REPLY: We would like to thank Drs. Hornof and Koblik for their comments, however, we do not agree with their conclusions. The question of the placement of the region of interest (ROI) is relevant. The authors did not provide more extensive images showing that the activity leaving the ROI, in fact, passed through the pyloric sphincter into the small intestine. A review of these images clearly shows that the activity in the gastrointestinal tract, well outside of the stomach, continually increases in relationship to the decrease in the stomach. Future work in this area should include more extensive regional images so that questions concerning redistribution are adequately resolved. Based upon review of this information, we conclude that redistribution is not evident.

Hornof and Koblik are correct in concluding that all four of the initial data points are superimposed at 100% at t = 0, and that t = 0 is the end of the 15-min ingestion period. Although Elashoff et al. (*1*) stated that t = 0 should be the time of beginning of ingestion, we were faced with the practical concern that we did not have completely compliant subjects. That is, the cats, at times, would delay ingesting any food until near the end of the feeding period, and then eat quite rapidly. At times, they would eat at a steady rate throughout the period. We therefore felt that the standardization of the time to the end of the feeding period more accurately reflected the total amount of ingested food. The method of Elashoff et al. sets the fraction remaining at t = 0 to 1.0, i.e., 100%, therefore, apart from standardizing the time to the end of the feeding period to accommodate the feeding characteristics of animals, we feel we have used previously accepted methods of curve normalization and that the error associated with this method is acceptable by published procedures.

Furthermore, their concerns over the statistical conclusions seem to be based upon a misinterpretation of Table 1, which is data for control animals only. These data were provided to show that variability does exist from animal to animal and between control experiments. Our article's Figure 3, comparing untreated to treated animals, is based upon raw data not provided as a table within the paper. The statistical conclusions were based on using each animal as its own control and provides a conservative analysis of effect. Even when all nonresponders at 3 mg/kg were included in the overall analysis, there was statistical significance. We conclude that as seen in a similar clinical trial (*2*) CCK antagonists and in particular, MK-329, accelerates gastric emptying.

REFERENCES

1. Elashoff JD, Reedy TJ, Meyer JH Analysis of gastric emptying data. *Gastroenterology* 1982;83:1306–1312.
2. Meyer B, Beglinger C, Jansen J, et al. Role of cholecystokinin in regulation of gastrointestinal motor functions. *Lancet* 1989;2:12–15.

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The Nuclear Pharmacist's Role in Compounding Radioactive Drugs

TO THE EDITOR: The Nuclear Regulatory Commission (NRC) interim final rule entitled "Authorization to Prepar Radiopharmaceutical Reagent Kits and Elute Radiopharmaceutical Generators; Uses or Radiopharmaceuticals for Therapy" (*1*) continues to disenfranchise nuclear pharmacists from the NRC recognized pool of skilled health care providers.

Nuclear pharmacists are not permitted to compound radioactive drugs except by following the manufacturer's instructions or in cases in which an authorized user-physician directs a specific departure, a precise description of the departure, and a brief description of why the departure from the manufacturer's instructions would obtain medical results not otherwise attainable or would reduce medical risks to particular patients because of their medical condition.

The author(s) of the new regulation erroneously assumes that: (1) the package insert direction for compounding cannot be improved upon by the pharmacist; (2) the manufacturer will file an amended new drug application whenever improved compounding procedures are developed; and (3) the "authorized user-physician" rather than the nuclear pharmacist is the expert in the compounding of radioactive drugs.

The new regulations, as they define the pharmacist's role in the compounding of radioactive drugs, fail to recognize the professional contribution of the pharmacist in the compounding of drugs. The pharmacist is the professional responsible to serve society in the appropriate use of radioactive drugs and serves to achieve optimal therapeutic (diagnostic) outcome (*2*).

Consider the case in which a nuclear physician wishes to prescribe for his patient 10 mCi of technetium-99m-autologous leukocytes for a nuclear imaging study. There is no package insert that describes the compounding procedure for this drug. There are package inserts for some of the radioactive and nonradioactive drug components. How will the physician write the prescription? The regulatory requirement is that the instructions must be precise. The nuclear physician must be intimately familiar with the compounding procedure and must flawlessly transmit the compounding procedure to the nuclear pharmacist. The physician must also transmit a brief statement of why the departure from the manufacturer's instructions would obtain medical results not otherwise attainable or would reduce medical risks to particular patients because of their medical condition.

The regulations should permit physicians to prescribe the radioactive drugs they need for their patients and allow pharmacists to compound those drugs in accordance with the directions from the prescriber and state-of-the-art technology. For example, a nuclear physician should be able to present the following prescription to a nuclear pharmacist:

From: Dr. Sam Jones, Anyhospital, Anywhere, USA 00000.
For: Mr. John J. Patient, Room 402, Anyhospital, Anywhere, USA 000000.
Rx: 10 mCi technetium-labeled autologous leukocytes injection.
Mix and make according to the art.
Sig: Administer intravenously for scintigraphic evaluation of inflammatory process.
Physician signature: _____

This apparently valid prescription would not meet the NRC's requirements. In the prescription displayed above, the physician relies upon the pharmacist to compound a drug that meets the requirements set forth in the prescription.

