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Review paper

Inter-relationships between rheumatoid arthritis and periodontal disease

A review

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Abstract

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.

Rheumatoid arthritis (RA) is a chronic destructive inflammatory disease characterized by the accumulation and persistence of an inflammatory infiltrate in the synovial membrane that leads to synovitis and the destruction of the joint architecture. RA occurs worldwide and affects approximately 1% of the world population in a female/male ratio of 3:1 and has a peak incidence of onset in women in the fourth and fifth decades of life (Arnett et al. 1988, Harris 1997).

Whether or not RA is positively, negatively, or not associated at all with the progression of existing inflammatory conditions elsewhere in the body, such as periodontitis, is still controversial. Although several studies have reported contradicting results regarding a relationship between RA and periodontitis, recent studies have reported a significant association between RA and periodontal disease (Kasser et al. 1997, Gleissner et al. 1998, Albandar 1990, Mercado et al. 2000, Mercado et al.

2001). One report indicates that the incidence of RA in patients suffering from periodontitis is 3.95% compared to 1% prevalence in the general population (Mercado et al. 2000). Despite these reports, the literature is still lacking studies correlating the severity of RA and the severity of periodontitis. It seems that carefully controlled, longitudinal population-based, laboratory and clinical (molecular epidemiology) studies are needed to verify the immunological and biological associations between RA and periodontal disease.

The aim of this review is to discuss the remarkable similarities between two of the most common chronic inflammatory diseases affecting humans. The similar pattern of natural history of RA and periodontitis provides useful insights into these diseases. For both diseases the host response, dictated by immunogenetics, determines to a large extent the inflammatory responses.

Furthermore, the cells, enzymes and cytokines which determine the degree of tissue damage all share a common pathologic process in both RA and periodontitis. Finally, because of common shared pathologic processes, management strategies aimed at modulating these responses are similar.

Natural History of RA And Periodontitis
Rheumatoid arthritis

The traditional view of RA has been that in the majority of patients, disease progression can be controlled satisfactorily with well-accepted conservative regimens (McCarty 1985), with suggestions that RA may be ''controlled'' in 70–80% of the patients using aspirin and first-line non-steroidal anti-inflammatory drugs (NSAIDs) and in 95% of patients using second-line drugs such as gold, penicillamine or anti-malarials (Kelley et al. 1993).

In contrast to these traditional views, clinical studies indicate that RA is a progressive disease over 5 years or longer. The majority of patients show radiographic damage within the first few years (Fuchs et al. 1989), further radiographic progression over the next 5–10 years (Fuchs et al. 1989), with severe functional decline (Scott et al. 1987) and increased mortality rates (Mitchell et al. 1986). Almost 50% of the patients have evidence of radiographic joint space narrowing and/or erosion within the first year of disease (Fuchs et al. 1989) and functional status declines are seen in most patients with RA over periods longer than a decade (Rasker & Cosh, 1984, Scott et al. 1987).

However, despite the differences noted between the epidemiological and clinical studies of the natural history of RA, at least three types of disease manifestation can be observed in RA populations (Table 1). These have been termed self-limiting, easily controlled and progressive. Based on epidemiological studies of individuals originally presenting for RA, more than 75% of cases are self-limiting. Around 27% of the individuals originally diagnosed with RA may belong to the easily controlled category (O'Sullivan & Cathart 1972), although this group has been identified in some populations as high as 85% (Pincus et al. 1992a). In rheumatology clinics, most patients appear to have progressive disease, generally requiring second-line drugs, which still do not fully control the disease (Pincus et al. 1992b). In general, these patients have a number of poor prognostic indicators such as the presence of rheumatoid factor, rheumatoid nodules, HLA-DR4 haplotype and numbers of affected joints in the early form of the disease (Sherrer et al. 1986; Roberts et al. 1988; Callin et al. 1989; Van Zeben et al. 1991).

Periodontitis

As for RA, longitudinal studies on the natural history of untreated periodontal disease in humans have indicated the presence of three distinct subpopulations experiencing rapid progression (10–15%), moderate progression (80%) and little or no progression of periodontal disease (5–10%) (Hirschfeld & Wasserman 1978, McFall 1982, Löe et al. 1986). These distributions seem to be independent of access to dental care or relative proportions of plaque deposits.

From etiological and pathogenesis viewpoints, the similar prevalence of severe forms of periodontitis in untreated and treated populations suggests that the amount of plaque does not determine the severity of the disease. Rather, the host response to the varying degrees of plaque challenge may determine the end point of periodontal disease. Increased risk of progressive periodontal disease has been associated with a multitude of factors including microbial parameters, smoking, familial or genetic background, diabetes mellitus, HLA-DR complex and IL-1β polymorphism (Michalowicz 1991a, b, Alley et al. 1993, Bergström & Preber 1994, Hart et al. 1994, Kornman et al. 1997)

Clinical features of RA and Periodontitis
Clinical features of RA

The clinical characteristics of RA vary not only from one patient to another but also within the same patient over the course of the disease. Pain, swelling and deformity of joints are the prominent features of RA. The most common joints affected include the joints of the hands, wrist and feet. Other organ systems can also be affected as a result of microvessel vasculitis leading to the formation of nodules, pleural effusions, pulmonary fibrosis, cardiac disease and ocular disease (Lee & Manolios 1999).

As a response to inflammation, muscles and tendons around an inflamed joint may shorten and undergo spasms. Ligaments that stabilize the joints can be weakened or severed by the erosive properties of inflamed synovium or pannus. Damaged ligaments destabilize the joint, altering the lines of force and the axis of rotation. In the severe stages of the disease, synovitis and pannus denude the surface of cartilage and erode juxta-articular bone, creating incompatible articular surfaces. With the complete disappearance of cartilage, the opposing bone surfaces may fuse when immobilized (Goronzy & Weyand 1997).

Clinical features of periodontitis

The periodontal tissues in health, exist in a steady-state equilibrium of tissue degradation and repair. With constant mechanical and chemical assaults, the periodontium for the most part manages to maintain its structural and functional integrity. However, if the balance between host response and bacterial virulence is disturbed, disease and consequent tissue destruction will occur (Bartold 1995). With developing inflammation, there is a marked accumulation of lymphocytes and monocytes within the connective tissue resulting in tissue swelling and matrix degradation. In contrast to RA, the development of periodontitis is not associated with pain.

The clinical consequences of periodontal tissue destruction are gingival bleeding on probing, increased pocket probing depth due to apical migration of the junctional epithelium, periodontal bone loss and increased tooth mobility and ultimately, tooth loss if, disease activity continues.

Table 1. Patterns of disease progression in RA and periodontitis

Rheumatoid arthtitis	Periodontitis
Self-limited RA	*Well-maintained periodontitis*
Disease commences, but does not progress to cause significant damage	Disease commences, but with simple treatment it can be controlled such that little or no further progresssion occurs
Easily controlled RA	*Downhill periodontitis*
Disease becomes established, but can be controlled with ''first-line'' medications	Disease becomes established and with a mixture of simple and complex therapies it can be largely controlled, although some slight ongoing destruction over time may be noted
Progressive RA	*Extreme downhill periodontitis*
Disease becomes established and continues to progress. Use of second-line medications may be of little help in arresting disease progression	Disease becomes established and despite simple and complex therapies continues to progress and cause further tissue damage and tooth loss

Laboratory Tests in Common

There is no single test that can assess and predict the status of RA and periodontal disease. However, it seems that the combination of clinical and laboratory markers give more meaningful measures of disease activity and severity than a single test (van Zeben & Breedveld 1996). Laboratory markers such as levels of rheumatoid factors, prostaglandins, collagen degradation products and C-reactive protein are altered in inflammatory conditions such as periodontitis and RA. Accordingly, a multitude of factors including clinical parameters, immuno-pathology and microbiology should be considered in order to reach an acceptable diagnosis and predictive ability for both RA and periodontal disease.

Rheumatoid factors

Rheumatoid factors (RFs) are autoantibodies that react to multiple epitopes on the Fc portion of IgG. RFs are found in more than two-thirds of adult patients with RA, but they are not specific to RA as they are found in patients with a number of other chronic inflammatory conditions (Geraci & Wilson 1982, Hirsch et al. 1989). Studies indicate that RF titers and MHC class II HLA-DRB1*0401 allele tend to correlate with severe and unremitting disease, nodules and extra-articular lesions (Weyand et al. 1992). However, in the individual patient, RF titer is of little prognostic value (Weyand et al. 1992).

Numerous studies have reported the detection of RF in patients with periodontitis (Gargiulo et al. 1982, Hirsch et al. 1989, DeNardin et al. 1991, The & Ebersole 1991, Davidson et al. 1994). Compared to the RF seronegative periodontitis patients, the RF seropositive patients show significantly elevated serum IgG and IgM antibody levels to oral microorganisms (The & Ebersole 1996). Increases in IgM-RF noted in periodontitis could result from chronic antigenic stimulation by the bacterial plaque or by specific members of the microbiota with cross-reactive epitopes as has been suggested with streptococcal antigen (Schroder et al. 1987, Moore et al. 1989). The definite role of periodontitis-induced RF on the severity and progression of RA is still unknown.

