

Bone Scintigraphy Following Intravenous Pamidronate for Paget's Disease of Bone

Paul J. Ryan, Terence Gibson, and Ignac Fogelman

Departments of Nuclear Medicine and Rheumatology, Guy's Hospital, London, United Kingdom

Pamidronate is one of several powerful bisphosphonates able to produce prolonged remissions of Paget's disease. This study examined to what extent bone scan changes parallel the clinical response and whether there is variability in the behavior of individual lesions. Twenty-five patients with pagetic bone pain for more than 2 yr were examined with bone scintigraphy before and on average 8 mo after six 30-mg infusions of pamidronate given weekly. Serum alkaline phosphatase and urinary hydroxyproline-to-creatinine ratios were measured before and 6 mo after treatment. A second course of pamidronate was given to 13 patients who had clinical or biochemical relapse. Of 136 pagetic lesions, 13 (10%) completely resolved, 90 (65%) improved and 33 (24%) remained unchanged. There was no significant difference in response between bony sites, although less active lesions were more likely to resolve completely. In conclusion pamidronate has a powerful effect on bone scan appearances in Paget's disease. Most lesions improve but complete resolution is uncommon. Less active lesions are more likely to resolve and are less likely to require further therapy.

J Nucl Med 1992; 33:1589-1593

For many years, Paget's disease has been treated with either injectable calcitonin or oral etidronate. However, in many patients, these treatments are ineffective or only give temporary relief of pain (1-3). Furthermore, at present in the U.K., calcitonin has to be given by injection, which often leads to distressing side effects, and etidronate, although generally well-tolerated, cannot be given in high doses or for long periods because of the risk of osteomalacia (3-5).

Pamidronate is a second generation bisphosphonate, which is more powerful than etidronate, and is not associated with impaired bone mineralization (6). Several studies have demonstrated its efficacy in Paget's disease (7,8). However, the changes in bone scintigraphy following pamidronate are less well established and the role of the bone scan in assessing response to pamidronate treatment has

not yet been defined (9,10). With the advent of powerful bisphosphonates, it has been suggested that a permanent cure could be achieved if the bone scan appearances were normalized following treatment (11).

For patients with Paget's disease who receive a standard treatment regimen of parenteral pamidronate, this study examined the changes in bone scan appearances following therapy.

METHODS

Twenty-five patients with a least 2 yr of bone pain due to Paget's disease were examined. Bone scintigraphy of the whole body and distal limbs was undertaken an average of 2.6 mo (range 1-5 mo) before treatment and 8 mo (range 6-12 mo) following treatment. Imaging was done 3-4 hr following injection of 550 MBq ^{99m}Tc -methylene diphosphonate (MDP). Pamidronate was administered weekly as 30-mg infusions in 500 ml of normal saline given intravenously for 6 wk. Clinical assessment was performed, and serum alkaline phosphatase (sAP) and urinary hydroxyproline-to-creatinine ratio (OHp/Cr) were measured before and 6 mo after treatment.

Scans were scored visually using a semiquantitative scale described by Patel et al. (10) as follows:

- 0 = No lesion apparent (see Fig. 1B).
- 1 = Increased activity just detectable (Fig. 2B).
- 2 = Increased activity easily detectable without loss of definition of adjacent bone (see Fig. 1A).
- 3 = Activity easily detectable but with loss of definition of adjacent bone (see Fig. 2A).
- 4 = Activity easily detectable from lesion with none visualized from adjacent normal bone.

Bone scans were reported without knowledge of whether they were pre- or post-treatment films by a physician (PR). A summated score for each patient was obtained by adding the scores for individual lesions. A mean score was obtained by dividing the summated score by the number of lesions. In addition to being scored, each lesion was also described as predominately uniform or focal. Pain response was assessed by patient interview 6 mo after treatment and noted to be unchanged or little improvement, improved, or pain free. Statistical analysis was undertaken using the Mann Whitney U-test.

RESULTS

There were 136 bone scan lesions, whose distribution is shown in Table 1. No significant difference was found in

Received Jan. 31, 1992; revision accepted Apr. 29, 1992.
For reprints contact: Dr. P.J. Ryan, Department of Nuclear Medicine, Guy's Hospital, St. Thomas Street, London, SE1 9RT, UK.