The radiation protection for the patient should be regulated in the licensure of the physician and the pharmacist to practice their respective professions. The regulations should be amended in order to allow the pharmacist to serve a professional role with respect to compounding radioactive drugs.

The nuclear pharmacist is the best trained health care provider to assume that role.

REFERENCES

1. *Federal Register*. 1990; 55, 34513-34518.
2. The proposed mission of pharmacy. *Am Pharm* 1990; NS 30:36.

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Radioimmune Imaging of Bone Marrow in Patients

TO THE EDITOR: We have read with interest the paper of Duncker et al. (*1*), which caused us to raise some questions and to offer some comments.

Questions

1. With regard to the staging of patients as mentioned in Table 1, does it correspond to initial staging before surgery or to the staging at the time of the bone marrow imaging? Three patients (7, 10, and 16) would indeed have to be Stage IV because of metastasis in other organs (lung and bone, liver, peritoneum, respectively) and eight others on the basis of the bone scan results.

2. Would the authors clarify the notion of "extension" used in Table 1 as well? Do they mean—again— at the initial (clinical) staging before surgery, the anatomopathologic status of the surgically removed axillary nodes ("lympathic nodes") or the classification at the time of bone marrow imaging? The presence of involved lymphatic nodes or local extension would mean in the last case that these patients are relapsing ones?

3. What do the authors mean by "benign bone scan" (as stated for Patients 6, 10, and 23)? Do they mean abnormal bone scan presentations that might be interpreted as non-metastatic? If yes, we cannot agree with Duncker et al. because in breast cancer, as well as in all cancerous diseases, all bone scan abnormalities have to be controlled regardless of their diagnostic interpretation.

4. In their discussion, the authors say that they applied only local treatment in patients where a single metastatic lesion is seen on the bone scan. Do they mean local x-ray therapy? Their therapeutic attitude is somewhat surprising and their conclusion "modification of treatment" only reflects this situation.

5. Do the authors consider that marrow activity at the skull level is normal? In our experience, normal patients without cancerous diseases and without hematopathy (the term being largely understood) may normally present no marrow activity at either the skull level or at the level of the mid-third of the femur. We therefore consider that there is marrow extension if there is clear activity in the skull and in the mid-third of the femur or if we have clear activity up to the distal part of the femur.

Comments

1. Unfortunately, we cannot agree with the authors' comment: ". . . it seems possible that sometimes bone marrow is not affected by these (benign) diseases." Based on our experience, we can say that in some presentations of Paget's disease, fresh fractures and osseous hemangiomas (*2*), appear as cold defects on bone marrow scans and that the differential diagnosis of bone marrow defects remains to be established, since there is hyperactive foci on conventional bone scans. On the other hand, irradiated regions (*3,4*) also appeared as cold defects on marrow scans.

2. Patients with abnormal bone marrow expansion would have to be followed carefully, because they are at risk of relapse; nevertheless, they often remain disease-free for longer intervals than others without marrow expansion (*4*). One possible reason for this situation that was not addressed by the authors is an activated reticuloendothelial status due to micrometastatic disease either in the bone marrow or in other organs as suggested previously on the basis of our results (*4*).

3. The use of monoclonal antibodies for the imaging of the bone marrow is highly questionable mainly as a systematic attitude for screening of bone marrow metastasis. Not only because of the possible development of human antimouse antibodies (a major drawback from a medical point of view) but also for economic reasons. What will be the price of such an imaging agent and its definitive contribution with respect to what can currently be obtained with less expensive products, such as colloids (*2-8*)? The authors do not compare and discuss their results with regard to these facts. We agree that the accumulation of these agents in the liver represents a main drawback. In a review of 77 patients with bone metastasis, however, isolated lesions involving the last thoracic and first lumbar vertebras represented only 6.5% (*2*). We agree that marrow imaging with labeled leukocytes or monoclonal antibodies shows more lesions and gives more impressive pictures than colloidal scans, but their use would really modify the staging of the patients in as much as *only* 6.5% of those with skeletal metastasis. On the other hand, the realization of hepatic SPECT investigations with small-sized colloids (human serum albumin nanocolloids or Sb2S3 colloids) allows the detection of liver metastasis [in 19/53 patients with Stage IV breast carcinomas (*4*)] that cannot be obtained with antibodies. Finally, marrow imaging with antibodies will probably meet the same limitations as marrow scans using colloidal agents. Small (and sometimes large) metastases detected on bone scans that involve the skull, the ribs, and femurs may indeed be missed (*2-5*) regardless of the tracer used (*2,9*).

We agree with the authors that bone marrow imaging is useful in cases of dubious bone scan presentation as well as in cases of clinical suspicion of bone metastasis, as has been previously concluded by several authors (*3-7*). The use of antibodies in such circumstances should be limited in the future to situations where the use of colloidal agents are not