interval; instrument(s) used; types of view obtained; information density image-enhancement, etc.

f. For diagnostic imaging procedures a description of all normal and abnormal image findings, including an evaluation of image quality (with reasons, if unacceptable), and interpreter's conclusions.

g. Correlation of image findings with other diagnostic modalities—e.g., radiographs, blood chemistries, biopsies, clinical course, autopsy findings, other nuclear medicine procedures, etc.

h. Overall evaluation of utility in each patient—e.g., "diagnostic," "confirmatory of prior data," "resulted in alteration of therapeutic plan," "resulted in misdiagnosis due to false-positive (or false-negative) result," etc.

i. Adverse reactions—subjective and objective. Include any changes in physical findings, laboratory data, etc. Also, information regarding product defects should be noted, such as size of aggregates, drug deposits in wrong organ (tissue), etc.

E. Considerations in Evaluation, Summarization, and Presentation of Completed Studies

1. Plan for evaluation of the data. In evaluating and comparing diagnostic products the statistical methods for assessing the accuracy and reliability of the diagnostic RDP should be presented in detail. In most cases the objectives of the studies will include the assessment of the sensitivity, specificity, and misclassification rates of RDP's. From a statistical viewpoint these terms are defined as:

Sensitivity—the ability of a test to give a positive finding when the subject tested truly has the disease under study.

Specificity—the ability of a test to give a negative finding when the person tested is free of the disease under study.

Misclassification rates—the frequency of false-negatives and false-positives, which is a function of sensitivity and specificity. Suitable statistical methods should be employed that may assist in the study design—e.g., whether reliability, accuracy, or false-positives/negatives are a function of investigator technique, differences in instrumentation, dosage, etc. In particular, the plan for evaluation should include the allowable statistical risks (Type I and Type II errors) and the precision with which the false-positive, false-negative, and misclassification rates will be estimated.

2. Plan for summarization and presentation of data and findings. In keeping with the study objectives, the summary findings should be presented in sufficient detail to allow judgments to be made concerning whether findings are consistent across relevant subgroups, and the extent to which safety and efficacy of the RDP under study are demonstrated. Such presentation should at least contain:

a. For each study, a separate tabulation of the data and laboratory findings, so that it may be analyzed independently of the other studies.

b. If applicable, a rationale and justification for combining findings from more than one investigator.

c. Displays of findings by relevant subgroups (i.e., sex, severity of condition, dose, imaging equipment, time of test) and by those factors that the protocol designated as being controlled.

d. Displays of all clinical and laboratory findings obtained before and after the RDP is administered and an appropriate statistical evaluation of the changes of the pre- and postadministration findings.

e. A detailed explanation and documentation of the methods of statistical analysis used in the study, along with the appropriate conclusions derived from the analysis.

f. A well-organized presentation of all the pertinent data upon which the statistical analyses and summaries were based.

IV. SPECIAL CONSIDERATIONS FOR THERAPEUTIC RADIOPHARMACEUTIC DRUG PRODUCTS

The section on therapeutic RDP's has been omitted in this publication to save space. This information may be obtained as a part of the HEW Publication No. 77-3044 from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402, at a cost of $.90.

STEVEN M. LARSON
BARRY A. SIEGEL
RALPH G. ROBINSON
Subcommittee of the FDA Radiopharmaceutical Drugs Advisory Committee

FOOTNOTES

* Section III, D, 2 contains guidelines for Phase II and Phase III protocols; much of the material therein will apply also to Phase I studies.

† Type I and Type II errors are terms used in the statistical theory of hypothesis testing. A Type I error is defined as the probability of rejecting the null hypothesis when it is true. A Type II error is the probability of accepting the null hypothesis when it is false. A statistician may be consulted for a more detailed explanation and for assistance in planning of study sample sizes.

Tc-99m Phytate as an Imaging Agent for Lymph Nodes

We read with misgiving the article by Alavi et al. (*1*), noting particularly some contradictory statements. Technetium-99m stannous phytate, the agent that the authors have termed a "unique radiotracer for lymph node imaging," would appear to be uniquely unsuitable for lymph node imaging in view of their own introductory statements indicating high extranodal concentration in liver, spleen, kidneys, and bladder, requiring the additional qualification that "the agent appears suitable for lymph node imaging in areas where the extranodal concentration does not interfere." The poor target-to-background ratio inherent in Tc-99m stannous phytate for lymphoscintigraphy should have induced the authors to restrain their enthusiasm and more carefully review alternate agents.

We have compared the lymphatic uptake and dynamics of Tc-99m stannous phytate and of Tc-99m antimony sulphide colloid, the agent we consider optimum for interstitial lymphoscintigraphy. Following dorsal pedal injection in rabbits and subcostal injection in patients, respectively, the lymphatic images are consistently superior with Tc-99m antimony colloid. The stannous phytate agent yielded inconsistent, poor quality images and showed generally decreased lymph node uptake.

