Disease activity in rheumatoid arthritis

Studies in interleukin-6, tumour necrosis factor alpha, monocyte activity, acute phase markers, glucocorticoids, and disability

BY

NILS GUNNAR ARVIDSON

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In the present studies, aspects of some disease activity measures in rheumatoid arthritis (RA) have been investigated, including the effect of glucocorticoids on this activity.

In RA, serum interleukin(IL)-6 levels were elevated and were shown to have a circadian rhythm, with peak levels in the morning, declining towards low or normal levels in the afternoon and evening. In contrast, serum levels of tumour necrosis factor(TNF)\(\alpha\) were low and stable. In other connective tissue diseases, serum TNF\(\alpha\) levels were elevated but without circadian variation, while IL-6 levels were low and stable.

Nocturnal administration (at 2:00 a.m.) of low-dose prednisolone a few hours before the early morning peak of IL-6 was shown to be significantly more effective in reducing clinical symptoms of disease activity and serum IL-6 levels than the traditional morning administration (at 7:30 a.m.) of the same dose of prednisolone.

Circulating monocytes are activated in RA, expressing receptors related to adhesion and phagocytosis. Treatment with glucocorticoids suppressed the expression of these receptors on monocytes, and this may be one mechanism of the beneficial effect of glucocorticoids in RA. Endogenous levels of cortisol may suppress leucocyte-endothelial interactions in RA.

The different acute phase markers used to assess disease activity in RA showed good correlations with each other and with serum IL-6 levels. There were especially strong correlations between C-reactive protein (CRP) and Serum amyloid A (SAA) protein, and between fibrinogen and erythrocyte sedimentation rate (ESR). Fibrinogen and CRP showed stronger correlation than ESR with the Modified Health Assessment Questionnaire (MHAQ) score and with the neutrophil count.

Four simple objective function tests were each compared with the MHAQ score and with a radiological joint damage score (Larsen score). The objective function tests correlated with the MHAQ score, and each of these two methods of assessing physical disability correlated with pain, CRP and ESR. In addition, most of the objective function tests correlated significantly with radiological joint damage, while the MHAQ score did not.

Key words: acute phase markers, circadian rhythm, disability, disease activity, glucocorticoids, monocyte activation, rheumatoid arthritis.

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DENNA VÄRLD

Det visar sig ha varit ett missförstånd.
Bokstavligt tog man det som var på försök.
Snart skall floderna återgå till källorna,
vinden skall upphöra att vandra.
Istället för att knoppas skall träden söka rötterna.
Åldringar skall springa efter bollen,
se sig i spegeln där de är barn på nytt.
De döda skall vakna och ingenting fatta.
Tills allt som har gjorts skall göras ogjort.
Vilken lättnad! Andas ut, ni som har lidit så.

(Czesław Miłosz, ur Vid flodens strand)

TIL ANNE GRETHE
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<td>American college of rheumatology (former ARA)</td>
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<td>American rheumatism association</td>
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<td>ADL</td>
<td>Activities of daily life</td>
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<td>CD</td>
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<td>Clinical health assessment questionnaire</td>
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<tr>
<td>CNS</td>
<td>Central nervous system</td>
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<td>COMP</td>
<td>Cartilage oligomeric matrix protein</td>
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<td>CR</td>
<td>Complement receptor</td>
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<td>CRH</td>
<td>Corticotropin releasing hormone</td>
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<td>CRP</td>
<td>C-reactive protein</td>
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<td>DAS</td>
<td>Disease activity score</td>
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<td>DHAQ</td>
<td>Difficult 8 item health assessment questionnaire</td>
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<td>DMARD</td>
<td>Disease modifying antirheumatic drugs</td>
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<tr>
<td>ESR</td>
<td>Erythrocyte sedimentation rate</td>
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<tr>
<td>Fc</td>
<td>Fragment crystallised</td>
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<td>FITC</td>
<td>Fluorescing isothiocyanate</td>
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<td>HAQ</td>
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<td>HNL</td>
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<td>HPA</td>
<td>Hypothalamic pituitary adrenal</td>
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<tr>
<td>ICAM</td>
<td>Intercellular adhesion molecule</td>
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<td>IFNγ</td>
<td>Interferon gamma</td>
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<td>Ig</td>
<td>Immunoglobulin</td>
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<td>IL</td>
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<td>IL-1 ra</td>
<td>IL-1 receptor antagonist</td>
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<td>MACTAR</td>
<td>McMasterToronto arthritis patient preference</td>
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<td></td>
<td>disability questionnaire</td>
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<td>MCAF</td>
<td>Macrophage chemoattractant and activating factor</td>
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<td>MCP</td>
<td>Metatarsophalangeal joints</td>
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<td>MCTD</td>
<td>Mixed connective tissue disease</td>
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<td>MD-HAQ</td>
<td>Multidimensional health assessment questionnaire</td>
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<td>MFI</td>
<td>Mean fluorescence intensity</td>
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<td>Abbreviation</td>
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<tr>
<td>MHAQ</td>
<td>Modified health assessment questionnaire</td>
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<td>Monoclonal antibodies</td>
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<td>MPO</td>
<td>Myeloperoxidase</td>
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<td>NBS</td>
<td>New-born foetal calf serum</td>
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<tr>
<td>NHP</td>
<td>Nottingham health profile</td>
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<tr>
<td>NSJ</td>
<td>Number of swollen joints</td>
</tr>
<tr>
<td>PBS</td>
<td>Phosphate-buffered saline</td>
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<tr>
<td>PIP</td>
<td>Proximal interphalangeal joints</td>
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<td>RA</td>
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<td>RA-HAQ</td>
<td>Rheumatoid arthritis health assessment questionaire</td>
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<td>RFs</td>
<td>Rheumatoid factors</td>
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<td>SAA</td>
<td>Serum amyloid A protein</td>
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<td>SLE</td>
<td>Systemic lupus erythematoses</td>
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<td>SOFI</td>
<td>Signals of functional impairment index</td>
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<td>SS</td>
<td>Sjögren´s syndrome</td>
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<tr>
<td>SSc</td>
<td>Systemic sclerosis</td>
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<tr>
<td>sTNFR</td>
<td>Soluble tumour necrosis factor receptor</td>
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<tr>
<td>Th cells</td>
<td>T helper cells</td>
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<tr>
<td>TNFα</td>
<td>Tumour necrosis factor alpha</td>
</tr>
<tr>
<td>UK</td>
<td>United kingdom</td>
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<tr>
<td>USA</td>
<td>United states of america</td>
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LIST OF PAPERS

The thesis is based on the following papers, which will be referred to in the text by their Roman numerals:


VI. Arvidson NG, Larsson A, Larsen A. Simple function tests, but not the modified HAQ, correlate with radiological joint damage in rheumatoid arthritis. Scand J Rheumatol 2002; 31: 146-50.

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INTRODUCTION

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a systemic inflammatory connective tissue disease with polyarthritis as a prominent feature. However, extraarticular symptoms and signs are always present. In Europe and USA, the prevalence of the disease in women is about 1% and in men about 0.5%, and the peak incidence in UK, Norway and USA occurs at the age of 55-64 years in women, and 65-75 years in men (reviewed by Symmons 2002). The overall female/male incidence ratio is about 2.5/1. In younger patients the female/male ratio is around 4/1, but in patients with older age onset, the incidence ratio is nearly equal (Lee and Weinblatt 2001; Symmons 2002).

Patients with RA are often affected in many ways, with physical disability, psychological and socio-economic decline and reduced quality of life. The mortality is increased especially in that small proportion of patients suffering from the most severe disease (reviewed by Callahan and Pincus 1995). The direct and indirect costs of RA to the society are tremendous (Allaire 1994; Pincus 1995; reviewed by Pugner et al. 2000).

The association with genetic factors in RA is marked. Studies on twins show that genetic factors account for about 60% of the population’s predisposition to RA (MacGregor et al. 2000). Although the genetic part may dominate in the aetiology of RA, non-genetic and environmental factors probably play a role.

RA has been regarded by many as an autoimmune disease, based upon the findings of autoreactivity to collagen type II (Tarkowski et al. 1989; Cook et al. 1996; discussed by Fujii et al. 1999), and to non-cartilaginous proteins, for example filaggrin or citrullinated peptides (Shellekens et al. 1998; Vincent et al. 2002). In experimental
animals, immunization with collagen type II, proteoglycans or cartilage oligomeric matrix protein (COMP), has been shown to induce arthritis which corresponds to the appearance of antibodies to these cartilage constituents (Trentham et al. 1977; Clague et al. 1980; Wooley et al. 1981; Holmdahl et al. 1985; Glant et al. 1987; Carlsén et al. 1998).

However, the relevance of these findings in the pathophysiology of RA is unclear. Host factors, such as age, gender, hormonal and lifestyle factors, e.g. smoking, also seem to play a role for the development of RA (Uhlig et al. 1999). The variable and unpredictable course of RA, with quiescent periods alternating with periods of flare, could possibly indicate that exogenous factors, for example environmental antigens, are involved.

A further support for RA as an autoimmune disease is the presence of rheumatoid factors (RFs), commonly regarded as autoantibodies against the Fc region of human IgG. RFs are present in about 80% of RA patients, using the latex fixation test (Wolfe 1991). The inclusion of positive RF in the criteria for RA of course increases the proportion of seropositive patients. RFs can belong to any immunoglobulin class, but IgM RF is the most studied and measured. It has been suggested that on the basis of immunogenetic profiles (HLA Class II associations), seronegative and weakly seropositive patients differ from the clearly seropositive subgroup (Ploski et al. 1994). RFs are not specific for RA, but occur in many inflammatory disorders, and in symptomless individuals and transiently in many infectious diseases. The current status of RFs was reviewed by Newkirk, 2002.

Based on many studies, it is often stated in textbooks that RFs levels are predictors of severe disease, especially radiographic progression (van Zeben et al. 1992; Listing et al. 2000; Rau et al. 2000; reviewed by Scott 2000a; Combe et al. 2001; Kaltenhäuser et
al. 2001). However, many reports do not confirm this finding (Amos et al. 1977; Bradlow and Movat 1985; Larsen 1988; Möttönen 1988; Lindqvist et al. 2002).

Unfortunately, there are neither specific histo-pathological changes nor specific clinical findings for RA. However, in practice radiological changes are the most specific features of RA. The clinical appearance of RA differs so much between individual patients, that one sometimes is tempted to believe that the patients do not have the same disease.

The American Rheumatism Association (ARA) in 1987 revised criteria for the classification of RA was used in this report (Arnett et. 1988):

- Morning stiffness (>1 hour before maximal improvement).
- Arthritis of at least three joint areas (must be observed by a physician).
- Arthritis of the hands.
- Symmetric arthritis.
- Rheumatoid nodules.
- Serum rheumatoid factor.
- Radiographic joint changes typical of RA (i.e., periarticular bony decalcifications or erosions = structural joint damage).

Four or more criteria must be satisfied for at least 6 weeks to diagnose RA.

**Disease activity in rheumatoid arthritis**

Disease activity in RA is a complex phenomenon, impossible to define and discern, like "das Ding an sich" of Immanuel Kant. The disease activity in RA is an expression of a cascade of immunological and inflammatory reactions, probably initiated by an unknown stimulus, and perpetuated for unknown reasons. At the present time no single test of disease activity in RA is effective because RA may cause various kinds of
symptoms and signs. Thus, the disease activity variables can be considered as surrogate markers for the in itself unmeasurable process.

Clinical symptoms of disease activity are e.g. morning stiffness, fatigue, pain, impaired function, and psychological and sleep disturbances. Clinical signs include joint swelling and deformity, reduced objective function, low-grade fever, osteoporosis and weight loss. Other extraarticular signs are serositis, pulmonary fibrosis, myositis, Sjögren’s syndrome, neuropathy and vasculitis. Some of these symptoms and signs are used to assess disease activity, e.g. the number of swollen and tender joints (reviewed by Prevo et al. 1993), graded, ungraded or weighted joint indices (Ritchie 1968; Thompson 1987), pain and fatigue (Ferraz et al. 1990; Mengshoel and Forre 1993), duration of morning stiffness and different scores for functional decline (Fries et al. 1980; Pincus et al. 1983). The patient’s own global assessment of the disease activity is sometimes added. Laboratory markers of disease activity are for instance acute phase proteins and ESR. In some instances, clinical and laboratory markers for disease activity are combined, including the patient’s global assessment of disease activity, into compound indices of disease activity, e.g. the Stoke index (Davis et al. 1990) or the disease activity score (DAS) (van der Heijde et al. 1992).

Histological changes in the synovial tissue are also related to the disease activity (reviewed by Bresnihan et al. 2000; and Katrib et al. 2002). The level of pro-inflammatory cytokines may correlate with disease activity giving rise to localised bone loss (erosions) and general bone loss (osteoporosis) (Gough et al. 1994; Forslind et al. 2002; Gravallese 2002; Harrison et al. 2002; Holstead et al. 2002). The disease activity, especially in early RA, correlates with the reported function of the patient and with objective function tests.
RA is a chronic disease, but the disease activity is a fluctuating process, showing great variation even during one day and during longer time periods.

**Pro-inflammatory cytokines**

The main way for lymphocytes to communicate with each other and with other cells is regulated by small proteins initially called lymphokines (in the late 1960s). Later on it was observed that also monocytes and macrophages synthesize such molecules, being therefore also called monokines. About ten years later, the term interleukins was proposed, and this nomenclature is still partly in use (e.g. interleukin(IL)-1, IL-2, IL-6). Today these molecules are often referred to as cytokines.

Cytokines are produced mainly by cells within the immune system, e.g. monocytes, macrophages, lymphocytes and T-cells (Th1- and Th 2-cells), but also by other cells, e.g. mast cells, fibroblasts and endothelial cells (Gordon et al 1990; Borish and Rosenwasser 1996; reviewed by Evangelos et al. 2002). Cytokines are small proteins, mostly glycoproteins, being active in small quantities (picograms). They have a short biological half-life (minutes), acting mainly locally in the tissues, primarily on immediately neighbouring cells.

Cytokines interact in a complicated way, inducing or inhibiting the production and effects of each other. Cytokines generally affect more than one cell type, and one cytokine may have several different effects on one type of cells, depending on the circumstances. A cytokine may at the same time activate one type of cells and suppress another type of cells.

The production of many cytokines, e.g. interferon(IFN) γ, TNFα, IL-1, IL-6 and IL-12 have been shown to exhibit a circadian variation or pulsatility in healthy volunteers (Liciano et al. 1994; Sothern et al. 1995; Petrovsky et al. 1998). Sometimes, especially
in inflammation, cytokines appear in the circulation most often in order to regulate the gene expression in a specific organ or cell type. This is the case when IL-1 and IL-6 induce the hepatic synthesis of acute phase proteins (Andus et al. 1988; Morrone et al. 1988; Castell et al. 1989), or when they stimulate the synthesis of CRH, ACTH, and cortisol (reviewed by Chrousos 1995; and Papanicolaou et al. 1998). Cytokines act on the hypothalamus to elevate the body temperature (“endogenous pyrogens”), as fever is generally beneficial for the host defence (reviewed by Bendtzen 1988; and Akira et al. 1990).

Cytokines are involved in a wide range of activities, such as tissue breakdown and repair, cell growth and differentiation, inflammation and regulation of immune responses. The cytokines most important in arthritic diseases such as RA seem to be the pro-inflammatory cytokines, especially IL-1, IL-6 and TNFα, and possibly IL-8, being detected in elevated levels in the synovial membrane and in the synovial fluid and in the circulation (Tetta et al. 1990; Westacott et al. 1990; Arvidson et al. 1994; McNiff et al. 1995; Ulfgren et al. 1995; Steiner et al. 1999; Al-Awadhi et al. 2002). The quantity and profile of cytokines varies between different RA patients, and even between different joints in the same patient (Ulfgren et al. 2000).

IL-1 and TNFα induce each other (Nawroth et al. 1986; reviewed by Akira et al. 1990). Both IL-1 and TNFα induce the production of IL-6, at least in vitro (Bender et al. 1990; Tosato and Jones 1990; Passeri et al. 1994). Treatment with the TNFα blocker infliximab was shown not only to reduce circulating levels of immunoreactive TNFα and soluble tumour necrosis factor receptor (sTNFR), but also levels of IL-1 ra and IL-6, suggesting that TNFα regulates the IL-6 production in RA (Charles et al. 1999). IL-17, another recently described pro-inflammatory cytokine in the RA synovium (Chabaud et al. 1999), has been reported to stimulate the production of other pro-
inflammatory cytokines from different cell types, and to have synergistic effects with TNFα on the production of IL-1, IL-6 and IL-8 from synovial fibroblasts (Fossiez et al. 1996; Katz et al. 2001).

IL-1 and TNFα have many important functions in RA. Both cytokines stimulate endothelial cells to express adhesion molecules, which is important for the attraction of inflammatory cells into the synovium (Lindsley et al. 1993; reviewed by Choy and Panayi 2001). IL-1 and TNFα stimulate the proliferation of synovial cells resulting in pannus formation and they activate chondrocytes, fibroblasts and osteoclasts to secrete proteolytic enzymes which degrade cartilage and bone (reviewed by Choy and Panayi 2000; and Evangelos et al. 2002). TNFα, IL-1, IL-6, IL-8 and some other cytokines have been detected in the cartilage/pannus junction in RA patients (Chu CQ et al. 1992; Deleuran et al. 1994).

Suppression of the effects of TNFα and IL-1 with TNFα antibodies (infliximab, adalimumab) or with a soluble TNFα receptor (etanercept), or with an IL-1 receptor antagonist (IL-1 ra) (anakinra), respectively, has shown promising results in the treatment of RA (Maini et al. 1999; Moreland et al. 1999; Lipsky et al. 2000; Cohen et al. 2002; Furst et al. 2002; Weinblatt et al. 2003).

IL-6 has been detected in synovial tissue in RA (Ulfgren et al. 1995), and is thought to take part in the local destructive processes in the joints (Kotake et al. 1996), and to induce some of the systemic symptoms in RA (Papanicolau et al. 1998). There is some uncertainty about the contribution of IL-6 to the local pathology of the disease, or whether it serves mainly as a mediator for the synthesis of hepatic acute phase proteins. In experimental arthritis, evidence supporting a direct role of IL-6 in the arthritic process has been demonstrated (Alonzi et al. 1998; Ohshima et al. 1998; Boe et al. 1999). IL-6, in combination with TNFα and IL-1, induce osteoclast differentiation and
activation, which is suggested to contribute to focal bone erosions in RA (Kotake et al. 1996; Goldring 2002). In addition to the accepted pro-inflammatory actions of IL-6, it has been suggested to have anti-inflammatory effects in some experimental systems (reviewed by Tilg et al. 1997).

Some cytokines, such as IL-4, IL-5, IL-10 and IL-13 are thought to have anti-inflammatory properties, and are present in the rheumatoid synovium (Katsikis et al. 1994; Cush et al. 1995; Isomäki et al. 1996a; Isomäki et al. 1996b; Steiner et al. 1999). In RA, the balance between pro-inflammatory cytokines, natural cytokine inhibitors and anti-inflammatory cytokines seem to be disrupted, and for some reasons homeostasis is not restored which is the case in self-limiting conditions.

**Monocyte activation**

The cellular elements of blood derive from the haematopoetic stem cells in the bone marrow. The myeloid progenitor cell is the precursor of granulocytes, monocytes and macrophages. The monocytes can be regarded as an immature form of macrophages, circulating in the blood, and differentiating into macrophages a few hours after leaving the blood stream. Monocytes and macrophages play a crucial role in the innate immunity, participating in both humoral and cellular immune responses. Macrophages (and neutrophils) constitute the phagocytes of the immune system, and are distributed all over in the body.

The monocytes are the biggest of all cells in the blood, and get even bigger when they are transformed into macrophages. The half-life of circulating monocytes is about three days (Whitelaw 1966), and once the monocytes have entered into the tissues, they stay there. In the tissues, the macrophages either migrate or are residents. The number
of macrophages is lower than the number of neutrophils at the site of inflammation, and the macrophages survive much longer than the neutrophils.

The cytoplasm of monocytes contains numerous lysosomal granule, but the macrophages are more active cells, synthesizing and secreting well over 100 substances (Rappolee and Werb 1988). Monocytes express adhesion receptors on their cell membranes, and macrophages express a large number of surface receptors, allowing these two types of cells to recognise and interact with the surroundings.

The leucocytes migrate from the circulation into the peripheral tissues. In the case of an inflammatory event, the local recruitment of leucocytes is greatly increased (extravasation). Initially neutrophils and somewhat later lymphocytes and monocytes reach the site of inflammation. The enhanced migration of leucocytes is brought about by interactions of adhesion molecules on the endothelial cells of local blood vessels and leucocytes, induced by cytokines, and is thought to occur in four steps (reviewed by Cronstein and Weissmann 1993; and Gumbiner 1996).

The first phase involves a reversible binding of leucocytes to the vascular endothelium through the interaction of selectins expressed on the endothelial cells (E- and P-selectins), and their ligands on the leucocytes (L-selectin). This initial binding between the endothelium and the leucocytes is weak, and cannot resist the force from the flowing blood. The leucocytes roll along the endothelium without making firm contact.

In the second step of adhesion, a stronger binding is established by the expression of leucocyte integrins cluster designations(CD)11a/CD18 and CD11b/CD18, which interact with an immunoglobulin related adhesion molecule (ICAM)-1 on the endothelium. The integrins have α- and β-chains, and are divided into different groups by differences in the β-chains. Chemokines like IL-8 are important in this process as
they further increase the adhesive capacity of the integrins. The result is that the rolling of the leucocytes will stop.

During the third phase, the leucocytes cross the vessel wall by squeezing between the endothelial cells. The integrins CD11a/CD18 and CD11b/CD18 on the leucocytes, and the molecule CD31 located on the leucocytes and on the junction between endothelial cells, are required for extravasation. To reach the extravascular tissue, the leucocytes must penetrate the basement membrane. Proteolytic enzymes that disintegrate the proteins in the basement membrane achieve this.

The final step in the recruitment of leucocytes to the site of inflammation is the movement of leucocytes through the tissues. A special group of cytokines, chemokines, are responsible for this migration. They are produced by phagocytes, endothelial cells and fibroblasts. The chemokine IL-8 acts on neutrophils, and the human macrophage chemoattractant and activating factor (MCAF) acts on monocytes. The concentration of chemokines increases in the direction of the site of inflammation to direct the migration of leucocytes.

In addition to adhesion molecules, monocytes express receptors that are important to phagocytosis, to the respiratory burst and to secretion (Fcγ receptors and complement receptors) (Venge et al. 1997). The circulating monocytes express two types of Fcγ receptors, CD64 and CD32 that bind monomeric immunoglobulin (Ig) G and IgG complexes, respectively. The complement receptors (CRs) expressed by monocytes are CD35 and CD11b/CD18.

In RA, elevated expression of CD 11b/CD18, CD14, CD64 and CD32 on blood monocytes has been reported (Gadd et al. 1992; Shinohara et al. 1992; Higaki et al. 1992; Highton et al. 1995), and also elevated expression of the β2-integrins, but not the β1-integrins (Liote et al. 1996).
The rheumatoid synovium is infiltrated by lymphocytes, plasma cells, mast cells and macrophages. The adhesion of circulating monocytes to the endothelial cells plays an important role for the recruitment of macrophages to the synovial membrane (Cutolo 1993). The expression of ICAM-1 on endothelial cells seems to be almost always present in synovial tissue from patients with chronic arthritis, while the expression of e.g. E-selectin in the vessel walls is substantially lower than that of ICAM-1 (Mellbye et al. 1996). The macrophages, fibroblasts, mast cells and infiltrating leucocytes produce cytokines of the pro-inflammatory type. In addition, they secrete metalloproteinases and reactive oxygen intermediates, which all contribute to the destruction of cartilage and bone (Yanni et al. 1994; Deleuran 1996). Additionally, these cytokines, of which some are detected in the circulation, e.g. IL-1, IL-6 and TNFα (Eastgate et al. 1988; Tetta et al. 1993; Arvidson et al. 1994), could stimulate the expression of β2-integrins on the monocytes.

The induction of leucocyte and vascular endothelium adhesion molecules in the synovial membrane is thus one part of the complicated immunological and inflammatory events that take place in RA. Substances that inhibit the expression of adhesion molecules are being developed for treatment of RA and other chronic inflammatory diseases (reviewed by Yusuf-Makagiansar et al. 2002).

Acute phase markers

Many different processes, sharing features of tissue injury or inflammation, such as trauma, infection, tumour necrosis, ischemia and connective tissue diseases, are associated with a substantial change in the protein components of plasma. All the mentioned processes generate a variety of cytokines that alter the metabolic activity of hepatocytes. The pro-inflammatory cytokines IL-1, TNFα, and IL-6 in particular,
increase the production of several plasma proteins such as C-reactive protein (CRP), fibrinogen, α1-antitrypsin, haptoglobin, α1-acid glycoprotein and Serum amyloid A (SAA) protein (Castell et al. 1989; Ganpathi et al. 1991; Suffredini et al. 1999). Also clotting factors, ferritin and some complement components are produced at an accelerated rate, while the synthesis of some other proteins, e.g. albumin, transthyretine and transferrin, is suppressed. The term "the acute-phase plasma protein response" is collectively used for these alterations. The most commonly measured laboratory markers of the acute phase response are the erythrocyte sedimentation rate (ESR) and CRP.

ESR is the oldest method to assess the acute phase response. Fåhæreus introduced ESR in the 1920s, based on his clinical observation that red blood cells separated from plasma quicker in sick than in healthy people (Fåhæreus 1921). Erythrocytes in plasma normally repel each other due to the negative electrical charge on the erythrocyte surface. Some plasma proteins, and especially fibrinogen, decrease this negative charge and increase the aggregation and the sedimentation of erythrocytes. Elevated immunoglobulins levels also increase the tendency for erythrocytes to aggregate (Stuart and Whicher 1988). The ESR is further influenced by age, sex, anaemia, renal failure, pregnancy and abnormal red blood cell morphology (reviewed by Zlonis et al. 1993; and Brigden et al. 1998). In response to an appropriate stimulus, ESR rises over 2-4 days and may not return to normal before 2-4 weeks have passed.

In rheumatology, ESR plays an important role in different criteria assessing disease activity and improvement and as a laboratory activity measure in clinical trials (Scott et al. 1993; Moreland et al. 1997; Lipsky et al. 1999; Smolen et al. 1999; Strand et al. 1999; Cohen et al. 2002). In RA, ESR has been shown to correlate with outcome and to influence radiological progression in many studies (Amos et al. 1977; Dawes et al.
1986; Möttönen 1988; Hassell et al. 1993; Combe et al. 2001), although the correlation with radiographic progression was weak or absent in some studies (Larsen 1988; Sjöblom et al. 1984). In some recent large clinical trials, ESR was not included as a laboratory marker (Charles et al. 1999; Weinblatt et al. 2003).

Despite its old age, ESR retains an important place in medical practice, because it is inexpensive and readily performed, without specialised equipment. Currently, ESR is preferred in USA and CRP is preferred in Europe (Wolfe 1997).

The discovery of a protein that precipitated the C-polysaccharide from pneumococci in the late 1920s (Tillett and Francis 1930) was eventually followed by the introduction of CRP in the clinic in the 1940s (Hedlund 1947). One of the first large studies to support the usefulness of CRP in RA dates back to 1972 when McConkey et al., studying 187 patients with RA for 3 years, concluded that CRP well mirrors the exacerbations and remissions of RA, and the overall course of the disease (McConkey et al. 1972).

There is evidence that CRP is present at low levels in asymptomatic individuals, possibly reflecting a baseline activity of circulating cytokines (Ross 1999; Herity 2000). CRP is synthesized by hepatocytes in response to pro-inflammatory cytokines, in particular IL-6 (Castell et al. 1989; Heinrich et al. 1990). Although IL-6 shows circadian variation in healthy subjects and RA patients (Arvidson et al. 1994; Sothern et al. 1995; Crofford et al. 1997), there is no circadian variation of CRP neither in healthy individuals, nor in RA patients (Sitton et al. 1984; Meier-Ewert et al. 2001).

The synthesis of CRP starts immediately after tissue injury, and elevated plasma levels can be detected within 6-10 hours, and peak levels occur after 1 to 3 days (Stuart and Whicher 1988; reviewed by Blackburn 1994). In response to inflammation, the level of CRP may increase up to 1000-fold or more. The major determinant of the
plasma concentration is the rate of synthesis, while the half-life is estimated to about 19 hours.

CRP belongs to a family of proteins, including SAA, with functional and structural similarities. These proteins are called pentraxins because of their chemical structure. CRP has opsonic properties, stimulating phagocytosis of erythrocytes, bacteria and fungi, and it participates in the activation of monocytes, and it activates the classical complement pathway (Mold et al. 1982; Kilpatrick and Volanakis 1985; Tebo 1990; Richardson et al. 1991; Mortensen 1994). CRP has been suggested to mediate part of the complement activation in RA (Molenaar et al. 2001). It has been reported that CRP increases the expression of IL-1 and TNFα in human alveolar macrophages (Galve de Rochemonteix et al. 1993), and induces the production of IL-1 receptor antagonist by human mononuclear cells (Tilag 1993). The biological functions of CRP in immunity and rheumatology was reviewed by Atkinson, 2001.

CRP has been shown to be of great value as an inflammatory marker in RA, and its correlation with an increased rate of radiological progression has been shown in many studies (Amos et al. 1977; Dawes et al. 1986; Larsen 1988; van der Heide et al. 1995; reviewed by Scott 2000; Combe et al. 2001). In a study by van Leeuwen et al., 1993, the correlation between time integrated CRP and the rate of radiological progression over 3 years was used to predict subsequent radiological progression. The development of generalised bone loss in early RA has been shown to correlate closely with persistently elevated levels of CRP (Gough et al. 1994). In clinical practice, a fall in CRP level represents the first objective sign of improvement in response to treatment with disease modifying drugs (reviewed by Emery and Luqmani 1993).

CRP must be considered an exact measure of the acute phase response, while ESR is additionally affected by events that accompany (or do not accompany) the
inflammation, e.g. anaemia, elevated immunoglobulins levels, and other not inflammatory and strictly confounding factors with respect to the acute phase response (e.g. sex and age).

Fibrinogen, being the major determinant of the plasma viscosity, has important functions in the normal haemostasis. Due to the asymmetry and high molecular weight of the fibrinogen molecule, more than 80% of the total fibrinogen pool is located intravascularly. Fibrinogen is secreted into the circulation with a half-life of 3-4 days, and the normal level of fibrinogen in plasma is approximately 2 – 4 g/l (reviewed by Dang 1989). In inflammation or tissue injury, pro-inflammatory cytokines may increase the synthesis from hepatocytes 2- to 3-fold. Increased plasma levels can be detected one to two days after stimulus, and maximum levels are seen in 3-4 days. Without further stimulus, the fibrinogen concentration returns to normal within 3-4 weeks (Stuart and Whichner 1988; reviewed by Emery and Luqmani 1993).

Fibrinogen has many physiologic functions. It is important for the aggregation of platelets and for the coagulation of plasma. It also induces reversible aggregation of red blood cells, and is therefore responsible (about 50%) for the erythrocyte sedimentation observed in the ESR during an inflammatory response (Stuart and Weicher 1988). In addition, fibrinogen has cellular functions, binding to endothelial cells, monocytes and macrophages (reviewed by Cook and Ubben 1990). Elevated levels of fibrinogen, like elevated levels of CRP and ESR, predict cardiovascular disease (Wilhelmsen et al. 1986; Kannel et al. 1987; Woodward et al. 1998; Ridker et al. 2000; Danesh et al. 2000). Patients with RA have an increased risk for cardiovascular and cerebrovascular events, which could relate to elevated fibrinogen levels (Wållberg Jonsson 1996; Charles et al. 1999; Wållberg Jonsson et al. 1999; Jarenros et al. 2002; Wolfe et al. 2003).
As expected, strong mutual correlations have been found between fibrinogen, ESR and CRP (Stuart and Whicher 1988; Arvidson et al. 1998; Arvidson et al. 2002). Fibrinogen and CRP, but not the ESR, showed a good correlation with radiological joint damage (Sjöblom et al. 1984). Fibrinogen correlated with reduced bone mineral density of the forearm in RA, while ESR and CRP did not (Péres-Edo et al. 2002).

SAA is an apolipoprotein associated with high-density lipoproteins (HDL). Sometimes SAA dissociates from HDL and precipitates in peripheral tissues to constitute the principal component of amyloid deposits. As an acute phase marker SAA shows similarities with CRP with respect to the rapidity and extent it elevates from normal levels when stimulated. The changes in SAA levels in response to inflammatory stimuli even surpass those of CRP (de Beer et al. 1982; Malle and de Beer 1996). Like CRP, SAA participates in the inflammatory reaction. It has been suggested that SAA may contribute to the recruitment of monocytes and neutrophils into inflamed tissues (Badolato et al. 1994).

Some cross-sectional studies suggest that SAA levels correlate with disease activity in RA (Benson and Cohen 1979; de Beer et al. 1982), and that SAA may be a more sensitive marker of inflammation in RA than is CRP (Chambers et al. 1983; Grindulis et al. 1985; Maury 1985).

The anti-inflammatory effects of the acute phase proteins (APPs) were reviewed by Tilg et al., 1997.

Analysis of other acute phase proteins, e.g. haptoglobin and α1-acid glycoprotein, or the analysis of pro-inflammatory cytokines, to assess or monitor disease activity in RA, have not been widely used.
**Glucocorticoids**

Molecules like cholesterol, sex hormones and corticosteroids are collectively called steroids because they have a common multiple ring structure. In the adrenal cortex, two classes of corticosteroids are synthesized: androgens with 19 carbon atoms, and other corticosteroids with 21 carbon atoms. The latter class of corticosteroids is divided into glucocorticoids and mineralocorticoids, depending on differences in effects on the regulation of the carbohydrate metabolism and the electrolyte balance. The anti-inflammatory effects of corticosteroids correlate with the effects on glucose metabolism. These compounds are therefore called glucocorticosteroids or glucocorticoids (Buttgereit et al. 2002a). The main endogenous glucocorticoid is cortisol (hydrocortison).

Glucocorticoids influence inflammatory reactions and immune responses in a variety of ways. They inhibit prostaglandin synthesis and suppress leucocyte trafficking and the activation of monocytes, macrophages and neutrophils, thereby suppressing the synthesis and release of pro-inflammatory cytokines and chemokines. Glucocorticoids inhibit directly and indirectly (by the suppression of cytokine production) the expression of adhesion molecules on leucocytes and endothelial cells, thus inhibiting the access of leucocytes to inflammatory sites. They may stimulate the production of anti-inflammatory proteins such as lipocortin 1. Glucocorticoids modulate the functions of fibroblasts and chondrocytes, thereby suppressing the release of cartilage and bone degrading enzymes. All these effects are important for the clinical improvement observed in RA patients treated with glucocorticoids.

