

TECHNETIUM-99m-PYROPHOSPHATE KINETICS AND IMAGING IN METABOLIC BONE DISEASE

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A study was undertaken to investigate the behavior of $^{99m}\text{Tc-Sn-pyrophosphate}$ complex in metabolic bone disease. Of clinical importance was the generalized increased periarticular bone accumulation of the radiopharmaceutical in osteomalacia and in combined osteomalacia and osteitis fibrosa as found in patients with chronic renal failure. The pattern in primary hyperparathyroidism was variable. There was no correlation between the initial rates of accumulation of the radiophosphate complex or its bone to soft-tissue uptake ratio at 5 hr when compared with the degree of osteomalacia and osteitis fibrosa. It is postulated that the $^{99m}\text{Tc-Sn-pyrophosphate}$ complex has a greater affinity for immature collagen than the crystal surface.

A review of the literature reveals contradictory evidence on the kinetics of bone-seeking radiopharmaceuticals obtained by external monitoring of the skeleton in patients with metabolic bone disease. In one publication the uptake of ^{47}Ca in the knee region is stated to be low in patients suffering from rickets and osteomalacia (1,2). On the other hand, another report showed an increased accretion of ^{85}Sr in a patient with osteomalacia (3). Normal accretion was observed in a case of hyperparathyroidism using ^{18}F (4) whereas there was an increased accumulation with ^{47}Ca (3).

This communication contains our initial observations on the use of $^{99m}\text{Tc-pyrophosphate}$ ($^{99m}\text{TcPP}$) in metabolic bone disease. Included are patients on

chronic hemodialysis, osteomalacia due to vitamin D deficiency, hyperparathyroidism, and Paget's disease. A parallel in vitro and in vivo experimental study on normal and rachitic rats will be reported separately (5).

METHODS AND MATERIALS

Thirty-eight patients served as controls. These included cases of lumbar disc disease and primary soft-tissue neoplasm with no known evidence of spread. Excluded from the group were patients with inflammatory arthritis, moderate to advanced osteoarthritis of the knees, hematopoietic disorder, and a history of a fractured or infected femur as these may all be associated with an increased concentration of $^{99m}\text{TcPP}$ in the areas monitored in this study. Ages ranged from 21 to 76 years. The experimental group of patients included 20 who were on chronic hemodialysis, 6 with primary hyperparathyroidism, 3 with Paget's disease, and 2 with osteomalacia.

Iliac crest bone biopsies were obtained on 14 out of the 20 patients on hemodialysis, 3 patients with hyperparathyroidism, and 2 with osteomalacia. One core was decalcified and stained with hematoxylin and eosin, the other was embedded in plastic, sectioned at 5 microns using a Jung microtome, and stained by the v. Kossa technique using toluidine

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blue as counterstain. Osteoid was quantitated both as a percentage of surface and as a percent of total bone. Resorptive surface was measured on the decalcified bone as described previously (6). Only trabecular bone was used for analysis. Serum alkaline phosphatase was measured by autoanalyzer using phenolphthalein monophosphate as substrate. Normal values are 3–13 King-Armstrong units. Patients with liver disease and those who were malnourished or who were growing were excluded from the study.

About 20 mCi $^{99m}\text{TcPP}$ were injected intravenously and a time-activity histogram of the accumulation of activity in the distal femur was obtained for the first 20 min. This was achieved by a single external scintillation detector with the 2-in. bore collimator placed against the anterior patella. Readout was procured with a ratemeter strip chart assembly. Five hours after administration of $^{99m}\text{TcPP}$ the patient was placed under the gamma camera with the detector head positioned over the anterior distal femur. A parallel-hole low-energy collimator was used and counts were accumulated for 5 min and stored on videotape. On playback, cursors were placed over the distal femur and medial soft-tissue mass of the thigh as shown in Fig. 1. Total counts within each cursor for a 3-min time interval were determined, corrected for disparity in cursor size, and expressed as a ratio of bone to soft tissue. The areas of the cursors were normalized by utilizing a uniform sheet source of ^{57}Co against the collimator of the gamma camera and procuring counts through the cursors positioned as they were in measuring the bone/soft-tissue ratio. This also corrected for nonuniformity of the camera response. No attempt was made to correct for the contributions of bone and soft tissue to the cursors over soft tissue and bone, respectively. Following this procedure, images of the hands, wrists, costocartilage area, lateral knees, and calvarium were obtained with the gamma camera.