Alavi et al. comment on the small particle size of Tc-99m stannous phytate, but we question whether they actually measured the particle size of this preparation. By electron microscopic analysis, we have determined the particle size distribution of Tc-99m antimony colloid to be log normal, with an optimum between 8–12 nm (*2*). With combined electron microscopic analysis and centrifugation, we found only 8–10% Tc-99m stannous phytate is colloidal in nature, and these particles were approximately 8 nm in size. It is likely that when calcium complexes with phytate in vivo, the resulting colloid may be an aggregate of a rather large

size, since calcium is a strong flocculating ion. On comparison of the liver uptake of Tc-99m stannous phytate and Tc-99m antimony sulphide colloid, the higher liver concentration of the stannous phytate preparation is obvious. This greater liver uptake with the phytate preparation is probably due to the rapid movement of ionic Tc-99m stannous phytate through the lymphatic pathways into the vascular channels with the consequent formation of colloid calcium-complexed Tc-99m stannous phytate, which is then extracted by the liver. In addition, ionic stannous phytate may diffuse from the injection site across the tissues into the blood and at this point also form calcium complexes. Though there may be some colloid formation at the injection site, our hypothesis is supported by early visualization of the liver in rabbit scintigrams and the high background activity noted on scintigraphy during the first hour by Alavi and colleagues. Using the rabbit animal model and quantitated body and node uptake, we have been able to compare radiocolloids for lymphoscintigraphy and predict uptake characteristics in humans.

In reference to the work of Ege (*3*), using Tc-99m antimony sulphide colloid in internal mammary lymphoscintigraphy, Alavi et al. comment on the variable clearance of this preparation from the injection site. These absorption data were taken in patients, some with diseased lymphatics, following interstitial subcostal injection. It must be appreciated that the uptake of radiocolloid varies with the animal model studied, the injection site, and the state of the lymphatics.

There are considerable experimental and clinical data available to suggest that interstitially injected Tc-99m antimony sulphide colloid has unique features that may not be simulated by Tc-99m stannous phytate, despite apparent similarities (personal communication, W. Kaplan; our unpublished data). Unless such limitations are recognized, the substitution of Tc-99m stannous phytate for Tc-99m antimony sulphide colloid may jeopardize the quality and accuracy of the lymphoscintigraphic procedure.

GUNES N. EGE
ANN WARBICK
The Princess Margaret Hospital
Toronto, Canada

REFERENCES

1. ALAVI A, STAUM MM, SHESOL BF, et al: Technetium-99m phytate as an imaging agent for lymph nodes. *J Nucl Med* 19: 422–426, 1978

2. WARBICK A, EGE GN, HENKELMAN G, et al: An evaluation of radiocolloid sizing techniques. *J Nucl Med* 18: 827–834, 1977

3. EGE GN: Internal mammary lymphoscintigraphy—The rationale, technique, interpretation and clinical application: A review based on 848 cases. *Radiology* 118: 101–107, 1976

Reply

We believe that technetium-99m stannous phytate (*1*) is a unique lymph-node imaging agent because it is different from other radiopharmaceuticals available for lymphoscintigraphy. When this agent is injected as a solution, the particles are formed in vivo in contrast to other agents that are administered as preformed particles.

In our opinion, a significant fraction of the lymph node imaging agent should be cleared from the site of injection, not only to outline all the lymph nodes along its path, but to visualize the liver and the spleen as well. The latter aspect is important to ensure that the particles have traveled through the lymphatic system and entered the systemic circulation, thereby producing a baseline pattern useful in the evaluation of abnormal states. When an agent is used that does not consistently visualize the liver/spleen (*2*), minimal decrease in lymphatic flow due to a diseased node may prevent visualization of lymph nodes proximal and distal to the abnormal site and may result in an overestimation of the extent of the involvement. Thus, the presence of extranodal activity in the liver and the spleen is probably an essential feature rather than a disadvantage with a lymph node imaging technique.

Since the particles are rapidly cleared from the circulation by the liver and the spleen, background activity is transient and minimal. Radioactivity in the liver, spleen, and kidneys in human subjects will not interfere with lymph node imaging, since these organs are usually located away from the nodes to be studied. Therefore, the statement in our paper that "Tc-99m stannous phytate appears to be a suitable agent for lymph node imaging in areas where the extranodal concentration does not interfere" is spplicable only to animals with different anatomy (such as the presence of a large bladder in rabbits) and should not be applied to human studies. An additional advantage of significant clearance of the activity from the site of injection is the reduction of radiation dose to the area of administraiton.

We did not attempt to measure the particle size of calcium stannous phytate. As part of the investigation, however, we injected prepared Tc-99m calcium stannous phytate for lymph node imaging in vitro and found that this preparation resulted in consistently poor lymph node images. In view of these findings we believe that when Tc-99m stannous phytate is used as an imaging agent, in vivo particle size cannot be inferred from in vitro particle measurements. Furthermore, one should bear in mind that the method of preparation of Tc-99m stannous phytate solution may alter its behavior in vivo. It has been shown that when Tc-99m stannous phytate is autoclaved before i.v. injection, its behavior is that of a bone-seeking agent and not as a reticuloendothelial tracer (*3*). We have used Tc-99m stannous phytate preparation (without autoclaving it) both in animals and humans and have obtained satisfactory reticuloendothelial scans (unpublished data). Our images demonstrate that the liver activity becomes apparent only after the lymph nodes are well visualized, indicating that Tc-99m stannous phytate is cleared through the lymphatics and enters the systemic circulation through the lymphatico-venous communications.

We have no experience with Tc-99m antimony sulphide colloid as a lymph-node imaging agent and no access to pertinent data, so it is not possible for us to discuss the superiority of one agent over the other.

In conclusion, more clinical and experimental data are needed before one agent can be proposed as a superior and optimal preparation for lymph node imaging.

ABASS ALAVI
MUNI STAUM
University of Pennsylvania
Philadelphia, Pennsylvania

REFERENCES

1. ALAVI A, STAUM MM, SHESOL BF, et al: Technetium-99m stannous phytate as an imaging agent for lymph nodes. *J Nucl Med* 19: 422–426, 1978

2. EGE GN: Internal mammary lymphoscintigraphy—The rationale, technique, interpretation and clinical application: