10%; $p<0.001$; chi-squared test) and displayed greater prevalence of periodontal disease, with an odds ratio of 48.06 (95% CI: 5.96-387.72; $p<0.001$). Notably, a positive correlation between probing depth and the levels of *P. gingivalis* in ischemic stroke was found ($r=0.60$; $p=0.03$; Spearman's rank correlation coefficient test). *A. actinomycetemcomitans* DNA was not detected in any of the groups by conventional or real-time PCR. CONCLUSIONS: Stroke patients had deeper pockets, more severe attachment loss, increased bleeding on probing, increased plaque indexes, and in their pockets harbored increased levels of *P. gingivalis*. These findings suggest that periodontal disease is a risk factor for the development of cerebral hemorrhage or infarction. Early treatment of periodontitis may counteract the development of cerebrovascular episodes.] Ghizoni JS, Taverira, LA, et al. *J. Appl. Oral Sci*. vol 20 no 1 Bauru Jan/Feb 2012 http://www.ncbi.nlm.nih.gov/pubmed/22437687

733. **Interactions of oral pathogens with toll-like receptors: possible role in atherosclerosis. [**Toll-like receptors (TLR) function as important signal transducers that mediate innate immune and inflammatory responses to pathogens through pattern recognition of virulence molecules. Although TLRs mediate protection against infection, it is also likely that they may have a pathophysiologic role in certain inflammatory diseases, such as atherosclerosis. In atherosclerotic lesions, endothelial cells and macrophages have been shown to upregulate TLR expression and may respond to TLR agonists of microbial origin, resulting in detrimental inflammatory reactions. Some of these potential TLR-activating virulence factors may be of oral origin. The detection in atherosclerotic plaques of DNA specific for Porphyromonas gingivalis and other periodontal pathogens suggests that these pathogens disseminate into the systemic circulation and localize in atheromas. The potential of periodontal and some other oral pathogens to activate TLRs in vivo is suggested by findings from cell culture experiments on interactions of selected virulence protein adhesins with TLRs and their coreceptors. Specifically, we have shown that proinflammatory cytokine induction by P. gingivalis fimbriae was inhibited by monoclonal antibodies to TLR2, TLR4, CD14, and beta2 integrins, but not by immunoglobulin isotype controls. Cytokine induction by Bacteroides forsythus protein A depended heavily on CD14 and TLR2. We also found that the ability of Streptococcus mutans protein AgI/II to stimulate cytokine release was partially dependent on CD14 and TLR4. Moreover, P. gingivalis fimbriae induced TLR-dependent activation of nuclear factor-kappaB and upregulation of costimulatory molecules in monocytic cells. These proinflammatory activities have been implicated in the pathogenesis of periodontitis, and similar inflammatory mechanisms could potentially operate in atherosclerosis. Studies by other groups have shown that P. gingivalis is capable of stimulating low-density lipoprotein oxidation, foam cell formation, and rupture of atherosclerotic plaque through induction of matrix metalloproteinases. Interestingly, at least some of these activities can be induced by TLR agonists (lipopolysaccharide and heat-shock protein-60) from Chlamydia pneumoniae, a major risk factor in atherosclerosis. Future research in animal models and in vitro cellular systems with defined mutations in TLRs may implicate TLR participation in oral pathogen-mediated atherosclerotic processes, thereby providing a mechanistic basis for the epidemiological findings linking oral pathogens to atherosclerotic disease.] Hajishengallis G, Sharma A, et al. *Ann Periodontol*. 2002 Dec;7(1):72-8. http://www.ncbi.nlm.nih.gov/pubmed/16013219

734. **Leukotoxin Confers Beta-Hemolytic Activity to *Actinobacillus actinomycetemcomitans***. [*Actinobacillus actinomycetemcomitans* is the etiologic agent of localized aggressive periodontitis, a rapidly progressing oral disease that occurs in adolescents. *A. actinomycetemcomitans* can also cause systemic disease, including infective endocarditis. In early work on *A. actinomycetemcomitans* workers concluded that this bacterium is not beta-hemolytic. More recent reports have suggested that *A. actinomycetemcomitans* does have the potential to be beta-hemolytic. While growing *A. actinomycetemcomitans* on several types of growth media, we noticed a beta-hemolytic reaction on media from one manufacturer. Beta-hemolysis occurred on Columbia agar from Accumedia with either sheep or horse blood, but not on similar media from other manufacturers. A surprising result was that mutants of *A. actinomycetemcomitans* defective for production of leukotoxin, a toxin that is reportedly highly specific for only human and primate white blood cells, are not beta-hemolytic. Purified leukotoxin was able to lyse sheep and human erythrocytes in vitro. This work showed that in contrast to the accepted view, *A. actinomycetemcomitans* leukotoxin can indeed destroy erythrocytes and that the production of this toxin results in beta-hemolytic colonies on solid medium. In light of these results, the diagnostic criteria for clinical identification of *A. actinomycetemcomitans* and potentially related bacteria should be reevaluated. Furthermore, in studies on *A. actinomycetemcomitans* leukotoxin workers should now consider this toxin's ability to destroy red blood cells.] Balashova NV, Crosby JA, et al. Infection and Immunity, April 2006, p. 2015-2021, Vol. 74, No. 4 http://iai.asm.org/cgi/content/abstract/74/4/2015?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=Leukotoxin+Confers+Beta-Hemolytic+Activity+&searchid=1&FIRSTINDEX=0&volume=74&issue=4&resourcetype=HWCIT

735. **Low-Abundance Biofilm Species Orchestrates Inflammatory Periodontal Disease through the Commensal Microbiota and Complement. [***Porphyromonas gingivalis* is a low-abundance oral anaerobic bacterium implicated in periodontitis, a polymicrobial inflammatory disease, and the associated systemic conditions. However, the mechanism by which *P. gingivalis* contributes to inflammation and disease has remained elusive. Here we show that *P. gingivalis*, at very low colonization levels, triggers changes to the amount and composition of the oral commensal microbiota leading to inflammatory periodontal bone loss. The commensal microbiota and complement were both required for *P. gingivalis*-induced bone loss, as

germ-free mice or conventionally raised C3a and C5a receptor-deficient mice did not develop bone loss after inoculation with *P. gingivalis*. These findings demonstrate that a single, low-abundance species can disrupt host-microbial homeostasis to cause inflammatory disease. The identification and targeting of similar low-abundance pathogens with community-wide impact may be important for treating inflammatory diseases of polymicrobial etiology.] Hajishengallis G, Liang S, et al. *Cell Host & Microbe***,** Volume 10, Issue 5, 497-506, 27 October 2011. http://www.cell.com/cell-host-microbe/abstract/S1931-3128(11)00299-X

736. **Major surface protein complex of Treponema denticola induces the production of tumor necrosis factor alpha, interleukin-1beta, interleukin-6 and matrix metalloproteinase 9 by primary human peripheral blood monocytes.** [Gaibani P, Caroli F, Nucci C, Sambri V. Major surface protein complex of Treponema denticola induces the production of tumor necrosis factor alpha, interleukin-1beta, interleukin-6 and matrix metalloproteinase 9by primary human peripheral blood monocytes. Background and Objective: Treponema denticola is a micro-organism that is involved in the pathogenesis of periodontitis. Major surface protein complex (MSPc), which is expressed on the envelope of this treponeme, plays a key role in the interaction between T. denticola and gingival cells. The peptidoglycan extracted from T. denticola induces the production of a large variety of inflammatory mediators by macrophage-like cells, suggesting that individual components of T. denticola cells induce the inflammatory response during periodontal disease. This study was designed to demonstrate that MSPc of T. denticola stimulates release of proinflammatory mediators in primary human monocytes. Material and Methods: Primary human monocytes were separated from the blood of healthy donors and incubated for up to 24 h with varying concentrations of MSPc. The production of tumor necrosis factor alpha (TNF-alpha), interleukin-1beta (IL-1beta), interleukin-6 (IL-6) and matrix metalloproteinase 9 (MMP-9) was measured at different time points with commercially available enzyme-linked immunosorbent assays. Results: T. denticola MSPc induced the synthesis of TNF-alpha, IL-1beta, IL-6 and MMP-9 in a dose- and time-dependent manner. Similar patterns of TNF-alpha, IL-1beta and IL-6 release were observed when cells were stimulated with 100 and 1000 ng/mL of MSPc. The production of MMP-9 was significant only when cells were treated with 1000 ng/mL of MSPc. Conclusion: These results indicate that T. denticola MSPc, at concentrations ranging from 100 ng/mL to 1.0 mug/mL, activates a proinflammatory response in primary human monocytes.] Gaibani P, Caroli F, et al. *J Periodontal Res*. 2010 Mar 9. http://www.ncbi.nlm.nih.gov/pubmed/20337896

737. **Managing the complexity of a dynamic biofilm.** [Background. This article provides an overview of the history of oral microbiology, a discussion of dental plaque as both a microbial community and a biofilm, and a review of the measures available to control the oral microflora. Types of Studies Reviewed. The authors reviewed the literature related to oral microbiology and associated infectious diseases. They also examined articles that detailed the structure and physiology of biofilms, including dental plaque biofilms. Conclusions. Biofilms cannot be eliminated. The pathogenic nature of the dental plaque biofilm can be diminished in the oral cavity by reducing the bioburden and effectively maintaining a normal oral flora via oral hygiene procedures that include daily toothbrushing, flossing and rinsing with an antimicrobial mouthrinse. An oral hygiene regimen that includes rinsing with an antimicrobial mouthrinse is a practical approach to the prevention and management of periodontal diseases. This strategy may have wider benefits when the link between periodontal disease and certain systemic diseases is considered.] Thomas JG, Nakaishi LA. *J Am Dent Asoc,* Vol 137, No Suppl_3, 10S-15S. http://jada.ada.org/cgi/content/abstract/137/suppl_3/10S

738. **Mast cells in gingival inflammations** [Mast cells are the normal components of the connective tissues. They are found in different densities and different regions of the inflamed and healthy gingival tissues. The role of mast cell mediators in periodontal disease progression were not studied in detail. Since the roles of mast cells in periodontal tissues are not clear, this study aimed to count the number of mast cells in gingival tissues of healthy volunteers and patients with gingival inflammation. Numbers of mast cells were found increased on inflamed tissues comparing to healthy tissues. This increase is closely related with the degree of inflammation on the fields which counting made on.] Gunhan M. *Ankara Univ Hekim Fak Derg*. 1989 Sep;16(3):481-3. http://www.ncbi.nlm.nih.gov/pubmed/2489499

739. **Microbial biofilms.** [Direct observations have clearly shown that biofilm bacteria predominate, numerically and metabolically, in virtually all nutrient-sufficient ecosystems. Therefore, these sessile organisms predominate in most of the environmental, industrial, and medical problems and processes of interest to microbiologists. If biofilm bacteria were simply planktonic cells that had adhered to a surface, this revelation would be unimportant, but they are demonstrably and profoundly different. We first noted that biofilm cells are at least 500 times more resistant to antibacterial agents. Now we have discovered that adhesion triggers the expression of a sigma factor that derepresses a large number of genes so that biofilm cells are clearly phenotypically distinct from their planktonic counterparts. Each biofilm bacterium lives in a customized microniche in a complex microbial community that has primitive homeostasis, a primitive circulatory system, and metabolic cooperativity, and each of these sessile cells reacts to its special environment so that it differs fundamentally from a planktonic cell of the same species.] Costerton JW, Lewandowski Z, et al. *Annu Rev Microbiol.* 1995;49:711-45. http://www.ncbi.nlm.nih.gov/pubmed/8561477

740. **Microbial ecology comes of age and joins the general ecology community**. [The article by Boles *et al.* (1) in a recent issue of PNAS is profoundly important because it addresses a major change in the etiology of human bacterial diseases that has passed unnoticed during the last half of the past century. Acute diseases caused by mobile cells of specialized pathogens have largely disappeared because we have identified the pathogens and countered with vaccines and antibiotics. Diphtheria, typhoid fever, and posttraumatic gangrene have ceased to threaten us. However, these acute epidemic diseases have been largely replaced (2) by environmental organisms that gain a foothold in the human body, especially in compromised organs (like the lung in cystic fibrosis), and initiate the invidious twin processes of inflammation and chronic disease. The new

microbial enemies are common and ubiquitous in nature, they live in protected biofilms where they resist antibiotics and host defenses, and they can mount small or large acute attacks on the host that may eventually succeed when his or her defenses are depleted.] Costerton B. *Proceedings of the National Academy of Sciences of the USA.* http://www.pnas.org/content/101/49/16983.full?ck=nck

741. **Microbiology of Odontogenic Bacteremia: beyond Endocarditis.** [Summary: The human gingival niche is a unique microbial habitat. In this habitat, biofilm organisms exist in harmony, attached to either enamel or cemental surfaces of the tooth as well as to the crevicular epithelium, subjacent to a rich vascular plexus underneath. Due to this extraordinary anatomical juxtaposition, plaque biofilm bacteria have a ready portal of ingress into the systemic circulation in both health and disease. Yet the frequency, magnitude, and etiology of bacteremias due to oral origin and the consequent end organ infections are not clear and have not recently been evaluated. In this comprehensive review, we address the available literature on triggering events, incidence, and diversity of odontogenic bacteremias. The nature of the infective agents and end organ infections (other than endocarditis) is also described, with an emphasis on the challenge of establishing the link between odontogenic infections and related systemic, focal infections.] Parahitiyawa NB, Jin LJ, et al. *Clinical Microbiology Reviews*, January 2009, p. 46-64, Vol. 22, No. 1. http://cmr.asm.org/cgi/content/full/22/1/46#INTRODUCTION

742. **Minocycline HCl Microspheres Reduce Red-Complex Bacteria in Periodontal Disease Therapy**. [Background: The objective of this trial was to measure the antimicrobial effects of a minocycline HCl microsphere (MM) local drug-delivery system when used as an adjunct to scaling and root planing (SRP). DNA probe analysis for 40 bacteria was used to evaluate the oral bacteria of 127 subjects with moderate to advanced chronic periodontitis. Methods: Subjects were randomly assigned to either SRP alone (N = 65) or MM + SRP (N = 62). The primary endpoints of this study were changes in numbers and proportions of the red-complex bacteria (RCB) and the sum of *Porphyromonas gingivalis*, *Tannerella forsythia* (formally *T. forsythensis*), and *Treponema denticola* relative to 40 oral bacteria at each test site from baseline to day 30. Numbers of RCB from the five test sites were averaged to provide a value for each subject. Results: MM + SRP reduced the proportion of RCB by 6.49% and the numbers by 9.4×10^5. The reduction in RCB proportions and numbers by SRP alone (5.03% and 5.1×10^5, respectively) was significantly less. In addition, MM + SRP reduced probing depth by 1.38 mm (compared to 1.01 mm by SRP alone), bleeding on probing was reduced by 25.2% (compared to 13.8% by SRP alone), and a clinical attachment level gain of 1.16 mm (compared to 0.80 mm by SRP alone) was achieved. Conclusion: These observations support the hypothesis that RCBs are responsible for periodontal disease and that local antimicrobial therapy using MM + SRP effectively reduces numbers of RCBs and their proportions to a greater extent than SRP alone.] Goodson JM, Gunsolley JC, et al. *Journal of Periodontology*, 2007, Vol. 78, No.8, pp1568-1579. http://www.joponline.org/doi/abs/10.1902/jop.2007.060488?journalCode=jop

743. **Molecular signaling mechanisms of the periopathogen, Treponema denticola**. [treponemes thrive and become a dominant component of the bacterial population. Oral treponemes are uniquely adept at capitalizing on the environmental conditions that develop with periodontal disease. The molecular basis of adaptive responses of oral treponemes is just beginning to be investigated and defined. The completion of several treponeme genome sequences and the characterization of global regulatory systems provide an important starting point in the analysis of signaling and adaptive responses. In this review, we discuss existing literature focused on the genetic regulatory mechanisms of Treponema denticola and present an overview of the possible roles of regulatory proteins identified through genome analyses. This information provides insight into the possible molecular mechanisms utilized by oral spirochetes to survive in the periodontal pocket and transition from a minor to a dominant organism.] Frederick JR, Sarkar J, et al. J Dent Res. 2011 Oct;90(10):1155-63. doi: 10.1177/0022034511402994. Epub 2011 Mar 29. http://www.ncbi.nlm.nih.gov/pubmed/21447698

744. **New insights into the emerging role of oral spirochaetes in periodontal disease. [**Clin Microbiol Infect 2011; 17: 502-512 ABSTRACT: Spirochaetes are prominent in the polymicrobial infections that cause periodontal diseases. Periodontitis is a chronic inflammatory condition of the periodontium, characterized by proinflammatory soft tissue damage and alveolar bone loss. Treponema denticola is the most well-understood oral spirochaete, expressing a wealth of virulence factors that mediate tissue penetration and destruction as well as evasion of host immune responses. This review focuses on emerging knowledge of virulence mechanisms of Treponema denticola as well as mechanisms of other less-studied oral treponemes.] Visser MB, **Ellen RP. *Clin Microbiol Infect.* 2011 Apr;17(4):502-12 http://www.ncbi.nlm.nih.gov/pubmed/21414084**

745. **Occurrence of red complex microorganisms and Aggregatibacter actinomycetemcomitans in patients with diabetes.** [AIM: The aim of the present study was to analyze the occurrence of Porphyromonas gingivalis (P. gingivalis), Tannerella forsythia (T. forsythia), Treponema denticola (T. denticola), and Aggregatibacter actinomycetemcomitans (A. actinomycetemcomitans) in patients with diabetes. METHODS: Periodontal and diabetic parameters and subgingival biofilm samples were obtained from 60 patients with diabetes and 62 patients without diabetes. By using polymerase chain reaction, the prevalence of red complex microorganisms (P. gingivalis, T. forsythia, and T. denticola) and A. actinomycetemcomitans were determined. Descriptive and non-parametric statistical analyses between groups were performed (Kruskal-Wallis, Mann-Whitney U-test, and Fisher's exact test). RESULTS: Patients with diabetes presented significantly higher periodontal attachment loss levels compared to patients without diabetes. Red complex microorganisms were detected in lower frequencies in patients with diabetes. The detection of A. actinomycetemcomitans was higher in patients with diabetes and periodontitis compared to systemically-healthy patients without periodontitis ($P < 0.05$). P. gingivalis was associated with periodontitis in non-diabetic patients ($P < 0.05$), whereas A. actinomycetemcomitans was associated with periodontitis in diabetic patients ($P < 0.05$). CONCLUSIONS: The findings of the present study indicate that there might be differences in the subgingival microbiota between diabetic and non-diabetic patients. In addition, P. gingivalis

and A. actinomycetemcomitans were associated with periodontitis in patients without diabetes and patients with diabetes, respectively.] Castrillon CA, Hincapie JP, et al. *J Investig Clin Dent.* 2013 Jul 16. http://www.ncbi.nlm.nih.gov/pubmed/23857867

746. **Oral Biofilm Architecture on Natural Teeth.** [Periodontitis and caries are infectious diseases of the oral cavity in which oral biofilms play a causative role. Moreover, oral biofilms are widely studied as model systems for bacterial adhesion, biofilm development, and biofilm resistance to antibiotics, due to their widespread presence and accessibility. Despite descriptions of initial plaque formation on the tooth surface, studies on mature plaque and plaque structure below the gum are limited to landmark studies from the 1970s, without appreciating the breadth of microbial diversity in the plaque. We used fluorescent in situ hybridization to localize in vivo the most abundant species from different phyla and species associated with periodontitis on seven embedded teeth obtained from four different subjects. The data showed convincingly the dominance of Actinomyces sp., Tannerella forsythia, Fusobacterium nucleatum, Spirochaetes, and Synergistetes in subgingival plaque. The latter proved to be new with a possibly important role in host-pathogen interaction due to its localization in close proximity to immune cells. The present study identified for the first time in vivo that Lactobacillus sp. are the central cells of bacterial aggregates in subgingival plaque, and that Streptococcus sp. and the yeast Candida albicans form corncob structures in supragingival plaque. Finally, periodontal pathogens colonize already formed biofilms and form microcolonies therein. These in vivo observations on oral biofilms provide a clear vision on biofilm architecture and the spatial distribution of predominant species.] Zijnge V, van Leeuwen BM, et al. *PLoS One.* 2010 Feb 24;5(2):e9321. http://www.ncbi.nlm.nih.gov/pubmed/20195365

747. **Oral Biofilm: Entry and Immune System Response** [This article demonstrates how the oral biofilm functions and the effects this biofilm has on the host immune system. Various components of the oral biofilm affect the immune system through a variety of ways with a resulting systemic inflammatory response. Treatment of the biofilm is an integral aspect to decrease the immune system responses, along with decreasing the host systemic inflammation.] Keller D, Costerton JW. *Compendium of Continuing Education in Dentistry.* Jan Feb 2009, Vol. 30, No 1, pp24-32. http://www.ncbi.nlm.nih.gov/pubmed/19263762

748. **Oral sepsis and the elective localization of bacteria. [**Six years have elapsed since Billings[1] published the extensive clinical observations made by himself and his co-workers to demonstrate the importance of septic foci, even when small, as sources of chronic infection conveyed by the blood stream. It was shown that these foci may harbor the same type of bacteria as are found in distant lesions, and that specific types tend to localize in definite organs or tissues. Rosenow,[2] in particular, has been most energetic in the attempt to demonstrate conclusively the elective localizing power of freshly isolated streptococci found in the focus or systemic lesions of a number of diseases, including appendicitis, ulcer of the stomach, chronic endocarditis, and rheumatic fever. Inevitably the possible relationship between ill health and oral sepsis has come into prominence in connection with the recent studies on what has lately been termed focal infection.] *J Am Med Assoc.* 1920;74(10):677-678. http://jama.ama-assn.org/cgi/content/summary/74/10/677

749. **Periodontal Disease and Coronary Heart Disease.** [*Background*— Results from studies relating periodontal disease to cardiovascular disease have been mixed. Residual confounding by smoking and use of clinical measures of periodontal disease rather than measures of infection have been 2 major criticisms. The aims of this study were to investigate relationships between prevalent coronary heart disease (CHD) and 2 exposures, (1) clinical periodontal disease and (2) IgG antibodies to 17 oral organisms, and to evaluate the role of smoking in these relationships. *Methods and Results*— Our study is based on a subset of participants in the Atherosclerosis Risk in Communities (ARIC) Study, who received a complete periodontal examination during visit 4 (1996–1998). The exposures were periodontal status and serum IgG antibody levels against 17 periodontal organisms, and the outcome was prevalent CHD at visit 4. Multivariable analyses indicate that periodontal status is not significantly associated with CHD in either ever smokers or never smokers. Similar analyses evaluating antibodies indicate that high antibodies (above the median) to *Treponema denticola* (odds ratio [OR]=1.7; 95% CI, 1.2 to 2.3), *Prevotella intermedia* (OR=1.5; 95% CI, 1.1 to 2.0), *Capnocytophaga ochracea* (OR=1.5; 95% CI, 1.1 to 2.1), and *Veillonella parvula* (OR=1.7; 95% CI, 1.2 to 2.3) are significantly associated with CHD among ever smokers, whereas *Prevotella nigrescens* (OR=1.7; 95% CI, 1.1 to 2.6), *Actinobacillus actinomycetemcomitans* (OR=1.7; 95% CI, 1.2 to 2.7), and *Capnocytophaga ochracea* (OR=2.0; 95% CI, 1.3 to 3.0) were associated with CHD among never smokers. *Conclusions*— Clinical signs of periodontal disease were not associated with CHD, whereas systemic antibody response was associated with CHD in ever smokers and never smokers. These findings indicate that the quality and quantity of the host response to oral bacteria may be an exposure more relevant to systemic atherothrombotic coronary events than clinical measures. "We reviewed evidence indicating that the chronic inflammatory burden of periodontal infection and the host response provide the basis for the observed association between periodontal disease and atherosclerosis and CHD… Thus, we conservatively interpret the results of this study to indicate that systemic exposure to oral organisms is related to the prevalence of detected CHD.] Beck JD, Eke P, et al. *Circulation.* 2005;112:19-24. http://circ.ahajournals.org/cgi/content/abstract/112/1/19

750. **Periodontal Microbiota and Carotid Intima-Media Thickness.** [*Background*— Chronic infections, including periodontal infections, may predispose to cardiovascular disease. We investigated the relationship between periodontal microbiota and subclinical atherosclerosis. *Methods and Results*— Of 1056 persons (age 69±9 years) with no history of stroke or myocardial infarction enrolled in the Oral Infections and Vascular Disease Epidemiology Study (INVEST), we analyzed 657 dentate subjects. Among these subjects, 4561 subgingival plaque samples were collected (average of 7 samples/subject) and quantitatively assessed for 11 known periodontal bacteria by DNA-DNA checkerboard hybridization. Extensive in-person

cardiovascular risk factor measurements, a carotid scan with high-resolution B-mode ultrasound, white blood cell count, and C-reactive protein values were obtained. In 3 separate analyses, mean carotid artery intima-media thickness (IMT) was regressed on tertiles of (1) burden of all bacteria assessed, (2) burden of bacteria causative of periodontal disease (etiologic bacterial burden), and (3) the relative predominance of causative/over other bacteria in the subgingival plaque. All analyses were adjusted for age, race/ethnicity, gender, education, body mass index, smoking, diabetes, systolic blood pressure, and LDL and HDL cholesterol. Overall periodontal bacterial burden was related to carotid IMT. This relationship was specific to causative bacterial burden and the dominance of etiologic bacteria in the observed microbiological niche. Adjusted mean IMT values across tertiles of etiologic bacterial dominance were 0.84, 0.85, and 0.88 (P=0.002). Similarly, white blood cell values increased across tertiles of etiologic bacterial burden from 5.57 to 6.09 and 6.03 cells x10^9/L (P=0.01). C-reactive protein values were unrelated to periodontal microbial status (P=0.82). *Conclusions*— Our data provide evidence of a direct relationship between periodontal microbiology and subclinical atherosclerosis. This relationship exists independent of C-reactive protein.] Desvarieux M, Demmer RT, et al. *Circulation. 2005;111:576-582.*
http://www.circ.ahajournals.org/cgi/content/full/111/5/576

751. **Polymorphonuclear neutrophils in post traumatic osteoyelitis: Cells recovered from the inflamed site lack chemotactic activity but generate superoxides.** [The pathogenesis of posttraumatic osteomyelitis, one of the major complications after orthopedic surgery, is not yet understood. Formation of bacterial biofilms on the implant is presumed, conferring resistance to antibiotic therapy and probably also to the host defense mechanisms. In that context, the polymorphonuclear neutrophils (PMN) having infiltrated the infected site were recovered and characterized phenotypically and functionally. Loss of CD62L and upregulation of CD14 were seen, as was expression of CD83. Expression of the latter is dependent on *de novo* protein synthesis and thus is indicative of an extended life span and a transdifferentiation of the PMN at the infected site. The infiltrated PMN had lost their chemotactic activity, whereas the capacity to produce superoxides was preserved and in some patients even enhanced. *In vitro* experiments done in parallel showed that long-term culture with interferon-γ resulted in similar alterations of PMN: loss of chemotactic activity, whereas other functions of PMN, such generation of superoxides and phagocytosis of opsonized bacteria, were preserved or even enhanced. The loss of the migratory capacity of PMN having already emigrated from the blood vessel to the infected site is not expected to affect the host defense negatively. Assuming, however, that bacteria are organized as a biofilm and that infiltration into this biofilm is required for phagocytosis of the bacteria, our data could to some extent explain why despite being activated, the PMN are not able to control the infection. By releasing their cytotoxic, proteolytic, and collagenolytic potential, PMN might instead contribute to tissue destruction and eventually to osteolysis.] Wagner C, Alexander K, et al. *Shock Injury, Inflammation, and Sepsis: Laboratory and Clinical Approaches*, Vol. 22(2)August 2004 pp 108-115. http://www.shockjournal.com/pt/re/shock/abstract.00024382-200408000-00003.htm;jsessionid=JGXXlzG9zb2ThvyJ5H6LgGL2F7zbXKj4jYFm5crmplM2K43gG1qN!-269263472!181195628!8091!-1
752. **Polysaccharide intercellular adhesin (PIA) protects Staphylococcus epidermidis against major components of the human innate immune system..** [The skin commensal and opportunistic pathogen Staphylococcus epidermidis is the leading cause of nosocomial and biofilm-associated infections. Little is known about the mechanisms by which S. epidermidis protects itself against the innate human immune system during colonization and infection. We used scanning electron microscopy to demonstrate that the exopolysaccharide intercellular adhesin (PIA) resides in fibrous strands on the bacterial cell surface, and that lack of PIA production results in complete loss of the extracellular matrix material that has been suggested to mediate immune evasion. Phagocytosis and killing by human polymorphonuclear leucocytes was significantly increased in a mutant strain lacking PIA production compared with the wild-type strain. The mutant strain was also significantly more susceptible to killing by major antibacterial peptides of human skin, cationic human beta-defensin 3 and LL-37, and anionic dermcidin. PIA represents the first defined factor of the staphylococcal biofilm matrix that protects against major components of human innate host defence.] Vuong C, Voyich JM et al. *Cell Microbiol.* 2004 mar;6(3):269-75. http://www.ncbi.nlm.nih.gov/pubmed/14764110
753. ***Porphyromonas gingivalis* accelerates inflammatory atherosclerosis in the innominate artery of ApoE deficient mice.** **[**Objective:Studies in humans support a role for the oral pathogen *Porphyromonas gingivalis* in the development of inflammatory atherosclerosis. The goal of this study was to determine if *P. gingivalis* infection accelerates inflammation and atherosclerosis in the innominate artery of mice, an artery which has been reported to exhibit many features of human atherosclerotic disease, including plaque rupture. Methods and results: Apolipoprotein E-deficient (ApoE$^{-/-}$) mice were orally infected with *P. gingivalis*, and magnetic resonance imaging (MRI) was used to monitor the progression of atherosclerosis in live mice. *P. gingivalis* infected mice exhibited a statistically significant increase in atherosclerotic plaque in the innominate artery as compared to uninfected mice. Polarized light microscopy and immunohistochemistry revealed that the innominate arteries of infected mice had increased lipids, macrophages and T cells as compared to uninfected mice. Increases in plaque, total cholesterol esters and cholesterol monohydrate crystals, macrophages, and T cells were prevented by immunization with heat-killed *P. gingivalis* prior to pathogen exposure. Conclusions: These are the first studies to demonstrate progression of inflammatory plaque accumulation in the innominate arteries by *in vivo* MRI analysis following pathogen exposure, and to document protection from plaque progression in the innominate artery via immunization.] Hayashi C, Genco C, et al. *Atherosclerosis*, Vol. 215, Issue 1, pp 52-59, March 2011. http://www.atherosclerosis-journal.com/article/S0021-9150(10)01029-4/abstract
754. **Porphyromonas gingivalis-host interactions: open war or intelligent guerilla tactics?** [This review summarizes and discusses virulence mechanisms whereby Porphyromonas gingivalis can persist in the oral cavity. It is proposed that the

virulence of P. gingivalis is dependent, at least in part, upon its ability to establish a complex host-pathogen molecular crosstalk which subverts innate immunity. The sophisticated stealth and sabotage tactics used by P. gingivalis may additionally benefit co-habiting organisms occupying the same niche.] Hajishengallisa G. *Microbes Infect*. 2009 May-Jun;11(6-7):637-45. Epub 2009 Apr 5. **http://www.ncbi.nlm.nih.gov/pubmed/19348960**

755. **Porphyromonas gingivalis induces its uptake by human macrophages and promotes foam cell formation in vitro. [**Porphyromonas gingivalis is an etiologic agent of periodontal disease in humans, which has been linked to an increased risk for atherosclerosis-related events. In this study, we examined the effect of P. gingivalis infection on human macrophages with respect to foam cell formation, the hallmark of early atherogenesis, and the potential of P. gingivalis to induce its uptake by these cells. Human monocyte-derived macrophages were incubated with low density lipoprotein and infected with P. gingivalis FDC381 or its fimbriae deficient mutant, DPG3. Consistent with a role for fimbriae in this process, strain 381 significantly increased foam cell formation as compared to DPG3. Recovery of viable P. gingivalis in antibiotic protection experiments was significantly higher for strain 381 than for DPG3. By transmission electron microscopy, the wild-type strain was shown to adhere to and enter THP-1 cells. These results suggest that properties of P. gingivalis which render it capable of adhering to/invading other cell types may also be operative in macrophages and play an important role in its atherogenic potential.] Giacona MB, Papapanou PN, et al. *FEMS Microbiol Lett*. 2004 Dec 1;241(1):95-101. http://www.ncbi.nlm.nih.gov/pubmed/15556715

756. **Porphyromonas gingivalis induces murine macrophage foam cell formation**. **[**Atherosclerosis is a complex pathologic process initialed by the formation of cholesterol-rich plaque. Macrophages play a central role in the development of atherosclerosis, specifically in the initial accumulation of cholesterol in the arterial wall. It has been suggested that infection and chronic inflammatory conditions such as periodontitis may influence the atherosclerosis process. Porphyromonas gingivalis, one of the major pathogens involved in periodontitis, has been detected in human atheromas, suggesting that P. gingivalis infection may be associated with atherosclerosis. However, a causal relationship between this pathogen and the disease process has not yet been established. The purpose of the present investigation was to determine whether P. gingivalis could induce macrophages to form foam cells using the murine macrophage cell line (J774) as a model system. For inocula smaller than one bacterium per ten cells, P. gingivalis 381, as well as its lipopolysaccharide (LPS), induced foam cell formation of macrophages when cultured in the presence of human low-density lipoprotein (LDL). Infection of macrophages with increasing doses of P. gingivalis resulted in higher levels of foam cell formation. More than 70% of the cultured macrophages form cholesterol ester droplet-rich cells in the presence of 100 mug/ml of LDL when the inocula was more than 10 bacteria per cell. Low concentrations of P. gingivalis outer membrane vesicles also induced foam cell formation in the presence of LDL. In addition, it was demonstrated that P. gingivalis LPS alone was able to induce macrophage foam cell formation. P. gingivalis and its vesicles not only promoted LDL binding to macrophages but also induced macrophages to modify native LDL, which plays an important role in foam cell formation and the pathogenesis of atherosclerosis. Therefore, P. gingivalis cells or its vesicles released from periodontal lesions into the circulation may deliver virulence factor(s) such as LPS to the arterial wall to initiate or promote foam cell formation in macrophages and contribute to atheroma development.] Qu M, Miyakawa H, et al. *Microb Pathog*. 2003 Dec;35(6):259-67. http://www.ncbi.nlm.nih.gov/pubmed/14580389

757. **Porphyromonas gingivalis lipopolysaccharide alters atherosclerotic-related gene expression in oxidized low-density-lipoprotein-induced macrophages and foam cells.** [Background and Objective: The molecular mechanism linking atherosclerosis formation and periodontal pathogens is not clear, although a positive correlation between periodontal infections and cardiovascular diseases has been reported. The aim of this study was to determine whether stimulation with Porphyromonas gingivalis lipopolysaccharide (LPS) affected the expression of atherosclerosis-related genes, during and after the formation of foam cells. Material and Methods: Macrophages from human THP-1 monocytes were treated with oxidized low-density lipoprotein (oxLDL) to induce the formation of foam cells. P. gingivalis LPS was added to cultures of either oxLDL-induced macrophages or foam cells. The expression of atherosclerosis-related genes was assayed by quantitative real-time PCR, and the production of granulocyte-macrophage colony-stimulating factor, monocyte chemotactic protein-1, interleukin (IL)-1β, IL-10 and IL-12 proteins was determined using ELISA. Nuclear translocation of nuclear factor-kappaB (NF-κB) P(65) was detected by immunocytochemistry, and western blotting was used to evaluate inhibitory kappa B-α (IκB-α) degradation to confirm activation of the NF-κB pathway. Results: P. gingivalis LPS stimulated atherosclerosis-related gene expression in foam cells and increased the oxLDL-induced expression of chemokines, adhesion molecules, growth factors, apoptotic genes and nuclear receptors in macrophages. Transcription of the proinflammatory cytokines IL1β and IL12 was elevated in response to LPS in both macrophages and foam cells, whereas transcription of the anti-inflammatory cytokine, IL10, was not affected. Increased activation of the NF-κB pathway was also observed in macrophages costimulated with LPS + oxLDL. Conclusion: P. gingivalis LPS appears to be an important factor in the development of atherosclerosis by stimulation of atherosclerosis-related gene expression in both macrophages and foam cells via activation of the NF-κB pathway.] Lei L, Li H, et al. *J Periodontal Res*. 2011 Mar 21. doi: 10.1111/j.1600-0765.2011.01356.x. http://www.ncbi.nlm.nih.gov/pubmed/21418223

758. **Porphyromonas gingivalis mediated periodontal disease and atherosclerosis: disparate diseases with commonalities in pathogenesis through TLRs.** [Toll-like receptors (TLRs) are a group of pathogen-associated molecular pattern receptors, which play an important role in innate immune signaling in response to microbial infection. It has been demonstrated that TLRs are differentially up regulated in response to microbial infection and chronic inflammatory diseases such as atherosclerosis. Furthermore hyperlipidemic mice deficient in TLR2, TLR4, and MyD88 signaling exhibit diminished inflammatory responses and decreased atherosclerosis. Accumulating evidence has implicated specific infectious agents

including the periodontal disease pathogen Porphyromonas gingivalis in the progression of atherosclerosis. Evidence in humans suggesting that periodontal infection predisposes to atherosclerosis is derived from studies demonstrating that the periodontal pathogen P. gingivalis resides in the wall of atherosclerotic vessels and seroepidemiological studies demonstrating an association between pathogen-specific IgG antibodies and atherosclerosis. We have established that the inflammatory signaling pathways that P. gingivalis utilizes is dependent on the cell type and this specificity clearly influences innate immune signaling in the context of local and distant chronic inflammation induced by this pathogen. We have demonstrated that P. gingivalis requires TLR2 to induce oral inflammatory bone lose in mice. Furthermore, we have demonstrated that P. gingivalis infection accelerates atherosclerosis in hyperlipidemic mice with an associated increase in expression of TLR2 and TLR4 in atherosclerotic lesions. Our recent work with P. gingivalis has demonstrated the effectiveness of specific intervention strategies (immunization) in the prevention of pathogen-accelerated atherosclerosis. Improved understanding of the mechanisms driving infection, and chronic inflammation during atherosclerosis may ultimately provide new targets for therapy.] Gibson FC, Genco CA. Curr Pharm Des. 2007;13(36):3665-75. http://www.ncbi.nlm.nih.gov/pubmed/18220804

759. **Porphyromonas gingivalis, Treponema denticola, and Tannerella forsythia: the "red complex", a prototype polybacterial pathogenic consortium in periodontitis.** [ ] Holt SC, Ebersole Jl. Periodontol 2000. 2005;38:72-122. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15853938
760. **Role of dentilisin in Treponema denticola epithelial cell layer penetration. [**Treponema denticola is an oral anaerobic spirochete implicated in periodontal diseases. The chymotrypsin-like protease, dentilisin (PrtP), has been suggested to be an important virulence factor of T. denticola. In this study, we examined the role of dentilisin in T. denticola epithelial monolayer penetration by comparing the wild type and prtP mutant. Wild-type T. denticola can disrupt transepithelial resistance (TER) and substantially penetrate the HEp-2 cell layer. The prtP mutant altered the monolayer only slightly and penetrated the Hep-2 layer in very low numbers. The membrane fraction of wild-type T. denticola is able to complement the prtP mutant in monolayer penetration, while the comparable fraction from the mutant has no such effect. Immunofluorescence studies suggested that wild-type T. denticola altered the TER by likely degrading the tight junctional proteins such as ZO-1. Cytotoxicity was not a major factor in the disruption of TER. The outer membrane vesicles (OMVs) of wild-type T. denticola also disrupted epithelial barrier function and penetrated the epithelial layers. Taken together, these results suggest that T. denticola penetrates the epithelial cell monolayers by altering cellular tight junctions.] Chi B, Qi M, et al. Res Microbiol. 2003 Nov;154(9):637-43. http://www.ncbi.nlm.nih.gov/pubmed/14596901 PMID: 14596901 .
761. **Role of Treponema denticola in periodontal diseases. [**Among periodontal anaerobic pathogens, the oral spirochetes, and especially Treponema denticola, have been associated with periodontal diseases such as early-onset periodontitis, necrotizing ulcerative gingivitis, and acute pericoronitis. Basic research as well as clinical evidence suggest that the prevalence of T denticola, together with other proteolytic gram-negative bacteria in high numbers in periodontal pockets, may play an important role in the progression of periodontal disease. The accumulation of these bacteria and their products in the pocket may render the surface lining periodontal cells highly susceptible to lysis and damage. T. denticola has been shown to adhere to fibroblasts and epithelial cells, as well as to extracellular matrix components present in periodontal tissues, and to produce several deleterious factors that may contribute to the virulence of the bacteria. These bacterial components include outer-sheath-associated peptidases, chymotrypsin-like and trypsin-like proteinases, hemolytic and hemagglutinating activities, adhesins that bind to matrix proteins and cells, and an outer-sheath protein with pore-forming properties. The effects of T. denticola whole cells and their products on a variety of host mucosal and immunological cells has been studied extensively (Fig. 1). The clinical data regarding the presence of T. denticola in periodontal health and disease, together with the basic research results involving the role of T. denticola factors and products in relation to periodontal diseases, are reviewed and discussed in this article.] Sela MN. *Crit Rev Oral Biol Med*. 2001;12(5):399-413. http://www.ncbi.nlm.nih.gov/pubmed/12002822 PMID: 12002822.
762. **Self-generated diversity produces “insurance effects” in biofilm communities** [Diversity generally protects communities from unstable environmental conditions. This principle, known as the “insurance hypothesis,” has been tested in many different ecosystems. Here we show that the opportunistic pathogen *Pseudomonas aeruginosa* undergoes extensive genetic diversification during short-term growth in biofilm communities. The induced genetic changes are produced by a *recA*-dependent mechanism and affect multiple traits, including the behavior of the bacteria in biofilms. Some biofilm-derived variants exhibit an increased ability to disseminate, whereas others manifest accelerated biofilm formation. Furthermore, the presence of these functionally diverse bacteria increases the ability of biofilms to resist an environmental stress. These findings suggest that self-generated diversity in biofilms provides a form of biological insurance that can safeguard the community in the face of adverse conditions.] Boles BR, Thoendel M. et al. *Proceedings of the National Academy of Sciences of the USA*. http://www.pnas.org/content/101/47/16630.abstract?ijkey=817d7b65b944ce4ba115f85b9144ac6a22f49847&keytype2=tf_ipsecsha
763. **Streptococcus tigurinus sp. nov., isolated from blood of patients with endocarditis, meningitis and spondylodiscitis.** [Four Gram-stain-positive, catalase-negative, coccus-shaped bacterial strains were isolated from multiple blood cultures of patients with endocarditis, meningitis and spondylodiscitis. The isolates were tentatively identified as viridans streptococcal species based on phenotypic characteristics. Comparative 16S rRNA gene sequencing studies showed that the organisms were members of the Streptococcus mitis group but did not correspond to any recognized species. The nearest phylogenetic relative was Streptococcus mitis ATCC 49456(T) with 98.6% sequence similarity. The representative strain AZ_3a(T)

showed similarity values of less than 96.8%, 97.6%, 94.5% and 95.5% to the phylogenetically most closely related species by recA, rpoB, sodA and groEL gene sequence analysis, respectively. DNA-DNA hybridization analyses showed a low reassociation value of 32.2% between strain AZ_3a(T) and S. mitis DSM 12643(T). Reassociation values with other S. mitis group species ranged from 27.3% to 49.7%. The G+C content of the DNA is 40.0 mol%. Based on our biochemical and molecular analyses, the novel isolates represent a new species, for which the name Streptococcus tigurinus sp. nov. is proposed. The type strain is AZ_3a(T)(=CCOS 600(T) =DSM 24864(T)).] Abinden A, Mueller NJ, et al. Int J Syst Evol Microbiol. 2012 Feb 21 http://www.ncbi.nlm.nih.gov/pubmed/22357776

764. **Supragingival and subgingival plaque: paradigm of biofilms. [**Most microorganisms in nature live in multispecies communities attached to a substratum-biofilms. Within these communities, organismal interaction is spatiotemporally defined. Because biofilms exist at an interface, their environment is characterized by gradients of nutrients that encourage spatial and metabolic diversity within the population. Oral bacterial biofilms were among the first human-associated biofilms to have been extensively investigated. They are diverse in species, and that diversity reflects the range of habitats within the oral cavity. Oral bacterial communities can be studied in vitro and in vivo. These studies have yielded information on interorganismal interactions and the developmental patterns within the communities. The wealth of information on these communities, coupled with their accessibility in their natural state, firmly establishes them as paradigm systems in biofilm research.] Palmer RJ Jr. *Compend Contin Educ Dent.* 2010 Mar;31(2):104-6, 108. http://www.ncbi.nlm.nih.gov/pubmed/20344897

765. **Synergistic virulence of Porphyromonas gingivalis and Treponema denticola in a murine periodontitis model**. [Chronic periodontitis is characterized by the destruction of the tissues supporting the teeth and has been associated with the presence of a subgingival polymicrobial biofilm containing Porphyromonas gingivalis and Treponema denticola. We have investigated the potential synergistic virulence of P. gingivalis and T. denticola using a murine experimental model of periodontitis. An inoculation regime of four intra-oral doses of 1 × 10(10) P. gingivalis cells induced significant periodontal bone loss compared with loss in sham-inoculated mice, whereas doses of 1 × 10(9) cells or lower did not induce bone loss. Inoculation with T. denticola with up to eight doses of 1 × 10(10) cells failed to induce bone loss in this model. However, four doses of a co-inoculum of a 1 : 1 ratio of P. gingivalis and T. denticola at 5 × 10(8) or 1 × 10(9) total bacterial cells induced the same level of bone loss as four doses of 1 × 10(10) P. gingivalis cells. Co-inoculation induced strong P. gingivalis-specific T-cell proliferative and interferon-γ-dominant cytokine responses, and induced a strong T. denticola-specific interferon-γ dominant cytokine response. Only at the higher co-inoculum dose of 1 × 10(10) total cells was a T. denticola-specific T-cell proliferative response observed. These data show that P. gingivalis and T. denticola act synergistically to stimulate the host immune response and to induce alveolar bone loss in a murine experimental periodontitis model.] Orth RK, O'Brien-Simpson NM, et al. *Mol Oral Microbiol*. 2011 Aug;26(4):229-40. doi: 10.1111/j.2041-1014.2011.00612.x. Epub 2011 May 2. http://www.ncbi.nlm.nih.gov/pubmed/21729244

766. **Systemic antibiotics in the treatment of periodontal disease.** [Nonsurgical scaling and root planing may remove subgingival *Campylobacter rectus* but is frequently ineffective against *Porphyromonas gingivalis,Prevotella intermedia, Bacteroids forsythus,* staphylococci and enteric rods, and may not significantly reduce *Actinobacillus actinomycetemcomitans.* Mechanical debridement may fail to remove pathogenic organisms because of their location in subepithelial gingival tissue, crevicular epithelial cells, collagenous substrata, altered cementum and radicular dentinal tubuli, subgingival hard deposits or furcations or other anatomic features complicating adequate instrumentation. Moreover, periodontal pathogens frequently colonize oral mucosa, tongue dorsum, tonsils and other oral domains and may translocate from non-periodontal sites to periodontal crevices.] Slots J, Ting M. *Periodontology 2000*, Vol. 28;2002, 106-176. http://onlinelibrary.wiley.com/doi/10.1034/j.1600-0757.2002.280106.x/abstract

767. **The Biofilm Concept: Consequenes for Future Prophylaxis of Oral Diseases?** [Biofilm control is fundamental to oral health. Existing oral prophylactic measures, however, are insufficient. The main reason is probably because the micro-organisms involved organize into complex biofilm communities with features that differ from those of planktonic cells. Micro-organisms have traditionally been studied in the planktonic state. Conclusions drawn from many of these studies, therefore, need to be revalidated. Recent global approaches to the study of microbial gene expression and regulation in non-oral micro-organisms have shed light on two-component and quorum-sensing systems for the transduction of stimuli that allow for coordinated gene expression. We suggest interference with two-component and quorum-sensing systems as potential novel strategies for the prevention of oral diseases through control of oral biofilms. Information is still lacking, however, on the genetic regulation of oral biofilm formation. A better understanding of these processes is of considerable importance.] Scheie AA, Petersen FC. *Crit Rev Oral Biol Med (International and American Associations for Dental Research),* 15(1):4-12 (2004). http://cro.sagepub.com/cgi/content/full/15/1/4

768. **The major surface protein complex of Treponema denticola depolarizes and induces ion channels in HeLa cell membranes.** [The oral spirochete Treponema denticola is closely associated with periodontal diseases in humans. The 53-kDa major surface protein (Msp) located in the outer membrane of T. denticola serovar a (ATCC 35405) has both pore-forming activity and adhesin activity. We have used standard patch clamp recording methods to study the effects of a partially purified outer membrane complex containing Msp on HeLa cells. The Msp complex was free of the chymotrypsin-like proteinase also found in the outer membrane of T. denticola. Msp bound to several HeLa cell proteins, including a 65-kDa surface protein and a 96-kDa cytoplasmic protein. The Msp complex depolarized and increased the conductance of the HeLa cell membrane in a manner which was not strongly selective for Na+, K+, Ca2+, and Cl- ions. Cell-attached patches of HeLa cell membrane exposed to Msp complex exhibited short-lived channels with a slope conductance of 0.4 nS in physiologically

normal saline. These studies show that Msp binds both a putative epithelial cell surface receptor and cytoplasmic proteins and that the Msp complex can form large conductance ion channels in the cytoplasmic membrane of epithelial cells. These properties may contribute to the cytopathic effects of T. denticola on host epithelial cells.] Mathers DA, Leung WK, et al. Infect. Immun., 08 1996, 2904-2910, Vol 64, No. 8 http://iai.asm.org/cgi/content/abstract/64/8/2904

769. ***Treponema denticola* in Disseminating Endodontic Infections.** [Treponema denticola is a consensus periodontal pathogen that has recently been associated with endodontic pathology. In this study, the effect of mono-infection of the dental pulp with T. denticola and with polymicrobial "red-complex" organisms (RC) (Porphyromonas gingivalis, Tannerella forsythia, and T. denticola) in inducing disseminating infections in wild-type (WT) and severe-combined-immunodeficiency (SCID) mice was analyzed. After 21 days, a high incidence (5/10) of orofacial abscesses was observed in SCID mice mono-infected with T. denticola, whereas abscesses were rare in SCID mice infected with the red-complex organisms or in wild-type mice. Splenomegaly was present in all groups, but only mono-infected SCID mice had weight loss. T. denticola DNA was detected in the spleen, heart, and brain of mono-infected SCID mice and in the spleen from mono-infected wild-type mice, which also had more periapical bone resorption. The results indicate that T. denticola has high pathogenicity, including dissemination to distant organs, further substantiating its potential importance in oral and linked systemic conditions.] Foschi F, Izard J, et al. *JDR* August 2006 vol. 85 no. 8 761-765, doi: 10.1177/154405910608500814 **http://jdr.sagepub.com/content/85/8/761.short** **http://www.ncbi.nlm.nih.gov/pubmed/16861296**

770. **Use of the carbon dioxide laser in retarding epithelial migration: a pilot histological human study utilizing case reports.** [This is the first reported observation of human histologic evaluation using CO2 laser for de-epithelization and may warrant further study.] Israel M, ; Rossmann JA, et al. *J Periodontol* 1995 Mar;66(3):197-204. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7776164&dopt=Abstract

771. **Virulence Factors of the Oral Spirochete Treponema Denticola. [**There is compelling evidence that treponemes are involved in the etiology of several chronic diseases, including chronic periodontitis as well as other forms of periodontal disease. There are interesting parallels with other chronic diseases caused by treponemes that may indicate similar virulence characteristics. Chronic periodontitis is a polymicrobial disease, and recent animal studies indicate that co-infection of Treponema denticola with other periodontal pathogens can enhance alveolar bone resorption. The bacterium has a suite of molecular determinants that could enable it to cause tissue damage and subvert the host immune response. In addition to this, it has several non-classic virulence determinants that enable it to interact with other pathogenic bacteria and the host in ways that are likely to promote disease progression. Recent advances, especially in molecular-based methodologies, have greatly improved our knowledge of this bacterium and its role in disease.] Dashper SG, Seets CA, et al. *J Dent Res.* 2010 Oct 12. http://www.ncbi.nlm.nih.gov/pubmed/20940357 PMID: 20940357

Probiotics

772. **From Structure to Function: the Ecology of Host-Associated Microbial Communities**. [Summary: In the past several years, we have witnessed an increased interest in understanding the structure and function of the indigenous microbiota that inhabits the human body. It is hoped that this will yield novel insight into the role of these complex microbial communities in human health and disease. What is less appreciated is that this recent activity owes a great deal to the pioneering efforts of microbial ecologists who have been studying communities in non-host-associated environments. Interactions between environmental microbiologists and human microbiota researchers have already contributed to advances in our understanding of the human microbiome. We review the work that has led to these recent advances and illustrate some of the possible future directions for continued collaboration between these groups of researchers. We discuss how the application of ecological theory to the human-associated microbiota can lead us past descriptions of community structure and toward an understanding of the functions of the human microbiota. Such an approach may lead to a shift in the prevention and treatment of human diseases that involves conservation or restoration of the normal community structure and function of the host-associated microbiota.] Robinson CJ, Bohannan BJM, et al. *Microbiology and Molecular Biology Reviews*, September 2010, p. 453-476, Vol. 74, No. 3 http://mmbr.asm.org/cgi/content/abstract/74/3/453

773. **Microbiological evaluation of a probiotic with Lactobacillus reuteri in gingivitis**. [Objective: To assess the microbiological effets of commercially prepared probiotic tablets containing two strains of *Lactobacillus reuteri* in patients with gingivitis. Methods: The study was a doubled-blind, placebo-controlled, cross-over, prospective, randomized clinical trial in patients with gingivitis. After supragingival prophylaxis participants were instructed to take one tablet (either the test or the placebo tablet) per day, in addition to conventional hygiene, during 1 month. A wash-out period of 1 month was allowed between the two test periods. Microbiological outcome variables were studied (by culture and PCR) from subgingival samples and unstimulated saliva samples, taken every 15 days during the three months of study. Chi-square and Mann-Whitney tests were used to compare the results. Results: 40 patients participated in the study. A statistically significant reduction in total bacterial counts in saliva was observed in the test group. A reduction in counts for different periodontal pathogens such as *A. actinomycetemcomitans, T. forsythia, C. rectus* and *Capnocytophaga* sp., was also detected in the subgingival niche in test group. Simultaneously, an increase in counts of *Lactobacillus* sp. was observed. *L. reuteri* strain 2 was frequently found in both saliva (27.5%) and subgingival samples (25.6%), whereas *L. reuteri* strain 1 was less frequent (10.6% in saliva and 2.5% in subgingival samples). Conclusions: *L. reuteri* from probiotic tablets may be able to colonize the saliva and the subgingival niches of gingivitis patients. The use of the test pills was associated with a reduction in the

amounts of selected periodontal pathogens.] Iniesta M, Montero E, et al. *IADR General Session*, San Diego, CA, March 2011. http://iadr.confex.com/iadr/2011sandiego/webprogram/Paper150752.html

774. **Using Probiotics to Help Patients be Proactive; Novel approach can enable the prevention of root caries in a periodontal geriatric population. [**As the US population ages, people are becoming increasingly health conscious, and, similarly, a greater percentage of patients are keeping more teeth. The desire to remain fit as people age has led to an increasing desire to maintain a healthy, functional dentition. The major cause of tooth loss for adults is from periodontal diseases. Therefore, teeth retention for a large portion of adults may require some periodontal therapy. A common result of periodontal therapies is gingival recession and, ultimately, root exposure. Additionally, as people age and become less self-reliant, their oral hygiene measures typically diminish and the likelihood of developing root caries increases. Age- or medication-induced xerostomia also diminishes the innate ability of saliva's protective response. Root surfaces are uniquely more susceptible to caries as they are more porous and likely to develop biofilms and, ultimately, dental caries. *Streptococcus mutans* is the known acidogenic etiologic pathogen in dental caries. Consequently, myriad approaches have been suggested to prevent these exposed roots from developing dental caries. Recently, a new oral probiotic entered the marketplace that can uniquely help prevent root surface decay. By continually inoculating the oral cavity with probiotic bacteria that out-compete naturally occurring *S. mutans*, an environment is created that combats the development of dental caries.] Oxford GE. *Inside Dentistry*, March 2011, Vol 7, Issue 3. http://www.dentalaegis.com/id/2011/03/using-probiotics-to-help-patients-be-proactive

Nutrition

775. **A unique function for ascorbate.** [Vitamin C is a reducing substance, an electron donor. When vitamin C donates its two high-energy electrons to scavenge free radicals, much of the resulting dehydroascorbate is re-reduced to vitamin C and therefore used repeatedly. Conventional wisdom is correct in that only small amounts of vitamin C are necessary for this function because of its repeated use. The point missed is that the limiting part in nonenzymatic free radical scavenging is the rate at which extra high-energy electrons are provided through NADH to re-reduce the vitamin C and other free radical scavengers. When ill, free radicals are formed at a rate faster than the high-energy electrons are made available. Doses of vitamin C as large as 1-10 g per 24 h do only limited good. However, when ascorbate is used in massive amounts, such as 30-200+ g per 24 h, these amounts directly provide the electrons necessary to quench the free radicals of almost any inflammation. Additionally, in high concentrations ascorbate reduces NAD(P)H and therefore can provide the high-energy electrons necessary to reduce the molecular oxygen used in the respiratory burst of phagocytes. In these functions, the ascorbate part is mostly wasted but the necessary high-energy electrons are provided in large amounts.] Cathcart RF. Med Hypotheses. 1991 May;35(1):32-7. http://www.ncbi.nlm.nih.gov/pubmed/1921774

776. **Active oxygen free radicals are scavenged by condensed tannins.** Uchida S, Ohta H, et al. *Prog Clin Biol Res*. 1988;280:"135-8. http://www.ncbi.nlm.nih.gov/pubmed/2845431

777. **α-Lipoic Acid Inhibits Inflammatory Bone Resorption by Suppressing Prostaglandin E_2 Synthesis.** [α-Lipoic acid (LA) has been intensely investigated as a therapeutic agent for several pathological conditions, including diabetic polyneuropathy. In the present study, we examined the effects of LA on osteoclastic bone loss associated with inflammation. LA significantly inhibited IL-1-induced osteoclast formation in cocultures of mouse osteoblasts and bone marrow cells, but LA had only a marginal effect on osteoclastogenesis from bone marrow macrophages induced by receptor activator of NF-κB ligand (RANKL). LA inhibited both the sustained up-regulation of RANKL expression and the production of PGE_2 induced by IL-1 in osteoblasts. In addition, treatment with either prostaglandin E_2 (PGE_2) or RANKL rescued IL-1-induced osteoclast formation inhibited by LA or NS398, a specific cyclooxygenase-2 (COX-2) inhibitor, in cocultures. LA blocked IL-1-induced PGE_2 production even in the presence of arachidonic acid, without affecting the expression of COX-2 and membrane-bound PGE_2 synthase. Dihydrolipoic acid (the reduced form of LA), but not LA, attenuated recombinant COX-2 activity in vitro. LA also inhibited osteoclast formation and bone loss induced by IL-1 and LPS in mice. Our results suggest that the reduced form of LA inhibits COX-2 activity, PGE_2 production, and sustained RANKL expression, thereby inhibiting osteoclast formation and bone loss in inflammatory conditions.] Ha H, Lee JH, et al. *The Journal of Immunology, 2006, 176: 111-117.* http://www.jimmunol.org/cgi/content/full/176/1/111

778. **Alpha-lipoic acid inhibits TNF-alpha-induced NF-kappaB activation and adhesion molecule expression in human aortic endothelial cells**. [Endothelial activation and monocyte adhesion are initiating steps in atherogenesis thought to be caused in part by oxidative stress. The metabolic thiol antioxidant alpha-lipoic acid has been suggested to be of therapeutic value in pathologies associated with redox imbalances. We investigated the role of (R)-alpha-lipoic acid (LA) vs. glutathione and ascorbic acid in tumor necrosis factor alpha (TNF-alpha) -induced adhesion molecule expression and nuclear factor kappaB (NF-kappaB) signaling in human aortic endothelial cells (HAEC). Preincubation of HAEC for 48 h with LA (0.05-1 mmol/l) dose-dependently inhibited TNF-alpha (10 U/ml) -induced adhesion of human monocytic THP-1 cells, as well as mRNA and protein expression of E-selectin, vascular cell adhesion molecule 1 and intercellular adhesion molecule 1. LA also strongly inhibited TNF-alpha-induced mRNA expression of monocyte chemoattractant protein-1 but did not affect expression of TNF-alpha receptor 1. Furthermore, LA dose-dependently inhibited TNF-alpha-induced IkappaB kinase activation, subsequent degradation of IkappaB, the cytoplasmic NF-kappaB inhibitor, and nuclear translocation of NF-kappaB. In contrast, TNF-alpha-induced NF-kappaB activation and adhesion molecule expression were not affected by ascorbic acid or by manipulating cellular glutathione status with l-2-oxo-4-thiazolidinecarboxylic acid, N-acetyl-l-cysteine, or d,l-buthionine-S,R-sulfoximine. Our data show that clinically relevant concentrations of LA, but neither vitamin C nor

glutathione, inhibit adhesion molecule expression in HAEC and monocyte adhesion by inhibiting the IkappaB/NF-kappaB signaling pathway at the level, or upstream, of IkappaB kinase.] Zhang WJ, Frei B. *FASEB J*. 2001 Nov;15(13):2423-32. http://www.ncbi.nlm.nih.gov/pubmed/11689467?dopt=Abstract

779. **Advanced glycation and lipoxidation end products--amplifiers of inflammation: the role of food.** [Chronic diseases (CD) represent the main cause of mortality in developed countries. The increase in the prevalence of of CD is associated with changes in lifestyle habits, including those related to the consumption of processed foodstuffs. In these foods advanced glycation end products (AGE) and advanced lipoperoxydation products (ALE) are formed as a consequence of the reactivity of proteins, carbohydrates, lipid and other components. The aim of the present review is to offer a perspective of how AGE and ALE affect the physiology and development of CD. Continous intake of AGE and ALE contributes to the exccesive accumulation of these products into body tissues, which in turn negatively influence the innate immune system, inflammatory responses, and resistance to diseases. This is achieved by direct interaction of AGE and ALE with specific cell AGE receptors (RAGE) that have a key role as master switches regulating the development of CD. Long-life molecules, namely collagen and myelin, and low-turnover tissues, e.g. connective, bone and neural tissues, are the main targets of AGE and ALE. In these tissues, AGE and ALE lead to the synthesis of insoluble compounds that severely alter cellular functionality. It has been reported associations of AGE and ALE with allergic and autoimmune diseases, Alzheimer disease and other degenerative disorders, catarats, atherosclerosis, cancer, and diabetes mellitus type 2, as well as a number of endocrine, gastrointestinal, skeleton-muscle, and urogenital alterations. Controlling all those pathologies would need further dietary recommendations aiming to limit the intake of processed foods rich in AGE and ALE, as well as to reduce the formation of those products by improving technological processes applicable to foods.] Gil A, Bengmark S. *Nutr Hosp*. 2007 Nov-Dec;22(6):625-40. http://www.ncbi.nlm.nih.gov/pubmed/18051988

780. **Advanced glycation and lipoxidation end products--amplifiers of inflammation: the role of food.** [BACKGROUND: High levels of glycated and lipoxidated proteins and peptides in the body are repeatedly associated with chronic diseases. These molecules are strongly associated with activation of a specific receptor called RAGE and a long-lasting exaggerated level of **inflammation** in the body. METHODS: PubMed reports over 5000 papers plus >13,500 articles about the related HbA(1c), most of them published in the past 5 years. Most of the available abstracts have been read and approximately 800 full papers have been studied. RESULTS: RAGE, a member of the immunoglobulin superfamily of cell surface molecules and receptor for **advanced glycation end products**, known since 1992, functions as a master switch, induces sustained activation of nuclear factor kappaB (NFkappaB), suppresses a series of endogenous autoregulatory functions, and converts long-lasting proinflammatory signals into sustained cellular dysfunction and disease. Its activation is associated with high levels of dysfunctioning proteins in body fluids and tissues, and is strongly associated with a series of diseases from allergy and Alzheimers to rheumatoid arthritis and urogenital disorders. Heat treatment, irradiation, and ionization of foods increase the content of dysfunctioning molecules. CONCLUSIONS: More than half of the studies are performed in diabetes and chronic renal diseases; there are few studies in other diseases. Most of our knowledge is based on animal studies and in vitro studies. These effects are worth further exploration both experimentally and clinically. An avoidance of foods rich in deranged proteins and peptides, and the consumption of antioxidants, especially polyphenols, seem to counteract such a development.] Bengmark S. *JPEN J Parenter Enteral Nutr*. 2007 Sep-Oct;31(5):430-40. **http://www.ncbi.nlm.nih.gov/pubmed/17712153**

781. **Amplifiers of systemic inflammation - The role advanced glycation and lipoxidation end products in foods. [**Chronic diseases are repeatedly associated to accumulation in the body of glycated and lipoxidated proteins and peptides. PubMed reports in excess of 5000 papers plus about 14,000 articles about the related HbA(1c) RAGE, a member of the immunoglobulin super-family of cell surface molecules and receptor for advanced glycation end products, functions as a master switch, induces sustained activation of NF-kappa B, suppresses a series of endogenous auto-regulatory functions and converts long-lasting pro-inflammatory signals into sustained cellular dysfunction and disease. RAGE is activated by high levels of dys-functioning proteins in body fluids and tissues and is strongly associated with chronic diseases from allergy and Alzheimer to rheumatoid arthritis and urogenital disorders. Heat-treatment, irradiation and ionization of foods increase the content in foods of advanced glycated end-products (AGE) and advances lipoxidated end-products (ALE). Some processed foods, much like tobacco smoking are major contributors to accumulation of glycated and lipoxidated molecules in the tissues. Change of life style: avoidance of foods rich in deranged proteins and peptides and increased consumption of antioxidants, especially polyphenols counteracts such a development.] Bengmark S. Kuwait Medical Asoc, Maar 2008, Vol 40, Issue 1, p3-17. https://iris.ucl.ac.uk/research/browse/show-publication?pub_id=295371&source_id=3

782. **Antihistamine effect of supplemental ascorbic acid and neutrophil chemotaxis.** [Renewed interest in the antihistamine action of ascorbic acid has emerged with the recently recognized immunosuppressive role of histamine. We examined the antihistamine effect of acute and chronic vitamin C (VC) administration and its effect on neutrophil chemotaxis in healthy men and women. In the chronic study, 10 subjects ingested a placebo during weeks 1, 2, 5 and 6, and 2 g/day of VC during weeks 3 and 4. Fasting blood samples were collected after the initial 2-week period (baseline) and at the end of weeks 4 and 6. Plasma ascorbate rose significantly following VC administration compared to baseline and withdrawal values. Neutrophil chemotaxis rose 19% (NS) during VC administration, and fell 30% after VC withdrawal, but these changes were not correlated to plasma ascorbate levels ($r = 0.01$). Chemotaxis was inversely correlated to blood histamine ($r = -0.32$, $p = 0.045$), and, compared to baseline and withdrawal values, histamine levels were depressed 38% following VC supplementation. Blood histamine and neutrophil chemotaxis did not change 4 hours following a single 2 g dose of ascorbic acid, although plasma ascorbate rose 150%. These data indicate that VC may indirectly enhance chemotaxis by detoxifying

histamine in vivo.] Johnston CS, Martin LJ, Cai X. *Journal of the American College of Nutrition*, vol 11, Issue 2,172-176. http://www.jacn.org/cgi/content/abstract/11/2/172

783. **Anti-inflammatory activity of gallic acid.** [Gallic acid was found to possess antiinflammatory activity towards zymosan-induced acute food pad swelling in mice. In vitro studies on the mode of action of gallic acid revealed that this compound interferes with the functioning of polymorphonuclear leukocytes (PMNs). Scavenging of superoxide anions, inhibition of myeloperoxidase release and activity as well as a possible interference with the assembly of active NADPH-oxidase may account for the inhibition of inflammatory process by gallic acid. Structure-activity relationship analysis showed that the o-dihydroxy group of gallic acid is important for the inhibitory activity in vitro.] Kroes BH, Vanden Berg AJ, et al. *Planta-Med* 1992 Dec;58(6):499-504. http://grande.nal.usda.gov/ibids/index.php?mode2=detail&origin=ibids_references&therow=585201
784. **Anti-inflammatory Activity of a High-molecular-weight Cranberry Fraction on Macrophages Stimulated by Lipopolysaccharides from Periodontopathogens.** [The continuous, high production of cytokines by host cells triggered by periodontopathogens is thought to be responsible for the destruction of tooth-supporting tissues. Macrophages play a critical role in this host inflammatory response to periodontopathogens. The aim of this study was to investigate the effect of (polyphenols) … on the pro-inflammatory cytokine response of macrophages induced by lipopolysaccharides.... Results clearly indicate that the cranberry fraction was a potent inhibitor of the pro-inflammatory cytokine and chemokine responses induced by LPS. Their results indicated that red wine polyphenols significantly modulate several inflammatory components released by macrophages (a population of host immune cells) in response to bacterial stimuli. Specifically, polyphenols efficiently scavenged and inhibited free-radical generation by host immune cells by controlling intracellular proteins involved in their release. These anti-oxidant properties of red wine polyphenols could be useful in the prevention and treatment of inflammatory periodontal diseases as well as other disorders involving free radicals.] Bodet C. et al., Laval University, Montreal, Canada. *J Dent Research* 85[3]:235-239, 2006. http://jdr.iadrjournals.org/cgi/content/abstract/85/3/235?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&author1=Bodet%2C+c&title=Anti-inflammatory+Activity+&andorexacttitle=and&andorexacttitleabs=and&andorexactfulltext=and&searchid=1&FIRSTINDEX=0&sortspec=relevance&resourcetype=HWCIT http://www.rxpgnews.com/research/dental/article_3641.shtml
785. **Antioxidant and pro-oxidant properties of ascorbic acid and gallic acid**.] The antioxidant and pro-oxidant properties of ascorbic acid (AA) and gallic acid (GA) were investigated. AA and GA, at a concentration of 1.65 mM, accelerate the oxidation of deoxyribose induced by Fe^{3+}–EDTAJH_2O_2. The reducing power of these two compounds increased upon increasing the concentration. AA and GA showed no chelating ability toward iron (II). At a concentration of 4.17 mM, AA and GA exhibited 42.1 and 43.9% scavenging effects on DPPH radicals, respectively. They exhibited 60% scavenging effects on hydrogen peroxide at a concentration of 4.17 mM. No toxicity was found in AA and GA toward human lymphocytes. AA, at 0.82 mM, and GA, at 0.6 mM, exhibited the maximal DNA damage, the means of tail DNA% were 14.8 and 28.8%, respectively. When AA and GA were mixed with H_2O_2, they exhibited a slight inhibitory effect on DNA damage induced by H_2O_2 on pre-incubating both the compounds with human lymphocytes for 30 min before exposure to H_2O_2. The antioxidant activities of AA and GA at a higher concentration were mainly due to the scavenging of hydrogen peroxide in this system. The pro-oxidant mechanism for AA and GA acid is most likely due to the strong reducing power and weak metalchelating ability.] Gow-Chin Y, Pin-Der D, et al. Food Chemistry, Vol 79, Issue 3, Nov 2002, pp 307-313. http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6T6R-458N9NT-2&_user=10&_rdoc=1&_fmt=&_orig=search&_sort=d&_docanchor=&view=c&_searchStrId=1116521918&_rerunOrigin=google&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=c25771711775e91b166fe369b67a0fb3
786. **Antioxidant Enzymes Activity in Polymorphonuclear Leukocytes in Chronic Renal Failure.** [In the present study, activity of polymorphonuclear leukocyte (PMNL) intra-cellular antioxidant enzymes, i.e. catalase, superoxide dismutase (SOD) and glutathione peroxidase (GPX), was assessed in CRF patients on hemodialysis (HD), or continuous ambulatory peritoneal dialysis (CAPD) and in healthy controls. The activity of SOD and GPX was reduced in HD and in CAPD (SOD: by 34.2 and 42%, respectively, and GPX 66 vs. 42%, respectively, taking the activity in normal controls as 100%). Catalase activity, on the other hand, was significantly augmented (298 and 175%, respectively) as compared to the healthy controls. This impairment in antioxidant enzymes activity, involved in the respiratory burst and phagocytosis, may contribute to the understanding of the reduced bactericidal ability of PMNL activity found in these patients.] Shurtz-Swirski R, Mashiach E, et al. *Nephron* 1995;71:176-179. http://content.karger.com/ProdukteDB/produkte.asp?Doi=188708
787. **Antioxidant, gallic acid, induces apoptosis in HL-60RG cells.** [Gallic acid, a naturally occurring plant phenol with antioxidative activity, was found to induce cell death in promyelocytic leukemia HL-60RG cells, although many antioxidants are well known to protect the cell from oxidative stress. Morphological and biochemical studies indicated that the gallic acid-induced cell death is apoptosis. Flow cytometric analysis revealed that the apoptosis was not triggered at a specific phase of the cell cycle and that 2 h exposure of gallic acid to HL-60RG cells was enough to induce apoptosis. The inhibitory assay suggested that gallic acid-induced cell death was mediated by reactive oxygen species such as hydrogen peroxide, superoxide anion in addition to Ca2+ ion, calmodulin-dependent enzymes. Structure-activity analysis suggests that gallic acid induces apoptosis in HL-60RG cells, depending on its distinctive feature derived from the structure but not on its antioxidative activity.] Inoue M, Suzuki R, et al. *Biochem Biophys Res Commun*. 1994 Oct 28;204(2):898-904. http://www.ncbi.nlm.nih.gov/pubmed/7980558

788. **Antioxidants and Atherosclerotic Heart Disease**. [Epidemiologic studies have demonstrated an association between increased intake of antioxidant vitamins such as vitamin E and vitamin C and reduced morbidity and mortality from coronary artery disease. This association has been explained on the basis of the "oxidative-modification hypothesis" of atherosclerosis, which proposes that atherogenesis is initiated by oxidation of the lipids in low-density lipoprotein (LDL), also termed lipid peroxidation. As a corollary to this hypothesis, antioxidants that inhibit lipid peroxidation in LDL should limit atherosclerosis and its clinical manifestations, such as myocardial infarction and stroke. In this review, we will evaluate the current literature involving antioxidants and vascular disease, with particular attention to the potential mechanism or mechanisms of action.] Diaz MN, Frei B, et al. *NEJM*, vol 337:408-416, Aug 7, 1997, No 6. http://content.nejm.org/cgi/content/extract/337/6/408
789. **Ascorbic acid metabolism in diabetes mellitus.**. [In contrast to normal subjects diabetic patients and very low plasma ascorbic acid and significantly high (p less than 0.001) dehydroascorbic acid irrespective of age, sex, duration of the disease, type of treatment, and glycemic control. However, there was no significant difference between the mean leukocyte ascorbate concentrations of the two populations. The in vitro rates of dehydroascorbate reduction in the hemolysate and the erythrocyte reduced glutathione levels and the glucose-6-phosphate dehydrogenase activities, which regulate the dehydroascorbate reduction, were similar in normal and diabetic subjects. The turnover of ascorbic acid was higher in the diabetics than that in the normal volunteers. Experiments with diabetic rats indicated that the increased turnover of ascorbic acid was probably due to increased oxidation of ascorbate to dehydroascorbate in tissue mitochondria. Ascorbic acid supplementation at a dose of 500 mg per day for a brief period of 15 days resulted in an increase in the plasma ascorbate level temporarily, but it did not lower the blood glucose level of the diabetic patients.] Som S, Basu S, et al. *Metabolism*. 1981 Jun;30(6):572-7. http://www.ncbi.nlm.nih.gov/pubmed/7231193
790. **Association of antioxidants with memory in a multiethnic elderly sample using the Third National Health and Nutrition Examination Survey.** [Oxidative stress has been implicated both in the aging process and in the pathological changes associated with Alzheimer's disease. Antioxidants, which have been shown to reduce oxidative stress in vitro, may represent a set of potentially modifiable protective factors for poor memory, which is a major component of the dementing disorders. The authors investigated the association between serum antioxidant (vitamins E, C, A, carotenoids, selenium) levels and poor memory performance in an elderly, multiethnic sample of the United States. The sample consisted of 4,809 non-Hispanic White, non-Hispanic Black, and Mexican-American elderly who visited the Mobile Examination Center during the Third National Health and Nutrition Examination Survey, a national cross-sectional survey conducted from 1988 to 1994. Memory is assessed using delayed recall (six points from a story and three words) with poor memory being defined as a combined score less than 4. Decreasing serum levels of vitamin E per unit of cholesterol were consistently associated with increasing levels of poor memory after adjustment for age, education, income, vascular risk factors, and other trace elements and minerals. Serum levels of vitamins A and C, beta-carotene, and selenium were not associated with poor memory performance in this study.] Perkins AJ, Hendrie HC, et.al. Am J Epidemiol. *1999 Jul 1;150(1):37-44.* http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10400551&dopt=Abstract
791. **Association of some specific nutrient deficiencies with periodontal disease in elderly people: A systematic literature review.** [Objective: Deficiency of vitamin B complex, vitamin C, vitamin D, calcium, and magnesium has been associated with periodontal disease. This article systematically reviews the currently available literature on the feasible association of vitamin B complex, vitamin C, vitamin D, calcium, and magnesium deficiencies with periodontal disease in elderly people. Methods: We performed a systematic review of relevant English- and Dutch-language medical literature published from January 1990 to May 2007, with critical appraisal of those studies evaluating the association of vitamin B complex, vitamin C, vitamin D, calcium, and magnesium deficiencies with periodontal disease in elderly people. Results: None of the studies meeting the selection criteria included institutionalized elderly people. In the studies on non-institutionalized elderly people, no significant or consistent association was found between vitamin B complex, vitamin C, vitamin D, calcium, and magnesium dietary intakes and serum levels and periodontal disease. Although in those studies decreased dietary vitamin C intake was found to be associated with increased risk of periodontal disease, no conclusive evidence could be demonstrated. Conclusion: There is no evidence of an association of vitamin B complex, vitamin C, vitamin D, calcium, and magnesium deficiencies with periodontal disease in non-institutionalized elderly people. To produce conclusive evidence on the subject of this systematic literature review, longitudinal cohort studies and follow-up randomized controlled trials are needed.] Van der Putten G, Vanobbergen J, et al. *Nutrition*, 2009, vol. 23, No 7-8 pp 717-722. http://cat.inist.fr/?aModele=afficheN&cpsidt=21660917
792. **Binding and Neutralization of Lipopolysaccharides by Plant Proanthocyanidins**. [Proanthocyanidins (PACs), polyphenolic metabolites that are widely distributed in higher plants, have been associated with potential positive health benefits including antibacterial, chemotherapeutic, and antiatherosclerotic activities. In this paper, we analyze the binding of PACs from cranberries, tea, and grapes to lipopolysaccharide (LPS), a major component of the outer membrane of Gram-negative bacteria and the cause of several human illnesses. We demonstrate that in the case of cranberries, the most potent LPS-binding activity is contained within a PAC fraction composed of polymers with an average degree of polymerization of 21. The PAC fraction modestly inhibits the binding of LPS to the surface of HEK 293 cells expressing the full complement of LPS receptors (TLR4/MD2 and CD14), while it significantly abrogates the endocytosis of LPS. This PAC fraction also inhibits LPS-induced nuclear factor-κB activation in a manner that is not readily overcome by excess LPS. Such an effect is mediated through the inhibition of LPS interaction with TLR4/MD2 and the partial abrogation of LPS interaction with CD14. Importantly, PAC concentrations that mediate effective LPS neutralization elicit minimal *in vitro* cytotoxicity. Our results identify PACs as a new class of LPS-binding compound and suggest that they have potential utility

in applications that necessitate either the purification and removal of LPS or the *in vivo* neutralization of LPS.] Delehanty JB, Johnson BJ, et al. *Journal of Natural Products*, 2007,70(11),pp1718-1724. http://pubs.acs.org/doi/abs/10.1021/np0703601

