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A Twenty-year Follow-up Study of Seropositive Rheumatoid Arthritis and Seronegative Oligoarthritis

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To my family

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INTRODUCTION

Undifferentiated arthritis can be a self-limiting disease but not infrequently develops into rheumatoid arthritis (RA) or evolves into some other form of chronic arthritis. It remains a clinical and scientific challenge to understand the relationhip between these phenotypes, to determine their aetiologies and predict the course and outcome for individual patients (Ollier et al. 2001).

Rheumatoid factor (RF)-positive RA is typically a long-lasting and usually an erosive disease. Only long-term prospective studies concerning the course and outcome of the disease can provide a reliable conception of its ultimate prognosis. There are few prospective studies of inception cohorts covering a period up to 20 years (Rasker and Cosh 1987, Scott et al. 1987).

Spondyloarthropathies comprise a cluster of interrelated and overlapping chronic inflammatory rheumatic diseases which includes ankylosing spondylitis (AS), reactive arthritis (ReA), arthritides associated with psoriasis (PsA) and inflammatory bowel diseases (IBD), and undifferentiated spondyloarthropathies (uSpA).They are typically RF-negative and apart from PsA are strongly associated with HLA-B27 (Khan 2002).

A prospective study covering patients with various forms of recent-onset arthritis collected from a defined area, called the Heinola Follow-up Survey of Arthritis, was initiated in 1973. Follow-up of patients with RA and seronegative oligoarthritis has now continued for a period of 20 years. This present work reviews the accumulated data on seropositive RA and seronegative oligoarthritis derived from the Heinola Follow-up Survey.

ABSTRACT

Rheumatoid factor (RF)-positive rheumatoid arthritis (RA) is a continuously progressive destructive inflammation of joints with systemic features, causing, when not controlled with proper treatment, work disability, deterioration of life quality, and even premature death. The aim of the present study was to ascertain the outcome and characteristics of 103 RF-positive RA patients and of 64 subjects with seronegative oligoarthritis followed prospectively for 20 years.

The predictive value of a total of 19 demographic, laboratory and radiographic entry markers in auguring the 20-year outcome of 66 RA patients was poor. Only the baseline Larsen score of 0-100 to some degree explained the 20-year joint destruction (OR 1.4).

During 20 years cumulatively 80% of subjects at work at onset of disease gave up work because of RA. The disabled patients had higher mean Health Assessment Questionnaire (HAQ) index and Larsen scores than subjects retired because of age or other diseases. There was also a statistically significant although weak association between the HAQ index and work disability (OR 1.13), whereas no independent role remained for the Larsen score.

If the Larsen score (0-100) on 20 joints in hands and feet in 102 RF-positive and erosive subjects did not worsen more than one point between the 1-, 3-, 8-, 15- and 20-year check-ups, nor thereafter, the patient was considered to be in permanent radiographic remission. Most of the radiographic remissions occurred after the 15-year check-up and the number of patients in remission was at endpoint 27 (26%). The patients with radiographic progression were more often on disease-modifying antirheumatic drug (DMARD) and/or prednisolone treatment than subjects in radiographic remission.

There is no international agreement on the criteria for severity in RA. When a Larsen score of 67-100 or HAQ index 2-3 or three large-joint arthroplasties performed were the criteria used, the incidence of severe RA was 29% (30/103) in RF-positive RA patients after 20 years. The cumulative incidence of amyloidosis was 14%.

In contrast, the outcome of 64 patients with seronegative oligoarthritis during the 23-year follow-up was generally good: only three subjects had retired because of arthritis. The putative diagnoses on re-evaluation of the patients were as follows: psoriatic arthritis (PsA) in 19, seronegative mono/oligo arthritis in 16, HLA-B27-associated oligoarthritis in 14, reactive arthritis (ReA) in 6, osteoarthrosis in 4, posttraumatic arthritis in 2, and one case each of ankylosing spondylitis (AS), RA and systemic lupus erythematosus (SLE).

In conclusion, RF-positive RA is mostly a severe disease for the patient and expensive for the community. The outcome is nonetheless almost impossible to predict at baseline. Early proper diagnosis and intensive treatment are the most prominent challenges. The outcome of seronegative oligoarthritis is mostly favourable.

CONTENTS:

ABBREVIATIONS

AA	Amyloid A
ACR	American College of Rheumatology
AI	Aortic insufficiency
AKA	Antikeratin antibody
ARA	American Rheumatism Association
APF	Antiperinuclear factor
AS	Ankylosing spondylitis
CCP	Citrullinated cyclic peptide
CI	Confidence interval
CRP	C-reactive protein
DAS	Disease activity score
DMARD	Disease-modifying antirheumatic drug
ELISA	Enzyme-linked immunosorbent assay
ESSG	European Spondylarthropathy Study Group
ESR	Erythrocyte sedimentation rate
GSTM	Gold sodium thiomalate
HAQ	Health Assessment Questionnaire
HLA	Human leukocyte antigen
IBD	Inflammatory bowel disease
IIF	Indirect immunofluorescence
IQR	Interquartile range
JIA	Juvenile idiopathic arthritis
MCP	Metacarpophalangeal
MTP	Metatarsophalangeal
NSAID	Nonsteroidal anti-inflammatory drug
OR	Odds ratio
PsA	Psoriatic arthritis
PsSpA	Psoriatic spondyloarthropathy
PIP,IP	Proximal, interphalangeal
RA	Rheumatoid arthritis
ReA	Reactive arthritis
RF	Rheumatoid factor
SAA	Serum amyloid A
SE	Shared epitope
SD	Standard deviation
SLE	Systemic lupus erythematosus
SMR	Standardized mortality ratio
SpA	Spondyloarthropathy
uSpA	Undifferentiated spondyloarthropathy
VAS	Visual analogue scale

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, referred to in the text by the Roman numerals I-V:

I. Jäntti JK, Kaarela K, Luukkainen RK, Kautiainen HJ (2000): Prediction of 20-year outcome at onset of seropositive rheumatoid arthritis. Clin Exp Rheumatol 18:387-90.

II. Jäntti J, Aho K, Kaarela K, Kautiainen H (1999): Work disability in an inception cohort of patients with seropositive rheumatoid arthritis: a 20-year study. Rheumatology 38:1138-41.

III. Jäntti J, Kaarela K, Kautiainen H, Isomäki H, Aho K (2001): Radiographic remission in seropositive rheumatoid arthritis. A 20-year follow-up study. Clin Exp Rheumatol 19:573-76.

IV. Jäntti JK, Kaarela K, Belt EA, Kautiainen HJ (2002): Incidence of severe outcome in rheumatoid arthritis during 20 years. J Rheumatol 29:688-92.

V. Jäntti JK, Kaarela K, Lehtinen KES (2002): Seronegative oligoarthritis: a 23-year follow-up study. Clin Rheumatol 21:353-56.

1. REVIEW OF THE LITERATURE

1.1. Classification criteria for rheumatoid arthritis

For any epidemiological study to proceed, the disease in question ought to have a clear definition, and one basic problem with RA is that there is no single criterion which applies exclusively to it. Thus, RA is a condition defined from a set of somewhat arbitrarily devised criteria. RF-positive patients tend to have a progressive disease, while RF-negative RA most likely comprises a heterogeneous group of disease conditions. For example, a patient may have HLA-B27-associated peripheral arthritis without evidence of spinal involvement, hidden psoriatic arthritis without overt skin lesions, or juvenile idiopathic arthritis of adult onset. On average, RF-negative patients tend to have a more favourable course than RF-positive patients, and many go on to complete remission. There remains, however, a variable but relatively small proportion of RF-negative patients who develop a chronic progressive disease which may prove resistant to conventional therapies.

Diagnostic criteria primarily apply to individuals and are needed for daily clinical practice. They should have high sensitivity at the expense of lower specificity. In contrast, classification criteria are used in epidemiological research for groups of patients. A basic requirement is that such criteria be applicable as widely as possible. For instance, taking foot radiographs, although supplementing hand radiographs in a valuable fashion, is not included in the routine evaluation of patients in all countries, which renders it difficult to use foot radiographs for comparative purposes. The primary purpose of classification criteria is to facilitate accurate communication. In daily clinical practice the classification criteria, although not primarily intended for diagnostic purposes, are often used more or less consciously (Berthelot et al. 2001, 2002).

The first consensus on classification criteria for RA was reached in 1956 when the committee of the American Rheumatism Association (ARA) published, and in 1958 revised, their criteria for RA (Ropes et al. 1956, 1958). RA was defined at three levels of certainty: definite, probable and possible RA, in 1958 also classical RA. The specificity of probable and possible RA was low. The concepts classical, definite and probable RA were retained in a symposium in Rome in 1961, and the symposium in New York in 1966 specified concepts for active and inactive RA.

The criteria used nowadays are based on the American Rheumatism Association, subsequently the American College of Rheumatology (ACR) 1987 revised criteria for classification of RA (Arnett et al. 1988). Their formulation was based on an analysis of 262 RA and 262 control subjects with rheumatic diseases other than RA. In these ACR 1987 criteria the previous eleven criteria were reduced to seven: 1) morning stiffness in and around joints lasting at least 1 hour before maximal improvement, 2) soft-tissue swelling (arthritis) in 3 or more joint areas observed by a physician, 3) swelling (arthritis) of proximal interphalangeal (PIP), metacarpophalangeal (MCP) or wrist joints, 4) symmetric swelling (arthritis), 5) rheumatoid nodules, 6) the presence of RF, and 7) radiographically detectable erosions and/or periarticular osteopenia in hand and/or wrist joints. Criteria 1 through 4 must have been present for at least 6 weeks. RA is defined by the presence of 4 or more criteria, and no further qualifications (classical, definite or probable) or list of exclusions are needed.

A number of studies have evaluated the ACR 1987 criteria. For instance in Heinola, Finland, the ACR 1987 criteria were tested in early (< 6 months) RA patients and were reported fit for use at that stage (Kaarela et al. 1995). In Northern Finland the feasible accuracy of the criteria was

assessed in a population-based study of RA patients with a mean disease duration of 16 years (Hakala et al. 1993). However, in a study from the Norfolk Arthritis Register, Harrison et al. (1998) reported that the 1987 ACR criteria had low efficacy among subjects with newly presenting inflammatory polyarthritis in discriminating between those who developed persistent, disabling, erosive disease and those who did not. In this study the sensitivity of the ACR 1987 criteria was good but the specificity poor. Wiles et al. (1999) reported increasing accuracy of ACR 1987 criteria in patients with early polyarthritis over time. If up to 5 years elapsed between onset of symptoms and notification, and the criteria were applied cumulatively, the estimates of annual incidences of RA rose by 75% and 93% for women and men, respectively, compared with the 1-year data, reaching an annual incidence of 54/100 000 and 24.5/100 000, respectively. Concerning the 7th ACR 1987 criterion, Paimela (1992) emphasized the radiographic evaluation of the feet as improving the classification of recent-onset RA.

