the amount of time one will have to spend scanning, or the amount of radioactivity that one will have to administer, it relates more to radiation dose considerations than to biologic considerations. The authors have excluded the radiation dose considerations from their rating system. Therefore, this parameter should be excluded as well.

Because of these drawbacks, it is difficult to imagine what, if anything at all, their rating system represents. To prove my point, let us consider two hypothetical agents, A and B, with the following experimental data for the four components used in their rating system:

Agent	% ad. dose per gram	Tumor-to-brain	Tumor-to-blood	Tumor-to-skin
A	2	10	10	1
B	3	3	3	2

According to their rating system, both agents should be rated equal, whereas with such high tumor-to-brain and tumor-to-blood ratios, and with only slightly inferior % administered dose/g and tumor-to-skin ratios, Agent A will be a far better choice than Agent B.

This fundamental weakness of their rating system is also evident in their radiopharmaceutical rankings. I am reproducing experimental data for the 4th ranked (one of the best) and 15th ranked (one of the worst) radiopharmaceuticals from Table 1 of their first paper (*1*).

	% ad. dose per gram	Tumor-to-brain	Tumor-to-blood	Tumor-to-skin
4th rank	3.04	6.8	0.25	1.13
15th rank	2.80	6.6	0.21	0.56

A glance at the data makes it clear that there is not a large difference between a good and a bad agent. The differences in the first three pairs of numbers are probably statistically insignificant. The only numbers that seem different are the tumor-to-skin ratios, which alone have pushed one to 4th place and the other to 15th place. Incidentally, when these authors used their experimental results in the rating system, they completely ignored the statistical significance of the differences between the measurements. Consequently, a tumor-to-blood ratio of 0.21 rated better than one of 0.19. Due to the want of the standard deviation data in their papers, I am unable to make a definite statement as to whether these two numbers are statistically different, but, from my own experience, it seems highly unlikely.

In conclusion, I feel there is a vital need for a suitable biologic parameter (figure of merit) with which to compare different radiopharmaceuticals in an experimental model system for brain scanning. I do not think, however, that the parameter used by Haynie et al. meets the desired need.

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Reply

The letter of Dr. Chandra concerning "Rating of Radiopharmaceuticals for Brain Imaging" is acknowledged with thanks, since it stresses problems encountered by every investigator who attempts to study tumor-localizing agents. We respond not to justify the defects in our rating system but rather to emphasize again our previous admonition that these data should not be translated into the clinical sphere without due caution.

Point 1 in Dr. Chandra's letter is well taken. The rating system does not provide an index of how agents differ or how much they differ. From inspection it is apparent that some are quite close, others quite different in their values. In our previous papers we have provided figures for statistical significance. We did not think it appropriate in the rating system, which was more an attempt at "optimization" than at judging differences.

With regard to point 2, we cannot agree with Dr. Chandra that the percentage administered dose per gram of tumor does not belong in the rating system. It certainly is a measure of the avidity of the tumor for the substance. Limitations on available scanning time and radioactivity that can be administered also make this of importance. We do recognize that some rapidly excreted agents may achieve good ratios with low percentage uptake per gram. It is for this reason that we now also use percentage *retained* dose/g tumor as an alternate means of evaluation (*1,2*). We agree that tumor-to-skin ratios are not an entirely satisfactory substitute for "calvarial" contribution, but technical difficulty with this model confined us to this. The proximity of the calvarium to the detector, however, leads us to believe that its contribution to count rate makes it of considerable importance. Dr. Chandra's hypothetical case will be of importance if we ever encounter an agent with the bizarre characteristics that he postulates.

Among our suggestions for future developments has been the need for comparisons between existing tumor models and the results obtained in humans, in order to understand better the relationship between animal and human tumors (*3*). It should be our goal in laboratory research with tumor models to indicate to clinicians those trends and phenomena that can be observed repeatedly and that may be applicable to a better understanding of malignant disease in man. As Dr. Chandra points out, we have a long way to go.

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Dry Aerosol Delivery System Compared with Ultrasonic Nebulizer

We have previously described a compressed-air system to

TABLE 1

	Ultrasonic nebulizer	B.A.R.C. nebulizer
Optimum volume of solution to be nebulized	10 ml	1 ml
Rate of nebulization	0.66 ml/min at speed position 7	0.0826 ml/min at 25 psi pressure*
Mass median diameter of aerosol particles	1.02 μm	0.84 μm
Geometric standard dev. in aerosol particle size	1.52 μm	2.08 μm
Range (66% limit)	0.67 μm to 1.55 μm	0.40 μm to 1.74 μm
Nature of aerosol	wet	dry
Cost in arbitrary units	100	10

* = ca. 1300 mm Hg.

produce dry aerosol particles containing $^{99m}TcO_4^-$ for lung imaging (*1*). We have now compared the performance of this aerosol generation and delivery system (called B.A.R.C.* nebulizer) with that of an ultrasonic nebulizer†.