793. **Binding of proanthocyanidins with bacteria and bacterial components.** [PACs from the American cranberry {Vacciniwn macrocarpon) are well documented in their ability to protect the urinary tract against the adherence of iiropathogenic bacteria and drinking cranberry juice is a recommended treatment for various urinary tract infections and prostatitis. It has been shown that cranberry PACs inhibit the adherence of P-fimbriated Escherichia coli to cellular surfaces bearing α-Gal (l→ 4) β-Gal receptor sequences similar to those on epithelial cells of the urinary tract (Foo). This effect is mediated largely via A-type PAC-induced conformational changes within the fimbriae proteins which undermine their ability to interact with cell surface receptors on uroepithelial cells.] http://www.wipo.int/pctdb/ja/ia.jsp?ia=US2007%2F077833&IA=US2007077833&DISPLAY=DESC
794. **Bioenergetics in clinical medicine. IX. Gingival and leucocytic deficiencies of coenzyme Q10 in patients with periodontal disease.**. [The specific activities of the succinate dehydrogenase-coenzyme Q10 reductase in mitochondria were determined for patients from a normal periodontal practice. The criteria for selection were patients having a bone score of 1.0-4.0 and a pocket depth of 2.5-5.2 mm. All 29 patients showed a deficiency of 20-63% of CoQ10-enzyme activity in gingival biopsies. The mean value was elevated (P less than 0.001) over that of controls. For corresponding blood samples, 24/28 (86%) showed deficiencies of 20-66% and a higher (P less than 0.001) mean value than that of controls. Periodontal patients frequently have significant gingival and leucocytic deficiencies of CoQ10. The leucocytic deficiency indicates a systemic nutritional imbalance and is not likely caused by neglected oral hygiene. A gingival deficiency could predispose this tissue to periodontitis and this disease could even augment the deficiency. These results support previously suggested adjunctive use of CoQ10 with oral hygiene for improved treatment presumably through bioenergetics.] Hansen IL, Iwamoto Y, et al. *Res Commun Chem Pathol Pharmacol*. 1976 Aug;14(4):729-38. http://www.ncbi.nlm.nih.gov/pubmed/959667
795. **Carvacrol, a component of thyme oil, activates PPAR and γ and suppresses COX-2 expression.** [Cyclooxygenase-2 (COX-2), the rate-limiting enzyme in prostaglandin biosynthesis, plays a key role in inflammation and circulatory homeostasis. Peroxisome proliferator-activated receptors (PPARs) are ligand-dependent transcription factors belonging to the nuclear receptor superfamily and are involved in the control of COX-2 expression, and vice versa. Here, we show that COX-2 promoter activity was suppressed by essential oils derived from thyme, clove, rose, eucalyptus, fennel, and bergamot in cell-based transfection assays using bovine arterial endothelial cells. Moreover, from thyme oil, we identified carvacrol as a major component of the suppressor of COX-2 expression and an activator of PPARα and γ. PPARγ-dependent suppression of COX-2 promoter activity was observed in response to carvacrol treatment. In human macrophage-like U937 cells, carvacrol suppressed lipopolysaccharide-induced COX-2 mRNA and protein expression, suggesting that carvacrol regulates COX-2 expression through its agonistic effect on PPARγ. These results may be important in understanding the antiinflammatory and antilifestyle-related disease properties of carvacrol.] Hotta M, Nakata R, et al. Journal of Lipid Research, Vol. 51, 132-139, January 2010. http://www.jlr.org/cgi/content/abstract/51/1/132?ck=nck
796. **Changes in the antioxidant content of mononuclear leukocytes from mice with endotoxin-induced oxidative stress.** [Abstract : Oxidative stress, associated with a high production of reactive oxygen species (ROS) by immune cells, is involved in the endotoxic shock caused by endotoxin. This oxidative stress is linked to the inability of the immune cells to maintain adequate levels of antioxidants with free radical-scavenging action. Glutathione (GSH) and ascorbic acid (AA) are intracellular and extracellular antioxidants (ROS scavengers) that improve the leukocyte functions. Therefore, in the present work we have determined the reduced GSH and AA content in axillary nodes, spleen, thymus and peritoneal mononuclear leukocytes from BALB/c mice subjected to lethal endotoxic shock produced by intraperitoneal injection of *E. coli* lipopolysaccharide (LPS, 100 mg/kg), at several times (0, 2, 4, 12 and 24 h) after LPS injection. Endotoxic shock decreased the levels of AA in the leukocytes from the three organs as well as the levels of GSH in axillary nodes and spleen cells while it increased the GSH levels in thymus and peritoneum. These results are in agreement with the oxidative stress and the altered function previously observed in those leukocytes, and they suggest that antioxidant administration may be useful for the treatment of endotoxic shock and other oxidative stress situations with altered immunological responses.] Victor VM, Guayerbas N, et al. *Molecular and Cellular Biochemistry*, Volume 229, Numbers 1-2 / January, 2002 pp 107-111. http://www.springerlink.com/content/y9ryhxbh95rp5ant/
797. **Chocolate consumption and cardiometabolic disorders: systematic review and meta-analysis.** [Objective To evaluate the association of chocolate consumption with the risk of developing cardiometabolic disorders. Design Systematic review and meta-analysis of randomised controlled trials and observational studies. Data sources Medline, Embase, Cochrane Library, PubMed, CINAHL, IPA, Web of Science, Scopus, Pascal, reference lists of relevant studies to October 2010, and email contact with authors. Study selection Randomised trials and cohort, case-control, and cross sectional studies carried out in human adults, in which the association between chocolate consumption and the risk of outcomes related to cardiometabolic disorders were reported. Data extraction Data were extracted by two independent investigators, and a consensus was reached with the involvement of a third. The primary outcome was cardiometabolic disorders, including cardiovascular disease (coronary heart disease and stroke), diabetes, and metabolic syndrome. A meta-analysis assessed the risk of developing cardiometabolic disorders by comparing the highest and lowest level of chocolate consumption. Results From 4576 references seven studies met the inclusion criteria (including 114 009 participants). None of the studies was a randomised trial, six were cohort studies, and one a cross sectional study. Large variation was observed between these seven studies for

measurement of chocolate consumption, methods, and outcomes evaluated. Five of the seven studies reported a beneficial association between higher levels of chocolate consumption and the risk of cardiometabolic disorders. The highest levels of chocolate consumption were associated with a 37% reduction in cardiovascular disease (relative risk 0.63 (95% confidence interval 0.44 to 0.90)) and a 29% reduction in stroke compared with the lowest levels. Conclusions Based on observational evidence, levels of chocolate consumption seem to be associated with a substantial reduction in the risk of cardiometabolic disorders. Further experimental studies are required to confirm a potentially beneficial effect of chocolate consumption.] Buitrago-Lopez A, Sanderson J, et al. *BMJ* 2011; 343:d4488. http://www.bmj.com/content/343/bmj.d4488.full

798. **Clinical Evaluation of a Nutraceutical for the Treatment of Periodontal Disease**. Munoz, CA Kiger R. Loma Linda University. [PerioTherapy is effective at reducing gingivitis, bleeding and periodontal pockets, but not attachment levels.] http://www.yourcelebritysmile.com/pdf/pharmaden.pdf ; http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11913269&dopt=Abstract
799. **COQ10** http://www.vistamagonline.com/articles/page.php?tp=3&p=1&id=17&s=coq10_heart_therapy
800. **Cranberry Derived Proanthocyanidins Reduce Bacterial Adhesion to Selected Biomaterials.** [Catheter associated urinary tract infections (CAUTI) linked with the uropathogens *Escherichia coli* (*E. coli*) and *Enterococcus faecalis* (*E. faecalis*) account for the majority of nosocomial infections acquired in the clinical environment. Because these infections develop following initial adhesion of the bacterial pathogens to the catheter surface, there is increased interest in developing effective methods to inhibit attachment of cells to biomaterials used in the manufacture of indwelling devices. High molecular weight proanthocyanidins (PAC) extracted from the North American cranberry (*Vaccinium macrocarpon*) were examined for their potential to reduce the initial adhesion of uropathogenic bacteria (*E. coli* CFT073 and *E. faecalis* 29212) to two model biomaterials, poly(vinyl chloride) (PVC) and polytetrafluoroethylene (PTFE). Well-controlled experiments conducted in a parallel-plate flow chamber (PPFC) demonstrated decreased attachment of both bacteria to PVC and PTFE when either the bacteria, biomaterial or both surfaces were treated with PAC. Most significant inhibition of bacterial adhesion was observed for the condition where both the bacteria and biomaterial surfaces were coated with PAC. Additional experiments conducted with nonbiological model particles demonstrate comparable extents of adhesion inhibition, supporting a nonbiospecific mechanism of PAC action. The results of this study are promising for the implementation of PAC in the clinical milieu for prevention of device associated infection as the proposed functional modification is independent of antibacterial mechanisms that may give rise to resistant strains.] Eydelnant IA, Tufenkji N. *Langmuir*, 2008,24(18),pp10273-10281. http://pubs.acs.org/doi/abs/10.1021/la801525d
801. **Dietary patterns and risk of mortality from cardiovascular disease, cancer, and all causes in a prospective cohort of women.** [Background: The impact of overall dietary patterns that reflect actual eating behaviors on mortality caused by cardiovascular or other chronic diseases is largely unknown. METHODS AND RESULTS: We prospectively evaluated the relation between dietary patterns and risk of cardiovascular, cancer, and all-cause mortality among 72,113 women who were free of myocardial infarction, angina, coronary artery surgery, stroke, diabetes mellitus, or cancer and were followed up from 1984 to 2002. Dietary patterns were derived by factor analysis based on validated food frequency questionnaires administered every 2 to 4 years. Two major dietary patterns were identified: High prudent pattern scores represented high intakes of vegetables, fruit, legumes, fish, poultry, and whole grains, whereas high Western pattern scores reflected high intakes of red meat, processed meat, refined grains, french fries, and sweets/desserts. During 18 years of follow-up, 6011 deaths occurred, including 1154 cardiovascular deaths and 3139 cancer deaths. After multivariable adjustment, the prudent diet was associated with a 28% lower risk of cardiovascular mortality (95% confidence interval [CI], 13 to 40) and a 17% lower risk of all-cause mortality (95% CI, 10 to 24) when the highest quintile was compared with the lowest quintile. In contrast, the Western pattern was associated with a higher risk of mortality from cardiovascular disease (22%; 95% CI, 1 to 48), cancer (16%; 95% CI, 3 to 30), and all causes (21%; 95% CI, 12 to 32). CONCLUSIONS: Greater adherence to the prudent pattern may reduce the risk of cardiovascular and total mortality, whereas greater adherence to the Western pattern may increase the risk among initially healthy women.] Heidemann C, Schulze MB, et al Circulation. 2008 Jul 15;118(3):230-7. http://www.ncbi.nlm.nih.gov/pubmed/18574045
802. **Dietary supplementation with antioxidants improves functions and decreases oxidative stress of leukocytes from prematurely aging mice.** [Objectives: Aging is accompanied by chronic inflammation and oxidative stress, which lead to a marked impairment of immune function and therefore increased mortality. This study assessed the effect of dietary supplementation, for 15 wk, with 5% and 20% (w/w) of biscuits enriched with nutritional doses of vitamins C and E, zinc, selenium, and β-carotenes on function and oxidative stress parameters of peritoneal leukocytes from middle-aged, prematurely aging mice (PAM) and non-prematurely aging mice (NPAM). Methods: After supplementation we measured leukocyte functions (adherence, chemotaxis, phagocytosis, intracellular reactive oxygen species levels, lymphoproliferation, natural killer activity, and interleukin-2 release), antioxidant defenses (superoxide dismutase, glutathione peroxidase, and reduced glutathione), oxidant compounds (extracellular O_2^-, glutathione disulfide, glutathione disulfide/reduced glutathione ratio, tumor necrosis factor-a, nitric oxide, and prostaglandin E_2), and lipid and DNA oxidative damage, measured by malondialdehyde and 8-oxo,7,8-dihydro-2'-deoxyguanosine levels, respectively. Results: In general, leukocyte functions were improved and redox homeostasis was restored after intake of antioxidants. In consequence, malondialdehyde and 8-oxo,7,8-dihydro-2'-deoxyguanosine in PAM and NPAM were strikingly decreased after 5% and 20% supplementation (malondialdehyde, $P < 0.001$ in PAM; $P < 0.01$ in NPAM after both treatments; 8-oxo,7,8-dihydro-2'-deoxyguanosine, $P < 0.01$ after 5% supplementation and $P < 0.001$ after 20% supplementation in PAM and NPAM). Moreover, the effect of the antioxidants was stronger in PAM than in NPAM, and 20% supplementation was more effective than 5%. Conclusion: Our

data suggest that improvement of leukocyte function and restoration of redox balance after consumption of adequate levels of antioxidants from adulthood may be useful to attain healthy aging, especially in animals with premature aging.] Alvarado C, Alvarez P, et al. *Nutrition*, 2006, Vol. 22, No 7-8, pp. 767-777. http://cat.inist.fr/?aModele=afficheN&cpsidt=17952921

803. **Direct characterization of caffeoyl esters with antihyaluronidase activity in crude extracts from Echinacea angustifolia roots by fast atom bombardment tandem mass spectrometry.** [Fast atom bombardment (FAB-MS) and fast atom bombardment tandem mass spectrometry (FAB-MS/MS) techniques (negative ions) have been successfully applied for identification of the constituents responsible for the antihyaluronidase activity of Echinacea angustifolia roots, whose extracts are widely employed for the adjuvant therapy of chronic inflammatory diseases. Crude extracts from different solvents were tested for antihyaluronidase activity, and those with the greatest inhibitory action (the ethylacetate, butylacetate and chloroform fractions, IC50 0.44, 0.50 e 0.62 mg/ml) were directly analyzed by MS. Full scan mass spectra produced intense molecular anions: collisional activation of these resulted in tandem mass spectra rich in significant product ions. Four main caffeoyl conjugates were detected and identified by tandem mass spectrometry (daughter and parent ion mode): 2,3-O-dicaffeoyltartaric acid (chicoric acid) and 5-O-dicaffeoylquinic acid (cynarine) and 2-O-caffeoyltartaric acid (caffaric acid) in the ethylacetate fraction. Among these caffeoyl conjugates, chicoric and caftaric acids had the greatest antihyaluronidase activity: IC50 = 0.42 and 0.61 mM, while the IC50 of cynarine and chlorogenic acid were 1.85 and 2.25 mM.] Facino Rm, Carini M, et al. *Farmaco*. 1993 Oct;48(10):1447-61. http://www.ncbi.nlm.nih.gov/pubmed/8117383

804. **Does overall diet in midlife predict future aging phenotypes? A cohort study**. [Background: The impact of diet on specific age-related diseases has been studied extensively, but few investigations have adopted a more holistic approach to determine the association of diet with overall health at older ages. We examined whether diet, assessed in midlife, using dietary patterns and adherence to the Alternative Healthy Eating Index (AHEI), is associated with aging phenotypes, identified after a mean 16-year follow-up. METHODS: Data were drawn from the Whitehall II cohort study of 5350 adults (age 51.3±5.3 years, 29.4% women). Diet was assessed at baseline (1991-1993). Mortality, chronic diseases, and functioning were ascertained from hospital data, register linkage, and screenings every 5 years and were used to create 5 outcomes at follow-up: ideal aging (free of chronic conditions and high performance in physical, mental, and cognitive functioning tests; 4%), nonfatal cardiovascular event (7.3%), cardiovascular death (2.8%), noncardiovascular death (12.7%), and normal aging (73.2%). RESULTS: Low adherence to the AHEI was associated with an increased risk of cardiovascular and noncardiovascular death. In addition, participants with a "Western-type" diet (characterized by high intakes of fried and sweet food, processed food and red meat, refined grains, and high-fat dairy products) had lower odds of ideal aging (odds ratio for top vs bottom tertile: 0.58; 95% confidence interval, 0.36-0.94; P=.02), independently of other health behaviors. CONCLUSIONS: By considering healthy aging as a composite of cardiovascular, metabolic, musculoskeletal, respiratory, mental, and cognitive function, the present study offers a new perspective on the impact of diet on aging phenotypes.] Akbaraly T, SAbia S, et al. Am J Med. 2013 May;126(5):411-419.e3. doi: 10.1016/j.amjmed.2012.10.028. http://www.ncbi.nlm.nih.gov/pubmed/23582933

805. **Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial. [**Folic acid supplementation for 3 years significantly improved domains of cognitive function that tend to decline with age.] Durga J, Van boxtel MP, et al. Lancet. 2007 Jan 20;369(9557):208-16. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=17240287&dopt=Abstract

806. **Effect of antioxidant vitamins on the transient impairment of endothelium-dependent brachial artery vasoactivity following a single high-fat meal.** [CONTEXT: Much has been written about the potential role of antioxidants in the prevention of atherosclerosis. OBJECTIVE: To assess the short-term effect of a single high-fat meal with and without pretreatment with antioxidant vitamins on endothelial function in healthy, normocholesterolemic subjects. DESIGN: Observer-blinded randomized trial. SETTING: University hospital. PARTICIPANTS: Twenty healthy, normocholesterolemic (total and low-density lipoprotein cholesterol <5.2 mmol/L and <3.4 mmol/L [<200 mg/dL and <130 mg/ dL], respectively), male (7) and female (13) hospital employee volunteers, aged 24 to 54 years. INTERVENTION: Three randomly administered breakfasts: (1) a high-fat meal (3766 J [900 calories], 50 g of fat); (2) a low-fat meal (3766 J [900 calories], 0 g of fat); and (3) a high-fat meal and pretreatment with oral administration of vitamins C (1 g) and E (800 IU) (high-fat meal with vitamins). A subgroup of 10 subjects also ate the low-fat meal with the same vitamin pretreatment (low-fat meal with vitamins). MAIN OUTCOME MEASURE: High-resolution ultrasound assessed flow-mediated (endothelium-dependent) brachial artery vasodilation measured as percent diameter change before and hourly for 6 hours following each meal. RESULTS: Flow-mediated vasodilation fell from a mean+/-SD of 20%+/-8% before to 12%+/-6%, 10%+/-6%, and 8%+/-9% at 2, 3, and 4 hours, respectively, after the high-fat meal (P<.001). No significant changes in flow-mediated vasodilation occurred after the low-fat meal, high-fat meal with vitamins, or low-fat meal with vitamins. The change in flow-mediated vasodilation after the low-fat and high-fat meals correlated inversely with the 2-hour postprandial change in triglyceride levels (r=-0.54; P<.001). CONCLUSION: A single high-fat meal transiently reduces endothelial function for up to 4 hours in healthy, normocholesterolemic subjects, probably through the accumulation of triglyceride-rich lipoproteins. This decrease is blocked by pretreatment with antioxidant vitamins C and E, suggesting an oxidative mechanism.] Plotnick GD, Corretti MC, et al. *JAMA*. 1997 Nov 26;278(20):1682-6. http://www.ncbi.nlm.nih.gov/pubmed/9388088

807. **Effects of a nutritional supplement on periodontal status. [**Among the recommendations for the maintenance of gingival and periodontal health, few have focused on the value of nutritional supplements. The purpose of this study was to compare the effect of certain nutritional and plant-derived nutraceuticals and a placebo tablet in the reduction of gingivitis, bleeding,

probing depths, and attachment levels in a 60-day two-cell, randomized, parallel clinical trial for patients with Type II periodontal disease. The vitamin therapy was introduced as an adjunct to patient homecare to determine if there was a quantifiable improvement to soft-tissue health and periodontal damage. Sixty-three patients were randomly divided into two groups of 32 and 31 subjects and given either a vitamin tablet containing seven active ingredients (experimental treatment) or a placebo tablet. The clinical parameters assessed were the gingival index (GI), bleeding index (BI), periodontal pocket depth (PD), and attachment levels (AL), and were recorded at baseline and 60 days. Patients took the assigned tablet at breakfast and at dinner after brushing their teeth twice daily. After 60 days, the data showed a clinical reduction in the GI, BI, and PD for the experimental group ($P < .0001$). There were no significant changes for AL with either the experimental or the placebo group. When the data were further analyzed for pocket depths of > or = 4 mm in patients receiving the experimental treatment, there were clinically significant improvements in the GI and PD from baseline to 60 days ($P < .0001$), but no significant differences in the BI and AL. There were no statistical differences in any of the indices when the data were compared between men and women. The results of the present study suggest that a multi-vitamin nutritional supplement might be a beneficial adjunct to the required established periodontal treatment.] Munoz CA, Kiger RD, et al. *Compend Contin Educ Dent*. 2001 May;22(5):425-8. http://www.ncbi.nlm.nih.gov/pubmed/11913269

808. **Effects of specific nutrients on periodontal disease onset, progression and treatment.** [OBJECTIVES: The aim of this paper is to review the available literature pertaining to the effects of specific nutritional elements (e.g. vitamin B-complex, vitamin C and dietary calcium) on general wound healing, periodontal disease status and response to periodontal therapy. METHODS: Critical appraisal of various studies that have evaluated the effects of calcium, ascorbic acid and vitamin B-complex in wound healing and periodontal treatment. RESULTS: Periodontal disease onset, progression and response to therapeutic interventions have been shown to be influenced by several systemic, local and environmental modifying factors. Nutritional supplementation has been suggested as a possible influencing factor on periodontal status and wound healing. Several studies have reported various degrees of association between nutritional elements/supplements and periodontal status, and others have reported possible positive influences of nutritional supplementation on periodontal therapeutic outcomes. Future research needs to more fully explore the presence and strength of association between nutrition and periodontal health. CONCLUSIONS: Data collected from the literature suggests that nutrient supplementation causes minimal or no side effects. However, the efficacy of prophylactic nutrient supplementation for the prevention of the onset and progression of periodontal disease, or for the enhancement of periodontal wound healing, remains to be determined.] Neiva RF, Steigenga J, et al. *J Clin Periodontol*. 2003 Jul;30(7):579-89. http://www.ncbi.nlm.nih.gov/pubmed/12834494

809. **Effects of Vitamin-B Complex Supplementation on Periodontal Wound Healing**. [Background: Reports have demonstrated that nutrient supplements, in particular vitamin-B complex (Vit-B), can positively influence wound healing processes. However, limited information is available on the effects of Vit-B on periodontal wound healing. Methods: A total of 30 patients (13 males, 17 females) presenting with generalized moderate to severe chronic periodontitis were enrolled in this study. All subjects presented ≥ two teeth in the same sextant with probing depth (PD) ≥5 mm and bleeding upon probing (BOP) in need of access flap surgery (AFS). This study was a randomized, double-masked, placebo-controlled clinical trial. Subjects were instructed to take one capsule a day of either Vit-B (50 mg of the following: thiamine HCl, riboflavin, niacinamide, d-calcium pantothenate, and pyridoxine HCl; 50 µg each of d-biotin and cyanocobalamin; and 400 mcg of folate) or placebo for 30 days following AFS. Clinical attachment levels (CAL) and N-benzoyl-dl-arginine-2- naphthylamide (BANA) test scores were measured at baseline and at 90 and 180 days following surgical intervention. Assessments of the healing response were also performed using BOP, gingival index (GI), and plaque index (Pl) at baseline and 7, 14, 30, 90, and 180 days. The mean results of each parameter were averaged within a group. Differences between groups were analyzed by using repeated measures analysis of variance (ANOVA). Results: Both groups experienced comparable levels of PD reduction following AFS (test: -1.57 ± 0.34; control: -1.50 ± 0.21). Changes in mean CAL were more favorable in Vit-B supplemented subjects (test: $+0.41 \pm 0.12$; control: -0.52 ± 0.23; $P = 0.024$). Stratified data demonstrated significantly better results for the test group in both shallow (test: -0.08 ± 0.03; control: -1.11 ± 0.27; $P = 0.032$) and deep sites (test: $+1.69 \pm 0.31$; control: $+0.74 \pm 0.23$; $P = 0.037$). No significant differences were observed between groups regarding PI, GI, and BOP. BANA test values were significantly reduced in both groups after surgical treatment and no significant differences were noted between groups. Conclusion: Vitamin B-complex supplement in combination with AFS resulted in statistically significant superior CAL gains when compared to placebo.] Al-Shammari K, Nociti FH, et al. *Journal of Periodontology*, July 2005, Vol. 76, No. 7, Pages 1084-1091. http://www.joponline.org/doi/abs/10.1902/jop.2005.76.7.1084?journalCode=jop

810. **Efficacy of dietary fiber in lowering serum cholesterol.**[in the last few years, increasing attention has been given to lowering serum cholesterol levels to reduce high rates of coronary artery disease in the U.S. population. …In this issue of the *Journal*, Hunninghake et al report the results fo a nearly year-long multicenter trail of the efficacy of dietary fiber in the treatment of hypercholesterolemia…. Although the same level of dietary fiber intake can be achieve by consuming fruits, vegetables, and grain products rick in fibers, as shown by Jenkins et al, such intake may require drastic changes in eating habits. This may be particularly difficult for onvegitarian patients whose consumption of dietary fiber is quite low. Therefore, for some patients, dietary fiber may be provided as supplements for serum cholesterol reduction.] Garg, A. *The American Journal of Medicine*, Volume 97, Issue 6, December 1994, Pages 501-503. http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6TDC-4CM94GX-6N&_user=10&_rdoc=1&_fmt=&_orig=search&_sort=d&_docanchor=&view=c&_searchStrId=1159448691&_rerunOrigin=google&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=43d387f7ebd630cc033743330423063a

811. **Efficacy of lycopene in the treatment of gingivitis: a randomised, placebo-controlled clinical trial.** [PURPOSE: The aim of the present study was to compare the effect of systemically administered lycopene (LycoRed) as a monotherapy and as an adjunct to scaling and root planing in gingivitis patients. MATERIALS AND METHODS: Twenty systemically healthy patients showing clinical signs of gingivitis were involved in a randomised, double-blind, parallel, split-mouth study. The subjects were randomly distributed between the two treatment groups: experimental group (n = 10), 8 mg lycopene/day for 2 weeks; and controls (n = 10), placebo for 2 weeks. Quadrant allocation within each group was randomised with two quadrants treated with oral prophylaxis (OP) and two quadrants not receiving any form of treatment (non-OP). Bleeding index (SBI) and non-invasive measures of plaque (PI) and gingivitis (GI) were assessed at baseline, 1 and 2 weeks. Salivary uric acid levels were also measured. RESULTS: All the treatment groups demonstrated statistically significant reductions in the GI, SBI and PI. Treatment with OP-lycopene resulted in a statistically significant decrease in GI when compared with OP-placebo ($p < 0.05$) and non-OP-placebo ($p < 0.01$). Treatment with non-OP-lycopene resulted in a statistically significant decrease in GI when compared with non-OP-placebo ($p < 0.01$). The OP-lycopene group showed a statistically significant reduction in SBI values when compared with the non-OP-lycopene group ($p < 0.05$) and the non-OP-placebo group ($p < 0.001$). There was a strong negative correlation between the salivary uric acid levels and the percentage reduction in GI at 1 and 2 weeks in the OP-lycopene group ($r = -0.852$ and -0.802 respectively) and in the non-OP-lycopene group ($r = -0.640$ and -0.580 respectively). CONCLUSIONS: The results presented in this study suggest that lycopene shows great promise as a treatment modality in gingivitis. The possibility of obtaining an additive effect by combining routine oral prophylaxis with lycopene is also an exciting possibility, which deserves further study.] Chandra RV, Prabhuji ML, et al. *Oral Health Prev Dent*. 2007;5(4):327-36. http://www.ncbi.nlm.nih.gov/pubmed/18173095

812. **Efficacy of Subgingival Irrigation Using Herbal Extracts on Gingival Inflammation.** [Background: The aim of the present study was to investigate the efficacy of an herbal-based mouthrinse in combination with an oral irrigator in reducing gingival inflammation. Methods: A total of 89 patients (45 females, 44 males; mean age 49.1 ± 1.31 years) were included in this prospective, randomized, double-blind clinical study and allocated to 3 treatment groups: group 1 (n = 34), treated with an oral irrigator with subgingival tips and an herbal-based mouthrinse; group 2 (n = 29), the oral irrigator was applied in combination with a conventional mouthwash; and group 3 (n = 26), treated with the conventional mouthwash without subgingival irrigation. Data collected at baseline and after 4, 8, and 12 weeks included gingival index (GI), sulcus bleeding index (SBI), plaque index (PI), and probing depth (PD). Over a period of 3 months, GI decreased from 1.80 ± 0.04 to 1.56 ± 0.04 in group 1; from 1.79 ± 0.05 to 1.68 ± 0.04 in group 2; and remained nearly constant in group 3 (from 1.79 ± 0.05 to 1.81 ± 0.04). Differences between the groups were significant (analysis of variance, $P < 0.05$). SBI values in group 1 were reduced from 2.51 ± 0.06 to 2.13 ± 0.06 after 3 months and were significantly lower than in group 2 ($P = 0.001$) and 3 ($P = 0.002$), with SBIs of 2.44 ± 0.06 and 2.42 ± 0.07, respectively, after 12 weeks. A reduction in PI was noted for all 3 groups throughout the follow-up period, with no statistically significant differences. Probing depths were not reduced significantly in any group. Conclusion: Subgingival irrigation with an herbal-based mouthrinse led to a significant reduction in both SBI and GI. This regimen can, therefore, be recommended as an adjunctive procedure to reduce gingival inflammation.] Pistorius A, Willershausen B, et al. *Journal of Periodontology*, May 2003, Vol. 74, No. 5, Pages 616-622. http://www.joponline.org/doi/abs/10.1902/jop.2003.74.5.616?journalCode=jop

813. **Folic acid, homocysteine, and cardiovascular disease: judging causality in the face of inconclusive trial evidence.** [The conclusion that homocysteine is a cause of cardiovascular disease explains the observations from all the different types of study, even if the results from one type of study are, on their own, insufficient to reach that conclusion. No single alternative explanation can account for all the observations. Since folic acid reduces homocysteine concentrations, to an extent dependent on background folate levels, it follows that increasing folic acid consumption will reduce the risk of heart attack and stroke by an amount related to the homocysteine reduction achieved. We therefore take the view that the evidence is now sufficient to justify action on lowering homocysteine concentrations, although the position should be reviewed as evidence from ongoing clinical trials emerges.] Wald DS, Wald NJ, et al. BMJ 2006;333:1114-1117 . http://www.bmj.com/cgi/content/full/333/7578/1114

814. **Free radicals, antioxidants in disease and health.** [Free radicals and oxidants play a dual role as both toxic and beneficial compounds, since they can be either harmful or helpful to the body. They are produced either from normal cell metabolisms in situ or from external sources (pollution, cigarette smoke, radiation, medication). When an overload of free radicals cannot gradually be destroyed, their accumulation in the body generates a phenomenon called oxidative stress. This process plays a major part in the development of chronic and degenerative illness such as cancer, autoimmune disorders, aging, cataract, rheumatoid arthritis, cardiovascular and neurodegenerative diseases. The human body has several mechanisms to counteract oxidative stress by producing antioxidants, which are either naturally produced in situ, or externally supplied through foods and/or supplements. This mini-review deals with the taxonomy, the mechanisms of formation and catabolism of the free radicals, it examines their beneficial and deleterious effects on cellular activities, it highlights the potential role of them antioxidants in preventing and repairing damages caused by oxidative stress, and it discusses the antioxidant supplementation in health maintenance.] Pham-Huy LI, He H, et al. Int J Biomed Sci 2008; 4(2): 89-96. http://ykameelah.wordpress.com/

815. **Gingival and leucocytic deficiencies of coenzyme Q10 in patients with periodontal disease.** [The specific activities of the succinate dehydrogenase-coenzyme Q10 reductase in mitochondria were determined for patients from a normal periodontal practice. The criteria for selection were patients having a bone score of 1.0-4.0 and a pocket depth of 2.5-5.2 mm. All 29 patients showed a deficiency of 20-63% of CoQ10-enzyme activity in gingival biopsies. The mean value was elevated (P less than 0.001) over that of controls. For corresponding blood samples, 24/28 (86%) showed deficiencies of 20-66% and a higher

(P less than 0.001) mean value than that of controls. Periodontal patients frequently have significant gingival and leucocytic deficiencies of CoQ10. The leucocytic deficiency indicates a systemic nutritional imbalance and is not likely caused by neglected oral hygiene. A gingival deficiency could predispose this tissue to periodontitis and this disease could even augment the deficiency. These results support previously suggested adjunctive use of CoQ10 with oral hygiene for improved treatment presumably through bioenergetics.] *Res Commun Chem Pathol Pharmacol*. 1976 Aug;14(4):729-38. http://www.ncbi.nlm.nih.gov/pubmed/959667

816. **Guar gum and plasma cholesterol. Effect of guar gum and an oat fiber source on plasma lipoproteins and cholesterol in hypercholesterolemic adults. [The hypolipidemic effect of guar gum (GG, 15 g/day) was compared with that of an oat fiber source (OFS, 77 g/day). Both** treatments supplied the same amount of total dietary fiber (11 g/day) and were taken with water three times a day for 3 weeks at mealtime. Thirteen free-living adult men and women participated in the study. Their total plasma cholesterol (TC) was 244 +/- 21 mg/dl (mean +/- SD), and plasma triglycerides (TGLYs) were 149 +/- 93 mg/dl before the intervention. Diets were monitored to ensure that no changes occurred other than the replacement of carbohydrate calories for the 200 kcal/day supplied by the OFS. Combined averages for both of the crossover phases showed that GG induced a reduction in TC of 26 +/- 10 mg/dl and in low density lipoprotein cholesterol of 25 +/- 9 mg/dl. The OFS induced a reduction in TC of 9 +/- 13 mg/dl and in low density lipoprotein cholesterol of 11 +/- 4 mg/dl. Although both treatments were effective in reducing elevated TC, GG at the levels fed was significantly more effective (p less than 0.001) in reducing TC. Neither treatment induced significant changes in high density lipoprotein cholesterol or very low density lipoprotein cholesterol.] Spiller GA, Farquhar JW, et al. *Arteriosclerosis and Thrombosis*, Vol 11, 1204-1208. http://atvb.ahajournals.org/cgi/content/abstract/11/5/1204

817. **Grape seed extract induces apoptotic death of human prostate carcinoma DU145 cells via caspases activation accompanied by dissipation of mitochondrial membrane potential and cytochrome c release.** [Results suggest that GSE possibly causes mitochondrial damage leading to cytochrome c release in cytosol and activation of caspases resulting in PARP cleavage and execution of apoptotic death of human prostate cancer DU145 cells.] Agarwal C, Singh RP, *Carcinogenesis. 2002 Nov;23(11):1869-76.* http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&itool=pubmed_docsum&list_uids=12419835&query_hl=8

818. **Graying of the immune system: can nutrient supplements improve immunity in the elderly?** [It is recognized that nutrient intake should not only prevent the classic deficiency diseases, but also could reduce illness and improve health. The type of nutrients and the quantity required to achieve such a beneficial effect varies with the index being studied and whether more than one nutrient is being administered simultaneously. For some nutrients, the amounts proposed as being healthful apparently cannot be provided by a reasonable quantity and variety of natural foods. Thus, nutrient supplements may be important for health promotion and prevention of certain chronic diseases.[1,2] This view goes against the prevailing dogma in nutritional science that a balanced diet is sufficient to achieve all nutritional objectives.] Chandra RL, *J Am Med Assoc*, May 7, 1997 Vol. 277, No. 17. http://www.faqs.org/abstracts/Health/Graying-of-the-immune-system-can-nutrient-supplements-improve-immunity-in-the-elderly.html http://www.nutritionhealthinfo.com/nutrition/nutrition_0162_001.pdf

819. **Histamine degradative potential of ascorbic acid: Considerations and evaluations.** [Conclusion The above points clearly bring out the histamine degradative potential of ascorbic acid and its beneficial effect in stress. However, it should not be assumed that this indicates an almost universal therapeutic action of this vitamin. Obviously, as plain reasoning suggests, such a small molecule cannot be the curative factor for handling a number of unrelated maladies. It is probably the removal of excess histamine, elevated under stress situations, which leads to the suppression of the side effects which otherwise would have been triggered by histamine. Hence there is a better resistance and apparent relief. Other effects, like influencing the cyclic AMP levels etc., have also been suggested to account for the medical potential of vitamin C. A co-therapy of ascorbic acid along with the antihistamines or other drugs could be doubly effective in handling situations arising due to increased histamine in the system.] Subramanian N. *Inflammation Research*, Vol 8, Num 5 / October,1978,pp484-487. http://www.springerlink.com/content/t47j81v316144183/

820. **Incorrect nutrition as a risk factor for periodontal disease.** [Knowledge of the cause, prevention, and treatment of periodontal disease has increased rapidly during the past several decades; however, periodontal disease is still a prevalent infection, the treatment of which consumes vast amounts of financial and manpower resources. The intention of this article is to explore the role of nutrition in both the initiation and treatment of periodontal disease and to suggest that dental health professionals should consider nutritional guidance as a part of routine periodontal care.] Riley M. *Alpha Omegan*. 2007;100(2):85-8. http://www.ncbi.nlm.nih.gov/pubmed/17824397

821. **Increase in Plasma Endotoxin Concentrations and the Expression of Toll-Like Receptors and Suppressor of Cytokine Signaling-3 in Mononuclear Cells After a High-Fat, High-Carbohydrate Meal Implications for insulin resistance.** [**OBJECTIVE** To compare the effect of a high-fat, high-carbohydrate meal (HFHC) with that of a high-fiber and fruit meal on the concentrations of endotoxin (lipopolysaccharide [LPS]), LPS-binding protein (LBP), the expression of toll-like receptors (TLRs), and the suppressor of cytokine signaling-3 (SOCS-3) in mononuclear cells. RESEARCH DESIGN AND METHODS Healthy lean subjects were given 910 calories of either an HFHC meal (n = 10) or an American Heart Association (AHA)-recommended meal rich in fiber and fruit (n = 10) after an overnight fast. Blood was collected before and at 1, 2, and 3 h after the meal. Cellular indexes of oxidative and inflammatory stress; the expression of SOCS-3, TLR2, and TLR4 in mononuclear cells; and plasma concentrations of LPS and LBP were measured. RESULTS HFHC meal intake induced an increase in plasma LPS concentration and the expression of SOCS-3, TLR2, and TLR4 protein, reactive oxygen

species generation, and nuclear factor-κB binding activity ($P < 0.05$ for all). These increases were totally absent after the AHA meal rich in fiber and fruit. CONCLUSIONS The novel changes described after the HFHC meal elucidate further the mechanisms underlying postprandial inflammation and also provide the first evidence explaining the pathogenesis of insulin and leptin resistance mediated by SOCS-3 after such meals. In contrast, an AHA meal does not induce these effects.] Ghanim H, Abuaysheh S, et al. Diabetes Care December 2009 vol. 32 no. 12 2281-2287. http://care.diabetesjournals.org/content/32/12/2281.abstract

822. **Inhibition of activator protein-1 transcription factor activation by [omega]-3 fatty acid modulation of mitogen-activated protein kinase signaling kinases.** [Background: Lipopolysaccharide (LPS)-stimulated macrophages (M[Phi]) produce excess tumor necrosis factor (TNF), and the direct inhibition of I[kappa]B phosphorylation and its subsequent separation from the nuclear factor [kappa]B (NF[kappa]B)-I[kappa]B complex has been experimentally supported as a mechanism for [omega]-3 fatty acid (FA) inhibition of this TNF response. However, TNF production is a "late" event in the LPS-mduced M[Phi] inflammatory cascade, and in addition to NF[kappa]B-associated pathways, a separate transcription factor, activator protein-1 (AP-1) is an important pathway for M[Phi] proinflammatory cytokine production. The mitogen-activated protein kinase (MAPK) cascade regulates both NF[kappa]B-I[kappa]B-and AP-1-associated gene transcription through several cross-amplifying phosphorylation kinases, specifically p44/42 [ie, extracellular signal-regulated kinase (ERK) 1/2], p38, and c/jun N-terminal kinase (JNK)/stress-activated protein kinase (SAPK). The activation of these kinases occurs in the proximal MAPK cascade and activation modulates AP-1 activation. In this set of experiments, it was hypothesized that inhibition of MAPK signaling phosphorylation kinases by [omega]-3 fatty acids in a model of LPS-stimulated M[Phi]s would alter the activation of the proinflammatory cytokine transcription factor AP-1. …Conclusions: [omega]-3 FA inhibited p44/42 and JNK/SAPK phosphorylation; however, p38 remained unchanged. Phosphorylation of p44/42 and JNK/SAPK are the immediate prior steps in AP-1 activation. Attenuated AP-1 activation and subsequent attenuated gene-level proinflammatory cytokine elaboration is anticipated after inhibition of these MAPK intermediates and is confirmed by the reduction in AP-1 activity. These results provide further evidence for the transcriptional level regulation in the elaboration of proinflammatory cytokines by [omega]-3 FA in this M[Phi] model.] Babcock TA, Kurland A, et.al. *Journal of Parenteral and Enteral Nutrition 27:176-181, 2003.* *http://findarticles.com/p/articles/mi_qa3762/is_200305/ai_n9216984*

823. **Inhibition of protease activities of periodontopathic bacteria by extracts of plants used in Kenya as chewing sticks (mswaki).** [Extracts from five plants used as chewing sticks, and tannic acid, gallic acid and methyl ester of gallic acid, were tested for their ability to inhibit proteolytic activities of three strains of Bacteroides gingivalis, three strains of Bacteroides intermedius and two strains of Treponema denticola. Aqueous extract from the plants Rhus natalensis and Euclea divinorum were the most inhibitory of those tested, inhibiting by 50% the proteolytic activity of the test organisms, at concentrations of up to 200 micrograms/ml. Tannic and gallic acids had similar effects at concentrations of less than 10 micrograms/ml, while the methyl ester of gallic acid was less inhibitory. These findings suggest that extracts from plants used as chewing sticks may possess enough inhibitory components to interfere with the virulence and growth of periodontopathic bacteria in vivo, provided they are able to gain access to the subgingival sites such bacteria preferentially inhabit.] Homer KA, Manji F, et al. *Arch Oral Biol.* 1990;35(6):421-4. http://www.ncbi.nlm.nih.gov/pubmed/2142592 Arch Oral Biol.

824. **Interleukin-1 genotype-selective inhibition of inflammatory mediators by a botanical: a nutrigenetics proof of concept**. [Objective: Although observational studies have shown that genotype may influence nutritional effects on target outcomes, there are few reported studies that stratified subjects by genotype before a nutritional intervention. This proof-of-concept trial determined whether specifically formulated botanical mixtures reduced inflammation in individuals with genetic variations that predispose to overexpression of interleukin-1β (IL-1β) and early heart disease. Methods: Healthy adults with elevated C-reactive protein (CRP) were stratified into genetic groups based on being positive (IL1Pos) or negative (IL1Neg) for the at-risk IL-1 gene variations. IL1Pos ($n = 39$) and IL1Neg ($n = 40$) subjects were then randomized to the candidate botanical formulation or placebo. The botanical formulation included rose hips, a blueberry and blackberry mixture, and a grapevine extract. Results: At 12 wk of dosing with the botanical formulation, IL-1β gene expression by stimulated peripheral blood mononuclear cells was significantly lower than at baseline and significantly lower than placebo in IL1Pos and IL1Neg subjects. Mean IL-1β gene expression treatment effect over the 12-wk period was greater in IL1Pos than in IL1Neg subjects. At 12 wk of dosing the botanical mixture produced no mean change in serum CRP levels. However, in IL1Pos subjects, significantly more subjects achieved a reduction in CRP with the botanical mixture than with placebo. No CRP effect was observed in the IL1Neg subjects. Conclusion: This study represents one of a few prospective clinical trials in which genetic variations were shown to differentially influence nutrient effects on outcomes.] Kornman Ken, Rogus J, et al. Nutrition, Vol 23, Issue 11, pp 844-852, Nov 2007. http://www.nutritionjrnl.com/article/S0899-9007(07)00246-8/abstract

825. **Long-term treatment of hypercholesterolemia with dietary fiber.** [PURPOSE: To evaluate the hypocholesterolemic effects of long-term treatment (36 to 51 weeks) with a mixture of dietary fibers (guar gum, pectin, soy, pea, corn bran) administered twice a day. PATIENTS AND METHODS: Fifty-nine subjects with moderate hypercholesterolemia who completed a 15-week, placebo-controlled study with the dietary fiber were treated for an additional 36 weeks with 20 g/day of fiber. Subjects were counseled and monitored on a National Cholesterol Education Program (NCEP) Step-One Diet before starting and during treatment. Analyses of changes in lipoprotein values during the additional 36 weeks of treatment took into account changes in weight, diet, and other variables that might have affected the response to treatment. RESULTS: There were no significant effects on the levels of either triglycerides or high-density lipoprotein cholesterol (HDL-C). Levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) and the LDL/HDL ratio were significantly reduced

during treatment. The mean percentage reductions from baseline after 51 weeks of treatment were approximately 5% for TC, 9% for LDL-C, and 11% for the LDL/HDL ratio. Changes were apparent after 3 weeks of treatment, with the maximum reductions occurring by the 15th week of treatment. CONCLUSIONS: For subjects on a Step-One Diet who complied with the treatment regimen, the moderate cholesterol-lowering effects of the fiber persisted throughout the 36-to-51 week treatment period.] Hunninghake DB, Miller VT, et al. *Am J Med*. 1994 Dec;97(6):504-8. http://www.ncbi.nlm.nih.gov/pubmed/7985708

826. **Long-term vegetarians have low oxidative stress, body fat, and cholesterol levels**. [Excessive oxidative stress and abnormal blood lipids may cause chronic diseases. This risk can be reduced by consuming an antioxidant- and fiber-rich vegetarian diet. We compared biomarkers of oxidative stress, antioxidant capacity, and lipid profiles of sex- and age-matched long-term vegetarians and omnivores in Korea. Forty-five vegetarians (23 men and 22 women; mean age, 49.5 ± 5.3 years), who had maintained a vegetarian diet for a minimum of 15 years, and 30 omnivores (15 men and 15 women; mean age, 48.9 ± 3.6 years) participated in this study. Their 1-day, 24-h recall, and 2-day dietary records were analyzed. Oxidative stress was measured by the levels of diacron reactive oxygen metabolites (d-ROM). Antioxidant status was determined by the biological antioxidant potential (BAP) and levels of endogenous antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. We observed that vegetarians had a significantly lower body fat percentage (21.6 ± 6.4%) than that of omnivores (25.4 ± 4.6%; $P < 0.004$). d-ROM levels were significantly lower in vegetarians than those in omnivores (331.82 ± 77.96 and 375.80 ± 67.26 Carratelli units; $P < 0.011$). Additionally, total cholesterol levels in the vegetarians and omnivores were 173.73 ± 31.42 mg/dL and 193.17 ± 37.89 mg/dL, respectively ($P < 0.018$). Low-density lipoprotein cholesterol was 101.36 ± 23.57 mg/dL and 120.60 ± 34.62 mg/dL ($P < 0.005$) in the vegetarians and omnivores, respectively, indicating that vegetarians had significantly lower lipid levels. Thus, oxidative stress, body fat, and cholesterol levels were lower in long-term vegetarians than those in omnivores.] Kim MK, Cho SW, et al. Nutr Res Pract. 2012 April; 6(2): 155–161. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3349038/

827. **Nutrients and micronutrients: progress in science-based understanding.** [Oral tissues and fluids exquisitely mirror subtle changes in nutritional status and are often the first sites of the body to exhibit clinical signs of malnutrition and micronutrient excesses, deficiencies or imbalances. The relatively high rates of epithelial stem cell division in the oral mucosal tissues, the production of saliva and its constituents, the rates of alveolar bone growth and resorption, and the inability of enamel to remodel all provide readily available opportunities to monitor the physiological status of humans throughout the life span. Virtually every classical nutritional deficiency disease, such as scurvy and pellagra, as well as a host of immune deficiencies, have signs and symptoms in the oral cavity. The lips, tongue, oral mucosa, gingiva, periodontal ligament and alveolar bone can all reflect nutritional status. Nutrients interact with physiological systems in the oral cavity such as cell division, deoxyribonucleic acid, or DNA, repair, protein synthesis and secretion, and immune-response mechanisms in such a manner as to increase or decrease the risk of disease. As oral health professionals, we realize that the oral epithelium acts as a protection against microbes such as viruses, bacteria, yeast and parasitic opportunistic infections. We appreciate that these microbes produce toxic substances, particularly antigens derived from oral microbes that invade the underlying collagenous connective tissues. We also appreciate that dental procedures and devices as well as oral lesions can alter a patient's food selection and oral hygiene behavior, further increasing the risk of oral and systemic disease.] Slavkin HC, *J Am Dent Assoc*, 1997;128;1306-1313. http://jada.ada.org/cgi/reprint/128/9/1306

828. **Nutrition and inflammatory markers [**Inflammation underlies many chronic diseases. The goal of nutritional support in such diseases is to provide adequate energy and nutrients to meet the increased requirements for synthesis of acute phase proteins, inflammatory mediators, antioxidant defenses and the promotion of tissue repair and restoration of cellular function. Systemic inflammation alters utilization of various nutrients (fats, carbohydrates and protein) and promotes increased cellular consumption of key antioxidant vitamins and minerals. Some nutrients play a direct role in the resolution of inflammation. These relationships necessitate consideration of the adjunctive role of diet in the natural history of periodontitis. Little is known about the role of nutrition in periodontitis. With rapid advances in molecular biology and nutritional genomics in particular, oral health scientists can address this important area of study.] Enwonwu CO, Ritchie CS. *J Am Dent Assoc, Vol 138, No 1, 70-73.* http://jada.ada.org/cgi/content/abstract/138/1/70

829. **Nutrient-Gene Interaction: Metabolic Genotype-Phenotype Relationship.** [The U.S. Department of Health and Human Services (DHHS)/USDA *Dietary Guidelines for Americans* is a science and population evidence-based guide on diet and physical activity, providing advice and recommendations to promote a healthier lifestyle and reduce the risk of chronic diseases, including cancer. These recommendations are supported by the comprehensive evidence-based review on diet and cancer prevention conducted by the American Institute for Cancer Research, National Cancer Institute, World Health Organization/International Agency for Research on Cancer, and others. However, influencing dietary effects are the individual genetic predispositions that are the basis for considerable interindividual variations in cancer risk within the population and in nutrient homeostasis, which is maintained by genomic-nutrient and metabolic-phenotype interactions. Although genetics is an important component, it accounts for only a portion of this variation. An individual's overall phenotype, including health status, is achieved and maintained by the sum of metabolic activities functioning under differing circumstances within the life cycle and the complex interactions among genotype, metabolic phenotype, and the environment. In this postgenomic era, high-throughput groups of technologies in genomics, proteomics, and metabolomics measure and analyze DNA sequences, RNA transcripts, proteins, and nutrient-metabolic fluxes in a single experiment. These advances have transformed biomarker studies on nutrient-gene interactions from a reductionist concept into a holistic practice in which many regulated genes involved in metabolism, along with its metabolic phenotypes, can be measured through functional

genomics and metabolic profiling. The overall integration of data and information from the building blocks of metabolism-based nutrient-gene interaction can lead to future individualized dietary recommendations to diminish cancer risk.] Go VLW, Nguyen CTH, et al. *American Society for Nutrition J. Nutr*. 135:3016S-3020S, December 2005. http://jn.nutrition.org/cgi/content/full/135/12/3016S

830. **Nutritional Supplement program halts progression of early coronary atherosclerosis documented by ultrafast computed tomography. [**ABSTRACT: The aim of this study was to determine the effect of a defined nutritional supplement program on the natural progression of coronary artery disease. This nutritional supplement program was composed of vitamins, amino acids, minerals, and trace elements, including a combination of essential nutrients patented for use in the prevention and reversal of cardiovascular disease. The study was designed as a prospective intervention before-after trial over a 12 month period and included 55 patients (age 44-67) with various stages of coronary heart disease. Changes in the progression of coronary artery calcification before and during the nutritional supplement intervention were determined by Ultrafast Computed Tomography (Ultrafast CT). The natural progression rate of coronary artery calcification before the intervention averaged 44% per year. The progression of coronary artery calcification decreased on average 15% over the course of one year of nutritional supplementation. In a subgroup of patients with early stages of coronary artery disease, a statistically significant decrease occurred, and no further progression of coronary calcification was observed. In individual cases, reversal and complete disappearance of previously existing coronary calcifications were documented. This is the first clinical study documenting the effectiveness of a defined nutritional supplement program in halting early forms of coronary artery disease within one year. The nutritional supplement program tested here should be considered an effective and safe approach to prevention and adjunct therapy of cardiovascular disease.] Rath M, Niedzwiecki A. *J Applied Nutrition*, Vol 48, No. 3, 1996. http://md-phc.com/nutrition/cell_ess.htm

831. **Oxygen free radical scavenging abilities of vitamins C and E, and a grape seed proanthocyanidin extract in vitro.** [Proanthocyanidins, a group of polyphenolic bioflavonoids, have been reported to exhibit a wide range of biological, pharmacological and chemoprotective properties against oxygen free radicals. We have assessed the concentration-dependent oxygen free radical scavenging abilities of a grape seed proanthocyanidin extract (GSPE), vitamin C and vitamin E succinate (VES) as well as superoxide dismutase, catalase and mannitol against biochemically generated superoxide anion and hydroxyl radical using a chemiluminescence assay and cytochrome c reduction. A concentration-dependent inhibition was demonstrated by GSPE. At a 100 mg/l concentration, GSPE exhibited 78-81% inhibition of superoxide anion and hydroxyl radical. Under similar conditions, vitamin C inhibited these two oxygen free radicals by approximately 12-19%, while VES inhibited the two radicals by 36-44%. The combination of superoxide dismutase and catalase inhibited superoxide anion by approximately 83%, while mannitol resulted in an 87% inhibition of hydroxyl radical. The results demonstrate that GSPE is a more potent scavenger of oxygen free radicals as compared to vitamin C and VES.] Bagchi D, Garg A, et al. *Res Commun Mol Pathol Pharmacol*. 1997 Feb;95(2):179-89. http://www.ncbi.nlm.nih.gov/pubmed/9090754

832. **Pilot study of dietary fatty acid supplementation in the treatment of adult periodontitis.** [The anti-inflammatory effects of both n-3 and n-6 polyunsaturated fatty acids (PUFA) have been demonstrated in vitro and in many disease states, in particular in the treatment of rheumatoid arthritis. The benefit of n-3 PUFA supplementation has been documented in animal models of periodontal inflammation and a trend towards reduced inflammation has been seen in human experimental gingivitis. The purpose of this study was to examine the potential anti-inflammatory effects of PUFA supplementation, by administration of fish oil as a source of the n-3 PUFA, eicosapentaenoic acid, and borage oil as a source of the n-6 PUFA, gamma-linolenic acid (GLA), to adults with periodontitis. Thirty adult human subjects with periodontitis were administered either fish oil 3000 mg daily; borage oil 3000 mg daily; fish oil 1500 and borage oil 1500 mg daily, or placebo. The modified gingival index, the plaque index (PI), periodontal probing depths and β-glucuronidase levels in gingival crevicular fluid were measured at baseline and after 12 weeks of treatment. Improvement in gingival inflammation was observed in subjects treated with borage oil (P<0.016), with a trend apparent in subjects treated with fish oil or a combination of PUFA. There was no statistically significant improvement in PI, although a trend was apparent in those receiving borage oil. Improvement in probing depth was seen in those subjects treated with either fish oil alone or borage oil alone, but statistical significance was only seen for the comparison of borage oil and placebo (P<0.044). No change was seen in gingival crevicular fluid (GCF) β-glucuronidase levels. The use of borage oil supplementation, a source of the n-6 PUFA, GLA, can have beneficial effects on periodontal inflammation. n-6 PUFA supplementation seemed to offer more impressive results than either n-3 PUFA supplementation or the combination of lower doses of the two supplements. Additional studies will be necessary to more fully assess the potential of these agents to favorably affect periodontal inflammation.] Rosenstein ED, Kushner LJ, et al. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, Volume 68, Issue 3, March 2003, Pages 213-218. http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6WPH-47X1C3V-4&_user=10&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_version=1&_urlVersion=0&_userid=10&md5=da238c0a177930c9e38a288336d9caea

833. **Polyol-combinant saliva stimulants and oral health in Veterans Affairs patients--an exploratory study.** [An exploratory study investigated the root caries incidence in Department of Veterans Affairs patients with exposed root surfaces. For a period of six to 30 months, the subjects were systematically assigned to groups which used chewable dragees or chewing gums that contained either xylitol or sorbitol as bulk sweeteners. The mean treatment time was 1.8 years (standard deviation = 0.8). The consumption levels of both polyols was up to 8.5 g daily, used typically in five episodes during a 16-hour period. The subjects were examined every six months in connection with their standard scheduled visits at the Veterans Affairs Medical Center. The risk for a root-surface lesion in the xylitol group was only 19% of that for a surface in the sorbitol group

(relative risk, 0.19; 95% confidence interval, 0.06-0.62; p < or = 0.0065). Simultaneous study in periodontal patients showed that both polyols significantly reduced the gingival index scores, and slightly (but not significantly) reduced the plaque index scores. Collectively, both studies suggest that frequent daily consumption of chewable, saliva-stimulating products containing essentially nonfermentable or slowly fermentable dietary carbohydrate sweeteners (xylitol and sorbitol) may have an oral-health-improving effect in Department of Veterans Affairs Medical Center patients. It is necessary to evaluate if these procedures would be efficacious in larger and expanded patient cohorts.] Makinen KK, Pemberton D, et al. *Spec Care Dentist*. 1996 May-Jun;16(3):104-15. http://www.ncbi.nlm.nih.gov/pubmed/9084323

834. **Polyphenolic flavanols as scavengers of aqueous phase radicals and as chain-breaking antioxidants.** [The purpose of this investigation was to establish the relative antioxidant activities in vitro of the flavanolic polyphenols, the catechins, and catechin-gallate esters. The relative antioxidant potentials were measured against radicals generated in the aqueous phase and against propagating lipid peroxyl radicals. The results show that in the aqueous phase their order of effectiveness as radical scavengers is epicatechin gallate (ECG) > epigallocatechin gallate (EGCG) > epigallocatechin (EGC) > gallic acid (GA) > epicatechin congruent to catechin; against propagating lipid peroxyl radical species, epicatechin and catechin are as effective as ECG and EGCG, the least efficacious being EGC and GA. This is consistent with their relative abilities to protect against consumption of LDL alpha-tocopherol. The results are discussed in the context of the most relevant antioxidant constituents of green tea extracts.] Salah N, Miller NJ, et al. *Arch Biochem Biophys*. 1995 Oct 1;322(2):339-46. http://www.ncbi.nlm.nih.gov/pubmed/7574706

835. **Polyunsaturated fatty acids and inflammation.** [The n-6 polyunsaturated fatty acid arachidonic acid gives rise to the eicosanoid family of mediators (prostaglandins, thromboxanes, leukotrienes and related metabolites). These have inflammatory actions in their own right and also regulate the production of other mediators including inflammatory cytokines. Consumption of long chain n-3 polyunsaturated fatty acids decreases the amount of arachidonic acid in cell membranes and so available for eicosanoid production. Thus, n-3 polyunsaturated fatty acids decrease production of arachidonic acid-derived eicosanoids. These fatty acids also decrease the production of the classic inflammatory cytokines tumour necrosis factor, interleukin-1, and interleukin-6 and the expression of adhesion molecules involved in inflammatory interactions between leukocytes and endothelial cells. These latter effects may occur by eicosanoid-independent mechanisms including modulation of the activation of transcription factors involved in inflammatory processes. The anti-inflammatory actions of long chain n-3 fatty acid-induced effects may be of therapeutic use in conditions with an acute or chronic inflammatory component.] Calder PC. *Prostaglandins Leukot Essent Fatty Acids*. 2006 Sep;75(3):197-202. http://www.ncbi.nlm.nih.gov/pubmed/16828270

836. **Polyunsaturated fatty acids and inflammatory processes: New twists in an old tale.** [The n-6 fatty acid arachidonic acid (AA; 20:4n-6) gives rise to eicosanoid mediators that have established roles in inflammation and AA metabolism is a long recognised target for commonly used anti-inflammatory therapies. It has generally been assumed that all AA-derived eicosanoids are pro-inflammatory. However this is an over-simplification since some actions of eicosanoids are anti-inflammatory (e.g. prostaglandin (PG) E(2) inhibits production of some inflammatory cytokines) and it has been discovered quite recently that PGE(2) inhibits production of inflammatory leukotrienes and induces production of inflammation resolving lipoxin A(4). The n-3 fatty acids from oily fish and "fish oils", eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3), are incorporated into inflammatory cell phospholipids in a time- and dose-dependent manner. They are incorporated partly at the expense of AA, but also of other n-6 fatty acids. EPA and DHA inhibit AA metabolism. Thus production of AA-derived eicosanoids is decreased by these n-3 fatty acids; this occurs in a dose-dependent manner. EPA gives rise to an alternative family of eicosanoids (e.g. PGE(3)), which frequently, but not always, have lower potency than those produced from AA. Recently a new family of EPA- and DHA-derived lipid mediators called resolvins (E- and D-series) has been described. These have potent anti-inflammatory and inflammation resolving properties in model systems. It seems likely that these mediators will explain many of the antiinflammatory actions of n-3 fatty acids that have been described. In addition to modifying the profile of lipid-derived mediators, fatty acids can also influence peptide mediator (i.e. cytokine) production. To a certain extent this action may be due to the altered profile of regulatory eicosanoids, but it seems likely that eicosanoid-independent actions are a more important mechanism. Indeed effects on transcription factors that regulate inflammatory gene expression (e.g. nuclear factor kappaB) seem to be important.] Calder PC. *Biochimie*. 2009 Jun;91(6):791-5. http://www.ncbi.nlm.nih.gov/pubmed/19455748

837. **Potential Mechanisms Underpinning the Nutritional Modulation of Periodontal Inflammation. [Background. Periodontitis results from an inappropriate host response to pathogenic biofilms**. Because traditional management approaches have failed to reduce disease prevalence, the research focus has shifted toward managing host-mediated inflammation. In this article, the author reviews the role of nutrition in the development and resolution of inflammation. Methods. The author reviewed the biomedical literature to elucidate mechanisms by which dietary factors affect inflammatory processes and to establish what evidence exists for macronutritional and micronutritional modulation of inflammation at a cellular and molecular level.Conclusions. Hyperinflammation characterizes the periodontitis phenotype, and oxidative stress is a key orchestration point for the diverse signaling pathways, which control inflammation. Oxidative stress is modulated by diet, as well as by infection. Recent research has demonstrated that subtle shifts in nutritional status are associated independently with the prevalence of periodontitis. Moreover, the results of contemporary animal and human studies have demonstrated the role of specific micronutrients in the modulation of the host's inflammatory response by reducing inflammatory biomarkers and bone loss. Clinical Implications. The scientific community is starting to realize the health benefits of diets containing foods naturally rich in antioxidants and omega-3 polyunsaturated fatty acids, as well as the

dangers of diets that are high in refined carbohydrates. Nutritional intervention studies in patients with inflammatory periodontitis are needed to evaluate the effect of nutritional approaches to periodontal management.] Chapple ILC, *J Am Dent Assoc*, Vol 140, No. 2, 178-184. http://jada.ada.org/cgi/content/short/140/2/178

838. **Procyanidolic oligomers (OPCs). [**Proanthocyanidins(polyphenols)found in high concentration in the grape pip, outer seed membrane), attach to the polymeric filaments in bacterial membranes, thereby inhibiting their aggregation and thus preventing the key initiating factor that leads to periodontal disease.] Masquelier J. *J. Parfums Cosmet Arom*, 95: 89-97, 1990
839. **Procyanidins from Vitis vinifera seeds: In vivo effects on oxidative stress**. [The purpose of this study was to evaluate the effect of supplementation with procyanidins from Vitis vinifera on markers of oxidative stress. Ten healthy volunteers received a daily dose of 110 mg of procyanidins for 30 days. Fasting venous blood samples were taken before and at the end of the supplementation period and after 7 days of wash-out. The total antioxidant activity and the plasma concentrations of α-tocopherol were not modified. Conversely, the levels of α-tocopherol in red blood cell membranes increased significantly from 1.8 ± 0.1 to 2.8 ± 0.2 mg/g. Similarly, the lymphocyte oxidized DNA [8-oxo-7,8-dihydro-2'-deoxyguanosine/2'-deoxyguanosine ratio] was reduced from 7.23 ± 2.47 to 2.34 ± 0.51, and the red blood cell membrane fatty acid composition shifted to a higher level of polyunsaturated fatty acids. On the basis of these results, it may be suggested that dietary procyanidins exert their antioxidant protection in vivo by sparing liposoluble vitamin E and reducing DNA oxidative damage.] Simonetti P, Ciappellano S, et al. *Journal of Agricultural and Food Chemistry*, 2002, vol. 50, No 21, pp 6217-6221. http://cat.inist.fr/?aModele=afficheN&cpsidt=13974316
840. **Protective role of antioxidative food factors in oxidative stress caused by hyperglycemia. [**Hyperglycemia causes the autoxidation of glucose, glycation of proteins, and the activation of polyol metabolism. These changes accelerate generation of reactive oxygen species (ROS) and increases in oxidative chemical modification of lipids, DNA, and proteins in various tissues. Oxidative stress may play an important role in the development of complications in diabetes such as lens cataracts, nephropathy, and neuropathy. Glycation reactions, especially Maillard reactions, occur in vivo as well as in vitro and are associated with the chronic complications of diabetes mellitus and aging and age-related diseases by increases in oxidative chemical modification of lipids, DNA, and proteins. In particular, long-lived proteins such as lens crystallines, collagens, and hemoglobin may react with reducing sugars to form advanced glycation end products (AGEs). Recently, we found a novel type of AGE, named MRX, and we found that MRX is a good biomarker for detecting oxidative stress produced during Maillard reaction. We also examined in detail the role of lipid peroxidation reaction in hyperglycemia and found that hexanoyl modification formed by the reaction of oxidized lipids and proteins must be important for oxidative stress. Detailed analyses of the formation mechanism of hexanoyl lysine (HEL) moiety in proteins were conducted, and excretion of HEL into urine was quantified by using LC/MS/MS. Macrophages and neutrophils play an important role in oxidative stress during hyperglycemia, and we determined that oxidatively modified tyrosines are a good biomarker for formation of oxidative stress at an early stage. Immunochemical analyses by application of monoclonal antibodies specific to lipid hydroperoxide-modified proteins produced by polyunsaturated fatty acids including docosahexaenoic acid (DHA) in oxidative stress caused by hyperglycemia were conducted, and the relationship between glycation and lipid peroxidation reactions both by chemical and immunochemical approaches are discussed. Recently, we put much more focus on dietary antioxidants for prevention of diabetic complications. Curcuminoids, the main yellow pigments in Curcuma longa (turmeric), have been used widely and for a long time in the treatment of sprain and inflammation in indigenous medicine. Curcumin is the main component of turmeric, and two minor components are also present as the curcuminoids. Curcuminoids possess antioxidant activity. Protective effects of curcumin (U1) and one of its major metabolites, tetrahydrocurcumin (THU1), have been examined for development of diabetic cataract in 25% galactose-fed SD rats. Through detailed examination of protective mechanisms of THU1, it was found that THU1 showed that scavenger ROS not only formed during hyperglycemia, but also induced antioxidative enzymes including detoxification enzymes such as glutathine S-transferase. THU1 also showed significant increase of glutathione concentration in the cultured rat lens. Glutathione (gamma-glutamylcysteinyl glycine [GSH]) is thought to be an important factor in cellular function and defense against oxidative stress, and we found that dietary GSH suppresses oxidative stress in vivo in prevention of diabetic complications such as diabetic nephropathy and neuropathy.] Osawa T, Kato Y. *Ann N Y Acad Sci.* 2005 Jun;1043:440-51. http://www.ncbi.nlm.nih.gov/pubmed/16037265
841. **PYCNOGENOL chewing gum minimizes gingival bleeding and plaque formation.** [PYCNOGENOL is an antioxidant phytochemical shown to have antiinflammatory activity in both the in vitro and in vivo models. This study compared the effects of chewing gums with and without PYCNOGENOL on gingival bleeding and plaque formation in 40 human subjects. In this double-blind study, subjects were assigned randomly to receive either control gums without PYCNOGENOL or experimental gums containng 5 mg PYCNOGENOL. Subjects used chewing gums for 14 days. Gingival bleeding and plaque scores were taken before and after the experiment. PYCNOGENOL chewing gums significantly reduced gingival bleeding, while no changes were noted in bleeding indexes in control subjects who used regular chewing gums. Subjects using regular control gums had significant increases of dental plaque accumulation during the two-week period. No increases in plaque accumulation were noted in subjects using PYCNOGENOL chewing gums. The data of this study suggest that the use of Pycnogenol chewing gums can minimize gingival bleeding and plaque accumulation.] Kimbrough C, Chun M, et al. *Phytomedicine*. 2002 Jul;9(5):410-3. http://www.ncbi.nlm.nih.gov/pubmed/12222660
842. **Relationship of Blood Plasma Vitamin C Level to Gingival and Periodontal Disease.** [Vitamin C is one of several vitamins which may be necessary for maintenance of oral health. The oral effects of a deficiency of vitamin C may be confused with, and complicated by, a number of other factors. … Deficiencies of several vitamins at once might produce changes in the mouth comparable to changes caused by more severe deficiencies of vitamin C alone. … When guinea pigs

are kept on a diet deficient in vitamin C, changes occur in the gingival, periodontal membrane and alveolar bone similar to the changes observed in mouths of humans suffering from gingivitis and periodontal disease.] Burrill DY. Journal of Dental Research, Vol. 21, No. 4, 353-363. http://jdr.sagepub.com/cgi/content/refs/21/4/353

843. **Renal Transplantation Normalized Hydrogen Peroxide Production of Neutrophils within the First Day.** [*Background:* Hemodialysis patients are in a state of oxidant stress. In renal transplantation reactive oxygen species (ROS) are considered to be important factors of ischemia-reperfusion injury. Neutrophils produce ROS as part of the host defense against invading bacteria. This study was designed to investigate whether neutrophil function in hemodialysis patients is immediately affected by renal transplantation. *Methods:* We evaluated the neutrophil respiratory burst and phagocytic activity in renal transplant patients with living-related donor (LRD) and cadaveric donor (CAD) grafts using flow cytometry techniques. Twenty patients (LRD = 6, CAD = 14) and 20 healthy volunteers were included in the study. Venous blood samples were drawn before anesthesia, 5 min before reperfusion, 1 h and 1, 3 and 7 days after reperfusion. *Results:* Before surgery, a significant increase in hydrogen peroxide production in neutrophils was seen for both renal transplantation groups compared to healthy subjects. Within 24 h after reperfusion hydrogen peroxide production almost decreased to normal values. The phagocytic capacity of neutrophils was continuously depressed. There were no differences between the CAD and LRD groups. *Conclusions:* We found that the enhanced respiratory burst activity of patients with chronic renal failure decreased to normal values within 1 day following renal transplantation. Our results suggest that reduced respiratory burst activity resulting in a diminished risk of tissue damage by the uncontrolled production of ROS.] Juttner B, Gehrmann A, et al. *Am J Nephrol* 2008;28:531-538. http://content.karger.com/ProdukteDB/produkte.asp?doi=10.1159/000114097

844. **Salivary antioxidants and periodontal disease status**. [Periodontal disease is a common chronic adult condition. The bacterium *Porphyromonasgingivalis* has been implicated in the aetiology of this disease, which causes destruction of the connective tissue and bone around the root area of the tooth. It has been observed that invading *P. gingivalis* bacteria trigger the release of cytokines such as interleukin 8 and tumour necrosis factor α, leading to elevated numbers and activity of polymorphonucleocytes (PMN). As a result of stimulation by bacterial antigens, PMN produce the reactive oxygen species (ROS) superoxide via the respiratory burst as part of the host response to infection. Patients with periodontal disease display increased PMN number and activity. It has been suggested that this proliferation results in a high degree of ROS release, culminating in heightened oxidative damage to gingival tissue, periodontal ligament and alveolar bone. Antioxidant constituents in plasma have been welldocumented, being chiefly ascorbate, albumin and urate, and these are known to display sensitivity to dietary antioxidant intakes. The concentration of antioxidants in saliva does not appear to mirror those of plasma. The extent of dietary influence upon salivary antioxidant status is unclear. Urate is the predominant salivary antioxidant, with albumin and ascorbate providing minor contributions. Previous research has found reduced salivary antioxidant activity in patients suffering from periodontal disease. An improved understanding of the role antioxidants play in periodontitis, and the influence of nutrition on antioxidant status, may lead to a possible nutritional strategy for the treatment of periodontal disease.] Sculley DV, Langley-Evans SC. *Proceedings of the Nutrition Society* (2002), 61, 137-143. http://journals.cambridge.org/download.php?file=%2FPNS%2FPNS61_01%2FS0029665102000198a.pdf&code=801edc0ef316eba4535dff80e4f96db5

845. **Sanguinaria toothpaste and oral rinse regimen clinical efficacy in short- and long-term trials.** [Short- and long-term testing of sanguinaria toothpaste and oral rinse used individually have yielded both positive and negative results. This review evaluates the results of a number of clinical trials testing the regimen use of sanguinaria products for periods ranging from 14 days to six months. Review of these trials establishes the clinical efficacy of the two products in combination. The regimen approach produces consistently positive reductions in plaque, gingival inflammation and bleeding parameters for up to six months with no adverse hard tissue effects and only one reversible adverse soft tissue effect observed among the 260 subjects tested. In addition, no adverse microbiological shifts in the normal oral flora were observed.] Kuftinec MM, Mueller-Joseph LJ, et al. *J Can Dent Assoc*. 1990;56(7 Suppl):31-3. http://www.ncbi.nlm.nih.gov/pubmed/2207852

846. **Serial coronary angiographic evidence that antioxidant vitamin intake reduces progression of coronary artery atherosclerosis.** [OBJECTIVE--To explore the association of supplementary and dietary vitamin E and C intake with the progression of coronary artery disease. DESIGN--A subgroup analysis of the on-trial antioxidant vitamin intake database acquired in the Cholesterol Lowering Atherosclerosis Study, a randomized, placebo-controlled, serial angiographic clinical trial evaluating the risk and benefit of colestipol-niacin on coronary artery disease progression. SETTING--Community- and university-based cardiac catheterization laboratories. SUBJECTS--A total of 156 men aged 40 to 59 years with previous coronary artery bypass graft surgery. INTERVENTION--Supplementary and dietary vitamin E and C intake (nonrandomized) in association with cholesterol-lowering diet and either colestipol-niacin or placebo (randomized). OUTCOME--Change per subject in the percentage of vessel diameter obstructed because of stenosis (%S) determined by quantitative coronary angiography after 2 years of randomized therapy on all lesions, mild/moderate lesions (< 50%S), and severe lesions (> or = 50%S). RESULTS--Overall, subjects with supplementary vitamin E intake of 100 IU per day or greater demonstrated less coronary artery lesion progression than did subjects with supplementary vitamin E intake less than 100 IU per day for all lesions (P = .04) and for mild/moderate lesions (P = .01). Within the drug group, benefit of supplementary vitamin E intake was found for all lesions (P = .02) and mild/moderate lesions (P = .01). Within the placebo group, benefit of supplementary vitamin E intake was not found. No benefit was found for use of supplementary vitamin C exclusively or in conjunction with supplementary vitamin E, use of multivitamins, or increased dietary intake of vitamin E or vitamin C. CONCLUSIONS--These results indicate an association between supplementary vitamin E intake and angiographically demonstrated reduction in coronary artery lesion progression. Verification from carefully designed, randomized, serial

arterial imaging end point trials is needed.] Hodis HN, Mack WJ, et al. *JAMA.* 1995 Jun 21;273(23):1849-54. http://www.ncbi.nlm.nih.gov/pubmed/7776501

847. **Serum C-Reactive Protein Concentrations Are Inversely Associated with Dietary Flavonoid Intake in U.S. Adults. [**Serum C-reactive protein (CRP) is a biomarker for chronic inflammation and a sensitive risk factor for cardiovascular diseases. Though CRP has been reported to be related to food intake, there is no documentation of a direct association with flavonoid intake. We aimed to test the associations between dietary flavonoid intake and serum CRP concentrations among U.S. adults after adjusting for dietary, sociodemographic, and lifestyle factors. Data from the NHANES 1999–2002 were used for this cross-sectional study. Subjects were ≥19-y-old adults (n = 8335), and did not include pregnant and/or lactating women. Flavonoid intake of U.S. adults was estimated by the USDA flavonoid databases matched with a 24-h dietary recall in NHANES 1999–2002. The serum CRP concentration was higher in women, older adults, blacks, and smokers, and in those with high BMI or low exercise level, and in those taking NSAID, than in their counterparts ($P < 0.01$). Intakes of apples and vegetables were inversely associated with serum CRP concentrations after adjusting for covariates ($P < 0.05$). Total flavonoid and also individual flavonol, anthocyanidin, and isoflavone intakes were inversely associated with serum CRP concentration after adjusting for the covariates ($P < 0.05$). Among the flavonoid compounds investigated, quercetin, kaempferol, malvidin, peonidin, daidzein, and genistein had inverse associations with serum CRP concentration ($P < 0.05$). These associations did not change even after the additional adjustment for fruit and vegetable consumption. Our findings demonstrate that intake of dietary flavonoids is inversely associated with serum CRP concentrations in U.S. adults. Intake of flavonoid-rich foods may thus reduce inflammation-mediated chronic diseases.] Chun OK, Chung SJ, et al. *J. Nutr.* 138:753-760, April 2008. http://jn.nutrition.org/cgi/content/short/138/4/753

848. **Soluble fiber and serum lipids: a literature review.** [Although fiber has been increasingly recognized as an important dietary constituent, controversy and confusion still exist about the physiologic effects of fiber. Specifically, the independent ability of dietary fiber to lower serum lipid levels is controversial. The purpose of this article is to review available evidence regarding the impact of soluble fibers on serum lipid levels. Soluble fibers appear to have a greater potential to alter serum lipid levels than do insoluble fibers. Significant reduction in the level of serum total cholesterol by soluble fiber was found in 68 of the 77 (88%) human studies reviewed. Of the studies measuring low-density lipoprotein cholesterol, 41 of 49 (84%) reported significant reductions. No significant changes were reported in 43 of the 57 (75%) studies that reported high-density lipoprotein cholesterol and/or in 50 of the 58 (86%) studies that measured triglyceride levels.][Glore SR, Treeck V, at al. *Am Diet Assoc.* 1994 Apr;94(4):425-36. http://www.ncbi.nlm.nih.gov/pubmed/8144811

849. **Supplement Containing Vitamins C, E and Grape Seed Extract Improves Smokers' Response to Gum Disease Treatment.** [Researchers showed that giving smokers a supplement containing the antioxidant vitamins C and E and grape seed extract improved the response to treatment, shown by better gum attachment and improved oral health in general.] Grossi S., *Department of Oral Biology, UB School of Dental Medicine.* http://www.buffalo.edu/news/fast-execute.cgi/article-page.html?article=66410009

850. **The antioxidant and pro-oxidant activities of green tea polyphenols: a role in cancer prevention.** [Green tea (Camellia sinensis) is rich in catechins, of which (-)-epigallocatechin-3-gallate (EGCG) is the most abundant. Studies in animal models of carcinogenesis have shown that green tea and EGCG can inhibit tumorigenesis during the initiation, promotion and progression stages. Many potential mechanisms have been proposed including both antioxidant and pro-oxidant effects, but questions remain regarding the relevance of these mechanisms to cancer prevention. In the present review, we will discuss the redox chemistry of the tea catechins and the current literature on the antioxidant and pro-oxidative effects of the green tea polyphenols as they relate to cancer prevention. We report that although the catechins are chemical antioxidants which can quench free radical species and chelate transition metals, there is evidence that some of the effects of these compounds may be related to induction of oxidative stress. Such pro-oxidant effects appear to be responsible for the induction of apoptosis in tumor cells. These pro-oxidant effects may also induce endogenous antioxidant systems in normal tissues that offer protection against carcinogenic insult. This review is meant point out understudied areas and stimulate research on the topic with the hope that insights into the mechanisms of cancer preventive activity of tea polyphenols will result.] Lambert JD, Elias RJ. *Arch Biochem Biophys.* 2010 Sep 1;501(1):65-72. http://www.ncbi.nlm.nih.gov/pubmed/20558130