TABLE 1
Distribution of Lesions with Average Pre- and Post-treatment Bone Scan Scores and Numbers of Normal Scans Post-treatment

Site	No.	Average scan score		Normal (%)
		Pre-treatment	Post-treatment	
Pelvis	33	2.59	1.56	3 (9)
L. Spine	20	2.70	1.65	1 (5)
Femur	19	2.37	1.75	0
Tibia	14	2.08	1.23	3 (20)
T. Spine	13	2.61	1.69	1 (8)
Skull	9	2.77	1.67	1 (11)
Scapula	8	2.37	1.37	2 (25)
Humerus	6	2.17	1.50	0
Patella	3	2.33	1.67	0
Clavicle	3	2.33	1.37	1 (33)
Talus	2	3.00	2.50	0
Sacrum	2	2.50	2.00	0
Ulna	1	3.00	2.00	0
Mandibule	1	3.00	0.00	1 (100)
Maxilla	1	3.00	1.00	0
Calcaneus	1	3.00	2.00	0
Total	136	341.44	215.03	13
Mean	8.5	2.51	1.58	0.8 (13)

the average fall in bone scan score for different bony sites. There was no site of Paget's disease in which a bone scan improvement following treatment was not obtained in some patients. Of individual lesions, 13 (10%) resolved completely, 90 (65%) improved, 33 (24%) remained unchanged and none worsened. There were no lesions with an initial score of 4. Seventy-eight lesions had an initial scan score of 3 and showed an average fall in scan score of 36% following treatment with 5% completely resolving and 20% remaining unchanged. Fifty lesions had an initial score of 2 and showed an average fall of 44% following treatment, with 20% completely resolving and 24% remaining unchanged. Eight lesions had an initial score of 1 and showed an average fall of 25% following treatment, with 25% completely resolving and 75% unchanged. Figures 1A and 1B show the resolution of a grade 2 pagetic lesion at L1 and Figures 2A and 2B show the marked improvement of a grade 3 lesion of the left hemipelvis to grade 1 following treatment.

The summated bone scan score improved in 24 patients (96%) and remained unchanged in 1 patient (Table 2). The mean summated score fell with treatment from 2.28 to 1.39. Completely resolved lesions were found in 12 (48%) patients, lesions that improved were found in 24 (96%) and lesions that remained unchanged were found in 16 (64%). Multiple lesions with the same initial bone scan score were found in 21 patients, in only 3 (14%) of whom did such lesions respond uniformly to treatment. The average difference between the greatest and least bone scan score response in each patient was 62%. The greatest variation was in one patient in whom a lesion of scan score 3 fully resolved and another lesion with the same scan score remained unchanged. In 15 (11%) lesions, the

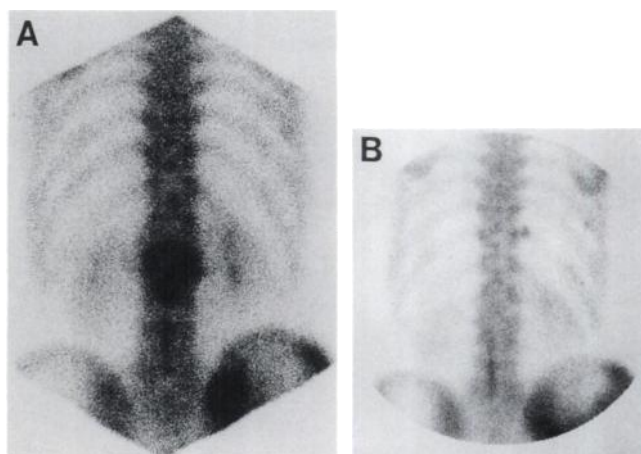


FIGURE 1. (A) Increased pagetic activity at L1 grade 2 pre-treatment. (B) Resolution of increased activity (grade 0) in same patient after treatment with pamidronate.

scan appearances changed from uniform to predominantly focal (Fig. 3A-B). Sites where this was noted were pelvis (2), femur (3), skull (3), lumbar spine (4) and tibia (3). Patients were divided into those where the bone scan score fell by more than 38% and less than 38%. No significant differences were found between changes in bone scan score and biochemical measurements in the two groups.