RESULTS

Time-activity histograms of the initial accumulation of the $^{99m}\text{TcPP}$ obtained over the distal femurs was found by regression analysis to be represented by the power function $C = Kt^m$ where C , K , t , and m denote counting rate, a constant, time in minutes, and slope of the log C versus log t plot, respectively. The coefficient of correlation for the interval 1.25–20 min exceeded 0.95 in all patients. The ratio of counting rate at 7.5–1.25 min, i.e., $C_{7.5}/C_{1.25}$, was calculated for each curve and the values of the control and abnormal groups compared. This ratio, $C_{7.5}/C_{1.25}$, is related to m by the expression $C_{7.5}/C_{1.25} = 6^m$; therefore, the ratio is a valid parameter

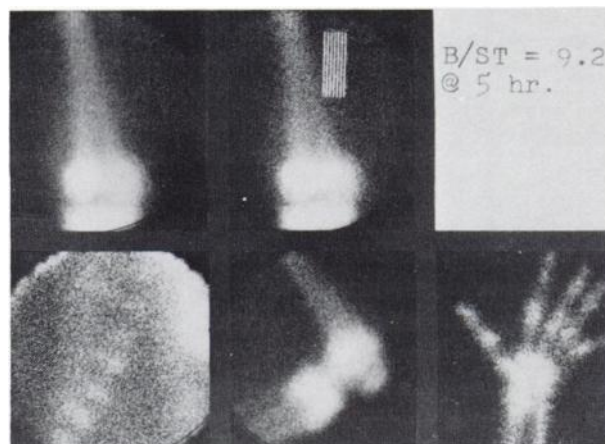


FIG. 1. Patient on chronic hemodialysis showing increased concentration of $^{99m}\text{TcPP}$ at knees, rib ends, points of hand, and wrist. Cursors over medial soft-tissue mass and distal femur are shown in second frame. Bone/soft-tissue ratio at 5 hr was 9.2. Images were obtained 1 week postparathyroidectomy for secondary hyperparathyroidism.

of the slope or the rate of accumulation of activity in the stated time interval.

The average $C_{7.5}/C_{1.25}$ ratio in the 38 controls was 1.64 ± 0.20 with a range of 1.26–2.12 (Fig. 2). Patients on chronic hemodialysis had an average ratio of 1.75 ± 0.24 with a range of 1.24–2.28. There was no significant difference between the two groups by the Student's t -test analysis ($0.10 > P > 0.05$). Unexpectedly, three patients with Paget's disease had normal ratios of 1.58, 1.97, and 2.0, respectively, although their bone/soft-tissue activity ratios at 5 hr

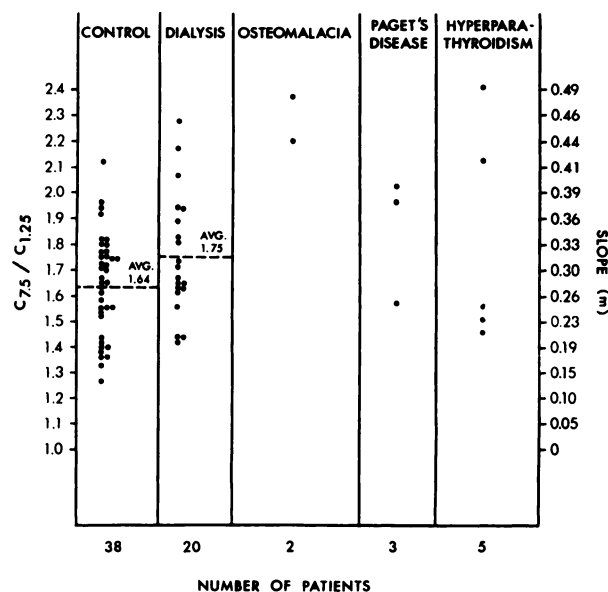


FIG. 2. Value of $C_{7.5}/C_{1.25}$ ratios and equivalent slope, m , obtained in five groups of patients under study.