851. **The effect of chronic hypovitaminosis C on the metabolism of cholesterol and atherogenesis in guinea pigs**. [Guinea pigs with varying intakes of ascorbic acid (0.5, 5 and 50 mg per 24 h) were receiving an atherogenic diet with addition of 0.3 % cholesterol during 140 days. In guinea pigs with a chronic deficiency of vitamin C (0.5 mg for 24 h) a significantly higher accumulation of cholesterol in liver, adrenal glands and small intestine was observed in comparison with the group receiving 50 mg of vitamin C for 24 h. Concentrations of cholesterol in the same organs of the group receiving 5 mg of vitamin C per 24 h were within these extreme data. A significantly negative correlation was confirmed to exist between cholesterol concentration in liver, adrenal glands and small intestine and saturation of tissues with vitamin C; with decreasing saturation of tissues with vitamin C, the accumulation of cholesterol in the relevant tissue was increasing. Cholesterol levels in brain and blood serum were not significantly influenced by differing intake of vitamin C. The most advanced atheromatous changes were found in aorta and coronary arteries of the hypovitaminous group (0.5 mg of vitamin C per 24 h). High doses of vitamin C (50 mg per 24 h) did not prevent the appearance of morphological changes in vascular system but only slowed down the process of atheromatous reconstruction.] Ginter E, Babala J, et al. *AtherosclerosisI*, Vol. 10, Issue 3, Pp 341-352. http://www.journals.elsevierhealth.com/periodicals/jar/article/PIIS0368131969800372/abstract

852. **The effect of dietary supplements on periodontal disease.** [four individuals with a clinical history of mile, moderate, or severe periodontal disease reported improvement with the initiation of a program of nutritional supplementation that included

glyconutritionals, phytonutritionals, vitamin/mineral supplements and a supplement developed for support of the endocrine system. A questionnaire was completed by the individuals to assess the effect, if any, that dietary supplementation had ontheir gingival tissues. Patients were evaluated for changeds in severity, plaque/calculus accumulation, periodontal pocket depth, gingival tissue color and texture, bleeding points and tooth mobility. All of these subjects reported improvement in their fgingival tissue health after taking the nutritional supplements, and theres improvements were confirmed clinically.] McKinley RN. *JANA*, August 1997, Supplement 1, p. 21-23. http://www.ana-jana.org/jana_journal.cfm

853. **The effect of folic acid on gingival health.**. [On days 0 and 30 of a double blind study, two groups of 15 subjects each were evaluated using a plaque index, a gingival index, a gingival exudate flow and fasting plasma folic acid levels. Group I received 2 mg of folic acid twice daily for 30 days while Group II received a placebo. Results of the study seem to indicate that folic acid supplemented to the diet may increase the resistance of the gingiva to local irritants and thus lead to a reduction in inflammation.] Vogel RI, Fink RA, et al. *J Periodontol.* 1976 Nov;47(11):667-8. http://www.ncbi.nlm.nih.gov/pubmed/789852
854. **The effects of dietary deficiencies upon the oral structures.** [The oral tissues are particularly sensitive to nutritional deficiencies and dietary aberrations. They are often the first to show the effects of such deficiencies, particularly if the latter are subclinical in nature.] Schour I, Massler M. *Physiol. Rev.* 25:442-482, 1945. http://physrev.physiology.org/cgi/pdf_extract/25/3/442
855. **The effects of glucose on ascorbic acid uptake in heart endothelial cells: possible pathogenesis of diabetic angiopathies.** [Glucose in concentrations of 20 mg% (or greater) significantly inhibited 14C-labelled ascorbic acid (1.25 mg%) uptake in endothelial cells in the presence of insulin (1600 microU/ml). The absence of insulin also significantly reduced ascorbic acid uptake. Furthermore, this reduction could be exacerbated by glucose (40, 160 mg%) but not equimolar concentrations of fructose. Increased ascorbic acid concentrations (two-fold) in the absence of insulin (1) significantly enhanced uptake, and (2) reversed the inhibition of glucose. These findings support earlier reports that ascorbic acid uptake into the cell may be compromised by decreased insulin and/or increased extracellular glucose levels. Since previous animal studies have correlated experimental ascorbic acid deficiencies with atherogenic processes (presumably by altering glycosaminoglycan metabolism), the postulation that the "diabetic condition" (low insulin, hyperglycemia) accelerates the cellular changes leading to atherosclerosis by impairing ascorbic acid uptake into the vascular endothelium, may now be supported.] Kapeghian JC, Verlangieri AJ. *Life Sci*. 1984 Feb 6;34(6):577-84.. http://www.ncbi.nlm.nih.gov/pubmed/6363863
856. **The impact of edentulousness on food and nutrient intake.** [The authors collected dietary intake data about the food and nutrient intake of 49,501 male health professionals. Edentulous participants consumed fewer vegetables, less fiber and carotene, and more cholesterol, saturated fat and calories than participants with 25 or more teeth. These factors could increase the risks of cancer and cardiovascular disease. Mean differences in intake ranged from 2 to 13 percent, independent of age, smoking, exercise and profession. Longitudinal analyses suggest that tooth loss may lead to detrimental changes in diet.] Joshipura KJ, Willett WC, et al. *J Am Dent Assoc*. 1996 Apr;127(4):459-67. http://www.ncbi.nlm.nih.gov/pubmed/8655866
857. **The Importance of Optimal Nutrition**. [ABSTRACT: Balanced and optimal macro- and micro- nutrient intake provides an important foundation for good health. Micronutrients are essential for a myriad of body functions, playing indispensable and diverse roles as coenzymes, structural components, pro-hormones, components of body fluids, antioxidants, and many more. Today's lifestyles and eating habits often result in "unbalanced" diets with many people not even meeting RDA levels of all essential nutrients. Also, because each individual has his or her own "biochemical individuality," or distinct nutritional needs which must be met for optimal well-being, the RDAs may not be adequate. Many factors can further increase individual nutrient requirements, such as smoking, alcohol abuse, chronic dieting, use of prescription or other drugs, chronic illness, etc. Marginal nutrient deficiencies can be found in all segments of the population, often manifesting vague, non-classic symptoms that make it difficult to recognize and supplement the deficiency. Eating a well-balanced diet rich in fruits and vegetables and taking a high-quality, scientifically balanced multiple vitamin/mineral supplement is an excellent way to ensure that our individual nutrient needs are met.] Pervical M. *Clinical Nutrition Insights*, Vol 5, No. 3. http://acudoc.com/Optimal%20Nutrition.PDF
858. **The interaction between two antioxidants, sodium ascorbate and gallic acid : Radical intensity and apoptosis induction.** [ESR spectroscopy revealed that both the radical intensity and degradation rate of sodium ascorbate were increased with increasing pH. Gallic acid significantly reduced the radical intensity of sodium ascorbate, which in turn reduced the radical intensity of gallic acid. Sodium ascorbate inhibited the apoptosis-inducing activity of gallic acid, and gallic acid inhibited the intracellular incorporation of ascorbic acid. These data suggest that interaction between sodium ascorbate and gallic acid might modify their biological activity.] Sakagami H, Satoh K. *Anticancer Research*, 1996, Vol 16, No 3A, pp. 1231-1234. http://cat.inist.fr/?aModele=afficheN&cpsidt=3113603
859. **The protective role of gallic acid esters in bacterial cytotoxicity and SOS responses induced by hydrogen peroxide.** [The effects of gallic acid and its esters on H2O2-induced cytotoxicity, mutagenicity and SOS response were investigated in bacterial assay systems, i.e., the Ames test with Salmonella typhimurium TA104 and the SOS chromotest with E. coli PQ37. In the Ames test, gallic acid esters showed protective effects against H2O2-induced cytotoxicity and no effects on the number of revertant colonies. In the SOS chromotest, gallic acid esters lowered the SOS induction factor raised by H2O2. Throughout the study, the effects of gallic acid itself were weak or negligible, and lauryl gallate was most effective among the three gallic acid esters. This structure-activity relationship indicates the similarity of the protective effects of gallic acid esters on the H2O2-induced damages to both bacterial and mammalian cells.] Nakayama T, Hiramitsu M, et al. *Mutat Res*. 1993 Sep;303(1):29-34. http://www.ncbi.nlm.nih.gov/pubmed/7690903

860. **The role of ascorbic acid deficiency in human gingivitis--a new hypothesis.**. [Periodontal disease is one of the most prevalent health problems in the world and is the major cause of tooth loss in the adult population. Its two major subdivisions are gingivitis where disease is confined to the gingiva, and periodontitis where disease is present both in the gingiva and the supporting periodontal tissues. During the first stage there is a vasculitis of vessels subjacent to the junctional epithelium which is followed by exudation of fluid from the gingival sulcus and migration of leukocytes. There is variable expression of this stage throughout the mouth with new areas of involvement appearing in place of healed areas. Mast cells which are present in the gingival connective tissues may participate in this inflammatory response by liberating histamine. Ascorbic acid deficiency has been shown to be a conditioning factor in the development of gingivitis. When humans are placed on ascorbic acid deficient diets there is increased edema, redness and swelling of the gingiva. These changes have been attributed to deficient collagen production by gingival blood vessels. However, this may be due to an antihistamine role of ascorbic acid. This vitamin may act to directly detoxify histamine or effect a change in the level of enzymes responsible for histamine metabolism. This could occur through the influence of ascorbic acid in altering cyclic AMP (c-AMP) levels. Such changes in the level of this regulatory molecule could result in increased histamine-N-methyl transferase and other enzymes responsible for the breakdown of histamine] Nakamoto T, McCroskey M, et al. *J Theor Biol*. 1984 May 21;108(2):163-71. http://www.ncbi.nlm.nih.gov/pubmed/6748685

861. **The role of omega-3 long-chain polyunsaturated fatty acids in health and disease of the retina.** [In this work we advance the hypothesis that omega-3 (omega-3) long-chain polyunsaturated fatty acids (LCPUFAs) exhibit cytoprotective and cytotherapeutic actions contributing to a number of anti-angiogenic and neuroprotective mechanisms within the retina. omega-3 LCPUFAs may modulate metabolic processes and attenuate effects of environmental exposures that activate molecules implicated in pathogenesis of vasoproliferative and neurodegenerative retinal diseases. These processes and exposures include ischemia, chronic light exposure, oxidative stress, inflammation, cellular signaling mechanisms, and aging. A number of bioactive molecules within the retina affect, and are effected by such conditions. These molecules operate within complex systems and include compounds classified as eicosanoids, angiogenic factors, matrix metalloproteinases, reactive oxygen species, cyclic nucleotides, neurotransmitters and neuromodulators, pro-inflammatory and immunoregulatory cytokines, and inflammatory phospholipids. We discuss the relationship of LCPUFAs with these bioactivators and bioactive compounds in the context of three blinding retinal diseases of public health significance that exhibit both vascular and neural pathology. How is omega-3 LCPUFA status related to retinal structure and function? Docosahexaenoic acid (DHA), a major dietary omega-3 LCPUFA, is also a major structural lipid of retinal photoreceptor outer segment membranes. Biophysical and biochemical properties of DHA may affect photoreceptor membrane function by altering permeability, fluidity, thickness, and lipid phase properties. Tissue DHA status affects retinal cell signaling mechanisms involved in phototransduction. DHA may operate in signaling cascades to enhance activation of membrane-bound retinal proteins and may also be involved in rhodopsin regeneration. Tissue DHA insufficiency is associated with alterations in retinal function. Visual processing deficits have been ameliorated with DHA supplementation in some cases. What evidence exists to suggest that LCPUFAs modulate factors and processes implicated in diseases of the vascular and neural retina? Tissue status of LCPUFAs is modifiable by and dependent upon dietary intake. Certain LCPUFAs are selectively accreted and efficiently conserved within the neural retina. On the most basic level, omega-3 LCPUFAs influence retinal cell gene expression, cellular differentiation, and cellular survival. DHA activates a number of nuclear hormone receptors that operate as transcription factors for molecules that modulate reduction-oxidation-sensitive and proinflammatory genes; these include the peroxisome proliferator-activated receptor-alpha (PPAR-alpha) and the retinoid X receptor. In the case of PPAR-alpha, this action is thought to prevent endothelial cell dysfunction and vascular remodeling through inhibition of: vascular smooth muscle cell proliferation, inducible nitric oxide synthase production, interleukin-1 induced cyclooxygenase (COX)-2 production, and thrombin-induced endothelin 1 production. Research on model systems demonstrates that omega-3 LCPUFAs also have the capacity to affect production and activation of angiogenic growth factors, arachidonic acid (AA)-based vasoregulatory eicosanoids, and MMPs. Eicosapentaenoic acid (EPA), a substrate for DHA, is the parent fatty acid for a family of eicosanoids that have the potential to affect AA-derived eicosanoids implicated in abnormal retinal neovascularization, vascular permeability, and inflammation. EPA depresses vascular endothelial growth factor (VEGF)-specific tyrosine kinase receptor activation and expression. VEGF plays an essential role in induction of: endothelial cell migration and proliferation, microvascular permeability, endothelial cell release of metalloproteinases and interstitial collagenases, and endothelial cell tube formation. The mechanism of VEGF receptor down-regulation is believed to occur at the tyrosine kinase nuclear factor-kappa B (NFkappaB). NFkappaB is a nuclear transcription factor that up-regulates COX-2 expression, intracellular adhesion molecule, thrombin, and nitric oxide synthase. All four factors are associated with vascular instability. COX-2 drives conversion of AA to a number angiogenic and proinflammatory eicosanoids. Our general conclusion is that there is consistent evidence to suggest that omega-3 LCPUFAs may act in a protective role against ischemia-, light-, oxygen-, inflammatory-, and age-associated pathology of the vascular and neural retina.] SanGiovanni JP, Chew EY. *Prog Retin Eye Res.* 2005 Jan;24(1):87-138. http://www.ncbi.nlm.nih.gov/pubmed/15555528

862. **The specificity of proanthocyanidin-protein interactions.** [The proanthocyanidins or condensed tannins, phenolic polymers which are synthesized by many plants, characteristically bind and precipitate proteins. The specificity of the interaction was investigated using a competitive binding assay to compare directly the affinities of various proteins and synthetic polymers for the tannin obtained from Sorghum bicolor (Lin.) Moench. At pH 4.9, the relative affinities range over more than 4 orders of magnitude, indicating that this proanthocyanidin interacts quite selectively with protein and protein-

like polymers. The affinity for tannins is an inverse function of the size of the polymer, and peptides with less than six residues interact very weakly with tannin. Proteins are precipitated by proanthocyanidins most efficiently at pH values near their isoelectric points. Proline-rich proteins and polymers have very high affinities for tannin. Tightly coiled globular proteins have much lower affinities for tannin than conformationally loose proteins.] Hagerman AE, Butler LG. *Journal of Biological Chemistry*. 256, 4494-4497. May 10, 1981. http://www.jbc.org/content/256/9/4494.abstract

863. **Understanding Antioxidants.** [Oxidative stress has been implicated as a contributory factor in many disease processes. Natural antioxidant defenses have been found to be defective in many of the same diseases. If disease is associated with an imbalance of oxidative stresses and antioxidant defenses, it should be possible to limit oxidative damage and prevent disease progression by supplementing and/or enhancing natural antioxidant defenses.1 Potential health promoting interventions might support natural enzyme antioxidants, natural preventative antioxidants, and/or scavenging antioxidants.] McDaniel CF. Fisher Institute for Medical Research. http://www.fisherinstitute.org/antioxidents.htm
864. **Vegetable, fruit, and cereal fiber intake and risk of coronary heart disease among men.** [OBJECTIVE--To examine prospectively the relationship between dietary fiber and risk of coronary heart disease. DESIGN--Cohort study. SETTING--In 1986, a total of 43,757 US male health professionals 40 to 75 years of age and free from diagnosed cardiovascular disease and diabetes completed a detailed 131-item dietary questionnaire used to measure usual intake of total dietary fiber and specific food sources of fiber. MAIN OUTCOME MEASURE--Fatal and nonfatal myocardial infarction (MI). RESULTS--During 6 years of follow-up, we documented 734 cases of MI (229 were fatal coronary heart disease). The age-adjusted relative risk (RR) for total MI was 0.59 (95% confidence interval [CI], 0.46 to 0.76) among men in the highest quintile of total dietary fiber intake (median, 28.9 g/d) compared with men in the lowest quartile (median, 12.4 g/d). The inverse association was strongest for fatal coronary disease (RR, 0.45; 95% CI, 0.28 to 0.72). After controlling for smoking, physical activity and other known nondietary cardiovascular risk factors, dietary saturated fat, vitamin E, total energy intake, and alcohol intake, the RRs were only modestly attenuated. A 10-g increase in total dietary fiber corresponded to an RR for total MI of 0.81 (95% CI, 0.70 to 0.93). Within the three main food contributors to total fiber intake (vegetable, fruit, and cereal), cereal fiber was most strongly associated with a reduced risk of total MI (RR, 0.71; 95% CI, 0.55 to 0.91 for each 10-g increase in cereal fiber per day). CONCLUSIONS--Our results suggest an inverse association between fiber intake and MI. These results support current national dietary guidelines to increase dietary fiber intake and suggest that fiber, independent of fat intake, is an important dietary component for the prevention of coronary disease.] Rimm EB, Ascherio A, et al. *JAMA.* 1996 Feb 14;275(6):447-51. http://www.ncbi.nlm.nih.gov/pubmed/8627965
865. **Vegetarian Dietary Patterns Are Associated With a Lower Risk of Metabolic Syndrome; The Adventist Health Study 2.** [OBJECTIVE The study objective was to compare dietary patterns in their relationship with metabolic risk factors (MRFs) and the metabolic syndrome (MetS). RESEARCH DESIGN AND METHODS Cross-sectional analysis of 773 subjects (mean age 60 years) from the Adventist Health Study 2 was performed. Dietary pattern was derived from a food frequency questionnaire and classified as vegetarian (35%), semi-vegetarian (16%), and nonvegetarian (49%). ANCOVA was used to determine associations between dietary pattern and MRFs (HDL, triglycerides, glucose, blood pressure, and waist circumference) while controlling for relevant cofactors. Logistic regression was used in calculating odds ratios (ORs) for MetS. RESULTS A vegetarian dietary pattern was associated with significantly lower means for all MRFs except HDL (***P*** for trend < 0.001 for those factors) and a lower risk of having MetS (OR 0.44, 95% CI 0.30–0.64, ***P*** < 0.001) when compared with a nonvegetarian dietary pattern. CONCLUSIONS A vegetarian dietary pattern is associated with a more favorable profile of MRFs and a lower risk of MetS. The relationship persists after adjusting for lifestyle and demographic factors.] Rizzo NS, Sabate J, et al. Diabetes Care. 2011 May; 34(5): 1225–1227. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3114510/
866. **Vegetarian Dietary Patterns and Mortality in Adventist Health Study 2. [Importance** Some evidence suggests vegetarian dietary patterns may be associated with reduced mortality, but the relationship is not well established. Objective To evaluate the association between vegetarian dietary patterns and mortality. Design Prospective cohort study; mortality analysis by Cox proportional hazards regression, controlling for important demographic and lifestyle confounders. Setting Adventist Health Study 2 (AHS-2), a large North American cohort. Participants A total of 96 469 Seventh-day Adventist men and women recruited between 2002 and 2007, from which an analytic sample of 73 308 participants remained after exclusions. Exposures Diet was assessed at baseline by a quantitative food frequency questionnaire and categorized into 5 dietary patterns: nonvegetarian, semi-vegetarian, pesco-vegetarian, lacto-ovo–vegetarian, and vegan. Main Outcome and Measure The relationship between vegetarian dietary patterns and all-cause and cause-specific mortality; deaths through 2009 were identified from the National Death Index. Results There were 2570 deaths among 73 308 participants during a mean follow-up time of 5.79 years. The mortality rate was 6.05 (95% CI, 5.82-6.29) deaths per 1000 person-years. The adjusted hazard ratio (HR) for all-cause mortality in all vegetarians combined vs nonvegetarians was 0.88 (95% CI, 0.80-0.97). The adjusted HR for all-cause mortality in vegans was 0.85 (95% CI, 0.73-1.01); in lacto-ovo–vegetarians, 0.91 (95% CI, 0.82-1.00); in pesco-vegetarians, 0.81 (95% CI, 0.69-0.94); and in semi-vegetarians, 0.92 (95% CI, 0.75-1.13) compared with nonvegetarians. Significant associations with vegetarian diets were detected for cardiovascular mortality, noncardiovascular noncancer mortality, renal mortality, and endocrine mortality. Associations in men were larger and more often significant than were those in women. Conclusions and Relevance Vegetarian diets are associated with lower all-cause mortality and with some reductions in cause-specific mortality. Results appeared to be more robust in males. These favorable associations should be considered carefully by those offering dietary guidance.] Orlich MJ, Singh PN, et al. *JAMA Intern Med. 2013;():1-8. doi:10.1001/jamainternmed.2013.6473.* http://archinte.jamanetwork.com/article.aspx?articleid=1691919

867. **Vitamin D and Cardiovascular disease.** [Substantial evidence suggests that a large portion of the population have suboptimal levels of vitamin D, which may adversely affect the cardiovascular (CV) system, including increasing levels of parathyroid hormone, activating the renin-angiotensin-aldosterone system, and increasing insulin resistance, thus leading to hypertension and left ventricular hypertrophy, metabolic syndrome/diabetes mellitus, systemic inflammation, and increased risk of atherosclerosis and CV disease events. We review the evidence that vitamin D deficiency is associated with incident CV disease events, as well as evidence that vitamin D supplementation is associated with reduction in CV diseases. Although the current evidence has created substantial hype, randomized controlled trials are needed to determine whether routine vitamin D assessment and supplementation will improve CV outcomes.] Lavie CJ, Lee JH, et al. *J Am Coll Cardiol*. 2011;58(15):1547-1556. http://www.medscape.com/viewarticle/750679?src=mp&spon=34
868. **Vitamin D controls T cell antigen receptor signaling and activation of human T cells.** [Phospholipase C (PLC) isozymes are key signaling proteins downstream of many extracellular stimuli. Here we show that naive human T cells had very low expression of PLC-γ1 and that this correlated with low T cell antigen receptor (TCR) responsiveness in naive T cells. However, TCR triggering led to an upregulation of ~75-fold in PLC-γ1 expression, which correlated with greater TCR responsiveness. Induction of PLC-γ1 was dependent on vitamin D and expression of the vitamin D receptor (VDR). Naive T cells did not express VDR, but VDR expression was induced by TCR signaling via the alternative mitogen-activated protein kinase p38 pathway. Thus, initial TCR signaling via p38 leads to successive induction of VDR and PLC-γ1, which are required for subsequent classical TCR signaling and T cell activation.] von Essen MR, Kongsbak M, et al. *Nature Immunology*, March 7, 2010. http://www.nature.com/ni/journal/vaop/ncurrent/abs/ni.1851.html
869. **Vitamin D deficiency linked to Parkinson's disease, cognitive decline.** [Vitamin D deficiency not only causes rickets, a skeletal disorder in which the bones are soft and weak, but has also been associated with a rapidly increasing range of chronic conditions like cancer, heart disease, and type 2 diabetes. Now, two new studies suggest a link between vitamin D and neurological disorder: older people with insufficient vitamin D levels may be more likely to develop Parkinson's disease and experience cognitive decline.]. Zeliadt N. *Scientific American Observations*, Jul 13, 2010. http://www.scientificamerican.com/blog/post.cfm?id=vitamin-d-deficiency-linked-to-park-2010-07-12&sc=DD_20100713
870. **Vitamin D discovery outpaces FDA decision making** [The US FDA currently encourages the addition of vitamin D to milk and cereals, with the aim of reducing rickets in children and osteoporosis in adults. However, vitamin D not only regulates the expression of genes associated with calcium homeostasis, but also genes associated with cancers, autoimmune disease, and infection. It does this by controlling the activation of the vitamin D receptor (VDR), a type 1 nuclear receptor and DNA transcription factor. Molecular biology is rapidly coming to an understanding of the multiplicity of roles played by the VDR, but clinical medicine is having difficulty keeping up with the pace of change. For example, the FDA recently proposed a rule change that will encourage high levels of vitamin D to be added to even more foods, so that the manufacturers can claim those foods "reduce the risk of osteoporosis". The FDA docket does not review one single paper detailing the transcriptional activity of vitamin D, even though, on average, one new paper a day is being published on that topic. Nor do they review whether widespread supplementation with vitamin D, an immunomodulatory secosteroid, might predispose the population to immune dysfunction. This BioEssay explores how lifelong supplementation of the food chain with vitamin D might well be contributing to the current epidemics of obesity and chronic disease] Marshall TG. BioEssays 30:173-182, 2008. http://www3.interscience.wiley.com/journal/117885976/abstract?CRETRY=1&SRETRY=0 http://trevormarshall.com/BioEssays-Feb08-Marshall-Preprint.pdf
871. **Vitamin D, periodontal disease, tooth loss, and cancer risk.** [(Suggestion is made that the underlying factor between the periodontal disease / tooth loss link with cancer is low serum 25-hydroxyvitamin D – calcidiol – levels. Vitamin D lowers risk for periodontal disease by induction of human cathelicidin, LL-37 and by this decreases the risk of several cancers by decreasing the risk of viral infections such as Epstein-Barr virus.] Grant WB. *Lancet Oncol*. 2008 Jul;9(7):612-3. http://www.ncbi.nlm.nih.gov/pubmed/18598929
872. **Vitamin D-mediated induction of innate immunity in gingival epithelial cells.** [Human gingival epithelial cells (GEC) produce peptides, such as β-defensins and the cathelicidin LL-37, that are both antimicrobial and that modulate the innate immune response. In myeloid and airway epithelial cells, the active form of vitamin D(3) [1,25(OH)(2)D(3)] increases the expression and antibacterial activity of LL-37. To examine the activity of vitamin D on the innate immune defense of the gingival epithelium, cultured epithelial cells were treated with either 10(-8) M 1,25(OH)(2)D(3) or ethanol for up to 24 h. A time-dependent induction of LL-37 mRNA up to 13-fold at 24 h in both standard monolayer and three-dimensional cultures was observed. Induction of the vitamin D receptor and the 1-α-hydroxylase genes was also observed. The hydroxylase was functional, as LL-37 induction was observed in response to stimulation by 25(OH)D(3). Through microarray analysis of other innate immune genes, CD14 expression increased 4-fold, and triggering receptor expressed on myeloid cells-1 (TREM-1) was upregulated 16-fold after 24 h of treatment with 1,25(OH)(2)D(3). TREM-1 is a pivotal amplifier of the innate immune response in macrophages, leading to increased production by inflammatory response genes. Activation of TREM-1 on the GEC led to an increase in interleukin-8 (IL-8) mRNA levels. Incubation of three-dimensional cultures with 1,25(OH)(2)D(3) led to an increase in antibacterial activity against the periodontal pathogen Aggregatibacter actinomycetemcomitans when the bacteria were added to the apical surface. This study is the first to demonstrate the effect of vitamin D on antibacterial defense of oral epithelial cells, suggesting that vitamin D(3) could be utilized to enhance the innate immune defense in the oral cavity.] McMahon L, Schwartz K, et al. *Infect Immun*. 2011 Jun;79(6):2250-6 http://www.ncbi.nlm.nih.gov/pubmed/21422187

Omega-3, PUFA, Resolvins, Resveratrol, Pycnogenol

873. **A novel bioactivity of omega-3 polyunsaturated fatty acids and their ester derivatives**. [Fish oil, enriched in omega-3 polyunsaturated fatty acids (n-3 PUFA), is widely used as a dietary or nutritional supplement with numerous benefits, including as an anti-inflammatory particularly linked to atherosclerosis. While n-3 PUFA have been suggested to be able to improve oral health through a reduction in inflammation through elevations in these fatty acids in serum and cellular membranes, information is lacking for the possibility that these fatty acids could directly impact the survival and growth of the oral bacteria that trigger the chronic inflammatory responses. The n-3 fatty acids, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and α-linolenic acid (ALA), and their fatty acid ethyl esters, ALAEE, EPAEE, DHAEE were analysed for antibacterial activity against oral pathogens. This study demonstrated a novel bioactivity of the three major n-3 PUFA, EPA, DHA, and ALA, and their ester derivatives. Our experimental data indicated that n-3 PUFA and their ester derivatives exhibited strong antibacterial activity against various oral pathogens, including *Streptococcus mutans*, *Candida albicans*, *Aggregatibacter actinomycetemcomitans*, *Fusobacterium nucleatum*, and *Porphyromonas gingivalis*. This study suggested that n-3 PUFA could have a positive therapeutic effect for improving oral health via their antibacterial activities, besides their anti-inflammatory effects.] Huang CB, Ebersole JL. *Molecular Oral Microbiology*, Vol. 25, Issue 1, pp 75-89. http://www3.interscience.wiley.com/journal/123261446/abstract?CRETRY=1&SRETRY=0

874. **An Antiinflammatory and Reactive Oxygen Species Suppressive Effects of an Extract of *Polygonum Cuspidatum* Containing Resveratrol.** [Background: Resveratrol have been shown to exert an antiinflammatory and antiaging effects *in vitro* and in animal models. Objective: The objective of the study was to investigate the effect of a *Polygonum cuspidatum* extract (PCE) containing resveratrol on oxidative and inflammatory stress in normal subjects. Research Design and Methods: Two groups (10 each) of normal-weight healthy subjects were randomized to placebo or PCE containing 40 mg resveratrol daily for 6 wk. Fasting blood samples were obtained prior to and after treatment at 1, 3, and 6 wk. Mononuclear cells were prepared for reactive oxygen species generation, RNA isolation, nuclear extract, and total cell homogenate preparation. Indices of oxidative and inflammatory stress, suppressor of cytokine signaling-3, phosphotyrosine phosphatase-1B, jun-N-terminal kinase-1, and inhibitor of κB-kinase-β were measured by RT-PCR and Western blotting. Results: The extract induced a significant reduction in reactive oxygen species generation, the expression of $p47^{phox}$, intranuclear nuclear factor-κB binding, and the expression of jun-N-terminal kinase-1, inhibitor of κB-kinase-β, phosphotyrosine phosphatase-1B, and suppressor of cytokine signaling-3 in mononuclear cells when compared with the baseline and the placebo. PCE intake also suppressed plasma concentrations of TNF-α, IL-6, and C-reactive protein. There was no change in these indices in the control group given placebo. Conclusions: The PCE-containing resveratrol has a comprehensive suppressive effect on oxidative and inflammatory stress.] Ghanim H, Sia CL, et al. *Journal of Clinical Endocrinology & Metabolism*, doi:10.1210/jc.2010-0482 June 9, 2010. http://jcem.endojournals.org/cgi/content/abstract/jc.2010-0482v1?maxtoshow=&hits=10&RESULTFORMAT=1&author1=Dandona+Paresh+&andorexacttitle=and&andorexacttitleabs=and&andorexactfulltext=and&searchid=1&FIRSTINDEX=0&sortspec=relevance&resourcetype=HWCIT

875. **An inverse relationship between plasma n-3 fatty acids and C-reactive protein in healthy individuals. [**High sensitivity C-reactive protein (hs-CRP) is a marker of low-grade sustained inflammation. Omega-3 (n-3) fatty acids have anti-inflammatory properties and are associated with reduced cardiovascular disease (CVD) risk. The aim of this study was to investigate whether plasma n-3 fatty acid concentration is related to hs-CRP concentration. A total of 124 free-living adults, were divided into tertiles of plasma hs-CRP (<1.0, 1.0-3.0 and >3.0 mg/l). Body composition and anthropometric measurements were recorded. Hs-CRP was analysed using immunoassays and fatty acids were measured by gas chromatography. Plasma hs-CRP concentration was negatively correlated with total n-3 fatty acids (P=0.05), eicosapentaenoic acid (EPA; P=0.002) and docosapentaenoic acid (DPA; P=0.01). The highest hs-CRP tertile (>3.0 mg/l) had significantly lower concentrations of total n-3 fatty acids, EPA and DPA, when compared with the other tertiles (P<0.05). This study provides evidence that in healthy individuals, plasma n-3 fatty acid concentration is inversely related to hs-CRP concentration, a surrogate marker of CVD risk.] Micallef MA, Munro IA, Garg ML. *Eur J Clin Nutr*. 2009 Sep;63(9):1154-6. Epub 2009 Apr 8. http://www.ncbi.nlm.nih.gov/pubmed/19352379

876. **Antioxidant activity and inhibition of matrix metalloproteinases by metabolites of maritime pine bark extract (pycnogenol). [**The procyanidin-rich maritime pine bark extract Pycnogenol has well-documented antioxidant and anti-inflammatory activity. After oral administration of Pycnogenol two major metabolites are formed in vivo, delta-(3,4-dihydroxyphenyl)-gamma-valerolactone (M1) and delta-(3-methoxy-4-hydroxyphenyl)-gamma-valerolactone (M2). We elucidated the effects of these metabolites on matrix metalloproteinases (MMPs) and determined their antioxidant activity to understand their contribution to the effects of maritime pine bark extract. We discovered strong inhibitory effects of M1 and M2 toward the activity of MMP-1, MMP-2, and MMP-9. On a microgram-per-milliliter basis both metabolites appeared more active than Pycnogenol. The metabolites were more effective than their metabolic precursor (+)-catechin in MMP inhibition. On a cellular level, we detected highly potent prevention of MMP-9 release by both metabolites, with concentrations of 0.5 microM resulting in about 50% inhibition of MMP-9 secretion. M1 was significantly more effective in superoxide scavenging than (+)-catechin, ascorbic acid, and trolox, while M2 displayed no scavenging activity. Both metabolites exhibited antioxidant activities in a redox-linked colorimetric assay, with M1 being significantly more potent than all other compounds tested. Thus, our data contribute to the comprehension of Pycnogenol effects and provide a rational basis for its use in prophylaxis and therapy of disorders related to imbalanced or excessive MMP activity.] Grimm T, Schafer A, et al. *Free Radic Biol Med*. 2004 Mar 15;36(6):811-22. http://www.ncbi.nlm.nih.gov/pubmed/14990359

877. **Association of Marine Omega-3 Fatty Acid Levels With Telomeric Aging in Patients With Coronary Heart Disease.** [Context: Increased dietary intake of marine omega-3 fatty acids is associated with prolonged survival in patients with coronary heart disease. However, the mechanisms underlying this protective effect are poorly understood. Objective: To investigate the association of omega-3 fatty acid blood levels with temporal changes in telomere length, an emerging marker of biological age. Design, Setting, and Participants**:** Prospective cohort study of 608 ambulatory outpatients in California with stable coronary artery disease recruited from the Heart and Soul Study between September 2000 and December 2002 and followed up to January 2009 (median, 6.0 years; range, 5.0-8.1 years). Main Outcome Measures: We measured leukocyte telomere length at baseline and again after 5 years of follow-up. Multivariable linear and logistic regression models were used to investigate the association of baseline levels of omega-3 fatty acids (docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA]) with subsequent change in telomere length. Results: Individuals in the lowest quartile of DHA+EPA experienced the fastest rate of telomere shortening (0.13 telomere-to-single-copy gene ratio [T/S] units over 5 years; 95% confidence interval [CI], 0.09-0.17), whereas those in the highest quartile experienced the slowest rate of telomere shortening (0.05 T/S units over 5 years; 95% CI, 0.02-0.08; $P < .001$ for linear trend across quartiles). Levels of DHA+EPA were associated with less telomere shortening before (unadjusted β coefficient x 10^{-3} = 0.06; 95% CI, 0.02-0.10) and after (adjusted β coefficient x 10^{-3} = 0.05; 95% CI, 0.01-0.08) sequential adjustment for established risk factors and potential confounders. Each 1-SD increase in DHA+EPA levels was associated with a 32% reduction in the odds of telomere shortening (adjusted odds ratio, 0.68; 95% CI, 0.47-0.98). Conclusion: Among this cohort of patients with coronary artery disease, there was an inverse relationship between baseline blood levels of marine omega-3 fatty acids and the rate of telomere shortening over 5 years.] Farzaneh-Far R, Lin J, et al. *JAMA*, 2010;303(3):250-257. http://jama.ama-assn.org/cgi/content/abstract/303/3/250

878. **Dietary fats and health: dietary recommendations in the context of scientific evidence.** [Although early studies showed that saturated fat diets with very low levels of PUFAs increase serum cholesterol, whereas other studies showed high serum cholesterol increased the risk of coronary artery disease (CAD), the evidence of dietary saturated fats increasing CAD or causing premature death was weak. Over the years, data revealed that dietary saturated fatty acids (SFAs) are not associated with CAD and other adverse health effects or at worst are weakly associated in some analyses when other contributing factors may be overlooked. Several recent analyses indicate that SFAs, particularly in dairy products and coconut oil, can improve health. The evidence of ω6 polyunsaturated fatty acids (PUFAs) promoting inflammation and augmenting many diseases continues to grow, whereas ω3 PUFAs seem to counter these adverse effects. The replacement of saturated fats in the diet with carbohydrates, especially sugars, has resulted in increased obesity and its associated health complications. Well-established mechanisms have been proposed for the adverse health effects of some alternative or replacement nutrients, such as simple carbohydrates and PUFAs. The focus on dietary manipulation of serum cholesterol may be moot in view of numerous other factors that increase the risk of heart disease. The adverse health effects that have been associated with saturated fats in the past are most likely due to factors other than SFAs, which are discussed here. This review calls for a rational reevaluation of existing dietary recommendations that focus on minimizing dietary SFAs, for which mechanisms for adverse health effects are lacking.] Lawrence GD. *Adv Nutr*, 2013 May 1;4(3):294-302. doi: 10.3945/an.113.003657. http://www.ncbi.nlm.nih.gov/pubmed/23674795

879. **Effects of a fish oil containing lipid emulsion on plasma phospholipid fatty acids, inflammatory markers, and clinical outcomes in septic patients: a randomized, controlled clinical trial.** [Introduction: The effect of parenteral fish oil in septic patients is not widely studied. This study investigated the effects of parenteral fish oil on plasma phospholipid fatty acids, inflammatory mediators, and clinical outcomes. Methods: Twenty-five patients with systemic inflammatory response syndrome or sepsis, and predicted to need parenteral nutrition were randomized to receive either a 50:50 mixture of medium-chain fatty acids and soybean oil or a 50:40:10 mixture of medium-chain fatty acids, soybean oil and fish oil. Parenteral nutrition was administrated continuously for five days from admission. Cytokines and eicosanoids were measured in plasma and in lipopolysaccharide-stimulated whole blood culture supernatants. Fatty acids were measured in plasma phosphatidylcholine. Results: Fish oil increased eicosapentaenoic acid in plasma phosphatidylcholine ($P < 0.001$). Plasma interleukin (IL)-6 concentration decreased significantly more, and IL-10 significantly less, in the fish oil group (both $P < 0.001$). At Day 6 the ratio PO_2/FiO_2 was significantly higher in the fish oil group ($P = 0.047$) and there were fewer patients with PO_2/FiO_2 <200 and <300 in the fish oil group ($P = 0.001$ and $P = 0.015$, respectively). Days of ventilation, length of intensive care unit (ICU) stay and mortality were not different between the two groups. The fish oil group tended to have a shorter length of hospital stay (22 ± 7 vs. 55 ± 16 days; $P = 0.079$) which became significant (28 ± 9 vs. 82 ± 19 days; $P = 0.044$) when only surviving patients were included. Conclusions: Inclusion of fish oil in parenteral nutrition provided to septic ICU patients increases plasma eicosapentaenoic acid, modifies inflammatory cytokine concentrations and improves gas exchange. These changes are associated with a tendency towards shorter length of hospital stay.] Barbosa VM, Miles EA, et al. *Critical Care* 2010, 14**:**R5 . http://ccforum.com/content/14/1/R5

880. **Evaluation of the Effect of Neptune Krill Oil on Chronic Inflammation and Arthritic Symptoms.** [Objectives: To evaluate the effect of Neptune Krill Oil (NKO™) on C-reactive protein (CRP) on patients with chronic inflammation and b) to evaluate the effectiveness of NKO™ on arthritic symptoms. Methods: Randomized, double blind, placebo controlled study. Ninety patients were recruited with confirmed diagnosis of cardiovascular disease and/or rheumatoid arthritis and/or osteoarthritis and with increased levels of CRP (>1.0 mg/dl) upon three consecutive weekly blood analysis. Group A received NKO™ (300 mg daily) and Group B received a placebo. CRP and Western Ontario and McMaster Universities (WOMAC) osteoarthritis score were measured at baseline and days 7, 14 and 30. Results: After 7 days of treatment NKO™ reduced CRP by 19.3% compared to an increase by 15.7% observed in the placebo group ($p = 0.049$). After 14 and 30 days of treatment

NKO™ further decreased CRP by 29.7% and 30.9% respectively ($p < 0.001$). The CRP levels of the placebo group increased to 32.1% after 14 days and then decreased to 25.1% at day 30. The between group difference was statistically significant; $p = 0.004$ at day 14 and $p = 0.008$ at day 30. NKO™ showed a significant reduction in all three WOMAC scores. After 7 days of treatment NKO™, reduced pain scores by 28.9% ($p = 0.050$), reduced stiffness by 20.3% ($p = 0.001$) and reduced functional impairment by 22.8% ($p = 0.008$). Conclusion: The results of the present study clearly indicate that NKO™ at a daily dose of 300 mg significantly inhibits inflammation and reduces arthritic symptoms within a short treatment period of 7 and 14 days.] Luisa Deutsch. *Journal of the American College of Nutrition*, Vol. 26, No. 1, 39-48 (2007). http://www.jacn.org/cgi/content/abstract/26/1/39

881. **Fish-oil supplementation induces antiinflammatory gene expression profiles in human blood mononuclear cells.** [BACKGROUND: Polyunsaturated fatty acids can have beneficial effects on human immune cells, such as peripheral blood mononuclear cells (PBMCs). However, the mechanisms of action of polyunsaturated fatty acids on immune cells are still largely unknown. OBJECTIVE: The objective was to examine the effects of supplementation with the polyunsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on whole-genome PBMC gene expression profiles, in healthy Dutch elderly subjects participating in a double-blind trial, by using whole-genome transcriptomics analysis. DESIGN: The subjects were randomly allocated to 1 of 3 groups: 1) consumption of 1.8 g EPA+DHA/d (n = 36), 2) consumption of 0.4 g EPA+DHA/d (n = 37), or 3) consumption of 4.0 g high-oleic acid sunflower oil (HOSF)/d (n = 38). All supplements were given in capsules. Before and after 26 wk of intervention, blood samples were collected. Microarray analysis was performed on PBMC RNA from 23 subjects who received 1.8 g EPA+DHA/d and 25 subjects who received HOSF capsules. Quantitative real-time polymerase chain reaction was performed in all 111 subjects. RESULTS: A high EPA+DHA intake changed the expression of 1040 genes, whereas HOSF intake changed the expression of only 298 genes. EPA+DHA intake resulted in a decreased expression of genes involved in inflammatory- and atherogenic-related pathways, such as nuclear transcription factor kappaB signaling, eicosanoid synthesis, scavenger receptor activity, adipogenesis, and hypoxia signaling. CONCLUSION: These results are the first to show that intake of EPA+DHA for 26 wk can alter the gene expression profiles of PBMCs to a more antiinflammatory and antiatherogenic status.] Bouwens M, Van de Rest O, et al. *Am J Clin Nutr*. 2009 Aug;90(2):415-24. http://www.ncbi.nlm.nih.gov/pubmed/19515734

882. **Inhibition of NF-kappaB activation and MMP-9 secretion by plasma of human volunteers after ingestion of maritime pine bark extract (Pycnogenol). [**French maritime pine bark extract (Pycnogenol) displays a variety of anti-inflammatory effects in vivo. Aim of this study was to determine whether human plasma after oral intake of Pycnogenol contains sufficient concentrations of active principles to inhibit key mediators of inflammation. Blood samples from seven healthy volunteers were obtained before and after five days administration of 200 mg Pycnogenol per day. Plasma samples statistically significantly inhibited matrix metalloproteinase 9 (MMP-9) release from human monocytes and NF-kappaB activation. Thus, we provide evidence that bioavailable active principles of Pycnogenol exert anti-inflammatory effects by inhibition of proinflammatory gene expression which is consistent with documented clinical observations. We suggest that our ex vivo method is suitable to substantiate molecular pharmacological mechanisms of complex plant extracts in a more focussed and rational way compared to in vitro studies by taking into account the processes of absorption and metabolism.] Grimm T, Chovanova Z, et al. *J Inflamm (Lond)*. 2006 Jan 27;3:1. http://www.ncbi.nlm.nih.gov/pubmed/16441890

883. **Modulation of inflammatory cytokines by omega-3 fatty acids.** [Many human diseases have been linked to inflammation, which is mediated by a number of chemical molecules including lipid mediators and cytokines. Polyunsaturated fatty acids (omega-6 and omega-3 fatty acids) are the precursors of the lipid mediators and play an important role in regulation of inflammation. Generally, omega-6 fatty acids (e.g. arachidonic acid) promote inflammation whereas omega-3 fatty acids (e.g. eicosapentaenoic acid and docosahexaenoic acid) have anti-inflammatory properties. Omega-3 fatty acids dampen inflammation through multiple pathways. On the one hand, omega-3 fatty acids inhibit the formation of omega-6 fatty acids-derived pro-inflammatory eicosanoids (e.g. PGE2 and LTB4), and on the other hand these fatty acids can form several potent anti-inflammatory lipid mediators (e.g. resolvins and protectins). These together directly or indirectly suppress the activity of nuclear transcription factors, such as NFkappaB, and reduce the production of pro-inflammatory enzymes and cytokines, including COX-2, tumor necrosis factor (TNF)-alpha, and interleukin (IL)-1beta. This chapter focuses on the evidence from recent studies using new experimental models.] Kang JX, Weylandt KH. *Subcell Biochem*. 2008;49:133-43. http://www.ncbi.nlm.nih.gov/pubmed/18751910

884. **n-3 polyunsaturated fatty acids, inflammation, and inflammatory diseases.** [Inflammation is part of the normal host response to infection and injury. However, excessive or inappropriate inflammation contributes to a range of acute and chronic human diseases and is characterized by the production of inflammatory cytokines, arachidonic acid-derived eicosanoids (prostaglandins, thromboxanes, leukotrienes, and other oxidized derivatives), other inflammatory agents (e.g., reactive oxygen species), and adhesion molecules. At sufficiently high intakes, long-chain n-3 polyunsaturated fatty acids (PUFAs), as found in oily fish and fish oils, decrease the production of inflammatory eicosanoids, cytokines, and reactive oxygen species and the expression of adhesion molecules. Long-chain n-3 PUFAs act both directly (e.g., by replacing arachidonic acid as an eicosanoid substrate and inhibiting arachidonic acid metabolism) and indirectly (e.g., by altering the expression of inflammatory genes through effects on transcription factor activation). Long-chain n-3 PUFAs also give rise to a family of antiinflammatory mediators termed resolvins. Thus, n-3 PUFAs are potentially potent antiinflammatory agents. As such, they may be of therapeutic use in a variety of acute and chronic inflammatory settings. Evidence of their clinical efficacy is reasonably strong in some settings (e.g., in rheumatoid arthritis) but is weak in others (e.g., in inflammatory bowel diseases and asthma). More, better designed, and larger trials are required to assess the therapeutic potential of long-chain n-3

PUFAs in inflammatory diseases. The precursor n-3 PUFA alpha-linolenic acid does not appear to exert antiinflammatory effects at achievable intakes.] Calder PC. *Am J Clin Nutr.* 2006 Jun;83(6 Suppl):1505S-1519S. http://www.ncbi.nlm.nih.gov/pubmed/16841861

885. **Omega-3 Fatty Acid Effect on Alveolar Bone Loss in Rats**. [Gingival inflammation and alveolar bone resorption are hallmarks of adult periodontitis, elicited in response to oral micro-organisms such as *Porphyromonas gingivalis.* We hypothesized that omega (ω)-3 fatty acids (FA) dietary supplementation would modulate inflammatory reactions leading to periodontal disease in infected rats. Rats were fed fish oil (ω-3 FA) or corn oil (n-6 FA) diets for 22 weeks and were infected with *P. gingivalis*. Rats on the ω-3 FA diet exhibited elevated serum levels of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), documenting diet-induced changes. PCR analyses demonstrated that rats were orally colonized by *P. gingivalis*; increased IgG antibody levels substantiated this infection. *P. gingivalis*-infected rats treated with ω-3 FA had significantly less alveolar bone resorption. These results demonstrated the effectiveness of an ω-3 FA-supplemented diet in modulating alveolar bone resorption following *P. gingivalis* infection, and supported that ω-3 FA may be a useful adjunct in the treatment of periodontal disease.] Kesavalu L, Vasudevan B, et al. *J Dent Res*. 2006 July; 85(7):648-652. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2220053/

886. **Omega-3 fatty acid regulates inflammatory cytokine/mediator messenger RNA expression in Porphyromonas gingivalis-induced experimental periodontal disease.** [INTRODUCTION: Porphyromonas gingivalis is strongly implicated in the etiology of adult periodontitis by inducing inflammatory cytokines, resulting in gingival and periodontal tissue inflammation and alveolar bone resorption. This study tested the hypothesis that supplementing the diet with omega-3 fatty acid (omega-3 FA; i.e. fish oil) would exert anti-inflammatory effects in the gingival tissues of P. gingivalis-infected rats. METHODS: Rats were fed either fish oil or corn oil diets ad libitum for 22 weeks and infected with P. gingivalis strain 381 or strain A7A1-28. After sacrifice, rat gingival tissues were excised and the RNA was isolated and analyzed for proinflammatory mediators [interleukin-1beta (IL-1beta), tumor necrosis factor-alpha (TNF-alpha), IL-6], T helper type 1 and type 2 cytokines [interferon-gamma (IFN-gamma), IL-4, IL-10), antioxidant enzymes [catalase (CAT), superoxide dismutase (SOD)], and genes critical for eicosanoid mediator production [cyclo-oxygenase-2 (COX-2), 5-lipoxygenase (5-LO)] by reverse transcription-polymerase chain reaction using rat-specific primers. RESULTS: Rats on the omega-3 FA diet exhibited decreased proinflammatory cytokine gene expression (IL-1beta, TNF-alpha) and enhanced IFN-gamma, CAT and SOD messenger RNA expression compared to rats fed a corn oil diet, supporting a diet-induced modulation of host inflammatory reactions. Analyses of alveolar bone resorption in the rats related to gene expression profiles demonstrated significant positive correlations with IL-1beta, IL-6 and COX-2 and negative correlations with CAT and SOD. CONCLUSION: These findings suggest that diets enriched for omega-3 FA modulate the local gingival inflammatory milieu of the host following oral P. gingivalis infection, which impacts on alveolar bone resorption in rats.] Kesavalu L, Bakthavatchalu V, et al. *Oral Microbiol Immunol.* 2007 Aug;22(4):232-9. http://www.ncbi.nlm.nih.gov/pubmed/17600534?ordinalpos=1&itool=PPMCLayout.PPMCAppController.PPMCArticlePage.PPMCPubmedRA&linkpos=1

887. **Omega-3 PUFA derived anti-inflammatory lipid mediator resolvin E1.** [Inflammation is a defensive response to injury and infection, but excessive or inappropriate inflammation contributes to a range of acute and chronic human diseases. Clinical assessment of dietary supplementation of omega-3 polyunsaturated fatty acids (PUFA) including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) indicate their beneficial impact on human diseases in which inflammation is suspected as a key component of the pathogenesis. Although the mechanism of EPA and DHA action is still not fully defined in molecular terms, recent studies have revealed that, during the course of acute inflammation, omega-3 PUFA-derived mediators including resolvins and protectins with potent anti-inflammatory and pro-resolving properties are produced. In this review, we provide an overview of the formation and actions of EPA-derived anti-inflammatory lipid mediator resolvin E1.] Seki H, Tani Y, et al. *Prostaglandins Other Lipid Mediat.* 2009 Sep;89(3-4):126-30. http://www.ncbi.nlm.nih.gov/pubmed/19737659

888. **Resolvins and protectins: novel lipid mediators in anti-inflammation and resolution.** [A well-integrated inflammatory response and its natural resolution are essential to homeostasis. Hence, it is important to achieve a complete understanding of the molecular events that govern termination of acute inflammation. Recent studies uncovered endogenous pathways in inflammatory exudates taken from the resolution phase that actively generate new families of locally acting mediators from the essential fatty acids eicosapentaenoic acid and docosahexaenoic acid. These new chemical families were coined resolvins and protectins because in animals specific members of these families control the duration and magnitude of inflammation. Hence, mapping of these resolution circuits, mediators and their target signaling pathways of these potent agonists of resolution has provided new avenues for appreciating the molecular basis of many inflammatory diseases. This overview covers recent advances on the biosynthesis and actions of these novel anti-inflammatory lipid mediators, with a focus on the stereochemical basis of the potent actions of resolving E1 and protectin D1. These previously unappreciated families of lipid-derived mediators were originally isolated from experimental murine models of acute inflammation captured during natural self-limited resolution. Since they have proven anti-inflammatory, proresolving, and protective properties in experimental models of disease, it follows that potential defective.] Serhan CN. *Scandinavian Journal of Food and Nutrition*, 2006; 50(52):68-78. http://www.foodandnutritionresearch.net/index.php/fnr/article/viewFile/1579/1447

889. **Resolvin D1 a Novel Docosahexaenoic Acid-Derived Mediator Resolves Experimental Periodontitis.** Objective: Resolvin D1 (RvD1; 7*S*, 8*R*, 17*S* trihydroxy-4*Z*, 9*E*, 11*E*, 13*Z*, 15*E*, 19*Z*-docosahexaenoic acid) is a newly identified lipid mediator with potent anti-inflammatory and pro-resolving properties derived from docosahexaenoic acid (DHA). RvD1

provides protection against tissue damage in several systemic inflammation models. The purpose of this study was to evaluate the proresolving actions of topically applied RvD1 in experimental periodontitis compared to vehicle control. Conclusions: In a rabbit model of human periodontal disease, local application of RvD1 a novel pro-resolving lipid mediator in small amounts results in complete resolution of inflammation and regeneration of bone.]Hasturk H, Kantarci A, et al. IADR General Session, Miami FL, April 1-4, 2009 http://iadr.confex.com/iadr/2009miami/webprogram/Paper120016.html

890. **Resolvin E1, an endogenous lipid mediator derived from omega-2 eicosapentaenoic acid, protects against 2,4,6-trinirobenzene sulfonic acid-induced colitis.** [Resolvin E1 is an anti-inflammatory lipid mediator derived from omega-3 fatty acid eicosapentaenoic acid (EPA). At the local site of inflammation, aspirin treatment enhances EPA conversion to 18R-oxygenated products, including Rv#1, which cary potent anti-inflammatory signals. Here, we obtained evidenc for reduced leukocyte infiltration in a mouse peritonitis model, where the administration of EPA and aspirin initiated the genertino of RvE1 in the exudates. Similar results were obtained with the administration of synthetic RvE1, which blocked leukocyte infiltration. RvE1 also protected against the development of 2,4,6-trinitrobenzene sulfonic acid IgG, decreased leukocyte infiltration, and proinflammatory gene expression including IL-12 p40, TNF-a, and inducible nitric oxide synthase. Thus, the endogenous lipid mediator RvE1 counter-regulates leukocyte-mediated tissue injury and proinflammatory gene expression. These findings show an endogenous mechanism that mayunderlie the beneficial actions of omega-3 EPA and provide targeted approaches for the treatment of intestinal inflammation.] Arita M, Yoshida M, et al. *PANS*, Vol 102, No. 21, p 7671-7676, May 24, 2005. http://www.jstor.org/pss/3375593

891. **Resolvin E1, an EPA-derived mediator in whole blood, selectively counterregulates leukocytes and platelets.** [Resolvin E1 (RvE1) is an omega-3 eicosapentaenoic acid (EPA)–derived lipid mediator generated during resolution of inflammation and in human vasculature via leukocyte-endothelial cell interactions. RvE1 possesses anti-inflammatory and proresolving actions. Here, we report that RvE1 in human whole blood rapidly regulates leukocyte expression of adhesion molecules. RvE1 in the 10- to 100-nM range stimulated L-selectin shedding, while reducing CD18 expression in both neutrophils and monocytes. When added to whole blood, RvE1 did not stimulate reactive oxygen species by either neutrophils or monocytes, nor did it directly stimulate cytokine/chemokine production in heparinized blood. Intravital microscopy (IVM) demonstrated that RvE1 rapidly reduced leukocyte rolling (~ 40%) in venules of mice. In human platelet-rich plasma (PRP), RvE1 selectively blocked both ADP-stimulated and thromboxane receptor agonist U46619 -stimulated platelet aggregation in a concentration-dependent manner. In contrast, Δ6,14-*trans*-RvE1 isomer was inactive. RvE1 did not block collagen-stimulated aggregation, and regulation of ADP-induced platelet aggregation was not further enhanced with aspirin treatment. These results indicate RvE1 is a potent modulator of leukocytes as well as selective platelet responses in blood and PRP, respectively. Moreover, the results demonstrate novel agonist-specific antiplatelet actions of RvE1 that are potent and may underlie some of the beneficial actions of EPA in humans.] Dona M, Fredman G, et al. Blood, 1 August 2008, Vol. 112, No. 3, pp. 848-855. http://bloodjournal.hematologylibrary.org/cgi/content/full/112/3/848

892. **Resolvin E1 promotes mucosal surface clearance of neutrophils: a new paradigm for inflammatory resolution**. [Migration of neutrophils (PMN) across epithelia is a pathological hallmark of numerous mucosal diseases. Whereas lesions at mucosal surfaces are generally self-limiting, endogenous mechanisms of resolution are incompletely understood. Previous studies revealed that resolvins directly act on PMN to attenuate transendothelial migration, less is known about the influence of resolvins on PMN-epithelial interactions and whether they act on epithelia. We studied the dynamics of resolvin E1 (RvE1) actions on leukocyte transepithelial migration. PMN exposure to RvE1 or chemerin (peptide agonist of ChemR23) reduced transepithelial migration in a concentration-dependent manner. Conversely, activation of epithelial ChemR23 promoted apical clearance of PMN. A nonbiased screen of known PMN ligands expressed on epithelial cells in response to RvE1 revealed selective induction of CD55, an apically expressed antiadhesive molecule. CD55 promoter analysis demonstrated that both RvE1 and chemerin activate the CD55 promoter. Inhibition of CD55 by neutralizing antibody prevented RvE1-dependent augmentation of apical PMN clearance. Taken together these findings implicate a "two-hit" model of inflammatory resolution, whereby activation of the PMN RvE1 receptor attenuates transepithelial migration and subsequent actions on the epithelium promote CD55-dependent clearance of PMN across the epithelial cell surface promoting active inflammatory resolution.] Campbell EL, Louis NA, et al. *The FASEB Journal*. 2007;21:3162-3170. http://www.fasebj.org/cgi/content/full/21/12/3162

893. **Resolvin E1 Regulates Inflammation at the Cellular and Tissue Level and Restores Tissue Homeostasis In Vivo.** [Resolvin E1 (RvE1) is a potent proresolving mediator of inflammation derived from omega-3 eicosapentaenoic acid that acts locally to stop leukocyte recruitment and promote resolution. RvE1 displays potent counter-regulatory and tissue-protective actions in vitro and in vivo. Periodontal disease is a local inflammatory disease initiated by bacteria characterized by neutrophil-mediated tissue injury followed by development of a chronic immune lesion. In this study, we report the treatment of established periodontitis using RvE1 as a monotherapy in rabbits compared with structurally related lipids PGE_2 and leukotriene B_4. PGE_2 and leukotriene B_4 each enhanced development of periodontitis and worsened the severity of disease. Promotion of resolution of inflammation as a therapeutic target with RvE1 resulted in complete restoration of the local lesion, and reduction in the systemic inflammatory markers C-reactive protein and IL-1β. This report is the first to show that resolution of inflammation by a naturally occurring endogenous lipid mediator results in complete regeneration of pathologically lost tissues, including bone.] Hasturk H, Kantarci A, et al. *The Journal of Immunology*, 2007, 179, 7021 -7029 http://www.jimmunol.org/cgi/content/full/179/10/7021

894. **Resolvins, docosatrienes, and neuroprotectins, novel omega-3-derived mediators, and their endogenous aspirin-triggered epimers**. [Abstract **:** The molecular basis for the beneficial impact of essential omega-3 (n−3) FA remains of

interest. Recently, we identified novel mediators generated from eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) that displayed potent bioactions identified first in resolving inflammatory exudates and in tissues enriched with DHA. The trivial names *resolvin* (resolution phase interaction products) and *docosatrienes* were introduced for the bioactive compounds from these novel series since they possess potent anti-inflammatory and immunoregulatory actions. … In this article, we provide an overview of the formation and actions of these newly uncovered pathways and products.] Serhan CN, Arita M, et al. *Lipids*, Vol 39, Num 11, Nov 2004, PP 1125-1132. http://www.springerlink.com/content/m664850147247830/

895. **Resolvins: A Family of Bioactive Products of Omega-3 Fatty Acid Transformation Circuits Initiated by Aspirin Treatment that Counter Proinflammation Signals. [**Aspirin (ASA) is unique among current therapies because it acetylates cyclooxygenase (COX)-2 enabling the biosynthesis of *R*containing precursors of endogenous antiinflammatory mediators. Here, we report that lipidomic analysis of exudates obtained in the resolution phase from mice treated with ASA and docosahexaenoic acid (DHA) (C22:6) produce a novel family of bioactive 17 *R*-hydroxy-containing di- and tri-hydroxy-docosanoids termed resolvins. Murine brain treated with aspirin produced endogenous 17 *R*-hydroxydocosahexaenoic acid as did human microglial cells. Human COX-2 converted DHA to 13-hydroxy-DHA that switched with ASA to 17 *R*-HDHA that also proved a major route in hypoxic endothelial cells. Human neutrophils transformed COX-2-ASA–derived 17 *R* -hydroxy-DHA into two sets of novel diandtrihydroxy products; one initiated via oxygenation at carbon 7 and the other at carbon 4. These compounds inhibited microglial cell cytokine expression and in vivo dermal inflammation and peritonitis at ng doses, reducing 40–80% leukocytic exudates. These results indicate that exudates, vascular, leukocytes and neural cells treated with aspirin convert DHA to novel 17 *R*-hydroxy series of docosanoids that are potent regulators. These biosyntheticpathways utilize omega-3 DHA and EPA during multicellular events in resolution to produce a family of protective compounds, i.e., resolvins, that enhance proresolution status.] Serhan CN, Hong S, et al. *J. Exp. Med*, Vol 196, No. 8, Oct 21, 2002, pp 1025-1037. http://jem.rupress.org/cgi/reprint/196/8/1025.pdf

896. **Resveratrol suppresses TNF-induced activation of nuclear transcription factors NF-kappa B, activator protein-1, and apoptosis: potential role of reactive oxygen intermediates and lipid peroxidation.** [Resveratrol (trans-3,4',5-trihydroxystilbene), a polyphenolic phytoalexin found in grapes, fruits, and root extracts of the weed Polygonum cuspidatum, exhibits anti-inflammatory, cell growth-modulatory, and anticarcinogenic effects. How this chemical produces these effects is not known, but it may work by suppressing NF-kappaB, a nuclear transcription factor that regulates the expression of various genes involved in inflammation, cytoprotection, and carcinogenesis. In this study, we investigated the effect of resveratrol on NF-kappaB activation induced by various inflammatory agents. Resveratrol blocked TNF-induced activation of NF-kappaB in a dose- and time-dependent manner. Resveratrol also suppressed TNF-induced phosphorylation and nuclear translocation of the p65 subunit of NF-kappaB, and NF-kappaB-dependent reporter gene transcription. Suppression of TNF-induced NF-kappaB activation by resveratrol was not restricted to myeloid cells (U-937); it was also observed in lymphoid (Jurkat) and epithelial (HeLa and H4) cells. Resveratrol also blocked NF-kappaB activation induced by PMA, LPS, H2O2, okadaic acid, and ceramide. The suppression of NF-kappaB coincided with suppression of AP-1. Resveratrol also inhibited the TNF-induced activation of mitogen-activated protein kinase kinase and c-Jun N-terminal kinase and abrogated TNF-induced cytotoxicity and caspase activation. Both reactive oxygen intermediate generation and lipid peroxidation induced by TNF were suppressed by resveratrol. Resveratrol's anticarcinogenic, anti-inflammatory, and growth-modulatory effects may thus be partially ascribed to the inhibition of activation of NF-kappaB and AP-1 and the associated kinases.] Manna SK, Mukhopadhyay A, et al. J *Immunol*. 2000 Jun 15;164(12):6509-19. http://www.ncbi.nlm.nih.gov/pubmed/10843709

897. **Stereochemical assignment, antiinflammatory properties, and receptor for the omega-3 lipid mediator resolvin E1.** [The essential fatty acid eicosapentaenoic acid (EPA) present in fish oils displays beneficial effects in a range of human disorders associated with inflammation including cardiovascular disease. Resolvin E1 (RvE1), a new bioactive oxygenated product of EPA, was identified in human plasma and prepared by total organic synthesis. Results of bioaction and physical matching studies indicate that the complete structure of RvE1 is 5S,12R,18R-trihydroxy-6Z,8E,10E,14Z,16E-EPA. At nanomolar levels, RvE1 dramatically reduced dermal inflammation, peritonitis, dendritic cell (DC) migration, and interleukin (IL) 12 production. We screened receptors and identified one, denoted earlier as ChemR23, that mediates RvE1 signal to attenuate nuclear factor-kappaB. Specific binding of RvE1 to this receptor was confirmed using synthetic [(3)H]-labeled RvE1. Treatment of DCs with small interference RNA specific for ChemR23 sharply reduced RvE1 regulation of IL-12. These results demonstrate novel counterregulatory responses in inflammation initiated via RvE1 receptor activation that provide the first evidence for EPA-derived potent endogenous agonists of antiinflammation.] Arita M, Bianchini F, et al. *J Exp Med.* 2005 Mar 7;201(5):713-22. http://www.ncbi.nlm.nih.gov/pubmed/15753205

898. **Water-soluble extract of Pacific Krill prevents triglyceride accumulation in adipocytes by suppressing PPARγ and C/EBPα expression.** [BACKGROUND: Pacific Krill (Euphausia pacifica) are small, red crustaceans, similar to shrimp, that flourish in the North Pacific and are eaten in Japan. METHODS AND FINDINGS: We investigated the effect of a water-soluble extract of Pacific Krill on adipocytes and discovered that this extract suppressed triglyceride accumulation in adipocytes. Furthermore, the water-soluble extract of Pacific Krill suppressed the expression of two master regulators of adipocyte differentiation, peroxisome proliferator-activated receptor gamma (PPARγ) and CCAAT enhancer binding protein alpha (C/EBPα). C/EBPβ promotes PPARγ and C/EBPα expression, but the water-soluble extract of Pacific Krill did not inhibit the expression of C/EBPβ or C/EBPβ-mediated transcriptional activation. The Pacific Krill extract was more effective than a PPARγ antagonist in suppressing PPARγ and C/EBPα expression. CONCLUSIONS: These results indicated that the water-soluble extract of Pacific Krill was not simply a PPARγ antagonist, but that it prevented triglyceride accumulation in

adipocytes by suppression of PPARγ and C/EBPα via a pathway that is independent of C/EBPβ.] Yamada H, Ueda T, et al. *PLoS One*. 2011;6(7):e21952. Epub 2011 Jul 7. http://www.ncbi.nlm.nih.gov/pubmed/21760932

Nutritional Genomics, Nutrient-Gene

899. **An antiinflammatory dietary mix modulates inflammation and oxidative and metabolic stress in overweight men: a nutrigenomics approach.** [BACKGROUND: Low-grade chronic inflammation in overweight subjects is thought to play an important role in disease development. OBJECTIVE: It was hypothesized that specific dietary components are able to reduce low-grade inflammation as well as metabolic and oxidative stress. DESIGN: Dietary products [resveratrol, green tea extract, alpha-tocopherol, vitamin C, n-3 (omega-3) polyunsaturated fatty acids, and tomato extract] selected for their evidence-based antiinflammatory properties were combined and given as supplements to 36 healthy overweight men with mildly elevated plasma C-reactive protein concentrations in a double-blind, placebo-controlled, crossover study with treatment periods of 5 wk. Inflammatory and oxidative stress defense markers were quantified in plasma and urine. Furthermore, 120 plasma proteins, 274 plasma metabolites (lipids, free fatty acids, and polar compounds), and the transcriptomes of peripheral blood mononuclear cells and adipose tissue were quantified. RESULTS: Plasma adiponectin concentrations increased by 7%, whereas C-reactive protein (principal inflammation marker) was unchanged. However, a multitude of subtle changes were detected by an integrated analysis of the "omics" data, which indicated modulated inflammation of adipose tissue, improved endothelial function, affected oxidative stress, and increased liver fatty acid oxidation. CONCLUSION: An intervention with selected dietary products affected inflammatory processes, oxidative stress, and metabolism in humans, as shown by large-scale profiling of genes, proteins, and metabolites in plasma, urine, and adipose tissue. This trial was registered at clinical trials.gov as NCT00655798.] Bakker GC, van Erk MJ, et al. *Am J Clin Nutr*. 2010 Apr;91(4):1044-59. Epub 2010 Feb 24. http://www.ncbi.nlm.nih.gov/pubmed/20181810

900. **Common genetic determinants of vitamin D insufficiency: a genome-wide association study.** [Background: Vitamin D is crucial for maintenance of musculoskeletal health, and might also have a role in extraskeletal tissues. Determinants of circulating 25-hydroxyvitamin D concentrations include sun exposure and diet, but high heritability suggests that genetic factors could also play a part. We aimed to identify common genetic variants affecting vitamin D concentrations and risk of insufficiency. Methods: We undertook a genome-wide association study of 25-hydroxyvitamin D concentrations in 33 996 individuals of European descent from 15 cohorts. Five epidemiological cohorts were designated as discovery cohorts (n=16 125), five as in-silico replication cohorts (n=9367), and five as de-novo replication cohorts (n=8504). 25-hydroxyvitamin D concentrations were measured by radioimmunoassay, chemiluminescent assay, ELISA, or mass spectrometry. Vitamin D insufficiency was defined as concentrations lower than 75 nmol/L or 50 nmol/L. We combined results of genome-wide analyses across cohorts using *Z*-score-weighted meta-analysis. Genotype scores were constructed for confirmed variants. Findings: Variants at three loci reached genome-wide significance in discovery cohorts for association with 25-hydroxyvitamin D concentrations, and were confirmed in replication cohorts: 4p12 (overall p=1·9×10−109 for rs2282679, in *GC*); 11q12 (p=2·1×10−27 for rs12785878, near *DHCR7*); and 11p15 (p=3·3×10−20 for rs10741657, near *CYP2R1*). Variants at an additional locus (20q13, *CYP24A1*) were genome-wide significant in the pooled sample (p=6·0×10−10 for rs6013897). Participants with a genotype score (combining the three confirmed variants) in the highest quartile were at increased risk of having 25-hydroxyvitamin D concentrations lower than 75 nmol/L (OR 2·47, 95% CI 2·20—2·78, p=2·3×10−48) or lower than 50 nmol/L (1·92, 1·70—2·16, p=1·0×10−26) compared with those in the lowest quartile. Interpretation: Variants near genes involved in cholesterol synthesis, hydroxylation, and vitamin D transport affect vitamin D status. Genetic variation at these loci identifies individuals who have substantially raised risk of vitamin D insufficiency .] Wang TJ, Zhang F, et al. The Lancet, Early Online Publication, 10 June 2010. http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(10)60588-0/abstract

901. **Effect of comprehensive lifestyle changes on telomerase activity and telomere length in men with biopsy-proven low-risk prostate cancer: 5-year follow-up of a descriptive pilot study.** [**Background** Telomere shortness in human beings is a prognostic marker of ageing, disease, and premature morbidity. We previously found an association between 3 months of comprehensive lifestyle changes and increased telomerase activity in human immune-system cells. We followed up participants to investigate long-term effects. **Methods** This follow-up study compared ten men and 25 external controls who had biopsy-proven low-risk prostate cancer and had chosen to undergo active surveillance. Eligible participants were enrolled between 2003 and 2007 from previous studies and selected according to the same criteria. Men in the intervention group followed a programme of comprehensive lifestyle changes (diet, activity, stress management, and social support), and the men in the control group underwent active surveillance alone. We took blood samples at 5 years and compared relative telomere length and telomerase enzymatic activity per viable cell with those at baseline, and assessed their relation to the degree of lifestyle changes. **Findings** Relative telomere length increased from baseline by a median of 0·06 telomere to single-copy gene ratio (T/S)units (IQR—0·05 to 0·11) in the lifestyle intervention group, but decreased in the control group (−0·03 T/S units, −0·05 to 0·03, difference p=0·03). When data from the two groups were combined, adherence to lifestyle changes was significantly associated with relative telomere length after adjustment for age and the length of follow-up (for each percentage point increase in lifestyle adherence score, T/S units increased by 0·07, 95% CI 0·02—0·12, p=0·005). At 5 years, telomerase activity had decreased from baseline by 0·25 (—2·25 to 2·23) units in the lifestyle intervention group, and by 1·08 (—3·25 to 1·86) units in the control group (p=0·64), and was not associated with adherence to lifestyle changes (relative risk 0·93, 95% CI 0·72—1·20, p=0·57). **Interpretation** Our comprehensive lifestyle intervention was associated

with increases in relative telomere length after 5 years of follow-up, compared with controls, in this small pilot study. Larger randomised controlled trials are warranted to confirm this finding.] Ornish D, Lin J, et al. *The Lancet Oncology*, Volume 14, Issue 11, Pages 1112 - 1120, October 2013. http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(13)70366-8/abstract

902. **Nutrient-Gene Interaction: Metabolic Genotype-Phenotype Relationship.** [The U.S. Department of Health and Human Services (DHHS)/USDA *Dietary Guidelines for Americans* is a science and population evidence-based guide on diet and physical activity, providing advice and recommendations to promote a healthier lifestyle and reduce the risk of chronic diseases, including cancer. These recommendations are supported by the comprehensive evidence-based review on diet and cancer prevention conducted by the American Institute for Cancer Research, National Cancer Institute, World Health Organization/International Agency for Research on Cancer, and others. However, influencing dietary effects are the individual genetic predispositions that are the basis for considerable interindividual variations in cancer risk within the population and in nutrient homeostasis, which is maintained by genomic-nutrient and metabolic-phenotype interactions. Although genetics is an important component, it accounts for only a portion of this variation. An individual's overall phenotype, including health status, is achieved and maintained by the sum of metabolic activities functioning under differing circumstances within the life cycle and the complex interactions among genotype, metabolic phenotype, and the environment. In this postgenomic era, high-throughput groups of technologies in genomics, proteomics, and metabolomics measure and analyze DNA sequences, RNA transcripts, proteins, and nutrient-metabolic fluxes in a single experiment. These advances have transformed biomarker studies on nutrient-gene interactions from a reductionist concept into a holistic practice in which many regulated genes involved in metabolism, along with its metabolic phenotypes, can be measured through functional genomics and metabolic profiling. The overall integration of data and information from the building blocks of metabolism-based nutrient-gene interaction can lead to future individualized dietary recommendations to diminish cancer risk.] Go VLW, Nguyen CTH, et al. *American Society for Nutrition J. Nutr.* 135:3016S-3020S, December 2005 http://jn.nutrition.org/cgi/content/full/135/12/3016S

903. **Nutrigenomic analysis of diet-gene interactions on functional supplements for weight management.** [Recent advances in molecular biology combined with the wealth of information generated by the Human Genome Project have fostered the emergence of nutrigenomics, a new discipline in the field of nutritional research. Nutrigenomics may provide the strategies for the development of safe and effective dietary interventions against the obesity epidemic. According to the World Health Organization, more than 60% of the global disease burden will be attributed to chronic disorders associated with obesity by 2020. Meanwhile in the US, the prevalence of obesity has doubled in adults and tripled in children during the past three decades. In this regard, a number of natural dietary supplements and micronutrients have been studied for their potential in weight management. Among these supplements, (-)-hydroxycitric acid (HCA), a natural extract isolated from the dried fruit rind of Garcinia cambogia, and the micronutrient niacin-bound chromium(III) (NBC) have been shown to be safe and efficacious for weight loss. Utilizing cDNA microarrays, we demonstrated for the first time that HCA-supplementation altered the expression of genes involved in lipolytic and adipogenic pathways in adipocytes from obese women and up-regulated the expression of serotonin receptor gene in the abdominal fat of rats. Similarly, we showed that NBC-supplementation up-regulated the expression of myogenic genes while suppressed the expression of genes that are highly expressed in brown adipose tissue in diabetic obese mice. The potential biological mechanisms underlying the observed beneficial effects of these supplements as elucidated by the state-of-the-art nutrigenomic technologies will be systematically discussed in this review.] Lau FC, Bagchi M, et al. *Curr Genomics.* 2008 Jun;9(4):239-51. http://www.ncbi.nlm.nih.gov/pubmed/19452041

904. **Nutrigenomics: from molecular nutrition to prevention of disease.** [Until recently, nutrition research concentrated on nutrient deficiencies and impairment of health. The advent of genomics-interpreted broadly as a suite of high throughput technologies for the generation, processing, and application of scientific information about the composition and functions of genomes-has created unprecedented opportunities for increasing our understanding of how nutrients modulate gene and protein expression and ultimately influence cellular and organismal metabolism. Nutritional genomics (nutrigenomics), the junction between health, diet, and genomics, can be seen as the combination of molecular nutrition and genomics. The diverse tissue and organ-specific effects of bioactive dietary components include gene-expression patterns (transcriptome); organization of the chromatin (epigenome); protein-expression patterns, including posttranslational modifications (proteome); as well as metabolite profiles (metabolome). Nutrigenomics will promote an increased understanding of how nutrition influences metabolic pathways and homeostatic control, how this regulation is disturbed in the early phases of diet-related disease, and the extent to which individual sensitizing genotypes contribute to such diseases. Eventually, nutrigenomics will lead to evidence-based dietary intervention strategies for restoring health and fitness and for preventing diet-related disease. In this review, we provide a brief overview of nutrigenomics from our point of view by describing current strategies, future opportunities, and challenges.] Afman L, Muller M. *J Am Diet Assoc.* 2006 Apr;106(4):569-76. http://www.ncbi.nlm.nih.gov/pubmed/16567153

905. **Nutrigenomics, proteomics, metabolomics, and the practice of dietetics.** [The human genome is estimated to encode over 30,000 genes, and to be responsible for generating more than 100,000 functionally distinct proteins. Understanding the interrelationships among genes, gene products, and dietary habits is fundamental to identifying those who will benefit most from or be placed at risk by intervention strategies. Unraveling the multitude of nutrigenomic, proteomic, and metabolomic patterns that arise from the ingestion of foods or their bioactive food components will not be simple but is likely to provide insights into a tailored approach to diet and health. The use of new and innovative technologies, such as microarrays, RNA

interference, and nanotechnologies, will provide needed insights into molecular targets for specific bioactive food components and how they harmonize to influence individual phenotypes. Undeniably, to understand the interaction of food components and gene products, there is a need for additional research in the "omics" of nutrition. It is incumbent upon dietetics professionals to recognize that an individual's response to dietary intervention will depend on his or her genetic background and that this information may be used to promote human health and disease prevention. The objectives of this review are to acquaint nutritional professionals with terms relating to "omics," to convey the state of the science to date, to envision the possibilities for future research and technology, and to recognize the implications for clinical practice.] Trujillo E, Davis C, et al. *J Am Diet Assoc*. 2006 Mar;106(3):403-13. http://www.ncbi.nlm.nih.gov/pubmed/16503231

