Scintigraphic Aspects of the Recurrence of Treated Paget's Disease of Bone

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The value of bone scintigraphy in the prediction and detection of a relapse of Paget's disease of bone after treatment, as well as the pattern of such a recurrence, were studied in a group of 40 patients. Thirty of these received a combination of calcitonin and HEDP, ten were treated alternately with calcitonin and HEDP. Scintigraphic deterioration is reliable evidence for a recurrence of Paget's disease of bone; one third of all recurrences was noted first on the bone scintigram. In another third of the cases of recurrence, however, the scintigram showed virtually no signs of deterioration. Scintigraphically a recurrence appears as a diffuse and homogeneous increase in activity in an affected part of the skeleton, or a focal and spotty increase of uptake in a diseased area, or a progression of a lesion beyond its original boundaries into healthy bone. Recurrence is usually not a generalized process occurring throughout the skeleton, but remains restricted to one or several lesions. Recurrence after combined treatment appeared to differ in nature from that seen after the use of calcitonin alone; the former was probably due to local exacerbation of the disease, probably caused by insufficient suppression of the Pagetic cells at these sites. The chance of recurrence could not be predicted on the basis of the pretreatment bone scintigram.

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In an earlier report we described the scintigraphic patterns in a population of 30 patients with Paget's disease of bone, as well as the changes in these patterns during treatment with a combination of calcitonin and disodium ethylidene diphosphonate (HEDP) (*1*). In the present study we have included data on ten additional patients receiving HEDP and calcitonin in an alternating sequence. The present study—thus comprising 40 patients—focuses on bone scintigrams made after clinical remission or at plateau stages. A plateau stage is defined as follows: as a result of treatment, alkaline phosphatase and/or hydroxyproline values stabilize at a lower but still elevated level.

Clinical remission—defined as the persistence of normal serum alkaline phosphatase activity and normal urinary hydroxyproline excretion for at least 6 mo—was achieved in 30 of the 40 patients. In half of these patients remission was maintained for 12–42 mo; in the rest both of the biochemical indicators increased with time. Seven of the ten patients with biochemical plateau levels suffered a relapse.

We studied the value of bone scintigraphy in the prediction and detection of a relapse as well as the pattern of such a recurrence after treatment.

METHODS

The serum alkaline phosphatase and urinary hydroxyproline levels were determined every month during treatment, and less frequently afterwards. The patients were admitted every 6 mo to the clinical investigation unit of our Department of Endocrinology for physical examination, bone biopsy, radiological studies, and bone scintigraphy. The methods were described by Bijvoet et al. (*1*).

The scintigrams were made with a gamma camera,* 3 hr after the injection of 20 mCi of Tc-99m(Sn)HEDP. Since at the time of the present study our department did

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not have a computer, we used a scoring method with a range from 6 to 1, in which Score 6 indicated an extremely high uptake of the radionuclide and Score 1 was normal (unpublished data). The scoring was carried out by two observers simultaneously (E.K.J. P. and C.J.L.R. V.).

We discriminated between biochemical recurrence, in which the alkaline phosphatase and/or hydroxyproline levels rose after normal levels had been achieved, and scintigraphic recurrence, in which the uptake of radionuclide (usually still elevated during remission) increased further. When remission of Paget's disease was not attained but the levels of serum alkaline phosphatase and urinary hydroxyproline stabilized at levels higher than normal (plateau stage) and then increased again, a recurrence was also considered to have occurred.

PATIENTS

Included in this study were 40 patients with Paget's disease. Of these, 30 were treated with a combination of HEDP and calcitonin (Patients 1–30) and ten received either HEDP or calcitonin or an alternating sequence of both drugs (Patients 37, 43, 52, 59, 61, 71, 74, 78, 84, and 88). In general, treatment was discontinued when the biochemical levels remained normal for at least 6 mo. The follow-up for the combined treatment group lasted 1.5–4 yr: 22 were followed for more than 2.5 yr. The clinical and biochemical data for these patients were described by Bijvoet et al. (*1*), and the scintigraphic results by Vellenga et al. (unpublished data). In the present investigation the follow-up of Bijvoet's patients has been extended 1 yr (*1*). The group of patients treated with either HEDP or calcitonin was followed for 2–5 yr.

