Radiological evaluation of erosions: a quantitative method for assessing long-term remittive therapy in rheumatoid arthritis

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1 The most reliable method for evaluating possible remission-inducing properties in a drug is to measure how well it prevents the appearance of new erosions in serial X-rays of the hands.

2 I have reviewed the literature on the development, over the last 25 years, of a standard method for quantitatively assessing the progress of erosions radiologically.

3 The only drugs thus far shown to be genuinely remission-inducing are cyclophosphamide, high-dose penicillamine, and (most consistently over several decades) gold-thiols, all drugs with life-threatening toxicity.

4 The search for a non-steroidal drug with remission-inducing properties is crucial in our efforts to find a safe drug to control the progression of rheumatoid arthritis.

Keywords rheumatoid arthritis remission erosion non-steroidal cyclophosphamide

Introduction

Half a century ago Gilbert Scott suggested that radiological evidence of changes in the hands, including 'erosion of articular bone,' was the most accurate and the earliest measure of disease activity in rheumatoid arthritis (RA) and related diseases (Scott, 1932). Despite all the research and the discoveries in immunology during the last 25 years, we still have no clear, consistent immunologic criteria for the early determination of which patients with RA will go on to develop deformity and disability. Thus, the assessment of erosions on X-ray remains, the best method for measuring long-term disease effects; erosion and bone destruction are the ultimate anatomical consequences of rheumatoid arthritis.

Radiological assessment gives a vivid and precise anatomic record of the progression of disease; minute detail can be seen in a hand film, especially if a fine-grain industrial film is

used without intensifying fluorescent screens. (Fluorescent screens diffuse the X-rays and make the image fuzzier). Readings by skilled diagnostic radiologists are not usually helpful in measuring the progress of the disease. Though these are useful diagnostically in differentiating various rheumatic diseases, the lack of careful comparison of films before and after therapy makes it impossible to determine whether or not the progression has been slowed. An approach which is comparative and at least partly quantitative—ideally, a careful, blinding comparison of 'before' and 'after' films, using standardized ordinal and quantitative reading scales—is needed to assess the effects of possibly remission-inducing drugs on the progression of disease.

The importance of the topic is indicated by the appearance of several recent editorials (Gofton, 1983) and reviews (Ingeman-Nielsen

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et al., 1983; Scott *et al.*, 1985). Questions about technique, reproducibility of readings, and correlations with other aspects of the disease process continue to be raised. A summary of all pertinent studies is therefore indicated.

The methodology for assessing X-ray progression

The development of ordinal scales for grading erosion

Over the last 25 years rheumatologists in a number of countries have developed something approaching a standard methodology (and have applied it in trials of various drugs) to measure the progress of RA by grading erosions in the hands. Erosions (also referred to as 'bone destruction' or 'defect score' by some writers) are the most significant lesions which occur in RA, and will be discussed in detail.

The assessment is based chiefly on the 5-point ordinal scale (0–4) developed in the mid-fifties by J. H. Kellgren, first with Bier (Kellgren & Bier, 1956) and later with Lawrence (Kellgren & Lawrence, 1957) in a trial which involved readings by such eminent international rheumatologists as Bunim, McEwen, Ragan and Bywaters. These early studies found 'a satisfactory measure of agreement' among different readers (and between different readings by the same observer) in regard to the severity of RA and the presence or absence of erosions, but less interobserver consistency in evaluating the severity of erosions, especially in borderline cases. They also found osteoporosis to be difficult to assess. Over the last quarter of a century, Kellgren's method of reading new erosions has been used both in population surveys such as those conducted by the National Institutes of Health (O'Brien *et al.*, 1967), the Public Health Service (Mikkelsen *et al.*, 1970), and the Health Examination Survey (National Health Survey, 1966 a, b), and in therapeutic trials.

More recently, Larsen and his Scandinavian colleagues, using a six-point grading scale (0–5), have likewise found fairly high consistency among observers in evaluating erosions and joint space narrowing, though less in interpreting osteoporosis and soft tissue swelling (Larsen *et al.*, 1979). Like Kellgren and Lawrence, Larsen has suggested the usefulness of a set of standard X-rays in evaluating the progress of RA (Larsen *et al.*, 1977); indeed, two atlases of standard films (Empire Rheumatism Council Field Unit, 1963; Larsen *et al.*, 1975) have been published in an effort to increase interobserver consistency in reading X-rays.