There was complete resolution of symptoms at 12 painful sites, improvement in 19 and no change in 4. The pelvis with additional osteoarthritis of the hip joints was the site of pain in two patients where there was no clinical response. The other two sites were the pelvis and the lumbar spine where there was improvement in scan score without full resolution. There was no significant difference in pre- or post-treatment bone scan score, or percentage score change, between those sites where there was a complete disappearance of pain and those where pain improved (Table 3). Those sites that were pain free after treatment had significantly higher fall in OHP/Cr ($p < 0.05$), although other biochemical measures were not significantly different in the two groups. Minor side effects, which were mostly a transient increase in pain or mild

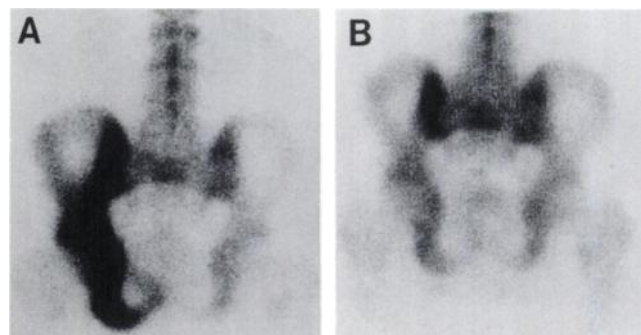


FIGURE 2. (A) Pagetic lesion grade 3 left hemipelvis before treatment. (B) Same patient in (A) after pamidronate treatment with marked resolution of the left hemipelvis lesion (grade 1).

TABLE 2

Average Bone Scan Scores for Individual Patients Pre- and Post-treatment and Numbers of Sites Where Lesions Completely Resolved

Patient no.	No. lesions	Bone scan score (range)		Normal
		Pre-treatment	Post-treatment	
1	2	2.00 (2)	0.50 (0-1)	1
2	4	2.00 (2)	1.00 (1)	0
3	2	2.00 (2)	0.50 (0-1)	1
4	1	2.00 (2)	2.00 (2)	0
5	2	1.50 (1-2)	0.50 (0-1)	1
6	15	2.73 (2-3)	1.80 (1-2)	0
7	2	2.00 (2)	1.50 (1-2)	0
8	4	2.75 (2-3)	1.00 (0-2)	1
9	9	2.25 (1-3)	1.25 (0-3)	1
10	2	2.50 (2-3)	1.50 (1-2)	0
11	3	2.67 (2-3)	2.33 (1-3)	0
12	3	2.67 (2-3)	1.67 (0-3)	1
13	3	2.33 (1-3)	1.33 (1-2)	0
14	6	3.00 (3)	2.00 (2)	0
15	6	2.50 (2-3)	1.67 (1-2)	0
16	3	2.00 (1-3)	1.33 (1-2)	0
17	7	2.57 (2-3)	1.57 (0-2)	1
18	17	2.82 (2-3)	1.88 (0-3)	1
19	8	2.25 (2-3)	1.25 (0-2)	1
20	5	2.40 (1-3)	1.60 (0-3)	1
21	8	2.50 (1-3)	1.12 (1-2)	0
22	5	2.80 (2-3)	1.00 (0-2)	0
23	1	3.00 (3)	2.00 (2)	0
24	9	1.78 (1-2)	1.11 (0-2)	2
25	9	2.78 (2-3)	2.56 (0-3)	1
Total	136	57.02	35.97	13
Mean	5.4	2.28	1.39	0.52

pyrexia (<38 C) were noted in 50% of the patients and have been described more fully elsewhere (8).

Six patients were retreated 1-2 yr and seven patients 2-3 yr following their first treatment because of a relapse of pain. Bone scan score and biochemistry results in these patients were compared to those not requiring retreatment

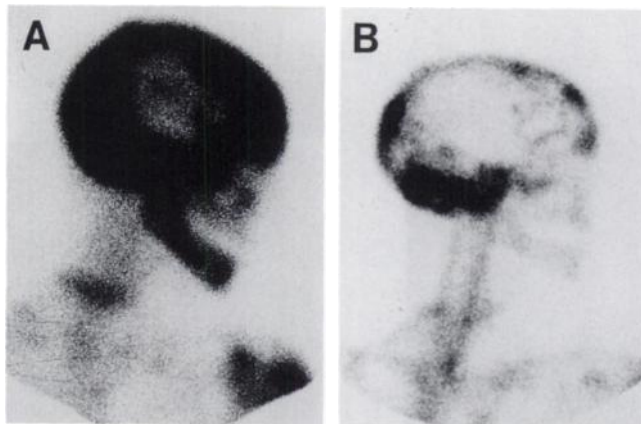


FIGURE 3. Paget's disease of the skull and mandible before treatment. (B) Same patient in (A) after pamidronate treatment. The mandibular lesion has resolved and the skull lesion has become multifocal.