were the highest in the study. Both osteomalacias had $C_{7.5}/C_{1.25}$ ratio determinations and they exceeded normal by two and three standard deviations, respectively. The mean $C_{7.5}/C_{1.25}$ of the five hyperparathyroid patients was 1.81 ± 0.43 . This did not differ significantly from the control group ($0.4 > P > 0.3$).

In 33 controls the average 5-hr bone/soft-tissue ratio was 2.63 ± 0.65 (1.75 to 4.3) compared with an average of 6.22 ± 2.16 (2.2–9.4) in 14 patients on chronic hemodialysis (Fig. 3). The difference between the two groups was significant ($P < 0.001$). Eleven of the 14 patients in the dialysis group had ratios which exceeded normal by at least three standard deviations. Three patients with Paget's disease had bone/soft-tissue ratios ranging from 19 to 21 even though their initial rates of accumulation were within normal range (Fig. 2). Both of the osteomalacias had abnormal 5-hr bone/soft-tissue ratios (Figs. 3 and 4).

Only four of the five patients with primary hyperparathyroidism had 5-hr bone/soft-tissue ratio determinations. The mean was 2.62 ± 0.65 and dif-

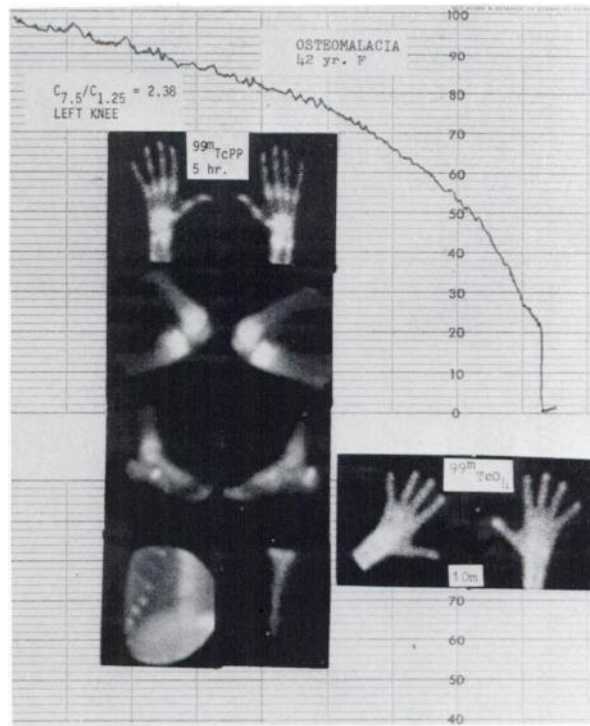


FIG. 4. A 42-year-old woman suffering from anorexia nervosa and osteomalacia. Tracing represents initial accumulation of ^{99m}TcPP obtained over distal femur. $C_{7.5}/C_{1.25} = 2.38$. At 5 hr there was high periarticular bone accretion of ^{99m}TcPP in hands, wrists, knees, ankles, feet, rib ends, and tibial shaft. Comparative ^{99m}TcO₄ images of both hands show no abnormality of synovia.

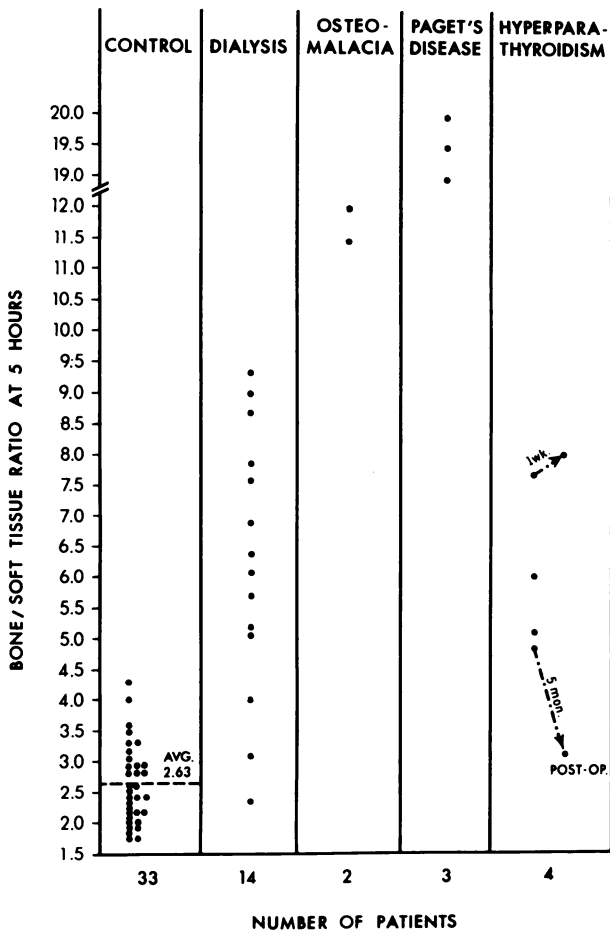


FIG. 3. Comparative 5-hr bone/soft-tissue ratios in five groups of patients.

fered significantly from the control group ($P < 0.001$). A sixth patient, not plotted in Figs. 2 and 3, had an adenocarcinoma of the parathyroid gland and hyperparathyroidism. The right knee had a normal bone/soft-tissue ratio but the distal femur and proximal tibia on the left registered high accretions of ^{99m}TcPP due to the presence of brown cell tumors (Fig. 5).

One patient with hyperparathyroidism due to an adenoma had no significant change in the 5-hr ratio 1 week postparathyroidectomy (Fig. 3). Similarly, a second patient on chronic hemodialysis had a parathyroidectomy for secondary hyperparathyroidism and exhibited no appreciable alteration in the 5-hr ratio 1 week postsurgery (Fig. 1). Five months postparathyroidectomy for primary hyperparathyroidism a third patient showed a decrease in the 5-hr bone/soft-tissue ratio from a value of 5.1 to a normal level of 3.0 (Fig. 3). Eight months after a medical regimen of calcium and vitamin D, a patient with osteomalacia exhibited a significant favorable decrease in the 5-hr ratio to a normal level.

The increased bone/soft-tissue ratio of ^{99m}TcPP at 5 hr can also be discerned qualitatively by imaging the peripheral joints and costochondral junctions (Figs. 1, 4–6).

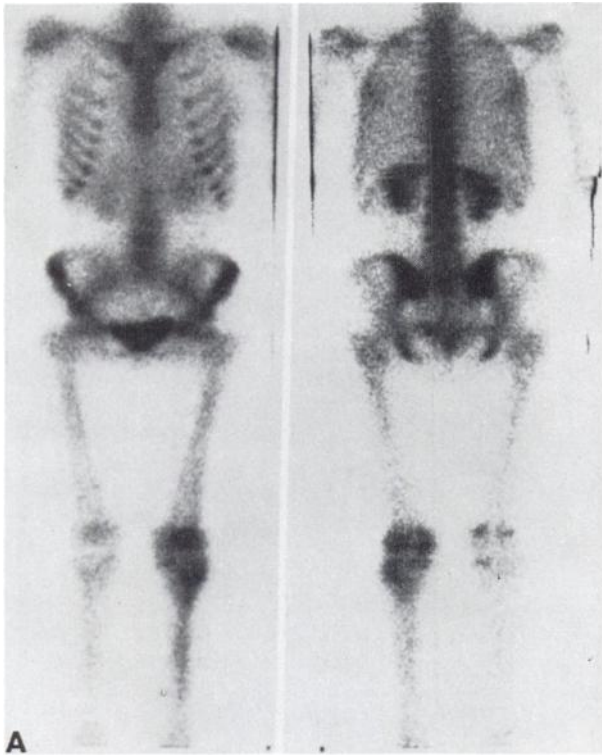
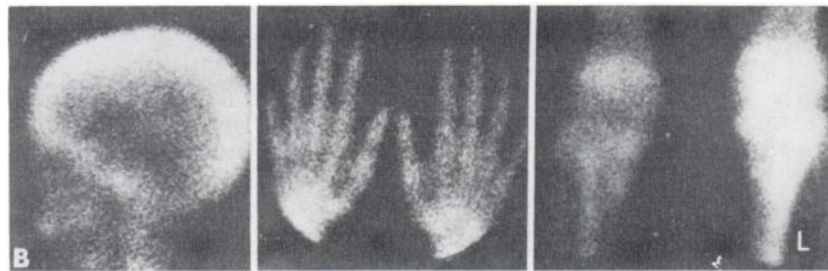


FIG. 5. Hyperparathyroidism secondary to parathyroid adenocarcinoma. (A) Total-body images with $^{99m}\text{TcPP}$ showing increased concentration at rib ends. Right knee was normal but distal left femur and left tibia are abnormal due to presence of brown cell tumor. (B) High accretion of $^{99m}\text{TcPP}$ in calvarium and wrists. Peri-articular bone concentration in hands is normal. Gamma camera images of knees exhibit marked difference between normal right knee and abnormal left knee.



No correlation was obtained between the bone/soft-tissue ratio at 5 hr compared with the percent bone surface covered with osteoid. A similar lack of correlation was found when the ratio was plotted against the percent of bone occupied by osteoid. Nor was there a significant relationship between the 5-hr bone/soft-tissue ratio compared with percent bone surface undergoing resorption. There was, however, a significant relationship between the level of serum alkaline phosphatase and the bone/soft-tissue ratio ($r = 0.58$, $P < 0.01$) (Fig. 7).

The coefficient of correlation, r , between $C_{7.5}/C_{1.25}$ and bone/soft-tissue ratios at 5 hr in the control group was 0.28 ($0.2 > P > 0.1$). A similar coefficient of correlation of 0.28 ($0.25 > P > 0.20$) was obtained for the patients on chronic hemodialysis. The correlation in both categories was not significant.

DISCUSSION

The time-activity histograms of the initial accumulation of $^{99m}\text{TcPP}$ over the distal femurs did not yield

the expected results. If it is postulated that the rate of uptake is primarily a function of blood flow, then the three cases of Paget's disease should have shown a markedly higher $C_{7.5}/C_{1.25}$ ratio relative to the normal group. Instead, the values were within normal range. However, at 5 hr the bone/soft-tissue ratio of Paget's diseased patients exceeded the normal average by a factor of 8. A comparison of the knees in one patient with Paget's disease (Fig. 8) showed the affected femur had a $C_{7.5}/C_{1.25}$ ratio of 2.0 compared with 1.48 on the normal side. This difference may be due to a larger blood flow on the abnormal side although both values were within normal range. Unexplained, however, is the vast disparity at 5 hr. The implication of this observation is the presence of another mechanism of concentration. It does not exclude the role of increased blood flow, which is known to occur in Paget's disease, in the accumulation of $^{99m}\text{TcPP}$, but apparently it is not the predominantly contributing factor. To a lesser degree, patients with hyperparathyroidism and those on