About 10 years ago Sharp and his associates (1971) in this country, in an attempt to quantify X-ray readings of the hand and wrist more reliably than Kellgren had done, developed a third variation of the basic method. They devised two scores: one for joint space narrowing and ankylosis, which they found did not correlate well with most clinical measures of disease activity; and one for erosions (the 'defect score'), which correlates quite well with most clinical indices. Sharp's numerical scale differs from those of Kellgren and Larsen in being truncated and discontinuous: for each joint read, 0 = no erosions, 1 = a single erosion (regardless of size), 2 = two erosions, and 3 = three erosions; but 4 = four or more erosions, and 5 = destruction of the articular surface or juxta-articular area. Despite this unusual scale, Sharp was able to derive some extremely useful ratios: a 'corrected defect score,' derived by summing the scores for individual joints and dividing by the maximum possible score (number of joints times 5); and a 'rate of progression,' derived by dividing the defect score by the number of months elapsed since the onset of RA.

Kellgren's, Larsen's and Sharp's methods, which are really three versions of a common method for radiologically measuring disease progression, all depend heavily on the rate of appearance of new erosions in the hands. New erosions have fuzzy edges, almost as if the cortex had been 'erased;' severity is indicated by the size of the eroded area. Old, stable erosions—those with well-defined edges and reparative sclerosis, usually referred to as 'healed erosions'—can also be enumerated.

Correlation of erosion with other measures of disease activity

Not only does Kellgren's method provide a clear, comparative, and quantitative measure of the progress of erosions associated with RA, but, over the last decade, a number of studies have shown that the appearance of new erosions on X-rays of the hand-wrist (and, in some studies, of the feet) correlates very closely with a broad range of clinical measures: the clinical outcome of RA (Brook *et al.*, 1977), global assessment of joint activity (Young *et al.*, 1980), duration of morning stiffness (Karten *et al.*, 1972), rheumatoid factor and nodules (Gram & Christiansen, 1975; Karten *et al.*, 1972), elevated erythrocyte sedimentation rate (Amos *et al.*, 1977; De Carvalho & Graudal, 1980; Karten *et al.*, 1972; Scott *et al.*, 1984), and elevated levels of serum C-reactive protein (Amos *et al.*, 1977). Brook & Corbett (1977) have also shown

that X-ray evidence of erosion is particularly effective in measuring the early course of the disease. They found that in almost 90% of a group of patients with early rheumatoid disease, radiologically detectable erosions appeared within 2 years of the first joint symptoms.

Special radiographic techniques

More elaborate techniques than the standard film have not produced better results. Special views, often referred to in Britain as the 'ball catcher's position,' or in the United States as the 'you're in good hands with Allstate view,' have not improved the results (Edwards *et al.*, 1983). Special X-ray machines giving microfocal views (Buckland-Wright, 1984) or magnified images have not improved the method. With fine-grain film a simple magnifying glass will do as well!

Grading osteoporosis, joint space narrowing, etc.

As Kellgren and his associates suggested in the mid-nineteen fifties and numerous other studies have also reported (Empire Rheumatism Council, 1955; Fletcher & Rowley, 1952; Kellgren & Bier, 1956; Larsen *et al.*, 1979), it is considerably more difficult to make a reliable assessment of osteoporosis than of new erosions. Despite that fact, various alternative methods have been proposed which rely exclusively or chiefly on some measurement of osteoporosis. Barnett & Nordin (1960) devised a fairly precise 'metacarpal index' for measuring generalized (as opposed to juxta-articular) osteoporosis of the hand. This index was shown to have a significant inverse correlation both with age and with duration of RA (Havelka *et al.*, 1973), and a variation of it revealed a significant inverse correlation with manual grip strength and positive correlations with erosions and erythrocyte sedimentation rate (Virtama *et al.*, 1968). The metacarpal index, however, has seldom been used to measure disease progression in large-scale drug trials.

Other efforts to use osteoporosis in measuring the course of RA have generally succeeded in demonstrating only what was already fairly obvious: e.g., that mineral content and density in metacarpals vary according to age and sex (Smith *et al.*, 1969); that bone density correlates with grip strength in both normal and rheumatic patients (Dickson *et al.*, 1973); that significant bone loss occurs in both metacarpals (Kennedy *et al.*, 1974) and femurs (Kennedy *et al.*, 1975) of patients with RA; that osteoporosis correlates both with age of patients and with extent and duration of disease (McConkey *et al.*, 1962).

