clinician. Surely, before making their positive recommendation for *all* cameras, some attempt should have been made to enable the results to be assessed by a panel rather than by a single clinician only.

Furthermore, their "liver phantom of average size (17 cm × 17 cm)" (no scintigrams of which were shown) in which "the focal lesion was simulated using various thicknesses of aluminum discs, 2 cm in diameter" is probably not very realistic clinically, unlike that used by the United Kingdom DHSS (*2*). A liver of average shape is difficult to define, as can be seen from the literature (*3, 4*), and a better policy might have been to adapt the DHSS phantom so that three or four of the most commonly occurring normal variants of liver shape had been available.

Baimel and Bronskill also concluded that since 256 of 1973 (13%) Ontario Cancer Institute liver studies had been read as equivocal or suspicious during 1975–76, motion correction could be of *considerable* benefit in that institute. Without a detailed followup analysis on as many of the 1975–76 patients as possible, and a resulting assessment of false-positive, false-negative, and equivocal reports, no such strongly worded statement should be made.

Finally, since the liver is a large organ of variable thickness, I am not fully convinced that the displacement of its periphery is the same as that of the center of activity within the liver. If the motion is more complicated than that assumed by Baimel and Bronskill, motion correction will in turn become more complicated—although, we hope, not to the extent that an increase in false positives will occur! Perhaps, therefore, while we are investigating new mathematical tools we should find it rewarding and informative also to assess in detail our present diagnostic efficiency in liver scintigraphy. For example, are we really seeing a 2-cm tumor when we think we are? Such an exercise, involving good prospective record keeping of patient data, including any subsequent followup for eventual correlation studies, could in itself lead to a reduction in the number of equivocal scintigram reports—even without any liver-motion correction. This suggestion also has the advantage that only a minimum of mathematics is required!

R. F. MOULD
Westminster Hospital
London, United Kingdom

REFERENCES

1. BAIMEL NH, BRONSKILL MJ: Optimization of analog-circuit motion correction for liver scintigraphy. *J Nucl Med* 19: 1059–1066, 1978
2. POTTER DC, MCCREADY VR, MOULD RF, et al: (DHSS Working Party Members): A survey of some radionuclide imaging instruments with an anthropomorphic liver phantom. DHSS publication, STB/3/78, 1978.
3. MCAFEE JG, AUSE RG, WAGNER HN: Diagnostic value of scintillation scanning of the liver. *Arch International Med* 116: 95, 1965
4. MOULD RF: An investigation of the variations in normal liver shape. *Br J Radiol* 45: 586–590, 1972

Reply

Our article (*1*) described a general mathematical model for analog motion-correction circuits. The validity of this model was verified by experimental measurements and a simple detection test that simulated clinical liver scintigrams. The purpose of our article, as clearly stated in the title, was to provide a general technique for optimizing the performance of analog-circuit motion correction.

I draw Dr. Mould's attention to the work of Turner et al. (*2*), which was published before our article. They not only showed liver scintigrams with and without motion correction, but they also analyzed liver scintigrams for 102 patients in which the true state of the liver was established. Their results with five observers were expressed as receiver operating characteristic curves and their conclusion was that "analogue motion correction is an effective, inexpensive method for improving hepatic scintigraphy with a scintillation camera." With this background information available, I do not find at all "premature" our conclusion that analog motion correction be provided in all scintillation cameras used for liver scintigraphy.

Our liver phantom was constructed to duplicate the film-density distribution measured from a liver scintigram of a patient with a normal liver. To that extent our phantom certainly was "clinically realistic." The DHSS phantom may well be a more common (and commercial) variant; its use in our experiments would not change our results or conclusions.

Because a large fraction (13%) of our 1975 and 1976 liver studies were interpreted as suspicious or equivocal, we considered as worthy of comment the indication that motion correction is most likely to clarify the interpretation of suspicious or equivocal. We were merely pointing to a large fraction of our liver scintigraphy studies in which we believed motion correction *could* be of benefit. The adjective "considerable" was apparently too strong for Dr. Mould. Although about 10% of our liver images are still obtained with a rectilinear scanner, we have observed, since implementing analog motion correction, a decrease in the fraction of total liver images interpreted as suspicious or equivocal from 13% to 10.5% (206 out of 1967) in 1977 and to 7.5% (139 out of 1863) in 1978. I consider this benefit worth considering (i.e., "considerable").

