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# Healing of erosive changes in rheumatoid arthritis

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## ABSTRACT

*This is an overview over the history and present state of knowledge of radiographic signs of erosion healing. The existence of healing or repair has been confirmed; different observers agree in the identification of healing; it may be identified without knowing the sequence of the films. As healing indicates that inflammation has discontinued for several months in an individual joint, it might represent a good additional outcome measure in RA clinical trials.*

## Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that historically resulted in substantial structural damage in affected joints in most patients. Conventional radiography remains the "gold standard" to document and quantify this damage (1) for several reasons: (1) Bone and joint damage can be objectively documented and quantified using standardized scoring methods. Although these methods are generally applied to the small joints of the hands and feet, damage in the large joints can also be estimated, as there is a strong correlation between the damage in the small and large joints. While functional disability in the early stages of the disease is predominantly caused by inflammation (i.e. joint swelling), it is correlated with radiographic scores at higher levels in late disease (2).

(2) Radiographs are permanent documents, which can be evaluated by other investigators, both in a similar time frame or at a later time.

For these reasons, radiographs are very useful to document the course of RA in clinical trials and in long-term observational studies. Inhibition of progression, as documented radiographically, remains a most important criterion for disease modification or disease control (3). Logically, radiographs have been included in the core set of endpoint measures in RA clinical trials that include observation over a period of one year or longer (4).

## Is radiographic improvement of joint damage possible?

Until recently, RA was generally found to be a disease with steady radiographic progression, which has been documented in one study for over 25 years (5). Progressive disability was also seen in the majority of patients (6) associated with increased mortality rates (6, 7). These conclusions are based mainly on the investigation, treatment and follow-up of RA patients seen in tertiary rheumatology centers where they were referred only after several years of disease, usually after having "failed" to respond to previous treatments. Therefore, patients included in most reports are selected negatively, since the patients who responded well to their initial therapy or spontaneously entered a state of low disease activity or even remission are excluded. Moreover, the results of clinical trials or long-term observations in these patients are presented as mean values with little quantitative information concerning the proportion of patients in whom progression was seen. From experience with studies in which these data have been analyzed, we know that only a minority of patients show substantial radiographic progression, while the majority of patients do not. Patients with later disease and greater radiographic damage at baseline have lower responses to treatment and poorer outcomes than patients treated and followed from the beginning of their disease (8, 9).

If there are a large number of patients who show no progression, as demonstrated by scoring methods, we must consider the following questions:

(1) Do erosions stay unaltered over time or do they change? Erosions represent "wounds" of the bone. Healing of wounds or of fractures is a common biological process.

(2) Why should healing not occur in wounds caused by inflammation? In the European literature, the term "secondary osteoarthritis," meaning osteoarthritis which is the result of remodel-

ing a joint after (rheumatoid) arthritis has "burnt out," has been used for many years. A pre-condition for the development of secondary osteoarthritis is the arrest of inflammation.

(3) What happens over time in the transition from an actively inflamed joint to an (inactive) osteoarthritic joint?

### Conventional scoring methods are not designed to measure improvement

We are unable to answer these questions, in part because the most frequently used scoring systems (10-12) and their multiple modifications (13-18) are designed to quantify damage and its progression over time in selected joints of the hands, wrists, and feet, and are not designed to document improvement. Bone reconstruction and remodeling of a joint, which may result from the healing of erosions, are disregarded and not scored. Until recently, the opinion of most rheumatologists was that erosions cannot heal. A healed erosion, or a joint with "secondary" osteoarthritis, is assigned a score that is identical to that of an actively eroded joint of the same shape.

Some authors, notably the developers of the two most widely used scoring systems, have previously excluded the possibility of a score reduction *expressis verbis* ("once an erosion, always an erosion") (19, and Sharp and Larsen: personal communications). This viewpoint indicates that an erosion must be scored even if it is no longer visible. In most clinical trials, radiographs have been scored by reviewing them in chronological order. Since a reduction in the score is not allowed, the score can only increase or remain constant. If the measurement scale can be changed only in one direction, towards progression, treatment has no capacity to improve the score; the best that can be achieved is a reduction in the rate of destruction.