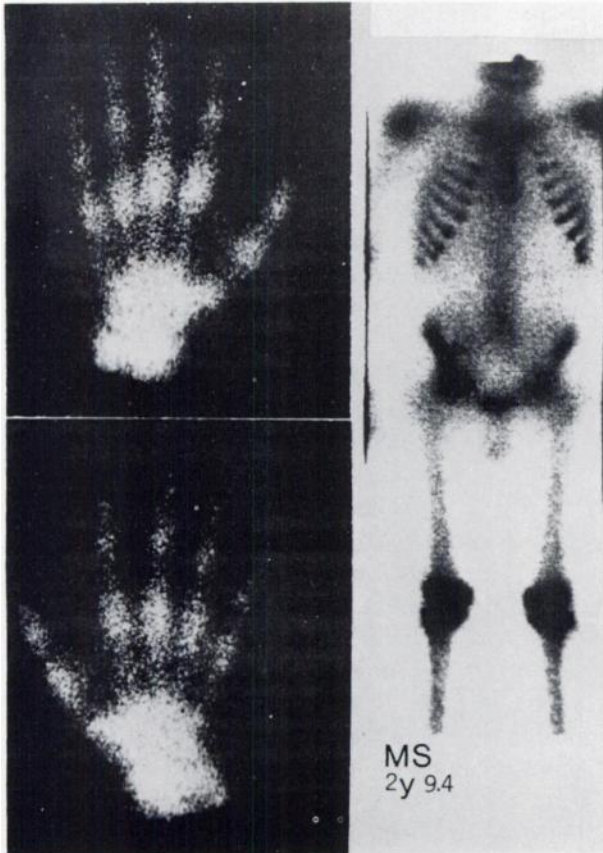


FIG. 6. This patient has been on hemodialysis for 2 years. Images clearly demonstrate increased periarticular bone accretion in hands, wrists, knees, and rib ends. The 5-hr bone/soft-tissue ratio was 9.4.

chronic hemodialysis also had inappropriately high bone/soft-tissue ratios at 5 hr for the initial rate of accumulation of ^{99m}TcPP. Furthermore, there was no significant correlation between the $C_{7.5}/C_{1.25}$ and the 5-hr bone/soft-tissue ratios in either normal or chronic hemodialysis patients. The two parameters probably reflect different phenomena.

No physiologic significance was attached to the power function $C = Kt^m$. It was used merely as an expedient to compare the rate of accumulation of ^{99m}TcPP about the knees of the same patient and from patient to patient in the time interval 1.25–20 min. Originally our data were analyzed in terms of the inverse exponential function $C = C_0(1 - e^{-kt})$. However, the tracings were not obtained for a sufficient length of time to accurately assess the asymptote C_0 . It is obvious from the equation that for a given C and t , k will vary with C_0 . On the other hand, no assumptions or arbitrary values are used in the power function.

Of practical significance is the visually marked uptake of ^{99m}TcPP in the peripheral periarticular areas of bone in patients with pure osteomalacia and

those on chronic hemodialysis wherein there is usually both osteomalacia and secondary hyperparathyroidism (7). The pattern in patients with primary hyperparathyroidism was variable as shown in Table 1. An interesting feature is the frequent occurrence in both osteomalacia and chronic hemodialysis of an accumulation of ^{99m}TcPP at the costochondral junction giving a beaded appearance to the rib ends. This latter feature, when it occurs, distinguishes metabolic disease from diffuse rheumatoid arthritis. The shafts of the long bones also exhibit a higher than normal concentration of ^{99m}TcPP at 5 hr both visually and in the few cases that were quantitated but the ends of the long bones showed the greater change. This may in part be related to the lesser amount of soft tissue about the periarticular regions. The immediate postparathyroidectomy hypoparathyroid state did not induce any decrease in the 5-hr bone/soft-tissue ratio in the two patients tested. However, there was a decrease 5 months after surgery in a third patient.

Reduced excretion of ^{99m}TcPP in anephric patients is not an appreciable factor contributing to increased bone concentration. Three patients on chronic hemodialysis had normal 5-hr bone/soft-tissue ratios. A fourth patient had a solitary kidney excised for renal carcinoma and 1 week postsurgery the 5-hr bone/soft-tissue ratio was normal.

