tigation, we were unable to detect thiols using Ellman's reagent on a Sandoglobulin IgG purified from ascorbate after treatment. Although the measurement was performed immediately after purification, a possibility exists that the absence of detectable thiols was due to the reformation of antibody disulfides once ascorbate was removed. Therefore, we also measured thiol concentrations without the ascorbate purification by measuring the absorbance at a fixed time after the addition of ascorbate to the antibody and to the cysteine standards. Once again, we were unable to detect thiols. Furthermore, we also used dithiodipyridine as a thiol indicator in place of Ellman's since the former is less sensitive to interference by ascorbate. Again, we were unable to detect thiols in samples of Sandoglobulin IgG treated with ascorbate and even without ascorbate purification. By contrast, we did observe a definite thiol signal in each study in which dithionite was present. Although these are difficult measurements and prone to experimental error, our results have the plausibility of consistency: in each case, a thiol signal was detected with dithionite but not ascorbate. We concluded that treatment of this antibody with ascorbate at a tenfold higher molar ratio to that recommended could not have generated more than about 1%–2% of the possible thiols (the upper limit on the assays), whereas dithionite treatment at fivefold higher concentrations did generate about 1%–5% of the possible thiols. On this basis, we feel that dithionite played a more important role in antibody reduction than did ascorbate.

Our experimental protocols were reproduced as faithfully as possible to those reported and when it was necessary to make changes, they were carefully described. For example, we were unable to achieve good labeling efficiencies unless the dithionite concentration was increased by a factor of five. We went up to a 35,000:1 ascorbate-to-antibody molar ratio (i.e., an increase by a factor of ten) for the thiol measurements to increase the concentration of thiols generated. We prepared ascorbate solution at pH 6 by adding ascorbic acid to solutions of ascorbate rather than the reverse and the dithionite was freshly prepared in nitrogen-purged 0.05 *M* carbonate buffer at pH 11.5 rather than bicarbonate buffer at pH 11.

The pH at a reduction of 5.5–6 measured by Thakur for our conditions contrasts with the pH value of 7.8–9 used in his work and was suggested as possibly generating artifact in our radiolabelings (*3*). Presumably this low pH was a result of adding a tenfold excess of ascorbate. However, we added the excess ascorbate primarily for the thiol measurements; most of the radiolabeling was performed with the lower ascorbate-to-antibody molar ratios. More importantly, elimination of the ascorbate entirely would have maintained the acidity and we observed no difference in labeling efficiency with or without ascorbate.

The yet unpublished studies with FITC and iodoacetate treatment of antibodies are interesting and may shed some light on the mechanism of the ascorbate/dithioinite labeling method (*3*). However, the issue of whether ascorbate is capable of disulfide reduction of antibodies can only be addressed by assaying for thiols after antibody treatment with ascorbate. These studies should be expanded. Meanwhile, useful information on the role of ascorbate could result simply from multiple labeling studies on a variety of different antibodies with and without ascorbate. It is possible that under certain circumstances the role of ascorbate is to stabilize reduced ^{99m}Tc and prevent colloid formation, as suggested by Thakur (*3*).

REFERENCES

1. Hnatowich DJ, Virzi F, Winnard P Jr., et al. Investigations of ascorbate for direct labeling of antibodies with technetium-99m. *J Nucl Med* 1994;35:127–134.
2. Thakur ML, DeFulvia D. Technetium-99m-labeled monoclonal antibodies for immunoscintigraphy. Simplified preparation and evaluation. *J Immunol Method* 1991;137:217–224.
3. Thakur ML. Ascorbate plays a major role in labeling proteins with ^{99m}Tc [Letter]. *J Nucl Med* 1994;35:1566–1567.

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May *Randoms* Evolve into *Scatter*?

TO THE EDITOR: We read with great interest the recent editorial "Something Borrowed, Something Blue" in the January issue of the *Journal* (*1*). However, we were somewhat bewildered when we learned about the intention that "*Randoms* will evolve into *Scatter* to denote a more generic and fundamental phenomenon . . . ." In our opinion, there must be a profound misunderstanding.

We fully agree that scatter is a basic physical phenomenon and "tends to degrade information unless dealt with appropriately." Compton scattering is the predominant interaction mechanism of gamma-quanta from radionuclides with body tissues in nuclear medicine. Most of the scattered photons can be suppressed by using an appropriate energy window, although in practice this may not be sufficient due to the limited energy resolution of the radiation detection devices. Thus, additional techniques to "correct" the measured data for scattered events are mandatory for accurate quantitation of local radiotracer concentrations.

Randoms, or more explicitly, random *coincidences*, on the other hand, are intimately connected to coincidence detection techniques as commonly used in PET. The terms random, chance or accidental coincidences simply denote the fact that two (or more) spatially and temporally independent events have been registered within the resolution time of the coincidence unit. These random coincidences increase rapidly with counting rate, as there is an increasing probability that unrelated events will accidentally produce overlapping timing signals. In principle, random coincidences cannot be distinguished from truly coincident events and will occur even in the absence of true coincidences. The contribution of the randoms to the recorded total coincidence rate, however, can be taken into account on a statistical basis either directly by an additional measurement with an appropriate time delay inserted in either branch of the coincidence unit or, in the case of a twofold coincidence system, by estimating the random coincidence rate from the uncorrelated *singles* input rates and the resolving time of the coincidence device (*2*).

In conclusion, both scatter and randoms do degrade information in PET. In any quantitative study, each of them must carefully be taken into account. The origin of both phenomena, however, is different (fundamental physical process versus coincidence counting technique) and should not be mixed up.

