istration, there will be no added radiation dose to the soft tissues surrounding the port.

Michele Beauvais
Christine Dickinson
Helen Anne D'Alessandro
Vince McCormick
Parul Patel
Helena Balon
Cheryl Culver-Schultz
Darlene Fink-Bennett
William Beaumont Hospital
Royal Oak, Michigan

Disseminated Intravasular Coagulation in Metastatic Prostate Cancer

TO THE EDITOR: The article by Leong et al. (*J Nucl Med* 1994;35: 1662–1664) merits further discussion of the factors to consider in selecting patients who will receive ^{89}Sr therapy for palliation of pain from osseous metastases.

The patient described had pre-existing anemia and thrombocytopenia, which the authors term "low-grade DIC," prior to ^{89}Sr therapy. There is no mention of the active management of the DIC with heparin and blood products in the article. No platelet levels are given between Day 10, when they were 53×10^9 per liter, or Day 31, when the first platelet infusions were given. There is no detail on the progression of the condition. The anemia was actively managed by packed red cell infusions. No evidence, however, is given of the coagulopathy being managed prior to Day 31.

In clinical trials, we have seen no evidence of suppression of the red cell series or of coagulopathy as a result of ^{89}Sr therapy. We do report thrombocytopenia and leukopenia as a result of the marrow suppression by ^{89}Sr. We previously reported two cases of DIC or consumptive coagulopathy (which is typically associated with severe infections, septic shock and advanced malignancy) in patients who were given ^{89}Sr, but this was ascribed to the underlying disease. This represents three known cases in a total of over 12,000 patients treated so far.

Although the authors concede that no causal relationship was established, this article does highlight the need for caution in patients with compromised bone marrow, as mentioned in the package insert and, importantly, emphasizes the need for active specific management of treatable hematological conditions prior to therapy.

Alastair J. Riddell
Amersham International
Buckinghamshire, United Kingdom

Bisphosphonate Effect on Bone Scintigraphy

TO THE EDITOR: We read with interest the article by Pecherstorfer et al. on the effect of bisphosphonate treatment on bone scintigraphy (*1*) and their reply (*3*) to the letter to the editor by Kayano et al. (*2*). Bisphosphonates are powerful inhibitors of osteoclast-mediated bone resorption. They are used not only for the treatment of hypercalcemia, but also for the treatment of Paget's disease and bone metastasis. Among various bisphosphonates, etidronate is the first generation bisphosphonate and has a unique action for bone metabolism; that is, etidronate action prevents bone resorption in a range of small amount but etidronate produces bone resorption above the threshold amount. Etidronate was reported to disturb the bone scintigraphy (*4,5*), but clodronate did not (*1*).

We recently observed that YM-175, a new bisphosphonate 7–10 times as potent as pamidronate, had no significant effect on bone scintigraphy (*6*). We intended to treat the bone metastatic pain with YM-175. Some of the patients were monitored by bone scintigraphy. We administered YM-175 (at a dose of 10 mg once a week for 5 wk intravenously). Bone scintigraphy was performed at pre-, 4- and 8-wk. Quantitative bone scintigraphy was performed according to the methods of Pecherstorfer et al. (*1*). Briefly, a region of interest was placed on bone metastasis and opposite nonmetastatic site, and the ratio of bone metastatic site to nonmetastatic counterpart was calculated. As shown in Table 1, no statistical difference was shown between pre-, 4- and 8-wk bone scintigraphic values. Furthermore, in one patient in whom bone scintigraphy was performed just after administration of YM-175 and no change was shown. Only etidronate appears to interfere with bone scintigraphy.

TABLE 1
Bone Scan Index

Patient no.	Pretreatment	4 wk	8 wk
1	3.47 ± 2.50*	2.83 ± 1.55	3.35 ± 1.58
2	3.10 ± 1.05	3.66 ± 1.79	4.03 ± 2.04
3	3.15 ± 1.79	3.17 ± 1.21	3.30 ± 1.16
4	2.66 ± 0.71	3.15 ± 1.33	2.90 ± 0.73
Average†	3.09 ± 1.58	3.16 ± 1.35	3.30 ± 1.33

*Mean value and 1 s.d. of the ratio of abnormal uptake sites and normal counterparts (5–6 sites in each patient) was shown.
†No statistical significance was detectable by ANOVA.

REFERENCES
1. Pecherstorfer M, Schelling T, Janisch S, et al. Effect of clodronate treatment on bone scintigraphy in metastatic breast cancer. *J Nucl Med* 1993;34:1039–1044.
2. Kayano H, Schimizu T, Shishiba Y. The bisphosphonate dilemma [Letter]. *J Nucl Med* 1995;36:705.
3. Pecherstorfer M. The bisphosphonate dilemma [Letter]. *J Nucl Med* 1995;36:705–706.
4. Sandler ED, Parisi MT, Hattner RS. Duration of etidronate effect demonstrated by serial bone scntigraphy. *J Nucl Med* 1991;32:1633–1634.
5. Krasnow AZ, Collier BD, Isitman AT, et al. False-negative bone imaging due to etidronate disodium therapy. *Clin Nucl Med* 1988;13:264–267.
6. Koizumi M, Nomura E, Sekine H, et al. Effect of bisphosphonate treatment on bone scintigraphy in metastatic breast cancer [Abstract]. *J Nucl Med* 1994;35(suppl):P119–P120.

