Observations on Serial Radionuclide Blood-Flow Studies in Paget's Disease: Concise Communication

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Twenty-four symptomatic patients with symptoms of active Paget's disease of bone were evaluated, during the course of their therapy, a total of 71 times (24 baseline and 47 follow-up examinations) by serial alkaline phosphatase levels (AP), Tc-99m MDP bone scans, and radionuclide blood-flow studies. The flow study correlated with disease activity in all of the baseline studies and in at least 85% of the follow-up studies. In five patients (seven follow-up studies) the changes in local blood flow correctly anticipated the eventual rise or fall of AP. In comparison with the bone scan, the changes in blood flow preceded the bone-scan alterations or were more reliable indicators of disease activity in 12 of the 13 follow-up studies in which the results of the two examinations disagreed. We conclude that the radionuclide flow study provides useful additional clinical information in the management of Paget's disease.

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In the investigation and follow-up of patients with Paget's disease of bone, several imaging and biochemical modalities are available. In this paper we examine the value of the radionuclide blood-flow study as an adjunctive index of bone hyperemia, in the management of patients undergoing therapy for Paget's disease.

PATIENTS AND METHODS

Twenty-four symptomatic patients with clinical, biochemical, and radiographic evidence of Paget's disease were studied sequentially with Tc-99m methylene diphosphonate (MDP) (18 mCi-666 MBq) bone scanning. Twenty-four baseline and 47 follow-up scans with blood-flow studies were performed. The lesions investigated by the flow study were distributed as follows: skull 1; hemipelvis/sacrum 11; femur 3; tibia 9. The flow study of the abnormal bone was obtained at two frames per second and was followed by an immediate 1-min postsequential blood-pool image. A gamma camera was used, equipped with a general-purpose, low-energy collimator. The scans were obtained 2 hr after injection. After an initial baseline study, the timing of the scintigraphic post-therapy follow-up was determined by the sole referring physician and depended on the drug administered and the patient's response to therapy. Alkaline phosphatase (AP) levels were determined before each scan study. Our upper limit of normal is 100 IU/cc.

The therapeutic regimen involved calcitonin, disodium etidronate, and mithramycin, either alone or in combination. A discussion of these therapeutic regimens and their indications is given in Refs. *2*, *4*, *5*. Clinical and biochemical responses to these agents were then correlated with the findings of the scintigraphic studies, which had been independently interpreted. Flow studies were rated on a scale of 0 to 3+. A score of 0 reflected no difference between normal and Pagetic bone, 1+ mild differences, 2+ moderate differences, and 3+ marked differences. The scoring was based on consensus of two independent observers.

Occasionally it was difficult to classify the flow study

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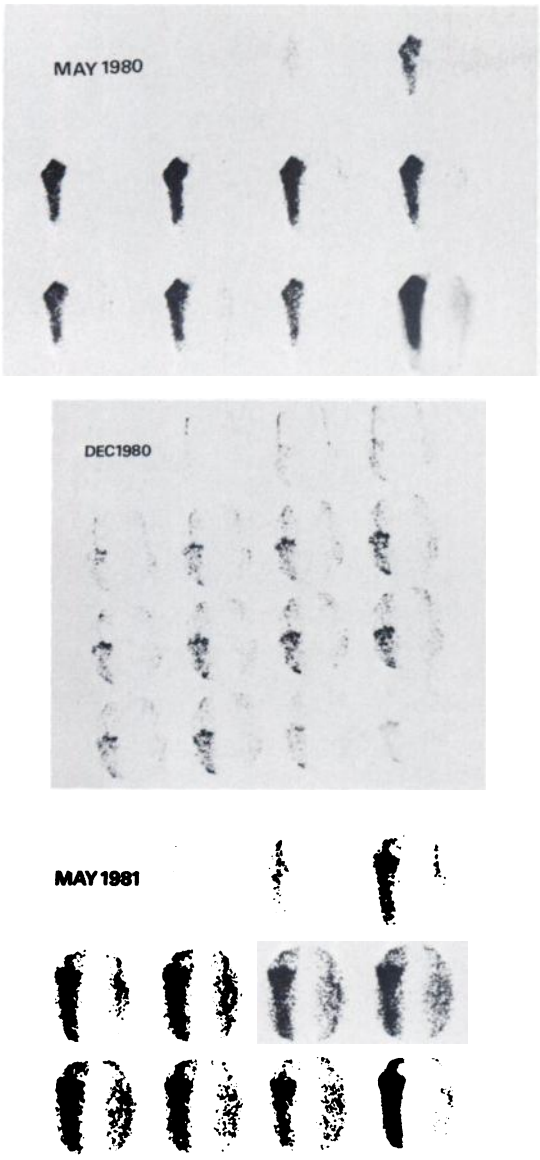

