Quantitative Gated SPECT

TO THE EDITOR: We write to point out several issues related to the article by Vallejo et al. (*1*) on experimental validation of gated SPECT for determining left ventricular volumes and ejection fraction.

Although one of the stated goals of this article was validating left ventricular ejection fraction (LVEF) and volume determinations by quantitative gated SPECT (QGS) against an MRI standard, Vallejo et al. (*1*) did not quote six separately published articles and abstracts from independent groups showing excellent agreement in humans between QGS and MRI LVEF ($r = 0.85–0.94$), end-diastolic volume ($r = 0.81–0.95$), and end-systolic volume ($r = 0.90–0.97$). Limitations on the number of references allowed in Letters to the Editor prevent us from explicitly quoting every one of these studies (*2–4*), but the reader can find the complete list at http://www.csmc.edu/aim/vallejo. By contrast, Vallejo et al. found poor correlation for LVEF in one canine model.

Additionally, the contention of Vallejo et al. (*1*) that QGS overestimates volumes in the presence of perfusion defects contradicts 12 published findings by 8 independent investigators studying humans. Again, we explicitly quote six of those studies (*5–10*), and the complete list can be found at http://www.csmc.edu/aim/vallejo. Interestingly, these studies are not listed in the bibliography of the article.

It is possible that the discrepancies between the findings of Vallejo et al. (*1*) and those in published QGS articles are caused by the fact that they imaged dogs. Animal studies are, of course, a valuable tool when patient data are unavailable, but they often may not be relevant to clinical practice because of the obvious differences in acquisition, positioning, type and mode of (simulated) occlusion, and degree of overlap from the liver. The last is likely to have been of particular importance in the animal model and may explain many of the problems noted with quantitation in this article. Unfortunately, the omission by Vallejo et al. of the failure rate of QGS in their canine population (both in the totally automatic mode and in the manual mode) makes it difficult to assess the specific problems they may have encountered. Also, no images are shown of studies in which successful and unsuccessful segmentation was attained by QGS.

Finally, it might have been appropriate to disclose that at least one of the authors and one of the consultants acknowledged in the article by Vallejo et al. (*1*) are involved in the development of a commercially available software package for the quantification of ejection fraction, wall motion, and wall thickening from gated SPECT images. The software, distributed under the name Wackers–Liu CQ (Eclipse Systems, Branford, CT), has been licensed to several nuclear medicine companies. It competes directly with QGS, the Cedars–Sinai (Los Angeles, CA) software tested in the article.

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REPLY: We appreciate Germano and Berman's interest in our recent publication (*1*), which evaluated their commercially available software program (QGS) for evaluation of gated SPECT in experimental models. They are correct in stating that one of our three aims was to compare the accuracy of QGS for estimation of left ventricular end-diastolic (ED) and end-systolic (ES) volume in our experimental model with that derived using a true three-dimensional analysis of MR images. We also explored the effect of a perfusion defect on this relationship. Admittedly, we put their algorithm to a real test by analyzing a group of hearts with large, dense anteroapical perfusion defects. However, this type of anteroapical defect is often seen in patients after acute anterior myocardial infarction. Obviously, all experimental animal models have strengths and weaknesses. One potential weakness of our study was that the position of the dog heart in relation to the liver was slightly different from that in humans. The healthy dog heart may also be slightly smaller than the average human heart. This potential limitation was stated in our article. However, coronary occlusion in the dog generally causes immediate left ventricular dilatation. The average QGS ES volume we observed in our dogs (group I, without defects: 24 ± 3 mL; group II, with defect: 41 ± 5 mL) was similar to the ES volumes (males: 37.4 ± 13.7 mL; females: 21 ± 11 mL) reported by Kang et al. (*2*) in patients using QGS. This study was referenced in our article.

Germano and Berman brought to the reader's attention six additional references (three abstracts, three manscripts) comparing QGS volumes with MR-derived volumes. All but two of the references were published after submission of our article in Feb-

ruary 1999. The two references published before submission of our article (*3*,*4*) represent the same study; the former is the abstact and the latter is the article. This study did not evaluate true three-dimensional volume from MR images but simply applied Simpson's rule to short- and long-axis dimensions derived from MR image sets. This situation represents an important limitation of that study for estimation of true left ventricular volume using MRI. A recent study (*5*) comparing two-dimensional and three-dimensional echocardiography and MRI suggested that performing true three-dimensional analysis of left ventricular volume is more important than the method by which the data are derived. Only one of the cited studies (*6*) computed true three-dimensional volume using MRI. Although each of the clinical studies cited by Germano and Berman showed a reasonable correlation between QGS and MR-derived volumes, all of the studies revealed a large SEE, ranging from 7 to 29 mL. This result represents a significant error, considering the average left ventricular volumes.