TABLE 1. TEMPORAL RELATIONSHIP BETWEEN THE SCINTIGRAPHIC AND BIOCHEMICAL EVIDENCE OF RECURRENCE OF PAGET'S DISEASE

Scintigraphic activity	Biochemical parameters	Patient identification	Rise in scintigraphic activity after x months*	Rise in biochemical activity after x months†
Increasing	rise			
(21 patients)	(17 patients)	10	12	19
		43	14	22
		4	18	25
		25	18	25
		12	18	26
		23	18	38
		17	24	18
		18	24	18
		5	25	24
		61	25	26
		6	26	30
		71	27	27
		28	27	29
		20	29	26
		3	33	27
		84	43	36
		37	48	36
	no rise	1	23	—
	(2 patients)	7	29	—
	indeterminate	14	28	?
		27	26	?
No increase	rise	11	—	26
(19 patients)	(4 patients)	13	—	21
		15	?	28
		21	—	15
	no rise	2, 8, 9, 16,	—	—
	(15 patients)	19, 22, 24, 26,		
		29, 30, 52, 59,		
		74, 78, 88.		

* When scintigraphic deterioration occurred with respect to the initiation of therapy.

† Time of the earliest biochemical change (alkaline phosphatase or hydroxyproline) with respect to the start of treatment.

RESULTS

During and after treatment, clinical remission was achieved in 30 out of 40 patients; in the other ten patients, the alkaline phosphatase and hydroxyproline levels dropped to plateau levels (i.e., stable but elevated values).

Table 1 shows the incidence of relapse for the 40 patients studied and the data indicating possible biochemical and/or scintigraphic deterioration. In the total group, scintigraphic deterioration was seen in 21 patients; 17 of these also showed biochemical recurrence. For two other patients (14 and 27) the occurrence of a biochemical relapse was uncertain: in Patient 14 there was a temporary, slight rise in the alkaline phosphatase level (only one observation); Patient 27 had an elevated alkaline phosphatase after deterioration of the bone scintigram, but died soon afterwards of cancer of the lung. In fact, this patient's scintigram showed changes in the skull compatible with both a focal increase in Paget's disease and metastasis, but a diffuse increase in activity in the tibia had the same unequivocal pattern as the original Pagetic lesion in this area. For two other patients with scintigraphic deterioration (1 and 7) there was no biochemical evidence of a recurrence until 14 and 22 mo, respectively, after the onset of the scintigraphic recurrence. In Patient 7 a slight increase in pathological uptake was seen in several locations, but the scintigram improved spontaneously 6 mo later. In Patient 1 (Fig. 3) a small circumscribed focus of high activity originated in the diffusely affected skull. Although the biochemical levels suggested that this patient was still in remission, a radiograph showing an osteolytic lesion corresponding with the foci of increased activity confirmed the presence of a disease process in the vault of the skull (Fig. 4). The differential diagnosis included recurrence of Paget's disease, metastasis, myeloma, and osteosarcoma.

The second part of Table 1 shows that in three cases (13, 11, and 21), the biochemical recurrence was not reflected in the scintigram. In Patient 13 the scintigraphic activity in the solitary lesion in the tibia was still extremely high at the time of the relapse, which hampered evaluation of minor changes. Patients 11 and 21 showed no appreciable increase in tracer uptake until 4 and 6 mo later, respectively. Patient 15 was not examined scintigraphically during the 3-yr period following his remission, so it is not known whether there was scintigraphic deterioration.

It appeared that an early rise in alkaline phosphatase was not always accompanied by scintigraphic deterioration in an early stage, nor was there early scintigraphic deterioration when urinary hydroxyproline increased before serum alkaline phosphatase did.

