# LETTERS TO THE EDITOR

## Re: Colloidal Particle-Size Determination by Gel Filtration

In their article on particle-size determination by gel filtration, Billinghurst and Jette (*1*) state that for particle-size measurements gel filtration indicates "the proportion of radioactivity in the size ranges rather than the number of particles."

At a time when we do not understand the effects of radiocolloid particle size, shape, charge, chemical nature, or any combination of these characteristics on biological systems, it would be more useful to state the activity per total particle number within a particular size class. To propose gel filtration and nucleopore filtration as a rapid screening technique for particle-size analysis is premature, as we do not even understand the significance of particle size on biological distribution.

Until such time when we truly understand the physical properties of radiocolloidal dispersions, gel filtration (*2*) and nucleopore filtration (*3*) should serve only to complement electron-microscopic analysis (*4*).

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*2*. PERSSON RBR, STRAND SE, KNOOS T: Radioanalytical studies of $^{99m}$Tc-labeled colloids and macromolecules with gel chromatography column scanning technique. *J Radioanalytical Chem* 43: 275-286, 1978
*3*. DAVIS MA, JONES AG, TRINDADE H: A rapid and accurate method for sizing radiocolloids. *J Nucl Med* 15: 923-928, 1974
*4*. WARBICK A, EGE GN, HENKELMAN RM, et al: An evaluation of radiocolloid sizing techniques. *J Nucl Med* 18: 827-834, 1977

## Reply

I agree with Ann Warbick-Cerone that currently we do not understand the effects of radiocolloid particle size, shape, charge, and chemical nature on biological systems, and that any data on colloidal localization should ideally provide as much information as possible on these physical characteristics of the colloid. Nevertheless I do not see how electron-microscopic analysis helps in this aim other than by supplying data on particle size. It may be true that the ideal way to express the radioactivity would be as activity per total particle number within a particular size class, but there is no way that the electron microscope will enable one to do this unless the particles are of uniform size. In such a case the sizing technique is unimportant. Gel filtration and nucleopore filtration, when coupled with the radioactive assay, do enable one to express the radioactivity in terms of the activity within a particle-size class. Thus they approach the ideal more closely than electron microscopy.

The advantages of electron microscopy that should not be overlooked are that it provides more definitive particle-size data as well as particle numbers. The actual numbers of particles cannot be obtained by any other method. Unfortunately, however, it does not relate the number of particles to their radioactivity, so that without additional data relative to the radioactivity of the particles in a size range it can be rather misleading. Take for example the case of the sulfur colloid preparation referred to in our article (*1*), where (a) only 0.5% of the particles are over 800 nm but represent 25% of the radioactivity, (b) 9.5% of the particles are between 200 and 600 nm but represent 73% of the radioactivity, and (c) 90% of the particles fall in the 5- to 15-nm range but account for only 1.5% of the radioactivity. Since nuclear medicine techniques indicate the biological distribution of radioactivity, clearly the most important information is the radioactivity in a certain particle-size range, rather than the number of particles in that range.

Thus I believe that while the ideal analysis of a radiocolloidal preparation should include all the physical aspects, the particle-size aspect must address the relationship between radioactivity and particle size. One way of doing this is by the nucleopore and gel-filtration technique we proposed. Where the electron microscope is available, it is a valuable analytical tool that can complement the data on the radioactivity in various size ranges but is adequate as a "stand alone" analysis only when the radiocolloidal preparation has a uniform particle size.

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REFERENCE

*1*. BILLINGHURST MW, JETTE D: Colloidal particle-size determination by gel filtration. *J Nucl Med* 20: 133-137, 1979

## Toxicity and Safety Factors Associated with Lung Perfusion Studies with Radiolabeled Particles

I read with great interest the articles by Allen et al. (*1*) and Davis and Taube (*2*), dealing with the toxicity and safety factors associated with lung perfusion studies with radiolabeled particles. It should be pointed out, however, that only adult animals were used in these studies. With the growing use of krypton-81m ventilation studies, it is likely that the use of technetium-99m-labeled particles for the evaluation of pulmonary perfusion will be used more frequently in infants. Since there is significant postnatal growth and development of the lung, these safety factors are likely to be more demanding in the very young.

In the human infant the alveoli increase in number rapidly during the first year, and then more gradually, reaching adult levels at about 8 years of age (*3*). Similarly there is an increase in the number of small pulmonary arteries, particularly between the ages of 4 mo and 3 yr (*4*). While the precise age at which alveolar multiplication ceases is not certain, one estimate showed a rapid increase from about 1/10 to 1/3 of adult values during the first year of life and to 1/2 the adult number by 3 yr (*5*).

This means that if 500,000 particles are regarded as safe in the adult, the number should not exceed 50,000 in the newborn or 165,000 at 1 yr. If the macroaggregated albumin kit contains an average of 5 million particles*, and it is reconstituted with high

concentration Tc-99m (say 150 mCi/3 cc), then a newborn dose of 0.5 mCi would contain 17,000 particles. However, preparations containing less than 50 mCi would deliver more than 50,000 particles.

The importance of using a high concentration of Tc-99m is obvious, but should be emphasized. Alternatively, if lower Tc activities are considered in order to avoid waste, a single kit can be split to provide several doses, each delivering a smaller number of particles.

