Detection and pathogenesis of visceral calcification in dialysis patients and patients with malignant disease

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Scintiscanning to detect the uptake of bone-seeking radioactive isotopes by soft tissue is a promising technique for the in vivo study of visceral calcification. Visceral uptake of such radioisotopes was studied in 40 patients: 22 undergoing long-term dialysis, 9 with malignant disease and hypercalcemia and 9 with primary hyperparathyroidism and hypercalcemia.

Fifteen patients, 11 undergoing dialysis and 4 with malignant disease, had radioisotope uptake in the lungs, and 5, 3 undergoing dialysis and 2 with malignant disease, had uptake in the stomach. None of the patients with primary hyperparathyroidism had visceral uptake, nor did the patients with uptake have radiologic evidence of pulmonary or gastric calcification. The dialysis patients with visceral uptake had a mean calcium × phosphate product of 84.3 ± 23.7 (standard deviation), which was significantly greater ($P < 0.001$) than that of patients without such uptake (59.2 ± 14.0). Similarly, in patients with malignant disease and visceral uptake the Ca × P product was 72.2 ± 6.4 — significantly greater ($P < 0.005$) than that of patients without such uptake (49.3 ± 6.7).

These findings indicate that scintiscanning for the visceral uptake of a bone-seeking radioisotope is a simple and effective technique for the in vivo study of visceral calcification. An elevation in the Ca × P product seems to be the single most important factor in the production of visceral calcification.

La scintigraphie utilisée comme moyen de déceler la captation par les tissus mous des isotopes radioactifs ayant une affinité pour l'os représente une technique prometteuse pour l'étude in vivo de la calcification viscérale. La captation viscérale de tels radioisotopes a été étudiée chez 40 patients: 22 sous dialyse à long terme, 9 souffrant de maladies malignes et d'hypercalcémie et 9 ayant une hyperparathyroïdie primaire et de l'hypercalcémie.

Quinze patients, 11 sous dialyse et 4 porteurs d'une maladie maligne, ont présenté une captation des radioisotopes dans les poumons, et 5, 3 sous dialyse et 2 ayant une maladie maligne, montraient une captation dans l'estomac. Aucun des patients atteint d'hyperparathyroïdie primaire n'a eu de captation viscérale, et les patients montrant une captation n'ont eu aucun signe radiologique de calcification pulmonaire ou gastrique. Les patients sous dialyse présentant une calcification viscérale avaient un produit moyen calcium × phosphate de 84.3 ± 23.7 (écart-type), qui était significativement plus grand ($P < 0.001$) que celui des patients sans captation (59.2 ± 14.0). De la même façon, le produit Ca × P chez les patients souffrant de maladie maligne et ayant une captation viscérale était de 72.2 ± 6.4, ce qui est significativement plus grand ($P < 0.005$) que celui des patients sans captation (49.3 ± 6.7).

Ces observations indiquent que la scintigraphie de la captation viscérale d'un radioisotope ayant une affinité pour le tissu osseux est une technique simple et efficace pour étudier in vivo la calcification viscérale. Une augmentation du produit Ca × P semble être le facteur isolé le plus important dans le développement de la calcification viscérale.

In the past, metastatic calcification of the lungs and stomach has been described in patients with renal failure and malignant disease,[1] but until recently diagnosis rested on histologic examination of biopsy or postmortem material.[2-4] On the rare occasions when it was demonstrated by roentgenography, metastatic calcification of the lungs was a terminal event.[3,5-7]

The use of bone-seeking radioactive isotopes in bone scintiscanning has disclosed occasional uptake of the radioisotope by the lungs or the stomach. This observation has been made in five patients with chronic renal failure, five with malignant disease and hypercalcemia and two with hypercalcemia of uncertain cause[3,4,6,8-12] (Table I). Histologic examination was performed in six such patients and calcium deposits were found in five. This correlation suggests that uptake of bone-seeking radioisotopes by lungs or stomach is a reliable index of diffuse metastatic calcification of these organs, and potentially provides a noninvasive means by which to study this complication during life.