FIG. 1. Pretherapy blood-flow study of Patient 22 (May 1980) shows very intense (3+) flow to right tibia (top). Left tibia is barely visible. Following HEDP therapy, flow study of December 1980 shows only mildly increased (1+) flow to right tibia (center). By May 1981, flow to right tibia is now moderately increased (2+) (bottom). As can be seen in Table 1, this increasing hyperemia preceded rise in AP levels.

exactly into one of these categories. For example, the flow may have improved from 1+ but still not quite to normal. There were five such cases and the flow was classified as 0/1+ in the fourth, and 1+/2+ in the fifth to represent these intermediate but discernible changes. Flow studies from Patient 22 are presented in Fig. 1 to illustrate the grading system. A flow study is easier to interpret when comparison with a contralateral structure is possible. If no such structure was present, the distribution of flow normally seen in the region could be compared with the study to be interpreted. For example, Fig. 2 shows the flow studies of Patient 8, who had extensive Paget's disease of the skull. The first examination shows markedly increased calvarial flow compared with cerebral flow (Fig. 2, top). The flow pattern returned to normal following mithramycin therapy (Fig. 2, bottom). The intensity of radiotracer uptake on the bone scan was also graded as unchanged, increased, or decreased relative to the previous study, based on a comparison of the degree of uptake in the lesion with normal bone.

RESULTS

All data are summarized in Table 1. Before therapy, all patients showed increased uptake on the bone scan and an initial hyperemia of at least 1+ on the baseline flow study. Figure 3 compares the flow changes with AP levels in 47 follow-up studies. Thirty-three studies were in immediate agreement while 14 studies disagreed. An analysis of these discordant studies was performed, based on the overall assessment of the patient and his or her subsequent course. The flow study was judged to be correct in seven studies (five patients): in three studies the flow increased before the AP finally rose; in three others the flow study decreased before or was faster than the decrease in AP levels; and in one instance the AP rose and there was no change in flow, but the flow had already

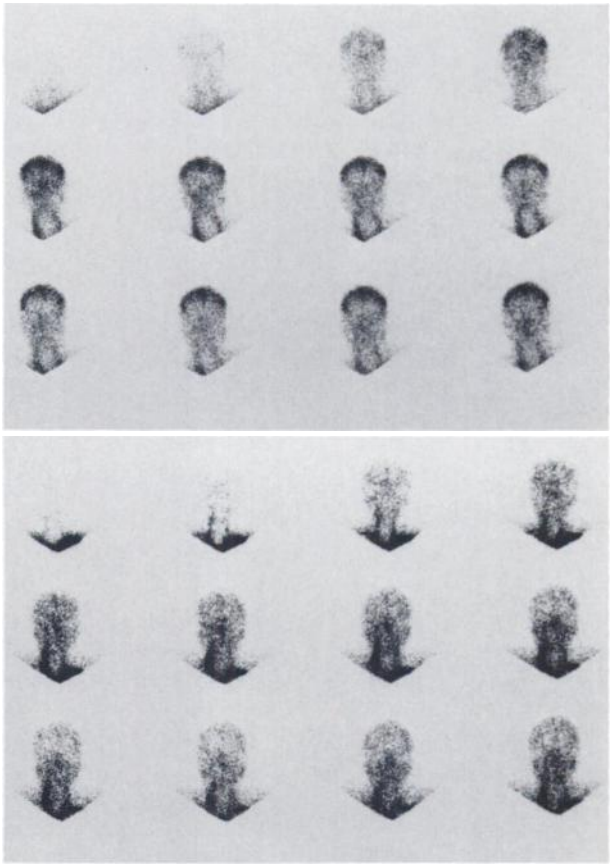

FIG. 2. Pretherapy blood-flow study of Patient 8 (November 1978) shows 2+ hyperemia in skull (top). This dramatically resolved following mithramycin therapy (February 1979) (bottom).