1.2. Criteria for spondyloarthropathies

Spondyloarthropathies were classified up to the 1950s as atypical, possible or special forms of RA. The concept of seronegative spondarthritides was formulated by Wright and Moll in Leeds, UK, in 1960 (Wright and Moll 1976). Nowadays this interrelated group of chronic inflammatory joint diseases covered under the umbrella term of spondyloarthropathies consists of ankylosing spondylitis, reactive arthritis, psoriatic arthritis, arthritis associated with inflammatory bowel diseases, and undifferentiated spondyloarthropathies (Table 1). These complaints tend to have a number of features in common, for example overlapping family history, involvement of the axial skeleton and of the lower limb joints especially the knees, enthesopathies, sacroiliitis, extra-articular manifestations in the gut, eye and aortic valve, negativity for RF and a more or less firm association with the HLA allele B27 (Khan 2002).

Table 1. Clinical presentation of spondyloarthropathies.
Dougados M (1999): Scand J Rheumatol 28:336-9.

Disease subgroups:	Clinical features:
* Ankylosing spondylitis	Rheumatic manifestations:
* Psoriatic arthritis	* Axial involvement
* Reactive arthritis	* Peripheral arthritis
* IBD-related arthritis	* Enthesopathy
* Undifferentiated SpA	Extra-articular features:
	* Acute anterior uveitis
	* Endocarditis
	Genetic background:
	* Family history
	* HLA-B27 antigen
	Specific manifestations:
	* Psoriasis
	* IBD

IBD inflammatory bowel disease
SpA spondyloarthropathy

Criteria have been proposed for AS (Bennett et al. 1967, van der Linden et al. 1984) and also for PsA and ReA (Wilkens et al.1981, Vasey et al. 1984). The arthritis associated with IBD has recently been studied (Palm et al. 2001, Salvarani et al. 2001). The preliminary classification criteria for spondylarthropathies issued by The European Spondylarthropathy Study Group (ESSG) are to a certain degree useful to classify patients with typical characteristics (Table 2) (Dougados et al. 1991). Although most subjects with RF-negative oligoarthritis, dactylitis, and/or heel pain due to periostitis are diagnosed as suffering from spondyloarthropathy, up to 27% of patients in a study of 403 patients could not be classified with the ESSG criteria and uSpA was one of the most frequent spondyloarthritides (Dougados et al. 1991). The ESSG criteria are criticized for lack of consensus on the nosology of early SpA and for the only limited help in differentiating early SpA from other forms of arthritis at the initial presentation (Berthelot et al. 2002).

Table 2. European Spondylarthropathy Study Group (ESSG) classification criteria for spondylarthropathies.
Dougados M (1999): Scand J Rheumatol 28:336-9.

INFLAMMATORY SPINAL PAIN	OR	SYNOVITIS:
		* Asymmetrical or * Predominantly in the lower limbs
	AND one or more of the following:	
	* Alternate buttock pain * Sacroiliitis * Enthesopathy * Positive family history * Psoriasis * Inflammatory bowel disease * Urethritis or cervicitis or acute diarrhea occurring within one month before arthritis	

1.3. Prognostic factors for rheumatoid arthritis

The prognosis of inflammatory joint diseases varies within wide limits: some cases have a tendency to spontaneous remission without prolongation of the disease, while others progress to chronic inflammation with destruction of joints, disability and handicap. Occasionally the disease can lead to serious systemic complications such as amyloidosis and vasculitis (Nissilä et al. 1983, Reilly et al. 1990). A risk factor may constitute genetic, behavioural or environmental characteristics with different occurrence among patients and controls and preceding the onset of clinically manifest disease. In order to overcome the problem of balancing risks, benefits and costs of treatment before the full severity and extent of a patient's RA has become apparent, prediction methods are needed.

1.3.1. Rheumatoid factor

Several different autoantibodies are associated with RA and some of these are sufficiently specific to serve as diagnostic and prognostic markers (Aho and Palosuo 2002). Most attention has been paid to RF. This is one of the most frequently ordered tests in the evaluation of patients with rheumatic complaints and is clearly associated with poor prognosis (Ragan et al. 1962, Sherrer et al. 1986, van Zeben et al. 1993). Brennan et al. (1996) evaluated nine separate studies covering at least 100 RA subjects published over the past 20 years; in all of them positive RF was strongly associated with unfavourable radiographic outcome.

Bukhari et al. (2002) in a large inception cohort of 439 patients from the Norfolk Arthritis Register Study reported that a high RF titre of 160 or more was an independent predictor of radiographic deterioration over a follow-up period of 5 years. Individuals with an initially high RF level evinced a radiographic progression in their Larsen score which was 2.3 times (95% CI 1.7-3.2) higher than that in RF-negative RA patients. In the Dutch Cobra trial (Boers et al. 2001) involving 155 RA patients with early (< 2 years) and active disease, followed for 80 weeks, Knijff-Dutmer et al. (2002) assessed the relationship of RF as a continuous variable with disease activity parameters and radiographic damage in hands and feet in individual patients. Both IgA-RF and IgM-RF could be regarded as disease activity parameters. All disease activity parameters, including RF, were associated with continuous radiographic damage. Moreover, there appeared to be a linear relationship between duration of exposure to disease activity and progression of radiographic damage.

1.3.2. Antiperinuclear factor and anticitrullin antibody

A number of closely related antibodies are targeted against epidermal filaggrin. This is an intermediate filament-associated protein involved in the aggregation of cytokeratin filaments during cornification of the epidermis. The early tests, antikeratin antibody (AKA) and antiperinuclear factor (APF), were based on immunofluorescence. They had been fairly consistently used in certain research laboratories but technical problems took them beyond the scope of most general laboratories. More recently, synthetic peptides containing reactive antigenic sites have been used in the enzyme-linked immunosorbent assay (ELISA). Crucial for the antigenicity is the enzymatic conversion of a proportion of arginine residues to citrulline during the maturation of filaggrin. Peptide cyclitization resulted in higher specific binding of RA sera and a somewhat higher frequency of positive reactions than use of linear peptides. Commercial test kits are now available for citrullinated cyclic peptide (CCP) antibody determination (Aho and Palosuo 2002).

In testing for prevalent RA and non-RA sera, the anti-CCP test proved to be 98% specific and 68% sensitive for RA. On the other hand, IgM-RF was 96% specific and 70% sensitive for RA. However, RF-positivity occurs in diseases other than RA and also in elderly healthy people and is thus of limited diagnostic value (Aho and Palosuo 2002). Palosuo et al. (2003) reported that anti-CCP is more specific than antibodies against filaggrin among the aged.

Using anti-CCP and RF tests together, the positive predictive value for RA may be further increased (positive predictive value 91% and negative predictive value 78%) compared with the IgM-RF test alone (Schellekens et al. 2000). van Jaarsveld et al. (1999) followed 249 early (< 1 year) RA patients for 3 years to study the prognostic value of APF as determined by an indirect immunofluorescence (IIF) test and anti-CCP ELISA together with RF. APF had prognostic

value, in addition to RF, for joint involvement and radiographic damage in early RA. Moreover, more large-joints were affected in APF-positive and RF-positive than in APF-negative and RF-positive patients. In this respect, the results of anti-CCP and APF were comparable. Reliable identification of progressive disease for the individual patient at baseline is still not possible. Also Meyer et al. (2003) in their study of 145 RA patients followed for 5 years concluded that antibodies to citrullinated proteins/peptides determined by APF IIF or anti-CCP ELISA early in the course of RA are good predictors of radiographic joint damage.

1.3.3. Genetics

The evidence in support of a genetic contribution to RA disease susceptibility comes from the consistent association observed between alleles in the highly polymorphic HLA-DRB1 gene of HLA class II. The initial discovery of the association between HLA-DR4 and RA (Stastny 1978) has been replicated in different populations in many studies. On the other hand, Paimela et al. (1993) reported no prognostic value of HLA-DR4 or HLA-B27 in early RA.

High-resolution DNA methods for HLA typing have identified a number of different alleles within HLA-DRB1 which are associated with RA. The key discovery was that all of the DRB1 alleles associated with RA share a very similar amino-acid sequence in the third hypervariable region in the DRB1 encoded molecule. This shared sequence is commonly referred to as the RA shared epitope (SE) and is controversially connected with unfavourable outcome of RA (Calin et al.1989, Scott 2000). The distribution of SE-bearing alleles varies considerably between populations.

In several studies the prognostic impact of radiographic evidence on severe joint destruction was seen in SE-positive and RF-positive RA patients (Gough et al. 1994, Wagner et al. 1997, Conaghan et al. 1999, Meyer et al. 1999, Valenzuela-Castano et al. 2000). In England, a prognostic correlation was found between the SE and RF-negative but not RF-positive RA patients (Mattey et al. 2001). RF-negative patients carrying an SE allele had higher mean Larsen scores than RF-negative subjects lacking the SE. The mean Larsen score was significantly higher in RF-positive than in RF-negative patients, but there were no differences between RF-positive subjects with or without the SE. However, no prognostic significance of HLA-DR4 or SE with regard to the functional or radiographic outcome of early RA was found in Finnish RA patients (Möttönen et al.1998).

Gorman and Criswell (2002) reviewed the association of the shared epitope and severity of RA and reported that after two decades of research involving thousands of RA patients, it was not possible to define precisely the relation of the SE alleles to the severity of RA. Genetic markers available for prognostic evaluation in early RA are probably of no significance in daily clinical practice.

1.3.4. Other prognostic factors

According to a review of 36 publications on factors prognostic of RA, a poor outcome was associated with RF, HLA-DR4, high disease activity, rheumatoid nodules, radiographic abnormalities, impaired functional status and lowered grip strength (van Zeben and Breedveld 1996). The accuracy of prediction of each individual factor was low, but together they predicted erosions with a precision of 70-80%. There are numerous studies of predictive factors in RA. For instance Combe et al. (2001) assessed a cohort of 191 RA patients, with a disease duration shorter than one year and followed them for three years. Prognostic factors for radiographic

damage and progression were evaluated. Sex, age, disease activity score (DAS), swollen or tender joint counts, extra-articular manifestations, HAQ score, Ritchie Articular Index, patient's assessment of pain, anti-RA33 antibodies, or AKA proved to bear no correlation with radiographic scores and progression in follow-up. Logistic regression analysis revealed that the only baseline values predictive of the three-year radiographic scores were IgM RF, DRB1*04 genes, pain score, and total radiographic score. Radiographic progression of joint damage was predicted by ESR, IgM-RF-positivity, DRB1*04 genes, and erosions at baseline.

Fex et al. (1996) reported a higher radiographic progression rate in female than in male subjects. At the onset of RA, elderly patients evinced more radiographic destruction than younger subjects (Kuiper et al. 2001). Also Papadopoulos et al. (2003) reported that elderly RA patients presented with more severe joint involvement at disease onset than younger subjects, whereas after a follow-up of 19 years no differences were seen in respect of radiographic changes and functional disability. Other factors predicting poor outcome are numerous, including cigarette smoking, poverty, co-morbidities, race, multiple joint involvement, high CRP and ESR, rheumatoid nodules and slow onset of the disease (Scott 2000, Albano et al. 2001).

1.4. Work disability in rheumatoid arthritis

Work disability consists in leaving the paid labour force by reason of health problems and constitutes a particularly serious social problem for RA patients and a good touchstone of outcome. In an inception cohort of RA patients, permanent work disability was already noted at a three-year check-up (Nissilä et al. 1983). Considering studies from different periods and from different countries, one must bear in mind differences in social security systems, changes in the structures of occupations (less agricultural work) and changes in disease-modifying antirheumatic drug (DMARD) treatment towards more aggressive measures during recent decades.

A Dutch study has shown that after a mean disease duration of two years (range 1-4), 60% of the group of RA patients still working had a nonmanual job, 20% were sales and service workers, and 20% were manual workers (Doeglas et al. 1995). Of the RA patients with work disability, 16% were non-manual workers, 34% were sales and service workers, and 50% belonged to the manual worker category. Mau et al. (1996) followed gainfully employed 73 subjects with early (< 12 months) RA for seven years. Determinants for work disability were age over 50 years, heavy (blue collar) work, a joint count exceeding 15, and ESR more than 60 mm/h. The fastest decline in the employment rate was found within the first three years of onset. At the endpoint, 27 of the initial 73 RA patients (37%) were permanently unable to work.

Barrett et al. (2000) followed two cohorts of RA patients in the Norfolk Arthritis Register. The first consisted of 160 RA subjects recruited between 1989 and 1992 and followed for a mean period of 8.6 years from onset. A total of 110 of them had population-based controls matched for age, gender and employment status at baseline. The second cohort consisted of 134 RA patients recruited between 1992 and 1997 with a mean follow-up of 4.1 years. At the endpoint, one third of the RA patients in the first cohort had given up work. The baseline HAQ score was the most important predictor of work disability. The risk of disability was 32 times higher in the RA cohort than in the matched control group. The disability rates for RA patients at 1, 2, 5 and 10 years after the disease onset were 14%, 26%, 33% and 39%, respectively. For the second cohort the rates of work disability at one and two years from onset were 23% and 33%, respectively. Earlier and more aggressive DMARD treatment had no effect on these rates.

In another UK study, Young et al. (2002) followed 732 early RA patients for five years. Of the patients 353/721 (49%) were fully employed at the onset of RA, and of these 211 (60%) were still working at the 5-year check-up, 104 (29%) had stopped because of the disease, and 31 (9%) had retired for reasons other than RA. Manual workers were more likely to become work-disabled, likewise patients with a baseline HAQ score of more than 1.5. In combination with other baseline variables (ESR, sex, age at disease onset, and radiographic erosions) employment outcome was predicted in 78% using multivariate analysis.

Sokka et al. (1999 a) in Finland studied 82 RA patients who had been treated with a "sawtooth" strategy over a 10-year period. The frequency of disability was 19% and 44% after two and 10 years from the onset of disease, respectively. The type of work rather than disease-related factors at baseline predicted permanent work disability. In contrast, a random sample of 1056 RA patients aged 16-59 years from 17 rheumatology practices in The Netherlands was assessed by Chorus et al. (2000). Of those with a mean disease duration of 12 years, 36 % held a paid job (men 57%, women 28%). When adjusted for age, sex and educational level, the participation of RA patients in the labour force was 61% compared with 67% for the general population. Disease duration of six years or more was associated with giving up work.

In the FIN-RACo Trial comparing the COMBI (combination of DMARDs) versus SINGLE therapies in the treatment of 195 recent-onset (median six months) RA subjects (Möttönen et al. 1999), a total of 162 patients were working at baseline (80 COMBI, 82 SINGLE). The preliminary results showed that after five years, permanent work disability was less in patients treated with the COMBI than in those treated with SINGLE DMARD strategy (20% and 29%, respectively) (Puolakka et al. 2002).

1.5. Remission in rheumatoid arthritis

Clinical remission is most often defined according to the preliminary ARA remission criteria (Pinals et al. 1981). Five or more of the following criteria must be fulfilled for at least two consecutive months: 1) duration of morning stiffness not exceeding 15 minutes, 2) no fatigue, 3) no joint pain (by history), 4) no joint tenderness or pain on motion, 5) no soft-tissue swelling of joints or tendon sheats, 6) ESR (Westergren method) < 30 mm/h for female or < 20 mm/h for male. However, Prevoo et al. (1996) criticized the ARA preliminary remission criteria and proposed the disease activity score (DAS) as a tool to define remission, as absence of disease activity should be measured using the same method as for higher levels of disease activity, preferably on a continuous scale.

In a Finnish study (Möttönen et al. 1996) of RA patients with early disease (mean 8 months) treated with "sawtooth" strategy, 27% were in ARA-defined remission at the 2-year check-up and 32% at the 6-year check-up. Wolfe and Hawley (1985) reported a remission rate of 18% among RA patients after a follow-up of seven years. The median length of remission was 10 months, regardless of therapy, and only 15% of remissions lasted longer than 24 months. Eberhardt and Fex (1998) investigated prospectively a total of 183 RA patients with early disease (mean disease duration 11 months) and followed them for five years to relate course to outcome and try to identify prognostic features. Twenty per cent achieved ARA-defined remission periods of at least six months' duration; 21 of them were spontaneous and 18 drug-induced. The average length of remission was 20 months. The remission periods constituted 7% of follow-up for all patients. A total of 56% of patients had a relapsing and remitting disease pattern and 44% a persistent disease pattern. More patients with persistent disease were treated with DMARDs and had more severe joint damage than those with relapsing and remitting

disease. The disease pattern had prognostic implications and it seemed that long-lasting remissions were rare.

In a follow-up study of 210 patients with established RA from the United States, Callahan et al. (1997) reported that most of the measures of inflammatory activity remained unchanged and sometimes even improved, while measures of radiographic damage indicated deterioration in status in the same patients over five years. Measures of inflammatory activity may underestimate long-term outcomes in RA, and long-term studies should include measures of radiographic damage. Molenaar et al. (2002) investigated the relationship between functional disability, disease activity and radiographic damage in 186 RA patients in ARA-defined remission or with low disease activity. When disease activity was measured by the DAS score (range from 0 to 10), and remission was defined by a DAS < 1.6 (Prevoo et al. 1996), it emerged that 82% of the initial 186 patients were in remission.

1.6. Severity of rheumatoid arthritis

In the classic evaluations, some 10% of patients had been confined to wheelchair or bed 10-15 years after the onset of RA (Ragan 1949, Duthie et al.1964). In the Droitwich study initially including 112 RA patients, Scott et al. (1987) observed that most patients (54%) had either died (35%) or were severely disabled (19%). At that time the mean Larsen score for hands and wrists was 51% of the maximum. Reilly et al. (1990) assessed a cohort of 100 RA patients after a follow-up period of 25 years. Of this total, 63 had died and in one third of them RA caused death directly or was at least a contributing factor. Large-joint replacements were performed on 18 out of 35 survivors who were seen for review. Only eleven patients were well with no functional impairment.

Premature death is the absolute outcome measurement in RA. Myllykangas-Luosujärvi et al. (1995) studied 1666 RA subjects in Finland who died in 1989. In 12% of cases the underlying cause of death was RA. Of all excess deaths in RA patients, 40% were due to cardiovascular diseases, 30% to infections and 15% to amyloidosis. About 10% of the excess mortality was treatment related. In a study in Manchester, UK (Symmons et al. 1998), the endpoint analysis in a cohort of initially 448 patients with RA assembled during 1968-74 and followed up to 22 years revealed that a total of 266 patients (59%) had died. The standardized mortality ratio (SMR) of RA patients was 2.5 compared with the general population. Patients who presented early continued to do well and most excess deaths were due to cardiovascular diseases. Mortality due to infection, renal failure and non-Hodgkin's lymphoma increased with disease duration.

Gordon et al. (2001) followed 289 patients with established RA for 10 years at Guy's Hospital, in London, UK. At the endpoint, 71 patients had died (SMR 1.3) and 92 were lost to follow-up. Median joint tenderness, morning stiffness, grip strength and blood hemoglobin were not significantly different at 0, 5, and 10 years. By contrast, HAQ scores and joint destruction worsened between 0 and 10 years. At 10 years, 54 patients (19%) of the original cohort had undergone at least one large-joint replacement. There was a continuous requirement for surgical large-joint replacement over time.The results of the study also suggested that the long-term effects of DMARD treatment may be less marked than the expectations evoked by short-term studies.

In a Japanese study the outcome of RA patients with multiple large-joint arthroplasties was markedly worse than that among patients with only two lower limb joint replacements (Kagyeama et al.1998). In a study involving 1600 RA patients followed for 23 years Wolfe and

Zwillich (1998) estimated that 25% had undergone total joint arthroplasty within 22 years from disease onset. In that study population 57% had knee arthroplasties.

In a 15-year study of RA subjects Rasker and Cosh (1978) reported a correlation between radiographic signs of damage in the MCP and carpal bones and both the degree of damage and subluxation in the cervical spine, emphasizing the significance of destruction in peripheral joints. An increased incidence of cervical myelopathy has also been reported in RA patients with multiple lower limb arthroplasties (Kirk et al. 1987).

In a prospective follow-up study of 109 RA subjects Graudal et al. (1998) assessed the progression of radiographic damage to joints as a mathematical function over a time period of up to 30 years. At the 20-year check-up all the patients had at least 10% radiographic events out of the maximum and 40% were considered to have a severe joint disease (50% radiographic events out of the maximum). A sigmoid function (slow onset, fast acceleration and subsequent deceleration) was the most prominent pattern.

1.6.1. Amyloidosis

During earlier decades, chronic infections like tuberculosis and osteomyelitis were the main reasons for secondary (AA) amyloidosis, but in the developed countries, with the decline in chronic infections, RA has become the most common cause (Gertz and Kyle 1991). Reliable epidemiological studies on amyloidosis are not available and the true prevalence is not known. Amyloidosis is rare in the United States, occurring in less than 1% of persons with chronic inflammatory diseases, but is more common in Europe, occurring in 5 to 10% of such patients (Husby 1985, Gertz and Kyle 1991, David et al. 1993).

The prevalence of amyloidosis in RA patients has ranged from 5 to 20% depending upon the severity and duration of RA and the population investigated (Husby 1985, Tiitinen et al. 1993). In a Japanese study during the period 1989-1991 Kobayashi et al. (1996) confirmed gastrointestinal amyloidosis in 54 (13%) of 407 RA subjects on whom they performed gastrointestinal endoscopy.

In a Spanish study of 313 RA patients with more than five years` disease duration (Comez-Casanovas et al. 1998), the prevalence of amyloidosis in abdominal fat aspirates after 14 years was 19.5%. Only 43% of these showed proteinuria or renal insufficiency or both. The investigators concluded that possibly only a minority of patients who develop histopathological deposits of amyloid also develop signs of organ dysfunction. In a Finnish study from the Rheumatism Foundation Hospital in Heinola (Laiho et al. 1999) the annual number of biopsies staining positively for amyloid decreased over the period 1987-1997 from 68 to 3. In contrast, no decline was noted in another Japanese study (Nakano et al. 1998) where amyloidosis was present in 18% of renal biopsy specimens in patients with RA in 1979-1988 and in 19% in 1989-1996.
In Lyon, France (Chevrel et al. 2001) over the years 1977-1999, the cumulative incidence of renal amyloidosis in RA subjects observed among 6931 renal biopsies was 0.68 cases/year and 0.22% (15/6931). Two out of six treated patients (33%) and all nine untreated patients (100%) died during the follow-up period. In a 10-year Finnish mortality study of 1000 RA patients aged 40 years or more, Laakso et al. (1986) found an excess of mortality from infections and cardiovascular and renal diseases. During their follow-up, 31 patients (3.1%) with RA (12 men and 19 women) had died of amyloidosis and 42 (4.2%) of other renal diseases (chronic nephritis and renal infections). In the study of 1666 RA patients who had died in 1989, the prevalence of amyloidosis was 5.8% (Myllykangas-Luosujärvi et al. 1999). The prevalence of histologically

confirmed amyloidosis and definite or probable renal amyloidosis in a cross-sectional study of 1042 RA patients living in Tampere in 1988 was 2.7% (2.3% in females and 4.2% in males) (Korpela 1993).