Table 2 shows the relationship between the biochemical and scintigraphic parameters and the relapse of Paget's disease of bone. In 17 patients both methods indicated deterioration; in seven of these the scintigraphic deterioration was noted 4–20 mo before the increase in the alkaline phosphatase or hydroxyproline levels, in five patients this time difference was less than 3 mo, and in five patients the biochemical changes preceded the scintigraphic changes. In 15 patients both methods indicated continuation of remission or the plateau state. In three patients (14, 15, and 27) the change in the biochemical or scintigraphic parameter was unknown or uncertain; in five there was frank disagreement between the parameters.

Scintigraphically the recurrence became manifest in one of three ways. The most common appearance is a diffuse increase in uptake of the bone-seeking agent in the diseased part (Table 3, Fig. 1). Another possible type of scintigraphic relapse is a focal increase in uptake (Figs. 2 and 3). This pattern was encountered most often in the skull, but sometimes also in the spinal column, sacrum, and long bones; it was never seen in the pelvis.

TABLE 2. RELATIONSHIP BETWEEN SCINTIGRAPHIC AND BIOCHEMICAL EVIDENCE OF RELAPSE OF TREATED PAGET'S DISEASE

	Biochemical change	No biochemical change	Biochemically indeterminate
Scintigraphic change	17*	2	2
No scintigraphic change	3	15	
Scintigraphically indeterminate	1		

* Scintigraphic deterioration preceded biochemical relapse by 4–20 mo in seven, was almost simultaneous (<3 mo) in five other patients, and followed biochemical deterioration by 8–12 mo in five patients.

TABLE 3. TYPES OF SCINTIGRAPHIC ABNORMALITY (n = 21)

Scintigraphic appearance of the recurrence*	No. of lesions
Diffuse increase†	39
Focal increase‡	14
Progression‖	5
New lesions	6
No change	50

* More than one type of scintigraphic deterioration may be encountered simultaneously in the same patient.

† Activity in the diseased part increases homogeneously.

‡ Focal radioactivity originates in the affected skeletal part; elsewhere the activity remains constant.

‖ Progression of activity beyond the original lesion.

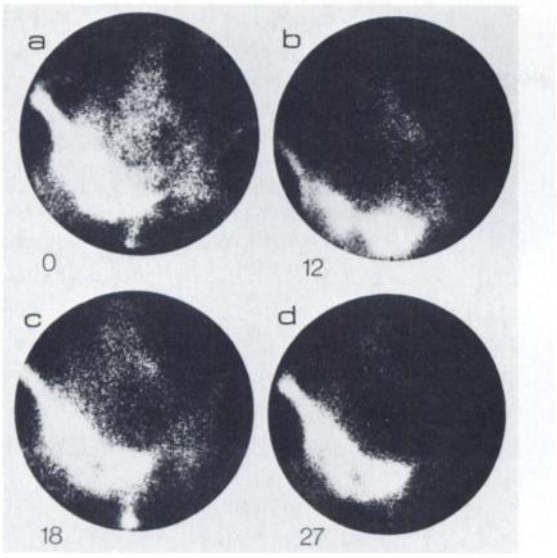

FIG. 1. Anterior scintigrams of Patient 28. (a) Before treatment: High activity in right hemipelvis, consistent with Paget's disease. (b) After 1 yr of treatment: Improvement is obvious and score has dropped from 5 to 3. (c) After 18 mo of treatment: Activity in right hemipelvis has increased slightly but distinctly. Biochemical parameters remained normal. (d) After treatment was stopped: Alkaline phosphatase level also started to rise, and scintigraphic deterioration increased to Score 4.

The third and least frequent appearance is progression of Paget's disease beyond the boundaries of the original lesion into adjacent normal bone (Fig. 5).

Increase in scintigraphic activity can occur in previously involved areas that have become completely normal by scintigram following treatment. In six instances a lesion originated in a part of the skeleton that had not yet been affected by Paget's disease; this occurred most often in the skull, but also in the foot and the pelvis.