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Table I—Details* of reported cases of uptake of a bone-seeking radioactive isotope by lung or stomach

Year and reference no.	Sex, age (yr)	Radioisotope†	Serum values (mg/dL) Ca	Serum values (mg/dL) P	Histologic site of calcification	Site of uptake	Primary disease
1970[3]	—	^{85}Sr	—	—	Lung	Lung	Chronic renal failure
1970[3]	—	^{85}Sr	—	—	—	Lung	Chronic renal failure
1972[8]	F, 46	^{87}Sr	12–13	—	None	Lung	Multiple myeloma
1974[9]	F, 56	^{99m}Tc-pyrophosphate	11.6	8.9	Lung	Lung	Multiple myeloma
1974[9]	F, 72	^{99m}Tc-pyrophosphate	18.8	5.8	—	Lung, stomach	Metastatic carcinoma
1974[4]	M, 48	^{99m}Tc-polyphosphate	16.8	5.3	Stomach	Lung, stomach	Lymphoma or myeloma
1975[10]	M, 52	^{99m}Tc-polyphosphate	16.4	—	Lung	Lung	Leiomyosarcoma, obstructive uropathy
1976[11]	M, 22	^{99m}Tc-HEDP	—	—	Lung	Lung	Chronic renal failure
1976[11]	F, 16	^{99m}Tc-HEDP	13.1	5.5	—	Lung	Hypercalcemia
1976[11]	M, 82	^{99m}Tc-HEDP	—	—	—	Lung	Hypercalcemia
1976[12]	M, 68	^{99m}Tc-polyphosphate	13	—	—	Lung	Chronic renal failure, Hodgkin's disease
1976[6]	M, 35	^{99m}Tc-diphosphate	8.9	7.8	—	Lung	Chronic renal failure, Hodgkin's disease

* – = not reported.
† HEDP = hydroxyethylene diphosphonate.

Table II—Details* of cases of uptake of a bone-seeking radioisotope by lung or stomach, or both, in patients with chronic renal failure

Patient no. and date of bone scan	Sex, age (yr)	Serum values: Mean during 3 months before scan: Ca (mg/dL)	P (mg/dL)	Ca × P product	Maximum during 3 months before or between scans: Ca (mg/dL)	P (mg/dL)	Ca × P product	Abnormal uptake* on scan: Lung	Stomach	Bone
1. 14/5/75	M, 50	9.7	6.1	58.7	11.0	8.1	70.4	+	—	+
2. 12/6/75	F, 19	9.5	8.9	84.9	9.8	9.9	95.0	+++	—	+++
3. 11/7/75	M, 70	10.1	5.6	57.9	10.6	6.4	67.8	+	—	+
4. 11/7/75	M, 27	9.5	10.8	99.9	11.4	14.7	124.9	++	—	+++
5. 16/7/75	F, 56	9.6	6.4	70.1	9.9	7.0	90.2	+	—	++
20/9/76		8.6	5.7	49.1	9.5	6.1	57.9	+	—	++
6. 6/1/76	M, 55	9.6	6.9	66.7	9.9	6.7	70.8	—	—	+++
3/6/76		11.2	5.5	63.8	15.0†	6.9	89.5	++	++	++
13/8/76		8.4	6.8	61.8	9.4	7.7	72.3	++	++	+
7. 7/5/76	F, 56	9.1	2.8	25.6	10.4	3.1	26.3	—	—	+++
30/8/76		9.2	9.1	84.2	9.4	11.1	102.1	++	—	+++
4/10/76		8.9	12.1	110.4	9.4	12.9	121.2	+++	—	++
8. 6/10/76	F, 52	9.6	4.4	43.2	10.0	6.2	62.0	++	—	+++
9. 19/8/76	M, 52	10.1	8.3	84.2	10.5	11.7	113.4	++	—	+++
10. 10/10/76	M, 52	9.4	5.3	51.6	10.5	6.8	71.4	++	—	+++
13/9/76		11.3	5.9	67.6	12.2	6.8	82.9	++	+++	+++
11. 23/9/76	M, 28	10.9	3.8	40.0	11.7	4.3	44.7	—	+	+
14/10/76		11.6	3.3	38.4	15.1	4.4	44.4	+	+	+
Mean ± standard deviation		9.7 ± 0.9	6.9 ± 2.4	68.3 ± 20.6	10.9 ± 1.8	8.4 ± 2.9	84.3 ± 23.7			

*— = none; + = minimal; ++ = moderate; +++ = marked.
†After parathyroidectomy because of hypercalcemia secondary to vitamin D intoxication.

This paper describes studies of visceral uptake of bone-seeking radioisotopes in 40 patients — 22 undergoing long-term dialysis, 9 with malignant disease and hypercalcemia, and 9 with primary hyperparathyroidism and hypercalcemia.

Methods

On the morning of the test each patient (except those with anuria or oliguria) was asked to ingest 500 mL of extra fluid, and later technetium-99m-polyphosphate (New England Nuclear, North Billerica, Massachusetts) or ^{99m}Tc-stannous methylene disphosphonate (TcMDP; Charles E. Frosst, Montreal), 10 mCi/m^2 of body surface, was injected intravenously (mean dose per patient, 17 mCi; range, 13 to 20 mCi). Approximately 3.5 hours after administration of the ^{99m}Tc-polyphosphate and 2.5 hours after the injection of TcMDP scintigraphy was carried out with a 12.7-cm, dual-probe rectilinear scanner (Ohio-Nuclear, Solon, Ohio: model 84), with 10% background subtraction and 10% contrast enhancement.