1.7. Undifferentiated spondyloarthropathy

The seronegative spondyloarthritides include entities which fail to meet the established criteria for definite categories, and are designated undifferentiated spondyloarthropathies. This diagnosis is only a working label with the implicit demand to solve the clinical conundrum by follow-up or even by identifying the causative or triggering infectious agents (Zeidler et al. 1992). A clinical diagnosis of seronegative oligoarthritis can frequently be regarded as a manifestation of uSpA at the onset of complaints, depending on the mode of arthritis in question. On the other hand, some patients with seronegative oligoarthritis have features of juvenile idiopathic arthritis (JIA) of adult onset (Säilä et al. 2003).

There are but scant solid data on the total incidence of SpA. Some evidence however exists for subtypes such as AS, ReA and PsA. Information from early arthritis clinics does not seem to be useful for the assessment of the true incidence of SpA, as there is no sufficiently general consensus on the nosology of early RA and early SpA. In addition, the classification of atypical early arthritis has not been resolved by the currently available criteria for RA and SpA and the ESSG criteria provide only limited help in the differentiation of early SpA from other forms of arthritis at baseline (Berthelot et al. 2001, 2002).

When the ESSG criteria were used to evaluate the frequency of SpA among blood donors in Berlin, Germany (Braun et al. 1998), an estimated overall SpA prevalence of 1.9% was calculated, AS and uSpA being the most frequent forms with prevalences of 0.87% and 0.67%, respectively. The prevalence of PsA was estimated to be 0.29%, while chronic ReA was less frequent.

Gladman et al. (1993) compared the spondyloarthropathy of AS with that of PsA. Forty patients with AS and 66 with PsA underwent a complete assessment including radiography and HLA typing. The patients with AS had a higher frequency of inflammatory neck and back pain and stiffness, limitation of back movements, grade 4 sacroiliitis, and syndesmophytes, while peripheral arthritis was more common and more severe in patients with PsA. A lower frequency of HLA-B17, and a higher frequency of HLA-B27, and Cw2 was found in AS than in PsA There are thus, clinical, radiographic, and genetic differences in disease expression of the spondyloarthropathy of AS and PsA, supporting the conception that they should be classified as distinct entities. Concerning the risk factors for progression of PsA, Gladman and Farewell (1995) stated that the HLA class I antigens B27 and B39 and the HLA Class II antigen DQw3 are the dominant predictors of disease progression in combination with clinical measures.

The relative contribution of the HLA-B27 antigen to susceptibility to psoriatic spondyloarthropathy (PsSpA) and to disease expression has been assessed by Queiro et al. (2002 a) in a cross-sectional study of 70 patients. PsSpA was defined according to radiographic findings (at least grade 2 sacroiliitis). Altogether 24 patients (34%) carried the HLA-B27 antigen. Of the 16 patients with isolated axial disease, 56% had this antigen, compared with 24% of the 25 patients with a polyarthritis axial pattern and with 31% of 29 patients with oligoarthritis and axial disease. HLA-B27-negative patients developed more erosions in peripheral joints than HLA-B27-positive subjects. No correlation was found between HLA-B27 and clinical symptoms of back involvement, syndesmophytes or functional impairment. In another study of 155 PsA

patients, Queiro et al. (2002 b) reported a strong association between HLA-Cw6 and a positive family history of psoriasis among first-degree relatives, and that the age at onset of PsA was significantly lower in HLA-B27-positive than in HLA-B27-negative subjects. Although in the case of psoriasis, whole genome scans have demonstrated a linkage with loci on chromosomes 17q, 4q, and especially on 6p, none of the linkage studies has attempted to identify the susceptibility genes related to PsA (Gladman and Rahman 2001).

In the Heinola Follow-up Study of Recent Arthritis (Isomäki et al. 1978), nonspecific arthritis was found in 40% of patients corresponding to an incidence of 88/100 000/year. In a two-year prospective German follow-up study, Hülsemann and Zeidler (1995) assessed 320 patients with arthritic complaints lasting less than one year at presentation. They used clinical, immunological and microbiological investigations to search for reactive arthritis. A total of 217 patients had inflammatory rheumatic disease, but for only 100 subjects (46%) could a definite diagnosis be made, while 117 subjects (54%) were considered as having undifferentiated arthritis. The joint manifestations were oligoarticular in 68%, polyarticular in 18% and monoarticular in 14% of the subjects. RF-positivity was noted in 17%, HLA-B27 in 27%, and a history of recent infection in 21% of the patients. After two years, of the 28 (24%) patients with undifferentiated arthritis complete remission was seen in 15 subjects (54%), and partial remission in 10 (36%). Only two patients (7%) developed RA and one AS (4%). Most patients with early synovitis remained unclassified and had a favourable outcome.

To determine the prevalence of SpA, Bruges-Armas et al. (2002) investigated a cohort of 490 subjects of Caucasian origin on Terceira Island, the Azores, Portugal. These subjects were assessed by dorsal, lumbar and pelvic radiography. Sacroiliitis was identified in eight patients on whom sacroiliac computed tomography had been performed. SpA was present in eight (1.6%), including seven men (2.7%) and one woman (0.4%). Three (1.2%) male patients with definite AS were HLA-B27-positive. Only one person had a previous diagnosis of SpA.

Vargas-Alarcon et al. (2002) in Mexico assessed the role of HLA-B and HLA-DR genes as contributors to genetic susceptibility and clinical expression of the spondyloarthropathies. The study involved 182 patients with SpA (uSpA in 73, AS in 84, and ReA in 25 patients) and 99 healthy controls. Increased frequencies and significant associations of HLA-B27, HLA-DR1, and HLA-B15 alleles with SpA were noted. HLA-B27 was associated with younger age at onset and increased disease severity and HLA-DR1 with older age at onset.

Amor et al. (1994) assessed factors predictive of outcome after onset of spondyloarthropathy. Determinators of poor long-term outcome were hip arthritis, ESR > 30 mm/h, limitation in the lumbar spine, dactylitis, oligoarthritis, age of 16 years or less at onset, and poor efficacy of NSAIDs. When none of these factors was present at entry, a favourable outcome could be predicted (Amor et al. 1994).

One additional manifestation of SpA can be aortic valve insufficiency (AI). In a study of 100 subjects with AI, Qaiyumi et al. (1985) found four patients with AS and three with ReA. Six of these evinced cardiac conduction abnormalities and four required insertion of a permanent pacemaker. All seven patients were HLA-B27-positive, whereas only five out of 89 patients with no evidence of spondylitis had this antigen. The investigators concluded that seronegative spondyloarthropathy is apparently associated with AI. In a Swedish study, Bergfeldt et al. (1988) investigated a group of 91 patients with AI by HLA typing and clinical and radiographic examination. HLA-B27-associated inflammatory rheumatic disease was identified as the probable cause of AI in 15% of patients. Furthermore, HLA-B27 was found in 88% of the male

patients with the combination of AI and severe conduction system abnormalities. The authors suggested that this combination of cardiac abnormalities should be regarded as an HLA-B27-associated syndrome, sometimes as a part of AS or ReA, but equally often presenting without obvious rheumatic disease.

2. PURPOSE OF THE STUDY

The activity of RA may last for decades, whereas seronegative oligoarthritis often quietens down without serious consequences. Thus, long-term prospective inception cohort studies are needed to reveal the true outcome of RA and seronegative oligoarthritis. The present 20-year follow-up study sought for answers on the following issues:

I. Is it possible to predict the long-term outcome in early RF-positive RA?

II. How prevalent is work disability in patients with RF-positive RA over 20 years?

III. How often does RF-positive RA end in permanent radiographic remission over 20 years?

IV. What is the incidence of severe outcome in RF-positive RA?

V. What is the outcome of patients with seronegative oligoarthritis over 23 years?

3. PATIENTS AND METHODS

3.1. Patients

A cohort of recent-onset arthritis was collected at the Rheumatism Foundation Hospital in Heinola, Finland in 1973-75 according to the following selection criteria: age 16 years or more, swelling in at least one joint, and duration of this complaint lasting not more than six months (Kaarela 1985). At onset, 441 patients fulfilling the admission criteria were studied. The patients were evaluated thereafter at one and three years from entry (Nissilä et al. 1983). At the 8-year follow-up in 1982, 266 patients with a diagnosis of RA or non-specific arthritis were recruited for examination. Of these, 35 were excluded in view of another specific diagnosis, and 30 patients were lost to follow-up, 7 due to death and 23 for other reasons (Kaarela 1985). The remaining 198 patients formed the following subgroups: 113 patients with seropositive arthritis, 21 patients with seronegative polyarthritis and 64 patients with seronegative oligoarthritis. Ten seropositive patients were excluded by reason of putative diagnosis other than RA (Kaarela et al. 1993). Thus the RA cohort in the present studies consisted of 103 seropositive patients (33 men and 70 women) of whom 102 had radiographically detectable erosions. The age at onset ranged from 17 to 70 years, mean 45.0 (SD 13.2) and median 45 years.

A total out of 83 of 103 RA patients attended the 15-year follow-up, and 66 the 20-year follow-up in 1995-96. Thirty had died and 7 could not attend on account of other severe diseases. All 64 patients with seronegative oligoarthritis (20 men, 44 women) were RF-negative and had one to four swollen joints during the first six months. The age at onset was 16-68 years, mean 35.5 (SD 13) (Kaarela and Sarna 1984). Seronegative oligoarthritis patients were asked to attend for the 23-year follow-up examination in 1997. Of these, eleven had died, six could not attend, and two patients were interviewed by phone, so that 47 subjects participated in the check-up.

3.2. Methods

Study I

Out of the 103 RF-positive RA patients seen at their 8-year check-up, 66 attended the 20-year follow-up. Radiographic destruction was graded by the Larsen method (Larsen et al. 1977). Radiographs of hands and feet were taken in dorsovolar projection. The radiographs to be interpreted were compared with a standard series consisting of a scale from 0 to 5 based on the degree of destruction in each joint. Joints with only soft-tissue swelling or osteoporosis were assigned to Larsen grade 0. Joints with pre-erosive changes or marked joint space narrowing were graded Larsen grade 1. The grades for the I-V metacarpophalangeal (MCP) joints and wrists and II-V metatarsophalangeal (MTP) joints (20 joints) were added to form a Larsen score of 0-100.

Disability was assessed by the Health Assessment Questionnaire (HAQ) index (Fries et al. 1980). A continuous scale (0-3) of functional disability indices was applied. The highest score for each of the eight areas of activity on daily living was summed (range 0-24) and divided by eight to yield a continuous scale (0-3) for a functional disability index.

The following entry variables were compared with the Larsen score and HAQ index: sex, age, grip strength, function score (Kaarela 1985), number of swollen joints (proximal interphalangeal (PIP), MCP, wrist, elbow, shoulder, sternoclavicular, jaw, MTP, subtalar, ankle, knee; maximum

46), the number of ACR criteria (Arnett et al. 1988), erosiveness (erosion in any joint), the Larsen score, HLA-B27, ESR, blood hemoglobin, blood platelets, serum IgA, IgG, and IgM, serum C1 esterase inhibitor, and serum orosomucoid.