In addition, glucocorticoids have multi-system effects, influencing the carbohydrate and lipid metabolism, the muscles and skeleton, CNS and the cardiovascular system.
Both natural and synthetic glucocorticoids exert their effects by binding to the cytoplasmatic glucocorticoid receptor (GR)-α, and most cells in the body possess this receptor, which leads to the modulation of gene transcription (Buttgereit et al. 1998). GR-mediated events are therefore classified as genomic. These glucocorticoid actions take at least 30-60 minutes, and seem to take place at any dosage that may be relevant in clinical practice (Buttgereit 2002b). Non-genomic effects are rapid, within seconds or minutes, and are mediated via cell surface GR. The non-genomic actions are seen at higher glucocorticoid concentrations (Lipworth et al. 2000). The relative potencies for different glucocorticoids to act by genomic mechanisms do not parallel those for non-genomic mechanisms (Lipworth et al. 2000; Schmid et al. 2000).

The hypothalamic-pituitary-adrenal (HPA) axis is an important part of the neuroendocrine immune mechanisms acting to maintain immune homeostasis (Bijlsma et al. 2002). The hypothalamic corticotropin-releasing hormone (CRH) induces the secretion of the adrenocorticotropic hormone (ACTH) from the pituitary gland, and this hormone stimulates the synthesis of cortisol from the adrenal cortex.

CRH, ACTH and cortisol secretions have circadian rhythms, which are thought to correspond to the normal sleep-wake cycle (reviewed by Tsigos and Chrousos 1994). Peak levels of plasma cortisol are found at about 8:00 a.m., and the nadir is found at about 2:00 a.m. Superimposed on the circadian rhythm of these hormones are additional pulses in response to exercise, food or stress. Furthermore, pro-inflammatory cytokines, particularly IL-1 and IL-6, stimulate the secretion of CRH, ACTH and cortisol (Chrousos 1995; Mastorakos et al. 1995). In RA, the elevations of ACTH and cortisol seem to be inappropriately low in relation to the degree of inflammation (Chikanza et al. 1992; Straub et al. 2002a). The ACTH/cortisol ratio is increased in RA, suggesting an impaired adrenal response to ACTH (Hall et al. 1994; Gudbjörnsson et al. 1996). An
altered stress response of the HPA axis and the sympathetic nervous system in RA have been suggested (Straub et al. 2002b).

It has recently been observed, that the expression of CRH and the CRH receptor is up-regulated in inflamed synovial tissue. CRH receptor mediated signalling seems to play a role in the vascular and pathological changes associated with joint inflammation (Bijlsma et al. 2002; Webster et al. 2002).

In workshops published by official health authorities, considerable doubts about the use of glucocorticoids in RA emerge (Swedish Medical Products Agency 1998; Norwegian Medicines Agency 2001), but in clinical practice the use of glucocorticoids has been widespread and may be increasing (Pincus et al. 1992; Conn 2001). They are used in combination with DMARDs or sometimes as monotherapy.

Glucocorticoids reduce levels of pro-inflammatory cytokines and suppress disease activity (Amano et al. 1993; Arvidson et al. 1994; Saag et al. 1996; Arvidson et al. 1997; Steer et al. 1997; Steer et al. 1998). Disease-modifying effects of low-dose (5-7.5 mg daily) prednisolone was documented by Kirwan et al., 1995, and by Rau et al., 2000. The clinical benefit of prednisolone 10 mg/d and the inhibition of progression of radiological joint damage were observed in a recent study by van Everdingen et al., 2002.

In a review by Boers 1999, the following conclusions were made on the effects of glucocorticoid therapy in RA: the symptomatic effect of glucocorticoids may be as large or larger than of any DMARD, including new biological agents. There is a beneficial effect on joint damage progression already at low doses, and the effects may continue to be apparent well after treatment is stopped.
However, arguments against the use of glucocorticoids in RA have also been presented (reviewed by Morrison and Capell 1999; and Moreland and O’Dell 2002; Saag 2001).

The side effects of glucocorticoids such as weight gain and skin atrophy are well known, but probably of minor importance with lower doses. The most feared side effect of glucocorticoids is bone loss (Laan et al. 1993; Khosla et al. 1994; Saag et al. 1994; Hougardy et al. 2000; Gudbjörnsson et al. 2002; Paget 2002).

The question of bone loss in RA is complex. Bone loss in RA is related to disease activity (Gough et al. 1994; Hansen et al. 1996), and pro-inflammatory cytokines cause bone resorption. In addition, the reduced physical mobility of RA patients is a contributing factor to bone loss. Many patients with RA are women in older ages when postmenopausal bone loss is common. As glucocorticoids reduce disease activity and inflammation, thereby increasing mobility, the effects on the skeleton may be beneficial in active RA, despite the negative skeletal effects of glucocorticoids in non-inflammatory conditions. It is a matter of the dose of glucocorticoids used in RA, which is much discussed.

Some studies show that long-term treatment with prednisolone at a dose of 5-15 mg/d is associated with adverse events, such as fractures (Saag et al. 1994), and reduced BMD of the lumbar spine (Laan et al. 1993; Buckley et al. 1995; Hansen et al. 1999; van Everdingen et al. 2002), while bone loss was not obvious in a systematic review of glucocorticoid effects on bone density in RA in prospective studies (Verhoeven and Boers 1997). Thus, the data from different studies do not permit any firm conclusion on a harmless dose of glucocorticoids in RA. In clinical practice, prednisolone 5 mg daily for women and 7.5 mg daily for men is supposed to be rather safe.
There is a prominent circadian variation in symptoms in most RA patients, with pronounced joint stiffness and pain late at night and in the early morning hours, these symptoms often subsiding spontaneously later in the day. The circadian rhythm of symptoms in RA has been confirmed by objective measurements of joint stiffness and grip strength (Kowanko et al. 1981; Harkness et al. 1982). The mechanism of this circadian rhythm is unknown, but could be related to a nocturnal flare up in the inflammatory process. This is probably related to the circadian variation of the levels of endogenous cortisol, with lowest values at about 2:00 a.m., the inflammatory process being poorly suppressed around that time. When maximum serum cortisol levels occur, at about 8:00 a.m., the inflammatory process is again suppressed, with decreased joint symptoms afterwards. Mechanical reasons (fluid retention in the tissues) may also be involved in the morning stiffness.

**Physical disability**

According to the International Classification of Impairments, Disabilities and Handicaps (World Health Organisation 1980), impairment in RA is defined as the losses of mental, anatomical or physiological structure or function directly attributable to the disease. Impairment can result in disability, which refers to limitations in physical or mental function in carrying out normal duties ("functional limitation"). Handicap means the inability to do things that are important for the given person.

The distinction between physical disability and handicap is not always straightforward. A professional violin player with a minor damage in a finger may not have a physical disability, i.e. the activities of daily life (ADL) functions are normal, but the player has a handicap, because she or he cannot play the violin properly. On the other hand, a philosopher may suffer from severe physical disability, i.e. reduced ability
to carry out normal duties, but still there is no handicap because the philosopher can do abstract thinking as usual. Furthermore, the methods that assess impairment and physical disability are overlapping, as methods for impairment sometimes include moments where impairment is tested and other moments where physical disability is tested.

Impairment in RA can be assessed by observer-based indices, e.g. the Keitel function index and the Signals of Functional Impairment index (SOFI) (Eberhardt et al. 1988; Kalla et al. 1995).

The Keitel index is a measure of impairment in RA, and scores observed limitations of joint movements. The test assesses range of motion in the hands, wrists, shoulders, and lower limbs containing 24 items. The score ranges from 4 to 100 (normal to severely disabled). The Keitel index has been shown to correlate with the Ritchie articular index, with acute phase markers and with a disability questionnaire (Kalla et al. 1988), and to improve in patients treated with disease modifying and remission inducing drugs (DMARDs) (Bombardier et al. 1986; Kalla et al. 1995). Impairment according to the Keitel index has been reported to correlate with the patient’s self-reported functional ability (Hakala et al. 1994).

SOFI is based on the same idea as the Keitel test. It has been designed to detect early functional impairment in particular joints, and includes more elaborate tests on function. Three parts are included, testing the functions of the hands, upper limbs and lower limbs. SOFI has been shown to correlate with the range of motion, with the Ritchie index, with the grip strength and with the Health Assessment Questionnaire (HAQ) disability score (Eberhardt et al. 1988).

Both the Keitel test and SOFI are too comprehensive and too time consuming to be suitable for clinical practice, but may be used in research or in special situations.
Simple quantitative measures of function, such as grip strength (Lee et al. 1973), walking time (DeCeulaer and Dick 1981) and the button test (Clawson et al. 1971) are easier to use in daily practice, and have been shown to provide good intraobserver and interobserver reliability (Pincus et al. 1991), and to predict long-term morbidity as well as mortality in RA (Pincus et al. 1987; Pincus et al. 1992).

Despite the value of objective or semi-objective function tests, some problems remain. It is difficult to reach consensus on which function tests to use, and the long time required to perform the tests, and their dependence on the observer. As these aspects of function tests were almost impossible to overcome, a new approach to assess disability in RA was introduced by Fries et al., 1980, the Stanford Health Assessment Questionnaire (HAQ) (see Appendix). They developed a structure of patient outcome representing five separate dimensions: Death, Disability, Discomfort, Drug (therapeutic) toxicity and Dollar cost. The quantification of these outcome dimensions was performed at interview or by patient questionnaire, and similar results were obtained by both methods. The questionnaires became soon popular, because they are independent of an observer, and they are quick and inexpensive.

The Full HAQ assesses all the abovementioned five dimensions of health outcome. The Short HAQ questionnaire that only assesses disability (HAQ Disability Index, HAQ-DI) is often used by itself, and is here referred to as HAQ (reviewed by Bruce and Fries 2003).

HAQ is by large the most widely used patient questionnaire to assess functional disability, and is today used in a slightly different version compared to the original HAQ by Fries at al. HAQ is a self-administered questionnaire, with one or more specific questions on each of eight dimensions of activities of daily life (dressing and grooming, arising, eating, walking, hygiene, reach, grip and outdoor activities). Each question is
scored from 0 to 3, according to the following scale: Functions that can be performed without difficulty = 0; any function performed with some difficulty = 1; functions performed with great difficulty = 2; and inability to perform a function = 3. The item with the highest score within each dimension is the score for that dimension. The scores for the eight different dimensions are added and divided by eight to get the mean value, i.e. the HAQ score.

Shortly after the introduction of HAQ, a modified version appeared, the modified HAQ (MHAQ) (Pincus et al. 1983; see Appendix). The scoring of MHAQ is the same as for HAQ, but the number of items has been reduced to eight.

Further modifications of the original HAQ have been introduced in the last years, such as RA-HAQ, DHAQ, CLINHAQ and multi-dimensional HAQ (Wolfe 1989; Pincus et al. 1999; Wolfe 2001), but these later modifications are seldom used.

HAQ and MHAQ are feasible and thus they are suitable for large-scale studies where physical examinations of joints or functions are impractical (Smedstad et al. 1997; Kvien et al. 1997; Scott and Strand 2002). HAQ and MHAQ have been shown to correlate with short-term (up to one year) variations in disease activity and outcome (Bombardier et al. 1986; Fries et al. 1986; Eberhardt et al. 1988; Jansen et al. 2000; Molenaar et al. 2002), with pain (Sokka et al. 2000; Molenaar et al. 2002), and with depression (Smedstad et al. 1997), and to predict disability and severe long-term (minimum 3.1 years) morbidity and mortality in RA (Pincus et al. 1984; Wolfe et al. 1988; Pincus et al. 1994; Callahan et al. 1997; Yelin et al. 2002; Lindqvist et al. 2002).