It is seen from Table 1 that the B.A.R.C. system delivers at a very low rate compared with the ultrasonic nebulizer, but the volume used for nebulization is also proportionately small, so that the wasted, unnebulized fraction becomes almost equal in both. Furthermore, the small volume required in the B.A.R.C. nebulizer makes it possible to use high-specific-activity solutions. Size distribution studies of aerosol particles from both nebulizers were made by using an Anderson Cascade Impactor (*2*). Both nebulizers were found to give comparable aerosol sizes, the particle-size distribution from the ultrasonic nebulizer being less dispersed. The great advantage of the B.A.R.C. nebulizer is that it produces dry aerosols. It is known that wet aerosols tend to deposit in major bronchi on their way to the alveoli, thus producing a heavy bronchial pattern in lung aerosol images. Figure 1 shows aerosol images obtained from a subject with the two nebulizers operating at the same compressed-air pressure. In both, the patient inhaled through the nose. As seen from the figure, the wet aerosol from the ultrasonic nebulizer tends to produce heavier deposition in the major bronchi. The rate of nebulization in the ultrasonic nebulizer is nearly ten times that of the B.A.R.C., and hence the compressed air used for drying the ultrasonic aerosols is insufficient. To obtain completely dry aerosols from the ultrasonic nebulizer, ten times the air flow would be required, which is uneconomical and inefficient. The inexpensiveness of the B.A.R.C. nebulizer is an attractive factor when resources are limited. This nebulizer is now in routine use with us for clinical studies in patients with chronic obstructive pulmonary disease, and there have been no problems.

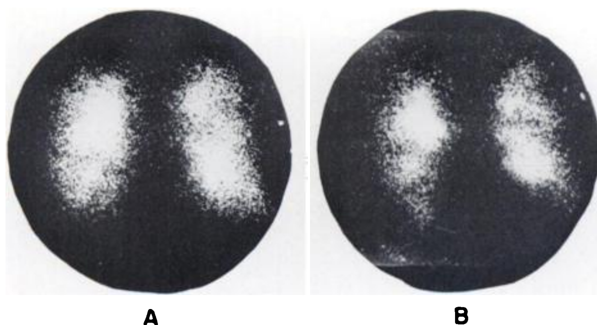

FIG. 1. Posterior views of a patient made with (A) B.A.R.C. nebulizer, and (B) ultrasonic nebulizer.

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FOOTNOTES

* B.A.R.C. = Bhabha Atomic Research Center.
† De Vilbiss 35A, 1.35 MHZ.

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Effect of Phenobarbital on Liver Uptake of Ga-67

After i.v. administration, gallium-67 citrate is taken up by liver cells. Subcellular Ga-67 is associated with lysosomes and probably also with a microsomal fraction within the cell (*1,2*). One possible explanation for this subcellular distribution is that Ga-67 may have a specific affinity for certain enzymes within these organelles. Various metals can substitute for iron in enzymes during iron deficiency (*3*) and Ga-67 does compete with iron for binding sites on the blood protein transferrin. In this context, binding of Ga-67 to one or more microsomal enzymes could account for at least some of the observed localization.

Phenobarbital is known to increase the amount of enzymes of the microsomal system, i.e. cytochrome P-450, cytochrome b_5, aniline hydroxylase, and aminopyrine demethylase. An increase is also found in smooth endoplasmic reticulum (SER), in protein concentration (including the anionic transport proteins Y and Z), in liver weight, and possibly in the RNA content of liver cells (*4,5*). These represent only a few of the known effects phenobarbital has on the body, but the relationship of Ga-67 to these effects can be looked at rather easily.

Balb/c mice were given daily intraperitoneal injections (0.1 ml $\approx$ 1.2 mg) of phenobarbital for six days. Control mice were injected with 0.1 ml soybean oil (the delivery solution for the phenobarbital) at the same time as test mice. On day eight, all mice were injected with 0.25 μCi Ga-67 citrate in 0.20 ml saline (a dose found to give high percentage uptake in this laboratory). On the ninth day the mice were killed and body samples were weighed and counted in a gamma counter. A standard dose was counted at the same time to be used in the calculation of a percentage dose uptake.

The liver-to-body weight ratio was significantly* higher