Germano and Berman also cited 11 additional clinical studies supporting the accuracy of QGS for estimation of left ventricular volume in the presence of a perfusion defect. Again, 6 of the 11 cited studies were published only in abstract form. All of the studies involved relatively small numbers of patients (population sizes, 20–72 patients; average, 43 patients). These studies compared QGS with a host of other methods, including echocardiography, MRI, equilibrium radionuclide blood-pool imaging, and radionuclide first-pass imaging. Most of these studies focused on the comparison of ejection fraction and not volumes. These clinical studies showed inconsistent differences in ED and ES volumes. None of these referenced studies specifically addressed the issue of perfusion defect size in relation to calculation of ventricular volumes.

Our group recently evaluated QGS in 400 unselected patients for estimation of ejection fraction in comparison with radionuclide first-pass imaging (*7*). The correlation of left ventricular ejection fraction (LVEF) derived using QGS and first-pass imaging was only fair ($r = 0.66$, SEE = 12%). The automated program failed in 9% of the studies. When the fully automated program worked, the correlation was better ($r = 0.74$); however, the SEE remained high (SEE = 10%). In this large clinical study, we observed a better correlation for high-count images ($r = 0.81$, SEE = 9%) than for low-count images ($r = 0.61$, SEE = 11%). This observation was similar to our experimental canine study. As expected, we observed a better correlation of QGS and first-pass radionuclide angiography in very large hearts, with ED volumes > 104 mL. We also evaluated the effect of quantitative perfusion defect size on estimation of ejection fraction. Unlike the experimental study, in our clinical study we observed a better correlation of first-pass and QGS LVEF in patients with the largest defects. However, these patients also had the largest left ventricular sizes, making it difficult to separate the potentially opposing effects of myocardial perfusion defect size and left ventricular size. In any event, we would not necessarily expect to see the same differences between QGS and MRI and other imaging modalities. In fact, the studies referenced by Germano and Berman using MRI showed conflicting results regarding over- and underestimation of volumes.

As stated on page 877, paragraph 4, of our article (*1*), the QGS program failed in 21% of our canine images, which was more frequently than observed in our clinical study. This failure was generally associated with adjacent background activity. Our original submission included a figure of canine images obtained 15 and 45 min after injection of a radiotracer. We were asked to remove the figure from our article by the editor to reduce the number of figures. This figure showed the excellent image quality of our canine studies and visually acceptable QGS-defined endocardial and epicardial contours, using the fully automated program. In this example, serial images obtained only 30 min apart yielded significantly different LVEFs (15 min: LVEF = 41%; 45 min: LVEF = 52%). We found this particular observation quite troubling.

When our article was accepted for publication in August 1999, we did not feel that a potential conflict of interest existed for any of the authors. In August 1999, our group did enter into an agreement with a vendor (Eclipse Systems, Branford, CT) to commercialize our software (Wackers–Liu CQ) for quantification of static SPECT myocardial perfusion images. We receive royalties for our program for quantitative analysis of static SPECT images. However, when we entered into this agreement, our program did not include an algorithm for calculation of LVEF or left ventricular volume. In January 2000, well after acceptance of our revised article, we began development of a program for the calculation of left ventricular volume and LVEF. These programs remain under development and testing and currently await Food and Drug Administration approval. We plan to put our own program, as well as the other available programs for analysis of gated SPECT, through the same rigorous testing.

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Nuclear Translocation of Somatostatin Analogs

TO THE EDITOR: We read with great interest the recent article by Hornick et al. (*1*) on the subcellular distribution of ^{111}In- and ^{125}I-labeled somatostatin analogs. We applaud the authors for addressing the important question of where radiolabeled soma-

tostatin analogs localize inside tumor cells, because there is considerable clinical interest in using somatostatin analogs labeled with Auger and conversion electron emitters as antitumor agents. We believe it is crucial to determine whether these compounds or their radiolabeled metabolites gain access to the nucleus. However, we find several inconsistencies in the data and have significant reservations regarding the authors' conclusion.

