

Identification of Radiologic Healing Phenomena in Patients with Rheumatoid Arthritis

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ABSTRACT. Objective. Conventional radiographic scoring methods in rheumatoid arthritis (RA) are designed to quantify progression and disregard any improvement. Reparative changes observed during longterm followup of RA have rarely been described as healing phenomena. Healing may become increasingly important with the availability of more potent antirheumatic drugs. We investigated whether radiologic healing phenomena can be identified by different observers in a blinded fashion.

Methods. Healing phenomena were defined as (1) reappearance (and sclerosis) of the cortical plate, (2) partial or complete filling in of an erosion, or (3) subchondral bone sclerosis with osteophyte formation (secondary osteoarthritis). Pairs of radiographs of hands, wrists, and forefeet [taken 2 to 8 (mean 4.8) yrs apart] of 34 patients were selected from longterm studies: 24 sets with healing phenomena and 10 with progressive disease without healing. The radiographs were blinded and read in pairs in random order by 3 observers unaware of the patients selected for the study. One observer read the set a second time after 8 weeks, resulting in a total of 4 observations. Thirty-eight joints were rated 0 to 5 depending on the amount of surface destruction. In addition an attempt was made to identify joints with healing phenomena. The data were analyzed with help of descriptive statistics such as means, standard deviations, and frequency tables.

Results. Out of 1292 joints scored at the second time point, 74 had healing phenomena. These joints were identified in a mean of 89% (95/89/88/82%, respectively) in the 4 observations performed by the 3 readers. Patients without healing phenomena were correctly identified by all observers. In 54 joints less typical healing phenomena were seen in all observations. Sixty-two joints with healing in addition to the 74 joints were seen in 3 observations, 76 in 2, and 127 in one observation. All observers agreed that 1090 joints had no healing phenomenon. The 24 patients with healing had a slight reduction in the Ratingen score, while the 10 patients without healing showed a moderate progression. In the group with healing an increase and decrease in the score occurred in the same patients at different joints.

Conclusion. In patients with RA followed for several years healing or reparative changes of erosions can be observed. These phenomena can be identified by different observers with high sensitivity even when the observers are blinded to chronological sequence of the films. (J Rheumatol 2001;28:2608–15)

Key Indexing Terms:

RHEUMATOID ARTHRITIS
SCORING METHODS

RADIOGRAPHY

HEALING PHENOMENA
RATINGEN SCORE

Rheumatoid arthritis (RA) is a chronic inflammatory disease leading to substantial structural damage in affected joints in a considerable proportion of patients. Conventional radiography is still considered the gold standard¹ to demonstrate and quantify this damage because: (1) it best reflects the

amount of destruction that can be quantified by means of generally accepted scoring methods; (2) the technology for taking radiographs is easily available all over the world; and (3) radiographs are lasting documents that do not depend on an immediate evaluation by the observer; they can be randomized and blinded and evaluated later by other investigators. Therefore, radiographs are very helpful means to document the course of the disease in clinical trials or longterm observational studies. Inhibition of progression as documented with radiography is still considered the most important and reliable criterion for disease modification². Consequently, in addition to clinical and biochemical variables of disease activity, radiographs have been included in the core set of endpoint measures in RA clinical trials that follow patients longer than one year³.

The most frequently used scoring systems⁴⁻⁶ and their multiple modifications⁷⁻¹⁷ are designed to quantify the speed

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Submitted March 22, 2001; revision accepted July 31, 2001.

of progressive destruction over time in selected joints of hands, wrists, and feet. However, they are not designed to document improvement: at least when reading films with known chronological sequence phenomena of healing of erosions, bone reconstruction and remodeling of a joint are usually disregarded. Some authors exclude the possibility of a score reduction *expressis verbis* (“once an erosion, always an erosion”)¹⁸ (Sharp, personal communication; Larsen, personal communication). Since in most clinical trials scoring of radiographs was done knowing the chronological order of the films and this method is regarded to be most sensitive to change¹⁸, a change is possible only in the direction of deterioration or — at best — halt of progression, but never a reduction of the score. The Ratingen method¹⁹, however, allows to reduce the score if the eroded joint surface is reduced by (partial) filling in of the erosion with newly formed bone. The same is true for the Genant method^{9,10}. The impossibility to reduce the score is one basis for the opinion that our treatment so far is unable to induce a repair of joint destruction and at best can reduce the pace of deterioration. However, trials where films were scored with unknown sequence²⁰⁻²² have demonstrated that a reduction of the score is possible, indicating improvement.