### Which morphological features may indicate healing or repair on radiographs?

When reading and scoring radiographs of patients in long-term routine observation in our department, we recognized

that repair does occur. We began to collect radiographs that show examples of healing phenomena. Since the early 1980s, we have presented oral and written reports of images of these findings at German and international meetings and in full publications (20-27). For example, we observed a decrease in the number of "active" joints (i.e. joints with signs of active inflammation) and an increase in the number of "inactive" joints (without signs of active inflammation) under long-term treatment with methotrexate (24). A series of images demonstrating different forms of the healing process over time in 6 patients treated with conventional disease modifying anti-rheumatic drugs (DMARDs) (predominantly parenteral gold) has been reported (25). Examples of healing phenomena include (25):

- (1) Re-cortication, or the reappearance of a clear visible cortical plate at a site at which it had been destroyed.
- (2) Partial or complete filling in of erosions or cysts by the formation of new bone.
- (3) "Complete restoration," or a complete filling-in of an early erosion, regaining a normal shape of the joint, including a normal trabecular structure of the subchondral bone. In this case, the restored joint cannot be distinguished from the same joint before the onset of arthritis.
- (4) Change in the trabecular structure with increased density or sclerosis of the subchondral bone.
- (5) Reshaping or re-modelling of a partially damaged joint to restore more normal function, a process which may be accompanied by formation of osteophytes. This state had been termed "secondary osteoarthritis".

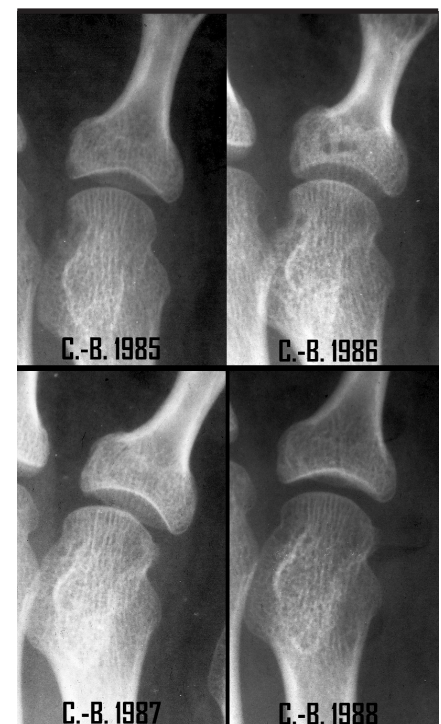
### Examples of healing (Figs. 1-3)

Most of these phenomena can be identified only in good quality radiographs and are difficult to detect in a series of radiographs with inconsistent quality. In our experience, healing occurs only after joints have been clinically inactive for at least several months. The absence of the cause of destruction – inflammation – is necessary for reparative processes to begin. At least a few

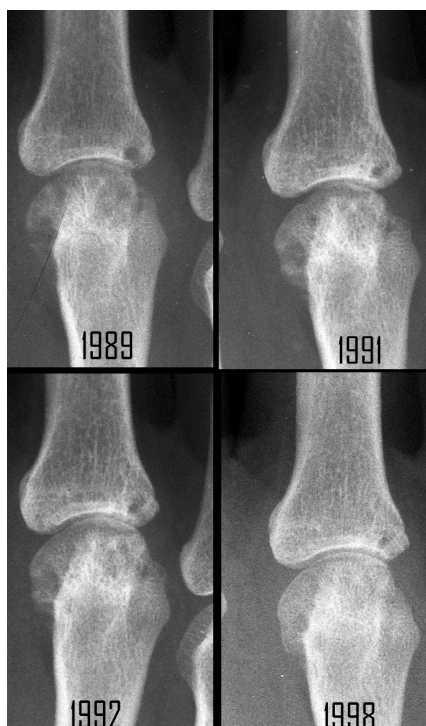
months are required until the formation of new bone by osteoblasts is detectable on radiographs. Healing represents a biologic attempt to repair bone "wounds" and to smooth eroded joint surfaces in order to improve functional capacity towards normal. Although most joints with reparative changes do not resemble completely normal joints, the term "healing" is adequate at least in the sense of defect healing with "scars".