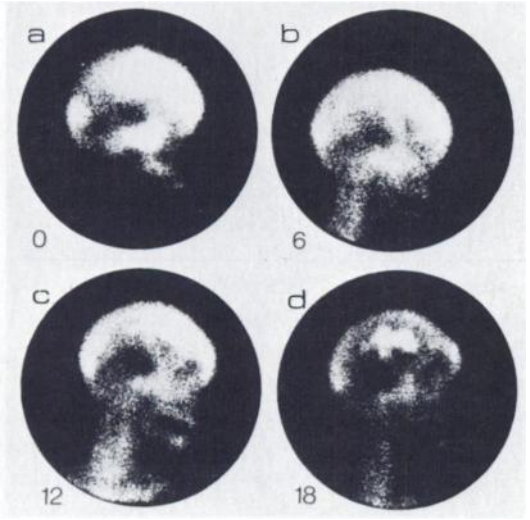

FIG. 2. Patient 12. (a) Before treatment: High activity (Score 5) is seen in skull. (b) After 6 mo of treatment: There is distinct improvement, to Score 4. (c) Another 6 mo later: There is further decrease in activity to Score 3, but focal increase in activity can be seen. (d) After 18 mo of treatment: Focal relapse, which has become more intense, is clearly demarcated from rest of skull, which seems to have improved even further.

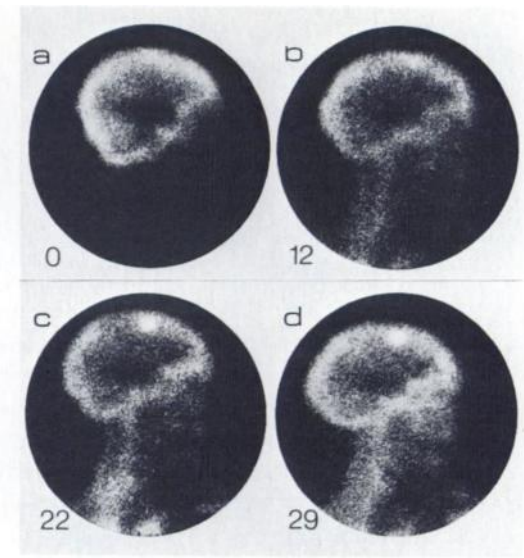

FIG. 3. Patient 1. (a) Before treatment: Very high activity is seen in skull; imaging time was so short that cervical spine is not visualized (Score 6). (b) After a year of treatment: There is marked improvement (to Score 4) and cervical spine is visible. Focal activity in vault of skull is somewhat higher. (c and d) 10 and 17 mo later: There is a distinct area of increased activity that could be due to relapse of Paget's disease or metastasis. Biochemical values remained normal. Treatment was stopped after 17 mo.

There are differences in the tendency toward deterioration. The incidence of deterioration was 60% for the skull (14 of 23), 45% (10 of 22) for frequently affected bones such as the tibia, and only 25% (11 of 46) for less frequently affected bones. Of the seriously affected bones (Score 5) 40% relapsed, whereas 25% of the Score 4 and 21% of the Score 3 bones relapsed. In bones with Score 1 (originally not affected) the incidence of deterioration (i.e., generation of a new Pagetic lesion) was 1%.

In Table 4 the pretreatment scintigrams of the patients

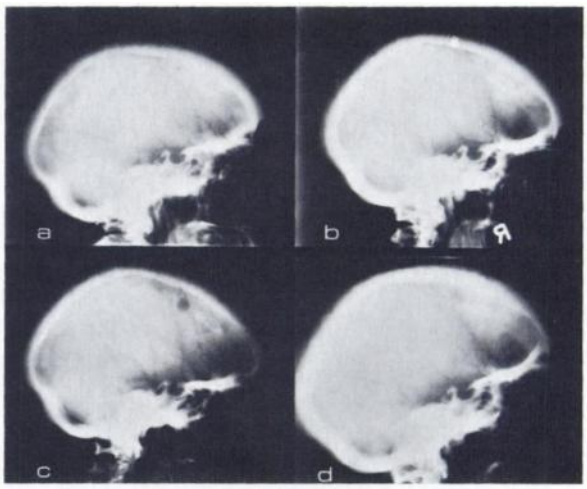

FIG. 4. Patient 1 (as in Fig. 3). (a) Radiograph shows Paget's disease of entire skull. (b) One yr later: There is possible focal osteolysis in vault of skull. (c and d) 10 and 17 mo still later: Distinct lesion is visible, consistent with either metastasis or osteoporosis circumscripta.

