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# Early arthritis and rheumatoid arthritis in Germany

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## ABSTRACT

*Early arthritis is challenging because the clinical picture often does not allow a distinction between rheumatoid arthritis (RA), self-limiting disease, and other forms of inflammatory arthritis. In Germany the first early synovitis clinic and several inception cohorts of patients with early RA were initiated and evaluated during the 1980s and 1990s to learn more about diagnostic classification, psycho-social problems and socio-economical status including sick-leave, work loss, and indirect costs of patients with early arthritis and early RA. Unclassified arthritis was described as the most frequent diagnosis and the term "undifferentiated arthritis" was chosen to underline the heterogeneity of these arthritides and the preliminary state of this classification as a working diagnosis.*

*A large National Databank of the German Regional Collaborative Arthritis Centres has been established over the last 10 years. In total, there are some 170,000 cases in the database. Moreover, a prospective multicentre inception cohort of early RA of less than 1 year's disease duration has been started recently to evaluate parameters of potential relevance for the pathogenesis of RA and eventually for the prediction of erosive disease. Studies are in progress to test the diagnostic performance of specific antibodies and antibody patterns for RA. Another topic of research addresses the identification of bacterial DNA in synovial fluid and synovial tissues to improve the differentiation of patients with reactive arthritis from those with early RA and to narrow the working diagnosis of undifferentiated arthritis.*

## Introduction

Early arthritis has long been a challenging and controversial area. There are difficulties in making an accurate diagnosis in patients with early disease because signs and symptoms frequently are very similar for rheumatoid arthritis (RA), self limiting disease or other forms of inflammatory arthritis. Lawrence and Bennett were the first to draw attention to a benign, self-limiting, seronegative arthritis which they called benign polyarthritis (1). Further epidemiological and clinical descriptions over the following years clearly established that unclassified arthritis represented the most common type of early arthritis (2, 3). For this type of arthritis, we adapted the term "undifferentiated arthritis" (UA) from Calin and Marks' case against seronegative RA, and emphasized not only the undefined origin but also the heterogeneity of these arthritides (Table I) (4,5). Moreover, the term "undifferentiated" underlines the preliminary state of this classification as a working diagnosis, which indicates a regular follow-up and willingness to change the diagnosis to a definite disease category whenever possible.

With this issue in mind, two initiatives were begun in Germany during the 1980s with the aim to investigate and to better understand early RA and undifferentiated arthritis. Raspe and Mau in Hannover followed an inception cohort of patients with early arthritis and early RA to learn more about the nosography, nosology, and diagnostic criteria for early arthritides and, in cases of early RA, to describe the associated social and emotional problems (6,7). At the same time we established in

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**Table I.** Heterogeneity of the diseases included and the preliminary state of classification as "undifferentiated" arthritis.

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- \* Early stage of a definite rheumatic disease, that will be differentiated later on
  - \* Undifferentiated = forme fruste of a definite rheumatic disease
  - \* Overlap syndrome, that can not be differentiated into only one definite rheumatic disease
  - \* Arthritis of unknown origin, which may be differentiated in the future
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Düsseldorf an early synovitis out-patient clinic with the intention to better differentiate between early RA and other arthritides. Furthermore, a comprehensive diagnostic program of serological, microbiological, and immunogenetic laboratory tests was applied to differentiate reactive arthritides and spondylarthropathies from early RA (2, 3, 5).

In the 1990s the Regional Collaborative Arthritis Centres were established in Germany which implemented the national databank to collect annually a large number of patients with rheumatic diseases including early RA (8). Finally, in 1999, supported by a grant from the German Ministry of Research, the German Rheumatology Competence Network was funded to connect basic research, clinical research, and health outcome research, with the ultimate aim of improving high quality research by the horizontal and vertical integration of the most active rheumatology research groups in Germany. Inception cohorts of early RA of less than 2 years duration and of spondy-

larthropathies including undifferentiated spondylarthropathy and juvenile spondylarthropathy of less than 3 years are included in this program.