There are occasional reports in the literature that consider healing of erosions as an endpoint of the disease. In the European literature, the term “secondary osteoarthritis” has been used to describe degenerative joint disease as a consequence of inflammatory joint disease implying an arrest of inflammation. Sharp⁴ mentioned the same sequence of events in the first publication of his method. Dihlmann²³ described healing of erosions and remodeling without the development of deformity as “arthritis reformans.” McCarty²⁴ noted that “erosion healing often accompanies clinical remission.” In clinical trials, healing phenomena have rarely been described since they can be seen only after a complete arrest of inflammation in a particular joint, and clinical trials are too short to capture these events. In our department, we have collected radiographs that show examples of healing phenomena during longterm treatment with disease modifying antirheumatic drugs since the early 1980s and have repeatedly described images of these findings²⁵⁻³⁰. A decrease in the number of joints with “active erosions” and an increase in the number of joints with “inactive” changes during methotrexate (MTX) treatment has been described²⁶. Examples of these phenomena include: (1) the reappearance of a clear visible cortical plate at a site where it was destroyed, (2) partial or complete filling in of erosions and cysts, and (3) sclerosis of the subchondral bone and formation of osteophytes^{18,24}. In addition, subchondral osteoporosis may disappear and bone structure normalize. These phenomena occur only after joints have been clinically inactive for several months. In many cases eroded joint surfaces may become smooth again with time thereby improving functional capacity. Similar to healed bone frac-

tures most joints with reparative changes do not look normal, but the term “healing” seems to be adequate at least in the sense of defect healing with “scars.”

With the availability of more potent antirheumatic drugs (e.g., biologic agents), we may find more reparative changes after shorter periods of treatment and radiologically detectable improvement will be attainable in investigational drug testing.

We aimed to test if phenomena denoted “healing” by one observer can be identified by other observers, and if this is possible even when reading radiographs in random time sequence. Scoring radiographs in clinical trials at random without knowing the chronological order (“paired reading”) was preferred in recent trials^{20-22,31} to avoid the bias of scoring with known chronological sequence (“chronological reading”) and because of better interobserver reliability^{32,33}.

The aim for the participants in this study was to reidentify obvious examples of healing. It was not our intention to investigate the agreement of the readers regarding the identification of all observable healing phenomena.

MATERIALS AND METHODS

One of the authors (GH), who follows many outpatients with RA that were included in longterm studies performed in our department, selected from among these patients 24 cases with — in her opinion — typical healing phenomena. The sets of radiographs of these patients were of hands, wrists, and forefeet taken at 2 time points: (1) at the time of the first radiograph in our department and (2) when healing was clearly visible according to GH. The time points were 2–8 years apart (mean 4.8). Each set had at least one joint with a healing phenomenon; altogether the 24 sets included 74 “index” joints with healing, but obviously in addition there were joints with less typical or less convincing healing phenomena. These joints were not indexed by GH.

In addition to the sets with healing, GH selected at random from her outpatient clinic 10 sets of radiographs with moderate disease progression but without any healing phenomena. All sets were copied and blinded by removing the name of the patient and the date of radiography. Each copy was randomly assigned a 3 digit number to allow films to be read in any order, including single films in random order, pairs at single time points, pairs at random chronological sequence, and pairs in correct chronological order. For this study the radiographs were read setwise in pairs without knowing the chronological order of the films (paired reading).

Readers did not know the number of cases showing healing but they knew the number was large within the study group. Radiographs were read by 3 readers (RR, SW, WP) within 3 days. Two of the 3 readers were experienced in scoring. One of the experienced readers read the radiographs a second time 8 weeks after the first reading.

The following data were recorded: (1) time sequence of the films in the opinion of the readers; (2) the radiographic score of 38 joints scored from 0 to 5 depending on the amount of joint surface destruction¹⁹; (3) identification of joints with healing phenomena (this implies identification of the correct order of the films); and (4) the time needed to read one set of films (readers were assisted by a secretary who recorded the data on a special sheet. Time for mounting and dismounting was not considered).

The raters had discussed which phenomena should be termed healing but there had been no formal training session. They agreed to regard the following changes as healing: (1) reappearance of the cortical plate at a site where it had been destroyed; (2) partial or complete filling in of an erosion; and (3) subchondral bone sclerosis and osteophyte formation (secondary osteoarthritis).