Mitsuru Koizumi
Etsuro Ogata
Cancer Institute Hospital
Tokyo, Japan

Radioiodine Therapy of the Autonomous Thyroid Nodule in Patients with or without Visible Extranodular Activity

TO THE EDITOR: The interesting paper by Clerc et al. (*1*) describes the outcome of 88 patients ~6 yr after radioiodine therapy (intended dose of 80 Gy) for an autonomous thyroid nodule. Forty-nine patients without scintigraphically visible extranodular activity fulfilled the criteria of scintigraphic decompensation, another 39 did not; 9 of 88 patients had nonsuppressed TSH levels (TSH > 0.1 mU/liter or TRH test > 2 mU/liter). Uptake monitoring and calculation of the doses absorbed by the autonomous thyroid nodule and the heterolateral extranodular area (in patients with and without extranodular activity) are beautifully presented. Unfortunately, the effectively measured results are disappointing in that 72 Gy (in case of extranodular activity) or 57 Gy (no extranodular activity) to the nodule are rather low doses to eradicate an autonomous thyroid nodule [a monoclonal growth due to mutations of the TSH receptor genes (*2,3*)], whereas doses of 8.5 Gy or 49 Gy absorbed by the extranodular area are too high to preserve full function. Thus, while late hypothyroidism is not prevented, hardly tolerable rates of therapy failures result.

As compared to our results, based on an internationally established dosimetric approach (*4*), 72 patients treated with 300 Gy to their autono-

mous thyroid nodule (*5*) showed no therapy failure one year after treatment (i.e., no residual hyperthyroidism and no recurrence within 9 yr) against 13.6% and 10% [(*1*), all autonomous thyroid nodules and decompensated autonomous thyroid nodules, respectively]. The incidence of hypothyroidism, due in part to spontaneous involution of thyroid function, even in the absence of therapy (*5*), was comparable under both dosage regimens: 11.9% in Berne against 9.6% in Paris [both 75 mo after treatment; calculation based on an annual cumulative hypothyroidism rate of 1.9% in Berne, see Table 4 in Ref. *5*]. Moreover, no long-term sequelae, such as bone marrow depression, were registered in the Bernese patients up to 9 yr after treatment.

Thus, the authors' objective, "... rapid elimination of hyperthyroidism is desirable ...," validated by their patient survival data, was met more effectively with our higher dose [or with surgery (*5*)]. The statement "... hypothyroidism is a lesser evil compared to failure of treatment ..." is clearly also valid for a higher dose, e.g., 300 Gy, that leads to similar rates of hypothyroidism and cures hyperthyroidism by eradicating its cause (*5*).

What is the physiological justification for uniformly treating autonomous thyroid nodules with a dose of 80 Gy independently of a suppressed or nonsuppressed TSH? Why treat euthyroid autonomous thyroid nodule patients by therapeutic doses of radioiodine without protecting the perinodular tissue by suppressive doses of thyroid hormone?

The life-table estimates for death were 22% at 75 mo (*1*). In Berne, with an expected death rate of 17.5% of the overall age-related population, the estimates for the patients were 20% after 9 yr [radioiodine and surgery together (*5*)]. The average age of the investigated autonomous thyroid nodule patient population was slightly higher in Paris than in Berne (64.5 versus 61.5 yr), as was the age of the patients who died [74 ± 4 yr (*1*), versus 62 ± 10 yr (*5*)]. The authors deduce that "... hyperthyroidism and its related complications are responsible for this fatal outcome." To support this statement, some additional information is missing, such as the mortality rate of a control population, matched for age and sex and the number of residual "supraventricular arythmias ... and left ventricular hypertropies" after radioiodine therapy as causes of death.

The authors treated "... single hot nodules ..." only, but in some cases postulate a transition into multifocal functional autonomy under therapeutic doses of ^{131}I: "... autonomous millimetric nodules ... often imaged with ... and sonography. ..." Doesn't sonography image and measure morphologic changes and no more? A detailed case report would have been helpful, particularly because we (*6*) and others (*7*) have been unable to substantiate a spontaneous evolution from an autonomous thyroid nodule to multifocal functional autonomy, despite interesting hypotheses based on in vitro experimentation concerning such a development.

Antithyroid antibodies were determined and related to some unclear causative effect on the late outcome after radioiodine therapy, but the titers were not documented. Did the authors register secondary basedowification?