Somers' *d* coefficient for asymmetrical association (Siegel and Castellan 1988) was used to measure the relationship between the individual variables at the start of the follow-up and the 20-year Larsen score and HAQ. In addition, stepwise logistic regression analysis was used to explain the endpoint Larsen score. Larsen scores were formed dichotomically using the median as the intersection. Spearman's rank correlation was used to study the correlation between the 20-year Larsen score and HAQ index.

Study II

Clinical check-up took place for the 103 RF-positive RA patients at onset and at 1, 3, 8, 15 and 20 years from entry. Radiographs of hands and feet were taken at each check-up. Destruction was graded by Larsen score 0-100. Disability was assessed at the 20-year check-up by the HAQ index. Patients were considered unable to work due to RA if they had retired on a disability pension under the National Pension Act available to the entire population of working age (16-64 year). People with a working history are additionally insured under the employment pension system. The disability pension is payable to persons who are incapable to work, i.e. unable to do their usual work, any kind of work which given their age, occupation and similar circumstances would be suitable for them.

Analysis of the development of work disability was carried out according to the life table method. Spearman's non-parametric correlations were counted for correlations between the endpoint HAQ index, the endpoint Larsen score and the age of the patient. Logistic regression analysis was used to explain retirement due to RA.

Study III

Radiographs of hands and feet were taken at onset and at 1, 3, 8, 15 and 20 years from entry in the 102 cases of recent-onset (< 6 months) seropositive and erosive RA. The Larsen score of 0-100 was formed to describe destruction in 20 joints of hands and feet. If the score did not worsen by more than one point between one of the above-mentioned time points and the end of the study, the patient was considered to be in radiographic remission.

ESR and CRP were registered at entry and at the 8-and 20-year check-ups. The number of swollen joints was counted at entry and at 8 years. The 72 joints investigated were as follows: distal interphalangeal (DIP), PIP of hand and foot, MCP, wrist, elbow, shoulder, sternoclavicular, jaw, MTP, subtaloid, ankle and knee. Use of DMARDs and prednisolone was recorded.

The results are expressed as the mean or median, and interquartile range (IQR). The Mann-Whitney U test and Chi square or Fisher's exact test were used to compare patients with and without radiographic remission. No adjustment was made for multiple testing.

Study IV

Follow-up examinations were made of 103 RF-positive RA patients at onset and at 1, 3, 8, 15 and 20 years from entry. Radiographs of hands and feet were evaluated by the Larsen score of 0-

100. The progression rate was calculated in relation to the remaining score. The formula used to calculate relative progression was the score of the designated year minus the score of the previous year divided by the total score minus the score of the previous year, i.e, the score change per amount of score available to change per year (Graudal et al. 1998).The HAQ index was used to evaluate disability.The scores were available only at the 15- and 20-year check-ups, and the endpoint disability was studied in 81 of the 83 patients. The use of DMARDs, prednisolone and their combinations were registered at each check-up.

At the 15-year check-up, a subcutaneous fat biopsy was taken in all patients to assess the presence of amyloidosis (Tiitinen et al. 1993). At the 20-year check-up, biopsy was performed if the patient had proteinuria or a high serum creatinine value. At the end of follow-up the number of arthroplasties performed on hip, knee, shoulder and elbow joints was counted.

The outcome of RF-positive RA was considered severe if the Larsen score (0-100) was 67-100 or the HAQ index 2-3 or if the patient had had three or more large-joint arthroplasties.
Analysis of the cumulative proportion of endpoint Larsen scores was made according to the life table method. The Mann-Whitney test was used to compare patients with and without amyloidosis.

Study V

A total of 64 patients with a diagnosis of seronegative oligoarthritis seen at the 8-year follow-up were re-examined in 1997. Numbers of swollen joints were counted, ESR and CRP tests were carried out. Hands, feet and sacroiliac joints were radiographed. Destruction in hands and feet was evaluated by Larsen score 0-100. Changes in sacroiliac joints were graded according to the New York Classification (Bennett et al. 1967) from 0 to 4 without knowledge of the history of the patients. Disability was rated by the HAQ index and ability to work was assessed. The clinical history, HLA-B antigens, number of swollen joints and the ACR 1987 criteria for RA at onset were re-evaluated.

4. RESULTS

4.1. Prediction of outcome of rheumatoid arthritis (I)

The prognostic value of 19 demographic, laboratory, clinical and radiographic markers was studied. Blood platelets (0.17, 95% CI 0.02 to 0.33), serum IgG (0.18, 95% CI 0.03 to 0.36) and moderately the Larsen score (0.33, 95% CI 0.17 to 0.50) correlated with the end-stage destruction of the peripheral joints. Old age (0.30, 95% CI 0.16 to 0.45), function score (0.28, 95% CI 0.11 to 0.45), duration of morning stiffness (0.28, 95% CI 0.00 to 0.55), grip strength (-0.24, 95% CI -0.40 to -0.08) and serum orosomucoid (0.17, 95% CI 0.00 to 0.35) correlated with the HAQ index. In stepwise logistic regression analysis only the baseline Larsen score entered and explained the later joint destruction (OR = 1.4, 95% CI 1.1 to 1.8). In this analysis RF was not included since all of the patients were RF-positive.

4.2. Work disability in rheumatoid arthritis (II)

The study indicated the deleterious nature of RF-positive RA. Already after one year from the onset of RA, 31% (95% CI 21 to 40) of working patients had given up work. The disability reached 80% (95% CI 70 to 89) over 20 years. The mean HAQ index was lowest among those still working (0.3, 95% CI 0.1 to 0.6), but the difference was small between the disabled RA patients (1.2, 95% CI 0.9 to 1.4) and those retired because of age (1.0) or other diseases (1.0). The mean Larsen score was highest among those who had retired because of RA (50, 95% CI 42 to 59) or high age (50) and lowest among those who were still working (33, 95% CI 16 to 50).

The mean endpoint HAQ index in this study was 0.96 and the mean Larsen score 45% of the maximum. The HAQ index showed a correlation with both the Larsen score and age. The age-adjusted correlation coefficient between the HAQ index and Larsen score was 0.46. The HAQ index was statistically significantly, albeit weakly associated with work disability when the Larsen score had been taken into account in multiple regression analysis; in contrast, no independent role remained for the Larsen score. The Odds ratio with its 95% CI was 1.13 (1.02-1.37) for the HAQ index and 1.01 (0.95-1.04) for the Larsen score.

4.3. Radiographic remission in rheumatoid arthritis (III)

Of the 102 patients with seropositive and erosive RA, radiographic remission was followed for over 20 years. Remission was confirmed in 27 (26%) of the patients and had rarely started by the first year check-up. In most cases the remission was not noted until the 15-year check-up. Some of these cases had a mild disease from the outset, whereas in some joint destruction was marked before the remission. Regarding total, participating patients ended up in remission during follow-up as follows: after 1-8 years 14 patients, after 15 years 27 patients.

Comparison of different disease characteristics at the 8-year and 20-year check-ups in patients with and without radiographic remission showed that ESR (mm/h) was significantly lower in RA patients in remission than in those with continuing radiographic progression (remission: median 18 and 16, radiographic progression: median 33 and 28), $p < 0.001$ at both check-ups. Correspondingly serum CRP (mg/l) values were significantly lower in subjects in remission than in patients with progression at the 8-year and 20-year check-ups, (remission: median 5 and 0, progression: median 17 and 20), $p = 0.001$ and 0.002, respectively. Likewise, the Larsen score was significantly lower (remission: median 8 and 16, radiographic progression: median 28 and

50), $p < 0.001$ at both check-ups respectively. The difference was also significant in respect of the number of swollen joints at the 8-year check-up between subjects with (median 2) and without radiographic remission (median 10), $p < 0.001$.

RA patients with continuing radiographic progression were more often on DMARD and/or prednisolone treatment. At the 8-year check-up a total of 12 (44%) of those in remission and 59 (79%) of those without were on treatment, $p = 0.001$. Further, at the 20-year check-up, on treatment were 13 subjects in remission (57%) and 41 (93%) with radiographic progression, $p < 0.001$.

4.4. Severe outcome in rheumatoid arthritis (IV)

The occurrence of severe outcome and the treatment among the 103 RA patients during 20 years were assessed. The initial DMARD treatment at the beginning of RA was gold sodium aurothiomalate (GSTM) in 58, hydroxychloroquine in 37, and d-penicillamine in two patients. Single DMARD therapy was used in 62 (60%) patients, single therapy with prednisolone in 25 (24%), combination therapy in only four patients (4%), while 10 (10%) subjects were without any DMARD treatment. After 1982, when sulphasalazine and methotrexate were introduced, and at endpoint, eight patients were receiving methotrexate and 13 sulphasalazine. At the 15-year follow-up, no DMARD treatments were in use in 29 (35%) of cases, and after 20 years the corresponding number was 17 (25%).

The median progression in destruction of the 20 peripheral joints was estimated to be yearly 2-3% according to the Graudal method (Graudal et al. 1998). At endpoint the degree of destruction was 2/3 (67%) or more of the maximum (a Larsen score of 67-100) in 24 (23%) patients.The cumulative number of patients deteriorating to a Larsen score of 67 % of maximum was considerably augmented after the 8-year check-up. The endpoint HAQ index in 81 cases indicated that 13 (16%) patients had the poorest (HAQ 2-3), and 49 (60%) the best outcome (HAQ 0-0.9).

At the end of the study, a total of 29 large-joint arthroplasties had been performed in 16 cases, and of these, three patients had 3 and one had 6 large-joint arthroplasties. The mean Larsen score of 59.2 (SD 30.7) in those with joint replacements was significantly higher ($p = 0.015$) than the 39.2 (SD 25.4) in patients not operated. Also the HAQ index of 1.7 (SD 0.77) was higher ($p = 0.001$) than that in patients without arthroplasties 0.78 (SD 0.72).

The cumulative occurence of amyloidosis at the 20 year check-up was confirmed in 14 patients, (14%) and eight (57%) of them had died. The mean endpoint Larsen score was 57 (median 54) in 14 patients with amyloidosis compared to the patients without amyloidosis with the mean Larsen score of 40 (median 35), $p = 0.026$.

If the definition of severe disease is a Larsen score of 67-100 or HAQ of 2-3 or three large-joint arthroplasties performed, the 20-year incidence of severe outcome in RA was 29% (30/103). There were six patients with an HAQ index of 2-3 (mean 2.25) who had Larsen scores of 0-47 (mean 22.8). Two of them had had one large-joint arthroplasty performed and one patient had three. The other three patients with 3-6 arthroplasties had Larsen scores of 76-100. Thus, requirement of at least three arthroplasties did not add to the severity figure of 29%, and the HAQ index contributed only 6%. Only two patients with three and six arthroplasties respectively fulfilled all three severity criteria: the Larsen score was 76-100, HAQ 2-2.6.