TABLE 1. RESULTS

Case	Date	Drug*	AP(IU/l)	Blood flow	Scan†	Symptoms‡
1.	12/79	HEDP	120	1+	+	+
	2/80	MITH	115	1+	↔	↔
	3/80		115	1+	↔	↔
	4/80		115	1+	↔	↔
2.§	1/80	HEDP	145	1+	+	+
	12/80		105	0	↓	↓
	6/82**		116	1+	↑	↔
3.	8/81	HEDP	234	3+	+	+
	11/81		156	0	↓	↓
4.	5/81	HEDP	510	2+	+	+
	11/81		480	2+	↔	↓
	7/82		936	3+	↑	↑
5.	1/81	HEDP	235	2+	+	+
	6/81**		105	1+	↔	↓(0)
	10/81**		103	1+	↓	0
6.	2/81	HEDP	3270	2+	+	+
	4/81**		1750	1+	↔	↓
7.	2/80	MITH	117	1+	+	+
	8/80**	MITH	162	3+	↔	↔
	11/80**		156	2+	↓	↓
	4/81**	HEDP	170	3+	↔	↑
	9/81		220	2+	↔	↔
8.	11/78	MITH	1392	2+	+	+
	2/79		320	0	↓	↓
9.	5/80	MITH	1860	2+	+	+
	5/80		711	0/1+	↓	↓
	6/80**		225	0	↔	0
10.	11/79	HEDP	270	1+	+	±
	10/80		275	1+	↔	±
11.	6/79	MITH	2100	3+	+	+
	9/79	HEDP	—	—	—	—
	4/80		1750	2+	↓	↓
	5/80		1380	2+	↔	↓
	6/80**		1188	1+/2+	↔	↓
12.	4/79	HEDP	1375	2+	+	+
	12/80		220	0/1+	↓	↓
13.	12/80	HEDP	175	2+	+	+
	7/81**		210	3+	↔	↔
14.	10/80	MITH	1020	2+	+	+
	1/81**		894	1+	↔	↓
15.	12/81	HEDP	720	3+	+	+
	3/82		432	1+	↓	↓(0)
16.	5/80	MITH	570	2+	+	+
	5/80	CALC	330	2+	↔	↓
	8/80		350	2+	↔	↔
	3/81		250	1+	↓	↓(0)
17.	10/81	HEDP	741	1+	+	+
	7/82		525	1+	↔	↔
18.	1/82	HEDP	1470	1+	+	+
	6/82		459	1+	↔	↓(0)
19.	3/81	HEDP	122	2+	+	+
	8/81		105	1+/0	↓	↓
	12/81		77	0	↓	↓
	6/82**		90	0	↓(0)	↓(0)

(*continued*)

TABLE 1. (*continued*)

Case	Date	Drug*	AP(IU/l)	Blood flow	Scan†	Symptoms‡
20.	11/81	HEDP	175	1+	+	±
	7/82		153	0	↓(0)	±
21.	1/80	HEDP	795	2+	+	+
	12/80		208	1+	↓	↓
22.	5/80	HEDP	717	3±	+	+
	12/80		150	1+	↓	↓(0)
	5/81**		97	2+	↔	↔
	1/82**	HEDP	257	2+	↔	↑
23.	3/79	HEDP	360	2+	+	±
	1/80**		462	1+	↓	±
	10/80		231	0/1+	↓¶	±
	11/81		420	0/1+	↓	±
24.	9/79	MITH	2200	3+	+	+
	1/80**		565	0	↓	↓
	6/80**		155	0	↓	↓
	7/81		1140	2+	↑	↑
	9/81	MITH	1350	2+	↔	↑
	11/81		612	0	↓	↓

* HEDP = disodium etidronate; MITH = mithramycin; CALC = calcitonin.

† + = increased uptake, ↓ = less intense uptake; ↑ = more intense uptake, ↔ = no change in uptake; 0 = normal, − = no data.