Dr. Mould's final paragraph restates the basic assumption of analog motion correction: that only translatory motion of the organ occurs. I, too, am not convinced that the motion of the periphery of the organ is the same as the motion of the center of activity. The fact remains that, within this limitation, properly executed analog motion correction is a simple, effective, and inexpensive technique for improving spatial resolution in liver scintigraphy.

M. J. BRONSKILL
The Princess Margaret Hospital
Toronto, Canada

REFERENCES

1. BAIMEL NH, BRONSKILL MJ: Optimization of analog-circuit motion correction for liver scintigraphy. *J Nucl Med* 19: 1059–1066, 1978
2. TURNER DA, FORDHAM EW, ALI A, et al: Motion corrected hepatic scintigraphy: an objective clinical evaluation. *J Nucl Med* 19: 142–148, 1978

Reticuloendothelial Distribution of a Colloid-Like Material in 6β-[^{131}I]-Iodomethyl-19-Norcholesterol (NP-59)

We have recently observed a previously unreported occurrence involving the apparently reticuloendothelial distribution of a colloid-like impurity in the adrenal imaging agent 6β-[^{131}I]-iodomethyl-19-norcholesterol (NP-59). The radiodiagnostic agent* was obtained as 6β-[^{131}I]-iodomethyl-19-norcholesterol in 1.5% polysorbate (Tween 80) and 6.6% absolute ethanol, in a final specific concentration of 2.33 mCi/ml at the time of calibration. Sterility and limulus lysate pyrogenicity testing, performed in our department, proved negative. A radiochemical purity check with ITLC-silica gel media and normal saline

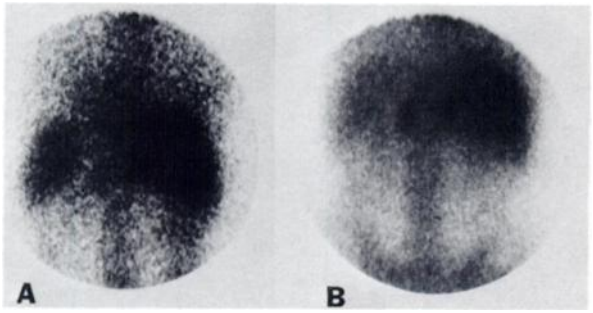

FIG. 1. Posterior scintiphotos obtained at (A) 48 hr and (B) 96 hr with 6β-[^{131}I]iodomethyl-19-norcholesterol. RES activity persists through 96-hr image.

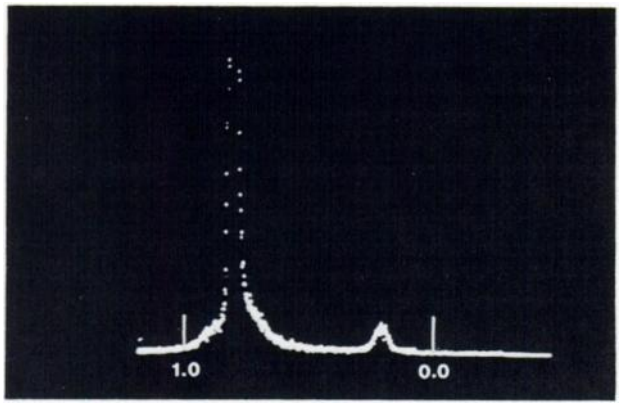

FIG. 2. Radiochromatography with ITLC-silica gel and chloroform, showing primary region of activity at R_f 0.80, with free iodide (6.8%), R_f 0.10.

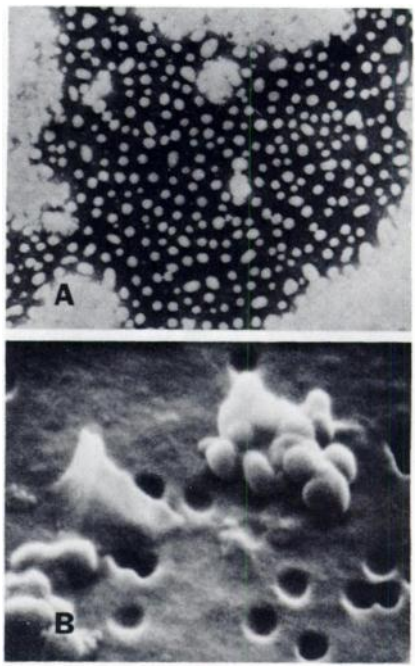

FIG. 3. Electron micrographs performed on NP-59 (lot no. 061378NP5975). Spherical particles are seen both individually and as aggregates. (A) Sample negatively stained with 1% phosphotungistic acid × 75,000 and (B) scanning micrograph showing larger particles on a filter membrane × 50,000.

yielded a small region of free iodide activity (1.2%) near the solvent front, and a primary peak of activity at an R_f of 0.15 representing NP-59 activity (*1*). The patient was pretreated with Lugol's solution and was injected with 1.8 mCi of NP-59 slowly over a 3-min period.