A reduction in the score was also counted as healing. Further, healing

was assumed if the reader diagnosed a progression when failing to state the correct order of the films. It may not be possible for the investigator to state the correct chronological order if an (early) erosion is completely filled in and the joint appears absolutely normal.

Thirty-eight joints in hands and feet had to be evaluated at 2 time points in 34 sets of radiographs, with a total of 2584 joints. In 74 of these 2584 joints characteristic healing phenomena had to be detected. The readers had to identify the first and the second time point in each set, score all joints, and look for healing phenomena in joints with destructive changes.

Statistical analysis. The time for rating, the Ratingen score, and the joint count determined at the 2 readings by the different raters were evaluated with the help of means and standard deviations as descriptive measures of location and scale. The detection rates of healing phenomena and the identification of the true chronological sequence were described using frequency tables.

RESULTS

The mean net reading time for scoring one set of radiographs ranged from 274 to 521 seconds (4.6–9.4 min) for the 3 readers (Table 1). Reader 3, with the least experience in reading and scoring radiographs, needed the most time.

For the experienced readers 1 and 2 (3 readings) the mean Ratingen score increased from around 16.5 at the first time point (T0) to around 20.5 at the second time point (T1), representing a progression from about 8 to 11% of the maximum possible score. Reader 3 scored 13.6, which is 7% of the maximum possible score, and found no increase in the score between T0 and T1.

A mean of 5.0 to 8.3 joints with healing per patient were identified in the 24 patients with healing selected by GH. Out of 1292 joints scored at the second time point, 74 “indexed joints” clearly had “typical” healing phenomena according to GH. These joints were identified in a mean of 89% (95/89/88/82%, respectively) in the 4 readings (Table 2). In addition to these 74 joints, all readers agreed on the presence of (less typical) healing phenomena in another 54 joints. Sixty-two with healing in addition to the 74 joints were seen in 3 ratings (1, 2B, 3). An additional 76 joints were diagnosed by 2 raters and 127 by one rater. All observers agreed that 1090 joints had no healing phenomena. The 10 patients without healing were correctly identified by all observers.

The correct sequence of the films was identified in 29–33 of the 34 patients (85–97%, mean 90.2%) (Table 3). The

Table 2. Number of joints with healing identified out of the 74 joints with typical healing.

	No. of Recognized Healing Phenomena
Rater	
1	70 of 74, 95%
2A	66 of 74, 89%
2B	65 of 74, 88%
3	61 of 74, 82%
Mean	65.5 of 74, 89%

Table 3. Number (%) of patients with correct or wrong identification of the sequence of the films.

Rater	Identification of the Sequence	
	Correct (%)	Wrong (%)
1	29 (85.3)	5 (14.7)
2A	31 (91.2)	3 (8.8)
2B	33 (97.1)	1 (2.9)
3	30 (88.2)	4 (11.8)

reader who most frequently misinterpreted the time sequence also had the highest number of healing phenomena: part of these “healings” in fact were progression. Among the 2 experienced readers the reader with the better result in judging time sequence of the films (2A, 2B) needed much more time (see Table 1).

To compare the radiographic progression between patients with healing according to GH and those without healing, the Ratingen score for these 2 groups was calculated separately. In the group with healing there was no change or only a slight (insignificant) reduction in the score seen by all raters (Table 4A), while patients without healing showed a significant increase in the score, again documented by all raters (Table 4B). As shown in Table 4A there were nearly as many joints showing progression (increase of the score) as improvement (decrease of the score). Around 50% of healing phenomena were not associated with a change in the score. The mean baseline value, calculated from raters 1 and 2 (A + B), was 14.1 in patients without

Table 1. Time for reading one set of radiographs; Ratingen score at T0 and T1; and mean and total number of joints with healing.

Rater	Time for rating, s	Ratingen Score, T0	Ratingen Score, T1	Joints with Healing, Mean No. /Patient	Joints with Healing, Total No.
1	274 ± 106 (4.6 min)	15.94 ± 13.82	19.52 ± 17.24	8.3 ± 5.8	199
2A	437 ± 140 (7.3 min)	15.85 ± 13.30	19.94 ± 19.15	5.0 ± 4.1	120
2B	400 ± 130 (6.7 min)	17.59 ± 13.97	21.42 ± 19.67	5.7 ± 4.6	137
3	521 ± 200 (8.7 min)	13.59 ± 11.76	13.19 ± 12.04	6.7 ± 4.6	151

Table 4. Mean Ratingen score at T0 and T1 in patients with healing phenomena (A) and in patients without healing phenomena (B). Percentage of joints with progression and reduction of the score.