Uptake of the radioisotope by the lungs or stomach was considered to be abnormal when it was equal to or greater than that of the ribs. Patients with generalized soft-tissue activity and those in whom other radioisotope scans (especially of the lungs) had recently been done were excluded from the study. Abnormal uptake by the lungs was graded arbitrarily as minimal (+), moderate (++) or marked (+++), depending on whether the activity was less than, equal to or greater than that seen over the spine in the posterior view. Similarly, uptake by the stomach was graded by comparison with sternal activity in the anterior view.

Results

Patients with chronic renal failure

Of the 22 patients with chronic renal failure (12 men and 10 women) 20 were undergoing long-term peritoneal dialysis and 2 were undergoing long-term hemodialysis.

Of the 11 patients (6 men and 5 women) (Table II) with abnormal uptake of the bone-seeking radioisotope in the lungs or stomach 9 were undergoing

Table III—Details* of cases of 11 patients with chronic renal failure and 5 patients with malignant disease and hypercalcemia whose bone scan showed no visceral uptake of the radioisotope

Patient no. and date of bone scan	Sex, age (yr)	Serum values: Mean during 3 months before scan: Ca (mg/dL)	P (mg/dL)	Ca × P product	Maximum during 3 months before or between scans: Ca (mg/dL)	P (mg/dL)	Ca × P product
Chronic renal failure							
1. 8/4/75	M, 59	8.8	5.3	46.9	9.0	5.7	49.5
2. 19/6/75	M, 72	8.2	6.3	52.2	9.3	6.7	58.5
3. 21/6/75	M, 51	8.4	7.5	63.2	8.8	8.0	67.2
4. 24/8/76	M, 58	8.2	4.7	38.4	9.0	6.1	46.3
5. 30/8/76	F, 47	9.6	4.6	44.6	10.0	5.8	58.0
6. 21/5/76	F, 26	8.3	5.8	48.8	8.4	6.6	55.4
7. 24/3/75	M, 39	7.2	6.3	45.8	7.9	7.4	48.8
8. 6/6/74	F, 49	9.7	6.1	59.6	10.0	7.5	75.0
31/1/75		9.3	6.6	61.7	9.5	7.3	68.4
2/6/75		9.7	5.7	55.5	10.3	6.0	57.0
9. 15/9/75	M, 42	8.8	5.8	51.3	9.9	6.3	57.4
10. 23/9/75	F, 50	9.0	7.9	72.2	11.2	8.2	91.8
11. 21/5/76	F, 52	7.2	4.7	34.1	7.4	5.2	36.4
Mean ± SD		8.6 ± 0.8	5.9 ± 0.8	51.8 ± 10.5	9.2 ± 1.0	6.6 ± 0.9	59.2 ± 14.0
Malignant disease							
1. 14/7/75	F, 69	12.6	3.3	41.8	13.8	3.4	46.9
2. 17/7/75	F, 50	13.5	3.1	42.3	16.2	3.3	53.4
3. 29/1/75	F, 81	13.4	2.5	33.7	16.5	3.2	52.8
4. 25/3/74	M, 62	14.8	1.9	28.1	16.8	2.3	38.6
5. 12/12/73	F, 61	—	—	—	12.2	4.5	54.9
Mean ± SD		13.5 ± 0.9	2.7 ± 0.6	36.4 ± 6.8	15.1 ± 2.0	3.3 ± 0.7	49.3 ± 6.7

*— = not reported.

long-term peritoneal dialysis and 2 were undergoing long-term hemodialysis. Four of the 11 (nos. 1, 4, 9 and 11) had chronic glomerulonephritis, 2 (nos. 8 and 10) had chronic pyelonephritis, 2 (nos. 3 and 5) had polycystic kidney disease and the remaining 3 (nos. 2 6 and 7) had, respectively, medullary cystic disease, Alport's disease and glomerulosclerosis secondary to arterial hypertension. All 11 patients were treated with aluminum hydroxide; 8 also received vitamin D or dihydrotachysterol (DHT) and 3 also received calcium supplements.

Of the other 11, who did not have visceral uptake of the radioisotope, all of whom were undergoing chronic peritoneal dialysis (Table III), 10 were receiving aluminum hydroxide, 5 were receiving vitamin D or DHT and 3 were receiving calcium supplements.