Some of these and other studies have found a correlation between osteoporosis and corticosteroid therapy (Hahn & Hahn, 1976; Kennedy *et al.*, 1975; O'Brien *et al.*, 1968), while other investigators have disputed such a link (McConkey *et al.*, 1962; Virtama *et al.*, 1968).

Other readings, such as joint space narrowing, subluxation, cyst formation, etc., are too unreliable to be of value in assessing drug effects. Erosion rates have been measured in other joints (De Carvalho *et al.*, 1980). Including foot films would probably detect more erosion; however, erosion in large joints tends to occur late in the course, and adding such films would provide little help.

Observer bias

Obviously it is essential, in such studies, that X-ray readings be unbiased; if the observer knows the sequence of the films, he may tend to ignore certain lesions which appear to be new erosions on the initial film since he knows that to read them would result in 'mistakes' (Bland *et al.*, 1969). Indeed, if the observers assessing X-rays are totally 'blind' and do not know which was the initial film, they do occasionally make 'mistakes.' Presumably, erosions do not disappear; if they do heal, they leave a characteristic sclerotic lesion without the fuzzy edges typical of an acute erosion. So, if the observer reports erosions in the earlier film which he does not also detect in the later film, he has in a sense made a mistake. Such inconsistencies can result from minor differences in positioning of the hands in different films, or simply from errors made by the reader; in any event, it is very unlikely that erosions would actually disappear without trace. Despite the fact that such inconsistencies cannot be wholly eliminated, this controlled, comparative methodology has been widely used in standardizing the assessment of progression of tuberculosis in clinical trials (Yerushalmy *et al.*, 1950), and in standardizing other laboratory tests (Horvath, 1964).

Observer error is a major concern, and blinding the individual observer and independent assessments by more than one observer are essential. Nevertheless careful studies of observer variation have demonstrated that assessment of progression by the use of ordinal scales is highly reproducible (Scott *et al.*, 1985; Sharp *et al.*, 1985).

One must be extremely cautious in assessing rates of erosion. To say that the erosive process is essentially linear means that the rate of erosion is constant over time *for each patient*—not that it is essentially the same for all patients

(indeed, we all know from clinical experience that it is not). Any changes in rates must therefore be calculated (as they were by Sharp) for each individual patient; pooling patients to estimate rates of erosive progression can be extremely misleading. Let us assume, for example, that patients with severe disease do not fare well on non-steroidal anti-inflammatory agents and tend to be treated with gold (or other major therapy) relatively early in the course of their disease. Assume, conversely, that patients with milder RA tend to respond to non-steroidal therapy and thus to be put on gold only later in their disease (if at all). If those patients with severe disease are treated early and those with mild disease are treated late, the net result is that the 'pooled' erosions may appear to be nonlinear; patients with early disease, i.e., those who receive major therapy early, may appear to have a very high erosion rate, while those with longer disease may appear to have a low erosion rate. In fact, however, this tendency towards early vigorous treatment of severe disease is not evidence of non-linearity in the rate of erosions *in an individual patient*. Both Sharp's data and our own data for patients receiving placebo in the ARA gold trials indicate that the erosion rate is fairly constant for a given patient with a given severity of disease.

Problems in the radiological evaluation of disease activity

Erosions do not heal or go away, while a swollen joint will respond to successful treatment by decreasing in size. The sedimentation rate rises and falls with variation in disease activity. Thus, the end point looked for when measuring erosion rates is the absence of progression rather than improvement.

Devastating and prolonged disease destroys joints; thus there may be very little left to measure. In a patient in whom the erosive process is far advanced, further erosion might not be possible. The patient with severe, advanced RA might not seem to respond to gold (or another drug) simply because there might be nothing left to erode, and thus no erosions to be slowed or stopped by remittive therapy. Reassuringly, in at least one previous study (Singler *et al.*, 1974), the investigators eliminated patients with especially high scores (advanced disease) and essentially found that their removal did not affect the results of the trial. To avoid any such concern, a trial group should be studied early in the course of their disease but over an adequate period of time. Erosion occurs slowly, and very brief trials will not detect changes (De Carvalho, 1981; Scott *et al.*, 1984).