The final remark in the abstract which recommends administering amounts of radioactivity as fixed doses does not conform to standard terminology in nuclear medicine and could thus be misunderstood. Moreover, the systematic, individual calculation of the administered activity is a minimal but very useful expense in this context.

Treatment of autonomous thyroid nodule with radioiodine is reliable, successful and rather predictable in its outcome if appropriate precautions are taken (*4,5*). The "recommendations for standard protocols on therapy with radioiodine in nonmalignant diseases of the thyroid" (*4*), which "aim to achieve a general consistency within the nuclear medicine community," were published in 1991. These guidelines, which present adequate definitions and precise dose recommendations, represent a consensus reached after study of many long-term experiences in Continental Europe. These guidelines may not have been followed from 1979 to 1989 but, hopefully, have been applied since.

REFERENCES

1. Clerc J, Dagousset F, Izembart M, et al. Radioiodine therapy of the autonomous thyroid nodule in patients with or without visible extranodular activity. *J Nucl Med* 1995;36:217–223.
2. Parma J, Duprez L, Van Sande J, Cochaux P, Gervy C, Mockel J, Dumont J, Vassart G. Somatic mutations in the thyrotropin receptor gene cause hyperfunctioning thyroid adenomas. *Nature* 1993;365:649–651.
3. Porcellini A, Ciullo I, Laviola L, Amabile G, Fenzi G, Avvedimento VE. Novel mutations of thyrotropin receptor gene in thyroid hyperfunctioning adenomas. Rapid identification by fine needle aspiration biopsy. *J Clin Endocrinol Metab* 1994;79:657–661.
4. EANM-taskgroup on therapeutic use of radioidotopes. Recommendations for standard protocols on therapy with radioiodine in non-malignant disease of the thyroid. *Eur J Nucl Med* 1991;18:11–13.
5. Kinser JA, Rösler H, Furrer T, Grütter D, Zimmermann H. Nonimmunogenic hyperthyroidism: cumulative hypothyroidism incidence after radioiodine and surgical treatment. *J Nucl Med* 1989;30:1960–1965.
6. Als C, Listewnik M, Rösler H, Bartkowiak E. Immunogenic and non-immunogenic hyperthyroidism: recent trends in pre-alpine Switzerland and coastal Poland. *Nucl Med* 1995;34:92–99.
7. Wiener JD. On the natural history of Plummer's disease. *Clin Nucl Med* 1979;4:181–190.

Claudine Als
Helmuth Rösler
Jane A. Kinser
University of Berne
Berne, Switzerland

REPLY: As usual, when ^{131}I therapy is used for thyrotoxicosis, the question is to know whether there is a best intended absorbed dose and, correlatively, a best dosing scheme for activity calculation.

The best intended absorbed dose level remains controversial because the success of treatment, its cost, convenience for the patient and the limitation of whole-body irradiation must all be considered at the same time. In such a context, it is helpful to dispose of objective dosimetric criteria. Our intended absorbed dose of 80 Gy is indeed low, but was previously used by both us and others with acceptable clinical success rates, especially in a subset of patients diagnosed earlier at younger ages and who presented with low toxic forms (*1,2*). We recommended the higher intended absorbed dose (130–150 Gy) for other patients. An intended absorbed dose of 300 Gy or more will obviously cure patients but at the cost of higher individual whole-body irradiation. In addition, a higher intended absorbed dose mainly shortens the time to cure without excessively affecting the percentage of patients cured at one year. Not only does the intended absorbed dose level reflect a medical strategy, which is partly unavoidable due to local habits and legal constraints, but it may be adjusted according to the patients. Indeed, there is no firm evidence that the intrinsic radiosensitivity of AFTN is comparable among individuals. If such evidence were to exist, it is likely that it would be erroneous since AFTN correspond in fact to miscellaneous mutations of the TSH receptor or of the stimulatory Gs protein (*3,4*). Variations in the stable intrathyroidal iodine stores (*5*), histologic variations, the presence of necrosis and of factors affecting the dosimetry at the multicellular level are numerous and not well apprehended. Finally, comparisons between series are difficult, if not impossible, because basic dosimetric data are often missing, and because pathologic definitions vary from one center to another. What is called nonimmunogenic nodular hyperthyroidism corresponds to a variety of diseases ranging from the single toxic AFTN to a series of multinodular toxic goiters which may require higher intended absorbed dose. For example, patients with toxic adenoma may also have multiple nodules, some of which may also be cold (*6*), which is an exclusion criterion in our study. Finally, the physicians in the Berlin task group meeting who recommended higher intended absorbed dose were mainly from Eastern and Central Europe, where single toxic AFTN may be less frequent than multifocal autonomy (*7*).

Until now, little has been done to compare the efficacy of a simple fixed dose to more sophisticated dosing schemes. We clearly showed that the more sophisticated the dosing scheme, the less the resulting coefficient of variation of absorbed dose to the target: 45% with the fixed dose, about 25% with the uptake-based methods and only 13% with Marinelli method.