TABLE 3

A Comparison of Clinical Response with Mean and Range Bone Scan Score, Serum Alkaline Phosphatase (sAP, IU/liter) and Urinary Hydroxyproline-to-Creatinine Ratio (OHP/Cr, mmol/mol)

Scan score/Biochemistry	Clinical response	
	Resolution of pain (12 pts)	Improvement of pain (13 pts)
Pre-bone scan score	2.4 (1-3)	2.7 (1-3)
Post-bone scan score	1.9 (1-3)	1.8 (1-3)
%Change bone scan score	22 (0-66)	36 (0-100)
%Lesions normal post-treatment	0	5
Pre-sAP	1929 (321-4461)	1247 (431-4400)
Post-sAP	412 (203-1216)	450 (157-913)
%Fall sAP	66 (33-92)	60 (35-81)
Pre-OHP/Cr	160 (16-450)	74 (12-300)
Post-OHP/Cr	29 (7-58)	30 (7-106)
%Fall OHP/Cr	71 (55-84)	57 (38-87)

Numbers in parentheses are range bone scores.

after 3 yr (Table 4). Higher sAP and OHP/Cr ratios both before and after treatment ($p < 0.05$), but not percentage change in these values, were significantly associated within the requirement for further therapy. Higher bone scan scores, both before and after treatment, and a smaller percentage fall in bone scan score were also associated with requirement for further therapy ($p < 0.05$). One patient with a painful site where there was complete resolution of bone scan appearances did not require further treatment by 3 yr after initial therapy. No patient with a grade 1 lesion after treatment (seven patients) required further treatment until 2-3 yr.

DISCUSSION

Treatment with pamidronate leads to improvement of most pagetic lesions visualized on bone scans and the complete resolution of some lesions. However, a minority are unchanged following treatment. There were wide variations in response of lesions to treatment, with complete resolution of some with a high initial score and no change in others with a low initial score. There were variations in response of lesions, with the same initial score in 86% of patients. This variation in response was also found by Patel et al. (10) in a study where some patients received etidronate and others pamidronate, but it differs from a study using a combination of calcitonin and etidronate (12), in which a constant reduction in uptake on bone

TABLE 4

A Comparison of Mean and Range Bone Scan Score, Serum Alkaline Phosphatase (sAP, IU/liter) and Urinary Hydroxyproline-to-Creatinine Ratio (OHp/Cr, mmol/mol) with the Requirement for Further APD Therapy

Biochemistry/Scan score	Retreatment with APD		
	1-2 yr (6 pts)	2-3 yr (7 pts)	None by 3 yr (5 pts)
Pre-treatment sAP	2248 (641-4400)	903 (54-2170)	528 (321-1083)
Post-treatment sAP	682 (226-1513)	304 (214-406)	209 (156-282)
%Fall sAP	66.5 (46-86)	58.3 (43-81)	53.2 (33-81)
Pre-treatment OHp/Cr	182 (50-450)	63 (19-169)	29 (16-46)
Post-treatment OHp/Cr	51 (8-106)	19 (5-35)	7 (0-12)
%Fall OHp/Cr	70 (40-86)	56 (12-97)	70 (44-100)
Pre-treatment bone scan score	3 (3-3)	2.6 (2-3)	2 (1-3)
Post-treatment bone scan score	2.5 (2-3)	1.7 (1-3)	0.8 (0-1)
%Fall bone scan score	16.5 (0-33)	33 (0-66)	52 (0-100)

Numbers in parentheses are the range of bone scan scores.

scintigraphy was found following treatment, and a subsequent study by the same authors using pamidronate, in which scintigraphic improvement was proportional to initial uptake (13).

In this study, although there was also a wide variation in responses of lesions in the same patient, complete resolution of lesions was associated with a lower initial bone scan score. This was also found in the study by Patel et al. for the 10 patients receiving pamidronate (10). However, Patel et al. reported that some lesions worsened following treatment and in some patients the summated bone scan score remained unchanged or deteriorated. They also reported the development of new lesions, which were not found in this study. However, it should be noted that in the study of Patel et al., follow-up scans were performed much later than in the present study—a mean of 21 mo (range 12-48) following treatment. A mixed group of patients were also used, some receiving etidronate and others pamidronate, and the medication dosages were not stated. Possible explanations for the variable response of lesions of the same intensity to pamidronate include differences in vascularity of lesions (14), the amount of woven bone present (15) or the thickness of involved bone (9).