In this chapter, we summarize the major results and perspectives from these German experiences which are related to the topic of early RA and early arthritides.

#### Undifferentiated arthritis and undifferentiated spondyloarthritis as a challenge for classification and diagnosis

When we started the early synovitis out-patient clinic in Düsseldorf the intriguing phenomenon of unclassified arthritis was widely recognized, but none of the available studies gave a comprehensive description including not only clinical parameters, routine laboratory tests, and HLA-B27 tissue typing, but also a laboratory screening program for reactive arthritis in all patients. This comprehensive analysis was to be conducted in all patients, and not only in subgroups of patients with a positive serology or with unclassified

arthritis, in order to compare early definite RA with early unclassified arthritis. The search for reactive arthritis included, in addition to the history of urogenital, gynecological, gastrointestinal, or other infections in all patients, serologic tests for *Streptococci*, *Chlamydia trachomatis*, *Yersinia enterocolitica* and *Pseudotuberculosis*, and *Campylobacter jejuni*. This program was complemented by optional serology for *Borrelia burgdorferi*, *Gonococci*, *Brucella abortus*, and *Salmonella*. Urogenital smears were investigated for *Chlamydia trachomatis* and in case of history of enteritis, stool probes were cultured for pathogenic bacteria.

Diagnoses were made at the first visit on the basis of a clinical decision by one of us (H.Z.), i.e. they were expert diagnoses and not criteria-based. All diagnoses were also retrospectively classified according to the 1958 ARA-criteria and the 1987 revised ACR criteria for RA. All previous "possible" and "probable" RA cases according to the 1958 ARA criteria were reclassified as undifferentiated arthritis in the second analysis (9-11).

As a primary result, only 46% of the patients (n = 217) with inflammatory rheumatic diseases could be given a definite diagnosis (RA 19%, reactive arthritis 11%, ankylosing spondylitis 5%, polymyalgia rheumatica 5%, psoriatic arthritis 3%, others 3%), whereas 54% were regarded as having undifferentiated arthritis (UA) (10). This frequency of UA is in good agreement with a report by Wolfe *et al.* evaluating a cohort of consecutive patients seen within the first two years of disease in a private practice out-patient rheumatological clinic (12). Wolfe *et al.* reported undifferentiated polyarthritis with a frequency of 55.9%, more frequent than RA with 44.1%. Other earlier incidence or cohort studies (7, 13-16) described unclassified arthritis in only 20 - 45% of patients. The major reason for these differences is probably the application of the new 1987 ACR criteria instead of the older 1958 criteria which classified RA as definite, probable and possible. Excluding all other diagnoses and using only the two diag-

**Table II.** How changes in terminology and classification have changed the distribution of diagnoses in early arthritis cohorts (expressed as percentages).

Diagnosis	Follow-up study of arthritis Heinola (14) 1978 (n = 332)		Early synovitis out-patient clinic Düsseldorf (2, 3, 10) 1987 (n=149)		1995 (n=217)
"Non-defined" or "undifferentiated" arthritis	22	] 45	41	] 49	54
Probable RA	23		8		-
Definite RA	19		15		19
Reactive arthritis	7	] 13	14	] 15	11
Reiter's disease	6		1		
Ankylosing spondylitis	4		5		5
Psoriatic arthritis	3		3		3
Sarcoidosis	1		2		1
Systemic CTDs, SLE*	3		2		1*
Others	12		9		6
Total	100		100		100

CTD: connective tissue disease; SLE: systemic lupus erythematoses.

nostic categories, RA and UA, as in the study of Wolfe *et al.*, the relative frequency of UA compared to RA would be even higher, 75% and 25%, respectively.

In this study, in contrast to other reports of early arthritis, we specifically looked for reactive arthritis based on a history of infections and extensive laboratory testing. Nevertheless, the rate of diagnosis of reactive arthritis was not increased, and a large percentage of early synovitis cases could only be classified as "undifferentiated arthritis". Therefore, we concluded that UA remains a challenge to clinics dealing with early synovitis and rheumatic diseases.

