The pertechnetate joint scan*

I. Timing

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Joint scanning has been used for the study of patients with arthritis for several years. Although the authors of the original reports used ^{131}I labelled human serum albumin (Weiss, Maxfield, Murison, and Hidalgo, 1965), and some workers have advocated the use of $^{99\text{m}}\text{Tc}$ labelled albumin (Cohen and Lorber, 1971), $^{99\text{m}}\text{Tc}$ -pertechnetate (McCarty, Polcyn, Collins, and Gottschalk, 1970b); Alarcón-Segovia, Trujeque, Tovar, and Adame, 1967; Whaley, Pack, Boyle, Dick, Downie, Buchanan, and Gillespie, 1968) is at present the most common radioisotope used for this purpose. Identification of inflamed joints by scanning techniques has been shown to correlate well with other clinical parameters (McCarty, Polcyn, and Collins, 1970a; Green and Hays, 1969, 1972). The best time after injection of pertechnetate for the scan has not yet been established, although McCarty, Polcyn, and Collins (1969) have stated that small joints should be scanned immediately after injection, while large joints, particularly the knees, should be scanned later. However, the value of delayed pertechnetate knee scanning has been questioned by Cohen and Lorber (1971), who observe that even normal knees show relative concentration of pertechnetate after a sufficiently long delay. Recently, McCarty and others (1970b) have modified their earlier opinion, advocating late scanning of large joints only when large effusions are present.

In order to clarify this issue, and to establish an appropriate routine for clinical studies, we undertook a systematic study of the rate of isotope concentration by inflamed and normal joints, and the relationship of these concentrations to simultaneous serum and joint fluid radioactivity. In addition, we hoped to shed light on the mechanism of joint scan positivity.

Methods

EXPERIMENTAL ANIMALS

Eight mongrel dogs, weighing approximately 12 kg., were anaesthetized with pentobarbital. $^{99\text{m}}\text{Tc}$ -pertechnetate was administered intravenously. All areas of the animal except the two hind knees (equal exposed areas) were carefully screened with flexible lead shielding. Six of the animals were positioned under the crystal of an Anger-type scintillation camera in a manner allowing both knees to be viewed simultaneously. With the field of the camera crystal split, the radioactivity in the two unshielded areas was recorded graphically. Repeated Polaroid photographs of the image were made to confirm the graphical information. These showed no evidence of overlap between the two knees. The other two dogs were studied using a matched pair of scintillation probes attached to a dual channel scaler spectrometer. Intravenous cannulae were placed in five animals to facilitate repeated blood sampling. In one dog, synovial fluid was sampled repeatedly through a needle left in place throughout the experimental period. Single synovial fluid samples were obtained in the other dogs by needle puncture.

In order to induce acute synovitis in the dogs, sodium urate crystals (50–100 mg.) were injected into the hind knee joint as described by Faires and McCarty (1962). Synovial fluid removed after several hours from the injected joint regularly revealed intraleucocytic, negatively birefringent crystals by polarizing microscopy. No significant bloody contamination was found. Experiments with urate injected joints were of two types: study of the immediate effects of trauma on pertechnetate concentration by the joint ('early' experiments) (4 dogs), and study of the concentration of a dose of pertechnetate in a previously traumatized joint ('delayed' experiments) (5 dogs).

In the 'early' experiments, the anaesthetized animal was given an intravenous dose of pertechnetate, and a baseline established by repeated counting of both knees. Samples of blood for plasma radioactivity were obtained at 2, 5, 10, 20, 30, 40, 50, and 60 mins and hourly thereafter. After

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* The term, 'scan', although technically imprecise for scintiphotographs, will be employed in the text because of general usage.

establishment of baseline external counts, at times varying from 15 to 90 mins after administration of pertechnetate, sodium urate crystals were injected into one knee joint. Scintillation counting and photography was then continued up to 5 hrs subsequently. In one experiment, a second dose of intra-articular urate was given at 3 hrs. In another, intravenous pertechnetate was repeated at 2½ hrs.

Four dogs were prepared for 'delayed' experiments by repeated intra-articular injection of urate crystals into one knee, receiving two or three daily injections. The 99m-pertechnetate experiment was performed 24 hrs after the last injection in four and after 72 hrs in one. In one animal, with the usual narrow shielding of both knees, curves of external counts were performed and correlated with the blood plasma curve after injection of 99m-pertechnetate. In another dog, appearance of the tracer in synovial fluid was correlated with simultaneous plasma radioactivity. In the latter animal, intermittent external counting was performed between withdrawals of synovial fluid after careful repositioning of the probe. The other three dogs' knees were monitored externally in a manner similar to that used in patients.