In total, 18 bone scans were performed in the 11 patients with abnormal uptake of the radioisotope; lung uptake was observed on 15 occasions and stomach uptake on 5 occasions. Only one patient had stomach uptake without uptake by the lungs. Roentgenograms of the chest failed to show pulmonary calcification even with repeated restrospective review. However, all 11 patients had radiologic evidence of arterial calcification elsewhere and two had articular calcification. Nine of the 11 patients had radiologic evidence of secondary hyperparathyroidism — that is, subperiosteal resorption. In two patients (nos. 6 and 9) a bone scan was available before and after subtotal parathyroidectomy; in one (no. 6) we observed a marked shift of radioisotope uptake (Fig. 1) from the skull and legs to the lungs and stomach after parathyroidectomy. A similar shift of uptake from the skull and legs to the lungs, but not the stomach, was seen in another patient (no. 7, Fig. 2), who received vitamin D therapy but did not undergo parathyroidectomy. This shift was not a simple redistribution of the radioisotope because it did not involve all parts of the skeleton equally: uptake was reduced in the skull and to a lesser extent in the legs, but no obvious change was detected in the spine, pelvis or sacroiliac joints.

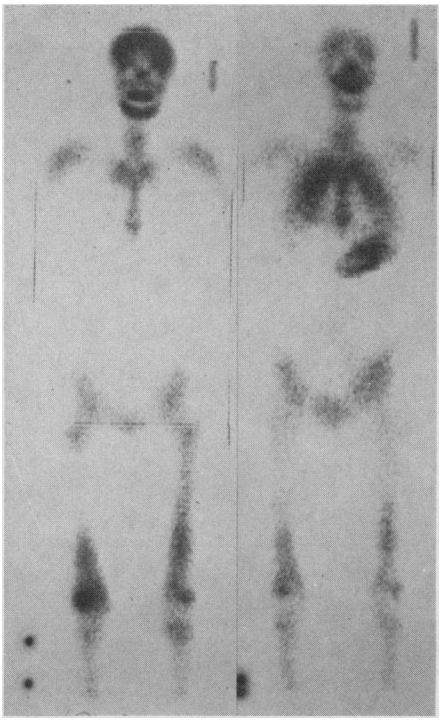

FIG. 1—Left: Anterior bone scan of patient with chronic renal failure (no. 6, Table II) on Jan. 6, 1976, showing markedly increased uptake of radioisotope in vault of skull, mandible and leg bones. Right: Scan on Aug. 13, 1976, 8 months after parathyroidectomy, showing moderate uptake in lungs and stomach and less activity in skull and leg bones.

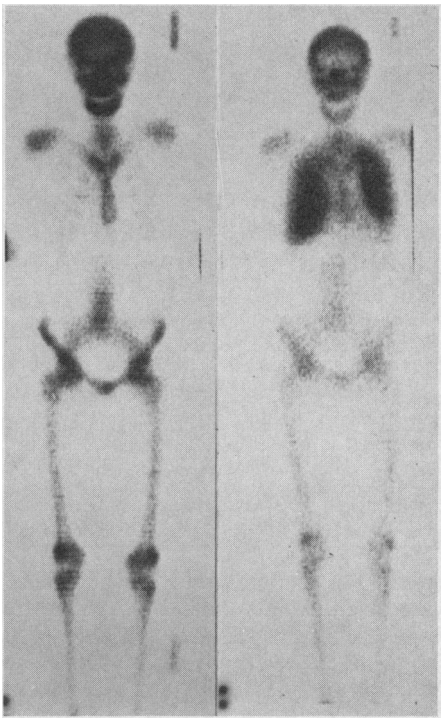

FIG. 2—Left: Anterior bone scan of patient with chronic renal failure (no. 7, Table II) on May 7, 1976, showing markedly increased uptake of radioisotope in skeleton, especially cranium, mandible and long bones. Right: Scan on Oct. 4, 1976, after 9 months of therapy with DHT, showing marked uptake in lungs and relative decrease in activity in skeleton.

Biochemical values during the 3 months before bone scanning in the 11 patients with chronic renal failure and abnormal uptake of the radioisotope are given in Table II. Six of the patients had at least one elevated serum calcium value (range of values, 10.6 to 15.1 mg/dL), 10 had an elevated serum phosphorus value (6.1 to 14.7 mg/dL), and 7 had an elevated serum alkaline phosphatase value (105 to 1020 IU/L). During the 3-month period before the scan their mean calcium × phosphate (Ca × P) product ranged from 38.4 to 110.4, with an overall mean (± standard deviation) of 68.3 ± 20.6; the maximum Ca × P product for each patient during this period varied from 44.4 to 124.9, with a mean of 84.3 ± 23.7. For the 11 patients with chronic renal failure and no evidence of visceral uptake of the radioisotope the mean Ca × P product during the 3 months before the scan ranged from 34.1 to 72.2, with an overall mean of 51.8 ± 10.5 (Table III). The maximum Ca × P product for each patient ranged from 36.4 to 91.8, with a mean of 59.2 ± 14.0; this value was significantly lower ($P < 0.001$) than the mean maximum value for those with visceral uptake.