A						
Rater	Ratingen Score, T0	Ratingen Score, T1	Joints with Score Increase		Joints with Score Decrease	
			%	Mean	%	Mean
1	17.36 ± 14.52	16.96 ± 16.07	7	1.17	8	1.20
2A	16.28 ± 12.97	16.67 ± 16.93	7	1.47	9	1.16
2B	18.24 ± 13.73	17.29 ± 16.71	7	1.41	11	1.21
3	14.56 ± 12.17	11.00 ± 11.71	6	1.51	14	1.29

B				
Rater	Ratingen Score T0	Ratingen Score, T1	Joints with Score Increase	
			%	Mean
1	12.00 ± 11.49	26.33 ± 19.37	30	1.36
2A	14.67 ± 14.92	28.67 ± 22.91	28	1.45
2B	15.78 ± 15.32	32.44 ± 23.62	32	1.40
3	10.89 ± 10.73	19.75 ± 11.18	26	1.47

healing and 17.3 for patients with healing phenomena, corresponding to 7 and 9% of the maximum possible Ratingen score.

Some examples of different types of healing defined for this study are shown in Figures 1–6.

DISCUSSION

The occurrence of healing phenomena in patients with RA indicates a halt of inflammation and the predominance of reparative over destructive processes. The documentation of healing during RA clinical trials may become more important in the future when highly effective and rapidly acting antirheumatic drugs become more available.

Our study was undertaken to test if healing phenomena in patients selected by an experienced rheumatologist could be reidentified by other observers. For this purpose 3 observers (not involved in selection of patients for this investigation) scored 24 sets of radiographs of hands and feet taken a mean of 4.8 years apart (T0 and T1) containing 74 typical healing phenomena according to the rheumatologist who selected the cases. To render the task more difficult 10 cases without healing were added to the 24 cases with healing. Cases with and without healing had been recruited from the outpatient clinic of GH and were unknown to the raters. The radiographs were read without knowing the identity of the patients or the chronological sequence of the films. The 3 observers (performing 4 readings) successfully identified 82–95% (mean 89%) of the 74 indexed joints with typical healing phenomena. Moreover, all readers were also able to recognize the 10 patients without healing phenomena.

In addition to the predefined (indexed) joints with healing all 4 ratings agreed in the finding of 54 other joints also showing healing phenomena. However, there was less

agreement in a number of further joints with healing, presumably because these healing phenomena were less convincing and did not unanimously fulfil the criteria for healing.

It is of interest that the patients with healing also showed no progression in the Ratingen score, while patients without healing had clear progression. Patients with healing had nearly as many joints with an increase as with a decrease in score. Healing can be diagnosed without knowing the time sequence of the films mainly for 2 reasons: First, in most cases it is possible to find out the correct sequence of films by analyzing all features of the radiographs including the appearance of irreversible signs of progression, i.e., the development of subluxation or luxation, changes in bone structure and density, appearance of degenerative changes absent in the corresponding (previous) film, etc. This analysis, however, is time consuming. Second, the radiographic appearance of the individual's joint may fulfill the criteria of healing: while an active erosion has an indistinct, fuzzy margin and may be accompanied by soft tissue swelling, juxtaarticular osteoporosis, irregularity, and unclear delineation of the trabecular structure, etc., an inactivated (healed) erosion is characterized by the disappearance of soft tissue swelling, reappearance of the cortical plate, normalization of the trabecular structure of subchondral bone, diminution of the erosion by formation of new bone with partial or complete filling in of the erosion, and subchondral sclerosis of the bone, etc. These phenomena have been described^{4,18,23,24} and included in a scoring system designed by Barbara Weissman³⁴; they help to distinguish a healed lesion from an active lesion and/or normal joint, even without knowing the chronological sequence of the films. However, there must be a time interval of at least one or 2



Figure 1. Complete filling in of an erosion in a patient. There is an active erosion at the scaphoid in May 1986, which is completely filled in in August 1992.