‡ + = symptomatic, ↓ = less pain, ↑ = increased pain, ↔ = no change, 0 = asymptomatic, ± = unable to assess pain clinically.

§ Patient's subsequent AP was 145 in 10/82.

¶ A new lesion had appeared, uptake in the symptomatic lesion was less intense.

** Studies in which the flow study was particularly helpful in assessing disease activity compared with the bone scan and/or AP levels.

increased on the previous study to show greater disease activity. In four studies the AP levels fell before the flow decreased. In one instance the AP levels rose due to the appearance of a new lesion, whereas the original lesion examined with the flow study had improved. In two studies it was not possible to arrive at a firm conclusion, within the period of evaluation, as to which study was correct, but the AP was assumed to reflect the overall trend of disease activity. Thus hyperemia appeared to correlate well with disease activity in at least 40 of the 47 follow-up studies (85%). If we include the 24 baseline studies, all of which showed hyperemia and increased AP, then exclude the two studies in which no conclusion was reached, we obtain an overall correlation of the flow study with disease activity in 64 of 69 studies (93%).

In Fig. 4 the flow study is compared with the bone scan in the assessment of changes in disease activity during therapy. Of the 47 follow-up studies, 34 showed changes in the same direction and 13 were in disagreement. Three of these discordant studies showed decreases in the degree of uptake on the bone scan that lagged behind prior improvement and stabilization of the flow study. In four patients, the flow study showed increasing local hyperemia with no change on the bone scan; two of these four patients also showed increased AP levels at the same time as the increased hyperemia, although in the other two the AP levels increased only on the subsequent study. In six patients the hyperemia decreased whereas the scan showed no change. Five of these patients also showed a decrease in the AP levels, whereas in the sixth the AP levels rose and the flow study appeared to be falsely negative. In summary, the changes in disease activity were indicated more reliably by the blood-flow study

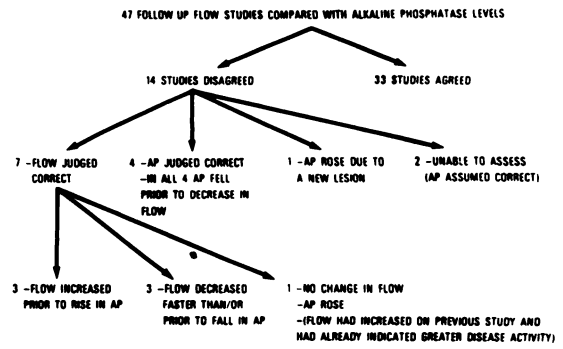

FIG. 3. Flow chart comparing results of 47 follow-up studies with changes in Patients' AP levels. All 24 baseline studies showed hyperemia and increased AP. Further discussion in text.

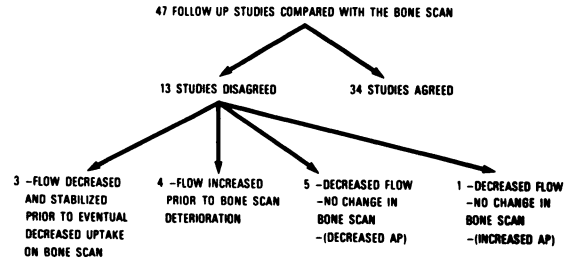

FIG. 4. Flow chart comparing results of 47 follow-up blood-flow studies with bone scans. All 24 baseline studies showed hyperemia and increased uptake on scan. Further discussion in text.

than by the bone scan in 12 of the 13 follow-up studies in which the results disagreed.

Table 2 compares the results of the flow changes with clinical symptoms. Only 42 follow-up studies are included, since three patients (five studies) had complex symptoms that were difficult to assess clinically. The flow study and symptom changes agreed in 29 of 42 follow-up studies (69%). An examination of the 13 discordant studies showed five instances in which symptoms decreased without any change in flow; in three of these the AP levels also fell, in one there was no change in AP, and in one the flow was already normal while symptoms and AP were still diminishing. There were four studies where the flow increased with no change in symptoms; in two the AP also increased, in two the increased flow preceded the rise in AP. These latter two cases gave rise to the two instances with increasing symptoms but no change in flow (in both the flow had already increased on the previous study). Finally, there were two cases where flow decreased with no change in symptoms; in one the AP was also falling, in one the AP rose. All 24 of the baseline studies showed hyperemia of the symptomatic lesions. If we include these 24 baseline studies with the 42 follow-up studies, hyperemia correlated with symptoms in 53 out of 66 studies (80%).

