

Yttrium-90 therapy and ^{99m}Tc pertechnetate knee uptake measurements in the management of rheumatoid arthritis

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SUMMARY Twenty-eight knees with chronic arthritis and effusion were treated with intra-articular ^{90}Y . Synovial activity was assessed by measuring ^{99m}Tc pertechnetate uptake. There was a significant difference in uptake between controls and patients. Those who had a good response to ^{90}Y (15 patients) showed a significant decrease in uptake, not seen in those who failed to respond. The pattern of ^{90}Y distribution was examined and appeared to correspond to areas of increased synovial activity; these patterns and their significance have not been previously reported. Factors which could help to predict response to ^{90}Y are discussed.

Radioactive colloids have been used for almost 20 years¹ in the treatment of chronic synovitis. The initial work was done with radioactive gold (^{198}Au) but radioactive yttrium (^{90}Y) is now preferred because of the greater penetration of beta radiation, the absence of undesirable gamma radiation, and probable greater retention within the joint.^{2,3}

Objective assessment of the effects of ^{90}Y on disease activity is desirable, and can be done by measuring radioactive technetium (^{99m}Tc) uptake in inflamed joints.⁴ The accumulation of ^{99m}Tc pertechnetate correlates with the intensity of inflammation, and the degree of activity can be assessed by joint scanning or counting.⁵

The aims of this study were to irradiate with ^{90}Y the synovium of the knee joint in patients with chronic synovitis and effusions, measure ^{99m}Tc uptake before and after treatment, and try to correlate response with uptake and clinical and radiological parameters. We also studied the pattern of ^{90}Y deposition and its significance.

Patients and methods

Twenty-two patients were selected with chronic effusion and arthritis of one or both knee joints. Thirty-three knees were studied in total. Treatment with systemic chemotherapy and repeated intra-articular

injection of steroids had been ineffective, and most were candidates for surgical synovectomy. Twenty-one of the patients had classical or definite rheumatoid arthritis by ARA criteria; one had a monoarticular arthritis of the knee with chronic recurrent effusion. The mean age was 63.24 years (range 49-76 years) and 15 were female. Disease duration ranged from 1 to 29 years, with a mean of 8.86 years. Eleven patients were receiving second-line drugs or steroids at the time of treatment, and all but 3 were seropositive.

Knee uptake measurements were based on the technique of Dick *et al.*⁶ The patient was positioned with a 2-inch (5-cm) scintillation counter over each knee, the end of the collimator being in line with the patellar surface. 100 μCi of ^{99m}Tc TcO_4^- (pertechnetate) was injected intravenously. The activity measured within the field of each counter at 15 and 20 minutes was expressed as a percentage of the injected dose by reference to a phantom counted with similar geometry. Control subjects receiving pertechnetate for thyroid scans were used to establish the normal range and to calculate baseline values corrected for body weight. After baseline uptake measurements had been obtained, the effusion was tapped and 4 mCi of ^{90}Y injected, the standard Amersham silicate colloid preparation being used. ^{90}Y was flushed in to prevent needle track burns with 50 mg hydrocortisone to reduce any local radiation reaction within the joint. After the knee had been flexed several times to distribute the radioactive material throughout the joint cavity the limb was

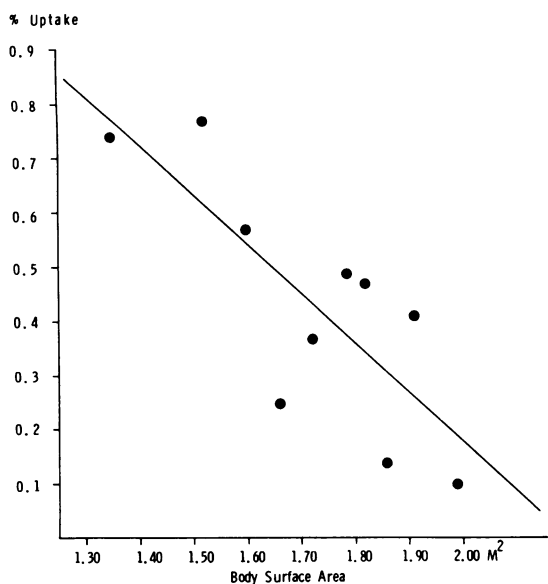


Fig 1 Knee uptake measurements in 10 control subjects; each point represents the mean of both knees. $y = 2.42 - 0.92x$ $r = 0.796$.

immobilised in a splint for 2 days to minimise leakage from the joint. The final distribution of activity at 48 or 72 hours was determined by scanning, with a wide energy channel set to record Bremsstrahlung. Activity distribution was assessed as 'localised', 'diffuse,' or 'mixed'. In half the patients ^{90}Y was injected under x-ray control to determine whether 'localised' distribution was due to loculation. Counting over groin and liver was done at the same time as scanning, to estimate leakage.