Prostaglandins

Prostaglandins, which are derivatives of arachidonic acid metabolism, are among the most important mediators of inflammation. Pro-inflammatory cytokines are capable of stimulating resident and migrating cells to produce copious amounts of prostaglandins, particularly prostaglandin E_2 (PGE_2). These are potent vasodilators and inducers of cytokine production by various cells and may be responsible for some of the bone resorption and cartilage destruction seen in RA (Dayer et al. 1986).

The ability of PGE_2 to act on fibroblasts and osteoclasts to induce the synthesis of matrix metalloproteinases (MMPs), IL-1β and other cytokines has been considered crucial to tissue turn-over and degradation in periodontitis. It has been demonstrated that PGE_2 levels increase from health to gingivitis, and reach very high concentrations during periods of periodontal disease progression (Offenbacher et al. 1993).

Type I carboxy terminal peptide (ICTP) levels

As a consequence of excessive cartilage-collagen (Type II) and bone-collagen (Type I) breakdown in RA, elevated bone and collagen-specific breakdown products become apparent in serum and/or urine (Hakala et al. 1995). Several studies have examined ICTP levels in RA (Hakala et al. 1995, Lems et al. 1993, Paimela et al. 1994). Serum ICTP is elevated in RA patients and this correlates well with clinical indices, radiologic damage scores and disease severity (Hakala et al. 1993, Kotaniemi et al. 1994).

ICTP levels may be up to 100-fold higher in gingival crevicular fluid and 3–4 times higher in serum of patients with periodontitis than in control subjects (Talonpoika & Hamalainen 1994). ICTP levels have also been shown to reduce in the GCF after treatment (Talonpoika & Hamalainen 1994, Giannobile et al. 1995, Palys et al. 1998). Increases in the GCF-ICTP levels have also been associated with periodontal disease progression and decreases in the GCF-ICTP levels with disease remission.

C-reactive protein

C-reactive protein (CRP) is an acute-phase reactant secreted by the liver in response to various inflammatory conditions such as trauma, hypoxia and infection (Pepys & Baltz 1983). Opsonization enhancement, phagocytosis faciliation, classical complement pathway activation, growth factor inhibition and modulation of PMN function are some of the suggested functions of CRP (Szalai et al. 1997). CRP is known to have a protective role during an acute-phase inflammatory response by recognizing foreign pathogens and initiating their elimination, most probably by activating the classical complement pathway (Szalai et al. 1997).

Studies concerning the relationship between CRP and radiographic changes have shown that progressive bone erosions occur when serum CRP is persistently elevated regardless of the presence or absence of rheumatoid factors (Amos et al. 1977). Suppression of elevated CRP in patients with active RA is associated with improvement in functional score and persistent CRP elevation is associated with functional deterioration (Devlin et al. 1997).

Acute-phase proteins have also been implicated in the pathogenesis of periodontitis (Sibraa et al. 1991, Slade et al. 2000). The severity of periodontal bone loss may correlate with CRP levels in gingival crevicular fluid (Ebersole et al. 1997, Gleissner et al. 1998). Measurement of serum acute-phase proteins may help to identify a subset of patients who are at higher risk for destructive disease (Johnson et al. 1988). The findings from these studies support the concept that localized inflammation and/or infection may have systemic manifestations within the affected host.

Etiological Considerations
Etiology of RA

The cause of RA is unknown, with many different arthritogenic stimuli being capable of activating the immune and inflammatory response. Consequently, research has focused on exogenous infectious candidates as the causative agent or agents, as well as endogenous substances, such as connective-tissue proteins (e.g. collagen and proteoglycans) and altered immunoglobulins.

The concept that RA is an infectious disease has been around for over 70 years. The possibility that RA patients acquire an infection that elicits an immune response in the synovial membrane would account for some of the clinical features as well as the accumulation of immunocompetent T and B cells in the lesions. The early pathologic findings of endothelial swelling and

synovial hyperplasia are non-specific, but have been viewed as evidence for blood-borne pathogens (Stransky et al. 1993). Numerous agents such as human T-cell lymphotropic virus Type I, Epstein–Barr virus, Parvovirus, Rubella, herpesvirus, mycobacteria and Gram-negative bacteria have been proposed as etiologic agents of RA (Izui et al. 1979, Phillips 1988, Venables 1989, Nishioka et al. 1996).

A study by van Den Broek et al. (1988) provided direct evidence that bacterial stimuli can result in an anti-cartilage response. It was demonstrated that priming *in vivo* with cell wall fragments of *Streptococcus pyogenes* or *Eschrichia coli* could induce a cellular and humoral anti-cartilage response in Balb/c mice *in vitro*. T cells isolated from these mice can be stimulated *in vitro* by small bacterial components and diverse antigens of cartilagenous origin (van Den Broek et al. 1988). A cross-reactive response occurred *in vivo* in certain circumstances, manifested as a delayed-type hypersensitivity reaction that could be elicited in cell-wall-primed mice by challenge with cartilage extract (van Den Broek et al. 1988). The characteristics and requirements for microorganisms to stimulate the development of RA are as tabulated in Table 2.

Another important piece of evidence supporting the role of exogenous bacterial antigens in RA is the ability of one bacterial species to cross-react with the immune response initially elicited by another bacterial species (van Den Broek et al. 1988). This observation has important implications with regard to the maintenance and persistence of arthritis. Once an anti-bacterial response and an anti-cartilage response have been triggered in a susceptible individual, other bacterial species or their degradation products (e.g. LPS) may reactivate not only the anti-bacterial but also the anti-cartilage response (van Den Broek et al. 1988). A possible source of bacteria and bacterial by-products is the oral cavity, especially when infected with periodontitis, where the primary pathogens are Gram-negative anaerobes.

Etiology of periodontitis

Gingivitis and periodontitis are classic examples of chronic inflammatory diseases. These diseases are the result of an induction of host inflammatory responses to the accumulation of bacteria on tooth surfaces adjacent to the supra- and sub-gingival tissues.

Gingivitis is a generalized acute inflammatory response to the bacterial colonization of tooth surfaces adjacent to the gingiva. With continuing plaque accrual, gingivitis becomes well established, but still confined to the superficial gingival connective tissues. The processes resulting in the progression of gingivitis to periodontitis are unclear. In some cases, gingivitis may represent the early stage in the evolution of periodontitis. However, in some individuals, gingivitis may exist as an independent clinical condition without progressing into periodontitis (Page et al. 1997).

Periodontitis presents in several different forms which differ in their etiology, rate and pattern of progression, natural history and response to therapy. This variability can be attributed to differences in composition of the sub-gingival microbial flora, together with the factors that modify the host response to microbial assault. While the host response and environmental factors that impact on this response are important for disease manifestation, periodontitis cannot commence without the presence of bacteria. Nonetheless, it must be noted that, although bacteria are necessary for disease initiation, they are not sufficient to cause disease progression unless there is an associated inflammatory response (Page et al. 1997).

For gingivitis to develop, the types of bacteria present appear to be inconsequential since gingivitis is a non-specific inflammatory response to dental plaque. However, for periodontitis to develop approximately 20 microbes, which inhabit the subgingival environment, are considered to be significantly pathogenic and associated with various forms of periodontitis. The most significant of these associated with periodontitis are *Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis* and *Bacteroides forsythus*. It is important to note that the sub-gingival microflora behaves as a ''biofilm'' that permits the occupants to survive as a community and resist common host defense mechanisms as well antibiotic exposure during therapy.

Could periodontal pathogens be involved in the development of RA?

Interestingly, many of the characteristics that microorganisms exhibit in order to induce RA in a genetically susceptible host may also be observed in microorganisms that are associated with periodontitis (Table 2).

Periodontal pathogens are organized in a biofilm with the other groups of bacteria and may be able to incite a chronic continuous infection (Requirement 1, Table 2). The suspected period-

Table 2. Requirements for microorganisms to stimulate RA and how dental plaque biofilm and periodontal pathogens measure up to these requirements

Requirements for microorganisms to initiate RA	Do periodontal pathogens have these requirements? (YES/NO)
(1) Pathogens must be able to produce a continuous low-grade infection without significantly harming the host	YES
(2) Pathogens should be common and have universal distribution	YES
(3) Pathogens must express proteins that share sequence identities with the third hypervariable region of HLA-DRB10401 and HLA-DRB10101, the part of the molecule that carries susceptibility to RA (e.g. *EBV, E. coli, Mycobacteria*)	YES (?)
(4) Pathogens must be able to persist in the host to produce a chronic continuous LPS exposure and be able to form complexes with antibodies	YES
(5) Pathogens must be able to cross-react with cartilage and be able to produce an anti-cartilage response. Also, the pathogens must be able to continuously reactivate this cross-reactivity through the constant release of components (e.g. release of LPS)	Not been demonstrated

ontal pathogens have been shown repeatedly to be present in most individuals suffering from various forms of periodontal disease (Requirement 2, Table 2). The biofilm in periodontitis serves as an abundant supply of LPS, thereby easily fulfilling the fourth requirement of chronic LPS exposure. Furthermore, the local production of IgA and IgM RF in periodontal disease has been demonstrated (Hirsch et al. 1989, The & Ebersole 1991). Although the ability of the LPS from the periodontal biofilm to cross-react with the cartilage to cause an anti-cartilage response has not been demonstrated, it is logically possible.

