REPLY: We would like to thank Drs. van Beek, Büller and Bounameaux for reemphasizing some of the points of our paper. We agree that D-dimer results, whether determined by latex agglutination or by ELISA, should definitely not be interpreted in a vacuum. To quote ourselves, "Ideally, the D-d latex agglutination assay would be used . . . in addition to clinical evaluation and V/Q scanning." "It should be stressed that a negative D-D latex agglutination assay should never be used to deny further evaluation (e.g., PAG) to a patient for whom the clinical suspicion of PE is high (1)." I would add that this applies to the ELISA assay as well. Stated another way, use D-dimer studies together with clinical signs and symptoms, lung scintigraphy and other commonly used diagnostic tests in formulating a level of clinical suspicion for pulmonary embolus and determining the necessity for further evaluation.

The statement regarding 95% confidence intervals (CI) for sensitivity is less relevant to the point of our paper than is the negative predictive value (NPV). We consider positive results to be indeterminate. Our NPV of 0.97 derived from 28 of 29 D-dimer negative patients found not to have pulmonary embolus results in a 95% CI lower limit of 0.84, very nearly the same as that found in the paper by Bounameaux et al. using ELISA methodology. He found a 0.98 NPV in his study (45 of 46 D-D negative patients were free of embolus) with a 95% CI lower limit of 0.87 despite using softer criteria for final diagnosis of pulmonary embolus (2). The suggestion that clinical management studies should be undertaken which examine the safety of withholding anticoagulation in those patients with negative D-dimer results would be advisable if we were advocating using D-dimer as a sole predictor of pulmonary embolus. However, as we view this test as only one of many factors to be considered in the overall clinical evaluation of patients with suspected embolus, this approach is perhaps more rigorous than is necessary.

On the other hand, we would hope that continuing studies regarding the clinical usefulness of D-dimer, perhaps comparing different manufacturers' latex agglutination kits and ELISA assays in patients with angiographically proven presence or absence of pulmonary embolus, would be performed to further elucidate the role of these tests.

Repeated references are made to a paper by Dr. van Beek et al. It is truly difficult to respond to the data from this paper as it has not yet been published and is therefore not available for our review.

Dr. Franco's experience with C-reactive protein emphasizes the point that D-dimer is but one of a number of laboratory tests which may potentially prove useful in the evaluation of intravascular coagulation, including pulmonary embolism. Some of these assays may prove to be cost-effective screening tools in the proper setting. In at least one of our institutions (University of Nebraska Medical Center) the cost of performing a D-dimer latex agglutination assay is approximately 40% less than that of C-reactive protein, although both are relatively inexpensive.

The practice of medicine has always allowed for the liberal use of experience (clinical judgement) in the interpretation of any diagnostic test. We would be the last to suggest that any test is 100% accurate and should supplant every other factor in making a diagnosis. As always, the patient's welfare is the primary consideration. However, in many instances when the D-dimer latex agglutination or ELISA result is negative and the overall clinical suspicion of pulmonary embolus is low, it may be reasonable not to subject that patient to invasive and expensive procedures.

REFERENCES


Katherine A. Harrison
William D. Haire
Karen P. Holdeman
Glenn V. Dalrymple
University of Nebraska Medical Center
Omaha, Nebraska

Alex A. Pappas
Gary L. Purnell
University of Arkansas for Medical Sciences
Little Rock, Arkansas

Sharon Palmer
Lou M. Fink
John L. McClellan Memorial Medical Center
Little Rock, Arkansas

Wall Dose Estimates

TO THE EDITOR: Several issues in the excellent paper by Breitz et al. (1) merit further comment. Regarding dose to the wall of hollow organs: MIRDSE2, as the authors quite correctly point out, estimates the dose to the wall of a hollow organ from "nonpenetrating" emissions as 0.5 times the average dose to the contents. This has been a convention for some time (2). This dose is meant to estimate the maximum dose that the wall receives, i.e., right at the inner surface of the wall. It is always true that this dose drops off throughout the wall at a rate dependent on the range of the "nonpenetrating" emissions. The photon dose is thought to be fairly uniform across the wall. To calculate the average dose to the wall in the general case is not trivial; therefore the maximum is used as a prospective estimate which is thought to be conservative.

The authors are correct, I think, in trying to estimate the average wall dose when correlation with some biological effects may be expected. In general, however, this is not done because of the complexity of the calculations. In MIRD Pamphlet No. 14 (3), a depth dose from electrons and beta particles was calculated, from which average doses can be obtained. The use of single factors to convert the conventional maximum wall dose to an average dose (as Breitz et al. have done) merits some study. Perhaps members of the MIRD Committee or others in the dosimetry community could comment on this. This could be routinely applied to the bladder, GI tract, gallbladder and heart doses calculated in MIRDSE if this is the most appropriate dose to use for most purposes. Another issue here, however, is whether or not there is always a clean interface between the organ contents (which contain the activity) and the wall (which presumably does not). If there is some "seepage" of activity into the tissues of the wall or nonuniform distribution of activity in folds of the wall, e.g., characterization of this average will be further complicated.