The authors suggested that radiolabeled somatostatin analogs were delivered intact to the nucleus. This conclusion is difficult to reconcile with other studies indicating that ^{111}In-pentetreotide, ^{125}I-[Tyr^{11}]-somatostatin, and other somatostatin analogs are degraded after internalization. Viguerie et al. (*2*) previously showed that ^{125}I-[Tyr^{11}]-somatostatin was rapidly degraded by pancreatic acini, and the radiolabeled metabolite was thought to represent monoiodotyrosine. On the basis of a series of subcellular fractionation and metabolism studies, we previously proposed that ^{111}In-pentetreotide was delivered to tumor cell lysosomes in a tumor-bearing rat model and degraded (*3*). Two separate studies also determined that ^{111}In-pentetreotide is metabolized to ^{111}In-diethylenetriaminepentaacetic acid-D-Phe in vivo (*4*,*5*). We are uncertain why these data were not addressed by Hornick et al. (*1*). Although it is possible that different cell types may metabolize radiolabeled somatostatin analogs differently or may even deliver them to different compartments, we doubt that this is the explanation for the discrepant results.

Nuclei and lysosomes are dense intracellular compartments, and they often copurify during subcellular fractionation. It is crucial to realize that the fractionation scheme used by Hornick et al. (*1*) did not separate lysosomes from nuclei, because Figure 1 shows that both DNA and *N*-acetyl-β-glucosaminidase are concentrated in fractions 12–15. Thus, the subcellular fractionation data (Figs. 5 and 7) with ^{111}In-pentetreotide could simply represent accumulation of the radiolabel within lysosomes. The data in Figure 9 concerning copurification of DNA and radiolabeled somatostatin analogs lack key controls. If ^{111}In-pentetreotide does bind specifically to DNA, it should be straightforward to prove that the binding is specific and saturable. It is crucial to recognize that copurification of DNA with a radiolabeled somatostatin analog does not prove colocalization in the nucleus or specific binding as a receptor–ligand pair.

The subcellular fractionation data with ^{125}I-WOC 4a shown in Figure 4 suffer from the limitations discussed above. However, the finding that 65% of the radiolabel sedimented with nuclei under conditions where >90% of lysosomal enzymes were recovered in the supernatant deserves further consideration because this is the best evidence that the radiolabel was delivered to the nucleus. Important controls would include fractionation after cell surface binding at 4°C. It would also be important to determine the kinetics of nuclear translocation at 37°C and whether this translocation could be inhibited by agents that disassemble the cytoskeleton. Another concern about the experiment is whether the DNA extracting process destroyed the lysosomal membrane, because the preparation kit for genomic tissue DNA isolation contains surfactant. As a result, the radiolabels in the lysosomes may have been released and then may have migrated to the DNA fractions. No control experiments were reported that confirmed that the lysosomes remained intact during the DNA extraction process.

Additional questions include the following:

- If 44% of the ^{111}In-pentetreotide counts can still be stripped from the cell surface by acid washing at 24 h (data from Table 1, 20,220 cpm stripped/45,569 total cpm), why is there not a corresponding radioactivity peak that copurifies with the plasma membrane marker 5′nucleotidase in Figure 4C?
- Figure 1 shows that the DNA is concentrated in fractions 13 and 14; however, a 24-h incubation in tumor cells with either ^{125}I-WOC 4a or ^{111}In-pentetreotide (Figs. 4C and 5C) shows that the radioactivity is concentrated in fractions that contain less dense subcellular material (fractions 12 and 13 for ^{125}I-WOC 4a and fractions 11 and 12 for ^{111}In-pentetreotide). This discrepancy persists when the marker beads (triangular symbols) are used as internal controls. In Figure 1, DNA copurifies with the heaviest marker beads, but in Figure 4C, this internal standard is found in fraction 15. In Figure 5C, this marker is found in fraction 12.
- Why should ^{111}In-pentetreotide distribute nearly uniformly in a Percoll (Sigma Chemical Co., St. Louis, MO) gradient (Fig. 8)? Soluble proteins and peptides should be found at the very top of the gradient.

In summary, the authors should be commended for carrying out research that addresses an important question for the success of the future development of targeted radiotherapy agents. However, we would like to raise awareness of alternative interpretations of their data.

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REPLY: We appreciate the careful critique of our recently published article (*1*) by Duncan et al. and would like to respond to their insightful comments. They suggested that our results showing intact radiolabeled somatostatin analogs in the nucleus of cells are difficult to reconcile with those of Viguerie et al. (*2*), who showed that ^{125}I-[Tyr^{11}]-somatostatin was rapidly degraded by pancreatic acini. Viguerie et al. did show degradation of a labeled somatostatin with a short biologic half-life to iodotyrosine "at the plasma membrane level," whereas "intracellular and membrane-bound radioactivity was mainly intact ^{125}I-[Tyr^{11}]-somatostatin." However, these same authors found that 96.3% of the label in the cell interior was intact and that a substantial unmetabolized portion was localized in a nuclear fraction. This result is similar to our

findings. However, Viguerie et al. did not specifically isolate lysosomes, although the centrifugal spin used to pellet their nuclear fraction (1500$g \times 12$ min) would not be expected to effectively pellet lysosomes from the cell homogenate. In response to the observation that "rapid intracellular degradation of iodinated proteins and peptides. . .has been shown by other groups," we would like to point out that a substantial body of research has also shown that numerous radiolabeled peptides and growth factors, including insulin, prolactin, growth hormone, epidermal growth factor, fibroblast growth factor 2, and nerve growth factor are internalized by endocytosis, translocated to the cytoplasm, and accumulate in the nucleus often bound to chromatin (*3*,*4*).

We agree that it is important to realize that our fractionation scheme does not separate lysosomes from nuclei. This is why we refer to the peak in the dense portion of the gradient as "nuclear lysosomal." This is also why we performed the experiment shown in Figure 6, contrasting the distribution of radioactivity in the gradients with and without nuclei present. These experiments showed that two thirds of the label in the nuclear-lysosomal peak are concentrated in the nuclei.

It is also true, as Duncan et al. suggested, that the DNA extraction procedure would likely lyse the lysosomal membrane, possibly resulting in the release of the radiolabel. We did not control for this possibility, other than by performing the short-term experiment in which the radiolabel was added to the cell homogenate before gradient centrifugation (Fig. 9). This experiment showed no binding to the nuclear fraction.

With respect to questions about the DNA peak and internal consistency, we believe that an internal standard such as density marker beads is essential when comparing gradients with each other. In our study, DNA in Figure 1 is concentrated in the fractions corresponding to the heaviest marker beads and in the one fraction beyond that. In Figures 5B and C and 6, the peaks that show the presence of label in the nucleus correspond exactly to the heaviest marker beads, whereas in Figure 7, the highest peak is in the fraction just beyond that. In all these cases, the highest density marker bead appears in either fraction 12 or fraction 13, whereas in Figure 4C, although our dense peak again comes out in fractions 12 and 13, the highest density marker appears in fraction 15. We believe that the density beads were too dry in this experiment because the density profile does not resemble any of the other experiments. Furthermore, the results of Duncan et al. are sorted by fraction number rather than by density, making comparisons of the two techniques unreliable.

Finally, Duncan et al. compared our work with theirs (*5*) and suggested that the predominant target for the intracellular localization of the ^{111}In-diethylenetriamine pentaacetic acid–octreotide (^{111}In-DTPA-octreotide) is the lysosome. In contrast to our studies, these authors injected ^{111}In-DTPA-octreotide into tumor-bearing animals and harvested liver, kidney, pancreas, and pancreatic tumors, both 1 h and 20 h after injection. This protocol is very different from our studies, in which human neuroblastoma cells were cultured in a medium that provided a continuous exposure to radioligand for protracted periods. At the cellular level, the difference between these studies is a comparison of a bolus injection with a constant infusion. Our system provides for a protracted exposure of cells to a high environmental concentration of radioligand, exposing cells to a constant receptor-dependent "pressure" to internalize. It can easily be seen that the internal routing of ligand may well be different under these two experimental conditions. Clearly, these two experimental systems cannot be directly compared.

In their studies, Duncan et al. noted that they studied lysosomes in their gradients but made no effort to study the translocation of ligand to a potential nuclear target. However, with respect to our study, these authors have brought up many worthwhile questions. It is unknown what fraction of the nuclear radioligand remains intact after prolonged exposure of somatostatin receptor subtype 2 (sst-2) expressing cells to constant levels of radioligand. Preliminary studies from our laboratory indicate that some of the radioactivity that is progressively translocated to the nucleus is not intact peptide; however, these same studies indicate that up to 30% of the nuclear-associated radioligand is intact ^{111}In-DTPA-octreotide. Clearly, the continuous exposure of receptor-bearing cells to a peptide translocates unmetabolized peptide into the cell in a continuous fashion. In conclusion, it appears that prolonged exposure of sst-2–expressing cells to a constant level of peptide promotes internalization and may provide a significant benefit for the cytotoxic effect of Auger-emitting radiopeptides regardless of their ultimate intracellular destination.

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What Is the Best Strategy to Treat and Study Patients After Near-Total Thyroidectomy?

TO THE EDITOR: We read the interesting article by Cholewinski et al. (*1*) about the absence of thyroid stunning after a diagnostic dose of 185 MBq ^{131}I. Their conclusion was that there is no thyroid stunning when the ablative dose is administered 72 h after the diagnostic dose (185 MBq). The authors reported their experience in 122 patients referred for radioiodine ablation of thyroid remnants or metastases. All of their patients had some residual thyroid tissue in the neck, and all received 1,110–7,400 MBq ^{131}I (104 of the patients received 5,550 MBq). Seventeen patients had functioning metastases. Our experience is similar to that of the authors, but our diagnostic and treatment strategy is different. Because all (or almost all) of the near-total thyroidectomy patients have residual tissue in the neck, we avoid the diagnostic whole-body scanning and replace it with the therapeutic

dose and whole-body scanning after 3–5 d. According to a clinical risk stratification (i.e., age, tumor size, extension, metastasis, and histology), the therapeutic dose is between 3,700 and 7,400 MBq. We add a 24-h thyroid uptake with a tracer dose (0.37–1.85 MBq) and a thyroid scan with ^{99m}Tc-pertechnetate. Usually, the studies confirm the existence of residual tissue in the neck, and we use this result to convince endocrinologists that they do not need a previous diagnostic whole-body scan. The iodine uptake gives us quantitative information, and the scan provides information about the localization and distribution of the functioning tissue.

Patients with palpable cervical lymphadenopathies, very high clinical risk, or suspected metastases are studied by whole-body scanning with ^{99m}Tc-sestamibi. This strategy implies lower cost (no diagnostic whole-body scanning), no thyroid stunning risk, and fewer delays to treatment (if we need to wait for a whole-body diagnostic scan to order the therapeutic dose). Occasionally, whole-body posttherapeutic scanning shows nonpredicted metastases. We believe that the routine ablative dose of 3,700 MBq (instead of 1,110 MBq) helps to obtain a therapeutic dose, even for patients with metastases. A potential disadvantage may be the use of an ablative dose in a patient without any residual tissue or metastases. This circumstance is very infrequent, as shown by Cholewinski et al. (*1*) and our personal experience.

In summary, in the first treatment after near-total thyroidectomy, we propose examination of the patient, correlation with surgical and anatomicopathologic information, risk stratification, administration of a therapeutic dose, and whole-body posttherapeutic scanning. The diagnostic ^{131}I dose (37, 111, 185, or 370 MBq) and whole-body diagnostic scanning would be omitted.

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REPLY: We thank Sarmiento et al. for their letter supporting our conclusion (*1*) of the absence of stunning after 185-MGq doses of ^{131}I, based on their experience. We note with interest their different diagnostic and treatment strategies and respond as follows to the points raised.

Although the majority of patients receive a fairly standard dose, the whole-body scan does play an important role in increasing or decreasing the dose to any individual patient for any given episode. We feel that the ability to calculate a dose based on tangible evidence is an important part of our management strategy.

Although Sarmiento et al. propose avoiding diagnostic whole-body scanning with ^{131}I, they usually obtain similar information with an uptake and ^{99m}Tc-pertechnetate scan or, if required, with ^{99m}Tc-sestamibi. We agree that any study intended to confirm the presence and assess the amount of residual tissue is valuable in gaining the cooperation of both the referring physician and the patient. However, the diagnostic whole-body scan with 185 MBq ^{131}I compares favorably with these agents in terms of cost, stunning risk, and treatment delay. The cost of 185 MBq ^{131}I, with our strategy of delivery well in advance of the calibration date and dispensing in our own radiopharmacy, is approximately (\$380/10,360 MBq) $\times$ 185 MBq = \$6.79 on the day of delivery and thus rises only to a range of \$10–\$15 before the shipment is used up. This result compares favorably with the cost of the ^{131}I uptake capsule (\$12), in addition to the cost of 185 MBq pertechnetate (approximately \$1–\$3) and a dose of ^{99m}Tc-sestamibi (\$90). Of course, these estimates do not take into account the costs of imaging, but we can assume them to be fairly similar. Regarding the risk factor, we have shown that stunning is not a risk using our strategy. This is a point with which Sarmiento et al. already agree, in light of their experience. Finally, the delay of 72 h introduced by our management enables us to complete the paperwork with the insurance companies and gives patients time to arrange their home and work matters without any clinical detriment.