Several factors may contribute to this strong concentration of UA in the early synovitis out-patient clinic. Changes in terminology and classification significantly change the frequency and distribution of diagnoses in early arthritis cohorts, as shown in Table II. Our classification of early synovitis was derived from expert diagnoses, not primarily based on the ARA classification criteria as in all previous studies other than Wolfe's. Additionally, recent arthritis was defined as a disease duration of up to 12 months, in contrast to the shorter interval between onset and examination of 6 months in studies (13,14,17) other than those of Mau *et al.* (7) and Wolfe *et al.* (12). The longer disease duration would increase the number of non-self-limiting, early unclassified synovitis. Finally, 74% of the patients diagnosed as having RA were rheumatoid factor positive, a figure which is in agreement with the frequency of 81% positive in Wolfe's study, but in contrast to only 0-53% in the other series (7, 13).

One could therefore assume that classical, seropositive RA would be detected by expert diagnosis, but seronegative RA would be misclassified as UA. Nevertheless, the retrospective use of the modified 1987 ACR criteria for RA in this data set, which was presented in detail in a subsequent paper (11), showed a good diagnostic performance for RA, with a sensitivity of 90% and a specificity of 90%. These figures argue against an assumption that seronegative RA might be misclassified as UA.

The heterogeneity of UA has been emphasized in earlier reports (2-4). In particular, HLA-B27 associated arthritis has been described as an important subgroup of early seronegative peripheral arthritis which may be frequently diagnosed as seronegative RA (18). Rheumatoid factor is another parameter discriminating in follow-up studies between self-limiting early synovitis and persisting arthritis which can develop into RA (12, 19). Therefore, we looked for both subgroups in our cohort of UA. Only 15% were RF-positive and 22% were HLA-B27 positive. Both groups might be in the early stages of RA or spondyloarthropathy, which will develop the typical and definite features of the diseases in the future. Alternatively, they may represent patients with abortive disease, who will never develop the classical picture, or with self-limiting disease going into remission. Data from several studies (7, 12, 17) indicate that "undefined arthritis" and "possible RA" often lead to remission, whereas HLA-B27 positive undifferentiated spondyloarthropathy generally tends to be chronic and to develop into definite AS (20, 21). Based on the follow-up of a limited number of patients with UA in our study, in accordance with other observations (12), most patients (54%) went into complete remission and only a few with active disease developed definite RA (7%) or AS (4%) over the short term of a mean of 26 (range 4-38) months (11).

#### **The national database of the German Regional Collaborative Arthritis Centres**

From 1993 to 1998 the German government funded the implementation of 24 Regional Collaborative Arthritis Centres which are now integrated in the German Society of Rheumatology as a working group devoted to improving the care of rheumatic patients by the integration of all health care providers. These centres comprise rheumatologists with a background in internal medicine or orthopaedics at universities, non-university hospitals, or in individual practices. The national database of the German Collaborative Arthri-

tis Centres was implemented in 1993 as a tool for health services research in rheumatology (8). It has been steadily continued and further developed within the Competence Network Rheumatology since 1999. Presently, 22 centres with 111 rheumatologic care units are participating. In 2000, 30,438 patients with inflammatory rheumatic diseases were recruited. In total, there are some 170,000 cases in the database.

This national database comprises newly referred as well as prevalent cases. Patients seen regularly are registered once a year, if possible in the same month or at least the same quarter of the year as in the previous year. For these patients, the same type of information is available for successive years. Rheumatologists are instructed to register every outpatient with inflammatory rheumatic disease except for those who refuse to participate. In addition, in-patients as well as patients with osteoarthritis, soft tissue disorders, or back pain are recorded by some of the centres for their own study purposes.