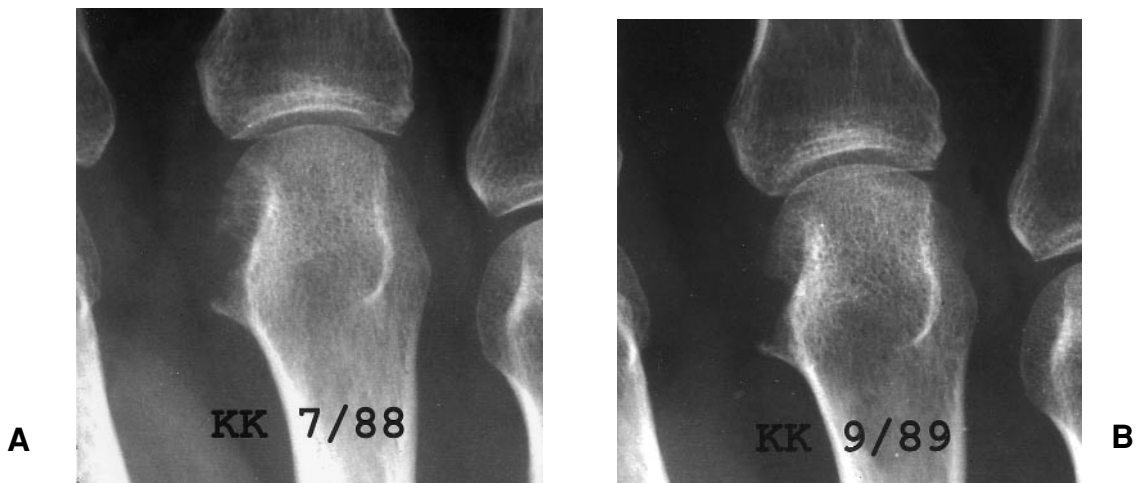


Figure 2. Recortication. A patient's radiographs show active erosion at the 3rd metacarpal head in July 1988 that is smoothed and recorticated in September 1989.

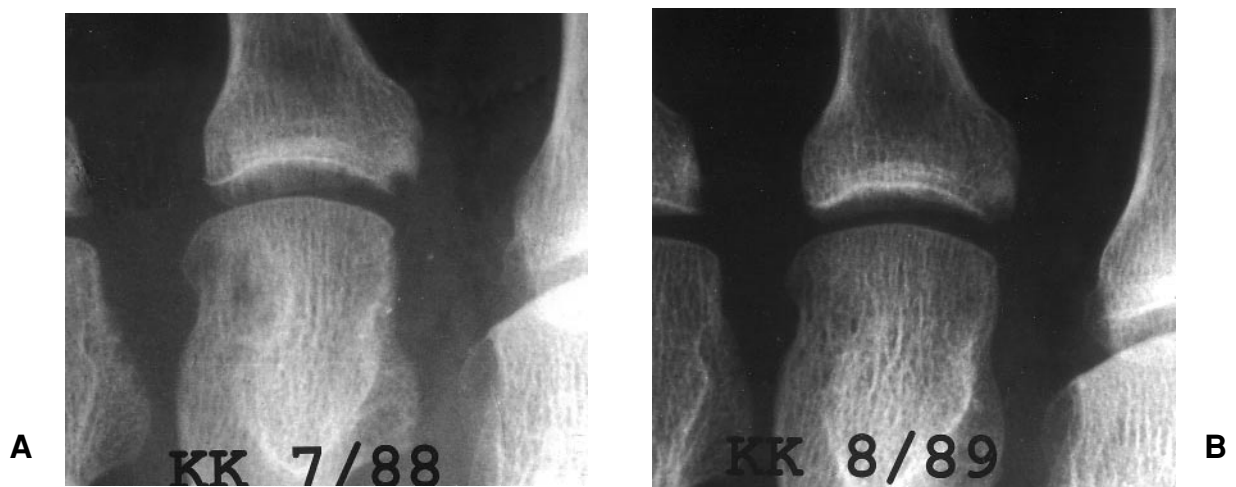


Figure 3. Recortication and filling in. There is superficial erosion at a metatarsal head and an erosion at the base of the proximal phalanx in July 1988. In August 1989 the metatarsal head is recorticated and the erosion at the base of the phalanx is filled in.

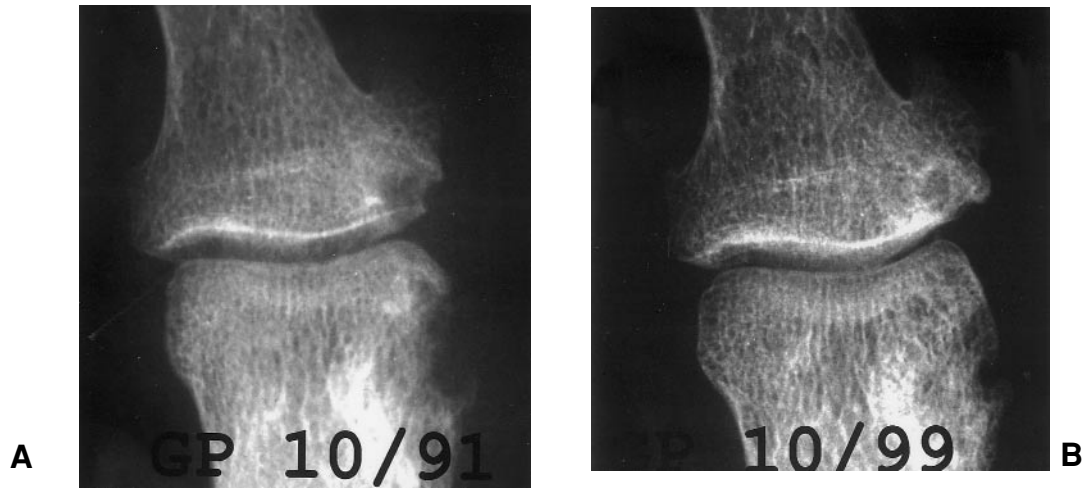


Figure 4. Partial filling in. In October 1991 a radiograph shows active erosions at the proximal and the distal phalanx of the great toe. These erosions are partially (nearly completely) filled in in October 1999.

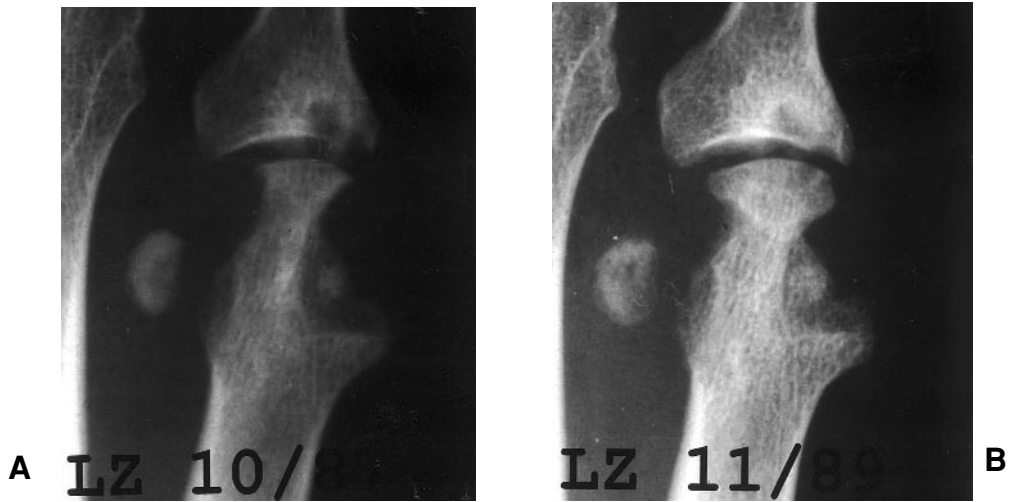


Figure 5. Partial filling in of erosions by new bone formation at the 5th metatarsal head and the base of the proximal phalanx between October 1987 and November 1989.

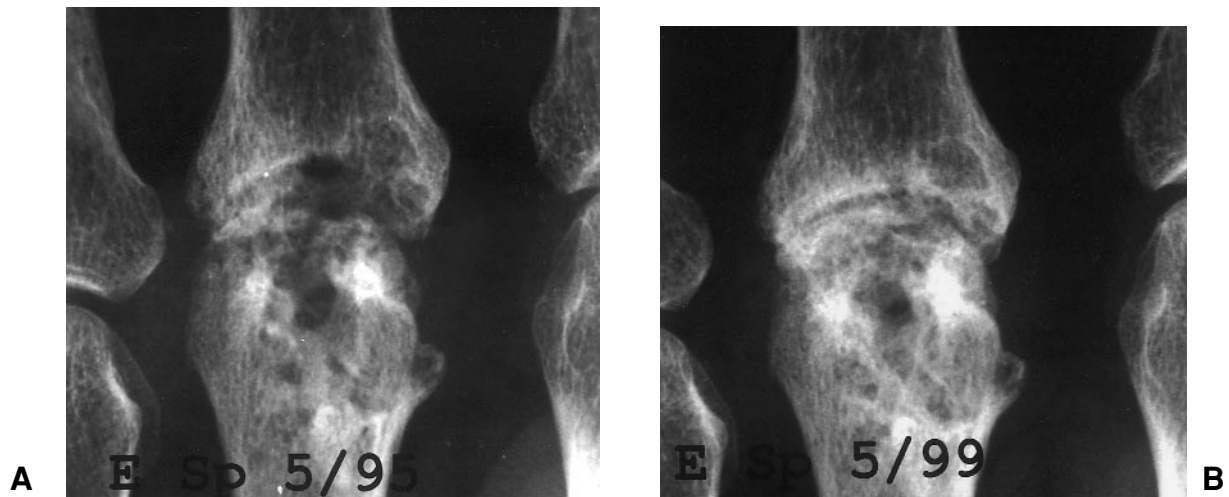


Figure 6. Filling in of multiple lesions at a metacarpal head and smoothing of the articulating surface between May 1995 and May 1999. At the same time the base of the proximal phalanx is also reconstructed and smoothed. This remodeling of the joint should clearly improve function.

years to clearly distinguish between both possibilities. In our study it was possible to identify the correct sequence of the films in 85–97% of the cases. The rater with a 15% error regarding the sequence of the films also diagnosed most healing phenomena (in part because of assuming the wrong time sequence). On the other hand, the reader with the best results (3% and 9% error in 2 readings) needed 50% more time.

Unfortunately, identifying healing increases the time requirement for scoring significantly. In our study the mean net time for scoring a set of radiographs with 2 time points was 6.8 minutes in a selected group of patients with relatively early disease reaching around 10% of the maximum possible score at the second time point. This compares to a mean of 7.6 minutes for scoring (without looking for healing) sets with 7 time points in cases with more severe disease reaching a mean of 20% of the maximum possible score at the last time point¹⁹.

Healing phenomena as defined for erosions have not been routinely identified heretofore because of short duration of clinical trials where radiologic changes have been carefully scored. Trials have often involved patients with long standing destructive disease, where it can be extremely difficult to see change and decide if reparative processes have occurred. Finally, criteria for repair have not yet been defined.

In addition to the above, there are further reports of healing in the literature: 2 single and multiple case reports show radiographs with healing^{30,35}. In a longterm trial of low dose MTX improvement of radiologic lesions has been reported in 5 of 14 patients³⁶. We found a decrease in active joints and a significant increase in the number of joints with secondary osteoarthritis defined as sclerosis of the subchondral bone and osteophyte formation in patients treated with longterm MTX²⁶. Cabral³⁷ reported on bone remodeling and osteophyte formation in patients achieving remission. In an additional study a greater prevalence of reparative compared to destructive changes was reported in the third half-year period of a parenteral gold treatment regimen³⁸. Menninger, *et al*³⁹ also reported an increased rate of repair during treatment of early erosive RA in patients treated with MTX or parenteral gold.

In several recent studies paired reading with unknown sequence of the films resulted in a reduction of the radiographic score in a certain proportion of RA patients treated with biologics²². In part this reduction may be explained by “uncertainty” or “error,” in part it may represent true healing.

However, the majority of healing phenomena do not change the score. The integration of healing in the numerical scale of scoring methods may not be easy because the interpretation of score changes would be difficult: which score change is due to deterioration and which to healing? Therefore, healing should be indicated on a separate scale in

addition to the radiographic score used to indicate progression. At the end of the trial the number of joints with healing could be counted and be related to the total number of joints with erosions.

Different types of healing, e.g., reappearance of the cortical plate, filling in, osteophyte formation, etc., could be defined and rated separately (i.e., A, B, C). A system classifying different types of healing would have to be agreed upon by an international panel and would need to be validated in clinical studies. Quantifying healing requires good quality films and increases the burden and time for scoring. On the other hand, it can improve our ability to show an arrest of rheumatic inflammation. As shown in our study (although with selected cases), healing is more likely to occur in patients with an arrest of radiologic progression than in patients with an increase in the radiologic score.

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