The mean Ca × P products of both

Table IV—Means* of the average values for serum calcium, phosphorus and the Ca × P product and of the maximum Ca × P products before scanning

Group of patients, by disease and radioisotope uptake		Mean Ca	Mean P	Mean Ca × P product	Maximum Ca × P product	Comparisons
Chronic renal failure						
With visceral uptake	11	9.7 ± 0.9	6.9 ± 2.4	68.3 ± 20.6	84.3 ± 23.7	1 v. 2: $P < 0.001$
Without visceral uptake	11	8.6 ± 0.8	5.9 ± 0.8	51.8 ± 10.5	59.2 ± 14.0	2 v. 6: $P < 0.001$
Malignant disease						
With visceral uptake	4	11.9 ± 2.5	4.2 ± 1.4	50.5 ± 27.7	72.2 ± 6.4	3 v. 4: $P < 0.005$
Without visceral uptake	5	13.5 ± 0.9	2.9 ± 0.6	36.4 ± 6.8	49.3 ± 6.7	4 v. 6: $P < 0.001$
Primary hyperparathyroidism	9	11.4 ± 2.1	2.5 ± 0.6	30.4 ± 7.1	35.0 ± 8.0	5 v. 6: not significant
Normal	94	9.5 ± 0.4	3.5 ± 0.5	33.9 ± 5.4	—	

* — = not calculated.

Table V—Details of cases of visceral uptake of a radioisotope in patients with malignant disease

Patient no. and date of bone scan	Sex, age (yr)	Primary disease	Serum values: Mean during short period before scan — Ca (mg/dL)	P (mg/dL)	Ca × P product	Serum values: Maximum throughout period of disease or between scans — Ca (mg/dL)	P (mg/dL)	Ca × P product	Abnormal uptake* on scan — Lung	Stomach	Bone
1. 18/4/75	F, 20	Widespread malignant disease (probably	13.0	4.5	58.9	14.7	4.5	66.1	—	—	+
2/9/75		malignant lymphoma)	10.8	4.9	46.3	17.1	3.9	66.6	+	—	++
2. 27/7/74	M, 52	Lymphoma	9.6	3.8	36.6	11.7	4.4	51.4	—	—	+
21/6/76		(mixed lymphocytic–histiocytic)	15.6	5.9	90.9	16.5	4.7	77.5	++	+	++
3. 14/6/76	F, 63	Multiple myeloma	9.6	3.1	29.7	15.6	5.0	78.0	+++	+++	+++
4. 13/6/74	M, 72	Plasma cell leukemia (and mild renal failure)	11.8	3.0	35.4	13.9	4.8	66.7	+	—	+
Mean ± SD			11.9 ± 2.5	4.2 ± 1.4	50.5 ± 27.7	15.7 ± 1.3	4.6 ± 0.4	72.2 ± 6.4			

*Definition as in Table II.

groups of patients with renal failure were significantly higher ($P < 0.001$) than the mean Ca × P product of a group of 94 healthy persons — 33.9 ± 5.4 (range, 23.1 to 44.7) (Table IV).

Patients with malignant disease

This group consisted of nine patients with hypercalcemia secondary to malignant disease. The underlying diseases were malignant lymphoma (in two), multiple myeloma (in two), carcinoma of the lungs (in two), carcinomatosis (in two) and plasma cell leukemia (in one).

Four patients had visceral uptake of the radioisotope (Table V) — two with malignant lymphoma, one with multiple myeloma and one with plasma cell leukemia. Two bone scans were performed in the patients with malignant lymphoma at intervals of 5 and 20 months, respectively. In each instance the first scan did not show visceral uptake, while the second scan showed increased uptake by the lungs in both and by the stomach in one. At autopsy both patients were found to have metastatic calcification in the lungs (Figs. 3 and 4).

The patients with multiple myeloma (no. 3) and plasma cell leukemia (no. 4) had increased lung uptake on routine bone scans performed 1 month after the initial diagnosis. The patient with multiple myeloma also had increased uptake by the stomach. Both patients showed increased values of serum calcium, phosphorus and alkaline phosphatase, although in the patient with multiple myeloma the value had returned to normal shortly before scanning and after treatment. The patient with plasma cell leukemia also had mild renal failure (serum creatinine concentration, 2.9 mg/dL).