In a few patients, the bone scan appearances of lesions changed from predominately uniform to predominately focal. In some of these individuals, the bone scan might have been reported as demonstrating metastases, without prior knowledge of this pattern of response to treatment.

The semiquantitative score used in this study is a relatively crude method of bone scan assessment, but it has been validated against quantitative approaches (16). By using this technique, we failed to demonstrate an association between bone scan score and biochemical changes or clinical response. An absence of a relationship between bone scan changes and sAP was also noted by Patel et al. (10). We found improvement in the bone scan score at almost every painful site, but this did not significantly correlate with clinical improvement over the first 6 mo. The biochemical measures also failed to show an association with clinical response except for a percent fall in OHp/Cr which was just significant.

The requirement for further treatment was associated with bone scan appearances, as was also found by Vellenga et al. (12), and it may therefore help in the assessment of the need for further therapy or deciding which therapeutic regimen is most appropriate. However, the sAP and OHp/Cr were also significantly associated with requirement for further therapy and in most cases would be used instead of the bone scan.

We have demonstrated that normalization of bone scan appearances is not required for relief of symptoms. However, whether normalization of scan appearances is associated with prevention of recurrence of disease remains uncertain. Nevertheless, it is of note that those patients not requiring further treatment by 3 yr following treatment all had average summated post-treatment bone scan scores of 0 or 1.

In conclusion, pamidronate has a powerful effect on bone scintigraphy in patients with Paget's disease. There is a large variation in response to treatment of individual lesions, and an awareness that diffuse involvement of bone may become focal should be noted to avoid possible confusion with metastatic disease. The bone scan, together with biochemistry measurements, can predict the need for further therapy.

REFERENCES

- De Rose DJP, Singer F, Auramides A, et al. Response of Paget's disease to porcine and salmon calcitonins: effects of long term treatment. *Am J Med* 1974;56:858-866.
- Johnston CC Jr, Khairi MRA, Meunier PJ. Use of etidronate in Paget's disease of bone. *Arth Rheumatism* 1980;23:1172-1175.
- Khairi MRA, Altman RD, De Rosa GP, Zimmerman J, Schank RK, Johnston CC. Sodium etidronate in the treatment of Paget's disease of bone. *Ann Intern Med* 1977;87:656-663.
- Boyce BF, Fogelman I, Rabston S, Smith L, Johnston E, Boyle IT. Osteomalacia due to low dose diphosphonate therapy in Paget's disease. *Lancet* 1984;1:821-824.
- Gibbs CB, Aaron JF, Peacock M. Osteomalacia in Paget's disease treated with short term, high dose sodium etidronate. *Br Med J* 1980;20:127-129.
- Frijlink WB, Te Velde J, Bijvoet OLM, Heynen G. Treatment of Paget's disease of bone 3 amino-1-hydroxypropylidene 1-1 bisphosphonate (APD). *Lancet* 1979;1:799-803.
- Hamick HJ, Papapoulos SF, Blahnsma HJ, Moolenaar AJ, Vermeij P, Bijvoet OLM. Paget's disease of bone: early and late responses to three modes of treatment with amino-hydroxypropylene bisphosphonate (APD). *Br Med J* 1987;295:1301-1305.

