# A Quantitative Evaluation of Rheumatoid Arthritic Activity with Tc-99m HEDP

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***In an attempt to develop a quantitative method of evaluating rheumatoid arthritic activity, Tc-99m HEDP joint uptake values and joint-to-bone ratios were studied in ten adult rheumatoid arthritic patients and 17 nonarthritic patients.***

***A joint-to-bone activity ratio of 1.8 at the fourth hour after injection (RA Index) discriminated clinically active rheumatoid arthritic joints from control joints with 95% accuracy. Serial studies on five patients during drug trial demonstrated a positive correlation between RA Index and the clinical manifestations of rheumatoid arthritic activity. The RA Index may be a useful quantitative parameter for evaluation of rheumatoid arthritic activity following therapy.***

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A number of clinical indications have been used to assess the degree of inflammatory reaction in rheumatoid arthritis. These include grip strength, joint size, 50-ft walking time, degrees of morning stiffness, pain, fatigue or discomfort, range of motion, and number of painful joints. These parameters, although helpful, are somewhat subjective since findings may vary according to the cooperation of the patient and the skill of the observer.

Various radiopharmaceuticals have been used to study arthritides (*1*). An excellent agreement between clinical examination and [Tc-99m] pertechnetate joint scintigraphy has been observed (*2*). In comparison with pertechnetate images, those using Tc-99m phosphorus compounds were found to have higher sensitivity in detecting arthritic joints (*3,4*). The present study was undertaken to determine the value of quantitative measurement of Tc-99m HEDP uptake by joints in the assessment of rheumatoid arthritic activity.

## METHODS AND MATERIALS

A total of ten adult patients (7 female, 3 male, mean age of 49.3 years) with classical rheumatoid arthritis (R.A.) diagnosed on the basis of the American Rheumatoid Association criteria were compared with 17 nonarthritic control patients (12 female, five male; mean age of 54.5 yr) referred for bone scanning to evaluate metastases or for other reasons. We excluded patients with clinical evidence of osteoarthritis, multiple skeletal metastases, R.A. patients with radiographic evidence of superimposed osteoarthritis, and those with joint prostheses.

The Tc-99m HEDP used in this study was prepared using the MPI Bone Scintigraphin Reagent® and Tc-99m from a molybdenum generator. The radiopharmaceutical contains less than 1% free pertechnetate as determined by chromatography using Whatman 3-mm chromatography paper and 85% methanol solvent.

The administered dose of Tc-99m HEDP was approximately 20 mCi. Syringes were assayed before and after injection. Gamma-camera images of the joints were obtained after 3 hr as is usual for bone imaging. At the fourth hour, counts from various joints and from nonarticular bones were obtained

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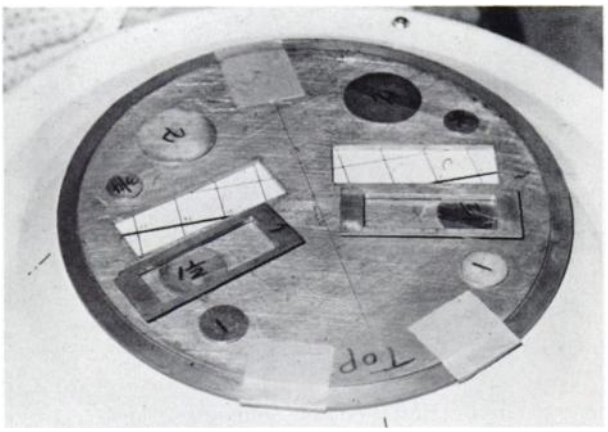

**FIG. 1.** Lead template with paired windows, to be attached to camera detector. It provides constant size and shape of "regions of interest". Rectangular inserts on template fit into the rectangular holes for the counting of small hands.