The maximum Ca × P product for all four patients with malignant disease and visceral uptake varied from 66.6 to 78.0, with a mean of 72.2 ± 6.4

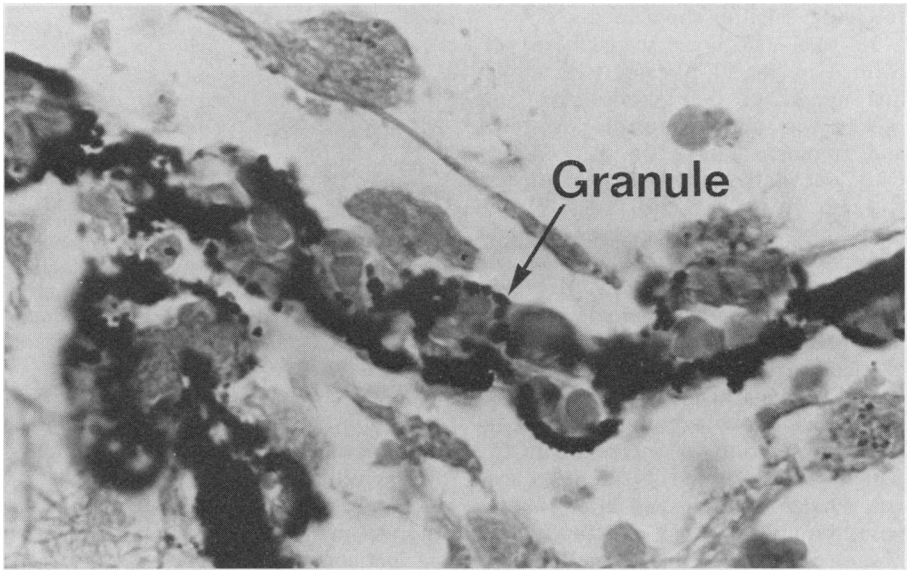

FIG. 3—Granular deposits of calcific material, stained black, in alveolar walls, in close association with capillaries of lung. Material is apparently noncrystalline and may be amorphous calcium phosphate (von Kossa's stain; ×400, reduced by 30%).

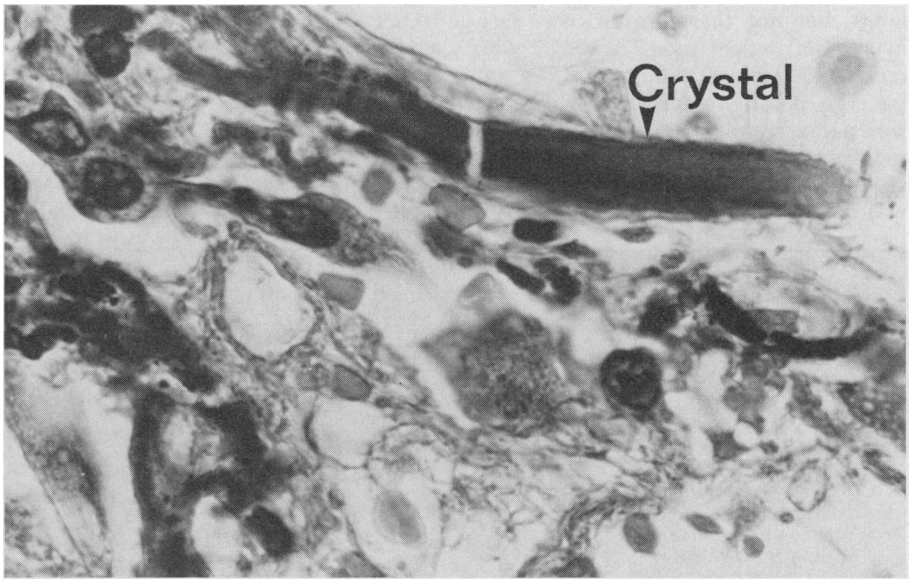

FIG. 4—Higher magnification of granular calcific deposits as in Fig. 3 and plate of more organized calcification with definite crystalline appearance. Fracture towards one end of crystal appears to have formed through organization of granular deposits (von Kossa's stain; ×1000, reduced by 30%).

(Table V). The maximum Ca × P product for the other five patients with malignant disease, who did not have abnormal radioisotope uptake, ranged from 38.6 to 54.9, with a mean of 49.3 ± 6.7 (Table III); this mean was significantly lower ($P < 0.005$) than that of the four patients with visceral uptake.