There are several possible explanations for the changes that have been described in this paper. Theoretically, increased delivery of nuclide, due to hyperemia, to a normal or abnormal skeleton could be responsible. Alternatively, there could be an increase in the binding affinity for the tracer. The latter could be due to either some change in the bone mineral so that more crystal surface was available for

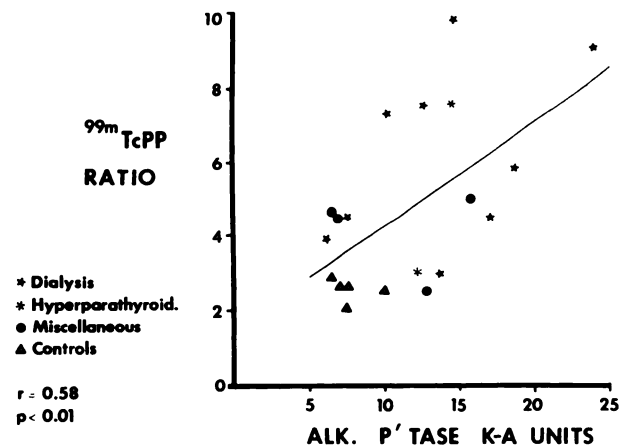


FIG. 7. Scatter diagram of ^{99m}TcPP 5-hr bone/soft-tissue ratio versus alkaline phosphatase. Coefficient of correlation, r , was 0.58 ($p > 0.01$).

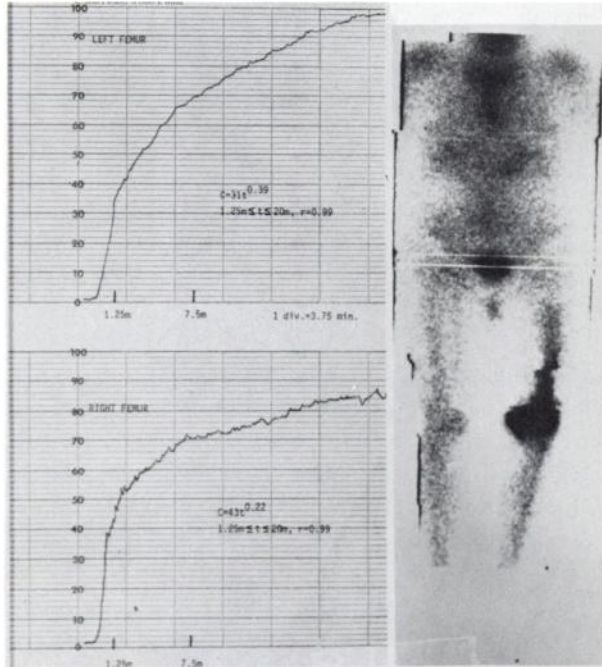


FIG. 8. $^{99m}\text{TcPP}$ time-activity histograms obtained over the distal femora of patient with Paget's disease of left femur. Slope, m , was 0.39 on left corresponding to $C_{7.5}/C_{1.25} = 2.0$. On the right $m = 0.22$ which is equivalent to $C_{7.5}/C_{1.25} = 1.48$.

exchange or to an alteration in the bone organic matrix. Regarding a possible increase in regional blood flow, the data employing the $C_{7.5}/C_{1.25}$ ratio make this unlikely as there was no significant difference between the control and chronic hemodialysis groups and disparity in blood flow should be observed in the early accumulation curves. Furthermore, the experimental determination of blood flow in animals with rickets has shown that it is not increased even though there is selective uptake of $^{99m}\text{TcPP}$ (5). An alternate hypothesis is that increased skeletal uptake is associated with higher rates of bone "turn-over," indicative of a more rapid accretion and resorption of mineral with presumably more of the bone surface available for exchange. The present data are not in accord with this view because some correlation would have been expected between the number of trabecular bone resorptive sites and the bone uptakes whereas none was found. Perhaps more convincing evidence is the unaltered bone uptake in patients with primary hyperparathyroidism immediately following removal of the involved gland(s) at a time when each patient was clearly hypoparathyroid as evidenced by hypocalcemia and in need of additional calcium. A marked decrease in turnover would be expected, yet $^{99m}\text{TcPP}$ deposition was unaltered. Furthermore, in osteomalacia mineral accretion is reduced whereas in hyperparathyroidism it is