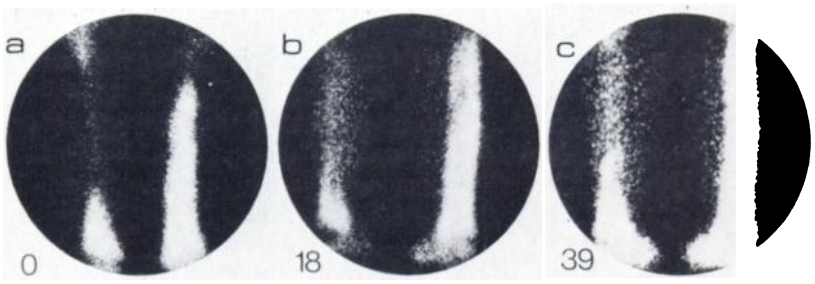

FIG. 5. Patient 17. (a) Both femora are affected by Paget's disease (Score 4). (b) After 18 mo of treatment: Activity has decreased (Score 3) but there is some cephalad progression of front of activity in left femur. (c) 21 mo later: Both femurs show increased activity, with cephalad progression into normal bone.

with relapse are compared with those of the group without a relapse. Remarkably enough, the incidence for the skull is approximately the same in the two groups; by contrast, in the group with relapse the other bones (spine, pelvis, femur, etc.) seem to be affected more often. However, the differences are not significant by Student's t-test, and the same applies to the small differences between the number of affected bones, number of high scores and average scintigraphic scores for the pretreatment scintigrams. There were no differences in biochemical values between the two groups (Table 4).

DISCUSSION

In the course of the past 10 yr, patients with Paget's disease of bone under the care of the clinical investigation unit of the Department of Endocrinology have been treated with calcitonin (*2*), ethane-hydroxy-diphosphonate (*3*), an alternating half-yearly regimen of calcitonin and HEDP or, finally, a combination of these drugs. The combination therapy in particular appeared to be very successful (*1*). Despite these good results, we saw a reactivation of Paget's disease in some instances in all groups.

TABLE 4. COMPARISON OF THE PRETREATMENT BONE SCINTIGRAMS SHOWING RECURRENCE AND WITHOUT RECURRENCE

	Recurrence (n = 21)	No recurrence (n = 19)	Student's t-test
Incidence in skull	0.57	0.53	
Incidence in spine	0.71	0.57	
Incidence in hemipelvis*	1.19	0.81	
Incidence in femur	0.62	0.19	
Incidence in tibia	0.52	0.14	
Incidence in other	1.00	0.48	
Average number of affected bones	4.67	3.21	1.87 ($p > 0.05$) (NS)
Number of high scores (5 or 6)	2.29	1.94	0.72 ($p > 0.05$) (NS)
Average initial score	1.94	1.67	1.67 ($p > 0.05$) (NS)
Urinary hydroxyproline (average value)	1155	1214	

* Not infrequently a patient with recurrence had both sides of the pelvis involved.

Although Lavender (*4*) mentions deterioration of the bone scintigram in some patients receiving calcitonin, the scintigraphic patterns of a relapse of Paget's disease have never been described in detail to our knowledge. In our patients a recurrence of Paget's disease—characterized by a rise in the serum alkaline phosphatase and urinary hydroxyproline levels, sometimes accompanied by increased pain—usually went together with a deterioration of the bone scintigram.

Out of the group of 40 patients there was no recurrence, either biochemical or scintigraphic, in 15 patients, whereas both parameters together indicated the presence of recurrence in 17 patients (Table 2). Table 2 further indicates that in the event of scintigraphic deterioration (21 cases), one may expect a biochemical relapse within 4–20 mo in approximately one third of the cases (seven patients), a simultaneous increase in the biochemical levels in about one third of the cases (five patients), and biochemical changes before the scintigraphic changes in another third of the cases (five patients).