4.5. Seronegative oligoarthritis (V)

The outcome of the seronegative 64 oligoarthritis patients was generally good. Only one patient with HLA-B27 antigen developed bilateral sacroiliitis, and three patients were retired because of arthritis; two with post-traumatic complaints and one with putative psoriatic arthritis. He had the highest Larsen score (0-100) of 14. Usually erosions were mild and were found in only seven patients, in whom the range of endpoint Larsen score was 2-14, mean 6. The HAQ index was 0 in 33, ranging from 0.1 to 0.9 in 12 subjects. By reclassification, the patients were divided in nine diagnostic groups. A total of 62 patients did not fulfil any rheumatological criteria, and thus only putative diagnoses were suggested:

1. PsA (Table 3) was suggested in 19 patients, among whom some psoriasis-related HLA-B antigens were found in 16 patients: seven patients had B13, four Bw16, two B17, one B13 and w16, one Bw16 and 17, one Bw16 and 27. One patient had HLA-B27. Eight patients had relatives with skin psoriasis. Five out of 19 patients had nail changes and seven had suspicion of psoriatic skin disease. One patient had suffered from anterior uveitis and one from dactylitis. Two patients had developed significant AI. One patient evinced erosive sternoclavicular monoarthritis and unilateral scroiliitis at the 8-year check-up, but 12 swollen joints, grade 3 unilateral sacroiliitis and a Larsen score of 14 at the 23-year follow-up.
2. Fourteen patients had HLA-B27-positive oligoarthritis. Two of them suffered from grade 1 unilateral sacroiliitis. In 10 patients the arthritis was predominantly in the lower limbs, seven presenting as monoarthritis at onset. The knee joint was involved in half of these patients (7/14). In one case the talocrural and MCP joints and in three only the MCP joints were affected.
3. ReA was suspected in three HLA-B27-positive and in three B27-negative patients. The reasons were: preceding mild gastrointestinal symtoms in two, erythema nodosum in one B27-negative, low-titre *Yersinia enterocolitica* type 3 antibodies in one, and leukocyturia in two patients. It should be mentioned that these six patients did not from the outset meet the Heinola Follow-up Study criteria for reactive arthritis. In this group, only one B27-positive patient developed grade 1 unilateral sacroiliitis with peripheral chronic reactive arthritis with a Larsen score of 13.
4. Osteoarthrosis was observed in four elderly patients.
5. Two patients had posttraumatic joint swelling and/or arthrosis.
6. One patient had high antinuclear antibody titre on four occasions without any radiographic joint changes. Her disease was proposed to be mild systemic lupus erythematosus (SLE).
7. One patient already fulfilled four ACR 1987 criteria at the outset and later evinced erosions in two MTP joints; obviously she had RA.
8. Although 37% (21/57) of the arthritic patients had HLA-B27, only one of them developed bilateral grade 2 sacroiliitis after the 8-year check-up. A diagnosis of AS in this patient was proposed.
9. In 16 of the original 64 patients (25%) the final diagnosis remained seronegative mono- or oligoarthritis without the smallest other stigma of any specific arthritis.

Table 3. Clinical findings in 19 patients with seronegative oligoarthritis and possible psoriatic arthritis

Patient N:o	HLA B types	Onset of arthritis	Skin disease	Nail disease	Relatives with psoriasis	Other
69	13	Knee			father, brother, sister	
89	13	Knee	head	present	mother, 2 brothers	
168	w16	I IP, knees				
169	w16	Ankles	plantar pustulosis	present		grade I sacroiliitis
172	13, w16	I IP, wrist, knees				
185	27	PIP II, knee, MTP I			brother	
193	13	Ankles				
207	13	Knee	head			iritis
219	w16	Knees	head, elbows			grade I sacroiliitis
265	13	Knee	ankle			
280	w16, 27	knee, ankle, wrist	head	present		periosteal changes
289	17	MCP IV			sister´s daughter	dactylitis, aortic valve insufficiency operated
294	w16, 17	Knees	legs		mother, brother	
303	w35, 40	Knee			mother	
340	13	Knee				painful jaws for five years
353	w16	Knee	balanitis			
458	13	Knee		present		
465	12, w40	Sternoclavicular			aunt	grade III unilateral sacroiliitis
1039	17	Knee		present	2 sisters	aortic valve insufficiency

PIP, IP: Proximal, interphalangeal. MCP: Metacarpophalangeal. MTP: Metatarsophalangeal.

5. DISCUSSION

5.1. Representativity of patient cohort

The Heinola Follow-up Survey of Arthritis constitutes a unique inception cohort study of arthritis. Since only about a third of the incident cases of arthritis from the study area had been caught, the question arises of possible selection biases in the series. On the other hand, in a later study of the incidence of chronic inflammatory rheumatic diseases in Finland during 1975-1990, based on the nationwide sickness insurance scheme (Kaipiainen-Seppänen and Aho 2000), incidence rates for RA, AS and PsA were very close to those recorded in the Follow-up Survey of Arthritis (Isomäki et al. 1978). Similar annual incidence figures for inflammatory joint diseases were observed in a population-based study in Sweden (Söderlin et al. 2002). Thus, the arthritis cases in the present studies may be regarded as representative of Finnish arthritis patients.

5.2.Treatment

On follow-up commencement in 1973 GSTM and hydroxychloroquine were the only DMARDs used. The present epidemiological series is the first in which as many as 90% of the patients had been treated with DMARDs during the first six months. However, GSTM treatment was often discontinued because of side-effects, which would appear to be the reason for the high rate of joint destruction seen at the 8-year check-up in the Heinola Follow-up Survey of Arthritis. After that check-up, carried out in 1982, treatment of RA had become more vigorous with the advent of methotrexate, sulphasalazine and azathioprine, and it will thus in the future be possible to determine whether more aggressive DMARD therapy instituted early in the disease course will lead to better long-term results in RF-positive patients (Möttönen et al. 1999).

5.3. Outcome measurements in rheumatoid arthritis

The definition of outcome in RA is somewhat controversial. The classic suggestion for outcome measures is that by Fries, including death, discomfort, disability, drug toxicity, and dollar cost (Fries et al. 1980). Subsequently Fries expanded the goals of measuring outcome in RA from control of synovitis to minimizing side-effects of therapy, maintaining function, improving quality of life and cost effectiveness (Fries 1983).
In practice, joint destruction is emphasized and the strength of the relationship between structural damage and functional disability is of particular interest. The methods used should match together and follow-up studies should be long enough to achieve plausibility. Previously Steinbrocker's functional classes from I to IV (Steinbrocker et al. 1949) and after 1980 the HAQ index (Fries et al. 1980) have been widely used to measure disability.

Structural damage, the result of long-lasting inflammation, is usually assessed by the Larsen or Sharp methods or their modifications. Already the 8-year follow-up study in the present series confirmed that radiographic scores showed high correlations with joint score, function score, ESR and CRP (Kaarela and Sarna 1993).

The relationship between functional disability and structural damage was recently reviewed by Scott et al. (2000). The annual increase in radiographic joint damage is fairly constant, amounting to 1.6-1.9% of possible maximal damage when the average annual rise in HAQ index remains 1%. In the earliest phase of RA, radiographic damage and the HAQ index are not

related. Most patients with early RA (during the first 5 to 8 years of the disease) evince little radiographic damage but considerable disability. Thus, the correlation coefficient between radiographic damage and HAQ index is no higher than 0.3-0.5. In a later phase (> 8 years), as the radiographic damage in joints increases, the relationship becomes more pronounced, rising to 0.68 in 10-12 years (Scott et al. 2000). This would mean that in early phases of the disease the HAQ index is mainly a measure of the inflammatory process and in later phases of structural damage, as also suggested by Kirwan (1999).

In a study by Kagyeama et al.(1998) it became apparent that patients with three or more lower limb arthroplasties of large joints have significantly poorer life prognosis than those with fewer replacements. Drossaers-Bakker et al. (2000) in the Netherlands determined the relative contributions of radiographic damage to large and small joints, of disease activity and the HAQ index to each other in a 12-year follow-up study of 105 female patients with RA of recent onset. At the endpoint 54 % of the subjects had at least one erosive large joint and the median Larsen score in 12 large-joints (range from 0 to 60) was 3 and the median Sharp score (range 0 to 428) in hands and feet 145. The correlation between the HAQ score and radiographic damage to either the small or the large joints was similar, and the univariate correlations of the Larsen score in large-joints with the Sharp score in small joints and the HAQ index were 0.76 and 0.60, respectively. Disease activity and radiographic damage in large joints were the major determinants of the HAQ index. Structural damage in joints, as assessed on plain films can be used as a surrogate marker for clinical outcome (van der Heijde 2001).

5.4. Prediction of outcome in rheumatoid arthritis

Outcome in a chronic disease is multifactorial and quite obviously related to disease severity or factors on which the physician has little influence (Gordon et al. 1990). Genetically related and environmentally associated determinants interact over time, contributing to the development of RA. The genetic component is probably oligogenic and patients labelled as having RA show a wide spectrum of clinical phenotypes (Ollier et al. 2001). Most subjects with RF-positive RA already start to deteriorate radiographically within one to two years from the beginning of the disease (Brook et al. 1977, Isomäki et al. 1988, Belt et al. 1998). However, even a highly destructive RA can begin slowly, and the institution of effective therapies thus may be delayed. Although some patients with RF-positive RA may have a good prognosis, in 20% the outcome is poor (Möttönen et al. 1996).
The ideal clinical predictor would be one which is readily available in all types of rheumatological practice, acceptable to patients, easy to administer and cheap, and potentially useful in many contexts, reflecting pathogenesis, pathophysiology or psychological coping mechanisms (Kirwan and Quilty 1997).

Predicting RA outcome is crucial for optimal clinical management. It would be desirable to distinguish with high likelihood patients with an untoward outcome with an eye to treating them with appropriately aggressive therapy at an early stage. This is now even more important since new DMARDs, including leflunomide, combination DMARD therapies, and biological therapies are available which can markedly retard the progression of RA (Maini et al. 1999, Möttönen et al. 1999, Smolen et al. 1999, Weinblatt et al. 1999).

In the present study (I) only RF-positive RA patients were included, and thus RF could not be taken into account as a prognostic factor. According to this study the prognostic value of 19 different entry variables in predicting the late outcome in RA patients as measured by Larsen

score and HAQ index was poor. The highest association (0.33) was observed between the onset and the endpoint Larsen scores. An association of old age at onset (0.30), morning stiffness (0.28) and grip strength (0.24) was found with the 20-year HAQ index.

In the previous Heinola Follow-up Study of Arthritis a total of 98 symptoms and signs were recorded at entry and were chosen as putative predictive factors. At the 8-year follow-up of 200 subjects with probable RA, seronegative and seropositive RA, the outcome was measured by joint score, function score, the sum of ESR and CRP values, a Larsen score of 0-200 and outcome index composed of the preceding (Kaarela 1985). Depending on the measure of outcome, from 10 to 39 of the predicting factors correlated highly significantly ($p < 0.001$) with the outcome, but at best only 14 variables showed $0.40 < r < 0.58$ correlations (Pearson's correlation coefficient). Symmetrical polyarthritis in peripheral joints, the presence of RF, radiographically detectable joint changes, morning stiffness, high ESR, and advanced age, mainly in this order, correlated best with the poorest outcome. It might be mentioned, in view of the heterogeneity of that series, that features typical of RA had the highest coefficients, emphasizing the significance of early diagnosis of RA (Kaarela 1985).

In several studies the strength of evidence concerning predictive factors for RA is generally negligible. Similarly the results of the present prospective 20-year study in ascertaining whether the variables at onset would correlate with the endpoint outcome in RF-positive RA were mostly insignificant. The Larsen score and functional status were of some benefit. Nonetheless, the best prognostic approach is to monitor the patient and to extinguish the inflammation in the joints. Early and effective immunosuppressive treatment is the only relevant prognostic factor in RA (Albers et al. 2001).