However, all these considerations remain purely speculative unless the causative agent can be unequivocally identified. Despite close investigation by, and intense efforts of, many investigators, no infectious agents have been identified as the cause of RA. Data collected from electron microscopy, molecular biology or molecular analysis of tissue infiltrating T cells do not support the concept that a single antigen is driving the synovial inflammation. It is possible that there is no single primary cause of RA and that several different mechanisms may lead to the initial tissue injury and precipitate synovial inflammation.

Immunogenetics of RA and Periodontitis

Immunogenetic studies in peridontitis and RA indicate that the genetic code for the extent and behavior of inflammatory cells determines the progression and severity of chronic inflammatory diseases.

Immunogenetics of RA

Although the pathogenesis of RA has not been fully clarified, the recognition that RA is an autoimmune disease and is primarily not a disease of tissue degeneration has aroused the attention of geneticists and immunologists. Family and twin studies have shown that RA has several features typical of a complex genetic disease, such as genetic variance, incomplete penetrance and multiple gene involvement (Winchester 1994). To date, the strongest genetic association for RA is found within the HLA complex (Nepom & Nepom 1992). The application of DNA sequen-

cing and molecular-based typing to detect HLA-DRB1 alleles showed that the actual disease-conferring portion of the D region is confined to a short sequence encompassing amino-acid positions 67–74 of the third hypervariable region of the HLA-DRB1 gene (Nepom & Nepom 1992). The disease-associated alleles include the HLA-DRB1 *0401, 0404 and 0408* in the white population, HLA-DRB1 0405 in the Asian population and HLA-DRB1 1402 in the Greek population (Nepom & Nepom 1992).

Despite the above, some studies have found no or only a weak correlation of this complex with RA (De Jongh et al. 1984, Thomson et al. 1993). Considerable debate is still focused on whether these genes are associated with susceptibility to the development of RA, or with a poorer prognosis among sufferers. To date, the results from most studies point towards a complex genetic model, and that the disease-associated HLA-DRB1 alleles are important in disease progression, rather than in initiating disease, and act in cooperation with other HLA genes as well as background genes (Weyand et al. 1992, 1995).

Immunogenetics in periodontitis

As for RA, immunogenetics has been the subject of considerable interest in peridontics. Greater than 50% of the variance seen in adult periodontitis may be explained by genetic factors (Michalowicz et al. 1991a, b, Hassell & Harris 1995).

In an infectious disease such as periodontal disease, the association between the HLA antigens and various forms of the disease has been of interest with several studies reporting the incidence of various class I and II HLA antigens in patients with early-onset periodontal disease. In particular, the HLA antigens A9, A28, BW15 and DR4 have been found to be associated with early-onset forms of periodontitis (Reinholdt et al. 1977, Katz et al. 1987a, b, Shapira et al. 1994). Of interest is the observation that the HLA-A9 and HLA-BW15 antigens have been associated with the generalized, but not localized, forms of juvenile periodontitis, implying differing genetic factors may be responsible for these two conditions (Takashiba et al. 1994). Furthermore, unique intronic gene variations have been noted in the gene for HLA-DQβ in patients (and some other normal family

members) manifesting with early-onset periodontitis (Takashiba et al. 1994). However, other studies have indicated that there are no HLA associations with manifestations of various types of periodontal disease (Cullinan et al. 1980, Saxen & Koskimies 1984). Thus, it is unclear whether there is an association between HLA antigens and periodontal disease due to either an inherited periodontal disease susceptibility factor that is close to the gene for HLA, or segregation of HLA antigens in families that have a high risk for developing early-onset forms of periodontitis.

Immunogenetic features in common

In humans, many of the genes that regulate monocytic cytokine responses have been mapped to the HLA-DR region of chromosome 5 in the area of the TNF-β genes (Bendtzen et al. 1988, Pociot et al. 1993). Both RA and progressive periodontitis are associated with this HLA complex (Ollier & Thomson 1992, Garrison & Nichols 1989), which suggests a genetic basis for the observed monocyte trait, linking RA, progressive periodontitis and other systemic diseases. It is reasonable to suggest that the inter-individual differences in the severity of RA and periodontal disease are partly due to intrinsic differences in the monocyte/T cell response traits. In both diseases, antigenic challenge (e.g. LPS) to the monocytic/lymphocytic axis would result in the secretion of catabolic cytokines and inflammatory mediators, of which PGE$_2$, IL-1, TNF-α and IL-6 would appear to dominate (Fig. 1).

Mechanisms of Tissue Destruction in RA and Periodontal Disease

There is no doubt about the importance of cytokines in the pathogenesis of both RA and periodontitis. Cytokines can be classified into functional groups based on the cells of origin. For example, interleukin-2 (IL-2), interleukin-3 (IL-3), interleukin-4 (IL-4) and interferon-gamma are the products of T cells, and most of their recognized functions are related to the activation and amplification of cellular and humoral immune responses. Interleukin-1 (IL-1), IL-6, colony-stimulating factor-1 and tumor necrosis factor-α (TNF-α) are produced primarily by

Pathogenesis of Rheumatoid Arthritis

Chronic inflammatory disease

Bacteria/peptide as adjuvant antigen in autoantibody production

Role of macrophage and dendritic cells

Interleukin-1, Tumor necrosis factor-a, prostaglandin-E2

Immunoregulatory imbalance

Th1=Th2

Role of Nitric Oxide

Genetic and environmental influences

Persistence of antigen/peptide

Pathogenesis of Periodontitis

Chronic inflammatory disease

Bacteria as aetiological agent

Role of macrophage and dendritic cells

Interleukin-1, Tumor necrosis factor-a, prostaglandin-E2

Immunoregulatory imbalance

↓Th1,↑Th2

Role of Nitric Oxide

Genetic and environmental influences
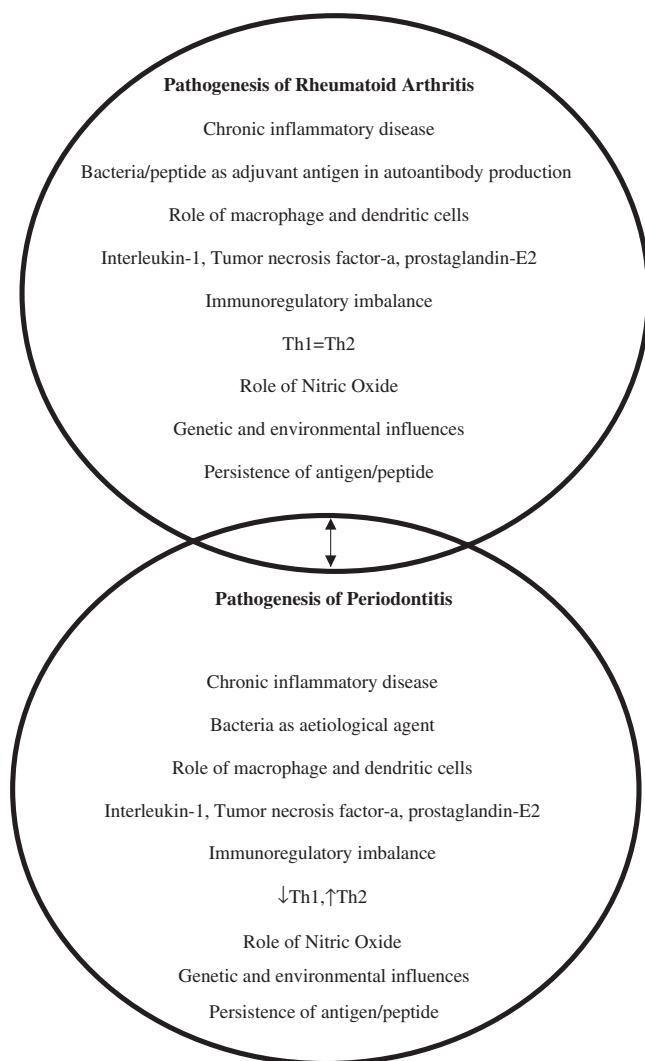
Persistence of antigen/peptide

Fig. 1. Pathogenic features in common between RA and periodontitis.

macrophages and fibroblasts. Although involved in the initiation of immune responses, these cytokines have broad effects on many cells, leading to cell proliferation, increased prostaglandin and matrix-degrading protease activity and bone resorption.

In RA, lymphocyte-associated cytokines are present in low concentrations in the rheumatoid synovial membrane (Firestein et al. 1988), whereas the levels of macrophage and fibroblast-associated products are high (Miyasaka et al. 1988). Moreover, pro-inflammatory cytokines including TNF-α, IL-1, IL-6, GM-CSF and chemokines such as IL-18 are abundant in RA patients regardless of therapy (Feldmann et al. 1996).