The absence of scintigraphic deterioration does not guarantee that a relapse has not taken place, since out of the 21 biochemical recurrences there was no evidence of increased scintigraphic activity in three cases, and five of the scintigrams did not change until later. This means that the recurrence of Paget's disease is detected initially (or only) by means of the biochemical values in 40% of the cases. Since 15 scintigrams correctly indicated the absence of a relapse, whereas five scintigrams revealed a recurrence in a late stage and three scintigrams did not show it at all, it appeared that out of 23 unchanged scintigrams a recurrence was present in eight instances (Table 2). This means that the chance of a relapse in a patient without scintigraphic evidence of a relapse is ~35%.

Similarly the persistence of normal biochemical values does not in itself imply the absence of a relapse, since about 30% of the patients with relapses visible by scintigram (seven of 21) had normal alkaline phosphatase and hydroxyproline levels. In such cases the bone scintigram can help in the early detection of a relapse, thus

leading to early treatment or prevention of the relapse in ~30% of the cases.

In fact, deterioration of the bone scintigram is a rather reliable sign of a relapse, since in the long run this relapse was not confirmed biochemically in only two patients. For one of these patients, not only the scintigram but also the radiographs showed progression of disease, although the biochemical values remained normal (Figs. 3 and 4). Relapse might not become manifest until 20 mo later.

An intriguing question is why the relapse on the scintigram is visible 6 mo before the rise in biochemical parameters in 30% of the cases but 6 mo after the biochemical evidence in another 30%. There was some tendency toward early detection of the relapse on the scintigram when the increase in alkaline phosphatase (index of osteoblastic activity) preceded elevation of the urinary hydroxyproline level (osteoclastic activity), but the differences were very small. Thus, there seems to be no support for the hypothesis that the rise in scintigraphic activity occurs in an earlier stage when osteoblastic activity predominates during reactivation of Paget's disease than when osteoclastic activity is the main feature of the recurrence. The differences between scintigraphic and biochemical recurrence are probably due to the entirely different factors that govern the parameters. Whereas the alkaline phosphatase level depends mainly on osteoblastic activity, there are multiple determinants of the uptake of bone-seeking agents, such as vascularity (*5–8*), extracellular fluid in bone (*9,10*), exchangeable bone pool (*6,7,10*), vascular permeability (*6,11*), amount of osteoid (*12*), concentration of enzymes like alkaline phosphatase (*13*), and the rate of bone metabolism (*6,7*).

Another question is whether an increase in tracer uptake really reflects deterioration of the disease, or is it merely an expression of bony healing, with increased bone turnover, during treatment. There are several strong arguments in support of the theory of elevated disease activity.

1. The scintigraphic deterioration is almost always accompanied by rising biochemical values, confirming the fact that the disease is becoming active once again. Moreover, in some instances an increase in osteoclastic activity in the histological specimen was established or an increase in pain was noted.

2. Bony healing in Pagetic lesions always accompanies an impressive drop in the pathological uptake on the bone scintigram, as was observed for all patients receiving the combination treatment. Healing was confirmed by biochemical and histological methods (*1*). Thus it appears that the equivalent of alleviating Paget's disease is an improvement in the bone scintigram rather than an increase in uptake.

3. The increase in scintigraphic activity that we observed, and thought to be an expression of the relapse, occurs at least 18 mo after the start of treatment, whereas clinical, biochemical, histological, and scintigraphic evidence of improvement or remission generally occurs during the first 12 mo of treatment (*1*). In many cases the relapse developed after treatment was discontinued.

4. Although a minor point, we note that scintigraphic deterioration takes place in just one or a few bones, whereas the other lesions remain quiescent scintigraphically. Thus it seems that there is local resistance of the disease to treatment.