5.5. Remission in rheumatoid arthritis

Although RA is a chronic, frequently progressive disorder, a certain proportion of patients remit spontaneously (Corrigan et al. 1974, Harrison et al. 1996,) or with therapy (Rothermich et al. 1976, Sharp et al. 1982). Since the 1920s, numerous studies have examined remission in patients with RA. The definition of remission used in these studies was often imprecise and early studies of RA through the 1920-40s and even later included patients who today would not be considered to have RA (Wolfe and Hawley 1985).

Regardless of clinical remission, radiographic deterioration in joints may proceed. It should be pointed out that Mulherin et al. (1996) found a striking contrast between improvement in measures of disease activity and simultaneous radiographic progression of joint destruction. On the other hand Fex et al. (1996) in a prospective follow-up study of subjects with RA, reported that values for morning stiffness, pain scores, general health, Ritchie Articular Index for tender joints, HAQ scores, ESR, and blood hemoglobin were similar to baseline after 5-6 years, while radiographic scores indicated significant progression.

The radiographic image of a peripheral joint is a reliable and cumulatively useful document of permanent destruction of bone and cartilage. A number of inception cohorts have been followed for progression of radiographic changes to 5-10 years, but only limited data are available covering a period up to 20 years (Scott et al. 1987, Kaarela and Kautiainen 1997, Graudal et al. 1998, Wolfe and Zwillich 1998). It seems that there are patients in whom this radiographic progression does not continue but ends in radiographic remission. However, very few data have been published dealing with this issue. The desirable patient outcome in RA is to achieve a clinical and radiogaphic stable remission.

Radiographic remission was noted in 27 (26%) out of 102 RA patients over 20 years in the Heinola Follow-up Survey of Arthritis (Study III). This remission figure was not seen before the 20-year check-up because half of the remissions occurred between the 15- and 20-year check-ups. The role of DMARD treatment in inducing remission remained elusive. Significant differences in activity measures of RA were noted at the 8-year and 20-year check-ups between patients with radiographic remission and those with evidence of continuing progression, suggesting that radiographic remission was often associated with diminishing activity of RA. Estimation of serial radiographs combined with clinical data thus gives a reliable assessment of remission in RA.

5.6. Severe outcome in rheumatoid arthritis

The concept of severity is difficult to define. Patients with severe disease are those who will ultimately have the worst outcome, that is, those who will die prematurely or have the poorest quality of life.

In 1934 Holsti and Rantasalo assessed 1177 subjects with chronic arthritis of whom 29% were partially and 41% totally disabled (Holsti and Rantasalo 1936). However, no definition was given for the expressions partial and total disablement. In another classic study, Rasker and Cosh (1987) reported that only 30 of their initial 100 patients with definite or classical RA had no or only moderate restriction of physical activity after a follow-up of 20 years; on the other hand, 46 patients had died and in 17 of them death was due to or related to RA.

A RF-positive RA patient with a high number of swollen joints and very high ESR and serum CRP is generally considered to have a severe disease, but with effective treatment its outcome is not necessarily severe. It is indeed possible, although by no means proven, that such patients may respond well to modern drug regimens (Maini et al. 1999, Weinblatt et al. 1999). On the other hand, RA with severe outcome may develop slowly, manifesting as disability measured by the HAQ index, high Larsen score for peripheral joints, need to perform large-joint arthroplasties, and cumulative incidence of amyloidosis. Using these parameters, the 20-year incidence of severe outcome of RA was 29% (30/103) in the present study (IV), where the median progression of destruction in patients with RF-positive RA was 2-3% yearly. No severe destruction of peripheral joints appeared during the first three years, but was noted at the 8-year check-up. Theoretically, the outcome according to different yearly progression rates is shown in Figure 1. A yearly progression rate of 5% augurs severe outcome after 20 years.

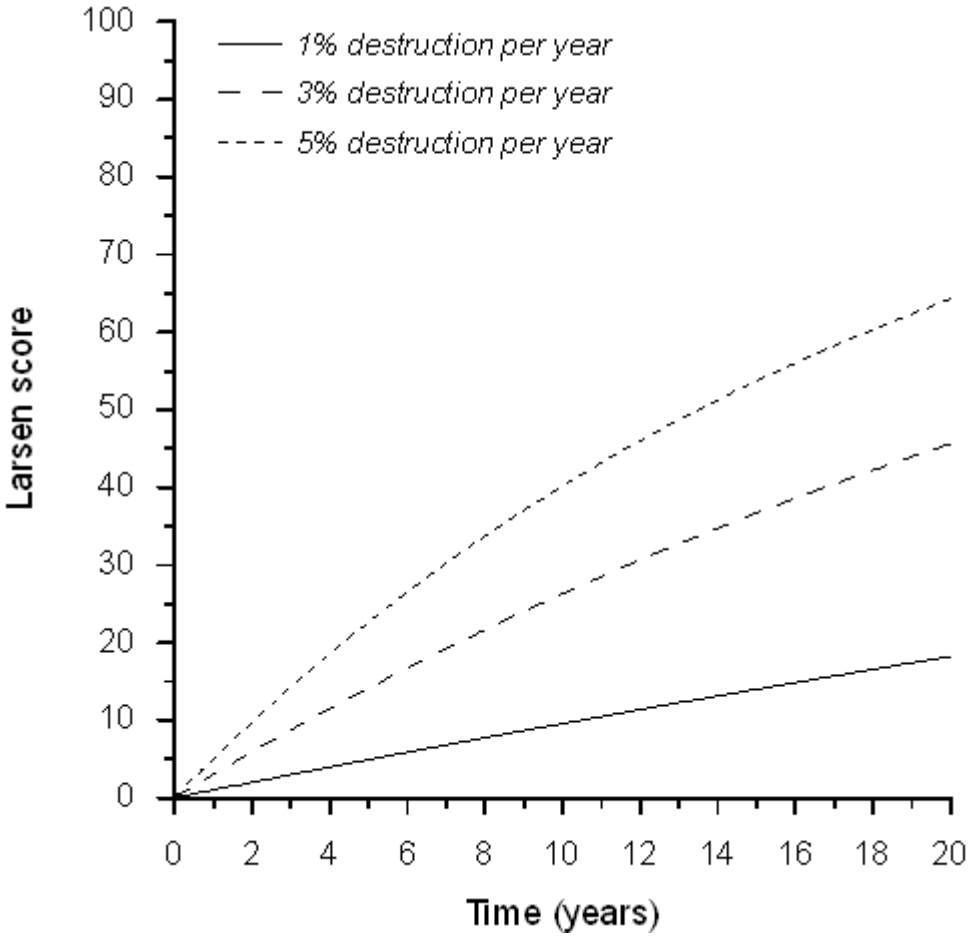

Figure 1. Theoretical progression of joint damage according to yearly destruction measured by Larsen score of 0-100

In the present work of the Heinola Follow-up Survey of Arthritis, hips were the joints most frequently replaced over the 20 years (15 hips, 10 knees). It has been shown that in RF-positive RA a Larsen score of 0-100 for peripheral joints correlates significantly with destruction in hips, glenohumeral, acromioclavicular and elbow joints over 15 years (Lehtimäki et al. 1998, Lehtinen et al. 1999, 2000, 2001). In the afore-mentioned study by Drossaers-Bakker et al. (2000) a significant correlation (0.76 Spearman) was also observed between radiographic damage in hands and feet, and in all large-joints. Peripheral joint destruction settled the degree of variance in HAQ index almost as well as that in all joints: 59% versus 61%, respectively.

As already noted, most of the patients in the present study (IV) were treated with GSTM and/or hydroxychloroquine at the start of the follow-up in 1973. GSTM was often discontinued because of side-effects. The arsenal of DMARDs became more extensive in Finland only after 1982, when at that 8-year check-up a high number of destructive joints were already seen.

The 20-year mortality among 121 RA patients (40 men and 81 women) in The Heinola Follow-up Survey of Arthritis was 35 (29%) (Isomäki et al. 1995). The cause of death was cardiovascular disease in 17, cancer in 8, RA in 5 and other disease in 5 patients. Amyloidosis was the cause of death in three patients, rheumatoid pulmonary disease in one, and in one patient the cause was unknown.The standardized mortality ratio (SMR) was 1.09. In a population-based US study (Gabriel et al. 2003) covering over 40 years in 1994, patients with RA had a significantly shorter survival than that expected in the population ($p < 0.001$). The SMR for RA

was 1.27 (in women 1.41, in men 1.08) and the presence of extra-articular manifestations was the strongest predictor of mortality after adjusting for sex, age, body mass index, smoking and RF positivity, respectively.

The simultaneous use of the Larsen score of 0-100, the HAQ index, and the number of arthroplasties performed in large joints together with the frequency of amyloidosis provides one means of measuring the severity of RA. The present result is the first community-based epidemiological survey in which the 20-year severity of RF-positive RA has been determined using these four different endpoint characteristics.

5.7. Amyloidosis

The AA (secondary) type of amyloidosis is a complication of severe, long-lasting inflammation occurring in rheumatic diseases or in chronic infections. The diagnosis of amyloidosis in a subject with RA and proteinuria, when not controlled with proper treatment, often means marked dysfunction of organs and premature death (Gillmore et al. 2001).

The Heinola Follow-up Survey of Arthritis was the first inception cohort in which an attempt was made to study the incidence of amyloidosis in RA. The cumulative incidence after 15 years was 11% (Tiitinen et al. 1993), after 20 years 14% (Study IV), and after 25 years 16% (Kaarela 2002). Nowadays, with the use of more effective DMARDs, several authors have suggested that the incidence of amyloidosis is decreasing (Laiho et al. 1999, Sokka et al.1999 b). The present study also revealed that subjects with amyloidosis had a more severe disease and at the same time worse joint destruction than patients without amyloidosis.

5.8. Work disability in rheumatoid arthritis

The consequences of RA for the individual and for society are serious in that ability to work is lost in the paid labour force. In Finland this means withdrawal from work life prior to the normal retirement age of 65 years. Most of the data on work disability in RA have been collected retrospectively in patients with longstanding disease. Frequently, work disability is the final outcome of a long process of accomodating work to the disease, this involving changes in working conditions and changes in jobs. In many studies concerning work disability in RA, physician's clinical ratings have not been especially important, and often these have not been included in the variance explained in work disability models.

In a cross-sectional study of residents in Turku, Finland, Sourander and Laine observed (1969) that 21% of 367 RA patients were permanently unable to work, 10% of men and 15% of women on light work and correspondingly 43% of men and 39% women on heavy work. Mäkisara and Mäkisara (1982) found that 40% of RA patients were permanently unable to work after 5 years from falling ill with RA, 50% after 10 years and 67% after 15 years, respectively. Almost all patients with light work and extensive education nevertheless retained their work capacity.