Another possible complication of the statistical analysis of X-ray readings is worth mentioning. One peculiarity which might skew figures is that males involved in heavy manual labour may develop rapidly progressive erosions (Castillo *et al.*, 1965). Such an occupational bias might skew the results of a trial.

Effects of anti-rheumatic drugs on erosion rates

Corticosteroids

The earliest application of the Kellgren method of reading new erosions of X-ray came in the mid-nineteen fifties in the original Empire Rheumatism Council trials of cortisone *vs* aspirin. The investigators who planned these trials believed that cortisone would prove to be categorically superior to aspirin, and would stop or at least slow the development of erosions. The results, however, were far from such expectations. At both 1 year (Empire Rheumatism Council, 1955) and 3 years (Empire Rheumatism Council, 1957) there was no clinical difference between the aspirin and cortisone groups, and radiological deterioration continued quite rapidly in both groups, though slightly—but not significantly—less rapidly in the cortisone treated group. These trials thus confirmed the disappointing findings of two earlier, smaller studies (Medical Research Council, 1954, 1955; Medical Research Council, Nuffield Foundation, 1954). There is no 'striking advantage' (Empire Rheumatism Council, 1955) of cortisone therapy over high-dose aspirin therapy; neither cortisone nor the most widely used non-steroidal is capable of stopping the erosive process.

With cortisone shown to have no significant remittive power, the English next turned to prednisolone. A 2-year trial of prednisolone *vs* aspirin, conducted by a Joint Committee of the Medical Research Council and the Nuffield Foundation, produced encouraging results (Joint Committee of the Medical Research Council and Nuffield Foundation, 1959). Clinically, the prednisolone patients fared significantly better. More importantly, radiological deterioration, which continued rapidly in the patients on aspirin, was slowed significantly in the prednisolone treated group, especially in the feet. (The hand films showed continued erosion in 17 of the 41 prednisolone patients, but the rate of erosion was significantly slower than in the aspirin group). On the other hand, the prednisolone patients showed a significant rise in the sheep cell agglutinating titre, and some disquieting side effects: six patients had collapsed vertebrae:

and, of eight patients on high-dose prednisolone therapy (20 mg day⁻¹), four developed peptic ulcers and a fifth developed psychosis—'a proportion of serious complications which is clearly unacceptable', as the investigators put it.

A decade later, an American investigator, McCarty, studied the possible remission-inducing effects of depot corticosteroids injected directly into inflamed joints (McCarty, 1972). Though the large local doses produced positive clinical responses, the injected joints showed continued progression of erosion. Recent studies from Bath suggest that corticosteroids have no effect on disease progression, and actually increase the rate of subluxation and mutilans deformity of the hand (Rasker & Cosh, 1978).

Other American workers have studied the effects of high-dose methylprednisolone pulse therapy (1 g intravenously every month for 6 months) on a small sample of patients with RA unresponsive to less drastic treatment (Liebling *et al.*, 1981). Though they (again) found a statistically significant improvement by most clinical measures, X-ray erosions continued to appear and progress in the methylprednisolone treated patients. Thus the remission-inducing power of prednisolone remains questionable.

Gold-thiols

For the last 50 years gold salts have provided the chief hope of clinicians seeking a means to arrest the erosive course of RA. The first major controlled trial of gold-thiol therapy was conducted by the Empire Rheumatism Council (ERC) more than twenty years ago. The course of sodium aurothiomalate therapy in this trial was only 20 weeks. At 18 months after the beginning of the trial (i.e., about 1 year after the course of injections), the gold treated patients showed statistically significant improvement by all clinical criteria (The Research Sub-Committee of the Empire Rheumatism Council, 1960). At month 30, however (2 years after the cessation of gold-thiol therapy), most of the earlier advantages of the gold cohort had disappeared (The Research Sub-Committee of the Empire Rheumatism Council, 1961). Radiologically, the results were both more consistent and less dramatic: hand films revealed a slight but not statistically significant superiority for the gold group, in percentage of narrowed joints, new erosions per joint and 'progression index,' both at 18 months and over 30 months (The Research Sub-Committee of the Empire Rheumatism Council, 1961).