Tissue destruction in RA is made more effective not only by cytokines but also by the constant and prolonged secretion of other effector molecules by resident and migrating cells. These effector molecules are able to enhance matrix degradation either through direct or indirect means. In RA, a significant means of matrix degradation is effected through the action of matrix metalloproteinases (MMPs). The major MMP-producing cells are synovial fibroblasts and monocytic phagocytes in the synovial lining layer. Both IL-1 and TNF-α may induce the production of MMPs by synovial fibroblasts and chondrocytes located in the adjacent articular cartilage (Lotz et al. 1995). Chondrocytes respond to these cytokines with a decrease in collagen and proteoglycan synthesis and the synthesis of collagenase and stromelysin leading to further tissue destruction (Lotz et al. 1995).

Periodontitis has remarkably similar cytokine profiles to RA (Snyderman &

McCarty 1982, Greenwald & Kirkwood 1999). As for RA, disease progression seen in periodontitis consists of the continuing presence of high levels of pro-inflammatory cytokines including IL-1β and TNF-α and low levels of IL-10 and transforming growth factor β, cytokines that suppress the immunoinflammatory response. Furthermore, low levels of tissue inhibitors of metalloproteinases (TIMPs) and high levels of MMPs and PGE_2 secreted by macrophages, fibroblasts and other resident and inflammatory cells describe the active stages of both RA and periodontitis.

In both RA and periodontitis, tissue destruction is not unidirectional, but an iterative process that is constantly being adjusted by the host response to inciting agents. The destruction of extracellular matrix in both diseases is determined by the balance of MMPs and their inhibitors. Bone destruction in periodontitis and RA is a result of the uncoupling of the normally coupled processes of bone resorption and bone formation, with PGE_2, IL-1, TNF-α, IL-6 as mediators of bone destruction. It is evident in both diseases that the host's immune response is controlled by genes that regulate differences in the monocyte/T cell response traits to different antigens that determine both the nature of the protective antibody response and the magnitude of tissue-destructive inflammatory response (Fig. 2).

Treatment Implications for RA and Periodontitis Based on common pathogenesis

The currently available antirheumatic drugs give limited control over RA. They rarely induce long-term remission and seldom affect the progression of joint destruction (American College of Rheumatology 1996). Furthermore, many of these drugs have serious side-effects that contraindicate their use for early-stage RA and interfere with long-term therapeutic use for more severe cases (Pincus 1992).

Current therapies

NSAIDs such as aspirin, naproxen, diclofenac and ibuprofen, are the current mainstream ''first-line'' modes of treatment for RA. Owing to their inhibitory effects on cyclooxygenase, which catalyzes the conversion of
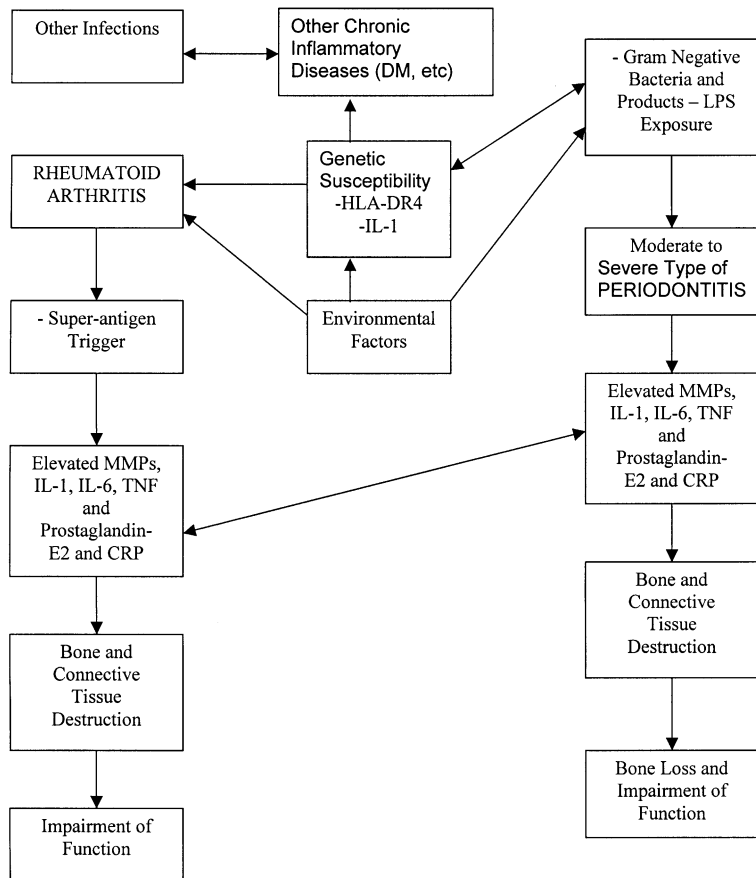
Fig. 2. Possible model of inter-relationship of RA, periodontitis and other chronic inflammatory diseases with genetic factors, environmental and microbial exposures as the common link.

arachidonic acid to prostaglandins and thromboxanes, NSAIDs have both analgesic and antipyretic properties. Although these drugs are capable of reducing the pain symptoms in RA, they do not significantly alter the course of RA (Lipsky 1991).

The use of NSAIDs for the management of periodontal disease has been extensively studied and the results seem promising: patients taking NSAIDs for at least 5 years have less alveolar bone loss than patients not taking NSAIDs (Feldman et al. 1983, Jeffcoat et al. 1991). In contrast, a retrospective study showed that patients taking NSAIDs demonstrated no significant differences in plaque index, gingival index, probing depth, attachment loss or bone loss in the control and rheumatoid group (Heasman & Seymour 1990).

Disease-modifying anti-rheumatic drugs (DMARDs) are second-line drugs that differ greatly in their chemical structure and pharmacokinetics, presumed mode of actions, toxicity profiles

and clinical indications (Cash & Klippel 1994). To be designated as a DMARD, a drug must change the course of RA for at least 1 year as evidenced by sustained improvement in function, decreased synovitis and prevention of further joint damage (Paget 1997). Gold (parenteral gold salts), methotrexate, sulfasalazine, hydroxychloroquine (antimalarial drug), penicillamine, azathioprine and leflunomide are examples of drugs that belong to this category. A number of short-term randomized controlled trials showed DMARDs to be more effective than, if not equally effective, as placebo with regard to controlling inflammatory parameters associated with RA and functional assessment scales (Conaghan & Brooks 1995, Ward 1994). The ability of DMARDs to prevent long-term bone destruction is questionable. DMARDs are associated with considerable toxicity. Thus, their use requires frequent monitoring, as many patients are able to tolerate the drugs for only 1 or 2 years before they are forced to discontinue the

treatment (American College of Rheumatology 1996).

The effect of gold salts has been tested in experimental periodontitis (Novak et al. 1984). It was concluded that the administration of systemic gold salts was associated with significantly less periodontal destruction. Further studies are needed to ascertain the role and benefit of systemic administration of DMARDs, such as gold salts in the management of periodontal disease (Novak et al. 1984).

Emerging treatments for RA and periodontal disease

The development of new paradigms and acquisition of new knowledge have allowed the development of novel drugs that inhibit different aspects of the inflammatory cascade. Chemically modified antibiotics and genetically engineered proteins (monoclonal antibodies and pro-inflammatory cytokines inhibitors) that can target specific molecules or enzymes have been developed to try to correct the imbalance between the pro-inflammatory and anti-inflammatory effects of the immune system involved in the pathogenesis of RA and periodontitis.

Tenidap (designed as one of the first COX-2 inhibitors) has been shown to inhibit cyclooxygenase and PGE_2 production with inhibition of IL-1, IL-6 and TNF-α production being a secondary feature of the PGE_2 inhibition. Its inhibition of IL-1 reduces *in vitro* bone resorption and cartilage degradation as well as the activation of collagenase and stromelysin in RA patients (Dingle et al. 1993).

Since MMPs have been implicated as important mediators of connective tissue breakdown, their inhibition has been tapped as one of the possible agents that can inhibit tissue destruction in RA and other diseases with connective tissue breakdown.

The discovery that tetracylines can inhibit MMP activity by a mechanism that is independent of their antimicrobial property (Golub et al. 1983) paved the way for investigating the effects of such MMP-inhibition effect on tissue destruction seen in chronic inflammation. Chemically modified tetracyclines (CMT) that retain anti-MMP properties, but have lost their antibacterial efficacy, have also been developed (Golub et al. 1987). Several clinical trials have demonstrated mild-to-moderate clinical

improvements in RA patients taking tetracyclines (Tilley et al. 1995, O'Dell et al. 1997). The role of MMP inhibitors in the long-term prognosis of RA is still unknown, but it appears promising. In an animal study, it was reported that the administration of a combination of CMT-1 plus an NSAID such as Flurbiprofen or Tenidap, synergistically inhibited severe bone destruction in arthritic rats, with the suppression of MMP activity in the joints (Greenwald et al. 1992, Leung et al. 1995).

In periodontitis, low-dose regimens of doxycycline (LDD) can reduce pocket depth, improve periodontal attachment levels and inhibit alveolar bone loss (Goren et al. 1994, Crout et al. 1996). However, the role of LDD in the prevention of progression and prognostic improvement in periodontal disease is still unknown.