Patients with primary hyperparathyroidism

This group included nine patients with surgically proven primary hyperparathyroidism and hypercalcemia. All had a bone scan and none had evidence of visceral uptake of the bone-seeking radioisotope. The maximum Ca × P product before the scan ranged from 23.8 to 49.9, with a mean of 35.0 ± 8.0; this was significantly lower ($P < 0.001$) than the mean Ca × P product for the patients with renal failure and those with malignant disease who had evidence of visceral uptake (Table IV).

Discussion

Lung calcification is detected on histologic examination in 60% of patients with chronic renal failure[7] and 85% of patients with metastatic bone disease.[1] Similarly five of the patients previously described[3,4,6,8-12] and two of our patients with lung uptake of a bone-seeking radioisotope were found at autopsy to have metastatic pulmonary calcification. These observations suggest that pulmonary uptake of radioisotopes used in bone scanning provides a reliable indication of pulmonary metastatic calcification.

Chaudhuri and colleagues[8] have challenged this view because they could not demonstrate lung calcification at autopsy in a patient with multiple myeloma, hypercalcemia and renal failure whose lungs showed uptake of radioactive strontium during life. They concluded that the strontium formed macroaggregates with calcium and phosphorus that subsequently were trapped in the pulmonary capillaries. Their findings have at least two possible explanations: first, during the interval between bone scanning and death, an unspecified interval, the hypercalcemia may have improved and the calcification resolved; and, second, the histologic examination may have been performed on tissues maintained in nonbuffered formalin, which would have dissolved any calcium. In addition, their postulate of microaggregate formation and subsequent trapping would not explain the escape of the radioisotope from the pulmonary capillary system and its appearance in the skeleton or the stomach.[4] The simultaneous presence of pronounced arterial calcification in all our patients with renal failure, only two of whom were older than 60 years, also supports our contention that pulmonary uptake of a bone scan radioisotope indicates pulmonary metastatic calcification; only 6 of the 11 patients without visceral uptake had evidence of arterial calcification, and it was less pronounced. In Mulligan's[1] series of 23 patients with chronic renal failure, 12 had lung calcification and 15 also had arterial calcification; similarly, among 35 patients with osteolytic bone disease, calcification was detected in the lungs in 30 and in the arteries in 12.

Our findings support the earlier observation that metastatic calcification in the stomach is less frequent than that in the lungs.[1] One of the two previously described patients[4,9] who had gastric uptake of a bone-seeking radioisotope and came to autopsy showed histologic evidence of calcification,[4] which again suggested that uptake by the stomach is due to the presence of calcification.

The mechanism by which bone takes up ^{99m}Tc-polyphosphate is unknown, but it may include such factors as osteoblastic activity of bone, affinity of the radioisotope for immature collagen[13] and ion exchange of the agent at deposits of calcium phosphate, especially if they are in the form of hydroxyapatite crystals.[14,15] The last mechanism may explain our findings. Figs. 3 and 4 suggest that the calcification was both amorphous and crystalline, but we cannot exclude the possibility of ion exchange between the radioisotope and the amorphous calcium phosphate frequently found in calcifications of uremic viscera.[16]

Factors in the occurrence of soft-tissue calcification are not well understood. Rachitic rat cartilage can calcify with a Ca × P product as low as 20 in aqueous solutions and as low as 35 in normal serum;[17] 35 is well below the value indicating saturation of normal serum with respect to calcium phosphate, 58 to 60, above which spontaneous precipitation may occur.[18] Our findings confirm the previous suggestion that a Ca × P product of 60 is the saturation product, above which metastatic calcification may occur spontaneously.[18] Only 2 of the 15 patients who had visceral uptake of the radioisotope had a Ca × P product lower than 60; similarly only 4 of the 25 patients without visceral uptake had a Ca × P product higher than 60. Hence, although the Ca × P product may be the most critical factor in the production of metastatic calcification, other factors, such as the pH of the environment and the presence or absence of inhibitors, may be important. The influence of regional pH is clear in that calcification is prone to occur in tissues rendered alkaline because of acid excretion, such as the lungs (because of expiration of carbon dioxide), gastric mucosa (because of secretion of hydrochloric acid), kidneys (because of excretion of hydrogen ion), and left chambers of the heart and systemic arteries (tissues with a low content of carbon dioxide). On the other hand, the significance of the inhibitors in uremic serum[17] has been demonstrated by the observation that while normal serum calcifies rachitic rat cartilage when the Ca × P product is above 36, most uremic serum inhibits calcification.