Several cohort studies of recent onset RA have shown that about one third of RA patients of working age are already on disability pension after three years from the onset of disease (Nissilä et al. 1983, Doeglas et al. 1995, Fex et al. 1998), and many had stopped working during the first year after onset of RA and even before inclusion in the study (Fex et al. 1998).
In the 8-year analysis in the Heinola Follow-up Survey of Arthritis, Kaarela et al. (1987) assessed 103 RA patients; 15% had more than the basic compulsory education, while the figure

for the whole Finnish population in 1970 was 16%. Vocational training had been completed by 32% of subjects as against 34% of the population aged 26-64, correspondingly. The extent of education was approximately the same in patients able vs. unable to work. At the 8-year check-up the degree of physical effort for the 37 working subjects was light work in 25%, moderately heavy work in 65% and heavy work in 8%. The corresponding figures for 44 subjects unable to work were 20%, 48% and 32%, respectively. Only as regards heavy work did the groups differ significantly ($p < 0.01$). The influence of educational level and profession on work disability was not obvious in that Heinola Follow-up Survey of Arthritis study by reason of the typical low educational level in the 1970s, but the effect of education on work abilities has been evident in subsequent studies.

There are only few work disability studies covering a period of 15 years or more among patients suffering from RA. In a study by Yelin et al. (1987), 50% of patients had stopped working at 10 years, 60% in 15 years and 90% at 30 years. Wolfe and Hawley (1998) found work disability to occur in 25% of the patients by 6 years and in 50% by 21 years. The figures are similar to those described by Hakala et al. (1994) in a study including 91 RA patients from Northern Finland with a mean duration of disease of 16 years, where the mean HAQ index was 0.86 and the mean Larsen score 40% of maximum at endpoint.

Proper function of the hand is a crucial prognostic factor of work ability in many occupations. The wrists are involved early in RA and deterioration proceeds rapidly (Wilson 1986, Hämäläinen et al. 1992, Terrano et al. 1995), contributing markedly to work disability.

In the Heinola Follow-up Survey of Arthritis the work disability among patients with RA reached 31% after one year and 80% after 20 years (Study II). A significant association was found between the HAQ index and work disability when the Larsen score had been taken to account in multiple regression analysis, whereas no independent role remained for the Larsen score itself. The results of this long-term inception cohort study are fairly similar to those in other studies from that epoch, although RF-negative patients were not included. The significance of treament was not the same as in later studies with more effective DMARD treatment and better results (Sokka et al. 1999 a, Puolakka et al. 2002). In any case it must be taken into account that work disability rates may be influenced by differences between the social security systems in Central and Northern Europe compared to American and other societies, as well as by employment rates and other characteristics of the labour market (Mau et al. 1996).

The burden of severe RA for society lies in the economic impact of the disease (Meenan et al. 1981, Pincus 1995). Using the Markov model (Kobelt et al. 1999), Jönsson et al. (1997) calculated that the total expected costs for the RA cohort in the present studies over a 15-year period amounted to 114 000 € and to 494 000 € (discounted 3%) when state of health was defined according to HAQ and Larsen scores, respectively. Indirect costs accounted for 70–75% of the total costs. The Markov model is a simulation model which can be used to assess disease progression and costs of RA and constitutes a useful tool in calculating the cost-effectiveness of different interventions aimed at changing the progression of disease.

In conclusion, the most important predictors for work disability are high disease activity, low educational level, blue-collar work, and age over 50 years.

5.9. Seronegative oligoarthritis

The seronegative spondyloarthritides comprise a group of inflammatory joint diseases which are classified together because they share many clinical, epidemiological and genetic features. Although once considered variants of RA they are now known to be distinct entities, and are characterized by axial and peripheral arthritis, absence of RF, increased frequency of HLA-B27, overlapping syndromes, familial aggregation, and mutual association within patients and families (Francois et al.1995).

In the group of SpAs the most common condition is uSpA, which has a frequency close to that of AS. USpA has not often been an object of investigation, partly because the criteria for diagnosing this entity have not until recently been strictly adhered to (Dougados et al. 1991). In a Swedish study, the annual incidence of undifferentiated arthritis was 41/100 000 (Söderlin et al. 2002). At the 8-year check-up in the Heinola Follow-up Survey of Arthritis, patients with nonspecific arthritis were assessed, and 64 were classified with the more specific term of seronegative oligoarthritis. They were followed for up to 23 years and their relations to spondyloarthropathies were re-evaluated and the outcome measured. At the 14-year check-up a quarter of the patients with seronegative oligoarthritis were estimated to have hidden psoriatic arthritis (Kaarela et al. 1989). In the present study this seemed to be the suggested diagnosis in 30 % (19/64) of patients (Study V). Although the prevalence of true PsA was quite low at the 3-year check-up in the Heinola Follow-up Survey of Arthritis (14/446) (Nissilä et al. 1983), it seems that the group of hidden PsA was the largest among the subjects with seronegative oligoarthritis.

There are only few studies available regarding the incidence and prevalence of PsA in the population. The earlier prevalence figures for psoriasis and PsA were 1.2% and 0.1%, respectively (Baker et al. 1966, Wright et al. 1976), while one recent work in the primary care setting has found prevalences of 1.7 and 0.3% (Kay et al. 1999). The annual incidence of PsA in the Finnish population was estimated to be 6.1/100 000 adults (Kaipiainen-Seppänen and Aho 2000). Several studies have proposed genetic factors for susceptibility to PsA and its expression (Gladman et al. 1986, 1995, 1998). It has become evident that there are genes on the short arm of chromosome 6 which predispose to PsA. The HLA antigens B13, B17, B38, B39, Cw6, and DR7 have been implicated (Eastmond et al. 1994, Elder et al. 1994, Gladman et al. 1998) and molecular DNA techniques have been applied to identify alleles of HLA-C locus. (Elder et al. 1994, Enerback et al. 1997). The HLA-Cw*0602 allele has been found to be increased among patients with PsA as compared to controls, and was associated with an earlier age of onset of psoriasis and PsA (Gladman et al. 1998).

In the present study (V), 33% (16/57) of arthritic patients had at least one of the psoriasis-related HLA antigens. Table 4. shows the prevalence of some HLA antigens in 14 752 Finnish bone marrow donors. The HLA antigens are after all only suggestive markers of psoriasis and careful clinical examination and a search for psoriasis in first-degree relatives are more important issues. In a Swedish cross-sectional study of 88 subjects with PsA, Alenius et al. (2002) reported that HLA-B17, B37 and B62 were significantly increased. However, in multivariate analyses clinical manifestations were more reliable predictors of joint damage than were specific HLA antigens. These antigens seemed rather to modify the expression of joint disease than to be involved in disease susceptibility.

Table 4. Prevalence (%) of some HLA antigens in 14 753 Finnish bone marrow donors. Dr. Jukka Partanen, Finnish Red Cross Blood Transfusion Service 2003.

HLA antigens	Prevalence (%)
HLA-B7	25.8
HLA-B12	15.3
HLA-B13	5.9
HLA-B16	9.6
HLA-B17	3.2
HLA-B22	4.6
HLA-B27	15.3
HLA-B35	26.4
HLA-B40	17.3
HLA-DR1	32.9
HLA-DR4	26.2
HLA-DR7	11.7

HLA-B27 was found in 37% (21/57) of the patients with seronegative oligoarthritis in the present study (V), while only one subject developed bilateral sacroiliitis after 8 years` follow-up when 19 of the original 441 patients had the diagnosis AS (Kaarela et al. 1995). In the Finnish prevalence figures, HLA-B27 is observed in 15.3% and AS respectively only in 0.15% of the population (Kaipiainen-Seppänen et al. 1997). It is thus obvious that HLA-B27 positivity is not as such sufficient to predispose to AS. Studies in AS patients have detected a linkage to chromosome 19, providing evidence that genes on it may be involved in AS (Reveille 2002). Schattenkirchner and Krüger (1987) reported that 26% of patients with HLA-B27 positivity had a diagnosis of seronegative oligoarthritis at entry and 34% of the subjects attained remission.

The putative diagnosis of the study was ReA in 11%. The occurrence of ReA varies among populations and the susceptibility to it is the greatest in young adults, in whom 0.2-12% fall ill after a triggering infection. HLA-B27-positivity regulates rather the severity of than the susceptibility to arthritis (Aho et al. 1975, Leirisalo-Repo et al. 1982, 1987, Inman et al. 1988). In this present study, only one HLA-B27-positive patient with reactive arthritis evinced grade 1 unilateral sacroiliitis and chronic arthritis with four swollen joints and a Larsen score of 13 at endpoint.

Preliminary European criteria for the classification of spondylarthropathy (ESSG Criteria) were published in 1991 (Dougados et al.1991). In 25% of the patients (16/64) in the present study the diagnosis remained seronegative oligoarthritis. Correspondingly, in 27% (109/403) of the patients in the above-mentioned European study, the disease could not be classified and remained undifferentiated spondyloarthropathy. The basis for the ESSG criteria is inflammatory spinal pain or synovitis, whereas in this inception cohort it was preliminarily a swollen joint. This explains the small number of AS cases (4.5%, 20/441) in the whole Heinola material.

Arnett et al. (1988) stated that one reason for the revision of the ARA 1987 classification criteria for RA was that seronegative oligoarthritis is not RA. In the present study, only one patient with seronegative oligoarthritis fulfilled four ARA 1987 criteria for RA. The outcome of seronegative oligoarthritis would appear to be mostly favourable as in uSpA, in contrast to seropositive RA (Kaarela et al. 1984, 2003). Only one of the arthritic patients had retired from work because of joint disease complaints. The functional outcome was also excellent when analysed by HAQ index. This should have implications for therapy at onset of the disease avoiding unnecessary heavy drug therapy, and most of all, in declaring a probable good prognosis to the patient (Dougados and Hochberg 2002).

6. SUMMARY AND CONCLUSIONS

1. When 19 prognostic factors were investigated at the very early onset of RA in 103 RF-positive patients, only blood platelets, serum IgG and a moderately elevated Larsen score augured the 20-year Larsen score of 0-100, and on the other hand, old age, function score, morning stiffness, grip strength and serum orosomucoid the 20-year HAQ score. The correlations were however poor. According to the literature, early effective DMARD therapy seems to be the best prognostic factor.

2. During the follow-up period of 20 years, work disability increased rapidly among the 103 RF-positive RA patients of working age investigated: after 1 year it was 31% (95% CI 21-40) and after 20 years as high as 80% (95% CI 70-89). The mean HAQ index was 0.96 and the mean Larsen score 45% of the maximum value at endpoint of observation. These results are illustrative of the serious nature and the economic impact of RF-positive RA.

3. One quarter of RF-positive RA patients ended up in permanent radiographic remission over 20 years, half of these after only 15 years. The patients in radiographic remission had fewer or no DMARDs at the start of remission. Thus the result portrays rather the natural course of RA than the effectiveness of traditional DMARDs.

4. With three simple yardsticks, the Larsen score of 0-100, the HAQ index, the number of large-joint arthroplasties performed, and the cumulative number of patients with amyloidosis, severe outcome of RF-positive RA over 20 years was assessed for the first time. Approximately one third of RA patients ended up in severe, one third in moderate and one third in mild disease. The 20-year incidence of amyloidosis was 14 %, indicating the ineffectiveness of the reported treatments. Patients with amyloidosis had significantly more severe disease than those without.

5. Seronegative oligoarthritis is a benign arthritis of variable causes mostly affecting the knee joint. PsA was the putative diagnosis in about a third of subjects and in 37% the HLA-B27 antigen was present. Most patients were probably suffering from mild spondyloarthropathy with excellent 23-year outcome. In one quarter of the patients the clinical diagnosis remained seronegative oligoarthritis.

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