In a recent analysis of 1817 RA patients from leflunomide trials, it was suggested that HAQ is a relatively good indicator of disease activity in groups of patients given DMARDs, and that changes in HAQ scores mainly reflect changes in pain and other subjective measures of disease activity (Scott and Strand 2002). HAQ and MHAQ have
also been suggested to improve efficiency and to document care in the clinic (Wolfe and Pincus 2000).

HAQ and structural joint damage have been shown to correlate in some studies, especially in patients with longer disease duration (Pincus et al. 1989; Hakala et al. 1993; Möttönen et al. 1998; Drossaers-Bakker et al. 1999; Drossakaers-Bakker et al. 2000; Molenaar et al. 2002). In other studies, the correlation between the radiographic score and the HAQ score was lower or absent (Fex et al. 1996; Sokka et al. 2000; Combe et al. 2001).

Scott et al., 2000b, reviewed the link between structural joint damage and functional disability in RA according to questionnaires. The link between damage and disability was observed in late disease (>8 years disease duration), but not in early and intermediate disease (<5 years disease duration). About 25% of the disability in established RA was estimated to be due to structural joint damage.

In early RA, there is no correlation between the HAQ score and Larsen score (Eberhardt et al. 1990), while serial measurements of HAQ in early RA show variation with fluctuations in disease activity (Eberhardt et al. 1988). In several follow-up studies over five years or more, no significant deterioration in the HAQ score was observed, despite a marked radiographic progression (Gardiner et al. 1993; Eberhardt et al. 1995; Fex et al. 1996; Kroot et al. 2000; Uhlig et al. 2000). This may indicate that self-reported questionnaires are not optimal to document the true rate of progression in physical disability in RA.

The routine use of HAQ or other questionnaires in clinical practice to document functional disability in individual patients has been questioned (Wiles et al. 1999; Greenwood et al. 2001). Psychological variables have been shown to be important determinants of disability, and self-reported functioning significantly correlated with
mental and general health perceptions, and psychological well being was a significant predictor of good functioning for all subjective scales (McFarlane and Brooks 1988; Spiegel et al. 1988). It was recently shown that in RA patients negative illness cognitions related to neuroticism may act as a common (and confounding) factor behind pain and questionnaire scores (Persson and Sahlberg 2002).

In an analysis of HAQ and MHAQ (and some further modifications of HAQ) in 2491 RA patients following leflunomide initiation, it was concluded that HAQ is better (more efficient) than MHAQ (Wolfe 2001). The shortened questionnaire shows less sensitivity to change. The room for improvement of functional status questionnaires was further discussed by Wolfe in a recent review (Wolfe 2002).

In addition to HAQ and MHAQ, there are several other self-reported instruments to assess the physical function in RA. The Arthritis Impact Measurement Scales (AIMS), and its modifications, AIMS 2, or short-form, AIMS2-SF, the Nottingham Health Profile (NHP), and the McMaster Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR), have all been shown to be effective to monitor patient status in clinical trials (Houssien et al. 1997; Haavardsholm et al. 2000; Verhoeven et al. 2000). However, they are rather comprehensive and time consuming. The simpler HAQ seems too be the instrument of choice for standard clinical trials and clinical care.
AIMS OF THE INVESTIGATION

The aims of this investigation were:

- To study the circadian rhythm of disease activity (paper I).
- To study the integrin and phagocytosis receptor expression on peripheral blood monocytes in RA, and the effects of endogenous and exogenous glucocorticoids on the expression of these receptors (paper II).
- To investigate the correlations between several acute phase markers in RA, and the correlations of these markers with some clinical indices of disease activity (paper III).
- To study fibrinogen as a laboratory marker for the slow component of the acute-phase response in RA and its correlation with ADL function (paper IV).
- To test the hypothesis that the timing of low dose glucocorticoid administration might be critical in determining its effect on the diurnal rheumatoid inflammatory process (paper V).
- To investigate the influence of disease activity on physical disability in RA, and to compare subjective and objective methods to assess physical disability with each other and with structural joint damage (paper VI).
MATERIALS AND METHODS

Laboratory methods

Cytokine analysis: The serum samples were collected in glass tubes without anticoagulant and stored for one hour at room temperature, centrifuged at 0°C, and aliquoted in plastic tubes before being stored at −70°C for later analysis of IL-6 and TNFα. In paper I, the levels of free IL-6 and TNFα in serum were measured using commercial ELISA-type kits (MEDGENIX Diagnostics, Brussels, Belgium). In paper III and V, the IL-6 assay was performed with Quantikine IL-6 immunoassay kit (R&D Systems, Minneapolis, MN, USA).

Preparation of leucocytes: Leucocytes were labelled with monoclonal antibodies (MoAbs) to cell surface receptors using a method described earlier (Hamblin et al. 1992). Venous blood (2 ml) treated with heparin and processed within 2 h was diluted with 10 ml phosphate-buffered saline (PBS)-citrate buffer with 2% new-born foetal calf serum (NBS) and centrifuged for 5 min at 160G. The supernatant was removed and the remaining 2 ml was incubated for 4 min at 37°C with an equal volume of 0.4% paraformaldehyde to fixate the blood cells. The blood sample was then incubated with 0.83% NH4Cl in 0.01M Tris-HCl buffer pH 7.4 for 15 min at 37°C to haemolyse the erythrocytes. The cells were then centrifuged for 5 min at 160G and the supernatant and the erythrocytes were removed, and the remaining leucocytes were then washed twice with PBS-citrate buffer. The cells were diluted with 0.5 ml PBS-citrate-0.2% NBS and counted. The concentration of the granulocytes was adjusted to 1.7-2.5 x 10^6/ml. The cells were incubated on ice with the following fluorescing isothiocyanate (FITC)-conjugated antibodies for 30 min: control antibodies for IgG1, IgG2, and IgG2b (Dako, Glostrup, Denmark) and CD11a, CD14, CD16, CD18, CD29 (Dako); CD11b, CD35,
Flow cytometric analysis: Monocytes were gated on the basis of their forward scatter and side scatter pattern and checked by staining with anti-CD14. The control antibodies were used to set the background levels. The relative number of positive monocytes and the mean fluorescence intensity (MFI) for each antibody were measured.

Analysis of acute phase proteins: In paper I, III and V, CRP was analysed in serum on a Hitachi 717 (Boehringer Mannheim, Mannheim, Germany). In paper IV and VI, CRP was analysed by turbimetry (CP2572, Randos Laboratories, Crumlin, UK).

SAA was analysed by an ELISA (BioSource International, Inc., Camarillo, CA).

In paper III, fibrinogen and haptoglobin were analysed in EDTA-plasma by rate nephelometry on a Beckman Array protein system (Beckman Instruments, Brea, CA) according to the recommendations by the manufacturer except that goat anti-human fibrinogen (Atlantic Antibodies, Stillwater, MN) was used for the fibrinogen analysis. The assay was calibrated against a human plasma standard (Behring, Marburg, Germany).

In paper IV, plasma fibrinogen was measured by clot detection (Fibrinosticon, Organon Teknika, Boxtel, The Netherlands).

Clinical methods

Joint indices: The Ritchie index (Ritchie et al. 1968) is based on joint tenderness in 53 joints when the observer applies a moderate pressure to the joint. The tenderness is
graded 0 - 3, where 0 = no tenderness, 1 = slight tenderness, 2 = moderate tenderness and 3 = maximal tenderness. The following joints are included: the temporomandibular joints, the sterno-clavicular joints, the acromio-clavicular joints, the shoulder joints, the elbows, the wrists, the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints, the hips, the knees, the ankles, the subtalar joints, midfoot joints and the metatarsophalangeal (MTP) joints. The range of Ritchie index is 0 – 78.

The Thompson index (a modified Lansbury index) (Thompson et al. 1987), combines tenderness and swelling of joints weighting different joints according to the size of the joints. A score (= 1) is only given if there are both joint swelling and pain, otherwise the score is 0. The following joints are included: the elbows, the wrists, the MCP and PIP joints, the knees and the ankles, and the MTP joints. The range of Thompson index is 0 - 534.

The number of swollen joints (NSJ) was counted in paper III, as it is probably a more reliable clinical sign of joint inflammation than the number of tender joints. The scoring was either 0 = no swelling or 1 = swelling of the joint. The following joints were included: the elbows, the wrists, the MCP and PIP joints, the knees, and the ankles. The range of NSJ is 0 - 28.

The duration of early morning stiffness was recorded in minutes.

Joint pain was measured on a visual analogue scale, either in cm (0 = no pain to 10 = most severe pain) or in mm (0 = no pain to 100 = most severe pain) (Scott et al. 1970).

A score for the global effect of treatment, i.e. a patient self assessment score on a five grade scale concerning the overall response and satisfaction throughout the study protocol, was used in paper V. The scoring was: 0 = no effect, 1 = poor effect, 2 = fair effect, 4 = good effect and 5 = excellent effect.
The Stoke index (Davis et al. 1990) is a compound disease activity index combining laboratory and clinical variables for disease activity. Levels of CRP and ESR, duration of morning stiffness, a PIP joint synovitis score and the Ritchie articular index are included.

HAQ was introduced by Fries et al. in 1980 (see Appendix) and it is currently used in a slightly different version. The patient completes a questionnaire including 20 items on ADL. These questions cover eight dimensions of ADL (dressing and grooming, arising, eating, walking, hygiene, reach, grip and outdoor activities). The functions that can be performed without difficulty are graded as 0. The functions that are performed with some difficulty are graded 1, and functions performed with great difficulty as 2. Inability to perform a function is graded as 3. The item with the highest score within each dimension is the score for that dimension. The scores for the eight different dimensions are added and divided by eight to get the mean value, i.e. the HAQ score.

MHAQ was introduced by Pincus et al. in 1983 (see Appendix). It is a short form of HAQ including only eight items of the 20 items used in HAQ, and based on the same scoring system as HAQ. The sum of the scores for the eight items is divided by eight to get the MHAQ score. In paper VI, a Norwegian version of MHAQ was used (see Appendix).

Arvidson and Larsen invented the objective function tests used in paper VI as an easy and quick way to assess objective function.

Walk test: The walking ability was judged on a scale from 0 to 3, where 0 = normal; 1 = halting; 2 = use of walking stick; 3 = use of wheel frame/wheel chair. Half points were used if the performance was in between two points.

Chair test: The ability to get up from a chair was judged on a scale from 0 to 3, where 0 = normal, i.e. without support of arms; 1 = with the support of one arm; 2 = with the
support of two arms; 3 = unable to get up. Half points were used if the performance was in between two points.

Upper extremity mobility test: The patient tried to place the right hand behind the neck and the left hand behind the back and then tried to move the fingertips as near as possible. The same manoeuvre was performed with opposite hands. The distance between fingertips on both sides was recorded in cm and summed up. Thus, higher values mean worse mobility (see cover illustration).

Grip strength: The patient inflated a blood pressure cuff to 20 mm Hg, and was then asked to make three subsequent squeezes as hard as possible. The result after the third squeeze minus 20 mm Hg was reported.