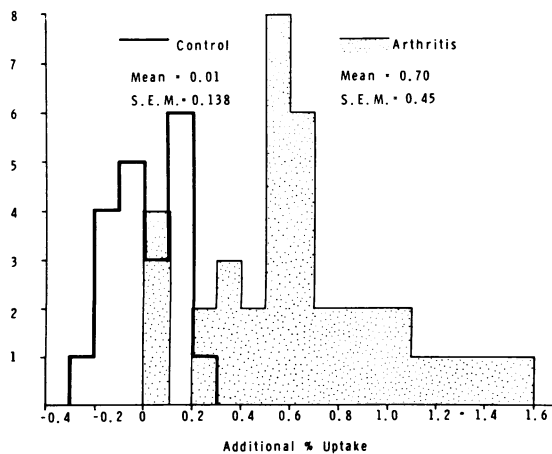


Fig 2 Uptake measurements corrected for body surface area.

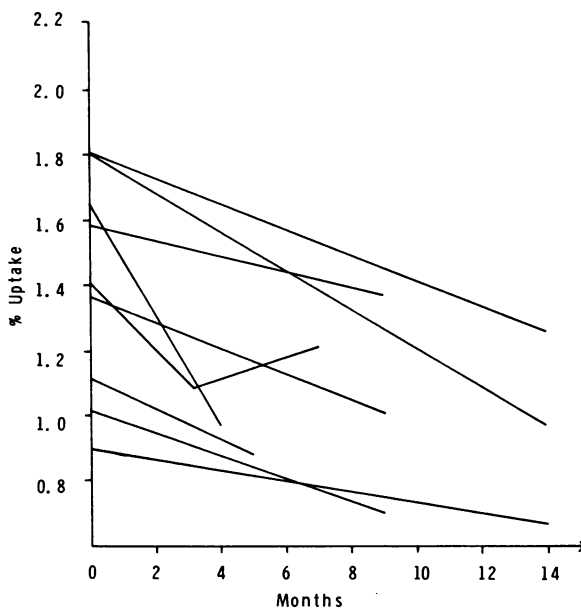


Fig 3 Serial uptake measurements following $^{90}\text{yttrium}$ therapy in those who had a good clinical response.

Sequential measurements of knee uptake in 12 cases, involving 18 treated knees, were done at intervals of 2-14 months, median 7.5 months. Clinical assessment was also carried out at at least 3 monthly intervals for a minimum of 6 months. The response to ^{90}Y was graded as 'good' if there was symptomatic improvement and the knee remained effusion free

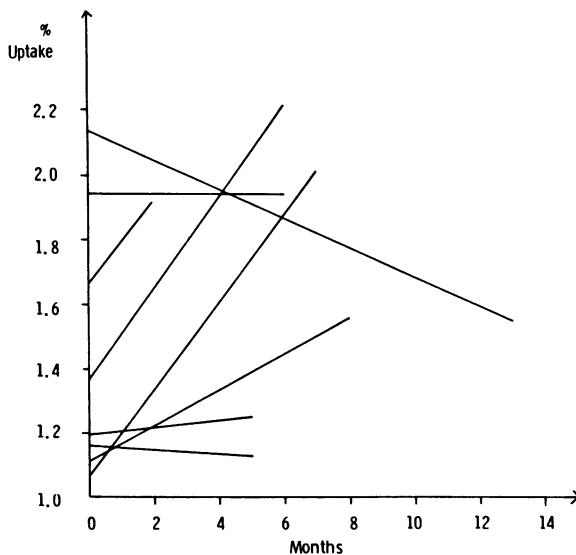


Fig 4 Serial uptake measurements following $^{90}\text{yttrium}$ therapy in those who had a poor clinical response.

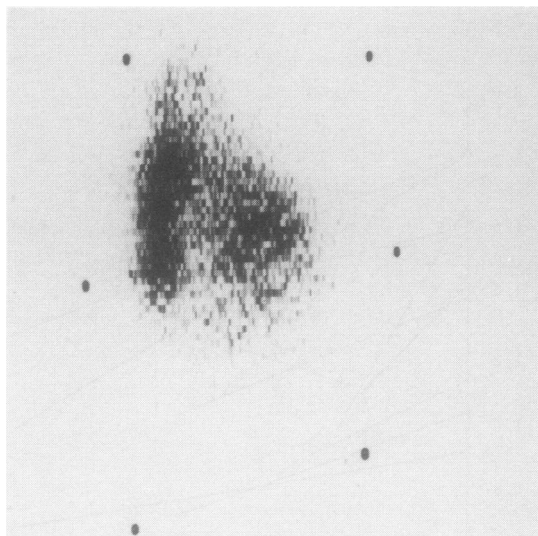


Fig. 5 Uniform distribution throughout synovial membrane (assessed as 'diffuse').

for more than 6 months and 'poor' if these criteria were not fulfilled. Radiological grading was carried out before treatment in 20 patients as described by Steinbrocker *et al.*⁷

Results

Percentage uptake in 10 controls was found to vary with body weight. The regression formula derived by plotting these figures was used to calculate expected soft-tissue activity, (Fig. 1) and thus the predicted baseline percentage uptake.

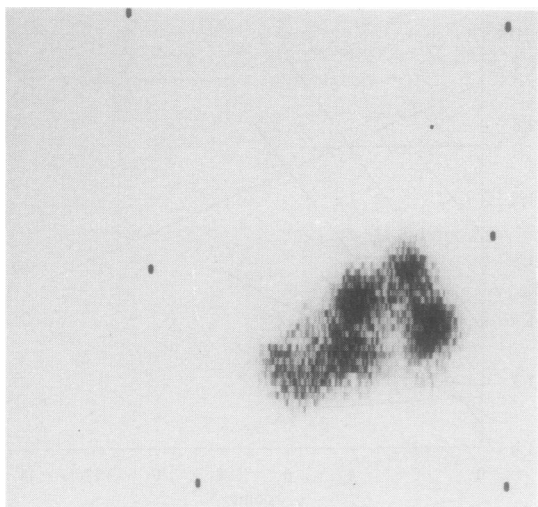


Fig. 6 Focal areas of activity additional to diffuse synovial uptake (assessed as 'mixed').

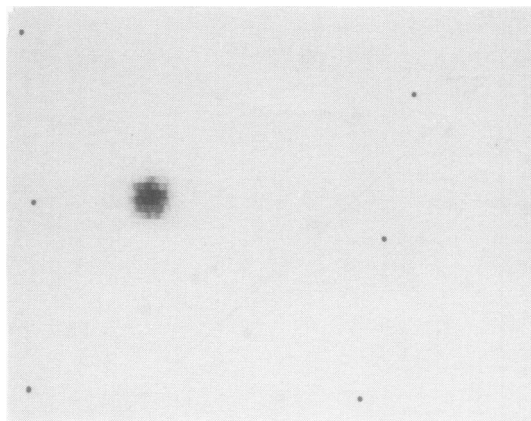


Fig. 7 Uptake of yttrium concentrated in single small focus (assessed as 'localised').

The percentage increase in uptake from the predicted baseline was then calculated at 20 minutes in 20 controls and 38 knees of 22 patients. Non-parametric statistical analysis of these results by the Mann-Whitney test showed a highly significant difference in uptake between the 2 groups ($p < 0.001$). These data are shown in Fig. 2.

Three patients (5 knees) were excluded from analysis of results, 2 because of death from unrelated causes and 1 because of a change in treatment which could have affected response. Of the remaining 28 knees (19 patients) 15 showed a 'good' response and 13 a 'poor' response to ⁹⁰Y injection. The repeat uptake values at 20 minutes decreased in all patients with a 'good' response (Fig. 3). These figures were analysed by the Wilcoxon signed rank test, and the change in uptake was significant ($p < 0.02$). All but one of those whose clinical response was poor showed no change in uptake or a further increase; statistical analysis confirmed that these changes were not significant (Fig. 4).