### Can healing be identified without knowing the time sequence of the films?

As noted above, scoring of radiographs in clinical trials traditionally was performed with a known time sequence of the films ("paired reading"). In recent clinical trials, scoring without knowing the chronological order has been preferred (28-31), both in order to avoid



**Fig. 1.** Filling-in, recortication and restoration of an eroded MTP joint with gold treatment. MTP III right, of patient CB. **1985:** There is an active erosion with interruption of the cortical plate and bone loss at the tibial aspect of the metatarsal head. **1986:** The erosion has partially filled in and a new cortical plate has formed. **1987:** Normal appearing cortical plate, normal subchondral bone structure. **1988:** The MTP joint appears to be absolutely normal. There is no indication that there has been an erosion before. This is an example of restoration.



**Fig. 2.** Recortication and filling-in with conventional DMARD treatment.

Right MCP joint of patient HG. **1989:** There are clear active erosions and subchondral cysts at the metacarpal head and the base of the proximal phalanx. Subchondral osteoporosis. **1991:** The cortical plate has been nearly completely rebuilt. The bone structure is more dense, and the subchondral cysts have been filled in in part. **1992:** There is further filling-in of the subchondral cysts, and the cortical plate is completely rebuilt. **1998:** There is only little indication of previous cysts. The bone structure is nearly normalized.



**Fig. 3.** Destruction and remodeling of an IP joint with anakinra treatment.

Right IP of patient KP. **1991:** The IP joint of the right great toe appears normal. There is an erosion at the fibular aspect of the phalanx. **1995:** Both joint surfaces are severely eroded with loss of bone. **1997:** A new cortical plate has been formed. There is no active erosion. The joint has been remodeled; both joint surfaces have a curved shape. The joint space appears normal. **1999:** The appearance of the joint is different from the appearance in 1991. The joint surface is curved. The width of the joint space is normal. There is some indication for osteophyte formation on the fibular aspect. This is an example of a remodeled joint with secondary osteoarthritis.

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the bias towards progression and because some investigators claimed it resulted in better inter-observer reliability (32,33). We performed a blinded study to determine whether healing phenomena noted by one observer could be identified by other observers when reading radiographs in random time sequence. It should be emphasized that the existence of joint healing was not accepted by most authorities at the time of that study.

In that study (34), an experienced rheumatologist in our group (G.H.), who was not involved in reading the radiographs in that study, selected 34 sets of radiographs of hands, wrists and feet. Each set consisted of radiographs of the hands and feet taken at two time points (T0 and T1) 2-8 years (mean 4.8 years) apart. Of the 34 sets, 24 were selected because they showed clear healing phe-

nomena in at least one joint in the opinion of G.H. The total number of joints with typical healing, according to G.H., was 74. However, there could be other joints with healing as well. Ten sets of radiographs with moderate disease progression, but without any healing phenomena were randomly added to the other sets. Three readers performing four readings scored the radiographs according to the Ratingen score (35) without knowing the identity of the patients or the chronological sequence of the films. In addition, the readers had to identify the time sequence of the films and the joints with healing.

Of the 1,292 joints scored at the second time point (T1), the 74 joints with healing were correctly identified at a mean level of 89% (95%, 89%, 88%, and 82%, respectively) in the four readings. All observers agreed that 1,090 joints

showed no healing phenomena. The 10 patients without healing were correctly identified by all observers. In the group of 24 patients with healing, a slight decrease in the mean Ratingen score was observed, while moderate progression in scores was seen in the 10 patients who showed no healing.

In our view, the results of this study indicate that different observers can agree on the existence of healing phenomena, even without knowing the time sequence of the radiographs, and that patients with healing also tend to have no radiographic progression or even a slight improvement.