In addition, our strategy allows us to sit down with patients and their families to show them exactly what the issues are and why the treatment is required. There is no issue as to whether the lack of pertechnetate uptake but positive ^{131}I uptake indicates a residual tumor. If there is abnormal ^{131}I uptake on a whole-body scan, treatment is initiated. The development of rapport is, in our opinion, extremely valuable in establishing a strong clinical relationship that will endure through all future follow-up visits. Also, achieving a negative scan at some point after the necessary episodes of therapy and being able to show a negative scan in comparison with prior scans can do wonders for the patient's morale and ensure further regular follow-up.

Recently, we have added the monitoring of thyroglobulin levels and the use of recombinant thyroid-stimulating hormone to our protocol as well, to further streamline management by offering suitable patients the option of not becoming hypothyroid for follow-up whole-body scanning.

If a decision is reached, usually in a later stage of follow-up, to go after residual tissue surgically (i.e., small amount, low uptake [$<$1%]), the ^{131}I remaining may be used with a probe system to assist the surgeon in localization in a reoperated neck.

In conclusion, we are grateful to Sarmiento et al. for confirming the lack of stunning in their experience and also for indicating that some sort of tangible information before ^{131}I treatment in the form of a scan is useful. In view of the above, we feel that our protocol works well for our patient population, including the first postoperative whole-body scan. We agree that the necessity of this first scan needs to be determined by each center in view of issues related to radiopharmaceutical supply, attitude of the referring physician, and desire of the patient.

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A Combined PET/CT Scanner: The Choices

TO THE EDITOR: I would like to comment on the viewpoint expressed by Akhurst and Chisin (*1*) with respect to Wagner's Newsline article on fused image tomography (*2*). As a member of the team that designed and built a prototype combined PET and CT scanner (*3*), I would like to share some of the thinking that led to our choice of clinical PET and clinical CT scanners for the first hybrid device.

Akhurst and Chisin (*1*) asked if the quality of the CT images should be maximized and, in particular, if the anatomic image should be a clinical-quality CT image. As they pointed out, such a hybrid device provides anatomic images, low-noise transmission scans for attenuation correction of the PET data, and fused functional and anatomic images. They highlighted several drawbacks in offering clinical-quality CT with a hybrid design. These included the difficulty of matching a CT image acquired during a breath-hold to a PET image acquired with the patient breathing normally, the need for subcentimeter registration to answer questions about the exact localization of the PET tracer, artifacts caused by respiratory and cardiac motion that result in incorrect quantitation and image fusion, the requirement for a power injector to administer contrast material, the need to provide a PET technologist trained to perform clinical CT protocols, the demand on the nuclear medicine physician to be trained to recognize anatomic details, and reimbursement issues associated with whether the CT image can be considered the clinical CT image for the patient. They thus suggested that such a hybrid device should combine PET with improved anatomic imaging—improved, that is, compared with current PET transmission scans.

Our prototype design was not foreseen as a PET device with improved anatomic imaging. Instead, we chose to provide full, clinical-quality anatomic images from helical CT, aligned with functional PET images. It is, of course, well known that anatomic and functional images can be acquired on different scanners and aligned retrospectively using software procedures. However, such procedures are not widely used for studies outside the brain because of the technical and logistic difficulties of implementation on a routine basis, even though the advantages of having the CT images available for the interpretation of clinical PET images is well documented (*4*). The goal of the PET/CT prototype was to overcome some of the technical and logistic difficulties associated with the software approaches by acquiring both clinical-quality anatomic images and clinical-quality functional images in a single scanning session. We feel that such a device will encourage involvement in molecular imaging of other medical specialists such as radiologists, surgeons, and oncologists—specialists who are more familiar with high-resolution anatomic imaging than with the tracer techniques of functional imaging.

The prototype combined PET/CT scanner was designed and built as a collaboration between the University of Pittsburgh and CTI PET Systems, Inc. (Knoxville, TN). The device has been installed in the University of Pittsburgh PET facility since June 1998, occupying a room equipped for the operation of a CT scanner. PET technologists certified in nuclear medicine and with additional training in CT protocols operate the PET/CT scanner, and all scanning is performed with the authorization of the University of Pittsburgh Institutional Review Board governing the use of an investigational device for human studies. A power injector is provided for the administration of intravenous contrast agents during the helical CT scanning, and a radiologist is present during contrast administration. Since the scanner became operational in June 1998, more than 200 patients have been scanned, primarily for oncologic indications. All studies are corrected for attenuation using CT-based attenuation correction factors scaled to account for the difference in energy (*5*). The studies are read jointly by a radiologist board certified in nuclear medicine and PET-trained nuclear medicine physicians. Additional consultation is available with radiologists specializing in CT of the particular region of the body under examination (e.g., head and neck, thorax, or abdomen).

The ability to perform essentially noiseless transmission scanning and CT-based scatter and attenuation correction is seen as an additional advantage and not as the primary motivation for such a device. Nevertheless, Akhurst and Chisin (*1*) made a good point concerning the alignment of PET and CT images acquired under different breathing conditions. In this situation, a potential mismatch may compromise the accuracy of both the image fusion and the CT-based attenuation correction factors. Such a mismatch is maximized in the thorax, particularly for the anterior part of the chest wall. Strategies to minimize the mismatch include allowing shallow breathing during both CT and PET scanning, even though the breathing may slightly compromise the diagnostic quality of the CT image. We have conducted several lung studies using this approach, and although some motion artifacts are discernable in the region of the diaphragm and base of the lungs, they generally do not affect the diagnostic quality of the fused image. We have also observed a maximum 5- to 6-mm misalignment of the PET and CT images for tumors in the anterior region of the lungs. Again, such a mismatch does not affect the diagnostic accuracy of the fused image. We have recently begun acquiring CT images with intravenous contrast material for head and neck and oral contrast material for abdominal studies and have verified that contrast-enhanced CT images can also be used for attenuation correction of the PET data. Nevertheless, further validation of CT-based attenuation correction will undoubtedly occur when combined PET/CT scanners become more widely available.

An interesting aspect of the availability of clinical-quality CT images has been the direct participation of radiologists, who raise specific questions related to the location and extent of the FDG uptake and the involvement of adjacent anatomic structures. To answer such questions, precise anatomic localization of the functional abnormality is required. Even with a combined PET/CT scanner, registration accuracy will potentially be affected by patient movement, lesion location, and other study-dependent factors. Therefore, procedures to monitor the quality of the image alignment on a study-by-study basis will be essential to ensure accurate responses to increasingly specific questions.

As Akhurst and Chisin (*1*) pointed out, good arguments have been made for improving the quality of current PET transmission scans and, at the same time, providing low-resolution anatomic images aligned to functional PET images. However, the prototype PET/CT scanner at the University of Pittsburgh looks beyond that objective to providing radiologists, surgeons, and oncologists the clinical-quality anatomic images with which they are familiar, automatically coregistered with corresponding clinical-quality PET images. Our approach opens up new imaging possibilities and applications and improves a current imaging technology. Admittedly, by potentially crossing existing boundaries, the introduction of such a device into clinical practice will not be simple, straightforward, or rapid. However, if the benefits brought by dual-modality imaging to the management of disease are, as we believe, significant, solutions to issues of technologist training, the availability of nuclear physicians skilled in reading anatomy, and reimbursement will undoubtedly be found. At this early stage in the development of the combined PET/CT scanner, our primary concern has been establishing its role in and contribution to patient care and disease management.

ACKNOWLEDGMENT

This work was supported by National Cancer Institute grant CA65856. David W. Townsend is a consultant for CTI PET Systems, Inc., the company that designed and built the prototype PET/CT scanner.

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Erythema Multiforme Reaction to Sestamibi

TO THE EDITOR: Allergic reactions to radioisotopes are uncommon, but all nuclear physicians need to be aware of possible reactions to radioisotopes in everyday practice. We would like to draw your attention to a previously unreported reaction to ^{99m}Tc-sestamibi experienced by a woman having parathyroid imaging.

^{99m}Tc-sestamibi was prepared and administered according to the manufacturer's guidelines. There was no past history of allergy or dermatologic disorder. Over 48 h, the patient developed an erythematous papulovesicular rash on the trunk, arms, and scalp with target lesions typical of erythema multiforme. A skin biopsy confirmed histologic features consistent with erythema multiforme.

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