Two naturally occurring inhibitors of IL-1 exist: the IL-1 receptor antagonist (IL-1ra) and the soluble IL-1 receptor (sIL-R). IL-1ra acts as a specific inhibitor of IL-1 by blocking IL-1 binding to its cell surface receptors without exerting agonist activity. A multi-center double-blind study demonstrated significant differences between placebo and rhIL-1ra-treated patients for several standard parameters (Campion et al. 1996, Drevlow et al. 1996). Gene therapy using IL-1ra aims to increase the level of anti-inflammatory molecules in the joint. Two animal gene therapy studies have successfully increased the level of IL-1ra in the joints (Bandara et al. 1993, Roessler et al. 1993). The preliminary results of the injection of retroviral ex vivo human IL-1ra cDNA into the synovium of patients with RA appear promising (Evans et al. 1999).

Another useful therapeutic approach to RA is the inhibition of TNF-α, one of the cytokines responsible for the acute-phase response and the production of destructive proteases in the joint. Recent studies have shown the therapeutic efficacy, in RA patients, of multiple intravenous infusions of anti-TNF-a monoclonal antibody combined with a weekly low-dose of methotrexate and recombinant TNF-a receptor:Fc fusion protein (Maini et al. 1998, Weinblatt et al. 1999). Similar studies using antibodies that block either the receptors or the TNF-α 1 molecules have also provided clinical benefits (Elliott et al. 1994, Moreland et al. 1996).

To assess the roles of IL-1 and TNF antagonists in experimental periodontitis, studies have been performed in a *Macaca fascicularis* primate model of experimental periodontitis (Assuma et al. 1998). Injection of soluble receptors to IL-1 and TNF inhibited the recruitment of inflammatory cells in close proximity to bone by approximately 80% (Assuma et al. 1998). The formation of osteoclasts was reduced by 67% at the experimental sites and the amount of bone loss was reduced by 60% (Assuma et al. 1998).

To date, these biologic agents have provided promising clinical outcomes for RA and periodontal disease. Future studies now focus on combination therapies of these biologic agents to block multiple pathways in the pathogenesis. It seems that various sites may have to be targeted before a significant and lasting clinical improvement can occur. As the etiology and pathogenesis of RA and progressive periodontitis are better understood, new therapies that target key substances and mechanisms in the disease process hold far greater promise for patients than mere symptomatic relief.

It should be kept in mind that since the bacterial etiology of periodontitis is well accepted, in addition to modulation of the host response, controlling the bacteria that cause periodontal infections remains a significant focus for periodontal treatment and prevention. Unlike periodontal disease, no specific bacterial etiology has been identified for RA.

Conclusions

RA and periodontitis have remarkably similar pathobiology. Microbiologically, chronic LPS exposure secreted from periodontal pathogens in the biofilm could serve as a source of super-antigens inciting the inflammatory cascade seen in RA. On the other hand, due to immune dysregulation in RA, manifested as increased pro-inflammatory cytokines such as IL-1 TNF-a and IL-6 as a result of hyper-responsive monocytes (a trait related to the HLA complex), patients susceptible to RA in the presence of periodontal pathogens and proper local environment may be susceptible to developing periodontitis, possibly a progressive form.

The data seem compelling to indicate that a relationship exists between the

extent and severity of periodontal disease and RA. While this relationship is unlikely to be causal, it is clear that individuals suffering from advanced RA are more likely to experience more significant periodontal problems compared to their non-RA counterparts. The possibility that a general and underlying dysregulation of the host inflammatory response is present in both conditions seems very likely.

With the realization that an imbalance between pro-inflammatory and anti-inflammatory cytokines exists in the pathogenesis of RA and periodontitis, emerging therapies are focusing on the inhibition of pro-inflammatory cytokines and destructive proteases. The development of chemically engineered bio-active molecules, gene therapy and MMP inhibitors are being aimed at restoring the dysregulation in the pathogenesis of chronic inflammatory diseases. These new therapies hold great promise for patients in altering the course of progressive forms of RA and periodontitis.

Zusammenfassung

Zusammenhänge zwischen rheumatoider Arthritis und Parodontalerkrankung – Eine Literaturübersicht
Diese Übersicht berücksichtigt die beträchtlichen Ähnlichkeiten zwischen einer Parodontalerkrankung und der rheumatoiden Arthritis. Während die Ätiologie dieser zwei Erkrankungen sich unterscheiden kann, sind die zugrundeliegenden Pathogenitätsmechanismen bemerkenswert ähnlich. Und es ist möglich, dass Personen bei denen sich sowohl eine Parodontitis als auch eine rheumatoide Arthritis manifestiert hat, an einer verbindenden zugrundeliegenden systemischen Dysregulation der Entzündungsreaktion leiden könnten. Unter Berücksichtigung dieser Ergebnisse ist es offensichtlich, dass, bei der Beherrschung dieser zwei chronischen entzündlichen Zustände, die Verwendung von die Erkrankung modifizierenden Medikamenten, indiziert ist. Weitere Longitudinalstudien und Interventionsstudien mit Medikamenten sind notwendig, um zu bestimmen, wie nahe diese zwei Zustände verwandt sind.

Résumé

Relations entre arthrite rhumatoïde et maladie parodontale. Une revue
Cette revue considère les similarités considérables qui existent entre la maladie parodontale et l'arthrite rhumatoïde. Tandis que l'étiologie de ces deux maladies peut être différente, les mécanismes pathogéniques sous-jacents sont remarquablement semblables et il est possible

que les individus avec arthrite rhumatoïde puissent souffrir d'une dérégularisation systémique sous-jacente unifiée de la réponse inflammatoire. A la lumière de ces découvertes, les implications de l'utilisation de médicaments modifiant la maladie dans le traitement de ces deux conditions inflammatoires chroniques est apparent. Davantage d'études longitudinales et d'études où il y a une intervention médicamenteuse sont requises pour déterminer le proportion de proximité de ces deux conditions.

References

Albandar, J. M. (1990) Some predictors of radiographic alveolar bone height reduction over 6 years. *Journal of Periodontal Research* **25**, 186–192.

Alley, C., Reinhardt, R. & Maze, E. (1993) HLA-D and T-lymphocyte reactivity to specific periodontal pathogens in type 1 diabetic periodontitis. *Journal of Periodontology* **64**, 974–979.

American College of Rheumatology Ad Hoc Committee on Clinical Guidelines (1996) Clinical guidelines for the management of rheumatoid arthritis. *Arthritis and Rheumatism* **39**, 713–722, 723–731.

Amos, R. S., Constable, T. J., Crockson, R. A., Crockson, A. P. & McConkey, B. (1977) Rheumatoid arthritis: relation of serum C-reactive protein and erythrocyte sedimentation rate to radiographic changes. *British Medical Journal* **1**, 195–197.

Arnett, F., Edworthy, S., Bloch, D. A., McShane, D. J., Fries, J. F., Cooper, N. S., Healey, L. A., Kaplan, S. R., Liang, M. H. & Luthra, H. S. (1988) The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis and Rheumatism* **31**, 315–324.

Assuma, R., Oates, T., Cohran, D., Amar, S. & Graves, D. T. (1998) IL-1 and TNF Antagonists inhibit the inflammatory response and bone loss in experimental periodontitis. *Journal of Immunology* **160**, 403–409.

Bandara, G., Mueller, G. M., Galea-Lauri, J., Tindal, M. H., Georgescu, H. I., Suchanek, M. K., Hung, G. L., Glorioso, J. C., Robbins, P. D. & Evans, C. H. (1993) Intraarticular expression of biologically active interleukin-1 receptor antagonist protein by ex vivo gene transfer. *Proceedings of the National Academy of Science USA* **90**, 10764–10768.

Bartold, P. M. (1995) Turnover in periodontal connective tissues; dynamic homeostasis of cells, collagen and ground substances. *Oral Diseases* **1**, 238–253.

Bendtzen, K., Morling, N., Fomsgaard, A., Svenson, M., Jakobsen, B., Odum, N. & Svejgaard, A. (1988) Association between HLA-DR2 and production of tumour necrosis factor α and interleukin-1 by mononuclear cells activated by lipopolysaccharide. *Scandanavian Journal of Immunology* **28**, 599–606.

Bergström, J. & Preber, H. (1994) Tobacco use as a risk factor. *Journal of Periodontology* **65**, 545–556.

Callin, A., Elswood, J. & Klouda, P. T. (1989) Destructive arthritis, rheumatoid factor, and HLA-DR Susceptibility versus severity, a case control study. *Arthritis and Rheumatism* **32**, 1221–1225.

Campion, G. V., Lebsack, M. E., Lookabaugh, J., Gordon, G. & Catalano, M. (1996) Dose-range and dose-frequency study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis. *Arthritis and Rheumatism* **39**, 1092–1101.

Cash, J. M. & Klippel, J. H. (1994) Second-line drug therapy for rheumatoid arthritis. *New England Journal of Medicine* **330**, 1368–1375.