The patient, a 57-year-old woman with a history of hypercalcemia and hypokalemia, had undergone surgical removal of a parathyroid adenoma 2 wk before imaging. Serum electrolyte levels obtained 2 days before imaging were within normal limits.

Scintigrams obtained at 48 and 96 hr showed persistent uptake of the agent in the liver, spleen, and bone marrow (Fig. 1), with bilateral adrenal uptake observed at 96 hr. Later images were not obtained. Radiochromatography with ITLC-silica gel and analytical-grade chloroform was performed on the remaining sample of the radiopharmaceutical at that time. The radiochromatogram (Fig. 2) indicates the presence of a chloroform-soluble component that migrates to an R_f of 0.80, and a lesser fraction (6.8%) that appears at an R_f of 0.10 and would be representative of free iodide activity (*1*). Electron micrographs (Fig. 3) demonstrate the presence of spherical particles with diameters in the range of 30-200 nm. When prepared by negative staining for transmission electron microscopy, the individually dispersed particles had ultrastructure characteristics similar to those of similarly prepared plasma lipoproteins. These were seen by scanning EM both individually and in small aggregates.

In correlation with the scintillation images, the in vitro analyses show the presence of a colloid-like radiochemical impurity. The initial radiochromatogram, performed with normal saline immediately before injection, failed to quantify the presence of any radiochemical impurity other than free iodide ion, which was within the acceptable limits (≤ 3%) used by our department. The follow-up radiochromatogram with analytical-grade chloroform showed a primary radiocomponent at an R_f of 0.80, which is in contrast to that reported for NP-59 (*1*). Radiochromatography with chloroform and ITLC-silica gel performed by the supplier on their remaining sample of this same lot demonstrated the expected results with NP-59 at an R_f of 0.6 and some free iodide at an R_f of 0.15. (Personal communication, Dennis Swanson). A check with other adrenal investigators did not yield any similar occurrences of the altered biodistribution pattern that we experienced.

The relative insolubility of cholesterol can be a serious obstacle in the preparation and stability of aqueous solutions. Nevertheless, our previous experience with this formulation of NP-59 has been favorable. Because a sufficient quantity of this material was not available for additional testing, we could not further investigate the presence of a radiocholesterol colloid. We believe, however, that the impurity did most likely exist in the radiopharmaceutical at the time of chromatography with normal saline, but was not detected. Normal saline has been suggested by one author (*2*) as the solvent of choice for the homoallyic isomer of NP-59, 19-[^{131}I]-iodocholesterol, and by another as a secondary solvent for NP-59 (personal communication, Dennis Swanson). Our experience, however, shows that normal saline is not a satisfactory solvent for the radiochemical analysis of NP-59. Additionally, the slight difference between R_f values for the primary radiochemical component that we saw (0.8) and that expected with NP-59 (0.6) could make resolution of a colloid component difficult.

The performance of thorough quality-control analysis of NP-59, and all radiopharmaceuticals, is of paramount importance. At the moment, analytical-grade chloroform may be the pre-

ferred solvent for NP-59, although should this problem become more frequent in the future, the difficulty of accurately resolving a radiocholesterol colloid from NP-59 could negate this usefulness in favor of a more desirable solvent system.

HANK CHILTON
JON C. LEWIS
STEVEN F. MOTSINGER
ROBERT J. COWAN
Bowman Gray School of Medicine
Winston-Salem, North Carolina

FOOTNOTE

* Lot No. 061378NP5975, University of Michigan Nuclear Pharmacy, Ann Arbor, MI.

REFERENCES

1. VIVIAN A, ICE RD, SHEN V, et al: Radiochemical Purity of Radiopharmaceuticals Using Gelman Seprachrom Chromatography, Gelman Instrument Co., Ann Arbor, 1977
2. ZIMMER AM, DAVEL DG: Rapid miniaturized chromatographic quality control procedures for iodinated radiopharmaceuticals. *Am J Hosp Pharm* 35: 426–428, 1978

Altered Biodistribution of 6β-[^{131}I]-Iodomethyl-19-Norcholesterol (NP-59): Radiopharmaceutical Contamination or Patient Idiosyncracy?