In general, scintigraphic deterioration, which was easily detected, manifested itself in one of three ways. The most common appearance was a diffuse increase throughout a Pagetic lesion (Fig. 1); this was seen 39 times (Table 3). The second most frequent type of recurrence showed a focal increase in uptake in an affected part of the skeleton (Fig. 2); this was encountered 14 times (Table 3). The foci of uptake can become so vivid and clearly defined that differentiation from metastatic disease may be impossible on the basis of the scintigraphic image alone (Figs. 3 and 4). Sometimes the rate of scintigraphic improvement is not constant throughout one affected bone, resulting in a steep drop in uptake in most of the lesion, with small foci within the healing bone retaining their activity. These foci, which were not visible before treatment because the surrounding bone had the same high level of activity, now appear as areas of increased activity, simulating the development of new lesions. One must be aware of this deceptive phenomenon, which can be detected by means of computerized, quantitative evaluation. The pretreatment scintigrams of patients with the focal type of recurrence were similar to the scintigrams of the other patients, i.e., diffusely elevated uptake throughout all or a part of a bone. The third and least common appearance (Table 3) is extension of Paget's disease beyond the boundaries of the original lesion into adjacent normal bone (Fig. 5). In addition we saw a new Pagetic lesion originating in initially normal bone in six instances. These new lesions, which also herald a relapse of the disease, were seen most often in the skull.

Table 3 also shows that the different types of scintigraphic deterioration can occur in the same patient and that as a rule the scintigram will show deterioration in only one or several sites, while the other bones remain normal, retain the same activity, or even improve. This finding, together with the relatively common appearance of focal increases in activity, led us to the theory that the relapse of Paget's disease of bone is local and the cause of this relapse is insufficient suppression of a nidus of Pagetic osteoclasts. A direct implication of this theory is that longer or more efficient treatment could prevent the relapse.

Nagant de Deuxchaisne (*14*) demonstrated radiologically that Pagetic lesions always improve during treatment with calcitonin, whereas immediately after

discontinuation of treatment radiological bone resorption increases once again. Therefore it would seem that the introduction of HEDP into the therapeutic regimen has added a new element to the efficacy of therapy in comparison with calcitonin alone. Indeed, the relapse after combination treatment—if present—seems to differ in nature from that after calcitonin. In the first place, after treatment with calcitonin alone there is always an increase in bone resorption, which seems to take place in every bone affected by Paget's disease before treatment. In contrast, recurrence after combined treatment with calcitonin and HEDP is not as frequent, and when it does occur, only one or several bones will be affected (Table 3). In the second place, the rebound after calcitonin therapy is diffuse, with progression into healthy bone, whereas in many instances the recurrence after combined treatment seems instead to be a local flaring up of a nidus of osteoclasts that resisted therapy.

The initial levels of serum alkaline phosphatase or urinary hydroxyproline were not indicative of the probability of recurrence. The scintigram also does not seem to be a suitable guide in this respect, because some bones showed deterioration although they had been completely normal, and many bones did not deteriorate although they were not normal scintigraphically. Deterioration was somewhat more frequent in the skull than elsewhere; moreover it appeared that the higher the initial scintigraphic score, the greater the chance of deterioration, although the differences were small.

We tried to find a correlation between the frequency of deterioration and the initial scintigraphic image by comparing the following factors for the group of patients with recurrence of Paget's disease with those for the group without recurrence: (a) initial anatomical distribution of the lesions; (b) number of severely affected bones (Score 5 or 6); and (c) average initial scintigraphic score. Table 4 shows that although the group of patients with recurrence tends to have a greater number of foci, a higher incidence of heavily affected bones, and a higher initial score, the differences are not significant. Thus we can conclude that no prediction can be made on the basis of the pretreatment scintigram as to whether or not there will be recurrence, especially in an individual patient.

CONCLUSIONS

A recurrence of treated Paget's disease of bone is generally visible on the bone scintigram, usually as a diffuse increase in activity, less frequently through the generation of vivid foci in the old Pagetic lesions, and sometimes as progression of the disease beyond the boundaries of the original lesion.

The relapse of Paget's disease after combined calcitonin and HEDP treatment is usually not a generalized process, but instead occurs locally in one or several bones, whereas the other lesions remain quiescent scintigraphically. Furthermore the scintigraphic appearance of the deteriorating lesions is not always identical to that on the pretreatment bone scintigram, since it is not unusual for the renewed activity to be more localized than the initial activity. These two facts suggest that the relapse of Paget's disease after combined calcitonin and HEDP treatment differs in nature from that seen after the use of calcitonin alone in that the former is due to local exacerbation of the disease, probably due to insufficient suppression of the Pagetic cells at these sites.