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FOOTNOTE

* Pulmolite, New England Nuclear Corp., Boston MA.

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4. DAVIES G, REID L: Growth of the alveoli and pulmonary arteries in childhood. *Thorax* 25: 669-681, 1970
5. EMERY JL, MITHAL A: The number of alveoli in the terminal respiratory unit of man during late intrauterine life and childhood. *Arch Dis Child* 35: 544-547, 1960

## Reply

We appreciate the interest in our work expressed by Dr. Heyman and fully concur with his concern for safety in pediatric pulmonary perfusion scintigraphy. Although this particular aspect of safety was beyond the scope of our investigation, we welcome the opportunity to comment here.

It is our belief that all adult lung scanning with commercially available MAA kits (particle size 10-60 $\mu$m) should be performed with no fewer than $10^5$ and no more than $10^6$ particles. In our clinics we formerly added 60 mCi of $^{99m}TcO_4^-$ to the MAA vial. This gave 250,000 MAA particles per 3-mCi dose immediately after preparation (8:00 am) and approximately 750,000 particles at the end of the day (5:00 pm). In the event of an emergency lung scan after 5:00 pm, a new vial of MAA was prepared. Under these circumstances, a pediatric dose of 0.5 mCi involved 42,000 aggregates at 8:00 am and 125,000 at 5:00 pm. With the recent widespread use of the fission $^{99}Mo$-$^{99m}Tc$ generator, which yields higher concentrations of pertechnetate, and the increased use of pediatric pulmonary perfusion scintigraphy, we have made it mandatory to add at least 120 mCi of pertechnetate to our MAA vial, giving an equivalent pediatric dose of 21,000 particles at 8:00 am and 63,000 at 5:00 pm.

Since we are a central radiopharmacy serving seven Harvard-affiliated hospitals, we use 120 to 150 mCi of Tc-99m-MAA daily. Therefore, we are able to achieve safety and economy simultaneously. For smaller institutions, which cannot afford to reconstitute their MAA kits with 120 mCi of pertechnetate, may we suggest either using unit dose kits containing $10^6$ or fewer particles, or splitting the kit by reconstitution with 2 ml of generator eluent (saline), then removing and discarding an appropriate amount (say 1.5 ml containing 3,750,000 particles), and adding 30 mCi to the remaining 1,250,000 MAA particles.

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## Scanning Dose and the Detection of Thyroid Metastases

Němec and coworkers (*1*) have again demonstrated that the quantity of I-131 administered to a patient before scanning for thyroid metastases alters the number of lesions detected by the technique (*2*). They conclude that machine setting, absolute quantity of I-131 concentrated by the lesion, and the background are important in this phenomenon. That these factors affect the detection of thyroid metastases by radionuclide imaging is undoubtably true, but the problem is more complex than the authors imply.

To begin with, the types of thyroid cancer that concentrate I-131 are rarely "pure" even when they appear so by light microscopy (*3*); neither are they a homogeneous group regarding differentiation (*4*). Furthermore, what the microscope reveals as a state of differentiation may not be reflected in the malignant tissues' ability to carry out enzymatic processes necessary for trapping and organification (*5*). It would not be unusual, therefore, if the acquisition of the radiopharmaceutical proceeded at different rates from site to site. The end result of this would be varying concentrations of I-131 (on a per-gram basis) in the metastatic deposits.

Secondly, it cannot be assumed that the blood flow per gram of tissue is the same to all metastatic areas. Certainly it is not the same to all parts of a primary tumor (*6*). If all other parameters remained constant, blood flow alone would be an important reason for the detection of one lesion in preference to another.

The size of a metastasis would be yet another variable, since the detector would be more likely to "see" a 10-g lesion that concentrated very little I-131 than a 1/2-g tumor that concentrated twice that amount per gram.

Differing rates of egress of radiopharmaceutical from the viable tumor (*7*) could also play a part in detectability. Stanbury and Brownell have shown (*8*) that the half-times for release of tracer in patients administered diagnostic and therapeutic quantities of I-131 for metastatic thyroid cancer are the same, ranging from 3 to 12 days. This is much faster than the total-body half-times for I-131 in normal patients following the same procedures. Thus, the rapid rate of egress of I-131 from a thyroid metastasis following a diagnostic (low) dose could shift a lesion from the detectable to the nondetectable level. This same rate of egress following a therapeutic dose would be less critical in detection, however, because of the large amount of I-131 initially in the lesion.

The one common denominator that could affect all of these variables is the plasma level of the radiopharmaceutical. In general, the higher the plasma level of tracer at time zero, the higher will be the plasma level at some distant time. A large dose of I-131 might produce plasma levels such that those tumor cells slow in acquiring I-131 could sufficiently concentrate the tumor to be detectable by our techniques; "low dose" on the other hand might not. Indeed, it is partly the plasma levels of I-131 that determine our ability to detect thyroid metastases that are not obvious before removal of a normal thyroid. The normal thyroid acts as a sump and, along with renal excretion, drops the plasma level of radioiodine at a very rapid rate. Remove the thyroid and the plasma iodine levels fall more slowly. It should not be surprising, therefore, to find the same phenomenon at work when the plasma levels are kept high by the administration of large quantities of radiopharmaceutical.