Conaghan, P. G. & Brooks, P. (1995) Disease-modifying antirheumatic drugs, including methotrexate, gold, antimalarials, and D-penicillamine. *Current Opinion in Rheumatology* **7**, 167–173.

Crout, R. J., Lee, H. M., Schroeder, H., Ramamurthy, N. S., Wiener, M. & Golub, L. M. (1996) The ''cyclic'' regimen of low-dose doxycycline for adult periodontitis: a preliminary study. *Journal of Periodontology* **67**, 506–514.

Cullinan, M. P., Sachs, J., Wolf, E. & Seymour, G. J. (1980) The distribution of HLA-A and -B antigens in patients and theeir families with periodontitis. *Journal of Periodontal Research* **15**, 177–184.

Davidson, A., Keiser, H., del Puente, A., Bennett, P. H., Schrohenloher, R. & Koopman, W. J. (1994) Expression of RF idiotypes 17.109, 636 and 419 in the sera of PIMA Indians. *Autoimmunity* **18**, 251–258.

Dayer, J., de Rochemonteix, B., Burrus, D., Demczuk, S. & Dinarello, C. A. (1986) Human recombinant IL-1 stimulates collagenase and prostaglandin production by human synovial cells. *Journal of Clinical Investigation* **77**, 645–648.

De Jongh, B., van Ronunde, J. & Valkenberg, H. (1984) Epidemiological study of HLA and GM in rheumatoid arthritis and related symptoms in an open Dutch population. *Annals of Rheumatic Diseases* **43**, 613–619.

De Nardin, A., Sojar, H., Grossi, S., Christersson, L. A. & Genco, R. J. (1991) Humoral immunity of older adults with periodontal disease to *Porphyromonas gingivalis*. *Infection and Immunity* **59**, 4363–4370.

Devlin, J., Gough, A., Huissoon, A., Perkins, . P., Holder, R., Reece, R., Arthur, V. & Emery, P. (1997) The acute phase and function in early rheumatoid arthritis C-reactive protein levels correlate with functional outcome. *Journal of Rheumatology* **24**, 9–13.

Dingle, J. T., Leeming, M. R. G. & Martindale, J. J. (1993) Effect of Tenidap on cartilage integrity in vitro. *Annals of the Rheumatic Diseases* **52**, 292–299.

Drevlow, B. E., Lovis, R., Haag, M. A., Sinacore, J. M., Jacobs, C., Blosche, C., Landay, A., Moreland, L. W. & Pope, R. M. (1996) Recombinant human interleukin-1 receptor type I in the treatment of patients with active rheumatoid arthritis. *Arthritis and Rheumatism* **39**, 257–265.

Ebersole, J., Machen, R., Steffen, M. J. & Willmann, D. E. (1997) Systemic acute phase reactants, C-reactive proteins and haptoglobin, in adult periodontitis. *Clinical and Experimental Immunology* **107**, 347–352.

Elliot, M. J., Maini, R. N., Feldmann, M., Kalden, J. R., Antoni, C., Smolen, J. S., Leeb, B., Breedveld, F. C., Macfarlane, J. D. & Bijl, H. (1994) Randomised double-blind comparison of chimeric monoclonal antibody to tumor necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. *Lancet* **344**, 1105–1110.

Evans, C. H., Ghivizzani, S., Kang, R., Muzzonigro, T., Wasko, M. C., Herndon, J. H. & Robbins, P. D. (1999) Gene therapy for rheumatoid arthritis. *Arthritis and Rheumatism* **42**, 1–16.

Feldmann, M., Brennan, F. & Maini, R. (1996) Role of cytokines in rheumatoid arthritis. *Annual Review of Immunology* **14**, 397–440.

Feldman, R. S., Szeto, B., Chauncey, H. H. & Goldhaber, P. (1983) Non-steroidal anti-inflammatory drugs in the reduction of human alveolar bone loss. *Journal of Clinical Periodontology* **10**, 131–136.

Firestein, G. S., Xu, W., Townsend, K., Broide, D., Alvaro-Gracia, J., Glasebrook, A. & Zvaifler, N. J. (1988) Cytokines in chronic inflammatory arthritis. I. Failure to detect T-cell lymphokines (IL-2 and Il-3) and presence of macrophage colony-stimulating factor (CSF-1) and a novel mast cell growth factor in rheumatoid arthritis. *Journal of Experimental Medicine* **168**, 1573–1586.

Fuchs, H., Kaye, J., Callahan, L. F., Nance, E. P. & Pincus, T. (1989) Evidence of significant radiographic damage in rheumatoid arthritis within the first 2 years of disease. *Journal of Rheumatology* **16**, 585–591.

Gargiulo, A. V. Jr., Robinson, J., Toto, P. D. & Gargiulo, A. W. (1982) Identification of rheumatoid factor in periodontal disease. *Journal of Periodontology* **53**, 569–577.

Garrison, S. W. & Nichols, F. C. (1989) LPS elicited secretory response in monocytes: altered release of PGE_2 but not IL-1 beta in patients with adult periodontitis. *Journal of Periodontal Research* **24**, 88–95.

Geraci, J. & Wilson, J. (1982) Symposium on infective endocarditis III. Endocarditis due to Gram negative bacteria report of 56 cases. *Mayo Clinical Proceedings* **57**, 145–148.

Giannobile, W. V., Lynch, S. E., Denmark, R. G., Paquette, D. W., Fiorellini, J. P. & Williams, R. C. (1995) Crevicular fluid osteocalcin and pyridinoline cross-linked terminal telopeptide of type I collagen (ICTP) as markers of rapid bone turn-over in periodontitis. *Journal of Clinical Periodontology* **21**, 903–910.

Gleissner, C., Willershausen, B., Kaesser, U. & Bolten, W. W. (1998) The role of risk factors for periodontal disease in patients with rheumatoid arthritis. *European Journal of Medical Research* **3**, 387–292.

Golub, L. M., Lee, H. M., Lehrer, G., Nemiroff, A., McNamara, T. F., Kaplan, R. & Rama-

murthy, N. S. (1983) Minocycline reduces gingival collagenolytic activity during diabetes: preliminary observations and a proposed new mechanism of action. *Journal of Periodontal Research* **18**, 516–526.

Golub, L. M., McNamara, T. F., D'Angelo, G., Greenwald, R. A. & Ramamurthy, N. S. (1987) A non-antibacterial chemically modified tetracycline inhibits mammalian collagenase activity. *Journal of Dental Research* **66**, 1310–1314.

Goren, A. D., Dunn, S. M. & Wolff, M. (1994) Effect of a 6-month regimen of low-dose doxycycline on alveolar bone loss in adult periodontitis patients: preliminary evaluation of digital subtraction results. Proceedings of the 45th meeting of the American Academy of Oral and Maxillofacial Radiology; New Orleans (LA): p. 73.

Goronzy, J. & Weyand, C. (1997) Epidemiology, pathology and pathogenesis. In: *Primer on rheumatic diseases*, ed. Klippel, J., 11th edition, pp. 155–161. Atlanta, GA: Arthritis Foundation.

Greenwald, R. & Kirkwood, K. (1999) Adult periodontitis as a model for rheumatoid arthritis. *Journal of Rheumatology* **26**, 1650–1653.

Greenwald, R. A., Moak, S. A., Ramamurthy, N. S. & Golub, L. M. (1992) Tetracyclines suppress matrix metalloproteinase activity in adjuvant arthritis, and in combination with flurbiprofen, ameliorate bone damage. *Journal of Rheumatology* **6**, 927–938.

Hakala, M., Aman, S., Luukkainen, R., Risteli, L., Kauppi, M., Nieminen, P. & Risteli, J. (1995) Application of markers of collagen metabolism in serum and synovial fluid for assessment of disease process in patients with rheumatoid arthritis. *Annals of the Rheumatic Diseases* **54**, 886–890.

Hakala, M., Risteli, L., Manelius, J., Nieminen, P. & Risteli, J. (1993) Increased type I collagen degradation correlates with disease severity in rheumatoid arthritis. *Annals of the Rheumatic Diseases* **52**, 866–869.

Harris, E. D., Jr. (1997) Clinical features of rheumatoid arthritis. In: *Textbook of rheumatology*, eds. Kelly, W. N., Harris, E. D. & Sledge, C. B., 5th edition, p. 898. Philadelphia: WB Saunders.

Hart, T., Shapira, L. & Van Dyke, T. (1994) Neutrophil defects as risk factor for periodontal diseases. *Journal of Periodontology* **65**, 521–525.

Hassell, T. & Harris, E. (1995) Genetic influences in caries and periodontal diseases. *Critical Reviews in Oral Biology and Medicine* **6**, 319–342.

Heasman, P. A. & Seymour, P. A. (1990) An association between long-term nonsteroidal antiinflammatory drug therapy and the severity of periodontal disease. *Journal of Clinical Periodontology* **17**, 654–658.

Hirsch, H. Z., Tarkowski, A., Koopman, W. J. & Mestecky, J. (1989) Local production of IgA- and IgM-rheumatoid factors in adult periodontal disease. *Journal of Clinical Immunology* **9**, 273–278.