The distribution of radioactivity is shown in Table 1 and does not appear to correlate with clinical response, though numbers are too small for formal

Table 1 Clinical response and scan appearances

	Localised	Diffuse	Mixed
Good response	5	8	2
Poor response	4	5	4

Table 2 Clinical response and radiological grading

	I	II	III	IV
Good response	7	2	1	1
Poor response	3	7	1	1

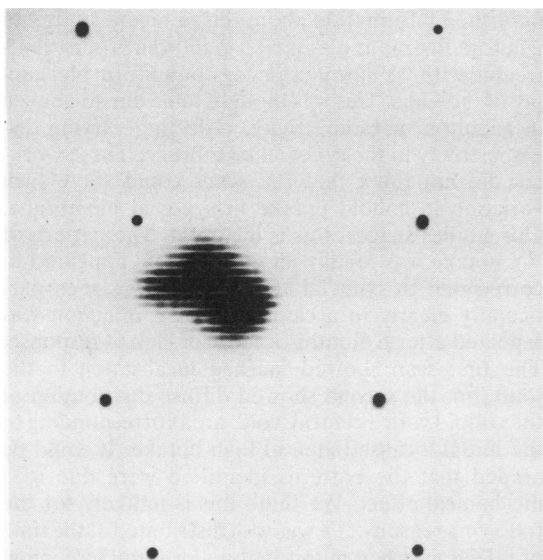


Fig. 8a Localised uptake at initial treatment.

analysis. Injections under *x*-ray control established that there was free flow through the joint cavity even if scans subsequently showed localisation of activity. Examples of typical patterns are shown in Figs. 5–7. One patient whose scan showed marked localisation had a second injection of ^{90}Y because of lack of response to the first. The second scan showed diffuse distribution of colloid but with a central ‘cold’ area corresponding to the initial area of localised high uptake (Figs. 8a, b). There was no correlation between initial uptake values and clinical response.

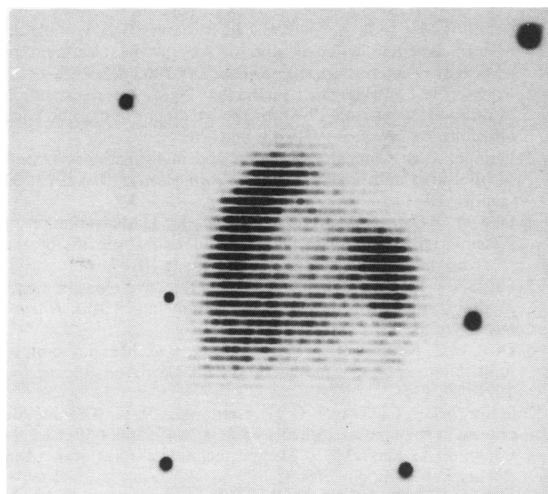


Fig. 8b Diffuse uptake on retreatment 8 months later with apparent reduced activity centrally.

Radiological grading did not appear to be related to response, but again the numbers were too small for analysis (Table 2).

The estimated uptake counts over groin and liver at 48–72 hours were insignificant in all cases (groin range 0.3–2.5 K, mean 1.31, liver 0–1.5 K, mean 1.05, background 0.5 K).

Discussion

Increased uptake of radionuclide in inflamed joints occurs because of hyperaemia in the inflamed synovial membrane, and also increased synovial permeability in the presence of an effusion.^{8,9} McCarty's group⁹ demonstrated a late ‘peak’ of increased activity in patients with extensive joint effusions, thought to be due to ^{99m}Tc binding to proteins in the joint fluid. Bone vascularity is also increased in inflamed joints, but joint deformity, fibrotic changes, and muscle wasting do not influence uptake.⁴ Our results show a significant difference in the percentage uptake of ^{99m}Tc at 20 minutes in inflamed joints when compared with controls. Those patients who responded well to ^{90}Y showed a significant decrease in uptake. We did not observe the late ‘peak’ reported by McCarty *et al.* Presumably the alteration in uptake reflects changes in the synovial membrane which are secondary to the inflammatory process.

Intra-articular injection of radioactive colloid has an established role in the treatment of chronic synovitis and effusions.^{10,11} Gumpel *et al.*¹² showed in 1975 that it is as effective as surgical synovectomy after 2 years, although a more recent study¹³ cast doubt on the benefit of radioactive yttrium. The destruction of inflamed synovial membrane occurs when it is irradiated by colloidal particles removed from the suspension in the joint cavity. Radioactivity seems to be concentrated in the synovial membrane; autoradiographs have shown that the cartilaginous surface is not usually affected.¹⁴ Kershbaumer *et al.*,¹⁵ however, reported marked degenerative change in human chondrocytes after 5 mCi of ^{90}Y , suggesting that colloid caused cartilage necrosis, but this study was uncontrolled, and the damage could have been due to chronic inflammation. The risks from the radiation dose to lymphocytes and lymph nodes have been examined by several groups.^{16–19} Most groups report an increased frequency of chromosomal aberrations in circulating lymphocytes after treatment with ^{90}Y ; immobilising patients after injection seemed to reduce this. Roberts and Gillespie,¹⁹ however, did not find any increase in abnormal chromosomes. There is in any case no clear evidence that such abnormalities are significant; to date there are no reported cases of leukaemia or other malignancies. Because the penetration of beta radiation is only