using a thyroid-uptake probe with the collimator in contact with the skin. Twelve-second counts were obtained over the volar aspect of each elbow, the dorsal aspect of each knee, and the medial aspect of each ankle. At 3 cm beyond the collimator's rim, the umbra was 6.5 cm in diameter and the penumbra 11 cm. Counts were also obtained over the mid-forearms, mid-thighs, and mid-legs, then serving as reference values for the corresponding elbows, knees and ankles. To secure constant sizes of the areas of interest and convenience in obtaining counts from small hand joints, a gamma camera was fitted with a 9-mm-thick lead template with paired windows of different sizes and shapes (Fig. 1). The field uniformity of the detector is checked daily by obtaining an image from a uniform Co-57 sheet source. The second through fifth metacarpophalangeal joints (MCPs) were counted as a group through one rectangular window, while simultaneously the opposite mid-forearm was counted through another window. A pair of lead inserts was used for smaller hands. The template also had round windows of varying diameters to be used for counting individual joints. Using the camera's 100-channel analyzer, two-minute counts were obtained simultaneously over the joints and the corresponding background bones. Joint counting was performed in the same sequence in all patients.

In the first five rheumatoid arthritic patients and three control patients, activity counting was done every hour for over the knee joints and over the tibiae the first 5 hr after injection. In all patients, joint-to-bone activity counts were obtained at the fourth hour over the second through fifth metacarpophalangeal joints, elbows, knees, and ankles. The time required to obtain these counts was less than 20 min. In a few patients, serial counts were obtained before and after treatment over various time intervals.

## RESULTS

The mean hourly uptakes (counts per second per millicurie administered) in the clinically active rheumatoid knee joints were greater than those for the normal control joints at all times. Both involved knee joints, and normal joints appeared to show two exponential components in their accumulation of Tc-99m HEDP activity. The first components are fast:

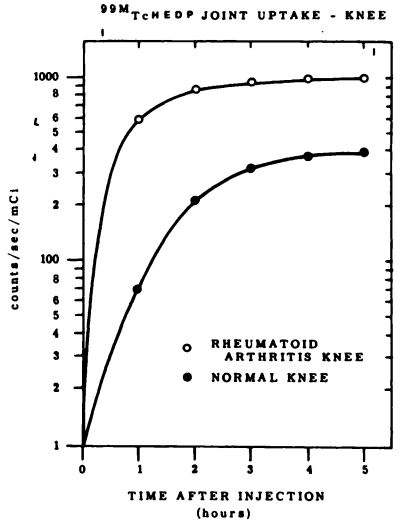


**FIG. 2.** Mean Tc-99m HEDP knee-joint uptakes on 5 arthritic patients and 3 nonarthritic patients. Arthritic joints show a more rapid early uptake.

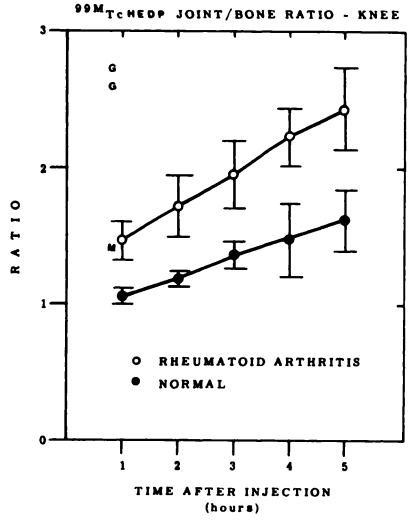


**FIG. 3.** Ratios of Tc-99m HEDP knee-joint activity to reference bone. Arthritic joints (5 patients) show greater ratios than non-arthritic joints (3 control subjects) and continue to rise during the five-hour study period.

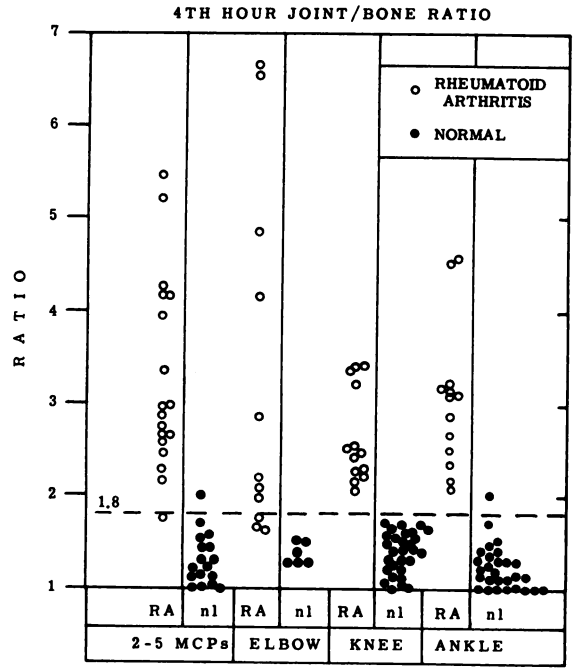


**FIG. 4.** The 4th-hour joint/bone ratio (RA Index) of various joints. RA Index of 1.8 distinguished between control joints and 130 of 136 arthritic joints.

$t_{1/2}$ = 6.5 min for rheumatoid arthritic joints and 16.6 min for normals; the second components are much slower: $t_{1/2}$ = 11.3 hr for the rheumatoid arthritic, 5.8 hr for normal joints. The involved joints appear to have a more rapid early component (Fig. 2). The hourly ratio of joint counts to reference bone counts was also greater for rheumatoid knee joints than for the normal joints and continued to rise during the 5-hr study (Fig. 3).

In all patients the fourth-hour ratio of joint counts to reference bone counts was significantly higher (range: 1.6–6.7) for the joints involved with rheumatoid arthritis than for the normal joints (range: 1.0–2.0). The means of the ratios in normal joints, ankles, and knees were significantly different (P = 0.02) while all other pairs were not. Using an arbitrary value of 1.8 as the upper limit of normal, 130 out of 136 (95%) joints or joint groups studied could be reliably distinguished (Fig. 4). We have designated this fourth-hour joint-to-bone ratio as the Radionuclide Arthritis Index (RA Index). The mean and standard deviations of the RA Index for rheumatoid arthritis and normal joints are shown in Table 1. Applying student's t-test, the P value was less than 0.001 for the second through fifth metacarpophalangeal joints, the knees, and the ankles, and it was less than 0.01 for elbows. The serial RA Indices obtained in a 46-year-old female volunteer are shown in Fig. 5. She had a 6-yr history of rheumatoid arthritis and had been on Butazolidine, aspirin and prednisone for a number of years. When the Butazolidine and aspirin were discontinued, and prednisone was reduced from 10 mg to 5 mg per day, the arthritis flared up and the RA Indices rose. When Fenoprofen was started and prednisone increased to 7.5 mg, she showed rapid clinical improvement and RA Indices decreased (Fig. 5). Serial studies in five patients with rheumatoid arthritis who volunteered for the same drug trial showed a 5 to 57% fall from baseline RA Indices accompanying a subsequent clinical improvement (Table 2).

**TABLE 1. FOURTH-HOUR Tc-99m HEDP JOINT-TO-BONE RATIO**

| | 2–5 MCPs* | Elbow | Knee | Ankle |
|---|---|---|---|---|
| Active R.A. joints | | | | |
| Mean | 3.24 | 3.29 | 2.62 | 3.00 |
| (S.D.) | (1.0) | (1.94) | (0.52) | (0.78) |
| Normal joints | | | | |
| Mean | 1.29 | 1.38 | 1.38 | 1.22 |
| (S.D.) | (0.28) | (0.12) | (0.22) | (0.23) |
| p† | <0.001 | <0.01 | <0.001 | <0.001 |

* Metacarpophalangeal joints.
† Standard student t test.