increased (8-12). These two opposite kinetic findings yield similar results on scanning with $^{99m}\text{TcPP}$. Turning to the bone matrix, one possibility requiring consideration is that the osteoid tissue itself has an increased affinity for $^{99m}\text{TcPP}$. In support of this view is the increased amount of osteoid that is always present in patients with osteomalacia (13) and it is frequently found in both primary hyperparathyroidism and Paget's disease (9,13), all conditions where the bone accumulation of $^{99m}\text{TcPP}$ is elevated. Against this are the in vitro data where rachitic tibia accumulated tracer to the same extent as normal bone (5) as well as the complete lack of any correlation between the quantitative assessment of osteoid by bone biopsy and the skeletal uptake of $^{99m}\text{TcPP}$. A recent study utilizing autoradiography following injection of $^{99m}\text{TcPP}$ showed clearly that areas of osteoid did not contain the radionuclide but rather the deposition was in the "less mineralized and less mature bone" (14).

Our conclusion, therefore, supported by the data in a separate paper (5), is that the increase in skeletal uptake that has been described in this report is caused predominantly by affinity of the tracer for the non-osteoid organic matrix rather than the crystal surface although some binding undoubtedly occurs there as well. If these preliminary observations are correct, the binding could be due to either protein polysaccharide or to immature collagen. Evidence in favor of the latter is described in the companion paper (5).

Abnormal bone collagen metabolism is characteristically found in the same conditions as described in this study as showing increased skeletal uptake of $^{99m}\text{TcPP}$. Urine or serum hydroxyproline is elevated indicating increased collagen breakdown or the rapid synthesis and breakdown of immature collagen. The evidence, although preliminary, suggests that immature collagen is responsible for the increased accre-

TABLE 1. SITE OF VISIBLE ACCRETION OF $^{99m}\text{TcPP}$ IN PATIENTS WITH ILIAC CREST BONE BIOPSIES POSITIVE FOR OSTEITIS FIBROSA

| Patient | Hands | Wrists | Knees | Ribs | Calvarium |
|---------|-------|--------|-------|------|-----------|
| OS* | +ve | +ve | +ve | -ve | -ve |
| BG* | -ve | +ve | +ve | -ve | -ve |
| HS* | +ve | +ve | +ve | -ve | +ve |
| CD* | -ve | +ve | -ve | +ve | +ve |
| AA† | +ve | +ve | +ve | -ve | +ve |
| AAb | -ve | -ve | +ve | +ve | -ve |
| BJ* | -ve | +ve | +ve | -ve | +ve |
| LH | +ve | +ve | +ve | -ve | -ve |

* Proved primary hyperparathyroidism.

† No bone biopsy. Surgical proof of primary hyperparathyroidism.

tion of ^{99m}TcPP. The correlation between the bone uptake of ^{99m}TcPP and serum alkaline phosphatase, Fig. 7, also supports this interpretation as this enzyme is known to be elevated in bone disease associated with high urine hydroxyproline levels (15).

The characteristic increased uptake of ^{99m}TcPP in the distal ends of the long bones is difficult to explain satisfactorily. It may be due, in part, to the greater thickness of osseous tissue at these sites and its content of cancellous bone. The metabolic turnover rate is higher in the cancellous bone than in the compacta and any abnormality would be evident earlier. The separate vascular supply to the long bones may also be related to more active collagen renewal in these sites.

Finally, although our conclusions regarding the physiopathology must at this stage be considered tentative, we believe the technique of measuring the 5-hr bone/soft-tissue ratio and imaging the hands and wrists for qualitative ^{99m}TcPP deposition is of considerable value to the clinician in the early recognition of metabolic bone disease.

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