The clinical data sheet includes demographic data (age, sex, insurance), year of onset of symptoms, first visit to the institution, and up to 3 diagnoses made by the rheumatologist. Rheumatologists are asked to make their diagnoses in accordance with agreed classifications, which means that diagnoses (e.g., RA) are based upon the doctor's clinical judgement. RA is only recorded as "definite" if the ACR 1987 criteria are met. All other cases are recorded as "suspected". Drug treatment and physiotherapy are reported as "current treatment" (day of registration) and "treatment within the previous 12 months". In addition, the type of surgeries are recorded as "within the previous 12 months" and "ever before".

The doctor gives a global assessment of the current disease activity (based on a numerical rating scale from 0 to 10) and the severity of disease (based on a 5-item Likert scale). The Steinbrocker functional class is used in a modified form. For patients with RA, 28 joint counts for swollen and tender joints as well as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are recorded by the doctor. The

**Table III.** Characteristics of out-patients from the year 1998 in the National Database of the German Regional Collaborative Arthritis Centres (8).

	No. of cases	Definite disease (%)	Mean age at onset (years)	Mean age duration (years)
Rheumatoid arthritis, RF+	8,104	93.4	45.7	10.3
Rheumatoid arthritis, RF-	4,888	77.9	47.7	7.9
Ankylosing spondylitis	1,486	82.8	28.5	14.5
Other seronegative SpA	1,524	80.9	35.9	7.7
Psoriatic arthritis	2,119	86.5	39.5	8.6
Reactive arthritis	672	48.7	35.6	3.2
Other arthritides	2,029	73.6	36.3	6.8
SLE	1,211	88.3	32.2	9.6
Scleroderma	323	80.2	44.8	7.8
Sjögren's syndrome	453	75.5	41.2	9.3
Other CTDs	1,287	68.0	39.9	6.9
Polymyalgia rheumatica	998	81.6	63.6	3.2
Other vasculitides	559	78.1	43.7	6.2
Total	25,653	83.0	42.7	8.7

SLE: systemic lupus erythematosus; CTDs: connective tissue diseases; SpA: spondyloarthropathy.

patient's assessment of his/her general health is also recorded. These four measures – swollen joints, tender joints, ESR or CRP, and patient global health – allow a 28-joint count disease activity score (DAS 28) to be calculated.

Diagnoses are registered using a list of 190 diagnoses of the musculoskeletal system which was developed by a sub-committee of the German rheumatological association before the implementation of the database. Eighty of these diagnoses comprise inflammatory rheumatic diseases. This list is more specific and detailed than the International Classification of Disease (ICD), but all diagnoses based on it can be transformed into ICD-9 or ICD-10 codes by a unified dictionary developed by a consensus group.

In addition to the one-page data sheet for the physician, patients are asked to complete a self-administered questionnaire in which they give their treatment histories, admissions to hospitals or rehabilitation clinics, and any in-patient and out-patient treatment. Other questions refer to self-help, social support, and degree of help needed, as well as days of sickness or absence from work. Patients record their current pain and global function (for the previous 7 days) on numerical rating scales (0-10)

and their global well-being on a 5-item scale. Disability is recorded using an 18-item scale, the Hannover functional status questionnaire (FFbH), which is comparable with the HAQ (Health Assessment Questionnaire) but is more widely used in Germany (22, 23).

An initial report described the patient case mix, institutional context, and demographic features of 25,653 patients from the year 1998 (8) (Table III). Additionally, two publications reported the medical and non-medical treatment of patients with RA (n= 12,982) and analysed in a subgroup (n=7,326) practice variations in the treatment of RA among German rheumatologists (24, 25).

In this large database, 64% of the patients with RA had seen a rheumatologist within the first year after disease onset, but overall patients with RA saw a rheumatologist for the first time on average after 1.7 years (20 months). The mean time lag between first symptoms and first consultation of a family doctor was 3 months in RA. These data show that early referral and initiation of treatment by the rheumatologist should be improved, although the time lag between symptom onset and first contact with a rheumatologist has shortened considerably compared with the

1970s and 1980s, when a 3 to 7-year delay in referral to the rheumatologist was reported for most patients with early RA in Germany (26).