8. Ryan PJ, Sherry M, Gibson T, Fogelman I. Treatment of Paget's disease by weekly infusions of 3 amino-hydroxypropylidene 1-1 bisphosphonate (APD). *Br J Rheum* 1992;31:97-101.
9. Fogelman I. Bone scanning in Paget's disease. In: Freeman LM, ed. *Nuclear medicine annual* 1991. New York: Raven Press Ltd, 1991:1.
10. Patel U, Gallaher SJ, Boyle IT, McKillop JH. Serial bone scans in Paget's disease: development of new lesions, natural variation in lesion intensity and nature of changes seen after treatment. *Nucl Med Commun* 1990;1: 747-760.
11. Anderson DC, O'Driscoll JB, Buckler HM, Cantrill J, Brown JDK. Relapse of osteoporosis circumscripta as a lytic ring after treatment of Paget's disease with intravenous 3-amino-1 hydroxypropylidene-1,1-bisphosphonate. *Br J Radiol* 1988;61:996-1001.
12. Vellenga CJLR, Pauwels EKJ, Bijvoet OLM, Hosking DJ, Frijlink WB. Bone scintigraphy in Paget's disease treated with combined calcitonin and diphosphonate (EHDP). *Metab Bone Dis Rel Res* 1982;4:103-111.
13. Vellenga CJLR, Pauwels EKJ, Bijvoet OLM, Hamieck MD, Frijlink WB. Quantitative bone scintigraphy in Paget's disease treated with APD. *Br J Radiol* 1985;58:1165-1172.
14. Fogelman I. Skeletal uptake of diphosphonate: a review. *Eur J Nucl Med* 1980;3:473-476.
15. Galasco CSB. The pathological basis for skeletal scintigraphy. *J Bone Joint Surg (Br)* 1975;57:353-359.
16. Vellenga CJLR, Pauwels EKJ, Bijvoet OLM. Comparison between visual assessment and quantitative measurement of radioactivity on the bone scintigram in Paget's disease of bone. *Eur J Nucl Med* 1984;9:533-537.

(continued from page 5A)

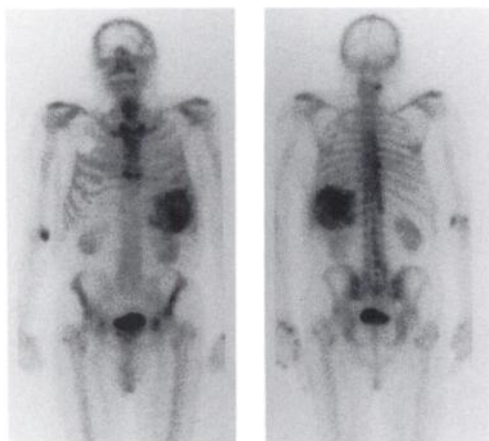


Figure 1 Ant Post

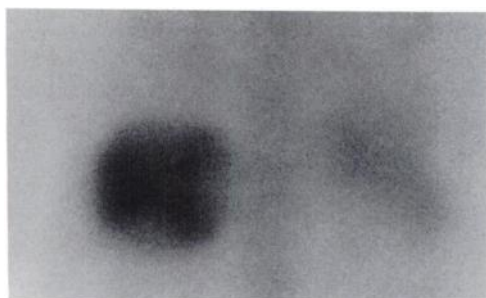


Figure 2 Post

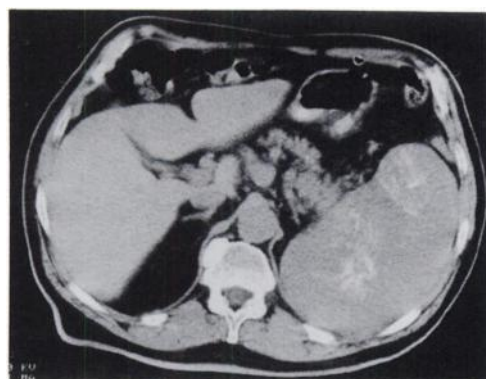


Figure 3

FIRST IMPRESSIONS

PURPOSE

A 75-yr-old male with no previous history of malignancy underwent a bone scan as part of a work-up for weakness and weight loss. A ^{99m}Tc -MDP bone scan demonstrated abnormal splenic activity (Fig. 1). A subsequent gallium scan also showed abnormal accumulation in the spleen (Fig. 2). A CT scan revealed splenomegaly and calcification in the spleen (Fig. 3). Pathology after splenectomy was reported as a large cell malignant lymphoma of the spleen.

TRACER

25 mCi of ^{99m}Tc -MDP and 12 mCi of ^{67}Ga -citrate

ROUTE OF ADMINISTRATION

Intravenous

TIME AFTER INJECTION

^{99m}Tc -MDP, 3 hr
 ^{67}Ga -citrate, 48 hr

INSTRUMENTATION

ADAC Genesis (large field of view) camera

CONTRIBUTORS

J. Hilger and E. Turbiner

INSTITUTION

Department of Radiology, Section of Nuclear Medicine, Mercy Hospital of Pittsburgh, Pittsburgh, Pennsylvania.