## DISCUSSION

Workers in the field of rheumatology agree that once a joint is involved with rheumatoid arthritis it is not likely to become completely normal again. Efforts to assess the efficiency of anti-inflammatory therapy must therefore rely upon changes in the degree of abnormality of the joint, i.e., relative quantitative changes. A few investigators attempted to

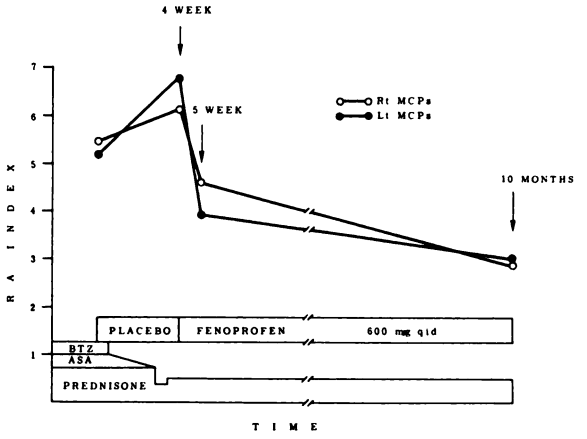


**FIG. 5.** Serial RA indices in a rheumatoid arthritic patient following therapeutic management. RA indices rose and fell with clinical exacerbation and improvement.

**TABLE 2. CHANGE IN RA INDEX PRE- AND POST-Rx**

| Patient's age | Patient's sex | RA index of 2–5 MCPs | | | Time interval |
|---|---|---|---|---|---|
| | | Before Rx | After Rx | Percent changed | |
| 47 | F | R 6.1 | 3.0 | −51 | 10 mo |
| | | L 6.9 | 3.0 | −57 | |
| 39 | M | R 3.4 | 2.1 | −39 | 4 mo |
| | | L 3.4 | 2.2 | −36 | |
| 62 | F | R 4.2 | 3.2 | −24 | 1 wk |
| | | L 3.3 | 2.5 | −25 | |
| 46 | M | R 2.1 | 2.0 | −5 | 1 wk |
| | | L 2.5 | 2.1 | −16 | |
| 45 | F | R 3.5 | 1.8 | −49 | 3 mo |
| | | L 4.9 | 2.9 | −41 | |

quantitate the inflammation of a joint by determining its uptake of pertechnetate (*5,6*). Such uptake by arthritic joints, however, is mostly due to increased blood flow to the inflamed and proliferated synovium, and the pertechnetate activity clears from the joint rapidly. Dick et al. (*6*) found that the time of maximum concentration of pertechnetate activity in rheumatoid joints was approximately 16 min and did not differ significantly from the normal time.

Since it is believed that practically all arthritic joints are associated with periarticular and subchondral bone erosions followed by increased osteoblastic activity in reaction to the inflammation, Tc-99m HEDP and other phosphorus bone-seeking agents have a theoretical advantage over pertechnetate. These Tc-99m phosphorus compounds are considered to be chemisorbed onto the hydroxyapatite crystals of bone and to remain there; hence, there is less fluctuation of the activity than with pertechnetate. Clinical studies have demonstrated the superiority of these agents in identifying arthritic joints (*3,4*).

From this work, it appears that Tc-99m HEDP joint uptake values (counts per second per millicurie administered) may be a usable quantitative parameter that may be superior to pertechnetate in assessing arthritic activity. Its calculation, however, requires background subtraction and correction for the decay, as well as assay of the syringe before and after injection of the radionuclide. The RA Index, on the other hand, is simple and easy to obtain. RA Indices, as well as the joint-uptake values, increased with time (although slowly) and thus reasonably accurate timing and obtaining the counts from individual joints in a prescribed order are important. Since the RA Index is a comparison of joint activity with the patient's own nonarticular bone activity, the patient serves as his own control. It is unlikely that the patient's body build will affect the index. One theoretical question is the possibility that generalized bone turnover is affected by the therapeutic regimen, especially by glucocorticoids. The anecdotal case illustrated in Fig. 5 has been on prednisone for many years and still showed changes in the RA Index when there was clinical exacerbation or improvement.

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