906. **Nutrigenomics. Scientific basis, status and perspectives of application** [Nutrigenomics investigates the interaction between nutrition and the genome, thereby combining nutritional research with functional genomics. Its aims are (1) to correlate heterogeneous effects of nutrients with sequence variations in the genome and (2) to investigate the effects of nutrients and other food components on gene expression at a genome-wide scale (mRNA profiling), and on patterns of metabolite alterations in serum (metabolite profiling). The field will provide important information as to the biological effects of food components, and to the functional consequences of genetic variance. This information will improve the prevention of nutrition-related diseases, e. g. by establishing personalised nutritional recommendations.] Joost HG. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2006 Oct;49(10):1011-9. http://www.ncbi.nlm.nih.gov/pubmed/17013774
907. **Nutritional genomics in practice: where do we begin?** [Nutritional genomics, which studies the genome-wide influences of nutrition, has far-reaching potential in the prevention of diet-related disease. It is highly likely that during the next decade the nutritional supplement and functional food industries will continue robust growth in response to advances in nutritional genomics research and its applications. Parallel to this growth will be impressive progress in understanding the specific influence of certain food components on metabolic pathways and on long-term risk for disease. As genetic information about individuals becomes available, such data are likely to redefine the current concept of preventive medicine. Dietetics professionals have the potential to harness this information and influence health promotion and disease prevention on a global scale. For these reasons, the dietetics profession has an exciting opportunity that, if seized and properly executed, could enhance the scientific foundation of clinical practice, improve therapeutic outcomes, and significantly expand career and economic opportunities for practitioners. The future of dietetics is unquestionably intertwined with nutritional genomics.] DeBusk RM, Kornman KS, et al. *J Am Diet Assoc*. 2005 Apr;105(4):589-98. http://www.ncbi.nlm.nih.gov/pubmed/15800562

Obesity and Inflammation

908. **Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance.** [Tumor necrosis factor-alpha (TNF-alpha) has been shown to have certain catabolic effects on fat cells and whole animals. An induction of TNF-alpha messenger RNA expression was observed in adipose tissue from four different rodent models of obesity and diabetes. TNF-alpha protein was also elevated locally and systemically. Neutralization of TNF-alpha in obese fa/fa rats caused a significant increase in the peripheral uptake of glucose in response to insulin. These results indicate a role for TNF-alpha in obesity and particularly in the insulin resistance and diabetes that often accompany obesity.] Hotamisligil GS, Shargill NS, et al., Science. 1993 Jan 1;259(5091):87-91., http://www.ncbi.nlm.nih.gov/pubmed/7678183?dopt=Abstract
909. **Are Metabolically Healthy Overweight and Obesity Benign Conditions?:** A Systematic Review and Meta-analysis. [Background: Recent interest has focused on a unique subgroup of overweight and obese individuals who have normal metabolic features despite increased adiposity. Normal-weight individuals with adverse metabolic status have also been described. However, it remains unclear whether metabolic phenotype modifies the morbidity and mortality associated with higher body mass index (BMI). Purpose: To determine the effect of metabolic status on all-cause mortality and cardiovascular events in normal-weight, overweight, and obese persons. …Conclusion: Compared with metabolically healthy normal-weight individuals, obese persons are at increased risk for adverse long-term outcomes even in the absence of metabolic abnormalities, suggesting that there is no healthy pattern of increased weight.] Kramer CK, Zinman B, et al. *Annals of Internal Medicine.* 2013 Dec;159(11):758-769. http://annals.org/article.aspx?articleid=1784291
910. **C-Reactive Protein in Healthy Subjects: Associations With Obesity, Insulin Resistance, and Endothelial Dysfunction.** [*Abstract*—C-reactive protein, a hepatic acute phase protein largely regulated by circulating levels of interleukin-6, predicts coronary heart disease incidence in healthy subjects. We have shown that subcutaneous adipose tissue secretes interleukin-6 in vivo. In this study we have sought associations of levels of C-reactive protein and interleukin-6 with measures of obesity and of chronic infection as their putative determinants. We have also related levels of C-reactive protein and interleukin-6 to markers of the insulin resistance syndrome and of endothelial dysfunction. We performed a cross-sectional study in 107 nondiabetic subjects: (1) Levels of C-reactive protein, and concentrations of the proinflammatory cytokines interleukin-6 and tumor necrosis factor-α, were related to all measures of obesity, but titers of antibodies to *Helicobacter pylori* were only weakly and those of *Chlamydia pneumoniae* and cytomegalovirus were not significantly correlated with levels of these molecules. Levels of C-reactive protein were significantly related to those of interleukin-6 (r=0.37, P<0.0005) and tumor necrosis factor-α (r=0.46, P<0.0001). (2) Concentrations of C-reactive protein were related to insulin resistance as calculated from the homoeostasis model assessment model, blood pressure, HDL, and triglyceride, and to markers of endothelial dysfunction (plasma levels of von Willebrand factor, tissue plasminogen activator, and cellular fibronectin). A mean standard deviation score of levels of acute phase markers correlated closely with a similar score of insulin resistance syndrome

variables (r=0.59, P<0.00005), this relationship being weakened only marginally by removing measures of obesity from the insulin resistance score (r=0.53, P<0.00005). These data suggest that adipose tissue is an important determinant of a low level, chronic inflammatory state as reflected by levels of interleukin-6, tumor necrosis factor-α, and C-reactive protein, and that infection with *H pylori*, *C pneumoniae*, and cytomegalovirus is not. Moreover, our data support the concept that such a low-level, chronic inflammatory state may induce insulin resistance and endothelial dysfunction and thus link the latter phenomena with obesity and cardiovascular disease.] Yudkin JS, Stehouwer CDA, et al. *Arteriosclerosis, Thrombosis, and Vascular Biology.* 1999;19:972-978.) http://atvb.ahajournals.org/cgi/content/abstract/19/4/972

911. **Circulating Mononuclear Cells in the Obese Are in a Proinflammatory State.[** *Background*— In view of the increase in plasma concentrations of proinflammatory mediators tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) in obesity, we investigated whether peripheral blood mononuclear cells (MNC) from obese subjects are in a proinflammatory state. *Methods and Results*— MNC were prepared from fasting blood samples of obese (n=16; body mass index [BMI]=37.7±5.0 kg/m^2) and normal-weight control (n=16; BMI=23.8±1.9 kg/m^2) subjects. Nuclear factor κB (NF-κB) binding to DNA in nuclear extracts was elevated (P<0.05) and the inhibitor of NFκB-ß (IκB-ß) was significantly lower (P<0.001) in the obese group. Reverse transcription–polymerase chain reaction revealed elevated levels of migration inhibitor factor (MIF), IL-6, TNF-α, and matrix metalloproteinase-9 (MMP-9) mRNA expression in the obese subjects (P<0.05). Plasma concentrations of MIF, IL-6, TNF-α, MMP-9, and CRP were also significantly higher. Plasma glucose, insulin, and free fatty acids (FFAs) were measured, and homeostasis model assessment of insulin resistance (HOMA-IR) was calculated. Plasma FFA concentration related significantly to BMI, IL-6, and TNF-α mRNA expression and plasma CRP levels but not to HOMA-IR. On the other hand, the inflammatory mediators were significantly related to BMI and HOMA-IR. *Conclusions*— These data show (1) for the first time that MNC in obesity are in a proinflammatory state with an increase in intranuclear NF-κB binding, a decrease in IκB-ß, and an increase in the transcription of proinflammatory genes regulated by NF-κB; (2) that plasma FFAs are a modulator of inflammation; and (3) that insulin resistance is a function of inflammatory mediators.] Ghanim H, Aljada A, et al. *Circulation.* 2004;110:1564-1571. http://circ.ahajournals.org/cgi/content/abstract/110/12/1564?etoc

912. **Diet-induced obesity increases NF-κB signaling in reporter mice.** [The nuclear factor (NF)-κB is a primary regulator of inflammatory responses and may be linked to pathology associated with obesity. We investigated the progression of NF-κB activity during a 12-week feeding period on a high-fat diet (HFD) or a low-fat diet (LFD) using NF-κB luciferase reporter mice. In vivo imaging of luciferase activity showed that NF-κB activity was higher in the HFD mice compared with LFD-fed mice. Thorax region of HFD females displayed fourfold higher activity compared with LFD females, while no such increase was evident in males. In male HFD mice, abdominal NF-κB activity was increased twofold compared with the LFD males, while females had unchanged NF-κB activity in the abdomen by HFD. HFD males, but not females, exhibited evident glucose intolerance during the study. In conclusion, HFD increased NF-κB activity in both female and male mice. However, HFD differentially increased activity in males and females. The moderate increase in abdomen of male mice may be linked to glucose intolerance.] Carlsen H, Haugen F, et al. *Genes Nutr.* 2009 September; 4(3): 215–222. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2745749/

913. **Elevated C-Reactive Protein Levels in Overweight and Obese Adults** [Context Human adipose tissue expresses and releases the proinflammatory cytokine interleukin 6, potentially inducing low-grade systemic inflammation in persons with excess body fat. Objective To test whether overweight and obesity are associated with low-grade systemic inflammation as measured by serum C-reactive protein (CRP) level. Design and Setting The Third National Health and Nutrition Examination Survey, representative of the US population from 1988 to 1994. Participants A total of 16,616 men and nonpregnant women aged 17 years or older. Main Outcome Measures Elevated CRP level of 0.22 mg/dL or more and a more stringent clinically raised CRP level of more than 1.00 mg/dL. Results Elevated CRP levels and clinically raised CRP levels were present in 27.6% and 6.7% of the population, respectively. Both overweight (body mass index [BMI], 25-29.9 kg/m^2) and obese (BMI, ≥30 kg/m^2) persons were more likely to have elevated CRP levels than their normal-weight counterparts (BMI, <25 kg/m^2). After adjustment for potential confounders, including smoking and health status, the odds ratio (OR) for elevated CRP was 2.13 (95% confidence interval [CI], 1.56-2.91) for obese men and 6.21 (95% CI, 4.94-7.81) for obese women. In addition, BMI was associated with clinically raised CRP levels in women, with an OR of 4.76 (95% CI, 3.42-6.61) for obese women. Waist-to-hip ratio was positively associated with both elevated and clinically raised CRP levels, independent of BMI. Restricting the analyses to young adults (aged 17-39 years) and excluding smokers, persons with inflammatory disease, cardiovascular disease, or diabetes mellitus and estrogen users did not change the main findings. Conclusion Higher BMI is associated with higher CRP concentrations, even among young adults aged 17 to 39 years. These findings suggest a state of low-grade systemic inflammation in overweight and obese persons.] Visser M, Bouter LM, et al. *JAMA.* 1999;282:2131-2135. http://jama.ama-assn.org/cgi/content/abstract/282/22/2131

914. **Elevation of serum C-reactive protein levels is associated with obesity in boys.** [This study aimed to reveal the relationships among C-reactive protein (CRP), obesity, blood pressure (BP), and serum lipids in children. This study revealed a significant relationship between CRP and obesity in children. Obese children tended to have high CRP levels, BP elevation, and slight dyslipidemia. These results support the findings that CRP is one of the useful indices of childhood obesity that would affect the progression to future atherosclerotic disease. We consider that a strategy of preventing obesity from childhood would contribute to a drop in the future incidence of metabolic syndromes.] Hiura M., Kikuchi T., *Hypertens Res. 2003 Jul;26(7):541-6.* http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12924621&dopt=Abstract

915. **Obesity Associated with Periodontal Disease: Retrospective Analysis, Dental School Population**. [Objectives: The worldwide prevalence of obesity (two-thirds of Americans are overweight or obese) is the public health challenge of our time. Obesity damages quality of life, boosts medical costs, and is recognized as a predisposing factor to major chronic diseases ranging from cardiovascular disease to cancer. Obesity might represent a systemic condition influencing onset and progression of periodontal disease through the gateway of metabolic syndrome, the pro-inflammatory state characterized by insulin resistance and oxidative stress, in a bi-directional relationship. We hypothesize that the prevalence of periodontal disease will be greater in obese individuals within a dental school patient population. Methods: Subjects identified retrospectively over two-year period using electronic health records from the University of Pittsburgh School of Dental Medicine. Patient records with documented weight, height, age, sex, Type II diabetes status and completed periodontal evaluation were included. Periodontal disease was classified as periodontal pocketing 4mm or greater. Body mass index (BMI) was calculated and patients were classified as obese (BMI>=30) or non-obese (BMI<30). Results: There were 4,537 unique individuals, 2,445 female, 2,092 male. Average age, 54 years. History of diabetes reported by 436 individuals. Prevalence of periodontal disease differed in obese and non-obese populations, being greater in obese populations. Thus we accept the hypothesis, that periodontal disease is more prevalent in obese individuals. Resulting chi-square values for all individuals and all individuals without diabetes were 48.17 (p<.001) and 38.36 (p<.001), respectively. Odds ratio (95% confidence intervals) for periodontal disease of obese versus non-obese individuals was 1.73 (1.48 – 2.02). Excluding diabetic individuals, odds ratio was 1.69 (1.43 – 2.00). Conclusion: Statistical analysis of the retrospective data collected establishes positive association between periodontal disease and obesity. Positive associations are repeatedly demonstrated between prevalent periodontal disease and obesity, but establishing any physiological mechanism behind this relationship will require well-designed prospective research.] Silverstein MS. *IADR General Session*, San Diego CA, March 2011. http://iadr.confex.com/iadr/2011sandiego/webprogram/Paper144341.html

916. **Obesity and Periodontitis.** [*To the Editor:* We recently noted a relation between obesity, which is a risk factor for various diseases, and periodontitis, which is a major cause of tooth loss in adults….] *NEJM* Vol 339:482-483, Aug 13, 1998, No 7. http://content.nejm.org/cgi/content/extract/339/7/482

917. **Obesity and Periodontal Disease in Young, Middle-Aged, and Older Adults**. [Background: The growing prevalence of increased body weight and obesity in the United States has raised significant public health concerns. Obesity has been implicated as a risk factor for several chronic health conditions, as well as being associated with increased mortality. Recently, an association between obesity and periodontal disease was found in a Japanese population. The purpose of the present study is to examine the relation between body weight and periodontal disease in a representative United States sample. Methods: Participants in the third National Health and Nutrition Examination Survey (NHANES III) who were ≥18 years and had undergone a periodontal examination were selected for the analysis (n = 13,665). Body mass index (BMI) and waist circumference (WC) were used as measures of overall and abdominal fat content, respectively. Univariable and multivariable logistic regression models were used to estimate the association between increased body weight and periodontal disease. BMI and WC were assessed independently in a multivariable logistic model containing the following variables: gender, race, education, poverty index, smoking, diabetes, and time elapsed since last dental visit. Significant interactions with age were found and analyses were then stratified by age: younger (18 to 34 years old), middle-aged (35 to 59 years old), and older (60 to 90 years old) adults. Results: A significant association between the measures of body fat and periodontal disease was found among the younger adults, but not middle or older adults. The adjusted odds ratios (OR) for having periodontal disease were 0.21 (0.080 to 0.565), 1.00 (0.705 to 1.407), and 1.76 (1.187 to 2.612) for subjects with BMI <18.5 kg/m^2, 25−29.9 kg/m^2, and ≥30 kg/m^2, respectively. Young subjects with high WC had an adjusted OR of 2.27 (1.480 to 3.487) for having periodontal disease. Conclusions: In a younger population, overall and abdominal obesity are associated with increased prevalence of periodontal disease, while underweight (BMI <18.5) is associated with decreased prevalence. Obesity could be a potential risk factor for periodontal disease especially among younger individuals. Promotion of healthy nutrition and adequate physical activity may be additional factors to prevent or halt the rate of progression of periodontal disease.] Al-Zahrani MS, Bissada NF, et al. *J Periodontol 2003;74:610-615.* http://www.joponline.org/doi/abs/10.1902/jop.2003.74.5.610

918. **Obesity Is an Important Determinant of Baseline Serum C-Reactive Protein Concentration in Monozygotic Twins, Independent of Genetic Influences.** [C-reactive protein (CRP) values predict atherothrombotic cardiovascular disease and type 2 diabetes mellitus. CRP was strongly related to total and central abdominal obesity, blood pressure, and lipid levels, independent of genetic influences. These relationships are likely to contribute significantly to prospective associations between CRP and type 2 diabetes and coronary events.] Greenfield J.R., Samaras K., *Circulation.* 2004;109:3022-3028. http://circ.ahajournals.org/cgi/content/full/109/24/3022

919. **Obesity related to periodontal disease.** [Obesity is significantly related to periodontal disease through the pathway of insulin resistance. Insulin resistance is a condition in which the body does not respond well to the action of insulin. Overweight people with an insulin-resistance index in the top 25 percent were nearly 50 percent more likely to have severe periodontal disease compared with those who had a high BMI and low insulin resistance. "We think bacteria from gum disease may interfere with fat metabolism, leading to elevated low-density lipoprotein cholesterol and total cholesterol," says Dr. Sara G. Grossi, lead author of the study. "Now we see a relationship between obesity, insulin resistance and periodontal disease in a large, population-based cohort. This relationship is important because obesity is an important risk factor for Type 2 diabetes and heart disease. It is possible that periodontal disease contributes to increased morbidity in overweight or obese individuals."] News. J Am Dent Assoc, Vol 131, No 6, 729. http://jada.ada.org/cgi/content/full/131/6/729-a

920. **Periodontal disease, obesity associated with heart disease marker: study . Periodontal disease, obesity associated with heart disease marker.** [Moderately elevated serum C-reactive protein (CRP) concentration is a systemic marker of inflammation and a documented risk factor for cardiovascular disease in otherwise healthy persons. Unrecognized infections, such as periodontal disease, may induce an acute-phase response, elevating CRP levels. We evaluated the association between periodontal disease and CRP levels in adults in the Atherosclerosis Risk in Communities study. Conclusions Extensive periodontal disease and BMI are jointly associated with increased CRP levels in otherwise healthy, middle-aged adults, suggesting the need for medical and dental diagnoses when evaluating sources of acute-phase response in some patients] Slade GD, Ghezzi EM, et al. *Arch Intern Med.* 2003;163:1172-1179. http://archinte.ama-assn.org/cgi/content/abstract/163/10/1172
921. **Periodontal innate immune mechanisms relevant to obesity.** [Obesity affects over 35% of the adult population of the USA, and obesity-related illnesses have emerged as the leading cause of preventable death worldwide, according to the World Health Organization. Obesity's secondary morbidities include increased risk of cardiovascular disease, type II diabetes, and cancer, in addition to increased occurrence and severity of infections. Sedentary lifestyle and weight gain caused by consumption of a high-fat diet contribute to the development of obesity, with individuals having a body mass index (BMI) score > 30 being considered obese. Genetic models of obesity (ob/ob mice, db/db mice, and fa/fa rats) have been insufficient to study human obesity because of the overall lack of genetic causes for obesity in human populations. To date, the diet-induced obese (DIO) mouse model best serves research studies relevant to human health. Periodontal disease presents with a wide range of clinical variability and severity. Research in the past decade has shed substantial light on both the initiating infectious agents and host immunological responses in periodontal disease. Up to 46% of the general population harbors the microorganism(s) associated with periodontal disease, although many are able to limit the progression of periodontal disease or even clear the organism(s) if infected. In the last decade, several epidemiological studies have found an association between obesity and increased incidence of periodontal disease. This review focuses on exploring the immunological consequences of obesity that exacerbate effects of infection by pathogens, with focus on infection by the periodontal bacterium Porphyromonas gingivalis as a running example.] Amar S, Leeman S. *Mol Oral Microbiol.* 2013 Oct;28(5):331-41. doi: 10.1111/omi.12035. http://www.ncbi.nlm.nih.gov/pubmed/23911141
922. **Regulation of visfatin by microbial and biomechanical signals in PDL cells**. [OBJECTIVES: This in vitro study was established to examine whether visfatin thought to be a link between periodontitis and obesity is produced by periodontal ligament (PDL) cells and, if so, whether its synthesis is modulated by microbial and/or biomechanical signals. MATERIALS AND METHODS: PDL cells seeded on BioFlex® plates were exposed to the oral pathogen Fusobacterium nucleatum ATCC 25586 and/or subjected to biomechanical strain for up to 3 days. Gene expression of visfatin and toll-like receptors (TLR) 2 and 4 was analyzed by RT-PCR, visfatin protein synthesis by ELISA and immunocytochemistry, and NFκB nuclear translocation by immunofluorescence. RESULTS: F. nucleatum upregulated the visfatin expression in a dose- and time-dependent fashion. Preincubation with neutralizing antibodies against TLR2 and TLR4 caused a significant inhibition of the F. nucleatum-upregulated visfatin expression at 1 day. F. nucleatum stimulated the NFκB nuclear translocation. Biomechanical loading reduced the stimulatory effects of F. nucleatum on visfatin expression at 1 and 3 days and also abrogated the F. nucleatum-induced NFκB nuclear translocation at 60 min. Biomechanical loading inhibited significantly the expression of TLR2 and TLR4 at 3 days. The regulatory effects of F. nucleatum and/or biomechanical loading on visfatin expression were also observed at protein level. CONCLUSIONS: PDL cells produce visfatin, and this production is enhanced by F. nucleatum. Biomechanical loading seems to be protective against the effects of F. nucleatum on visfatin expression. CLINICAL RELEVANCE: Visfatin produced by periodontal tissues could play a major role in the pathogenesis of periodontitis and the interactions with obesity and other systemic diseases.] Noqueira AV, Nokhbehsaim M, et al. *Clin Oral Investig*., 2013 Feb 13 **http://www.ncbi.nlm.nih.gov/pubmed/23404558**
923. **Release of C-Reactive Protein in Response to Inflammatory Cytokines by Human Adipocytes: Linking Obesity to Vascular Inflammation.** [Obesity, the most common nutritional disorder in industrialized countries, is associated with increased cardiovascular mortality and morbidity). C-reactive protein (CRP), an acute-phase protein and an important predictor of future cardiovascular events in apparently healthy men and women, has been thought to be synthesized in the liver following stimulation by cytokines, such as interleukin (IL)-1-beta, IL-6, and tumor necrosis factor (TNF)-alpha. Recently, however, the extrahepatic synthesis of CRP was found to occur under similar proinflammatory conditions. There is also some evidence for the presence of the CRP message in human adipose tissue. In the present study, we investigated whether CRP is produced by cells in adipose tissue in response to inflammatory stimuli using an in vitro model and whether this phenomenon might be modulated using anti-inflammatory drugs. … In conclusion, our study demonstrates that human adipocytes can produce CRP under the stimulation of several proinflammatory cytokines; moreover, CRP http://content.onlinejacc.org/cgi/content/full/46/6/1112 production may be modulated by selected pharmacologic intervention. The mechanism(s) underlying these findings are not fully defined, and further studies are needed in this area.] Calabro P, Chang DW, et al. *J Am Coll Cardiol*, 2005; 46:1112-1113. http://content.onlinejacc.org/cgi/content/full/46/6/1112
924. **Researchers find human fat cells produce C-reactive protein - Obesity, inflammation and vascular disease link. [**Researchers at The University of Texas M D Anderson Cancer Center and The University of Texas Health Science Center at Houston have found that human fat cells produce a protein that is linked to both inflammation and an increased risk of heart disease and stroke.] Yeh ETH, et al. http://www.medicalnewstoday.com/articles/30761.php
925. **Weight loss leads to reductions in inflammatory biomarkers after a very-low-carbohydrate diet and a low-fat diet in overweight men.** [In recent years, it has become apparent that low-grade vascular inflammation plays a key role in all stages

of the pathogenesis of atherosclerosis. Weight loss has been shown to improve blood inflammatory markers; however, it is unknown if weight-loss diets varying in macronutrient composition differentially affect inflammatory responses. The primary purpose of the present study was to compare a very-low-carbohydrate diet and a low-fat weight-loss diet on inflammatory biomarkers in overweight men. In a randomized cross-over design, 15 overweight men (body fat, >25%; body mass index, 34 kg/m2) consumed two experimental weight-loss diets for two consecutive 6-week periods: a very-low-carbohydrate diet (<10% energy via carbohydrate) and a low-fat diet (<30% energy via fat). Both the low-fat and the very-low-carbohydrate diets resulted in significant decreases in absolute concentrations of hsTNF-alpha (high-sensitivity tumour necrosis factor-alpha), hsIL-6 (high-sensitivity interleukin-6), hsCRP (high-sensitivity C-reactive protein) and sICAM-1 (soluble intercellular cell-adhesion molecule-1). There was no significant change in absolute sP-selectin (soluble P-selectin) concentrations after either diet. Normalized inflammatory values represented as the delta change per 1 kg reduction in body mass showed a significant difference between the two diets only for sP-selectin ($P<0.05$). In summary, energy-restricted low-fat and very-low-carbohydrate diets both significantly decreased several biomarkers of inflammation. These data suggest that, in the short-term, weight loss is primarily the driving force underlying the reductions in most of the inflammatory biomarkers.] Sharman MJ, Volek JS. *Clin Sci (Lond).* 2004 Oct;107(4):365-9.
http://www.ncbi.nlm.nih.gov/pubmed/15265001

Oral Hygiene Devices

926. **Biofilm Removal with a Dental Water Jet.** [Objective:The objective of this study was to evaluate the effect of a dental water jet on plaque biofilm removal using scanning electron microscopy (SEM). Methodology: Eight periodontally involved teeth were extracted. Ten slices were cut from four teeth and were inoculated with saliva and left for four days to further grow plaque biofilm (ex vivo). Four slices were treated with the standard jet tip, four slices were treated with the orthodontic jet tip, and two slices were used as controls. The remaining 4 teeth were treated with the orthodontic jet tip to evaluate the removal of calcified plaque biofilm (in vivo). All teeth were treated using medium pressure for three seconds and evaluated by SEM. Results: The standard jet tip removed 99.9% and the orthodontic jet tip removed 99.8% of the salivary biofilm after 3-second treatment on the 8 teeth slices as viewed by SEM. Observation of the remaining four teeth by the naked eye indicated that the orthodontic jet tip removed significant amounts of calcified (in vivo) plaque biofilm. This was confirmed by SEM evaluations. Conclusion: The Waterpik dental water jet can remove both ex vivo and in vivo plaque biofilm significantly.] Gorur A, Lyle DM, et al. *Compendium of Continuing Education in Dentistry – Supplement*, March 2009, Vol 30, p 1-6. http://www.waterpik.com/oral-health/whitepapers/WP_BiofilmStudyAbstract_0209_v2.pdf
927. **Comparison of the Hydrabrush Powered Toothbrush with Two Commercially-Available Powered Toothbrushes.** Patters MR, Bland PS, et al. Department of Periodontology and Department of Pediatric Dentistry and Community Oral Health, University of Tennessee Health Science Center, College of Dentistry, Memphis, TN. *Journal of the International Academy of Periodontology, July 2005.* http://www.perioiap.org/absjul05.htm
928. **The effect of oral irrigation with a magnetic water treatment device on plaque and calculus.** [The measurements of the group using an irrigator with a magnetic device showed a 44% greater reduction in calculus volume and a 42% greater reduction in area over the group using an unmagnetized irrigator. There appears to be a statistically significant difference in supragingival accretion volumes between conventional irrigation and using an irrigator with a magnetic water treatment device.] Watt DL, Rosenfelder C, et al. *J Clin Periodontol 1993; 20: 3J4-317.*
http://www.hydrofloss.com/oral_health.htm#JOURNAL%20OF%20CLINICAL%20PERIODONTOLOGY
929. **The effectiveness of a magnetized water oral irrigator (Hydro Floss®) on plaque, calculus and gingival health**. [Irrigation with magnetized water resulted in 64% less calculus compared to the control group.] Johnson KE, Sanders JJ, et al, *J Clin Periodontol* 1998; 25: 316-321.
http://www.hydrofloss.com/oral_health.htm#JOURNAL%20OF%20CLINICAL%20PERIODONTOLOGY
930. **A two-month study of the effects of oral irrigation and automatic toothbrush use in an adult orthodontic population with fixed appliances.** [Forty-seven adult orthodontic patients with fixed orthodontic appliances were divided into three study groups: (1) oral irrigation with automatic toothbrush, (n = 16); (2) oral irrigation with manual toothbrushing, (n = 16); (3) control group with continued normal toothbrushing only, (n = 15). Gingival and plaque indices, bleeding after probing, and gingival sulcus depths were assessed at baseline, 1-month, and 2-month periods. Marked and significant gingival and plaque improvements from baseline were measured in all three study groups. After 1 to 2 months use of the automatic toothbrush and/or the oral irrigation device, there was a significant reduction in plaque when compared with the control group who used only the manual toothbrush ($p = 0.026$). Also, there was a significant reduction in gingival inflammation ($p = 0.045$) and evidence for reducing bleeding after probing ($p = 0.037$). No significant differences were found in probe depths among the three study groups, however, use of both devices reduced the pocket depth significantly from baseline by 0.5 mm ($p < 0.0002$). For this population of orthodontic patients, significant reductions in plaque, gingival inflammation, and a tendency for reduced bleeding after probing occurred in both groups with the power device. These improvements were most attributable to the effect of the oral irrigation device.] Burch JG, Lanese R, et.al. *Am J Orthod Dentofacial Orthop. 1994 Aug;106(2):121-6.*
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8059746&dopt=Abstract

931. **Comparison of irrigation to floss as an adjunct to tooth brushing: effect on bleeding, gingivitis, and supragingival plaque.** [OBJECTIVE: The purpose of this twenty-eight day, randomized, single-blind clinical trial was to assess the efficacy of the addition of daily oral irrigation to both power and manual tooth brushing, compared to a traditional regimen of manual tooth brushing and flossing, to determine which regimen had the greatest effect on the reduction of gingival bleeding, gingivitis, and supragingival plaque. CONCLUSION: The results of this clinical trial indicate that when combined with manual or sonic tooth brushing, oral irrigation is an effective alternative to manual tooth brushing and dental floss for reducing bleeding, gingival inflammation, and plaque removal.] Barnes CM, Russell CM, et.al. *J Clin Dent. 2005;16(3):71-7.* http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=16305005&dopt=Abstract

Orthopedic, Transplantation & Heart Valve Procedures

932. **Antibiotic prophylaxis and invasive dental treatment in prosthetic joint patients.** [AIM: To describe current clinical practice among specialist orthopaedic surgeons in New Zealand in their recommendations regarding antibiotic prophylaxis for patients with prosthetic joints who undergo invasive dental treatment. METHODS: Data was collected from a single wave postal survey of all practicing orthopaedic surgeons in New Zealand. Literature review was performed using web-based online search engines and library resources. RESULTS: The response rate from the surgeons was high (75%). Almost 94% of respondents recommended antibiotic prophylaxis for prosthetic joint patients prior to invasive dental treatment as a general principle and 90% of respondents considered that antibiotic prophylaxis was necessary as long as there was a prosthetic joint in situ. The majority of clinicians follow the AHA guidelines; that is, a single preoperative oral dose of 2 g amoxicillin or 600 mg clindamycin if the patient was allergic to penicillin. Over half did not recommend a 6-hour postoperative dose. Patients with medical conditions placing them "at-risk" of prosthetic joint infection were correctly identified by most orthopaedic surgeons especially those with diabetes and other forms of immunosuppression. The setting in which dental surgery was performed was not seen as being important. No randomised controlled trials were identified and currently no definite scientific evidence exists for the systematic use of prophylactic antibiotics before dental procedures in patients with prosthetic joints. In view of the high clinical cost of bacterial infection in cardiac and prosthetic joint patients, most guidelines currently favour the use of prophylactic antibiotics before invasive dental procedures in all patients within 2 years of the index surgery and high risk patients for the rest of their life. CONCLUSIONS: In the absence of level 1 evidence for or against the use of prophylactic antibiotics in patients with prosthetic joints undergoing invasive dental treatment, the most recent ADA/AAOS guidelines provide the best available advice for dental practitioners and their patients. Further discussion between orthopaedic surgeons, general medical practitioners and dental practitioners should be encouraged in order to reach a consensus in New Zealand over this controversial issue.] Tong D, Theis JC. *N Z Med J*. 2008 Aug 22;121(1280):45-52. http://www.ncbi.nlm.nih.gov/pubmed/18791627?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_SingleItemSupl.Pubmed_Discovery_RA&linkpos=3&log$=relatedarticles&logdbfrom=pubmed

933. **Antibiotic prophylaxis before dental procedures in arthroplasty patients.** [Antibiotic prophylaxis is commonly prescribed to patients with total arthroplasties before a dental intervention. This attitude is not evidence-based for several reasons: 1) the usual pathogens of prosthetic joint infections are not of oral origin; 2) even if given, systemic antibiotic do not completely suppress the occult bacteraemia occurring during dental intervention and 3) humans may have up to twelve episodes of occult bacteraemia of dental origin per day. Routine antibiotic prophylaxis should be clearly distinguished from the antibiotic treatment required in case of established oral cavity infection. A constant optimal oral and dental hygiene is more important in terms of prevention and should be routinely recommended to every patient carrying a joint arthroplasty.] Uckay I, Hoffmeyer P, et al. Rev Med *Suisse*. 2010 Apr 7;6(243):727-30. http://www.ncbi.nlm.nih.gov/pubmed/20432994

934. **[Antibiotic prophylaxis for patients with joint prostheses undergoing dental treatment--a topic for discussion]** German [AIM: In accordance with international guidelines, the German Society for Cardiology and the Paul Ehrlich Society for Chemotherapy recently adapted their recommendations for antibiotic prophylaxis of infectious endocarditis. The new version reflected the statistically lower risk for such infections as compared to former considerations and reduced the group of patients who would benefit from the prophylaxis. That paper as well as an increasing number of statements of orthopaedic/traumatologic or dental societies stimulated our contribution on the prevention of prosthesis infections after dental care. With this article we intend to stimulate a position paper of the German Society for Orthopaedics and Traumatology. METHOD: For our study we screened the international literature on the association between bacteremia and dental treatment, bacteremia and prosthesis infections as well as on the availability and risks of antibiotic prophylaxis for prosthesis infections. In addition, we included data on the responsible microorganisms and the importance of biofilms both in the oral cavity and on the infected prosthesis. RESULTS: Generally, the risk of prosthesis infections after bacteremia is lower than that of endocarditis. Also, the range of involved microorganisms only partially overlaps in both diseases. Of note, bacteremia regularly occurs due to normal dental hygiene measures or even after chewing. Because of this high background risk and because of the extended latency period between dental care and symptomatic prosthesis infections, the causality of professional dental measures for prosthesis infections has never conclusively been demonstrated, e.g., by employing molecular methods. However, the association remains plausible and the consequences for such patients are severe. CONCLUSION: We suggest an oral prophylaxis with an aminopenicillin plus beta-lactamase inhibitor or clindamycin shortly before and 4 hours after dental care depending on the tissue invasiveness of the dental measures and the personal risk profile of the patient (prosthesis recently implanted, history of prosthesis infection, natural or iatrogenic conditions severely

affecting the immune status).] Podbielski A, Pahncke D, et al. *Z Orthop Unfall.* 2009 May-Jun;147(3):350-5. Epub 2009 Jun 23.
http://www.ncbi.nlm.nih.gov/pubmed/19551587?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_SingleItemSupl.Pubmed_Discovery_RA&linkpos=2&log$=relatedarticles&logdbfrom=pubmed

935. **Antibiotic prophylaxis for patients with joint prostheses - still a dilemma for dental practitioners.** [OBJECTIVES: To provide a critical review of the current evidence that implicates dental-induced bacteraemia as a risk for joint infections in patients fitted with joint prostheses and appraise the need for antibiotic prophylaxis. DESIGN: Retrospective analysis. SETTING: Mainly hospital-based patients or subjects. OUTCOME MEASURES: The relationship between joint infections and dental treatment is equivocal at the best and there is no evidence that antibiotic prophylaxis provides such patients with any protection. RESULTS: Microbiological evidence linking dental treatment-induced bacteraemia to joint infections is weak and if an oral commensal is implicated, it is more likely to have arisen either from a spontaneous bacteraemia or from a dental infection. As a consequence of the latter, we recommended the institution of good dental health prior to joint replacement. There may be a case for providing prophylaxis to the immuno-compromised patient, but only if the immuno-suppression is associated with a neutropenia. In such circumstances, only emergency treatment should be considered until the neutropenia is resolved. Antibiotic regimens that are recommended by orthopaedic surgeons have not been evaluated in a randomised placebo-controlled study and many of the drugs are not licensed for this purpose. The evidence on cost-risk benefit seems to demonstrate that antibiotic prophylaxis with either amoxicillin or penicillin is not cost effective when compared with no prophylaxis. CONCLUSION: The case for providing antibiotic prophylaxis prior to dental treatment in patients fitted with a joint prosthesis is weak or virtually non-existent. Furthermore, the risk from providing prophylaxis is greater than the risk of a joint infection.]Seymour RA, Whitworth JM, et al. *Br Dent J*. 2003 Jun 28;194(12):649-53.
http://www.ncbi.nlm.nih.gov/pubmed/12830173?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_SingleItemSupl.Pubmed_Discovery_RA&linkpos=1&log$=relatedarticles&logdbfrom=pubmed

936. **Antibacterial prophylaxis in dermatologic surgery: an evidence-based review.** [Clean, non-contaminated skin surgery is associated with low rates of surgical site infection (SSI), bacterial endocarditis, and joint prosthesis infection. Hence, antibacterial prophylaxis, which may be associated with adverse effects, the emergence of multidrug-resistant pathogens, and anaphylaxis, is generally not recommended in dermatologic surgery. Some body sites and surgical reconstructive procedures are associated with higher infection rates, and guidelines for SSI antibacterial prophylaxis have been proposed for these cases. Large prospective, controlled trials are needed to ascertain the role of oral SSI prophylaxis for these surgical sites and procedures especially in patients with diabetes mellitus who are intrinsically at greater risk of SSI. Topical antibacterial ointment and sterile paraffin appear to make no difference to healing or the incidence of SSIs in clean wounds. Although further research is needed, preliminary studies have shown that intraincisional antibacterials, which may be associated with fewer adverse effects and a lower risk of multidrug-resistant bacteria, could potentially be helpful for SSI prophylaxis. Trials using honey- and silver-impregnated dressings have found no advantage in the healing of chronic wounds. However, several case studies, which need corroboration in larger studies, suggest that these dressings may be helpful in preventing and treating SSIs. Bacterial endocarditis and joint prosthesis infection prophylaxis are not routinely recommended in cutaneous surgery. The updated 2007 American Heart Association guidelines now advocate bacterial endocarditis prophylaxis for high-risk cardiac patients having surgery involving the oral mucosa or infected skin. The latest American Dental Association/American Academy of Orthopaedic Surgery guidelines recommend considering antibacterial prophylaxis for oral procedures where bleeding is anticipated and for surgery involving acute orofacial skin infections if the patient has had a total joint replacement within 2 years or is in a high-risk group and has had a joint replacement at any time.] Rosengren H, Dixon A. *Am J Clin Dermatol*. 2010;11(1):35-44. http://www.ncbi.nlm.nih.gov/pubmed/20000873

937. **[Dental care and joint prostheses]** Article in French [PURPOSE OF THE STUDY: Infectious dental foci and oral dental care constitute one of the leading causes of arthroplasty infection after infections involving the skin and the urinary tract. There is however no formal evidence confirming the relationship between oral or dental care and arthroplasty infection. MATERIAL AND METHODS: We reviewed 44 cases of arthroplasty infection secondary to dental infections and searched for data in the literature. In our series, no risk factor could be identified for 24 cases. The median disease-free interval was five years and mean time from the oral-dental procedure to the first signs of prosthesis infection was one month. Tooth extraction was the most common oral-dental procedure involved (n=19). Most of the infections were caused by a single agent, predominantly Streptococci sp. (n=24) and Staphylococci sp. (n=12). DISCUSSION: It is well known that dental-related bacteriemia is a spontaneous daily event even without dental procedures. It is also probable that spontaneous bacteriemia induced by daily activities is much more frequent than dental-care induced bacteriemia. The presence of foreign material diminishes local antibacterial defense systems increasing the risk of hematogeneous contamination of the joint prosthesis after dental care. The oral flora is also modified in immunodepressed subjects, particularly carriage of Staphylococcus aureus in the oral cavity which is significantly more frequent in patients with rheumatoid arthritis. These changes increase the risk of contamination after dental care. For arthroplasty infection, the pathogenic power of Staphylococci sp. is certainly greater than that of Streptococci sp. even if the inoculum is less abundant. Antibiotic prophylaxis during dental care in patients with an arthroplasty remains a controversial subject and the most appropriate antibiotic remains to be defined. Successive episodes of spontaneous bacteriemia arising from an oral-dental foci are probably the main cause of arthroplasty infections, more so than bacteriemia triggered by dental care. CONCLUSION: Antibiotic therapy is not indicated for routine dental care in the majority of patients but is recommended whenever there is a high risk of arthroplasty contamination. In the event of oral-dental infection, antibiotic therapy is necessary. The

recommendations proposed by the ADA and the AAOS were revised in 2003. The most important point is to obtain and maintain a good state of oral hygiene. For prevention, awareness of the risk is essential, for the patient, the orthopedic surgeon and the primary care physician alike. Regular dental visits are necessary.] Bauer T, Maman L, et al. *Rev Chir Orthop Reparatrice Appar Mot.* 2007 Oct;93(6):607-18. http://www.ncbi.nlm.nih.gov/pubmed/18065872?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_SingleItemSupl.Pubmed_Discovery_RA&linkpos=5&log$=relatedreviews&logdbfrom=pubmed

938. **Dental Procedures as Risk Factors for Prosthetic Hip or Knee Infection: A Hospital-Based Prospective Case-Control Study.** [*Background.* The actual risk of prosthetic joint infection as a result of dental procedures and the role of antibiotic prophylaxis have not been defined. *Methods.* To examine the association between dental procedures with or without antibiotic prophylaxis and prosthetic hip or knee infection, a prospective, single-center, case-control study for the period 2001–2006 was performed at a 1200-bed tertiary care hospital in Rochester, Minnesota. Case patients were patients hospitalized with total hip or knee infection. Control subjects were patients who underwent a total hip or knee arthroplasty but without a prosthetic joint infection who were hospitalized during the same period on the same orthopedic floor. Data regarding demographic features and potential risk factors were collected. Logistic regression was used to assess the association of variables with the odds of infection. *Results.* A total of 339 case patients and 339 control subjects were enrolled in the study. There was no increased risk of prosthetic hip or knee infection for patients undergoing a high-risk or low-risk dental procedure who were not administered antibiotic prophylaxis (adjusted odds ratio [OR], 0.8; 95% confidence interval [CI], 0.4–1.6), compared with the risk for patients not undergoing a dental procedure (adjusted OR, 0.6; 95% CI, 0.4–1.1) respectively. Antibiotic prophylaxis in high-risk or low-risk dental procedures did not decrease the risk of subsequent total hip or knee infection (adjusted OR, 0.9 [95% CI, 0.5–1.6] and 1.2 [95% CI, 0.7–2.2], respectively). *Conclusions.* Dental procedures were not risk factors for subsequent total hip or knee infection. The use of antibiotic prophylaxis prior to dental procedures did not decrease the risk of subsequent total hip or knee infection.] Bebari EF, Osmon DR, et al. *CID*, 2010:50(1 Jan) p 8-16. http://iis-db.stanford.edu/pubs/22789/CID.Influenza.FINAL.pdf

939. **Hematogenous Infection in Total Joint Replacement. [**TOTAL joint replacement has been accepted as effective treatment for painful arthritis by the medical community. Indeed, between 1972 and 1976, an estimated 0.5 million joint prostheses were implanted in the United States.[1] Infection of a prosthesis is one of the most serious complications of total joint replacement and is associated with serious morbidity and mortality.[2,3] The pathogenesis of this infection, including portals of bacterial entry, is currently under debate, but evidence is accumulating to suggest that organisms are introduced by two routes: first, by local contamination at the time of surgery,[4] and later, by the hematogenous route.[5-7] Prophylactic antibiotics and local wound care precautions can substantially reduce the incidence of early infections, but appear to have little effect on late sepsis.] Lattimer GL, Keblish PA, et al. *JAMA*, 79;242(20):2213-2214. http://jama.ama-assn.org/cgi/content/summary/242/20/2213

940. **Identification of oral bacterial DNA in synovial fluid of patients with arthritis with native and failed prosthetic joints.** [OBJECTIVE: We examined the presence of bacterial DNA in synovial fluids of native or clinically aseptically failed prosthetic joints from patients having periodontal disease and arthritis to determine whether there is bacterial spread from the oral cavity to the joints. METHODS: A total of 36 subjects were enrolled in the study. Among these, 11 were diagnosed with rheumatoid arthritis (RA) and 25 were diagnosed with osteoarthritis (OA). Eight patients with OA and 1 patient with RA had failed prostheses. Synovial fluid was aspirated from the affected hip or knee joint. Pooled subgingival plaque samples were collected, followed by clinical periodontal examination. Bacterial DNA was extracted from the collected synovial fluid and dental plaque samples were followed by polymerase chain reactions and DNA sequence analysis of the 16S-23S rRNA genes. RESULTS: Of the 36 patients, bacterial DNA was detected in the synovial fluid samples from 5 patients (13.9%): 2 with RA (1 native and 1 failed prosthetic joints) and 3 with OA (1 native and 2 failed prosthetic joints). Of these 5 patients, 2 were diagnosed with periodontitis and had identical bacterial clones (Fusobacterium nucleatum and Serratia proteamaculans, respectively) detected in both the synovial fluid and the dental plaque samples. Fusobacterium nucleatum was the most prevalent, detected in 4 of the 5 positive samples. No cultures were done and no patients were treated with antibiotics or developed clinical infection. CONCLUSIONS: The present findings of bacterial DNA in the synovial fluid suggest the possibility of organisms translocating from the periodontal tissue to the synovium. We suggest that patients with arthritis or failed prosthetic joints be examined for the presence of periodontal diseases and be treated accordingly.] Temoin S, Chakaki A, et al. *J Clin Rheumatol*. 2012 Apr;18(3):117-21. **http://www.ncbi.nlm.nih.gov/pubmed/22426587**

941. **Incidence and sources of native and prosthetic joint infection: a community based prospective survey**. [*OBJECTIVES*—To determine the incidence and sources of bacterial arthritis in the Amsterdam health district and the maximum percentage of cases that theoretically would be preventable. *METHODS*—Patients with bacterial arthritis diagnosed between 1 October 1990 and 1 October 1993 were prospectively reported to the study centre by all 12 hospitals serving the district. Data were gathered on previous health status, source of infection, and microorganisms involved. *RESULTS*—188 episodes of bacterial arthritis were found in 186 patients. Most of the 38 children were previously healthy. Fifty per cent of the adults were 65 years or older. Of the adults 84% had an underlying disease, in 59% a joint disorder. Joint surgery constituted the largest part of direct infections (33%) and skin defects were the most important source of haematogenous infections (67%). Infection of joints containing prosthetic or osteosynthetic material by a known haematogenous source occurred 15 times (8%). *Staphylococcus aureus* was the causative organism in 44% of all positive cultures. *CONCLUSION*—The incidence of bacterial arthritis was 5.7 per 100 000 inhabitants per year. Preventive measures directed to patients with prosthetic joints or osteosynthetic material, and a known haematogenous source would have

prevented at most 8% of all cases.] Kaandorp C, Dinant H, et al. *Ann Rheum Dis*. 1997 August; 56(8): 470–475. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1752430/

942. **Infections associated with dental procedures in total hip arthroplasty.** [Dental procedures may lead to a transient bacteraemia lasting for up to 30 minutes. Of the numerous cases of total hip arthroplasty (THA) reported which have been infected from haematogenous sources, dental procedures have been involved only infrequently. We reviewed the records of 2973 patients after THA. Of the late infections identified in 52 patients, three (6%) were strongly associated with a dental procedure. Infection was diagnosed by culture from the affected joint; Streptococcus viridans was identified in two cases and Peptostreptococcus in one. One patient had diabetes mellitus and another rheumatoid arthritis, both conditions predisposing to infection. The dental operations all lasted for more than 45 minutes and no patient received perioperative antibiotics. Infection of a THA after dental procedures is more common than has been previously suspected. Patients with systemic disease, or who are undergoing extensive procedures, should be considered for prophylactic antibiotic treatment.] LaPorte DM, Waldman BJ, et al. *J Bone Joint Surg Br*. 1999 Jan;81(1):56-9. http://www.ncbi.nlm.nih.gov/pubmed/10068004
943. **Infections in total hips secondary to a primary source elsewhere.** [This is a report of 3 cases in which a primary infection in a site other than a total hip led to infection in the hip itself. One hip infection appeared to arise in a tooth abscess, a second in the urinary tract, and one from the respiratory tract. All infections resulted in the necessity of removing the components of the total hip. It is suggested that patients who have had previous total hip replacement should be warned to consult their physician when the possibility of an infection is present, and that antibiotic coverage be given during this period of time. Cultures of infected sites should be made in patients who have had total hip replacements, in order that organisms and their sensitivity may be identified in the event that antibiotic therapy is needed, subsequently.] *Clin Orthop Relat Res*. 1975 Jan-Feb;(106):99-101. http://www.ncbi.nlm.nih.gov/pubmed/1126095
944. **Late Hematogenous Infection of Total Joint Replacement.** [ABSTRACT: Late deep wound infection secondary to hematogenous spread of bacteria from a distant focus is an infrequent but devastating complication of total joint replacement. Nine patients (ten implants) with documented late hematogenous infection are reported, all of whom demonstrated several characteristic features. The initial operation was free of clinical evidence of infection and a long asymptomatiinc interval ensued, followed by a definite febrile illness and acute joint pain. The source of the infection often was not recognized until late and prophylactic antibiotics were not given when it was identified. Seven of the ten implants had to be removed. The primary responsibility for the prevention of this devastating complication lies with the surgeon, who must inform each patient of the risk of late hematogenous seeding from infection elsewhere in the body. It is also important to pay special attention to patients who are at particularly high risk, such as those with rheumatoid arthritis or other systemic diseases. A knowledge of the bacterial flora of the various areas of the human body is essential in choosing the appropriate prophylactic antibiotic.] Stinchfield FE, Bigliani LU, et al. *Journal of Bone and Joint Surgery*, Vol 62-!, No. 8, December 1980, pp 1345-1350. http://www.ejbjs.org/cgi/reprint/62/8/1345.pdf
945. ***Micromonas (Peptostreptococcus) micros*: unusual case of prosthetic joint infection associated with dental procedures, Case Report.**[*Micromonas (Peptostreptococcus) micros* is frequently associated with periodontal disease as well as respiratory, gastrointestinal and female genitourinary tract infections, but only rarely has been reported as a pathogenic agent of prosthetic joint infections. Here we describe a case of a 63-year-old woman with prosthetic joint infection of total hip arthroplasty caused by the anaerobic species *Micromonas micros*, associated with tooth extraction. Samples obtained intraoperatively and from the oral cavity were positive for the presence of *M. micros* by culture and by real-time PCR. This case report indicates that infections of prosthetic joints can be associated with dental procedures and that sensitive molecular techniques are necessary for their routine diagnostic.] Bartz J. Mpmmem,acjer C. et a;/ *International Journal of Medical Microbiology Volume 294, Issue 7*, 26 January 2005, Pages 465-470. http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B7GW0-4DXT7W0-1&_user=10&_coverDate=01%2F26%2F2005&_rdoc=1&_fmt=high&_orig=search&_sort=d&_docanchor=&view=c&_searchStrId=1232321679&_rerunOrigin=google&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=401824053678374ac79cff2ef7588f0e
946. **Necessity of surgical dental foci treatment prior to organ transplantation and heart valve replacement**. [Diagnosis and surgical treatment of septic foci (e.g., apical or marginal and profound periodontitis, cysts, unrestorable teeth, or abscesses) in patients awaiting organ transplants and heart valve replacement (HVR) have become a recommended, yet controversial standard procedure. This study aims to evaluate the numerical extent of the required oral surgical procedures removing septic foci in these patients. Data of 204 patients (115 males/89 females) of the Department of Oral- and Maxillofacial Surgery with an average age of 58 years were evaluated in terms of necessary oral surgical procedures before HVR or kidney (K), heart (H), or liver (L) transplant (T) and were compared with data from patients not undergoing transplantation or HVR, who were referred for other reasons such as oral surgery. The number of tooth extractions or apicoectomies per patient averaged two to five for each of the four patient groups (KT, 0-7 affected teeth; HT, 0-5; LT, 1-5; and HVR, 1-10). Treatment of periodontitis was necessary in 64% of patients. A total of 70% of patients required oral surgical procedures before HT, LT, and HVR, while 84% needed before KT. Removal of oral septic foci is necessary to avoid jeopardizing the success of transplantations. With regard to the surprisingly high need for surgical treatment in this patient population, assessment of these patients by the appropriate specialist and continuation with a follow-up program is still highly recommended.] Rustemeyer J, Bremerich A. *Clin Oral Investig*. 2007 Jun;11(2):171-4. http://www.ncbi.nlm.nih.gov/pubmed/17431693
947. **Prosthetic joint infections: update in diagnosis and treatment.** [The pathogenesis of prosthetic joint infection is related to microorganisms growing in biofilms, rendering these infections difficult to diagnose and to eradicate. Low-grade infections

in particular are difficult to distinguish from aseptic failure, often presenting only with early loosening and persisting pain, or no clinical signs of infection at all. A combination of preoperative and intraoperative tests is usually needed for an accurate diagnosis of infection of prosthetic joint infections. Successful treatment requires adequate surgical procedure combined with long-term antimicrobial therapy, ideally with an agent acting on adhering stationary- phase microorganisms. In this article, epidemiology, pathogenesis, diagnosis and treatment of prosthetic joint infections are reviewed…. Late infections present either with a suddenonset of systemic symptoms (in about 30%) or as a subacute infection following unrecognized bacteraemia (in about 70%). The most frequent primary (distant) foci of implant-associated infections are skin, respiratory, dental and urinary tract infections] Trampuz A, Zimmerli W. *Swiss Med Wkly*, 2005;135:243-251. P 243-251. http://www.smw.ch/docs/pdf200x/2005/17/smw-10934.pdf

948. **Relation between mouth and haematogenous infection in total joint replacements.** [Objective : To investigate the source of infections associated with orthopaedic prostheses. Design : Analysis of four infections of prosthetic joints with case records; minimum inhibitory and minimum bactericidal concentrations and sodium dodecylsulphate polyacrylamide gel electrophoresis of the cell wall polypeptides of the Streptococcus sanguis isolates from the mouth and infected prostheses; examination of the patients' mouths for periodontal disease and caries. Subjects : Four adults (three men) aged 58-83. Results : For each patient the strain of S sanguis isolated from the mouth was indistinguishable from that isolated from the prosthesis. All patients had severe periodontal disease and caries. Conclusions : The mouth was probably the source of bacterial infection in the prosthetic joints of these patients; the route of infection was possibly haematogenous. Incipient oral infection should be treated before joint replacement, and oral health should be maintained indefinitely.] Bartzokas CA, Johnson R, et al. *BMJ* 1994;309:506-508 (20 August) http://www.bmj.com/cgi/content/full/309/6953/506
949. **The use of antibiotic prophylaxis prior to dental procedures for the prevention of prosthetic joint infection.** [Prosthetic joint infection (PJI) is a severe illness which may cause pain and discomfort, may damage the quality of life and may even be life-threatening. A variety of studies have demonstrated the presence of bacteria in a small but potentially dangerous number of prosthetic joint infections that may have originated in the oral cavity. Some dental treatments such as calculus removal, extractions, dental implants placements etc. and daily oral hygiene routines such as tooth brushing may cause bacteremia. Recently the American Academy of Orthopaedic Surgeons (AAOS) published updated guidelines for antibiotic prophylaxis to prevent prosthetic joint infections. These guidelines suggest a direct and established connection between dental treatments and prosthetic joint infections, and expand the criteria to prescribe antibiotic prophylaxis prior to dental procedures associated with bacteremia. The purpose of this review is to introduce these new guidelines, and to review the literature regarding the relationship between dental care and prosthetic joint infections.]Volfin G, yarom N, et al. *Refuat Hapeh Vehashinayim*. 2011 Apr;28(2):35-45, 74. http://www.ncbi.nlm.nih.gov/pubmed/21848030
950. **Total Hip Replacement**. [Although infections after hip replacement are not common, an infection can occur if bacteria enter your bloodstream. Because bacteria can enter the bloodstream during dental procedures, you should consider getting treatment for significant dental diseases (including tooth extractions and periodontal work) before your hip replacement surgery. Routine cleaning of your teeth should be delayed for several weeks after surgery… The most common causes of infection following hip replacement surgery are from bacteria that enter the bloodstream during dental procedures, urinary tract infections, or skin infections. These bacteria can lodge around your prosthesis. Following your surgery, you may need to take antibiotics prior to dental work, including dental cleanings, or any surgical procedure that could allow bacteria to enter your bloodstream. For many people with joint replacements and normal immune systems, the American Academy of Orthopaedic Surgeons (AAOS) recommends antibiotic prophylaxis before dental work.] American Academy of Orthopaedic Surgeons. http://orthoinfo.aaos.org/topic.cfm?topic=A00377
951. **Total knee arthroplasty infections associated with dental procedures.** [Total knee arthroplasties are at risk for hematogenous seeding secondary to procedures that create a transient bacteremia. To define the risk of infection associated with dental surgery, a retrospective review of the records of 3490 patients treated with total knee arthroplasty by the authors between 1982 and 1993 was performed. Sixty-two total knee arthroplasties with late infections (greater than 6 months after their procedure) were identified, and of these, seven infections were associated strongly with a dental procedure temporally and bacteriologically. These seven cases represented 11% of the identified infections or 0.2% of the total knee arthroplasty procedures performed during this period. In addition, among 12 patients referred for infected total knee arthroplasties from outside institutions, two infections were associated with a dental procedure. Five of the nine (56%) patients had systemic risk factors that predisposed them to infection, including diabetes and rheumatoid arthritis. All dental procedures were extensive in nature (average, 115 minutes; range, 75-205 minutes). Eight of the patients received no antibiotic prophylaxis. One patient had only one preoperative dose. Infections associated with dental procedures may be more common than previously suspected. Eight of these patients had no prophylactic antibiotics, and one had inadequate coverage. The authors think that patients with a total knee arthroplasty who have systemic disease that compromises host defense mechanisms against infections and who undergo extensive dental procedures should receive prophylactic antibiotics. A first generation cephalosporin, given 1 hour preoperatively and 8 hours postoperatively would provide the best prophylaxis against the organisms identified in this study.] Waldman BJ, Mont MA, et al. *Clin Orthop Relat Res.* 1997 Oct;(343):164-72. http://www.ncbi.nlm.nih.gov/pubmed/9345222?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_SingleItemSupl.Pubmed_Discovery_RA&linkpos=1&log$=relatedarticles&logdbfrom=pubmed

Osteoporosis, Osteomyelitis and Inflammation

952. **Influence of Estrogen and Osteopenia/Osteoporosis on Clinical Periodontitis in Postmenopausal Women**. [**Background:** In Western societies, more than one-third of the female population above age 65 suffers from signs and symptoms of osteoporosis, a disorder characterized by low bone mass. Estrogen deficiency is the dominant pathogenic factor for osteoporosis in women. The impact of estrogen deficiency and osteopenia/osteoporosis on periodontitis is unclear, partially due to the lack of longitudinal studies evaluating clinical signs of gingival inflammation and periodontitis progression. The purpose of this investigation was to analyze prospectively the influence of serum estradiol levels and osteopenia/osteoporosis on common clinical measurements of periodontal disease over a 2-year period. Methods: Fifty-nine moderate/advanced adult periodontitis patients and 16 non-periodontitis subjects, all within 5 years after menopause at baseline, completed the study. Serum estradiol levels (E_2) were measured yearly by ^{125}I radioimmunoassay, and osteopenia/osteoporosis was determined by dual energy x-ray absorptiometry of the lumbar spine. Posterior interproximal clinical measurements were obtained every 6 months for the periodontitis patients, including explorerdetectable supragingival plaque, bleeding on probing (BOP) and relative clinical attachment level (RCAL). Baseline probing depths, smoking history, and demographic data also were collected. Results: Data indicated that baseline demographic measurements and bone mineral density (BMD) of the lumbar spine were not different between E_2-deficient and E_2-sufficient subjects. Smoking activity (packs smoked/day, years smoked) was higher in periodontitis patients (P=0.0001) . E $_2$-sufficient periodontitis subjects had a higher frequency of supragingival plaque without increasing gingival inflammation. E_2 status did not influence the percentage of sites losing RCAL for either periodontitis or non-periodontitis groups, but when non-smoking osteopenic/osteoporotic periodontitis patients were evaluated, E_2-deficient subjects had more BOP (43.8% versus 24.4%, P<0.04) and a trend toward a higher frequency of ≥ 2.0 mm RCAL loss (3.8% versus 1.2%, 2 P<0.1) than E -sufficient subjects. Conclusions: These data suggest that E_2 supplementation (serum E_2>40 pg/ml) is associated with reduced gingival inflammation and a reduced frequency of clinical attachment loss in osteopenic/osteoporotic women in early menopause.] Reinhardt RA, Payne JB, et al. *J Periodontol* 1999;70:823-828. http://www.joponline.org/doi/abs/10.1902/jop.1999.70.8.823

953. **Oral Health and Bone Disease.** [It is estimated that periodontal disease affects up to 80 percent of men and women in the United States. Periodontitis is a chronic infection that affects the gums and the bones that support the teeth. Bacteria and the body's own immune system break down the bone and connective tissue that hold teeth in place. Teeth may eventually become loose, fall out, or have to be removed. Although tooth loss is a well-documented consequence of periodontitis, the relationship between periodontitis and skeletal bone density is less clear. Some studies have found a strong and direct relationship among bone loss, periodontitis, and tooth loss. It is possible that the loss of alveolar bone mineral density leaves bone more susceptible to periodontal bacteria, increasing the risk for periodontitis and tooth loss.] National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH/DHHS. http://www.niams.nih.gov/Health_Info/Bone/Bone_Health/Oral_Health/default.asp#b

954. **Oral implications of osteoporosis.** [ObjECTIVES: The association between osteoporosis and oral health remains a matter of controversy. It is important to confirm whether there is a role of osteoporosis in bone loss in the jaws, periodontal diseases, tooth loss, and other oral tissue changes. The objective of this article is to review and summarize the published literature on the associations between osteoporosis and various oral conditions such as bone loss in the jaws, periodontal diseases, and tooth loss. METHODS: A search of the computerized database MEDLINE was conducted. Clinical information concerning systemic osteoporosis and animal studies reporting possible associations between osteoporosis and changes in the dental and oral tissues were included. The review focus was on studies involving (1) methods for assessing bone mineral density (BMD); (2) methods for assessing osteoporosis-related changes in intraoral sites; (3) associations between mandibular BMD and skeletal BMD; (4) changes in the jaws, periodontal tissues, and temporomandibular joint concurrent with osteoporosis; (5) changes in the oral tissues following estrogen deficiency; and (6) effects of estrogen-hormone replacement therapy and/or calcium and vitamin D on oral health. RESULTS: Ninety-seven studies conducted in various parts of the world were identified. Evidence from prospective studies supports the contention that individuals with osteoporosis may be at increased risk for the manifestations of oral osteoporosis; however, such risk is not definitively proven. Studies suggest that findings on dental panoramic radiographs may be used to detect individuals with low BMD. CONCLUSIONS: Further well-controlled studies are needed to better elucidate the inter-relationship between systemic and oral bone loss and to clarify whether dentists could usefully provide early warning for osteoporosis risk.] Dervis E. Oral Surg *Oral Med Oral Pathol Oral Radiol Endod*. 2005 Sep;100(3):349-56. http://www.ncbi.nlm.nih.gov/pubmed/16122665

955. **Oral Inflammation and Osteoporosis**. [Bone loss is a central, common feature of both periodontal disease and osteoporosis…In periodontal disease, oral inflammation due to chronic infection of the tissue around the teeth results in destruction of oral bone and periodontal ligament ultimately leading to tooth loss. Oral inflammation increases production of cytokines, such as interleukin-6, that stimulate osteoclast activity and promote bone resorption.5 A similar mechanism may contribute to osteoporosis, raising the question of whether people with low skeletal BMD are at increased risk of oral osteopenia. Several lines of evidence indicate that there is an association between osteoporosis and periodontal disease.] Krall EA. *Colgate White Papers – Oral Inflammation*, http://www.colgateprofessional.com/LeadershipUS/ProfessionalEducation/WhitePapers/Resources/pdf/profed_WP_oral-inflam-and-osteo.pdf

956. **Osteomyelitis of a Long Bone Due to *Fusobacterium nucleatum* and *Actinomyces meyeri* in an Immunocompetent Adult.** [Background**:***Fusobacterium* species are uncommon causes of osteomyelitis. These organisms are normal flora of the oral cavity. Therefore, they mostly cause osteomyelitis of the head and neck. Hematogenous osteomyelitis at distant sites other than the head and neck has rarely been reported in pediatric or immunocompromised patients. Here, we report the first case of osteomyelitis of a long bone combined with a muscle abscess due to *Fusobacterium nucleatum* in an otherwise healthy adult. Case presentation: A 59-year-old Korean man was admitted for pain and swelling of the right lower leg, which had been persistent for two weeks. Magnetic resonance imaging showed osteomyelitis of the right fibula with a surrounding muscle abscess of the right lower leg. Incision and drainage was performed, and repetitive tissue cultures grew *F. nucleatum.* In this patient, it was presumed that recurrent periodontitis caused hematogenous seeding of *F. nucleatum* to a distant site leading to osteomyelitis with a muscle abscess. The patient was successfully treated with intravenous ampicillin-sulbactam for three weeks and oral amoxicillin-clavulanate for eight weeks. He also underwent repeated surgical drainage. He has no evidence of recurrence after seven months of follow-up.Conclusions: Clinicians should be aware that *F. nucleatum* could be the etiologic agent of hematogenous osteomyelitis of a long bone in an immunocompetent patient. Lee MJ, Ha YE, et al BMC Infect Dis. 2012;12(161). http://www.medscape.com/viewarticle/776435?src=nl_topic

957. **Periodontal Diseases and Osteoporosis: Association and Mechanisms**. [There is increasing evidence that osteoporosis, and the underlying loss of bone mass characteristic of this disease, is associated with periodontal disease and tooth loss. Periodontitis has long been defined as an infection-mediated destruction of the alveolar bone and soft tissue attachment to the tooth, responsible for most tooth loss in adult populations. Current evidence including several prospective studies supports an association of osteoporosis with the onset and progression of periodontal disease in humans. The majority of studies have shown low bone mass to be independently associated with loss of alveolar crestal height and tooth loss. However studies that focus on the relation of clinical attachment loss and osteoporosis are less consistent. To date, the majority of studies on the relationship between periodontal disease and osteoporosis have been hindered by small sample sizes, limited control of other potential confounding factors, varying definitions of both periodontal disease and osteoporosis, and few prospective studies where the temporality of the association can be established. Potential mechanisms by which host factors may influence onset and progression of periodontal disease directly or indirectly include underlying low bone density in the oral cavity, bone loss as an inflammatory response to infection, genetic susceptibility, and shared exposure to risk factors. Systemic loss of bone density in osteoporosis, including that of the oral cavity, may provide a host system that is increasingly susceptible to infectious destruction of periodontal tissue. Studies have provided evidence that hormones, heredity, and other host factors influence periodontal disease incidence and severity. Both periodontal disease and osteoporosis are serious public-health concerns in the United States. Prevalence of both osteoporosis and tooth loss increase with advancing age in both women and men. Understanding the association between these common diseases and the mechanisms underlying those associations will aid health professionals to provide improved means to prevent, diagnose, and treat these very common diseases. This paper reviews the current evidence on the association between periodontal disease and osteoporosis.] Wactawski-Wende J. *Ann Periodontol* 2001;6:197-208. http://www.joponline.org/doi/abs/10.1902/annals.2001.6.1.197

958. **The Periodontal-Systemic Connection: Implications for Treatment of Patients With Osteoporosis and Periodontal Disease**. [Osteoporosis and osteopenia may influence periodontal disease and tooth loss. Medications such as hormone replacement therapy and nutritional supplements that are used to prevent or treat osteoporosis have been evaluated for beneficial effects on oral health in a small number of human studies. Hormone replacement therapy (HRT), which slows the rate of bone loss at skeletal sites such as the hip and spine, also appears to reduce the rate of alveolar bone loss in postmenopausal women. HRT use is consistently associated with greater tooth retention and a reduced likelihood of edentulism in studies of elderly women. The number of studies on the effects of calcium or vitamin D intake on oral outcomes is limited, but suggest that higher intake levels are associated with reduced prevalence of clinical attachment loss and lower risk of tooth loss. Data from a prospective study of oral health in men show a similar association between higher calcium intake and reduced alveolar bone loss. The number of teeth with progression of alveolar bone loss over a 7-year period was significantly lower among men whose calcium intake was at least 1,000 mg per day, compared to men with a calcium intake below this level. Future studies should confirm these findings and evaluate the oral effects of new medications for osteoporosis. If confirmed, the implications for dental professionals may include an expanded array of medications for the treatment of periodontal disease and a greater emphasis on nutrition education for patients.] *Ann Periodontol* 2001;6:209-213. http://www.joponline.org/doi/abs/10.1902/annals.2001.6.1.209?journalCode=annals

959. **The Relationship Between Bone Mineral Density and Periodontitis in Postmenopausal Women.** [Skeletal BMD is related to interproximal alveolar bone loss and, to a lesser extent, to clinical attachment loss, implicating postmenopausal osteopenia as a risk indicator for periodontal disease.] Tezal M, Grossi S.G., *J Periodontology* 2000, Vol. 71, No. 9, pp 1492-1498. http://www.joponline.org/doi/abs/10.1902/jop.2000.71.9.1492

960. **The Role of Osteopenia in Oral Bone Loss and Periodontal Disease.** [The relationship of osteopenia to oral bone loss and periodontal disease has been addressed in a limited number of studies. A review of current knowledge regarding this relationship is presented. Interpretation of the literature is complicated by the variety of methods used to assess osteopenia, oral bone mass, and periodontitis, as well as varying definitions of outcomes of interest. Results of a previously unpublished study are presented which suggest that severity of osteopenia is related to loss of alveolar crestal height and tooth loss in post-menopausal women.] Wactawski-Wende J, Grossi SG., et.al., *J Periodontol Vol 67 #10, Oct 1996.* http://www.electronicipc.com/JournalEZ/detail.cfm?code=02250010671019

Ozone

961. **An in vitro evaluation of the ability of ozone to kill a strain of Enterococcus faecalis.** [AIM: To evaluate the potential of ozone as an antibacterial agent using Enterococcus faecalis as the test species. METHODOLOGY: Ozone was produced by a custom-made bench top generator and its solubility in water determined by ultraviolet (258 nm) spectrophotometric analysis of solutions through which ozone was sparged for various time-periods. The antibacterial efficacy of ozone was tested against both broth and biofilm cultures. Ozone was sparged for 30, 60, 120 and 240 s, through overnight broth cultures of a strain of E. faecalis (E78.2) and compared with those that were centrifuged, washed and resuspended in water. Enterococcus faecalis (E78.2) biofilms were grown on cellulose nitrate membrane filters for 48 h and suspended in water through which ozone gas was sparged with stirring for 60, 120 and 240 s in a standard fashion. In a separate test, biofilms were also exposed to gaseous ozone. Sodium hypochlorite (NaOCl) was used as a positive control. All experiments were repeated four times. RESULTS: There were significant ($P < 0.05$) reductions of bacteria in the unwashed (2 log(10) reductions) and washed (5 log(10) reductions) broth cultures following 240 s applications. Biofilms incubated for 240 s with ozonated water showed no significant reduction in cell viability attributable to ozone alone, whereas with NaOCl no viable cells were detected over the same time. Gaseous ozone applied for 300 s had no effect on these biofilms. CONCLUSIONS: Ozone had an antibacterial effect on planktonic E. faecalis cells and those suspended in fluid, but little effect when embedded in biofilms. Its antibacterial efficacy was not comparable with that of NaOCl under the test conditions used.] Hems RS, Gulabivala K, et al. *Int Endod J*. 2005 Jan;38(1):22-9. http://www.ncbi.nlm.nih.gov/pubmed/15606819

962. **Antibacterial effect of an ozone device and its comparison with two dentin-bonding systems.** [Microorganisms remaining beneath restorations can cause secondary caries and pulp damage. Because of this, antimicrobial treatment could be useful. The aim of this study was to evaluate the antibacterial effect of the HealOzone device on Streptococcus mutans and to compare it with the already proven activity of two dentin-bonding systems. Thirty-five human molars were divided into 5 groups. Cavities were then cut into the teeth (n = 28 cavities per group). After sterilization, the teeth were left in broth cultures of 10(6) colony-forming units (CFU) ml(-1) of S. mutans at 36 degrees C for 48 h. The appropriate treatment followed (group A, control; group B, Clearfil SE Bond; group C, Clearfil Protect Bond; group D, 40 s of treatment with ozone; and group E, 80 s of treatment with ozone), and the cavities were then filled with composite resin. After 72 h, the restorations were removed, dentin chips were collected with an excavator, and the total number of microorganisms was determined. All treatments significantly reduced the number of S. mutans present compared with the control group. The antimicrobial effect of both bonding systems and treatment with 80 s of ozone was significantly higher than the 40 s ozone treatment. In conclusion, HealOzone and the bonding systems show striking antimicrobial effects against S. mutans.] Polydorou O, Pelz K, et al. *Eur J Oral Sci*. 2006 Aug;114(4):349-53 http://www.ncbi.nlm.nih.gov/pubmed/16911107

963. **Antibacterial effect of ozone on cariogenic bacterial species.** [OBJECTIVE: The aim was to evaluate the antibacterial effect of ozone on cariogenic bacterial species with and without the presence of saliva and a possible effect on the salivary proteins. METHODS: Suspensions of Actinomyces naeslundii (ACTCC 12104(T)), Lactobacilli casei (N CTC 151) and Streptococcus mutans (NCTC 10449), in salt buffer or in saliva, were exposed to ozone gas delivered by the ozone generator Healozone 2130C. Aliquots of the suspensions were taken after 10, 30 and 60s ozone exposures and cultivated on agar plates. Initial number of bacteria per ml was 8.0 x 10(7) (SD 2.2 x 10(7)) (A. naeslundii), 1.0 x 10(8) (SD 3.1 x 10(6)) (L. casei) and 1.0 x 10(8) (SD 7.0 x 10(5)) (S. mutans), respectively. The proteins were separated by SDS electrophoresis and visualized by silver staining. RESULTS: In salt buffer 92%, 73% and 64% of the initial numbers of A. naeslundii, S. mutans and L. casei, respectively, were killed already after 10s ozone exposure, while approximately 99.9% of the bacteria were dead after a 60s exposure. After 10 and 30s, but not after 60s exposure to ozone, S. mutans and L. casei were less efficiently killed in saliva compared to the salt buffer. Various saliva proteins were degraded by ozone after a 60s exposure. CONCLUSIONS: The cariogenic species S. mutans, L. casei and A. naeslundii were almost eliminated following 60s of ozone treatment. This killing was reduced in the presence of saliva although increasing the ozone application time to 60s overcame these reductants in saliva. Detection of altered salivary proteins indicates that saliva components constitute additional targets for ozone.] Johansson E, Claesson R, et al. *J Dent*. 2009 Jun;37(6):449-53. http://www.ncbi.nlm.nih.gov/pubmed/19342147

964. **Effectiveness of ozone against endodontopathogenic microorganisms in a root canal biofilm model.** [AIM: To assess the antimicrobial efficacy of aqueous (1.25-20 microg mL(-1)) and gaseous ozone (1-53 g m(-3)) as an alternative antiseptic against endodontic pathogens in suspension and a biofilm model. METHODOLOGY: Enterococcus faecalis, Candida albicans, Peptostreptococcus micros and Pseudomonas aeruginosa were grown in planctonic culture or in mono-species biofilms in root canals for 3 weeks. Cultures were exposed to ozone, sodium hypochlorite (NaOCl; 5.25%, 2.25%), chlorhexidine digluconate (CHX; 2%), hydrogen peroxide (H(2)O(2); 3%) and phosphate buffered saline (control) for 1 min and the remaining colony forming units counted. Ozone gas was applied to the biofilms in two experimental settings, resembling canal areas either difficult (setting 1) or easy (setting 2) to reach. Time-course experiments up to 10 min were included. To compare the tested samples, data were analysed by one-way anova. RESULTS: Concentrations of gaseous ozone down to 1 g m(-3) almost and aqueous ozone down to 5 microg mL(-1) completely eliminated the suspended microorganisms as did NaOCl and CHX. Hydrogen peroxide and lower aqueous ozone concentrations were less effective. Aqueous and gaseous ozone were dose- and strain-dependently effective against the biofilm microorganisms. Total elimination was achieved by high-concentrated ozone gas (setting 2) and by NaOCl after 1 min or a lower gas concentration (4 g m(-3)) after at least 2.5 min. High-concentrated aqueous ozone (20 microg mL(-1)) and CHX almost completely

eliminated the biofilm cells, whilst H(2)O(2) was less effective. CONCLUSION: High-concentrated gaseous and aqueous ozone was dose-, strain- and time-dependently effective against the tested microorganisms in suspension and the biofilm test model.] Huth KC, Quirling M, et al. *Int Endod J*. 2009 Jan;42(1):3-13. http://www.ncbi.nlm.nih.gov/pubmed/19125975

965. **Efficacy and safety of medical ozone (O(3)) delivered in oil suspension applications for the treatment of osteonecrosis of the jaw in patients with bone metastases treated with bisphosphonates: Preliminary results of a phase I-II study.** [Osteonecrosis of the jaw (ONJ) is an adverse event that has been reported in patients receiving cancer treatment regimens, including bevacizumab, bisphosphonates, and denosumab. We performed a preliminary open label, prospective phase I-II study in patients treated with bisphosphonate to evaluate the treatment effect and tolerability of medical ozone (O(3)) delivered in an oil suspension on BONJ lesions ≤2.5cm. Ten consecutive patients with BONJ lesions not responsive to conservative treatment were pre-treated with 10days of antibiotics to reduce purulent secretions on the gum. The exposed bone lesion and osteomucosal edge was cleaned with an ultrasonic scaler. The BONJ lesion was treated with 10 local applications of medical O(3) delivered in an oil suspension for 10min. In all patients, mucosal lesions resolved with complete reconstitution of oral and jaw tissue, with 3-10 applications. No toxicity was reported. Unexpectedly, total sequestration of the necrotic bone, with spontaneous expulsion in eight patients and new bone formation around the necrotic area in two patients was observed. No patient required surgical intervention. In two patients with pre-and post-treatment X-rays, no residual bone lesions were observed after treatment. These preliminary results show the efficacy and tolerability of O(3) delivered in an oil suspension applied directly to BONJ lesions ≤2.5cm, thus indicating that BONJ can be a manageable and potentially curable condition.] Ripamonti CI, Cislaghi E, et al. *Oral Oncol*. 2011 Mar;47(3):185-90. doi: 10.1016/j.oraloncology.2011.01.002. http://www.ncbi.nlm.nih.gov/pubmed/21310650

966. **Evaluation of Ozonated Oils on Osseointegration of Dental Implants under the Influence of Cyclosporine A: An In Vivo Study.** [Abstract Immunosuppressive agents have been recognized as factors that induce changes and modifications in bone metabolism. The purpose of this study was to evaluate the effect of ozonated plant extracts (herein termed 'ozonated oil') under the influence of Cyclosporine A (CsA) on osseointegration. Materials and methods: 20 dental implants were placed in 20 rabbits tibiae assigned to Group A or B. CsA was injected at an immunosuppressive dose in both groups A and B as a single dose treatment. At the day of surgery, Group A received a single topical ozonated oil treatment (0.55 ml) around dental implants; Group B, the control group, received no ozonated oil. Animals were sacrificed after 8 weeks. Radiographs were obtained at implant surgery and at the day of sacrifice. Bone quality was compared between the two groups. Radiographically osseointegration was microscopically evaluated using scanning electron and light microscopies. Results: In ozonated Group A specimens, light microscopic examination demonstrated evidence of more organized mature bone compared to Group B. Conclusion: Within the limits of this study, the results suggest that short-term administration of CsA, when administered with topical ozonated oil, may influence bone density and the quality of dental implant osseointegration.Therefore, topically-applied ozonated oil, may influence bone density and the quality of osseointegration around dental implants.] El Hadary A, Yassin H, et al. *J Oral Implantol.* 2010 Jun 14 http://www.ncbi.nlm.nih.gov/pubmed/20545531