Rheumatoid Arthritis Function score (RAF): This is the mean value of the four function tests scored on a 0-3-grade scale. The walk test and the chair test are already scored from 0 to 3. The upper mobility test turns into a 0 to 3 scale if the recorded value (i.e., the sum on left and right side in cm) is divided by 60. This is because the maximum value for the vast majority of the patients was 180 cm, and this is regarded as 3. Using the same principle, the grip strength is converted into a 0 to 3 scale by the formula: 120 minus recorded value (i.e., max value minus 20) divided by 40. It can also be written: 140 minus maximum value divided by 40, which is easier to remember. It may sometimes be an advantage to report the RAF scores for upper and lower extremities separately to get a more detailed picture of the functional limitation.

In paper VI, Larsen assessed the radiological joint damage according to his modified method (Larsen 1995). The following joints are scored on both sides: PIP joints 2-5, MCP joints 2-5, MTP joints 2-5, and four joint areas in the wrist. Each joint is graded using a 0 to 5-grade scale, where:

Grade 0: Intact bony outlines and normal joint space.
Grade 1: Erosions less than 1 mm in diameter or joint space narrowing.

Grade 2: One or several small erosions (diameter more than 1 mm).

Grade 3: Marked erosions.

Grade 4: Severe erosions: there is usually no joint space left; the original bony outlines are partly preserved.

Grade 5: Mutilating changes: the original bony outlines have been destroyed.

Larsen score is the mean of the sum of the grades in these 32 joints (or less if any joint is operated).
PRESENT INVESTIGATIONS

Participating subjects, study designs and results

Paper I

Circadian rhythm of serum interleukin-6 in rheumatoid arthritis

The presence of pro-inflammatory cytokines such as IL-1, IL-6 and TNFα in the synovial fluid and serum of RA patients, suggest that they play a role in the disease process. These cytokines have been shown to be arthritogenic in experimental animals, and IL-1 and TNFα blockade reduces inflammation and joint destruction.

It has been difficult to find association of in vitro effects of pro-inflammatory cytokines in arthritis with clinical and laboratory observations. In some studies, a correlation was found between synovial or serum levels of IL-6 and various laboratory and clinical disease activity measures (Houssiau et al. 1988; Swaak et al. 1988; Waage et al. 1989; De Benedetti et al. 1992; Manicourt et al. 1993; Cohick et al. 1994), while these correlations were poor or absent in other studies (De Benedetti et al. 1991; Dasgupta et al. 1992; Holt et al. 1992; Madhok et al. 1993). The prominent circadian variation of joint symptoms in most RA patients could possibly be of importance in this matter.

Serum levels of IL-6 and TNFα were therefore studied in 13 RA patients and 10 healthy controls, with 3 hour intervals from 07:30 a.m. to 22:30 p.m. Additionally, six patients with arthritides other than RA (unspecified polyarthritis, psoriasis arthropathy and juvenile chronic arthritis), and 25 patients with various inflammatory connective tissue diseases (systemic lupus erythematoses, SLE; systemic sclerosis, SSc; primary Sjögren’s syndrome, primary SS; and mixed connective tissue disease, MCTD), were included.
IL-6 and TNFα could not be detected in serum from healthy controls, whereas substantially increased serum IL-6 levels were observed in RA patients. Furthermore, there was a marked circadian variation of IL-6, with peak levels early in the morning and low levels in the afternoon and evening. Levels of TNFα were low in patients with RA and high in patients with other inflammatory connective tissue diseases, but without circadian rhythm. In the latter patient group, serum IL-6 levels were low and stable. After one week of treatment with prednisolone 15-20 mg daily in four of the patients with RA, the serum levels of IL-6 decreased significantly, but the circadian rhythm remained.

The diurnal variation of IL-6 in RA may explain the conflicting results previously reported on the correlation between systemic IL-6 levels and disease activity in RA. If serum IL-6 levels are not measured at the same time of the day, the results may be conflicting. The circadian rhythm of IL-6 can explain the prominent circadian variation of joint symptoms in RA patients, with pronounced joint stiffness and joint pain late at night and in the early morning hours, improving later in the day.

**Paper II**

**Monocyte activation in rheumatoid arthritis: increased integrin, Fcγ and complement receptor expression, and the effect of glucocorticoids.**

The background for paper II is the observation that in animal models of inflammation, treatment with metyrapone (an inhibitor of the cortisol synthesis), or a glucocorticoid antagonist or adrenalectomy, caused exacerbation of the inflammatory response, with increased concentrations of leucocytes, including enhanced adhesion and migration (Flower et al. 1986; Laue et al. 1988; Farsky et al. 1995). In RA patients, treatment with metyrapone resulted in decreased serum cortisol concentrations and significantly
increased joint pain and tenderness (Saldanha et al. 1986). These observations suggest that physiological amounts of cortisol modulate the inflammatory response.

It has been shown that treatment with low doses of prednisolone in RA normalises the enhanced expression of some adhesion molecules in neutrophils and eosinophils, while endogenous levels of cortisol had minor impact on the expression of adhesion and phagocytosis receptors on granulocytes (Torsteinsdottir et al. 1999a). In another study, serum levels of the leucocyte-derived granular proteins lysozyme and MPO, but not lactoferrin and HNL, were shown to be elevated in RA, and treatment with prednisolone decreased serum concentrations of lysozyme and MPO. Treatment with metyrapone did not influence the levels of these granular proteins (Torsteinsdottir et al. 1999b).

In paper II, the integrin and phagocytoses receptor expression on peripheral blood monocytes was investigated in twenty-two patients with RA at baseline, and in ten patients after treatment with low-dose prednisolone for 4-6 weeks. In eight of the RA patients, the effect on monocyte activation was studied after two days of treatment with metyrapone, a substance that reduces the synthesis of endogenous cortisol in the adrenal cortex by blocking the enzyme 11β-hydroxylase.

The results of paper II are that the expression of the β2 integrins and CD35, and the phagocytosis receptors CD32 and CD64 were elevated in patients with RA not treated with prednisolone compared to healthy controls, while β1 integrins were not. After treatment with low-dose prednisolone, the expression of most β2 integrins and complement receptors on monocytes were normalised, and the β1 integrins CD49d and CD49f also diminished significantly. After two days of treatment with metyrapone, which significantly lowered the serum cortisol levels (from 438 nmol/l to 162 nmol/l),
the expression of the complement receptor CD 35 and the β1 integrin CD49f was elevated.

The priming of the blood monocytes in RA may be one of the mechanisms behind the recruitment of mononuclear cells to the synovium. One of the many anti-inflammatory effects of glucocorticoids in RA may be the suppression of the adhesion and phagocytosis receptors on monocytes, thereby reducing the mononuclear cell infiltration of the synovium.

**Paper III**

*Concordant message of different inflammatory markers in patients with rheumatoid arthritis*

The pro-inflammatory cytokines IL-1, IL-6, and TNFα are central to the development of the acute phase response, and IL-6 in particular stimulates the hepatic synthesis of the acute phase proteins (Andus et al. 1988; Castell 1989; Heinrich et al. 1990; Suffredini et al. 1999).

In paper III, the correlations between the acute phase markes CRP, ESR, SAA, haptoglobin, fibrinogen and IL-6 were analysed in 26 patients with RA. The correlation of each of these acute phase markers with different clinical measures of disease activity was investigated (morning stiffness, swollen joint count, joint pain, Thompson and Ritchie articular indices and the Stoke compound disease activity index). In addition, the correlations between each of these clinical signs of disease activity were analysed.

Correlations were strong between all acute phase markers, and especially between CRP and SAA and between ESR and fibrinogen. The acute phase markers correlated only to the Stoke index among the clinical indices of disease activity. The two joint indices used correlated to each other and to the number of swollen joints, and
Thompson joint index correlated to the Stoke index. The duration of morning stiffness and joint pain at rest did not correlate to any of the other clinical signs of disease activity.

The strong correlations between the acute phase markers found in this study suggest that one rapid and one slow acute phase marker may be enough to assess disease activity in RA. The lack of correlation between the acute phase markers and clinical indices of disease activity in this study, and the rather weak correlations between different clinical signs of disease activity, may put in doubt the value of clinical indices in the assessment of disease activity in RA.

**Paper IV**

**Disease activity in rheumatoid arthritis: fibrinogen is superior to the erythrocyte sedimentation rate**

The relationships between CRP, ESR and fibrinogen in RA were studied more closely in paper IV, and each of these acute phase markers were correlated with a patient questionnaire score for activities of daily living (MHAQ), and with the neutrophil and platelet counts, and with haemoglobin levels.

The results from the previous paper III were confirmed, regarding highly significant mutual correlations between CRP, ESR and fibrinogen. The ADL score showed a highly significant correlation with CRP and fibrinogen, but not with ESR, and fibrinogen and CRP showed stronger correlations with the neutrophil count than ESR. These are important observation from a clinical point of view.

We suggest that ESR could be replaced by fibrinogen in the assessment of RA, in order to more accurately assess the slow component of the acute phase response, and to
have a variable that shows better correlation with disability. However, CRP remains a valuable marker for acute events.

**Paper V**

**The timing of glucocorticoid administration in rheumatoid arthritis**

The time of day of prednisolone administration in RA has been discussed for many years (Andrate et al. 1964; Kowanko et al. 1982). Most often glucocorticoids are given in the morning to mimic the normal circadian rhythm of endogenous cortisol secretion, which peaks in the morning. The observation of a circadian rhythm of serum IL-6 levels in RA, with peak values early in the morning and normal levels in the afternoon and evening (paper I), made us doubt the logic in the conventional way of administering glucocorticoids. In paper V, the hypothesis to be tested was that the timing of glucocorticoid administration might be important to obtain optimal anti-inflammatory effects in RA.

After oral administration of prednisolone, the peak plasma concentrations are attained after 1-3 hours, and maximum anti-inflammatory effects occur somewhat later (Meikle et al. 1977; Pickup 1978). In order to try to suppress the enhanced IL-6 synthesis early in the morning, prednisolone 5-7.5 mg daily was administered during five days to two groups of RA patients (n=13 in each group), either at 2:00 a.m. or at 7:30 a.m. Clinical signs of disease activity (morning stiffness, joint pain and a joint index), and acute phase proteins (levels of IL-6, CRP and SAA) were analysed on day 1 and on day 5 (after four doses of prednisolone).

The results showed that clinical disease activity and CRP and serum IL-6 levels measured after 5 days were improved in both groups, but there was a significant advantage in favour of the 2:00 a.m. administration group. In fact, it was necessary to
treat the patients in the 7:30 a.m. group with prednisolone 15-20 mg daily to obtain a comparable reduction in IL-6 levels to the 2:00 a.m. group (paper I). The patients’ self-assessment concerning the global effect of treatment was scored “good-excellent” in the 2:00 a.m. group, and “poor-fair” in the 7:30 a.m. group.

The conclusion of this study is that low doses of prednisolone seem to suppress acute rheumatoid arthritis symptoms and IL-6 levels more effectively if the administration precedes the morning peak of IL-6 synthesis with 5.5 hours.

**Paper VI**

**Simple function tests, but not the modified HAQ, correlate with radiological joint damage in rheumatoid arthritis**

Several methods have been used to assess disability in RA, but no one seems to be entirely valid. In paper VI, an effort was made to compare different methods to assess physical disability with each other and with radiological joint damage.

Physical disability in RA is associated with disease activity, more so in early arthritis than in chronic arthritis, where structural changes in tendons, ligaments, joint capsules, cartilage and bone play a relatively greater role (Sherrer et al. 1986; Zijlstra et al. 2000; Johnson et al. 2002). The main problem with questionnaires is their subjective nature, implying that factors others than the disease itself may influence the results (McFarlane and Brooks 1988; Spiegel et al. 1988; Persson and Sahlberg 2002). In some patients, questionnaires do not therefore reflect the real physical disability.