Hirschfeld, L. & Wasserman, B. (1978) A long-term survey of tooth loss in 600 treated periodontal patients. *Journal of Periodontology* **49**, 225–237.

Izui, S., Eisenberg, R. & Dixon, F. (1979) IgM rheumatoid factors in mice injected with bacterial LPS. *Journal of Immunology* **122**, 2096–2102.

Jeffcoat, M. K., Page, R., Reddy, M., Wannawisute, A., Waite, P., Palcanis, K., Cogen, R., Williams, R. C. & Basch, C. (1991) Use of digital radiography to demonstrate the potential of naproxen as an adjunct in the treatment of rapidly progressive periodontitis. *Journal of Periodontal Research* **26**, 415–421.

Johnson, N. W., Griffiths, G. S., Wilton, J. M., Maiden, M. F., Curtis, M. A., Gillett, I. R., Wilson, D. T. & Sterne, J. A. (1988) Detection of high-risk groups and individuals for periodontal diseases. Evidence for the existence of high risk groups and individuals and approaches to their detection. *Journal of Clinical Periodontology* **15**, 276–282.

Kasser, U. R., Gleissner, C., Dehne, F., Michel, A., Willershausen-Zonnchen, B. & Bolten, W. W. (1997) Risk for periodontal disease in patients with longstanding rheumatoid arthritis. *Arthritis and Rheumatism* **40**, 2248–2251.

Katz, J., Benoliel, R., Goultschin, J. & Brautbar, C. (1987a) Human leukocyte antigen (HLA) DRY positive association with rapidly progressive periodontitis. *Journal of Periodontology* **58**, 607–610.

Katz, R., Goutschin, J., Benoliel, P. & Brautbar, C. (1987b) Human Leukocyte antigen (HLA) DR4 positive association with rapidly progressive periodontitis. *Journal of Periodontology* **58**, 607–610.

Kelley, W. N., Harris, E. D. Jr. & Ruddy, S. (1993) *Textbook of Rheumatology*, 4th edition, Vol. 1. Philadelphia: WB Saunders.

Kornman, K., Crane, A. & Wang, H. (1997) The interleukine-1 genotype as severity factor in adult periodontal disease. *Journal of Clinical Periodontology* **24**, 72–77.

Kotaniemi, A., Isomaki, H., Hakala, M., Risteli, L. & Risteli, J. (1994) Increased type I collagen degradation in early rheumatoid arthritis. *Journal of Rheumatology* **21**, 1593–1596.

Lee, L. & Manolios, N. (1999) Therapeutic horizons for rheumatoid arthritis. *Today's Life Science* **July/August**, 42–48.

Lems, W. F., Jacobs, J. W., van den Brink, H. R., van Rijn, H. J. & Bijlsma, J. W. (1993) Transient decrease in osteoclacin and markers of type I collagen turnover during high-dose corticosteroid pulse therapy in rheumatoid arthritis. *British Journal of Rheumatology* **32**, 787–789.

Leung, M. K., Greenwald, R. A., Ramamurthy, N. S., Moak, S. A., Koszulinski, R., Dieudonne, D. & Golub, L. M. (1995) Tenidap and flurbiprofen enhance uptake of matrix metalloproteinase inhibitor 4-dedimethylamino tetracycline in inflamed joints of adjuvant arthritic rats. *Journal of Rheumatology* **22**, 1726–1731.

Lipsky, P. E. (1991) Rheumatoid arthritis. In: *Harrison's principles of internal medicine* (Wilson, J. D., Braunwald, E. & Isselbacher, K. J., 12th edition, pp. 1437–1443. New York: McGraw-Hill.

Löe, H., Anerud, A., Boysen, H. & Morrison, E. (1986) Natural history of periodontal disease in man. Rapid, moderate and no loss of attachment in Sri Lankan laborers 14 to 46 years of age. *Journal of Clinical Periodontology* **13**, 431–445.

Lotz, M., Blanco, F. J., von Kempis, J., Dudler, J., Maier, R., Villiger, P. M. & Geng, Y. (1995) Cytokine regulation of chondrocyte functions. *Journal of Rheumatology* **43**, 104–108.

Maini, R. N., Breedveld, F. C., Kalden, J. R., Smolen, J. S., Davis, D., Macfarlane, J. D., Antoni, C., Leeb, B., Elliott, M. J., Woody, J. N., Schaible, T. F. & Feldmann, M. (1998) Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low dose weekly methotrexate in rheumatoid arthritis. *Arthritis and Rheumatism* **41**, 1552–1563.

McCarty, D. (1985) Arthritis and allied conditions. In: *A textbook of rheumatology*, ed. Koopman, W. J. Philadelphia, PA: Lea and Febiger, P 675.

McFall, W. (1982) Tooth loss in 100 treated patients with periodontal disease. *Journal of Periodontology* **53**, 539–549.

Mercado, F., Marshal, R., Klestov, A. & Bartold, P. (2000) Is there a relationship between rheumatoid arthritis and periodontal disease? *Journal of Clinical Periodontology* **27**, 267–272.

Mercado, F., Marshal, R., Klestov, A. & Bartold, P. (2001) A relationship between rheumatoid arthritis and periodontal disease. *Journal of Periodontology* **72**, 779–787.

Michalowicz, B. S., Aeppli, D. P., Kuba, R. K., Bereuter, J. E., Conry, J. P., Segal, N. L., Bouchard Jr, T. J. & Pihlstrom, B. L. (1991a) A twin study of genetic variation in proportional radiographic alveolar bone height. *Journal of Dental Research* **70**, 1431–1435.

Michalowicz, B. S., Aeppli, D., Virag, J. G., Klump, D. G., Hinrichs, J. E., Segal, N. L., Bouchard, T. J. & Pihlstrom, B. L. (1991b) Periodontal findings in adult twins. *Journal of Periodontology* **62**, 293–299.

Mitchell, D. M., Spitz, P. W. & Young, D. Y. (1986) Survival, prognosis, and causes of death in rheumatoid arthritis. *Arthritis and Rheumatism* **29**, 706–714.

Miyasaka, N., Sato, K., Goto, M., Natsuyama, M., Inoue, K. & Nishioka, K. (1988) Augmented IL-1 production and HLA-DR expression in the synovium of rheumatoid arthritis patients: possible involvement in joint destruction. *Arthritis and Rheumatism* **31**, 480–486.

Moore, T., el-Najdawi, E. & Dorner, R. (1989) Antibody to streptococcal cell wall peptidoglycan–polysaccharide polymers in sera of patients with juvenile rheumatoid arthritis but absent in isolated immune complexes. *Journal of Rheumatology* **16**, 1069–1073.

Moreland, L. W., Margolies, G., Heck, L. W. Jr., Saway, A., Blosch, C., Hanna, R. & Koopman, W. J. (1996) Recombinant soluble tumor necrosis factor receptor (p80) fusion protein: toxicity and dose finding trial in refractory rheumatoid arthritis. *Journal of Rheumatology* **23**, 1849–1855.

Nepom, G. & Nepom, B. (1992) Prediction of susceptibility to rheumatoid arthritis by human leukocute antigen genotyping. *Rheumatic Disease Clinics of North America* **18**, 785–792.

Nishioka, K., Sumida, T. & Hasunuma, T. (1996) Human T lymphotropic virus type I in arthropathy and autoimmune disorders. *Arthritis and Rheumatism* **39**, 1410–1418.

Novak, M. J., Polson, A. M. & Freeman, E. (1984) Effects of gold salts on experimental periodontitis. *Journal of Periodontology* **55**, 69–77.

O'Dell, J. R., Haire, C. E., Palmer, W., Drymalski, W., Wees, S., Blakely, K., Churchill, M., Eckhoff, P. J., Weaver, A., Doud, D., Erikson, N., Dietz, F., Olson, R., Maloley, P., Klassen, L. W. & Moore, G. F. (1997) Treatment of early rheumatoid arthritis with minocycline or placebo: results of a randomised, double-blind, placebo controlled trial. *Arthritis and Rheumatism* **40**, 842–848.

O'Sullivan, J. & Cathart, E. (1972) The prevalence of rheumatoid arthritis: follow-up evaluation of the effect of criteria on rates in Sudbury, Masachusetts. *Annals of Internal Medicine* **76**, 573–577.

Offenbacher, S., Heasman, P. & Collins, J. (1993) Modulation of host PGE2 secretion as a determinant of periodontal disease progression. *Journal of Periodontology* **64**, 432–444.

Ollier, W. & Thomson, W. (1992) Population genetics of rheumatoid arthritis. *Rheumatic Disease Clinics of North America* **18**, 741–759.

Page, R. C., Offenbacher, S., Schroeder, H. E., Seymour, G. J. & Kornman, K. (1997) Advances in the pathogenesis of periodontitis: summary of developments, clinical implications and future directions. *Periodontolgy* **14**, 216–247.

Paget, S. (1997) Treatment. In: *Primer on the rheumatic diseases*, ed. Klippel, J., pp. 168–174. Atlanta, GA: Arthtritis Foundation.