The results of the ERC series were essentially confirmed by the smaller trial of sodium aurothiomalate conducted by the American

Rheumatism Association (O'Brien & Zvaifler, 1973). Only a qualitative assessment of erosion was done but review of these X-rays using the quantitative methods developed by Sharp (Sharp *et al.*, 1971) demonstrated differences between active drug therapy and placebo. The patients receiving gold showed 'slight, but definite, improvement in all parameters measured,' (though in most cases, because of the small size of the sample, the differences were not quite statistically significant). Radiologically, deterioration was seen in nine of 19 patients receiving placebo injections and in only three of 20 receiving gold ($P = 0.06$). A year later, the Detroit-Houston study (Singler *et al.*, 1974) also reported that chrysotherapy (over a 2 year period) not only caused significant improvement according to various clinical measures but also retarded disease progression as evaluated by X-ray (for most radiological criteria, $P < 0.025$). The retardation—and even, in several patients, the arrest—of erosion was clearly demonstrated.

During the seventies, two European investigators shed further light on gold therapy and X-ray progression. The Dutch trials conducted by Cats (1976) compared high-dose gold therapy (using aurothioglucose) to low-, and then maintenance-dose therapy and to placebo. On the whole, the low-dose gold patients fared as well as the high-dose group, and those receiving no maintenance dosage as well as those receiving maintenance dosage. Radiologically, however, deterioration was less rapid for the patients who received high-dose injections followed by maintenance therapy than for all three other groups, though the difference was not statistically significant.

Luukkainen and his colleagues at the Finnish Rheumatism Foundation Hospital at Heinola, using sodium aurothiomalate, studied the effects of both dosage levels and duration of RA before gold therapy. Unlike Cats (1976), they found a statistically significant difference between X-ray erosions (which they evaluated according to Larsen's six-step scale) in the low-dose group and those in the high-dose group, with the latter showing distinctly less deterioration (Luukkainen *et al.*, 1977). They found, in terms of radiologic progression of the disease, that patients who received high-dose chrysotherapy beginning within 10 months of the onset of RA fared highly significantly better than those who received the same therapy beginning more than 20 months after the onset of the disease—and that even high-dose therapy beginning 11 to 20 months after onset produced highly significantly better results (i.e., fewer erosions) than low-dose

therapy (Luukkainen *et al.*, 1977). In short, 'the best result in preventing development of erosions was achieved in patients with the high-dose of gold in the early phase of the disease' (Luukkainen *et al.*, 1978). The same distinct advantages for early, high-dose gold treatment were likewise observed in a follow-up study about 5 years after the initial treatment. Patients receiving low dosages, or high dosage initiated more than 20 months after the onset of RA, had significantly more new erosions and a highly significantly worse 'general joint index' than patients receiving early, high-dose chrysotherapy (Luukkainen, 1980). Thus Luukkainen has reached conclusions about the remittive efficacy of early gold therapy which are very similar to those of Adams and Cecil obtained 30 years ago (Adams & Cecil, 1950) and of Forestier 45 years ago (Forestier & Certonciny, 1936; Forestier, 1935), and this conclusion has again been confirmed in a recent American study from Denver (Sharp *et al.*, 1982).

The new oral gold compound, auranofin, has been studied, and does prevent the progression of erosions (Gofton & O'Brien, 1982; Gofton *et al.*, 1984).

Penicillamine

During the nineteen seventies, hopes for remittive therapy were raised by various studies of D-penicillamine, which appears to be clinically more effective than 'simple analgesics' (chiefly salicylates) alone (Multicentre Trial Group, 1973). Huskisson, in a small trial vs non-steroidal anti-inflammatories, found that penicillamine caused clinical improvement as well as a significant reduction in the technetium index, an 'objective measurement' of the progress of RA (Huskisson *et al.*, 1976). Huskisson and his colleagues also studied high-dose penicillamine vs sodium aurothiomalate. A preliminary report suggested that the two drugs were 'equally effective' in slowing the progress of RA (Huskisson *et al.*, 1974), but contained no radiologic data. The final report presented such data and concluded that 'penicillamine may be more effective than gold in delaying the progress of radiograph erosions' (Gibson *et al.*, 1976). This conclusion is called into question, however, by several elements in the methodology of that study: First, the investigators did not read the X-rays blind. Second, though Huskisson indicates that he was using Sharp's method of assessing erosions, the report presents only raw radiographic scores, not monthly rates based on such scores, as Sharp himself uses (Sharp *et al.*, 1971). Third, the gold cohort in Huskisson's trial had a much higher

initial erosion score than the penicillamine cohort, so that the two groups were not, in fact, matched for severity of disease. In proportion to their initial erosion scores, the gold patients' score increased only very slightly more than those of the penicillamine patients. What is more, Huskisson and his colleagues used such a high dosage of penicillamine (1750 mg day⁻¹) that the patients receiving it suffered about three times as many life-threatening side effects as the gold patients.