The University of Michigan Nuclear Pharmacy is naturally concerned with any reported problem in regard to the use of NP-59. Although we do not question the obviously abnormal biodistribution observed in the reported study, we are not totally convinced that this phenomenon was due to the presence of an insoluble colloidal contaminant in our original formulation.

In the manufacturing sequence of NP-59, an initial step involves the preparation of 10-mCi multiple-dose vials. These 10-mCi "bulk" vials are subsequently subdivided into five 2-mCi individual dose vials. Our followup conversation with each of the four other investigators who received *exactly* the same material from the same "bulk" vial as this investigator revealed no altered biodistribution patterns. We have received no other reports of problems with this batch of NP-59 (061378NP5975), nor did we observe reticuloendothelial uptake in four patients studied with the same material at our institution (Fig. 1).

FIG. 1. Posterior scintillation image (computer display) obtained in a Cushingnoid patient 5 days after administration of 1 mCi of NP-59 (Lot No. 061378NP5975).

Regarding the apparent demonstration of spherical particles in the electron micrographs, we note that the Tween-80 surfactant used in the formulation most likely exerts its solubilization effects on NP-59 via micellization. Micelles (association colloids) are spherical aggregates of colloidal dimensions, not to be confused with insoluble colloids routinely encountered in radiopharmaceutical preparations. This phenomenon would not only explain the presence of the uniform spherical particles, but also their ultrastructural similarity to a naturally occurring association colloid, the plasma lipoproteins (*1*).

If an *insoluble* colloidal impurity were present in this preparation of NP-59, one would have expected to visualize it at an R_f of 0.0 using an instant thin layer chromatography (ITLC) silica-gel: normal-saline system. Although your correspondents did not observe the presence of this impurity in their initial analysis, we agree that it may be difficult to separate its R_f peak from the R_f of NP-59 (0.15). On the other hand, they state that further in vitro analysis (ITLC silica-gel: analytical-grade chloroform) showed the presence of a colloid-like radiochemical impurity at an R_f of 0.8, which was in contrast to that reported for NP-59 (0.6). Careful inspection of the sample chromatogram presented in their reference for this chromatography system reveals that the R_f of 19-[^{131}I]-iodocholesterol is 0.6, with the R_f of NP-59 being somewhat higher (*2*). Our experience in the use of an ITLC silica-gel: chloroform system for the radiochemical analysis of NP-59 has been unsatisfactory, with considerable spreading of the radioactive peak; therefore we have recommended (*3*), and continue to recommend, the use of Thin-Layer Chromatography (TLC) silica-gel: analytical-grade chloroform (R_f of NP-59 = 0.4).

Another tenable explanation for the observed altered distribution of NP-59 is patient idiosyncracy. Although we have not witnessed such a pattern in over 200 patients studied at the University of Michigan, the relative lack of overall clinical experience with NP-59 leaves this as one possibility. Patient history, including laboratory values and current drug therapy (i.e., corticosteroids), is required to evaluate such a possibility and is, in fact, of paramount importance to the interpretation of any adrenal scintigraphic study.

In summary, the altered biodistribution of NP-59 reported may be a result of an insoluble radiochemical impurity in the preparation, or a patient idiosyncracy. Our followup analyses on this batch of NP-59 indicates that a radiocolloid contaminant was probably not present in the original formulation. We do recognize the possibility for radiochemical impurity formation as a result of the rigors of shipment or on-site manipulation of the agent, and therefore stress the importance of quality control by each investigator. However, we don't feel that the results of the quality control tests presented in the letter in question definitely indicate the presence of a colloidal impurity in the preparation, either before or after administration. Further analysis of this patient's history is necessary to evaluate properly the possibility of a patient idiosyncracy.

DENNIS P. SWANSON
NANCY E. WIRTH
MILTON D. GROSS
University of Michigan Medical Center
Ann Arbor, Michigan

REFERENCES

1. ELWORTHY PH, FLORENCE AT, MACFARLANE CB: *Solubilization by Surface-Active Agents*. Bungary, Suffolk, Great Britain, The Chaucer Press Ltd., 1968, pp 13-60
2. VIVIAN A, ICE RD, SHEN V, et al: *Radiochemical Purity of Radiopharmaceuticals Using Gelman Seprachrom Chromatography*, Ann Arbor, MI, Gelman Instrument Co., 1977, p 23