Paimela, L., Leirisalo-Repo, M., Risteli, L., Hakala, M., Helve, T. & Risteli, J. (1994) Type I collagen degradation product in serum of patients with early rheumatoid arthritis: relationship to disease activity and radiological progression in a 3 year-follow-up. *British Journal of Rheumatology* **33**, 1012–1016.

Palys, M. D., Haffajee, A. D., Socransky, S. S. & Giannobile, W. V. (1998) Relationship between C-telopeptide pyridinoline cross-links (ICTP) and putative periodontal pathogens in periodontitis. *Journal of Clinical Periodontology* **25**, 865–871.

Pepys, M. & Baltz, M. (1983) Acute phase proteins with special reference to C-reactive and related proteins (Pentaxins) and serum amyloid A protein. *Advances in Immunology* **34**, 141–212.

Phillips, P. (1988) Evidence implicating infectious agents in rheumatoid arthritis and juvenile rheumatoid arthritis. *Clinical and Experimental Rheumatology* **6**, 87–94.

Pincus, T. (1992) The paradox of effective therapies but poor long-term outcome in rheumatoid arthritis. *Seminars in Arthritis and Rheumatism* **21** (Suppl 3), 2–15.

Pincus, T., Marcum, S. & Callahan, L. (1992a) Long-term drug therapy for rheumatoid arthritis in seven rheumatology private practices. II. Second-line drugs and prednisone. *Journal of Rheumatology* **19**, 1885–1894.

Pincus, T., Marcum, S., Callahan, L., Adams, R. F., Barber, J., Barth, W. F., Gordon, G. V., Huston, J. W., Polk, J. R. & Whelton, J. C. (1992b) Long-term drug therapy for rheumatoid arthritis in seven rheumatology private practices. I. Non-steroidal anti-inflammatory drugs. *Journal of Rheumatology* **19**, 1874–1884.

Pociot, F., Briant, L., Jongeneel, C. V., Molvig, J., Worsaae, H., Abbal, M., Thomsen, M., Nerup, J. & Cambon-Thomsen, A. (1993) Association of tumor necrosis factor (TNF) and class II major histocompatibility complex alleles with the secretion of TNF-alpha and TNF-beta by human mononuclear cells: a possible link to insulin-dependent diabetes mellitus. *European Journal of Immunology* **23**, 224–231.

Rasker, J. & Cosh, J. (1984) The natural history of rheumatoid arthritis: a 15 year follow-up study. The prognostic significance of features noted in the first year. *Clinical Rheumatology* **3**, 11–20.

Reinholdt, J., Bay, I. & Svejgaard, A. (1977) Association between HLA-antigens and periodontal disease. I. *Journal of Dental Research* **56**, 1261–1263.

Roberts, W. N., Daltroy, L. H. & Anderson, R. J. (1988) Stability of normal joint findings in persistent classical rheumatoid arthritis. *Arthritis and Rheumatism* **31**, 267–271.

Roessler, B. J., Allen, E. D., Wilson, J. M., Hartman, J. W. & Davidson, B. L. (1993) Adenoviral gene transfer to rabbit synovium in vivo. *Journal of Clinical Investigation* **92**, 1085–1092.

Saxen, I. & Koskimies, S. (1984) Juvenile periodontitis – no linkage with HLA antigens. *Journal of Periodontal Research* **19**, 441–444.

Schroder, A. K., Gharavi, A. E., Steinitz, M., Johansson, P. J. & Christensen, P. (1987) Binding of monoclonal IgM rheumatoid factor to streptococci via the antibody combining site. *International Archives of Allergy and Applied Immunology* **83**, 88–91.

Scott, D. L., Symmons, D. P., Coulton, B. L. & Popert, A. J. (1987) Long-term outcome of treating rheumatoid arthritis: results after 20 years. *Lancet* **1**, 1108–1111.

Shapira, L., Eizenberg, S., Sela, M. N., Soskolne, A. & Brautbar, H. (1994) HLA A9 and B15 are associated with the generalised form, but not the localised form, of early-onset periodontal diseases. *Journal of Periodontology* **65**, 219–223.

Sherrer, Y. S., Bloch, D. A., Mitchell, D. M., Young, D. Y. & Fries, J. F. (1986) The development of disability in rheumatoid arthritis. *Arthritis and Rheumatism* **29**, 494–500.

Sibraa, P. D., Reinhardt, R. A., Dyer, J. K. & DuBois, L. M. (1991) Acute phase protein detection and quantification in gingival crevicular fluid by direct and indirect immunodot. *Journal of Clinical Periodontology* **18**, 101–106.

Slade, G. D., Offenbacher, S., Beck, J. D., Heiss, G. & Pankow, J. S. (2000) Acute-phase inflammatory response to periodontal disease in the US population. *Journal of Dental Research* **79**, 49–57.

Snyderman, R. & McCarty, G. A. (1982) Analogous mechanism of tissue destruction in rheumatoid arthritis and periodontal disease. In: *Host–parasite interaction in periodontal disease*. eds. Genco, R. J. & Mergenhagen, S. E., pp. 354–362. Washington, DC: American Society for Microbiology.

Stransky, G., Vernon, J., Aicher, W. K., Moreland, L. W., Gay, R. E. & Gay, S. (1993) Virus-like particles in synovial fluids from patients with rheumatoid arthritis. *British Journal of Rheumatology* **32**, 1044–1048.

Szalai, A. J., Agrawal, A., Greenhough, T. J. & Volanakis, J. E. (1997) C-reactive protein. Structural biology, gene expression, and host defense function. *Immunology Research* **16**, 127–136.

Takashiba, S., Noji, S., Nishimura, F., Ohyama, H., Kurihara, H., Nomura, Y., Taniguchi, S. & Murayama, Y. (1994) Unique intronic variations of HLQ-DQβ gene in early onset periodontitis. *Journal of Periodontology* **65**, 379–386.

Talonpoika, J. & Hamalainen, M. (1994) Type I collagen carboxy terminal telopeptide in human gingival crevicular fluid in different clinical conditions and after periodontal treatment. *Journal of Clinical Periodontology* **21**, 320–326.

The, J. & Ebersole, J. (1991) Rheumatoid factor (RF) distribution in periodontal disease. *Journal of Clinical Immunology* **11**, 132–142.

The, J. & Ebersole, J. (1996) Rheumatoid factor from periodontitis patients cross-reacts with epitopes on oral bacteria. *Oral Diseases* **2**, 253–262.

Thomson, W., Pepper, L., Payton, A., Carthy, D., Scott, D., Ollier, W., Silman, A. & Symmons, D. (1993) Absence of an association between HLA-DRB1*04 and rheumatoid arthritis in newly-diagnosed cases from the community. *Annals of the Rheumatic Diseases* **32**, 539–541.

Tilley, B. C., Alarcon, G. S., Heyse, S. P., Trentham, D. E., Neuner, R., Kaplan, D. A., Clegg, D. O., Leisen, J. C., Buckley, L. & Cooper, S. M. (1995) Minocycline in rheumatoid arthritis: a 48-week, placebo-controlled trial. *Annals of Internal Medicine* **122**, 81–89.

van Zeben, D. & Breedveld, F. (1996) Prognostic factors in rheumatoid arthritis. *Journal of Rheumatology Supplement* **44**, 31–33.

van Zeben, D., Hazes, J. M., Zwinderman, A. H., Cats, A., Schreuder, G. M., D'Amaro, J. & Breedveld, F. C. (1991) Association of HLA-DR4 with a more progressive disease course in patients with rheumatoid arthritis. Results of a follow-up study. *Arthritis and Rheumtism* **34**, 822–830.

van den Broek, M. F., van den Berg, W. B., Arntz, O. J. & van de Putte, L. B. (1988) Reaction of bacterium primed murine T cells to cartilage components: a clue for the pathogenesis of arthritis? *Clinical and Experimental Immunology* **72**, 9–14.

Venables, P. (1989) Infection and rheumatoid arthritis. *Current Opinion in Rheumatology* **1**, 15–20.

Ward, M. M. (1994) Clinical measures in rheumatoid arthritis: which are the most useful in assessing patients? *Journal of Rheumatology* **21**, 17–27.

Weinblatt, M. E., Kremer, J. M., Bankhurst, A. D., Bulpitt, K. J., Fleischmann, R. M., Fox, R. I., Jackson, C. G., Lange, M. & Burge, D. J. (1999) A trial of etanercept, a recombinant tumor necrosis factor:Fc fusion protein in patients with rheumatoid arthritis receiving methotrexate. *New England Journal of Medicine* **340**, 253–259.

Weyand, C., Hicok, K., Conn, D. & Goronzy, J. (1992) The influence of HLA-DRB1 genes on disease severity in rheumatoid arthritis. *Annals of Internal Medicine* **117**, 801–806.

Weyand, C., Mc Carthy, T. & Goronzy, J. (1995) Correlation between disease phenotype and genetic heterogeneity in rheumatoid arthritis. *Journal of Clinical Investigation* **95**, 2120–2126.

Winchester, R. (1994) Immunoelectron microscopic study of the distribution of cell subsets in rheumatoid synovium. *Journal of Experimental Medicine* **158**, 1191–1210.

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