There were seven patients who had a total of nine instances of relapse or deterioration during the study. In eight of these the AP increased, while one showed a definite increase in intensity of uptake on the scan. The flow study showed increased hyperemia in seven of these studies; four at the same time as the change in AP, and three before it. One patient developed a new lesion not assessed by the flow study, and one patient showed decreasing hyperemia from 3+ to 2+ as the AP levels rose. In contrast, the bone scan showed deterioration in only four of these nine relapses.

DISCUSSION

Hyperemia is known to be present in Pagetoid bone. We have shown that this hyperemia and its subsequent response to therapy can readily be demonstrated by the simple addition of a flow study to the routine bone scan. Our results indicate that regressing hyperemia correlates well with the clinical and biochemical response of the disease.

Note that the comparison of AP, scans, and blood flow presented in the Results section is not intended to show that one test is superior to another, but rather to determine whether the flow study of the abnormal bone contributes additional diagnostic information. The degree of uptake on the bone scan was not quantified, a technique that might have increased the sensitivity of the bone scan in detecting changes in disease activity. Instead, serial AP levels were used to monitor disease activity since previous studies have shown that, even with quantification, the bone-scan changes lag behind the AP alterations and show less marked changes (*1*). We likewise confirmed a similar lag in bone-scan changes in our patients as compared with AP fluctuations. In contrast, the flow study tended to follow the changes in AP levels more closely and even preceded the changes in AP in five patients.

Note that while AP levels are very useful clinically, they represent the total body response to the disease and its therapy, and are therefore not ideal. The patient may be improving symptomatically while a new lesion is developing, and thus the AP levels will rise or remain unchanged without reflecting the activity of the initial lesion. Similarly, small focal lesions may be associated with normal AP levels, yet show increased uptake on the scan (*1*). Also, AP is not specific for bone disease and its value may be misleading in the presence of liver disease.

The flow study was also shown to be useful in detecting recurrence or deterioration of disease. It has been demonstrated previously that recurrence of Paget's disease was detected initially by rising AP levels in only 40% of cases whereas the bone scan detected 30% of the recurrences before a change in AP (*3*). From these data it would appear that AP levels are less sensitive in detecting relapse than recovery. In our experience, there were three patients in whom the regional hyperemia

TABLE 2. RELATIONSHIP BETWEEN BLOOD-FLOW STUDY AND SYMPTOMS FOLLOWING THERAPY*

	↑ Symptoms	↓ Symptoms	No change in symptoms
↑ Flow	3	0	4
↓ Flow	–	20	2
No change in flow	2	5	6

* Only 42 follow-up studies are included as three patients had complex symptoms that were difficult to assess clinically.

increased, suggesting deterioration of disease before a rise in AP level occurred.

The flow study is useful not only in following therapy but also in the initial evaluation of the patient's disease. Patients with Paget's may be suffering pain from bone engorgement (with subsequent compression of perivascular nerves) or from one of the complications of Paget's disease, such as stress fracture, bowing, or arthritis. The flow study should distinguish the group of patients with pain secondary to bone engorgement. Assessing bone flow is also very useful if a bone biopsy or surgery is being considered, since a biopsy of very hyperemic Pagetic bone can lead to fatal hemorrage. In fact, one patient was referred to our institution because of excessive bone bleeding following biopsy. Unfortunately, the patient exsanguinated before medical therapy for Paget's disease could be initiated. Two more patients, who had not been treated for Paget's disease, bled profusely during surgery. In contrast, 12 patients who had undergone therapy for Paget's disease and had normal bone-flow studies preoperatively, showed no increased bleeding tendency during surgery. Similar clinical observations of decreased surgical bleeding in treated patients have been made (*6*), but the authors gave no objective assessment of bone vascularity before surgery.

We conclude that the flow study is a very useful adjuvant to the bone scan and AP levels in the management of Paget's disease. This finding is especially relevant because a flow study can be performed in minutes with a bone-seeking nuclide, and thus poses no increased danger or inconvenience to the patient.

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