In paper VI, observed physical disability, using four objective function tests, was correlated with a patient questionnaire score for activities of daily life (MHAQ). Each of the four function tests and the MHAQ score were compared with the Larsen score for radiological joint damage (Larsen 1995). Pain score (VAS) and laboratory variables
for inflammation were included in the analysis. To the author’s knowledge, this is the first time a set of objective function tests has been directly compared with MHAQ and radiological joint damage in RA.

In this study, objective function tests, MHAQ, pain and CRP showed highly significant mutual correlations. However, MHAQ did not correlate with Larsen score, while most function tests did. The superiority of function tests was even more pronounced after four years, but in patients with disease duration of four years or less, neither MHAQ nor objective function tests correlated with Larsen score. It was also observed that joint pain did not correlate with neither CRP, nor ESR.

The results in paper VI suggest that the MHAQ score are mainly associated with changes in the disease activity and pain, while the function tests studied here additionally seem to be associated with structural joint damage.
DISCUSSION

The concept of disease activity is essential in rheumatology, guiding the treatment and influencing the outcome in RA. However, the essence of the disease activity is hitherto unknown, and one should be modest enough to remember the famous concluding words in Tractatus of Ludwig Wittgenstein: "Worüber man nich reden kann, darüber muss man schweigen."

As the disease activity itself is an unmeasurable process, several surrogate markers are used, such as laboratory markers, clinical indices, function tests, questionnaires, radiological changes and perhaps measurement of BMD. Sometimes compound indices are used, where some of the aforementioned measurements of disease activity are summed up to an index (score), e.g. the Stoke index and DAS.

Disease activity variables can be used both in short- and long-term evaluation of RA. In paper I, low serum TNFα levels were observed in RA and levels remained stable during the day. The finding of low and stable TNFα levels is partly in agreement with a later study of 73 patients with active RA, where about half of the patients had detectable circulating TNFα, but these levels were low (Charles et al. 1999), but in disagreement with an earlier study, where elevated serum TNFα levels were observed (Altomonte et al. 1992). In a study by Tetta et al., 1990, high concentrations of TNF were found only in serum samples from patients with severe RA. The results are in disagreement with a recent study suggesting a diurnal variation in serum TNFα levels in RA patients, with lowest levels at about 10:00 a.m. and highest levels at about 6:00 a.m. (Zoli et al. 2002).

Concerning short-term changes (as defined by enhanced IL-6 synthesis), disease activity was shown to be a most dynamic process, varying substantially during one day
in a circadian pattern, with peak serum IL-6 levels early in the morning and low levels in the afternoon and evening. This is the first time the circadian rhythm of serum IL-6 has been reported in RA.

The circadian variation of serum IL-6 in RA has been confirmed in a later study (Crofford et al. 1997). A nighttime diurnal peaking of serum IL-6 levels also occurs in normal subjects (Sothern et al. 1995), but earlier in the night and is much lower. The circulating IL-6 may stimulate ACTH and cortisol secretions in RA, or cortisol may inhibit the production of IL-6 (Papanicoloau et al. 1996; Crofford et al. 1997). The circadian rhythm of the serum IL-6 concentrations may be associated with the circadian variation of symptoms in RA.

The circadian variation in IL-6 levels (and possibly other cytokines) in RA is important from a practical point of view. If analysis of pro-inflammatory cytokines are used to monitor disease activity, or to assess effects of treatment in clinical trials, care must be taken always to collect blood samples at the same time of the day, preferably in the morning. The same rule is true for the assessment of clinical symptoms of disease activity, because of the possible association of serum IL-6 levels with clinical symptoms in RA.

The timing of prednisolone administration in RA has been controversial for many years. In a study by Andrade et al., 1964, morning and evening administration of 5 mg prednisolone was compared, and the results showed that 28 out of 49 patients preferred the evening dose, while only two patients preferred the morning dose. In a study by Kowanko et al., 1982, twelve patients with RA received low-dose prednisolone, mean 5.6 mg daily, at 8:00 a.m., 1:00 p.m. or 11:00 p.m. The results suggested that prednisolone was equally effective on subjective and objective assessments irrespective of the time of prednisolone administration.
Assuming that the early morning peak of serum IL-6 in RA mirrors its production, and is correlated with a flare in inflammatory activity, an effort was made to try to minimise the IL-6 influence on the rheumatoid inflammatory process by administrating 5-7.5 mg of prednisolone at 2:00 a.m. In comparison with patients who received the same dose of prednisolone at 7:30 a.m., there was a dramatic improvement in morning stiffness, pain and joint indices and decreased serum IL-6 concentrations over the study period. However, the results in the two groups could not be properly compared as they had significantly unequal intervals between their last dose of prednisolone and outcome assessments (5.5 hours and 24 hours, respectively). Furthermore, the clinical observer was not blinded with respect to treatment regimes and the 7:30 a.m. group was not awakened at 2:00 a.m., which may have affected the results.

In spite of the limitations of the study, the results indicate that the conventional way of prednisolone administration in the morning, which has been used for 50 years, may be questioned. The timing of glucocorticoid administration in RA seems to be critical for the control of the diurnal rheumatoid inflammatory process. The results of the study suggest that nocturnal administration of glucocorticoids should be preferred. As compliance with this regime may be doubtful at least in the long run, administration as late as possible in the evening, or as early as possible in the morning, could be used. We have good experiences with all three regimes in our RA patients.

In RA synovitis is a key characteristic, and the synovial membrane has a dominant role in the local inflammatory and destructive processes. The synovial membrane shows increased vascularity and thickening, with both in situ proliferation and reduced apoptosis of fibroblast-like cells (Qu et al. 1994; Firestein et al. 1995). There is further infiltration of primarily CD4+ T cells, but also of B lymphocytes, plasma cells, mast cells and macrophages, the latter cells being recruited from peripheral blood monocytes.
In addition, alterations of the adhesion molecule expression take place (Bevilacqua 1993; Cronstein and Weissmann 1993).

In accordance with previous studies (Gadd et al. 1992; Shinora et al. 1992; Highton et al. 1995) blood monocyte activation related to adhesion and phagocytosis was observed in RA (paper II). A significant correlation was found between the monocyte expression of the CD64 receptor and CRP, and platelet count, respectively, emphasising the importance of common laboratory parameters in assessing disease activity, as pro-inflammatory cytokines stimulate the production of CRP, and induces thrombocytosis (Castell et al. 1989; Papanicolaou et al. 1998). However, there are no reports on the effect of IL-1, IL-6 and TNFα on the CD64 expression.

After 4-6 weeks of treatment with glucocorticoids, the increased expression of β2 and Fcγ receptors was reduced, and a significant correlation was observed between the decrease in expression of CD11b and clinical improvement as described by the Thompson index. When endogenous cortisol levels were reduced for two days, the expression of CD35 and CD49f was increased.

Thus, the priming of blood monocytes in RA may contribute to the infiltration of monocytes and macrophages into the rheumatoid synovium. Glucocorticoids reduce the expression of adhesion and phagocytosis receptors on monocytes, thereby diminishing the monocyte and macrophage infiltration into the synovium. This may be one of the mechanisms explaining the beneficial effects of glucocorticoids in RA.

The most commonly used acute phase markers ESR and CRP are of great value to monitor disease activity in RA. There are several other acute phase proteins that may work just as well or better, and fibrinogen and SAA have been the most discussed candidates. In paper III and paper IV, the relationships between different acute phase
markers were studied, including their correlations with some clinical indices of disease activity and the MHAQ score.

The correlations between different acute phase markers were shown to be good, and the correlations were especially strong between ESR and fibrinogen, and between CRP and SAA. Fibrinogen and CRP correlated better than ESR with the MHAQ score and with the neutrophil count. However, in accordance with some other studies (Kirwan et al. 1995; Coste et al. 1997) the correlations between clinical indices of disease activity and the acute phase markers were weak. On the other hand, correlations between these two aspects of disease activity have been observed in other studies (Prevoo et al. 1993). Generally, there is an association between many acute phase markers and radiographic progression (Amos et al. 1977; Dawes et al. 1986; Larsen 1988; Möttönen 1988; van Leeuwen et al. 1993; Listing et al. 2000; Combe et al. 2001), but in some studies the association with ESR was weak or nil (Larsen 1988; Sjöblom et al. 1984). The association between clinical indices and radiographic progression may be weaker (Coste et al. 1997; Combe et al. 2001). In a 10-year follow-up study including 168 RA patients, active joint count from the first month did not predict outcome for remission, HAQ disability, extra-articular manifestations and joint replacement, respectively (Lindqvist et al. 2002).

The results of paper III suggest that some clinical indices of disease activity, and especially the duration of morning stiffness and joint pain at rest, may be of limited value in the assessment of disease activity in RA. A lack of correlation between joint pain and acute phase markers was not only observed in paper III, but also in paper VI. However, any firm conclusions in this matter cannot be made from the present studies, as they are cross-sectional and include a limited number of patients.
In early arthritis, the patient’s assessment of the disease activity and/or the number of swollen joints are the most important bedside measures of disease activity. In late disease, this assessment is more difficult, but probably consists of the patient’s and the doctor’s global assessments of disease activity.

The results of these studies (papers III and IV) suggest that fibrinogen has a considerable potential to challenge ESR as a marker of the slower part of the acute phase response. In a study by Sjöblom et al. 1984, a good correlation was found between radiological joint damage and fibrinogen, and CRP, but not with ESR. In a recent study on bone mineral density in RA, values were significantly decreased at the forearm level and correlated with fibrinogen, but not with ESR and CRP (Péres-Edo et al. 2002). A further advantage of fibrinogen and CRP, contrary to the ESR, is that they can be analysed centrally from stored plasma, which is important in clinical research and trials.

In the long-term perspective, especially in established disease, disease activity causes reduced physical function and progression of structural joint damage. In paper VI, two different methods to assess physical disability were compared with each other, namely the subjective MHAQ method and the objective method, using four simple function tests as described previously. Both methods were then correlated with structural joint damage, with pain and with laboratory disease activity markers.

An overall correlation was observed in RA patients between radiological joint damage and most of the simple function test used in the study, and this correlation was even stronger in patients with more than four-year disease duration. However, there was no correlation between structural joint damage and MHAQ, neither for the whole group of patients, nor for those with disease duration of more than four years. The simple function tests and MHAQ correlated well with each other, and both methods to assess
physical disability correlated with pain, CRP levels and ESR. Thus, the MHAQ score seems mainly to be associated with changes in the inflammatory activity, while the function tests used in this study seem to be associated both with changes in inflammatory activity and with structural joint damage.

To the author’s knowledge, this is the first time several function tests have been directly correlated with structural joint damage and MHAQ. There is an earlier report (Pincus et al.1989), where a significant correlation between the MHAQ score and physical measures of functional capacity was found, and in their study the MHAQ score also correlated with the radiographic score.
CONCLUSIONS

■ In RA, a circadian pattern of IL-6 synthesis is evident, with peak serum IL-6 levels in the morning and low levels in the afternoon and evening, a pattern which may correspond to the circadian variation of symptoms in this disease.

■ Clinical and laboratory assessments of disease activity in RA should be performed at the same time of the day in patients participating in research studies or clinical trials.

■ Nocturnal administration of prednisolone therapy in RA may be more beneficial in controlling acute arthritis symptoms than the traditional administration of prednisolone in the morning.

■ The duration of morning stiffness and joint pain at rest neither correlated with each other, nor with some other commonly used clinical disease activity measures, nor with any of several acute phase markers.

■ Some of the cellular mechanisms explaining the disease-modifying effects of prednisolone in RA may be the influence of this glucocorticoid on monocyte activity.

■ Compared to ESR, fibrinogen has a considerable potential for allowing more accurate assessment of the slower component of the acute-phase response, while CRP remains a valuable marker for acute events.