STUDIES IN PATIENTS

Thirteen studies were carried out in eleven patients. Seven of these patients had rheumatoid arthritis, and spondylitis with peripheral joint involvement, gout, Reiter's disease, and monoarticular arthritis (aetiology not established) were each diagnosed in one patient. Only individuals with clear-cut unilateral ankle, knee, or wrist inflammation, together with a clearly normal contralateral joint for comparison were studied, except in Autofluoroscope studies of the small joints of the hand, when a corresponding joint on another finger was compared. In all cases, the joint in question was closely defined by lead shielding, except when this could be done by instrumentation. A variety of detection instruments were used for these studies: an Anger-type scintillation camera with analog recorder (4 studies), an Autofluoroscope (2 studies), a two-channel gamma spectrometer with simultaneous readout from two matched probes (4 studies), and a 400-channel analyser with capacity for sequential recording of 200 time periods with each of two matched probes (3 studies). Two patients were studied twice, using different instruments; in both cases, the findings were similar.

In five patients serial blood samples were obtained through an indwelling needle. Repeated synovial fluid samples, obtained in three patients, were drawn through a fine bore needle or polyethylene catheter left in place during the experimental period. Scrupulous attention was paid to maintaining a sterile field during these studies, with avoidance of trauma from the indwelling needle.

All patients were informed of the experimental nature of the study, and gave their informed consent. Routine joint scanning was also performed on these subjects.

Results

ANIMAL STUDIES

Acute effects of trauma

In the 'early' studies, no immediate effect of urate injection on the joint scan was observed. In one dog, a second dose of pertechnetate, given 1½ hrs after

urate injection, was distributed equally between the traumatized and the control knee. Another dog, 4 hrs after urate injection, had obvious swelling of the affected joint, with the presence of excess joint fluid. Nevertheless, this animal showed no asymmetry in joint scan appearance at that time. (This experience differs from that of Sholkoff, Glickman, Schachter, and Rowland (1969), who found asymmetrical $^{99m}\text{TcO}_4^-$ uptake in two of three rabbit knees studied 4 to 6 hrs after intra-articular *Bedsonia* organism administration.) This dog was re-studied briefly 24 hrs after the initial experiment, by simple scanning of the two knees after injection of a dose of 99m-pertechnetate. At that time, the injected knee (which had not concentrated pertechnetate 4 hrs after urate injection) showed a high concentration of the tracer. This observation led us to the study of animals with well-established experimental arthritis.

Studies of dogs with established urate-induced arthritis ('late' experiments)

Three of the dogs injected repeatedly with intra-articular sodium urate crystals were studied by continuous external counting over the two knees after intravenous pertechnetate (Fig. 1). The inflamed knee showed a rapid rise in radioactivity with a peak reached 6, 8, and 18 mins after injection. On the other hand, in the normal knees, the radioactivity level rose more slowly, and underwent a prolonged plateau with the decrease in radioactivity beginning at 17, 20, and 40 mins respectively after $^{99m}\text{TcO}_4^-$ injection. One of these animals received an additional sodium urate crystal injection into the already inflamed joint shortly after a second dose of pertechnetate. This new intra-articular sodium urate did not affect the shape of the pertechnetate curve in the inflamed joint.

FIG. 1 Counts recorded externally over the knees of a dog. The experimental knee had received three previous doses of intra-articular sodium urate crystals. Recording made on a strip-chart recorder (linear scale) with the scintillation camera. Note that the time scale begins at the right

A fourth dog, similarly injected, was studied with special attention to the rate of appearance of radio-

activity in the synovial fluid. The results of this study are presented in Fig. 2. Although the serum radioactivity in this animal fell in the multiphasic exponential fashion typical of most substances with wide distribution throughout the body, the concentration of radioactivity in the synovial fluid rose very gradually, and had not reached true parallelism with serum radioactivity at the end of 60 mins. Synovial fluid and serum from this animal taken 24 hrs after injection of pertechnetate showed a synovial fluid to serum ratio of 0.87, higher than any ratio attained during the acute experiment. It was felt that this difference at 24 hrs might be due to a different degree of binding of pertechnetate by the two fluids. For this reason, samples of these two fluids, enriched with additional ^{99m}Tc -pertechnetate, were subjected to ultrafiltration at 4°C . By the technique used, 16 per cent. of the radioactivity in the synovial fluid was found to be unbound, while only 13.2 per cent. of the radioactivity in the serum was free. In other work (Hays and Green, 1972), we have found this difference in ultrafiltrability of simultaneously studied samples to indicate a significant binding difference.