We believe that the Ca × P product, and not elevated secretion of parathyroid hormone per se, is significant in the production of soft-tissue calcification, since none of our patients with primary hyperparathyroidism had evidence of visceral uptake of the radioisotope; their Ca × P product ranged from 23.8 to 49.9 — well below that causing saturation. The only reported instance of visceral uptake of radioisotope and metastatic calcification in primary hyperparathyroidism was in a patient who had a Ca × P product of 70 to 75.[19] Similarly one of our dialysis patients with renal failure who had three serial scans made had no pulmonary uptake of the radioisotope when her Ca × P product was 26.3, but 3 months later, when the product was 102, the lungs showed abnormal uptake.

Since in uremic patients the elevated Ca × P product is due exclusively to high serum concentrations of phosphorus these observations emphasize the importance of control of the serum phosphorus concentration in patients with renal failure.

The predominance of patients undergoing long-term peritoneal dialysis among those with renal failure who had pulmonary and gastric uptake of the radioisotope may reflect the fact that in our unit most dialysis patients are receiving long-term peritoneal dialysis, but other factors should be considered. Peritoneal dialysis produces only slight phosphate clearance and little or no change in the serum phosphorus concentration at its end. This, combined with the simultaneous increase in serum pH and calcium concentration at the end of dialysis, produces an ideal environment for visceral calcification. Furthermore, it has been observed that peritoneal dialysis removes inhibitors of calcification, whereas hemodialysis does not;[17] hence the tendency to soft-tissue calcification is enhanced.

Metastatic calcification may be responsible for at least some of the abnormal pulmonary function ("stiff lung") exhibited by patients with renal failure,[3,7] an association we are currently investigating.

Demonstration of pulmonary calcifi-

cation by the uptake of ^{99m}Tc-polyphosphate is not necessarily ominous; all but one of our patients are alive 2 to 18 months after bone scans demonstrated such calcification.

We have demonstrated that visceral uptake of bone-seeking radioisotopes is a simple, noninvasive method of studying the pathogenesis and treatment of soft-tissue calcification.

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Management of anemia in a general city hospital: value of chart review in establishing deficiencies in care

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A retrospective review was done of the charts of 50 persons admitted to hospital for investigation of primary anemia. The duration of hospital stay was considered excessive for 80% of the patients and investigation was considered excessive for 34%. Nevertheless, underdiagnosis or misdiagnosis by the time of discharge was evident in 48% and was the result of inadequate investigation or faulty analysis of the results or both. Even when the type of anemia was established, investigations to determine the cause of specific deficiencies were frequently inadequate.

Understandably treatment was inadequate for undiagnosed or misdiagnosed conditions but it was also inadequate for many correctly diagnosed conditions. Parenteral administration of iron was prescribed more often than oral administration, and 30% of patients with iron deficiency anemia failed to receive iron by either route. Most patients with vitamin B_{12} deficiency anemia received treatment late. Blood transfusion was given to 40% of patients but could be justified in only 16%.

On a fait une étude rétrospective des dossiers de 50 personnes hospitalisées pour examen en rapport avec une anémie primaire. La durée d'hospitalisation a été jugée excessive pour 80% des patients et les examens ont été considérés excessifs pour 34%. Néanmoins, un diagnostic incomplet ou inexact était évident pour 48% des patients au moment de leur congé de l'hôpital, et était le résultat d'un examen insuffisant ou d'une analyse erronée des résultats, ou des deux. Même quand le type d'anémie a été établi, les examens destinés à déterminer la cause des carences spécifiques ont été fréquemment insuffisants.

Bien entendu, le traitement a été insatisfaisant dans les cas non diagnostiqués ou diagnostiqués incorrectement, mais il a aussi été insatisfaisant dans les cas où le diagnostic a été posé correctement. L'administration de fer par voie parentérale a été prescrite plus souvent que l'administration par voie orale, et 30% des patients souffrant d'anémie ferriprive n'ont pas reçu de fer. La plupart des patients souffrant d'anémie due à une déficience en vitamine B_{12} a été traité tardivement. Des transfusions sanguines ont été données à 40% des patients mais n'étaient justifiées que dans 16% des cas.

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A chart review for persons more than 14 years of age admitted with a primary diagnosis of anemia to the care of primary care physicians in a general city hospital was undertaken to establish the following:

1. The use of hematologic indices, the blood smear and the reticulocyte count, and the value of the findings in the prediction of the cause of anemia.
2. The extent of omission or delay in the performance of basic investigations important to diagnosis.
3. The degree of suboptimal therapy.
4. The extent to which "abnormal" findings, both hematologic and nonhematologic, are disregarded.
5. The outcome of management, including excessive stay in hospital and expense, misdiagnosis, illness and potential death.

Methods

A review of 50 charts of persons ad-