#### How can healing be identified without knowing the time sequence of the radiographs?

First, in most cases it is possible to identify the correct sequence of the films

by analyzing all features of all joints displayed on the radiographs of the hands and feet. If there are irreversible signs of progression in one film, for instance subluxation, degenerative changes which are absent from the other radiograph, it must be the second film. This analysis, however, is time consuming.

Secondly, the radiographic appearance of a single joint may fulfill the criteria of healing. An active erosion has an indistinct fuzzy margin and may be accompanied by soft tissue swelling, juxta-articular osteoporosis, irregularity and unclear delineation of the trabecular structure etc. In contrast, an inactivated (healed) erosion is characterized, as discussed before, by the re-appearance of the cortical plate (re-cortication), disappearance of subchondral osteoporosis, increased density or sclerosis of the subchondral bone or even normalization of the trabecular structure. A reduction in the size of the eroded area by formation of new bone with partial or complete filling-in of the erosion is a reliable sign. These phenomena help to distinguish a healed lesion from an active lesion and/or a normal joint, even without knowing the chronological sequence of the radiographs.

It should be noted, however, that in most cases a time interval of at least one or two years is necessary to clearly distinguish between an active and a healed erosion. Furthermore, discrimination may be impossible in many joints. A search for healing increases the time requirements for scoring significantly, because the reader must look for signs of healing in every joint.

#### **What is the biological significance of healing?**

Healing is a true biologic endpoint that may occur only after the reason for joint destruction – the inflammatory process – has been completely arrested. Under these circumstances, reparative processes predominate over destructive processes: formation of new bone by osteoblasts exceeds bone destruction caused by osteoclasts, enzymatic degradation and pannus infiltration. At least several months are required for bone formation to reach a level which

can be identified on radiographs. Healing, therefore, indicates disease remission, at least in an individual joint. Therefore, it could be utilized as an outcome measure in addition to the slowing or arrest of progression measured by a scoring method. As is the case with clinical remission, radiographic healing does not preclude re-activation in the future.

#### **Why have healing phenomena not been reported in patients with RA?**

1) Generally, the duration of clinical trials is too short to capture healing with certainty. In routine care, radiographs often are not taken in patients with low disease activity or who are in remission, although healing can be expected in these patients. As noted before, common scoring methods disregard healing. An "active" erosion is assigned the same score as an "inactivated" erosion. A reduction in size of an erosion is not taken into account in the original Sharp method or it may be too small to result in a change in the score. A complete filling in of an early erosion leading to a normal appearance of the joint – restoration – would reduce the score to zero by all methods.

2) Identification of healing is a time-consuming process, that must be added to the time for conventional scoring, as mentioned before.

3) The differing quality of radiographs between centers and/or over time, leads to considerable difficulty in evaluating the cortical plate, juxta-articular osteoporosis, trabecular structures, etc.

4) Most clinical trials have been conducted in patients with long-standing destructive disease, which again leads to extreme difficulty in identifying any change and determining whether reparative processes have occurred. It is more straightforward to detect clearly progression, regression, and healing on radiographs in patients with early disease.

Despite these difficulties, there have been occasional reports in the literature concerning healing. As noted above, the term "secondary osteoarthritis" has been used in the European literature for decades to refer to degenerative joint disease after the arrest of inflammatory

disease. Sharp mentioned this phenomenon in his first publication concerning scoring (10). As early as 1969, Dihlmann (36) described the healing of erosions and remodeling, without development of deformity, as "arthritis reformans". In his 1989 text, McCarty observed that "erosion healing often accompanies clinical remission" (37). Case reports (26, 27, 38, 39) and a multiple case report (25) demonstrated healing phenomena on radiographic images. Improvement of radiographic lesions was mentioned in 5 of 14 patients in a long-term trial of low dose methotrexate (40). We found a decrease in the number of "active" joints and a significant increase in the number of joints with "secondary osteoarthritis," defined as sclerosis of the subchondral bone and osteophyte formation, with methotrexate treatment over years (21, 41). Cabral *et al.* (42) also reported bone remodeling and osteophyte formation in patients who experienced clinical remission.