If deterioration is manifest on the bone scintigram, a relapse of Paget's disease is very likely. The biochemical evidence can be delayed for up to 20 mo.

If there is no scintigraphic deterioration, the chance of a (biochemical) recurrence is about 35%, since out of 23 patients with no scintigraphic evidence of a recurrence over a given period, eight suffered a reactivation of Paget's disease.

In our group of recurrences (21 patients), one third was detected by bone scintigraphy and one third by biochemical analysis; in the remaining 30% both parameters became abnormal at more or less the same time.

We are not able to predict the chance of recurrence on the basis of the bone scintigram before treatment.

FOOTNOTE

Toshiba 202 or 402 gamma camera.

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REFERENCES

1. BIJVOET OLM, HOSKING DJ, FRIJLINK WB, et al: Treatment of Paget's disease with combined calcitonin and diphosphonate (HEDP). *Metab Bone Dis Rel Res* 1: 251-261, 1978
2. BIJVOET OLM, VAN DER SLUYS VEER J, JANSSEN AP: Effects of calcitonin on patients with Paget's disease, thyrotoxicosis or hypercalcaemia. *Lancet* 1: 876-881, 1968
3. DE VRIES HR, BIJVOET OLM: Results of prolonged treatment of Paget's disease of bone with disodium ethane-1-hydroxy-1,1-diphosphonate (EHDP). *Neth J Med* 17: 281-298, 1974
4. LAVENDER JP, EVANS IMA, ARNDT R, et al: A comparison of radiography and radioisotope scanning in the detection of Paget's disease and in the assessment of response to human calcitonin. *Br J Radiol* 50: 3-250, 1977
5. JONES AG, FRANCIS MD, DAVIS MA: Bone scanning: radionuclidic reaction mechanisms. *Semin Nucl Med* 6: 3-18, 1976

6. KING MA, KILPPER RW, WEBER DA: A model for local accumulation of bone imaging radiopharmaceuticals. *J Nucl Med* 18: 1106-1111, 1977
7. GENANT HK, BAUTOVICH GJ, SINGH M, et al: Bone-seeking radionuclides: an in vivo study of factors affecting skeletal uptake. *Radiology* 113: 373-382, 1974
8. SIEGEL BA, DONOVAN RL, ALDERSON PO, et al: Skeletal uptake of ^{99m}Tc-diphosphonate in relation to local bone blood flow. *Radiology* 120: 121-123, 1976
9. CHARKES ND, MAKLER PT JR, PHILIPS C: Studies of skeletal tracer kinetics. I. Digital-computer solution of a five-compartment model of [^{18}F] fluoride kinetics in humans. *J Nucl Med* 19: 1301-1309, 1978
10. SAGAR VV, PICCONE JM, CHARKES ND: Studies of skeletal tracer kinetics. III. Tc-99m(Sn)methylenediphosphonate uptake in the canine tibia as a function of blood flow. *J Nucl Med* 20: 1257-1261, 1979
11. HUGHES SPF, DAVIES DR, KELLY PJ, et al: Extraction by bone of technetium-99m labeled ethane-1-hydroxy-1,1-diphosphonate. *Fed Proc* 34: 401, 1975 (abst)
12. ROSENTHALL L, KAYE M: Technetium-99m-pyrophosphate kinetics and imaging in metabolic bone disease. *J Nucl Med* 16: 33-39, 1975
13. ZIMMER AM, ISITMAN AT, HOLMES RA: Enzymatic inhibition of diphosphonate: A proposed mechanism of tissue uptake. *J Nucl Med* 16: 352-356, 1975
14. NAGANT DE DEUXCHAISNES C, ROMBOUTS-LINDEMANS C, HUAUX JP, et al: Roentgenologic evaluation of the efficacy of calcitonin in Paget's disease of bone. *Mol Endocrinol* 213-233, 1977