Schorn & Mowat (1977) showed that penicillamine can reverse the downward trend in the metacarpal index, thus apparently reversing osteoporosis, but they presented no evidence that the drug halts erosions. By contrast Golding and his colleagues, found that low-dose penicillamine therapy (500 mg/day), (while it may cause dramatic improvement in various clinical measures) did not halt the erosive process as seen in hand films (Golding *et al.*, 1977). Of 109 patients, 36% showed progression of subarticular erosion and 22% showed progression of joint erosion. Finally a recent report from Glasgow reported only a tendency for improvement on low doses of penicillamine (Pullar *et al.*, 1984). On balance, it seems clear that penicillamine, if it is to be genuinely remission inducing, must be administered at very high dosage, with the attendant risk of serious side effects.

Cyclophosphamide

The most striking decrease in the rate of new erosions seen in any trial was reported in the American Rheumatism Association trial of cyclophosphamide (Mainland *et al.*, 1970). Not only did high-dose cyclophosphamide therapy produce significant clinical improvement, but also it reduced the rate of new hand erosions to about one-tenth of that seen in most earlier trials. British data suggest that cyclophosphamide has a greater effect on erosion rate than azathioprine or gold (Currey *et al.*, 1974).

Unfortunately, at the same time that cyclophosphamide seems to be genuinely remission-inducing, it is also highly toxic at effective dosage levels. The complications of cyclophosphamide therapy (neutropaenia and overwhelming sepsis as well as induction of malignancy)—limit the use of the drug to the most severe and refractory cases.

Azathioprine

While this drug is effective in refractory RA, several studies in which serial radiographs have been studied have noted no effects on the

progression of erosions (Goebel *et al.*, 1976; Hunter *et al.*, 1975; Tausch & Siegmeth, 1973). The combined use of three remission-inducing drugs has been reported to stop erosions (McCarty & Carrera, 1982). However few would consider using polypharmacy with three dangerous drugs: cyclophosphamide, azathioprine and hydroxychloroquine. And one must ask if cyclophosphamide alone might have produced as good a result.

Antimalarials and methotrexate

Both of these drugs are used as remission-inducing agents, but neither has been subjected to rigorous trials in RA patients refractory to other therapies. Their effects on X-ray progression have not been studied.

Levamisole

Hopes for remittive therapy have also been raised by the immunostimulant, levamisole, which is being extensively tested in RA. As yet no reports have appeared concerning its effect on the erosive process. My own experience is that erosions progressed rapidly in 17 of 41 patients treated with levamisole over a 4 year period. Others have suggested that progression may occur (Pullar *et al.*, 1984).

Radiation therapy

Similarly, several workers have either directly irradiated inflamed joints or injected nondiffus-

able or colloidal radioisotopes into joints in the hope of slowing or stopping the erosive process. Despite yet another series of striking clinical effects, however, therapy erosions continued to progress both in those patients receiving radiation (Smyth *et al.*, 1941) and in those receiving injected radioisotopes (Bridgman *et al.*, 1973). Such treatment also carries with it an inherently large potential for inducing leukaemia.

Recent trials of total body and lymphoid irradiation have not assessed the effects on X-ray progression. In view of the tremendous risks of such trials, this omission is unfortunate.

Non-steroidal anti-inflammatory drugs

It is generally assumed that these drugs are palliative. The claim that benoxaprofen had effects on cell migration into inflamed joints led to studies of this drug on X-ray progression. It had no effect (Bluhm *et al.*, 1982). Studies on the effects of isoxicam are currently in progress.

Conclusion

The detection of erosion is the most accurate predictor of destruction and progression of joints affected by rheumatoid arthritis. The drugs which prevent the progression of erosion have major and serious adverse effects. The demonstration that a nonsteroidal drug would prevent progression would provide a major advance in our ability to manage this crippling disease.

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