FIG. 2 ^{99m}Tc in equal volumes of serum from a dog and synovial fluid from its previously sodium urate-injected knee

STUDIES IN HUMANS

Regardless of the joint studied, or the aetiology of the arthritis, we found that abnormal joints reached

a peak of radioactivity earlier than did the contralateral normal joints. An illustration of this phenomenon is shown in Fig. 3, in which the points represent 'volume of distribution' of pertechnetate within the unshielded area. These 'volumes' are the ratio of the percentage of the dose found within the area in question (estimated by comparison with an appropriately shielded standard), and the percentage of the dose found within 1 ml. of plasma. This notation is used in this instance to correct for changes in plasma radioactivity. The volume of distribution in the right, abnormal knee reaches a maximum after approximately 40 mins and does not increase thereafter. At the same time, the volume is increasing in the left knee, and continues to increase until the end of the experiment at 100 mins. Up to approximately 40 mins after the injection, separation of the radioactivity concentration in the right knee from that in the left knee appears to be greatest.

FIG. 3 Volume of distribution

$$\left(\frac{\text{percentage of dose measured by external counting}}{\text{percentage of dose in 1 ml. serum}} \right)$$

 of the normal left knee and the inflamed right knee of a patient with rheumatoid arthritis

A similar study, performed in conjunction with repeated measurement of synovial fluid radioactivity in the affected knee, is presented in Fig. 4. In this instance, the external counts from the knees are presented simply as the percentage of the dose 'seen' by the narrowly shielded probe rather than as 'volume of distribution'. Whereas the abnormal knee reaches peak radioactivity within approximately 20 mins, and subsequently falls quite abruptly, the normal knee radioactivity is slower to reach a peak and slower to fall. While the total radioactivity in the abnormal knee was falling rapidly, the concentration of radioactivity in synovial fluid from that knee was gradually rising. Even at the end of 100 mins, however, the synovial fluid radioactivity had not reached the concentration of that of the plasma bathing the joint.

Fig. 5 presents smoothed curves from counts made at $\frac{1}{2}$ min. intervals after injection of the $^{99m}\text{per-}$

FIG. 4 Simultaneous measurement of radioactivity (as seen externally) in arthritic knee compared with normal contralateral knee, compared with plasma and repeated synovial fluid radioactivity. The patient is a young man with Reiter's disease

FIG. 5 External counting over a normal right ankle and a markedly inflamed left ankle (containing a large effusion) in a patient with rheumatoid arthritis. This study was done using the multi-channel analyser, with counts made every 30 sec. The curves shown are smoothed from these multiple points. Maximum count rate for inflamed knee 146,000 c/min.; for normal knee, 36,000 c/min.

technetate, using a matched-probe system and the multi-channel analyser. In this case, the patient had a monoarticular arthritis of unknown cause of the left ankle. All other joints, including the right ankle, were clinically normal at the time of the study. Radioactivity in the left ankle reached maximum early after the pertechnetate injection, in this case after approximately 10 mins, and subsequently began to fall, roughly paralleling the expected simultaneous serum radioactivity concentrations. At the same time, the radioactivity in the normal joint increased slowly and had not begun to fall at the end of 40 mins.

Fig. 6 shows results of a study of a hand using the Autofluoroscope. After injection of the 99mTc -pertechnetate, counts were accumulated at 1-min. intervals for 60 mins. Subsequently, the anatomy of the hand was correlated with the oscilloscope pattern, and regions corresponding to the inflamed second metacarpophalangeal joint and the uninfamed third metacarpophalangeal joint were identified by

FIG. 6 Comparison of externally measured radioactivity in the inflamed second and the normal third metacarpophalangeal joints of a patient with rheumatoid arthritis. This study was done with the Autofluoroscope, with specific identification of the regions representing these two joints. The time scale begins at the right, and each deflection represents the counts accumulated during 1 min.

the light pen. The curves presented in Fig. 6 are those resulting from playback from magnetic tape of the areas corresponding to these two joints. It will be seen that in these small joints, just as for larger joints, the abnormal joint reaches its maximum radioactivity after approximately 15 mins., whereas the radioactivity in the normal joint continued to rise until approximately 50 mins.

Fig. 7 presents samples from a series of scintiphotos made of a hand at increasing intervals after injection of the pertechnetate. While the abnormality in the first metacarpophalangeal joint continues to be apparent even at the end of this sequence, its differentiation from the normal joints is most clearcut up to about 40 mins. after the injection. The abnormal fourth distal interphalangeal joint is apparent only in the early views.