Regarding "tumor-to-whole-body" dose ratios: I have seen this convention often in the evaluation of tumor-specific agents, but I often wince because "whole-body" dose is a misleading number.
for internal dosimetry in most cases, especially for radiolabeled antibody agents. Would "tumor-to-marrow" absorbed doses or some other ratio be more indicative of the efficacy from a dosimetry standpoint?

REFERENCES

Michael Stabin
Radiation Internal Dose Information Center
Oak Ridge, Tennessee

REPLY: I reported tumor-to-whole-body dose ratios as a means of comparing relative cumulative activity of different radiolabeled antibodies in tumors, not as a direct measure of efficacy (1). Whole-body dose is the absorbed dose that is estimated most consistently by all investigators. I agree that whole-body dose does not correlate reliably with any radiobiological effect but the tumor-to-whole-body ratio does seem to be useful for comparing localization of different radiolabeled antibodies.

In my paper I reported the tumor-to-liver, tumor-to-lung and tumor-to-kidney dose ratios. However, derivation of data for these ratios varies regarding exactly how regions of interest are drawn and how background is subtracted. Tumor-to-marrow dose ratios are not an accurate assessment of efficacy, because even if the marrow dose is accurate, the patients' marrow reserve is also important in determining the therapeutic index. Tumor-to-marrow dose ratios seem to be the least valuable as a comparison at this stage, because the methods used to estimate marrow dose are continually changing as we learn more about marrow dosimetry.

Another reason for reporting tumor-to-whole-body dose ratios was to compare them with those derived from theoretical modeling of radiolabeled antibodies (2). These ratios have also been developed in animal models in an attempt to predict clinical results (3).

REFERENCES

Hazel Breitz
Virginia Mason Medical Center
Seattle, Washington

Samarium-153-EDTMP Dosimetry

TO THE EDITOR: In a recent paper, Eary et al. (1) addressed the issue of the biodistribution and dosimetry of samarium-153-EDTMP. I would like to make a few comments about the dosimetry aspects of this article. In particular, I would like to comment on the statement reproduced below:

Radiation dose estimates for soft tissues were similar to those estimated by Logan et al. (2) and Heggie (3), which were human doses scaled from rat biodistribution data. Skeletal doses were several-fold higher, ranging from 20,000 to 32,000 mrad/mCi (5300–8800 Gy/MBq).

First, although the absorbed dose data of Logan et al. (2) is based on the rat model, the dosimetry in my article (3) makes no assumptions about biodistribution. Indeed, I calculated the bone and red marrow absorbed doses with respect to unit activity taken up by the bone surfaces. In that respect, it is not clear whether the bone dosimetry results of Eary et al. (1) refer to administered unit activity or unit activity on the bones. I suspect the former but it is not clear from their Table 4. In the absence of data reflecting the uptake to bone, direct comparison between my data and theirs is difficult. Assuming a bone uptake of 50% of injected dose (in line with data in Eary et al., Table 2), my calculations would suggest values of 0.93 mGy/MBq and 2.43 mGy/MBq for the absorbed dose to the red marrow and endosteal surfaces, respectively. These values are indeed lower, but not severalfold lower, than those estimated by Eary et al. (1). Incidentally, the SI dosimetry values shown in Table 4 and throughout the text of their work have been erroneously converted from traditional units; they are shown as being approximately a factor of a million larger than they should be.

The reason for the absorbed dose discrepancy between their work and my own is undoubtedly due to their adoption of the ICRP model of bone. As previously noted (3), the validity of the ICRP-30 dosimetry model for bone must be questioned on two counts. First, it was developed for radiation protection purposes and not accurate dosimetry. As such, it overestimates the absorbed fractions for electrons to the red bone marrow and the endosteal layer. Second, it uses bone structural data that is at odds with the work of Beddoe et al. (4) and others. Specifically, the adopted model underestimates the area of the endosteal surface layer associated with trabecular bone.

In the context of therapeutic treatment of bone metastases with 153Sm-EDTMP, the success or failure of the treatment hinges on an accurate determination of the absorbed dose to the red bone marrow, since it is the red bone marrow absorbed dose which limits the amount of radioactivity that can be safely administered. In view of this, it would be instructive to use the biodistribution data of Eary et al. (1) with my previously published S-factors (3).

REFERENCES

John C.P. Heggie
St. Vincent's Hospital
Fitzroy, Australia

REPLY: We appreciate Dr. Heggie's (1) comments about our paper on 153Sm distribution and dosimetry. He makes several