a few millimetres, the risk of irradiation to bone cells around the knee appears to be minimal. The dose to inguinal lymph nodes is usually negligible,^{18, 20} but other groups^{2, 21} reported node uptake of >10% amounting to several thousand rads. There is no relevant experience of the risks of malignancy from such doses to human lymph nodes: local irradiation of <1000 rads (equivalent to <2–3% of the injected ⁹⁰Y) seems to be innocuous,²² and leakage of amounts greater than this should be avoided if possible.

Our results showed improvement in just over half the patients treated with ⁹⁰Y, rather lower than in some other studies,^{23, 24} which may be partly explained by the varying criteria used in assessment. Although some of our patients had improved within 2 months, in some no change was apparent until more than 4 months. Menkes *et al.*²³ showed that a poor result at 6 months was unlikely to improve but that this was not the case at 3 months. They also found that initially good results rarely deteriorated, and a good result at 6 months was likely to remain so at 2 years.

Prediction of those most likely to respond well to ⁹⁰Y is unsatisfactory. Patients with marked articular damage rather than active synovitis of the knee joint are unlikely to benefit, and grades I and II radiological changes are associated with a better response.²³ Two patients who failed to respond in our study had knee arthroplasty performed shortly afterwards, and in both there was extensive bony damage but little active synovitis. As only 4 patients had radiological grades III or IV, correlation of grading with response was not possible. Winfeld and Gumpel²⁵ suggested patients with widespread active synovitis were unsuitable for ⁹⁰Y in the knee, but did not find the ESR helpful in predicting outcome. Seropositivity was associated with a lower failure rate in the study by Menkes *et al.*,²³ but as only 3 of our group were seronegative we could not confirm this. Scan distribution and disease duration did not appear to be related to response, but again numbers were too small for formal analysis. The initial 20-minute uptake value did not correlate with clinical outcome. Another possible factor affecting response is the degree of isotope retention. Numerous studies of this have been carried out.^{2, 12} Of the 4 commonly available yttrium colloids, citrate, ferric hydroxide, resin, and silicate, all have similar retention up to 24 hours, but by 5 days only resin and silicate preparations are consistently well retained and there is considerable variation in the other 2. Although no strict quantitative assessment of retention was made, the low counts over groin and liver in our study suggest there was little leakage of colloid from the knee joint.

An interesting feature was the varying distribution of yttrium within the knee joint. There is very little

published information about this; a recent study²⁶ of 2 autoradiographs of synovial membranes of patients treated with ⁹⁰Y silicate showed nonuniform blackening of the films. This was thought to be due to uneven distribution of radioactivity, reflecting varying disease activity in the synovial membrane. These workers did not think that ⁹⁰Y scans could show such variation in colloid uptake in synovial membrane. Our studies suggest this is incorrect. The pattern of ⁹⁰Y uptake was readily identifiable and appeared to correspond to synovial activity. This was seen particularly clearly in a case where ⁹⁰Y injection was repeated after 6 months because of lack of response. The first scan showed marked localisation in the joint, but the second showed diffuse distribution of the colloid with a central 'cold' area corresponding to the initial localised area of high uptake. It could be argued that the patterns identified were due to a mechanical effect. We think this is unlikely for the following reasons. ⁹⁰Y was well distributed at the time of injection, when monitored under x-ray screening. In all patients the knee was passively flexed after injection, which has been shown to result in widespread dispersal of injected fluids.²⁷ Further studies of ⁹⁰Y distribution, particularly in cases where the injection is repeated, would be of interest.

In summary, we confirmed the value of ⁹⁰Y in treating some patients, although it could not be predicted which would respond. We examined in some detail the distribution pattern of ⁹⁰Y, an aspect not previously discussed. Technetium uptake was useful both in confirming inflammation and in monitoring improvement after treatment.

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