A macroradiographic study demonstrated a greater prevalence of reparative, compared to destructive, changes in the 3rd half year of parenteral gold treatment (43). Menninger *et al.* (44) also reported an increasing rate of repair during the treatment of early erosive RA patients with methotrexate or i.m. gold. Weissman included "healing of erosions" and "reparative bone formation" in her scoring system used in a 36-week trial of methotrexate versus Auranofin, but found no difference between the groups, likely because of the short duration of the trial (45).

#### **How could healing phenomena be integrated into existing scoring systems?**

Until recently, radiographs were scored in chronological order, and improvement could not be documented because a reduction of the score was not permitted. The situation may be different with scoring in an unknown order. A change of the score should be possible with the van der Heijde modification (13) and the Ratingen score (35), if the decrease in size of the erosion is large enough to change the score. Where only the number of erosions is counted (10), the

score should decrease only with a complete filling-in of the erosion. Negative changes have been reported in some patients after one year of treatment with infliximab (29) or etanercept (30), as well as adalimumab (31). These negative changes may be the result of measurement error. However, in these trials with highly effective drugs, it is likely that – at least in part – negative changes in scores represent true healing, especially if the negative changes are greater than the minimal detectable change that represents the measurement error of the method.

At present we do not know which proportion of healing phenomena may be captured by standard scoring methods and which proportion cannot be computed using these methods. Moreover, this could change from trial to trial. It is not yet clear if and how healing could be integrated into existing scoring methods. Until a generally accepted method is established, healing could be indicated separately in addition to the standard score. The number of joints with healing could be counted at the end of a trial and evaluated in relation to the total number of joints with erosions.

### The existence of healing has been confirmed by an international committee

Thanks to the initiative of John Sharp and Desiree van der Heijde, a subcommittee on healing within the imaging committee of the OMERACT organization has been formed. This subcommittee includes international experts interested in this particular field of investigation, who have begun to perform several exercises as an "attempt to confirm whether healing occurs in rheumatoid arthritis, and if so, to determine how healing should be assessed" (46).

In one of the initial exercises, the committee members evaluated 28 pairs of images of single joints, 14 cases showing progression and 14 with improvement in a randomized double blind study. Most committee members were able to determine correctly which joint was improved. There was also a good agreement concerning the relative size of the erosion. Since the second films

were always judged to be better in the cases shown as examples of improvement, it was concluded that healing or repair of erosions really exists.

Agreement regarding the morphologic features of bone repair (re-cortication, filling in, sclerosis, restoration, re-modelling) was not impressive. This was in part due to a lack of agreement on the meaning or definition of these terms. The correct sequence of the films could be determined only by 65% of the committee members. Committee members with greater experience in scoring and evaluating healing determined the correct sequence of the films more frequently, which indicated that they were more successful in diagnosing healing. In images representing examples of healing, morphological features, presumably indicating bone repair, were much more pronounced than in images representing examples of progression, according to committee members.

Another workshop of the subcommittee was organized by John Sharp in March 2004 in Newtown, Pennsylvania. A small number of experts experienced in scoring and evaluating healing discussed the morphologic features of repair and their definition set at OMERACT 6. Thereafter, a large number of pairs of single joints showing improvement or deterioration were evaluated in a randomized double-blind exercise. The sequence of the films, improvement or progression, as well as a number of morphologic features of repair, were scored.

This exercise was repeated the next day after a new randomization displaying not only a single joint, but the whole hand or foot, to investigate whether the determination of the time sequence of the films is facilitated by considering the other joints. The pairs of images will be scored independently by other investigators. This exercise will answer the question concerning what proportion of healing is captured by regular scoring and how much agreement exists between investigators regarding the morphological features of healing.

### Conclusion

In conclusion we can say that healing detected on radiographs in RA exists,

different observers agree in the identification of healing, and healing appears to be identified without knowing the sequence of the films, although this remains to be confirmed. As healing can be observed only after active inflammation has discontinued in a particular joint for several months, it might be regarded as a good additional outcome measure in RA trials.

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