REFERENCES

1. Goldsmith SJ. Something borrowed, something blue [Editorial]. *J Nucl Med* 1994;35:168.
2. Knoll GF. *Radiation detection and measurement*, second edition. New York: Wiley and Sons; 1989:635–639.

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REPLY: I am delighted that the authors read my editorial "Something Borrowed, Something Blue" (*1*) and felt sufficiently moved to correspond to correct a literal misperception. I agree completely with the somewhat more detailed description of the physical phenomena "randoms" and "scatter" as described by Drs. Ostertag and Belleman, but I think that my allusion to these phenomena was correct.

The phenomenon of "randoms" is *limited* to distintegrations characterized by coincident events, whereas "scatter" involves the interaction of gamma photons and matter quite *independent* of count rate regardless of whether they are single or coincident photons. Hence, I characterized "scatter" as a "more generic and fundamental phenomenon" in the *literal* rather than the *physical* sense; that is in terms of the *frequency* with which it is encountered. In this regard, "frequency" is also used in the literal sense.

This correspondence confirms that *degradation* is inherent in the transfer of information as well as energy. This phenomenon needs to be understood by nuclear physicians, scientists and editors.

Stanley J. Goldsmith, Editor-in-Chief,
The Journal of Nuclear Medicine

REFERENCE

1. Goldsmith SJ. Something borrowed, something blue [Editorial]. *J Nucl Med* 1994; 35:168.

Adverse Allergic Reaction to Technetium-99m-Mebrofenin

TO THE EDITOR: Adverse reactions to radiopharmaceuticals are rare, with an estimated annual incidence in the United States of one to six reactions per hundred thousand (*1*). A much higher incidence, between 1/1,000 and 1/10,000 has been reported in the United Kingdom in a 7-yr period between 1977 and 1983 (*2*). In the United States, only two allergic reactions to ^{99m}Tc-DISIDA were described between 1976 and 1981 (*1*). True incidence of adverse reactions to radiopharmaceuticals is speculative since it is difficult to document cause and effect. Intradermal skin testing, however, may correlate well with systemic reactivity and predict and/or confirm allergic response (*3*). The following case strongly suggests an adverse reaction to ^{99m}Tc-mebrofenin.

A 53-yr-old, cholecystectomized, female volunteer underwent a hepatobiliary scintigraphy with ^{99m}Tc-mebrofenin (Cis Biointernational) as part of a clinical trial. Hepatobiliary scintigraphy was to be performed twice in a 1-wk interval. The routine biochemical tests and physical examination of this subject were normal. She was taking no medications but had a history of allergic reactions to penicillin.

Hepatobiliary scintigraphy was performed with 7 mCi of ^{99m}Tc-mebrofenin. Ninety minutes after injection, the subject was asymptomatic. After 1 wk, at the time of the second scheduled imaging session, she was complaining of fatigue, nausea, dizziness, headache, pruritis, flushing and a rash on her face and extremities. These symptoms and signs began 8–12 hr after radiopharmaceutical injection and gradually decreased during the following week. Upon physical examination, a maculo-papuler rash was seen on her face and extremities. An allergic reaction to ^{99m}Tc-mebrofenin was suspected prior to the second hepatobiliary scintigraphy session. An intradermal skin test was performed by injecting 0.02 ml of ^{99m}Tc-mebrofenin intradermal with a tuberculin syringe. Skin testing was read at 15 min; an 8 × 10-mm erythematous induration was observed at the injection site. This was accepted as a positive skin test and the second scintigraphy session was cancelled. The subject again complained of fatigue and dizziness after the radiopharmaceutical test dose. The patient's biochemical tests, blood counts were normal except for eosinophilia (8.8%).

Various allergic responses to radiopharmaceuticals have been reported. These allergic responses may occur as simple symptoms such as fatigue, nausea, dizziness, rushing and pruritis or as severe a systemic reaction as anaphylaxis (*3–6*). Intradermal skin testing may correlate well with systemic reactivity and predict an allergic response to bone imaging agents (*3*). In this case, the patient's symptoms secondary to an allergic reaction to ^{99m}Tc-mebrofenin is based on the positive skin test and the lack of another explanation.

REFERENCES

1. Cordova MA, Rhodes BA, Atkins HL, Glenn HJ, Hooglond DR, Solomon AC. Adverse reactions to radiopharmaceuticals. Report of the Adverse reactions Subcommittee of the Society of Nuclear Medicine. *J Nucl Med* 1982;23:550–551.
2. Keeling DH, Sompson CB. Adverse reactions to radiopharmaceuticals. United Kingdom 1977–1983. *Br J Radiol* 1984;57:1091–1096.
3. Gabatin AR, Orzel AJ, Maloney TR, Mumane JE, Barchert RD. Severe systemic reaction to diphosphanate bone imaging agents: skin testing to predict allergic response and a safe alternative agent. *J Nucl Med* 1986;27: 1432–1435.
4. Spicer JA, Preston DF, Stephens RL. Adverse allergic reaction to technetium-99m-methylene diphosphanate. *J Nucl Med* 1985;26:373–374.
5. Ponto JA. Adverse reactions to technetium-99m colloids. *J Nucl Med* 1987; 28:1781–1782.
6. Williams ES. Adverse reactions to radiopharmaceuticals: a preliminary survey in the United Kingdom. *Br J Radiol* 1974;47:54–59.

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Out of Sight, Out of Mind!

TO THE EDITOR: Recently, ^{99m}Tc-teboroxime (CardioTec™), a new myocardial perfusion agent (*1,2*), was recalled temporarily from the world market. Regrettably, this has implications in the clinic and for the industry. The chromatography procedure suggested in the manufacturer's product monograph indicated greater than 90% binding throughout the first 6 hr after reconstitution. The solution was clear immediately after preparation, but within