967. **Evidence for antibody-catalyzed ozone formation in bacterial killing and inflammation. [**Recently, we showed that antibodies catalyze the generation of hydrogen peroxide (H2O2) from singlet molecular oxygen (1O2*) and water. Here, we show that this process can lead to efficient killing of bacteria, regardless of the antigen specificity of the antibody. H2O2 production by antibodies alone was found to be not sufficient for bacterial killing. Our studies suggested that the antibody-catalyzed water-oxidation pathway produced an additional molecular species with a chemical signature similar to that of ozone. This species is also generated during the oxidative burst of activated human neutrophils and during inflammation. These observations suggest that alternative pathways may exist for biological killing of bacteria that are mediated by potent oxidants previously unknown to biology.] Wentworth P, McDunn JE, et al. *Science*. 2002 Dec 13;298(5601):2195-9 http://www.ncbi.nlm.nih.gov/pubmed/12434011

968. **Is it true that ozone is always toxic? The end of a dogma.** [There are a number of good experimental studies showing that exposure by inhalation to prolonged tropospheric ozone damages the respiratory system and extrapulmonary organs. The skin, if extensively exposed, may also contribute to the damage. The undoubtful strong reactivity of ozone has contributed to establish the dogma that ozone is always toxic and its medical application must be proscribed. Although it is less known, judiciously practiced ozonetherapy is becoming very useful either on its own or applied in combination with orthodox medicine in a broad range of pathologies. The opponents of ozonetherapy base their judgment on the ozone chemistry, and physicians, without any knowledge of the problem, are often skeptical. During the last 15 years, a clear understanding of the action of ozone in biology and medicine has been gained, allowing today to argue if it is true that ozone is always toxic. The fundamental points that are discussed in this paper are: the topography, anatomical and biochemical characteristics of the organs daily exposed to ozone versus the potent antioxidant capacity of blood exposed to a small and precisely calculated dose of ozone only for a few minutes. It is becoming clear how the respiratory system undergoing a chronic oxidative stress can release slowly, but steadily, a huge amount of toxic compounds able to enter the circulation and cause serious damage. The aim of this paper is to objectively evaluate this controversial issue.] Bocci V. *Toxicol Appl Pharmacol*. 2006 Nov 1;216(3):493-504 http://www.ncbi.nlm.nih.gov/pubmed/16890971

969. **The disinfecting effect of ozonized oxygen in an infected root canal: an in vitro study..** [OBJECTIVES: To determine the disinfecting effect of ozonized oxygen (120 seconds from the HealOzone generator, KaVo) on Enterococcus faecalis, representing bacteria that are difficult to eliminate in the root canals of human teeth, and to compare it with the conventional irrigants: sterile physiologic sodium chloride solution (negative control group), 3% hydrogen peroxide solution, 0.2%

chlorhexidine solution, 1.5% sodium hypochlorite solution, and 3% sodium hypochlorite solution (positive control group). METHOD AND MATERIALS: The roots (n = 10 in each group) were sterilized, contaminated with the test microorganisms in a quantitative preparation, rinsed with the test solutions, and dried. The residual concentration of E faecalis was determined through another irrigation stage with the sodium chloride solution. RESULTS: The positive control group showed a significantly lower concentration of microorganisms than all the other groups, whereas the negative control group showed a significantly higher concentration compared to the other groups. The test groups showed low concentrations. CONCLUSION: Ozonized oxygen appears to be suitable for disinfecting root canal systems in cases where sodium hypochlorite is not indicated.] Stoll R, Venne L, et al. *Quintessence Int.* 2008 Mar;39(3):231-6. http://www.ncbi.nlm.nih.gov/pubmed/18618038

970. **The dual action of ozone on the skin.** [The aim of this brief review is to summarize the recent literature on the effect of ozone (O3) on cutaneous tissues. Recently it has been reported that a chronic contact with O3 can be deleterious for the skin. Our group and others have shown a progressive depletion of antioxidant content in the stratum corneum and this can then lead to a cascade of effects resulting in an active cellular response in the deeper layers of the skin. Using an in vivo model we have shown an increase of proliferative, adaptive and proinflammatory cutaneous tissue responses. On the other hand the well known activity of O3 as a potent disinfectant and oxygen (O2) donor has been also studied for therapeutic use. Two approaches have been described. The first consists of a quasi-total body exposure in a thermostatically controlled cabin. This treatment has proved to be useful in patients with chronic limb ischaemia. The second approach is based on the topical application of ozonated olive oil in several kinds of skin infection (from soreness to diabetic ulcers, burns, traumatic and surgical wounds, abscesses and skin reactions after radiotherapy). We and other authors have observed a striking cleansing effect with improved oxygenation and enhanced healing of these conditions. It is now clear that, on the skin, O3, like other drugs, poisons and radiation, can display either a damaging effect from a long exposure or a beneficial effect after a brief exposure to O2 and O3 or to the application of ozonated oil to chronic wounds.] Valacchi G, Fortino V, et al. *Br J Dermatol.* 2005 Dec;153(6):1096-100. http://www.ncbi.nlm.nih.gov/pubmed/16307642

971. **The ozone paradox: ozone is a strong oxidant as well as a medical drug.** [After five decades characterized by empiricism and several pitfalls, some of the basic mechanisms of action of ozone in pulmonary toxicology and in medicine have been clarified. The present knowledge allows to understand the prolonged inhalation of ozone can be very deleterious first for the lungs and successively for the whole organism. On the other hand, a small ozone dose well calibrated against the potent antioxidant capacity of blood can trigger several useful biochemical mechanisms and reactivate the antioxidant system. In detail, firstly ex vivo and second during the infusion of ozonated blood into the donor, the ozone therapy approach involves blood cells and the endothelium, which by transferring the ozone messengers to billions of cells will generate a therapeutic effect. Thus, in spite of a common prejudice, single ozone doses can be therapeutically used in selected human diseases without any toxicity or side effects. Moreover, the versatility and amplitude of beneficial effect of ozone applications have become evident in orthopedics, cutaneous, and mucosal infections as well as in dentistry.] Bocci V, Borrelli E, et al. *Med Res Rev*. 2009 Jul;29(4):646-82. http://www.ncbi.nlm.nih.gov/pubmed/19260079

Periodontal Disease and Inflammation

972. **Accuracy of NHANES Periodontal Examination Protocols.** [This study evaluates the accuracy of periodontitis prevalence determined by the National Health and Nutrition Examination Survey (NHANES) partial-mouth periodontal examination protocols. True periodontitis prevalence was determined in a new convenience sample of 454 adults ≥ 35 years old, by a full-mouth "gold standard" periodontal examination. This actual prevalence was compared with prevalence resulting from analysis of the data according to the protocols of NHANES III and NHANES 2001-2004, respectively. Both NHANES protocols substantially underestimated the prevalence of periodontitis by 50% or more, depending on the periodontitis case definition used, and thus performed below threshold levels for moderate-to-high levels of validity for surveillance. Adding measurements from lingual or interproximal sites to the NHANES 2001-2004 protocol did not improve the accuracy sufficiently to reach acceptable sensitivity thresholds. These findings suggest that NHANES protocols produce high levels of misclassification of periodontitis cases and thus have low validity for surveillance and research.] Eke PI, Thornton-Evans GO, et al. *J Dent Res.* 2010 Sep 21. http://www.ncbi.nlm.nih.gov/pubmed/20858782?dopt=Abstract

973. **Activation of protease-activated receptors by gingipains from *Porphyromonas gingivalis* leads to platelet aggregation: a new trait in microbial Pathogenicity.** [The bacterium *Porphyromonas gingivalis* is a major etiologic agent in the pathogenesis of adult periodontitis in humans. Cysteine proteinases produced by this pathogen, termed gingipains, are considered to be important virulence factors. To further expand knowledge of the interaction between gingipains and the clotting cascade, this study examined their effects on cellular components of the coagulation system. Results indicate the existence of a novel pathway of host cell activation by bacterial proteinases. This mechanism not only represents a new trait in bacterial pathogenicity, but may also explain an emerging link between periodontitis and cardiovascular disease.] Lourbakos A, Yuan, Y, et.al., Hemostasis, Thrombosis, and Vascular Biology, *Blood, 15 June 2001, Vol. 97, No. 12, pp. 3790-3797.* http://www.bloodjournal.org/cgi/content/abstract/97/12/3790

974. **Acute-phase Inflammatory Response to Periodontal Disease in the US Population.** [Moderate elevation of serum C-reactive protein (CRP) is a risk factor for cardiovascular disease among apparently healthy individuals, although factors that create this inflammatory response in the absence of systemic illness have not been clarified. This study aimed to: (1) evaluate

associations among periodontal disease, established risk factors for elevated CRP, and CRP levels within the US population; and (2) determine whether total tooth loss is associated with reduced CRP. Data were obtained from the third National Health and Nutrition Examination Survey. A random sample of the US population was interviewed in their homes and examined at mobile examination centers. CRP was quantified from peripheral blood samples and analyzed as a continuous variable and as the prevalence of elevated CRP (≥ 10 mg/L). Some 12,949 people aged 18+ years who had periodontal examinations and an additional 1817 edentulous people aged 18+ years were included in the analysis. Dentate people with extensive periodontal disease (> 10% of sites with periodontal pockets 4+ mm) had an increase of approximately one-third in mean CRP and a doubling in prevalence of elevated CRP compared with periodontally healthy people. Raised CRP levels among people with extensive periodontal disease persisted in multivariate analyses ($P < 0.01$), with established risk factors for elevated CRP (diabetes, arthritis, emphysema, smoking, and anti-inflammatory medications) and sociodemographic factors controlled for. However, CRP levels were similarly raised in edentulous people. Furthermore, the established risk factors for elevated CRP modified relationships between oral status and CRP levels. Periodontal disease and edentulism were associated with systemic inflammatory response in the US population, most notably among people who had no established risk factors for elevated CRP.] Slade GD, Offenbacher S, et al. *Journal of Dental Research*, Vol. 79, No. 1, 49-57. http://jdr.sagepub.com/cgi/content/abstract/79/1/49

975. **Causes of Periodontal Disease.** [The main cause of periodontal disease is bacterial plaque, a sticky, colorless film that constantly forms on your teeth. Other causes include: Smoking, genetics, pregnancy, nutrition, stress, medications, clenching/grinding teeth, and diabetes.] http://www.perio.org/consumer/2a.html
976. **Cementum and Periodontal Wound Healing and Regeneration.** [For new cementum and attachment formation during periodontal regeneration, the local environment must be conducive for the recruitment and function of cementum-forming cells, and that the wound matrix is favorable for repair rather than regeneration.] http://crobm.iadrjournals.org/cgi/content/abstract/13/6/474
977. **Chronic Periodontitis as a Risk Marker for Systemic Diseases with Reference to Cardiometabolic Disorders:Common Pathways in their Progression.** [Abstract: Periodontitis, an inflammatory condition of the supporting structures of teeth resulting from dental plaque biofilm attached to tooth surfaces is potentially an important nidus of systemic inflammation and its sequelae. Relevant risk markers common to periodontitisco-existing with coronary heart disease and diabetes mellitus play an important role in their pathogeneses and abate in response to treatment. An over-exuberant host-response to periodontal pathogen- mediated inflammation, triggers a cycle of events which is not dissimilar to an autoimmune response in a cohort of susceptible individuals. Some variation in documented findings regarding correlations with co-morbidities and periodontitis could be explained by the lack of uniformity in studies with regard to stipulation of periodontal inflammatory status in the context of risk factors examined. There are several genetic and environmental factors which influence the progression of inflammatory periodontitis in response to plaque biofilm, also relevant to associated cardiometabolic disorders in the same subject. Some common mechanisms in the pathogeneses of periodontitis and cardiometabolic disorders based on regulation of inflammation are addressed in this review. There is some evidence of an improved systemic inflammatory profile in response to periodontal treatment which emphasizes the importance of periodontal management for systemic health in relevant cases.] Soory M. *Immunology and Immunogenetics Insights*, 2010:2 7-21. http://www.la-press.com
978. **Clinical Innovations in Managing Inflammation and Periodontal Diseases: The Workshop on Inflammation and Periodontal Diseases.** [This summary will highlight the clinical implications of the Workshop on Inflammation and Periodontal Diseases reported in this supplement of the *Journal of Periodontology*. In selecting clinical innovations, the objective criteria of present or potential clinical utility have been applied, as well as the context of these innovations in light of recent and past literature. However, in any such endeavor, there is likely to be unintentional selectivity based upon judgment about future developments and relevance. Clinical innovations will be discussed relative to a timeline of implementation with three categories discussed: those that may be applied in the short term (1 to 2 years), medium term (5 to 10 years), and long term (≥10 years). The medium-term innovations will require further research and development, whereas the long-term innovations will likely require extensive translation of science and technology to apply them to useful clinical practice. The risk/benefit ratios and cost/benefit ratios will be important considerations in final decisions to implement these innovations.] Genco RJ. *Journal of Periodontology, 2008, Vol. 79, No. 8s, Pages 1609-1611.* http://www.joponline.org/doi/full/10.1902/jop.2008.080305
979. **Collagenase activity of gingival tissue affected with periodontal disease.** Hazen SP, Beutner EH, et al. *J Periodontol*. 1968;39(1):45. http://www.ncbi.nlm.nih.gov/pubmed/4299699
980. **Collagenase and neutral metallo-proteinase activity in xtracts of inflamed human gingival** [Human gingiva was found to contain neutral proteolytic enzymes that degrade native and denatured collagen, and azocoll, a substrate for non-specific proteinases. The best enzyme recovery was obtained when an insoluble gingival homogenate was extracted at 40°C in the presence of 0.1 M $CaCl_2$. The proteinases were found to exist in the extracts mostly in a latent form that could be activated by compounds reacting with sulfhydryl groups of proteins. Enzyme inhibitor studies showed that all three enzymes belong to the group of metallo-proteinases. In gel filtration chromatography the enzyme activity degrading denatured collagen was separated from the two other proteinase activities. When the specific collagenase activity and the nonspecific proteinase activity were compared with Gingival Index, it was found that the enzyme activities were significantly higher in gingival samples that showed clear signs of inflammation than in clinically non-inflamed samples.] Uitto V, Appelgren R, et al. *Journal of Periodontal Research*, Vol 16, Issue 4, pp 417-424. Jun 30, 2006. http://www3.interscience.wiley.com/journal/119572326/abstract?CRETRY=1&SRETRY=0

981. **Controlling the Resolution of Acute Inflammation: A New Genus of Dual Anti-Inflammatory and Proresolving Mediators**. [A well-integrated host inflammatory response is essential in maintaining health and fighting disease. It is important to achieve a complete understanding of the cellular and molecular events that govern the resolution of acute inflammation. Because novel lipid-derived mediators, called resolvins and protectins in animal models, control the duration and magnitude of inflammation, the mapping of these resolution circuits may provide new ways of understanding the molecular basis of many inflammatory diseases. This article provides an overview of recent studies on resolvin and protectin biosynthesis and of advances in understanding the actions of these novel anti-inflammatory and proresolving lipid mediators. These new families of lipid-derived mediators were originally isolated from experimental murine models of acute inflammation identified during the natural spontaneous resolution phase. They are biosynthesized from omega-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid) and possess potent anti-inflammatory, proresolving, and antifibrotic actions in vivo. Taken together, these findings suggest that defective resolution mechanisms may underlie the inflammatory phenotypes that are believed to characterize many common human diseases. The new families of endogenous proresolving and anti-inflammatory agonists constitute a new genus of anti-inflammatories.] Serhan CN. *Journal of Periodontology*, Vol. 79. No. 8s, pp1520-1526, Aug 2008. http://www.joponline.org/doi/abs/10.1902/jop.2008.080231

982. **Demonstration of tissue collagenase activity in vivo and its relationship to inflammation severity in human gingiva.** Overall CM, Wiebkin OW, et al. *J Periodontal Res.* 1987 Mar;22(2):81-8. http://www.ncbi.nlm.nih.gov/pubmed/3035163

983. **Dental disease and risk of coronary heart disease and mortality.** [Among all 9760 subjects included in the analysis those with periodontitis had a 25% increased risk of coronary heart disease relative to those with minimal periodontal disease. Poor oral hygiene, determined by the extent of dental debris and calculus, was also associated with an increased incidence of coronary heart disease. In men younger than 50 years at baseline periodontal disease was a stronger risk factor for coronary heart disease; men with periodontitis had a relative risk of 1.72. Both periodontal disease and poor oral hygiene showed stronger associations with total mortality than with coronary heart disease. CONCLUSION--Dental disease is associated with an increased risk of coronary heart disease, particularly in young men.] DeStefano F, Anda RF et al, *Brit Med J* 13;306(6879):688-691, 1993. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8471920&dopt=Abstract

984. **Distribution of enzymatically pathogenic bacteria from periodontal pocket in advancing periodontitis.** [Production of 9 enzymatic activities of 527 strains freshly isolated from periodontal pockets in advancing periodontitis were investigated. Of these isolates, two strains showed lecithinase activity on egg yolk agar plate. Collagenase, plasmin and lipase were produced by 28 strains, 26 strains and 22 strains, respectively. Two lecithinase-producing strains were identified as Bacteroides intermedius. Nineteen strains of B. intermedius and 1 strain of Fusobacterium species produced lipase on egg yolk agar plate. All of the 28 collagenase-producing strains were B. gingivalis. B. gingivalis (20 strains) and non black-pigmented Bacteroides (6 strains) showed plasmin activity. These results indicate that Bacteroides species, mainly B. gingivalis and B. intermedius may exert an important influence on the exacerbation of the disease.] Inoue J, Fukushima H, et al. *Nippon Shishubyo Gakkai Kaishi*. 1990 Mar;32(1):199-205. http://www.ncbi.nlm.nih.gov/pubmed/1966847

985. **DNA methylation profiles of gingival tissues in periodontal disease.** [Objective: We have recently reported that periodontal pathogens can alter DNA methylation patterns of host genomic DNA. DNA methylation is an epigenetic phenomenon that controls gene expression without a change in DNA sequence. Changes in DNA methylation generally remain stable following cell division to permanently alter the tissue gene expression and response to challenge. The goal of this study was to determine whether the biofilm was inducing local alterations in host DNA methylation patterns that could potentially modulate gene expression. Material and Methods: Genome-wide alterations in DNA methylation patterns were performed by analyses using CpG island microarrays. Diseased gingival tissues collected from patients with severe periodontal disease were compared with healthy gingival tissues from either healthy or diseased patients. Genomic DNA was isolated and restrictively digested with MseI, ligated to linkers and subjected to restrictive digestion by two methylation-sensitive restrictive enzymes, BstUI and HpaII. Following PCR amplification, products were labeled by Cy5 for test samples and Cy3 for control samples, hybridized to a 12K Human CpG-island microarray and analyzed for differences in CpG methylation patterns comparing health to disease. Results: Altered DNA methylation patterns were found in samples from patients with periodontal disease suggesting a local epigenetic modulation of host DNA structure. Preliminary results suggest that many genes are differentially methylated at sites of periodontal disease compared to health. Hypermethylation, which is usually associated with gene silencing, was observed for many genes including SOCS3, VDR, MMP25 and BMP4. Conclusion: Chronic infection and underlying inflammation in gingival tissue is associated with altered DNA methylation of multiple genes. Such modification may significantly contribute to permanent alteration of the local environment to further enhance the inflammatory tissue phenotype.] Barros S, Zhang S, et al. IADR 86th General Session & Exhibition. http://iadr.confex.com/iadr/2008Toronto/techprogram/abstract_108338.htm

986. **Early Carotid Atherosclerosis in Subjects with Periodontal Diseases.** [The present results indicate that periodontal disease is associated with the development of early atherosclerotic carotid lesions.] Söder P, Söder B, *Stroke.* 2005;36:1195. http://stroke.ahajournals.org/cgi/content/full/36/6/1195

987. **Effect of locally delivered minocycline microspheres on markers of bone resorption.** [BACKGROUND: Gingival crevicular fluid (GCF) biomarkers associated with bone resorption may be useful to determine periodontal disease status and response to therapy. The pyridinoline cross-linked carboxy-terminal telopeptide of type I collagen (ICTP), a bone-specific degradation product, and interleukin 1-beta (IL-1), a potent bone-resorptive cytokine, have both been associated with periodontal disease activity. Minocycline is a tetracycline derivative possessing antimicrobial effects on periodontal

pathogens and inhibitory properties on matrix metalloproteinases (MMPs) associated with tissue destruction. The aim of this study was to evaluate the effect of periodontal treatment in the form of scaling and root planing (SRP) and locally administered minocycline microspheres on the GCF levels of ICTP and IL-1. METHODS: Forty-eight chronic periodontitis patients were randomly assigned to 2 groups (SRP plus subgingival application of vehicle control [SRP + V], or SRP plus subgingival application of minocycline microspheres [SRP + M]) and monitored at 8 sites per subject at baseline and 1, 3, and 6 months. Four shallow (PD < or = 3 mm) and 4 deep (PD > or = 5 mm) sites were evaluated for both marker levels and for probing depth (PD), clinical attachment level (CAL), and bleeding on probing (BOP). Eight periodontally healthy control subjects with no probing depths >3 mm and no loss of attachment were also monitored at the same time intervals. GCF levels of ICTP and IL-1 were determined using radioimmunoassay and enzyme-linked immunosorbent assay techniques, respectively. RESULTS: Significant differences (P<0.001) in GCF levels of ICTP and IL-1 were found between deep and shallow sites at all time points in both treatment groups. In addition, healthy subjects demonstrated significantly reduced levels of both markers compared to both shallow and deep sites in periodontitis patients (P <0.001). Only the SRP + M treated patients exhibited significant reductions (P <0.05) in both ICTP and IL-1 levels 1 month after treatment. Furthermore, the SRP + M group demonstrated significantly lower IL-1 levels (P <0.02) at 1 month compared to the SRP + V group. CONCLUSIONS: Results of this study indicate that GCF levels of ICTP and IL-1 correlate with clinical measures of periodontal disease and may aid in assessing disease status and response to periodontal therapy. Furthermore, local administration of minocycline microspheres led to a potent short-term reduction in GCF IL-1 levels. Additional studies are needed to address whether repeated administration of scaling and root planing along with minocycline microspheres will achieve long-term reductions in GCF ICTP and IL-1 levels.] Oringer RJ, Al-Shammari KF, et al.*J Periodontol*, 2002 Aug;73(8):835-42. http://www.ncbi.nlm.nih.gov/pubmed/12211491

988. **Effect of Periodontal Treatment on Markers of Systemic Inflammation.** [Periodontal disease has been associated with elevated levels of acute phase proteins (systemic inflammatory markers) namely C-reactive protein (CRP) and Fibrinogen. Objective: This randomized clinical trial assessed the effect of anti-infective periodontal treatment on these markers of systemic inflammation. Methods: One hundred and two (102) patients with chronic adult periodontitis were randomized to one of two groups, i.e. Scaling and Root Planing (SRP),and Subgingival application of Atridox, followed by Scaling and root Planing (ATX-SRP). Periodontal treatment was performed at baseline, 3, 6, and 9 months. Periodontal assessments included Plaque Index, Gingival Index, Probing depth and bleeding on probing. Blood samples to measure CRP and fibrinogen were collected at screening, baseline, 6 weeks, 3, 6, 9 and 12 months after treatment. Differences in PPD, CRP and fibrinogen between groups at all time points were assessed using ANOVA. Results: Mean reduction in PPD for both groups at 3, 6, 9 and 12 months ranged from 0.5 to 0.9 mm and 1.4 to 2 mm for sites with initial PPD 5-6 mm and ≥ 7 mm respectively. Statistically significant reductions in levels of CRP and Fibrinogen were seen in patients with elevated levels of these markers at baseline; CRP ≥ 3mg/L) and fibrinogen ((≥ 3g/L). Reduction in levels of CRP in the SRP group reached significance (p< 0.05) at 9 months and in the ATX-SRP group at 6 and 9 months following therapy (p < 0.05). The reduction in Fibrinogen levels in the SRP group reached significance at 6 weeks and 12 months (p< 0.05) and at all time-points following therapy in the ATX-SRP group (p < 0.01). Conclusion: Anti-infective periodontal treatment has an effect on systemic markers of inflammation measured by reduction in acute phase proteins namely CRP and Fibrinogen.] Farooqi OA, Grossi SG, et al., Int Assoc Dent Res 82nd General Session, Mar 10-13, 2004).
http://iadr.confex.com/iadr/2004Hawaii/techprogram/abstract_39952.htm

989. **Effect of periodontal treatment on the C-reactive protein and proinflammatory cytokine levels in Japanese periodontitis patients. [**BACKGROUND: Recent epidemiological studies have shown that individuals with periodontitis have a significantly increased risk of developing coronary heart disease. In addition to conventional risk factors, chronic infection and subsequent production of systemic inflammatory markers may be associated with this increased risk. OBJECTIVES: The aim of the present study was to determine whether the presence of chronic periodontitis and subsequent periodontal treatment could influence the serum levels of C-reactive protein (CRP), interleukin-6 and tumor necrosis factor-alpha (TNF-alpha) in a Japanese population. METHODS: Sera were obtained from 24 patients with moderate to advanced periodontitis at the baseline examination and at reassessment after completion of treatment. As a control, sera were also obtained from 21 subjects without periodontitis. High-sensitivity CRP (hs-CRP) was measured using nephelometry with a latex particle-enhanced immunoassay and interleukin-6 and TNF-alpha were determined by sensitive enzyme-linked immunosorbent assay. RESULTS: The levels of hs-CRP and interleukin-6 in the sera of this Japanese population seemed to be much lower than those reported in other populations. TNF-alpha on the other hand, demonstrated similar levels between this Japanese and other populations. Periodontal status demonstrated a significant improvement in all patients following treatment. There was a trend toward higher hs-CRP levels in patients at baseline compared with control subjects. Hs-CRP level tended to decrease with improvement of the periodontal condition following treatment and approached that of control subjects, although this decline was not statistically significant. interleukin-6 and TNF-alpha levels did not change following periodontal treatment. Furthermore, there was no difference in the serum levels of these inflammatory cytokines between patients either at baseline or at reassessment and control subjects. CONCLUSIONS: In this pilot study, we were unable to show that periodontal disease significantly affects the serum levels of systemic inflammatory markers. However, this does not necessarily mean that periodontitis does not contribute to the total burden of inflammation as there was a tendency for hs-CRP to decrease following successful periodontal treatment. Large-scale studies are clearly needed to determine the impact of periodontal disease on systemic inflammation.] Yamazaki K, Honda T, et al. *J Periodontal Res*. 2005 Feb;40(1):53-8.
http://www.ncbi.nlm.nih.gov/pubmed/15613080

990. **Effect of treating periodontitis on C-reactive protein levels.** [Periodontitis seems to increase C-reactive protein only in some individuals, presumably the ones reacting to it with a systemic inflammatory reaction. Periodontal treatment decreases C-reactive protein levels in these individuals and it may thus decrease their risk of coronary heart disease.] Mattila K, Vesanen M, *BMC Infect Dis.* 2002 Dec 10;2:30. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12475397&dopt=Abstract
991. **Elevation of Systemic Markers Related to Cardiovascular Diseases in the Peripheral Blood of Periodontitis Patients.** [Periodontitis is a common, often undiagnosed, chronic infection of the supporting tissues of the teeth, epidemiologically associated with cardiovascular diseases. Since C-reactive protein (CRP) and other systemic markers of inflammation have been identified as risk factors for cardiovascular diseases, we investigated whether these factors were elevated in periodontitis. Periodontitis results in higher systemic levels of CRP, IL-6, and neutrophils. These elevated inflammatory factors may increase inflammatory activity in atherosclerotic lesions, potentially increasing the risk for cardiac or cerebrovascular events.] *J Periodontology* 2000 Oct; 71(10):1528-34. http://www.joponline.org/doi/abs/10.1902/jop.2000.71.10.1528
992. **Enhanced monocyte migration and pro-inflammatory cytokine production by Porphyromonas gingivalis infection.** [Background and Objective: Porphyromonas gingivalis, a major periodontal pathogen, has been reported to be involved in atherogenesis. In order to further understand this pathogen's link with systemic inflammation and vascular disease, we investigated its influence on murine monocytes and macrophages from three different sources. Material and Methods: Concanavalin A-elicited peritoneal macrophages, peripheral blood monocyte-derived macrophages and WEHI 274.1 monocytes were infected with either P. gingivalis 381 or its non-invasive fimbriae-deficient mutant, DPG3. Results: Infection with P. gingivalis 381 markedly induced monocyte migration and significantly enhanced production of the pro-inflammatory cytokines, tumor necrosis factor-alpha and interleukin-6. Consistent with a role for this pathogen's major fimbriae and/or its invasive capacity, infection with DPG3 had a minimal effect on both monocyte attraction and pro-inflammatory cytokine production. Conclusion: Since monocyte recruitment and activation are important steps in the development of vascular inflammation and atherosclerosis, these results suggest that P. gingivalis infection may be involved in these processes.] Pollreisz A, Huang Y, et al. *J Periodontal Res.* 2009 Sep 23. http://www.ncbi.nlm.nih.gov/pubmed/19778327
993. **Induction of Bone Loss by Pathobiont-Mediated Nod1 Signaling in the Oral Cavity**. [Periodontitis is a common disease that is characterized by resorption of the alveolar bone and mediated by commensal bacteria that trigger host immune responses and bone destruction through unidentified mechanisms. We report that Nod1, an innate intracellular host receptor for bacterial peptidoglycan-related molecules, is critical for commensal-induced periodontitis in a mouse model. Mice lacking Nod1 exhibit reduced bone resorption as well as impaired recruitment of neutrophils to gingival tissues and osteoclasts to the alveolar bone, which mediate tissue and bone destruction. Further analysis showed that accumulation of a Nod1-stimulating commensal bacterium, NI1060, at gingival sites was sufficient to induce neutrophil recruitment and bone resorption. Genomic sequencing revealed that NI1060 is a mouse-specific bacterium that is related to bacteria associated with the development of aggressive periodontitis in humans. These findings provide insight into commensal-host interactions contributing to periodontitis and identify a potential target for preventing this common oral disease.]Jiao Y, Darzi Y, et al. Cell Host & Microbe**,** Volume 13, Issue 5, 595-601, 15 May 2013 , http://www.cell.com/cell-host-microbe/abstract/S1931-3128(13)00147-9
994. **Infection or Inflammation: The Link Between Periodontal Disease and Systemic Disease**. [There is increasing evidence that chronic infections are associated with cardiovascular diseases. A number of hypotheses have been put forward to explain these associations, including common susceptibility, systemic inflammation, direct infection of the blood vessels, and cross-reactivity or molecular mimicry between bacterial and self-antigens. In terms of common susceptibility, a person who is susceptible to progressive periodontal disease is also susceptible to atherosclerosis, but the periodontal disease does not cause the atherosclerosis. In recent years much research has been focused on the role of systemic inflammation and the increase in circulating cytokines and inflammatory mediators. These cytokines and mediators can lead to direct endothelial damage and ultimately to atherosclerosis. A number of studies have shown that periodontal bacteria can directly invade the endothelium and thereby lead to inflammation in the blood vessel wall resulting in atherosclerosis. In terms of molecular mimicry, it is proposed that because of the homology between bacterial GroEL antigens and human heat shock protein (HSP), the local immune response to the periodontopathic bacteria cross-reacts with self-HSP expressed on the endothelium leading to vascular inflammation and hence atherosclerosis. There is increasing evidence in support of this hypothesis; however, none of these possible mechanisms are mutually exclusive, and it is likely that in different people different mechanisms may explain the link between periodontal infection and cardiovascular disease.] Seymour GJ, Ford PJ, et al. *Inside Dentistry* Vol 2 (Special Issue 1) International Consensus Statement, http://www.colgateprofessional.com/ColgateProfessional/Home/US/EN/ProfessionalEd/Publications/PDFs/Seymour.pdf
995. **Inflammation and Bone Loss in Periodontal Disease.** [Inflammation and bone loss are hallmarks of periodontal disease (PD). The question is how the former leads to the latter. Accumulated evidence demonstrates that PD involves bacterially derived factors and antigens that stimulate a local inflammatory reaction and activation of the innate immune system. Proinflammatory molecules and cytokine networks play essential roles in this process. Interleukin-1 and tumor necrosis factor-alpha seem to be primary molecules that, in turn, influence cells in the lesion. Antigen-stimulated lymphocytes (B and T cells) also seem to be important. Eventually, a cascade of events leads to osteoclastogenesis and subsequent bone loss via the receptor activator of nuclear factor-kappa B (RANK)–RANK ligand (RANKL)–osteoprotegerin (OPG) axis. This axis and its regulation are not unique to PD but rather are critical for pathologic lesions involving chronic inflammation. Multiple

lines of evidence in models of PD clearly indicate that increases in RANKL mRNA expression and protein production increase the RANKL/OPG ratio and stimulate the differentiation of macrophage precursor cells into osteoclasts. They also stimulate the maturation and survival of the osteoclast, leading to bone loss. OPG mRNA expression and protein production do not generally seem to be increased in the periodontitis lesion. Studies of RANKL and OPG transgenic and knockout animals provide further support for the involvement of these molecules in the tissue loss observed in PD. Ironically, periodontal practitioners have focused on the bacterial etiology of PD and believed that plaque removal was aimed at eliminating specific bacteria or bacterial complexes. However, it seems that the reduction of inflammation and attenuation of the host's immune reaction to the microbial plaque, eventually leading to a decrease in the ratio of RANKL/OPG and a decrease in associated bone loss, are the actual and desired outcomes of periodontal therapy. Future therapeutic options are likely to have regulation of the RANK–RANKL–OPG axis as their goal.] Cochran DL. *Journal of Periodontology, 2008, Vol. 79, No. 8s, Pages 1569-1576* http://www.joponline.org/doi/full/10.1902/jop.2008.080233

996. **Inflammatory responses of a macrophage/epithelial cell co-culture model to mono and mixed infections with *Porphyromonas gingivalis, Treponema denticola,* and *Tannerella forsythia.*** [Accumulated evidence points to *Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia* as three major etiologic agents of chronic periodontitis. Epithelial cells and macrophages play a major role in the host response to periodontopathogens, and the secretion of inflammatory mediators and matrix metalloproteinases (MMPs) by these host cells is believed to contribute to periodontal tissue destruction. The aim of this study was to investigate the inflammatory response of a macrophage/epithelial cell co-culture model following mono or mixed infections with the above three periodontopathogens. An in vitro co-culture model composed of epithelial-like transformed cells (HeLa cell line) and macrophage-like cells (phorbol myristic acid-differentiated U937 monocytic cell line) was challenged with whole cells or lipopolysaccharides (LPS) of *P. gingivalis*, *T. denticola*, and *T. forsythia*, individually and in combination. Following stimulation, the production of interleukin-1 beta (IL-1β), IL-6, IL-8, tumor necrosis factor alpha (TNF-α), regulated on activation normal T cell expressed and secreted (RANTES), prostaglandin E_2 (PGE_2), and MMP-9 were quantified by enzyme-linked immunoassays. We observed that mono or mixed infections of the co-culture model induced the secretion of IL-1β, IL-6, IL-8, PGE_2, and MMP-9. *P. gingivalis* and *T. forsythia* induced an increase in RANTES secretion, whereas *T. denticola* alone or in combination resulted in a significant decrease in RANTES levels. All LPS challenges induced an increase in chemokine, MMP-9, and PGE_2 production. No synergistic effect on the production of cytokines, chemokines, PGE_2, and MMP-9 was observed for any of the bacterial or LPS mixtures tested. This study supports the view that *P. gingivalis*, *T. denticola*, and *T. forsythia* may induce high levels of pro-inflammatory mediators and MMP-9 in periodontal lesions, thus contributing to the progression of periodontitis.] Bodet C, Chandad F, Grenier D. *Microbes and Infection*, Vol 8, Issue 1, Jan 2006, Pp 27-35). http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6VPN-4GR32V5-1&_user=10&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=9b2788675d013e0b7bffcb32a059c2c8

997. **Inflammatory Responses Triggered by Oral Bacterial DNA-Induced Signaling Pathways**. [OBJECTIVE: Signaling pathways triggered by innate receptor activation help shape the final host response. We previously reported that Porphyromonas gingivalis (Pg) and Tannerella forsythia DNA stimulate cytokine production in human monocytic cells (THP-1) through Toll like receptor 9 (TLR9) and nuclear factor kappa B signaling pathway. Fusobacterium nucleatum, a periodontal pathogen, is implicated in periodontitis-associated adverse pregnancy outcomes. This study determined cytokine production from THP-1 cells in response to Fusobacterium nucleatum (Fn-DNA) and Streptococcus sanguinis DNA (Ss-DNA), a non-pathogenic oral bacteria, and further assessed whether inflammatory mediators triggered by whole pathogens or Pg-LPS are affected by the inhibitors of TLR9 signaling (chloroquine). METHODS: THP-1 cells were stimulated with Pg-DNA (100ng/µl), Fn-DNA (100ng/µl), Ss-DNA (100ng/µl), Pg-LPS (strain 381) (10ng/µl) and heat-killed whole bacteria (Multiplicity of Infection: 1:100) for 16 hours with or without chloroquine pre-treatment (10µg/ml). IL-1beta, IL-6, IL-8 and TNF-alpha levels were determined using enzyme-linked immunoabsorbent assay. Statistical analyses included analysis of variance with multiple comparisons using Tukey method and paired t-test. A value of $p<0.05$ was considered significant. RESULTS: Increased inflammatory mediator production was observed in response to all the stimuli with the exception of Ss-DNA ($p<0.05$). Chloroquine pre-treatment significantly decreased inflammatory mediator production from THP-1 cells in response to bacterial DNA, heat-killed bacteria and Pg-LPS with the exception of IL-6 production in response to whole F. nucleatum and S. sanguinis ($p<0.05$). CONCLUSION: DNA of certain oral pathogens can be as potent as whole bacteria or LPS. By altering the conditions in cytosolic compartments, we can modify the cellular responses triggered by extracellular receptor activation. Thus, alternative treatment approaches targeted to intracellular receptors might be of benefit in controlling periodontal inflammation.] Sahingur SE, Xia-Juan X, et al. *IADR/AADR/CADR* 89th General Session, March 2011, http://iadr.confex.com/iadr/2011sandiego/preliminaryprogram/abstract_149801.htm

998. **Mapping the Pathogenesis of Periodontitis: A new Look.** [Chronic adult periodontitis is a bacterially induced chronic inflammatory disease that destroys the connective tissue and bone that support teeth. Concepts of the specific mechanisms involved in the disease have evolved with new technologies and knowledge. Histopathologic observations of diseased human tissues were used previously to speculate on the causes of periodontitis and to describe models of pathogenesis. Experimental evidence later emerged to implicate bacterial plaque deposits as the primary factor initiating periodontitis. At the same time, specific bacteria and immunoinflammatory mechanisms were differentially implicated in the disease. In the mid-1990s, early insights about complex diseases, such as periodontitis, led to new conceptual models of the pathogenesis of periodontitis. Those models included the bacterial activation of immunoinflammatory mechanisms, some of which targeted control of the

bacterial challenge and others that had adverse effects on bone and connective tissue remodeling. Such models also acknowledged that different environmental and genetic factors modified the clinical phenotype of periodontal disease. However, the models did not capture the dynamic nature of the biochemical processes, i.e., that innate differences among individuals and changes in environmental factors may accelerate biochemical changes or dampen that shift. With emerging genomic, proteomic, and metabolomic data and systems biology tools for interpreting data, it is now possible to begin describing the basic elements of a new model of pathogenesis. Such a model incorporates gene, protein, and metabolite data into dynamic biologic networks that include disease-initiating and -resolving mechanisms. This type of model has a multilevel framework in which the biochemical networks that are regulated by innate and environmental factors can be described and the interrelatedness of networks can be captured. New models in the next few years will be merely frameworks for integrating key knowledge as it becomes available from the ''-omics'' technologies. However, it is possible to describe some of the key elements of the new models and discuss distinctions between the new and older models. It is hoped that improved conceptual models of pathogenesis will assist in focusing new research and speed the translation of new data into practical applications.] Kornman KS. *J Periodontol 2008;79:1560-1568.* http://www.joponline.org/doi/pdf/10.1902/jop.2008.080213

999. **Mechanical stress enhances production of cytokines in human periodontal ligament cells induced by Porphyromonas gingivalis.** [OBJECTIVE: We have previously reported that human periodontal ligament (hPDL) cells produced many kinds of cytokines as a result of bacterial stimulation, including stimulation with Porphyromonas gingivalis (P. gingivalis). However, the effects of mechanical stress on cytokine production in hPDL cells stimulated by periodontopathogenic bacteria are not clearly understood. In this study, we investigated the effects of mechanical stress on the production of inflammatory cytokines in hPDL cells induced by stimulation with P. gingivalis. METHODS: The hPDL cells were exposed to various levels of mechanical stress (1, 6, 10 and 50MPa) and costimulated with mechanical stress and P. gingivalis for 24h. Cytokine mRNA expressions were determined by RT-PCR. Cytokines in the culture supernatant were assessed by ELISA, and morphologic changes in hPDL cells were observed. RESULTS: The expressions of interleukin (IL)-6, IL-8 and tumor necrosis factor-α mRNA were observed in hPDL cells after exposure to mechanical stress. Moreover, the production of IL-6 and IL-8 increased significantly after exposure to mechanical stress ranging from 1 to 10MPa. The amount of IL-8 in the culture supernatants of hPDL cells costimulated with P. gingivalis and mechanical stress was significantly higher than the expected additive amount. The morphology of hPDL cells did not change after exposure to 6MPa, but these cells were partly detached from the Petri dish after exposure to 50MPa. CONCLUSIONS: These results suggest that local inflammation of the periodontal ligament may be induced mainly by periodontal bacteria, and mechanical stress may promote local inflammation.] Yamamoto T, Kita M, et al. *Arch Oral Biol*. 2011 Mar;56(3):251-7. **http://www.ncbi.nlm.nih.gov/pubmed/20970115**

1000. **Microcirculation and micromorphology of healthy and inflamed gingivae.** [Inflammation changes the microcirculatory and micromorphological dynamics of human gingiva. Laser Doppler flowmetry (LDF) and a replica technique for scanning electron microscopy (SEM) were used to examine the facial soft tissues of six maxillary anterior teeth, before and after treatment, in 12 patients exhibiting clinically healthy tissues and in 12 others with moderate gingivitis. All patients received oral hygiene instructions and scaling. The gingiva in the gingivitis group became healthy within 3 months after treatment. LDF results were recorded at the free gingivae, interdental gingivae, attached gingivae, and alveolar mucosae of the six maxillary anterior teeth. The gingival blood flows in the gingivitis group before treatment were significantly different from those in the healthy gingiva group. Flows were restored to the same level as the healthy gingiva, with no significant difference, at P>0.01, 3 months after treatment. However, there were significant differences among sites during the same period. In addition, blood flow was reduced to a normal level after the inflammation subsided. Initially, the gingival morphology of the inflamed sites exhibited irregular free gingival margins, in contrast to that of healthy gingivae, which were characterized by rounded margins closely adapted to the tooth. One month post-treatment, the gingivae exhibited a wrinkled appearance, but they had reverted to normal micromorphology by 3 months post-treatment. The replica impression technique can be used to record gingival micromorphology both before and after reduction of inflammation.] Kerdvongbundit V, Vongsavan N, et al. *Odontology*, 2003;91(1):19-25. http://sciencelinks.jp/j-east/article/200321/000020032103A0662719.php

1001. **Molecular Pathogenicity of the Oral Opportunistic Pathogen Actinobacillus Actinomycetemcomitans.** [Periodontitis is mankind's most common chronic inflammatory disease. The main causative organism of this disease is *Actinobacillus actinomycetemcomitans*. This organism also produces a plethora of proteins able to inhibit eukaryotic cell cycle progression and proteins and peptides that can induce distinct forms of proinflammatory cytokine networks.] Henderson B, Nair SP, et. al., *Annual Review of Microbiology* Vol. 57: 29-55 *http://arjournals.annualreviews.org/doi/abs/10.1146/annurev.micro.57.030502.090908*

1002. **Optimal Oral Health Reduces Degenerative Diseases. [**Despite regular brushing, flossing, and professional cleaning, it is challenging to *optimally* suppress plaque buildup. In an intriguing development, researchers have discovered two unique strains of bacteria that can *prevent* the buildup of plaque and biofilm on our teeth. As we have come to learn, plaque-induced gum disease causes more than just *halitosis* (bad breath). Chronically inflamed gums lead to a host of degenerative disorders including atherosclerosis, diabetes, and cancer. After years of study, a new oral probiotic *lozenge* may change how millions can achieve optimal oral health.] Goepp J. *Life Extension Magazine*, July 2009. http://www.lef.org/magazine/mag2009/jul2009_Optimal-Oral-Health-Reduces-Degenerative-Diseases_01.htm

1003. **Periodontal Antibiotic Treatment Reduces Inflammation.** *J Am Dent Assoc*, Vol 133, No 6, 701-703. http://jada.ada.org/cgi/content/full/133/6/701-b

1004. **Periodontal Bacteria and Novel Systemic Inflammatory Markers in INVEST**. [Objective: To investigate the relationship between periodontal bacterial colonization and novel inflammatory markers relevant to incident coronary artery disease. Methods: The Oral Infections and Vascular Disease Epidemiology Study(INVEST) enrolled subjects aged ≥55 years, in northern Manhattan. Participants in the current analysis (n=598) were 60% female, tri-ethnic (58% Hispanic, 22% Black, 18% White, 2% other) with mean age (±SD) 69±9). In the two most posterior teeth/quadrant eleven periodontal microbes were quantified from dental plaques (n=4,866) in 8 sites/mouth (mesio-lingual in the maxilla and mesio-buccal in the mandible) using DNA-DNA checkerboard hybridization. Secretory-phospholipase A2 (s-PLA2) activity and lipoprotein-associated PLA2 (Lp-PLA2) was assessed systemically from stored plasma samples. We examined the cross-sectional relationship between *Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Treponema denticola* and *Tannerella forsythia* and both s-PLA2 activity and Lp-PLA2 activity. A standardized bacterial burden score was computed by: 1) ln transforming laboratory derived bacterial values; and 2) dividing values for each individual bacteria and person, by the population standard deviation for that bacteria. Etiologic burden (EB) was defined by summing standardized values across the four bacteria and represents the absolute combined level of these species, equating standard deviation units (SDU) across bacteria. In separate analyses, we used ANOVA to assess levels of s-PLA2 or Lp-PLA2 across EB tertiles. Analyses were adjusted for age, gender, race/ethnicity, education, diabetes, smoking, systolic blood pressure, HDL-cholesterol and LDL-cholesterol. Results: Mean EB was 32±4 SDU and mean s-PLA2 activity and Lp-PLA2 activity values were 0.76±0.56 nmol/min/ml and 30.4±10.9 nmol/min/ml, respectively. s-PLA2 values increased across tertiles of EB, as follows: T1=0.71±0.05, T2=0.74±0.04, T3=0.83±0.05 nmol/min/ml (p for trend=0.12). Lp-PLA2 values were: T1=29.4±0.9, T2=29.1±0.74, T3=32.9 nmol/min/ml (p for trend=0.04). Conclusion: Bacteria believed to be important contributors to clinical periodontal disease are positively associated with novel inflammatory markers recently shown to have prognostic value for incident coronary artery disease.] Desvarieux M, Mallat Z, et al. *IADR* 86th General Session, July 2008. http://iadr.confex.com/iadr/2008Toronto/techprogram/abstract_106763.htm

1005. **Periodontal Disease: An Overview for Physicians.** [Periodontitis is now seen as resulting from a complex interplay of bacterial infection and host response, often modified by behavioral factors. Susceptibility to periodontitis increases with age, and all individuals are susceptible to severe periodontal disease.] Fenesy KE, Dept of Oral Pathology, Biology and Diagnostic Sciences, New Jersey Dental School, Univ. of Medicine and Dentistry of New Jersey, Newark, NJ. *Mt Sinai J Med*, 1998 Oct-Nov;65(5-6):362-9. http://www.mssm.edu/msjournal/65/08_fenesy.pdf http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9844364&dopt=Abstract

1006. **Periodontal diseases and health: Consensus Report of the Sixth European Workshop on Periodontology**. [Introduction: The remit of this group was to update the knowledge base on periodontal diseases and health. [Material and Methods: The literature was systematically searched and critically reviewed in five specific topics. Results: *Prevalence of periodontitis:* The data suggest a trend towards a lower prevalence of periodontitis in recent years. *Adverse pregnancy outcome:* The findings indicate a likely association between periodontal disease and an increased risk of adverse pregnancy outcomes. There is no evidence that treating periodontal disease decreases the rate of adverse pregnancy outcomes. *Prevalence and distribution of periodontal pathogens:* Genetic analysis of bacteria has demonstrated an unanticipated diversity within species. Carriage rates and particular subsets of these species vary between ethnic groups. Few of these differences can be related to differences in disease prevalence. *Diabetes mellitus:* Evidence on the association supports the concept of increased severity but not extent of periodontitis in subjects with poorly controlled diabetes. It is inconclusive that periodontal treatment results in improved metabolic control. *Cardiovascular diseases:* Evidence suggests that having periodontitis contributes to the total infectious and inflammation burden and may contribute to cardiovascular events and stroke in susceptible subjects. The impact of periodontal therapy must be further investigated.] Kinane D, Bouchard P, et al. *Journal of Clinical Periodontology*, Vol. 35, pp 333-337, Sept 2008. http://onlinelibrary.wiley.com/doi/10.1111/j.1600-051X.2008.01278.x/abstract

1007. **Periodontal Disease and Risk of Cerebrovascular Disease**. [Periodontal disease is an important risk factor for total CVA and, in particular, nonhemorrhagic stroke.] Wu T et al, *Arch Intern Med. 2000; 160:2749-2755*. http://archinte.ama-assn.org/cgi/content/abstract/160/18/2749

1008. **Periodontal disease and systemic health--what you and your patients need to know.** [For many years, dentists have recognized the importance of dental health to general health. Recent research findings point to possible associations between chronic oral infections such as periodontitis and systemic health problems. This article will review the evidence for some of these associations and explore factors that may underlie oral-systemic disease connections.] Otomo-Corgel J, Merin RL. Journal CA Dental Assoc. April 2002. http://www.cda.org/library/cda_member/pubs/journal/jour0402/systemic.html

1009. **Periodontal disease in mothers indicates risk in their children.** [Introduction. It is well established that severe periodontitis clusters in families, but there are no data about the relationship between mothers with chronic periodontitis and their children's periodontal status. Objective. To evaluate a risk for periodontal diseases in children of periodontally diseased and healthy mothers. Methods. Four study groups were included: (I) 20 female patients with untreated generalized severe chronic periodontitis, (II) their children (34), (III) 13 periodontally healthy mothers and (IV) their children (13). Material was collected from years 2004–2006. The clinical examination included registration of visible plaque index, modified gingival index and, bleeding sites on probing. Periodontal microbiological samples were obtained from all study subjects and the isolates were identified according to morphology and biochemical profiles; similar interfamilial pathogens were compared by

PCR-technique. Results. The children of diseased mothers more frequently had periodontal diseases, especially gingivitis. In addition, clinical parameters of gingival inflammation were more expressed and oral hygiene was worse in this group of children. VPI and VPI% of the diseased and healthy mothers differed significantly. The most common oral pathogens were *P. intermedia/nigrescens* and *A. actinomycetemcomitans*. The children of healthy mothers harboured pathogens less frequently than the children of diseased mothers. The sharing of *P. intermedia/nigrescens* was more frequent (5 families) than *A. actinomycetemcomitans* (2 families). Conclusion. Maternal indicators, such as periodontitis, hygiene habits, and periodontal microflora are risk factors for childhood periodontal diseases, and might be predictive of future childhood and adolescent periodontitis.] Pahkla E, Jogi E, et al. *International Journal of Paediatric Dentistry*, Vol 20, Issue 1, Pp 24-30, Dec 2009. http://www3.interscience.wiley.com/journal/123214954/abstract

1010. **Periodontal Infections Contribute to Elevated Systemic C-Reactive Protein Level.** [Periodontitis is a local inflammatory process mediating destruction of periodontal tissues triggered by bacterial insult. However, this disease is also characterized by systemic inflammatory host responses that may contribute, in part, to the recently reported higher risk for cardiovascular disease (CVD) among patients with periodontitis. Moderate elevation of C-reactive protein (CRP) has been found to be a predictor of increased risk for CVD. Elevated CRP levels in periodontal patients have been reported by several groups. In this study, we examined whether CRP plasma levels are increased in periodontitis and if there is a relation to severity of periodontal disease and to the periodontal microflora. there are elevated levels of CRP associated with infection with subgingival organisms often associated with periodontal disease, including *P.g., P.i., C.r.,* and *B.f.* Recent investigations emphasized the role of moderate elevated CRP plasma levels as a risk factor for CVD. The positive correlation between CRP and periodontal disease might be a possible underlying pathway in the association between periodontal disease and the observed higher risk for CVD in these patients.] Noack et al, *J Periodontol*. 2001 Sep;72(9):1221-7. http://www.joponline.org/doi/abs/10.1902/jop.2000.72.9.1221?cookieSet=1&journalCode=jop

1011. **Periodontal inflamed surface area: quantifying inflammatory burden.** [BACKGROUND: Currently, a large variety of classifications is used for periodontitis as a risk factor for other diseases. None of these classifications quantifies the amount of inflamed periodontal tissue, while this information is needed to assess the inflammatory burden posed by periodontitis. AIM: To develop a classification of periodontitis that quantifies the amount of inflamed periodontal tissue, which can be easily and broadly applied. MATERIAL AND METHODS: A literature search was conducted to look for a classification of periodontitis that quantified the amount of inflamed periodontal tissue. A classification that quantified the root surface area affected by attachment loss was found. This classification did not quantify the surface area of inflamed periodontal tissue, however. Therefore, an Excel spreadsheet was developed in which the periodontal inflamed surface area (PISA) is calculated using clinical Attachment Level (CAL), recessions and bleeding on probing (BOP). RESULTS: The PISA reflects the surface area of bleeding pocket epithelium in square millimetres. The surface area of bleeding pocket epithelium quantifies the amount of inflamed periodontal tissue. A freely downloadable spreadsheet is available to calculate the PISA. Conclusion: PISA quantifies the inflammatory burden posed by periodontitis and can be easily and broadly applied.] Nesse W, Abbas F, et al, *J Clin Periodontol*. 2008 Aug;35(8):668-73.
http://www.ncbi.nlm.nih.gov/pubmed/18564145
http://parsprototo.info/docs/PISA%20quantifying%20inflammatory%20burden.pdf

1012. **Periodontal status in the United States, 1988-1991: prevalence, extent, and demographic variation.**[This paper reports estimates of the periodontal status of US population derived from data from Phase 1 of the Third National Health and Nutrition Examination Survey conducted by the National Institute of Dental Research from 1988-1991. A total of 7,447 dentate individuals 13 years of age and older, representing approximately 160.3 million civilian non-institutionalized Americans, received a periodontal assessment. Measurements of gingival bleeding, gingival recession level, periodontal pocket depth, and calculus were made by dental examiners. Assessments were made at the mesiobuccal and mid-buccal sites of all fully erupted permanent teeth present in two randomly selected quadrants, one maxillary and one mandibular. All data were weighted and standard errors calculated by special software to adjust for the effect of sample design. Although over 90% of persons 13 years of age or older had experienced some clinical loss of attachment (LA), only 15% exhibited more severe destruction (LA > or = 5 mm). Prevalence of moderate and severe LA and gingival recession increased with age, while prevalence of pockets > or = 4 mm or > or = 6 mm did not. These data suggest that the increasing prevalence of LA with age is more associated with increasing prevalence of recession than with changes in the prevalence of pockets or age. The extent or number of affected sites with advanced conditions for loss of attachment, pocket depth, or recession was not large for any age group. Differences in prevalence of moderate and severe loss of attachment, moderate and deep pockets, and recession were found among gender and race-ethnicity groups. Females exhibited better periodontal health than males, and non-Hispanic whites exhibited better periodontal health than either non-Hispanic blacks or Mexican-Americans.] Brown LJ, Brunelle http://www.ncbi.nlm.nih.gov/pubmed/8594091

1013. **Periodontal Therapy Lowers Levels of Heart Disease Inflammation Markers.** [Treating periodontal disease with scaling and root planing combined with a topical antibiotic gel can significantly lower the levels of two inflammatory proteins associated with a heightened risk of heart disease. People who have high levels of CRP in their blood are at high risk of heart disease. Results showed that in people who had elevated levels of CRP at baseline, removal of dental plaque bacteria by scaling or scaling combined with topical antibiotics produced a statistically significant reduction, bringing CRP levels close to the low-risk level.] Grossi, S, et al. SUNY Buffalo, *ADA News* 04/21/2004.
http://www.ada.org/prof/resources/pubs/adanews/adanewsarticle.asp?articleid=841

1014. **Periodontitis, A True Infection.** [Periodontal infection is initiated by specific invasive oral pathogens that colonize dental plaque biofilms on tooth surface, and host immune response to inflammation plays a central role in disease pathogenesis. Periodontal diseases are recognized as infectious processes that require bacterial presence and a host response and are further affected and modified by other local, environmental and genetic factors. Association of periodontal infection with organ systems like cardiovascular system, endocrine system, reproductive system and respiratory system makes periodontal infection a complex multiphase disease. Periodontitis is defined as an inflammatory disease of supporting tissues of teeth caused by specific microorganisms or groups of specific microorganisms, resulting in progressive destruction of the periodontal ligament and alveolar bone with periodontal pocket formation, gingival recession or both. Periodontal disease is a complex infectious disease resulting from interplay of bacterial infection and host response to bacterial challenge, and the disease is modified by environmental, acquired risk factors and genetic susceptibility. Dental plaque represents a classic example of both a biofilm and a microbial community, in that it displays emer-gent properties, i.e., plaque displays properties that are more than the sum of its constituent members,[2] and microbial communities are ubiquitous in nature and usually exist attached to a surface as a spatially organized biofilm. Recent studies suggest that the environmental heterogeneity generated within biofilms promotes accelerated genotypic and phenotypic diversity that provides a form of "biological insurance" that can safeguard the "microbial community" in the face of adverse conditions, such as those faced by pathogens in the host.] Saini RM, Marawar PP, et al. *J Glob Infect Dis*. 2009 Jul-Dec; 1(2): 149–150. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2840950/

1015. **Periodontitis and Systemic Inflammation: Control of the Local Infection is Associated with a Reduction in Serum Inflammatory Markers.** [Severe periodontitis is associated with elevated inflammatory markers in otherwise healthy populations. periodontitis seems to contribute to systemic inflammation. The potential significance of the reported findings relates to the magnitude of the observed decreases in CRP, the high prevalence of periodontitis in the population, and the fact that periodontitis can be treated.] D'Aiuto F., Parkar M, et al. http://jdr.iadrjournals.org/cgi/content/full/83/2/156

1016. **Periodontitis as a component of hyperinflammation: treating periodontitis in obese diabetic patients.** [Increasing evidence points to periodontal disease as a significant risk factor in the etiology of other diseases with inflammatory components, such as cardiovascular disease and type 2 diabetes mellitus. Thus, it may be possible to reduce the risk for other diseases with an inflammatory component by maintaining a healthy periodontium. In addition to plaque and calculus, other factors such as diet, body weight, lifestyle, and environmental stress complicate the maintenance of a healthy periodontium. It is becoming more important for the general dentist to address these additional risk factors in addition to providing conventional treatment for periodontal disease. This review addresses a multifactorial approach to the treatment of periodontal disease and suggests that the "focal theory" of infection may still be relevant for oral inflammation.] Johnson RB. *Compend Contin Educ Dent*. 2007 Sep;28(9):500-4. http://www.ncbi.nlm.nih.gov/pubmed/17907373

1017. **Proinflammatory effect in whole blood by free soluble bacterial components released from planktonic and biofilm cells**. [Background *Aggregatibacter actinomycetemcomitans* is an oral bacterium associated with aggressive forms of periodontitis. Increasing evidence points to a link between periodontitis and cardiovascular diseases, however, the underlying mechanisms are poorly understood. This study investigated the pathogenic potential of free-soluble surface material, released from live planktonic and biofilm *A. actinomycetemcomitans* cells. Results By employing an *ex vivo* insert model (filter pore size 20 nm) we demonstrated that the *A. actinomycetemcomitans* strain D7S and its derivatives, in both planktonic and in biofilm life-form, released free-soluble surface material independent of outer membrane vesicles. This material clearly enhanced the production of several proinflammatory cytokines (IL-1β, TNF-α, IL-6, IL-8, MIP-1β) in human whole blood, as evidenced by using a cytokine antibody array and dissociation-enhanced-lanthanide-fluorescent-immunoassay. In agreement with this, quantitative real-time PCR indicated a concomitant increase in transcription of each of these cytokine genes. Experiments in which the LPS activity was blocked with polymyxin B showed that the stimulatory effect was only partly LPS-dependent, suggesting the involvement of additional free-soluble factors. Consistent with this, MALDI-TOF-MS and immunoblotting revealed release of GroEL-like protein in free-soluble form. Conversely, the immunomodulatory toxins, cytolethal distending toxin and leukotoxin, and peptidoglycan-associated lipoprotein, appeared to be less important, as evidenced by studying strain D7S *cdt*/*ltx* double, and *pal* single mutants. In addition to *A. actinomycetemcomitans* a non-oral species, *Escherichia coli* strain IHE3034, tested in the same *ex vivo* model also released free-soluble surface material with proinflammatory activity. Conclusion *A. actinomycetemcomitans*, grown in biofilm and planktonic form, releases free-soluble surface material independent of outer membrane vesicles, which induces proinflammatory responses in human whole blood. Our findings therefore suggest that release of surface components from live bacterial cells could constitute a mechanism for systemic stimulation and be of particular importance in chronic localized infections, such as periodontitis.] Oscarsson Jan, Karched M, et al. *BMC Microbiol*. 2008; 8: 206. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2612679/

1018. **Purification and characterization of a potent 70-kDa thiol lysyl- proteinase** (Lys-gingivain) from Porphyromonas gingivalis that cleaves kininogens and fibrinogen. { These data suggest that lys-gingivain is a very potent proteinase that would be fully functional in anaerobic periodontal crevices and might participate in the pathogenesis of periodontitis.] http://www.jbc.org/cgi/content/abstract/268/11/7935

1019. **Redox regulation of nuclear factor kappa B: therapeutic potential for attenuating inflammatory responses.** [Nuclear factor kappa B (NF-kappaB) is a protein transcription factor that is required for maximal transcription of a wide array of pro-inflammatory mediators that are involved in the pathogenesis of stroke. The purpose of this review article is to describe what is known about the molecular biology of NF NF-kappaB and to review current understanding of the interaction between reactive oxygen species (ROS) in NF-kappaB. ROS seem to play a duel role by participating in the NF-kappaB

activation cascade and by directly modulating DNA binding affinity. Exogenous and endogenous antioxidants are effective in blocking activation of NF-kappaB and preventing the consequences of pro-inflammatory gene expression. Phase II enzymes either directly or indirectly play a major in vivo role in minimizing oxidative stress by scavenging peroxides, peroxide breakdown products and dicarbonyls and in regeneration of lipid peroxidation chain-breaker, vitamin E. Dietary phase II enzyme inducers have been demonstrated to increase phase II enzyme activities in a variety of tissues. These data, together, suggest that phase II enzyme inducers could have therapeutic value for ameliorating inflammatory conditions.] Christman JW, Blackwell TS, et al. *Brain Pathol.* 2000 Jan;10(1):153-62. http://www.ncbi.nlm.nih.gov/pubmed/10668905 http://www.direct-ms.org/pdf/ImmunologyMS/Juurlink%20anti-ox%20brain.pdf

1020. **Relationship Between Periodontal Disease and C-Reactive Protein Among Adults in the Atherosclerosis Risk in Communities Study**. [[Background Moderately elevated serum C-reactive protein (CRP) concentration is a systemic marker of inflammation and a documented risk factor for cardiovascular disease in otherwise healthy persons. Unrecognized infections, such as periodontal disease, may induce an acute-phase response, elevating CRP levels. We evaluated the association between periodontal disease and CRP levels in adults in the Atherosclerosis Risk in Communities study. Methods Oral examinations were conducted between January 1, 1996, and December 31, 1998, on 5552 ARIC participants (aged 52-74 years) from 4 US communities. Periodontal disease was quantified as the percentage of periodontal sites with pocket depth of 4 mm or more. Serum CRP concentration was quantified in milligrams per liter using an enzyme-linked immunosorbent assay.Results Mean (SE) CRP level was 7.6 (0.6) mg/L among people with extensive periodontal pockets (>30% of sites with pocket depth ≥4 mm), approximately one-third greater than that for people with less extensive periodontal pockets (5.7 [0.1] mg/L). In a multivariable linear regression model that controlled for age, sex, diabetes mellitus, cigarette use, and nonsteroidal anti-inflammatory drug use, the association of extensive periodontal pockets with CRP concentration was modified by body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters). For people with a BMI of 20, the model predicted a 2-fold difference in mean CRP concentration between periodontal pocket groups (7.5 vs 3.6 mg/L), but the difference decreased with increasing BMI and was negligible when BMI equaled 35.Conclusions Extensive periodontal disease and BMI are jointly associated with increased CRP levels in otherwise healthy, middle-aged adults, suggesting the need for medical and dental diagnoses when evaluating sources of acute-phase response in some patients.] (Extensive periodontal disease and BMI are jointly associated with increased CRP levels in otherwise healthy, middle-aged adults, suggesting the need for medical and dental diagnoses when evaluating sources of acute-phase response in some patients.) Slade GD, Ghezzi EM, et al. *Arc Int Med*, Vol. 163 No. 10, May 26, 2003. http://archinte.ama-assn.org/cgi/content/abstract/163/10/1172.

1021. **Relationship Between Periodontal Disease, Tooth Loss, and Carotid Artery Plaque.** [Chronic infections, including periodontal infections, may predispose to cardiovascular disease. Data suggest that tooth loss is a marker of past periodontal disease in this population and is related to subclinical atherosclerosis, thereby providing a potential pathway for a relationship with clinical events.] *Stroke*. 2003;34:2120. http://stroke.ahajournals.org/cgi/content/abstract/34/9/2120?etoc%20

1022. **Resveratrol suppresses TNF-induced activation of nuclear transcription factors NF-kappa B, activator protein-1, and apoptosis: potential role of reactive oxygen intermediates and lipid peroxidation.** [Resveratrol (trans-3,4',5-trihydroxystilbene), a polyphenolic phytoalexin found in grapes, fruits, and root extracts of the weed Polygonum cuspidatum, exhibits anti-inflammatory, cell growth-modulatory, and anticarcinogenic effects. How this chemical produces these effects is not known, but it may work by suppressing NF-kappaB, a nuclear transcription factor that regulates the expression of various genes involved in inflammation, cytoprotection, and carcinogenesis. In this study, we investigated the effect of resveratrol on NF-kappaB activation induced by various inflammatory agents. Resveratrol blocked TNF-induced activation of NF-kappaB in a dose- and time-dependent manner. Resveratrol also suppressed TNF-induced phosphorylation and nuclear translocation of the p65 subunit of NF-kappaB, and NF-kappaB-dependent reporter gene transcription. Suppression of TNF-induced NF-kappaB activation by resveratrol was not restricted to myeloid cells (U-937); it was also observed in lymphoid (Jurkat) and epithelial (HeLa and H4) cells. Resveratrol also blocked NF-kappaB activation induced by PMA, LPS, H2O2, okadaic acid, and ceramide. The suppression of NF-kappaB coincided with suppression of AP-1. Resveratrol also inhibited the TNF-induced activation of mitogen-activated protein kinase kinase and c-Jun N-terminal kinase and abrogated TNF-induced cytotoxicity and caspase activation. Both reactive oxygen intermediate generation and lipid peroxidation induced by TNF were suppressed by resveratrol. Resveratrol's anticarcinogenic, anti-inflammatory, and growth-modulatory effects may thus be partially ascribed to the inhibition of activation of NF-kappaB and AP-1 and the associated kinases.] Manna SK, Mukhopadhyay A, et al. J *Immunol.* 2000 Jun 15;164(12):6509-19. http://www.ncbi.nlm.nih.gov/pubmed/10843709

1023. **Rethinking Periodontal Inflammation.** [Clinical signs and symptoms, as well as medical and dental history, are all considered in the clinical determination of gingival inflammation and periodontal disease severity. However, the “biologic systems model” highlights that the clinical presentation of periodontal disease is closely tied to the underlying biologic phenotype. We propose that the determination and integration of subject-level factors, microbial composition, systemic immune response, and gingival tissue inflammatory mediator responses will better reflect the biology of the biofilm–gingival interface in a specific patient and may provide insights on clinical management. Disease classifications and multivariable models further refine the biologic basis for the increasing severity of periodontal disease expression. As such, new classifications may better identify disease-susceptible and treatment–non-responsive individuals than current classifications that are heavily influenced by probing and attachment level measurements alone. New data also suggest that the clinical

characteristics of some complex diseases, such as periodontal disease, are influenced by the genetic and epigenetic contributions to clinical phenotype. Although the genetic basis for periodontal disease is considered imperative for setting an inflammatory capacity for an individual and, thus, a threshold for severity, there is evidence to suggest an epigenetic component is involved as well. Many factors long associated with periodontitis, including bacterial accumulations, smoking, and diabetes, are known to produce strong epigenetic changes in tissue behavior. We propose that we are now able to rethink periodontal disease in terms of a biologic systems model that may help to establish more homogeneous diagnostic categories and can provide insight into the expected response to treatment.] Offenbacher S, Barros SP, Beck JD. Journal of Periodontology, 2008, Vol. 79, No. 8s, Pages 1577-1584. http://www.joponline.org/doi/full/10.1902/jop.2008.080220

1024. **Risk assessment and management of periodontal disease.** [Background. As our understanding of periodontal diseases has increased, it has become clear that certain risk factors are associated with the diseases' incidence, severity and progression. This article focuses on the role of risk assessment and disease management in improving patient outcomes, both in the general population and in specific population groups with an increased risk of developing periodontal disease or with associated comorbidities. Types of Studies Reviewed. The author reviewed literature related to the efficacy of risk assessment and periodontal disease management in improving clinical outcomes. In addition, he examined studies demonstrating a link between periodontal disease and specific patient populations and other comorbidities. Conclusions. Risk assessment can help predict a patient's risk of developing periodontal disease and improve clinical decision making. In turn, patient adherence to a self-care oral health regimen is a key component to successful periodontal disease management. Clinical Implications. The clinical practice of risk assessment may reduce the need for complex periodontal therapy, improve patient outcomes and ultimately reduce oral health care costs. Patients are encouraged to become actively involved in periodontal disease management by following a daily three-step regimen of brushing, flossing and rinsing with an antimicrobial mouthrinse.] Douglass CW. J Am Dent Assoc, Vol 137, No suppl_3, 27S-32S. http://jada.ada.org/cgi/content/full/137/suppl_3/27S

1025. **Salivary infectious agents and periodontal disease status. [**Objectives: The potential of salivary microorganisms to diagnose periodontal disease and to guide periodontal treatment is a research topic of current interest. This study aimed to determine whether the salivary counts of periodontopathic microbes correlated with the periodontal pocket counts of the same infectious agents, and whether the salivary counts of the test infectious agents could distinguish among individuals with periodontal health and various types of periodontal disease. Material and Methods: The study included 150 systemically healthy adults, of whom 37 were periodontally healthy, 31 had gingivitis, 46 had chronic periodontitis and 36 had aggressive periodontitis. Each study subject contributed microbial samples from the two deepest periodontal pockets of the dentition and from whole saliva. Aggregatibacter actinomycetemcomitans, Campylobacter rectus, Fusobacterium nucleatum, Porphyromonas gingivalis, Prevotella intermedia, Tannerella forsythia and Epstein-Barr virus were identified using the TaqMan real-time PCR methodology. Statistical analysis was performed using the Mann-Whitney U-test and the receiver operating characteristic statistics. Results: C. rectus, F. nucleatum, P. gingivalis, P. intermedia and T. forsythia occurred with significantly higher copy-counts in salivary samples from patients with gingivitis, chronic periodontitis and aggressive periodontitis than from periodontally healthy individuals. A. actinomycetemcomitans only showed higher salivary copy-counts in subjects with aggressive periodontitis compared with subjects with healthy periodontium, and the salivary copy-counts of Epstein-Barr virus did not reveal any significant difference among the four subject groups studied. The diagnostic sensitivity for periodontitis was 89.19 for P. gingivalis and for T. forsythia and 86.49 for P. intermedia, with specificities ranging from 83.78 to 94.59. The optimal copy-counts per mL saliva for identifying periodontitis were 40,000 for P. gingivalis, 700,000 for T. forsythia and 910,000 for P. intermedia. Conclusion: Salivary copy-counts of P. gingivalis, T. forsythia and P. intermedia appear to have the potential to identify the presence of periodontitis, whereas the salivary level of the other test infectious agents may possess little or no diagnostic utility. Longitudinal studies are warranted to determine the ability of salivary copy-counts of major periodontopathic bacteria to predict future periodontal breakdown.] Saygun I, Nizam N, et al. *J Periodontal Res*. 2011 Apr;46(2):235-239. http://www.ncbi.nlm.nih.gov/pubmed/21261620

1026. **Salivary nitric oxide levels in inflammatory periodontal disease - a case-control and interventional study.** [BACKGROUND: Biochemical markers of inflammatory periodontal disease present in saliva can partially determine the extent of periodontal disease. Furthermore, collection of salivary constituents is a simple and non-invasive procedure. Nitric oxide (NO) has been linked to etiopathogenesis of inflammatory periodontal disease and is expressed in saliva. This study was conducted with the objective of estimating salivary NO levels in inflammatory periodontal diseases (gingivitis and periodontitis) and comparing these levels with control subjects. A re-assessment of these levels was also made after providing appropriate treatment with a view to ascertain its diagnostic and prognostic values. METHODS: This was a case-control as well as an interventional study including a total of 90 (30 control, 30 gingivitis and 30 periodontitis) subjects. Saliva samples were collected from each subject, and NO levels were assayed by Griess reaction. RESULTS: NO levels were increased significantly in gingivitis and periodontitis subjects as compared with controls. There was a statistically significant decrease in the NO levels in each study group after the healing period (corresponding to the reduced clinical signs of inflammation). Our study also correlated probing pocket depths with salivary NO levels in periodontitis group where we found a positive correlation between the two. CONCLUSION: Salivary NO levels can be utilized as a good indicator of the inflammatory status of the periodontium, and evaluating its levels in saliva by Griess reaction on a photoelectric colorimeter is a reliable, accurate and faster method to estimate the level of inflammation in periodontal tissues.] Parwani SR, Chitnis PJ, et al, *Int J Dent Hyg.*, 2012 Feb;10(1):67-73. doi: 10.1111/j.1601-5037.2011.00508.x. Epub 2011 May 12. http://www.ncbi.nlm.nih.gov/pubmed/21564536

1027. **Short-term Effects of Intensive Periodontal Therapy on Serum Inflammatory Markers and Cholesterol.** [Severe periodontitis has been associated with increased systemic inflammation. In a three-arm preliminary randomized trial, we investigated the impact of standard (SPT) and intensive periodontal therapy (IPT) on serum inflammatory markers and cholesterol levels. Medical and periodontal parameters, C-reactive protein (CRP), interleukin-6 (IL-6), total cholesterol, and LDL cholesterol were evaluated in 65 systemically healthy subjects suffering from severe generalized periodontitis. Two months after treatment, both SPT and IPT resulted in significant reductions in serum CRP compared with the untreated control (0.5 ± 0.2 mg/L for SPT, P = 0.030 and 0.8 ± 0.2 mg/L for IPT, P = 0.001). Similar results were observed for IL-6. Changes in inflammation were independent of age, gender, body mass index, and ethnicity, but a significant interaction between cigarette smoking and treatment regimen was found. The IPT group also showed a decrease in total and LDL cholesterol after 2 months. Analysis of these data indicates that periodontitis causes moderate systemic inflammation in systemically healthy subjects..] D'Aiuto F., Nibali, L, et al http://jdr.iadrjournals.org/cgi/content/abstract/84/3/269

1028. **Soluble antagonists to interleukin-1 (IL-1) and tumor necrosis factor (TNF) inhibits loss of tissue attachment in experimental Periodontitis.** [The inflammatory response is effective in preventing large-scale colonization of the gingival tissues by bacteria that lie in close proximity to the tooth surface or within the gingival sulcus. It has been postulated that the host-response in some individuals may lead to an over-reaction to invading oral pathogens resulting in the destruction of periodontal tissues.] http://www.blackwell-synergy.com/links/doi/10.1034/j.1600-051x.2001.028003233.x/abs/

1029. **Spokesman for the American Heart Association confirms the link between Perio and Heart Disease** – Healthday News, November 29 2005- ["People who have chronic infections -- and gum disease is one of the major chronic infections -- are at increased risk later in life for atherosclerosis (hardening of the arteries) and coronary heart disease," said American Heart Association spokesman Dr. Richard Stein] http://health.yahoo.com/news/141399;_ylt=Ahq5pJAqH2GCLGes3r4j7NX3tMUF

1030. **Systemic inflammation caused by chronic periodontitis in acute ischemic heart attack patients.** [OBJECTIVE: Infectious and inflammatory processes mediated by bacteria in distant sites have been described as a risk factor for acute ischemic heart disease (AIHD). METHODS: One hundred one patients with AIHD with and without chronic periodontitis (CP) were included in this study. Patients were admitted to the HC UNICAMP and stratified into three groups: in group 1, we selected patients with severe chronic periodontitis (31 men and 19 women, mean age 55.1 ± 11.29 years old); the group 2 with mild chronic periodontitis (40 men and 28 women, mean age 54.8 ± 10.37 years old) and group 3 represented by the toothless (43 men and 20 women, mean age 67.5 ± 8.55 years old). Blood samples were collected to measure the lipid profiles, hematological and blood glucose levels. In addition, biopsies of seventeen coronary arteries with atherosclerosis and an equal number of internal mammary arteries without atherosclerotic degeneration in group 1 were investigated. Statistical analysis by analysis of variance (ANOVA) and Scheffé test for multiple comparisons was performed. RESULTS: Triglyceride and LDL levels were elevated in group 1 than in group 2. HDL were reduced by 20% in group 1 and remained reduced by 8% in toothless. Blood glucose was higher in group 1. DNA of periodontal bacteria was detected in 58.8% of the coronary arteries. ONCLUSIONS: Patients with (AIHD) and severe chronic periodontitis may have altered lipid profile, as well as microorganisms associated with CP can permeate into coronary vessels.] de Oliverira F, Vieira RW, et al. Rev Bras Cir Cardiovasc vol.25 no.1 São José do Rio Preto Jan./Mar. 2010. http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0102-76382010000100013&lng=en&nrm=iso&tlng=en

1031. **The antimicrobial treatment of periodontal disease: changing the treatment paradigm.** [The recent observations that periodontal infections increase the risk of specific systemic health problems, such as cardiovascular disease, argue for the prevention and elimination of these periodontal infections. W.J. Loesche, Critical Reviews in Oral Biology & Medicine, Vol 10, 245-275. http://crobm.iadrjournals.org/cgi/content/abstract/10/3/245

1032. **The Concept of "Risk" and the Emerging Discipline of Periodontal Medicine.** [While the link between systemic disease and periodontitis was thought to be unidirectional, mounting evidence in the last decade suggests that the relationship may be bi-directional. Periodontitis triggers both local and systemic host inflammatory responses. A central hypothesis of periodontal medicine states that periodontal infection presents a chronic inflammatory burden at the systemic level. In addition to their products, whole bacterial pathogens can enter local host tissues where pocket epithelial integrity has been lost. Perio pathogens have evolved virulence factors that allow for direct tissue invasion. Systemic exposures to gram-negative pathogens, LPS and other products can trigger mediator expression and inflammatory events with consequences related to other organ systems. PGE2 causes oxidative stress, smooth muscle contraction and LDL oxidation. Cytokines IL-1b, TNFa and interleukin 6 (IL-6) can stimulate endothelial adhesion, hyperlipemia, metabolic wasting, hepatic release of acute phase reactants and connective tissue catabolism. Many of these events have been implicated in the natural histories of systemic conditions like cardiovascular disease and preterm low-birth weight.] Paquette DW, Madianos P., *The Journal of Contemporary Dental Practice*, Vol. 1 No. 1, Fall 1999. http://www.thejcdp.com/issue001/paquette/paquette.pdf

1033. **The effect of periodontal disease on medical and dental costs in a middle-aged Japanese population: a longitudinal worksite study.** [BACKGROUND: Although periodontal disease is one of the most common chronic diseases, it is not clear whether periodontal disease is associated with increased health care costs. The authors examined the effect of periodontal disease on medical and dental costs and use for 3.5 years prospectively. METHODS: The data were derived from health and dental examinations and health insurance claims of 4,285 Japanese civil officers aged 40 to 59 years. The subjects were divided into three categories: no pathological pocket, moderate periodontitis, and severe periodontitis. Age, gender,

smoking, body mass index, and hypertension were adjusted in a multivariate analysis after excluding subjects with any history of liver disease, heart disease, or diabetes mellitus. RESULTS: The cumulative cost for subjects with severe periodontitis was approximately 21% higher than for subjects with no pathological pocket, and the hospital admission rates of subjects with severe periodontitis were highest (male: odds ratio [OR]=.34; 95% confidence interval [CI]: 1.00 to 1.80; female: OR=1.29; 95% CI: 0.75 to 2.20). In males, the annual hospital costs of subjects with severe periodontitis were 75% higher than for subjects with no pathological pocket. There was no clear trend identified for outpatient care. The annual dental visit rates and costs for subjects with severe periodontitis were highest in both genders. Periodontal disease might increase the medical care costs for diabetes mellitus, digestive disease, and liver disease. CONCLUSION: Periodontal disease may have played an important role in the cumulative health care cost increases in middle-aged adults over a period of only a few years.] Ide R, Hoshuyama T, et al. *J Periodontol*. 2007 Nov;78(11):2120-6. http://www.ncbi.nlm.nih.gov/pubmed/17970678

1034. **The effect of periodontal treatment on serum leptin, interleukin-6, and C-reactive protein.** [Background: Previous studies have suggested that periodontitis is closely related to obesity and metabolic syndrome. Leptin, a pleiotrophic hormone produced by adipose tissue, has been reported to be related to periodontitis. This study investigated the effects of periodontal treatment on the serum levels of leptin and other cytokines in patients with chronic periodontitis (CP). Methods: Serum samples were taken from 33 CP patients (22 non-smokers, 11 smokers) and 18 healthy subjects. The serum leptin, adiponectin, tumor necrosis factor (TNF)-alpha, interleukin (IL)-6, and C-reactive protein (CRP) levels were measured before and after non-surgical periodontal treatment. Results: Significant differences between healthy and CP patients were found in serum leptin, IL-6, and CRP levels (P = 0.0018, P = 0.0064, and P = 0.0095, respectively). The serum leptin level was associated with mean probing pocket depth, mean clinical attachment level, mean alveolar bone loss and BMI. There were significant associations between serum leptin levels and IL-6 and CRP levels. After non-surgical periodontal treatment, serum leptin, IL-6, and CRP levels were significantly decreased (mean +/- SD; before, after, p-value, respectively; leptin, 8.02 +/- 5.5, 7.10 +/- 4.4, P = 0.015; IL-6, 1.73 +/- 1.02, 1.36 +/- 0.73, P = 0.048; CRP, 802.0 +/- 1065, 491.2 +/- 479.3, P = 0.047). Conclusion: Periodontal treatment is effective in reducing serum leptin, IL-6, and CRP levels. The results suggest that leptin, IL-6, and CRP could be mediating factors that connect metabolic syndrome and periodontitis.] Shimada Y, Komatsu Y, et al. *J Periodontol.* 2010 Apr 6 http://www.ncbi.nlm.nih.gov/pubmed/20370420

1035. **The Epidemiology, Consequences and Management of Periodontal Disease in Older Adults.** [Background. This review summarizes the literature on periodontal disease (PD) in older adults. The authors focused on significant sequelae of PD and therapy in this population. Types of Studies Reviewed. The authors conducted a search on PubMed for human studies using the terms "periodontal disease OR periodontitis" and "older adults." They retrieved 649 articles and excluded studies that had poor experimental design. For each topic of the review, they selected one to three of the most recent studies or reviews for inclusion and cited classic articles where appropriate. Results. PD is a common oral chronic inflammatory disease often found in older adults. In older patients, PD may lead to root caries, impaired eating and socialization. It also may increase patients' risk of developing systemic diseases such as diabetes mellitus, lung disease, heart disease and stroke. Treatment is not limited by chronological age but depends on the patient's medical and emotional status and the availability of financial resources. Clinical Implications. General dentists usually can treat the majority of older people with mild or moderate PD. For older adults who are medically compromised and dependent, the literature supports treatment that prevents PD progression.] Boehm TK, Scannapieco FA. J Am Dent Assoc, Vol 138, No suppl_1, 26S-33S. http://jada.ada.org/cgi/content/full/138/suppl_1/26S

1036. **The Junctional Epithelium: from Health to Disease.** [The junctional epithelium is located at a strategically important interface between the gingival sulcus, populated with bacteria, and the periodontal soft and mineralized connective tissues that need protection from becoming exposed to bacteria and their products. Its unique structural and functional adaptation enables the junctional epithelium to control the constant microbiological challenge. The antimicrobial defense mechanisms of the junctional epithelium, however, do not preclude the development of gingival and periodontal lesions. The conversion of the junctional to pocket epithelium, which is regarded as a hallmark in disease initiation, has been the focus of intense research in recent years. Research has shown that the junctional epithelial cells may play a much more active role in the innate defense mechanisms than previously assumed. They synthesize a variety of molecules directly involved in the combat against bacteria and their products. In addition, they express molecules that mediate the migration of polymorphonuclear leukocytes toward the bottom of the gingival sulcus. Periodontopathogens—such as *Actinobacillus actinomycetemcomitans* or, in particular, *Porphyromonas gingivalis*—have developed sophisticated methods to perturb the structural and functional integrity of the junctional epithelium. Research has focused on the direct effects of gingipains, cysteine proteinases produced by *Porphyromonas gingivalis*, on junctional epithelial cells. These virulence factors may specifically degrade components of the cell-to-cell contacts. This review will focus on the unique structural organization of the junctional epithelium, on the nature and functions of the various molecules expressed by its cells, and on how gingipains may attenuate the junctional epithelium's structural and functional integrity.] Bosshardt DD, Lang NP. *J of Dental Res*, Vol 84, No. 1, 9-20(2005). http://jdr.sagepub.com/cgi/content/abstract/84/1/9

1037. **The Management of Inflammation in Periodontal Disease.** [It has become clear in recent years that periodontitis is an inflammatory disease initiated by oral microbial biofilm. This distinction implies that it is the host response to the biofilm that destroys the periodontium in the pathogenesis of the disease. As our understanding of pathways of inflammation has matured, a better understanding of the molecular basis of resolution of inflammation has emerged. Resolution of inflammation is an active, agonist-mediated, well-orchestrated return of tissue homeostasis. There is an important distinction

between anti-inflammation and resolution; anti-inflammation is pharmacologic intervention in inflammatory pathways, whereas resolution is biologic pathways restoring homeostasis. A growing body of research suggests that chronic inflammatory periodontal disease involves a failure of resolution pathways to restore homeostasis. This article reviews the resolution of inflammation in the context of periodontal disease and the potential for the modification of resolution pathways for the prevention and treatment of periodontal diseases. Proof-of-concept studies in the 1980s demonstrated that pharmacologic anti-inflammation prevented and slowed the progression of periodontal diseases in animals and man. However, the side-effect profile of such therapies precluded the use of non-steroidal anti-inflammatory drugs or other enzyme inhibitors or receptor antagonists in periodontal therapy. The isolation and characterization of resolving agonist molecules has opened a new area of research using endogenous lipid mediators of resolution as potential therapeutic agents for the management of inflammatory periodontitis. Work in animal models of periodontitis has revealed the potential of this therapeutic approach for its prevention and treatment and forced the reconsideration of our understanding of the pathogenesis of human periodontal diseases.] VanDyke TE. *Journal of Periodontology, 2008, Vol. 79, No. 8s, Pages 1601-1608.* http://www.joponline.org/doi/full/10.1902/jop.2008.080173

1038. **The oral-medical connection - Exploring our role as health care providers.** [Periodontal disease is a chronic infectious disease that has been postulated to affect other chronic conditions through various pathways, including the generation of inflammatory mediators, by direct effect of bacterial colonization, or as a result of toxins produced by periodontal pathogens. Thousands of articles have discussed periodontal disease and its association with heart disease, stroke, pneumonia, preterm births, low–birth weight babies, osteopenia, osteoporosis and diabetes mellitus.] Michael Glick, Editor, *J Am Dent Assoc*, Vol 136, No 6, 716-718. http://jada.highwire.org/cgi/content/full/136/6/716

1039. **The role of gingival crevicular fluid and salivary interstitial collagenases in human periodontal diseases** [Interstitial collagenases (matrix metalloproteinase-1, EC 3.4.24.7), isolated from extracts of inflamed human gingiva, gingival crevicular fluid and saliva were characterized for their molecular weight, proteolytic and non-proteolytic activation and substrate specificity against soluble collagen types I, II and III. All three collagenases had Mr of 70 K. The enzymes existed predominantly in a latent form that could be activated by aminophenylmercuric acetate, gold thioglucose and hypochlorous acid. Among serine proteases tested, trypsin, chymotrypsin, neutrophil cathepsin G and a combination of trypsin and human gingival fibroblast prostromelysin activated gingival and salivary interstitial collagenases. Plasmin and plasma kallikrein, however, were relatively ineffective activators. The collagenases degraded soluble type I and II collagens at apparently equal rates but considerably faster than they did type III collagen. These findings suggest that the characteristics of interstitial collagenases found in inflamed human gingiva, gingival crevicular fluid and saliva are consistent with those of human neutrophil interstitial collagenase rather than the fibroblast-type interstitial collagenase. Thus, neutrophils are suggested to be the main source of such enzymes in inflamed human gingiva, crevicular fluid and saliva during adult periodontitis.] Sorsa T, Suomalainen K, et al. *Archives of Oral Biology*, Jan 2, 1990; 35 Suppl:193s-196s. https://www.researchgate.net/publication/21191123_The_role_of_gingival_crevicular_fluid_and_salivary_interstitial_collagenases_in_human_periodontal_diseases

1040. **Transmission of *Porphyromonas gingivalis* between spouses.** [*P. gingivalis* can be transmitted between spouses.] http://www.blackwell-synergy.com/doi/abs/10.1111/j.1600-051X.1993.tb00370.x

1041. **Understanding and Managing Periodontal Diseases: A Notable Past, a Promising Future.** [Throughout the 20th century, an understanding of the role of causative bacteria and the susceptible host in the initiation and progression of periodontal disease(s) has emerged from the research efforts of scientists and clinicians worldwide. Over time, specific bacterial types, such as *Porphyromonas gingivalis*, were discovered and shown to be important in the cause of periodontal disease. At the same time, inflammatory mediators, such as prostaglandins and interleukins, and enzymes, such as matrix metalloproteinases, were discovered and found to be important participants in the destruction of periodontal tissues. Acquired and inherited environmental risk factors began to emerge that could explain, in part, the susceptibility of individuals to periodontal disease. The discovery of antibiotics, beginning with sulfanilamide, penicillin, and streptomycin, led to additional strategies for managing periodontal disease. With the discovery of the mechanism of action of aspirin, scientists began to develop new strategies for treating diseases that focused on controlling inflammation. Thus, host-modulating therapies emerged for the management of periodontal disease through the control of inflammation. At the end of the 20th century, an old concept in medicine and dentistry reappeared: that the infection and inflammation of periodontal disease in the mouth could reach distant sites via the bloodstream. Apparently oral disease could, in fact, contribute to systemic diseases, such as atherosclerosis, diabetes, and adverse outcomes in pregnancy. This concept of the oral health–general health connection is now supported by sound and rational evidence-based observations. Clearly, the 21st century has arrived with a new understanding of the nature of periodontal diseases based on a notable era of discovery. There is a promising future for preventing and treating this common and troubling condition that affects not just the mouth but also the whole body.] Williams RC. *Journal of Periodontology, 2008, Vol. 79, No. 8s, Pages 1552-1559.* *http://www.joponline.org/doi/full/10.1902/jop.2008.080182*

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1042. **Antimicrobials for the treatment of aggressive periodontitis.** [Aggressive periodontitis is characterized by a considerable attachment loss over a relatively short period of time. It may be the consequence of either the presence of highly

aggressive pathogens or a highly susceptible host. In the first case, the use of antimicrobials should be beneficial in the treatment of those patients. However, due to the organization of the micro-organisms as a biofilm, the increasing incidence of allergies and resistance against antimicrobials and their side-effects, there is still controversy about their benefit in the treatment of periodontal disease. This paper discusses indications for the use of antimicrobials, the substances prescribed and the type of application under the conditions of aggressive periodontitis.] Dorfer CE. *Oral Dis*. 2003;9 Suppl 1:51-3. http://www.ncbi.nlm.nih.gov/pubmed/12974531

1043. **Antioxidative activities of some chemotherapeutics. A possible mechanism in reducing gingival inflammation.** [Inflammatory periodontal diseases are related to dental plaque formation. Increase in the perfusion of the inflamed tissue results in increased oxygen supply. Although oxygen has healing effects, it is bound to be a mediator of peroxidation in biological membranes. Chemotherapeutic agents such as chlorhexidine, listerine, sanguinarine, and cetylpridinium chloride and oral antibiotics such as tetracycline HCl and doxycyline were tested for their antioxidative activities. While doxycycline has the highest antioxidant activity in lower volumes (0.1 ml), sanguinarine, listerine and a pace after them, tetracycline HCl, had similar effects in higher volumes (0.3 and 0.4 ml). The results showed that in addition to their antiseptic or antimicrobial effects, these preparations have an antioxidative activity against spontaneous oxidation.] Firatli E, Unal T, et al. J Clin Periodontol. 1994 Nov;21(10):680-3. http://www.ncbi.nlm.nih.gov/pubmed/7852612

1044. **Chemically modified tetracyclines act through multiple mechanisms directly on osteoclast precursors.** [Chemically modified tetracyclines (CMTs) are thought to inhibit bone resorption primarily through their ability to inhibit matrix metalloproteinases (MMPs). We have previously demonstrated that some tetracycline compounds (TCs) induce apoptosis in mature rabbit osteoclasts and inhibit osteoclastic resorption in mouse osteoblast/marrow co-cultures in vitro. In this report, we now show that non-antibiotic analogues of doxycycline (CMT-3) and minocycline (CMT-8) are potent inhibitors of osteoclastogenesis in vitro from human peripheral blood mononuclear cells (PBMC) stimulated with macrophage colony stimulating factor (MCSF) and receptor activator of NF-kappaB ligand (RANKL), through an action that is independent of osteoblast-osteoclast interactions. Osteoclast formation over 20 days was completely abrogated when CMT-3 or CMT-8 were included in PBMC cultures at a concentration of 250 ng/ml, although doxycycline at this concentration reduced osteoclast formation to ca. 50% of control. CMT-3 and CMT-8 also significantly induced apoptosis over 24 h in mature osteoclasts generated over 20 days when added to cultures at 5 microg/ml or more. In a time-course experiment, apoptosis was evident after a delay of 1-2 h following treatment of mature osteoclasts with CMT-3 at 20 microg/ml. The broad-spectrum MMP inhibitor BB94 (Batimastat) did not recapitulate the apoptosis induced by CMT-3, even at a concentration where MMP-13 activity was completely inhibited. There was no evidence for an anabolic effect of any of the TCs on osteoblast lineage cells in a calcifying fibroblastic colony (CFU-f) formation assay, where CMT-3 partially inhibited CFU-f formation at 5 microg/ml. Our data indicate that inhibition of osteoclast formation and induction of osteoclast apoptosis are pharmacologically significant actions of CMTs in inhibiting bone resorption, and that osteoclast apoptosis cannot be attributed to the ability of CMTs to inhibit MMPs or to actions mediated by osteoblastic lineage cells.] Holmes SG, Still K, et al. *Bone.* 2004 Aug;35(2):471-8. **http://www.ncbi.nlm.nih.gov/pubmed/15268899**

1045. **C-reactive protein changes during Perio Protect treatment of periodontal disease.** [Objective: Pilot study to monitor blood levels of C-reactive protein (CRP) while treating periodontal disease in patients with and without co-morbidities. Methods: A retrospective analysis of clinical records from January 1-August 1, 2006 from a general dental practice was performed. Records with complete documentation and informed consent were included in the study. The resulting 29 patient sample included 19 females, 6 smokers, 2 patients with diabetes, 8 patients with cardiac disease and an age of 52.9+12.6 years. Three patients exhibited no periodontal disease, 3 had gingivitis, and 23 had periodontitis. All patients with signs of periodontal disease began treatment on day 1 (baseline) with the Perio Protect Method per established guidelines. Blood CRP samples were taken at day 1 and 14 days later through a standard clinical analysis (QuikRead CRP, Orion Diagnostica). All CRP values in the normal range were assigned a “4” for subsequent data analysis. Descriptive statistics were used to describe group differences. Results: In the no periodontal disease group, the baseline and 14 day CRP values were 4 mg/L. In the gingivitis group, baseline CRP values were 8.0+5.3mg/L (range=4-16) while 14 day CRP values were 4.0+0.0mg/L. In the periodontitis group, baseline CRP values were 7.7+5.7mg/L (range=4-27) while 14 day CRP values were 4.6+1.4mg/L (range=4-10). All normal values at baseline regardless of group stayed normal at 14 days. The baseline CRP values for smokers were 8.5+4.8mg/L (range=4-16) while 14 day CRP values were 4.3+0. mg/L (range=4-5). For the 10 patients with diabetes or cardiac disease, 100% of the baseline CRP readings were greater than normal (9.7+6.9mg/L; range=5-27). At 14 days, 70% were within normal (4.6+1.1mg/L; range=4-7) for an average decrease of 5.1+6.9mg/L (range=0-23). Conclusion: The Perio Protect Method produced a decrease in 14 days in the blood CRP levels in all patient population groups examined.] Steele C. Sindelar GJ, Keller DC. Abstract: #1195: 2007 IADR General Session & Exhibition. http://iadr.confex.com/iadr/2007orleans/techprogram/abstract_92806.htm

1046. **Effects of hyperbaric oxygen on aggressive periodontitis and subgingival anaerobes in Chinese patients.** [Objective: To investigate the effects of hyperbaric oxygen (HBO2) on aggressive periodontitis (AgP), and subgingival obligate anaerobes in Chinese patients. MATERIALS AND METHODS: Sixty cases of Chinese patients with AgP were randomly divided into two groups -the HBO2 group (30 cases) and the control group (30 cases). Study teeth were divided into four groups -: the HBO2 therapy, the HBO2 + scaling scaling group, the scaling group and the control group. Subgingival anaerobic organisms were measured with anaerobic culture, and number of obligate anaerobes and facultative anaerobes and Bacteroides melaninogenicus was counted. Comparisons of changes in the clinical indices, and subgingival anaerobes were made between the groups. RESULTS: Highly significant differences in gingival index (GI), probing depth

(PD), attachment loss (AL), and Plaque index (PLI), and tooth odontoseisis (TO) were seen in the HBO2, the HBO2 + scaling and the scaling groups when compared with the control group ($P<0.01$). The number of subgingival anaerobes as well as the types of obligate anaerobes and facultative anaerobes and the number of Bacteroides melaninogenicus were reduced markedly in these three treatment groups. Highly statistical differences in clinical indices, subgingival anaerobe number and types of obligate anaerobes and facultative anaerobes and Bacteroides melaninogenicus were found when comparisons were made between the HBO2 + scaling and the HBO2 groups, as well as between the HBO2 + scaling and the scaling groups. Clinical follow-ups indicated that the GI, PD, AL, TO, PLI and subgingival anaerobes number of the three therapeutic groups were reduced more severely than the control group. CONCLUSIONS: HBO2 had good therapeutic effects on Chinese patients with AgP. HBO2 therapy combined with scaling and root planing was the most beneficial in the treatment of AgP. The therapeutic effect of HBO2 on AgP is most likely through inhibition of the growth of subgingival anaerobes. Clinical follow-ups suggest that the effect could last more than 2 years.] Chen TL, Xy B, et al. J Indian Soc Periodontol. 2012 Oct;16(4):492-7. doi: 10.4103/0972-124X.106880. http://www.ncbi.nlm.nih.gov/pubmed/23493978

1047. **Evidence for Antibody-Catalyzed Ozone Formation in Bacterial Killing and Inflammation.** [Recently we discovered that antibodies catalyze the generation of hydrogen peroxide (H_2O_2) from singlet molecular oxygen ($^1O_2$*) and water. Here we show this process can lead to efficient killing of bacteria, regardless of the antigen specificity of the antibody. H_2O_2 production by antibodies was not alone sufficient for bacterial killing and further studies suggested that the antibody-catalyzed water-oxidation pathway produced an additional molecular species with a chemical signature similar to that of ozone. This species is also generated during the oxidative burst of activated human neutrophils and during inflammation. These observations suggest that alternative pathways may exist for biological killing of bacteria that are mediated by potent oxidants new to biology.] Wentworth P, McDunn JE, et al. *Science* 298/5601/2195. http://www.sciencemag.org/cgi/content/short/298/5601/2195

1048. **Hydrogen peroxide: a review of its use in dentistry.** [Several dentifrices that contain hydrogen peroxide are currently being marketed. The increased use of bleaching agents containing (or generating) H2O2 prompted this review of the safety of H2O2 when used in oral hygiene. Daily exposure to the low levels of H2O2 present in dentifrices is much lower than that of bleaching agents that contain or produce high levels of H2O2 for an extended period of time. Hydrogen peroxide has been used in dentistry alone or in combination with salts for over 70 years. Studies in which 3% H2O2 or less were used daily for up to 6 years showed occasional transitory irritant effects only in a small number of subjects with preexisting ulceration, or when high levels of salt solutions were concurrently administered. In contrast, bleaching agents that employ or generate high levels of H2O2 or organic peroxides can produce localized oral toxicity following sustained exposure if mishandled. Potential health concerns related to prolonged hydrogen peroxide use have been raised, based on animal studies. From a single study using the hamster cheek pouch model, 30% H2O2 was referred to as a cocarcinogen in the oral mucosa. This (and later) studies have shown that at 3% or less, no cocarcinogenic activity or adverse effects were observed in the hamster cheek pouch following lengthy exposure to H2O2. In patients, prolonged use of hydrogen peroxide decreased plaque and gingivitis indices. However, therapeutic delivery of H2O2 to prevent periodontal disease required mechanical access to subgingival pockets. Furthermore, wound healing following gingival surgery was enhanced due to the antimicrobial effects of topically administered hydrogen peroxide. For most subjects, beneficial effects were seen with H2O2 levels above 1%.**]** Marshall MV, Cancro LP, Fischman SL. *J Periodontol.* 1995 Sep;66(9):786-96. http://www.ncbi.nlm.nih.gov/pubmed/7500245

1049. **Initial Study of the Perio Protect™ Treatment for Periodontal Disease.** [A new treatment regimen, Perio Protect Method™, is being used to treat all stages of periodontal disease. While subjective clinical response has been positive, no studies have systematically examined this method that uses prescription trays to direct medications into the gingival sulcus. Objective: To evaluate outcomes of the Perio Protect Method™. Methods: A retrospective analysis compared pre-treatment and six months post-treatment records for 11 patients with periodontal disease and 2 with gingivitis (56.2±10.1 years; 8 females, 3 males; 5 smokers =39%). Sequential subjects with at least one molar in all quadrants and no standard periodontal treatment for 6 months pre-study were chosen to complete 6 months of the Perio Protect™ program. Disease severity was assessed by probing pocket depth (PPD) and bleeding and established treatment frequency and duration. Teeth exhibiting the worst symptoms of periodontal disease (PPD=5.7±1.8; range= 4-9) and those with the least evidence of disease (PPD=1) were considered in the subsequent analysis. Data was analyzed using paired t-tests. Results: Nine patients exhibited bleeding pre-treatment (20.7±14.0 sites). A significant decrease occurred post-treatment with only three patients exhibiting bleeding (2.7±4.4 sites; p=0.002). No patients developed any new bleeding sites post-treatment. A significant change in PPD occurred in the most severely diseased teeth with post-treatment PPD of 3.0±2.1 ($p<0.0001$). The percentage of closed pockets (PPD≤3 mm) in this group post-treatment was 70.8%. All teeth in the least severe range stayed within the normal range post-treatment (PPD≤3 mm). Conclusions: Treatment outcomes indicate the Perio Protect Method™ is effective in treating periodontal disease. Further studies are necessary to examine its effect on different patient populations over longer treatment times and to compare it to gold standard treatments.] Wentz LE, Blake AM, Keller DC, et al. Abstract: 2006 AADR and ADEA Annual Meeting. March 2006 http://iadr.confex.com/iadr/2006Orld/techprogram/abstract_75553.htm

1050. **Intracellular production and extracellular release of oxygen radicals by PMNs and oxidative stress on PMNs during phagocytosis of periodontopathic bacteria.** [Abstract In this study we investigated intracellular and extracellular oxygen radical production by polymorphonuclear leukocytes (PMNs) during the phagocytosis of periodontopathic bacteria. In in vitro assays, bacteria of the species *Porphyromonas gingivalis*, *Actinobacillus actinomycetemcomitans*, and *Fusobacterium nucleatum* were phagocytosed at 37°C for 4 h by purified peripheral human PMNs from healthy subjects (*n* =

6). Superoxide production during phagocytosis was determined by flow cytometry and with a fluorescence/luminescence microplate reader. After phagocytosis, oxidative stress was determined by flow cytometry. Both the intracellular and extracellular oxygen radical production by PMNs phagocytosing *F. nucleatum* was significantly greater than that of PMNs phagocytosing *P. gingivalis* and *A. actinomycetemcomitans*. Moreover, after 4 h of incubation, the oxidative stress of PMNs phagocytosing *F. nucleatum* was significantly greater than that of PMNs phagocytosing *P. gingivalis* and *A. actinomycetemcomitans*. We conclude that a high level of superoxide production by PMNs may damage not only periodontopathic bacteria but also PMNs themselves, and may be correlated with the destruction of periodontal tissue.] Katsuragi H, Ohtake M, et al. *Odontology*, Vol 91, No. 1, pp 13-18, Sept, 2003. http://www.springerlink.com/content/030d36dlnhj4b966/

1051. **Local delivery of antimicrobials: a new era in the treatment of adult periodontitis.** [This article discusses the principles, products, and techniques currently available for local delivery of antimicrobials in the treatment of adult periodontitis. Four principles provide the scientific basis for the treatment of periodontitis: it is caused by bacteria; it cannot be cured, but it can be controlled; clinicians cannot remove all the plaque and calculus; and periodontitis reinfects. This article stresses how the local delivery of antimicrobials can help the clinician achieve the goals of arresting the disease and maintaining the disease in the arrested or controlled state. Rationales for reevaluating the treated patient and treatment options are presented. Local-delivery systems are reviewed, stressing those available in the United States. Pharmacokinetics, multicenter randomized trials, and techniques are presented.] Killoy WJ. *Compend Contin Educ Dent. 1999*;20(4 Suppl):13-8; quiz 34-5. http://www.ncbi.nlm.nih.gov/pubmed/11908359

1052. **Low-dose doxycycline prevents inflammatory bone resorption in rats.** [Matrix metalloproteinases (MMP) are considered to be key initiators of collagen degradation, thus contributing to bone resorption in inflammatory diseases. We determined whether subantimicrobial doses of doxycycline (DX) (< or =10 mg kg-1 day-1), a known MMP inhibitor, could inhibit bone resorption in an experimental periodontitis model. Thirty male Wistar rats (180-200 g) were subjected to placement of a nylon thread ligature around the maxillary molars and sacrificed after 7 days. Alveolar bone loss (ABL) was measured macroscopically in one hemiarcade and the contralateral hemiarcade was processed for histopathologic analysis. Groups of six animals each were treated with DX (2.5, 5 or 10 mg kg-1 day-1, sc, 7 days) and compared to nontreated (NT) rats. NT rats displayed significant ABL, severe mononuclear cell influx and increase in osteoclast numbers, which were significantly reduced by 5 or 10 mg kg-1 day-1 DX. These data show that DX inhibits inflammatory bone resorption in a manner that is independent of its antimicrobial properties.] Bezerra MM, Brito GA, et al. *Braz J Med Biol Res*. 2002 May;35(5):613-6. http://www.ncbi.nlm.nih.gov/pubmed/12011948

1053. **Osteoblast-like cells complete osteoclastic bone resorption and form new mineralized bone matrix in vitro.** [Bone remodeling involves old bone resorption by osteoclasts and new bone formation by osteoblasts. However, the precise cellular mechanisms underlying these consecutive events remain obscure. To address this question in vitro, we have established a cell culture model in which the resorption lacunae are first created by osteoclasts and osteoblast-like cells accomplish the subsequent bone formation. We isolated osteoclasts from rat bone marrow and cultured them on bovine bone slices for 48 hours to create resorption lacunae. After removing osteoclasts, confluent differentiated primary osteoblast cultures were trypsinized and the cells were replaced on the resorbed bone slices for up to 14 days. The cultures were then examined by confocal microscopy, field emission scanning electron microscopy (FESEM), and transmission electron microscopy (TEM). Our data suggest that after osteoclastic bone resorption, osteoblast-like cells, not macrophages, remove the remaining organic matrix in the lacuna. After cleaning the lacuna, osteoblast-like cells deposit new collagen fibrils at the bottom of the lacuna and calcify the newly formed matrix only, as visualized by labeled tetracycline accumulation merely in the lacuna during the osteoblast culture. Furthermore, an electron-dense layer rich in osteopontin separates the old and new matrices suggesting formation of the cement line. Since the morphology of the newly formed matrix is similar to the natural bone with respect to the cement line and osteoid formation as well as matrix mineralization, the present method provides for the first time a powerful in vitro method to study the cellular mechanisms leading to bone remodeling also in vivo. Mulari MT, Qu Q, et al. *Calcif Tissue Int*. 2004 Sep;75(3):253-61. http://www.ncbi.nlm.nih.gov/pubmed/15148559

1054. **Periodontal antimicrobials: finding the right solutions.** [Strengthened by promising research data and commercial backing, interest in the field of anti-infective periodontal therapy is rapidly expanding. Management of the periodontal microbiota with antibiotic drugs and antiseptic agents in conjunction with mechanical debridement seems to be more effective than mechanical therapy alone, at least in the treatment of advanced periodontal disease. The choice of a periodontal chemotherapeutic regimen requires an understanding of the usual infecting flora, available antimicrobial agents, and pathogen susceptibility patterns. Systemic administration of combinations of metronidazole and either amoxicillin or ciprofloxacin has been widely used with great success; however the presence of subgingival yeasts and resistant bacteria can be a problem in some periodontitis patients. Valuable antiseptic agents for subgingival application include 10% povidone-iodine for professional use and 0.1-0.5% sodium hypochlorite for patient self-care. These antiseptics have significantly broader spectra of antimicrobial action, are less likely to induce development of resistant bacteria and adverse host reactions, and are considerably less expensive than commercially available antibiotics in controlled release devices. In practice, mechanical debridement combined with subgingival povidone-iodine application in the dental office and sodium hypochlorite irrigation for patient self-care are valuable antimicrobial remedies in the treatment of virtually all types of periodontal disease. Management of moderate to severe periodontitis may require additional systemic antibiotic and/or surgical treatment.] Jorgensen MG, Aalam A, Slots J. *Int. Dent J*, 2005, Vol. 55, No 1, pp. 3-12. http://cat.inist.fr/?aModele=afficheN&cpsidt=16531850

1055. **Periodontal therapy in humans. I. Microbiological and clinical effects of a single course of periodontal scaling and root planing, and of adjunctive tetracycline therapy.** [The present results showed that maarked and long-lasting changes in the subgingival microflora associated with periodontal disease could be achieved by a single course of periodontal treatment. Immediately following therapy, the total number of subgingival organisms decreased 10- to 100-fold and the proportions of cultivable Gram negative organisms and anaerobic organisms generally decreased 3- to 4-fold or more. After treatment, most periodontal pockets were populated by a scant microflora predominated by facultative Actinomyces and Streptococcus species. The kinetics of the subgingival bacterial recolonization revealed that the total cell counts and the proportions of spirochetes and Capnocytophaga species did not reach their pretreatment levels even after 6 months. Other Gram negative anaerobic species returned to pretreatment proportions after 3 to 6 months. Several Gram positive species exhibited higher posttreatment than pretreatment proportions throughout the 6 months study. The microbiological shifts paralleled significant changes in the clinical status of the periodontal tissues. Following therapy, the periodontal pocket depths decreased generally 1 to 4 mm, the gingival inflammatory index, the gingival fluid flow, and the suppurative index were generally lower, and nine of 33 test pockets examined showed apposition of alveolar bone. The microbiological and clinical changes described were exhibited by two patients treated with periodontal scaling and root planing alone and by two patients treated with the adjunctive use of systemic tetracycline therapy. In two other patients, mechanical periodontal therapy only slightly reduced the total number of subgingival organisms and the proportions of spirochetes and other Gram negative anaerobic rods. A shift in the subgingival microbial composition was achieved in these two patients after tetracycline therapy. The following model for treatment of periodontal disease is proposed: (1) Conventional therapy including thorough periodontal scaling and root planing; (2) Monitoring the subgingival flora and the clinical course; and (3) Use of antimicrobial therapy in refractory cases. Further studies are needed to develop means for rapid identification of refractory patients, and to determine the optimal antimicrobial agent, the optimal route of administration, and the optimal dosage regime.] Slots J, Mashimo P, et al. *J Periodontol.*. 1979 Oct;50(10):495-509. http://www.ncbi.nlm.nih.gov/pubmed/385821

1056. **Position Paper. Epidemiology of Periodontal Diseases.** [“5% to 20% of any population suffers from severe generalized periodontitis, even though moderate disease affects a majority of adults.” • “If the disease is defined as the identification of at least one site with clinical attachment loss (CAL) of 2 mm or more, around 80% of all adults are affected, and over 90% of those aged 55 to 64.8 “ • “When the case-definition is at least one site with CAL of 4 mm or more, the prevalence in those aged 55 to 64 drops to 64%.”] *J Periodontol* 1996;67:935-945.

1057. **Regulation of cytoplasmic calcium concentration in tetracycline-treated osteoclasts.** [The ability of low-dose tetracyclines to inhibit collagenase activity and inactivate osteoclasts suggests that these compounds have great potential as a prophylaxis for metabolic bone disease. However, the cellular mechanism by which tetracyclines interact with skeletal tissue is not yet clear. To better understand the effects of tetracyclines on bone metabolism, we examined their effect on osteoclast activity in vitro. Because tetracyclines can enter the cell and bind calcium and have been reported to directly interact with osteoclasts, we postulated that exposure to either of two tetracyclines, minocycline or doxycycline, would alter cytosolic Ca2+ regulation in rat osteoclasts. [Ca2+]i was measured in single rat osteoclasts utilizing fura-2. Addition of extracellular Ca2+ (5 mM CaCl2), a potent osteoclast inhibitor, increased [Ca2+]i in all osteoclasts, but 10(-6) M salmon calcitonin (sCT) did so only in a subpopulation of osteoclasts. Neither minocycline nor doxycycline (10 micrograms/ml) altered steady-state osteoclast [Ca2+]i. Further, neither minocycline nor doxycycline pretreatment affected the sCT-mediated increases in [Ca2+]i. However, tetracycline pretreatment significantly decreased the cytosolic Ca2+ response to extracellular CaCl2. Our results strongly suggest that tetracyclines have a specific effect on extracellular Ca(2+)-stimulated cytosolic Ca2+ mobilization in osteoclasts, which is not solely dependent on their ability to buffer Ca2+. Furthermore, these results point to the potential use of tetracyclines as probes to study cytosolic Ca2+ regulation. However, that tetracyclines attenuate a signal response associated with decreased osteoclastic resorption suggests that the reported antiresorptive attributes of tetracyclines must be achieved independently of an effect on osteoclastic cytosolic Ca2+.] Donahue HJ, Iijima K, et al. *J Bone Miner Res.* 1992 Nov;7(11):1313-8. **http://www.ncbi.nlm.nih.gov/pubmed/1466256**

1058. **Routine scale and polish for periodontal health in adults.** [BACKGROUND: Many dentists or hygienists provide scaling and polishing for patients at regular intervals, even if those patients are considered to be at low risk of developing periodontal disease. There is debate over the clinical effectiveness and cost effectiveness of 'routine scaling and polishing' and the 'optimal' frequency at which it should be provided. OBJECTIVES: The main objectives were: to determine the beneficial and harmful effects of routine scaling and polishing for periodontal health; to determine the beneficial and harmful effects of providing routine scaling and polishing at different time intervals on periodontal health; to compare the effects of routine scaling and polishing provided by a dentist or professionals complementary to dentistry (PCD) (dental therapist or dental hygienist) on periodontal health. … AUTHORS' CONCLUSIONS: The research evidence is of insufficient quality to reach any conclusions regarding the beneficial and adverse effects of routine scaling and polishing for periodontal health and regarding the effects of providing this intervention at different time intervals. High quality clinical trials are required to address the basic questions posed in this review.] Beirne P, Forgie A, et al. *Cochrane Database Syst Rev.* 2005 Jan 25;(1):CD004625. http://www.ncbi.nlm.nih.gov/pubmed/15674957

1059. **Scanning Electron Microscopy Study Confirms Effectiveness of Perio Protect Method™.** [One of the world’s leading microbiologists used scanning electron microscopy (SEM) to complete cellular evaluations to determine the effects of the Perio Protect Method™ on the infection causing subgingival biofilm. METHOD: Flexible polycarbonate carriers were placed into two 6 mm pockets and one 5mm pocket for 2 days allowing the subgingival biofilm to colonize the carrier.

Carriers were inserted before and during treatment using the Perio Tray™ with Perio Gel and Sumycin and subsequently examined by SEM at different time intervals and bacterial counts were completed (Schaudinn and Costerton). RESULTS: Cell analysis before treatment with the Perio Protect™ system determined the pocket ecosystem consisted of large numbers of fusiform-like bacteria, cocci-like, short rods and in one pocket, treponema-like. After two days using the Perio Tray most of the fusiform bacteria and treponema had disappeared. After 17 days there were less than .02% of the periopathogenic bacteria (99.98: kill) and what remained were some cocci-like and pleomorphic rods that were visible next to large numbers of eukaryotic cells. CONCLUSION: In this clinical case, the direct application of medication using the Perio Tray radically modifies the microbial ecosystem of periodontal pockets, so that only a few bacteria species and bacteria cells are capable of forming small colonies. SEM cell counts at 17 days determined that greater than 99.98% of the periopathogens were eradicated. The study confirms that the Perio Protect Method is effective in managing the microbial challenge by killing the periopathogens.] Keller DC, Costerton B. http://www.perioprotect.com/research.asp

1060. **The prevalence of Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, and Bacteroides forsythus in humans 1 year after 4 randomized treatment modalities.** [The relationship between probing attachment changes in treated periodontal pockets and the prevalence of selected periodontal pathogens was assessed in 10 patients with adult periodontitis 1 year following randomized therapy. All patients had at least 1 tooth in each quadrant with an inflamed pocket of probing depth > or =5 mm and clinical attachment loss and harbored at least one of the following 3 major periodontal pathogens: Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, or Bacteroides forsythus. The number of target organisms per site was determined preoperatively; at 1 week; and at 1, 3, 6, and 12 months postoperatively utilizing DNA probes. The following clinical parameters were measured and recorded preoperatively and at 1, 3, 6, and 12 months post-treatment: gingival fluid flow, gingival index, plaque index, probing depth, probing attachment level, gingival recession, and bleeding on probing. One quadrant in each patient was randomly assigned to 1 of the following 4 treatments: 1) scaling and root planing; 2) pocket reduction through osseous surgery and apically-positioned flap; 3) modified Widman flap; and 4) modified Widman flap and topical application of saturated citric acid at pH 1 for 3 minutes. All 4 treatments were rendered in one appointment using local anesthesia. No postoperative antibiotics were used, but patients rinsed with 0.12% chlorhexidine for the first 3 months postoperatively and received a prophylaxis every 3 months. This investigation revealed: 1) 30.0% of the sites were infected by at least 1 species at 3, 6, and 12 months postoperatively. 2) Failing sites were infected by a high number of both Pg and Bf These sites had a mean of 24.2+/-9.0 x 10(3) Pg and 93.1+/-42.0 X 10(3) Bf while stable sites had a mean of 6.8+/-0.5 x 10(3) Pg and 7.2+/-1.2 x 10(3) Bf (P = 0.06 and P = 0.05, respectively). 3) The infected sites lost significantly more mean clinical attachment at 12 months (1.5+/-0.5 mm compared to a loss of 0.2+/-0.3 mm for uninfected sites, P = 0.017). 4) The infected sites had a significantly greater BOP (67+/-14% versus 25+/-8% for uninfected sites at 12 months, P = 0.012). 5) The choice of treatment modality did not affect the prevalence of the target species at 1 year post-treatment. These results suggest that prevalence of microbial pathogens negatively affects the 1 year outcome of periodontal surgical and nonsurgical therapy.] Shiloah J, Patters MR, et al. *J Periodontol*. 1998 Dec;69(12):1364-72. http://www.ncbi.nlm.nih.gov/pubmed/9926766

Periodontal Disease

1061. **Essentials of Periodontal Medicine in Preventive Medicine.** [Influence of systemic disorders on periodontal diseases is well established. However, of growing interest is the effect of periodontal diseases on numerous systemic diseases or conditions like cardiovascular disease, cerebrovascular disease, diabetes, pre-term low birth weight babies, preeclampsia, respiratory infections and others including osteoporosis, cancer, rheumatoid arthritis, erectile dysfunction, Alzheimer's disease, gastrointestinal disease, prostatitis, renal diseases, which has also been scientifically validated. This side of the oral-systemic link has been termed Periodontal Medicine and is potentially of great public health significance, as periodontal disease is largely preventable and in many instances readily treatable, hence, providing many new opportunities for preventing and improving prognosis of several systemic pathologic conditions. This review article highlights the importance of prevention and treatment of periodontal diseases as an essential part of preventive medicine to circumvent its deleterious effects on general health.] Gulati M, Anand V, et al. *Int J Prev Med.* 2013 Sep;4(9):988-994. http://www.ncbi.nlm.nih.gov/pubmed/24130938

1062. **Prevalence of Periodontitis in Adults in the United States: 2009 and 2010.** [This study estimated the prevalence, severity, and extent of periodontitis in the adult U.S. population, with data from the 2009 and 2010 National Health and Nutrition Examination Survey (NHANES) cycle. Estimates were derived from a sample of 3,742 adults aged 30 years and older, of the civilian non-institutionalized population, having 1 or more natural teeth. Attachment loss (AL) and probing depth (PD) were measured at 6 sites per tooth on all teeth (except the third molars). Over 47% of the sample, representing 64.7 million adults, had periodontitis, distributed as 8.7%, 30.0%, and 8.5% with mild, moderate, and severe periodontitis, respectively. For adults aged 65 years and older, 64% had either moderate or severe periodontitis. Eighty-six and 40.9% had 1 or more teeth with AL $\geq$ 3 mm and PD $\geq$ 4 mm, respectively. With respect to extent of disease, 56% and 18% of the adult population had 5% or more periodontal sites with $\geq$ 3 mm AL and $\geq$ 4 mm PD, respectively. Periodontitis was highest in men, Mexican Americans, adults with less than a high school education, adults below 100% Federal Poverty Levels (FPL), and current smokers. This survey has provided direct evidence for a high burden of periodontitis in the adult U.S. population.] Eke PI, Eye BA, et al. *J Dent Res.* 2012 Oct;91(10):914-20. Epub 2012 Aug 30. http://www.ncbi.nlm.nih.gov/pubmed/22935673

1063. **Systemic Diseases Caused by Oral Infection**. [Recently, it has been recognized that oral infection, especially periodontitis, may affect the course and pathogenesis of a number of systemic diseases, such as cardiovascular disease, bacterial pneumonia, diabetes mellitus, and low birth weight. The purpose of this review is to evaluate the current status of oral infections, especially periodontitis, as a causal factor for systemic diseases. Three mechanisms or pathways linking oral infections to secondary systemic effects have been proposed: (i) metastatic spread of infection from the oral cavity as a result of transient bacteremia, (ii) metastatic injury from the effects of circulating oral microbial toxins, and (iii) metastatic inflammation caused by immunological injury induced by oral microorganisms. Periodontitis as a major oral infection may affect the host's susceptibility to systemic disease in three ways: by shared risk factors; subgingival biofilms acting as reservoirs of gram-negative bacteria; and the periodontium acting as a reservoir of inflammatory mediators. Proposed evidence and mechanisms of the above odontogenic systemic diseases are given.] Li X, Kolltveit KM, et al. *Clin Microbiol Rev.* 2000 Oct;13(4):547-58. http://www.ncbi.nlm.nih.gov/pubmed/11023956

Sleep Apnea

1064. **Obstructive sleep apnoea and periodontitis: a novel association?** [PURPOSE: Since both obstructive sleep apnoea (OSA) and periodontitis are associated with systemic inflammation and cardiovascular morbidity, we questioned whether there may be an association between these two disorders. MATERIALS AND METHODS: A standard periodontal examination was undertaken in a group of 66 (54 men and 12 women) treatment-naïve patients diagnosed with OSA [apnoea-hypopnoea index (AHI) >5/h] to derive a number of quantitative variables which could then be used to determine the prevalence of periodontitis in a group of patients. RESULTS: The prevalence of periodontitis in our study group was 77-79%, depending on the definition used. This was almost four times that of historical controls derived from a recent national survey. When sleep-related variables were compared against periodontal variables, significant correlations were found between periodontal **clinical** attachment level and total sleep time. CONCLUSION: Our pilot study suggests that OSA is associated with periodontitis. Further research is needed to elucidate the nature of this association.] Gunaratnam K, Taylor B, et al. Sleep Breath. 2009 Aug;13(3):233-9. doi: 10.1007/s11325-008-0244-0. Epub 2009 Feb 6. **http://www.ncbi.nlm.nih.gov/pubmed/19198909**

Pharmacology

1065. **Adverse effects of oral corticosteroids in relation to dose in patients with lung disease**. [*Background*—The adverse effects of oral corticosteroids are widely recognised but there are few quantitative data on which to base advice to patients. In a two part cross sectional study we compared adverse effects in patients with lung disease taking oral corticosteroids and control subjects and related the adverse effects to corticosteroid dose in the patient group. *Methods*—Data on oral corticosteroid use, lifestyle, fractures, and other possible adverse effects were collected by questionnaire and compared between a community based cohort of patients taking continuous or frequent intermittent oral corticosteroids for asthma, chronic obstructive pulmonary disease, or alveolitis and age and sex matched control subjects. Dose related effects were explored in the corticosteroid group using cumulative dose quartiles and multiple logistic regression. *Results*—A total of 367 patients (>50 years, 48% female) and 734 control subjects completed the questionnaire. The cumulative incidence of fractures since the time of diagnosis was 23% for patients taking oral corticosteroids and 15% in the control group (odds ratio (OR) 1.8; 95% confidence interval (CI) 1.3 to 2.6). Patients were more likely to have had a fracture of the vertebrae (OR 10; 95% CI 2.9 to 34), hip (OR 6; 95% CI 1.2 to 30), and ribs or sternum (OR 3.2, 95% CI 1.6 to 6.6) than control subjects. They also reported a significant increase in cataracts, use of antacids, muscle weakness, back pain, bruising, oral candidiasis, and having fewer teeth. The effects of oral corticosteroids were dose related: the odds ratio for patients in the highest compared with the lowest cumulative dose quartile (median prednisolone dose 61 g versus 5 g) ranged from 2 for all fractures to 9 for vertebral fractures and bruising. *Conclusions*—By quantifying the morbidity associated with the use of oral corticosteroids, this study should help to rationalise their long term use.] Walsh LJ, Wong CA, et al. *Thorax* 2001;56:279–284. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1746020/pdf/v056p00279.pdf

1066. **Current Oral Contraceptive Status and Periodontitis in Young Adults**. [Background: The aim of this study was to investigate the influence of current hormonal contraceptive medication on periodontal health in young females. Methods: Fifty women aged 20 to 35 years (mean ± SD: 29.7 ± 4.7 years) had a comprehensive periodontal examination. Current and previous contraceptive pill use was assessed by a questionnaire. Periodontal assessment included plaque index, gingival index, probing depth, and attachment level at six sites per tooth. The periodontal health of current pill users was compared to that of women not taking the pill. Results: Forty-two percent of subjects were taking the contraceptive pill at the time of periodontal examination. Current pill users had deeper mean probing depths compared to non-users (3.3 mm versus 2.7 mm; $P = 0.006$) and more severe attachment loss (2.6 mm versus 1.7 mm; $P = 0.015$). Pill users had more sites with bleeding on probing (44.0% versus 31.1%; $P = 0.017$). Conclusion: Current users of oral contraceptives had poorer periodontal health.] Mullally BH, Coulter WA. *Journal of Periodontology*, 2007, Vol. 78, No. 6, Pages 1031-1036. http://www.joponline.org/doi/abs/10.1902/jop.2007.060163

1067. **Oral health in patients on inhaled corticosteroid treatment**. [Objective: The aim of this study was to investigate the effects of long-term inhaled corticosteroids on bone mineral density (BMD) of the mandible in relation with the tooth loss. Design: Cross sectional analytic study. Subjects and methods: Patients ($n = 30$) with chronic obstructive pulmonary

disease under inhaled corticosteroid therapy for at least 1 year were compared with sex- and age-matched healthy controls (n = 30). BMD of the mandible was measured by dual-energy X-ray absorptiometry. The clinical examination included recording the number of teeth present together with periodontal condition. Levels of serum osteocalcin, alkaline phosphatase, calcium, phosphorus and cortisol were also assessed. Results: BMD of the mandible in patients on corticosteroid treatment was significantly lower than that in the control group (P = 0.001). Patients under treatment had more missing teeth than the control group but the difference did not reach statistical significance. The two groups exhibited similar clinical parameters of periodontal condition. Significantly lower levels of osteocalcin (P < 0.0001), calcium (P = 0.004) and cortisol (P = 0.03) were observed in the patients on corticosteroid treatment. Conclusion: Long-term use of inhaled corticosteroids may impair bone metabolism and lead to a marked decrease in the mandibular BMD.] Komerik N, Akkaya A, et al. *Oral Diseases*, Vol 11, issue 5, Pp 303-308. http://www3.interscience.wiley.com/journal/118666967/abstract

Subantimicrobial-Dose Doxycycline

1068. **Adjunctive Benefits of Subantimicrobial Dose Doxycycline in the Management of Severe, Generalized, Chronic Periodontitis.** [Background: Severe, generalized periodontitis is a form of chronic periodontitis that appears to be associated with an exaggerated host response. Little information is available on the benefits of using adjunctive host modulation in the management of this form of periodontal disease. Methods: Thirty subjects ≤ 45 years of age with severe, generalized periodontitis received subgingival debridement and oral hygiene instructions each week for 4 weeks, plus 6 months of adjunctive subantimicrobial doxycycline (SDD) or placebo. Periodontal status was monitored at baseline, and at 1 , 3, 5.25, and 8.25 months following completion of the hygiene sessions. Maintenance therapy was performed at 3, 5.25, and 8.25 months for both groups. Results: Ten subjects in each group completed all phases of the study. Subgingival debridement plus adjunctive SDD reduced deep pockets (≥7 mm at baseline) by an average of 3.02 mm after 9 months versus 1.42 mm for the placebo group. A significant clinical response was seen in both groups as soon as 1 month, but the response was always clinically and statistically greater in the SDD group. In the SDD group, nearly 40% of 237 pockets 27 mm were reduced by ≥4 mm, and 55% were reduced by ≥3 mm. In addition, only 2 pockets deepened by ≥4 mm in the SDD group versus 10 in the placebo group. Conclusions: The supplementation of hygienist-delivered full mouth subgingival and supragingival debridement with a hostmodulating agent, SDD, provides clinically and statistically significant benefits in the reduction of deep pockets in patients with severe, generalized periodontitis. In addition, adjunctive SDD is more effective than a placebo in preventing further increases in probing depth.] Novak MJ, Johns LP, et al. Journal of Periodontology, July 2002, Vol. 73, No. 7, Pages 762-769 http://www.joponline.org/doi/abs/10.1902/jop.2002.73.7.762

1069. **Adjunctive low-dose doxycycline therapy effect on clinical parameters and gingival crevicular fluid tissue plasminogen activator levels in chronic periodontitis.** [*Objective and design:* The present study examined effectiveness of low-dose doxycycline (LDD) in combination with nonsurgical therapy on gingival crevicular fluid (GCF) tissue plasminogen activator (t-PA) levels and clinical parameters in chronic periodontitis (CP) a over 12-month period. *Methods:* GCF samples were collected, probing depth (PD), clinical attachment level (CAL), gingival index (GI) and plaque index were recorded at baseline, 3, 6, 9 and 12 months. CP patients (n = 65) were randomized to LDD or placebo groups. LDD group received LDD (20 mg) b.i.d for 3-months plus and root planing (SRP), while placebo group was given placebo capsules b.i.d for 3-months plus SRP. GCF t-PA levels were determined by ELISA. Friedman, Wilcoxon and Mann-Whitney test was used for statistical analysis. *Results:* Significant improvement was observed in all clinical parameters in both groups over 12-month period ($p < 0.01$). LDD group had lower PD, CAL and GI scores than placebo group at 6, 9 and 12-months ($p < 0.05$). GCF t-PA levels reduced in both groups over 12-month period ($p < 0.01$). LDD group had lower GCF t-PA levels than placebo group at 6 and 9-months ($p < 0.05$). *Conclusions:* These results provide additional information about usefulness of LDD therapy as an adjunct to nonsurgical therapy in long-term management of periodontitis.] Emingil G, Gurkan A, et al. *Inflammation Research, Vol 55, Number 12 / Dec 2006.* http://www.springerlink.com/content/5330m6761105q5p3/

1070. **Adjunctive Treatment with Subantimicrobial Doses of Doxycycline: Effects on Gingival Fluid Collagenase Activity and Attachment Loss in Adult Periodontitis.** [Objectives: The therapeutic effects of doxycycline and other tetracyclines in the treatment of periodontitis involve, at least in part, mechanisms that are unrelated to their antimicrobial activity. Previous clinical studies have shown that doxycycline administered orally — at doses below those needed for antimicrobial efficacy — to human subjects with adult periodontitis resulted in significantly reduced collagenase activity in gingival crevicular fluid (GCF) and in extracts of inflamed gingival tissues. The purpose of the present study was to identify clinically effective dosing regimens using subantimicrobial dose doxycycline (SDD) as an adjunctive therapy in patients with adult periodontitis. Material and Methods: A total of 75 adult men and women qualified for enrollment into the 3-part, placebo-controlled, double-blind, parallel-group study. Patients were stratified based on repeatedly exhibiting pathologic levels of periodontal attachment (Alv) and GCF collagenase activity at several appointments prior to baseline. Patients received scaling and prophylaxis, then 1 of 5 treatment schedules for 12 weeks (part I), followed by a 12-week period of no drug therapy (part II), a second scaling and prophylaxis, and 12 additional weeks of treatment (part III). Primary determinants of efficacy included reductions in GCF collagenase activity and changes in relative Alv. Results: 66 patients completed the first 12 weeks (part I) of the 3-part, 36-week study; 51 patients completed the entire 36-week study. From baseline to week 12 (part I), treatment with specially formulated SDD capsules (20 mg) 2x daily (1x every 12 h) for up to 12 weeks was shown to significantly reduce GCF collagenase activity and to improve Alv; effects not seen in patients treated with placebo.

Continuous drug therapy over the 12-week treatment period was needed to maintain and maximize the reduction in GCF collagenase and the improvement in Alv. Improvements in periodontal disease parameters occurred without the emergence of doxycycline-resistant microorganisms. In patients administered an “on-off-on” regimen of SDD over 36 weeks (parts I-III), essentially no attachment loss occurred in patients receiving the highest of these SDD regimens (20 mg 2x daily during part I and 20 mg 1x daily in part III), whereas patients administered placebo capsules experienced a mean attachment loss of approximately 0.8 mm at the 24- and 36-week time periods. Conclusion: Doxycycline administered at subantimicrobial doses led to improvements in disease parameters with no apparent side effects, and it appears to have significant potential as an oral adjunctive therapy in the long-term management of adult periodontitis.] Golub LM, McNamara TF, et al. *J Clin Periodontol. 2001;28:146-156.* http://www.ncbi.nlm.nih.gov/pubmed/11168739

1071. **Can Systemic Diseases Co-induce (*Not* Just Exacerbate) Periodontitis? A Hypothetical "Two-hit" Model.** [The connection between systemic diseases and chronic destructive periodontitis (CDP) has received increasing attention in recent years. A major unanswered question is how disease in one part of the body (*e.g.*, the joints and skeletal tissues) can transmit signals to the periodontium to enhance or, as we hypothesize in this report, to co-induce CDP. The inflammatory mediators and effector molecules described below, carried by the circulation, are likely conduits. The purpose of this paper is to explore a proposed "two-hit" model of CDP, by interpreting the results of experiments with animal models and supported by evidence from human clinical studies. This model conceptualizes how bone- and connective-tissue-destructive diseases in one location (*e.g.*, the joints in patients with rheumatoid arthritis, the skeletal system during post-menopausal osteoporosis, and others) may communicate with the tissues in the periodontium (the 2nd "hit"), together with the microbial products (*e.g.*, endotoxin) generated by the subgingival biofilm (the 1st "hit"), to co-induce periodontitis. A similar "two-hit" model has recently been proposed to explain the pathogenesis of acute lung injury during acute respiratory distress syndrome (ARDS), mediated by essentially the same inflammatory mediators and effector molecules as proposed in this paper (Carney *et al.*, 1999; Steinberg *et al.*, 2005a). Our hypothesis and model are further supported by a wealth of evidence, accumulated over the past several decades, suggesting that inhibitors of these mediators and effector molecules (particularly pleotropic MMP-inhibitor drugs, notably the non-antimicrobial formulations of tetracycline compounds) can reduce the severity of several of these systemic diseases (*e.g.*, ARDS, rheumatoid arthritis, post-menopausal osteoporosis), as well as periodontitis, in experimental animals and, in some cases, in humans as well] Golub LM, Payne JB, et al. *J Dent Res* 85(2):102-105, 2006 http://jdr.iadrjournals.org/cgi/content/full/85/2/102

1072. **Clinical and Biochemical Results of the Metalloproteinase Inhibition with Subantimicrobial Doses of Doxycycline to Prevent Acute Coronary Syndromes (MIDAS) Pilot Trial.** [*Background*— Vulnerable plaque demonstrates intense inflammation in which macrophages secrete matrix metalloproteinases (MMPs) that degrade the fibrous cap, ultimately leading to rupture, in situ thrombosis, and an associated clinical event. Thus, inhibition of MMP activity or more general suppression of vascular inflammation are attractive targets for interventions intended to reduce plaque rupture. We hypothesized that subantimicrobial doses of doxycycline (SDD) (20 mg twice daily) would benefit patients with coronary artery disease by reducing inflammation and MMP activity and thus possibly prevent coronary plaque rupture events. *Methods and Results*— We conducted a prospective, randomized, double-blind, placebo-controlled pilot study of 6 months of SDD or placebo treatment to reduce inflammation and prevent plaque rupture events. A total of 50 patients were enrolled, of whom 24 were randomized to placebo and 26 to SDD. At 6 months, there was no difference in the composite endpoint of sudden death, fatal myocardial infarction (MI), non-fatal MI, or troponin-positive unstable angina in SDD compared with placebo-treated patients (8.4% versus 0%, P=0.491). Biochemical markers of inflammation were assessed in plasma at study entry and after 6 months of therapy in 30 patients. In SDD-treated patients, high-sensitivity C-reactive protein (CRP) was reduced by 46% from 4.8±0.6 μg/mL to 2.6±0.4 μg/mL (P=0.007), whereas CRP was not significantly reduced in placebo patients. Interleukin (IL)-6 decreased from 22.1±3.7 pg/mL at baseline to 14.7±1.8 pg/mL at 6 months in SDD-treated patients (P=0.025) but did not decrease significantly in placebo-treated patients. On zymography, pro-MMP-9 activity was reduced 50% by SDD therapy (P=0.011), whereas it was unchanged by placebo treatment. *Conclusion*— SDD appears to exert potentially beneficial effects on inflammation that could promote plaque stability. These findings should be investigated in a larger study.] Brown DL, Desai KK, et al. *Arteriosclerosis, Thrombosis, and Vascular Biology.* 2004;24:733. http://atvb.ahajournals.org/cgi/content/abstract/24/4/733

1073. **Clinical trials of a matrix metalloproteinase inhibitor in human periodontal disease. SDD Clinical Research Team.** [After demonstration by Golub et al. of the ability of the tetracyclines to inhibit elevated collagenolytic activity in animal models of periodontal diseases, a clinical development program was initiated to demonstrate the potential of a subantimicrobial dose of doxycycline (SDD) to augment and maintain the improvements in clinical parameters of adult periodontitis (AP) afforded by conventional nonsurgical periodontal therapy. Clinical trials were carried out in which a number of different SDD dosing regimens and placebo were compared in patients administered a variety of adjunctive nonsurgical therapies. Measured parameters included levels of collagenase activity in gingival crevicular fluid (GCF) and gingival specimens, clinical attachment levels (cALv), probing pocket depths (PD), bleeding on probing (BOP), and subtraction radiographic measurements of alveolar bone height. When used as an adjunct to either scaling and root planing or supragingival scaling and dental prophylaxis, SDD was shown to reduce collagenase levels in both GCF and gingival biopsies, to augment and maintain cALv gains and PD reductions, to reduce BOP, and to prevent loss of alveolar bone height. These clinical responses arose in the absence of any significant effects on the subgingival microflora and without evidence of an increase in the incidence or severity of adverse reactions relative to the control groups. It is proposed that one of the mechanisms of action of SDD is as an inhibitor of pathologically elevated MMPs, including neutrophil and bone cell

collagenases (MMP-8 and MMP-13), which are associated with the host response in chronic AP, and that SDD provides a novel systemic approach to the management of AP.] Ashley RA. *Ann N Y Acad Sci. 1999 Jun 30;878:335-46.* http://www.ncbi.nlm.nih.gov/pubmed/10415739

1074. **Could low dosage of doxycycline e considered for Alzheimer's disease treatment? [**Objectives: Alzheimer's disease (AD) is a neurodegenerative disease primarily of the elderly, and treatment modalities are limited. AD is characterized by the presence of senile plaques with its main component amyloid â , neurofibrillary tangles with phosphophorylated tau protein, and neuronal loss. These pathological components as well as inflammation are hypothesized to be involved in the pathogenesis of AD. When considering potential treatment modalities for AD, this pathogenesis should be considered. Periostat is a drug containing low dosages of Doxycycline and is used in long-term administration to treat periodontal disease without the side effects characterizing the anti-microbial doses of this medication. The objective of this study is to evaluate the possible use of Periostat for treating AD by critically analyzing the existing literature. Methods: a Medline search was undertaken using combinations of the following terms: doxycycline, tetracycline, minocycline, Alzheimer's disease, cognition, mild impairment cognition, metalloproteinase (MMP), amyloid, and inflammation. Then, the relevant papers were reviewed manually. Results: the database search resulted in a total 301 papers containing the search terms. Further evaluation resulted in 45 papers containing relevant data. The studies evaluated were based on in vitro, animal, and clinical data. Only one randomized control study was found. The review study found that tetracycline derivatives, including doxycycline: a) cross the brain blood barrier; b) have neuroprotective effects; c) destabilize the amyloid fibrils to make them susceptible to proteolysis; d) inhibit caspase-3 that has a role in tau protein neurotoxicity; e) inhibit the production of proinflammatory molecules; and f) slow cognitive decline. However, untoward effects have also been reported related to tetracyclines anti-MMPs activities. Conclusion: the available data suggest that in selective cases low dosage doxycycline may be effective in treating AD.] Kamer SA, Kamer AR. *IADR*, July 16, 2010. Barcelona Spain. http://iadr.confex.com/iadr/2010barce/webprogramcd/Paper140673.html

1075. **Doxycycline affects diet- and bacteria-associated atherosclerosis in an ApoE heterozygote murine model: Cytokine profiling implications .** [Background: It has been postulated that systemic infection with pathogens such as Porphyromonas gingivalis (Pg) elevates the inflammatory response and increases susceptibility to atherosclerosis. We hypothesized that Doxycycline would be beneficial in diet- and/or Pg-induced atherosclerosis given its role in various cell functions and matrix remodeling. Methods and results: ApoE± mice were inoculated weekly with Pg and treated with either Doxycycline or saline; animals were fed either a high-fat or chow diet. Animals were euthanized at 14 or 24 weeks and histomorphometric analysis of atheromatous lesions in proximal aorta, levels of SAA and serum cytokine profiling were performed. Histomorphometric analysis demonstrated that in non-infected mice fed a high fat diet, Doxycycline treatment resulted in a reduction of mean lesions from 10.5%±.49 to 1.09%±0.102 ($p<0.05$) at 14 weeks and a reduction from 21.5%±6.49 to 8.26%±0.162 ($p=0.106$) at 24 weeks. Chow-fed Pg mice treated with Doxyclycline also resulted in a reduction from 0.62%±0.128 to 0.0%±0.0 ($p<0.05$) at 14 weeks and a reduction from 0.92%±0.23 to 0.0%±0.0 ($p<0.05$) at 24 weeks. Administration of Doxycycline to mice fed a high fat diet and Pg-inoculated resulted in a reduction of mean percentage of atheromatous lesions from 16.46%±1.69 to 1.141%±0.23 ($p<0.05$) at 14 weeks and a reduction from 25.27%±1.734 to 0.428%±0.033 ($p<0.05$) at 24 weeks. At this timepoint, SAA levels in Pg-infected animals were reduced by five-fold and three-fold in Doxycycline-treated chow and high fat-diet groups, respectively. Cytokine antibody arrays revealed a marked reduction in the levels of pro-inflammatory cytokines in Doxycycline-treated groups whether Pg-infected or fed a high fat diet while anti-inflammatory cytokines were not affected. Consistent with the role of Doxycycline on matrix proteases, at 24 weeks MMP-9 Serum levels were markedly reduced by 60% ($p<0.05$) and 30% ($p<0.05$) with Doxycycline treatment in Pg-infected high fat and chow diet groups, respectively. Conclusions: Doxycycline decreases pro-inflammatory cytokines and results in reduction of atherosclerosis in ApoE± Pg-inoculated and/or high fat diet fed mice.] Madan M, Bishayi B, et al. *Atherosclerosis , Volume 190 , Issue 1, Pages 62 – 72.* http://linkinghub.elsevier.com/retrieve/pii/S0021915006000645

1076. **Doxycycline ameliorates vascular endothelial and contractile dysfunction in the thoracic aorta of diabetic rats.** [Studies have shown that tetracycline class antibiotics exhibit an ameliorating action with its antioxidant property on increased oxidative stress in tissues, including **heart**. Since endothelial vascular dysfunction in diabetes is associated with increased oxidative stress and prevented with antioxidants, herein, we aimed to test a hypothesis whether a low-dose doxycycline treatment of diabetic rats for 4 weeks can ameliorate endothelial vascular dysfunction of thoracic aortas. Results of the present study shows that both direct and alpha receptor-mediated contractile responses as well as endothelium-dependent and endothelium-independent vasodilatory responses were preserved with low-dose doxycycline treatment (30 μmol/kg, daily; for 4 weeks) compared with untreated diabetic group. Furthermore, doxycycline treatment normalized increased lipid peroxidation and cellular glutathione level measured in plasma and prevented diabetes-induced impaired body weight gain without significant effect on high blood glucose level. Increased membrane protein level of caveolin-1, elevated ratio of PKC in particulate and cytosolic fraction, and increased protein level of cytosolic endothelin-1 in diabetic rats were also significantly prevented with doxycycline treatment. Moreover, diabetes-induced another type of oxidative stress markers in rats, matrix metalloproteinases, MMP-2, and MMP-9 were also normalized with doxycycline treatment in blood. Taken together, our data address that amelioration and/or prevention of vascular endothelial and contractile dysfunction by doxycycline is accompanied by a clear reduction in oxidative stress markers of diabetes, which provides evidence for doxycycline's potential antioxidant action as a therapeutic agent for amelioration and/or prevention of vascular disorders in

diabetic subjects.] Zeydanli EN, Kandilci HB, et al. *Cardiovasc Toxicol*. 2011 Jun;11(2):134-47. http://www.ncbi.nlm.nih.gov/pubmed/21360312

1077. **Doxycycline reduces airway inflammation and hyperresponsiveness in a murine model of toluene diisocyanate-induced asthma**. [BACKGROUND: Toluene diisocyanate (TDI) is a leading cause of occupational asthma. Although considerable controversy remains regarding its pathogenesis, TDI-induced asthma is an inflammatory disease of the airways characterized by airway remodeling caused, at least in part, by an excess of extracellular matrix deposition in the airway wall. Matrix metalloproteinases (MMPs) are major proteolytic enzymes that are involved in extracellular matrix turnover because of their ability to cleave all proteins constituting extracellular matrix. Previous studies have reported that MMP-9 might play a role in chronic airway inflammation and remodeling in asthma. OBJECTIVE: An aim of the current study was to evaluate the effects of MMP-inhibiting antibiotic, doxycycline, and MMP inhibitors on hyperresponsiveness and inflammation of the airways in TDI-induced asthma. METHODS: We used a murine model for TDI-induced asthma to examine the effect of doxycycline or MMP inhibitors on bronchial inflammation and airway hyperresponsiveness. RESULTS: The following typical pathophysiologic features are observed in the lungs of the mice: airway inflammation, airway hyperresponsiveness, and increased expression of MMP-9 mRNA and protein. Administration of doxycycline and MMP inhibitors reduced all of these pathophysiologic findings. In addition, the increased phosphorylated Akt but not Akt protein levels in lung tissues after TDI inhalation were significantly reduced by the administration of doxycycline and MMP inhibitors. CONCLUSION: These findings suggest that doxycycline may reduce airway inflammation and hyperresponsiveness through phosphatidylinositol 3-kinase pathway in a murine model of TDI-induced asthma.] Lee KS, Jin SM, et al. *J Allergy Clin Immunol. 2004 May;113(5):902-9.* http://www.ncbi.nlm.nih.gov/pubmed/15131573

1078. **Effect of Subantimicrobial Dose Doxycycline as an Effective Adjunct to Scaling and Root Planing.** [**Background:** This study evaluated the efficacy and safety of a subantimicrobial dose of doxycycline (SDD) in conjunction with scaling and root planing (SRP). Methods: The study was a 9-month, double masked, randomized, placebo-controlled, parallel-group trial. A total of 41 patients with moderate chronic periodontitis who received SRP were randomly allocated to receive either a doxycycline hyclate or a placebo 2 weeks after SRP. Clinical attachment level (CAL), the probing depth (PD), gingival crevicular fluid (GCF) levels, and matrix metalloproteinase (MMP)-8 and -13 levels were measured throughout the study. The effect of SDD in conjunction with SRP on the dynamics of the periodontal microflora was also assessed using dark-field microscopic and culture analysis. Information on adverse events was collected throughout the study. Results: During the treatment period, per-patient reductions in PD and CAL were demonstrated for both treatment groups, with a significantly greater reduction for the SDD group. The mean value of per-patient change in the GCF was much greater for the SDD group. Microbial analysis showed there were a general tendency for cocci, non-motile rods, and aerobes to increase with increasing treatment duration and a general decreasing tendency for spirochetes, motile rods, and anaerobes and black pigmented bacteria in both treatment groups, but no significant difference between the groups. The MMP-8 and -13 levels of the SDD group gradually reduced with time, and the mean perpatient average was significantly higher than in the placebo group. The adverse events in the SDD group were similar to those in the placebo group. Conclusion: This study suggests that a submicrobial dose of doxycycline as an adjunct therapy with SRP might be safe and effective in the long-term management of chronic periodontitis.] Lee JY, Lee YM, et al. *Journal of Periodontology, November 2004, Vol. 75, No. 11, Pages 1500-1508* http://www.joponline.org/doi/abs/10.1902/jop.2004.75.11.1500

1079. **Effect of Systemic Matrix Metalloproteinase Inhibition on Periodontal Wound Repair: A Proof of Concept Trial.** [Background: The adjunctive use of matrix metalloproteinase (MMP) inhibitors with scaling and root planing (SRP) promotes new attachment in patients with periodontal disease. This pilot study was designed to examine aspects of the biological response brought about by the MMP inhibitor low dose doxycycline (LDD) combined with access flap surgery (AFS) on the modulation of periodontal wound repair in patients with severe chronic periodontitis. Methods: Twenty-four subjects were enrolled into a 12-month, randomized, placebo-controlled, double-masked trial to evaluate clinical, biochemical, and microbial measures of disease in response to 6 months therapy of either placebo capsules + AFS or LDD (20 mg b.i.d.) + AFS. Clinical measures including probing depth (PD), clinical attachment levels (CAL), and bleeding on probing (BOP) as well as gingival crevicular fluid bone marker assessment (ICTP) and microbial DNA analysis (levels and proportions of 40 bacterial species) were performed at baseline and 3, 6, 9, and 12 months. Results: Patients treated with LDD + AFS showed more potent reductions in PD in surgically treated sites of >6 mm (P <0.05, 12 months). Furthermore, LDD + AFS resulted in greater reductions in ICTP levels compared to placebo + AFS. Rebounds in ICTP levels were noted when the drug was withdrawn. No statistical differences between the groups in mean counts were found for any pathogen tested. Conclusions: This pilot study suggests that LDD in combination with AFS may improve the response of surgical therapy in reducing probing depth in severe chronic periodontal disease. LDD administration also tends to reduce local periodontal bone resorption during drug administration. The use of LDD did not appear to contribute to any significant shifts in the microbiota beyond that of surgery alone.] Gapski R, Barr JL, et al. Journal of Periodontology, March 2004, Vol. 75, No. 3, Pages 441-452. http://www.joponline.org/doi/abs/10.1902/jop.2004.75.3.441?journalCode=jop

1080. **Effects of scaling and root planing and sub-antimicrobial dose doxycycline on oral and systemic biomarkers of disease in patients with both chronic periodontitis and coronary artery disease.** [Objectives: This study evaluated the effects of scaling and root planing (SRP) ± sub-antimicrobial dose doxycycline (SDD) on gingival crevicular fluid (GCF) levels of matrix metalloproteinase (MMP) -1, -8, -13 and on serum levels of high-sensitivity C-reactive protein (HsCRP) and lipid fractions in patients with *both* chronic periodontitis (CP) and coronary artery disease (CAD). Material and Methods: Thirty-six patients were randomly distributed into two groups (Placebo or SDD; 6 weeks) and both received two regimens of

SRP. At baseline and 6 weeks, GCF and blood were collected and clinical indices were recorded. MMPs, HsCRP and lipid fractions were assayed. Results: There were statistically significant improvements for all clinical parameters, GCF volumes, GCF MMPs and serum levels of HsCRP, apolipoprotein-A (APO-A), high-density lipoprotein (HDL) and lipoprotein-a between pre- and post-treatment in both groups. Between groups, there were statistically significant greater improvements in pocket depth (PD), gingival index (GI), APO-A and HDL, favouring the group receiving SDD adjunctive to SRP ($p < 0.05$). Conclusion: Greater improvement was detected for PD and GI, and for serum levels of APO-A and HDL cholesterol when using SRP+SDD compared with SRP+placebo in this study. An investigation with larger numbers of patients and a longer duration of drug treatment is needed to confirm these preliminary findings.] Tuter G, Kurtis B, et al. *Journal of Clinical Periodontology, Volume 34 Issue 8, Pages 673 – 681*. http://www3.interscience.wiley.com/journal/118533353/abstract

1081. **of sub-antimicrobial dose doxycycline therapy on crevicular fluid MMP-8, and gingival tissue MMP-9, TIMP-1 and IL-6 levels in chronic periodontitis.** [Objective: To investigate whether sub-antimicrobial dose doxycycline (SDD) therapy for 120 d in chronic-adult periodontitis patients had significant effects on gingival crevicular fluid (GCF) matrix metalloproteinase-8 (MMP-8) levels, and on gingival tissue MMP-9, tissue inhibitor of matrix metalloproteinases-1 (TIMP-1) and interleukin-6 (IL-6) levels. Background: Tetracycline can significantly inhibit MMP activity in GCF and in gingival tissue, even in much lower dosage then a traditional antimicrobial dosage used in conventional therapy. Sub-antimicrobial dose doxycycline (SDD) therapy has been shown to reduce periodontal disease activity to control MMP and pro-inflammatory cytokines. Methods : A total of 32 patients with incipient to moderate (probing pocket depth 4-7 mm) chronic adult periodontitis were included in the study. Subjects were randomly assigned to two groups. After scaling and root planning (SRP), the SRP + SDD group received SDD, 20 mg bid, whereas the SRP + placebo group received placebo, 20 mg bid. In the follow-up, efficacy measures included the change in probing pocket depth (PD), clinical attachment level (CAL), bleeding on probing (BOP) and gingival crevicular fluid MMP-8 levels, gingival tissue MMP-9, TIMP-1 and IL-6 levels from baseline to 120 d. Results: After 120 d, PD and CAL improved significantly in the SRP + SDD group. Initial MMP-8 levels for the SRP + SDD group and the SRP + placebo group were 407.13 ± 114.45 ng/ml and 378.71 ± 189.39 ng/ml, respectively, with no statistical difference between the two groups. MMP-8 levels for the SRP + SDD group and the SRP + placebo group were: 235.35 ± 134.58 ng/ml and 364.04 ± 219.27 ng/ml at 30 d; 157.50 ± 95.95 ng/ml and 236.60 ± 186.16 ng/ml at 60 d; 102.70 ± 67.64 ng/ml and 208.56 ± 124.54 ng/ml at 90 d; and 63.77 ± 53.33 ng/ml and 229.13 ± 168.09 ng/ml at 120 d, respectively. The amount of decrease in MMP-8 levels for the SRP + SDD group was statistically significant compared to that for the SRP + placebo group, especially apparent at 120 d ($p < 0.05$). TIMP-1 levels in both groups increased from the baseline to 120 d with statistical significance (p-value < 0.05), but there was no significant difference between the two groups. Changes in MMP-9 and IL-6 levels were not statistically significant. Conclusion. Adjunctive SDD therapy can improve the clinical parameters and this clinical improvement is reflected by controlled level of MMP-8 in chronic adult periodontitis after the therapy.] Choi DH, Moon IS, et al. *Journal of Periodontal Research.* 2004, Vol 39, No.1, pp.20-26. http://cat.inist.fr/?aModele=afficheN&cpsidt=15517624

1082. **Efficacy of sub-antimicrobial dose doxycycline in post-menopausal women: clinical outcomes.[** AIMS: To determine the clinical efficacy of a 2-year continuous sub-antimicrobial dose doxycycline (SDD; 20 mg bid) in post-menopausal, osteopenic, oestrogen-deficient women on periodontal maintenance. MATERIALS AND METHODS: One-hundred and twenty-eight subjects were randomized to SDD (n=64) or placebo (n=64). Clinical measurements were performed at posterior interproximal sites at baseline and every 6 months during this 2-year randomized, double-blind, placebo-controlled clinical trial with adjunctive, no-cost 3-4-month periodontal maintenance. Statistical analyses of secondary outcomes from this clinical trial used Generalized Estimating Equations in primarily intent-to-treat analyses. RESULTS: For the placebo group, 3.4% of the sites showed improvement in clinical attachment levels (CAL) and 2.7% had progressive loss in CAL; for the SDD group, 5.0% of the sites showed an improvement in CAL and 2.2% had progressive loss in CAL. This difference (2.1% of sites) was more favourable in the SDD group than in the placebo [odds ratio (OR)=0.81 [corrected] 95% confidence interval (CI): 0.67-0.97, p=0.03] in these well-maintained patients, whereas probing depths, bleeding on probing and supragingival plaque did not differ significantly between groups (p>0.2). However, in exploratory subgroup analysis of non-smokers, SDD showed reduced bleeding versus placebo (27%versus 33%; p=0.05). In protocol-adherent subjects, the odds of bleeding were 34% lower for SDD (p=0.05). CONCLUSIONS: Analyses of secondary outcomes of this clinical trial indicated that SDD may be of benefit in reducing progressive attachment loss in post-menopausal females; additional research is needed to confirm these findings.] Reinhardt RA, Stoner JA, Golub LM, et al. *J. clin Periodontol*. 2007 Sep:34(9):768-75. http://www.ncbi.nlm.nih.gov/pubmed/17716312

1083. **Effect of Sub-antimicrobial Doxycycline on Biomarkers in Patients with Acute Coronary Syndromes.** [Objectives: Acute myocardial infarction may result from inflammation-induced, matrix metalloproteinase (MMP)-mediated breakdown of the connective tissue (collagen) cap, destabilizing the atherosclerosis plaque, followed by thrombosis. The current study determined whether an MMP-inhibitor, sub-antimicrobial doxycycline (SDD), affects biomarkers of systemic inflammation in patients with acute coronary syndromes (ACS). Methods: 50 patients with acute myocardial infarction and unstable angina (ACS) were randomly distributed into 2 groups administered either placebo (n=24 subjects) or SDD (n=26) b.i.d. for 6 months. Blood samples were taken before and after the 6 month regimen. The plasma was collected and analyzed for high sensitivity C-reactive protein (hs CRP) and IL-6 (& other cytokines) by ELISA, and for matrix metalloproteinases (MMP-2 & MMP-9) by densitometric scanning of gelatin zymograms and by western blot. Results: The 2 groups showed no significant differences in age, gender, hypertension, diabetes, smoking, or extent of cardiac disease at baseline. Although SDD did not significantly affect clinical end-points in this short-term pilot study, it did produce significant (p<0.05) 46%,

34% and 50% reductions in hs CRP, IL-6 and MMP-9, respectively (a 38% reduction in MMP-2 was not statistically significant). When the ACS patients were stratified into "higher" (>5 µg/ml) and “lower” (<5 µg/ml) baseline hs CRP levels, SDD therapy produced a 58% ($p<0.001$) and 23% ($p>0.05$) reduction of this biomarker, respectively. Placebo treatment had no significant effect on any parameters. Conclusions: These data suggest that sub-antimicrobial doxycycline (developed as adjunctive therapy for inflammatory periodontal disease) can reduce SYSTEMIC inflammation (including mediators of connective tissue destruction) and the risk for acute myocardial infarction in patients not referred for periodontal therapy. A longer-term study addressing clinical (both coronary and periodontal) end – points is being planned.] Brown DL, Golub L, et al. AADR 32nd Annual Meeting, March 12-15. 2003. http://iadr.confex.com/iadr/2003SanAnton/techprogram/abstract_24399.htm

1084. **Host Modulation: Conceptualization to Clinical Trials and Integration into Clinical Practice.** [A better understanding of the pathogenesis of periodontitis has resulted in pharmacotherapeutic advancements, addressing both the microbes and the host response, leading to improved management of this chronic progressive disease by the dental practitioner. The adjunctive use of host-modulatory agents can enhance therapeutic responses, slow the progression of the disease, and allow for more-predictable management of patients. This article will review the pathogenesis and risk factors associated with periodontitis and address in detail the concept and clinical utility of host modulation as a therapeutic strategy.] *Ryan ME. Journal CA Dental Association, April 2002, http://www.cda.org/library/cda_member/pubs/journal/jour0402/hostmodulation.html*

1085. **Host modulation with tetracyclines and their chemically modified analogues.** [Recent studies have suggested the use of drugs to modulate host response as a new approach in periodontal therapy. In this regard, the tetracycline antibiotics have been found to inhibit host-derived collagenases and other matrix metalloproteinases by a mechanism independent of the antimicrobial activity of these drugs; this effect may suppress connective tissue breakdown during periodontal disease and during a variety of medical disorders including (but not limited to) noninfected corneal ulcers, serious (sometimes life-threatening) skin-blistering diseases, rheumatoid arthritis and osteoarthritis, systemically--as well as locally--induced bone loss, and perhaps even tumor-induced angiogenesis. Two therapeutic strategies based on the host-modulating properties of tetracyclines are currently being developed: 1) the use of low-dose doxycycline (the most potent anticollagenase of commercially available tetracyclines) formulations, which do not appear to result in tetracycline side effects such as the emergence of antibiotic-resistant microorganisms; and 2) the production of a family of chemically modified tetracyclines that have lost their antimicrobial activity, but have retained their anticollagenase activity. A description of several of these compounds and a discussion of their efficacy in inhibiting collagenases in vitro and reducing tissue destruction in several animal models of periodontal and medical diseases is presented.] Golub LM, Suomalainen K, Sorsa T. Curr Opin Dent. 1992 Mar;2:80-90. http://www.ncbi.nlm.nih.gov/pubmed/1325849

1086. **Host-Response Therapeutics for Periodontal Diseases.** [Periodontal diseases are initiated by Gram-negative tooth-associated microbial biofilms that elicit a host response, with resultant osseous and soft tissue destruction. In response to endotoxins derived from periodontal pathogens, several osteoclast-related mediators target the destruction of alveolar bone and supporting connective tissues. Major drivers of this aggressive tissue destruction are matrix metalloproteinases (MMPs), cathepsins, and other osteoclast-derived enzymes. This article focuses on the downstream factors of the osteoclast responsible for the degradation of bone and soft tissues around teeth and oral implants. Furthermore, therapeutic approaches that target MMP-2, -8, and -9 inhibition, such as MMP inhibitors, chemically modified tetracyclines, and subantimicrobial formulations of tetracycline analogues, are discussed. The use of rapid, chair-side tests of MMP activity, in particular for MMP-8 and bone collagen fragments, show strong potential as non-invasive measures of tissue health or disease. In addition, studies using other agents for the preservation of bone mass, such as bisphosphonates that inhibit osteoclast recruitment, are highlighted. The application of these bone-preservation strategies to periodontal management and treatment are discussed in the context of high-risk patients susceptible to disease reactivation or disease complications.] Giannobile WV. Journal of Periodontology, 2008, Vol. 79, No. 8s, Pages 1592-1600. http://www.joponline.org/doi/full/10.1902/jop.2008.080174

1087. **Inhibition of alveolar bone loss by matrix metalloproteinase inhibitors in experimental periodontal disease.** [Periodontal disease is characterized by excessive host collagenase resulting in loss of gingival and periodontal ligament collagen and adjacent alveolar bone. Intragingival endotoxin injection induces a model of periodontal disease characterized by rapid bone loss with biochemical features similar to that of naturally occurring adult periodontitis. CH1766, a peptide with a zinc binding moeity which fits into the active site of the enzyme, and CH6631, a hydroxamic acid derivative with aryl-substituted sulphonamide residues, are inhibitors of matrix metalloproteinases (MMPIs) with differing inhibitory profiles as characterized by *in vitro* assays. In this study, endotoxin was injected into the gingivae of rats which were then treated orally with either 3 mg/kg or 30 mg/kg of one of the two inhibitory compounds. The gingival tissues were assessed for collagenase and gelatinase activity, plus three different pro-inflammatory cytokines. In addition, alveolar bone height in defleshed jaws was studied by computerized morphometric analysis and scanning electron microscopy. Both drugs reduced active and/or total MMP activity, in many cases to normal, and also partially normalized cytokine levels as well. A dose-response effect was seen with regard to amelioration of lipopolysaccharides -induced alveolar bone loss with both drugs. Other than studies with tetracyclines, this is the first report of beneficial effects of MMPIs in a model of periodontal disease, strongly suggesting that this class of agents could bring therapeutic benefit to patients with this disorder, and that periodontal disease can be used as a model to demonstrate *in vivo* efficacy of this class of drugs.] Ramamurthy NS, Xu J, et al. Journal of Periodontal Research, Volume 37 Issue 1**,** Pages 1 – 7. http://www3.interscience.wiley.com/journal/120770340/abstract

1088. **Long-term treatment with subantimicrobial dose doxycycline exerts no antibacterial effect on the subgingival microflora associated with adult periodontitis.** [BACKGROUND: The purpose of this study was to determine whether treatment with subantimicrobial dose doxycycline (SDD), 20 mg bid, exerted an antimicrobial effect on the microflora associated with adult periodontitis. METHODS: Following the approval of the protocol and informed consent forms by the respective IRBs at the University of Florida and West Virginia University, 76 subjects with adult periodontitis were entered and randomly assigned to receive SDD or placebo. A split-mouth design was utilized, with each subject receiving subgingival scaling and root planing (SRP) in two quadrants immediately following baseline data collection, while the remaining two quadrants were left unscaled (non-SRP). Microbial samples were collected prior to treatment, after 3, 6, and 9 months of treatment, and after 3 months of no treatment. The samples were examined by microscopy and by enumeration on selective and non-selective media. RESULTS: All treatments resulted in statistically significant decreases in the proportions of spirochetes and motile rods ($P < 0.05$) and in an increase in the proportion of coccoid forms ($P < 0.0001$) relative to baseline. No between-treatment differences were detected between the SDD and placebo treatments in either the SRP or non-SRP design, with the exception of the small and large spirochetal groups. The spirochetal proportions present in the SDD group were significantly lower ($P<0.05$) than the paired placebo group during the 9-month treatment and was preceded by a significant decrease ($P<0.01$) in the proportion of microbiologic sample sites that bled on probing. No between- treatment differences were detected in any of the other microbial parameters. CONCLUSION: The microbial differences observed were attributed to the anticollagenase and anti-inflammatory properties of SDD and not to an antimicrobial effect.] Walker C, Thomas J, et al. *J Periodontol. 2000 Sep;71(9):1465-71.* http://www.ncbi.nlm.nih.gov/pubmed/11022777

1089. **Long-term treatment with sub-antimicrobial dose doxycycline has no antibacterial effect on intestinal flora.** [Aim: The purpose of this study was to determine if a 9-month regimen of sub-antimicrobial doxycycline (20 mg, bid) had an effect on either the intestinal or the vaginal microflora. Material and Methods: A total of 69 periodontally diseased subjects were randomized to receive drug or placebo control for a 9-month period. Stool specimens and vaginal swabs were collected at baseline and after 3 and 9 months of therapy. Samples were examined for total anaerobic counts, opportunistic pathogens, and doxycycline-resistant (≥4 μg/ml) bacteria. All isolates that survived sub-culture were identified and their susceptibilities determined to six antibiotics. Analyses were performed to determine if treatment differences were present. Results: The only statistically significant differences ($p<0.05$) between the two treatment groups occurred in the doxycycline-resistant counts at the baseline sample period for the faecal samples. This imbalance was before treatment initiation and the administration of the study drug. No between-treatment differences were detected at either the 3- or 9-month sample period either in the predominant bacterial taxa present or in their antibiotic susceptibilities. Conclusions: There was no evidence that sub-antimicrobial doxycycline treatment exerted an effect on the composition or doxycycline resistance level of either the faecal or the vaginal microflora.] Walker C, Preshaw PM, Novak J. *J Clin Periodontol,* Vol. 32, 1163-1169, 2005.

1090. **Long-term Use of Subantimicrobial Dose Doxycycline Does Not Lead to Changes in Antimicrobial Susceptibility.** [**Background:** Adjunctive subantimicrobial dose doxycycline (SDD) with scaling and root planing leads to improved clinical parameters of adult periodontitis, but it has raised questions about potential changes in antibiotic susceptibility of the host microflora. These 4 studies assessed whether long-term SDD changes antibiotic susceptibility of the oral microflora in adults with periodontitis. Methods: In studies 1 and 2, adult patients with periodontitis were randomized to receive SDD 10 mg QD, 20 mg QD, 20 mg BID, or placebo. In study 3, patients were randomized to receive SDD 20 mg BID or placebo. No medication was administered in study 4, a follow-up to study 3. Subgingival plaque samples were collected at baseline (all studies) and at 12, 15 to 18, and 24 months (study 1); 12, 18, and 27 months (study 2); 3, 6, and 9 months (study 3); and 3 months poststudy 3 (study 4). Antimicrobial susceptibility of isolated bacteria was assessed by: 1) minimum inhibitory concentration (MIC) levels (studies 1 and 2); 2) cross-resistance to nontetracycline antibiotics (studies 2 and 3) and 3) the proportion of doxycycline-resistant isolates (studies 3 and 4). Results: Organism MIC levels remained constant among all treatment groups at 18 and 24 months compared with baseline (study 1). Observed changes in susceptibility at 12 and 18 months for the 20-mg groups were attributed to the limited number of isolates tested (study 1). There were no statistically significant differences in the proportion of doxycycline-resistant isolates among treatment groups (studies 3 and 4), and no evidence of multi-antibiotic resistance (studies 3 and 4) or cross-resistance (studies 2 and 3) at any time point. Conclusion: Long-term SDD does not contribute to changes in antibiotic susceptibility.] Thomas J, Walker C, Bradshaw M. *J Periodontol. 2000;71:1472-1483.* http://www.joponline.org/doi/abs/10.1902/jop.2000.71.9.1472?journalCode=jop

1091. **Low-dose doxycycline prevents inflammatory bone resorption in rats.** [Matrix metalloproteinases (MMP) are considered to be key initiators of collagen degradation, thus contributing to bone resorption in inflammatory diseases. We determined whether subantimicrobial doses of doxycycline (DX) (£10 mg kg^{-1} day^{-1}), a known MMP inhibitor, could inhibit bone resorption in an experimental periodontitis model. Thirty male Wistar rats (180-200 g) were subjected to placement of a nylon thread ligature around the maxillary molars and sacrificed after 7 days. Alveolar bone loss (ABL) was measured macroscopically in one hemiarcade and the contralateral hemiarcade was processed for histopathologic analysis. Groups of six animals each were treated with DX (2.5, 5 or 10 mg kg^{-1} day^{-1}, *sc*, 7 days) and compared to nontreated (NT) rats. NT rats displayed significant ABL, severe mononuclear cell influx and increase in osteoclast numbers, which were significantly reduced by 5 or 10 mg kg^{-1} day^{-1} DX. These data show that DX inhibits inflammatory bone resorption in a manner that is independent of its antimicrobial properties.] Bezerra MM, Brito BAC, et al. Braz J Med Biol Res, May 2002, Volume 35(5) 613-616. http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0100-879X2002000500015&nrm=iso&tlng=pt

1092. **Matrix metalloproteinases, tissue inhibitor of matrix metalloproteinase-1, and laminin-5 gamma2 chain immunolocalization in gingival tissue of endotoxin-induced periodontitis in rats: effects of low-dose doxycycline and alendronate.** [BACKGROUND: Matrix metalloproteinases (MMPs) play important roles in tissue destruction mechanisms of periodontitis. MMP-8 and -13 are the major collagenases that act in extracellular matrix degradation in periodontal tissues. MMP-14 is a membrane-type MMP, and laminin (Ln)-5 is a basal membrane component. The aim of the present study was to evaluate the effects of doxycycline and alendronate on gingival tissue expression of MMP-8, -13, and -14; tissue inhibitors of MMP (TIMP)-1; and Ln-5 gamma2 chain in experimental periodontitis induced by Escherichia coli endotoxin (LPS) in rats. METHODS: Experimental periodontitis was induced by repeated injection of LPS. Forty-four adult male Sprague-Dawley rats were divided into five study groups: saline control, LPS, LPS + doxycycline, LPS + alendronate, and LPS + doxycycline + alendronate. Doxycycline and alendronate were given as a single agent or as combination therapy during the 7 days of the experimental study period. On day 7, the rats were sacrificed, and the gingival tissues were analyzed immunohistochemically for expression of MMP-8, -13, and -14, Ln-5 gamma2 chain, and TIMP-1. Alveolar bone loss was evaluated morphometrically under a stereomicroscope. Data were tested statistically by Kruskal-Wallis and Mann-Whitney tests and Spearman correlation analysis. RESULTS: Alveolar bone loss was significantly higher in the LPS, doxycycline, alendronate, and combination groups than in the saline control group (all $P < 0.01$). MMP-8 expression was significantly higher in the LPS group than in the saline control group ($P = 0.001$). Individual administration of doxycycline or alendronate significantly decreased the expression of MMP-8 compared to LPS ($P = 0.01$). Combined drug administration reduced MMP-14 significantly compared to doxycycline ($P = 0.004$). No significant differences in Ln-5 gamma2 chain expression were found between the study groups ($P > 0.05$). MMP-14 significantly correlated with the Ln-5 gamma2 chain in the LPS + alendronate group ($P = 0.04$) and with the amount of alveolar bone loss in the LPS + doxycycline + alendronate group ($P = 0.03$). CONCLUSIONS: Our findings suggest that alendronate and/or doxycycline may inhibit MMP-8 expression significantly; particularly, their combined administration may provide beneficial effects in periodontal treatment. Moreover, individual administration of alendronate and doxycycline results in significant increases in TIMP-1 expression in gingiva. However, these effects of combined low-dose doxycycline and alendronate on MMPs and TIMP should be verified by clinical human trials before these agents are used in dental practice.] Buduneli E, Vardar-Sengul S, et al. *J Periodontol. 2007 Jan;78(1):127-34.* http://www.ncbi.nlm.nih.gov/pubmed/17199549

1093. **Modified-Release Subantimicrobial Dose Doxycycline Enhances Scaling and Root Planing in Subjects With Periodontal Disease.** [Background: Previous studies showed that adjunctive subantimicrobial dose doxycycline (SDD; 20 mg, twice daily) provides significant clinical benefits to scaling and root planing (SRP). A modified-release SDD formulation containing 40 mg doxycycline (SDD-40) to be taken once daily has been developed. The aim of this study was to investigate the efficacy of SDD-40 when used as an adjunct to SRP for the treatment of periodontitis. Methods: A 9-month, double-masked, randomized, placebo-controlled, multicenter study was conducted to test the efficacy of adjunctive SDD-40 in 266 subjects with periodontitis. Subjects were treated by SRP and randomized to receive SDD-40 or placebo for 9 months with evaluations at 3, 6, and 9 months. Results: Adjunctive SDD-40 provided significantly greater clinical benefits than placebo at all time points. At month 9, at sites with baseline probing depths (PD) ≥6 mm, 72% to 76% of sites in the SDD-40 group demonstrated clinically significant PD reductions and clinical attachment level (CAL) gains ≥2 mm compared to 56% to 58% of sites in the placebo group ($P < 0.0001$); 48% to 52% of sites in the SDD-40 group demonstrated PD reductions and CAL gains ≥3 mm compared to 32% of sites in the placebo group ($P < 0.0001$). In moderate sites (baseline PD 4 to 6 mm), adjunctive SDD-40 provided significant clinical benefits compared to placebo for mean CAL (all time points: $P < 0.05$), PD (3 months: $P = 0.002$; 6 and 9 months: $P = 0.001$), and bleeding on probing (BOP) (3 months: $P < 0.01$; 6 months: $P < 0.02$; 9 months: $P < 0.05$). In deep sites (baseline PD ≥7 mm), SDD-40 provided significant benefits over control for mean CAL (3 months: $P < 0.05$; 6 and 9 months: $P < 0.01$), PD (all time points: $P < 0.001$), and BOP (3 months: $P < 0.05$; 6 months: not statistically significant; 9 months: $P < 0.05$). Compliance with study medication was high (>92%) with no significant differences in adverse events between groups and no evidence of microbiologically significant changes or development of antibiotic resistance in the subgingival flora in either group. Conclusion: SDD-40 used as an adjunct to SRP resulted in significantly greater clinical benefits than SRP alone in the treatment of periodontitis.] Preshaw PM, Novak MJ, et al. *Journal of Periodontology, 2008, Vol. 79, No. 3, Pages 440-452.* http://www.joponline.org/doi/abs/10.1902/jop.2008.070375?journalCode=jop

1094. **Modulation of the Host Response in Periodontal Therapy.** [This paper was prepared by the Research, Science, and Therapy Committee of the American Academy of Periodontology to provide the dental profession an overview of current and potential methods to modulate the host response in the treatment of periodontal diseases. Specifically, it discusses components of periodontal disease pathogenesis (i.e., immune and inflammatory responses, excessive production of matrix metalloproteinases and arachidonic acid metabolites, and regulation of bone metabolism) and their modulation.] Academy Report – Informational Paper. *J Periodontol 2002;73:460-470.* http://www.perio.org/resources-products/pdf/35-hostresponse.pdf

1095. **New Applications of Doxycycline Hyclate in Medicine and Dentistry.** [Tetracyclines are used in medicine and dentistry because of their unique properties as bacteriostatic antimicrobials.[1] They function by inhibiting bacterial multiplication and growth. In addition to their antimicrobial effects, tetracyclines have anti-inflammatory properties. Another property of tetracyclines is their unexpected activity at su bantimicrobial doses. This property was discovered by Golub et al in 1983, when they administered minocycline to germ-free, diabetic rats with periodontal disease.[2] The experiment resulted in a 65% to 70% reduction in collagenase activity in the gingival tissue and was associated with preventing alveolar bone loss.

Subsequent studies by Golub with chemically modified tetracyclines (CMTs) helped to confirm their nonantimicrobial properties. By removing the dimethylamino group from the carbon-4 position of the "A" ring of the tetracycline molecule,[3] Golub and his colleagues were able to show that tetracycline exerted a unique property that was independent of its antimicrobial effects. The CMTs showed no antimicrobial effect but rather inhibited an enzyme called collagenase, which is produced by host neutrophils (white blood cells) and structural cells (eg, fibroblasts and osteoclasts). … Pharmacologic advancements in the treatment of inflammatory and immune diseases including periodontitis, acne vulgaris, and rosacea have skewed toward host-modulation therapy rather than traditional antibiotic therapy. This new approach has not been documented to cause bacterial resistance because it uses low-enough doses of doxycycline hyclate to avoid eliciting bacterial resistance. It is directed toward inhibiting collagenase and other MMPs, which are responsible for the pathological destruction of collagen, the major component of bone and soft tissues in the body. Many clinical studies demonstrate that doxycycline hyclate 20 mg is safe and effective in the adjunctive treatment of chronic periodontitis, and one completed clinical study in acne patients show that this formulation is also safe and effective in controlling inflammatory lesions.[36] Currently, clinical studies are being conducted to evaluate the effectiveness of doxycycline hyclate 20 mg tablets in the treatment of rosacea. Other studies will involve patients with blepharitis, periodontal implantitis, postmenopausal osteopenia, and perioral dermatitis. It is important for pharmacists to realize that the indications for doxycycline hyclate 20 mg tablets are not the same as for the tetracyclines, which are used as antibiotics. Rather than acting as an antimicrobial, doxycycline hyclate 20 mg is a nonantimicrobial that is used in subantimicrobial, low-dose formulation. Thus, this product should not be substituted for a less expensive, generic doxycycline formulation (eg, either used as 50-mg or split 50-mg tablets or capsules). Currently, there is no substitute for doxycycline hyclate 20 mg tablets (Periostat), and the product should be dispensed as written on the prescription. Substitution with other formulations of doxycycline may place the patient at risk for the emergence of antibiotic and bacterial resistance. Studies have demonstrated that doxycycline hyclate 20 mg tablets can be used safely and effectively for nine to 12 months.] Weinberg MA. *U.S. Pharmacist Vo..No:29:04, 4/15/2004.* http://www.uspharmacist.com/index.asp?show=article&page=8_1250.htm

1096. **Non-antibacterial tetracycline formulations: clinical applications in dentistry and medicine.** [In 1983, it was first reported that tetracyclines (TCs) can modulate the host response, including (but not limited to) inhibition of pathologic matrix metalloproteinase (MMP) activity, and by mechanisms unrelated to the antibacterial properties of these drugs. Soon thereafter, strategies were developed to generate non-antibacterial formulations (subantimicrobial-dose doxycycline; SDD) and compositions (chemically modified tetracyclines; CMTs) of TCs as host-modulating drugs to treat periodontal and other inflammatory diseases. This review focuses on the history and rationale for the development of: (a) SDD which led to two government-approved medications, one for periodontitis and the other for acne/rosacea and (b) CMTs, which led to the identification of the active site of the drugs responsible for MMP inhibition and to studies demonstrating evidence of efficacy of the most potent of these, CMT-3, as an anti-angiogenesis agent in patients with the cancer, Kaposi's sarcoma, and as a potential treatment for a fatal lung disease (acute respiratory distress syndrome; ARDS). In addition, this review discusses a number of clinical studies, some up to 2 years' duration, demonstrating evidence of safety and efficacy of SDD formulations in humans with oral inflammatory diseases (periodontitis, pemphigoid) as well as medical diseases, including rheumatoid arthritis, post-menopausal osteopenia, type II diabetes, cardiovascular diseases, and a rare and fatal lung disease, lymphangioleiomyomatosis.] Gu Y, Walker C, Golub LM, et al. *J Oral Microbiol*. 2012;4. doi: 10.3402/jom.v4i0.19227. Epub 2012 Oct 12. http://www.ncbi.nlm.nih.gov/pubmed/23071896

1097. **Periodontal Disease**. [Research on the protective effects of common no-steroidal anti-inflammatory drugs (NSAIDs) and tetracyclines led to the concept of host modulation as a therapy for the cessation of periodontitis progression.] William RC. N Engl J Med 1990;322:373-382. http://content.nejm.org/content/vol322/issue6/index.shtml

1098. **Periodontal Host Modulation with Antiproteinase, Anti-Inflammatory, and Bone-Sparing Agents.A Systematic Review.** [Background:The use of modulating agents, including inhibition of matrix metalloproteinases (MMPs) with antiproteinases, blocking production of proinflammatory cytokines and prostaglandins with antiinflammatory drugs, and inhibiting activation of osteoclasts with bone-sparing agents, has been postulated to be of therapeutic value as an adjunctive therapy to the management of chronic periodontitis. Rationale:The objective of this systematic review of the literature was to assess the adjunctive efficacy of antiproteinase, anti-inflammatory, and bone-sparing host-modulating agents in the treatment of gingivitis, aggressive periodontitis, and chronic periodontitis. … Reviewers' Conclusions: 1. Large multi-center trials are needed to evaluate the role of host-modulating agents in the treatment of periodontitis. 2. NSAIDS and bisphosphonate drugs may have a potential adjunctive role in periodontal therapy. 3. The adjunctive use of SDD with SRP is statistically more effective than SRP alone in reducing PD and in achieving CAL gain.] Reddy MS, Geurs NC, et al. *Annals of Periodontology, December 2003, Vol. 8, No. 1, Pages 12-37.* http://www.joponline.org/doi/abs/10.1902/annals.2003.8.1.12

1099. **Regulation of matrix metalloproteinase production by cytokines, pharmacological agents and periodontal pathogens in human periodontal ligament fibroblast cultures.** [Matrix metalloproteinases (MMPs), produced by both infiltrating and resident cells of the periodontium, play a role in physiologic and pathologic events. It is recognized that an imbalance between activated MMPs and their endogenous inhibitors leads to pathologic breakdown of the extracellular matrix during periodontitis. To date, little is known about the regulation of MMP synthesis and secretion in human periodontal ligament fibroblasts (PDLFs). The purpose of this study was to examine the effects of cytokines, pharmacological agents (protein synthesis inhibitor and protein kinase C inhibitors) and predominant periodontal pathogens (*Actinobacillus actinomycetemcomitans* and *Porphyromonas gingivalis*) on MMP production in human PDLFs using gelatin zymography. The gelatin zymograms revealed that the main gelatinase secreted by human PDLFs migrated at 72 kDa and represents

MMP-2. Minor gelatinolytic bands were also observed at 92 kDa regions that correspond to MMP-9. We found that *A. actinomycetemcomitans*, *P. gingivalis* and IL-1α can elevate MMP-2 secretion in human PDLFs. These results indicate that periodontal pathogens and inflammatory cytokines play an important role in tissue destruction and disintegration of extracellular matrix in periodontal diseases. Thus, activation of MMPs may be one of the distinct host degradative pathways in the pathogenesis of periodontitis. In addition, H7, staurosporine, cycloheximide and TGF-β could suppress MMP-2 production. Agents that target protein synthesis or the protein kinase C pathway in human PDLFs inhibit MMP-2 production, and such inhibition may contribute to the pathogenesis of periodontal inflammation. Taken together, these findings suggest a possible new therapeutic approach, involving the use of drugs that modify host-response mechanisms to suppress or inhibit MMP-mediated tissue destruction.] Chang YC, Yang SF, et al. *Journal of Periodontal Research*, Vol 37, Issue 3, Pp 196-203, Jun 28, 2008. http://www3.interscience.wiley.com/journal/118943882/abstract?CRETRY=1&SRETRY=0

1100. **Safety and Efficacy of sub-Antimicrobial-Dose Doxycycline Therapy in Patients with Adult Periodontitis.** [The objectives of the studies presented here were to assess the safety and efficacy of the adjunctive administration of sub-antimicrobial-dose doxycycline (SDD) for the treatment of adult periodontits and to confirm the optimal dosing regimen. The studies summarized including four double-blind, placebo-controlled, randomized clinical trials, conducted over a period of 9 to 12 months. Analysis of efficacy data demonstrated that adjunctive SDD treatment resulted in: (1) increases in clinical attachment levels; (2) decreases in probing pocket depths; and (3) reductions in bleeding on probing in patients with adult periodontitis. There were no significant adverse avents or unwanted long-term antimicrobial effects associated with orally administered SDD. The results of these clinical trials indicate that the adjunctive use of SDD 20 BID is an effective and well-tolerated regimen which can significantly improve several indices of periodontal health.] Ciancio S. *Adv Dent Res 12:27-31, November, 1998.* http://adr.iadrjournals.org/cgi/reprint/12/2/27.pdf

1101. **Subantimicrobial Dose Doxycycline as an Adjunct to Scaling and Root Planing: Post-treatment Effects.** [Background/objective: Subantimicrobial dose doxycycline (SDD 20 mg BID) plus scaling and root planing (SRP) significantly improved clinical attachment level (CAL) and reduced probing depth (PD) compared with placebo plus SRP in double-blind, placebo-controlled, multicenter study of patients with adult periodontitis (AP). In a study conducted as a follow-up, the posttreatment effects of SDD were assessed in patients who completed the SRP study. Methods: The SRP study was a 9-month, active-treatment study and the follow-up was a 3-month, no treatment study. In the SRP study, tooth sites in qualifying quadrants were scaled and root planed and patients were randomized to receive SDD 20 mg or placebo twice daily. In the follow-up, patients received no study drug; investigators and patients remained blinded to the previous treatment group assignments. Efficacy measures included the change in CAL and PD from baseline values determined at the start of the SRP study in tooth sites stratified by baseline PD (ie, 0-3 mm, 4-6 mm, = 7 mm). Safety was evaluated using adverse event data and the results of clinical laboratory tests, oral pathology examinations, and microbiological assessments. Results: Within each disease stratum, the incremental improvements in PD and CAL demonstrated in the SDD group over 9 months of active treatment were maintained through 3 additional months of no treatment. Treatment cessation did not result in an accelerated regression of periodontal health. No differences in the incidence of adverse events (including those related to infection) or laboratory or microbiological parameters were noted between the SDD group and the placebo group. Conclusion: The administration of SDD 20 mg BID for a period of up to 9 months is not associated with rebound effects or delayed or negative after-effects for a 3-month period after cessation of therapy.] *J Clin Periodontol.* 2001;28:782-789. http://www.ncbi.nlm.nih.gov/pubmed/11442739

1102. **Subantimicrobial Dose Doxycycline Effects on Alveolar Bone Loss in Postmenopausal Women.** [Recent studies demonstrate the ability of SDD to be used to maintain bone mass while reducing periodontal disease in patients with decreased bone mass (as in the situation of post-menopausal osteoporosis). In postmenopausal osteopenic women with periodontitis, SDD did not differ overall from placebo. Based on exploratory subgroup analyses, additional research is needed to determine the usefulness of SDD in non-smokers, subjects > 5 years postmenopausal and in deeper pockets] Payne JB, Stoner JA, et al. J Clin Periodontol. 2007 September; 34(9): 776–787.
http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2174266
http://www.joponline.org/doi/abs/10.1902/jop.2008.070623?journalCode=jop

1103. **Subantimicrobial Dose Doxycycline Efficacy as a Matrix Metalloproteinase Inhibitor in Chronic Periodontitis Patients Is Enhanced When Combined With a Non-Steroidal Anti-Inflammatory Drug.** [Background: Administration of subantimicrobial dose doxycycline (SDD) to chronic periodontitis (CP) patients has repeatedly been found to reduce mammalian collagenase and other matrix metalloproteinase (MMP) activity in gingival tissues and crevicular fluid, in association with clinical efficacy, without the emergence of antibiotic-resistant bacteria either orally or extra-orally. More recently, SDD adjunctive to repeated mechanical debridement resulted in dramatic clinical improvement in patients (>50% smokers) with generalized aggressive periodontitis. As an additional pharmacologic approach, non-steroidal anti-inflammatory drugs (NSAIDs) can reduce gingival inflammation and alveolar bone resorption, at least under experimental conditions. In the current study, we determined the effect of administering a combination (combination) of these two host-modulating drugs (SDD plus low-dose NSAID) to CP patients, on selected neutral proteinases in gingiva, enzymes believed to mediate periodontal breakdown. Earlier preliminary studies in humans with bullous pemphigoid, which is also associated with excessive levels of host-derived proteinases including MMPs, indicated improved clinical efficacy of combination therapy. Methods: Nineteen CP patients, scheduled for mucoperiosteal flap surgery bilaterally in the maxillary arch, were randomly distributed into three experimental groups administered either 1) low-dose flurbiprofen (LDF) alone, 50 mg q.d.; 2) SDD (20 mg b.i.d.) alone; or 3) a combination of SDD plus LDF (combination). The gingival tissues were biopsied during

surgery from right and left maxillary posterior sextants, before and after a 3-week regimen of medication, respectively. The tissues were then extracted, the extracts partially purified, then analyzed for the endogenous proteinase inhibitor, α1-PI, and its breakdown product, and for host-derived matrix metalloproteinases (i.e., collagenases, gelatinases) and neutrophil elastase activities. Results: Short-term therapy with SDD alone produced a significant reduction and LDF alone produced no reduction in host-derived neutral proteinases. However, the combination therapy produced a statistically significant synergistic reduction of collagenase, gelatinase, and serpinolytic (α1-PI degrading) activities (69%, 69%, and 75% reductions, respectively) and a lesser reduction of the serine proteinase, elastase (46%). Conclusions: Consistent with previous studies on animal models of chronic destructive disease (e.g., rheumatoid arthritis), the SDD and NSAID combination therapy synergistically suppressed MMP and other neutral proteinases in the gingiva of CP patients. A mechanism, suggested by earlier animal studies, involves the NSAID, in the combination regimen, increasing the uptake of the tetracycline-based MMP inhibitor in the inflammatory lesion, thus synergistically enhancing the efficacy of this medication.] Lee HM, Ciancio SG, Golub L, et al. *J Periodontol 2004;75:453-463.* http://www.joponline.org/doi/abs/10.1902/jop.2004.75.3.453?journalCode=jop

1104. **Subantimicrobial-Dose Doxycycline Modulates Gingival Crevicular Fluid Biomarkers of Periodontitis in Postmenopausal Osteopenic Women.** [Background: We recently demonstrated that a 2-year subantimicrobial-dose doxycycline (SDD) regimen (double-masked, placebo-controlled clinical trial) in postmenopausal (PM) women exhibiting mild systemic bone loss (osteopenia) and local bone loss (periodontitis) reduced the progression of periodontal attachment loss (intent-to-treat analysis) and the severity of gingival inflammation and alveolar bone loss (subgroups) without producing antibiotic side effects. We now describe SDD effects on biomarkers of collagen degradation and bone resorption in the gingival crevicular fluid (GCF) of the same vulnerable subjects. Methods: GCF was collected from SDD- and placebo-treated PM subjects (n = 64 each) at the baseline and 1- and 2-year appointments; the volume was determined; and the samples were analyzed for collagenase activity (using a synthetic peptide as substrate), relative levels of three genetically distinct collagenases (Western blot), a type-1 collagen breakdown product/bone resorption marker (a carboxyterminal telopeptide cross-link fragment of type I collagen [ICTP]; radioimmunoassay), and interleukin-1β (enzyme-linked immunosorbent assay). Statistical analyses were performed using generalized estimating equations; primary analyses were intent-to-treat. Results: Collagenase activity was significantly reduced by SDD treatment relative to placebo based on intent-to-treat (P = 0.01). ICTP showed a similar pattern of change during SDD treatment, and GCF collagenase activity and ICTP were positively correlated at all time periods (P <0.001). Matrix metalloproteinase (MMP)-8 accounted for ~80% of total collagenase in GCF, with much less MMP-1 and -13, and SDD reduced the odds of elevated MMP-8 by 60% compared to placebo (P = 0.006). Conclusion: These observations support the therapeutic potential of long-term SDD therapy to reduce periodontal collagen breakdown and alveolar bone resorption in PM women; effects on serum biomarkers of systemic bone loss in these subjects are being analyzed.] Golub LM, Lee HM, et al. *Journal of Periodontology, 2008, Vol. 79, No. 8, Pages 1409-1418* , http://www.joponline.org/doi/abs/10.1902/jop.2008.070623

1105. **Subantimicrobial Doses of Tetracycline.** [Editorial Response: We appreciate the interest of Dr Pallasch in our recent publication. However we are surprised that a manuscript that makes no claim regarding the impact of low doses of doxycycline on indigenous microbial flora or microbial resistance has stimulated his current letter. Although the in vitro studies on limited numbers of isolates cited by Dr Pallasch have shown a number of multiple resistance mechanisms, this finding has never been found to have clinical relevance in human populations. In fact, review of national data (400 000 isolates) by electronic surveillance has shown exactly the opposite. In tracking the sensitivity profiles to 23 different antibiotics in clinical specimens, patterns of tetracycline resistance have remained essentially unchanged after adjustment for CDC region, type of institution, consumption of tetracycline-containing food products, and the introduction of low-dose doxycycline for the treatment of periodontal disease (Periostat) in 1998. Furthermore, there was no evidence that tetracycline selected for cross-resistance. Nor did the development of tetracycline resistance promote the progression from cutaneous to blood-borne infection, indicating tetracycline resistance is neither a virulence factor nor a survival factor. Dr Pallasch seems unaware of the emerging science of Host Modulation Therapy (HMT) for chronic diseases in which biofilms are implicated in their pathogenesis. The recognition of the importance of biofilms in the pathogenesis of cystic fibrosis, otitis media, endocarditis, periodontitis, and indwelling catheter infections has led to a new era of research and treatment in which a combination of anti-infectives and immune modulators are complementary in disease management. Subinhibitory concentrations of tetracycline and macrolide antibiotics have both been used successfully as biologic modifiers without any evidence of the development of clinically significant microbial resistance. Finally, we agree with Dr Pallasch that construction of a risk-benefit ratio is always important when evaluating a potential new therapy. However, in this case it must be borne in mind that tetracyclines are rarely if ever used in the treatment of patients with life-threatening infections, and cardiovascular disease is the leading cause of death in industrialized nations. Thus, the risk-benefit ratio strongly favors further investigation of low-dose doxycycline to treat cardiovascular disease.] Pallasch T, Brown DL, Golub LM, et al. *Arteriosclerosis, Thrombosis, and Vascular Biology.* 2004;24:e163.) http://atvb.ahajournals.org/cgi/reprint/24/9/e163.pdf

1106. **Targeting the Host. [**For years, we believed that poor oral hygiene and age were the primary predictors of periodontal disease in humans. After 20 years of fighting plaque, I can truly appreciate the other side of the imbalance — the host immune response. … Dr. Ray Williams blames innate risk factors, which include gender, neutrophil function, and genetics. We finally have scientific evidence that much of periodontal disease can be attributed to heredity. So how do we incorporate that information into our practices? One thing is certain; no one wants to feel blamed or guilty about disease. Telling your patient that the problem is genetic often results in a sigh of relief. We still, however, must address oral hygiene

and do a thorough root planing. And we must educate our patients on the role of the host response in their disease. Recent research by Dr. Roy Page indicates that genetics are responsible for 50 percent of patients' susceptibility. The good news to our patients is that we can adjust the way our body reacts to pathogens. We now have a way to address the host response through host modulatory therapy (HMT). … At this time, there is only one HMT available. Periostat® (doxycycline hyclate) is a 20 mg tablet. The original concept for Periostat was developed by Dr. L.M. Golub.[2] When used as a subantimicrobial dosage, Periostat decreases the production of harmful enzymes, while having no effect on the level of periodontal microorganisms. By decreasing the activity of these enzymes there is a reduction in tissue and alveolar bone break down. When compared to scaling and root planing alone, mechanical therapy combined with Periostat results in statistically significant reduction in pocket depths, bleeding, better attachment, and prevention of disease progression.**]** Braswell L. Woman Dentist Journal. http://www.wdjournal.com/display_article/199715/76/none/none/FocPR/Targeting-the-host

1107. **The "Cyclic" Regimen of Low-Dose Doxycycline for Adult Periodontitis: A Preliminary Study.** Specially formulated low-dose doxycycline (LDD) regimens have been found to reduce collagenase activity in the gingival tissues and gingival crevicular fluid (GCF) of adult periodontitis subjects in short-term studies. In the current, double-blind, placebo-controlled study, adult periodontitis patients were administered a "cyclical" regimen of either LDD or placebo capsules for 6 months, and various clinical parameters of periodontal disease severity, both collagenase activity and degradation of the serum protein, and α_1-PI in the GCF were measured at different time periods. No significant differences between the LDD- and placebo-treated groups were observed for plaque index and gingival index. However, attachment levels, probing depth, and GCF collagenase activity and α_1-PI degradation were all beneficially and significantly ($P < 0.05$) affected by the drug regimen. We propose: 1) that LDD inhibits tissue destruction in the absence of either antimicrobial or significant anti-inflammatory efficacy; and 2) that long-term LDD could be a useful adjunct to instrumentation therapy in the management of the adult periodontitis patient.] Crout RJ, Lee HM, et al. *J Periodontol.* 1996;67:506-514. http://www.ncbi.nlm.nih.gov/pubmed/8724709

1108. **The Effect of Adjunctive Low-Dose Doxycycline Therapy on Clinical Parameters and Gingival Crevicular Fluid Matrix Metalloproteinase-8 Levels in Chronic Periodontitis.** [**Background:** Low-dose doxycycline (LDD) is recognized to have non-antimicrobial properties that can therapeutically modulate the host response. The aim of the present randomized, double-blind, placebo-controlled, parallel-arm study was to examine the effectiveness of LDD in combination with non-surgical periodontal therapy, compared to non-surgical periodontal therapy alone, on gingival crevicular fluid (GCF) matrix metalloproteinase-8 (MMP-8) levels and clinical parameters over a 12-month period in patients with chronic periodontitis. Methods: GCF samples were collected, and clinical parameters including probing depth (PD), clinical attachment level, gingival index (GI), and plaque index were recorded. Thirty chronic periodontitis patients were randomized either to a low-dose doxycycline (LDD) or placebo group. The LDD group received lowdose doxycycline (20 mg) b.i.d. for 3 months plus scaling and root planing (SRP), while the placebo group was given placebo capsules b.i.d. for 3 months plus SRP. The patients were evaluated every 3 months during the 12-month study period. At each visit, all clinical measurements and GCF sampling were repeated. GCF MMP-8 levels were determined by a time-resolved immunofluorescence assay. Intragroup comparisons were tested by the Friedman test followed by Wilcoxon signed-rank test to analyze significance of changes over time. The Mann-Whitney test was used to determine differences between the LDD and placebo groups. Results: Significant improvements were observed in all clinical parameters in both groups over the 12-month period (P <0.0125). The LDD group showed a significantly greater reduction in mean PD scores at 9 and 12 months and in mean GI scores at all time points than the placebo group (P <0.05). From baseline to 12 months, GCF MMP-8 levels were significantly reduced in both groups (P <0.0125). The GCF MMP-8 level in the LDD group was significantly lower than that of the placebo group at 6 months (P <0.05). Conclusions: The present results indicate that low-dose doxycycline therapy in combination with scaling and root planing can reduce GCF MMP-8 levels and improve clinical periodontal parameters in patients with chronic periodontitis. These results provide additional information about the usefulness of low-dose doxycycline therapy as an adjunct to non-surgical periodontal therapy in the long-term management of periodontal disease. The effectiveness and course of low-dose doxycycline therapy can be monitored conveniently by assessing GCF MMP-8 levels. *J Periodontol 2004;75:106-115.*] Emingil G, Atilla G, et al. *Journal of Periodontology, January 2004, Vol. 75, No. 1, Pages 106-115.* http://www.joponline.org/doi/abs/10.1902/jop.2004.75.1.106

1109. **The effects of the initial treatment phase and of adjunctive low-dose doxycycline therapy on clinical parameters and MMP-8, MMP-9, and TIMP-1 levels in the saliva and peripheral blood of patients with chronic periodontitis.** [*Introduction* The treatment of periodontal disease can consist of bacterial plaque reduction, risk factor elimination, and metalloproteinase inhibitor medication. The level of matrix metalloproteinases (MMPs) are regulated by endogenous tissue inhibitors of metalloproteinases (TIMPs) as well as therapeutic low-dose doxycycline. The aim of the study was to evaluate the effect of the initial phase of periodontal treatment and the effect of doxycycline on clinical parameters and the MMP-8, MMP-9, and TIMP-1 concentrations in the saliva and peripheral blood of patients with chronic periodontitis. *Materials and Methods* The study group consisted of 33 patients with chronic periodontitis. Conventional periodontal treatment (scaling and root planing) was conducted on all the patients and doxycycline (20 mg orally) was administered twice daily for three months. Thirty-three controls received the conventional treatment only. Clinical scores (PI, BI, PD, CAL) were recorded before and three months after the treatment. MMP-8, MMP-9, and TIMP-1 concentrations in saliva and peripheral blood were measured by ELISA before and after the treatment of 20 patients from the study group and 13 of the controls. *Results* The application of doxycycline 20 mg resulted in significant improvement in clinical parameters compared with the conventional periodontal treatment. Doxycycline did not produce significant reductions in MMP-8 and

MMP-9 levels in saliva observed after the conventional treatment. The study revealed increases in the TIMP-1 concentration and the MMP-8/TIMP-1 and MMP-9/TIMP-1 ratios in saliva and blood after treatment with doxycycline. *Conclusions* The study confirmed the modulating effect of doxycycline on the host response in chronic periodontitis.] Gorska R, Nedzi-Gora M. *Archivum Immunologiae et Therapiae Experimentalis, Vol 54, Number 6 / Dec, 2006.* http://www.springerlink.com/content/t2484m8362nru1vt/

1110. **Treatment with subantimicrobial dose doxycycline improves the efficacy of scaling and root planing in patients with adult periodontitis.** [BACKGROUND: In a previous study, subantimicrobial dose doxycycline (SDD) significantly improved clinical parameters associated with periodontal health in patients with adult periodontitis (AP) when used as an adjunct to a maintenance schedule of supragingival scaling and dental prophylaxis. In this double-blind, placebo-controlled, parallel-group, multicenter study, the efficacy and safety of SDD were evaluated in conjunction with scaling and root planing (SRP) in patients with AP. METHODS: Patients (n = 190) received SRP at the baseline visit and were randomized to receive either SDD 20 mg bid or placebo bid for 9 months. Efficacy parameters included the per-patient mean changes in clinical attachment level (CAL) and probing depth (PD) from baseline, the per-patient percentages of tooth sites with attachment loss (AL) > or = 2 mm and > or = 3 mm from baseline, and the per-patient percentage of tooth sites with bleeding on probing. Prior to analysis, tooth sites were stratified by the degree of disease severity evident at baseline RESULTS: In tooth sites with mild to moderate disease and severe disease (n = 183, intent-to-treat population), improvements in CAL and PD were significantly greater with adjunctive SDD than with adjunctive placebo at 3, 6, and 9 months (all P <0.05). In tooth sites with severe disease, the per-patient percentage of sites with AL > or = 2 mm from baseline to month 9 was significantly lower with adjunctive SDD than with adjunctive placebo (P<0.05). Improvements in clinical outcomes occurred without detrimental shifts in the normal periodontal flora or the acquisition of doxycycline resistance or multiantibiotic resistance. SDD was well tolerated, with a low incidence of discontinuations due to adverse events. CONCLUSIONS: The adjunctive use of SDD with SRP is more effective than SRP alone and may represent a new approach in the long-term management of AP.] Caton JG, Ciancio SG, et al. *J Periodontol. 2000 Apr;71(4):521-32.* http://www.ncbi.nlm.nih.gov/pubmed/10807113

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1111. **A Review of Premature Birth and Subclinical Infection.** [This article reviews the evidence linking subclinical infection and premature birth. Evidence of subclinical infection as a cause of preterm labor is raised by finding elevated maternal serum C-reactive protein and abnormal amniotic fluid organic acid levels in some patients in preterm labor. Biochemical mechanisms for preterm labor in the setting of infection are suggested by both in vitro and in vivo studies of prostaglandins and their metabolites, endotoxin and cytokines.] Gibbs RS, Romero R, et.al., *Am J Obstet Gynecol* 166:1515-28, 1992. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=92280938

1112. **Adverse Pregnancy Outcomes and Periodontal Disease.** [Periodontitis is a chronic inflammatory disease caused mainly by gram-negative bacteria. It is believed that periodontitis can contribute to adverse outcomes of pregnancy. Toxins or other products generated by periodontal bacteria in the mother can reach the blood circulation, cross the placenta, and harm the foetus. In addition, the response of the mother's immune system to the infection activates the release of inflammatory mediators, growth factors and other potent cytokines, which may trigger preterm labour.] World Health Organization, http://www.whocollab.od.mah.se/expl/systpreterm.html

1113. **Bacterial foci in the teeth, oral cavity, and jaw--secondary effects (remote action) of bacterial colonies with respect to bacteriospermia and subfertility in males**. [Bacteriospermia requiring medical treatment were diagnosed in more than 70% of the subfertile patients who had since 1988 attended the gynecological clinic at the RWTH hospital in Aachen. In 23% of all cases specific treatment with antibiotics did not reduce the concentrations of bacteria in sperma. Thirty-six patients with bacteriospermia resistant to antibiotic therapy were then subjected to dental examination. A high incidence of potential dental foci was found in all patients. In a test group of 18 patients these sources of potential infection were eliminated. Between dental operations and therapy swabs were taken to determine bacterial levels and bacteriological composition. It could be demonstrated that the bacterial spectrum of the intraoral samples was almost identical with the spermiograms. Six months following completion of dental treatment a further spermiogram analysis was carried out. In the test group about two thirds of the spermiograms proved sterile. Spermatological parameters, such as motility, density and morphology, had also clearly improved. In the control group the findings of the spermiogram remained poor. This study indicates that a direct causal relationship exists between bacterial colonies (dental foci) and therapy-resistant bacteriospermia which probably leads to subfertility.] Bieniek KW, Riedel HH. *Andrologia*. 1993 May-Jun;25(3):159-62. http://www.ncbi.nlm.nih.gov/pubmed/8517556

1114. **Bacterial Infection Promotes DNA Hypermethylation.** [Maternal oral infection, caused by bacteria such as *C. rectus* or *P. gingivalis*, has been implicated as a potential source of placental and fetal infection and inflammatory challenge, which increases the relative risk for pre-term delivery and growth restriction. Intra-uterine growth restriction has also been reported in various animal models infected with oral organisms. Analyzing placental tissues of infected growth-restricted mice, we found down-regulation of the imprinted *Igf2* gene. Epigenetic modification of imprinted genes *via* changes in DNA methylation plays a critical role in fetal growth and development programming. Here, we assessed whether *C. rectus* infection mediates changes in the murine placenta *Igf2* methylation patterns. We found that infection induced hypermethylation in the

promoter region-P0 of the *Igf2* gene. This novel finding, correlating infection with epigenetic alterations, provides a mechanism linking environmental signals to placental phenotype, with consequences for development.] Bobetsis YA, Barros SP, et al. Journal of Dental Research, Vol. 86, No. 2, 169-174 (2007). http://jdr.sagepub.com/cgi/content/abstract/86/2/169

1115. **Detection of *Fusobacterium nucleatum* in chorionic tissues of high-risk pregnant women.** [Aim: The present study was undertaken to investigate the existence of a periodontopathic bacterium, *Fusobacterium nucleatum* in chorionic tissues of pregnant women, and the effects of *F. nucleatum* on human chorion-derived cells. Materials and Methods: Oral and chorionic tissue samples were collected from 24 high-risk pregnant women and 15 normal pregnant women. The presence of *F. nucleatum* in the samples was detected by polymerase chain reaction. Chorion-derived cells and Toll-like receptor (TLR)-2 or TLR-4 gene-silenced chorion-derived cells were stimulated with *F. nucleatum* lipopolysaccharide (LPS). Interleukin (IL)-6 and corticotrophin-releasing hormone (CRH) levels in the culture supernatants were measured by ELISA. Results: *F. nucleatum* was detected in all oral samples and seven chorionic tissues from the high-risk pregnant women, but was not detected in chorionic tissues from the normal pregnant women. *F. nucleatum* LPS significantly increased IL-6 and CRH secretion by chorion-derived cells. The *F. nucleatum* LPS-induced IL-6 and CRH levels were significantly reduced in TLR-2 or TLR-4 gene-silenced chorion-derived cells. Conclusions: We suggest that *F. nucleatum* is detected in chorionic tissues of high-risk pregnant women, but not in chorionic tissues of normal pregnant women, and that *F. nucleatum* induces IL-6 and CRH production via both TLR-2 and TLR-4 in chorion-derived cells.] Tateishi F, Hasegawa-Nakamura K, et al. *Journal of Clinical Periodontology*, DOI: 10.1111/j.1600-051X.2012.01855.x. http://onlinelibrary.wiley.com/doi/10.1111/j.1600-051X.2012.01855.x/abstract?systemMessage=Wiley+Online+Library+will+be+disrupted+4+Feb+from+10-12+GMT+for+monthly+maintenance

1116. **Diseases of the masticatory system as possible causal factors in infertility.** [In this study 36 subfertile patients between 25 and 43 years, in whom asymptomatic bacteriosperms with a concentration of 10(5)/ml or higher could be shown despite an antibiotic directed therapy in which no count reduction was observed, were examined in the Dept. for Dental Prosthetics. A lot of intraoral foci were found, which got eliminated. Intra-operational bacterial specimens were taken and evaluated by a special diagnostic technique in the Dept. of Microbiology. It was shown, that the bacterial spectrum of the intraoral specimens and the spermiograms were identical. 6 months after completion of the dental therapy and intensive oral hygiene instructions a new andrological examination was performed. Two thirds of the spermiograms were already sterile. A direct causal relationship between dental primary diseases and asymptomatic bacteriosperms, which probably leads to subfertility, must be concluded.] Bieniek KW, Riedel HH. *ZWR*. 1989 Oct;98(10):850, 852, 854. http://www.ncbi.nlm.nih.gov/pubmed/2639537

1117. **Effects of periodontal therapy on rate of preterm delivery: a randomized controlled trial.** [OBJECTIVE: To test the effects of maternal periodontal disease treatment on the incidence of preterm birth (delivery before 37 weeks of gestation). METHODS: The Maternal Oral Therapy to Reduce Obstetric Risk Study was a randomized, treatment-masked, controlled clinical trial of pregnant women with periodontal disease who were receiving standard obstetric care. Participants were assigned to either a periodontal treatment arm, consisting of scaling and root planing early in the second trimester, or a delayed treatment arm that provided periodontal care after delivery. Pregnancy and maternal periodontal status were followed to delivery and neonatal outcomes until discharge. The primary outcome (gestational age less than 37 weeks) and the secondary outcome (gestational age less than 35 weeks) were analyzed using a chi test of equality of two proportions. RESULTS: The study randomized 1,806 patients at three performance sites and completed 1,760 evaluable patients. At baseline, there were no differences comparing the treatment and control arms for any of the periodontal or obstetric measures. The rate of preterm delivery for the treatment group was 13.1% and 11.5% for the control group (P=.316). There were no significant differences when comparing women in the treatment group with those in the control group with regard to the adverse event rate or the major obstetric and neonatal outcomes. Periodontal therapy did not reduce the incidence of preterm delivery.]. Offenbacher S, Beck JD, et al. *Obstet Gynecol* 2009;114(3):551-559. http://www.ncbi.nlm.nih.gov/pubmed/19701034

1118. **Evaluation of the Incidence of Preterm Low Birth Weight in Patients Undergoing Periodontal Therapy.** [Background: Preterm low birth weight was reported to be related to periodontal infections that might influence the fetus–placenta complex. The aim of this study was to provide periodontal treatment for pregnant women and to evaluate if this treatment can interfere with pregnancy duration and weight of the newborn. Methods: The sample consisted of 450 pregnant women who were under prenatal care at a polyclinic in Três Corações, Brazil. Women with risk factors, such as systemic alterations (ischemic cardiopathy, hypertension, tuberculosis, diabetes, cancer, anemia, seizure, psychopathology, urinary tract infection, sexually transmitted diseases, asthma, and human immunodeficiency virus), and/or users of alcohol, tobacco, and drugs were excluded from the study. Data related to age, socioeconomic level, race, marital status, number of previous pregnancies, and previous preterm delivery also were evaluated. Initially, the sample was divided into two groups: 122 healthy patients (group 1) and 328 patients with periodontal disease (group 2). In group 2, 266 patients underwent treatment and 62 patients dropped out. After mothers gave birth, pregnancy duration and the weight of all infants were analyzed and recorded. Results: There was no statistical difference between the healthy and treated groups. However, there was a difference in the non-treated group, with a 79% incidence of preterm low birth weight. Educational level, previous preterm birth, and periodontal disease were related significantly to preterm delivery (P <0.001). Conclusion: Periodontal disease was related significantly to preterm low birth weight.] Gazolla CM, Ribeiro A, et al. Journal of Periodontology, 2007, Vol. 78, No. 5, Pages 842-848. http://www.joponline.org/doi/abs/10.1902/jop.2007.060295

1119. **Exploring the relationship between periodontal disease and pregnancy complications.** [Obstetric complications not only are a significant health care expense, but also affect the well-being of the affected infants throughout life. Maternal infection with periodontal pathogens has a deleterious effect on fetal growth and viability. Treatments can be provided safely during pregnancy to improve the oral health of the mother. It is the responsibility of the dentist and the profession to inform patients about the biological plausibility that untreated periodontal disease may increase the risk not only of unfavorable pregnancy outcomes, but also of developing conditions that may affect the well-being of the offspring. There is no evidence of a down-side to providing care to mothers, which suggests that such treatment actually may be beneficial for two.] Bobetsis YA, Barros SP, et.al., *JADA, vol 137 Oct 2006 Supplement, pp.7s-13s.* http://jada.ada.org/content/vol137/suppl_2/index.dtl http://jada.ada.org/cgi/content/full/137/suppl_2/7S

1120. ***Fusobacterium nucleatum* Induces Premature and Term Stillbirths in Pregnant Mice: Implication of Oral Bacteria in Preterm Birth.** [*Fusobacterium nucleatum* is a gram-negative anaerobe ubiquitous to the oral cavity. It is associated with periodontal disease. It is also associated with preterm birth and has been isolated from the amniotic fluid, placenta, and chorioamnionic membranes of women delivering prematurely. Periodontal disease is a newly recognized risk factor for preterm birth. This study examined the possible mechanism underlying the link between these two diseases. *F. nucleatum* strains isolated from amniotic fluids and placentas along with those isolated from orally related sources invaded both epithelial and endothelial cells. The invasive ability may enable *F. nucleatum* to colonize and infect the pregnant uterus. Transient bacteremia caused by periodontal infection may facilitate bacterial transmission from the oral cavity to the uterus. To test this hypothesis, we intravenously injected *F. nucleatum* into pregnant CF-1 mice. The injection resulted in premature delivery, stillbirths, and nonsustained live births. The bacterial infection was restricted inside the uterus, without spreading systemically. *F. nucleatum* was first detected in the blood vessels in murine placentas. Invasion of the endothelial cells lining the blood vessels was observed. The bacteria then crossed the endothelium, proliferated in surrounding tissues, and finally spread to the amniotic fluid. The pattern of infection paralleled that in humans. This study represents the first evidence that *F. nucleatum* may be transmitted hematogenously to the placenta and cause adverse pregnancy outcomes. The results strengthen the link between periodontal disease and preterm birth. Our study also indicates that invasion may be an important virulence mechanism for *F. nucleatum* to infect the placenta.] Han YW, Redline RW, et al. *Infect Immun*. 2004 April; 72(4): 2272–2279. doi: 10.1128/IAI.72.4.2272-2279.2004. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC375172/

1121. **Healthy Births Initiative Blueprint.** [The role that infections play in preterm birth (particularly very early preterm birth) has been clearly established, and the interactions that occur with maternal and fetal immunity is increasingly understood. Microbes can cause LBW and preterm birth directly or through activation of maternal and fetal immune processes. Infection causes white blood cells (T-helper lymphocytes, TH 1) to specialize and release proteins called cytokines (i.e., gamma-interferon, tumor necrosis factor and interleukins) that increase the immune response and serve as crucial mediators of the body's immune-inflammatory responses. Considerable information from human studies and animal models is available regarding the mechanisms through which immune functioning mediates LBW and PTB. As part of the body's response to infection, a cascade of maternal and fetal enzymes (metalloproteases) that may precipitate preterm labor and preterm premature rupture of membranes (PPROM) can be released. Infections such as bacterial vaginosis (BV), asymptomatic bacteruria, sexually transmitted infections and periodontal infections have all been associated with increased risk for preterm delivery. Current investigations suggest that genetic variation in response to infection (e.g., increased inflammatory resonse) may place susceptible women at increased risk. A mother's ability to resist infection during pregnancy is dependent upon such factors as stress, nutritional status, and personal habits (e.g., smoking, substance use, douching) as well as genetics. Infection and inflammation during pregnancy may have other adverse consequences for the infant. Pro-inflammatory cytokines implicated in LBW and PTB have also been implicated in the pathogenesis of cerebral palsy in premature infants and maternal depression.] Los Angeles Best Babies Collaborative. http://www.first5la.org/docs/Projects/HB/LABBCHealthyBirthsBluePrint.pdf

1122. **Human Cytomegalovirus Transplacental Trasmission In Preeclamptics With Periodontitis**. [Cytomegalovirus infection of the placenta may be harmful leading to disorders in fetal growth, premature delivery, or major congenital abnormalities. Relationship between CMV and preeclampsia has been suggested. Although, transplacental CMV trasmission has been documented in preeclampsia the source of the CMV infection remains elusive. Subgingival CMV has been linked to increased periodontal disease severity. Very recently periodontal infection have been proposed as possible risk factor in preclampsia. Objectives:The aim of this study was to determine the frequency of transplacental CMV trasmission in hospitalized preeclamptics with periodontal inflammation. 29 preeclamptics with periodontitis and 10 with gingivitis were studied. Methods: CMV specific IgM and IgG antibodies were determined in placental blood samples from term placentae to examine fetal CMV infection and twice in maternal serum samples: a) at study enrollment 24 - 33 gestation weeks and, b) 24 hours after child delivery. In addition, CMV DNA was examined by PCR in the same samples and maternal Gingival Crevicular Fluid - GCF. Results: Six umbilical cord blood samples resulted IgM+. In five of those cases the mother had periodontitis and 1 case had gingivitis. Five mothers that trasmitted the CMV to their children were also CMV+ in the GCF (PCR) and only one was IgM+ in maternal serum at the study enrollment. Maternal blood samples were CMV negative by PCR at inclusion and postpartum. Conclusion: this study reported a very high rate (15%) of transplacental CMV transmission among preeclamptics with periodontitis as compared with a maximum rate of CMV congenital trasmission of 3% reported to the general population. Maternal gingival crevicular fluid may be a source of CMV in preeclamptics with periodontitis.] Consuegra J, Velez S, et al. *IADR General Session*, San Diego, CA, March 16-9, 2011. http://iadr.confex.com/iadr/2011sandiego/webprogram/Paper150722.html

1123. **Importance of Good Oral Health in Pregnant Women**. **[**WASHINGTON, D.C. – May 7, 2000 – The more of the mouth affected with periodontal disease, the more likely a woman is to deliver a premature baby, according to an ongoing study of more than 2,000 pregnant women. The results point to further evidence that periodontal disease may be a significant risk factor for preterm births.] Jeffcoat M. American Academy of Periodontology's Specialty Conference on Periodontal Medicine, 2000. http://www.perio.org/consumer/women_risk.htm

1124. **Innate inflammatory responses of human decidual cells to periodontopathic bacteria. [**OBJECTIVE: The purpose of this study was to test the hypothesis that periodontopathic bacteria exert potent proinflammatory effects in human decidua. STUDY DESIGN: The immunostimulatory effects of Gram-positive and negative periodontopathic bacteria and their lipopolysaccharides were tested in human decidual cell cultures in comparison with Escherichia coli. Cytokine production was measured by enzyme-linked immunosorbent assay; inflammatory gene expression was measured by oligonucleotide arrays and quantitative real time-polymerase chain reaction. RESULTS: All bacteria that were tested elicited an inflammatory response, although concentration-dependence and efficacy varied considerably with organism and culture. Lipopolysaccharides were more potent stimuli than intact bacterial cells, although bacteria exerted greater effects at high concentrations. Of 112 genes on the arrays, 18 genes were stimulated significantly by one or more lipopolysaccharide preparation. CONCLUSION: The ability of periodontopathic bacteria to stimulate a decidual inflammatory response is highly variable and partly dependent on the presence and structure of constituent lipopolysaccharides. This adds to our understanding of the causal association between periodontal disease and preterm birth.] Keelan JA, Wong PM, et al. *Am J Obstet Gynecol.* 2010 May;202(5):471.e1-11. http://www.ncbi.nlm.nih.gov/pubmed/20452492

1125. **Intrauterine Growth Restriction, Low Birth Weight, and Preterm Birth: Adverse Pregnancy Outcomes and Their Association With Maternal Periodontitis**. [It has been suggested that periodontitis is associated with systemic alterations such as adverse pregnancy outcomes. However, some conflicting results have been reported. This case-control study was conducted to determine the association between maternal periodontitis and preterm birth (PTB), low birth weight (LBW), and intrauterine growth restriction (IUGR)… Maternal periodontitis is associated with an increased risk for PTB, LBW, and IUGR. Results emphasize the importance of periodontal care in prenatal health programs.] Siqueira FM, Cota LOM, Costa JE. *Journal of Periodontology 2007, Vol. 78, No. 12, Pages 2266-2276* http://www.joponline.org/doi/abs/10.1902/jop.2007.070196

1126. **Is there a link between periodontal disease and preterm birth?** [Mounting evidence suggests that a chronic oral infection may lead to an immune reaction that either triggers premature parturition or contributes to its onset. Rresearchers have measured gingival crevicular levels of PGE_2 and IL-1ß in 48 mothers who delivered preterm, LBW infants and compared these levels to those found in control women.[23] They discovered that gingival crevicular fluid levels of PGE_2 were significantly higher in cases, compared to control women. In addition, among primiparous women with preterm, LBW infants, they found a significant inverse association between birthweight and gestational age and gingival crevicular PGE_2 levels.] Bogess KA. *Contemporary OB?GYN Aug.1,2003*. http://www.cedip.cl/Temas/PTDandPERIODONT/Is%20there%20a%20link%20between%20periodontal%20disease%20and%20preterm%20birth.htm

1127. **Male subfertility and oral bacterial diseases.** [More than 70% of the husbands consulting the Dept. of Gynecology and Obstetrics of the RWTH Aachen for sterility since June 1987 needed treatment for bacteriospermia with germ concentrations greater than 10(4) cfu/ml ejaculate. In 23% of the treated men however, no convincing reduction of germ concentration were achieved. 36 patients with therapy-resistant bacteriospermia were sent to the Dept. of Dentistry of the RWTH Aachen. A lot of intra-oral foci were found, which got eliminated. Intra-operational bacterial specimens were taken and evaluated by a special diagnostic technique in the Dept. of Microbiology. It was shown that the bacterial spectrum of the intraoral specimens and the spermiograms were identical. Six months after completion of the dental therapy a new andrological examination was performed. Two thirds of the spermiograms now were already sterile. There was an improvement of the spermparameters as well as motility, morphology and density. It can be concluded from these results that there is a direct causal relationship between a symptomatic dental primary disease and bacteriospermia which probably leads to subfertility.] Ensslen SC, Riedel HH, et al. *Zentralbl Gynakol*. 1990;112(13):823-5. http://www.ncbi.nlm.nih.gov/pubmed/2238984

1128. **Maternal periodontal disease and preterm low birthweight: case–control study.** [Periodontal disease has been suggested to be an important risk factor for preterm low birthweight (PLBW). Here we report a case-control study of 236 cases (infants < 37 wks and weighing < 2499 g) and a daily random sample of 507 controls (≥ 38 wks and weighing ≥2500 g). Clinical periodontal indices were measured on the labor wards. Associated risk factors for periodontal disease and PLBW were ascertained by means of a structured questionnaire and maternity notes. The risk for PLBW decreased with increasing pocket depth (odds ratio [OR] 0.83, 95% confidence interval [CI] 0.68 to 1.00). After adjustment for maternal age, ethnicity, maternal education, smoking, alcohol consumption, infections, and hypertension during pregnancy, this decreased further (OR 0.78, 95% CI 0.64 to 0.99). We found no evidence for an association between PLBW and periodontal disease. Our results do not support a specific drive to improve periodontal health of pregnant women as a means of improving pregnancy outcomes.] Davenport ES, Williams CECS, et.al. *J Dent Res* 81(5): 313-318, 2002 http://jdr.iadrjournals.org/cgi/content/abstract/81/5/313

1129. **Maternal periodontal disease and preterm or extreme preterm birth: an ordinal logistic regression analysis.** [BACKGROUND: Despite previous studies addressing the link between preterm or low birth weight infants and maternal periodontitis, extreme preterm births have received far less attention. This study is designed to address the possible

association between maternal periodontal disease and preterm or extreme preterm birth. METHODS: Immediately after childbirth, 1,207 women underwent an examination in which periodontal disease was assessed according to two alternative definitions: 1) four or more teeth with at least one site showing probing depth (PD) >or=4 mm and clinical attachment loss (AL) >or=3 mm, and 2) at least one site showing PD and clinical AL >or=4 mm. For each of these definitions, two types of multivariate analysis were conducted: a linear regression analysis for the number of gestation weeks, and a more specific ordinal logistic regression analysis for the ordinal variable gestation time categorized as normal (term) (n = 1,046 women) or mild-moderate (n = 146 women) or extreme preterm (n = 15 women). RESULTS: Periodontal disease was associated with fewer weeks of gestation by linear regression (definition 1: P = 0.012; definition 2: P <0.001) and with preterm (n = 161; mild-moderate and extreme) or extreme preterm births (n = 15) by ordinal logistic regression (definition 1: odds ratio [OR] = 1.83, 95% confidence interval [CI]: 1.28 to 2.62; definition 2: OR = 2.37, 95% CI: 1.62 to 3.46). CONCLUSION: Our findings suggest that periodontal disease is associated with a premature or extremely premature birth] Guimaraes AN, Silva-Mato A, et al. *J Periodontol*. 2010 Mar;81(3):350-8. http://www.ncbi.nlm.nih.gov/pubmed/20192860

1130. **Maternal Periodontal Disease Is Associated With an Increased Risk for Preeclampsia.** [OBJECTIVE: To determine if maternal periodontal disease is associated with the development of preeclampsia. METHODS: A cohort of 1115 healthy pregnant women were enrolled at less than 26 weeks' gestation and followed until delivery. Maternal demographic and medical data were collected. Periodontal examinations were performed at enrollment and within 48 hours of delivery to determine the presence of severe periodontal disease or periodontal disease progression. Preeclampsia was defined as blood pressure greater than 140/90 on two separate occasions, and at least 1+ proteinuria on catheterized urine specimen. The potential effects of maternal age, race, smoking, gestational age at delivery, and insurance status were analyzed, and adjusted odds ratios for preeclampsia were calculated using multivariable logistic regression. RESULTS: During the study period, 763 women delivered live infants and had data available for analysis. Thirty-nine women had preeclampsia. Women were at higher risk for preeclampsia if they had severe periodontal disease at delivery (adjusted odds ratio 2.4, 95% confidence interval 1.1, 5.3), or if they had periodontal disease progression during pregnancy (adjusted odds ratio 2.1, 95% confidence interval 1.0, 4.4). CONCLUSION: After adjusting for other risk factors, active maternal periodontal disease during pregnancy is associated with an increased risk for the development of preeclampsia.] Boggess KA, Lief S, et.al. *Obstetrics & Gynecology* 2003;101:227-231. http://www.greenjournal.org/cgi/content/abstract/101/2/227

1131. **Maternal periodontal disease, systemic inflammation, and risk for preeclampsia.** [Maternal periodontal disease, a chronic oral infectious and inflammatory disorder, is associated with an increased risk for preeclampsia. Our objective was to determine the relationship between maternal periodontal disease, maternal systemic inflammation, and the development of preeclampsia. **Conclusion:** Maternal periodontal disease with systemic inflammation as measured by C-reactive protein is associated with an increased risk for preeclampsia.] Ruma M, Boggess K, et al. *American Journal of Obstetrics and Gynecology, Vol 198, Issue 4, Pp 389.e1-389.e5 (April 2008)*, http://www.ajog.org/article/S0002-9378(07)02266-1/abstract.