■ Objective function tests are preferable to MHAQ in the assessment of physical disability in RA. However, MHAQ may be a substitute in large-scale studies, where objective function tests or physical joint examinations are impractical.
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Kronisk ledgångsreumatism – reumatoid artrit (RA) – är en inflammatorisk bindvävssjukdom som påverkar kroppen allmänt med trötthet, smärta, och ibland viktnedgång, samt med försämrad fysisk funktion och psykisk påverkan. RA är således en systemisk (generaliserad) inflammatorisk sjukdom, men svullnad, stelhet och ömhet till följd av inflammation i ledhinnan och lednära strukturer, är framträdande symtom vid sjukdomen.

RA är relativt vanlig, 0,5-1% av befolkningen anses lida av den och detta gäller internationellt med få undantag. Möjligen har antalet nyinsjuknade minskat de senaste 20-30 åren, men detta är omdiskuterat. Orsaken till RA är för närvarande okänd, men man tror att immunsystemet reagerar på något främmande ämne som kroppen ej kan göra sig av med. Det leder till kronisk inflammation. Under senare år har man påvisat ökad aktivitet hos Immunsystemets celler, tex de vita blodkropparna såsom monocyter, makrofager, lymfocyter och neutrofila celler. Härvid producerar cellerna cytokiner som är små äggviteämnen vilka i vanliga fall upprätthåller kommunikationen mellan immunsystemets celler och även andra slags celler. Vissa av cytokinerna är proinflammatoriska, dvs de ökar inflammationen, genom att frisätta brosk- och bennedbrytnande enzymer, tex metalloproteinaser. Till gruppen proinflammatoriska cytokiner räknas bla interleukin (IL)-1, tumör nekros faktor (TNF)α, IL-6 och IL-8.

En inflammatorisk process finns ständigt närvarande i kroppens vävnader och är oftast av godo. Sårläkning är ett exempel på en positiv inflammationsprocess. Vid RA har inflammationsprocessen skenat iväg och blivit okontrollerad, både till kvantitet och utsträckning i tiden. Man känner också till att flera cytokiner, tex IL-4 och IL-10, har inflammationsdämpande egenskaper, och de kan därför komma att användas för behandling av RA.
Sjukdomsaktivitet vid RA är ett centrat begrepp för reumatologer, och har stor betydelse för patienter med sjukdomen, eftersom graden av sjukdomsaktivitet avgör sjukdomens svårighetsgrad och prognos. Sjukdomsaktiviteten inbegriper en mängd inflammatoriska och immunologiska mekanismer, men vad den innerst inne är vet man ej. Sjukdomsaktiviteten kan liknas vid filosofen Immanuel Kants välkända begrepp ”das Ding an sich” (tinget i sig), dvs tillvarons innersta om vilket vi intet vet, och vår sinnevärld är blott ett brokigt sken kring detta innersta.

Även om sjukdomsaktivitets innersta kärna således förblir okänd, finns det många surrogat för sjukdomsaktivitet som används för att bedöma graden av aktivitet. Det hör laboratorieprover som sänkan och C-reaktivt protein (CRP), antal svullna och ömma leder, morgonstelhetens längd, olika ledindex, objektiv och subjektiv skattning av vardaglig funktion, radiologiska förändringar, mätning av bentäthet, och sammansatta aktivitetsmått som Stoke index och ”disease activity score” (DAS).

I denna avhandling behandlas vissa sidor av sjukdomsaktiviteten vid RA, och hur den påverkas av kortison.

I arbetet påvisas förhöjda blodnivåer av det proinflammatoriska cytokinet IL-6 hos RA patienter, och detta cytokin visar sig därtill ha en uttalad dygnsrytm med högsta blodnivåer tidigt på morgonen, vilka sjunker till normala nivåer på eftermiddagen och kvällen. I motsats till IL-6 var blodnivåerna av TNFα låga och stabila. Vid andra bindvävssjukdomar som systemisk lupus erythematoses (SLE), systemisk skleros (SSc), blandad bindvävssjukdom (MCTD) och primärt Sjögrens syndrom (SS) var blodnivåerna av TNFα förhöjda utan dygnsvariation, medan nivåerna av IL-6 vara låga och stabila.

Kortison minskar de förhöjda nivåerna av proinflammatoriska cytokiner, och effekten är olika stor beroende på när man tar prednisolon under dygnet. I avhandlingen
jämfördes effekten av 5-7,5 mg prednisolon på symtom och blodnivåer av IL-6 hos två grupper av RA patienter. Den ena gruppen fick prednisolon kl 02:00 på natten, och den andra gruppen fick prednisolon kl 07:30 på morgonen. De patienter som fick prednisolon kl 02:00 hade signifikant bättre effekt på symtom och blodnivåer av IL-6 än de patienter som fick prednisolon kl 07:30 på morgonen.

Monocyter, en slags immunologiska celler som spelar stor roll för inflammationen vid RA, är aktiverade och uttrycker receptorer för adhesion och fagocytos. Behandling med prednisolon minskade uttrycket för dessa receptorer på monocyter vilket kan vara en av orsakerna till den gynnsamma effekten av kortison vid RA. Kropps eget kortison, dvs kortisol, tycks spela en viss roll för att minska vidhäftningen av monocyter till kärlväggen i inflammerad vävnad, vilket visades genom att behandla RA patienter med metyrapone, en substans som minskar syntesen av kroppseget kortisol.

De olika laboratorieprover som används för att bedöma sjukdomsaktivitet vid RA (sänkan, CRP, fibrinogen, haptoglobin, IL-6 och Serum amyloid A (SAA) protein visar god överensstämmelse sinsemellan, och särskilt stark är sambandet mellan CRP och SAA och mellan fibrinogen och sänkan. Fibrinogen och CRP visade sig korrelera bättre än sänkan till ett patientanpassat frågeformulär för vardaglig funktion, Modified Health Assessment Questionnaire (MHAQ), och bättre än sänkan till antalet vita blodkroppar (neutrofiler). Observationerna är viktiga med tanke på den reumatologiska vardagsverksamheten.

Övriga mått på sjukdomsaktivitet såsom antal ömma och svullna leder, morgenstelhet, smärta, olika ledindex samt ett sammansatt aktivitetsmått (Stoke index) visade relativt liten inbördes överensstämmelse, och endast Stoke index korrelerade till de olika laboratorieproverna för sjukdomsaktivitet. Resultaten pekar på att vissa kliniska
undersökningar, fra morgonstelhetens längd och vilosmärta, kan ha begränsat värde för att bedöma sjukdomsaktiviteten vid RA.

Långtidseffekter av RA kan vara nedsatt vardagsfunktion och röntgenologiska inflammationsförändringar i det lednära skelettet (usurer). Bedömning av nedsatt vardagsfunktion är överraskande komplicerad, och det har varit svårt att finna tillförlitliga metoder för det. I avhandlingen jämfördes objektiva tester för funktionsnedsättning (framstagna av författaren för detta arbete) med MHAQ, som är ett internationellt använt och populärt subjektivt frågeformulär för bedömning av vardagsfunktion. Var och en av dessa metoder att bedöma funktionsnedsättning jämfördes sedan med en kvantitativ metod för bedömning av röntgenologiska ledförändringar vid RA, Larsen score.

De objektiva funktionstesterna korrelerade med MHAQ, och båda metoderna korrelerade med smärta, CRP och sänkan. Därtill korrelerade de objektiva funktionstesterna med röntgenologiska ledförändringar, vilket MHAQ inte gjorde. Detta samband var särskilt påtagligt hos patienter som haft RA mer än fyra år. Objektiva funktionstester är därför att föredra framför MHAQ när det gäller värdering av vardagsfunktion hos patienten med RA.
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APPENDIX

The Stanford Health Assessment Questionnaire (HAQ or HAQ-DI)
without with some difficulty? with some difficulty? unable
help from to do another person

1. DRESSING AND GROOMING
   Are you able to:
   a. get your clothes out of the closet and drawers .... .... .... .... ....
   b. dress yourself including handling of closures (buttons, zippers, snaps) .... .... .... .... ....
   c. shampoo your hair .... .... .... .... ....

2. ARISING
   Are you able to:
   a. stand up from a straight chair without using your arms for support .... .... .... .... ....

3. EATING
   Are you able to:
   a. cut your meat .... .... .... .... ....
   b. lift a full cup or glass to your mouth .... .... .... .... ....

4. WALKING
   Are you able to:
   a. walk outdoors on flat ground .... .... .... .... ....

5. HYGIENE
   Are you able to:
   a. wash and dry your entire body .... .... .... .... ....
   b. use the bathtub .... .... .... .... ....
   c. turn faucets on and off .... .... .... .... ....
   d. get on and off the toilet .... .... .... .... ....

6. REACH
   Are you able to:
   a. comb your hair .... .... .... .... ....
   b. reach and get down a 5 lb. bag of sugar which is above your head .... .... .... .... ....

7. GRIP
   Are you able to:
   a. open push-button car doors .... .... .... .... ....
   b. open jars, which have been previously
opened .... .... .... ....
c. use a pen or pencil .... .... .... ....

8. ACTIVITY
Are you able to:
  a. drive a car .... .... .... ....
     (for reasons other than arthritis,
      I do not drive ___)
  b. run errands and shop .... .... .... ....

     without somewhat limited to impossible
     any uncomfortable? certain because
     difficult? positions of arthritis?
     or very
     Uncomfortable?

9. SEX
Are you able to:
  a. have sex .... .... .... ....
      (I am not involved in a sexual
       relationship____)

The original HAQ (Fries et al. 1980).

The Modified Stanford Health Assessment Questionnaire (MHAQ)

AT THIS MOMENT, are you able to: without any with some with much unable to
  difficulty difficulty difficulty do

a. Dress yourself, including tying shoelaces and doing buttons? .... .... .... ....

a. Get in and out of bed? .... .... .... ....

b. Lift a full cup or glass to your mouth? .... .... .... ....

c. Walk outdoors on flat ground? .... .... .... ....

d. Wash and dry your entire body? .... .... .... ....
f. Bend down to pick up clothing from the floor?  

e. Turn regular faucets on and off?  
g. Get in and out of a car?  

The original version of MHAQ (Pincus et al. 1983).

The Norwegian version of MHAQ

I løpet av siste uken, kunne du:  

<table>
<thead>
<tr>
<th>Activity</th>
<th>UTEN problemer</th>
<th>med VISSE problemer</th>
<th>med STORE problemer</th>
<th>kunne IKKE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kle på deg selv, inkl. å knytte skolisser og å knepe knapper?</td>
<td>….</td>
<td>….</td>
<td>….</td>
<td>….</td>
</tr>
<tr>
<td>Komme opp i og ut av sengen?</td>
<td>….</td>
<td>….</td>
<td>….</td>
<td>….</td>
</tr>
<tr>
<td>Løfte en full kopp eller et fullt glas til munnen?</td>
<td>….</td>
<td>….</td>
<td>….</td>
<td>….</td>
</tr>
<tr>
<td>Gå utendørs på flat mark?</td>
<td>….</td>
<td>….</td>
<td>….</td>
<td>….</td>
</tr>
<tr>
<td>Vaske og tørke deg over hele kroppen?</td>
<td>….</td>
<td>….</td>
<td>….</td>
<td>….</td>
</tr>
<tr>
<td>Bøyde deg for å ta opp klær fra gulvet?</td>
<td>….</td>
<td>….</td>
<td>….</td>
<td>….</td>
</tr>
<tr>
<td>Skru vanlige kraner opp og igjen?</td>
<td>….</td>
<td>….</td>
<td>….</td>
<td>….</td>
</tr>
<tr>
<td>Komme inn og ut av en bil?</td>
<td>….</td>
<td>….</td>
<td>….</td>
<td>….</td>
</tr>
</tbody>
</table>

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