In summary, the German National Rheumatological Database of the Regional Collaborative Arthritis Centres, with its core set of items, provides information on a range of inflammatory rheumatic diseases including early RA. This database allows a nationwide overview of patient care and its development over time, the determination of practice variations between centres and single facilities, and analysis of the relationship between therapeutic guidelines and patient care practice. It is now a central evaluation instrument of the Competence Network Rheumatology. Additionally, the database has been the prerequisite for the successful start of the German registry of biologic agents in May 2001 as part of the Competence Network. It has been built up in close cooperation with the Swedish and British registries for biologic agents.

In the future, emphasis will be focused on analyses of longitudinal data which are presently available for 17,749 patients over at least 3 years. In addition, the item pool has recently been enhanced and now allows the performance of comprehensive analyses on the frequency of co-morbidities and the side effects of drugs, as well as on the cost of illness. A system of electronic data entry is under development to replace the present paper-and-pencil recording of data, which should make the database even more useful for the participating centres. They will be able to receive benchmarking data from the system on specific patients or patient groups. Also, longitudinal data concerning single patients will be immediately available to the physicians. This will improve the possibilities of multi-centre studies as well as readiness to contribute to the system.

#### German early RA inception cohort

As part of the Competence Network Rheumatology, a prospective multicentre study on early RA of less than one year's disease duration has been started to evaluate parameters of potential relevance for the pathogenesis of RA and

eventually for the prediction of an erosive disease (27).

In the spring of 2003, about 300 of the finally planned 400 patients were recruited in a network of close collaboration of general practitioners, rheumatologists, and arthritis care units. This cohort will be followed in a long-term observational study for at least 3 years, with a thorough clinical and radiographic documentation of the disease scores. The concomitant collection and central storage of patient material (e.g. sera, DNA) represents a valuable resource that will be made available to research projects on different aspects of RA pathogenesis.

Besides physical examination every 6 months, x-rays of the hands and feet will be evaluated annually to document disease progression. The endpoint of the study is radiological progression of joint destruction. A major focus will be the correlation between scores of radiographic progression and parameters of cartilage breakdown, titres of autoantibodies directed to cartilage matrix proteins and synovial or ubiquitously expressed autoantigenes. This prospective study on early RA constitutes an integral component of all the projects in the Competence Network Rheumatology dealing with aspects of the pathogenesis, diagnosis and treatment of RA. Finally, the RA cohort may serve as a reference group for the investigations on early spondylarthropathies which are currently underway in an inception cohort, collecting patients with ankylosing spondylitis, undifferentiated spondylarthropathy, reactive arthritis, and undifferentiated oligoarthritis (28).

### **Sick-leave, work loss and medical costs in early RA**

Mau and Raspe were the first to investigate prospectively in Germany the occurrence of permanent work disability in patients with early stage RA (disease duration  $\leq 12$  months) for a mean follow-up period of 6 years (29). Of the 132 patients who were referred between December 1982 and September 1987 to the out-patient clinic of the Division of Rheumatology, Medical School Hannover, and who entered into the longitudinal study, 109 (83%) were available

for a physical, laboratory and radiological re-examination after 6 years (S.D.  $\pm 2$  yr). A rapid decline in the employment rate was found within the first 3 years of disease onset. The group with the poorest prognosis was defined by an age  $\geq 50$  years with either an ESR  $\geq 60$  mm/hr or the combination of a modified functional class (1-7)  $\geq 4$  and a disease duration of  $\geq 7$  months.