Discussion

This study was undertaken with two aims:

(1) To settle the practical question of the best time for joint scanning after injection of ^{99m}Tc -pertechnetate;

(2) To elucidate the mechanism underlying joint scan positivity.

We feel that our data demonstrate unequivocally that, regardless of the size of the joint, the best differentiation between normality and abnormality is achieved in times up to 40 mins. after the injection of the tracer. For this reason, we have adopted the policy of discontinuing scanning in our laboratory at 40 mins., offering the option to the clinician of repeating the tracer if this time limit has been insufficient for the studies of interest. This policy was reinforced after we had encountered difficulties in interpretation of the equivocal results seen in late scanning.

Weiss and others (1965) using radioiodinated human serum albumin, and Maxfield and Weiss (1969), using pertechnetate, presented data showing slow concentration of radioactivity in both normal and abnormal joints. However, when pertechnetate

is the agent employed, most workers appear to agree that early scanning is best for small joints. On the other hand, there has been disagreement about the proper time to examine large joints such as the knee. Cohen and Lorber (1971) have recently shown that, when scanning is performed with pertechnetate rather than with an albumin-attached isotope, false-positive knee scans may be seen after an interval of 1 to 2 hrs. It is possible that the increased identification of inflamed knees observed by other workers after prolonged delay (McCarty and others, 1969) represent an accumulation of radioactivity in the synovial fluid, which is slow to reach equilibration with the serum. However, our observations and those of other workers (Weiss and others, 1965) suggest that synovial fluid radioactivity is not the primary mechanism of the positive joint scan. In our studies, despite the lag in concentration of radioactivity in the synovial fluid, this radioactivity never becomes greater than simultaneous plasma values.

The rapid uptake of radioactivity followed by rapid decrease demonstrated in the abnormal joints could be explained by increased vascularity in these regions. This is more than simple superficial vasodilation, as local heating and cooling did not affect the joint scan. In addition, these changes were not observed in experimental animals after acute injury to the joint, but only after sufficient delay had been allowed for increased blood flow to develop.

Increased disappearance rate of Na^{131}I from the joints has been previously described as specifically associated with active inflammation, even when a 'control' joint showed chronic changes (Hernborg, 1968) on x-ray. The same phenomenon has been demonstrated using ^{133}Xe injected intra-articularly by Dick, St. Onge, Gillespie, Downie, Nuki, Whaley, Boyle, and Buchanan (1970) with elegant documentation that this clearance is exclusively vascular. Extension of these observations to $^{99m}\text{TcO}_4^-$ is in progress in our laboratory.

We have postulated three possible causes of joint scan positivity:

(1) Increased transport of pertechnetate into the inflamed synovium;

FIG. 7 Serial scintiphotos of radioactivity in the hand of a patient with Reiter's disease. Note that, while the marked inflammation of the second metacarpophalangeal joint is apparent even at 70 min., the abnormality in the fourth distal interphalangeal joint has disappeared at 40 min. after isotope administration.

(2) Concentration of radioactivity in synovial fluid within the inflamed joint;

(3) Increased blood flow to the inflamed joint.

The first of these possibilities is not dealt with above. Studies with normal and abnormal synovium *in vitro*, to be reported elsewhere (Hays and Green, 1972), show that abnormal synovium concentrates pertechnetate slightly faster and more avidly than does normal synovium. As the inflamed joint has a larger amount of synovium than the normal joint, accumulation of the tracer by this increased mass of tissue partially accounts for the positive joint scan. The second possibility, radioactivity concentrated in the synovial fluid, usually plays a very minor role, as demonstrated above and confirmed by direct imaging (Weiss and others 1965; Green and Hays, 1972). However, McCarty and others (1970b) present one case in which they interpret this to be a major factor. The third mechanism, increased blood flow, appears from our studies to be a major factor in production of the positive joint scan.

Summary

In order to establish the best timing for joint scanning, a series of quantitative studies were performed in animals with experimentally-induced arthritis and patients with inflammatory joint disease. In all cases, an abnormal joint was compared with a corresponding normal joint. Regardless of the size of the joint studied, pertechnetate was found to be concentrated more rapidly and released earlier by the inflamed joint than by the corresponding control joint. Synovial fluid concentrates the radioactivity slowly, reaching maximum concentration long after the peak of radioactivity usually observed in the abnormal joint. These differences in timing suggest that, in most cases, increased vascularity of the inflamed joint is a major factor responsible for production of the positive joint scan, and that uptake by the synovial fluid is generally of minimal importance.

As a result of these studies, we recommend that joint scanning be performed immediately after the injection of radiopertechnetate, and that it be discontinued no later than 40 mins after the injection.

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