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## CLINICAL PEARLS UPDATE#23

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### *Rheumatoid arthritis*

March 1, 2004

Dear Colleague,

Our clinical pearl this week is on **rheumatoid arthritis (RA) diagnosis and management**. RA brings pain, swelling, and frustration to too many people and their physicians. More active inflammation, which we understand as cumulative blocked repair, is associated with more aggressive disease. Rather than inhibit the inflammatory process, we recommend identifying the cause of immune provocation, substitution for those items while a repair, energizing diet (the Alkaline Way), targeted supplementation to stimulate repair, and healing actions are combined into first line comprehensive care.

We encourage you to share this valuable clinical update newsletter with your colleagues and staff so they can learn more about how our comprehensive approach can be applied to their practice with beneficial results. Please also let us know if any of your colleagues or staff would like to be added to our email distribution list.

We are grateful for the opportunities to be of service to you and your patients.

Sincerely,

***Russ Jaffe, MD, Ph.D., CCN, NACB***  
***Lab Director***

Sattar N, McCarey DW, Capell H, McInnes IB. **Explaining how "high-grade" systemic inflammation accelerates vascular risk in rheumatoid arthritis.** *Circulation* 2003;108(24):2957-2963.

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There is intense interest in mechanisms whereby low-grade inflammation could interact with conventional and novel vascular risk factors to promote the atheromatous lesion. Patients with rheumatoid arthritis (RA), who by definition manifest persistent high levels of inflammation, are at greater risk of developing cardiovascular disease. Mechanisms mediating this enhanced risk are ill defined. On the basis of available evidence, we argue here that the systemic inflammatory response in RA is critical to accelerated atherogenesis operating via accentuation of established and novel risk factor pathways. By implication, long-term suppression of the systemic inflammatory response in RA should be effective in reducing risk of coronary heart disease. Early epidemiological observational and clinical studies are commensurate with this hypothesis. By contrast, risk factor modulation with conventional agents, such as statins, may provide unpredictable clinical benefit in the context of uncontrolled systemic inflammatory parameters. Unraveling such complex relationships in which exaggerated inflammation-risk factor interactions are prevalent may elicit novel insights to effector mechanisms in vascular disease generally.

Toussirot EA. **Oral tolerance in the treatment of rheumatoid arthritis.** *Curr Drug Targets Inflamm Allergy* 2002;1(1):45-52.

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Oral tolerance (OT) consists of the oral administration of antigens (Ag) that could alter the response of the immune system. This is a form of peripheral immune tolerance in which mature lymphocytes in the peripheral lymphoid tissues are rendered non functional or hyporesponsive by prior oral administration of Ag. It was first described in 1911 in animal models of anaphylaxis. This therapeutic approach requires the orally administration of Ag and the active participation of the gut-associated lymphoid tissue (GALT), a tissue comprising Peyer's patches, intraepithelial cells and villi containing epithelial cells which is a well organized immune network. The mechanisms by which OT is mediated included deletion or anergy and active cellular suppression. The primary factor determining which form of tolerance will be developed after oral administration

of Ag is the Ag dosage. Thus, it is thought that low doses of Ag induce the generation of active suppression, via regulatory T cells in the GALT, which then migrate to the systemic immune system. These regulatory T cells produce down-regulatory cytokines such as IL4, IL10 and TGFbeta, a Th2 / Th3 cytokine pattern. Conversely, high dose of Ag favors anergy or clonal deletion. The phenomenon in which regulatory cells, as generated by oral tolerization, are primed in an Ag specific manner, but act in the respective microenvironment in a non-Ag specific manner is called bystander suppression. This phenomenon is of particular interest and explained the use of OT in T cell mediated autoimmune diseases such as rheumatoid arthritis (RA), multiple sclerosis (MS) and type I diabetes, some diseases in which the autoAg remains unknown or where there are reactivities to multiple autoAgs. There were several studies demonstrating the effectiveness of orally administered Ag in different animal models of autoimmune diseases, such as experimental allergic encephalomyelitis, collagen induced arthritis, diabetes, but also uveitis, myasthenia gravis and transplantation. These mouse or rat models of autoimmune diseases gave the rationale for the therapeutic use of OT in human and this therapeutic approach has been tried in MS and RA, using oral myelin or oral collagen, respectively. In RA, 4 trials of oral type II collagen (CII) in RA have been published. Taken together, these studies suggested that oral CII in RA gave a trend toward clinical improvement, with significance in only 2 studies. Bacterial extract from Escherichia coli containing heat shock proteins has been tried in oral treatment for RA. Two placebo controlled trials and 2 comparative studies gave favorable results for this bacterial extract with no or mild adverse events. Although oral/mucosal tolerance has given successful results in animal models of autoimmune diseases, the enthusiasm for this therapeutic approach in human diseases must be tempered. The discrepancies between the effectiveness of OT in animal models and the results in human trials raise some questions, the identification of the subgroup of patients who might respond to this treatment and the source (or nature) of the administered Ag (homologous versus heterologous), for instance.