In the same cohort, Mau and colleagues examined whether measures of rehabilitative medicine and vocational rehabilitation were implemented during the course of early RA. Of those patients receiving a social security pension, only 63% had participated in in-patient rehabilitation programs (30). Despite frequently strenuous job-related physical requirements in 44-70% of the patients with work disability, measures of vocational rehabilitation had been taken in only 26%, vocational retraining in 4%, adaptation of the workplace because of RA in 8%, and reduced working time in 22%. These data demonstrated significant under utilization of rehabilitation medicine and vocational rehabilitation programs in the early phase of RA.

To confirm and to extend the investigations of this monocentric pilot study, Mau and colleagues initiated a second, larger, multicentre prospective study assessing the disease course, work disability, and costs in early RA ( $< 12$  months since first symptom of joint swelling). They recruited 317 consecutive out-patients with a mean disease duration of 6 months  $\pm 3.5$  and a mean age of  $53 \pm 14$  (31) in 5 centres (Division of Rheumatology, Medical School Hannover - H. Zeidler, W. Mau; Ev. Fachkrankenhaus Ratingen - R. Rau, G. Herborn; Klinik Niedersachsen Bad Nenndorf - H. G. Pott; Schoßparkklinik Berlin - R. Alten; and Klinikum Südstadt Rostock - M. Keysser). The patients were recruited from August 1992 to January 1994 and re-examined after one and two years. The total observation time was  $2.5 \pm 0.2$  years.

In a subgroup of this cohort ( $n = 134$ ) of gainfully employed RA patients, sick-leave (SL) due to RA occurred in 76% (32). The duration of SL because of RA was 11 days per month (about one-third

of the disease duration) in males and 8 days per month (1 quarter of the time since the onset of RA) in females. SL due to RA was 5 times longer than expected compared to controls. In addition to SL because of RA, SL due to other causes occurred with a similar duration as in controls. As early as the first year of RA, therefore, the large proportion of patients with SL due to RA and the long SL duration indicate the extent of substantial handicap concerning gainful employment (33).

To understand the significance of the demographic, disease and work characteristics of SL, several indicators – defined as the history of SL as certified by the treating physician – were recorded. In multivariate logistic regression analyses, significant indicators of SL were work conditions, disease activity, pain and age. Additionally, frequent time pressure at work and extra hours of work were important indicators of SL. From these data it was concluded that interventions focussing on an amelioration of the work capacity and thereby on the reduction of SL should concentrate on both control of the disease and very importantly also on the improvement of working conditions (33).

Work disability was assessed over a mean follow-up period of  $6.1 \pm 0.4$  years in this prospective cohort (34). Work disability due to RA occurred in 5% after 1 year of disease duration, and increased to 15% after 2 years, to 20% after 3 years, and to 28% after 6.5 years. Other reasons for leaving the labor force were found in 24%. In multivariate analyses, age  $> 45$  years and the following job-related prognostic indicators for work disability were identified: working under time pressure, limited joint motion interfering with job tasks, feeling overworked, and work status (unskilled blue-collar worker versus white-collar professionals and self-employed persons). In an alternative, final Cox-regression model the variables of "feeling overworked" and work status were replaced by SL duration  $> 8$  weeks within the first year of RA. Therefore, the authors concluded that adequate interventions must begin early in RA, as work disability

**Table IV.** Costs per gainfully employed patient (SE) in US\$. Period I includes the first and second year, and period II the third year after the onset of RA (35).

Period	Sick leave	Work disability	Other work loss	Total
I	10,530 (990)	1,210 (360)	840 (370)	12,580 (1030)
II	2,520 (580)	4,570 (960)	2,800 (780)	9,890 (1210)
I + II	7,640 (740)	2,520 (550)	1,590 (480)	11,750 (1120)

frequently occurs already within the first 3 years. Apart from rheumatological treatment and rehabilitation, the focus should be on pain reduction, improved coping with pain, reduced joint destruction and improved mobility, and working under time pressure should in particular be avoided. Efforts should be made to adjust the workplace in cases of limited joint motion interfering with job tasks. Sick-leave of several weeks duration already within the first year of RA is a "red flag" for impending work disability.