1132. **Maternal periodontitis and prematurity. Part I: Obstetric outcome of prematurity and growth restriction.** [Oral Conditions and Pregnancy (OCAP) is a 5-year prospective study of pregnant women designed to determine whether maternal periodontal disease contributes to the risk for prematurity and growth restriction in the presence of traditional obstetric risk factors. Full-mouth periodontal examinations were conducted at enrollment (prior to 26 weeks gestational age) and again within 48 hours postpartum to assess changes in periodontal status during pregnancy. Maternal periodontal disease status at antepartum, using a 3-level disease classification (health, mild, moderate-severe) as well as incident periodontal disease progression during pregnancy were used as measures of exposures for examining associations with the pregnancy outcomes of preterm birth by gestational age (GA) and birth weight (BW) adjusting for race, age, food stamp eligibility, marital status, previous preterm births, first birth, chorioamnionitis, bacterial vaginosis, and smoking. Interim data from the first 814 deliveries demonstrate that maternal periodontal disease at antepartum and incidence/progression of periodontal disease are significantly associated with a higher prevalence rate of preterm births, BW < 2,500 g, and smaller birth weight for gestational age. …In summary, the present study, although preliminary in nature, provides evidence that maternal periodontal disease and incident progression are significant contributors to obstetric risk for preterm delivery, low birth weight and low weight for gestational age. These studies underscore the need for further consideration of periodontal disease as a potentially new and modifiable risk for preterm birth and growth restriction.] Offenbacher S, Lieff S, et.al. *Ann Periodontol*. 2001 Dec;6(1):164-74.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11887460&dopt=Abstract

1133. **Maternal Periodontitis Treatment and Child Neurodevelopment at 24 to 28 Months of Age. [**BACKGROUND Some maternal infections are associated with impaired infant cognitive and motor performance. Periodontitis results in frequent bacteremia and elevated serum inflammatory mediators. OBJECTIVE The purpose of this study was to determine if periodontitis treatment in pregnant women affects infant cognitive, motor, or language development. METHODS Children born to women who had participated in a previous trial were assessed between 24 and 28 months of age by using the Bayley Scales of Infant and Toddler Development (Third Edition) and the Preschool Language Scale (Fourth Edition). Information about the pregnancy, neonatal period, and home environment was obtained through chart abstractions, laboratory test results, and questionnaires. We compared infants born to women treated for periodontitis before 21 weeks' gestation (treatment group) or after delivery (controls). In unadjusted and adjusted analyses, associations between change in maternal periodontal condition during pregnancy and neurodevelopment scores were tested by using Student's *t* tests and linear regression. RESULTS A total of 411 of 791 eligible mother/caregiver-child pairs participated. Thirty-seven participating children (9.0%) were born at <37 weeks' gestation. Infants in the treatment and control groups did not differ significantly for adjusted mean

cognitive (90.7 vs 91.4), motor (96.8 vs 97.2), or language (92.2 vs 92.1) scores (all $P > .5$). Results were similar in adjusted analyses. Children of women who experienced greater improvements in periodontal health had significantly higher motor and cognitive scores ($P = .01$ and .02, respectively), although the effect was small (~1-point increase for each SD increase in the periodontal measure). CONCLUSIONS Nonsurgical periodontitis treatment in pregnant women was not associated with cognitive, motor, or language development in these study children.] Michalowicz BS, Hodges JS, et al. Published online April 11, 2011. *PEDIATRICS* (doi:10.1542/peds.2010-3129).
http://pediatrics.aappublications.org/cgi/content/abstract/peds.2010-3129v1

1134. **Maternal Periodontitis and Prematurity, Part II: Maternal Infection and Fetal Exposure. [**Clinical data from the first 812 deliveries from a cohort study of pregnant mothers entitled Oral Conditions and Pregnancy (OCAP) demonstrate that both antepartum maternal periodontal disease and incidence/progression of periodontal disease are associated with preterm birth and growth restriction after adjusting for traditional obstetric risk factors. In the current study we present measures of maternal periodontal infection using whole chromosomal DNA probes to identify 15 periodontal organisms within maternal periodontal plaque sampled at delivery. In addition, maternal postpartum IgG antibody and fetal exposure, as indexed by fetal cord blood IgM level to these 15 maternal oral pathogens, was measured by whole bacterial immunoblots. The potential role of maternal infection with specific organisms within 2 bacterial complexes most often associated with periodontitis, conventionally termed "Orange" (Campylobacter rectus, Fusobacterium nucleatum, Peptostreptococcus micros, Prevotella nigrescens, and Prevotella intermedia) and "Red" (Porphyromonas gingivalis, Bacteroides forsythus, and Treponema denticola) complexes, respectively, to prematurity was investigated by relating the presence of oral infection, maternal IgG, and fetal cord IgM, comparing full-term to preterm (gestational age < 37 weeks). The prevalence of 8 periodontal pathogens was similar among term and preterm mothers at postpartum. There was a 2.9-fold higher prevalence of IgM seropositivity for one or more organisms of the Orange or Red complex among preterm babies, as compared to term babies (19.9% versus 6.9%, respectively, P = 0.0015, chi square). Specifically, the prevalence of positive fetal IgM to C. rectus was significantly higher for preterm as compared to full-term neonates (20.0% versus 6.3%, P = 0.0002, as well as P. intermedia (8.8% versus 1.1%, P = 0.0003). A lack of maternal IgG antibody to organisms of the Red complex was associated with an increased rate of prematurity with an odds ratio (OR) = 2.2; confidence interval (CI) 1.48 to 3.79), consistent with the concept that maternal antibody protects the fetus from exposure and resultant prematurity. The highest rate of prematurity (66.7%) was observed among those mothers without a protective Red complex IgG response coupled with a fetal IgM response to Orange complex microbes (combined OR 10.3; P < 0.0001). These data support the concept that maternal periodontal infection in the absence of a protective maternal antibody response is associated with systemic dissemination of oral organisms that translocate to the fetus resulting in prematurity. The high prevalence of elevated fetal IgM to C. rectus among premature infants raises the possibility that this specific maternal oral pathogen may serve as a primary fetal infectious agent eliciting prematurity.] Madianos RPN, Lieff S, et.al. *Obstetrical & Gynecological Survey. 58(7):438-339, July 2003.*
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11887461&dopt=Abstract

1135. **Optimal timing of periodontal disease treatment for prevention of adverse pregnancy outcomes: before or during pregnancy? [**Several large randomized controlled clinical trials failed to find that standard periodontal therapy during pregnancy reduces the incidence of adverse pregnancy outcomes (eg, preterm birth and low birthweight). However, treating periodontal disease during pregnancy may be too late to reduce the inflammation that is related to the adverse pregnancy outcomes. Moreover, periodontal treatment during pregnancy can cause bacteremia, which itself may initiate the pathway leading to the adverse pregnancy outcomes. Finally, the periodontal treatments provided during pregnancy are not always effective in preventing the progression of periodontal disease during pregnancy. Pregnancy may not be an appropriate period for periodontal intervention(s). We hypothesize that periodontal treatment before pregnancy may reduce the rates of adverse pregnancy outcomes. Future randomized controlled trials are needed to test if treating periodontal disease in the prepregnancy period reduces the rate of adverse pregnancy outcomes.] Xiong X, Buekens P, et al. *Am J Obstet Gynecol*. 2011 Mar 16. http://www.ncbi.nlm.nih.gov/pubmed/21620355

1136. **Oral health during pregnancy: an analysis of information collected by the pregnancy risk assessment monitoring system.** [BACKGROUND: Little is known about the use of dental services during pregnancy. Yet research suggests that a pregnant woman's oral health and her pregnancy outcome may be associated. METHODS: Four states collected oral health data a part of the Pregnancy Risk Assessment Monitoring System, or PRAMS, in 1998. PRAMS is an ongoing, population-based survey designed to obtain information from mothers who recently delivered live-born infants about their experiences and behaviors before, during and immediately after pregnancy. RESULTS: Reports of dental care use during pregnancy ranged from 22.7 to 34.7 percent. In three states, 12.2 percent to 25.4 percent of respondents reported having a dental problem and of these, 44.7 percent to 54.9 percent went for care. Among mothers reporting a dental problem, prenatal care, or PNC, insurance through public funding and late PNC entry were significantly associated with their not getting dental care. CONCLUSIONS: Most mothers did not go for dental care during their pregnancy; among those who reported having problems, one-half did not get dental care. PRACTICE IMPLICATIONS: Attention toward the oral health needs of pregnant women is warranted. A coordinated effort from the dental and obstetric communities to establish guidelines could benefit maternal oral health and perinatal outcomes.] Gaffield ML, Gilbert BJ, et al. *J Am Dent Assoc*. 2001 Jul;132(7):1009-16. http://www.ncbi.nlm.nih.gov/pubmed/11480627

1137. **Oral Health in Women During Preconception and Pregnancy: Implications for Birth Outcomes and Infant Oral Health. [**Maternal oral health has significant implications for birth outcomes and infant oral health. Maternal

periodontal disease, that is, a chronic infection of the gingiva and supporting tooth structures, has been associated with preterm birth, development of preeclampsia, and delivery of a small-for-gestational age infant. Periodontal disease is a destructive inflammatory condition of the gingiva and bone that supports teeth. It is most commonly associated with a gram-negative anaerobic infection of these structures. Fluid that bathes the tooth at the gingival margin often contains inflammatory mediators and oral pathogens associated with periodontal disease. The mechanisms underlying this destructive process involve both direct tissue damage resulting from plaque bacterial products, and indirect damage through bacterial induction of the host inflammatory and immune responses. Extrapolation from these data suggested that 18% of the preterm, low birth weight infants born annually might be attributable to periodontal disease, and thus account for a significant proportion of the $5.5 billion annual hospital costs associated with the care of preterm/low birthweight infants. These early studies led to the hypothesis that periodontopathic bacteria, primarily Gram-negative anaerobes, may serve as a source for endotoxin and lipopolysaccharides, which then increases local inflammatory mediators including PGE2, and cytokines, and that this increases systemic inflammatory mediators that can then lead to preterm birth.] Boggess KA, Edelstein BL, *Matern Child Health J. 2006 September; 10(Suppl 7): 169–174.* http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1592159

1138. **Periodontal disease activity measured by the benzoyl-dl-arginine-naphthylamide test is associated with preterm births**. [Background: Infection is a risk factor for preterm birth. This study was conducted in the field and addressed the link between periodontal pathogens measured with the benzoyl-DL-arginine-naphthylamide (BANA) test and preterm birth. Methods: This prospective study was performed in Changhua, Taiwan. Periodontal examinations included the plaque index, papillary bleeding scores, and measurement of the BANA enzyme in plaque samples at the second and third trimesters. Independent variables included maternal demographic characteristics, previous pregnancy histories, risk factors, plaque and gingivitis scores, and current pregnancy outcomes. Results: There were 19 (7%) preterm deliveries among the 268 subjects. A history of a previous preterm birth and low birth weight, frequency of prenatal visits, preterm uterine contractions, antepartum hemorrhages, placenta previae, and preterm premature rupture of membranes were significantly related to preterm birth (P = 0.035, 0.027, <0.001, 0.025, 0.006, 0.014, and <0.001, respectively). Maternal weight gain was higher with a normal term delivery (P = 0.003). Multivariable logistic regression analyses showed that the number of BANA-infected sites in the third trimester (odds ratio [OR]: 5.89; 95% confidence interval [CI]: 1.5 to 31.6), maternal weight gain (OR: 0.78; 95% CI: 0.65 to 0.91), antepartum hemorrhages (OR: 10.0; 95% CI: 2.2 to 46.9), and preterm premature rupture of membranes (OR: 12.6; 95% CI: 3.97 to 42.71) had significant influences on preterm-birth outcomes. Conclusions: BANA-positive plaque in the third trimester was associated with preterm births after controlling for other risk factors. The BANA test can be used to screen pregnant women at chairside and/or bedside to apply suitable intervention tactics.] Chan HC, WU CT, et al. *Journal of Periodontology*, 2010, Vol. 81, No. 7, Pages 982-991. http://www.joponline.org/doi/abs/10.1902/jop.2010.090532

1139. **Periodontal Disease and Preterm Birth: Results of a Pilot Intervention Study**. [This trial indicates that performing SRP in pregnant women with periodontitis may reduce PTB in this population.] Jeffcoat, MK, Hauth JC, et al, *J Periodontol 2003;74:1214-1218*. http://www.joponline.org/doi/abs/10.1902/jop.2003.74.8.1214?prevSearch=allfield%3A%28Jeffcoat+Pregnant%29

1140. **Periodontal Infection and Preterm Birth: Results of a Prospective Study.** [Babies born prematurely are at a significant risk of developing serious and lasting health problems. Preterm delivery, or PTD, is the major cause of neonatal mortality and of nearly one-half of all serious long-term neurological morbidity. Previous studies have suggested that chronic periodontal infection may be associated with preterm births. Chronic periodontitis has been proposed as a risk factor for preterm birth. The authors conducted a prospective study to test for this association. The authors' data show an association between the presence of periodontitis at 21 to 24 weeks' gestation and subsequent preterm birth. This study provides additional evidence that pre-existing periodontal disease in the second trimester of pregnancy increases the risk of preterm birth. The odds of increased prematurity were increased 4.5- to 7.0-fold.] Jeffcoat MK, Geurs NC, et al., *JADA 2001; 132:875-880.* http://jada.ada.org/cgi/content/abstract/132/7/875

1141. **Periodontal infection and preterm birth: successful periodontal therapy reduces the risk of preterm birth.** [Objective This study tested the hypothesis that successful periodontal treatment was associated with a reduction in the incidence of spontaneous preterm birth (PTB). Design This was a randomised, controlled, blinded clinical trial. Setting Hospital outpatient clinic. Population Pregnant women of 6–20 weeks of gestation were eligible. Methods Of 322 pregnant women with periodontal disease, 160 were randomly assigned to receive scaling and root planing (SRP, cleaning above and below the gum line), plus oral hygiene instruction, whereas the remaining 162 received only oral hygiene instruction and served as an untreated control group. Subjects received periodontal examinations before and 20 weeks after SRP, and were classified blindly according to the results of treatment into two groups: successful ('non-exposure') and unsuccessful ('exposure') treatment. Groups were compared using standard inferential statistics; dichotomous variables were compared using the chi-square test or logistic regression. Results are presented in terms of odds ratios. Main outcome measure The main outcome measure was spontaneous preterm birth before 35 weeks of gestation. Results No significant difference was found between the incidence of PTB in the control group (52.4%; n = 162) and the periodontal treatment group (45.6%; n = 160) (P < 0.13, Fisher's exact test). The incidence of PTB was compared within the periodontal treatment group, considering the success of therapy. A logistic regression analysis showed a strong and significant relationship between successful periodontal treatment and full-term birth (adjusted odds ratio 6.02; 95% CI 2.57–14.03). Subjects refractory to periodontal treatment were significantly more likely to have PTB. Conclusions A beneficial effect on PTB may be dependent on the success of periodontal treatment.] Jeffcoat M, Parry S , et al. *BJOG An International Journal of Obstetrics*

and Gynaecology. http://onlinelibrary.wiley.com/doi/10.1111/j.1471-0528.2010.02713.x/abstract;jsessionid=CD41EF4E86A8A1DBA9606F8527E41CE8.d02t01?systemMessage=Due+to+scheduled+maintenance+access+to+the+Wiley+Online+Library+may+be+disrupted+as+follows%3A+Saturday%2C+2+October+-+New+York+0500+EDT+to+0700+EDT%3B+London+1000+BST+to+1200+BST%3B+Singapore+1700+SGT+to+1900+SGT.

1142. **Periodontal disease activity as measured by the BANA test is associated with preterm births.** [Background: Infection is a risk factor for preterm birth. This study, conducted in the field, addressed the link between periodontal pathogens measured with the BANA test (N-benzoyl-DL-arginine-2-naphthylamide) and preterm birth. Methods: This prospective study was performed in Changhua, Taiwan. Periodontal examinations included plaque index, papillary bleeding scores, and measurement of BANA enzyme in plaque samples at the second and third trimester. Independent variables included maternal demographic characteristics, previous pregnancy histories, risk factors, plaque and gingivitis scores, and current pregnancy outcomes. Results: There were 19 (7%) preterm deliveries among the 268 subjects. A history of previous preterm birth and a low birth weight, frequency of prenatal visit, preterm uterine contraction, antepartum hemorrhage, placenta previa, and preterm premature rupture of membrane were significantly related to preterm birth (P = 0.035, 0.027, <0.001, 0.025, 0.006, 0.014, and <0.001, respectively). Maternal weight gain was higher with normal term delivery (P = 0.003). A multivariable logistic regression analysis showed that the number of BANA infected sites in the third trimester, [Odds ratio (OR) = 5.89, 95% confidence interval (CI)=1.5-31.6], maternal weight gain (OR = 0.78, 95% CI = 0.65-0.91), antepartum hemorrhage (OR = 10.0, 95% CI = 2.2-46.9) and preterm premature rupture of membrane (OR = 12.6, 95% CI = 3.97-42.71 had a significant influence on preterm birth outcomes. Conclusions: BANA-positive plaques in the 3rd trimester are associated with preterm births, after controlling for other risk factors. The BANA test could be used to screen at chair/bed-side pregnant women in order to apply suitable intervention tactics, since periodontal disease is treatable.] Chan HC, Wu CT, et al. J Periodontol. 2010 Apr 12 , http://www.ncbi.nlm.nih.gov/pubmed/20384462

1143. **Periodontal disease is associated with gestational diabetes mellitus: a case-control study**. [BACKGROUND: Few studies have specifically examined the relationship between periodontal disease and gestational diabetes mellitus (GDM). The objective of this study was to examine whether maternal periodontal disease is associated with GDM. METHODS: A case-control study was conducted of 53 pregnant women with GDM and 106 pregnant women without GDM at Woman's Hospital, Baton Rouge, Louisiana. The periodontal examinations were performed by a calibrated dentist who was masked to the diabetic status of the pregnant women. Periodontitis was defined as the presence of any site with a probing depth (PD) >or=4 mm or a clinical attachment loss (AL) >or=4 mm. The severity of periodontal disease was measured in quartiles of PD and clinical AL. Univariable analysis and multivariable logistic regression were used to examine the relationships between periodontal disease and GDM. RESULTS: The percentage of periodontitis was 77.4% in women with GDM and 57.5% in women without GDM, with an odds ratio (OR) of 2.5 and a 95% confidence interval (CI) of 1.2 to 5.3. After adjusting for confounding variables of maternal age, parity, race, marital status, education, family income, smoking, alcohol consumption, systemic antibiotics during pregnancy, family history of diabetes, income, dental insurance coverage, and body mass index, the adjusted OR (95% CI) was 2.6 (1.1 to 6.1). The adjusted ORs (95% CIs) of GDM comparing the highest-to-lowest quartiles of PD and clinical AL were 3.8 (1.0 to 14.0) and 4.5 (1.2 to 16.9). CONCLUSION: This study supports the hypothesis of an association between periodontal disease and GDM.] Xiong X, Elkind-Hirsch KE, et al. *J Periodontol*. 2009 Nov;80(11):1742-9. http://www.ncbi.nlm.nih.gov/pubmed/19905944

1144. **Periodontal Disease – The Emergence of a Risk for Systemic Conditions: Pre-term Low Birth Weight.** [There is compelling evidence that a link exists between pre-term low birth weight and periodontitis. A model explaining the plausible relationship is proposed based upon the concept of infection leading to a cascade of inflammatory reactions associated with pre-term labour and periodontal disease. Current evidence has pointed to an interest in dental intervention studies to control periodontal disease as one of the potential strategies to reduce pre-term labour.] Yeo BK, Lim LP, et. al. *Annals Academy of Medicine* January 2005, Vol. 34 No. 1. http://www.annals.edu.sg/pdf200502/YeoBK.pdf

1145. **Periodontal Infection as a Possible Risk Factor for Preterm Low Birth Weight.** [Peridontal diseases are gram-negative anaerobic infections that can occur in women of childbearing age (18 to 34 years). These data indicate that periodontal diseases represent a previously unrecognized and clinically significant risk factor for preterm low birth weight as a consequence of either pre-term labor or preterm rupture of membranes.] Offenbacher S, Katz V., et.al., *J Periodontol. 1996 Oct;67(10 Suppl):1103-13.* http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8910829&dopt=Abstract

1146. **Periodontal Therapy May Reduce Incidence of Preterm Births.** [Study shows that women with gingivitis who received periodontal therapy before 28 weeks of gestation had a significantly lower incidence of preterm low-birthweight babies than women who did not receive periodontal therapy. There is a significant association between gingivitis and preterm birth after adjusting for the major risk factors for preterm delivery, suggesting that gingivitis, the earliest form of periodontal disease, is an independent risk factor for preterm birth and low birthweight. If periodontal infection is diagnosed at any time during pregnancy, the treatment should be administered as soon as possible in order to reduce the risk of preterm birth and low birthweight.] *American Academy of Periodontology Media Release, Nov 2005* http://www.perio.org/consumer/pregnancy-therapy.htm

1147. **Periodontal Therapy May Reduce the Risk of Preterm Low Birth Weight in Women With Periodontal Disease: A randomized Controlled Trial.** [Pregnant women who receive treatment for their periodontal disease can reduce their risk of giving birth to a low birth-weight or pre- term baby. Of the women who received treatment during pregnancy, 2

percent gave birth to either a low birth-weight or pre-term infant. By comparison, 10 percent of the women who received treatment after birth had either a low birth-weight or pre-term baby.] Lopez NJ, et al. *J Periodontology 2002, Vol. 73, No. 8, Pages 911-924. http://www.joponline.org/doi/abs/10.1902/jop.2002.73.8.911*

1148. **Periodontal Therapy Reduces the Rate of Preterm Low Birth Weight in Women With Pregnancy-Associated Gingivitis.** [One hypothesis to explain the association between periodontal disease (PD) preterm/low birth weight (PT/LBW) is that PT/LBW may be indirectly mediated through translocation of bacteria or bacterial products in the systemic circulation. Periodontal treatment significantly reduced the PT/LBW rate in this population of women with pregnancy-associated gingivitis. Within the limitions of this study, we conclude that gingivitis appears to be an independent risk factor for PT/LBW for this population.] Lopez NJ, Da Silva I et.al, *J Periodontol 2005, Vol. 76,No.11-s:2144-2153.* http://www.joponline.org/doi/abs/10.1902/jop.2005.76.11-S.2144?journalCode=jop

1149. **Periodontal treatment did not prevent complications of pregnancy.** [DESIGN: A randomised controlled trial (RCT) was conducted. INTERVENTION: Women found to have a periodontal disease were randomly allocated to receive periodontal treatment in midpregnancy (this was the treatment group; n = 542) or after the pregnancy was concluded (the control group; n = 540). Periodontal disease was defined as presence of periodontal pockets of 4 mm or greater in depth at 12 or more probing sites in fully erupted teeth (typically excluding wisdom teeth). Treatments were conducted either by the hygienists or periodontists and included nonsurgical debridement of the subgingival and supragingival plaque, removal of local predisposing factors such as calculus, root planing, and adjustment of overhanging restorations. Comprehensive oral hygiene instructions and motivation were provided at each visit at a minimum of three weekly visits, with further visits if required. OUTCOME MEASURE: The primary outcomes were preterm birth or other major complications of pregnancy. RESULTS: There were no differences between the control and treatment groups in terms of: preterm birth [9.3% compared with 9.7%; odds ratio (OR), 1.05; 95% confidence interval (CI), 0.7-1.58; P 0.81); birthweight (3450 g versus 3410 g; P 0.12); pre-eclampsia (4.1% versus 3.4%; OR, 0.82; 95% CI, 0.44-1.56; P 0.55); or other obstetric endpoints. There were four unexplained stillbirths in the control group and no pregnancy losses in the treated group (P 0.12). Measures of foetal and neonatal wellbeing were similar in the two groups, including abnormalities in foetal heart rate recordings (P 0.26), umbilical artery flow studies (P 0.96), and umbilical artery blood gas values (P 0.37). The periodontal treatment was highly successful in improving health of the gums (P<0.01). CONCLUSIONS: The evidence provided by the present study does not support the hypothesis that treatment of periodontal disease during pregnancy in this population prevents preterm birth, foetal growth restriction, or pre-eclampsia. Periodontal treatment was not hazardous to the women or their pregnancies.] Niederman R. Evid Based Dent. 2010;11(1):18-9. http://www.ncbi.nlm.nih.gov/pubmed/20348894

1150. **Periodontitis, a marker of risk in pregnancy for preterm birth.** [Pregnant women with findings of elevated amniotic fluid levels of PGE_2, IL-6 and IL-8 in the 15–20 weeks of pregnancy and with periodontitis are at high risk for premature birth. The implication of this is that periodontitis can induce a primary host response in the chorioamnion leading to preterm birth.] Dörtbudak O, Eberhardt R., *Journal Of Clinical Periodontology. Volume 32 Page 45 - January 2005. http://www.cababstractsplus.org/abstracts/Abstract.aspx?AcNo=20053005877*

1151. **Periodontitis and Plasma C-Reactive Protein During Pregnancy.** [Periodontitis has been associated with increased risk of adverse pregnancy outcomes and elevated C-reactive protein (CRP) concentrations in non-pregnant adults. These findings suggest that periodontitis may increase CRP levels in pregnancy. CRP could potentially mediate the association of periodontitis with adverse pregnancy outcomes.] Pitiphat W,†‡ Joshipura KJ, *Journal of Periodontology, 2006.050193).* http://www.joponline.org/doi/abs/10.1902/jop.2006.050193

1152. **Persistently High Levels of Periodontal Pathogens Associated With Preterm Pregnancy Outcome.** [Background: Few studies examining the association between periodontal diseases and preterm birth have explored the underlying microbial and antibody responses associated with oral infection. Methods: A nested case-control study was performed using data from a recent interventional trial following the delayed-treatment control group of 31 subjects with periodontal diseases. The levels of eight oral bacteria and the maternal immunoglobulin G (IgG) responses in serum to these bacteria were measured at antepartum and postpartum visits to determine the relationship to cases (preterm delivery <37 weeks' gestation) and controls (term delivery). Results: Antepartum, the levels of periodontal pathogens tended to be higher in the preterm (case group) deliveries compared to the term deliveries (control group). Maternal anti–*Porphyromonas gingivalis* IgG was significantly lower in the preterm group compared to the term group ($P = 0.028$). Postpartum, levels of *P. gingivalis*, *Tannerella forsythia*, *Prevotella intermedia*, and *Prevotella nigrescens* were statistically significantly higher in preterm births compared to term deliveries, adjusting for baseline levels. The joint effects of red and orange microbial clusters were significantly higher in the preterm group compared to the term group. Conclusions: High levels of periodontal pathogens and low maternal IgG antibody response to periodontal bacteria during pregnancy are associated with an increased risk for preterm delivery. Further studies elucidating the role of the microbial load and maternal immune response as related to pregnancy outcome seem merited.] Lin D, Moss K, et al. *Journal of Periodontology. 2007, Vol. 78, No. 5, Pages 833-841. http://www.joponline.org/doi/abs/10.1902/jop.2007.060201*

1153. **Polymorphism in the interleukin-1 gene complex and spontaneous preterm delivery. [**Objective: We examined the association between preterm delivery and polymorphisms at position +3953 of the interleukin-1[beta] gene (IL1B+3953) and in intron 2 of the interleukin-1 receptor antagonist gene (IL1RN). Study Design: This was a case-control study that involved 52 pregnancies that resulted in spontaneous preterm delivery before 34 weeks of gestation and 197 pregnancies that resulted in birth at term. Polymorphisms were determined by polymerase chain reaction and restriction fragment length polymorphism analysis. Results: Homozygous carriage of IL1B+3953 allele 1 by fetuses of African descent was associated

with a risk of preterm delivery (P =.033). Fetuses of Hispanic descent that carried IL1RN allele 2 were found to be at an increased risk for preterm premature rupture of membranes and subsequent preterm delivery(P =.021; odds ratio, 6.5; 95% CI, 1.25-37.7). Conclusion: There are associations of spontaneous preterm delivery with the fetal carriage of IL1B+3953*1 and IL1RN*2 alleles in African and Hispanic populations, respectively.] Genc MR, Gerber S, et.al. **American Journal of Obstetrics & Gynecology July 2002, 187:1.** http://pt.wkhealth.com/pt/re/ajog/abstract.00000447-200207000-00024.htm;jsessionid=GFnPyPB6tdln2WTllFrd4qChqpkqThfGf18hThLvZDcK4yy7p2YN!-377544086!-949856144!8091!-1

1154. **Poor periodontal health of the pregnant woman as a risk factor for low birth weight.** [We conclude that poor periodontal health of the mother is a potential independent risk factor for LBW.] Dasanayake AP, *Ann Periodontol 1998 Jul;3(1):206-12.* http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9722704

1155. **Potential Pathogenic Mechanisms of Periodontitis – Associated Pregnancy Complications.** [Maternal inflammatory response appears to be an important effector mechanism underlying preterm low-birth-weight infants. This response involves genetic as well as environmental exposure components. There is a growing body of evidence indicating that periodontist may be a sufficient infectious challenge to result in PLBW. Data presented here indicates that perio disease (in hamster model) can induce elevations in intraamniotic PGE2 and TNF-ά and result in fetal growth retardation; and that mothers with PLBW have a significant 2-fold elevation in the BCF-PGE2 levels and a plaque microbiota, which is consistent with progressive periodontitis. The similarities in the mixed anaerobic infection of vaginosis and Periodontitis and the striking parallels in inflammatory mediator responses suggest that there is a common underlying pathophysiologic pathway or mechanism that warrants further investigation of the linkage between these infections and PLBW.] Offenbacher S, Jared HL, et. al., *Annals of Periodontology* Vol. 3, No. 1, July 1998. http://medweb.uni-muenster.de/institute/zmk/einrichtungen/par/bilder/offenbacher.pdf

1156. **Preterm birth: associations with genital and possibly oral microflora**. [Opportunistic pathogenic microbes are indigenous to the female lower genital tract and etiologic in many types of pelvic infections and, apparently, a portion of preterm birth (PTB) cases. Bacterial vaginosis (BV) is a clinical syndrome based on an altered genital microflora in which Gardnerella vaginalis; anaerobic species primarily among Prevotella, Porphyromonas, Bacteroides, Peptostreptococcus, and Mobiluncus; Mycoplasma hominis; and Ureaplasma urealyticum become predominant in vaginal secretions. This BV complex of microbes, compared to a normal vaginal microflora dominated by facultative lactobacilli, is associated with significantly increased risks for preterm labor, preterm premature rupture of membranes, PTB, and other perinatal infectious complications. Pathogenetic mechanisms include an ascending route of infection and/or inflammatory process due to microbial products and maternal and/or fetal response(s) with production of prostaglandins and cytokines. In the presence of periodontal disease, oral opportunistic pathogens and/or their inflammatory products also may have a role in prematurity via a hematogenous route. Fusobacterium nucleatum, a common oral species, is the most frequently isolated species from amniotic fluid cultures among women with preterm labor and intact membranes. Also, the species and subspecies of fusobacteria identified from amniotic fluid most closely match those reported from healthy and diseased subgingival sites, namely F. nucleatum subspecies vincentii and F. nucleatum subspecies nucleatum, compared to strains identified from the lower genital tract. Although these fusobacteria also could be acquired through cunnilingus from a partner, new data associating maternal periodontal disease with preterm low birth weight taken with the isolation of F. nucleatum, Capnocytophaga, and other oral species from amniotic fluid support further study of a possible additional route, oral-hematogenous, to PTB.] Hill GB.*Ann Periodontol*. 1998 Jul;3(1):222-32. http://www.ncbi.nlm.nih.gov/pubmed/9722706

1157. **Preterm low birth weight and periodontal disease among African Americans.** [African Americans consistently experience higher rates of preterm and low birth weight (LBW) deliveries than do whites. LBW and preterm infants are more likely to die before their first birthday and survivors may suffer from a number of health problems. Therefore, identification of modifiable risk factors for preterm deliveries and LBW has considerable public health significance. Pregnant women's poor periodontal health is emerging as one such factor. Maternal clinical periodontal status and bacteriologic and immunologic profiles related to periodontal disease have been associated with risk of fetal growth and preterm LBW, and periodontal treatment during pregnancy has reduced the incidence of preterm deliveries. This article reviews the literature on the above association and presents data from a previously published prospective study of predominantly African Americans to show that preterm LBW deliveries are associated with higher midtrimester maternal serum antibody levels against Porphyromonas gingivalis.] Dasanayake AP, Russell S. *The Dental clinics of North America. 2003, vol. 47, No.1 pp.115-12.*, http://cat.inist.fr/?aModele=afficheN&cpsidt=14624279

1158. **Progressive Periodontal Disease and Risk of Very Preterm Delivery.** [The OCAP study demonstrates that maternal periodontal disease increases relative risk for preterm or spontaneous preterm births. Furthermore, periodontal disease progression during pregnancy was a predictor of the more severe adverse pregnancy outcome of very preterm birth, independently of traditional obstetric, periodontal, and social domain risk factors.] Offenbacher S, Boggess KA, et. al. Obstetrics & Gynecology 2006;107:29-36. http://www.ncbi.nlm.nih.gov/pubmed/16394036

1159. **Research Presented Today Provides Further Evidence on the Importance of Good Oral Health in Pregnant Women.** [The more of the mouth affected with periodontal disease, the more likely a woman is to deliver a premature baby, according to an ongoing study of more than 2,000 pregnant women. The results point to further evidence that periodontal disease may be a significant risk factor for preterm births. Past studies have shown that women with periodontal disease may be up to seven times more likely to deliver a preterm low birth weight baby. Today at the American Academy of Periodontology's Specialty Conference on Periodontal Medicine in Washington, D.C., preliminary research was presented for

the first time suggesting that the risk for women who have generalized periodontal disease (meaning it affects at least 30 percent of their mouth) is even higher. Data tells us the best advice continues to be that women considering pregnancy have a periodontal screening and get any problems with their oral health under control before becoming pregnant. Women who are already pregnant should not shy away from dental care. Dentists should perform scaling and root planing, along with any supportive therapy, in the second trimester for pregnant patients with periodontal disease.] Jeffcoat M., American Academy of Periodontology Specialty Conference on Periodontal Medicine in Washington, DC, May 7, 2000. Univ of Alabama Birmingham School of Dentistry. American Academy of Periodontology Press Release May 2000. http://www.perio.org/consumer/women_risk.htm

1160. **Simultaneous detection of periodontal pathogens in subgingival plaque and placenta of women with hypertension in pregnancy**. [There are many studies documenting increased prevalence of periodontal infection in women with preeclampsia. But, very few studies have attempted to establish causal relationship between the two. OBJECTIVE: To find out causal circumstantial evidence by isolating specific periodontal pathogens in oral and placental samples. MATERIALS AND METHODS: Antenatal periodontal screening and subgingival plaque collection was carried out in ten women with hypertension in pregnancy and ten normotensive controls on their hospital admission at term for cesarean delivery. Placental biopsy was obtained after aseptic placental collection at the time of elective cesarean delivery. Subgingival plaque and placental biopsy were studied for Porphyromonas gingivalis, Fusobacterium nucleatum, Treponema denticola, Prevotella intermedia and Aggregatibacter actinomycetemcomitans using quantitative polymerase chain reaction technique. Periodontist and laboratory personnel were unaware of case or control status. Periodontal status was not informed to the obstetrician recruiting the cases and laboratory. Microbiology report was not revealed till end of the study. RESULTS: Periodontal pathogens were found to be high in the group with hypertension than the controls. P gingivalis was found in all the samples from subgingival plaque and placenta, irrespective of the periodontal disease status. CONCLUSION: In cases with hypertension, periodontal pathogens are present in higher proportion in subgingival plaque and placenta.] Swati P, Thomas B, et al. *Arch Gynecol Obstet*. 2012 Mar;285(3):613-9. Epub 2011 Aug 10. http://www.ncbi.nlm.nih.gov/pubmed/21830010

1161. **Study boosts suspected link between mothers' gum disease and both premature birth, low birth weight.** [Mothers who suffer from gum disease are significantly more likely to deliver their babies prematurely than women without that illness. In the five-year study, researchers evaluated periodontal disease in more than 850 women. This prospective study confirms our earlier case-control studies showing that both periodontal disease and periodontal disease progression during pregnancy have an effect on the fetus. Babies developing in women's wombs are being adversely affected by germs growing in their mothers' mouths such that they are born early or at lower than normal weight. Scientists find antibodies to specific organisms in placental blood at the time of delivery. One in 10 babies in the United States is born too small or too early, which is a major cause of sickness and mortality. This work is very important because it confirms a new and potentially modifiable risk factor that we should be able to reduce. Gum disease may be responsible for up to 18 percent of pre-term deliveries, he said the new study suggests. It's not just that periodontal disease is a surrogate marker for poor oral hygiene or other socioeconomic factors just sort of jumbled together," the scientist said. "The fact that we're finding specific organisms that can cause growth and delivery problems opens up a whole new avenue for preventive care.] Lieff, S., McKaig R.G., University of North Carolina at Chapel Hill, Duke University. http://www.eurekalert.org/pub_releases/2002-03/uonc-sbs030502.php

1162. **Term Stillbirth Caused by Oral Fusobacterium nucleatum.** [BACKGROUND: Intrauterine infection is a recognized cause of adverse pregnancy outcome, but the source of infection is often undetermined. We report a case of stillbirth caused by *Fusobacterium nucleatum* that originated in the mother's mouth. CASE: A woman with pregnancy-associated gingivitis experienced an upper respiratory tract infection at term, followed by stillbirth a few days later. *F. nucleatum* was isolated from the placenta and the fetus. Examination of different microbial floras from the mother identified the same clone in her subgingival plaque but not in the supragingival plaque, vagina, or rectum. CONCLUSION: *F. nucleatum* may have translocated from the mother's mouth to the uterus when the immune system was weakened during the respiratory infection. This case sheds light on patient management for those with pregnancy-associated gingivitis.] Han YW, Yann F, et al. *Obstetrics & Gynecology*, Feb 2010 - Volume 115 - Issue 2, Part 2 - pp 442-445. http://journals.lww.com/greenjournal/Abstract/2010/02001/Term_Stillbirth_Caused_by_Oral_Fusobacterium.18.aspx

1163. **The association between Porphyromonas gingivalis-specific maternal serum IgG and low birth weight.** [Low birth weight infants are about 20 times more likely to die before their first birthday compared to normal birth weight infants. While the rate of LBW has been consistently higher among African Americans compared to whites, there has been a gradual increase in LBW for both African Americans and whites over the last 15 years. In an attempt to identify modifiable risk factors for LBW, we have previously reported that a pregnant woman's poor periodontal health may be an independent risk factor for low birth weight. Porphyromonas gingivalis (P.g.)-specific maternal serum IgG levels were higher in the LBW group compared to the normal birth weight (NBW) group. Women with higher levels of Pg.-specific IgG had higher odds of giving birth to LBW infants. This association remained significant after controlling for smoking, age, IgG levels against other selected periodontal pathogens, and race. Conclusions: Low birth weight deliveries were associated with a higher maternal serum antibody level against P. gingivalis at mid-trimester.] Dasanayake AP, Boyd D, et.al., *Journal of periodontology 2001, vol. 72, n°11, pp. 1491-1497.* http://cat.inist.fr/?aModele=afficheN&cpsidt=13493073

1164. **The Association between Maternal Oral Health Experiences and Risk of Preterm Birth in 10 States, Pregnancy Risk Assessment Monitoring System, 2004–2006. [**The aim of this study is to investigate the association

between oral health experiences of women in the peripartum period and the risk of preterm delivery (<37 weeks). We analyzed 2004–2006 data from the CDC Pregnancy Risk Assessment Monitoring System (PRAMS), a population-based surveillance system that collects data on pregnancy and postpartum experiences of mothers who have recently delivered a live infant. Ten states included in the analysis had a ≥70% weighted response rate and three standard questions pertaining to oral health. White non-Hispanic (WNH), Black non-Hispanic (BNH), and Hispanic women were selected for analysis. Chi-squared analysis was performed for our bivariate analysis and multivariate logistic regression models were created to calculate adjusted odds ratios, controlling for socio-demographic characteristics and peripartum morbidities. Weighted percentages and standard errors were used for all analyses. Among the 35,267 women studied, in the multivariate analysis, mothers who did not receive dental care during pregnancy and did not have a teeth cleaning during pregnancy were at higher risk for delivering a preterm infant (OR 1.15, CI 1.02–1.30; OR 1.23, CI 1.08–1.41). In this population-based study, women who did not receive dental care or have a teeth cleaning during pregnancy were at slightly higher risk for preterm delivery after adjustment for pertinent confounders.] Hwang SS, Smith VC, et al. *Maternal and Child Health Journal*, November 2012, Volume 16, Issue 8, pp 1688-1695. http://link.springer.com/article/10.1007%2Fs10995-011-0870-1 http://www.medscape.com/viewarticle/778169?src=nl_topic

1165. **The association of Aggregatibacter actinomycetemcomitans with preeclampsia in a subset of Japanese pregnant women.** [AIM: To determine whether periodontitis and three prominent members of the periodontal flora are associated with the development of preeclampsia (hypertension plus proteinuria) Materials and Methods: The samples were composed of 127 systemically healthy women. Within 5 days after labour, clinical periodontal parameters and Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis and Prevotella intermedia in subgingival plaque were evaluated. Maternal serum IgG antibody specific for each bacteria was determined by enzyme-linked immunosorbent assay. Multivariate logistic regression analysis was used to control for confounders (maternal age, body mass index before pregnancy, parity, and smoking). RESULTS: Eighteen women were affected with preeclampsia. The number of A.actinomycetemcomitans was shown to be significantly associated with preeclampsia in the logistic regression model (odds ratio; 1.7, 95% confidence interval; 1.1–2.7). There were statistically significant differences between the preeclamptic and control groups in body mass index before pregnancy, pre-term birth and low birthweight (respectively, $p = 0.014$, $p = 0.010$ and $p < 0.0001$). We found no statistically significant association between preeclampsia and periodontal clinical parameters or the presence of periodontitis. CONCLUSION: In systemically healthy pregnant women, our findings suggested that the levels of maternal subgingival A. actinomycetemcomitans DNA were elevated in preeclamptic women.] Hirano E, Sugita N, et al. *J Clin Periodontol*. 2012 Mar;39(3):229-38. http://www.ncbi.nlm.nih.gov/pubmed/22393563

1166. **The Contribution of Preterm Birth to Infant Mortality Rates in the United States.** [Although two thirds of infant deaths in the United States occur among infants born preterm (<37 weeks of gestation), only 17% of infant deaths are classified as being attributable to preterm birth with the standard classification of leading causes of death. To address this apparent discrepancy, we sought to estimate more accurately the contribution of preterm birth to infant mortality rates in the United States. …On the basis of this evaluation, preterm birth is the most frequent cause of infant death in the United States, accounting for at least one third of infant deaths in 2002. The extreme prematurity of most of the infants and their short survival indicate that reducing infant mortality rates requires a comprehensive agenda to identify, to test, and to implement effective strategies for the prevention of preterm birth.] Callaghan WM, MacDorman MF, et al. *PEDIATRICS Vol. 118 No. 4 October 2006, pp. 1566- 1573.* http://pediatrics.aappublications.org/cgi/content/abstract/118/4/1566

1167. **The East London Study of Maternal Chronic Periodontal Disease and Preterm Low Birth Weight Infants: study design and prevalence data.** [The influence of subject-based and environmental factors on the balance between the subgingival microbial challenge and the host response in periodontal diseases illustrates the intimate link between oral and systemic health. From this stems the hypothesis that the persistent Gram-negative challenge and associated inflammatory sequelae in periodontal disease may have consequences extending beyond the periodontal tissues themselves. This paper addresses the design of a case-control study to examine the relationship between preterm low birth weight (PLBW) and maternal periodontal disease. We present preliminary data on the prevalence of these 2 conditions in a group of mothers at the Royal Hospitals Trust, London, U.K. Cases are defined as mothers delivering an infant weighing less than 2,500g before 37 weeks gestation and controls as mothers delivering an infant of more than 2,500g after 38 weeks. We estimated that a study involving 800 mothers (1:3 case:control) should have sufficient power to detect an association with a minimum odds ration of 3 at the 5% significance level. Demographic details of 177 subjects demonstrated that they were representative of the local population, and the prevalence of PLBW was within the expected range. However, the extent and severity of periodontal disease were higher than predicted and may have reflected elevations in gingival inflammation associated with pregnancy. The final outcome of the study should help determine the need for further interventionist studies to demonstrate a causal relationship between periodontal disease and PLBW, as well as provide information on the prevalence of periodontal diseases in this study population.] Davenport ES, Williams CE, et.al. *Ann Periodontol. 1998 Jul;3(1):213-21.* http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9722705&dopt=Citation

1168. **The origin of Fusobacterium nucleatum involved in intra-amniotic infection and preterm birth. [**Objective. To evaluate the potential oral origin of Fusobacterium nucleatum found in amniotic fluid of women at high risk of preterm birth. Methods. A transversal study nested into a cohort study of women with preterm labor and/or preterm premature rupture of membranes was undergone. Women with the presence of F. nucleatum in the amniotic fluid and their respective partners were invited to be examined for their periodontal health after delivery, and samples of saliva and subgingival plaque

were collected. For each couple, specific PCR detection of Fusobacterium species was performed on each oral sample, and the DNA sequences were compared with the one obtained from amniotic fluid. Results. Three women, all in preterm labor with intact membranes, were included. Intra-amniotic sludge was observed in all of them. A strain of F. nucleatum with 100% sequence identity with the strain detected in the amniotic fluid was found in the oral samples of one of them and of two partners. Conclusion. This study suggests that intra-amniotic F. nucleatum could originate from the patient's or the partner's oral microflora.] Gauthier S, Tetu A, et al. *J Matern Fetal Neonatal Med.* 2011 Feb 11. http://www.ncbi.nlm.nih.gov/pubmed/21314291

1169. **The Relationship Between Infections and Adverse Pregnancy Outcomes: An Overview**. [Preterm birth with its subsequent morbidity and mortality is the leading perinatal problem in the United States. Infants born before the thirty-seventh week of gestation account for approximately 6% to 9% of all births, but 70% of all perinatal deaths and half of all long-term neurologic morbidity. Current approaches focus on symptomatic treatment. Despite widespread use of drugs to arrest preterm labor (tocolytics), there has been no decrease in low birth weight or preterm infants in the last 20 years. It is likely that therapy directed at preventing or treating underlying causes would be more successful. Evidence from many sources links preterm birth to symptomatic infections, for example, of the urinary or respiratory tracts. In the last decade, great interest has been generated to support the hypothesis that subclinical infection is an important cause of preterm labor. Evidence to support this may be categorized as follows: histological chorioamnionitis is increased in preterm births; clinical infection is increased after preterm birth; there is significant association of some lower genital tract organisms and infections with preterm birth or preterm premature rupture of the membranes; there are positive cultures of amniotic fluid or membranes from some patients with preterm labor and preterm birth; there are markers of infections in preterm birth; bacteria or their products induce preterm birth in animal models; and some antibiotic trials have shown a lower rate of preterm birth or have deferred preterm birth. In the last 5 years, additional exciting information has suggested that not only is subclinical infection responsible for preterm birth but also many serious neonatal sequelae including periventricular leukomalacia, cerebral palsy, respiratory distress, and even bronchopulmonary dysplasia and necrotizing enterocolitis. In sum, a large body of clinical and laboratory information suggests that subclinical infection is a major cause of preterm birth, especially those occurring before 30 weeks. This concept holds promise that new approaches can be developed to prevent prematurity.] Gibbs RS. *Annals of Periodontology December 2001, Vol. 6, No. 1, Pages 153-163.* http://www.joponline.org/doi/abs/10.1902/annals.2001.6.1.153?journalCode=annals

1170. **Transmission of Diverse Oral Bacteria to Murine Placenta: Evidence for the Oral Microbiome as a Potential Source of Intrauterine Infection.** [Microbial infection of the intrauterine environment is a major cause of preterm birth. The current paradigm indicates that intrauterine infections predominantly originate from the vaginal tract, with the organisms ascending into the sterile uterus. With the improvements in technology, an increasing number of bacterial species have been identified in intrauterine infections that do not belong to the vaginal microflora. We have demonstrated previously that intrauterine infections can originate from the oral cavity following hematogenous transmission. In this study, we begin to systemically examine what proportion of the oral microbiome can translocate to the placenta. Pooled saliva and pooled subgingival plaque samples were injected into pregnant mice through tail veins to mimic bacteremia, which occurs frequently during periodontal infections. The microbial species colonizing the murine placenta were detected using 16S rRNA gene-based PCR and clone analysis. A diverse group of bacterial species were identified, many of which have been associated with adverse pregnancy outcomes in humans although their sources of infection were not determined. Interestingly, the majority of these species were oral commensal organisms. This may be due to a dose effect but may also indicate a unique role of commensal species in intrauterine infection. In addition, a number of species were selectively "enriched" during the translocation, with a higher prevalence in the placenta than in the pooled saliva or subgingival plaque samples. These observations indicate that the placental translocation was species specific. This study provides the first insight into the diversity of oral bacteria associated with intrauterine infection.] Fardini Y, Chung P, et al. Infection and Immunity, April 2010, p. 1789-1796, Vol. 78, No. 4 http://iai.asm.org/cgi/content/abstract/78/4/1789

1171. **Treatment of Periodontal Disease During Pregnancy: A Randomized Controlled Trial.** [OBJECTIVE: To investigate whether treating periodontal disease prevents preterm birth and other major complications of pregnancy. METHODS: This single-center trial was conducted across six obstetric sites in metropolitan Perth, Western Australia. Pregnant women identified by history to be at risk (n=3,737) were examined for periodontal disease. Approximately 1,000 women with periodontal disease were allocated at random to receive periodontal treatment commencing around 20 weeks of gestation (n=542) or 6 weeks after the pregnancy was completed (controls; n=540). The treatment included mechanical removal of oral biofilms together with oral hygiene instruction and motivation at a minimum of three weekly visits, with further visits if required. RESULTS: There were no differences between the control and treatment groups in preterm birth (9.3% compared with 9.7%, odds ratio [OR] 1.05, 95% confidence interval [CI 0.7–1.58], *P*=.81), birth weight (3,450 compared with 3,410 g, *P*=.12), preeclampsia (4.1% compared with 3.4%, OR 0.82, 95% CI 0.44–1.56, *P*=.55), or other obstetric endpoints. There were four unexplained stillbirths in the control group and no pregnancy losses in the treated group (*P*=.12). Measures of fetal and neonatal well-being were similar in the two groups, including abnormalities in fetal heart rate recordings (*P*=.26), umbilical artery flow studies (*P*=.96), and umbilical artery blood gas values (*P*=.37). The periodontal treatment was highly successful in improving health of the gums (*P*<.01). CONCLUSION: The evidence provided by the present study does not support the hypothesis that treatment of periodontal disease during pregnancy in this population prevents preterm birth, fetal growth restriction, or preeclampsia. Periodontal treatment was not hazardous to the women or

their pregnancies.] Newnham JP, Newnham IA, et al. Obstetrics & gynecology, Vo.. 114, Issue 6, pp 1239-1248. http://journals.lww.com/greenjournal/Abstract/2009/12000/Treatment_of_Periodontal_Disease_During_Pregnancy_.13.aspx

Prostate Disease and Periodontal Disease

1172. **Association Between Periodontal Disease and Prostate Specific Antigen Levels in Chronic Prostatitis Patients**. [Background: Prostate Specific Antigen (PSA) is an inflammatory marker produced by the epithelial cells of the prostate acini. In the presence of inflammation and/or malignancy of the prostate, PSA levels are higher than 4.0ng/ml. This preliminary study was conducted to evaluate any association between periodontitis and PSA levels in chronic prostatitis patients. Methods: Thirty-five subjects that underwent prostate biopsy because of abnormal findings on digital rectal exam and/or elevated PSA (>4.0 ng/ml) participated in the study. Periodontal examination: plaque and gingival indices, bleeding on probing, probing depth and clinical attachment level were determined. Two sided independent sample t-test assessed any significant differences in the PSA levels between/among the groups of prostatitis as well as periodontitis. Results: Mean PSA levels were significantly higher (P = 0.04) in subjects with moderate/severe prostate inflammation than those with none/mild (8.8 ± 5.8 vs 5.7 ± 3.1 ng/ml). Subjects with CAL ≥2.7 mm had higher but not statistically significant PSA levels than those with CAL <2.7 mm (7.7 ± 5.2 vs. 5.7 ± 3.2 ng/ml), respectively. Individuals having both moderate/severe prostatitis and CAL ≥2.7 mm (10.8 ± 7.0ng/ml) had significantly higher mean PSA levels (P = 0.05) than those with neither condition (5.6 ± 3.7 ng/ml) nor only CAL ≥2.7 mm (5.7 ± 2.4 ng/ml) or moderate/severe prostatitis (6.0 ± 1.9 ng/ml). Conclusion: Subjects having co-morbidity of CAL ≥2.7 mm and moderate/severe prostatitis have higher PSA levels than those with either condition alone.] Joshi N, Bissada NF, et al. *Journal of Periodontology*, Posted online on 10 February 2010. http://www.joponline.org/doi/abs/10.1902/jop.2010.090646

Salivary Diagnostics - OralDNALabs – Bacterial DNA & Periodontal Susceptibility Testing

1173. **Analysis of gingival crevicular fluid as applied to the diagnosis of oral and systemic diseases. [**Gingival crevicular fluid (GCF), a serum transudate or inflammatory exudate, can be collected from the gingival crevice surrounding the teeth. As such, the fluid reflects the constituents of serum, the cellular response in the periodontium, and contributions from the gingival crevice. The study of GCF has focused on defining the pathophysiology of periodontal disease, and identification of a potential diagnostic test for active periodontitis. The majority of markers that have been identified as potential candidates for such a test are measures of inflammation (i.e., prostaglandin E2 (PGE2), neutrophil elastase, and the lysosomal enzyme beta-glucuronidase). Further, analysis of inflammatory markers in GCF may assist in defining how certain systemic disorders (e.g., diabetes mellitus) can modify periodontal disease, and how periodontal disease/periodontal inflammation can influence certain systemic disorders (i.e., cardiovascular/cerebrovascular diseases). Methodological concerns related to the collection and analysis of GCF are important factors that need to be considered when studying GCF. Practical concerns argue against the widespread clinical application of GCF as an adjunct to periodontal diagnosis. Rather, analysis of GCF-derived mediators in saliva may serve as a means of rapid screening for periodontal disease.] Lamster IB, Ahlo JK. *Ann N Y Acad Sci*. 2007 Mar;1098:216-29. http://www.ncbi.nlm.nih.gov/pubmed/17435131

1174. **Evaluation of components of gingival crevicular fluid as diagnostic tests. [**Gingival crevicular fluid (GCF) is an inflammatory exudate that can be collected at the gingival margin or within the gingival crevice. The biochemical analysis of the fluid offers a noninvasive means of assessing the host response in periodontal disease. In recent years, the relationship of measures of the inflammatory response in GCF to risk for development of active periodontal disease (defined as clinical attachment loss or radiographic bone loss) has been studied in longitudinal trials. The greatest interest has focused on prostaglandin E2, an arachidonic acid metabolite; beta-glucuronidase and neutrophil elastase, markers of lysosomal enzyme release from neutrophils; and aspartate aminotransferase, a cytoplasmic enzyme indicative of cellular necrosis. Analysis of the data allows a number of conclusions to be drawn concerning the potential diagnostic significance of GCF: 1) an exuberant host inflammatory response is associated with progressive disease in patients with periodontitis; 2) collection of GCF using small precut strips is a reproducible and reliable collection technique; 3) the total amount of the mediator and not concentration of the mediator in the GCF sample can be reported when timed samples are collected; and 4) technology exists for GCF-based diagnostic tests to be performed in the dental office. Nevertheless, many questions remain. Still to be determined are: 1) the relationship of test results to the development of periodontitis in patients with gingivitis; 2) the level of test accuracy needed to justify use of these tests; 3) the unit of observation (patient, site) that is being evaluated by the test; and 4) the need for such tests as perceived by clinicians. While these questions are formidable, introduction of GCF-based diagnostic tests will provide clinicians with an improved, quantitative means of evaluating patients and offer specific criteria to assess the effectiveness of treatment.] Lamster IB. *Ann Periodontol*. 1997 Mar;2(1):123-37. http://www.ncbi.nlm.nih.gov/pubmed/9151549

1175. **Metabonomic analysis of saliva reveals generalized chronic periodontitis signature**. [The diagnoses of periodontal diseases (PD) are primarily based on clinical examination and radiographic parameters. In this pilot exploration we want to supply some evidence whether metabonomic profiling of saliva samples can provide a signature of the disease. Saliva samples were analyzed by Nuclear Magnetic Resonance (NMR) metabonomics from 22 healthy subjects (HS) and 32 patients with clinic and radiographic diagnosis of different PD: Gingivitis (G), Localized Chronic Periodontitis (LCP),

Generalized Chronic Periodontitis (GCP), Localized Aggressive Periodontitis (LAP), and Generalized Aggressive Periodontitis (GAP). Pattern recognition analysis of NMR profiles can discriminate GCP patients (n = 21) from HS (n = 22) with an accuracy of 84.1%. Metabolic profiles of GCP patients exhibited higher concentrations of acetate, γ-aminobutyrate, *n*-butyrate, succinate, trimethylamine, propionate, phenylalanine and valine, and decreased concentrations of pyruvate and *N*-acetyl groups compared with controls. Our results can provide a contribution to the understanding of the biochemical network and pathway in the GCP and other PD, however at this stage the method can not be extended to the general population as a ready-to-use clinical tool, due to the limited cohort recruited and the exploratory nature of this work. Anyway, a further validation of the statistical model on a larger cohort is in progress with the aim to demonstrate the potential impact in clinical practice of our findings.] Aimetti M, Cacciatore S, et al. *Metabolomic*s, Published Online 07 july 2011; DOI: 10.1007/s11306-011-0331-2. http://www.springerlink.com/content/y528l4035653m888/

Pathogen Threshold Levels and Bacterial Risk

1176. **Microbial etiological agents of destructive periodontal disease**. Periodontol 2000, Vol. 5; 1994, 78-111. http://www3.interscience.wiley.com/journal/119280617/abstract

1177. **Microbial Etiology of Periodontal Disease.** [The periodontal disease is a chronic, degenerative disease which is localised on the gingiva, periodontalligament, cementum and alveolar bone. The main etiological factor is oral biofilm with microorganisms. The search for the pathogens of periodontal diseases has been underway for more than 100 years, and continues up today. The currently recognized key Gram negative periodontopathogens include: Porphyromonas gingivalis, Prevotella intermedia, Bacteroides forsythus, Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum, Capnocytophaga species, Campylobacter rectus.All bacteria in the periodontal pocket could damage periodontal tissues, and good knowledge of these as well as an adequate treatment could be helpful in treatment of this disease.A full understanding of the microbial factors, their pathogenicity as well as host factors are of the essential importance for pathogenesis of periodontal disease. In this way, it could be possible to treat the periodontal patients adequately.] Mini Review. Kesic L, Milasin J, et al. Medicine and Biology Vol. 15, 2008, 1-6. http://facta.junis.ni.ac.rs/mab/mab200801/mab200801-01.pdf

1178. **Microbiological goals of periodontal therapy.** Teles RP, Haffajee AD**.** Periodontol 2000. 2006;42:180-218. http://www.ncbi.nlm.nih.gov/sites/entrez

1179. **The effect of periodontal therapy on the composition of the subgingival microbiota**. Haffajee AD, Teles RP, Socransky SS. Periodontol 2000, Vol. 42, 2006, 219-258. http://www.ncbi.nlm.nih.gov/pubmed/16930312

HPV – Cancer Diagnostics

1180. Body fluid biomarkers for early detection of head and neck squamous cell carcinomas. **[**Along with advancements in treatment, early detection of primary tumor, and relapse seems to remain a key factor for improving the survival rate of patients with head and neck squamous cell carcinoma (HNSCC), in which a high proportion of patients are diagnosed at an advanced stage. Recent advancements in basic research of molecular biology have improved the understanding of the molecular process of HNSCC progression and have led to identification and characterization of numerous biomarkers. Biomarkers of HNSCC are expected to facilitate the early detection of primary, and relapsed tumors. In the present article, we review the recent discoveries of potential biomarkers for the early detection of HNSCC. Most of the promising biomarkers have some limitations in clinical diagnosis. However, salivary interleukin-8 and melanoma-associated gene showed good sensitivity, specificity, convenience, and standardization. As HNSCC is a life-threatening disease, large-scale clinical validation is necessary for these two markers.] Lee KD, Lee HS, et al. *Anticancer Res.* 2011 Apr;31(4):1161-7. http://www.ncbi.nlm.nih.gov/pubmed/21508360

MyPerioPath℠ Description/Clinical Utility of Periodontal Testing

1181. **Dental Biofilms: difficult therapeutic targets**. Socransky SS, HaffajeeAD. Periodontol 2000, Vol. 28, 2002, 9-12. http://www.ncbi.nlm.nih.gov/pubmed/12013340

1182. **Microbial complexes in subgingival plaque.** [It has been recognized for some time that bacterial species exist in complexes in subgingival plaque. The purpose of the present investigation was to attempt to define such communities using data from large numbers of plaque samples and different clustering and ordination techniques. Subgingival plaque samples were taken from the mesial aspect of each tooth in 185 subjects (mean age 51 +/- 16 years) with (n = 160) or without (n = 25) periodontitis. The presence and levels of 40 subgingival taxa were determined in 13,261 plaque samples using whole genomic DNA probes and checkerboard DNA-DNA hybridization. Clinical assessments were made at 6 sites per tooth at each visit. Similarities between pairs of species were computed using phi coefficients and species clustered using an averaged unweighted linkage sort. Community ordination was performed using principal components analysis and correspondence analysis. 5 major complexes were consistently observed using any of the analytical methods. One complex consisted of the tightly related group: Bacteroides forsythus, Porphyromonas gingivalis and Treponema denticola. The 2nd complex consisted of a tightly related core group including members of the Fusobacterium nucleatum/periodonticum subspecies, Prevotella intermedia, Prevotella nigrescens and Peptostreptococcus micros. Species associated with this group included: Eubacterium nodatum, Campylobacter rectus, Campylobacter showae, Streptococcus constellatus and Campylobacter gracilis. The 3rd complex consisted of Streptococcus sanguis, S. oralis, S. mitis, S. gordonii and S. intermedius. The 4th complex was

comprised of 3 Capnocytophaga species, Campylobacter concisus, Eikenella corrodens and Actinobacillus actinomycetemcomitans serotype a. The 5th complex consisted of Veillonella parvula and Actinomyces odontolyticus. A. actinomycetemcomitans serotype b, Selenomonas noxia and Actinomyces naeslundii genospecies 2 (A. viscosus) were outliers with little relation to each other and the 5 major complexes. The 1st complex related strikingly to clinical measures of periodontal disease particularly pocket depth and bleeding on probing.] Socransky SS, Haffajee AD, et al. ; J Clin Periodontol Vol. 25, 134-144; 1998. http://www.ncbi.nlm.nih.gov/pubmed/9495612

1183. **Microbiological diagnostics in periodontics: biological significance and clinical validity**.[The identification of etiologic agents helps select the optimal drug therapy to support the patient in overcoming an infectious disease. Clinical microbiologyin dentistyis used in cariology, implant dentistry, and periodontis… Th present article discusses the rationale for applying clinical periodontal microbiology in the treatment of sever types of destructive periodontal disease.] van Winkelhoff AJ, Winkel EG. Periodontol 2000, Vol. 39, 2005, 40-52: Arie J, van Winkelhoff, Winkel http://www3.interscience.wiley.com/journal/118702649/abstract

1184. **Role of bacteria in health and disease of periodontal tissues.** Feng Z, Weinberg A; Periodontol 2000, Vol. 40, 2006, 50-76.. http://www.ncbi.nlm.nih.gov/pubmed/16398685

1185. **The effect of periodontal therapy on the composition of the subgingival microbiota**. Haffajee AD, Teles RP, et al. Periodontol 2000, Vol . 42, 2006, 219-258 . http://www.ncbi.nlm.nih.gov/pubmed/16930312

1186. **The relationship between periodontal disease and systemic conditions**. [In this year's report of the United States Surgeon General on oral health in America, two major themes evolved: 1) oral health means much more than healthy teeth, and 2) oral health is integral to general health. This article describes how oral diseases, in particular periodontal diseases, are associated with other health problems, including cardiovascular disease, diabetes mellitus, complications of pregnancies, and osteoporosis.] Rose LF, Steinberg BJ, Minsk L. *Compend Contin Educ Dent*. 2000 Oct;21(10A):870-7;quiz 878. http://www.ncbi.nlm.nih.gov/pubmed/11908364

MyPerioID℠PST® Reference

1187. **Self-reported periodontal disease in a Virginia twin population.** [To investigate the contribution of genetic factors in the etiology of periodontal disease, questionnaire data were collected on 4,908 twin pairs included in the population-based Virginia Twin Registry. A history of periodontal disease was reported in 420 individuals who were members of 116 monozygotic (MZ) and 233 dizygotic (DZ) twin pairs. The mean age at diagnosis in this sample was 31.4 +/- 0.7 years and was significantly earlier in females than males (30.1 vs. 33.0 years, P < 0.025). Proband-wise concordance rates were 0.38 for MZ and 0.16 for DZ twins. There were no differences in concordance rate between same and opposite-sexed dizygotic twins. These findings provide evidence that genetic factors make an important contribution to risk for adult-onset periodontal disease.]Corey LA, Nance WE, Hofstede P, Schenkein HA *J Periodontol*. Dec 1993;64(12):1205-1208. http://www.ncbi.nlm.nih.gov/pubmed/8106947

1188. **Interleukin-1 gene polymorphisms and long term stability following guided tissue regeneration**. [BACKGROUND: Specific interleukin (IL)-1 gene polymorphisms are associated with an increased susceptibility to severe periodontitis, increased inflammation, and increased likelihood of tooth loss during the maintenance phase after conventional periodontal therapy. The aim of the present study was to evaluate the impact of genotype on the maintenance of gained clinical attachment obtained after guided tissue regeneration (GTR) surgical therapy in deep intrabony defects. METHODS: Forty deep (> or =4 mm) interproximal angular bony defects with presurgical clinical attachment loss of >8 mm were treated by GTR using a non-absorbable expanded polytetrafluoroethylene (ePTFE) membrane. Membranes were surgically removed 4 to 6 weeks after surgery. Afterwards patients were placed on monthly recall for the first year and every 3 months for the following 3 years. At the 4-year re-evaluation, a IL-1 genetic susceptibility test was performed on all patients. RESULTS: Fourteen (35% of the 40 patients) were genotype-positive (+). At baseline no statistically significant differences were found between patients with different genotypes in full mouth plaque score (FMPS), full mouth bleeding score (FMBS), clinical attachment level (CAL), probing depth (PD), or gingival recession. At year 1 follow up visit, no statistically significant differences were noted between genotype + and genotype - patients in FMPS, FMBS, amount of CAL gain, decrease in PD, or increase in gingival recession. Sixteen patients had membrane exposure after the GTR procedures. In these patients, the amount of CAL gain (P <0.001) and PD reduction (P <0.01) 1 year after surgery was significantly lower than those observed in patients without membrane exposure. At the year 4 follow-up visit, no significant differences were found between genotype negative and positive patients in FMPS or FMBS and both groups showed a significant loss in CAL (P<0.001) and increase in PD (P<0.001) when compared to year 1 visit. No change in gingival recession was noted. Genotype + patients showed significantly more CAL loss (P<0.002) and increase in PD (P<0.001) between the years 1 and 4 when compared to genotype - patients. A significant association between genotype and stability of the regenerated attachment was also demonstrated. CONCLUSIONS: The results of this study demonstrate that genotype expression did not effect GTR treatment response at 1 year, but had a great impact on long-term stability (year 4). In a 3-year period, patients with positive IL-1 genotype lost about 50% of the first year gained CAL and were about 10 times more likely of experiencing > or = 2 mm CAL loss when compared to oral hygiene matched genotype-negative patients.] DeSanctis M, Zuchelli G. *J Periodontol*. Dec 2000;71:606-13. http://www.ncbi.nlm.nih.gov/pubmed/10807125

1189. **Periodontal disease in non-insulin dependent diabetes mellitus.** [The relationship between diabetes mellitus and oral health status was determined in Pima Indians from the Gila River Indian Community in Arizona. This tribe of native

Americans has the world's highest reported incidence and prevalence of non-insulin-dependent (type 2) diabetes mellitus. The probing attachment level, alveolar bone loss, age, sex, Calculus Index, Plaque Index, Gingival Index, fluorosis, and DMFT as well as the diabetic status was assessed in 1,342 Pima Indians who were at least partially dentate. The prevalence and severity of destructive periodontal disease was determined by measuring probing attachment loss and radiographically apparent interproximal crestal alveolar bone loss, two independent but correlated indicators of periodontal destruction. Only diabetic status, age, and the presence of subgingival calculus were significantly associated with both increased prevalence and greater severity of destructive periodontal disease in this population. Diabetic status was significantly and strongly related to both the prevalence and severity of disease after adjusting for the effects of demographic variables and several indices of oral health including the Plaque Index. Subjects with type 2 diabetes have an increased risk of destructive periodontitis with an odds ratio of 2.81 (95% confidence interval 1.91 to 4.13) when attachment loss is used to measure the disease. The odds ratio for diabetic subjects was 3.43 (95% confidence interval 2.28 to 5.16) where bone loss was used to measure periodontal destruction. These findings demonstrate tht diabetes increases the risk of developing destructive periodontal disease about threefold. Furthermore, diabetes increases the risk of developing periodontal disease in a manner which cannot be explained on the basis of age, sex, and hygiene or other dental measures.] Emrich LJ, Shlossman M, Genco RJ. J Periodontol. Feb 1991;62(2):123-131. http://www.ncbi.nlm.nih.gov/pubmed/2027060

1190. **IL-1 gene polymorphism and smoking as risk factors for peri-implant bone loss in a well-maintained population.** [The aim of the present study was (i) to investigate the relation between specific interleukin-1 (IL-1) gene polymorphisms and peri-implant bone loss at osseointegrated ITI(R) dental implants and (ii) to explore the association between these allelic variants of the IL-1 gene complex and peri-implant mucosal inflammation, in both smoking and non-smoking individuals. A sample of 90 consecutive Caucasian patients (aged 33-88 years), treated with at least one ITI-implant participated in this retrospective investigation. Standardized periapical radiographs were taken after prosthetic rehabilitation (133.6 days, SD 136.9 days) and at the time of the re-examination, on average 5.6 years (SD 2.5 years) thereafter. The radiographs were analyzed by a calibrated examiner for changes in peri-implant bone levels. The examiner was blind with respect to clinical parameters and IL-1 status. The distance between the implant shoulder and the first visible bone-implant contact (DIB) at the respective time points were measured using a computerized method. The absolute bone level difference during the years of service (ABL) and the annual bone loss (DeltaBL/year) were calculated for all the implants. Percentages of full mouth bleeding on probing (BOP), as well as of BOP calculated separately for teeth and implants, were determined for all visits and averaged for the entire observation period. Out of the total patient sample, there were 14 heavy smokers (= 20 cigarettes/day), 14 moderate smokers (5-19 cigarettes/day), 23 previous smokers (smoking cessation > 5 years) and 39 non-smokers. Twenty-eight (31.11%) patients were IL-1 genotype positive. Upon stratification for smoking status, significant differences were found for the variables ABL ($P < 0.04$, U-test) and DeltaBL/year ($P < 0.04$, U-test) between non-smokers and heavy smokers for the IL-1 genotype positive group but not for the IL-1 genotype negative group. Moreover, significant differences in ABL ($P < 0.04$, U-test) and DeltaBL/year ($P < 0.04$, U-test) were identified between former smokers and heavy smokers for the IL-1 genotype positive group. The differences in inflammatory parameters (BOP) did not reach statistical significance. This study suggests that in heavy cigarette smokers, carriage of a functionally significant IL-1 gene complex polymorphism is associated with an increased risk for peri-implant bone loss following prosthetic reconstruction and during the supportive periodontal care phase of the treatment.] Feloutzis A, Lang NP, Tonetti MS, Burgin W. Bragger U, Buser D, Duff GW, Kornman KS. *Clin Oral Implants Res*. 14: 10-7. http://www.ncbi.nlm.nih.gov/pubmed/12562360

1191. **The Interleukin-1 genotype as a severity in adult periodontal disease.** [Although specific bacteria, dental plaque, and age are associated with periodontal disease, there are currently no reliable predictors of periodontitis severity. Studies in twins have suggested a genetic contribution to the pathogenesis of periodontitis, but previous attempts to identify genetic markers have been unsuccessful. The pro-inflammatory cytokines interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF alpha) are key regulators of the host responses to microbial infection. IL-1 is also a major modulator of extracellular matrix catabolism and bone resorption. We report a specific genotype of the polymorphic IL-1 gene cluster that was associated with severity of periodontitis in non-smokers, and distinguished individuals with severe periodontitis from those with mild disease (odds ratio 18.9 for ages 40-60 years). Functionally, the specific periodontitis-associated IL-1 genotype comprises a variant in the IL-1B gene that is associated with high levels of IL-1 production. In smokers severe disease was not correlated with genotype. In this study, 86.0% of the severe periodontitis patients were accounted for by either smoking or the IL-1 genotype. This study demonstrates that specific genetic markers, that have been associated with increased IL-1 production, are a strong indicator of susceptibility to severe periodontitis in adults.] Kornman KS Crane A, Wang HY, et al. J Clin Periodontol. Jan 1997;24(1):72-77. http://www.ncbi.nlm.nih.gov/pubmed/9049801

Tobacco, Alchohol

1192. **Differences in microbiological composition of saliva and dental plaque in subjects with different drinking habits. [**Several foods have been shown to contain natural components (especially polyphenols) which display anti-adhesive properties against Streptococcus mutans, the aetiological agent responsible for dental crown caries, as well as inhibition of glucosyltransferases, which are the S. mutans enzymes involved in the synthesis of an adherent, water-insoluble glucan from sucrose. Other studies have demonstrated an in vitro action on oral plaque biofilm formation and desorption. This study evaluated whether the activity displayed in vitro by food compounds could affect the microbiological composition of saliva and dental plaque of subjects with a diet rich in these foods, comparing the results with those obtained from subjects with a

different diet. The foods considered were: coffee, barley coffee, tea and wine. A total of 93 subjects were recruited into the study. Six samples of both plaque and saliva were collected from each subject at roughly one-monthly intervals. Total bacteria, total streptococci, S. mutans and lactobacilli counts were determined by culture in both saliva and dental plaque. The highest bacterial titres were recorded for the control population, while each drinking habit subgroup showed counts roughly one log lower than the controls. These differences in bacterial counts proved statistically significant ($P<0.05$). As far as dental plaque was concerned, while total counts did not significantly vary per mg of plaque in the subjects belonging to the different drinking habit subgroups, a significant decrease ($P<0.05$) was observed in those subjects drinking coffee, tea, barley coffee and wine when mutans streptococci and lactobacilli were evaluated. In several cases a more than one log decrease was observed. Plaque indices were also determined, and a significant ($P<0.05$) reduction in values was recorded in the subjects belonging the specific drinking habit subgroups compared to the control group. This study indicates that there is a correlation between consumption of specific foods and oral health in terms of reduced plaque deposition and lower counts of odontopathogens.] Signoretto C, Burlacchini G, et al. *New Microbiol.* 2006 Oct;29(4):293-302. http://www.ncbi.nlm.nih.gov/pubmed/17201096

1193. **Drinking habits are associated with changes in the dental plaque microbial community.** [Caries and gingivitis are the most prevalent oral infectious diseases of humans and are due to the accumulation of dental plaque (a microbial biofilm) on the tooth surface and at the gingival margin, respectively. Several in vitro and in vivo studies have shown that many natural components of foods and beverages inhibit the adhesion of and/or exert activity against oral bacteria. These biological activities have mainly been attributed to the polyphenol fraction. In order to explore the possibility that diet can alter the dental plaque community, in this study we evaluated the composition of the microbiota of supra- and subgingival plaque samples collected from 75 adult subjects with different drinking habits (drinkers of coffee, red wine, or water for at least 2 years) by analyzing the microbial population through the separation of PCR-amplified fragments using the denaturing gradient gel electrophoresis (DGGE) technique. The mean numbers of bands of the DGGE profiles from all three categories were evaluated. There were no significant differences between the two kinds of plaque collected from the control group (water drinkers), and this group showed the highest number of bands (supragingival plaque, 18.98 +/- 3.16 bands; subgingival plaque, 18.7 +/- 3.23 bands). The coffee and wine drinker groups generated the lowest numbers of bands for both supragingival plaque (coffee drinkers, 8.25 +/- 3.53 bands; wine drinkers, 7.93 +/- 2.55 bands) and subgingival plaque (coffee drinkers, 8.3 +/- 3.03 bands; wine drinkers, 7.65 +/- 1.68 bands). The differences between coffee drinkers or wine drinkers and the control group (water drinkers) were statistically significant. A total of 34 microorganisms were identified, and the frequency of their distribution in the three subject categories was analyzed. A greater percentage of subjects were positive for facultative aerobes when supragingival plaque was analyzed, while anaerobes were more frequent in subgingival plaque samples. It is noteworthy that the frequency of identification of anaerobes was significantly reduced when the frequencies for coffee and wine drinkers were compared with the frequencies for subjects in the control group. The DGGE profiles of the organisms in both plaque samples from all groups were generated and were used to construct dendrograms. A number of distinct clusters of organisms from water, coffee, and wine drinkers were formed. The clustering of some of the DGGE results into cohort-specific clusters implies similarities in the microbiotas within these groups and relevant differences in the microbiotas between cohorts. This supports the notion that the drinking habits of the subjects may influence the microbiota at both the supragingival and the subgingival levels.] Signoretto C, Bianchi F, et al. *J Clin Microbiol.* 2010 Feb;48(2):347-56. Epub 2009 Dec 2. http://www.ncbi.nlm.nih.gov/pubmed/19955272

1194. **Response of Subgingival Bacteria to Smoking Cessation.** [It has been demonstrated that smoking cessation alters the subgingival microbial profile; however, the response of individual bacteria within this ecosystem has not been well studied. The aim of this investigation, therefore, was to longitudinally examine the effect of smoking cessation on the prevalence and levels of selected subgingival bacteria using molecular approaches for bacterial identification and enumeration. Subgingival plaque was collected from 22 smokers at the baseline and 12 months following periodontal nonsurgical management and smoking cessation counseling. The prevalence and abundance of selected organisms were examined using nested PCR and multiplexed bead-based flow cytometry. Eleven subjects successfully quit smoking over 12 months (quitters), while 11 continued to smoke throughout (smokers). Smoking cessation led to a decrease in the prevalence of *Porphyromonas endodontalis* and *Dialister pneumosintes* at 12 months and in the levels of *Parvimonas micra*, *Filifactor alocis*, and *Treponema denticola*. Smoking cessation also led to an increase in the levels of *Veillonella parvula*. Following nonsurgical periodontal therapy and smoking cessation, the subgingival microbiome is recolonized by a greater number of health-associated species and there are a significantly lower prevalence and abundance of putative periodontal pathogens. The results indicate a critical role for smoking cessation counseling in periodontal therapy for smokers in order to effectively alter the subgingival microbiome.] Delima SL, McBride RK, et al. Journal of Clinical Microbiology, July 2010, p. 2344-2349, Vol. 48, No. 7 http://jcm.asm.org/cgi/content/abstract/48/7/2344

1195. **Relationship of cigarette smoking to the subgingival microbiota.** [BACKGROUND: The relationship of cigarette smoking to the composition of the subgingival microbiota is not clear. Some studies indicated higher levels of certain species in smokers, while other studies failed to detect differences in the microbiota between subjects with different smoking histories. Thus, the purpose of the present investigation was to examine the prevalence, proportions and levels of the subgingival species in adult subjects who were current, past or never smokers. METHOD: 272 adult subjects ranging in age from 20-86 years with at least 20 teeth were recruited for study. Smoking history was obtained using a questionnaire. Clinical measures were taken at 6 sites per tooth at all teeth excluding third molars at a baseline visit. Subgingival plaque samples were taken from the mesial surface of all teeth excluding third molars in each subject at baseline and assayed individually for

counts of 29 subgingival species using checkerboard DNA-DNA hybridization. Subjects were subset according to smoking history into never (n=124), past (n=98) and current smokers (n=50). Uni-variate and multi-variate analyses were used to seek associations between smoking category and the counts, proportions and prevalence of subgingival species. RESULTS: Greater differences were observed for the prevalence (% of sites colonized) of the test species in the 3 smoking groups than were observed for counts or proportions of total counts. Members of the orange and red complexes including E. nodatum, F. nucleatum ss vincentii, P. intermedia, P. micros, P. nigrescens, B. forsythus, P. gingivalis and T. denticola were significantly more prevalent in current smokers than in the other 2 groups. The difference in prevalence between smokers and non-smokers was due to greater colonization at sites with pocket depth <4 mm. Stepwise multiple linear regression analysis indicated that combinations of the prevalence of 5 microbial species and pack years accounted for 44% of the variance for mean pocket depth ($p<0.000001$), while the prevalence of 3 microbial taxa along with age, pack years, current smoking and gender accounted for 31% of the variance in mean attachment level ($p<0.000001$). The difference in prevalence between current and never smokers of all members of the red complex and 8 of 12 members of the orange complex was significantly greater in the maxilla than in the mandible. CONCLUSIONS: The major difference between the subgingival microbiota in subjects with different smoking history was in the prevalence of species rather than counts or proportions. The greater extent of colonization in smokers appeared to be due to greater colonization at pocket depths <4 mm. Differences in colonization patterns between current and never smokers were greater in the maxilla than in the mandible.] Haffajee AD, Socransky SS. *J Clin Periodontol.* 2001 May;28(5):377-88. http://www.ncbi.nlm.nih.gov/pubmed/11350499

1196. **Subgingival microbial profiles of smokers with periodontitis.** [The subgingival microbiome is largely uncultivated, and therefore, cultivation-based and targeted molecular approaches have limited value in examining the effect of smoking on this community. We tested the hypothesis that the subgingival biofilm is compositionally different in current and never-smokers by using an open-ended molecular approach for bacterial identification. Subgingival plaque from deep sites of current and never-smokers matched for disease was analyzed by 16S sequencing. Smokers demonstrated greater abundance of Parvimonas, Fusobacterium, Campylobacter, Bacteroides, and Treponema and lower levels of Veillonella, Neisseria, and Streptococcus. Several uncultivated Peptostreptococci, Parvimonas micra, Campylobacter gracilis, Treponema socranskii, Dialister pneumosintes, and Tannerella forsythia were elevated in this group, while Veillonella sp. oral clone B2, Neisseria sp. oral clone 2.24, Streptococcus sanguinis, and Capnocytophaga sp. clone AH015 were at lower levels. The microbial profile of smoking-associated periodontitis is distinct from that of non-smokers, with significant differences in the prevalence and abundance of disease-associated and health-compatible organisms.] Shchipkov AY, Nagaraja HN, et al. *J Dent Res.* 2010 Nov;89(11):1247-53. Epub 2010 Aug 25. http://www.ncbi.nlm.nih.gov/pubmed/20739702

1197. **The effect of a supragingival plaque-control regimen on the subgingival microbiota in smokers and never-smokers: evaluation by real-time polymerase chain reaction. [**Background The aim of the present study was to evaluate the effect of strict supragingival plaque control on the subgingival microbiota in smokers and never-smokers. Research into the impact of supragingival plaque control on the number of subgingival bacteria has resulted in contradictory findings. Real-time polymerase chain reaction (PCR) has been suggested as a valid alternative to current microbiologic methods based on bacteria cultures. METHODS: Forty-five subjects with chronic periodontitis were selected. Twenty-four of them had never smoked, and 21 were active smokers. Four sites per patient were selected for sampling. Supragingival debridement was performed at baseline, and the subjects received weekly instructions on oral hygiene for 180 days. A clinical examination and subgingival plaque sampling were carried out at baseline and at 30, 90, and 180 days. A real-time PCR assay was used to detect and quantify Porphyromonas gingivalis, Parvimonas micra (previously Peptostreptococcus micros or Micromonas micros), Dialister pneumosintes, Aggregatibacter actinomycetemcomitans (previously Actinobacillus actinomycetemcomitans), and the total bacteria load (eubacteria) in the subgingival samples. Statistical analysis was performed using linear models adjusted for the clustering of observations within individuals. RESULTS: Smokers and never-smokers exhibited a similar and significant reduction in total bacteria counts over time. Irrespective of smoking status, deep sites consistently harbored greater quantities of total bacteria throughout the study. Higher numbers of the bacteria investigated were associated with bleeding on probing. CONCLUSION: Supragingival plaque control markedly reduced subgingival microbiota counts in smokers and never-smokers.] Gomes SC, Nonenmacher C, et al. J Periodontol. 2008 Dec;79(12):2297-304. http://www.ncbi.nlm.nih.gov/pubmed/19053920

1198. **Tobacco Smoking Affects Bacterial Acquisition and Colonization in Oral Biofilms** [Recent evidence suggests that smoking affects the composition of the disease-associated subgingival biofilm, yet little is known about its effects during the formation of this biofilm. The present investigation was undertaken to examine the contributions of smoking to the composition and proinflammatory characteristics of the biofilm during ***de novo*** plaque formation. Marginal and subgingival plaque and gingival crevicular fluid samples were collected from 15 current smokers and from 15 individuals who had never smoked (nonsmokers) following 1, 2, 4, and 7 days of undisturbed plaque formation. 16S rRNA gene cloning and sequencing were used for bacterial identification, and multiplex bead-based flow cytometry was used to quantify the levels of 27 immune mediators. Smokers demonstrated a highly diverse, relatively unstable initial colonization of both marginal and subgingival biofilms, with lower niche saturation than that seen in nonsmokers. Periodontal pathogens belonging to the genera ***Fusobacterium***, ***Cardiobacterium***, ***Synergistes***, and ***Selenomonas***, as well as respiratory pathogens belonging to the genera ***Haemophilus*** and ***Pseudomonas***, colonized the early biofilms of smokers and continued to persist over the observation period, suggesting that smoking favors early acquisition and colonization of pathogens in oral biofilms. Smokers also demonstrated an early proinflammatory response to this colonization, which persisted over 7 days. Further, a positive correlation between proinflammatory cytokine levels and commensal bacteria was observed in smokers but not in

nonsmokers. Taken together, the data suggest that smoking influences both the composition of the nascent biofilm and the host response to this colonization.]. Kumar PS, Matthews CR, et. al. *Infect. Immun*. November 2011 vol. 79 no. 11 4730-4738. http://www.ncbi.nlm.nih.gov/pubmed/21859855

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1199. **Are Dental Plaque, Poor Oral Hygiene, and Periodontal Disease Associated With *Helicobacter pylori* Infection?** [The microorganism *Helicobacter pylori* has been closely linked to chronic gastritis, peptic ulcer, gastric cancer, and mucosa-associated lymphoid tissue (MALT) lymphoma. Despite the current treatment regimens that lead to successful management of *H. pylori*-positive chronic gastritis, the reinfection rate is high. It has been suggested that one of the possible mechanisms of reinfection is the recolonization from dental plaque. *H. pylori* in dental plaque is seldom eliminated by *H. pylori*-eradication therapy, and this may act as a source for future reinfection. Hence, eradication of *H. pylori* from the dental plaque should be made an important part of comprehensive management of *H. pylori*-associated gastric diseases.] Anand PS, Nandakumar K. *Journal of Periodontology* 2006.050163. http://www.joponline.org/doi/abs/10.1902/jop.2006.050163