Productivity losses due to sick-leave, work disability and other work losses are the main components leading to indirect costs of RA to society. As yet no systematic evaluation of the impact of these indirect cost components associated with the early phase of RA have been carried out. Therefore, costs due to RA-related sick-leave, work disability, and other work losses were recently assessed using the human capital approach and the friction cost method (35). Variables associated with a reduction in lost productivity were tested by multivariate logistic regression analysis. The mean  $\pm$  SEM annual indirect costs were \$11,750  $\pm$  1,120 per person. During the 3-year period of observation, a marked reduction in costs due to sick-leave was seen, which exceeded the increase in costs due to work disability and other work losses (Table IV). This phenomenon resulted in an overall reduction in indirect costs of 21%. The final logistic regression model of reduced loss of productivity included 3 variables representing occupational aspects: no problems with standing at work (odds ratio [OR] 7.1), no problems with working speed (OR 4.1), and no problems with outdoor work (OR 3.1). Since the absence of problems due to strenuous working

conditions was found to be associated with a reduction in indirect costs, it may be assumed that early intensified vocational rehabilitation, apart from controlling disease activity by adequate treatment, might help to reduce indirect costs. Compared to cost-of illness studies in advanced RA, the results of the indirect cost assessment in early RA reveals similar costs related to productivity losses (35).

#### **Coping and control beliefs in early arthritis**

Attribution of causes, the degree of belief that one is in control of a situation, and anxiety play important roles in coping with arthritis. Therefore, Bräuer and colleagues used the opportunity provided by the German multicenter prospective study on early RA to examine the applicability of a questionnaire on control beliefs (31). In addition to patients fulfilling the ACR criteria for RA ( $n = 232$ ), they included patients classified as having undifferentiated arthritis ( $n = 94$ ). A total of 326 patients with early RA or UA with a disease duration of less than 12 months (mean duration 6 months  $\pm$  3.5, mean age 53  $\pm$  14) were assessed.

Full clinical investigations were performed and patient questionnaires were administered at the outset of the study, after 12 months and after 24 months. A marked influence on coping types could be demonstrated for the covariates of sex, age, cognitive components of anxiety, and the severity of RA. These results should be considered in patient education programs for RA, applying special techniques of behaviour therapy. Such interventions in the early phase of RA might lead to a reduction in cognitive anxiety and thus to more effective coping by patients with RA.

#### **Perspectives**

The diagnosis of arthritis of recent onset and early rheumatoid arthritis remains a challenge to rheumatologists in out-patient facilities and clinics. A large percentage of early synovitis cases can be classified only as undifferentiated arthritis, even if an extensive standardized clinical and laboratory work-up including HLA-B27 tissue typing and a microbiological program to search for reactive arthritis is carried out. The application of the 1987 ACR criteria for the diagnosis of early RA remains controversial. In our experience in an early synovitis out-patient clinic, the performance of the ACR 1987 criteria was very good, whereas other groups and clinics have described lower sensitivities and specificities in the diagnosis of early RA. Future research by the German Rheumatology Competence Network will focus on two approaches to this problem.

First, studies are in progress in the early RA inception cohort to test the diagnostic performance of specific antibodies and antibody patterns for RA. Second, the increasing rate of identification of bacterial DNA in the synovial fluid of patients with undifferentiated arthritis and the development of more sensitive and standardized PCR techniques for the identification of bacterial DNA in synovial fluid and synovial biopsies should ultimately lead to the differentiation of more patients with reactive arthritis from those with early RA and reduce the frequency of undifferentiated arthritis (36-38).

An additional focus must lie on the referral of patients with early arthritis, early RA and early spondylarthropathies. Recognizing that the referral of these patients from primary care physicians to rheumatologists occurs later in the disease course than appears optimal, a working group of the German Regional Collaborative Arthritis Centres is currently developing criteria for early referral to improve diagnosis and treatment, while taking into account health economic considerations.

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